CHIRAL ANION-MEDIATED CATALYSIS: THE CHEMISTRY OF VANOL-DERIVED BOROXINATE AND ZIRCONATE COMPLEXES

By

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ABSTRACT

CHIRAL ANION-MEDIATED CATALYSIS: THE CHEMISTRY OF VANOL-DERIVED BOROXINATE AND ZIRCONATE COMPLEXES

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A highly enantioselective asymmetric catalytic synthesis of *cis*- and *trans*-aziridines can be achieved with multi-component procedure with primary amines, aldehydes and diazo compounds mediated by a chiral boroxinate (BOROX) catalyst generated from VANOL, VAPOL or *t*-Bu_2VANOL ligands.

A catalyst controlled asymmetric aziridination is reported based on the previously developed method for the multi-component *cis*-aziridination. The stereochemistry of the newly formed aziridines is the function of chiral boroxinate catalyst and is independent of the chiral centers already present in the aldehyde substrates. A series of aldehydes with the chiral centers presented at either α- or β-positions are investigated to find out the diastereoselectivity of the corresponding aziridines from both enantiomers of the BOROX catalyst, as well as the evaluation of ligand control over the diastereoselectivity from the matched and miss-matched pairs. The synthesis of stereoisomers of isoleucine and polyoxamic acid will be discussed as the application of this method.

Meanwhile, The three-component catalytic asymmetric synthesis of *trans*-aziridines is introduced. This method provides direct aziridination of amines, aldehydes and diazoacetamides to give *trans*-aziridine-2-carboxamides with the chiral boroxinate catalyst. Taken together with our previous reported on the three-component catalytic asymmetric synthesis of *cis*-aziridines, the three-component aziridination can be controlled to give either *cis*- or *trans*-aziridines. The scope of the *trans*-aziridination is

discussed along with the application in the natural product synthesis. As the extension of this methodology, an asymmetric synthesis of α-amino-β-hydroxy amides is developed by the strategy of *trans*-aziridination/ring-opening cascade reactions with the presence of nucleophilic phenols and carboxylic acids, with decent yields and asymmetric inductions of aminohydroxy amides achieved. The substrate scope of aldehydes and oxygen-nucleophiles will be further explored.

In addition, a parallel kinetic resolution of racemic α-iminols is introduced based on the previously developed method of catalytic asymmetric α-iminol rearrangement based on a chiral zirconate complex derived from VANOL ligand. An excellent resolution of the racemic α-iminols with a phenyl and a alkyl migration group to afford a pair of amino ketone regioisomers with high enantiomeric purity. More studies will focus on the stereochemistry to reveal the mechanism of migration.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF SCHEMES

KEY TO ABBREVIATIONS

acac acetylacetone

AQN anthraquinone

Ac acetyl

ACDC asymmetric couteranion-directed catalysis

Bh benzhydryl

BINAP 1,1'-binaphthyl-2,2'-bis(diphenylphosphine)

BINOL 1,1'-bi(2-naphthol)

BPO benzoyl peroxide

Bu butyl

BUDAM tetra-*tert*-butyldianisylmethyl

CAN ceric ammonium nitrate

Cy cyclohexyl

DAM dianisylmethyl

DHDQ dihydroquinidine

DHQ dihydroquinine

DKR dynamic kinetic resolution

DMAP 4-dimethylaminopyridine

DMPAO 2,6-dimethylphenylaminooxalic acid

DNA Deoxyribonucleic acid

DOSP 1-(4-dodecylphenylsulfonyl)-2-pyrrolidine carboxylate

EDA ethyl diazoacetate

Et ethyl

Fmoc fluorenylmethyloxycarbonyl

HMDS hexamethyldisilazide

HMPA hexamethylphosphoramide

IBX 2-iodoxybenzoic acid

LDA lithium diisopropylamide

Me methyl

MEDAM tetramethyldianisylmethyl

NBS *N*-bromosuccinimide

NMI *N*-methylimidazole

Ns 4-nitrobenzenesulfonyl

Ph phenyl

PHAL phthalazine

phen phenanthroline

phth *o*-phthaloyl

Piv pivaloyl

PKR parallel kinetic resolution

PMP *para*-methoxyphenyl

PNB *para*-nitrobenzoate

Pr propyl

TADDOL α,α,α',α'-tetraaryl-2,2-disubstituted 1,3-dioxolane-4,5-dimethanol

TEMPO 2,2,6,6-(tetramethylpiperidin-1-yl)oxyl radical

Tf trifluoromethanesulfonyl

Tr triphenylmethyl

TRIP 3,3'-bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2-diyl hydrogenphosphate

Ts 4-toluenesulfonyl

VANOL 3,3’-diphenyl-2,2’-bi(1-naphthol)

VAPOL 2,2’-diphenyl-(4-biphenanthrol)

Chapter 1 Chiral Anions in Asymmetric Catalysis

1.1 Introduction

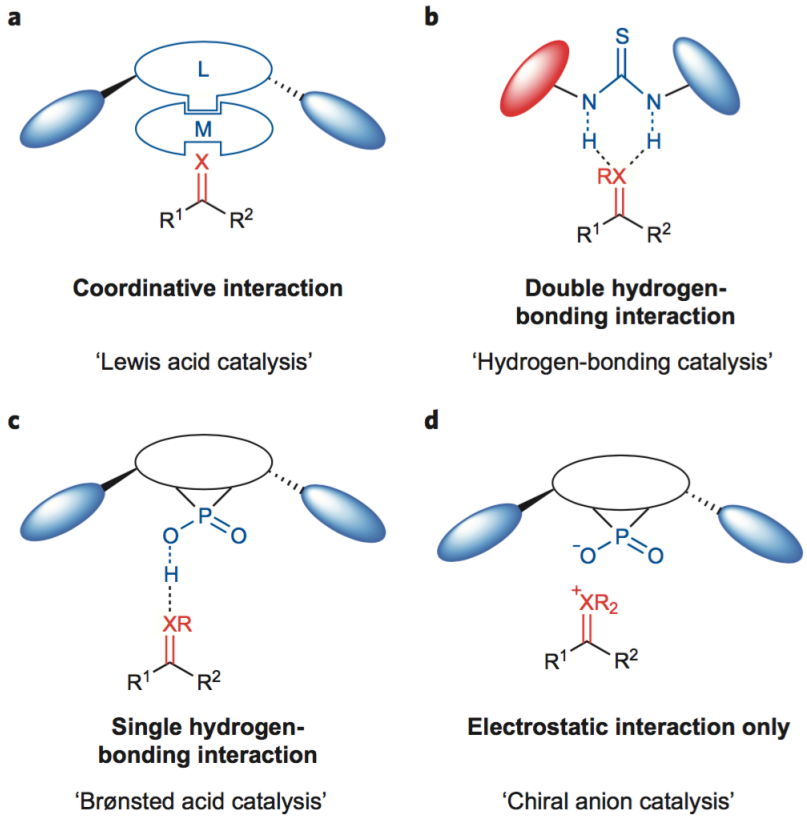
Chiral anions have been significantly highlighted in the field of asymmetric catalysis during the last score years. Cationic species, reagents and intermediates are frequently involved in many chemical reactions and processes as cations are often generated along the reaction pathways by Lewis/Brønsted acid catalysis or nucleophilic/electrophilic fragmentation. A great number of synthetic and biological processes are mediated by ammonium, iminium and imidazolium ions. Considering the purpose of asymmetric induction in asymmetric catalysis, people realized chiral anions can play an important role as counterion species in the asymmetric auxiliaries, ligands and reagents that provide electrostatic, hydrogen-bonding or coordinative interactions to be associated with cationic intermediates.[1]

A number of activation modes in asymmetric catalysis are fundamental to better understand the interactions of chiral anions with the targets.[2] In the most common scenario, the catalytic species can be a chiral Lewis basic ligand with the combination of a Lewis acidic reagent. The resulting chiral catalyst possessing the net Lewis acidity provides coordination with the target substrates at a nucleophilic site such as a carbonyl group that is effectively activated (Figure 1.1a).

Replacement of the Lewis acidic core in the catalyst with a proton gives an activation mode known as Brønsted acid catalysis that allows the formation of hydrogen-bonding of the proton to the nucleophilic site with the lone pairs of the target substrates. For weak Brønsted acids (pK_a 8-20), particularly for chiral ureas and thioureas[3], they are excellent

H-bond donors to develop double hydrogen-bonding interactions with the substrates providing high asymmetric inductions (Figure 1.1b).

Figure 1.1 Activation modes in Asymmetric catalysis[2]



Significant Brønsted acidity ($pK_a < 4$) of the catalysts, typically exemplified by BINOL-derived phosphoric acids[4], are likely to be totally deprotonated by the basic functional groups such as amines or imines. The enantioselectivity is likely to result from both electrostatic and hydrogen bonding interactions within the anionic conjugate base of the catalysts and protonated substrates (Figure 1.1c).

Since cationic species derived from the substrates are not all H-bond donors or acceptors, the chiral anionic catalysts can be the counterion of the substrates and provide the electrostatic ion-pair interactions as the effective activation mode known as asymmetric counteranion directed catalysis (ACDC) (Figure 1.1d). The substrate can form a cationic

intermediate and directly interact with the catalyst, or coordinate with Lewis acidic metals to form a cationic complex, which interacts with the catalysts as the ion pair.

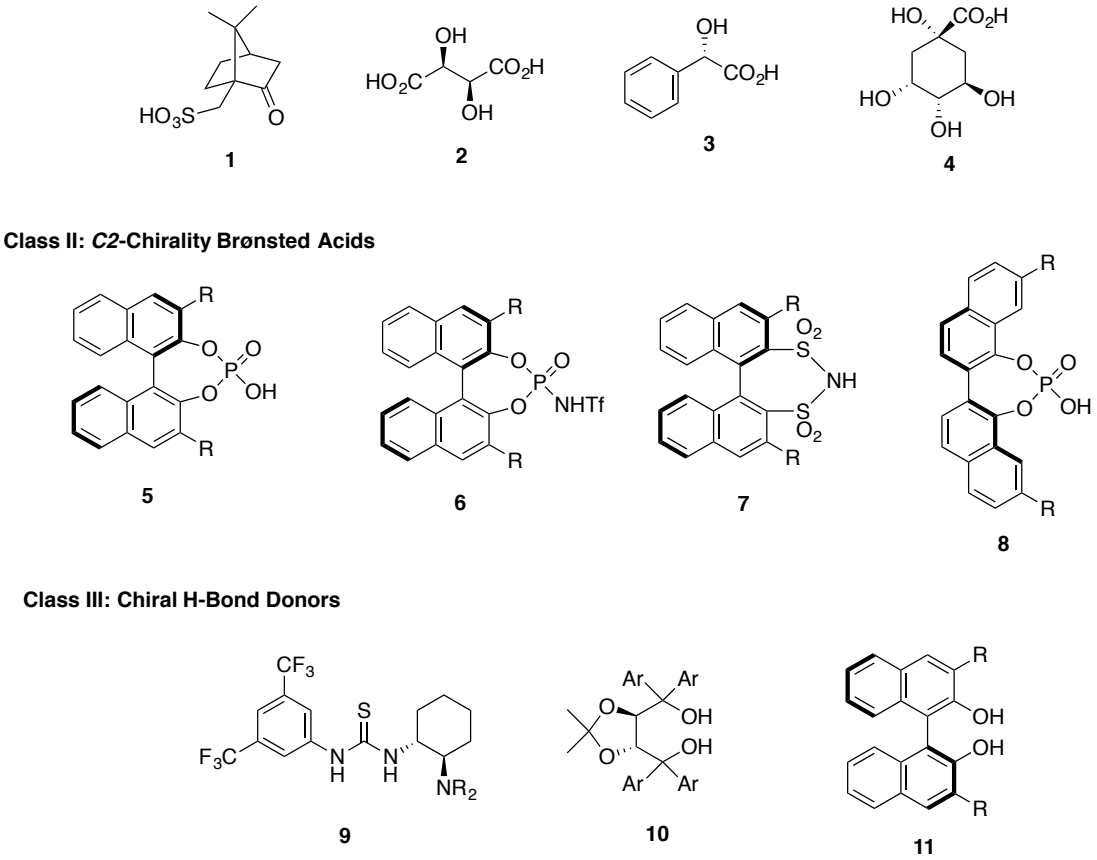
1.2 Chiral Anions Derived from Brønsted Acid Catalysts

A great number of chiral anionic catalysts are derived from its conjugate Brønstend acids. Since early last century, people made use of chiral anions and their conjugate acids from natural compounds from the chiral pool in the resolution and spectroscopic analysis of chiral molecules.[2] These natural chiral Brønsted acids include camphorsulfonic acid **1**, tartaric acid **2**, mandelic acid **3** and quinic acid **4**, which have been commonly used for the asymmetric induction (Figure 1.2, Class I).

For the purpose of superior performance and application in asymmetric synthesis, more powerful synthetic chiral Brønsted acids have received attention. As a commonly used type of specific Brønsted acid catalysts, binaphthol-derived phosphoric acids **5** and **8**, phosphoramides **6** and disulfonimides **7** have been widely used in the chemistry of carbonyl and imine activation (Figure 1.2, Class II). This type of chiral acids exhibits strong Brønsted acidity and effectively activates carbonyls and imines by protonation. Their anionic conjugate bases are also significant in asymmetric induction *via* ion-pair interactions or coordination with transition metal catalysts as the ligands.[4]

The other type of synthetic acids include thioureas **9**, TADDOL **10**, BINOL **11** and their derivatives behave as general acid catalysts due to their relatively weaker acidity that results in incomplete deprotonation and to the fact that they can only activate carbonyl compounds only by hydrogen bonding interactions (Figure 1.2, Class III).

Figure 1.2 Common classes of chiral Brønsted acid catalysts

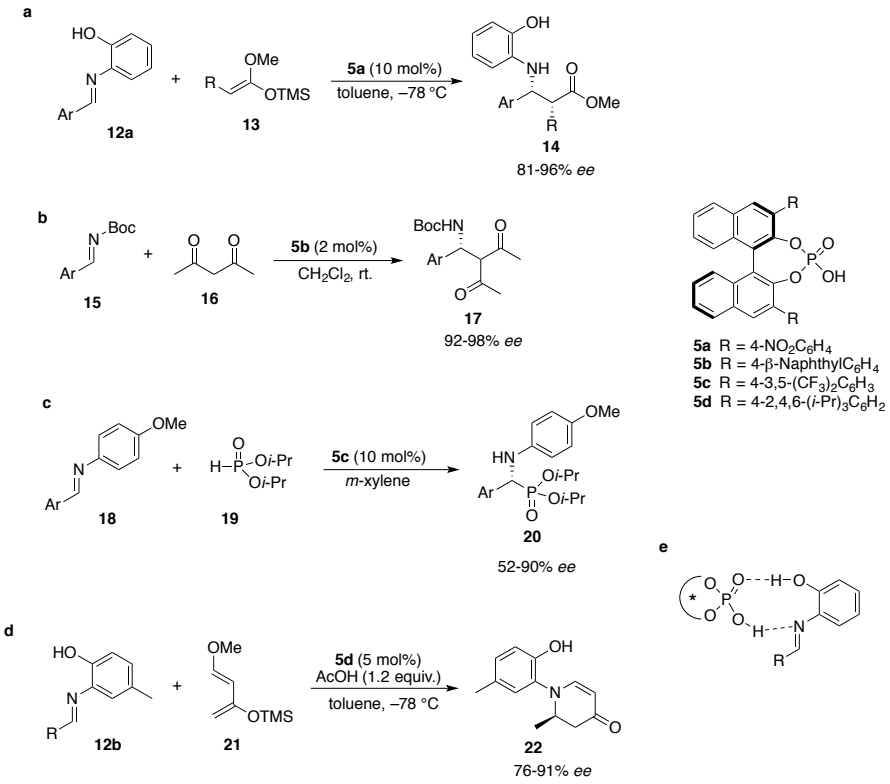


1.2.1 Chiral Anion Catalysis *via* Proton Activation

Over the recent decade, the family of chiral phosphoric acids has been greatly developed as a popular organocatalyst option in asymmetric transformations due to their strong acidity and promising asymmetric inductions. These substrates are particularly effective for imine activation and thus provide useful synthetic strategies for chiral nitrogen-containing molecules. Moderately basic imines are protonated by phosphoric acids and the resulting iminiums interact with the catalyst *via* hydrogen bonding and electrostatic attraction. Initial work on asymmetric imine transformation were done by Akiyama[6a,7,8] and Terada[6b] on the Mannich reaction (Scheme 1.1a, b), imine hydrophosphonylation (Scheme 1.1c) and aza-Diels-Alder reaction (Scheme 1.1d). A better interaction of imine

substrates and chiral phosphoric acid catalysts can be promoted by the effects of an adjacent functional group such as a hydroxyl group with the formation of an additional hydrogen bond, since the phosphonyl oxygen is a good H-bond acceptor that promotes a cyclic structure with double hydrogen bonds that stabilize the transition state (Scheme 1.1e).

Scheme 1.1 Chiral phosphoric acid catalyzed imine transformations

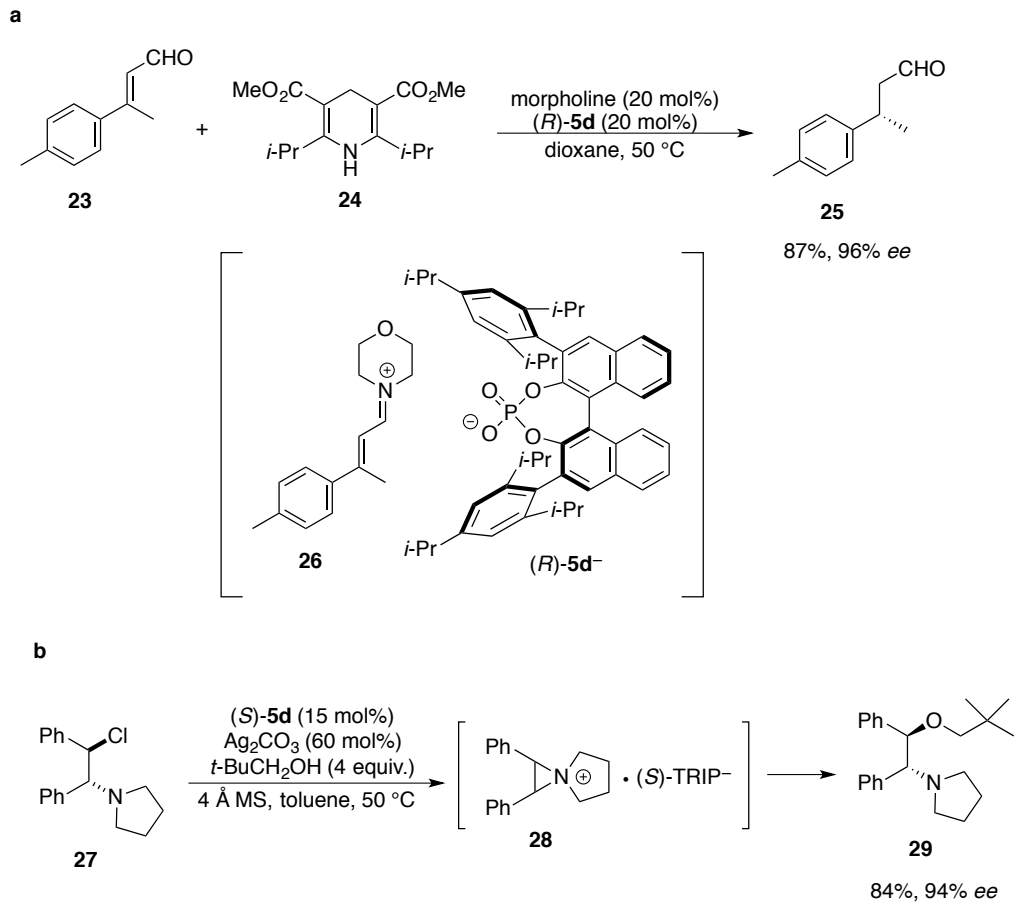


1.2.2 Chiral Anion Catalysis *via* Electrostatic Ion-Pair Interaction

In the asymmetric transformations of aldehydes and ketones, proton activation of carbonyls by chiral Brønsted acids is much less effective than it is for imines, since the carbonyl oxygen is much less basic than an imine. A most common strategy for carbonyl activation is realized by iminium-based organocatalysis[9] that is further activated by chiral phosphoric acids to achieve the asymmetric induction. Mayer and List have developed the methodology by the combination of secondary amines and the TRIP catalyst in the

asymmetric reduction of conjugated aldehydes **23** with excellent enantioselectivity.[10] As illustrated for the activated intermediate generated from the aldehyde **23** and morpholine, the asymmetric induction of the iminium substrate is directed by the TRIP anion only by ion-pair interaction, which is called asymmetric counterion-directed catalysis (ACDC) (Scheme 1.2a).[5]

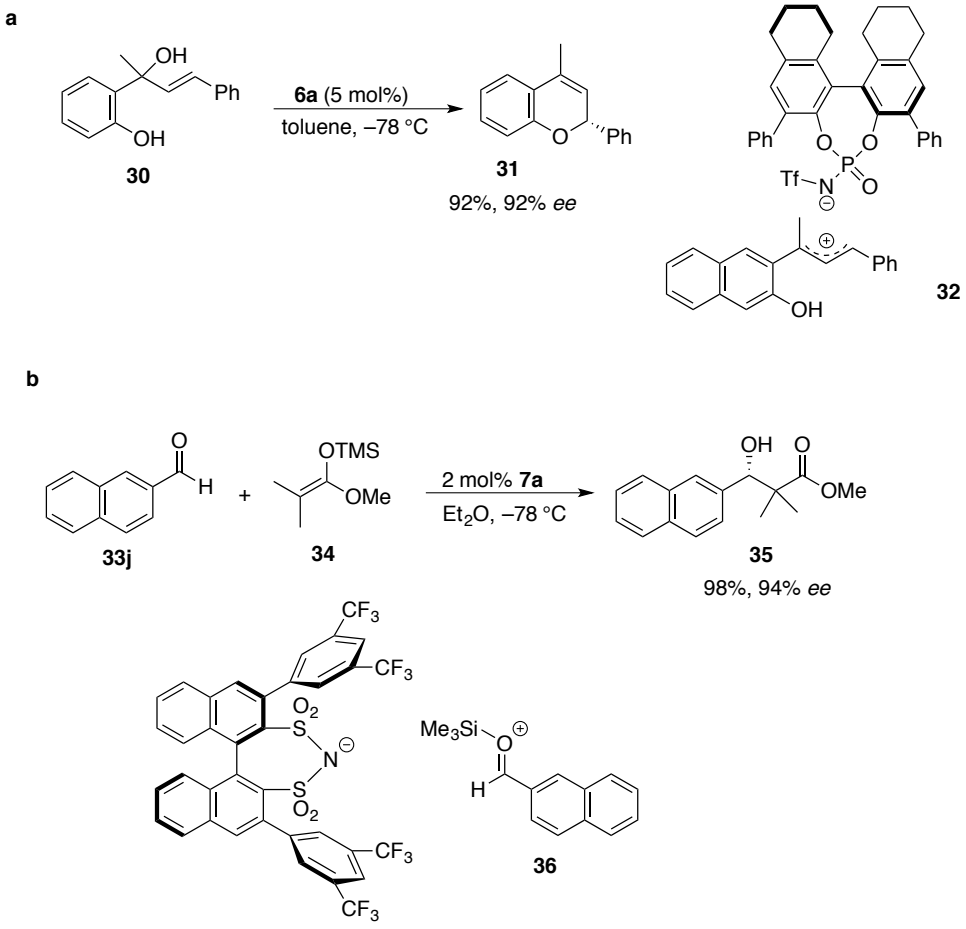
Scheme 1.2 ACDC *via* cationic activated intermediates



There are a couple of ways to generate chiral anionic catalysts from the conjugate Brønsted acid in ACDC. Toste made use of a stoichiometric amount of Ag_2CO_3, which serves both as a base to deprotonate TRIP and a chlorophile to abstract the chloride from racemic chloroamine **27**. An anionic conjugate base is generated to stabilize the quaternary *meso*-aziridinium intermediate **28** by ion-pair interaction without any other

directional interactions such as hydrogen bonds or proton activation.[11] The attack of *neo*-pentanol completes ring-opening of aziridinium **28** to deliver an amino ether **29** in high enantioselectivity (Scheme 1.2b).

Scheme 1.3 Cationic intermediates generated by the catalysis of strong chiral Brønsted acids



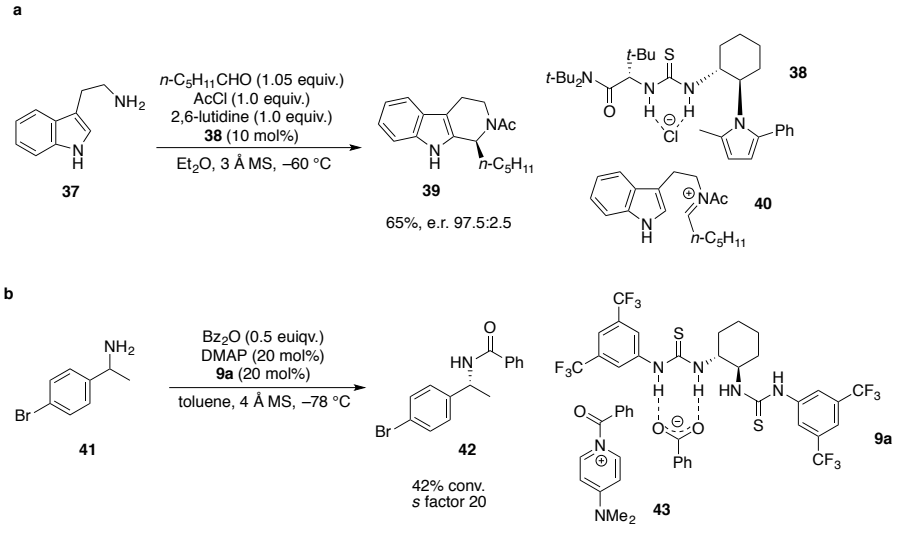
The other way of chiral anion generation is achieved *via* direct activation of carbonyls or even alcohols by a catalyst with significant Brønsted acidity. Rueping *et al.* have reported a highly enantioselective intramolecular allylic substitution by the *N*-triflylphosphoramide catalyst **6a**[12], which promotes the dehydration the racemic allylic alcohol **30** to afford an allylic carbocation **32** performing the ion-pair interaction with the catalyst (Scheme 1.3a). List and his co-workers have reported a novel BINOL-derived disulfonimide catalyst **7a** which was found to be highly effective in activation of

aldehyde **33j** in an asymmetric Mukaiyama aldol reaction.[13] The disulfonimide **7a** displays much greater Brønsted acidity than analogous phosphoric acids. It is proposed that the reaction includes oxonium cation **36**, which interacts with the catalyst by electrostatic attraction (Scheme 1.3b).

1.2.3 Chiral Anion Catalysis *via* Hydrogen-Bonding

Chiral Brønsted acids such as thioureas derivatives are not able to be completely deprotonated to generate an anionic conjugate base, but they are excellent H-bond donor catalysts that provide effective anion recognition. It has been reported that the thiourea catalysts can capture an anion such as halide or carboxylate *via* double hydrogen-bonding interaction to give a chiral anionic complex that performs as the couterion to provide an effective chiral induction to a cationic reaction intermediate.

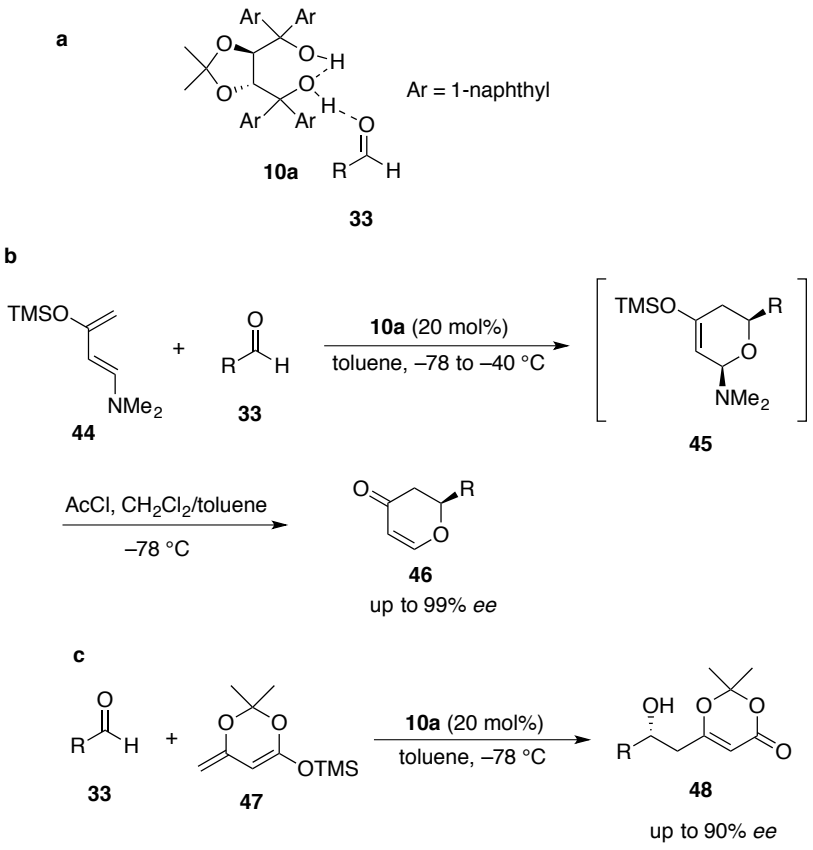
Scheme 1.4 Anion-binding chiral thioureas in asymmetric catalysis



For example, Jacobsen *et al.* have reported acyl-Pictet-Spengler reaction of tryptamine **37** with aldehydes catalyzed by chiral thiourea **38**.[14] It was believed that with the stoichiometric acetyl chloride, the reaction was involved in the chiral ion-pair intermediate consisted of *in-situ* generated acyl iminium **40** and hydrogen bonded

chloride by thiourea **38** (Scheme 1.4a). Seidel and his co-workers have made use of anion-binding thiourea catalysts in the kinetic resolution of a racemic benzylic amine **41** and its derivatives.[15] The formation of acylated DMAP intermediate **43** and benzoate binding with thiourea catalyst **9a** results in a chiral ion-pair which give selectivity factors of 7.1 to 24 (Scheme 1.4b).

Scheme 1.5 Aldehyde activation by TADDOL catalysts



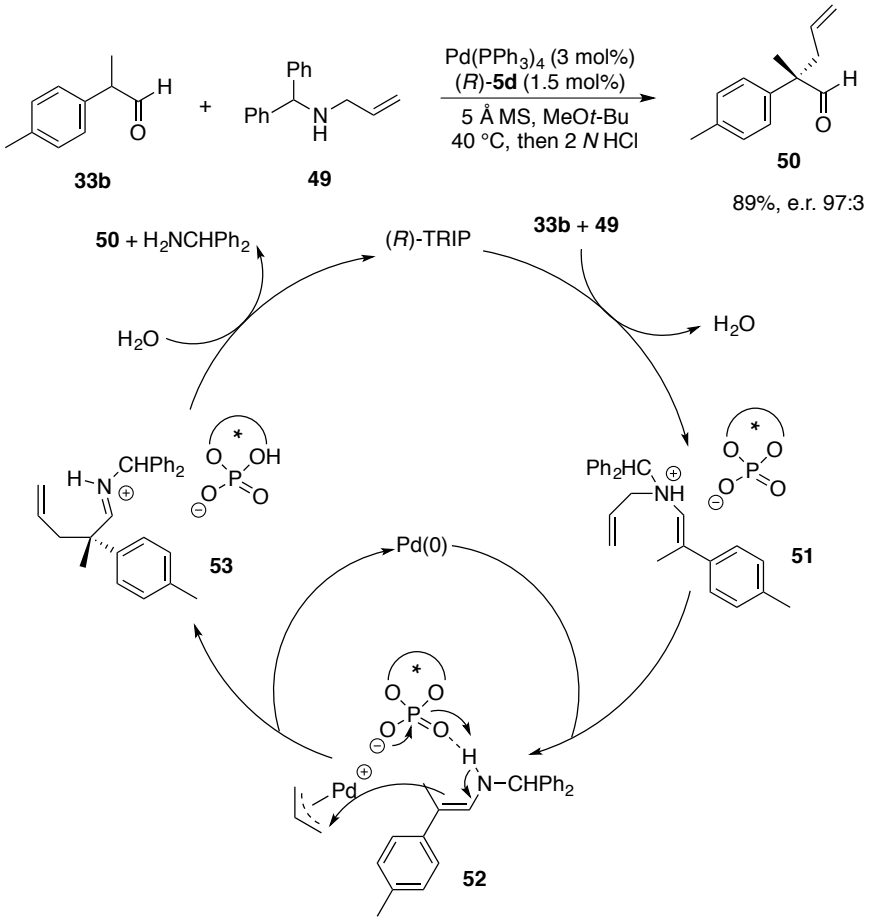
The chiral diol catalysts TADDOL **10** derivatives can activate z carbonyl by a single-point hydrogen bond mode as Brønsted acid-assisted Brønsted acid catalysis proposed by Yamamoto and Rawal.[16] The presence of intramolecular hydrogen bond between two hydroxyl groups of TADDOL greatly enhances the Brønsted acidity of the catalyst and effectively activates carbonyls by the formation of an intermolecular hydrogen bond (Scheme 1.5a). Rawal *et al.* have reported a hetero-Diels-Alder reaction of non-activated

aldehydes **33** and an aminodiene **44** with TADDOL **10a** as a highly effective catalyst to afford cycloadducts excellent enantioselectivity (Scheme 1.5b).[17a] They also demonstrated that TADDOL **10a** was effective in the vinylogous Mukaiyama aldol reaction to afford the aldol products **48** up to 90% *ee* (Scheme 1.5c).[17b]

1.2.4 Chiral Anion Catalysis *via* Transition Metal Coordination

The conventional ways of attempting to induce asymmetry in a transition metal-catalyzed reaction is to use a chiral ligand that tightly coordinates to the metal. However, in many cases the chiral ligand does not provide direct and effective interactions with the substrate and it results in poor enantioselectivity. People realized if there were the cationic intermediates of the substrate-metal complex involved in the catalytic cycle, they could be effectively recognized by the couteranion derived from a chiral Brønsted acid catalyst. For example, List *et al.* have reported an asymmetric Tsuji-Trost reaction of a racemic α-branched aldehyde **33b** and an allylamine **49** with a palladium catalyst and chiral phosphate **5d**.[18] To start the catalytic cycle, the corresponding enamine from **33b** and **49** is protonated by TRIP to give the ion-pair species **51**. This is followed by Pd(0) oxidative addition to afford π-allyl Pd(II) complex **52**. Meanwhile, the substrate enamine interacts with the chiral phosphate catalyst *via* hydrogen bonding that results in a catalyst assembly **52** that provides an excellent asymmetric induction by ion-pair recognition between chiral phosphate and cationic Pd(II) complex (Scheme 1.6).

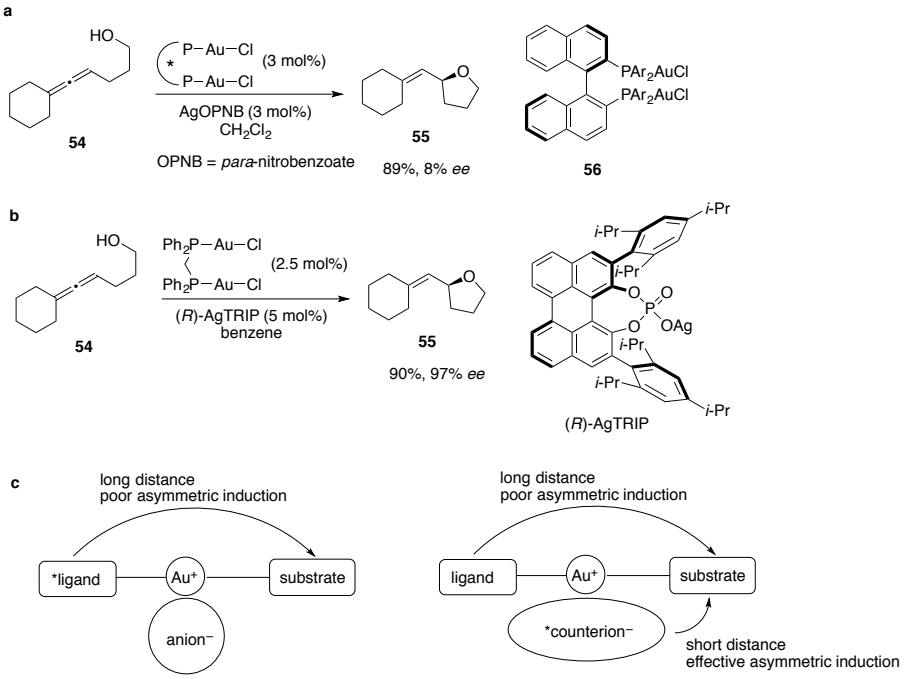
Scheme 1.6 Asymmetric Tsuji-Trost reaction with a palladium catalyst and TRIP couterion



An illustration of the difference in chiral ligand- and chiral counterion-direction asymmetric transition metal catalysis was reported by Toste *el at.*[19] in the gold-catalyzed intramolecular hydroalkoxylation of allenes **54**. The gold(I) chloride phosphine complexes **56** were used as the catalysts and silver salts were employed as the chloride precipitators. In their initial catalyst screening, the chiral phosphine ligand **56** and the non-chiral 4-nitrobenzoate as the counteranion of the silver salt were used resulting in poor asymmetric inductions (Scheme 1.7a). They realized that a chiral couteranion of the silver salt such as TRIP phosphate may give improved enantioselectivity. Even with a non-chiral phosphine ligand, an excellent induction was observed (Scheme 1.7b). They proposed that reaction proceeded *via* an π-allenyl gold(I) complex as the cationic

intermediate with the linear relationship of the phosphine ligand, gold(I) metal and the substrate. Instead of tight coordination of a chiral ligand to the gold(I) species, it is nonetheless far way from the substrate. On the other hand, inclusion of a chiral counterion with the gold(I) metal *via* electrostatic interaction would result in a chiral environment that is much closer to the substrate and thereby provides much a more effective asymmetric induction (Scheme 1.7c).

Scheme 1.7 Asymmetric induction by a chiral ligand and counteranion



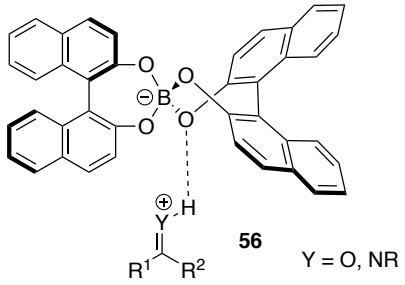
1.3 Chiral Anions Derived from Combined Acid Catalysts

1.3.1 Chiral Combined Acids in Asymmetric Catalysis

People have found the combination of a Lewis acid and a Brønsted acid can greatly promote the acidity of each other. Many strong inorganic combined catalysts include the well known examples such as $HF{\cdot}BF_3$, $HCl{\cdot}AlCl_3$, $HF{\cdot}SbF_5$ and so-called magic acid $HSO_3F{\cdot}SbF_5$.[20] In the area of organic chemistry, a Lewis acid activation of a Brønsted

acid can increase the acidity up to 24 units for a α-proton of acetaldehyde when it's carbonyl oxygen coordinates to a Lewis acid such as BF_3.[21]

Figure 1.3 BINOL Spiro-Boron Complex 56 as the Typical Example of A Combined Acid Catalyst[28]

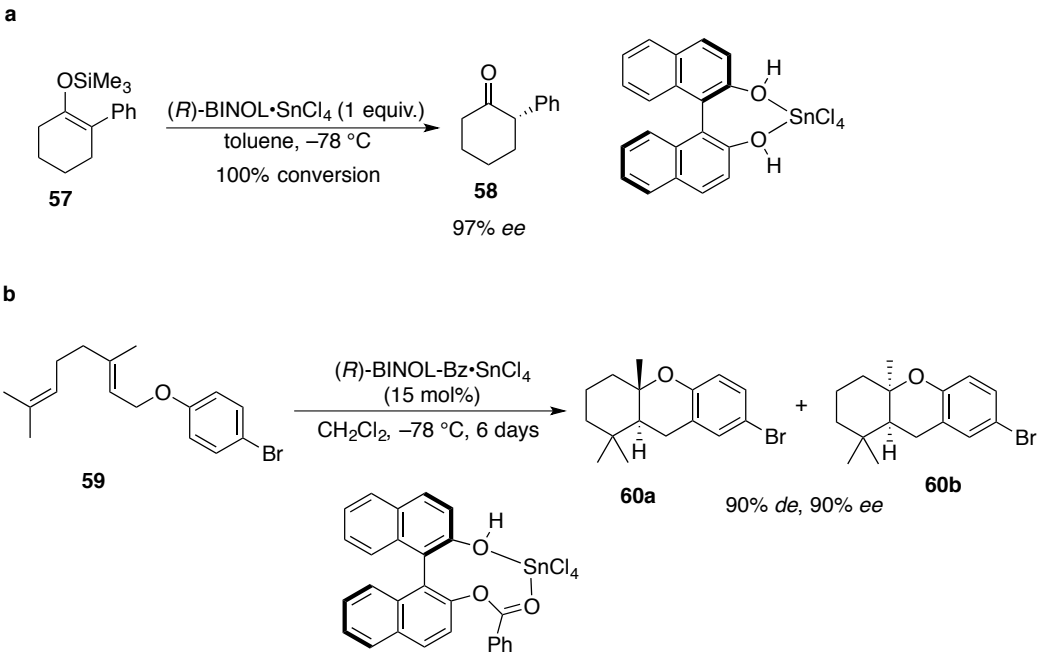


Yamamoto *et al.* developed a number of combined acid catalysts since early 1990s.[22a] The spiro-BINOL-derived borate **56** is the typical example which consists a boron Lewis acid core with two BINOLs as the chiral Brønsted acid ligands. The bis-BINOL borate **56** can function as a Lewis acid and has been proposed to activate both aldehydes and imines by forming a Lewis acid/Lewis base complex with the borate esters.[22a] a number of different combined acid catalysts have been established to function in different modes including Lewis acid-assisted Brønsted acids (LBA), Brønsted acid-assisted Lewis acids (BLA) and Lewis acid-assisted Lewis acids (LLA)[22].

1.3.2 Chiral Combined Acids as LBAs

Diol Brønsted acids such as TADDOL or BINOL can provide an effective asymmetric induction in asymmetric catalysis. However, they are relative weak Brønsted acids (pK_a 9-16) and less efficient in activating the reactive site of target substrates *via* interactions with their protons. Yamamoto and his co-workers have found that coordination of a Lewis acid to a weakly acidic Brønsted acid greatly increase the acidity of latter.[23] The combination of a Lewis acid and a chiral Brønsted acid can afford a strong acidic complex that can be used as a strong chiral Brønsted acid catalyst.

Scheme 1.8 LBAs in asymmetric catalysis



A LBA catalyst generated *in-situ* from BINOL and tin tetrachloride was reported by Yamamoto *et al.* as a stoichiometric acidic reagent in the enantioselective protonation of a non-chiral silyl enol ether **57** to give the α-substituted ketone **58** with 97% *ee* (Scheme 1.8a).[24] They further explored the asymmetric catalytic reactions of LBAs and found that the strong acidity of the catalysts can effectively activate the olefin double-bond and trigger cationic reactions. Thus, they reported the first LBA-catalyzed enantioselective biomimetic cyclization of polyprenoids **59**.[25] The LBA catalyst was prepared from (*R*)-BINOL mono-benzoate derivative and $SnCl_4$ and gave good recognition of the terminal trisubstituted olefin in the substrate **59** to generate site-selective carbocations (Scheme 1.8b).

1.3.3 Chiral Combined Acids as BLAs

In the complexes with a combination of Lewis acids and Brønsted acids, not only is Brønsted acidity greatly improved, but also the acidity of Lewis acids is enhanced

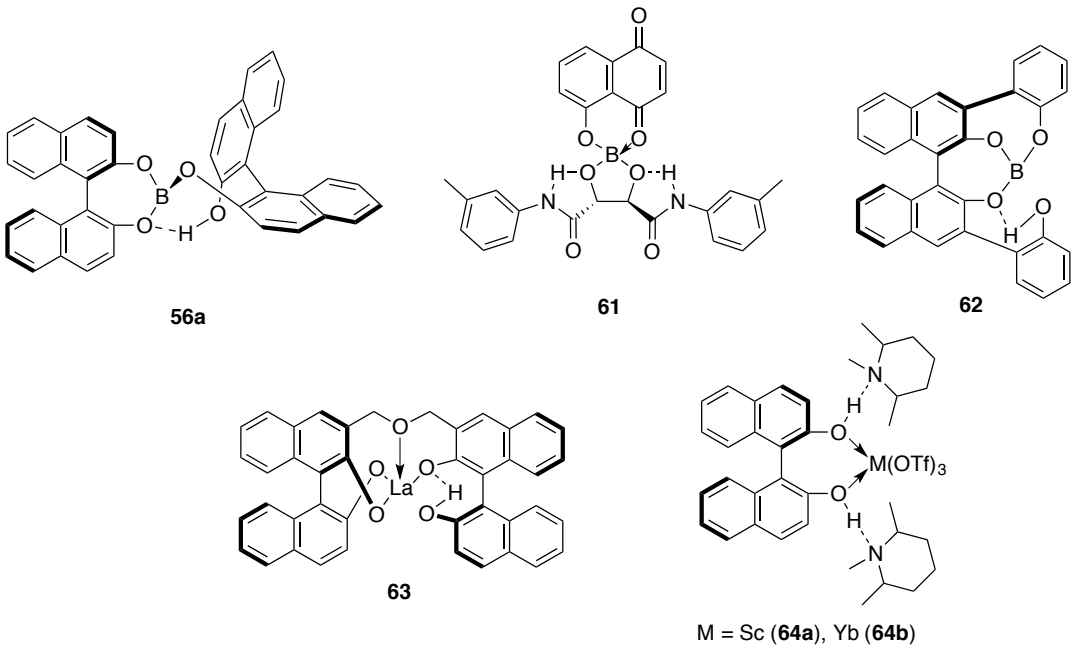
significantly. The BLA catalysts can be highly effective in activating the nucleophilic sites of the substrates, typically carbonyls, and also provide enhanced asymmetric inductions by the chiral Brønsted acid ligands. As shown in Figure 1.3, the spiro-BINOL borate can exist in a four-coordinate anionic form **56** or the three-coordinate neutral form **56a**. In the acid form **56a**, one of BINOL oxygens is not bonded to the boron and remains pronated. The free phenol group is hydrogen bonded to an oxygen of the other BINOL ligand and as a result improves the Lewis acidity of the boron.

During the past thirty years, a great number of BLA catalysts have been developed and explored in the applications of the Lewis acid-catalyzed asymmetric transformations (Figure 1.4). Yamamoto *et al.* reported the asymmetric Diels-Alder reaction in 1986 between naphthoquinone derivatives and siloxy dienes catalyzed by the BLA **61** derived from $B(OMe)_3$ and (*R*,*R*)-(+)-tartaramide.[26a] The high enantioselectivity observed for the BLA catalyst **62** in Diels-Alder reactions (1994) was proposed to the result from attractive π-π interactions with the substrate.[26b,c] BLA spiro-BINOL borate **56a** displays highly effective stereoselectivity for aza-Diels Alder reactions with chiral imines and Danishefsky dienes, as well as for Mannich reaction of chiral amines.[26d] In the unpublished work from our laboratories, there is an evidence that these reactions of imines occur *via* the Brønsted acid form of this catalyst **56a**.

In addition to boron, other Lewis acidic metals can also be used in BLA catalysis. In 2000, Shibasaki *et al.* developed a lanthanium-BINOL derived complex **63** for asymmetric Michael reactions of cyclohexenone and malonates.[26e] Kobayashi *et al.* (1994-1996) developed BLA catalyst **64** which has a piperidine adduct *via* hydrogen bonded with the BINOL oxygen. The piperidine moieties are effective in extending the

chiral scaffold which result in excellent enantioselectivity in Diels-Alder[26f] and aza-Diels-Alder reactions[26g].

Figure 1.4 Examples of BLA catalysts



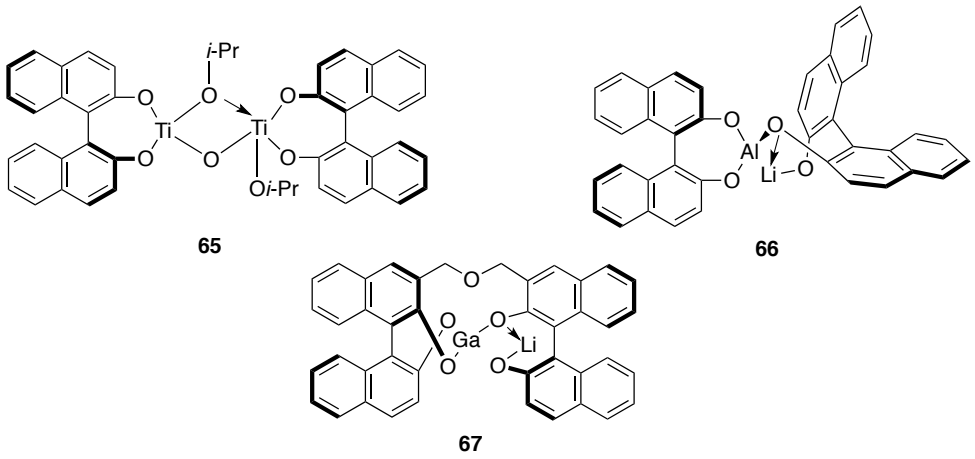
1.3.4 Chiral Combined Acids as LLAs

The replacement of the proton in a BLA catalyst with a Lewis acid metal will give an LLA complex (Figure 1.5). In this way, electron-deficient metals can be further activated by the second electrophilic Lewis acid. One way to assemble an LLA catayst is to have two of the same Lewis acidic metals in a homo-dimetallic complex. For example, LLA **65** designed by Maruoka *et al.* consists of two titanium cores that increase the interactions with the substrate compounds and provide a well-organized chiral environment. The bis-Ti(IV) oxide **65** was successful for the asymmetric allylation of aldehydes with allyltributylstannane to afford a secondary allylic alcohol in 99% *ee*. [27a]

The other type of LLA catalysts are those derived from BLA catalysts, where the free phenol is deprotonated and charge-balanced by lithium as the conjugate bases in the BLA

catalyst. The spiro-BINOL aluminum complex **66** has been used as an efficient LLA catalyst in the Michael addition of cyclohexenone and malonates.[27b,c] The chelation of lithium by BINOL oxygens further enhances the Lewis acidity of aluminum resulting in highly efficient interactions with non-activated ketones. And a number of ring-opening reactions were developed involving in a bridged-Ga-Li-BINOL complex **67** with up to 96% ee.[27d] An X-ray crystallographic analysis suggested that LLA **67** functions with a structure similar to that of the BLA catalyst **63**.

Figure 1.5 Examples of LLA catalysts

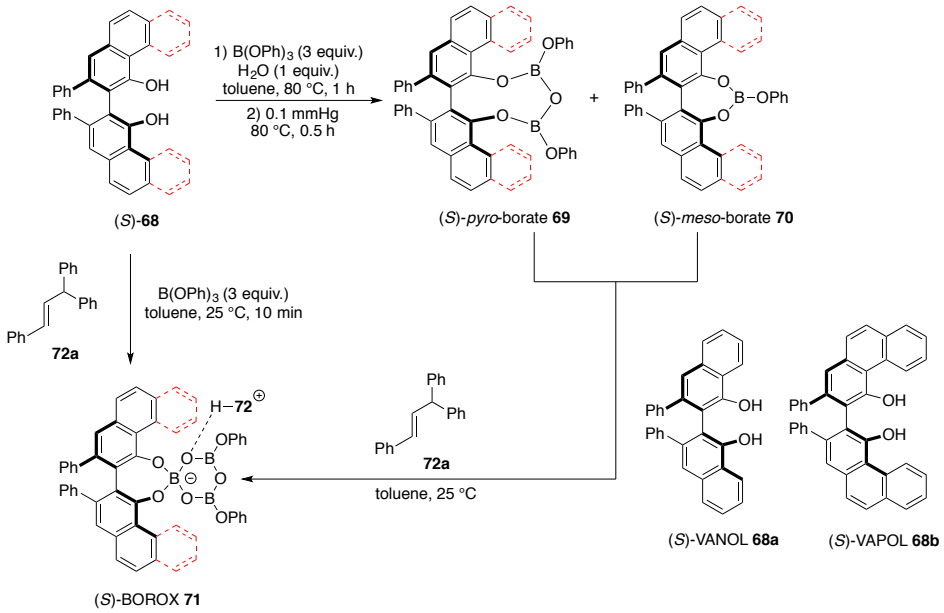


65 **66** **67**

1.3.5 Wulff's Chiral Boroxinate Catalysts

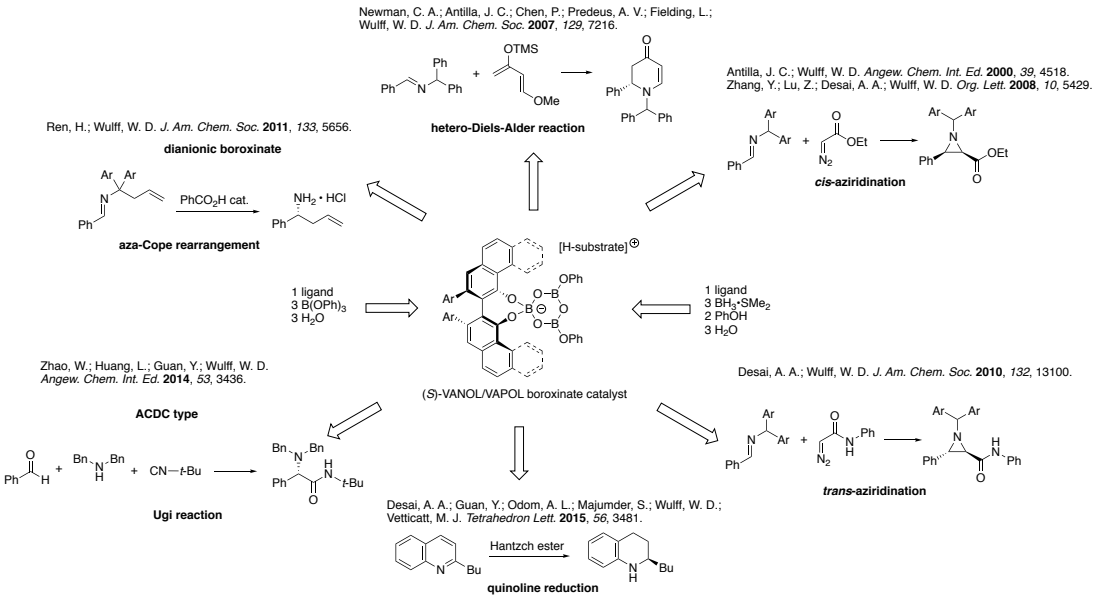
In 1999, Antilla and Wulff reported a novel chiral VANOL/VAPOL-derived boroxinate (BOROX) **71** as the combined acid-derived catalyst as applied to the *cis*-selective aziridination.[28a] The structure of this catalyst was not determined until 2010.[29] The chiral BOROX anion **71** was prepare by one equivalent chiral diol ligand VANOL **68a** or VAPOL **68b** with three equivalents of triphenylborate or borane dimethyl sulfide. The presence of imine substrate **72a** promoted deprotonation to complete the formation of the boroxinate ring, with the resulting iminium balancing the negative charge.

Scheme 1.9 Formation of VANOL/VAPOL-derived BOROX catalysts



Further investigation of the protocol for BOROX preparation revealed that a precatalyst was generated by heating VANOL or VAPOL with $B(OPh)_3$. The NMR study indicated the precatalyst was a mixture of a cyclic *pyro*-borate **69** and a linear *meso*-borate **70** with the *pyro*/*meso* ratio of 2.5:1 for VANOL and 8:1 for VAPOL.[29a] Both species **69** and **70** contain Lewis acidic three-coordinate borons. They are hydrolytically sensitive and easily deprotonated by basic imine substrates to afford BOROX anions. A recent study also found that the treatment of VANOL/VAPOL with imine **72a** and $B(OPh)_3$ afforded BOROX **71** within 10 min at room temperature and that the generation of precataysts **69** and **70** was not necessary.[29b]

Figure 1.6 Chiral BOROX anion in asymmetric catalysis



The BOROX anion consists of one four-coordinate boron and two three-coordinate borons that feature multiple reactive sites with good Lewis acidity, H-bond acceptors and the VANOL/VAPOL ligand as the chiral scaffold. A number of asymmetric imine transformations were reported by Wulff and his co-workers that exhibited excellent stereoselectivity. The BOROX catalysts can effectively interact with a protonated imine by hydrogen bonding and provide high asymmetric inductions in *cis*-selective aziridinations[28b,c], *trans*-selective aziridinations[30], hetero-Diels-Alder reactions[31], quinoline reduction[32], aza-Cope rearrangements[33] and the Ugi reaction[34].

Of articular interest is that benzoic acid was employed as a co-catalyst in the asymmetric aza-Cope rearrangement. It is believed that a dianionic catalytic BOROX species was generated as the result of benzoate coordination to one of the three-coordinate borons. The additional negative charge can strengthen the electrostatic attraction between the BOROX catalyst and the protonated iminium substrates substrate with an improvement of enantioselectivity. In the three-component Ugi reaction, a cationic iminium, generated

in-situ by an aldehyde and a secondary amine, is involved in the catalytic cycle. The BOROX anion provides an effective ACDC catalyst by ion-pair interaction with iminium cation to give a high enantioselectivity.

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Chapter 2 Multi-Component *cis*-Aziridination

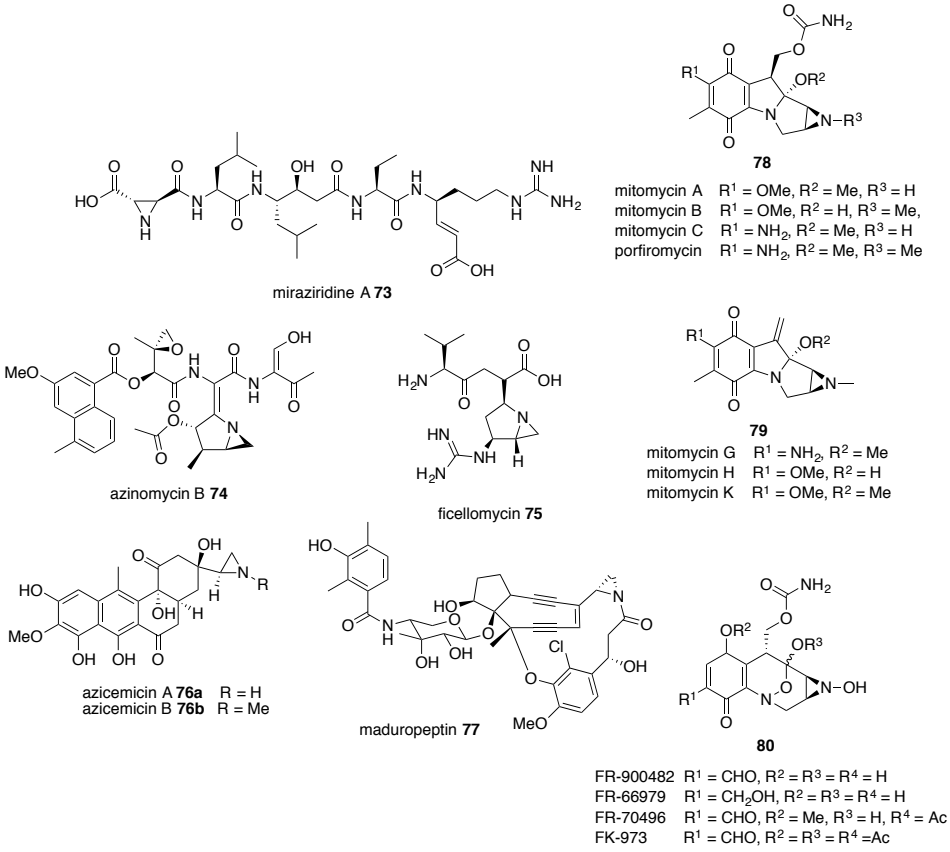
2.1 Literature Work on Catalytic Asymmetric Aziridination

2.1.1 Aziridines in natural products

Aziridines are important building blocks and many exist natural products and drug reagents that have biological properties including anti-tumor, anti-bacteria and anti-fungus activities.[1] A number of aziridine-containing natural products have been reported in thw literature. Miraziridine A **73** was isolated from the marine sponge *Theonella mirabilis*, which exhibites a variety of bioactivies such as anti-fungal properties and protease inhibitory.[2] Azinomycin B **74** is a natural product with potential anti-tumor activity isolated from *Streptomyces sahachiroi*.[3] Ficellomycin **75** was isolated from *Streptomyces ficellus* with antibiotic activity.[4] Azicemicins A **76a** and B **76b** are a class of antibiotics isolated from the culture broth of the strain MJ126-NF4.[5] Maduropeptin **77** is an antibiotic with anticancer activity isolated from *Actinomadura madurae*.[6]

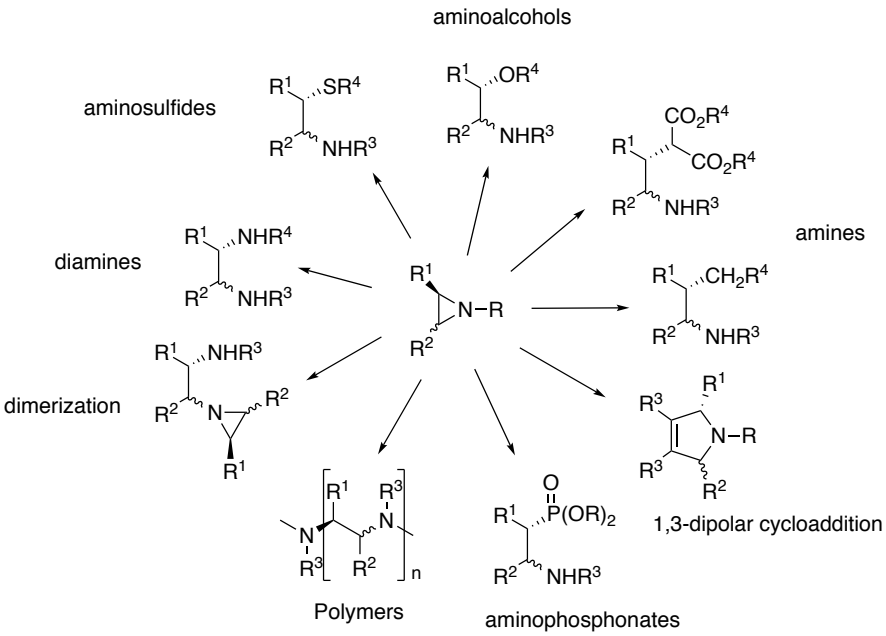
The best-known compounds containing aziridine-rings are the family of mitosanes **78** and **79**, which were first isolated from soil extracts of *Streptomyces verticillatus* and exhibit both anti-tumor and anti-biotic activity.[1a] The aziridine rings are essential in bioactivity of mitosanes that relies on a bioreductive activation to that results in DNA alkylation/aziridine ring-opening followed by DNA cross-linking *via* cationic intermediates.[1a] Danishefsky and his co-worker also proposed an alternative mode of action for mitosanes involving a semi-quinone radical anion as a key intermediate.[1c] Related compounds also known as FR and FK anti-cancer reagents **80** have similar interactions with DNA, which reveals an intimate relationship in the structural similarity with mitosanes.[1d]

Figure 2.1 Aziridine-containing natural products



Also, extensive reports have appeared on methods for the prepration of aziridines since they are useful synthetic intermediates and willing to undergo nucleophilic ring-opening process under the mild conditions to afford amino-containing compounds including aminoalcohols, aminosulfides and aminophosphonates, γ-aminocarbonyl compounds, dimerization products, polymers and 2,5-dihydropyrrole derivatives by 1,3-dipolar cycloaddition with alkynes (Figure 2.2).[7] In addition, there is a substantial body of literature that involves the use of aziridine compounds have been used as chiral ligands or chiral auxiliaries. For example, C_2-symmetric bisaziridines give decent stereoselectivity in various asymmetric transformations such as the asymmetric alkylations and *syn*-aldol reactions.[8] Chiral aziridino alcohols have been reported as effective chiral ligands in asymmetric reduction of imines and aldehydes.[9]

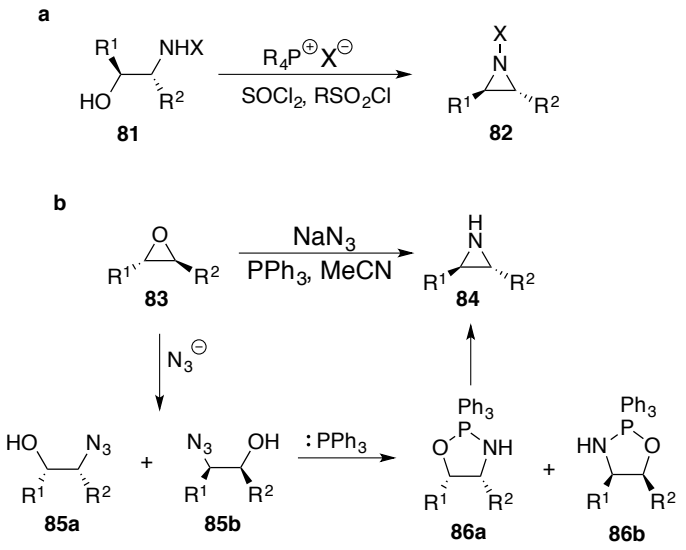
Figure 2.2 Transformations of disubstituted aziridines



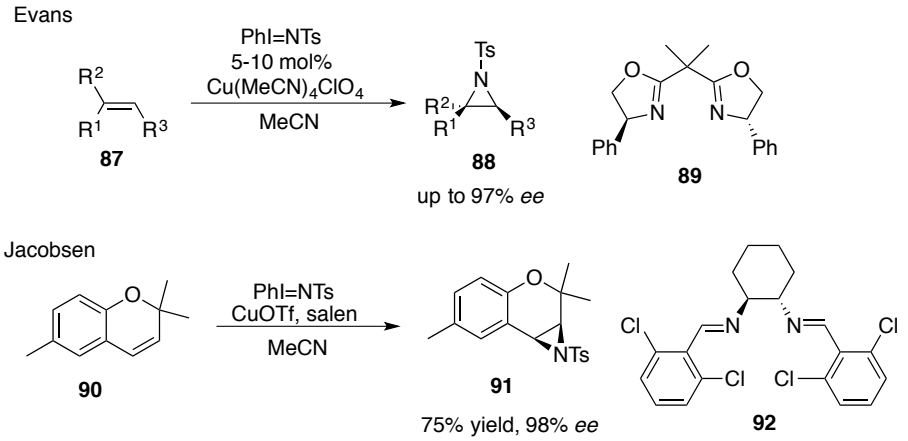
2.1.2 Catalytic Asymmetric Aziridination

The oldest and most conventional way to synthesize an aziridine ring is from a 1,2-aminoalcohol or 1,2-aminohalide through S_N2 ring-closure. As early as 1888, Grabriel synthesized aziridines in a two-step process, by chlorination of ethanolamines followed by cyclization (Scheme 2.1a).[10a] The stereochemistry of resulting aziridines was total dependent on the stereochemical configurations of the starting materials in avoid with the nature of the S_N2 process. Of particular note is reported by Sweeney and co-workers in 1997 that employed a Staudinger reaction in a phosphine-mediated ring-closure of azidoalcohols.[10b] They started from ring-opening of chiral epoxides **83** by sodium azide to afford the corresponding mixture of azidoalcohol regioisomers **85a** and **85b**, which was followed by triphenylphosphine mediated Staudinger reaction *via* five-membered ring oxazaphospholidine intermediates to give aziridines **84**, with the inversion of stereochemistry of both carbons in expoxides **83** (Scheme 2.1b).

Scheme 2.1 Aziridination from 1,2-amino functionzalized compounds



Scheme 2.2 Aziridination by nitrene addition to alkenes



In early studies of direct aziridination was achieved by nitrene addition to alkenes. Nitrenes are highly reactive intermediates and are typically generated by thermal or photochemical decomposition of azides. However, this method leads to a mixture of singlet and triplet nitrenes as only singlet nitrenes react with alkene through concerted processes but triplet ones react with alkenes *via* radical pathways.[10a] During the middle 1990s, Evans[11a], Jacobsen[11b,c] and Katsuki[11d] developed enantioselective aziridination of alkenes by metal-stabilized nitrenes, which were generated *in-situ* from nitrene precursor

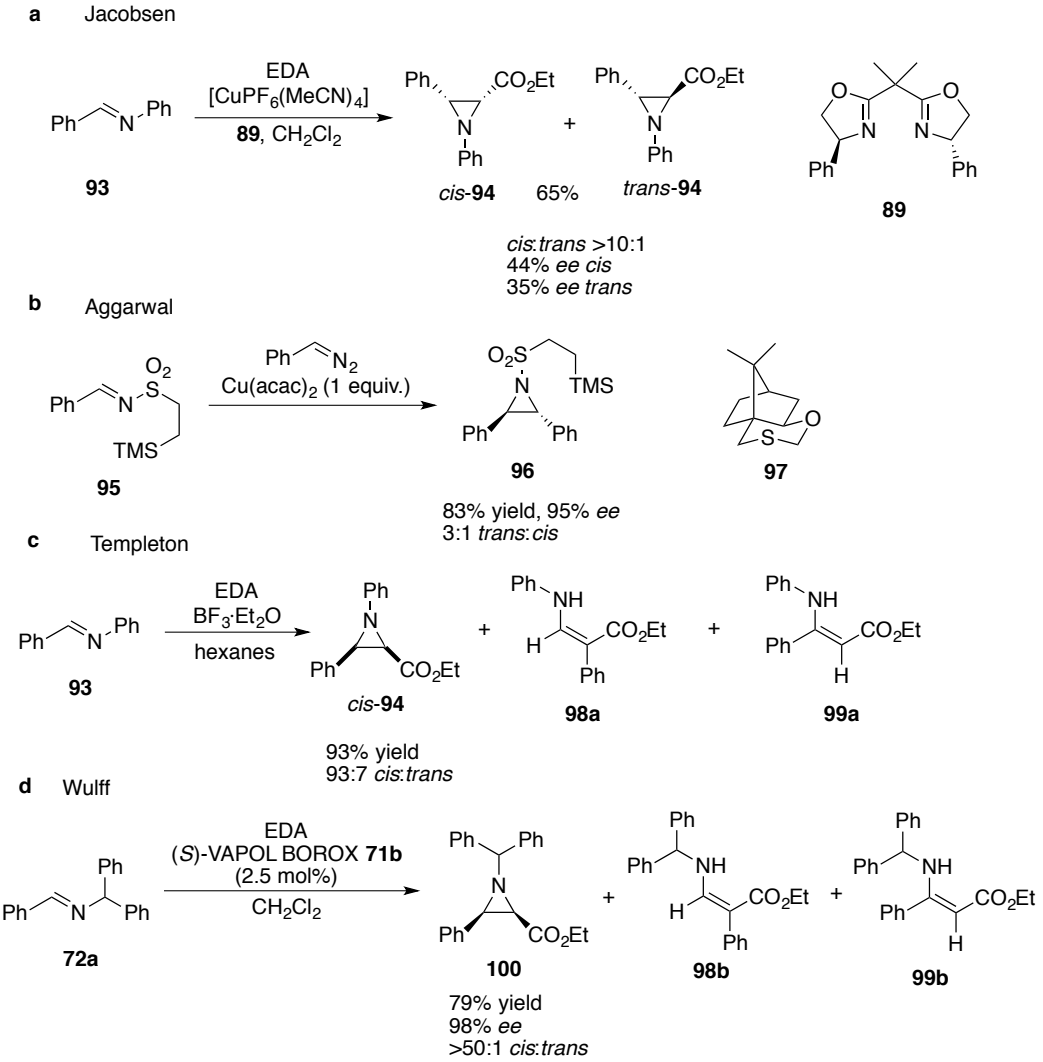
N-tosyliminophenyliodinane (Scheme 2.2). The utility of chiral bis-oxazoline **89** and 1,2-diimine **92** ligands afforded aziridines with high enantioselectivity.

As two C-N bonds form nearly simultaneously, the stereochemistry of aziridines from nitrene addition relies on the double bond configuration of the alkenes. A useful aziridination protocol was established in the late 1990s when it was found a carbene or ylide would react with an imine effectively to obtain the corresponding aziridine at a time when a number of groups explored a direct asymmetric catalytic synthesis of aziridines. It was believed the aziridination proceeds step-wise with the carbene lone-pair attacking an imine followed by nitrogen ring-closure. A number of chiral catalysts were developed to control the asymmetric induction during the carbene addition process.

Jacobsen *et al.* reported that a copper-carbenoid derived from ethyl diazoacetate (EDA) reacts with an *N*-arylaldimine **93** to afford a mixture of *cis*- and *trans*-aziridines **94** in a 10:1 selectivity, however, with relatively low enantioselectivity (Scheme 2.3a).[12a] The enantioselectivity was greatly improved in a *trans*-selective aziridination reported by Aggarwal *et al.* with benzaldimine **95** and diazotoluene.[12b] In their strategy, a sulfur-ylid intermediate was generated from an *in-situ* copper carbenoid in the presence of chiral sulfide reagent **97**. They obtained *trans*-aziridine **96** with a 3:1 *trans*:*cis* selectivity and 95% *ee* for the *trans*-isomer (Scheme 2.3b). However, a stoichiometric amount of $Cu(acac)_2$ was used to maintain a decent yield. The first Lewis acid catalyzed aziridination was reported by Templeton *et al.* with imine **93** and EDA in the presence of boron trifluoride diethyl etherate as the Lewis acid.[12c] A high selectivity for the *cis*-aziridine **94** was observed in 93% yield and 97:3 *cis*/*trans* ratio. They also observed a mixture of enamine regioisomers **98a** and **99a** derived from phenyl or hydride migration

of diazonium intermediate (Scheme 2.3c). Based on these results, Wulff and Antilla developed a highly efficient asymmtric *cis*-aziridination catalyzed by the chiral VAPOL-derived BOROX catalyst **71b** (Scheme 1.9) that afforded aziridine **100** in 79% yield, 98% *ee* and with a >50:1 *cis*-selectivity (Scheme 2.3d).[12d]

Scheme 2.3 Aziridination by carbene/ylid addition to imines

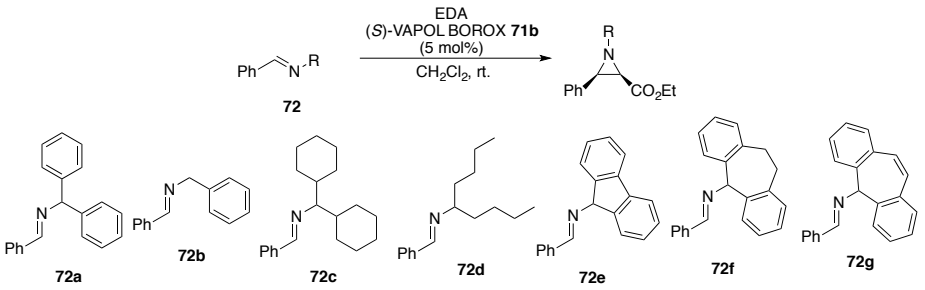


2.1.3 Wulff's BOROX-Catalyzed *cis*-Aziridination

In the early work on BOROX-catalyzed *cis*-aziridination, a benzhydryl (diphenylmethyl) group was employed as the *N*-substitution in the imine substrates it was later realized that the interactions between the BOROX catalyst and imines are not just limited to hydrogen

bonding, electrostatic attractions and Lewis acid-Lewis base coordination, but also potential CH-π and π- π stacking interactions. Further optimization of the asymmetric *cis*-aziridination was carried out by Yu Zhang, Zhenjie Lu and Aman Desai who focused on the diversity of the imine *N*-substition.[13a] The first set of experiments in screening a number of *N*-substituents revealed the presence of aromatic moieties in *N*-substituent of imines had a significant effect on the rection rate and the asymmetric induction (Table 2.1).

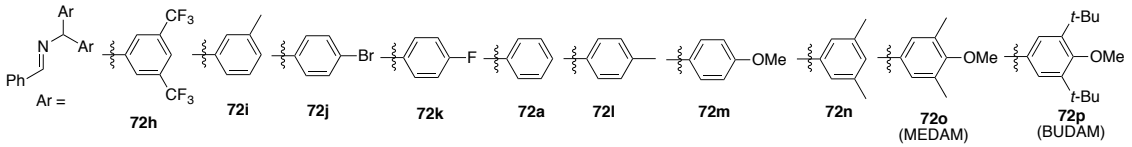
Table 2.1 Screening of imine N-substitution[13a]



imine	relative rates	yield%	*ee*%
72a	1.0	83	89
72b	1.7	51	43
72c	0.04	18	74
72d	0.23	27	84
72e	0.3	64	80
72f	1.0	75	95
72g	2.2	65	96

Imine **72f** and **72g** reacted with a higher induction and faster rates than imine **72a**, but with relatively lower yields. Thus, a series of electron-rich and electron-deficient benzhydryl imines were evaluated in the *cis*-aziridination in a second set of experiments (Table 2.2). Ten imines were explored that indicated electron-rich benzhydryls could greatly enhance the CH-π and π- π stacking interactions and 3,4,5-trisubstituted aromatic rings with outstanding inductions. Particularly, imine **72o** and **72p** display dramtic improvement in yield and *ee* in the *cis*-aziridination, with the tetramethyldianisylmethyl (MEDAM) and tetra-*tert*-butyldianisylmethyl (BUDAM) substituents as the optimum.

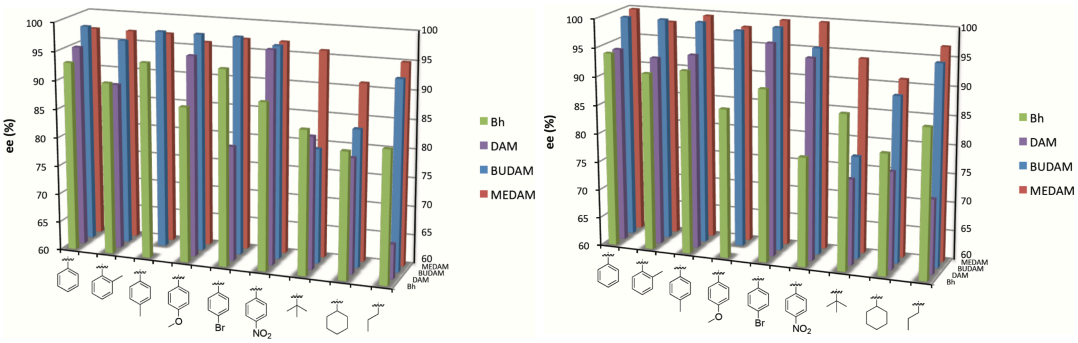
Table 2.2 Screening of benzhydryl substitution[13a]



imine	72h	72i	72j	72k	72a	72l	72m	72n	72o	72p
rel. r	0.02	0.05	0.28	0.45	1.0	2.3	3.8	10.0	11.5	16.3
yield%	48	63	80	70	83	82	78	89	89	96
ee%	37	86	88	88	89	92	90	95	98	99

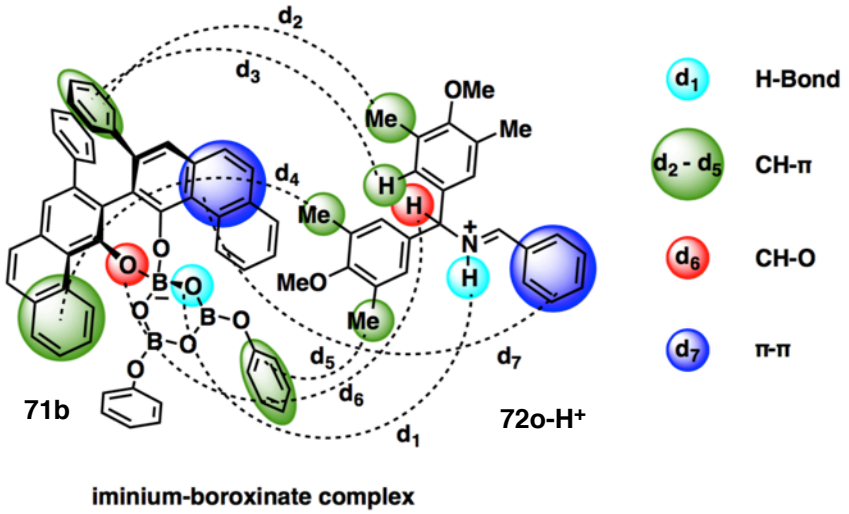
Munmun Mukherjee, Anil Gupta, Yu Zhang and Zhenjie Lu investigated on substrate scope with 36 imines with a combination of imines from nine different aldehydes including electron-rich and electron-poor phenyl and 1°, 2°, 3° alkyls and four diarylmethyl *N*-substituents (Bh, DAM, MEDAM and BUDAM) (Bh = benzhydryl, DAM = dianisylmethyl) which provided an extensive profile of asymmetric induction in the *cis*-aziridination.[13b] Based on the experimental results, MEDAM and BUDAM substituted imines displayed much better inductions than Bh and DAM imines with excellent *ee* for the *cis*-aziridines for all the substrates investigated. And MEDAM imines gave higher *ee* than BUDAM in most of the protocols as the optimal *N*-substitution in *cis*-aziridination (Figure 2.3). Both VANOL- and VAPOL-derived BOROX catalysts were investigated and it was shown VAPOL BOROX **71b** gave a better induction than VANOL BOROX **71a** for most of substrates, except for 2° and 3° imines.

Figure 2.3 Asymmetric induction with *N*-substitution for a) VANOL BOROX; b) VAPOL BOROX[13b]



a **b**

Figure 2.4 The non-covalent interactions in BOROX-iminium complex[14c]



A crystal structure of the active BOROX catalyst **71b** – iminium **72a-H**$^+$ complex obtained by Gang Hu, Anil Gupta, Rui Huang and Munmun Mukherjee[14a] helps to reveal the non-covalent interactions between BOROX **71b** and imine **72o** with the computational studies using ONIOM(B3LYP/6-31G*:AM1) calculation by Mathew Vetticatt and Aman Desai[14b]. The strongest interaction is the hydrogen bonding between imine NH^+ and one of the oxygens from the six-membered ring of broxinate anion (Figure 2.4, d1)[14c]. There are several CH-π interactions within CH_3, sp^2 C-H bonds of

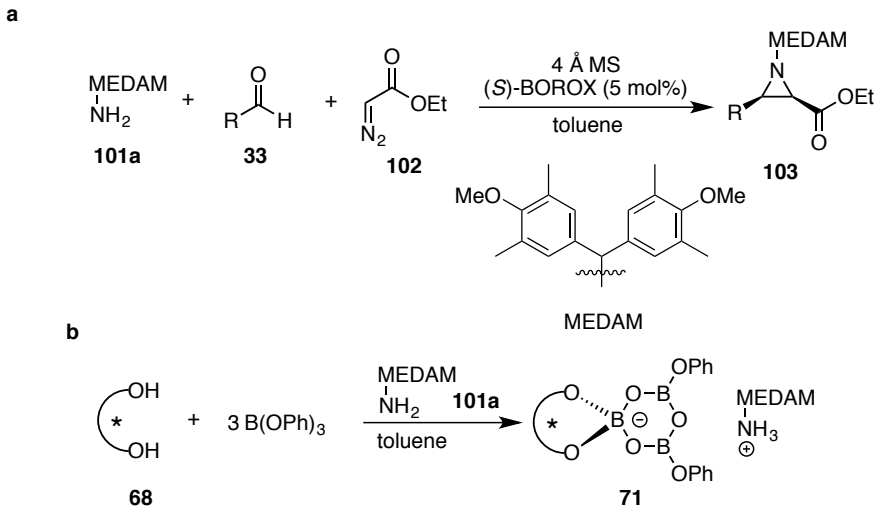
MEDAM group and aromatic systems of BOROX (Figure 2.4, d2-d5). In addition, there is a secondary interaction between the MEDAM methine and the VAPOL oxygen (Figure 2.4, d6). The presence of π-π stacking interaction between phenyl group of imine and aromatic ring of the phenanthrene unit in VAPOL may also play a role in the asymmetric induction (Figure 2.4, d7).

2.2 Catalytic Asymmetric Multi-Component *cis*-Aziridination

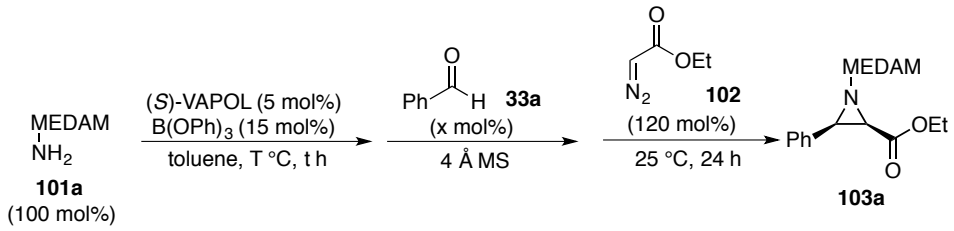
2.2.1 Optimization of Reaction Conditions

Multi-component reactions have been extensively studied and applied to asymmetric catalysis for the maximization of synthetic efficiency in the production of chiral molecules.[15] Imine substrates are usually less stable due to slow decomposition and in most protocols synthesized from the corresponding amines and aldehydes in advance. Purification of imines can also be a problem because most imines decompose during silica gel column chromatography or upon distillation and sublimation during heating. Thus, Anil Gupta and Munmun Mukherjee, our former lab members have reported the first strategy for the asymmetric multi-component *cis*-aziridination based on the BOROX-catalyzed *cis*-aziridination with imines and EDA (Scheme 2.4a).[16] In this multi-component procedure, an imine is generated *in-situ* as an intermediate which is consumed by EDA to afford a *cis*-aziridine. Given that amines are more basic than imines, the BOROX catalyst **71** could also prepared from VANOL/VAPOL ligands **68** with $B(OPh)_3$ in the presence of primary amines **101a** (Scheme 2.4b). The question is if the presence of amines and aldehydes could result in any byproducts. Also, different modes of interactions between the substrates and the catalysts are anticipated, which could have an effect on the asymmetric induction.

Scheme 2.4 BOROX-catalyzed multi-component *cis*-aziridination



Scheme 2.5 Multi-component *cis*-aziridination of benzaldehyde 33a[16]

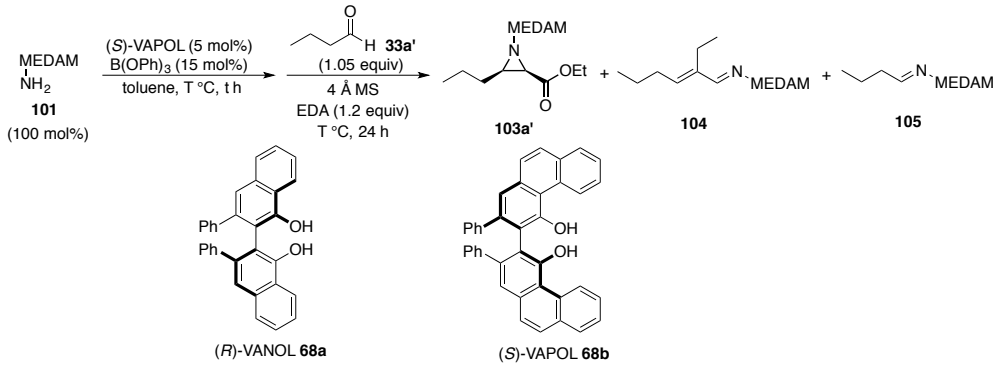


Procedure A (T = 25 °C, t = 1 h)	**33a** (105 mol%) added before **102** (98% yield, 98% *ee*) **102** added before **33a** (105 mol%) (94% yield, 98% *ee*) **33a** (60 mol%) added before **102** (<1% yield)
Procedure B (T = 80 °C, t = 0.5 h)	**33a** (105 mol%) added before **102** (97% yield, 98% *ee*)

Several experiments were conducted on the multi-component *cis*-aziridination of benzaldehyde **33a** in an effort to evaluated the effects of each component of substrates on the reaction. In the standard conditions, the (*S*)-VAPOL **68b** (5 mol%) was mixed with $B(OPh)_3$ (15 mol%) and MEDAM amine (1 equiv) in toluene at 25 °C for 1 h to generate the BOROX catalyst (Procedure A, Scheme 2.5). This was followed by the addition of molecular sieves, benzaldehyde **33a** (1.05 equiv) and EDA **102** (1.2 equiv). The resulting mixture was stirred at room temperature for 24 h to afford *cis*-aziridine **103a** in 98% yield and 98% *ee*. If EDA **102** was added before benaldehyde **33a**, a similar result was

obtained (94% yield, 98% *ee*). However, if only 60 mol% of benzaldehyde **33a** was added, no azirine was observed, which suggested that the excess amine could deactivate the catalyst since it is a stronger base than an imine. It was also found that generation of the BOROX catalyst at 80 °C for 0.5 h would also lead to a similar result (97% yield, 98% *ee*) (Procedure B, Scheme 2.5).

Table 2.3 Optimization of multi-component aziridination with *n*-butyraldehyde 33a' [a] [16]



entry	ligand	proc.	cat. x mol%	T (°C)	EDA (equiv.)	yield% **103a'** [b]	*ee*% **103a'** [c]	yield% **104** [d]	yield% **105** [d]
1	(*R*)-**68a**	A	5	25	1.2	25[d]	nd	20	38
2	(*R*)-**68a**	A	5	0	1.2	50[d]	nd	6	21
3	(*R*)-**68a**	B	5	0	1.2	53[d]	nd	6	17
4	(*R*)-**68a**	B	10	0	1.2	74	–95	2	<1
5	(*R*)-**68a**	B	10	–10	1.2	80	–96	<1	<1
6	(*S*)-**68b**	B	10	–10	1.2	82	98	<1	<1
7	(*S*)-**68b**	B	5	–10	8	91	96	<1	<1
8	(*S*)-**68b**	A	5	–10	8	94	96	<1	<1
9	(*S*)-**68b**	A	3	–10	2	92	96	<2	<2

[a] Unless otherwise specified, all reactions were performed with 0.5 mmol of amine **101a** (0.5 *M*) and 1.05 equiv of *n*-butyraldehyde **103a'** and 1.2 equiv EDA **102** with Procedure A or B (see Scheme 2.6) and went to 100% completion. [b] Isolated yield. [c] Determined by chiral HPLC. [d] Yield determined by ^{1}H-NMR with Ph_3CH as internal standard.

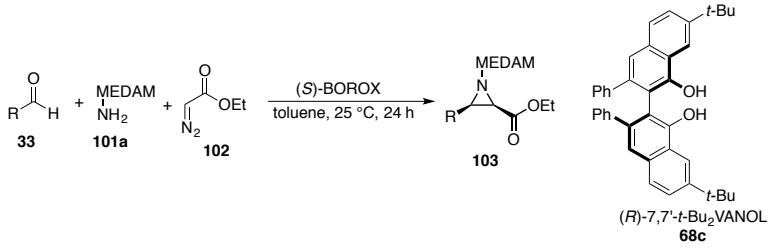
It was quite a different story when it came to aliphatic aldehyde substrates. For non-branched aliphatic imines, there is a problem in the clean *in-situ* generation of the imino reactor that leads to a very poor outcome in aziridination with non-purified substrate. In the initial study of the multi-component reaction with *n*-butyraldehyde **33a'**, it was found that the imine could not be generated in a clean fashion. The self-condensation byproduct conjugate imine **104** was observed in 20% yield after reaction for 24 h at room

temperature along with 38% of the imine **105** (Table 2.3, entry 1). Further optimization of the reaction conditions shown that the self-condensation product could be effectively retarded as the temperature was decreased to –10 °C. Excess EDA (2.0 equiv) could promote the conversion of *in-situ* imine **105** into *cis*-aziridine **103a'**. VAPOL **68b** also provides a better yield than VANOL **68a**, which affords **103a'** in 92% yield and 96% *ee* with the optimal conditions (Table 2.3, entry 9).

2.2.2 Substrate Scope and Screening of BOROX Catalysts

The screening of BOROX catalysts derived from the ligands VANOL **68a**, VAPOL **68b** and 7,7-di-*tert*-butyl VANOL **68c** has been reported with several aldehyde substrates **33**.[16,17] The reactions were allowed to proceed for 24 h with 5 mol% catalyst loading to ensure a full conversion of all substrates, however many of the aldehydes were completely converted in far less time. The data (Table 2.4) reveals that all three ligands **68a**, **68b**, **68c** gave significantly high asymmetric inductions for aromatic aldehydes. But for electron-rich 4-anisaldehyde, the yield was relatively low due to the slow *in-situ* formation corresponding imine. Ligand **68c** gave a slighly higher induction than either **68a** or **68b** for aliphatic aldehydes, which makes the ligand synthetically valuable, especially for the aziridination of *n*-pentadecanal as the key step in the sphinganine synthesis.

Table 2.4 Substrate scope of multi-component *cis*-aziridination with three ligands-derived catalysts[17]



entry	R	(*S*)-VANOL **68a**		(*S*)-VAPOL **68b**		(*R*)-^{t}Bu$_2$VANOL **68c**	
		yield% [b]	*ee*% [c]	yield% [b]	*ee*% [c]	yield% [b]	*ee*% [c]
1	*p*-$NO_2C_6H_4$	77	99	92	99	100	–99
2	*p*-$CH_3C_6H_4$	87	98	95	99	91	–99
3	*o*-$CH_3C_6H_4$	73	98	96	>99	97	–99
4	C_6H_5	87	97	98	98	100	–99
5	*p*-$CH_3OC_6H_4$	82	97	78	98	93	–99
6	2-pyridyl	95	96	96	90	97	–99
7	*n*-$C_{15}H_{31}$ [d]	60	95	85	96	97	–98
8	cyclohexyl	94	94	95	90	100	–96
9	*tert*-butyl	70	95	89	94	100	–97

[a] Unless otherwise specified, all reactions were run at 0.5 *M* in amine in toluene on a 0.5 mmol scale with EDA **102** (1.2 equiv) and aldehyde **33** (1.05 equiv) at 25 °C for 24 h and went to 100% completion with the catalyst (5 mol%) with Procedure B (see Scheme 2.6). The data for ligand **68a** is from Reference 17 and the data for ligand **68b** and **68c** are data from this thesis work. [b] Yield of isolated *cis*-aziridine **103** purified by silica gel column chromatography. [c] Determined by chiral HPLC. [d] Reaction was performed at –10 °C at 0.2 *M* with **102** (2.0 equiv).

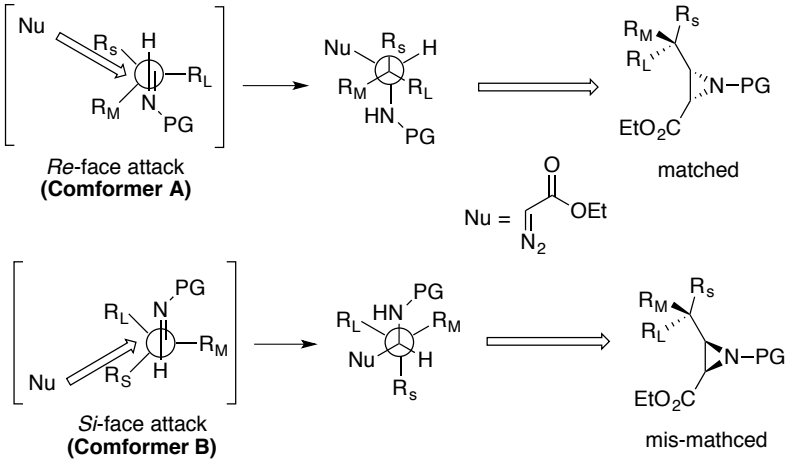
2.3 Catalyst Control in Multi-Component *cis*-Aziridination

2.3.1 Reaction Optimization and Substrate Scope

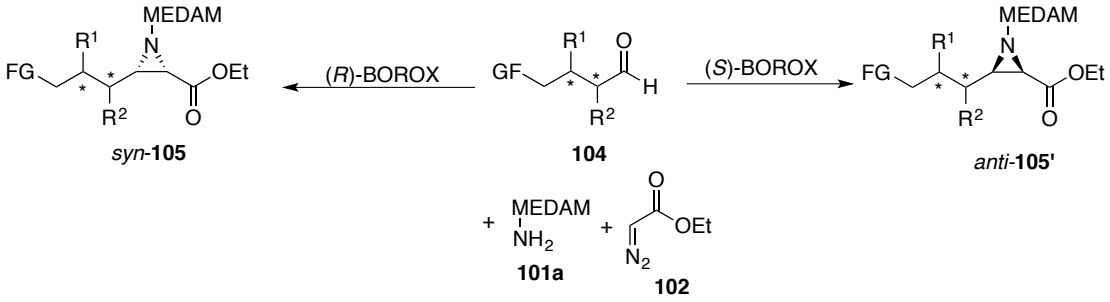
Among the range of asymmetric catalytic tactical methods, most do not display true catalyst control in setting the stereochemistry of new chiral centers independently from the chiral centers already present in the substrates. Typically, one finds matched and miss-matched pairs of the catalyst and substrate which affect the disatereoselectivity in the formation of new chiral centers.[18] The disatereoselective outcomes of aziridination with chiral imines can be predicted by the Felkin-Ahn Model[19] of nucleophilic attack on an imine. As shown in Figure 2.5, the preferential addition of the nucleophile to the C=N bond will be along Bürgi-Dunitz angle near the side of smallest substituent which is sterically favored. The chiral imine reacts *via* Conformer A in *Re*-face attack of the nucleophile, which is favored to afford the matched diastereomer of the aziridine.

Conformer B of the chiral imine reacts *via Si*-face attack of the nucleophile, which is disfavored to afford the miss-matched diastereomer.

Figure 2.5 Felkin-Ahn Model in *cis*-aziridination of chiral imines[19c]

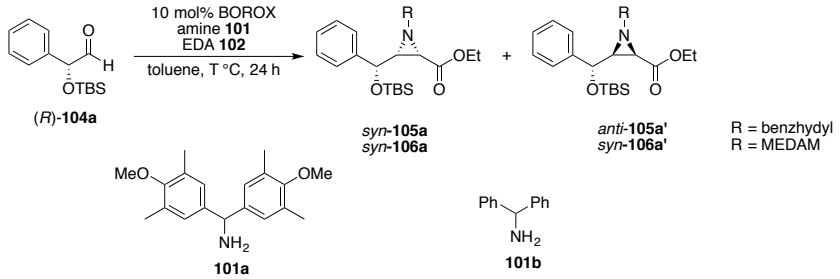


Scheme 2.6 Catalyst-controlled multi-component *cis*-aziridination[20]



Our laboratories have developed the first catalyst-controlled multi-component *cis*-aziridination of aldehydes where the absolute stereochemistry of the newly formed aziridines is a function of the catalyst and not of chiral centers in aldehyde present at either α- or β-positions (Scheme 2.6). One of the reasons that we were driven to develop the multi-component version of the catalyst-controlled aziridination was that in some cases epimerization of the pre-formed imines occurred to result in a poor stereoselectivity.

Table 2.5 Catalyst-controlled *cis*-aziridination of aldehyde (*R*)-104a [a] [20]



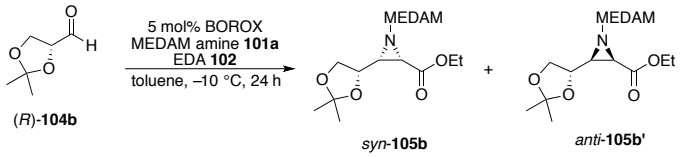
entry	amine	ligand	T (°C)	yield% [b]	aziridine	*syn*:*anti* [c]
1	**101a**	(*S*)-VAPOL	25	90	**105a**	4:96
2	**101a**	(*R*)-VAPOL	25	90	**105a**	97:3
3	**101a**	(*S*)-VAPOL	0	92	**105a**	3:97
4	**101a**	(*R*)-VAPOL	0	90	**105a**	99:1
5	**101a**	(*S*)-VAPOL	–10	90	**105a**	2:98
6	**101a**	(*R*)-VAPOL	–10	90	**105a**	99:1
7	**101a**	(*S*)-VANOL	–10	85	**105a**	2:98
8	**101a**	(*R*)-VANOL	–10	85	**105a**	98:2
9	**101b**	(*S*)-VAPOL	–10	50	**106a**	1:99
10	**101b**	(*R*)-VAPOL	–10	65	**106a**	94:6

[a] Unless otherwise specified, all reactions were run with 0.2 mmol amine **101** (1.0 equiv), EDA (1.2 equiv) and aldehyde (*R*)-**104a** (1.05 equiv) in toluene (0.4 *M*) for 24 h in the presence of powered 4 Å molecular sieves and went to 100% conversion. The BOROX catalyst was prepared with Procedure B (Scheme 2.6). [b] Isolated yield of *syn*-**105a**/**106a** and *anti*-aziridine **105a'**/**106a'** purified by silica gel column chromatography. [c] Determined by ^{1}H-NMR of the crude reaction mixture.

The initial investigations of the catalyst-controlled multi-component *cis*-aziridination with (*R*)-**104a** were done by Munmun Mukherjee and gave a 96:4 distereoselectivity of the *anti*-aziridine **105a'** over *syn*-aziridine **105a** with (*S*)-VAPOL-derived BOROX catalyst (Table 2.5, entry 1). The aziridination with (*R*)-VAPOL-derived BOROX catalyst gave 97:3 ratio of aziridines **105a** and **105a'** in favor of *syn*-isomer (Table 2.5, entry 2), which indicates a high level of catalyst control in the asymmetric induction, and in addition agrees with the previous experimental results in the *cis*-aziridination with the (*S*)-ligand BOROX catalysts giving addition to the *Si*-face of the non-chiral imines to afford *cis*-aziridine carboxylates with (2*R*)-configuration. The diastereoselectivity was slightly improved when the reaction temperature was decreased to –10 °C (Table 2.5, entry 3-6). The VANOL BOROX catalyst gave the comparable catalyst control level to those of the VAPOL BOROX catalyst (Table 2.5, entry 7, 8). However, replacement of

MEDAM amine **101a** with benzhydryl amine **101b** resulted in great drop in the yield, although decent catalyst control was still maintained.

Table 2.6 Catalyst-controlled *cis*-aziridination of (*R*)-glyceraldehyde acetonide 104b [a]



(*R*)-**104b** *syn*-**105b** *anti*-**105b'**

entry	ligand	yield% [b]	*syn*:*anti* [c]
1	(*S*)-VANOL	67	16:84
2	(*R*)-VANOL	86	92:8
3	(*S*)-VAPOL	73	16:84
4	(*R*)-VAPOL	90	94:6
5	(*S*)-^{t}Bu$_2$VANOL	99	3:97
6	(*S*)-^{t}Bu$_2$VANOL	99	97:3

[a] Unless otherwise specified, all reactions were run with 0.2 mmol MEDAM amine **101a** (1.0 equiv), EDA (1.2 equiv) and aldehyde (*R*)-**104b** (1.05 equiv) in toluene (0.4 *M*) for 24 h in the presence of powered 4 Å molecular sieves and went to 100% conversion. The BOROX catalyst was prepared with Procedure B (Scheme 2.6). [b] Isolated yield of *syn*-**105b** and *anti*-aziridine **105b'** purified by silica gel column chromatography. [c] Determined by ^{1}H-NMR of the crude reaction mixture.

As part of the work in this thesis, the ligand of the catalyst-controlled aziridination was also investigated with (*R*)-glyceraldehyde acetonide **104b**, which has potential synthetic utility of polyoxamic acid. All three ligands VANOL **68a**, VAPOL **68b** and 7,7'-di-*tert*-VANOL **68c** have been tested. It was found that the *anti*-isomer of aziridine **105b** was the miss-matched product with (*S*)-VANOL and VAPOL ligands and resulted in lower yields and disatereoselectivities than those of *syn*-**105a** with (*R*)-VANOL and VAPOL ligands (Table 2.6, entry 1 and 3 vs 2 and 4). However, complete catalyst control was observed with *t*-Bu$_2$VANOL ligands, since it gives 97:3/3:97 diastereomeric ratio in a 99% yield for both *syn*- and *anti*-**105b** (Table 2.6, entry 5, 6).

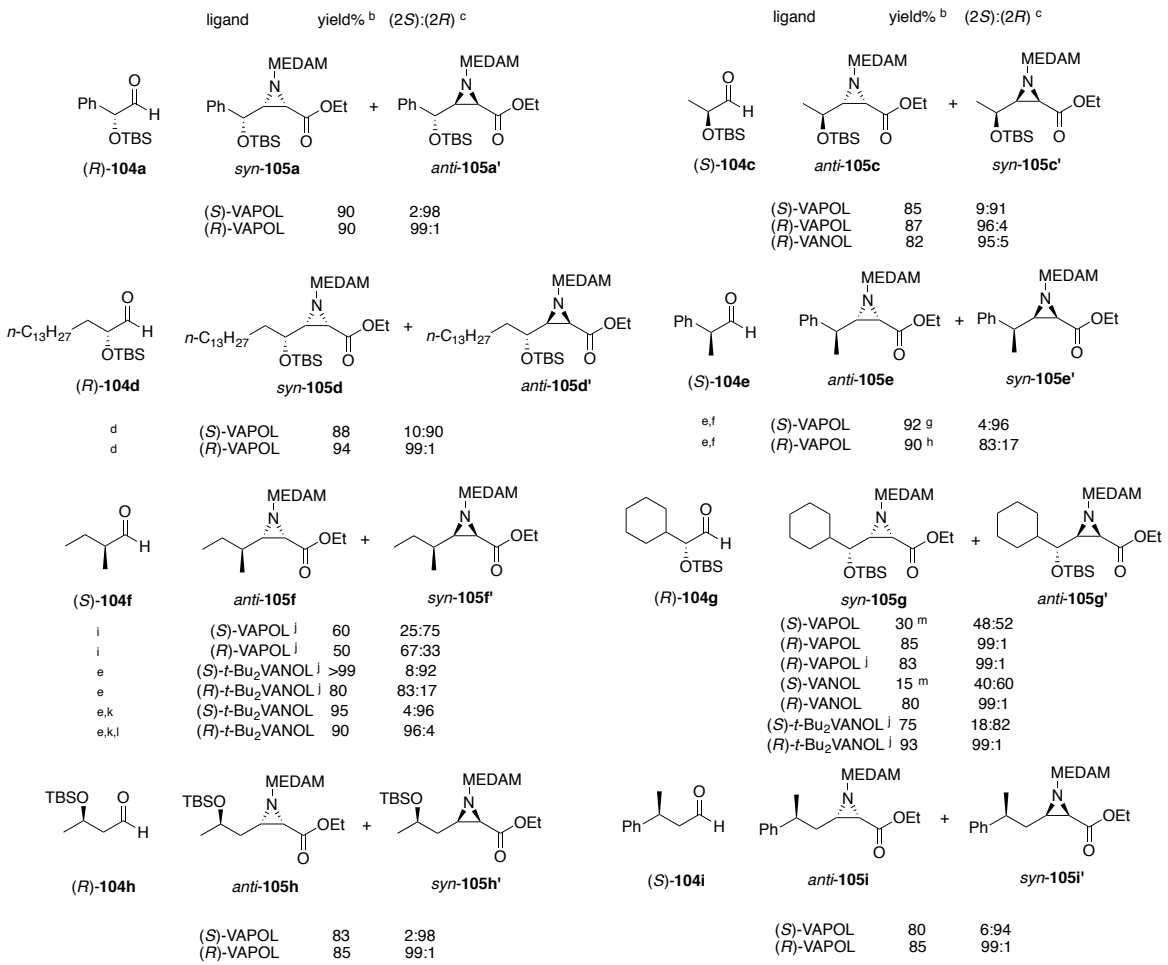
A number of different aldehydes with chiral centers at the α- or β-positions have been evaluated in the catalyst-controlled aziridination (Table 2.7). Replacement of the phenyl group in aldehyde **104a** with a methyl or a long chain *n*-tetradecyl group still results in very good catalyst control for the aldehydes (*S*)-**104c** and (*R*)-**104d**. However,

replacement of the *tert*-butyldimethylsiloxy group in **104a** with a methyl group results in drop in the diastereoselectivity for aldehyde (*S*)-**104e** to 83:17 ratio in favor of *anti*-**105e** in the miss-matched case due to racemization of the intermediate imine (see chapter 6.2.2 b2). The chiral aldehyde (*S*)-**104f** with an α-branched alkyl chain did not give a high level of catalyst control with the VAPOL ligand **68b**. However, it gave a perfect level of catalyst control with the *t*-Bu_2VANOL ligand **68c** at –40 °C. And the aldehyde (*R*)-**104g** with the a cyclohexyl and a *tert*-butyldimethylsiloxy group in the α-position is the substrate with a strongly miss-matched reaction even with the *t*-Bu_2VANOL ligand **68c** and affords 18:82 ratio at the best selectivity for this case. A high level of catalyst control could also be realized with aldehydes (*R*)-**104h** and (*S*)-**104i** bearing the chiral centers at β-positions. Comparing the case aldehydes **104h** with **104c** and **104i** with **104e**, we would expect that a higher level of catalyst control would be seen with the greater distance of the chirality from the reaction center, as the more remote chiral center exhibits weaker negative effects on the asymmetric induction for the miss-matched isomer. In addition, the β-chiral center would not be expected to undergo racemization of the *in-situ* generated imines.

Several chiral heterocyclic aldehydes were also examined with the catalyst-controlled aziridination (Table 2.8). The multi-component aziridination of (*S*)-**104j** exhibited very high yields and a decent level of catalyst control with the selectivity around 90:10 ratio for both isomers of the *t*-Bu_2VANOL ligand **68c**. A complete and significantly high level of catalyst control was seen for the aziridine carboxaldehyde (2*S*,3*S*)-**104k** and Garner's aldehyde (*S*)-**104m** giving **105k**, **105k'**, **105m** and **105m'** as single diastereomers.

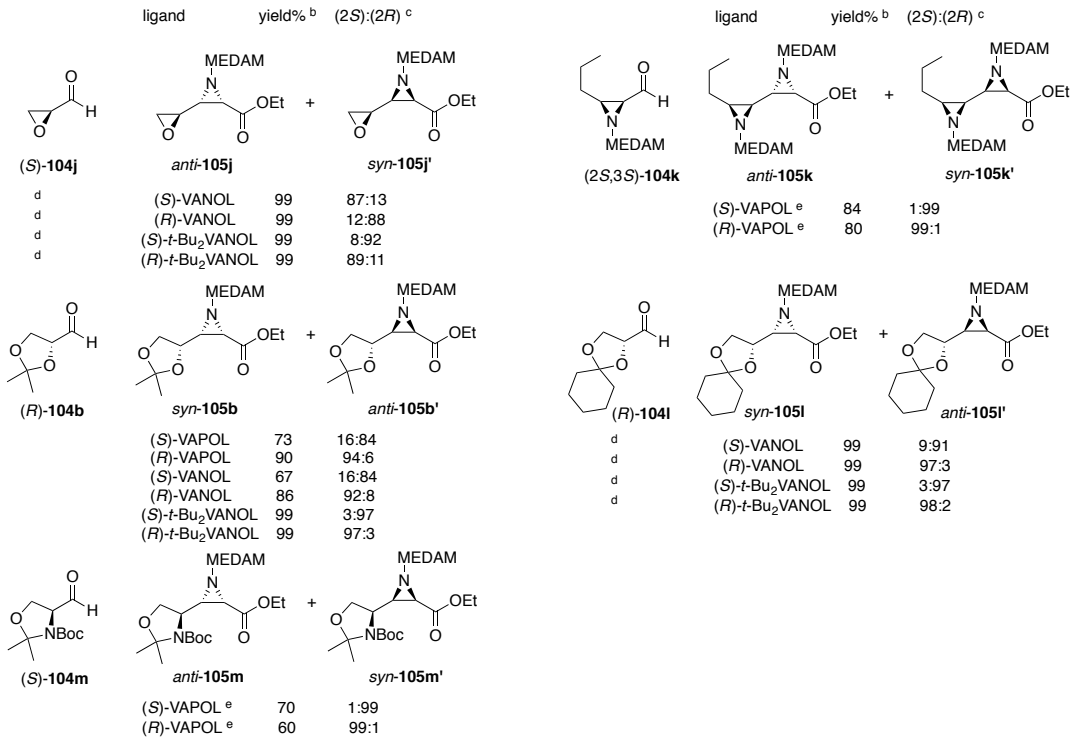
Slightly improved selectivity was seen with (*R*)-glyceraldehyde cyclohexanonide **104l** compared to (*R*)-**104b**.

Table 2.7 Catalyst-controlled *cis*-aziridination of α- and β-chiral aldehydes [a 20]



[a] Unless otherwise specified, all reactions were carried out as described in Table 2.5 at –10 °C for 24 h with 10 mol% catalyst. The concentration is 0.4 *M* in MEDAM amine **101a**. Substrates **104a**, **c**, **e**, **g**, **h** and **i** were done by Munmun Mukherjee. Substrate **104d** and **f** were done by Yijing Dai. [b] Yield of aziridine **105** diastereomers isolated together by silica gel column chromatography. [c] Determined by ^{1}H-NMR of the crude reaction mixture. [d] Reaction at 0.2 *M* instead of 0.4 *M*. [e] 4 equiv of EDA. [f] Reaction at 0.04 *M* instead of 0.4 *M*. [g] The *ee* of *anti*-**105e** was 80% and *syn*-**105e'** was 99% from (*S*)-VAPOL. [h] The *ee* of *anti*-**105e** was 99% and *syn*-**105e'** was 43% from (*R*)-VAPOL. [i] 2 equiv of EDA. [j] 5 mol% catalyst instead of 10 mol%. [k] Reaction at –40 °C. [l] Reaction for 48 h instead of 24 h. [m] Reaction did not go to completion.

Table 2.8 Catalyst-controlled *cis*-aziridination of chiral heterocyclic carboxaldehydes [a] [20]



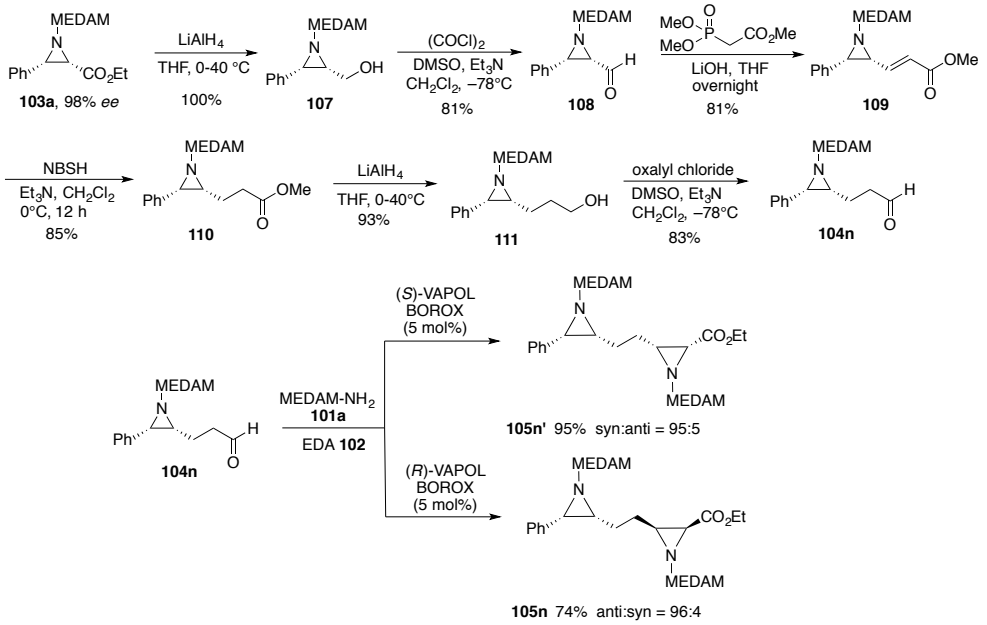
[a] Unless otherwise specified, all reactions were carried out as described in Table 2.5 at –10 °C for 24 h with 5 mol% catalyst. Substrates **104j**, **b** and **l** were done by this thesis. Substrate **104k** and **m** were done by Munmun Mukherjee. [b] Yield of aziridine **105** diastereomers isolated together by silica gel column chromatography. [c] Determined by ^{1}H-NMR of the crude reaction mixture. [d] 2 equiv of EDA. [e] 10 mol% catalyst instead of 5 mol%.

2.3.2 Synthetic Utility of Catalyst-Controlled *cis*-Aziridination

My research collaborator Yijing Dai has performed the application of catalyst-controlled aziridination in the synthesis of ethylene diaziridine **105n** and **105n'** as well as β^3-homo-D-isoleucine *anti*-**112** and β^3-homo-D-alloisoleucine *syn*-**112'**. The diastereomers ethylene diaziridine **105n** and **105n'** have been synthesized by multi-component aziridination of γ,δ-aziridinyl aldehyde **104n** with (*R*)- and (*S*)-VAPOL BOROX catalysts respectively. Aziridine **104n** was prepared in 43% total yield over six steps from aziridine **103a**, the synthesis of which was previously reported by multi-component *cis*-aziridination of benzaldehyde **33a** in 98% yield and 98% *ee* with (*R*)-VAPOL BOROX

(Table 2.4, entry 4). The *cis*-aziridination of **104n** with 5 mol% (*S*)-VAPOL BOROX gave the ethylene diaziridine **105n'** as a 95:5 mixture of *syn*- and *anti*-diastereomers in 95% yield. The *anti*-isomer **105n** was preferentially generated from (*R*)-VAPOL BOROX in 74% yield with a 96:4 selectivity (Scheme 2.7).

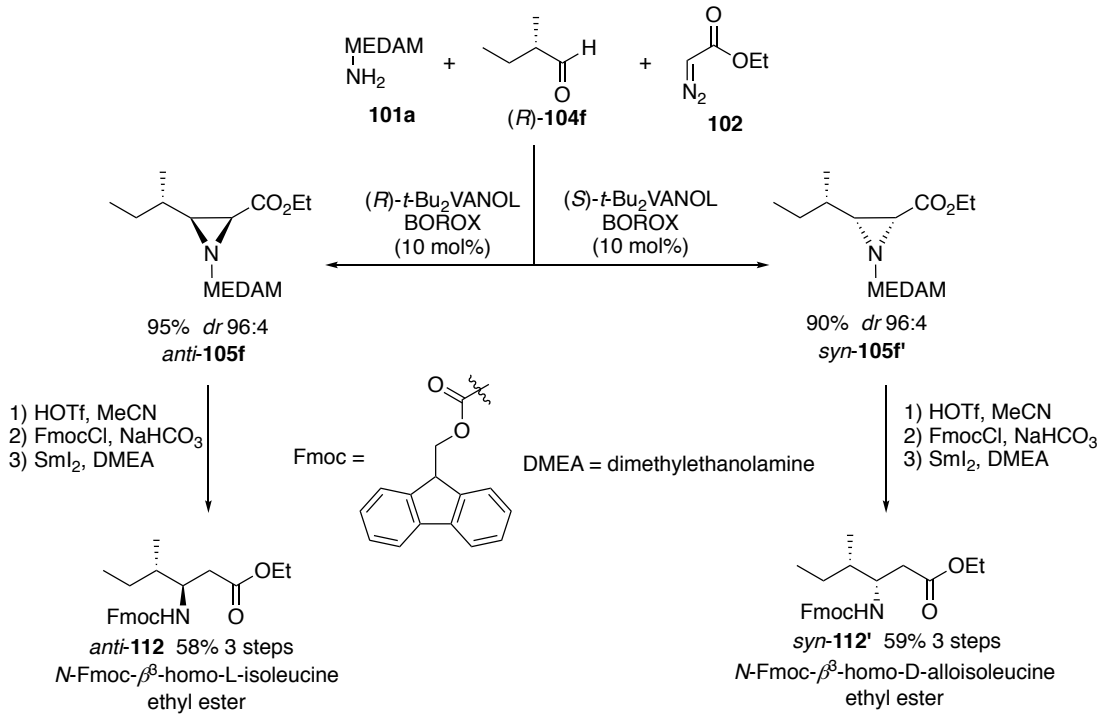
Scheme 2.7 Catalyst-controlled synthesis of ethylene diaziridines 105n and 105n'



β-amino acids have been of significant interest in research during the last score years[21, 22] because they are used as the important building blocks in the synthesis of β-peptides and β-lactams, which exhibits antibiotic resistance[23] and, in the case of the former, stability against proteolytic degradation *in vitro* and *in vivo*[24]. As an illustration of the synthetic utility of the catalyst-controlled multi-component aziridination, a concise synthesis of Fmoc-protected β^3-homo-D-isoleucine *anti*-**112** and β^3-homo-D-alloisoleucine *syn*-**112'** was carried out starting from the aldehyde (*R*)-**104f** prepared from commercially available (*S*)-2-methyl-1-butanol by Dess-Martin oxidation (Scheme 2.8). The aziridination of (*R*)-**104f** with *t*-Bu$_2$VANOL-derived BOROX catalysts gave 96:4 selectivity for each aziridine diastereomer (Table 2.7). The MEDAM group was then

removed and replaced by Fmoc, which was followed by the SmI_2-mediated reductive ring-opening of the aziridine based on the published procedure by Wenjun Zhao and Zhenjie Lu.[25] The β-amino esters *anti*-**112** and *syn*-**112'** were obtained in a decent overall yield as a single stereoisomer.

Scheme 2.8 Access to *β*^{3}-homo-D-isoleucine *anti*-112 and *β*^{3}-homo-D-alloisoleucine *syn*-112'[20]

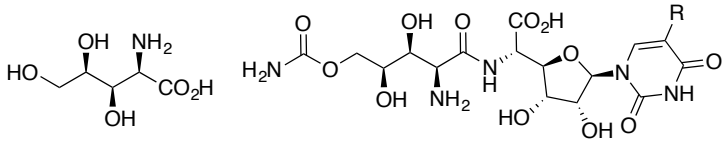


The synthesis of polyoxamic acid was also envisioned as an application of catalyst-controlled multi-component *cis*-aziridination. Polyoxamic acid **113** is a key component of the polyoxins **114** which are a family of important nucleoside antibiotics first isolated in 1960s as the inhibitors of chitin synthesis in a yeast (Figure 2.6).[26] They inhibit the growth of fungus and lack human toxicity.

A number of synthesis have been published of polyoxamic acid and various derivatives since the early 1990s in an effort to obtain improved biological activity.[27] Dolt and Zabel reported the synthesis of polyoxamic acid derivative **121** from aziridine carboxylate **117**,

which was prepared from (*R*)-glyceraldehyde acetonide **104b** by Wittig reaction followed by olefin hydroamination/aziridination cascade (Scheme 2.10a).[27b] Unfortunately, the aziridine **117** was obtained as a 1:1 mixture of diastereomers. The aziridine **119** underwent Lewis acid catalyzed deprotection of acetonide to the afford diol **120** and subsequent ring-opening with trifluoroacetic acid to give the target molecule **121**. Although the aziridine carboxylate *anti*-**105b'** could be obtained in a high yield and selectivity with a high level of catalyst control by multi-component *cis*-aziridination, the TFA-catalyzed ring-opening of the aziridine *anti*-**105b'** failed to give a clean reaction and afford a mixture of ring-opening and acetonide cleavage compounds. Thus, it's likely that following a similar synthetic strategy from **105b'**, involving acetonide deprotection, TFA ring-opening, ester saponification and MEDAM hydrogenolysis would afford polyoxamic acid **113** in four steps (Scheme 2.10b).

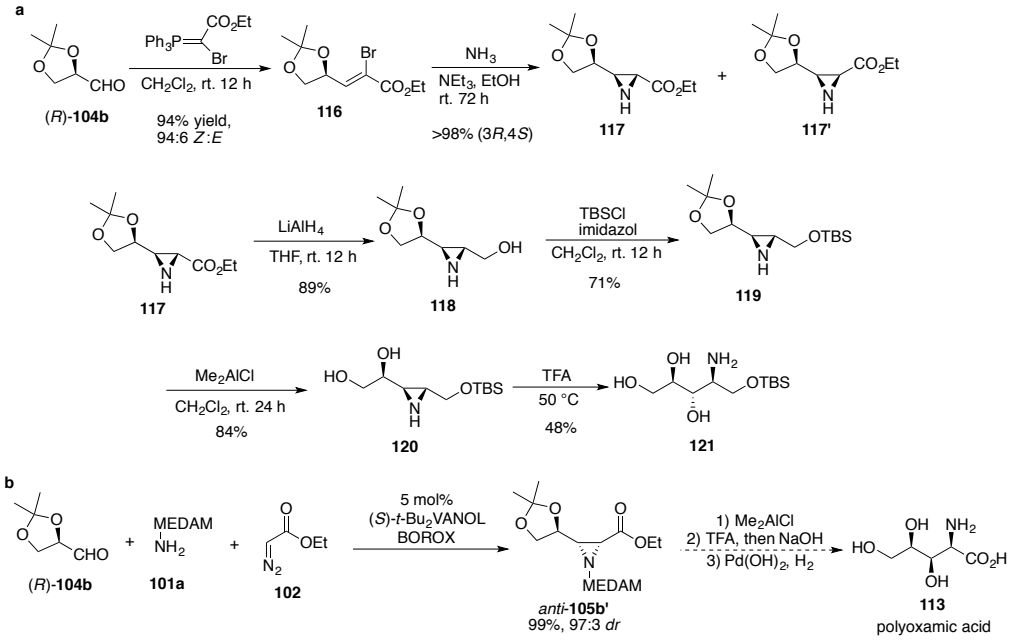
Figure 2.6 Polyoxamic acid 113 and polyoxins 114



113
polyoxamic acid

114
polyoxins

Scheme 2.9 Proposed synthesis of polyoxamic acid by catalyst-controlled aziridination



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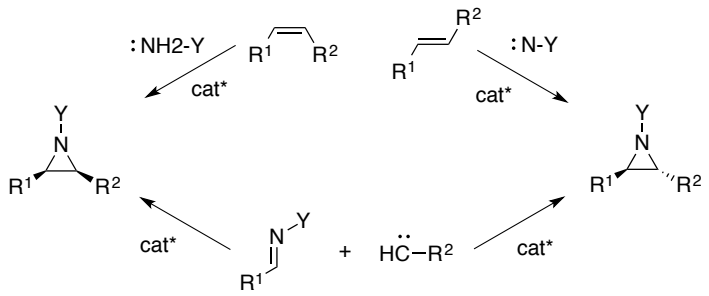
Chapter 3 Multi-Component *trans*-Aziridination

3.1 Catalytic Asymmetric *trans*-Aziridination

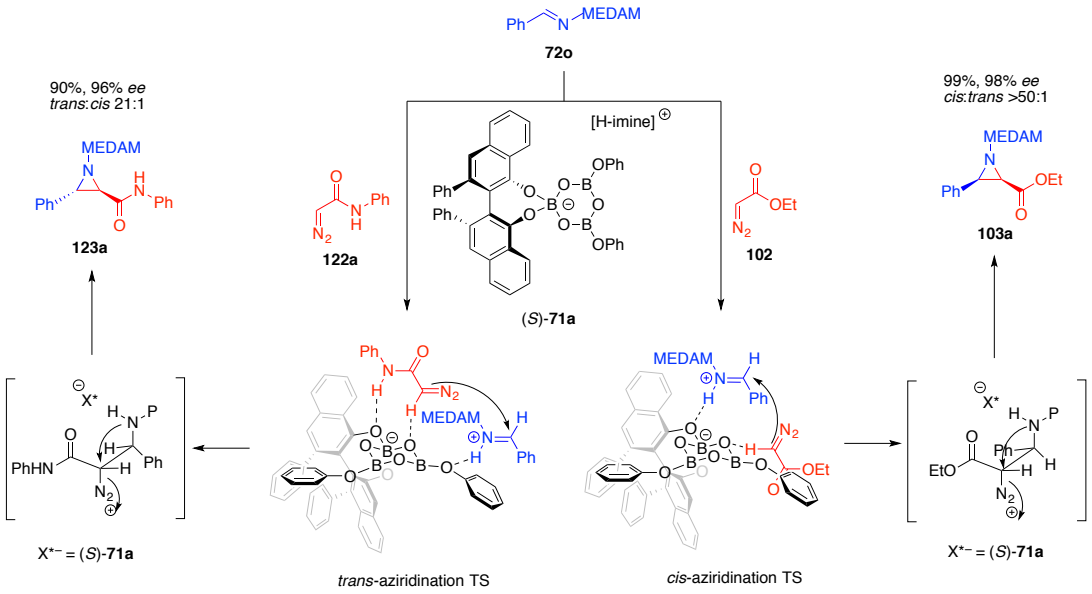
Our consideration of catalytic asymmetric aziridination has focused on the construction of two chiral centers. In the protocol of nitrene addition to alkenes, the stereochemistry of the disubsituted aziridines as either *cis*- or *trans*- is completely dependent on the configuration of double bond in the alkene. One of the limits of this method is that it requires a pure *Z*- or *E*-isomers of alkenes.[1] In contrast, this requirement would not exist in the preparation of aziridines from the formal addition of a carbene to an imine of the proper set of catalysts were available to selectively give either *cis*- or *trans*-aziridines (Scheme 3.1).

Scheme 3.1 Substrate control and catalysts control of stereoselective aziridination



Since the early 1990s, several efficient catalytic strategies for the aziridination by carbene addition to imine have been reported to realize either *cis*-selective aziridination[2,3] or *trans*-selective aziridination[4]. Based on the success of the BOROX-catalyzed asymmetric *cis*-aziridination of imines with ethyl diazoacetate (EDA) developed by Jon Antilla[3a,b], Aman Desai reported an asymmetric *trans*-aziridination of imines with diazoacetamides catalyzed by the same BOROX anion[5], which together provides a universal protocol for catalytic asymmetric aziridination process for either *cis*- or *trans*-stereoselectivity.

Figure 3.1 Universal BOROX-catalyzed asymmetric aziridination



The BOROX-catalyzed *trans*-aziridination with *N*-MEDAM benzaldimine **72o** and *N*-phenyl diazoacetamide **122a** afford the *trans*-disubstituted aziridine carboxamide **123a** in 90% yield and 96% *ee* with a 21:1 *trans*-selectivity, while the same imine **72o** and EDA **102** catalyzed by the same BOROX anion **71a** affords the *cis*-aziridine carboxylate **103a** in 99% yield and 98% *ee* with greater than 50:1 *cis*-selectivity[3h,j]. This is a significant strategy that allows the stereochemistry to be nicely controlled by the nature of the diazo compound with the same chiral catalyst and with the same imine substrate (Figure 3.1). Mathew Vetticatt and Aman Desai have shown that the hydrogen bonds between the diazo compounds and the BOROX catalyst govern the diasteroselection of aziridine formation.[6] The aziridination by carbene addition to the imines happens in step-wise manner with the initial C-C bond formation that is followed by C-N bond formation in the ring closure.[7] A previous study suggested that the C-C bond formation step is the enantio- and diastereoselectivity-determining step.[2b] The transition states have been studied by ONIOM (B3LYP/6-31G*: AM1) calculation to reveal that the substrate-

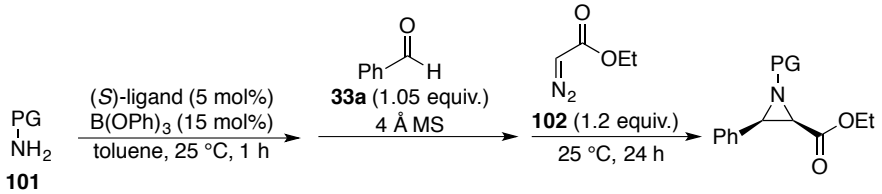
catalyst interactions in the most stable conformer controls the asymmetric induction (Figure 3.1).[6] In *cis*-aziridination transition state, a C–H···O interaction is present between the α-hydrogen of EDA **102** and an oxygen of the broxinate. In the *trans*-aziridination transition state, the similar C–H···O interaction exists between the α-hydrogen of diazoacetamide **122a** and one of the VANOL oxygens. In addition, additional H-bonding is provided by the secondary amide hydrogen and an oxygen of the boroxinate. This indicates the secondary amide is the crucial as the active site for *trans*-selective induction.

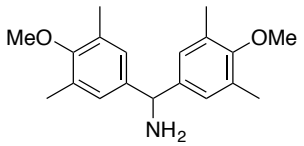
3.2 Multi-Component *trans*-Aziridination

3.2.1 *trans*-Aziridination with Aromatic Aldehydes

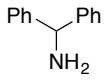
We have previously reported catalytic asymmetric multi-component *cis*-aziridination of an amine, aldehyde and EDA with high enantioselectivity catalyzed by the BOROX catalysts[3k], which were generated from either VANOL **68a** or VAPOL **68b** ligand in the presence of the amine **101** and triphenyl borate (Scheme 3.2). Catalyst generation was followed by the rapid addition of an aldehyde, molecular seives and EDA to give the *cis*-aziridine with high diasteroselectivity (up to 50:1 *cis*:*trans*). After screening three amines **101a**, **101b** and **101c**, the MEDAM protecting group of amine gives the best results in both yield and *ee* in aziridination. The VAPOL-derived BOROX catalyst also gives the better results than the VANOL-derived BOROX and thus the combination of MEDAM amine **101a** and VAPOL ligand **68b** was established as the optimal conditions in the multi-component *cis*-aziridination.

Scheme 3.2 Multi-component *cis*-aziridination of benzaldehyde 33a[8]



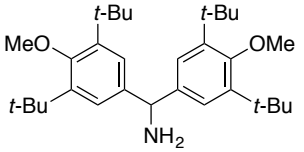


101a



101b

PG = MEDAM **103b**
PG = BUDAM **124a**
PG = benzhydryl **100**



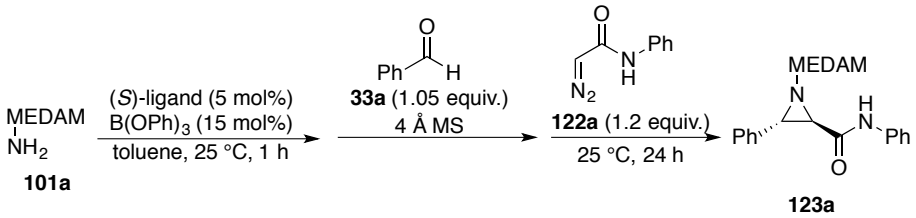
101c

amine	ligand	yield%	*ee*%	reference
101a	VAPOL	98	98	3m
101a	VANOL	95	95	3m
101b	VAPOL	77	92	3l
101b	VANOL	72	91	3l
101c	VAPOL	85	99	this work
101c	VANOL	91	97	this work

Since secondary diazoacetamides are known to react with imines to give *trans*-aziridines in a decent diastereoselectivity[5], it was believed a similar multi-component procedure could be applied to *trans*-aziridination. However, it was not clear that the optimal procedure for the multi-component *cis*-aziridination would be equally effective for the multi-component *trans*-aziridination, since *cis*- and *trans*-aziridination of imines react *via* different pathways involving different transition states. Nonetheless, our initial studies on the multi-component *trans*-aziridination of benzaldehyde employed the optimal conditions for the multi-component *cis*-aziridination with MEDAM amine **101a** at room temperature for 24 h (Scheme 3.3). With VAPOL- and VANOL-derived BOROX catalysts, only moderate yields of *trans*-aziridine **123a** was obtained, with only 2:1 *trans*/*cis* diastereoselectivity. There was drop in enantioselectivity for the VAPOL BOROX catalyst from 98% *ee* to 73% *ee*, but there was dramatic decreasing for the VANOL BOROX catalyst from 95% to 14% *ee* (Scheme 3.2 vs 3.3). This indicates that

there is a great difference in the reaction pathways for *cis*- and *trans*-aziridine formation and further optimization will be required to develop an effective procedure.

Scheme 3.3 Initial studies of multi-component *trans*-aziridination[8]

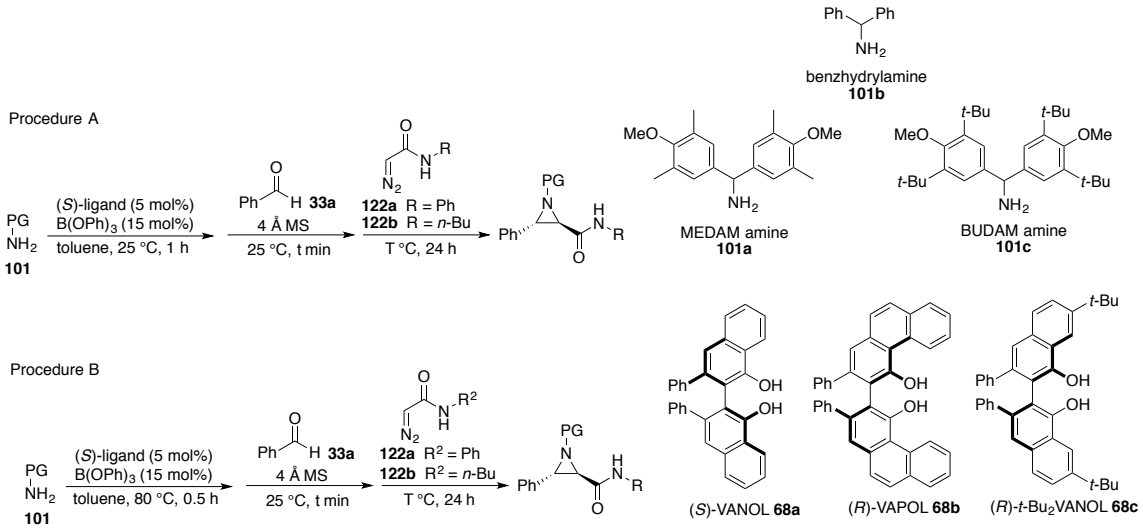


ligand	yield%	*ee*%	*trans*:*cis*
VAPOL	67	73	2:1
VANOL	63	14	2:1

The first effort to optimize the multi-component *trans*-aziridination was the exploration of the BUDAM *N*-substituted amine **101c** as it was found to be comparable or slightly better than MEDAM *N*-substitution in the *cis*-aziridination of imines.[3h] In the reaction of BUDAM amine **101c**, the VANOL-derived catalyst was superior to the VAPOL-derived catalyst (Table 3.1, entry 3, 4), while it was reversed in the reaction with MEDAM amine **101a** where the VAPOL-derived catalyst was found to be superior (Table 3.1, entry 1, 2). Dropping the temperature from ambient to –20 °C resulted in a significant slowing of the reaction with an only 14% yield of aziridine **125a** (Table 3.1, entry 5, 9). However, if the pre-catalyst was allowed to interact with the amine and aldehyde for 20 min prior to the addition of the diazoacetamide, a dramatic improvement in yield and *ee* was realized for aziridine **125a** (90% yield, 92% *ee*, Table 3.1, entry 10). In the diazoacetamide susbtrate, an *N*-phenyl substituent was found to be superior to an *N*-butyl substituent (Table 3.1, entry 10, 13). It was found that procedure A gave a lower yield than procedure B (80% vs 90% yield), although the asymmetric induction was slightly higher (95% *ee*) (Table 3.1, entry 10, 12). The combination of MEDAM amine **101a** and the VAPOL ligand **68b** was not as efficient as BUDAM amine **101c** and VANOL **68a** in the optimal conditions

(Table 3.1, entry 10, 14). Benzhydryl amine **101b** was also tested with both VANOL and VAPOL and found to be far less effective (Table 3.1, entry 15, 16). The ligand 7,7-di-*tert*-butyl VANOL **68c** was significantly less effective than VANOL in the *trans*-aziridination (Table 3.1, entry 11 vs entry 10), which was superior to VANOL in *cis*-aziridination (Table 2.4).

Table 3.1 Optimization of the multi-component *trans*-aziridination with benzaldehyde 33a [a] [8]



entry	Proc	amine	ligand	R^2	T/°C	t/min	aziridine	yield% [b]	*ee*% [c]	*trans*:*cis* [d]	imine% [e]
1	A	**101a**	*S*-**68a**	Ph	23	0	**123a**	63	14	2:1	18
2	A	**101a**	*R*-**68b**	Ph	23	0	**123a**	67	–73	2:1	22
3	A	**101c**	*S*-**68a**	Ph	23	0	**125a**	63	70	8:1	3
4	A	**101c**	*R*-**68b**	Ph	23	0	**125a**	43	–32	2:1	12
5	B	**101c**	*S*-**68a**	Ph	23	0	**125a**	38	67	7:1	15
6 [f]	A	**101c**	*S*-**68a**	Ph	23	20	**125a**	50	73	7:1	5
7 [g]	B	**101c**	*S*-**68a**	Ph	23	20	**125a**	38	71	8:1	5
8	B	**101c**	*S*-**68a**	Bu	23	0	**126a**	29	72	6:1	23
9	B	**101c**	*S*-**68a**	Ph	–20	0	**125a**	(14)	–	13:1	59
10	B	**101c**	*S*-**68a**	Ph	–20	20	**125a**	90	92	18:1	0
11	B	**101c**	*R*-**68c**	Ph	–20	20	**125a**	36	40	2:1	23
12	A	**101c**	*S*-**68a**	Ph	–20	20	**125a**	80	95	19:1	0
13	B	**101c**	*S*-**68a**	Bu	–20	20	**126a**	43	86	8:1	21
14	B	**101a**	*R*-**68b**	Ph	–20	20	**123a**	57	–87	2:1	32
15	B	**101b**	*S*-**68a**	Ph	–20	20	**127a**	62	69	4:1	20
16	B	**101b**	*R*-**68b**	Ph	–20	20	**127a**	49	–75	4:1	11

[a] Unless otherwise specified, all reactions were on a 0.5 mmol scale at 0.2 *M* in toluene with 10 mol% catalyst prepared by either Procedure A or B with 1.2 equiv of benzaldehyde **33a** and 1.4 equiv of diazo acetamides **112**. [b] Isolated yield. [c] Determined by HPLC. [d] Determined by the ^{1}H-NMR spectrum of the crude reaction mixture. [e] Determined by the ^{1}H-NMR spectrum of the crude reaction mixture with triphenylmethane as an internal standard. [f] A 24% yield of an amino amide was isolated which resulted from ring-opening of aziridine at the benzylic carbon and was found to be 93% *ee*. [g] An 18% yield of an amino amide was isolated which resulted from ring-opening of the aziridine at the benzylic carbon and was found to be 93% *ee*.

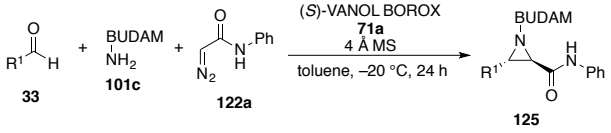
The scope of the multi-component *trans*-aziridination was investigated with a variety of electron-rich and electron-poor aromatic aldehydes (Table 3.2). Most of these aldehydes were found to be effective in giving high selectivity for *trans*-aziridines with high yields and excellent asymmetric inductions employing the optimal conditions (Table 3.1, entry 10). The reaction of 4-methoxybenzaldehyde was very sluggish and an only 9% yield of *trans*-aziridine **125f** was detected along with 76% yield of the imine generated from BUDAM amine **101c** and aldehyde **33f** (Table 3.2, entry 5). However, the acetoxy group could serve as a surrogate for aldehyde **33f** since aldehyde **33m** gave the *trans*-aziridine **125m** in 82% yield and greater than 99% *ee* with a 25:1 *trans*-selectivity (Table 3.2, entry 4).

Both of the electron-poor aldehyde **33c** and **33s** were very slowly converted to their corresponding *trans*-aziridines (Table 3.2, entry 13, 14). This is in contrast to the electron-poor aldehydes **33q** and **33r**, which gave the *trans*-aziridines **125q** and **125r** in decent yields and inductions (Table 3.2, entry 11, 12). The origin of the failure of the 4-nitro- and 4-cyano-substited remains unclear, but could possibly be due to the incompatibility with the BOROX-catalysts. Given that a 2-bromo substituent on benzaldehyde gave a much lower induction than the 4-bromo isomer (Table 3.2, entry 8, 10), it was surprising to find that the reverse is true for the corresponding methyl derivatives where the 2-methyl isomer gave a higher induction than 4-methyl isomer (Table 3.2, entry 6, 7).

Amino amide byproducts were detected in the reaction of aldehyde **33d** and **33k** that resulted from the nucleophilic ring-opening of *trans*-aiziridines by phenol, which was generated from triphenylborate during the catalyst formation (Scheme 4.11). It is

necessary to employ high vacuum to the pre-catalyst in order to remove all the volatile substances including phenol. Decent yields were obtained with the modified procedure for aziridine **125d** (73%, Table 3.2, entry 6) and **125k** (82%, Table 3.2, entry 2). The determination of the absolute configuration of the *trans*-aziridine **125a** from benzaldehyde **33a** was previously reported by Aman Desai[5] and the *trans*-aziridines from the other aromatic aldehydes were assumed to be homo-chiral.

Table 3.2 Aromatic aldehyde scope of multi-component *trans*-aziridination [a] [8]



entry	R^1	*trans*:*cis* [b]	yield% [c]	*ee*% [d]
1	C_6H_5	18:1	90	92
2 [e]	2-naphthyl	62:1	82	92
3	1-naphthyl	>99:1	88	87
4	*p*-$AcOC_6H_4$	25:1	82	>99
5	*p*-$MeOC_6H_4$	1.3:1	9[f]	–
6 [e]	*p*-MeC_6H_4	19:1	73	82
7	*o*-MeC_6H_4	>99:1	85	93
8	*p*-BrC_6H_4	23:1	82	96
9	*m*-BrC_6H_4	27:1	89	95
10	*o*-BrC_6H_4	19:1	89	72
11	*p*-$CF_3C_6H_4$	31:1	78	95
12	*p*-$CO_2MeC_6H_4$	42:1	89	–
13	*p*-$NO_2C_6H_4$	29:1	16[g]	>99
14	*p*-CNC_6H_4	13:1	8[h]	–

[a] Unless otherwise specified, all reactions were performed on a 0.2 mmol scale at 0.2 *M* of amine **101c** in toluene with 1.2 equiv aldehyde **33** and 1.4 equiv *N*-phenyl diazoacetamide **122a** with 10 mol% catalyst with procedure B under the conditions of Table 3.1, entry 10. [b] Determined by the ^{1}H-NMR spectrum of the crude reaction mixture. [c] Isolated yield. [d] Determined by HPLC. [e] Pre-catalyst was subjected to high vacuum at 80 °C for 30 min. [f] A 76% of imine was observed by the ^{1}H-NMR spectrum of the crude reaction mixture. [g] A 52% yield of imine was observed by the ^{1}H-NMR spectrum of the crude reaction mixture. [h] A 66% yield of imine was observed by the ^{1}H-NMR spectrum of the crude reaction mixture.

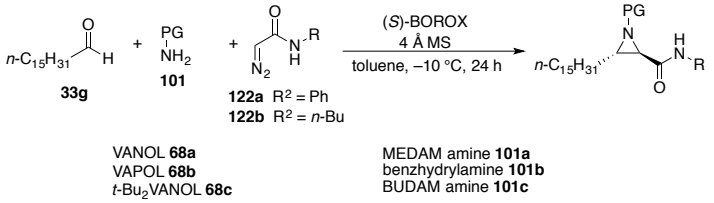
3.2.2 *trans*-Aziridination with Aliphatic Aldehydes

The optimal conditions for the *trans*-aziridination of aromatic aldehydes did not directly apply to that of aliphatic aldehydes. Re-optimization of the multi-component *trans*-aziridination of the aliphatic aldehydes were carried out with *n*-hexadecanal **33g** at –10 °C (Table 3.3), which was the optimal temperature for the multi-component *cis*-aziridination of *n*-hexadecanal **33g**. With the optimal conditions for benzaldehyde **33a**, *n*-

hexadecanal **33g** gave a 78% yield and 88% *ee* at –10 °C (Table 3.3, entry 9). The reaction of aldehyde **33g** with *N*-phenyl diazoacetamide **122a** with the VANOL BOROX catalyst gives superior results if the aldehyde and amine are allowed to interact for 20 min before the addition of the diazo compound (Table 3.3, entry 8 vs 9). In contrast, it was found that the reaction of aldehyde **33g** with *N*-butyldiazoacetamide **122b** was essentially the same, whether or not the aldehyde and amine were allowed to interact for 20 min before the addition of the diazo compound (Table 3.3, entry 6 vs 7).

Both VAPOL **68b** and *t*-Bu_2VANOL **68c** catalysts gave excellent results with BUDAM amine **101c**, but not as good as VANOL **68a** catalyst (Table 3.3, entry 6, 10, 11). this was in significant contrast to the reaction with benzaldehyde **33a** where it was found that the *t*-Bu_2VANOL **68c** catalyst was much less effective (Table 3.1, entry 11). All three ligands were slightly less satisfactory with the combination of MEDAM amine **101a** (Table 3.3, entry 3, 5). The reactions with benzhydryl amine **101b** were much slower and resulted in low yields (Table 3.3, entry 1, 2).

Table 3.3 Optimization of multi-component *trans*-aziridination with *n*-hexadecanal 33g [a] [8]



entry	amine	ligand	R^2	aziridine	*trans*:*cis*[b]	yield%[c]	*ee*%[d]
1	**101b**	*S*-**68a**	*n*-Bu	**128g**	14:1	33 (30)[e]	77
2	**101b**	*R*-**68c**	*n*-Bu	**128g**	14:1	45 (36)[f]	33
3	**101a**	*S*-**68a**	*n*-Bu	**129g**	8:1	67	88
4	**101a**	*S*-**68b**	*n*-Bu	**129g**	15:1	79	86
5	**101a**	*R*-**68c**	*n*-Bu	**129g**	2:1	49	–90
6	**101c**	*S*-**68a**	*n*-Bu	**126g**	24:1	85	96
7[g]	**101c**	*S*-**68a**	*n*-Bu	**126g**	21:1	88	96
8	**101c**	*S*-**68a**	Ph	**125g**	6:1	68	68
9[g]	**101c**	*S*-**68a**	Ph	**125g**	12:1	78	88
10	**101c**	*S*-**68b**	*n*-Bu	**126g**	14:1	91	91
11	**101c**	*R*-**68c**	*n*-Bu	**126g**	17:1	71	–90

[a] Unless otherwise specified, all reactions were performed at 0.2 *M* in amine **101** with 0.2 mmol of 1.0 equiv of amine **101**, 1.1 equiv of aldehyde **33g** and 1.2 equiv of diazoacetamides **122** with 10 mol%

Table 3.3 (cont'd)

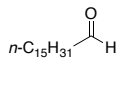
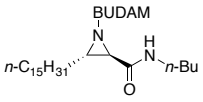
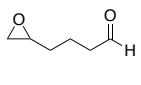
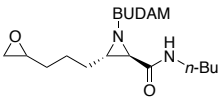
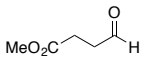
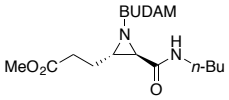
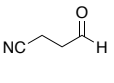
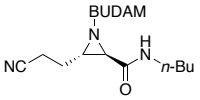
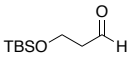
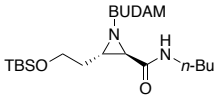
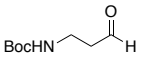
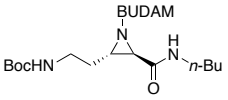
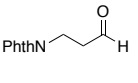
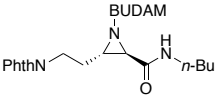
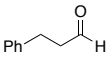
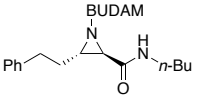
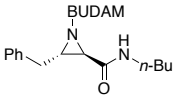
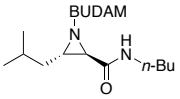
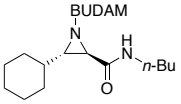
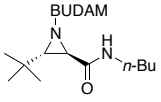
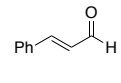
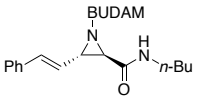
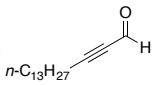
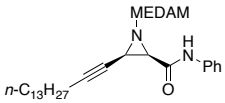
catalyst which was prepared by Procedure B in Table 3.1 with t = 0 min. [b] Determined by the ^{1}H-NMR spectrum of the crude reaction mixture. [c] Isolated yield of *trans*-aziridine. Yields in parentheses are ^{1}H-NMR yields with an internal standard. [d] Determined by HPLC. [e] Reaction went to 87% conversion. [f] Reaction went to 92% conversion. [g] The catalyst was stirred with the aldehyde **33g** and amine **101** for 20 min before the diazoacetamide **122** was added.

The substrate scope of the multi-component *trans*-aziridination with aliphatic aldehydes was also investigated (Table 3.4). The aziridination of unbranched aldehydes give the decent results by the optimal conditions of the multi-component procedure, but for the α-branched aldehydes **33h** and **33i**, a decent conversion in the multi-component method with the optimal conditions could not be achieved (Table 3.4, entry 11, 12). The reasons still remain unclear, but are most likely related to the steric hindrance resulting in the slow formation of the corresponding imines and the negative effect of potential interactions between the catalyst and the excess aldehyde, since the *trans*-aziridination of a purified imine with diazoacetamides is a successful methodology in Aman Desai's work.[5] Thus, the best method to obtain *trans*-aziridines from secondary and tertiary aldehydes involves the pre-preparation of imines as previously reported. However the β-branched aldehyde **33z** proceeds smoothyl to give the *trans*-aziridine **126z** in 88% yield and 95% *ee* as a single diastereomer when catalyzed by the VANOL BOROX catalyst (Table 3.4, entry 10).

The multi-component *trans*-aziridination of unbranched aliphatic aldehydes is fairly tolerant of a number of functional groups including silyl ethers, esters, epoxides, carbamates and phthalimides. The cyano group, on the other hand, seems to negatively impact the reaction as the aldehyde **33u** was converted to *trans*-aziridine **126u** with a low asymmetric induction (Table 3.4, entry 4). The *trans*/*cis* selectivity is generally higher than that for aromatic aldehydes. For a few substrtates (**33t** and **33u**) the *trans*/*cis* ratio

could not be determined due to overlap of key peaks in the ^{1}H-NMR spectrum of the crude reaction mixtures. There does not seem to be an ideal ligand for these substrates since when VANOL **68a** and *t*-Bu_2VANOL **68c** were directly compared VANOL gave better asymmetric inductions for five substrates (Table 3.4, entry 1, 2, 7, 8, 10) and *t*-Bu_2VANOL gave better *ee* for a different set of five substrates (Table 3.4, entry 3, 4, 5, 6, 9). Of particular interest is that the *trans*-aziridination of epoxide **33s** was carried out on the racemic aldehyde **33t** but there does not seem to be any effect in asymmetric induction by the chiral center of the substrate since the *trans*-aziridine **126s** was a mixture of isomers with 49:49:1:1 ratio catalyzed by VANOL BOROX catalyst and a mixture of isomers with 49.5:49.5:0.5:0.5 ratio when catalyzed by *t*-Bu_2VANOL BOROX catalyst (Table 3.4, entry 2). The conjugated unsaturated aldehyde **130b** could not give the *trans*-aziridine **131b** and it should be noted that it also failed in the *cis*-aziridination (Table 3.4, entry 13).[9] It was reported by Anil Gupta that the corresponding conjugated imine would undergo [3+2] cycloaddition with EDA instead of *cis*-aziridination.[9] It still remains unclear if a similar [3+2] cycloaddition pathway will be involved in the reaction with conjugate imines and diazoacetamides. Interesting, the propargyl aldehyde **132** was also investigated and found to give the *cis*-aziridine **133** instead of *trans*-isomer in an excellent yield and asymmetric induction with the VANOL catalyst (Table 3.4, entry 14). It is interesting that this result exactly matches the results reported by Yong Guan *et al.* in the synthesis of *cis*-alkynyl aziridines from propargyl imines and *N*-phenyl diazoacetamide.[10]

Table 3.4 Aliphatic aldehyde scope of multi-component *trans*-aziridination [a] [8]

entry	aldehyde	ligand	yield% [b]	*ee*% [c]	*trans*:*cis* [c]
1					
	33g			**126g**	
		(*S*)-VANOL	88	96	28:1
		(*R*)-*t*-Bu$_2$VANOL	71	–90	17:1
2					
	33s			**126s**	
		(*S*)-VANOL	89	96[e]	8:1[f]
		(*R*)-*t*-Bu$_2$VANOL	62	–98[e]	>99:1[g]
3					
	33t			**126t**	
		(*S*)-VANOL	78	86	nd
		(*R*)-*t*-Bu$_2$VANOL	59	–93	nd
4					
	33u			**126u**	
		(*S*)-VANOL	88	40	nd
		(*R*)-*t*-Bu$_2$VANOL	51	–60	nd
		(*R*)-VAPOL	61	–47	nd
5					
	33v			**126v**	
		(*S*)-VANOL	60	96	>99:1
		(*R*)-*t*-Bu$_2$VANOL	56	–98	>99:1
6					
	33w			**126w**	
		(*S*)-VANOL	67	85	25:1
		(*R*)-*t*-Bu$_2$VANOL	68	–88	10:1
7					
	33x			**126x**	
		(*S*)-VANOL	71	91	6:1
		(*R*)-*t*-Bu$_2$VANOL	64	–60	6:1
8					
	130a			**131a**	
		(*S*)-VANOL	87	98	>99:1
		(*R*)-*t*-Bu$_2$VANOL	77	–73	>99:1
9					
	33y			**126y**	
		(*S*)-VANOL	71	88	>99:1
		(*R*)-*t*-Bu$_2$VANOL	86	–96	>99:1
10					
	33z			**126z**	
		(*S*)-VANOL	88	95	>99:1
		(*R*)-*t*-Bu$_2$VANOL	70	–75	>99:1
11					
	33h			**126h**	
		(*S*)-VANOL	45	28	12:1
		(*S*)-VANOL [h]	61	8	nd
		(*R*)-VAPOL	56	–57	16:1
12					
	33i			**126i**	
		(*S*)-VANOL		no reaction	
		(*S*)-VANOL [i]	6 [j]	nd	nd
13					
	130b			**131b**	
		(*S*)-VANOL		no reaction	
14					
	132			**133**	
		0 °C	(*R*)-VANOL [i]	90	91	*cis* only
		–20 °C	(*R*)-VANOL [i]	71	95	*cis* only

[a] Unless otherwise specified, all reactions were run under the conditions of Table 3.3, entry 6. [b] Isolated yield. [c] Determined by HPLC on isolated *trans*-aziridine. [d] Determined by the ^{1}H-NMR spectrum of the crude reaction mixture. nd means not determined. [e] *de* instead of *ee*. [f] The isolated *trans*-isomer was a 49:49:1:1 mixture of isomers. [g] The isolated *trans*-isomer was a 49.5:49.5:0.5:0.5 mixture of isomers. [h] *N*-butyl diazoacetamide **122b** was added 20 min after the aldehyde as indicated in Table 3.1. [i] The MEDAM amine **101a** was used. [j] *N*-butyl diazoacetamide **122b** was added 20 h after the aldehyde as indicated in

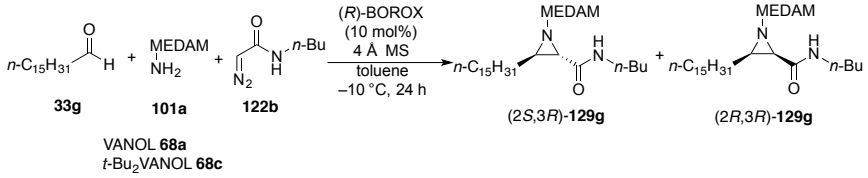
Table 3.4 (cont'd)

Table 3.1. [k] Reaction went to 24% conversion. Yield was determined by the ^{1}H-NMR spectrum of the crude reaction mixture with an internal standard.

3.2.3 Investigation of Absolute Stereochemistry

In the multi-component *trans*-aziridination for both aromatic and aliphatic aldehydes, BUDAM amine **101c** is superior to MEDAM amine **101a** and gives an excellent yield, asymmetric induction and *trans*/*cis* diastereoselectivity (Table 3.2 and 3.4). The multi-component *trans*-aziridination with MEDAM amine revealed a great difference in the *trans*/*cis* ratio between the ligands VANOL and *t*-Bu$_2$VANOL. For example, in the *trans*-aziridination of MEDAM amine **101a** and *n*-hexadecanal **33g**, VANOL BOROX-catalyzed reaction affords aziridine **129g** with relative high *trans*-selectivity (59% yield of *trans*-**129g** and 8% yield of *cis*-**129g**, Table 3.5, entry 1). However, *t*-Bu$_2$VANOL BOROX gives an almost 1:1 mixture of *trans*- and *cis*-isomers (Table 3.5, entry 2). It is necessary to determine the absolute stereochemistry of these aziridine diastereomers in the multi-component *trans*-aziridine strategy since it may reveal any difference in asymmetric inductions between the reaction with MEDAM amine and BUDAM amine.

Table 3.5 *trans*-Aziridination with MEDAM amine and *n*-hexadecanal [a 8]

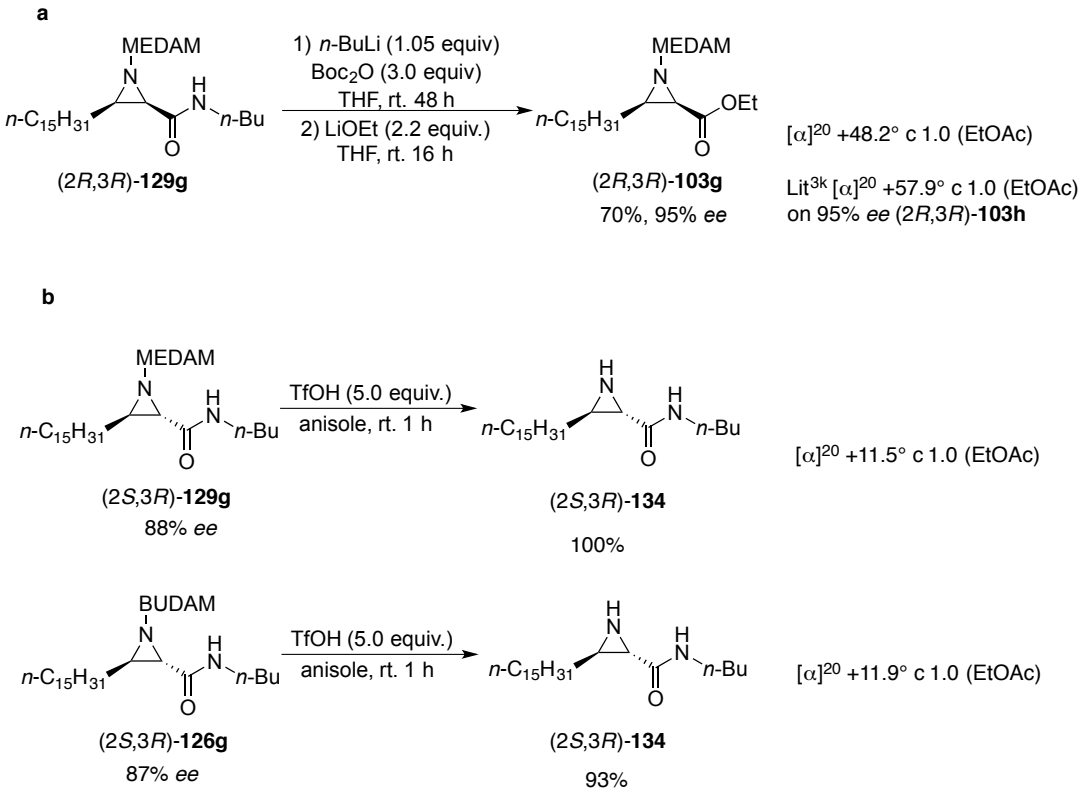


entry	ligand	(2*S*,3*R*)-129g% [b]	*ee*% [c]	$[\alpha]_D^{20}$ [d]	(2*R*,3*R*)-129g% [b]	*ee*% [c]	$[\alpha]_D^{20}$ [d]
1	(*R*)-**68a**	57	83	+13.6°	8[e]	nd	nd
2	(*R*)-**68c**	46	93	+19.1°	44	83	+7.0°

[a] Unless otherwise specified, all reactions were run under the conditions of Table 3.3, entry 6. [b] Isolated yield. [c] Determined by HPLC on isolated aziridines. [d] Determined by polarimeter on the solution of aziridines in ethyl acetate (c 1.0). [e] determined by the ^{1}H-NMR spectrum of the crude reaction mixture with an internal standard.

The absolute configuration of the *cis*- and *trans*-isomers of **129g** obtained from multi-component *trans*-aziridination of MEDAM amine **101a** and aldehyde **33g** were determined and confirmed by the conversion to the compounds with known absolute stereochemistry. The *cis*-**129g** was converted to the previously reported *cis*-aziridine carboxylate **103g**, with the (2*R*,3*R*)-stereochemistry upon the analysis of the optical rotation (Scheme 3.4a). The absolute stereochemistry of the BUDAM *trans*-aziridine (2*S*,3*R*)-**126g** was confirmed by the synthesis of sphinganine that will be discussed in the following section 3.3. To confirm that the MEDAM *trans*-aziridine **129g** has the same absolute stereochemistry as the BUDAM *trans*-aziridine (2*S*,3*R*)-**126g**, both were deprotected with triflic acid to give the same N-H aziridine with the same optical rotation. As a conclusion, the stereochemistry changes at the 2-position when a *trans*- and *cis*-isomer are produced in the multi-component *trans*-aziridination with MEDAM amine, aliphatic aldehydes and diazo acetamides. Interestingly, it gives (2*R*,3*R*)-stereochemistry for the *cis*-isomer in the *cis*-aziridination of aldehyde **33g** with (*S*)-ligand[3k], while the *cis*-isomer as the minor product from *trans*-aziridination of aldehyde **33g** gives the same (2*R*,3*R*)-stereochemistry with (*R*)-ligand.

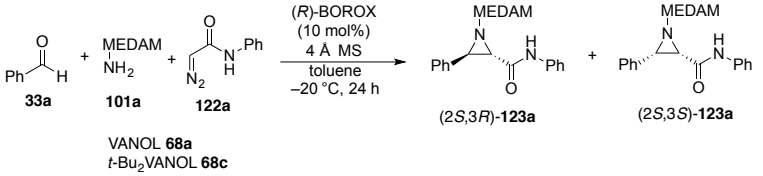
Scheme 3.4 Absolute stereochemistry of *N*-MEDAM alkyl aziridine carboxylamides 129g[8]



Given that the aromatic and aliphatic aldehydes require quite different optimal conditions in the multi-component *trans*-aziridination, it is necessary to investigate the absolute stereochemistry with MEDAM amine **101a** and aromatic aldehydes as well. A number of optimization experiments on the multi-component *trans*-aziridination reaction were conducted with benzaldehyde **33a**, MEDAM amine **101a** and *N*-phenyl diazoacetamide **122a** with both VANOL and *t*-Bu$_2$VANOL ligands (Table 3.6). The diastereoselectivity with MEDAM amine is much worse than that of the reaction with BUDAM amine (Table 3.1) that a 63% yield of *trans*-**123a** and a 17% yield of *cis*-**123a** were isolated by VANOL-BOROX catalysis (Table 3.6, entry 1). Surprisingly, the diastereoselectivity was reversed with the VANOL and *t*-Bu$_2$VANOL catalyst that the latter gave a 9% yield of *trans*-**123a** and a 75% yield of *cis*-**123a** (Table 3.6, entry 2). The *trans*-aziridination of

the corresponding imine **72o** and *N*-phenyl diazoacetamide **122a** was examined to understand the nature of ligand control on the diastereoselectivity. As reported by Aman Desai, it gave up to 21:1 *trans*:*cis* selectivity for aziridine **123a** with the VANOL catalyst.[5] However, this experiment was reported with the *t*-Bu_2VANOL catalyst to afford *cis*-**123a** as the major product in 73% yield and *trans*-**123a** in 23% yield, which gives the same trend in diastereoselectivity with the ligand effect (Scheme 3.5).

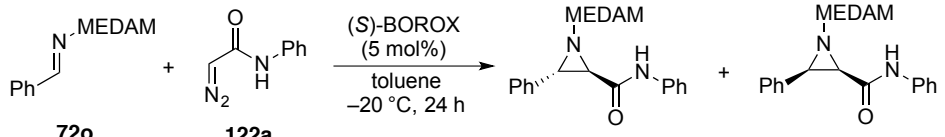
Table 3.6 *trans*-Aziridination with MEDAM amine, benzaldehyde and *N*-phenyl diazoacetamide [a] [8]



entry	ligand	(2*S*,3*R*)-123a% [b]	*ee*% [c]	$[\alpha]_D^{20}$ [d]	(2*R*,3*R*)-123a% [b]	*ee*% [c]	$[\alpha]_D^{20}$ [d]
1	(*R*)-**68a**	63	87	–4.6°	17	73	–13.6°
2	(*R*)-**68c**	9	55	–3.1°	75	95	–26.2°

[a] Unless otherwise specified, all reactions were run under the conditions of Table 3.1, entry 10. [b] Isolated yield. [c] Determined by HPLC on isolated aziridines. [d] Determined by automatic polarimeter on the solution of aziridines in ethyl acetate (c 1.0).

Scheme 3.5 Ligand-effects on the diastereoselectivity[8]

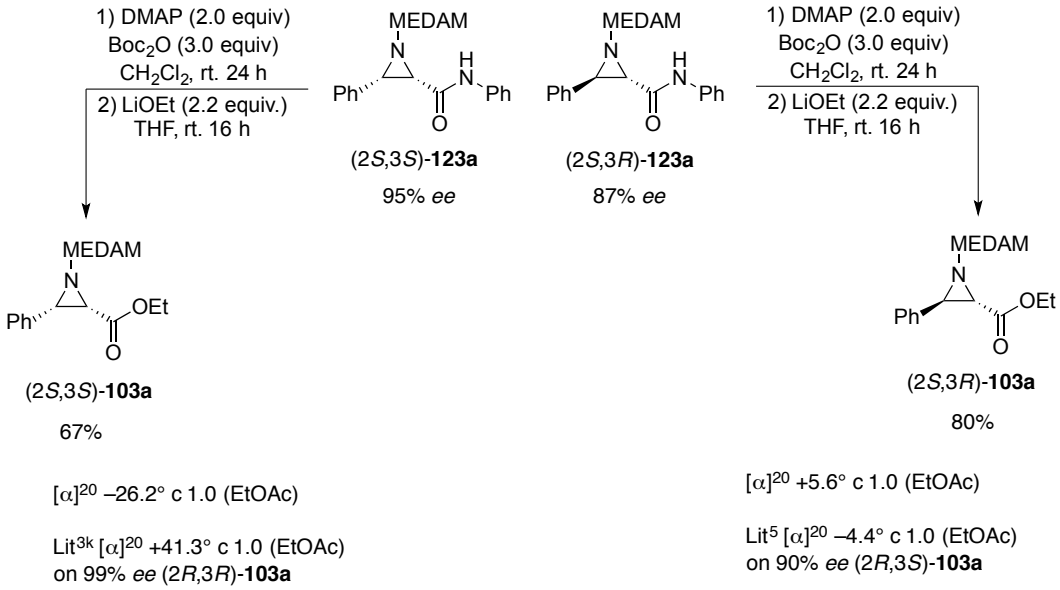


ligand	%yield	%*ee*	%yield	%*ee*
(*S*)-VANOL	90	96	<5	nd
(*S*)-^{t}Bu$_2$VANOL	21	65	73	96

The *trans*- and *cis*-isomers of aziridine **123a** could be converted into the corresponding aziridine carboxylates **103a** with a known optical rotation and compared with the optical rotation that is known for both the *cis*- and *trans*-isomers (Scheme 3.6). The *cis*-aziridine ester **103a** exhibits a negative rotation which is consistent with the (2*S*,3*S*)-stereochemistry based on a literature report.[3k] The *trans*-isomer of **103a** exhibits a

positive rotation with (2*S*,3*S*)-stereochemistry according to a literature report.[5] Notably, the configuration changes at the 3-position with *trans*- and *cis*-isomers in the multi-component of *trans*-aziridination with aromatic aldehydes, instead of at the 2-position where is the case for aliphatic aldehyde substrates. The stereochemical configuration of *cis*-aziridine is consistently obtained from either *cis*-aziridination as a major product or *trans*-aziridination as a minor product of aromatic aldehydes by the catalyst with the same chirality.

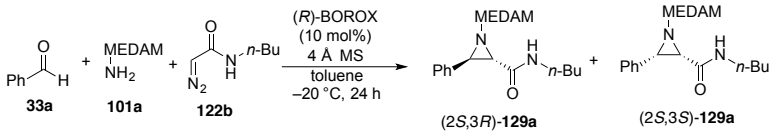
Scheme 3.6 Absolute stereochemistry of *N*-MEDAM alkyl aziridine carboxylamides 123a[8]



Finally, the multi-component *trans*-aziridination with MEDAM amine **101a**, benzaldehyde **33a** and *N*-butyl diazoacetamide **122b** was also studied to determine the diastereoselectivity as well as the absolute stereochemistry. With *N*-butyl diazoacetamide **122b**, the *cis*-isomer of aziridine **129a** was the major product with both the VANOL and *t*-Bu$_2$VANOL BOROX catalyst, while a greater *cis*-selectivity was observed with the *t*-Bu$_2$VANOL catalyst than that with the VANOL catalyst (Table 3.7). The *trans*- and *cis*-isomers of aziridine **129a** were also converted to the corresponding aziridine carboxylates

103a to confirm the stereochemistry as (2*S*,3*S*)- and (2*S*,3*R*)-aziridines, which are consistent with the protocol in the multi-component *trans*-aziridination strategy of MEDAM amine, aromatic aldehydes and *N*-phenyl diazoacetamide. The specific interactions between the BOROX catalyst and each of the three substrates are unclear, but these results indicate that a more complex process is involved in the multi-component procedure. It was found in this work that *cis*:*trans* selectivity could be effected and reversed in the proper combination of ligands, amines, aldehydes and diazoacetamides.

Table 3.7 *trans*-Aziridination with MEDAM amine, benzaldehyde and *N*-butyl diazoacetamide [a 8]

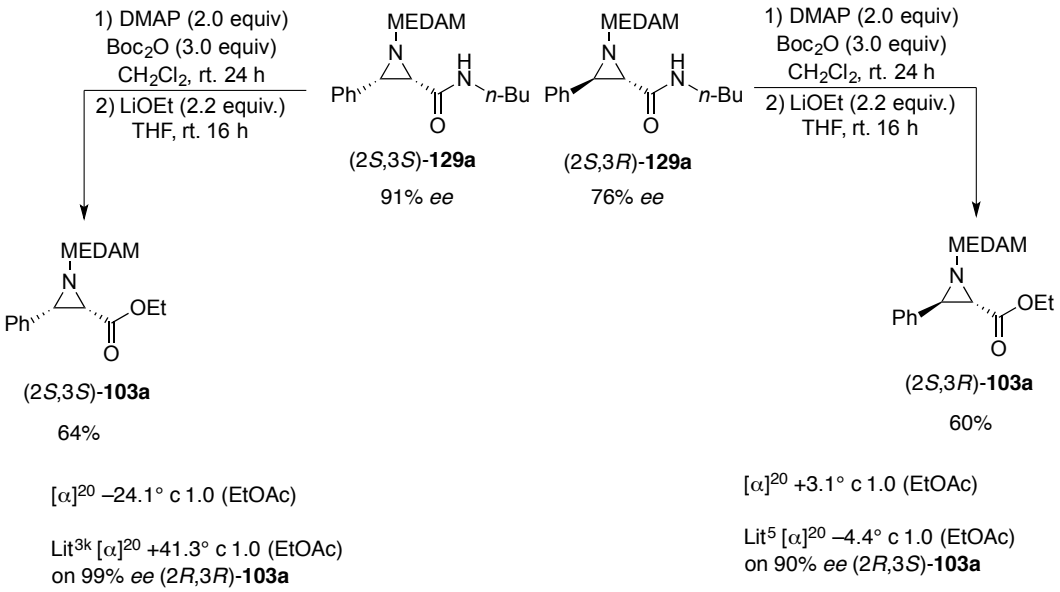


VANOL **68a**
t-Bu$_2$VANOL **68c**

entry	ligand	(2*S*,3*R*)-129a% [b]	*ee*% [c]	$[\alpha]_D^{20}$ [d]	(2*R*,3*R*)-129a% [b]	*ee*% [c]	$[\alpha]_D^{20}$ [d]
1	(*R*)-**68a**	36	76	+20.0°	50	86	–6.6°
2	(*R*)-**68c**	8	89	+22.9°	73	91	–7.5°

[a] Unless otherwise specified, all reactions were run under the conditions of Table 3.1, entry 10. [b] Isolated yield. [c] Determined by HPLC on isolated aziridines. [d] Determined by polarimeter on the solution of aziridines in ethyl acetate (c 1.0).

Scheme 3.7 Absolute stereochemistry of *N*-MEDAM alkyl aziridine carboxylamides 129a[8]



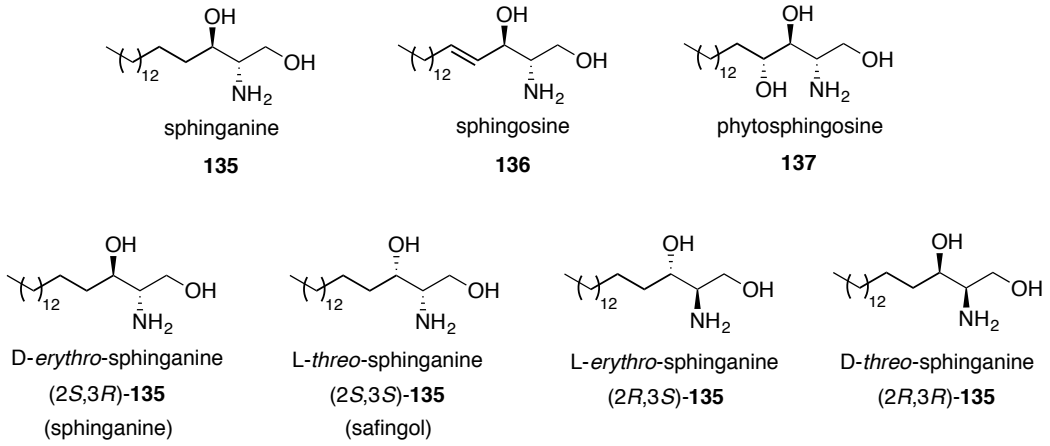
3.3 Synthetic Utility in Natural Products

3.3.1 Synthesis of Sphinganine Stereoisomers

Sphingolipids consist of several subclasses of compounds that were discovered in brain extracts in the 1870s and are involved in signal transmission and cell recognition.[11] They are a class of lipids containing a backbone of sphingoid bases.[12] The three major core units in sphingolipids are sphinganine **135**, sphingosine **136** and phytosphingosine **137** (Figure 3.2). *N*-acylated derivatives of the sphingoid bases are members of the ceramide family, of which the well-known members are glycosphingolipids with one or more sugar units attached to the hydroxy group at the 1-position and phosphosphingolipids with a phosphate ester bounded to the hydroxy group at the 1 position. The natural configuration of both sphinganine and sphingosine is the D-*erythro* isomer. However, it has been found that for both classes of compounds that the stereochemistry can play a large role in their bioactivity. For example, the L-*threo* diastereomer of sphinganine, usually called safingol (2*S*,3*S*)-**135**, is a lyso-sphingolipid protein kinase C inhibitor.[13] Medically, safingol has

demonstrated promising anticancer potential as a modulator of multi-drug resistance and as an inducer of necrosis.

Figure 3.2 Sphingoid bases and the four stereoisomers of sphinganine

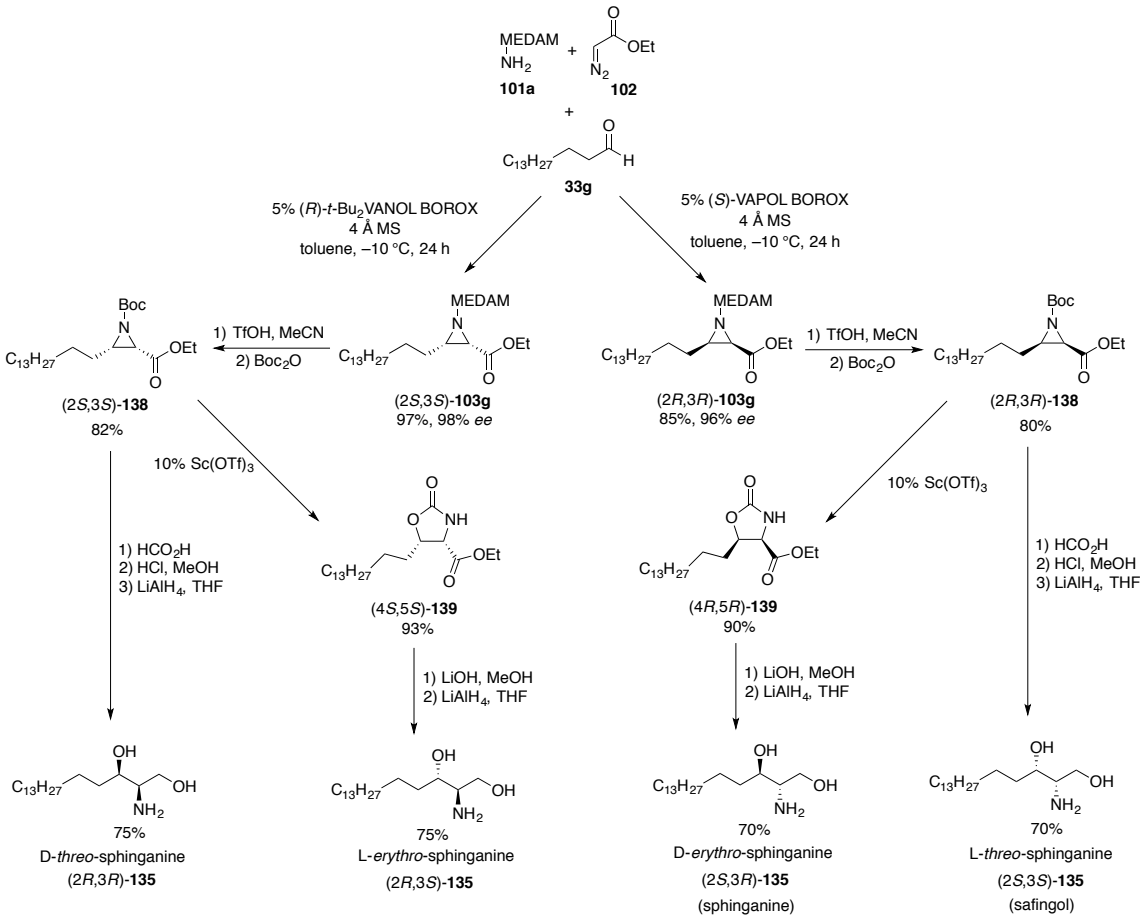


A great number of publications in the literature work has reported on the synthesis of sphinganine beginning in 1951.[14, 15] The earlier synthesis of sphinganines tended to be nonselective, giving mixtures of diastereomers that needed to be separated and enantiomers that needed to be resolved. The most successful applications with asymmetric catalysis involved the use of the Sharpless asymmetric dihydroxylation[16], Sharpless asymmetric epoxidation[17], and the Sharpless kinetic resolution of allylic alcohols[15n], the asymmetric hydrogenation of β-oxo esters[15m] and a proline-based Mannich reaction[15p], although it has not been demonstrated if these methods can be used for all four of the stereoisomers of the sphinganine. Notably, the shortest synthetic pathway (two steps from hexadecanal) demonstrated by Shibasaki and his co-worker involves an asymmetric catalytic reaction in which the chiral center at the nitrogen-substituted carbon atom is created in the stereogenic step.[18] They reported that a 1,1 -bi-2-naphthol (BINOL)–lanthanum catalyst will effect the nitroaldol reaction (Henry reaction) between 2-nitroethanol and hexadecanal. Although this reaction gave good

diastereoselectivity (91:9) and a good asymmetric induction (97 % *ee*), the reaction was limited in that it could produce only one diastereomer and prolonged reaction times were required: 10 turnovers required 6-7 days.

A synthesis of all four stereoisomers of sphinganine has been developed with the strategy of multi-component *cis*-aziridination and has been published (Scheme 3.8).[3m] Both enantiomers of *cis*-aziridine (2*R*,3*R*)- and (2*S*,3*S*)-**103g** were obtained in excellent yields and *ee* from aziridination of *n*-hexadecanal **33g** by BOROX catalysts with opposite chirality. The multi-component *cis*-aziridination was successful on gram scale (5 mmol, 1.5 g) to afford the *cis*-aziridine **103g** in 85% yield (2.6 g) and 96% *ee* with VAPOL-BOROX catalyst. The *cis*-aziridine (2*R*,3*R*)-**103g** was then converted to *N*-Boc-aziridine (2*R*,3*R*)-**138** in 80% yield, which could be ring-opened up by oxygen-nucleophiles with inversion of configuration at the 3-position in a known process that typically requires the electron-withdrawing group on the nitrogen.[3k, l] Thus, *N*-Boc-aziridine (2*R*,3*R*)-**138** was treated with neat formic acid which was resulted in ring-opening with formate and subsequent *O*- to *N*-formyl migration after Boc-deprotection. The *N*-formyl group was removed with hydrochloric acid and the ester was reduced to give L-*threo*-sphinganine (2*S*,3*S*)-**135** in 70% overall yield. On the other hand, *N*-Boc-aziridine (2*R*,3*R*)-**138** could undergo Lewis acid-catalyzed ring-expansion with retention of configuration at the 3-position with the aid of scandium triflate to afford oxazolidinone (4*R*,5*R*)-**139** in 90% yield. Finally, D-*erythro*-sphinganine (2*S*,3*R*)-**135** was prepared in 70% overall yield from (4*R*,5*R*)-**139** by hydrolysis of the oxazolidinone and reduction of the ester. The isomers of D-*threo*-sphinganine (2*R*,3*R*)-**135** and L-*erythro*-sphinganine (2*R*,3*S*)-**135** were synthesized in an analogous strategy from aldehyde **33g**.

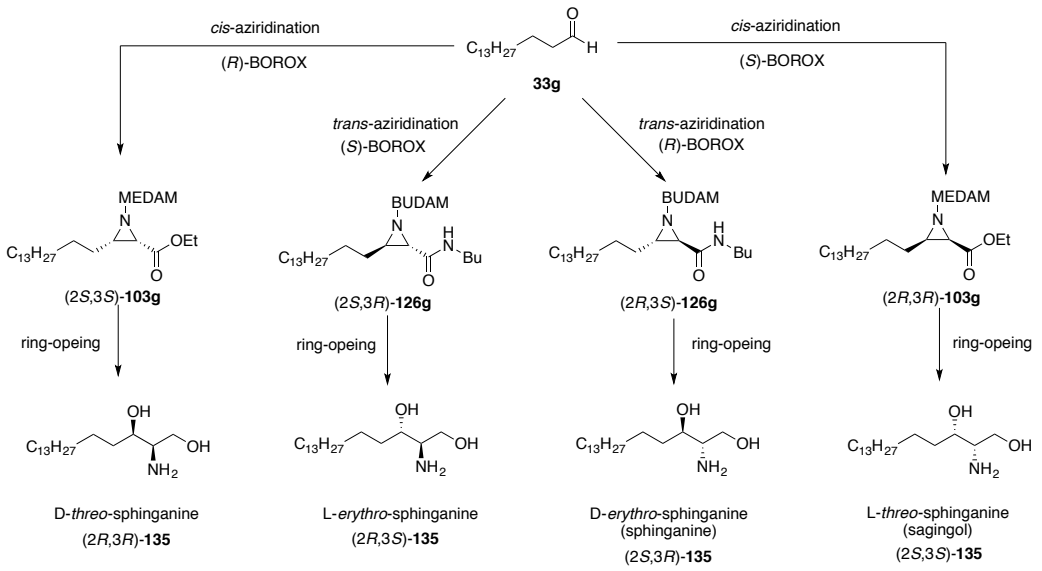
Scheme 3.8 Synthesis of all four stereoisomers of sphinganine by multi-component *cis*-aziridination[3m]



Since a successful method for the multi-component *trans*-aziridination has been developed, an alternative synthetic strategy to achieve all four stereoisomers of sphinganine could be considered from aldehyde **33g** (Scheme 3.9). The multi-component synthesis of aziridines can afford two enantiomers of *cis*-aziridine **103g** and two enantiomers of *trans*-aziridine **126g**. Each stereoisomer in aziridine ostensibly should undergo direct ring-opening with an oxygen nucleophilic attack at the 3-position following the published procedure in the presence of trifluroacetic acid (TFA) for the *cis*-aziridine with an *N*-MEDAM group nitrogen.[3m] In the initial exploration to extend this method to *trans*-aziridines, the *trans*-aziridine (2*S*,3*R*)-**126g** was prepared on gram-scale

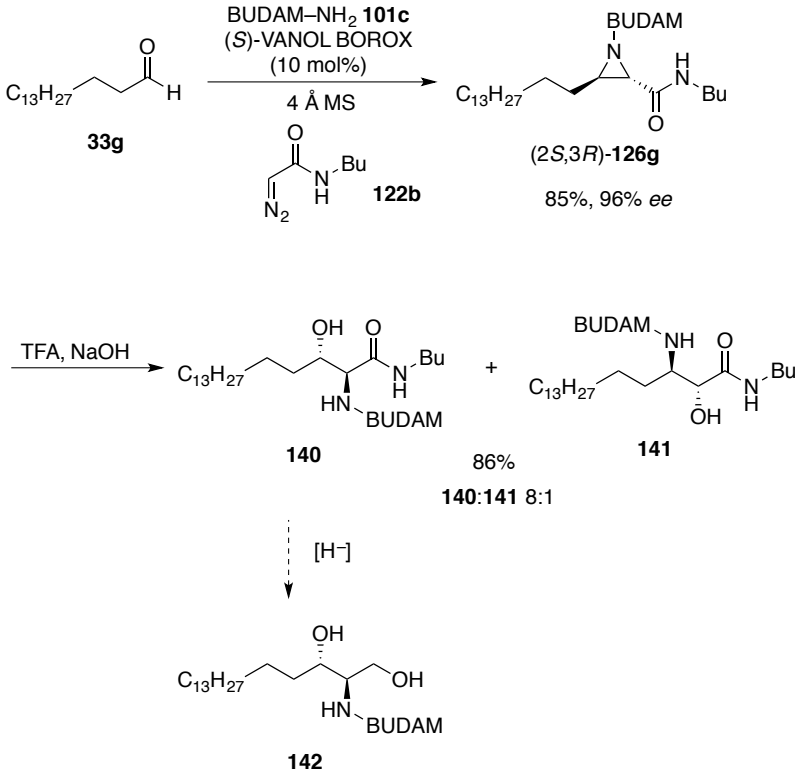
(3 mmol, 1.4 g) with an 88% isolated yield and 96% *ee*. It was then converted to the ring-opening compound **140** upon the treatment with TFA and subsequent basic hydrolysis. A regioisomer **141** was detected resulted from oxygen-nucleophilic attack at the 2-position. The regioselectivity was optimized to reach a 8:1 mixture of the regioisomers **140** and **141** in 86% total yield (Scheme 3.10).

Scheme 3.9 Alternative synthesis of all four sphinganine stereoisomers



Unfortunately, a number of strategies to obtain *N*-BUDAM sphinganine **142** by the reduction of amide in **140** to a primary alcohol were tested and came up a failure. The difficulty presumably comes from the bulky nature of *N*-BUDAM group, which makes the space proximity of the amide carbonyl quite sterically hindered and thus limits access by any hydride reductant. Attempts to force the reduction by heating or adding excess reductant such as LAH, $NaBH_4$, super hydride or $LiBH_3NH_2$ gives a mixture of amine and alcohol products and also results in racemization at the α-position of amide (Scheme 3.10).

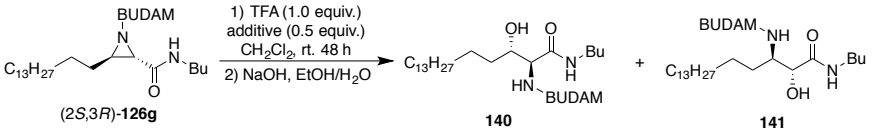
Scheme 3.10 Initial exploration of sphinganine synthesis by *trans*-aziridination



The experimental conditions were optimized for the ring-opening of *trans*-aziridine **126g** by TFA (Table 3.8). This reaction gave a 62% total yield of **140** and **141** with 4:1 regioselectivity from aziridine **140** treated with one equivalent of TFA (Table 3.8, entry 1). The reaction was not clean with a complex mixture of byproducts generated, which possibly due to acid-catalyzed polymerization of the aziridine. It was found that the presence of a weaker acid could improve the yield significantly, which indicated the conjugate base would be a better oxygen nucleophile than trifluoroacetate to accelerate the ring-opening. The effects of 0.5 equivalent of three carboxylic acids were examined as additive (Table 3.8, entry 2-4). Acetic acid gave a 3:1 mixture of **140** and **141** in 93% yield (Table 3.8, entry 2). It was found that a lower concentration of the substrate **126g** would afford a much greater selectivity (Table 3.8, entry 5-8). Although the yield slightly

dropped with a more diluted solution, the polymerization would presumbly be effectively inhibited to give a cleaner reaction mixture for the ring-opened products. In addition, without acetic acid as the additive and at the concentration of 0.1 *M*, the reaction will give an 86% yield of an 8:1 mixture of **140** and **141** which indicates that the substrate concentration has a key effect in the ring-opening (Table 3.8, entry 9).

Table 3.8 Ring-opening of *trans*-aziridine carboxylamide 126g [a] [8]

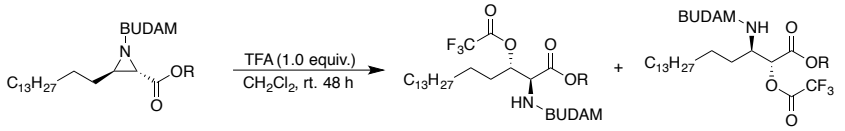


entry	additive	conc. (*M*)	yield% [b]	140:141 [c]
1	–	0.5	62	4:1
2	AcOH	0.5	93	3:1
3	HCO_2H	0.5	85	2:1
4	PivOH	0.5	92	3:1
5	AcOH	1.0	76	1.6:1
6	AcOH	0.2	88	7:1
7	AcOH	0.1	86	9:1
8	AcOH	0.05	86	8:1
9	–	0.1	86	8:1

[a] Unless otherwise specified, all the reactions were run in 0.2 mmol scale of aziridine **126** with 1 equiv of TFA in CH_2Cl_2 at room temperature for 48 h. It was followed by the basic hydrolysis of trifluoroacetate with aqueous NaOH. [b] Isolated yield of a mixture of regioisomers **140** and **141**. [c] Determined by the ^{1}H-NMR spectrum of the crude reaction mixture.

The ring-opening of aziridine carboxylate **143** and **143'** was also investigated (Table 3.9) since the strategy with amide reduction to an alcohol proved not to be feasible for sphinganine synthesis (Scheme 3.10). Both the methyl and ethyl esters were investigated at different concentrations in CH_2Cl_2. A protocol similar to that used for aziridine carboxylamide **126g** was employed with a lower concentration, on which was observed to give better regioselectivity and a higher yield of the ring-opened product for **126g**. However, the results were not as good as those for **126g**, giving up to a 61% yield of **144** and **145** and a 6:1 selectivity for methyl ester **143** at 0.05 *M* reaction solution (Table 3.9, entry 5).

Table 3.9 Ring-opening of *trans*-aziridine carboxylate 143 and 143' [a] [8]



(2*S*,3*R*)-**143** R = Me
(2*S*,3*R*)-**143'** R = Et

144 (144') **145 (145')**

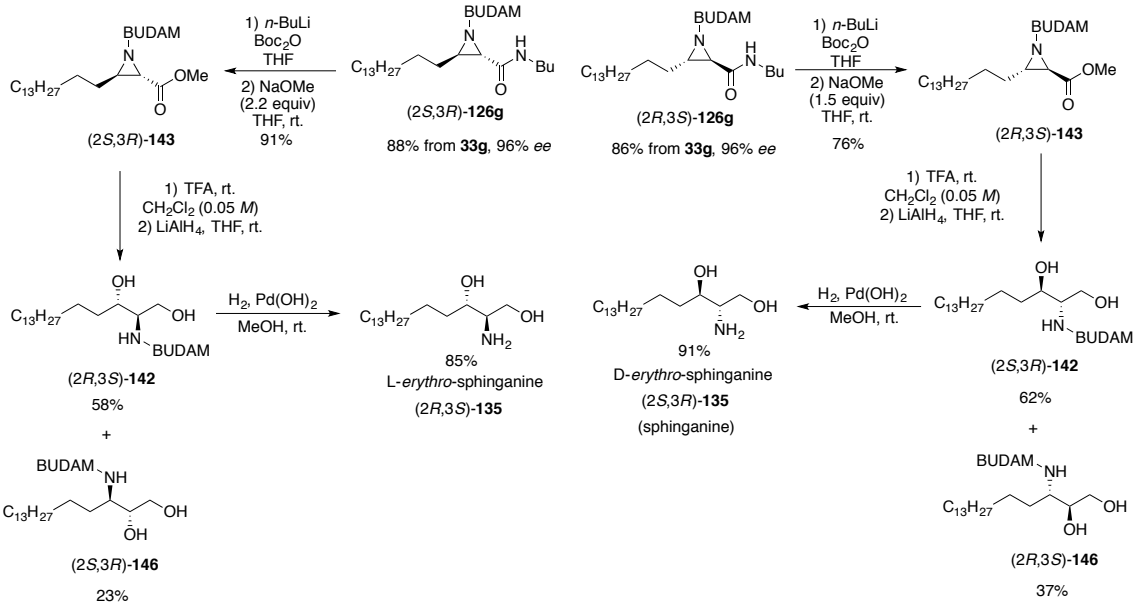
entry	R	conc. (*M*)	yield [b]	144:145 [c]
1	Me	0.2	46	2:1
2	Et	0.2	48	2:1
3	Me	0.1	55	5:1
4	Et	0.1	49	5:1
5	Me	0.05	61	6:1

[a] Unless otherwise specified, all the reactions were run in 0.2 mmol scale of aziridine **143** with 1 equiv of TFA in CH_2Cl_2 at room temperature for 48 h. The compound with a prime is the ethyl ester. [b] Isolated yield of a mixture of regioisomers **144** and **145**. [c] Determined by the ^{1}H-NMR spectrum of the crude reaction mixture.

With these optimization, a synthesis of D- and L-*erythro*-sphinganines was conceived as shown in Scheme 3.11 involving six steps from *n*-hexadecanal **33g**. Both enantiomers of *trans*-aziridine **126g** were prepared by the multi-component reaction of BUDAM amine **101c**, aldehyde **33g** and *N*-butyl diazoacetamide **122b** with either the (*S*)- or (*R*)-VANOL BOROX catalyst (Table 3.4). The amide **126g** could be converted to *N*-Boc-*N*'-butyl amide and then treated with sodium methoxide (1.5 equiv) to afford the corresponding methyl ester (2*S*,3*R*)-**143** in 76% yield over two steps. A larger excess of NaOMe (2.2 equiv) improved the overall yield significantly to 91% for the (2*R*,3*S*)-enantiomer of **143**. Given that the possible acidic hydrolysis of ester **143** and the relatively high yield in the reduction of both methyl carboxylate and trifluoroacetate to alcohols in **144** and **145** (80% yield), a one-pot procedure was developed to combine the TFA-mediated ring-opening and the $LiAlH_4$ reduction. This has a potential advantage that it could also convert any carboxylic acid byproducts and separate the desired alcohol. A mixture of regioisomers **142** and **146** were obtained from methyl aziridine carboxylate **143** and could be isolated and separated in a 56% yield of desired *N*-BUDAM sphinganine **142** and a 23% yield of

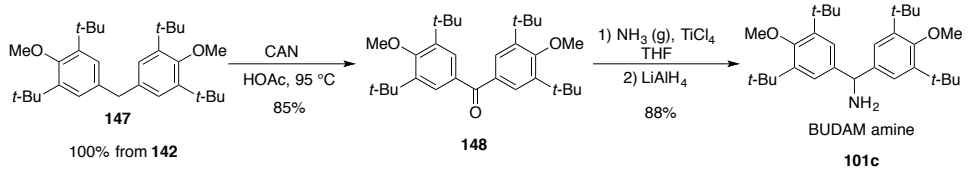
the regioisomer **146** over two steps. The *erythro*-sphinganines were finally prepared by the hydrogenolysis of the *N*-BUDAM substituent with Pearlman's catalyst in high yields.

Scheme 3.11 Synthesis of *erythro*-sphinganines from *trans*-aziridination of *n*-hexadecanal 33g[8]



Notably, BUDAM amine **101c** could be recycled to improve the atom economy from the BUDAM hydrocarbon compound **147** isolated in the hydrogenolysis of *N*-BUDAM sphinganine **142**. The hydrocarbon underwent benzylic oxidation by ceric ammonium nitrate to afford ketone **148**[19] and reductive amination to give BUDAM amine **101c** in three steps (Scheme 3.12).

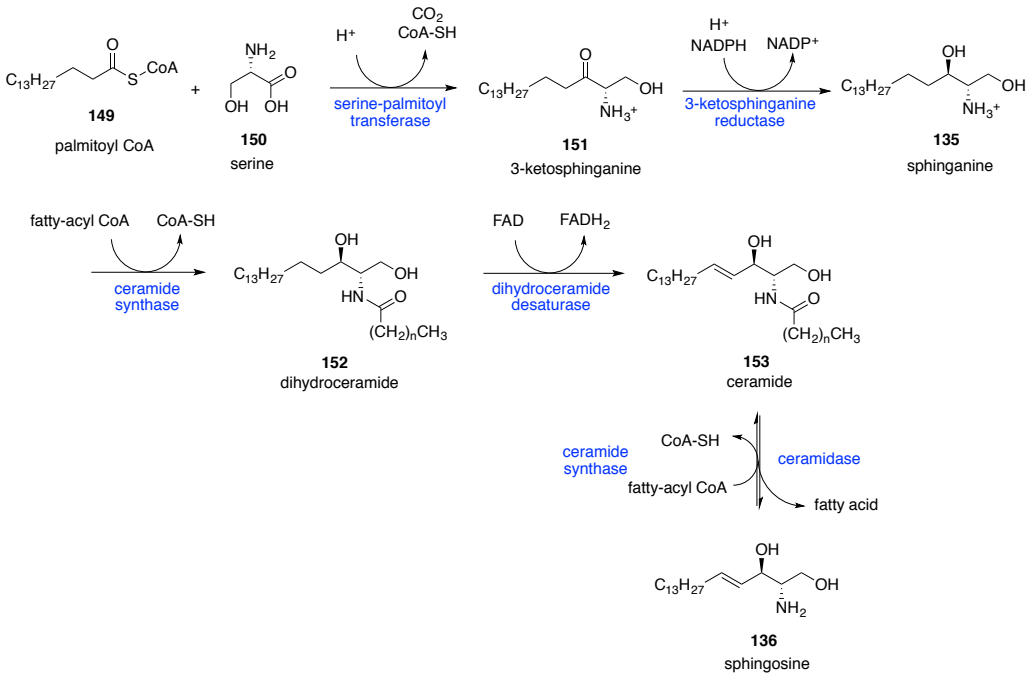
Scheme 3.12 Recycling of BUDAM amine 101c[8]



3.3.2 Synthesis of Sphingosine Stereoisomers

Sphingosine **136** is one of the three primary sphingoid bases which has an unsaturated hydrocarbon chain at the 4-position (Figure 3.2) as the important structural and functional component of sphingolipids widely occurring in the plasma membrane of eukaryotic cells. It is biologically synthesized from the condensation of palmitoyl CoA **149** and serine **150** to yield 3-ketosphinganine **151**, which is then reduced by NADPH to sphinganine **135**. Sphinganine can be acylated to dihydroceramide **152** with the presence of fatty acyl CoA, which was then dehydrogenated by FAD into ceramide **153** and hydrolyzed to sphingosine **136**.[20]

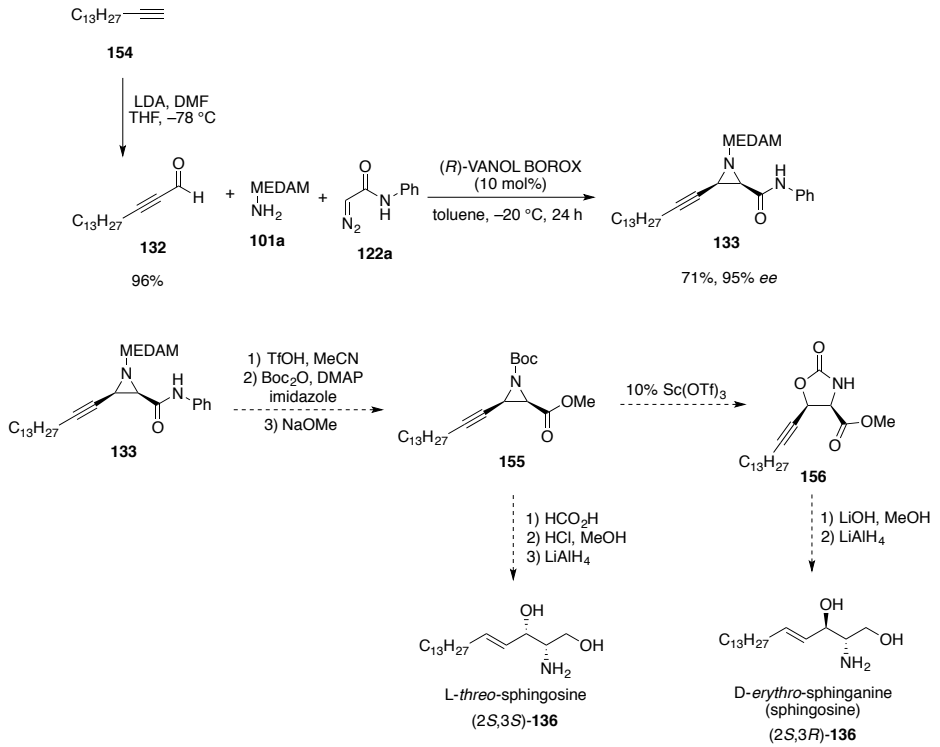
Scheme 3.13 ***De novo*** **biosynthesis of sphinganine and sphingosine**



The early work on sphingosine synthesis was lacking of any asymmetric catalysis, and instead involved the crystallization and resolution to separate the stereoisomers.[21a-c] Shapiro and Segal reported the first synthesis of sphingosine where they constructed the hydrocarbon chain by a Knoevenagel-Doebner condensation, obtained the *erythro*-

isomers by fractional crystallization and finally afforded D- and L-configured enantiomers by resolution with the aid of L-(+)-acetylmandeloyl.[21a] Other asymmetric synthesis of sphingosine have been achieved from the chiral pools including D-*ribo*-phytosphingosine and serine derivatives to promote the asymmetric induction and obtain the various stereoisomers of sphingosine.[21d, e] During recent years, several applications of asymmetric catalysis have been reported in successful synthetic strategies to sphingosine. For example, Castillón *et al.* induced three chiral centers by dynamic kinetic resolution of ring-opening of epoxides with subsequent Sharpless asymmetric dihydroxylation of alkenes.[21f] Kumar *et al.* developed an efficient synthetic route by employing the kinetic resolution of allylic alcohols by the Sharpless asymmetric epoxidation catalyst and the diastereoselective intramolecular aminohydroxylation of alkenes.[21g]

Scheme 3.14 Proposed synthetic strategy of *erythro*- and *threo*-sphingosines



Given that the alkynyl aldehyde **132** could be taken to the *cis*-aziridine **133** in a decent yield and asymmetric induction by the multi-component reaction of MEDAM amine **101a** and *N*-phenyl diazoacetamide **122a** catalyzed by VANOL-BOROX (Table 3.4, entry 14), the total synthesis of all four stereoisomers of sphingosine was proposed as shown in Scheme 3.14 based on the synthetic strategies developed for sphinganine. The synthesis starts from 2-hexadecynal **132** which was prepared from 1-pentadecyne **154** by treatment with LDA and then DMF. With the synthesis of *cis*-alkynylaziridine carboxylamide **133**, it should be possible to convert it to *N*-Boc-aziridine **155** carboxylate with a procedure that has been established for related aziridines[3m]. Upon treatment with $Sc(OTf)_3$, aziridine **155** should undergo the ring-expansion to afford oxazolidinone **156** with stereochemical retention at the 3-position. Subsequent hydrolysis of the oxazolidinone, ester and alkyne reduction would then complete the synthesis of *erythro*-sphingosine. On the other hand, the direct oxygen-nucleophilic ring-opening of aziridine **155** will have the stereochemistry at the 3-position inversed and thus preparation of *threo*-sphingosine could be completed by formamide hydrolysis and $LiAlH_4$ reduction.

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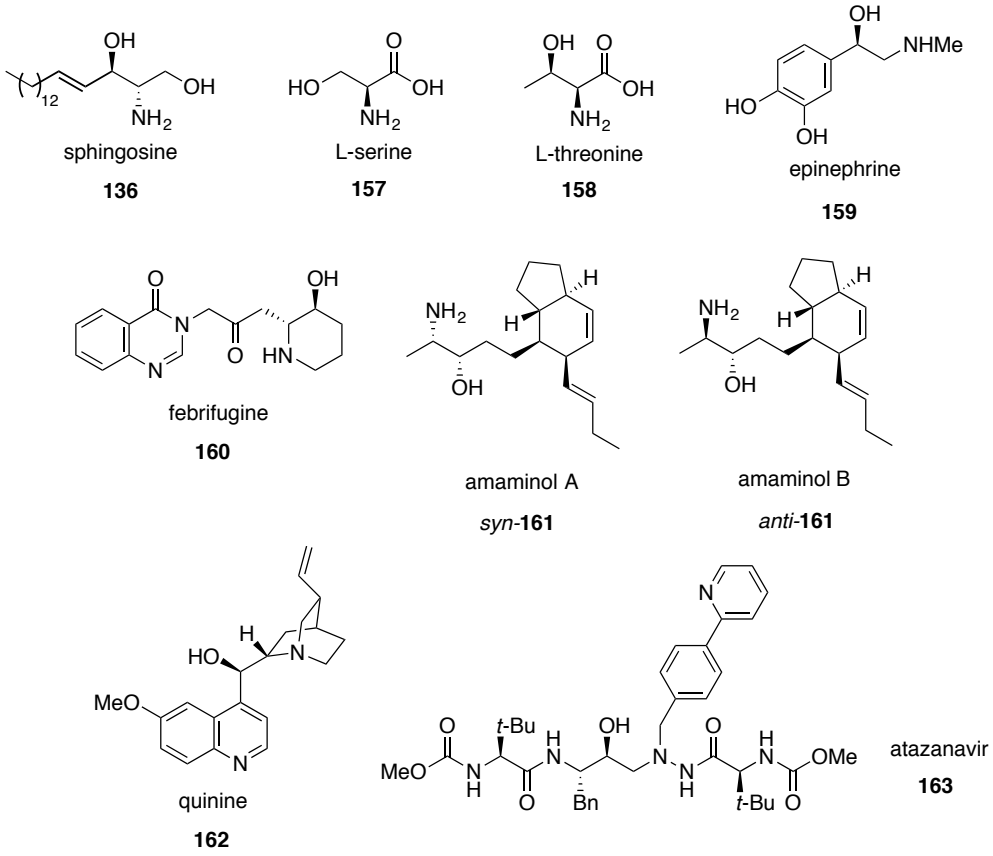
Chapter 4 Asymmetric Synthesis of Aminohydroxy Amide

4.1 Introduction of 1,2-Aminohydroxy Functionalization

4.1.1 β-Amino Alcohols in Natural Products

A β-Aminoalcohol is a common structural motif in biological natural products and important molecular moiety in amino acids, hormones, alkaloids and drugs (Figure 4.1). Sphingoids, such as sphingosine **136**, exist in cell memberanes and regulate the cell activities (Chapter 3, 3.2.2). Serine and threonine are common amino acids in organisms. Epinephrine **159** is a well-known medication and hormone that can treat severe asthma attacks and allergic reactions in the case of an emergency. Febrifugine **160** is a quinazolinone alkaloid first isolated from the Chinese herb *Dichroa fabrifuga* that has antimalarial properties.[1] Amaninol A *syn*-**161** and B *anti*-**161** were reported in 2000 and found to be cytotoxic against P388 murine leukemia cells.[2] Quinine **162** is a well-known alkaloid isolated from the bark of the cinchona trees and widely used for the treatment of malaria and babesiosis. Atazanavir **163** is an antiretroviral drug and a protease inhibitor and used to treat infection by HIV.

Figure 4.1 β-Aminoalcohols in natural products



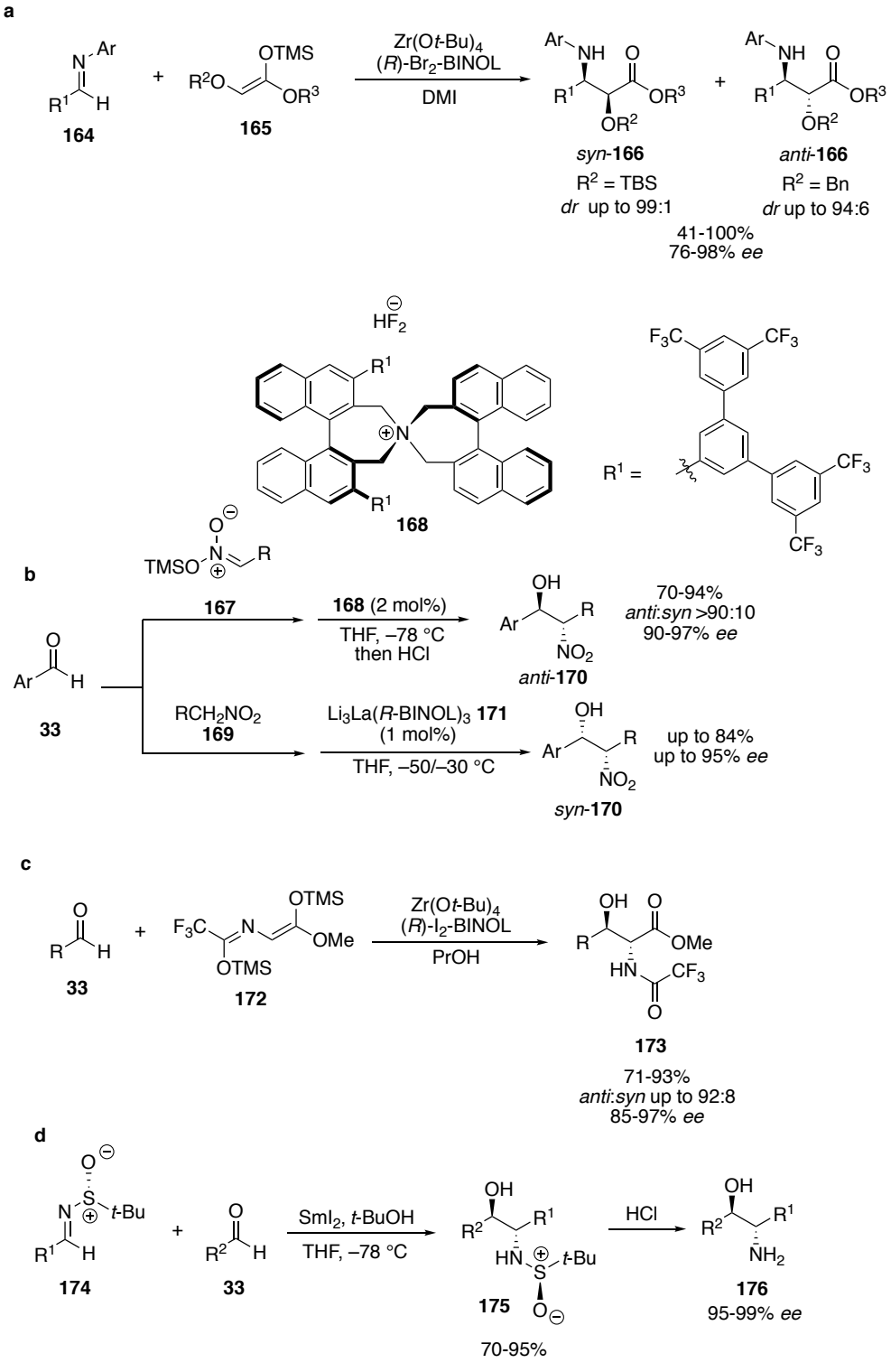
4.1.2 β-Amino Alcohols from C-C Bond Forming Reactions

The stereoselective synthetic routes to β-amino alcohols in early reports were limited to the derivatization of molecules from the chiral pool such as amino acids.[3] To access the broadest range of targets, a great number of routes have been developed for the asymmetric synthesis of β-amino alcohols. One of the common ways to construct the amino alcohol moiety is the coupling of two fragments by C-C bond formation, with one component containing oxygen functionalization and the other containing nitrogen functionalization. There are many strategies based reported in the literature for the synthesis of β-amino alcohols that are based on C-C bond formation. One of the strategies involves Mannich-type reaction with nucleophilic addition to imines by α-hydroxy carbonyls or α-alkoxy enolates. [4, 5] Kobayashi *et al.* have reported a nice

example of a stereoselective Mannich-type reaction of imine **164** with α-alkoxy Mukaiyama enolate **165** with the catalysis prepared from zirconium tetra-*tert*-butoxide and (*R*)-Br_2BINOL ligand. They have shown that the diastereoselectivity of the β-amino alcohols **166** was well controlled by the α-substituent. The reaction gives the *syn*-isomer of β-amino alcohols **166** with an α-TBS siloxy group while the *anti*-isomer of amino alcohols **166** can be obtained with an α-benzyloxy group (Scheme 4.1a).

The other strategy as the aldol-type reaction in the presence of aldehydes involves in Henry reaction with subsequent reduction of the nitro compounds[6, 7] (Scheme 4.1b) or the addition of glycine-derived enolates to aldehydes[8] (Scheme 4.1c). Maruoka *et al.* reported the addition of trimethylsilyl nitroates **167** to aromatic aldehydes **33** in the presence of chiral quaternary ammonium fluoride salt **168** to give greater than >90:10 *anti*-diastereoselevtivity and 90-97% *ee*.[7a] Shibasaki *et al.* reported a *syn*-selective Henry reaction of nitroalkanes **169** and aldehyde **33** catalyzed by a Lewis acid-assisted Chiral Lewis acid (LLA) lithium/lanthanum polymetallic complex **171**, which gave a *syn*-isomer of compound **170** in up to 84% yield and 95% *ee*.[7b-d] Particularly, a recent work reported a highly stereoselective synthesis of β-amino alcohols by asymmetric Pinacol cross coupling with an aldehyde and imine leading to an enantiomerically pure *anti*-β-amino alcohol in an excellent yield (Scheme 4.1d).[9]

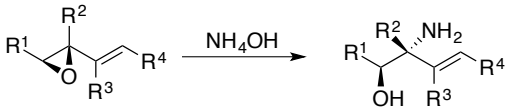
Scheme 4.1 Synthesis of β-amino alcohols by C-C bond formation



4.1.3 β-Amino Alcohols from Functional Group Transformations

β-Amino alcohols can also be approached by functional group transformations with the pre-existing carbon skeletons. One of synthetic routes commonly investigated is the asymmetric ring-opening of cyclic substrates such as epoxides[10], aziridines[11], sulfates[12] and carbonates[13]. The regioselectivity can be a challenge and usually controlled by the directing groups such as phenyl, vinyl or carbonyl groups (Scheme 4.2).

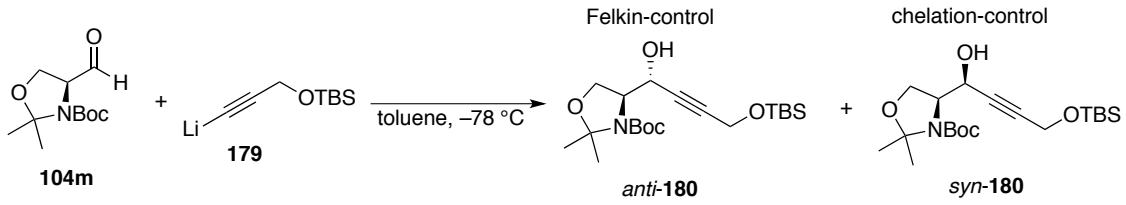
Scheme 4.2 Amminolysis of vinylepoxide 177



177 **178**

The alternative methods to β-amino alcohols by functional group transformations are related to stereoselective nucleophilic additions of chiral α-amino aldehydes[14] or ketones[15] through a Grignard addition or Mukaiyama aldol reaction, and also by diastereoselective reduction of α-amino carbonyl compounds[16]. Notably, with the presence of chirality in the α-amino carbonyl substrate, the diasteroselectivity of the β-amino alcohol formation could either be the *anti*-configuration by Felkin-Anh control or the *syn*-configuration by metal-chelation control.[14a, c] For example, the addition of lithium acetylide **179** to Garner's aldehyde **104m** gives a moderate *anti*-selectivity without any additive. However, the *anti*:*syn* ratio is improved to 19:1 in the presence of the polar aprotic reagent HMPA due to the breaking up of lithium aggregates. On the other hand, the presence of a chelating metal such as tin tetrachloride leads to the inversed diastereoselectivity with 1:19 *anti*:*syn* ratio (Scheme 4.3).[14a]

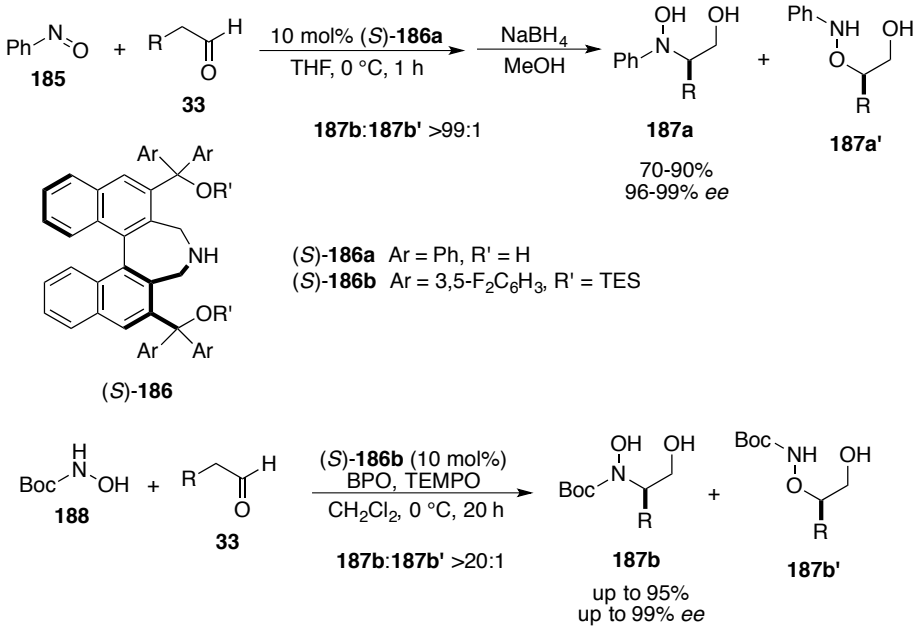
Scheme 4.3 Diastereoselectivity control in nucleophilic addition to chiral amino aldehyde 104m



addtive	*anti*:*syn*	yield%
none	3:1	80
HMPA	19:1	85
$SnCl_4$	1:19	46

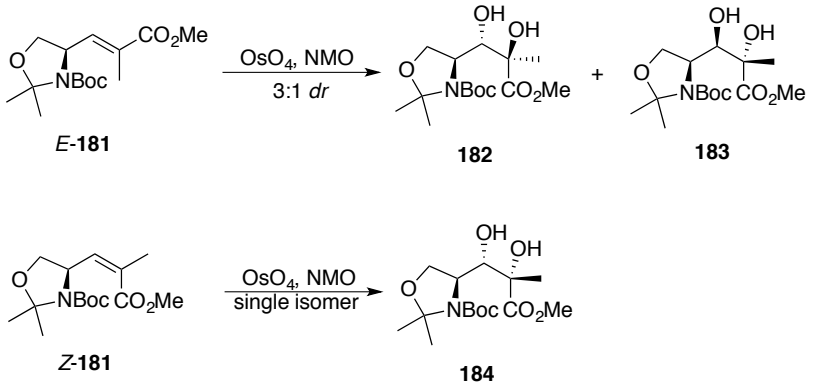
For the purpose to accessing enantiomerically pure amino aldehydes, Maruoka *et al.* reported a highly efficient one-pot procedure for the synthesis of β-amino alcohols by the direct asymmetric hydroxyamination of aldehydes with nitroso compounds. For ease of isolation, the aldehyde product was subsequently reduced to the corresponding hydroxyamino alcohol **187a**.[17] This involved a chiral secondary amine-catalyzed condensation of primary aldehydes **33** and nitrosobenzene **185** to afford β-amino alcohol **187a** in a good yield and excellent asymmetric induction.[17a] Trace amounts of the aminoxylation byproduct **187a'** was detected but in less than 1:99 ratio to hydroxyamination product **187a**. They also modified the procedure with hydroxycarbamate **188** as the substrate, however since the corresponding nitroso compound is unstable and highly reactive, it was *in-situ* generated by oxidation with BPO and TEMPO (Scheme 4.5).[17b,c]

Scheme 4.4 Asymmetric hydroxyamination of aldehydes



The third synthetic route to β-amino alcohol by functional group transformations involves oxidation of chiral allylic amines through epoxidation[18] or dihydroxylation[19]. Based on the literature reports, the stereochemical configuration of the product is greatly dependent on the alkene configuration in the substrates. The *Z*-isomer of allylic amine gives a mixture of diastereoisomers while the *E*-isomer gives the product as the single *anti*-isomer of the β-amino alcohol (Scheme 4.5).[19]

Scheme 4.5 Dihydroxylation of allyl amines 181

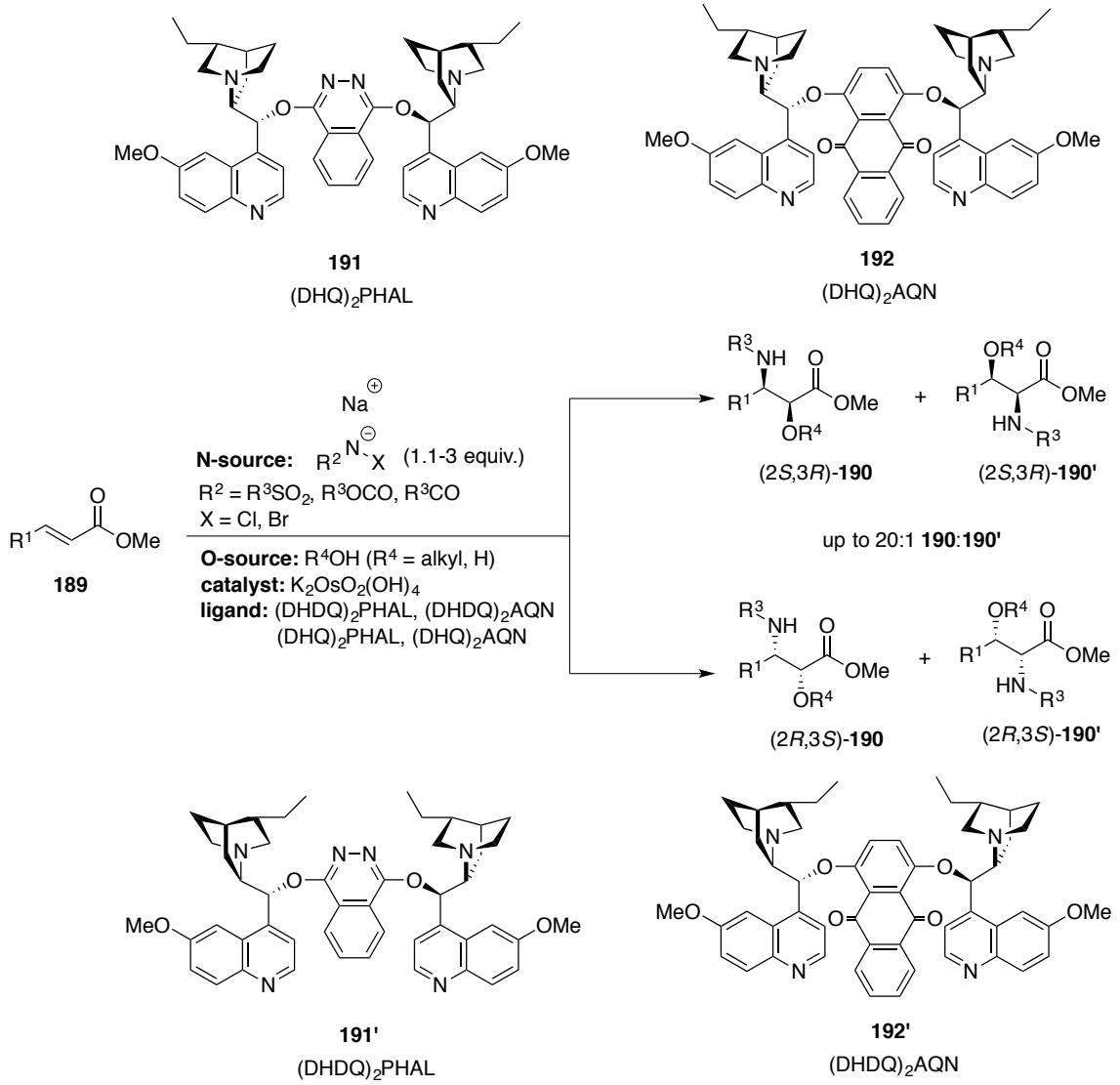


4.1.4 β-Amino Alcohols from Direct Alkene Aminohydroxylation

The most widely used method for the direct enantioselective indroduction of both amino and hydroxyl in the synthesis of β-amino alcohols is the Sharpless asymmetric aminohydroxylation of alkenes (Scheme 4.6).[20,21] It has been demonstrated that the α,β-unsaturated esters or phosphonates are the most suitable substrates which give the best regioselectivity for α-hydroxy-β-amino esters **190** over the regioisomer α-amino-β-hydroxy esters **190'**.[20a] The optimal conditions for the Sharpless aminohydroxylation allows for the *syn*-selective preparation of α-hydroxy-β-amino esters, untilizing the salts of *N*-halosulfonamides, amides, or carbamates as the nitrogen source, water or alcohol as the oxygen source and potassium osmate(VI) as the oxidant.[20b,c] The excellent enantioselectivity (>95% *ee* in most of cases) is achieved by dihydroquinine- or dihydroquinidine-derived chiral ligands.

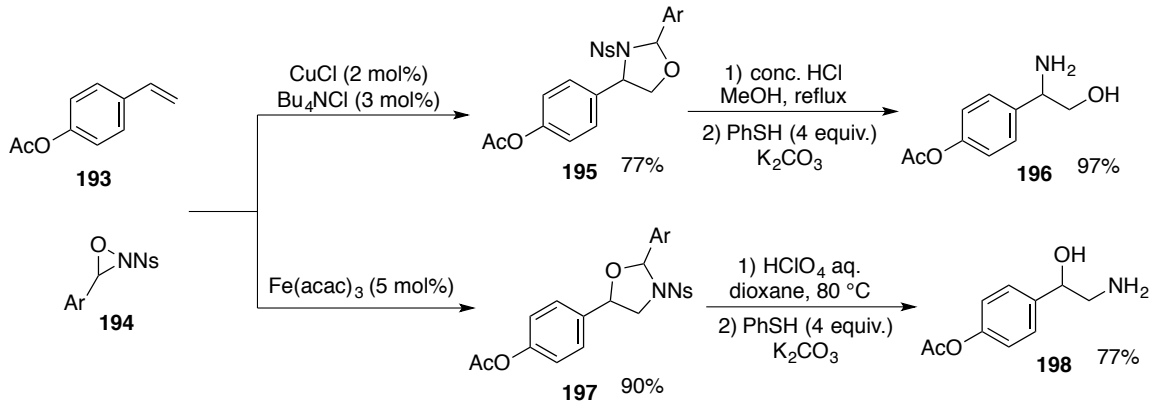
Based on the literature reports, the high regioselectivity of the Sharpless aminohydroxylation is limited to α,β-unsaturated esters, sulfonates, phosphonates, allylic alcohols and silanes.[21] A mixture of regioisomers are produced with unfunctionalized alkenes. Only the styrene derivatives were reported to stereoselectively give oxazolidinones by the Sharpless aminohydroxylation when treated with carbamates and bases.[22] Considering the high toxicity of osmium(VI) or (VIII) reagents, a number of alternative procedures for olefin aminohydroxylation have been developed in recent years with a broader range of substrate scope and better regioselectivity.[23]

Scheme 4.6 Sharpless asymmetric aminohydroxylation



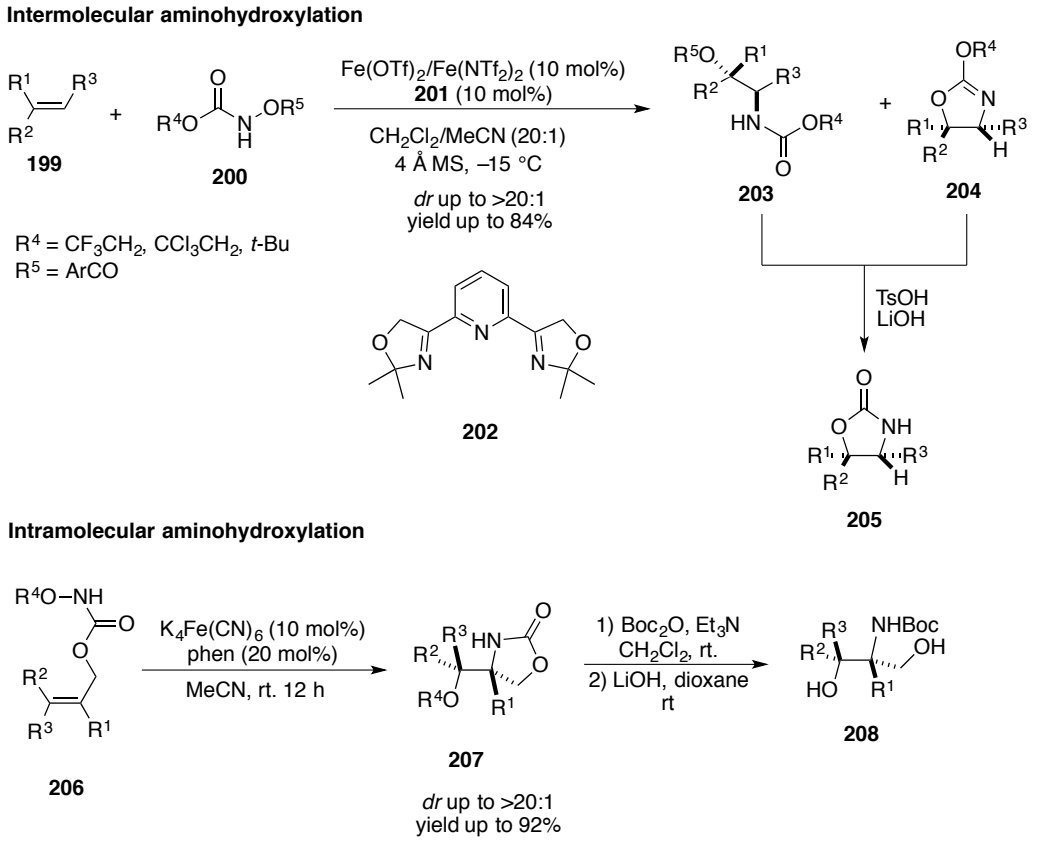
Yoon *et al.* have reported an example of catalyst-controlled in the regioselectivity of olefin aminohydroxylation.[23e-h] They reported a copper-catalyzed reaction of terminal styrene **193** with oxaziridines **194** to afford a 2,4-disubstitued oxazolidine **195**, while the reaction favored the opposite regioselectivity to give a 2,5-disubstituted oxazolidine **197** under iron catalysis (Scheme 4.7). Both regioisomers of β-amino alcohols **196** and **198** were obtained by the subsequent hydrolysis of the oxazolidines.

Scheme 4.7 Regioselective aminohydroxylation of styrene 193 and oxaziridines 194



Xu *et al.* developed a highly diastereoselective and atom-economic iron-catalyzed alkene aminohydroxylation with oxycarbamates in the presence of polydentate nitrogen ligands (Scheme 4.8).[23i-l] They proposed a iron nitrenoid-mediated mechanism that oxycarbamates **200** would allow either *syn*- or *anti*-addition to the olefin **199** which afforded β-amino alcohols **203** or cyclic imidates **204** and both could be converted to oxazolidinone **205**.[23k] With a tethered carbamate in the substrate **206**, an intramolecular aminohydroxylation to give an β-amino-γ-hydroxy alcohol **208** as the final product with the high diastereomeric purity.[23j]

Scheme 4.8 Aminohydroxylation of alkenes and oxycarbamates

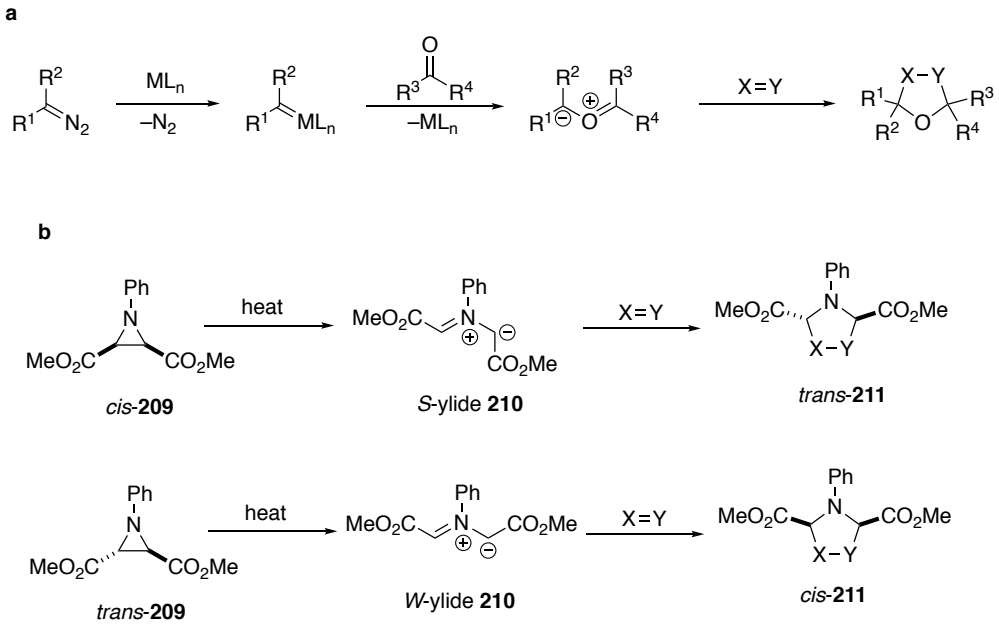


4.4.5 β-Amino Alcohols from 1,3-Dipole Cycloaddition

Ylides are highly reactive dipoles that have been used as key intermediates in a variety of organic tranforatmions. Carbonyl ylides can form by the reaction of carbonyls with electrophilic metallocarbenes and have been revealed as a 1,3-dipole.[24] The most significant reaction involving a carbonyl ylide is the 1,3-dipole cycloaddition with alkenes and alkynes to yield the corresponding five membered oxacycles (Scheme 4.9a).[25] Azomethine ylides are nitrogen-based analogs of carbonyl ylides that were first discovered and studied in 1965.[26] Huisgen and co-workers have shown that the thermolysis of 1-phenyl-2,3-dicarbomethoxyaziridines **209** could afford the stabilized *S*- or *W*-ylides **210** by a conrotary ring opening.[27] The *S*-dipole generated from *cis*-aziridine **209** reacts with most dipolarophiles to afford heterocycles *trans*-**211** stereospecifically,

while *W*-ylides **210** from *trans*-aziridine **209** afford heterocycles with only the *syn*-configuration (Scheme 4.9b).[28]

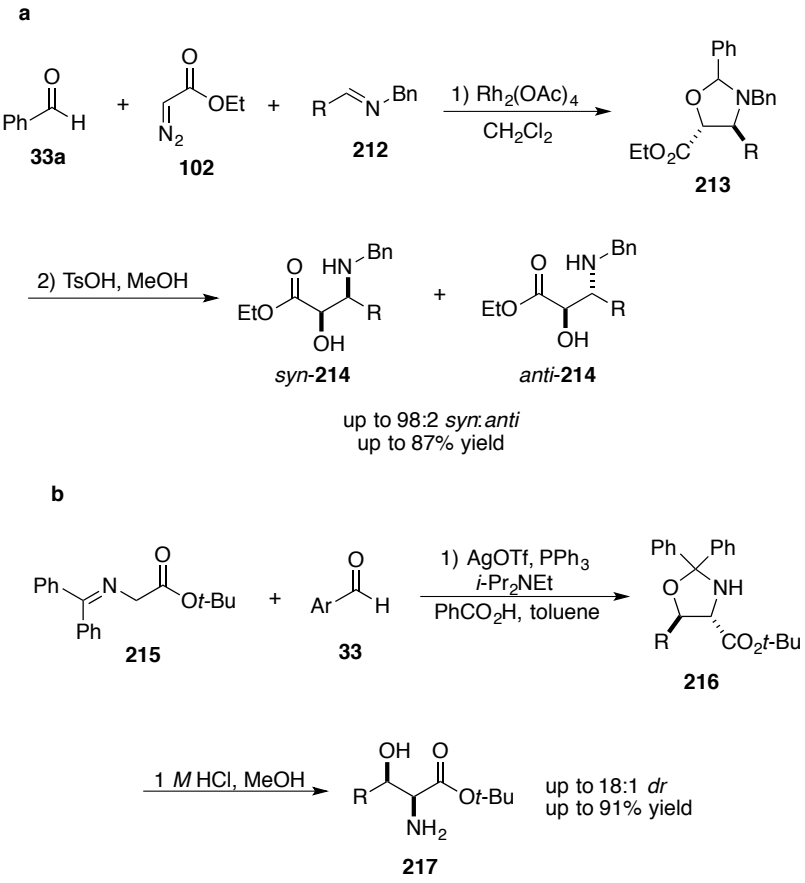
Scheme 4.9 Formation of carbonyl and azomethine ylides and 1,3-dipole cycloadditions



Somfai and co-workers have reported the *syn*-selective synthesis of aminohydroxycarboxylates *via* oxazolidine intermediates by 1,3-dipole cycloadditions.[29] They developed a three-component procedure involving aldehyde **33a**, ethyl diazoacetate (EDA) **102** and aldimines **212** (Scheme 4.10a). A carbonyl ylide is generated *in-situ* from benzaldehyde **33a** and EDA **102** and undergoes rhodium-catalyzed 1,3-dipole cycloaddition with imines **212** to give the *trans*-substituted oxazolidines **213**. Subsequent hydrolysis of the oxazolidine ring affords the β-amino-α-hydroxy esters **214** with up to 98:2 *syn*-selectivity.[29a, b] On the other hand, they also reported a 1,3-dipolar cycloaddition of aldehydes **33** and an azomethine ylide generated *in-situ* from an imino glycine ester **215** upon activation with silver triflate, which was followed by the hydrolysis of *trans*-oxazolidine intermediates **216** to afford the α-amino-β-hydroxy esters **217** with a 18:1

syn-selectivity and opposite regioselectivity observed by the carbonyl ylide (Scheme 4.10a vs 4.10b).[29c,d]

Scheme 4.10 Synthesis of β-amino alcohols by 1,3-dipole cycloadditions



4.2 BOROX-Catalyzed Aziridination/Ring-Opening Cascade Reaction

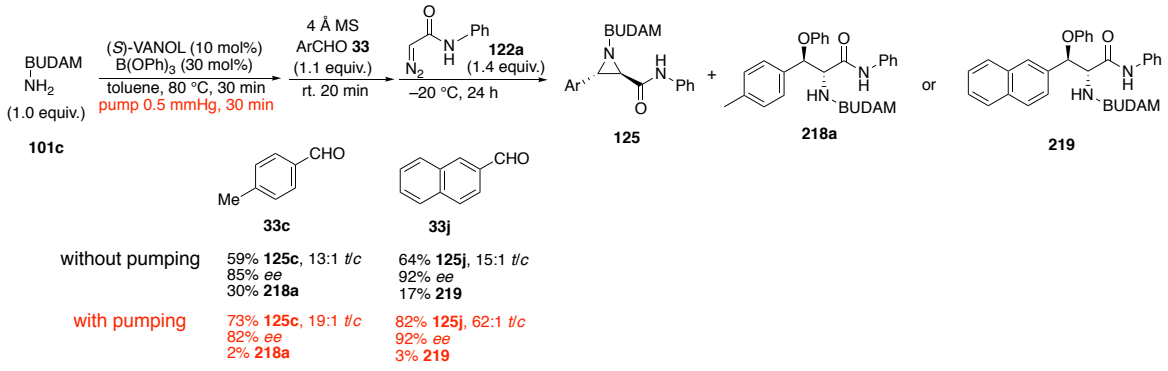
4.2.1 Catalytic Ring-Opening of *trans*-Aziridines

In the studies of the substrate scope in the multi-component *trans*-aziridination (Table 3.2), a byproduct **218a** or **219** was detected and isolated in the reaction of some of the aromatic aldehydes such as 4-tolualdehyde **33c** and 2-naphthaldehyde **33j** (Scheme 4.11). It was observed that the amount of the byproduct **218a** or **219** could be greatly reduced if after the catalyst formation step that al volatiles were removed by heating at 80 °C under a high vacuum. Thus, it could inferred that the structure of the unknown compound **218a**

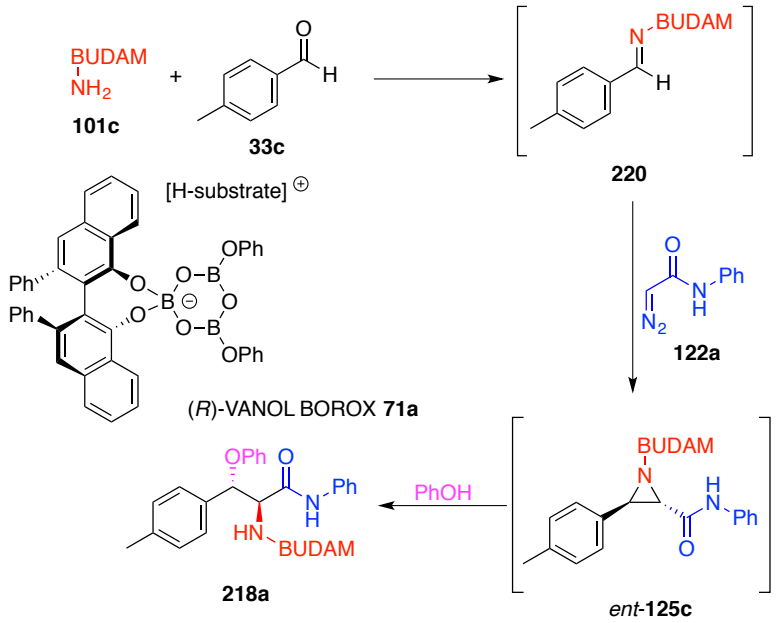
or **219** was an α-amino-β-hydroxy carboxamide generated by nucleophilic ring-opening of the aziridine product since previous experiment has shown that phenol is removed when the catalyst is subjected to a high vacuum at 80 °C.

The formation of aminohydroxy amide byproduct can be rationalized as a BOROX-catalyzed cascade process of *trans*-aziridination/nucleophilic ring-opening (Scheme 4.12). The *trans*-aziridine carboxamide *ent*-**125c**, generated from BUDAM amine **101c**, aldehyde **33c** and *N*-phenyl diazoacetamide **122a**, once formed, could be protonated and activated by the BOROX catalyst since the aziridine nitrogen has the similar basicity to an imine. A BOROX-catalyzed ring-opening of *trans*-aziridine *ent*-**125c** in the presence of phenol derived from triphenylborate would be expected to occurr to afford an 2-amino-3-phenoxy carboxamide **218a** by nucleophilic attack at the 3-position. The observation then supports for the assertion that the application of the pumping procedure can effectively remove phenol before the formation of *trans*-aziridine. Meanwhile, it can be inferred that a stoichiometric amount of phenol as a nucleophile should be able to give a complete conversion of the *trans*-aziridine intermediate into an aminohydroxy amide as a ring-opened product.

Scheme 4.11 Byproducts in multi-component *trans*-aziridination



Scheme 4.12 Formation of aminophenoxy amide 218a in *trans*-aziridination of 4-tolualdehyde 33c

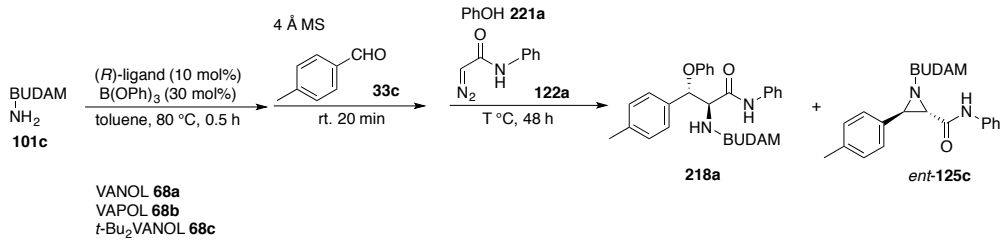


4.2.2 Asymmetric Synthesis of Aminohydroxy Amides with Phenols

The BOROX-catalyzed synthesis of aminohydroxy amides was optimized in the presence of a stoichiometric amount of phenol **221a** (Table 4.1). The *trans*-aziridination with the removal of phenol was present as the reference reaction where is was observed that a less than 2% yield of aminophenoxy amide **218a** was detected and *trans*-aziridine *ent*-**125c** was isolated in 73% yield and 82% *ee* (Table 4.1, entry 1). With the addition of a slightly excess phenol (1-2 equiv), a moderate yield of product **218a** was obtained (~40-50%) with significant high enantiomeric purity (>96% *ee*), while there was still a 20-30% yield of *trans*-aziridine *ent*-**125c** isolated, however with much lower enantiomeric purity (60-70% *ee*) compared to the results in entry 1 (Table 4.1, entry 2-4). This unexpected enantiomeric enrichment from the *trans*-aziridine intermediate *ent*-**125c** to aminophenoxy amide **218a** was presumably resulted from a kinetic resolution of *trans*-aziridine as a consequence of the action of the BOROX catalyst. Great drop in the yield of product **218a** was observed when the amout of phenol was further increased (3-10 equiv) and at

the same time, more *trans*-aziridine *ent*-**125c** remained unreacted. The decrease in *ee* of both product **218a** and *ent*-**125c** indicates that the BOROX catalyst is likely deactivated by the interaction with the large amount of excess phenol **221a** to give a poorer asymmetric induction (Table 4.1, entry 5-7).

Table 4.1 Optimization of asymmetric synthesis of aminohydroxy amide [a]



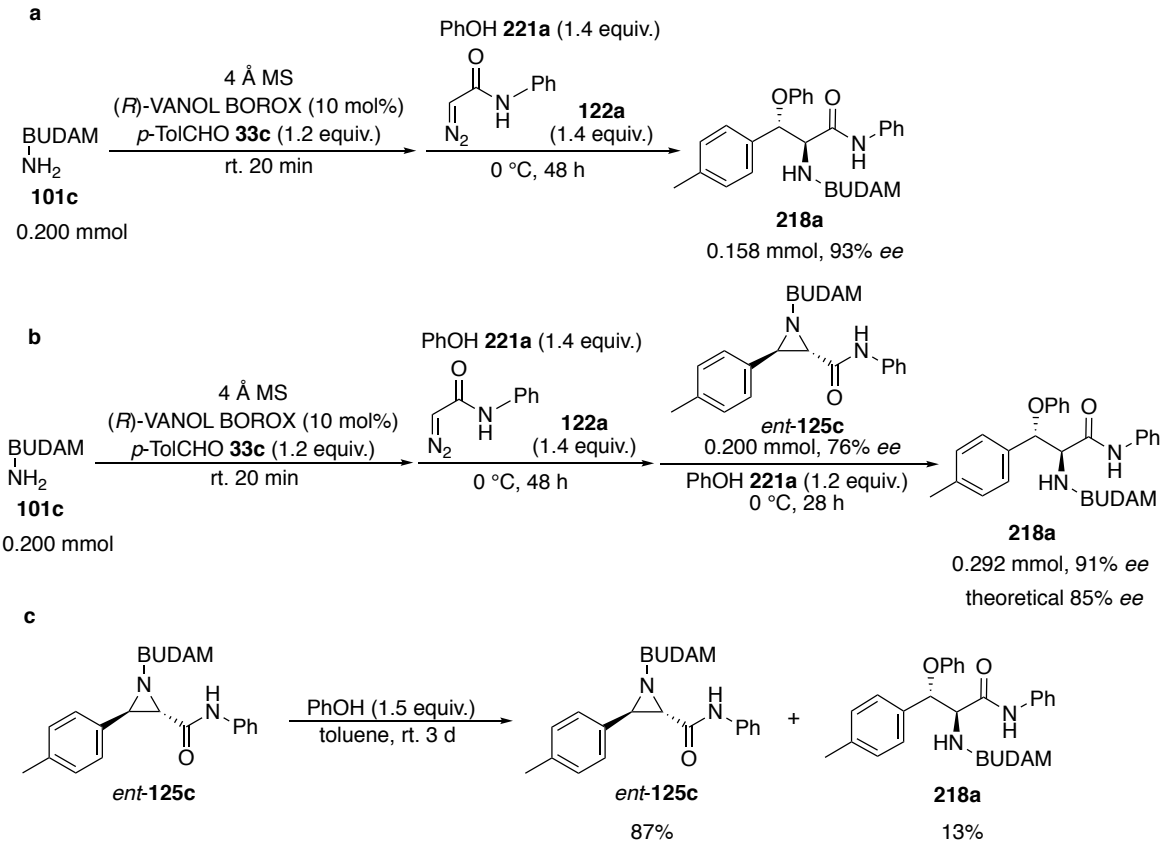
entry	ligand	PhOH/equiv.	T/°C	*trans*-aziridine		aminohydroxy amide	
				yield% [b]	*ee*% [c]	yield% [b]	*ee*% [c]
1 [d]	(*R*)-**68a**	0	–20	73	82	<2	nd
2	(*R*)-**68a**	1	–20	16	57	52	>99.5
3	(*R*)-**68a**	1.5	–20	21	69	48	99
4	(*R*)-**68a**	2	–20	36	69	44	96
5	(*R*)-**68a**	3	–20	42	70	39	95
6	(*R*)-**68a**	5	–20	51	72	30	90
7	(*R*)-**68a**	10	–20	53	55	16	72
8	(*R*)-**68a**	1.5	0	<1 [e]	nd	81	94
9 [f]	(*R*)-**68a**	1.5	25	<1 [e]	nd	65	87
10	(*R*)-**68b**	1.5	–20	4 [e, g]	nd	26	28
11	(*R*)-**68c**	1.5	–20	<1 [e, g]	nd	59	26

[a] Unless otherwise specified, all the reactions were run in 0.2 mmol scale of BUDAM amine **101c** (1 equiv), 4-tolualdehyde **33c** (1.2 equiv), *N*-phenyl diazoacetamide **122a** (1.4 equiv) and phenol **221a** with 0.2 *M* in toluene for 48 h. [b] Isolated yield. [c] Determined by HPLC. nd = not determined [d] The pumping at high vacuum was applied in the preparation of pre-catalyst to remove the volatile components. [e] Determined by the ^{1}H-NMR spectrum of the crude reaction mixture with an internal standard. [f] Reaction was run for 24 h. [g] 11% of *cis*-aziridine was detected. [h] 7% of *cis*-aziridine was detected.

The optimization of reaction temperature shows that the nucleophilic ring-opening of *trans*-aziridine *ent*-**125c** is greatly accelerated at 0 °C to give a complete conversion to the product **218a** in a high yield and *ee* (Table 4.1, entry 8). However, at the room temperature other byproducts are observed that the yield and *ee* drops even the reaction should be complete in a much shorter time (Table 4.1, entry 9). Finally, by screening the three chiral ligands VANOL **68a**, VAPOL **68b** and *t*-Bu$_2$VANOL **68c**, it was found that VANOL **68a** gives the much more decent results than the other two ligands (Table 4.1, entry 10, 11 vs entry 3). Notably, a small amount of *cis*-aziridine was detected with the

ligands VAPOL **68b** and *t*-Bu$_2$VANOL **68c**, which is consistent with the previously observed behavior of these ligands in the multi-component *trans*-aziridination (Table 3.1, 3.2). In addition, an experiment conducted for comparison has shown there is a background reaction of ring-opening of *trans*-aziridine *ent*-**125c** by phenol **221a** without the presence of the BOROX catalyst. The reaction is far slower than the catalytic one with an only 13% conversion of *trans*-aziridine after 3 days (Scheme 4.13c).

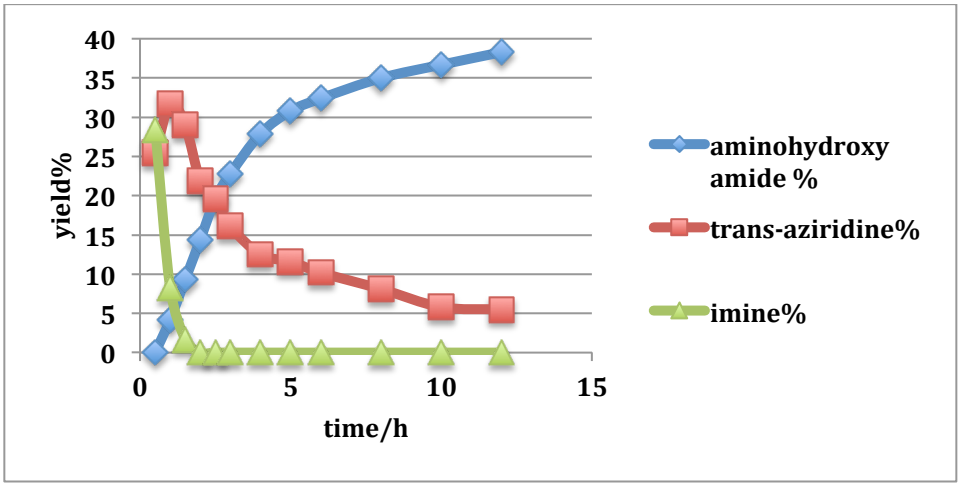
Scheme 4.13 Control experiments



A set of control experiments was carried out to confirm the enantiomeric enrichment involved in the catalytic ring-opening of *trans*-aziridine intermediate. In the first experiment on a 0.2 mmol scale, the optimal conditions were followed (Table 4.1, entry 8) to isolate the aminophenoxy amide **218a** (81% yield, 0.158 mmol) in 93% *ee* (Scheme 4.13a). In a parallel experiment also with 0.2 mmol scale was carried out in exactly the

same way and when the reaction was complete, additional phenol was added along with 0.2 mmol purified *trans*-aziridine *ent*-**125c** (76% *ee*). The enantiomeric purity of aminophenoxy amide **218a** was found to be 91% *ee*, and was isolated in the amount of 0.292 mmol (Scheme 4.13b). These experiments are consistent with the enantioenriched effects observed during the catalytic ring-opening, the theoretical *ee* of the product should be 85% if the additional 0.134 mmol of compound **218a** where 76% *ee* and is simply mixed with 0.158 mmol of the same material with 93% *ee*.

Figure 4.2 Reaction Tracking

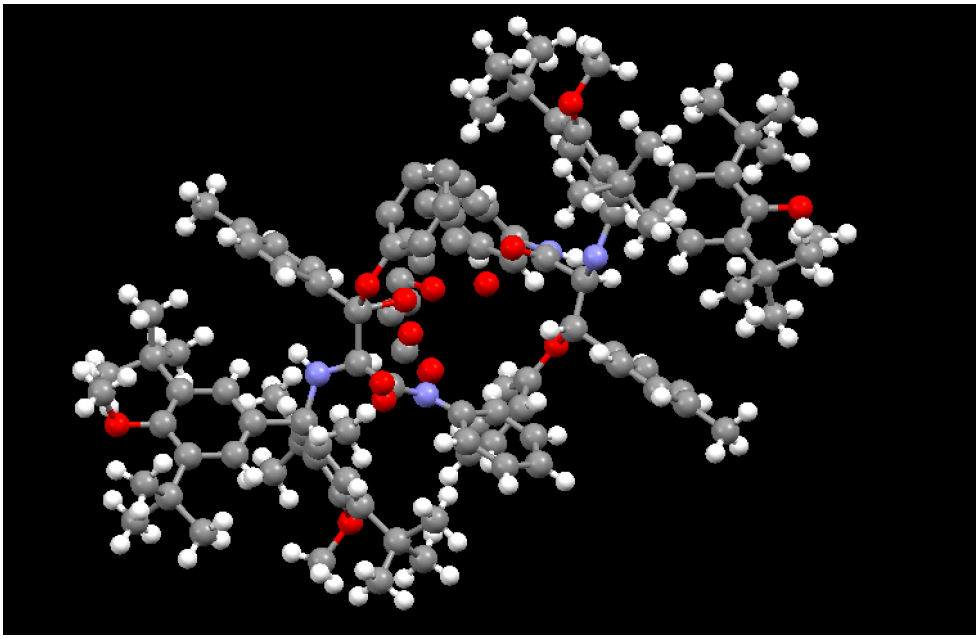


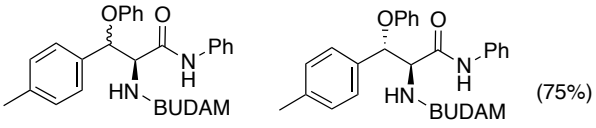
A plot obtained by tracking the percentage yield of the imine **220**, the *trans*-aziridine *ent*-**125c** and the aminophenoxy amide **218a** every 30 min by the ^{1}H-NMR spectrum of the reaction mixture with an internal standard (Figure 4.2). The amount of imine reached a 28% yield at 0.5 h and then kept decreasing indicating that the imine **220** was formed almost instantly and was rapidly converted to the *trans*-aziridine *ent*-**125c** within 2 h. The *trans*-aziridine *ent*-**125c** reached a maximum yield of 32% at 1 h and then was slowly converted to the product. Only around 5% yield of the aziridine was left at 12 h. Meanwhile, the amount of aminohydroxy amide kept increasing all the time. Given that the yield of aziridine was decreasing by 26 percentage from 1 h to 12 h, while the yield of

aminohydroxy amide was increased by 34 percentage in the same period of time, it suggests the evidence that the *trans*-aziridine can be the intermediate which is directly converted to the product. It is possible that this difference is due to inaccurate integration of the *trans*-aziridine that the peaks of the rotamers could be observed in the ^{1}H-NMR spectrum of the pure compound with $CDCl_3$ as the solvent. However, in the proton spectrum of the crude reaction mixture, these peaks could not be detected.

A single crystal of compound **218a** was obtained in the mixed solvent EtOH/H_2O, which was isolated and purified from the (*R*)-VANOL BOROX catalyzed reaction. The structure has two molecules in the unit cell as revealed by the X-ray crystallographic analysis (Figure 4.3). One of molecule (right) perfectly shows the stereochemistry of (2*S*,3*S*)-configuration. However, the other molecule (left) could only display the *S*-configuration at the 2-position, with the 3-position left unresolved due to the disorder in the crystal. The absolute stereochemistry of compound **218a** was eventually comfirmed by the independent synthesis of the compound with a known configuration (Scheme 4.17).

Figure 4.3 X-ray crystallographic analysis of aminophenoxy amide 218a

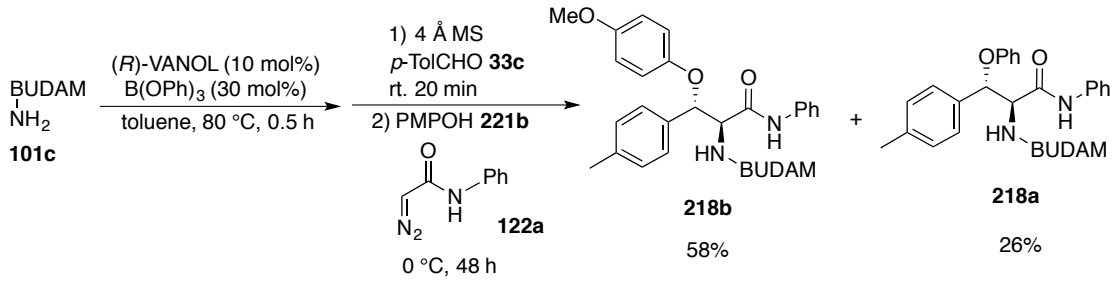




(2*S*,3*S*)-**218a**

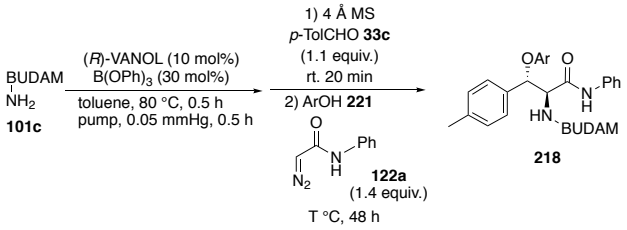
To investigate other phenol derivatives as the nucleophile, the optimal conditions with phenol need to be revised, as triphenylborate will always release free phenol during the catalyst formation to the reaction mixture which would result in a mixture of aziridine ring-opened products when there is another external phenol derivative added. For example, 4-methoxyphenol (PMPOH **221b**) was tested as a different nucleophile with the standard procedure of aziridination/ring-opening cascade reaction, which afforded a mixture of PMPOH ring-opened product **218b** in 58% yield as well as phenol ring-opened product **218a** in 26% yield (Scheme 4.14).

Scheme 4.14 Asymmetric synthesis of aminohydroxy amides with 4-methoxyphenol



In order to avoid the incorporation of phenol liberated during catalyst formation and generate a single aminohydroxy amide, the pumping procedure was applied with the high vacuum during the process of BOROX pre-catalyst preparation to remove the phenol liberated from triphenylborate. The reaction with the pumping procedure was first tested with phenol **221a** as the nucleophile at 0 °C and it was found that both the yield and the *ee* dropped (70% yield and 90% *ee*) compared to the reaction when the phenol liberated during the catalyst formation was not removed (Table 4.2, entry 1 vs Table 4.2, entry 8). If the reaction was run at –20 °C, an even lower yield was obtained, although the induction was improved to 97% *ee* (Table 4.2, entry 2). However, replacement of phenol **221a** with 4-methoxyphenol **221b** will give a reaction with an over 80% yield and excellent *ee* which suggests that an electron-rich phenol behaves as a better nucleophile. There was no significant difference for the yield and *ee* at 0 or –20 °C with PMPOH **221b** (Table 4.2, entry 3, 4).

Table 4.2 Optimization of the procedure with pumping at high vacuum [a]



entry	Ar	T/°C	yield% [b]	*ee*% [c]
1	Ph **221a**	0	70	90
2	Ph **221a**	–20	64	97
3	PMP **221b**	0	83	92
4	PMP **221b**	–20	85	93

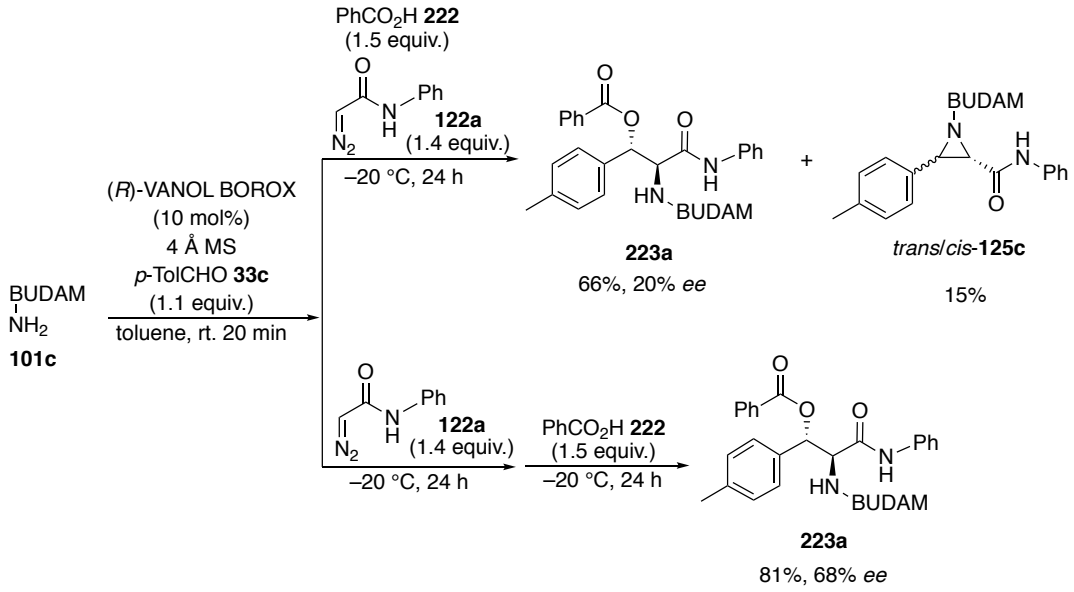
[a] Unless otherwise specified, all the reactions were run in 0.2 mmol scale of BUDAM amine **101c** (1 equiv), 4-tolualdehyde **33c** (1.2 equiv), *N*-phenyl diazoacetamide **122a** (1.4 equiv) and phenols **221** (1.5 equiv) with 0.2 *M* in toluene for 48 h. A pumping procedure was applied at high vacuum to remove the volatile components in the preparation of pre-catalyst. [b] Isolated yield. [c] Determined by HPLC.

4.2.3 Asymmetric Synthesis of Aminohydroxy Amides with Carboxylic Acids

In order expand the scope of nucleophiles, the BOROX-catalyzed *trans*-aziridination/ring-opening cascade reactions need to be evaluated with different types of nucleophilic reagents (Scheme 4.15). The reaction was examined with benzoic acid **222**, if it is successful, the aminobenzoyloxy amide **223a** should be easily hydrolyzed to afford the β-amino alcohol moiety. In the initial experiment, the optimal conditions in Table 4.2, entry 4 were followed and employed benzoic acid **222** instead of *para*-methoxyphenol **221b**. A moderate yield (66%) of aminobenzoyloxy amide **223a** was isolated, however, with an asymmetric induction of only 20% *ee*. In addition, a 1:1 mixture of *trans*- and *cis*-aziridines **125c** was detected in 15% yield. It is proposed that benzoic acid **222** can either be hydrogen bonded to the catalyst or protonate the imine intermediate that either way makes the catalyst less effective in interacting with the substrate intermediate, resulting in the poor asymmetric induction. A much better yield and improved asymmetric induction was obtained with for product **223a** in a experiment with a modified procedure that has the benzoic acid added to the reaction mixture after the

trans-aziridination was complete. Unlike the protocol in the reaction with phenol that gives improved enantiomeric purity during the ring-opening transformation, the reaction with benzoic acid results in drop in *ee* from the *trans*-aziridine to the aminobenzoyloxy amide **223a**. Given that the major difference of these two oxygen nucleophiles is their Brønsted acidity, future work should focus on studying the Hammett plot between the asymmetric induction and the pK_a values of phenols and benzoic acids, which the pK_a can be tuned by the electronic nature of the substituents on the aromatic ring.

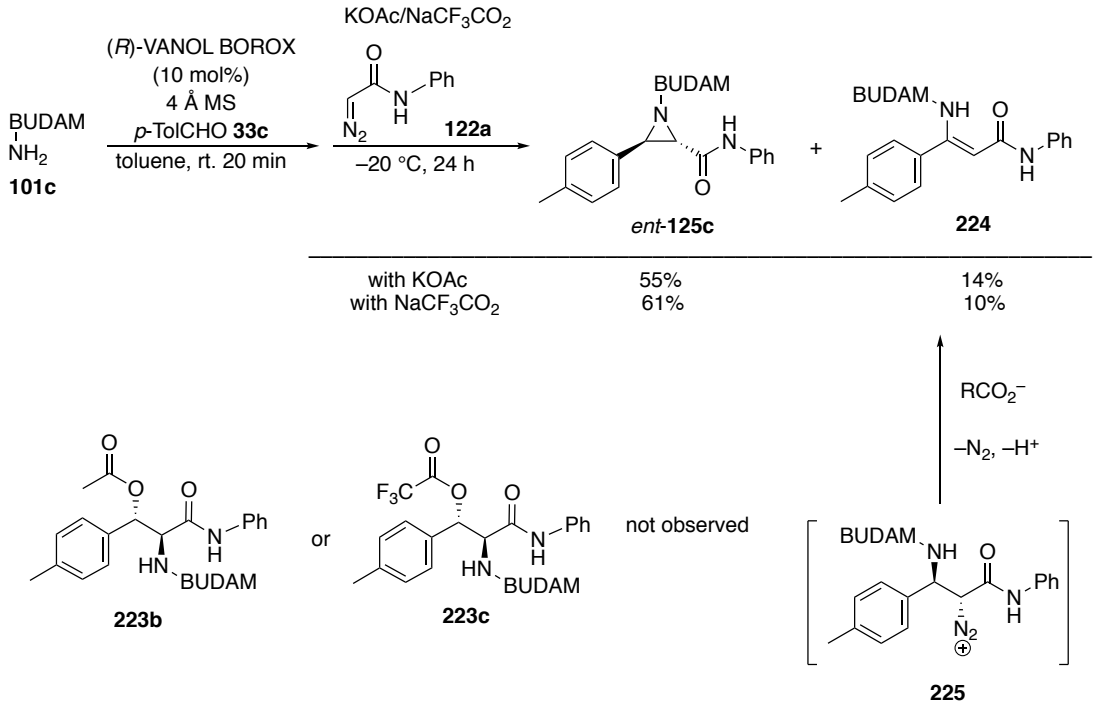
Scheme 4.15 ***trans*-Aziridination/ring-opening cascade reaction with benzoic acid 222**



The anionic carboxylate reagents potassium acetate and sodium trifluoroacetate were examined for the cascade reactions since they could be better nucleophiles than their acidic forms in the ring-opening of the aziridine intermediate (Scheme 4.16). Unfortunately, neither the aminoacetoxy amide **223b** nor aminotrifluoroacetoxy amide **223c**, could be detected in the reaction mixtures. Instead, only a moderate yield of the *trans*-aziridine *ent*-**125c** was isolated and thus the ring-opening step failed to occur. In addition, achiral compound **224** was detected in the mixture from both experiments in 10-

15% yield. This enamine compound **224** could be generated from the elimination of nitrogen from diazonium intermediate **225** facilitated by the basic nucleophiles. This is consistent with the previous studies that revealed a step-wise mechanism for the aziridination involving diazonium intermediate.[30]

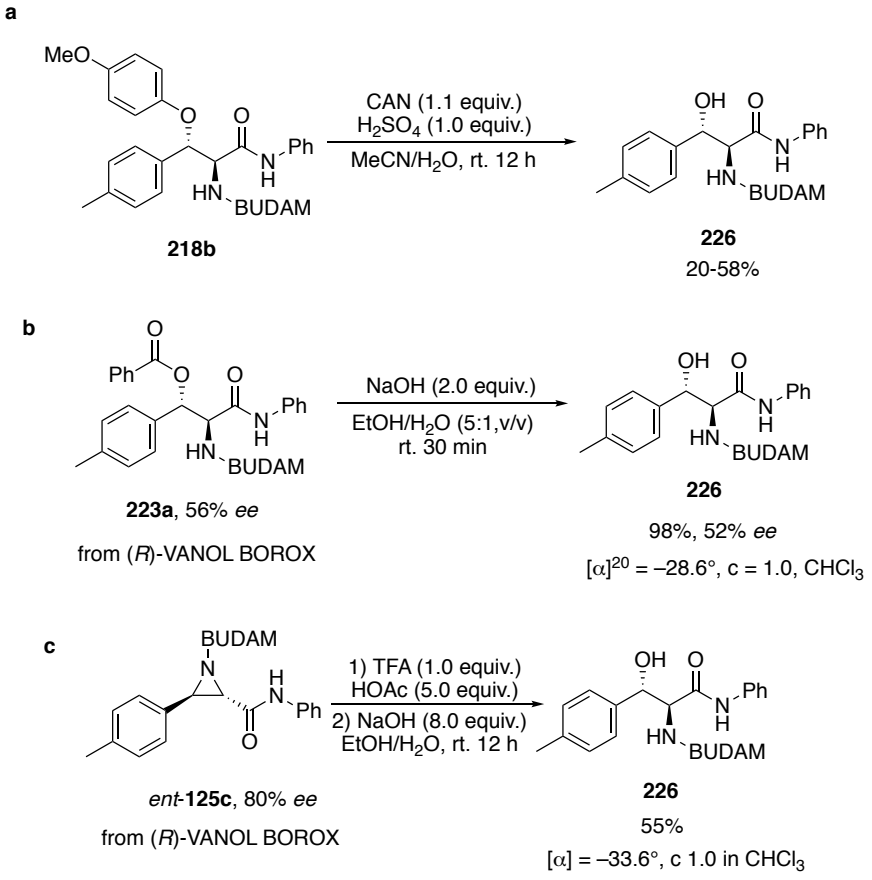
Scheme 4.16 ***trans*-Aziridination/ring-opening cascade reaction with carboxylate anions**



The PMP oxygen substituent in the aminophenoxy **218b** is expected to be cleaved by CAN oxidation, however, no reproducible yield of the product **226** could be obtained with severial trials and the reaction conditions were not further optimized (Scheme 4.17a). Fortunately, the aminobenzoyloxy amide **223a** prepared by (*R*)-VANOL BOROX-catalyzed cascade reaction was able to be hydrolyzed to the aminohydroxy amide **226**, which gives a negative optical rotation in $CHCl_3$ (Scheme 4.17b). Meanwhile, the same compound with the (2*S*,3*S*)-configuration and a negative rotation in $CHCl_3$ could be obtained by the TFA/HOAc-catalyzed ring-opening and basic hydrolysis of (2*S*,3*R*)-aziridine **125c** (Scheme 4.17c). These results match with the data from

crystallographic analysis that the cascade reactions give *anti*-diastereoisomers due to the inversion of stereochemistry at C3-position in the process of nucleophilic ring-opening. Based on the results in chapter 3 that (*R*)-VANOL BOROX catalyst gives aziridine **125c** with (2*S*,3*R*)-configuration, it reveals that the catalytic cascade reaction follows the same stereochemistry of product as that of *trans*-aziridination.

Scheme 4.17 Synthesis of α-amino-β-hydroxy carboxylamide 226



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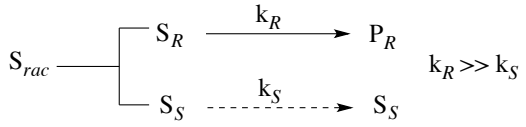
Chapter 5 Parallel Kinetic Resolution of Racemic α-Iminols

5.1 Parallel Kinetic Resolution (PKR)

Kinetic resolution refers to the rate differentiation of two enantiomers in a racemic compound. Chiral catalysts or reagents are often used to make two enantiomers react in different rates.[1] The more reactive enantiomer S_R gives a chiral product P_R, resulting in enantioenrichment of the less reactive enantiomer S_S. When the reaction rate of S_R is much greater than that of S_S ($k_R >> k_S$), the reaction affords high enantiomeric purity of both staring material and product with the overall result of synthetically useful in separation of chiral molecules (Scheme 5.1). A great number of publications have reported extremely effective kinetic resolutions for the preparation of enantiopure starting materials and products introducing alcohol acylation[2a], Sharpless epoxidation[2b, 2c], Sharpless dihydroxylation[2d, 2e], Jacobsen epoxide opening[2f, 2g], hydrogenation[2h] and ring-closing metathesis[2i] as typical examples of the practicality of kinetic resolution in asymmetric catalysis.

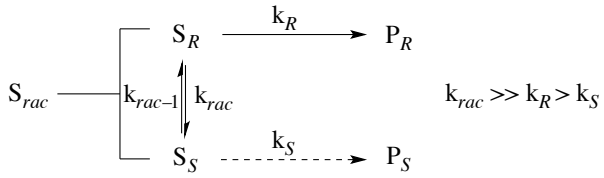
Scheme 5.1 Kinetic resolution of a racemic compound



To give an efficent kinetic resolution, the selectivity factor *s* should have a value (k_R/k_S) to be greater than 200.[1] However, in many cases the difference in reaction rate of both enantiomers is not great enough which results in a decrease in the enantiopurity of the product. The situation is even worse when the conversion passes 50% and the less reactive enantiomer rises to a relative high concentration. One way to avoid this situation is if there is an *in situ* racemization of two enantiomers of a starting material which has a

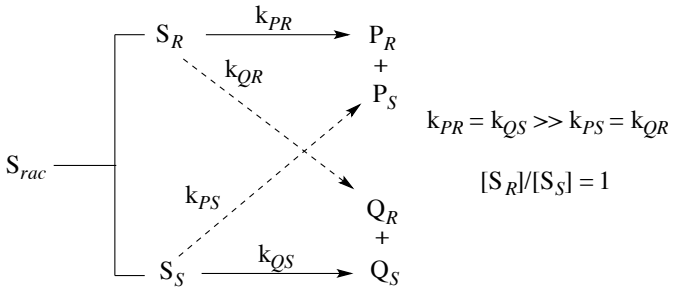
lower reaction barrier than the former reaction barrier for either of the enantiomers. This situation is called dynamic kinetic resolution (DKR) that is able to reach a theoretical 100% conversion of starting material into a single enantiomer of product (Scheme 5.2).[3]

Scheme 5.2 Dynamic kinetic resolution of a racemic compound



There is another way to maximize the enantiopurity as well as the conversion percentage by the use of two selective reagents in parallel. The more reactive enantiomer S_R and less reactive enantiomer S_S give two different enantiopure products P_R and Q_S through competing reactions, which is called parallel kinetic resolution (PKR) (Scheme 5.3).[4] Ideally, there should be an identical rate of parallel reactions maintaining 1:1 ratio of substrate enantiomers S_R and S_S and affording products P_R and Q_S with *ee* values that will depend on each reaction and a 50% theoretical yield for each product. Thus, PKR extends the process of conventional kinetic resolution by overcoming the limitation. The same efficiency can be reached when the *s* value is 49 in PKR, as when the *s* value is 200 in regular kinetic resolution. In conclusion, the following basic requirements necessary for a successful PKR process when the parallel reactions are a) totally independent without any mutual interference; b) with similar rate c) highly enantioselective; d) afford non-enantiomeric and easy separated compounds.[4]

Scheme 5.3 Parallel kinetic resolution of a racemic compound



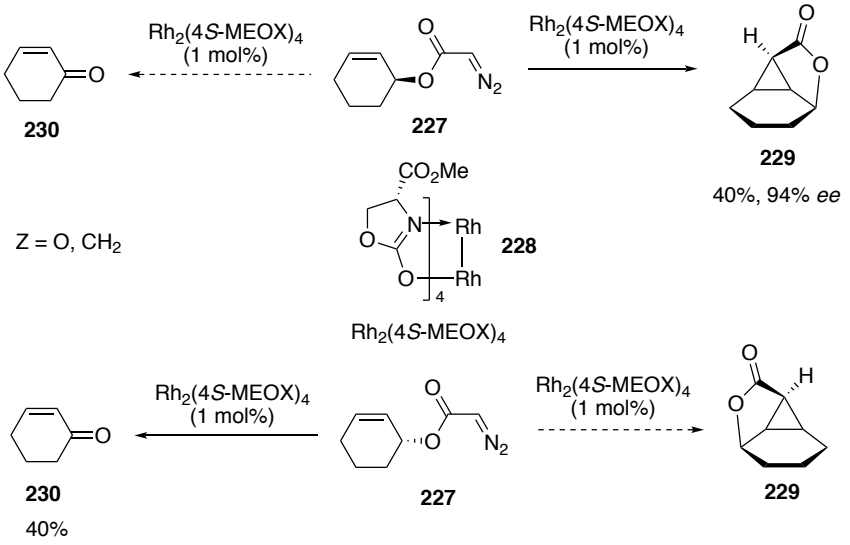
5.1.1 Chemodivergent PKR

Based on the structural relationship of both products, the processes of PKR can be chemodivergent, regiodivergent and stereodivergent.[5] In the chemodivergent PKR, the reactions yield two non-isomeric products. The early studies gave some examples of PKR that afforded two completely different compounds, however, one of them was useless due to the formation of a non-chiral molecule. A typical example is from the work done by Michael Doyle and his co-workers who reported a catalytic PKR that was found during the study of the intramolecular cyclopropanation of racemic cyclic allylic diazoacetate **227**.[6] With the chiral catalyst dirhodium(II) carboxamiate Rh_2(4*S*-MEOX)$_4$ **228**, the *S*-enantiomer of substrate gave the desired cyclopropanation product **229** in 94% *ee*, while the *R*-enantiomer surprisingly afforded a non-chiral cyclic unsaturated ketone **230** (Scheme 5.4).

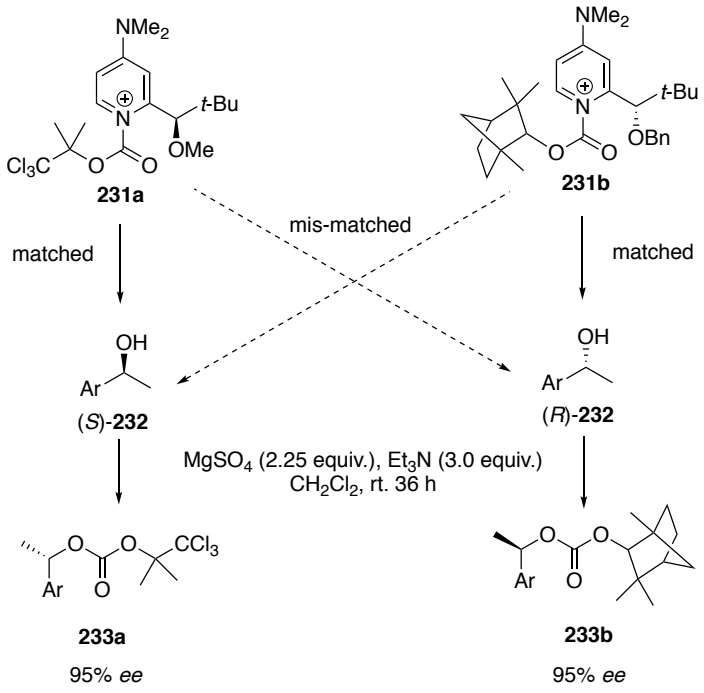
However, in most reported cases of chemodivergent PKR, a pair of pseudoenantiomeric reagents was used to afford two pseudoenantiomeric products possessing all the stereocenters with the opposite chirality and differing at a remote position. Vedejs, *et al.* reported the first application of this strategy in a magnesium bromide mediated acylation of 1 equivalent racemic 1-arylethanol **232** with two chiral DMAP-derived salts **231a** and **231b** (0.55 equiv), yielding the corresponding trichloro-*tert*-butyl carbonate **233a** and

fenchyl carbonate **233b** both in 95% *ee* after a complete conversion (Scheme 5.5).[4] In this process, trichloro-*tert*-butyl DMAP-derived salt **231a** formed a "matched-pair" with (*S*)-**232** and fenchyl DMAP-derived salt **231b** was the matched pair with (*R*)-**232** respectively.

Scheme 5.4 PKR affords non-chiral compound

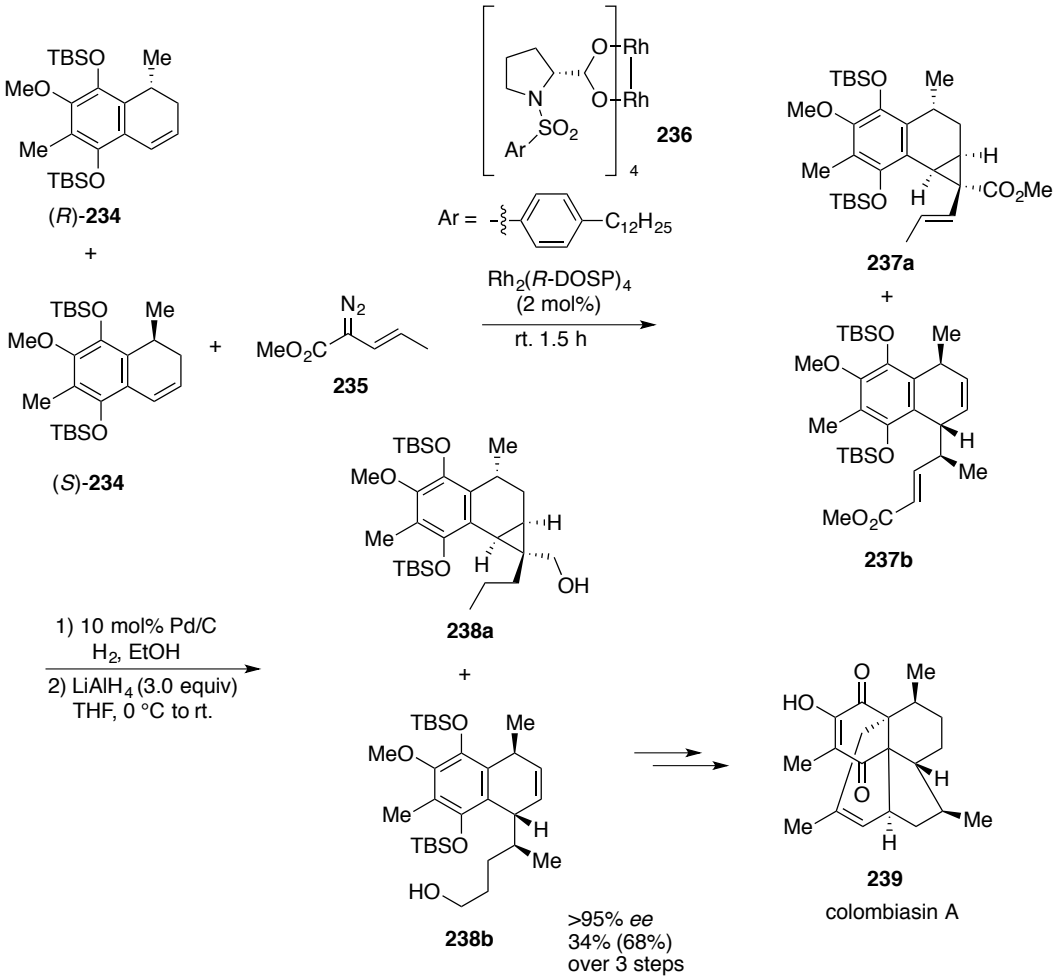


Scheme 5.5 PKR affords pseudoenantiomeric compounds



In a recent example of chemodivergent PKR, the catalytic process has been reported to afford two different enantioenriched compounds *via* dramatically different reaction pathways.[7] A beautiful application of chemodivergent PKR was reported by Davies and his co-workers as the key step in the total synthesis of (–)-colombiasin A **239**. With the catalysis of Rh_2(*R*-DOSP)$_4$ **236** and the presence of carbene precursor **235**, (*R*)-enantiomer of compound **234** gives a cyclopropane **237a**, while the (*S*)- enantiomer of compound **234** undergoes C-H activation/Cope rearrangement to afford compound **237b**. To separate the PKR products, the mixture was hydrogenated and reduced by $LiAlH_4$ to isolate the desired terminal alcohol **238b** as the synthetic intermediate on the way to colombiasin A **239** in 34% overall yield as a single distereoisomer with >95% *ee* (Scheme 5.6).[7b]

Scheme 5.6 Chemodivergent PKR in the total synthesis of (–)-colombiasin A



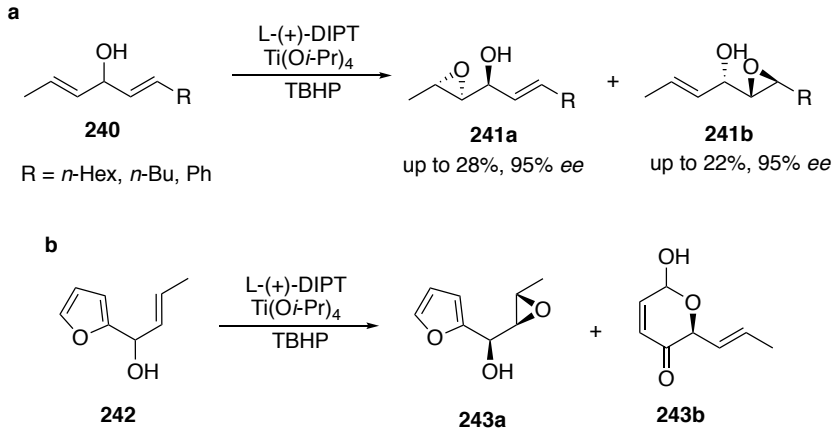
5.1.2 Regiodivergent PKR

The regiodivergent PKR includes substrates containing the same reactive functional groups but at different positions, or one functional group with two reactive sites, or even two different functional groups with similar reactivities.[8]

Several examples have been described with Sharpless asymmetric epoxidation of allylic secondary alcohols. Zhou, *et al.* have studied the Sharpless epoxidation of unsymmetrical divinyl methanols **240** which yielded a mixture of epoxides **241a** and **241b** with decent enantiopurity (Scheme 5.7a).[8a] Honda, *et al.* studied the Sharpless epoxidation of 2-

furylmethanol bearing an alkenyl moiety **242** resulted in the formation of epoxide **243a** and the rearrangement product pyranone **243b** (Scheme 5.7b).[8b]

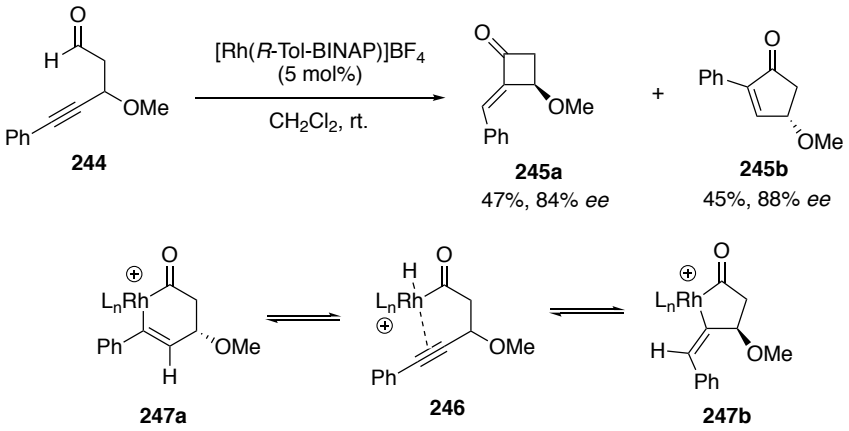
Scheme 5.7 Regiodivergent PKR in Sharpless epoxidation



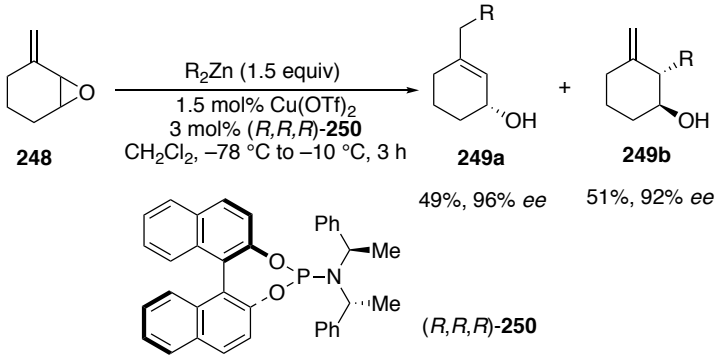
Fu, *et al.* reported the kinetic resolution of 4-alkynals by a chiral cationic rhodium bisphospine catalyzed intramolecular hydroformylation of a triple bond, which highlighted the impact of the ligand on the efficiency of the kinetic resolution. The highly regioselective alkyne insertion of cationic (Tol-BINAP)Rh^+ species with the two enantiomers of substrate **244** led to the formation of two different enones **245a** and **245b** with high enantioselectivity (Scheme 5.8).[8c]

An example of regiodivergent PKR involving different functional groups was reported by Feringa, *et al.* that involved treatment of the vinyloxiran **248** with dialkylzinc catalyzed by a copper complex of chiral phosphoramidite **250** which yielded two regioisomeric alcohols **249a** and **249b** in 99% *ee* (Scheme 5.9). The allylic alcohol **249a** was formed *via* a S_N2' mechanism while the homoallylic alcohol **249b** was formed by S_N2.[8d]

Scheme 5.8 Regiodivergent PKR in catalytic hydrofomylation



Scheme 5.9 Regiodivergent PKR in C-C bond formation



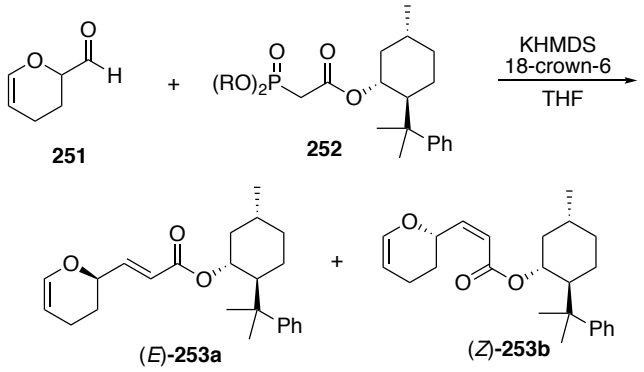
5.1.3 Stereodivergent PKR

PKR processes can also be stereodivergent that yield a pair of Z/E isomers or diastereomers. The Z/E selectivity in PKR usually happens through the formation of C-C double bond in an asymmetric Wittig-type reaction. Rein, *et al.* reported a Z/E-divergent PKR by an asymmetric Horner-Wadsworth-Emmons (HWE) reaction where each enantiomer of the Diels-Alder acrolein dimer **251** yields different geometric isomers of the (*E*)- and (*Z*)-olefins in compound **253** (Scheme 5.10).[9a]

The stereodivergent PKR can also be involved in the process that a new chiral center forms in the molecule, which already possesses a stereocenter. For example, Gotor, *et al.* carried out the bioreduction of racemic 1-methyl-2-oxocycloalkanecarbonitrile **254** by the

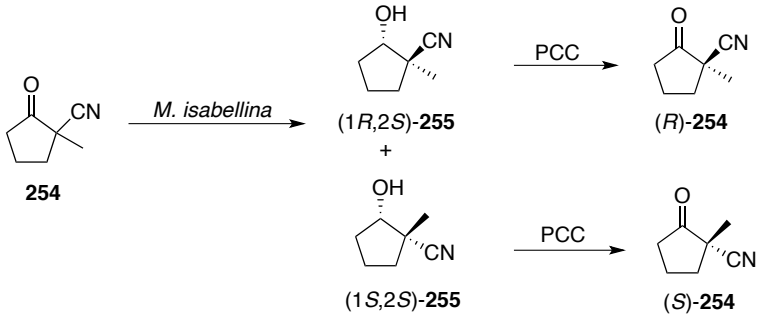
fungus *M. isabellina*, yielding a mixture of hydroxynitrile diastereomers (1*R*,2*S*)- and (1*S*,2*S*)-**255**, which could be re-oxidized by PCC to afford each enantiomer of starting material **254** (Scheme 5.11).[9b]

Scheme 5.10 Stereodivergent PKR in an asymmetric HWE reaction



251 252 (*E*)-253a (*Z*)-253b

Scheme 5.11 Stereodivergent PKR of β-keto nitriles



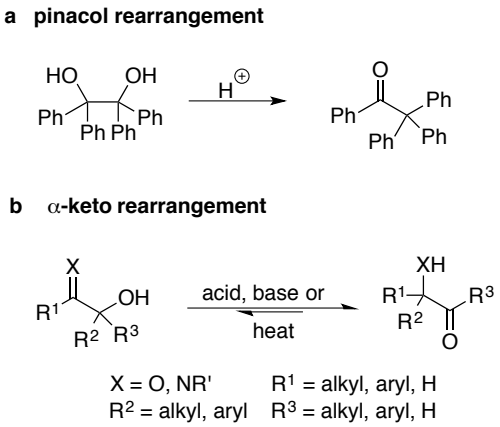
254

5.2 Literature Work on α-Ketol/Iminol Rearrangement

5.2.1 α-Hydroxy Ketones and Aldehydes

Since the adjacent carbocation triggered 1,2-rearrangement was first described by Fittig in 1860 (Scheme 5.12a) [10], more rearrangement reactions with α-hydroxy aldehydes and ketones involving cations were discovered with similar mechanisms. Treatment of α-ketols with a base, a Brønsted acid, a Lewis acid or even heat will arouse the 1,2-shift of an alkyl or aryl substituent to afford an isomeric compound (Scheme 5.12b).

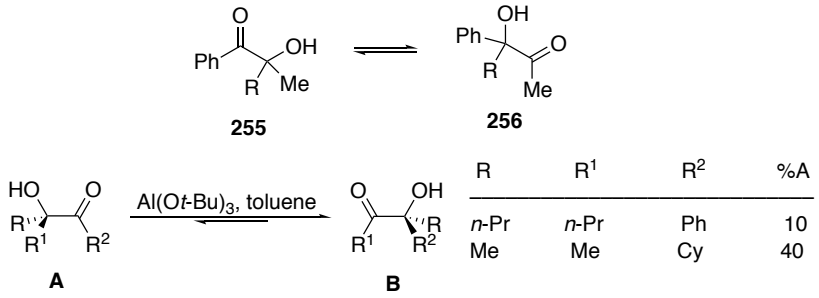
Scheme 5.12 Pinacol and α-keto rearrangement



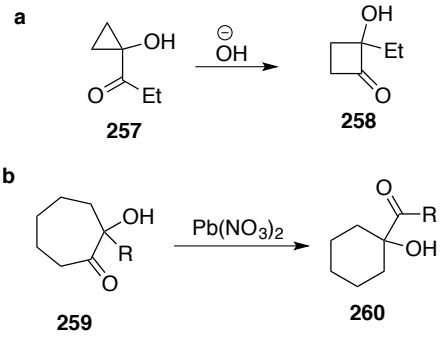
There is less synthetic utility for the rearrangement of acyclic α-ketols, since an equilibrium is usually exists between the two isomers. Efforts have been made to investigate the relative stability of isomers, which was believed to be on the basis of conventional electronic effects, however, more cases have shown there are additional factors which may determine the outcome (Scheme 5.13).[11] The α-keto rearrangement is more synthetically useful in the rearrangement of cyclic α-ketols as the ring strain release acts as a driving force to undergo ring expansion in small ring systems (Scheme 5.14a).[12a] Also, the larger cyclic α-ketol **259** irreversibly contracts to the cyclohexanol **260** under basic conditions (Scheme 5.14b).[12b, c]

The thermodynamically-controlled α-hydroxy aldehyde rearrangement is unidirectional progressing from the α-hydroxy aldehyde **261** to an α-hydroxy ketone **262** (Scheme 5.15a).[13a] The thermodynamic advantage associated with the ketone is also highlighted by the ring expansion from 1-hydroxycyclohexanecarboxaldehyde **263** to 2-hydroxycycloheptanone **264** in 80% yield (Scheme 5.15b).[13b] A common example of the synthetic utility of the α-hydroxy aldehyde rearrangement is the D-homoannulation of a steroid **265** when exposed to silica gel, heat or a Lewis acid(Scheme 5.15c).[13c]

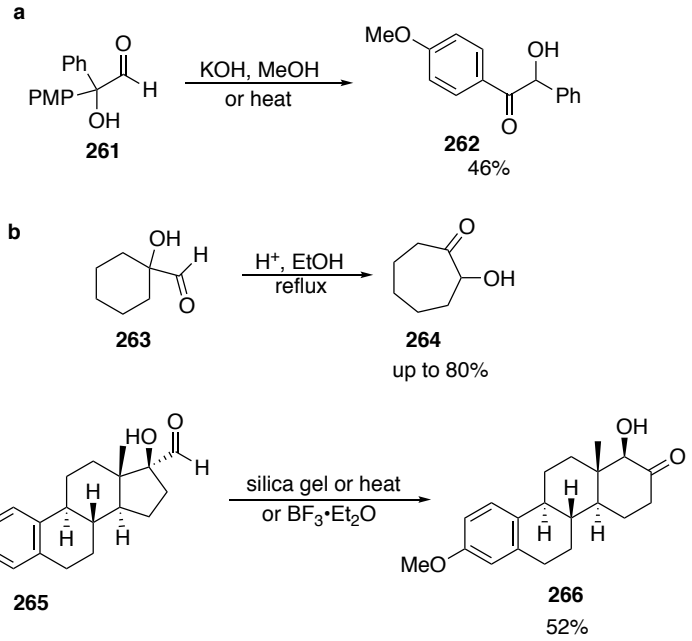
Scheme 5.13 Acyclic α-ketol rearrangement



Scheme 5.14 Cyclic α-ketol rearrangement



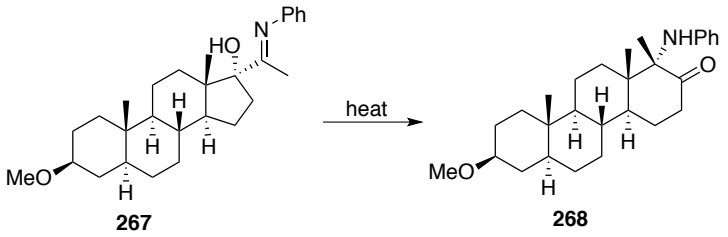
Scheme 5.15 α-hydroxy aldehyde rearrangement



5.2.1 α-Hydroxy Imines (α-Iminols)

The first example α-iminol rearrangement was reported by Schoppee and Prins in 1943 (Scheme 5.16) that the reaction was promoted by heat.[14a], there were lots of literature reports on the thermal rearrangement of α-iminols as the early work. The investigation on the mechanistic study has shown the thermal α-iminol rearrangement was unidirectional and concerted.[14]

Scheme 5.16 The first example of α-hydroxy imine rearrangement

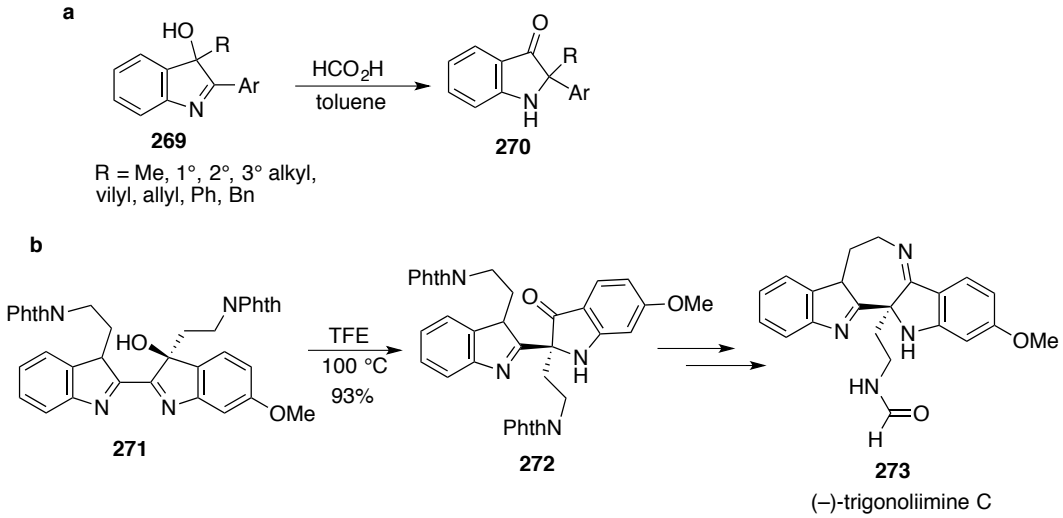


267 **268**

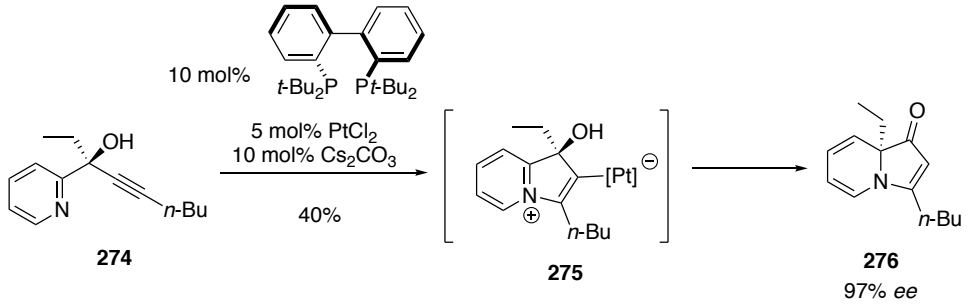
More approaches have been explored for the catalytic α-iminol rearrangement such that Brønsted acids, Lewis acids and Brønsted bases are commonly found in the literature. For example in weak bases such as imines (pK_a 4-5), the C=N double can be activated by strong Brønsted acids such as HCO_2H, TFA, H_2SO_4, *p*-TsOH, *etc.* promoting the migration of alkyl and aryl substituents. The Brønsted acid-catalyzed rearrangement of 3*H*-indol-3-ol **269** has been studied a lot since indol-3-ones are potentially useful intermediates in the synthesis of alkaloids and pharmaceuticals (Scheme 5.17a). The relative reactivity of migration substituents have been studied by McWhorter, Jr. *et al.* and they shown an increasing trend of migration in the order of CH_3, 1°, 2°, 3° alkyl, vinyl, allyl, phenyl and benzyl.[15a] Movassaghi, *et al.* reported a beautiful application in the total synthesis of (–)-trigonoliimine C **273** with 3*H*-indol-3-ol rearrangement as the key step (Scheme 5.17b).[15b]

Imines are good Lewis bases and easy to be activated by Lewis acids. This process is quite similar to iminol activation by Brønsted acids. In Particular, there are several examples of α-iminol rearrangement involving an iminium intermediate formed by organometallic Lewis acid catalysis. Sarpong, *et al.* reported a *trans*-metalation/α-iminol rearrangement cascade reaction of a pyridine with a tethered propargyl alcohol as in compound **274** (Scheme 5.18).[16] The cyclization to the pyridine was achieved by *trans*-aminoplatination of the alkyne to form the indolizinium intermediate **275**, followed by a stereoselective Wagner-Meerwein shift of ethyl group to afford the indolizinone product **276**.

Scheme 5.17 Brønsted acid promoted of α-iminol rearrangement

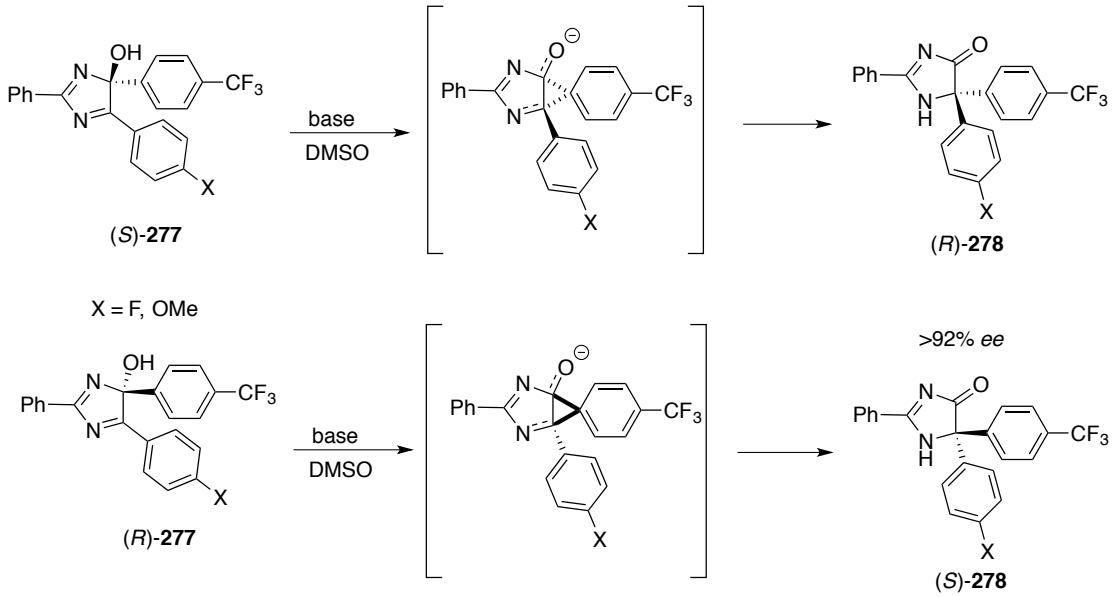


Scheme 5.18 α-Iminol rearrangement *via* an iminium intermediate



The acidic property of the hydroxyl group may allow for the activation of an α-iminol by deprotonation with base to promote the 1,2-shift. Lu, *et al.* reported a base-triggered 1,5-phenyl migration of imidazol-4-ol **277**. The stereoselectivity of migration was investigated for each enantiomer of substrate that afforded totally opposite stereochemical configurations of imidazol-4-one products **278**, which indicates that 1,5-phenyl migration happens through concerted pathway *via* an intramolecular three-membered ring (Scheme 5.19).[17]

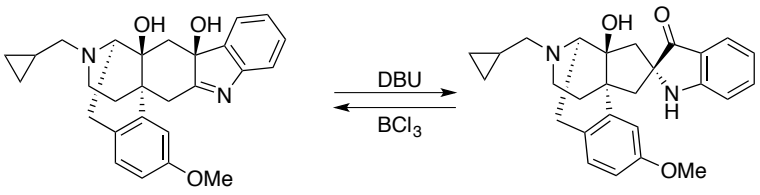
Scheme 5.19 Stereoselective base-promoted α-iminol rearrangement



Most α-iminol rearrangement reactions reported in the literature are unidirectional and irreversible, but there are sevel examples involving the reverse reaction from an α-amino ketone to corresponding α-iminol. Nagase and his co-workers reported an example of interconversion between a hydroxyindolenine **279** and a spiroindolinone **280** (Scheme 5.20).[18] They reported the base-promoted α-iminol rearrangement of hydroxyindolenine **279** to afford a spiroindolinone **280**. They could also convert the spiroindolinone **280**

back to the hydroxyindolenine **279** by treatment with a Lewis acid. This reveral is apparently favored by the ring-stress release from the spiro-ring to the bridged ring.

Scheme 5.20 Interconversion between a α-iminol and a α-amino ketone

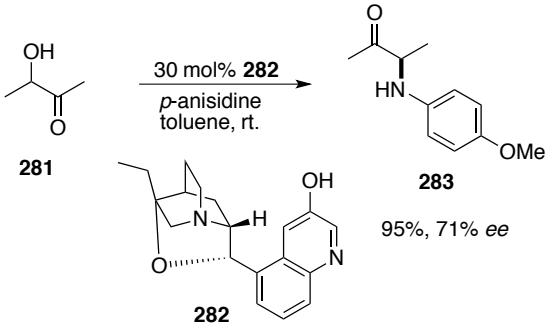


279 **280**

5.3 Asymmetric Catalytic Rearrangement with Non-Chiral α-Iminols

The literature examples of asymmetric catalytic α-iminol rearrangement are rare. Frongia and his co-workers have reported the synthesis of an optically active amino ketone *via* one-pot iminol synthesis/asymmetric imine-enamine tautomerization (Scheme 5.21).[19] They investigated the raction of acetoin with *p*-anisidine, using the chiral bifunctional amino alcohols as the catalysts. The β-isocupreidine was screened as the optimal catalyst to afford the corresponding amino ketone in 95% yield and 71% *ee*.

Scheme 5.21 One-pot catalytic asymmetric rearrangement of α-hydroxy ketones with anilines



281 **283**

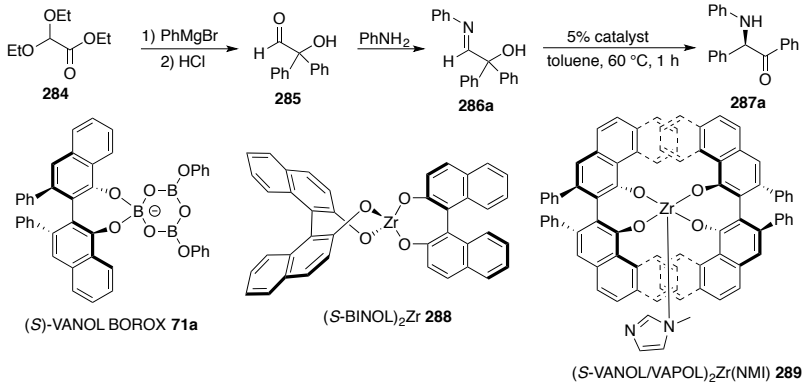
95%, 71% *ee*

282

Xin Zhang in our research group developed an effective strategy for Zr-catalyzed asymmetric α-iminol rearrangement in 2014.[20] The background reaction can be effectively catalyzed by Lewis acids to afford high conversions of the α-iminols. In the study to search for the most effective asymmetric catalyst, the BOROX catalyst **71a** with

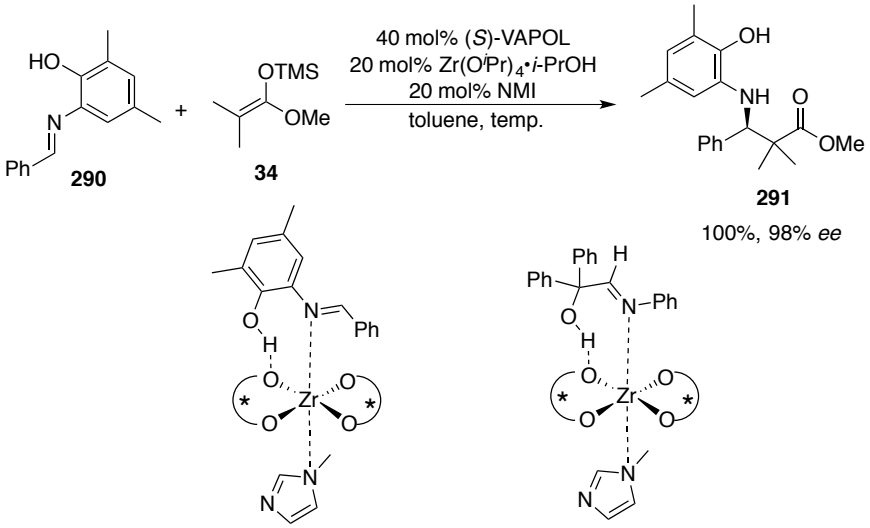
different ligands were examined but resulted in poor enantioselectivity (Table 5.1, entry 1). Considering that the similarity of the N,O-bifunctional units in the substrates from the previously published work on Mannich reaction of imine **290** to β-amino ester **291** indicates a possible way that a α-imino could interact with the zirconium catalyst (Scheme 5.22).[21] Thus, the VANOL-derived zirconate catalyst **289** was examined and found to be remarkably effective in asymmetric induction of the amino ketone **287a** with 97% *ee* (Table 5.1, entry 2). However, replacement of VANOL with VAPOL or BINOL gives a catalyst which fails to promote the enantioselectivity (Table 5.1, entry 3,4).

Table 5.1 Catalyst screen for α-iminol rearrangement[20]



entry	catalyst	ligand	yield%	*ee*%
1	boroxinate	(*S*)-VANOL	60	17
2	zirconate	(*S*)-VANOL	96	97
3	zirconate	(*S*)-VAPOL	86	28
4	zirconate	(*S*)-BINOL	66	10

Scheme 5.22 Zr-catalyzed Mannich reaction[21]

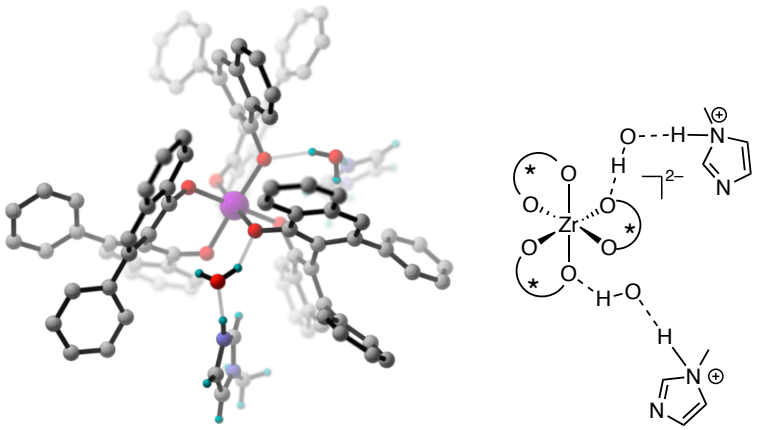


A single crystal of the VANOL zirconate catalyst was obtained and its solid state structure was analyzed by X-ray crystallography (Figure 5.1). It was revealed that the zirconium complex was homoleptically hexacoordinated with three VANOL ligands and the charge balanced by two protonated *N*-methyl imidazolium cations. The protonated imidazolium cations are not directly H-bonded to the oxy-zirconium core. Instead, a molecule of water interacts between each imidazolium cation and zirconate dianionic core by H-bonding. This is the first example of homoleptic zirconium complex with three *bis*-phenol ligands, although a number of rare earth complexes with three BINOL ligands have been reported but not for zirconium.[22]

However, the experimental evidence shows that it might be that the zirconium complex is a different species in solution and solid state. The single crystals were grown from a 1:2:1 mixture of Zr/ligand/NMI, which was the catalyst composition proposed in Mannich reaction, but actually the X-ray analysis shows a compose of 1:3:2 ratio. In addition, an *in-situ* generated catalyst from a 1:3:2 mixture of Zr/ligand/NMI gave a similar yield and enantioselectivity for the amino ketones as the catalyst generated from a 1:2:1 mixture.

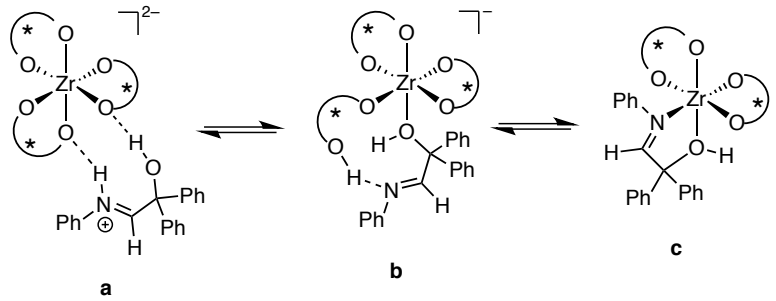
This indicated there could be a difference in the structure of the zirconium complex in the solid state and the solution form.

Figure 5.1 Single crystal structure of VANOL zirconate in the solid state[20]



Although the interactions between the catalytic zirconate species and the α-iminol substrates still remains unclear, it is possible that the dissociation of one of the VANOL ligands from zirconium can happen during the reaction process, which leaves room for the substrate to access the catalyst. Several possibilities have been proposed for the α-iminol activation with the zirconium complex (Scheme 5.23): a) both nitrogen and oxygen of an iminol were H-bonded to the *tris*-VANOL zirconium which functions as a Lewis acid-assisted chiral Brønsted acid catalyst; b) one of the oxygens is dissociated from the *tris*-VANOL zirconium to give a combined Brønsted/Lewis acid activation of an iminol, with the alcohol coordination with zirconium and the imine nitrogen H-bonded with the free VANOL hydroxyl group; c) one of the VANOL ligands is totally dissociated to afford a charge-neutral *bis*-VANOL zirconate which functions as a Lewis acid catalyst with bidentate coordination of the iminol nitrogen and oxygen.

Scheme 5.23 Proposed possible iminol activation by VANOL zirconium complex



5.4 Asymmetric Catalytic Rearrangement with Racemic α-Iminols

5.4.1 Non-chiral Iminols vs Racemic Iminols

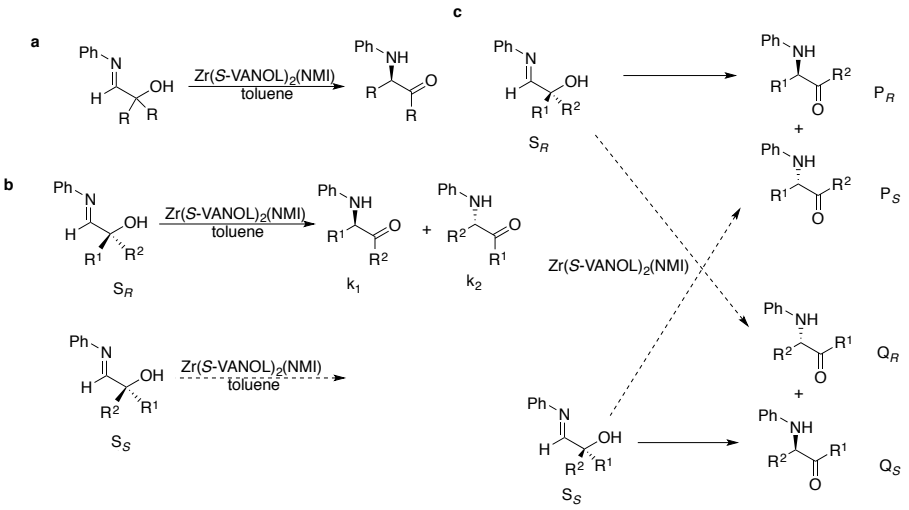
In Xin Zhang's work, all substrates are non-chiral and contain two identical alkyl or aryl groups that are under migration. The amino ketones were obtained as the single product of the reaction with an excellent enantiomeric induction (Scheme 5.24a, Table 5.1). We became interested in investigating the asymmetric catalytic rearrangement of α-iminols with two different groups that have the potential to migrate during the rearrangement process. The chemistry will be much more complicated than that with non-chiral α-iminols since it is difficult to predict that which group will migrate with the higher priority. For an optically pure substrate, the outcome will depend on the difference of migration rates between two groups R^1 and R^2. If R^1 migrates much faster than R^2 ($k_1 >> k_2$), the rearrangement will afford a single product by R^1 migration only. But if the rate selectivity is not great enough for R^1 and R^2, a mixture of amino ketone isomers would be expected as the products of rearrangement.

However, the reaction pathways of the two enantiomers could be different and lead to different asymmetric catalytic inductions in the rearrangement of a racemic substrate. Kinetic resolution will occur when one of the α-iminol enantiomers S_R reacts much faster than the other enantiomer S_S, while the selectivity of two amino ketone isomers would

still depend on the migration rate differential of the two groups. Thus, the reaction could afford three produtcs; two amino ketone isomers and unreacted substrate enantiomer S_S with a 50% conversion of the starting material (Scheme 5.24b).

On the other hand, a PKR effect will be expected when there is no great gap in the reaction rates between the two of the substrate enantiomers. For example, R^1 migration affording amino ketone P is favored with the substrate enantiomer S_R but disfavored with S_S. And R^2 migration affording Q is favored with S_S but disfavored with S_R. The better selectivity of R^1 and R^2 migration with both enantiomers will give higher enantioselectivity of amino ketones products. As the result, the reaction can give a 100% conversion of a racemic α-iminol to afford a pair of optically pure amino ketone regioisomers (Scheme 5.24c).

Scheme 5.24 The asymmetric catalytic rearrangement of α-iminols: a. Rearrangement of a non-chiral α-substrate; b. Kinetic resolution pathway in the rearrangement of a racemic α-iminol; c. Parallel kinetic resolution in the rearrangement of a racemic α-iminol

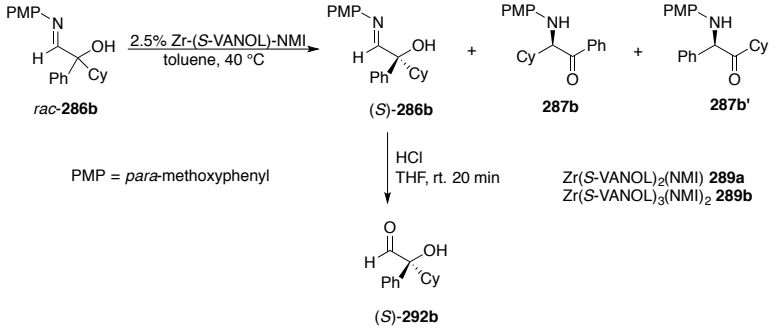


5.4.2 Initial Studies on the Rearrangement of Racemic α-Iminols

The initial studies investigated the kinetic resolution of the α-iminol *rac*-**286b** with a phenyl and a cyclohexyl substituent, which was treated with zirconium catalyst **289** prepared by one equivalent of zirconium isopropoxide, two equivalents of (*S*)-VANOL ligand **68a** and one equivalent of *N*-methylimidazole (NMI) with 2.5% catalyst loading (Table 5.2, entry 1). The reaction was quenched at the 50% conversion of the starting material after 12 h, which afforded a mixture of amino ketone regioisomers **287b** from cyclohexyl migration and **287b'** from phenyl migration. Amino ketones **287b** and **287b'** could not be separated by column chromatography due to similar polarities, and the yield of each regioisomer was determined by the NMR studies of the isolated mixture. The ratio of regioisomers **287b** and **287b'** was determined as 3:1 with amino ketone **287b** as the major product which indicates that cyclohexyl migration is faster than phenyl migration. The enantiomeric purity of the major amino ketone **287b** was significantly high with greater than 99% *ee*. A change of Zr/ligand/NMI ratio to 1:3:2 in the catalyst preparation, which mirrors the same composition of Zr-catalyst in the crystal state, gave similar 3:1 regioselectivity of amino ketone **287b** and **287b'** (Table 5.2, entry 2). When the catalyst loading was increased from 2.5% to 5%, the reaction was much faster and reached a 49% conversion of substrate **286b** in 7 h (Table 5.2, entry 3), and in addition the regioselectivity of amino ketone isomers **287b** and **287b'** was improved to 5:1. The asymmetric inductions of both products was extremely high with 99% *ee* for amino ketone **287b** and 95% *ee* for amino ketone **287b'**. Meanwhile, the enantioenriched α-iminol **286b** was recovered and hydrolyzed to the corresponding α-hydroxy aldehyde **292b** with for the enantiomeric purity determination, since the α-iminol **286b**

decomposes during column chromatographic isolation. The enantiomeric purity of α-hydroxy aldehyde **292b** is relatively poor which indicates a low efficiency of kinetic resolution.

Table 5.2 Initial studies on kinetic resolution of α-iminol *rac*-286b [a]

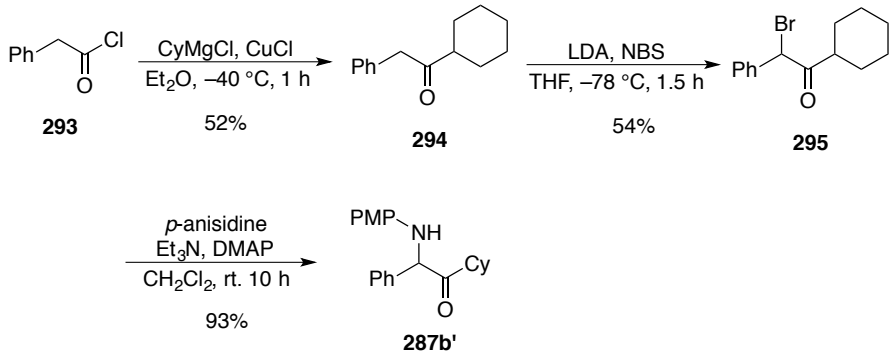


entry	cat.	time/h	conv.% [b]	(*S*)-292b		287b		287b'		287b:287b' [e]
				yield% [c]	*ee*% [d]	yield% [b]	*ee*% [d]	yield% [b]	*ee*% [d]	
1	**289a**	12	50	42	64	37	>99	12	nd	3.1:1
2	**289b**	12	48	46	58	35	>99	11	nd	3.2:1
3	**289a** [f]	7	49	37	60	39	>99	7.5	95	5.2:1

[a] Unless otherwise specified, the reaction was run by the racemic α-iminol **286b** of 0.4 *M* concetraction in toluene with 2.5% Zr-catalyst loading. The catalyst was prepared by Zr(O*i*-Pr)$_4$·*i*-PrOH, (*S*)-VANOL and NMI of 0.05 *M* in toluene resulting a fine suspension. [b] Determined by the ^{1}H-NMR spectrum of the crude reaction mixture with an internal standard. [c] isolated yield. [d] Determined by HPLC. [e] Determined by the ^{1}H-NMR spectrum of the crude reaction mixture. [f] 5% Zr-catalyst loading.

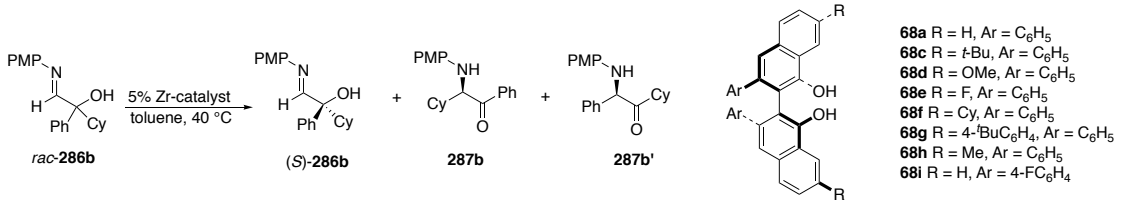
Since there was only small amount of amino ketone **287b'** produced as the minor product in the rearrangement of α-iminol *rac*-**286b** and since the regioisomers could not be separated, it was necessary to obtain the pure compound **287b'** by a different method to confirm its structure. The synthesis of compound **287b'** started from phenylacetyl chloride **293**, which could be converted to ketone **294** upon treatment with cyclohexylmagnesium chloride catalyzed by cuprous chloride. Benzylic bromination of ketone **294** afforded α-bromo ketone **295** which was followed by the coupling with *p*-anisidine in the presence of base to give the desired compound **287b'** (Scheme 5.25).

Scheme 5.25 Synthesis of amino ketone 287b' as the minor product in α-iminol rearrangement



To improve the *s* value of the kinetic resolution, a number of VANOL derivative ligands **68** were screened to investigate their effect on the rate differential of two enantiomers of the racemic substrate **286b** (Table 5.3). The results reveal that the ligands can significantly effect the *ee* of both amino ketones **287b** and **287b'**, the ratio of the amino ketone regioisomers and the *ee* of recovered α-iminol **286b** at around 50% conversion. As these results completely depend on the progress of the reaction, all the experiments were quenched within a narrow range of substrate conversions around 50% (44-53%). The reaction times for the 50% conversion vary a lot among the ligands, but it does not seems directly related to the degree of kinetic resolution. The *ee* of recovered α-iminol **286b** directly reflects the efficiency and is positively correlated to the ratio of amino ketone regioisomers. For example, VANOL ligand **68a** gives 60% *ee* of α-iminol **286b** with the ratio **287b**:**287b'** as high as 5.1:1 (Table 5.3, entry 1). However, 7,7'-dimethoxy VANOL **68d** gives only 33% *ee* of α-iminol **286b** and a 2.6:1 regioselectivity (Table 5.3, entry 3). Finally, the rearrangement gives excellent enantiomeric purity for both amino ketone isomers with all either ligands (>87% *ee*).

Table 5.3 Ligand screening for kinetic resolution of α-iminol rearrangement [a]



entry	ligand	time/h	(*S*)-286b		287b		287b'		287b:287b' [d]
			yield% [b]	*ee*% [c]	yield% [b]	*ee*% [c]	yield% [b]	*ee*% [c]	
1	**68a**	7	51	60	39	>99	7.5	95	5.1:1
2	**68c**	24	47	61	39	>99	10	97	3.9:1
3	**68d**	8	51	33	36	87	14	94	2.6:1
4	**68e**	14	52	60	40	90	9.4	95	4.3:1
5	**68f**	5.5	44	41	30	>99	14	99	2.1:1
6	**68g**	1.5	45	54	40	99	16	91	2.5:1
7	**68h**	23	48	41	40	93	17	>99	2.4:1
8	**68i**	38	53	58	41	96	8.1	>99	5.1:1

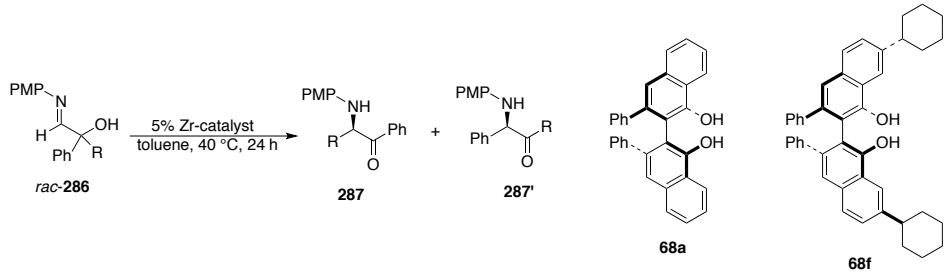
[a] Unless otherwise specified, the reaction was run by the racemic α-iminol **286b** of 0.4 *M* concetraction in toluene with 5% Zr-catalyst loading at 40 °C. The catalyst was prepared by Zr(O*i*-Pr)$_4$·*i*-PrOH (1 equiv), (*S*)-VANOL derivatives **68** (2 equiv) and NMI (1 equiv) of 0.05 *M* concentraction in toluene. [b] Determined by the ^{1}H-NMR spectrum of the crude reaction mixture with an internal standard. [c] Determined by HPLC. [d] Determined by the ^{1}H-NMR spectrum of the crude reaction mixture.

That the best *ee* for recovered α-iminol **286b** was only 60% with the VANOL ligand **68a** indicates that there is poor efficiency of kinetic resolution (Table 5.3, entry 1). However, in contrast it is noticed that both amino ketone regioisomers **287b** and **287b'** are formed with a significantly high asymmetric induction of 99% *ee* with with 7,7'-dicyclohexyl VANOL ligand **62f** (Table 5.3, entry 5). Further studies focused on the catalytic rearrangement with a 100% conversion of the racemic α-iminols to investigate the PKR effect since the two product amino ketone regioisomers are generated and indicate the possibility of parallel reactions involved in the process.

The Zr-catalyzed rearrangement of four racemic α-iminols with a phenyl and four different alkyl substituents has been examined with catalysts generated from VANOL **68a** and Cy_2VANOL **68f** ligands (Table 5.4). It was found that the racemic α-iminols with an ethyl, butyl and cyclohexyl groups afforded close to a 1:1 mixture of highly enantiometic pure amino ketone regioisomers with a 100% conversion of substrates

(Table 5.4, entry 3-7). However, in the rearrangement of the α-iminol with a methyl group, the phenyl migration product was the major isomer with around 1.5:1 regioselectivity, which is opposite to the regioselectivity seen in the experiments in Table 5.3 and indicates an unusual PKR process involving in the rearrangement of the methyl-substituted α-iminol. The *er* of the two products are dramtically different with the minor methyl migration product formed with significantly higher *er* up to 99:1, but the major phenyl migration product was obtained with much lower enantiomeric purity (Table 5.4, entry 1, 2). The reaction with the Cy_2VANOL ligand **68f** gave excellent enantiomeric purity for both amino ketones from the cyclohexyl-substituted α-iminol (Table 5.4, entry 7), but the same ligand was not as good as VANOL **68a** for all the other substrates.

Table 5.4 Zr-catalyzed rearragement of α-iminols [a]



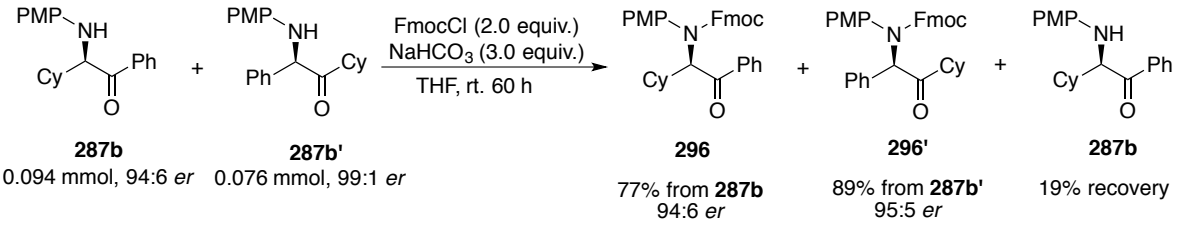
entry	R	ligand	R migration 287		Ph migration 287'	
			yield% [b]	*er* [c]	yield% [b]	*er* [c]
1	Me	**68a**	33	98.5:1.5	48	75.5:24.5
2	Me	**68f**	30	99:1	51	65.5:34.5
3	Et	**68a**	48	96.5:3.5	47	97:3
4	Et	**68f**	33	96:4	35	90:10
5	Bu	**68a**	46	96.5:3.5	46	98:2
6	Cy	**68a**	53 [d]	94:6	44 [d]	99:1
7	Cy	**68f**	42 [d]	99.5:0.5	42 [d]	99.5:0.5

[a] Unless otherwise specified, the reaction was run by the racemic α-iminols **286** of 0.4 *M* concetraction in toluene with 5% Zr-catalyst loading at 40 °C for 24 h. The catalyst was prepared by Zr(O*i*-Pr)$_4$·*i*-PrOH (1 equiv), (*S*)-VANOL derivatives **68a** or **68f** (2 equiv) and NMI (1 equiv) of 0.05 *M* concentraction in toluene. [b] Isolated yield. [c] Determined by HPLC. [d] Determined by the ^{1}H-NMR spectrum of crude reaction mixture with an internal standard.

The two amino ketone regioisomers are separable for the rearrangement of all of the α-iminol substrates except the cyclohexyl-substituted α-iminol *rac*-**286b**. A bulky Fmoc group was introduced in the amino ketones **287b** and **287b'** to better separate the

regioisomers (Scheme 5.26). The phenyl migration amino ketone **287b'** gave a 100% conversion to Fmoc-substituted product **296'** while the reaction of cyclohexyl migration amino ketone **287b'** was sluggish with an 81% conversion to the Fmoc-substituted product **296**. Meanwhile, slight drop in the enantiometic purity was observed for the phenyl migration amino ketone **296'** (99:1 vs 95:5 *er*) due to partial racemization of the benzylic position in the presence of base. This is supported by the evidence that the reaction was heated up to 60 °C resulting in the decrease of enantiometic purity of amino ketone **296'** without any improvement in the conversion of amino ketone **287b**.

Scheme 5.26 Synthesis and Separation of Fmoc-amino ketone regioisomers 296 and 296'



287b
0.094 mmol, 94:6 *er*

287b'
0.076 mmol, 99:1 *er*

296
77% from **287b**
94:6 *er*

296'
89% from **287b'**
95:5 *er*

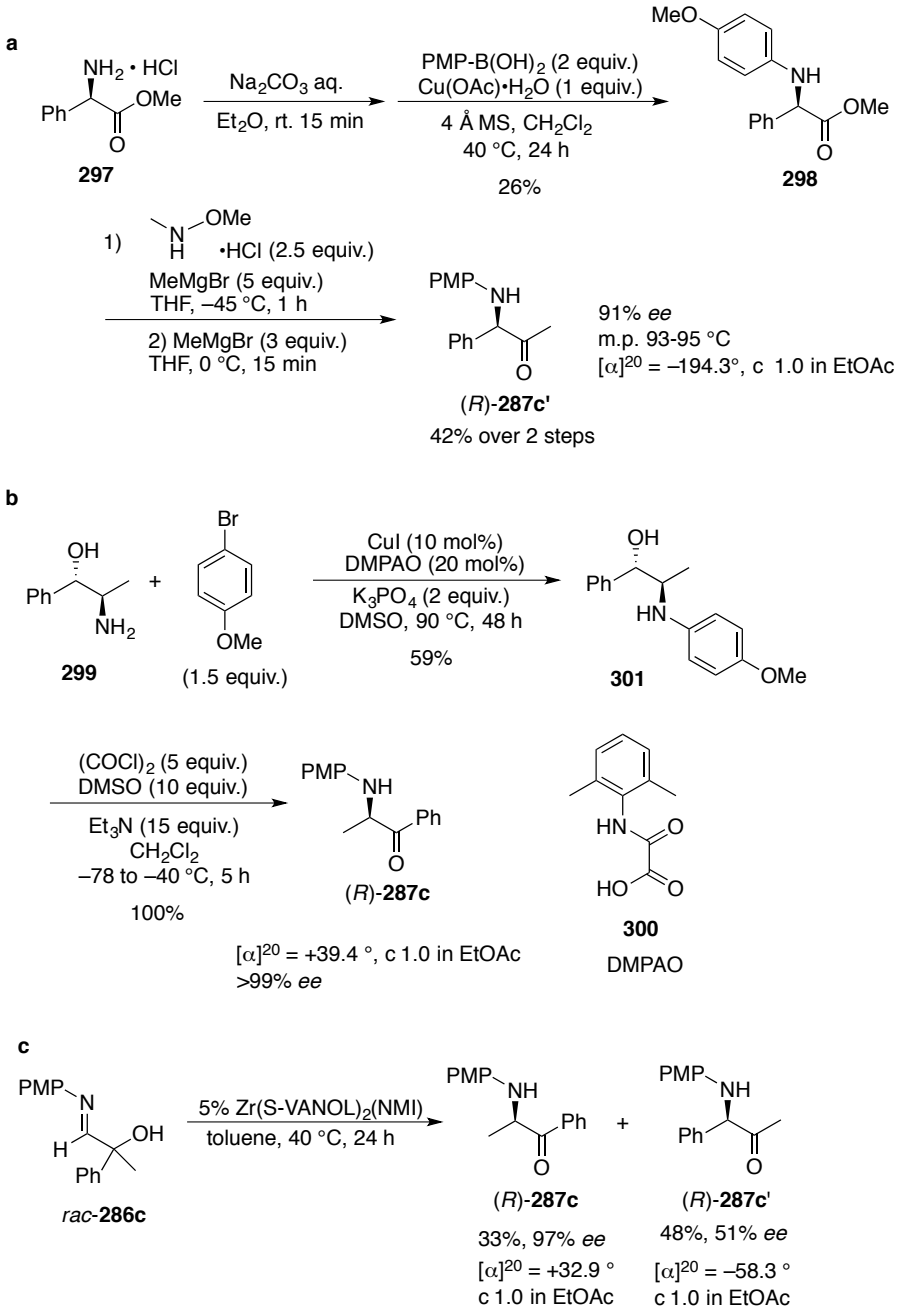
287b
19% recovery

5.4.3 Mechanistic Studies on the PKR in the α-Iminol Rearrangement

To help to understand the mechanism of PKR in the rearrangement of racemic α-iminols, it's necessary to make clear the stereochemistry involved in the migration for either the phenyl or alkyl group with the asymmetric induction of the chiral zirconium catalyst. In order to confirm the absolute stereochemistry of the amino ketone products, both amino ketone regioisomers **287c** and **287c'** were synthesized with the (*R*)-configuration. The synthesis of the phenyl migration amino ketone (*R*)-**287c'** starts from (*R*)-phenylglycine methyl ester **297** which undergoes C-N bond coupling to give a PMP-amino substituent in compound **298**. The amino ketone (*R*)-**287c'** was obtained by the Weinreb ketone synthesis by treatment of the Weireb's amide derived from compound **298** with methyl magnesium bromide and gave a product with a negative optical rotation, which allows the

assignment of the product **287c'** from the (*S*)-VANOL catalyst as the (*R*)-enantiomer (Scheme 5.27a). On the other hand, in the synthesis of the methyl migration amino ketone (*R*)-**287c**, (1*R*,2*S*)-norephedrine **299** was the starting material and coupling with 4-bromoanisile to afford compound **301**, which was in turn converted to the target (*R*)-**287c** by the Swern oxidation and had a positive rotation (Scheme 5.27b). So the absolute stereochemistry of both amino ketone regioisomers **287c** and **287c'** was found to be (*R*)-configuration in the rearrangement of racemic methyl-substituted α-iminol **286c** with the catalysis of (*S*)-VANOL zirconium complex (Scheme 5.27c).

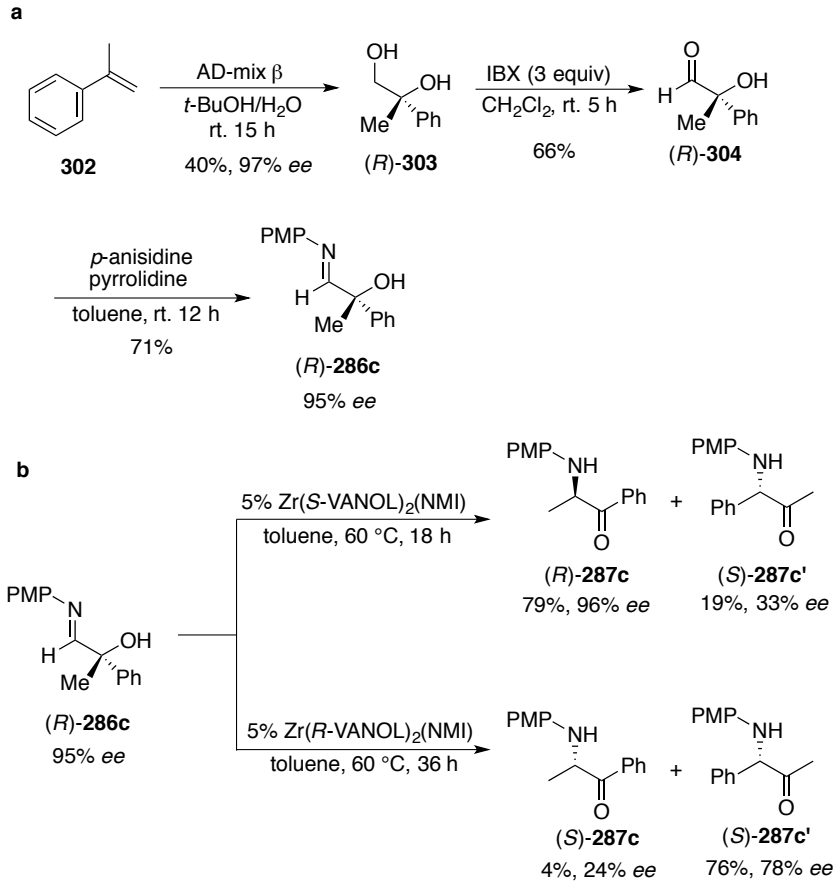
Scheme 5.27 Synthesis of amino ketones 287c and 287c' with known stereochemical configurations



To further understand the PKR in the Zr-catalyzed rearrangement of racemic α-iminols, a set of parallel experiments were done to study the mechanism and stereochemistry involved in the reaction of the enantiomerically pure α-iminol (*R*)-**286c** with phenyl and methyl substituents, which was prepared in 95% *ee* from α-methylstyrene **302** over three

steps by the Sharpless dihydroxylation, IBX oxidation and imine synthesis (Scheme 5.28a). Dramatically different results were observed in the rearrangement of α-iminol (*R*)-**286c** with the (*S*)- or (*R*)-VANOL zirconium catalysts. With (*S*)-VANOL ligand, the rearrangement of (*R*)-**286c** afforded the methyl migration amino ketone (*R*)-**287c** as the major product in 79% yield and 96% *ee* and the phenyl migration amino ketone (*S*)-**287c'** as the minor product in 19% yield and only 33% *ee*. However, the reaction with *rac*-**286c** gave an opposite 1.5:1 selectivity of **287c'** and **287c** with both (*R*)-configuration under the same conditions (Table 5.4, entry 1). With the (*R*)-VANOL ligand, the phenyl migration amino ketone (*S*)-**287c'** was almost the only product in 76% yield and 78% *ee* from the rearrangement of (*R*)-**286c**, and only a small amount of **287c** was detected, with surprisingly the same (*S*)-configuration in 24% *ee* (Scheme 5.28b). The relatively lower enantiomeric purity of amino ketone **287c'** compared to that for amino ketone **287c** is probably due to the partial racemization of benzylic position.

Scheme 5.28 Catalytic rearrangement of α-iminol (*R*)-286c

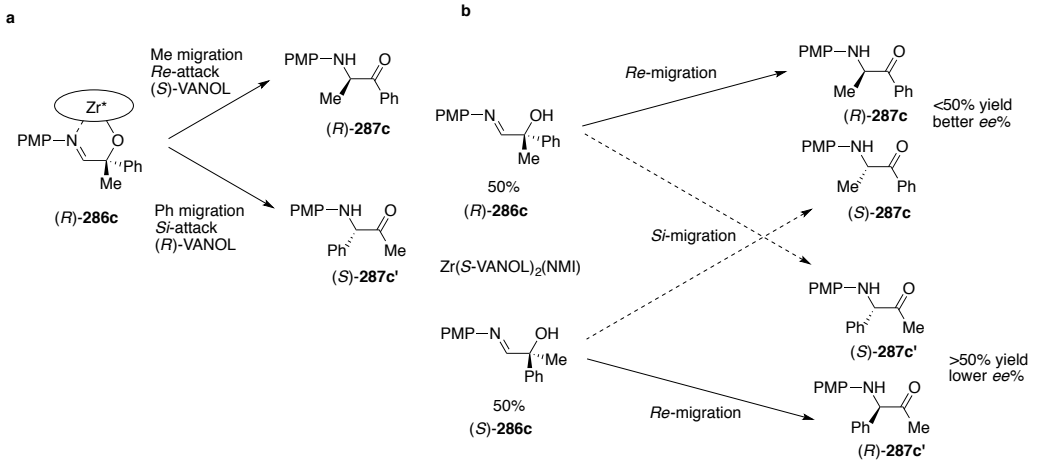


As the rationalization of the results in the rearrangement of (*R*)-**286c**, it is proposed that the zirconium catalyst provides the chiral environment which is source of migratory between the two different substituents. It is believed that zirconium can be chelated by a nitrogen and an oxygen in an α-iminol that inhibits the rotation of C-C bond and locks the conformer in the complex consisted of substrate (*R*)-**286c** and Zr-catalyst. Theoretically, in the rearrangement of substrate (*R*)-**286c**, the *Re*-face migration of methyl group will be favored with the induction of (*S*)-VANOL to afford amino ketone (*R*)-**287c**, while on the other hand, the *Si*-face migration of phenyl group is favored with the induction of (*R*)-VANOL to the product (*S*)-**287c'** (Scheme 5.29a). However, the results shown in Scheme 5.26 indicates that the *Si*-face migration of the phenyl group could also occurs to a small

extent in the reaction with (*S*)-VANOL since a 19% yield of (*S*)-**287c'** was generated. The *Re*-face migration of methyl group seems totally inhibited by (*R*)-VANOL since only a 4% yield of (*S*)-**287c** was generated from the small amount of (*S*)-enantiomer of the substrate **286c**. An experimental error could occur given that the enantiometic purity of the substrate (*R*)-**286c** was 95% *ee*, a 2.5% yield of (*S*)-**287c** would be expected.

In addition, with the racemic substrate **286c**, the (*R*)-enantiomer will undergo methyl migration to afford amino ketone (*R*)-**287c** while the (*S*)-enantiomer will give amino ketone (*R*)-**287c'** by phenyl migration, since *Re*-face migration is favored by the induction of (*S*)-VANOL (Scheme 5.29b). Considering that there is also a small amount of (*R*)-**286c** converting to amino ketone (*S*)-**287c'** by phenyl migration, it explains that (*R*)-**286c'** was the major product but with poor enantiomeric purity (Scheme 5.27c). But with a bulky alkyl substituent in a racemic α-iminol, phenyl migration will be greatly inhibited by the miss-matched ligand. Therefore, a perfect PKR with the asymmetric induction of the catalyst leads to a 1:1 mixture of amino regioisomers in a theoretical yield of 50% with significantly decent enantiomeric purity (Table 5.4, entry 3, 5, 6, 7).

Scheme 5.29 Mechanistic rationalization of PKR in the α-iminol rearrangement



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Chapter 6 Experimental Information

6.1 General Information

All experiments were performed under an argon atmosphere. Flasks were flame dried and cooled under argon before use. All solvents used were dried appropriately. Toluene, dichloromethane and acetonitrile were dried from calcium hydride under nitrogen. THF was dried from sodium with benzophenone as the indicator under nitrogen. The ligands VANOL **68b**, VAPOL **69c** and 7,7'-disubstituted VANOL derivatives **68d-i** were prepared according to the published procedure.[1] Phenol was sublimed and stored under argon in a dry desiccator; each batch was used for a maximum of 20 days. The commercially available aldehydes were purchased from Aldrich or other commercial sources and purified appropriately before use. Solid aldehydes were sublimed and liquid aldehydes were distilled. The aldehydes were stored under argon; each batch was used for a maximum of 5 days. Phenol, 4-methoxyphenol and benzoic acid were sublimed before use. Benzhydryl amine was used as purchased from Aldrich and distilled before use. The tetramethyldianisylmethyl (MEDAM) amine and the tetra-*tert*-butyldianisylmethyl (BUDAM) amine were prepared according to the procedures previously reported by our group.[2] The *n*-butyl diazoacetamide and phenyl diazoacetamide were also prepared according to the previously reported procedures.[3] All other reagents were used as freshly purchased either from Aldrich or other commercial sources, or purified appropriately.

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}H-NMR: 7.26 ppm, ^{13}C-NMR: 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) purchased from SiliCycle Inc.

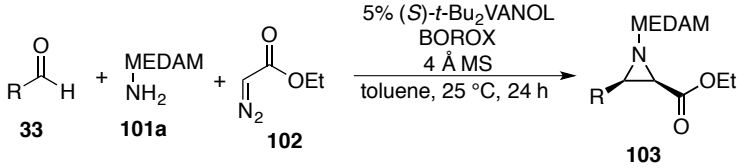
HPLC analyses were peformed using a Varian Prostar 210 Solvent Delivery Module with a Prostar 330 PDA Detector and a Prostar Workstation. Chiral HPLC data for the aziridines were obtained using a CHIRALCEL OD-H column, CHIRALPAK AD column and PIRKLE COVALENT (R, R) WHELK-O 1 column.

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.

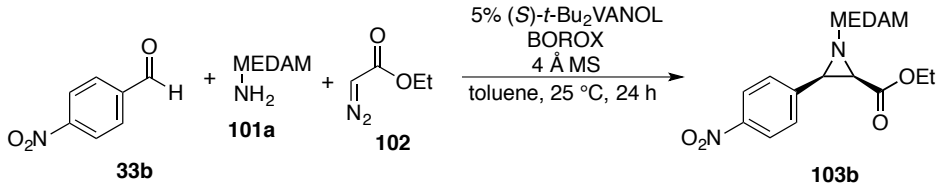
6.2 Experimental Information of Chapter 2

6.2.1 Multi-Component *cis*-Aziridination of Non-Chiral Aldehydes 33a-i

General Procure for Multi-Component *cis*-Aziridination



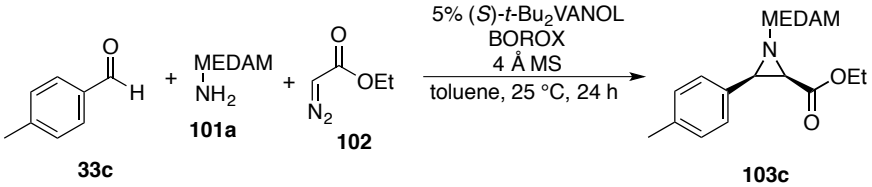
To a flame-dried 10 mL Schlenk flask filled with nitrogen was added (*S*)-*t*-Bu_2VANOL **68c** (13.8 mg, 0.0250 mmol), triphenylborate (21.8 mg, 0.0750 mmol) and MEDAM amine **101a** (150 mg, 0.500 mmol). The solid was dissolved in toluene (1 mL, freshly distilled) and the resulting solution was heated to 80 °C for 0.5 h with the flask filled with nitrogen and sealed with a Teflon valve. The resulting BOROX catalyst solution was allowed to cool down to room temperature before flame-dried 4 Å molecular sieves (~ 150 mg) were added, which was followed by the addition of aldehyde **33** (0.525 mmol) and ethyl diazoacetate **102** (63 μL, 0.60 mmol). Tiny bubbles of nitrogen were observed which indicated the initiation of aziridination. The reaction mixture was stirred at room temperature for 24 h. The reaction was quenched by filtering the mixture through a silica gel pad to a 250 mL round-bottom flask, with EtOAc (100 mL) as the eluent. The resulting light yellow colored solution was concentrated and dried under vacuum to give an oily crude residue. The *cis*/*trans* ratio was determined by comparing the H^1-NMR of the crude reaction mixture. The coupling constants of *cis*-aziridines (J = 6-7 Hz) and *trans*-aziridines (J = 2-3 Hz) were used to differentiate the two isomers. Purification of the crude mixture by silica gel chromatography (30 mm × 300 mm column, 9:1 hexanes/EtOAc as the eluent, gravity column) afforded pure *cis*-aziridine **103**. The enantiomeric purity was determined by HPLC analysis.



*(2R,3R)-ethyl-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-(4-nitrophenyl) aziridine-2-carboxylate **103b***: 4-Nitrobenzaldehyde **33** (83.1 mg, 0.550 mmol) was reacted

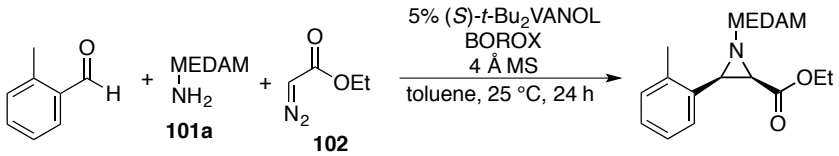
according to the general procedure **6.2.1** with (*S*)-*t*-Bu_2VANOL as the ligand. The aldehyde **33b** was allowed to dissolve in toluene (1 mL), which required gently warming of the solution due to its low solubility at the room temperature. The resulting solution of the aldehyde was introduced into the BOROX catalyst *via* a 1 mL syringe. Additional toluene (0.5 mL) was used to rinse the flask and was transferred to the catalyst solution. The pure *cis*-aziridine **103b** was separated by silica gel chromatography (9:1 hexanes/EtOAc, gravity column) to afford an off-white semi-solid in 100% yield (264 mg, 0.509 mmol); *cis*/*trans* >132:1. The enantiomeric purity was determined to be 99.3% *ee* by HPLC (CHIRALCEL OD-H column, 99:1 hexane/isopropanol at 226 nm, flow rate 0.7 mL/min); retention times, 19.2 min (major enantiomer, **103b**) and 26.5 min (minor enantiomer, *ent*-**103b**). The aziridination of aldehyde **33b** in the presence of (*S*)-VANOL catalyst afforded *cis*-aziridine **103b** in >99% *ee* and 77% yield (200 mg, 0.385 mmol).

Spectral data for **103b**: ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 1.04 (t, 3H, *J* = 7.0 Hz), 2.20 (s, 6H), 2.27 (s, 6H), 2.70 (d, 1H, *J* = 7.0 Hz), 3.17 (d, 1H, *J* = 7.0 Hz), 3.64 (s, 3H), 3.70 (s, 3H), 3.72 (s, 1H), 3.93-3.97 (m, 33m), 7.08 (s, 33m), 7.18 (s, 33m), 7.59 (d, 33m, *J* = 8.5 Hz), 8.12 (d, 33m, *J* = 9.0 Hz); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 14.08, 16.21, 16.26, 46.79, 47.26, 59.56, 59.61, 60.89, 76.86, 123.00, 127.22, 127.56, 128.81, 130.84, 130.87, 137.26, 137.47, 142.78, 147.22, 156.07, 156.22, 167.22. These spectral data match those previously reported for this compound.[4]



*(2R,3R)-ethyl-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-(4-tolyl)aziridine-2-carboxylate **103c***: 4-Tolualdehyde **33c** (62 μL, 0.52 mmol) was reacted according to the general procedure with (*S*)-*t*-Bu_2VANOL as the ligand. The pure *cis*-aziridine **103c** was separated by silica gel chromatography (9:1 hexanes/EtOAc, gravity column) to afford an off-white semi-solid in 91% yield (222 mg, 0.455 mmol); *cis*/*trans* >132:1. The enantiomeric purity was determined to be 99.6% *ee* by HPLC (CHIRALCEL OD-H column, 99:1 hexane/isopropanol at 226 nm, flow rate 0.7 mL/min); retention times, 7.9 min (major enantiomer, **103c**) and 11.5 min (minor enantiomer, *ent*-**103c**). The aziridination of aldehyde **33c** in the presence of (*S*)-VANOL catalyst afforded *cis*-aziridine **103c** in 98% *ee* and 87% yield (212 mg, 0.435 mmol).

Spectral data for **103c**: ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 1.03 (t, 3H, *J* = 7.0 Hz), 2.20 (s, 6H), 2.26 (s, 6H), 2.28 (s, 3H), 2.54 (d, 1H, *J* = 6.5 Hz), 3.10 (d, 1H, *J* = 6.5 Hz), 3.64 (s, 3H), 3.66 (s, 1H), 3.70 (s, 3H), 3.93-3.98 (m, 33m), 7.05 (d, 33m, *J* = 8.0 Hz), 7.11 (s, 33m), 7.20 (s, 33m), 7.26 (d, 33m, *J* = 8.5 Hz); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 14.05, 16.17, 16.22, 21.12, 46.16, 48.19, 59.52, 59.58, 60.48, 77.07, 127.37, 127.68, 127.77, 128.41, 130.55, 130.58, 132.19, 136.78, 137.84, 137.98, 155.84, 156.00, 168.14. These spectral data match those previously reported for this compound.[4]

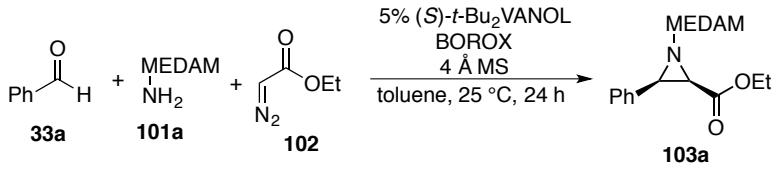


33d 103d

*(2R,3R)-ethyl-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-(2-tolyl)aziridine-2-carboxylate **103d***: 2-Tolualdehyde **33d** (61 μL, 0.52 mmol) was reacted according to the general procedure with (*S*)-*t*-Bu_2VANOL as the ligand. The pure *cis*-aziridine **103d** was

separated by silica gel chromatography (9:1 hexanes/EtOAc, gravity column) to afford an off-white semi-solid in 97% yield (236 mg, 0.485 mmol); *cis*/*trans* >260:1. The enantiomeric purity was determined to be 99.7% *ee* by HPLC (CHIRALCEL OD-H column, 99:1 hexane/isopropanol at 226 nm, flow rate 0.7 mL/min); retention times, 9.3 min (major enantiomer, **103d**) and 12.2 min (minor enantiomer, *ent*-**103d**). The aziridination of aldehyde **33d** in the presence of (*S*)-VANOL catalyst afforded *cis*-aziridine **103d** in 98% *ee* and 73% yield (178 mg, 0.365 mmol).

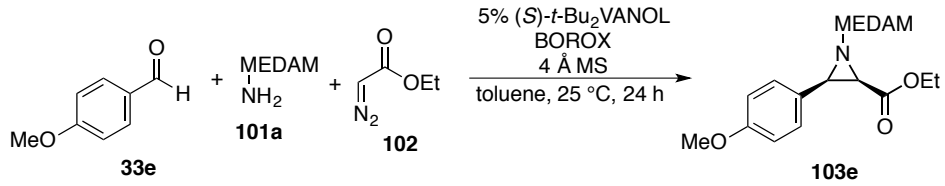
Spectral data for **103d**: ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 0.91 (t, 3H, *J* = 7.0 Hz), 2.22 (s, 6H), 2.26 (s, 6H), 2.28 (s, 3H), 2.63 (d, 1H, *J* = 7.0 Hz), 3.10 (d, 1H, *J* = 6.5 Hz), 3.64 (s, 3H), 3.68 (s, 1H), 3.70 (s, 3H), 3.90 (q, 33m, *J* = 7.0 Hz), 7.02 (dd, 1H, *J* = 7.0, 2.0 Hz), 7.09-7.12 (m, 33m), 7.15 (s, 33m), 7.20 (s, 33m), 7.54 (dd, 1H, *J* = 7.0, 2.0 Hz); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 13.90, 16.17, 16.24, 18.78, 45.51, 47.14, 59.54, 59.60, 60.39, 77.30, 125.28, 127.05, 127.28, 127.92, 128.59, 129.08, 130.62, 130.63, 133.42, 136.01, 137.83, 137.99, 155.85, 156.12, 168.18. These spectral data match those previously reported for this compound.[4]



*(2R,3R)-ethyl-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-phenylaziridine-2-carboxylate **103a***: 2-Benzaldehyde **33a** (53 µL, 0.52 mmol) was reacted according to the general procedure with (*S*)-*t*-Bu_2VANOL as the ligand. The pure *cis*-aziridine **103a** was separated by silica gel chromatography (9:1 hexanes/EtOAc, gravity column) to afford an off-white semi-solid in 100% yield (247 mg, 0.52 mmol); *cis*/*trans* >62:1. The enantiomeric purity was determined to be 99.7% *ee* by HPLC (CHIRALCEL OD-H

column, 99:1 hexane/isopropanol at 226 nm, flow rate 0.7 mL/min); retention times, 9.0 min (major enantiomer, **103a**) and 11.4 min (minor enantiomer, *ent*-**103a**). The aziridination of aldehyde **33a** in the presence of (*S*)-VANOL catalyst afforded *cis*-aziridine **103a** in 98% *ee* and 87% yield (206 mg, 0.435 mmol).

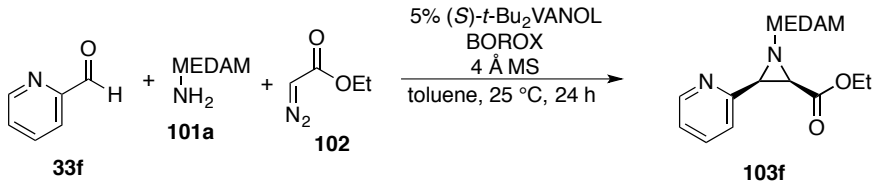
Spectral data for **103a**: ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 1.00 (t, 3H, *J* = 7.0 Hz), 2.20 (s, 6H), 2.26 (s, 6H), 2.58 (d, 1H, *J* = 7.0 Hz), 3.13 (d, 1H, *J* = 7.0 Hz), 3.64 (s, 3H), 3.68 (s, 1H), 3.70 (s, 3H), 3.90-3.97 (m, 33m), 7.11 (s, 33m), 7.20 (s, 33m), 7.23-7.26 (m, 3H), 7.38 (d, 33m, *J* = 7.0 Hz); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 14.00, 16.16, 16.22, 46.25, 48.20, 59.52, 59.58, 60.49, 77.03, 127.21, 127.40, 127.70, 127.78, 127.84, 130.58, 130.60, 135.30, 137.79, 137.95, 155.92, 156.07, 168.03. These spectral data match those previously reported for this compound.[4]



*(2R,3R)-ethyl-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-(4-anisyl)aziridine-2-carboxylate **103e***: 4-Anisaldehyde **33e** (64 μL, 0.52 mmol) was reacted according to the general procedure with (*S*)-*t*-Bu_2VANOL as the ligand. The pure *cis*-aziridine **103e** was separated by silica gel chromatography (9:1 hexanes/EtOAc, gravity column) to afford an off-white semi-solid in 93% yield (234 mg, 0.464 mmol); *cis*/*trans* >150:1. The enantiomeric purity was determined to be 99.9% *ee* by HPLC (CHIRALCEL OD-H column, 99:1 hexane/isopropanol at 226 nm, flow rate 0.7 mL/min); retention times, 13.4 min (major enantiomer, **103e**) and 20.6 min (minor enantiomer, *ent*-**103e**). The

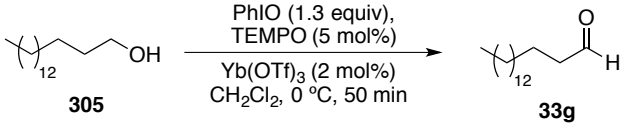
aziridination of aldehyde **33e** in the presence of (*S*)-VANOL catalyst afforded *cis*-aziridine **103e** in 97% *ee* and 82% yield (206 mg, 0.410 mmol).

Spectral data for **103e**: ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 1.04 (t, 3H, *J* = 7.0 Hz), 2.20 (s, 6H), 2.26 (s, 6H), 2.52 (d, 1H, *J* = 7.0 Hz), 3.07 (d, 1H, *J* = 7.0 Hz), 3.64 (s, 3H), 3.66 (s, 1H), 3.70 (s, 3H), 3.76 (s, 3H), 3.92-3.99 (m, 33m), 6.78 (d, 33m, *J* = 8.0 Hz), 7.10 (s, 33m), 7.19 (s, 33m), 7.30 (d, 33m, *J* = 8.5 Hz); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 14.10, 16.18, 16.23, 46.20, 47.90, 55.20, 59.54, 59.59, 60.47, 77.05, 113.17, 127.42, 127.78, 128.94, 130.56, 130.58, 137.83, 138.01, 155.91, 156.06, 158.84, 168.16 (one sp^2 carbon not located). These spectral data match those previously reported for this compound.[4]



*(2R,3S)-ethyl-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-(2-pyridyl)aziridine-2-carboxylate **8f***: 2-Pyridylcarboxaldehyde **33f** (50 μL, 0.52 mmol) was reacted according to the general procedure with (*S*)-*t*-Bu_2VANOL as the ligand. The pure *cis*-aziridine **8f** was separated by silica gel chromatography (9:1 hexanes/EtOAc, gravity column) to afford an off-white semi-solid in 97% yield (230 mg, 0.48 mmol); *cis*/*trans* >49:1. The enantiomeric purity was determined to be 100% *ee* by HPLC (CHIRALCEL OD-H column, 99:1 hexane/isopropanol at 226 nm, flow rate 0.7 mL/min); retention times, 20.4 min (major enantiomer, **8f**) and 33.6 min (minor enantiomer, *ent*-**8f**). The aziridination of aldehyde **33f** in the presence of (*S*)-VANOL catalyst afforded *cis*-aziridine **8f** in 96% *ee* and 95% yield (225 mg, 0.474 mmol).

Spectral data for **8f**: ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 1.03 (t, 3H, *J* = 7.0 Hz), 2.20 (s, 6H), 2.26 (s, 6H), 2.68 (d, 1H, *J* = 6.5 Hz), 3.29 (d, 1H, *J* = 7.0 Hz), 3.64 (s, 3H), 3.70 (s, 3H), 3.75 (s, 1H), 3.96 (q, 33m, *J* = 7.0 Hz), 7.10 (s, 33m), 7.11-7.13 (m, 1H), 7.18 (s, 33m), 7.61 (dd, 33m, *J* = 4.5, 1.5 Hz), 8.44 (dt, 1H, *J* = 4.5, 1.5 Hz); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 14.00, 16.16, 16.23, 45.91, 49.45, 59.54, 59.60, 60.63, 76.80, 122.29, 122.83, 127.36, 127.78, 130.65, 130.68, 135.87, 137.56, 137.77, 148.56, 155.47, 155.99, 156.12, 167.74. These spectral data match those previously reported for this compound.[4]

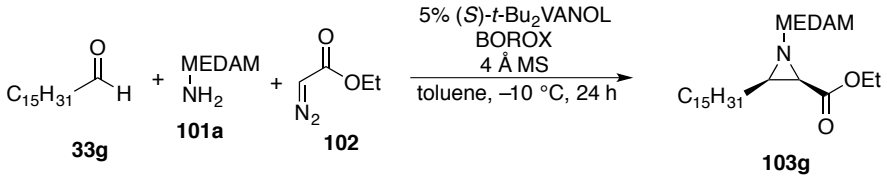


305 **33g**

*Hexadecanal **105g***: To a 100 mL flame-dried round bottom flask equipped with a stir bar was added 1-hexadecanol (1.21 g, 5.00 mmol). Dry CH_2Cl_2 (20 mL) was added to dissolve the alcohol. To the resulting solution were added TEMPO (39.1 mg, 0.250 mmol) and PhIO (1.43 g, 6.50 mmol). The suspension was cooled to 0 °C and $Yb(OTf)_3$ (62.5 mg, 0.100 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, 3:1 hexanes / dichloromethane as eluent, flash column) afforded pure aldehyde **105g** as a white solid (mp 36-38 ºC) in 88% isolated yield (1.06 g, 4.41 mmol).

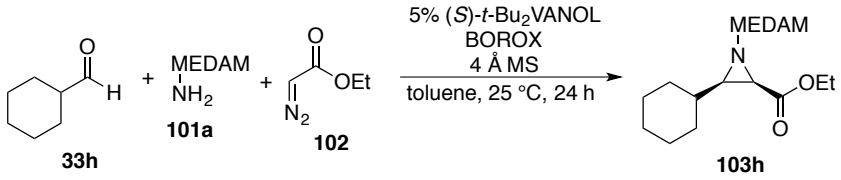
Spectral data for **105g**: R_f = 0.45 (1:1 hexanes/DCM). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.88 (t, 3H, *J* = 6.9 Hz), 1.30-1.25 (m, 24H), 1.62 (quintet, 33m, *J* = 7.3 Hz), 2.41 (td, 33m, *J* = 7.4, 1.9 Hz), 9.76 (t, 1H, *J* = 1.8 Hz); ^{13}C-NMR (126 MHz, $CDCl_3$): δ 14.09, 22.10, 22.68, 29.17, 29.35, 29.42, 29.57, 29.63, 29.64, 29.65, 29.67, 29.68, 31.92, 43.91,

202.85 (1 *sp3* carbon not located). These spectral data match those previously reported for this compound.[5]



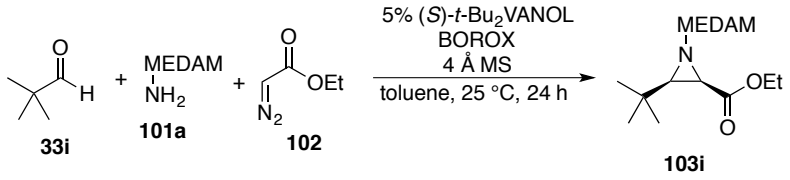
(2R,3R)-ethyl-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-pentadecylaziridine-2-carboxylate ***8g***:*n*-Hexadecanal **105g** (132 mg, 0.550 mmol) was reacted according to the general procedure with (*S*)-*t*-Bu_2VANOL as the ligand. The aldehyde **105g** was allowed to dissolve in toluene (1 mL) and then pre-cooled to −10 °C. The resulting solution of the aldehyde was then introduced into the BOROX catalyst solution *via* a 1 mL syringe after the catalyst solution was first cooled in an ethanol bath to −10 °C. Additional toluene (0.5 mL) was used to rinse the flask and was transferred to the catalyst solution. The pure *cis*-aziridine **8g** was separated by silica gel chromatography (9:1 hexanes/EtOAc, gravity column) to afford an off-white semi-solid in 97% (295 mg, 0.485 mmol). Only a single diastereomer was observed. The enantiomeric purity was determined to be 98.5% *ee* by HPLC (PIRKLE COVALENT (R, R) WHELK-O 1 column, 99.5:0.5 hexane/isopropanol at 226 nm, flow rate 0.7 mL/min); retention times, 26.6 min (major enantiomer, **8g**) and 47.8 min (minor enantiomer, *ent*-**8g**). The aziridination of aldehyde **105g** in the presence of (*S*)-VANOL afforded *cis*-aziridine **8g** in 95% *ee* and 60% yield (182 mg, 0.299 mmol). Spectral data for **8g**: ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 0.88 (t, 3H, J = 7.0 Hz), 1.14-1.33 (m, 29H), 1.45-1.56 (m, 33m), 1.96 (q, 1H, J = 6.5 Hz), 2.20 (d, 1H, J = 7.0 Hz), 2.24 (s, 125m), 3.40 (s, 1H), 3.68 (d, 6H, J = 8.0 Hz), 4.15-4.23 (m, 33m), 7.01 (s, 33m), 7.10 (s, 33m); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 14.11, 14.33, 16.11, 16.16, 22.67, 27.22, 27.92,

29.15, 29.34, 29.50, 29.61, 29.64, 29.68, 31.91, 43.54, 46.99, 59.57, 60.66, 77.31, 127.36, 128.07, 130.42, 130.47, 137.73, 138.14, 155.75, 156.10, 169.67 (five sp^3 carbons not located). These spectral data match those previous reported for this compound.[4]



(2R,3R)-ethyl-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-cyclohexylaziridine-2-carboxylate ***103h***: Cyclohexylcarboxaldehyde **33h** (64 μL, 0.52 mmol) was reacted according to the general procedure with (*S*)-*t*-Bu_2VANOL as the ligand. The pure *cis*-aziridine **103h** was separated by silica gel chromatography (9:1 hexanes/EtOAc, gravity column) to afford an off-white semi-solid in 100% yield (243 mg, 0.507 mmol); *cis*/*trans* >14:1. The enantiomeric purity was determined to be 96.0% *ee* by HPLC (CHIRALCEL OD column, 99:1 hexane/isopropanol at 223 nm, flow rate 0.7 mL/min); retention times, 10.4 min (major enantiomer, **103h**) and 13.1 min (minor enantiomer, *ent*-**103h**). The aziridination of aldehyde **33h** in the presence of (*S*)-VANOL catalyst afforded *cis*-aziridine **103h** in 94% *ee* and 94% yield (225 mg, 0.469 mmol).

Spectral data for **103h**: ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 0.49-0.56 (m, 1H), 0.83-1.16 (m, 4H), 1.24 (t, 3H, J = 7.0 Hz), 1.16-1.32 (m, 33m), 1.41-1.63 (m, 4H), 1.74 (dd, 1H, J = 9.5, 7.0 Hz), 2.18 (d, 1H, J = 6.5 Hz), 2.23 (s, 6H), 2.24 (s, 6H), 3.36 (s, 1H), 3.66 (s, 3H), 3.69 (s, 3H), 4.16-4.27 (m, 33m), 6.96 (s, 33m), 7.11 (s, 33m); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 14.33, 16.06, 16.17, 25.33, 25.52, 26.15, 30.08, 30.81, 36.33, 46.46, 52.25, 59.60, 59.65, 60.66, 77.47, 127.32, 128.52, 130.33, 130.46, 137.53, 138.08, 155.69, 156.22, 169.81. These spectral data match those previously reported for this compound.[4]

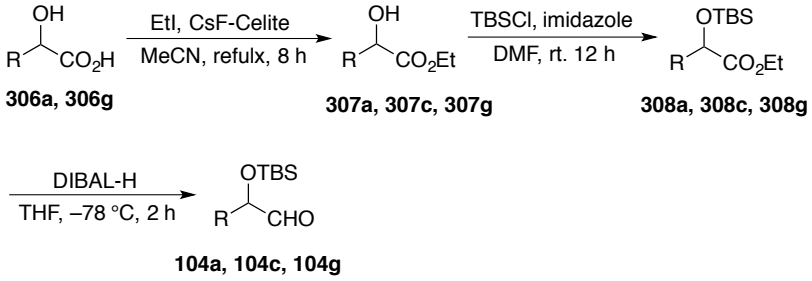


*(2R,3R)-ethyl-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-tert-butylaziridine-2-carboxylate **103i***: Trimethylacetaldehyde **33i** (57 μL, 0.52 mmol) was reacted according to the general procedure with (*S*)-*t*-Bu_2VANOL as the ligand. The pure *cis*-aziridine **103i** was separated by silica gel chromatography (9:1 hexanes/EtOAc, gravity column) to afford an off-white semi-solid in 100% yield (226 mg, 0.498 mmol); *cis*/*trans* >90:1. The enantiomeric purity was determined to be 97.0% *ee* by HPLC (CHIRALCEL OD column, 99:1 hexane/isopropanol at 226 nm, flow rate 1.0 mL/min); retention times, 7.1 min (major enantiomer, **103i**) and 11.0 min (minor enantiomer, *ent*-**103i**). The aziridination of aldehyde **33i** in the presence of (*S*)-VANOL catalyst afforded *cis*-aziridine **103i** in 95% *ee* and 70% yield (159 mg, 0.351 mmol).

Spectral data for **103i**: ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 0.69 (s, 9H), 1.30 (t, 3H, *J* = 7.0 Hz), 1.66 (d, 1H, *J* = 7.0 Hz), 2.09 (d, 1H, *J* = 7.0 Hz), 2.24 (s, 6H), 2.26 (s, 6H), 3.34 (s, 1H), 3.66 (s, 3H), 3.69 (s, 3H), 4.06-4.26 (m, 33m), 7.01 (s, 33m), 7.28 (s, 33m); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 14.15, 16.10, 16.21, 27.42, 31.60, 43.36, 56.15, 59.57, 59.64, 60.56, 78.43, 127.47, 128.34, 130.27, 130.30, 137.92, 138.85, 155.64, 156.10, 170.01. These spectral data match those previously reported for this compound.[4]

6.2.2 Preparation of α- or β-Chiral Aldehydes

General Procedure A for Aldehyde 104a, c, g



306a, 306g **307a, 307c, 307g** **308a, 308c, 308g**

104a, 104c, 104g

Esterification of α-hydroxy acids:[6] To a 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 the α-hydroxy acid (5.00 mmol). Dry acetonitrile (120 mL) was added to dissolve the acid. Thereafter, CsF-Celite (2.60 g) and iodoethane (1.20 mL, 15.0 mmol, 3.00 equiv) were added. The flask was placed in an oil (185 °C) 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 into 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. Purification of the product by silica gel chromatography (30 mm × 300 mm column, flash column) afforded the pure ester as a white solid.

Preparation of α-silyloxy esters: To a flame dried round bottom flask equipped with a stir bar and filled with nitrogen was added the α-hydroxy acid (2.50 mmol). Dry DMF (15 mL freshly distilled and stored over activated 4 Å MS) was added to dissolve the ester. The resulting solution was cooled to 0 °C. To the reaction flask was added imidazole

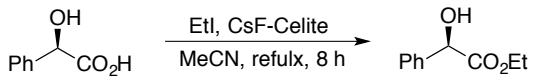
(3.00 mmol, 1.20 equiv) and *tert*-butyldimethylsilylchloride (3.00 mmol, 1.20 equiv). The flask was fitted with a rubber septum and a nitrogen balloon. The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was diluted by addition of hexanes (15 mL). Thereafter, brine was 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 α-silyloxy ester. Purification of the product by silica gel chromatography (30 mm × 300 mm column, flash column) afforded the pure ester as a colorless liquid.

Reduction of α-silyloxy esters to aldehydes: To a flame dried round bottom flask equipped with a stir bar and filled with nitrogen was added the appropriate α-(*tert*-butyldimethylsilyloxy) ester (2.00 mmol). Dry diethyl ether (10 mL) was added to dissolve the ester. The flask was fitted with a rubber septum and a nitrogen balloon. The solution was cooled to –78 °C. To the reaction flask was added DIBAL-H (4.0 mL, 1 M solution in hexanes, 4.0 mmol, 2.0 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 a mixture of methanol and water (0.50 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 a 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. Purification of the product by silica gel chromatography (20 mm × 300 mm column, flash column) afforded the pure aldehyde as a colorless liquid.

General Procedure B for Dess-Martin Oxidation from Alcohol to Aldehyde

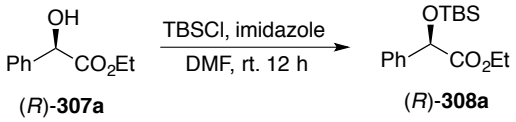
Dess-Martin Oxidation of Alcohols to Aldehydes: To a flame-dried 25 mL round bottom flask flushed with nitrogen and equipped with a stir bar was added the appropriate alcohol (1.00 mmol) and freshly distilled CH_2Cl_2 (5 mL). To the resulting clear solution was added Dess-Martin periodinane (509 mg, 1.20 mmol, 1.20 equiv). The turbid reaction mixture was stirred for 30 min at room temperature under a nitrogen atmosphere. Thereafter, a buffer solution made from dissolving NaH_2PO_4 (262 mg) and Na_3PO_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 product by silica gel chromatography (20 mm × 150 mm column, 9:1 hexanes/Et_2O as eluent, flash column) afforded the pure aldehyde as a colorless liquid.



(*R*)-**306a** (*R*)-**307a**

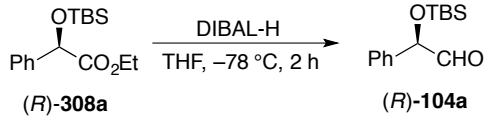
*Ethyl (R)-2-hydroxy-2-phenylacetate (R)-**307a***: (*R*)-mandelic acid (*R*)-**306a** (761 mg, 5.00 mmol) was reacted according to the first step of the general procedure A with CsF-Celite (2.60 g) and iodoethane (1.20 mL, 15.0 mmol, 3.00 equiv) in dry acetonitrile (120

mL). Purification of the product ester by silica gel chromatography (30 mm × 300 mm column, 4:1 hexanes/EtOAc, flash column) afforded pure ester (*R*)-**307a** as a white solid (mp 33–34 °C) in 70% isolated yield (631 mg, 3.50 mmol). Spectral data for (*R*)-**307a**: R_f = 0.16 (4:1 hexanes/EtOAc) ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.23 (t, 3H, *J* = 7.2 Hz), 3.51 (d, 1H, *J* = 6.0 Hz), 4.17-4.26 (m, 33m), 5.16 (d, 1H, *J* = 6.0 Hz), 7.33-7.44 (m, 104h); ^{13}C-NMR (125 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 $[\alpha]_D^{20}$ −135.0° (c 3.0, $CHCl_3$) (Sigma Aldrich).



(*R*)-**307a** (*R*)-**308a**

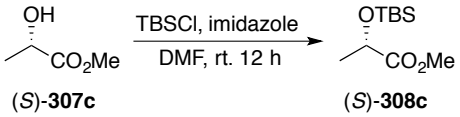
*Ethyl (R)-2-(tert-butyldimethylsilyloxy)-2-phenylacetate (R)-**308a***: The ester **(*R*)-307a** (901 mg, 5.00 mmol) was reacted according to the second step of the general procedure A with imidazole and *tert*-butyldimethylsilylchloride in dry DMF (15 mL). Purification of the product by silica gel chromatography (30 mm × 300 mm column, 50:1 hexanes/Et_2O as eluent, flash column) afforded pure ester **(*R*)-308a** as a colorless liquid in 92% isolated yield (1.35 g, 4.60 mmol). Spectral data for **(*R*)-308a**: 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, 3H, *J* = 7.1 Hz), 4.15 (q, 33m, *J* = 7.1 Hz), 5.23 (s, 1H), 7.50 - 7.27 (m, 104h); ^{13}C-NMR (75 MHz, $CDCl_3$) δ –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 1.5,$CHCl_3$). Lit[7] $[\alpha]_D^{20}$ +38.8° (c 1.5, $CHCl_3$, *S*-isomer).



(*R*)-**308a** (*R*)-**104a**

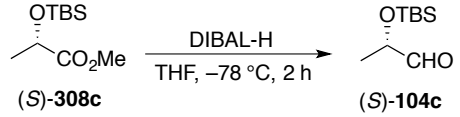
*(R)-2-(tert-butyldimethylsilyloxy)-2-phenylacetaldehyde (R)-**104a***: The ester **(*R*)-308a**

(581 mg, 2.00 mmol) was reacted according to the third step of the general procedure A with DIBAL-H (4.0 mL, 1 M solution in hexanes, 4.0 mmol, 2.0 equiv) in dry diethyl ether. Purification of the product by silica gel chromatography (30 mm × 300 mm column, 25:1 hexanes/Et_2O as eluent, flash column) afforded pure aldehyde **(*R*)-104a** as a colorless liquid in 85% isolated yield (423 mg, 1.70 mmol). Spectral data for **(*R*)-104a**: R_f = 0.35 (1:1 CH_2Cl_2/hexanes); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.04 (s, 3H), 0.12 (s, 3H), 0.95 (s, 9H), 5.01 (d, 1H, *J* = 2.1 Hz), 7.30-7.41 (m, 104h), 9.51 (d, 1H, *J* = 2.2 Hz); ^{13}C-NMR (125 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 0.60, ethanol). Lit[8] $[\alpha]_D^{22}$ –39.5° (c 0.61, ethanol).



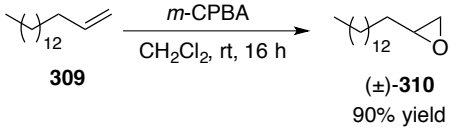
(*S*)-**307c** (*S*)-**308c**

*Methyl (S)-2-(tert-butyldimethylsilyloxy)propanoate (S)-**308c***: (*S*)-methyl lactate (*S*)-**307c** (520 mg, 5.00 mmol) was reacted according to the second step of the general procedure A with imidazole and *tert*-butyldimethylsilylchloride in dry DMF (15 mL). Purification of the product by silica gel chromatography (30 mm × 300 mm column, 100:1 hexanes/Et_2O as eluent, flash column) afforded pure ester **(*S*)-308c** as a colorless liquid in 85% isolated yield (928 mg, 4.25 mmol). Spectral data for **(*S*)-308c**: R_f = 0.55 (9:1 hexanes/EtOAc); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.07 (s, 3H), 0.10 (s, 3H), 0.90 (s, 9H), 1.40 (d, 3H, *J* = 6.7 Hz), 3.72 (s, 3H), 4.33 (q, 1H, *J* = 6.7 Hz); ^{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 0.90, $CHCl_3$). Lit[9] $[\alpha]_D^{26}$ –26.7° (c 0.86, $CHCl_3$).



(*S*)-**308c** (*S*)-**104c**

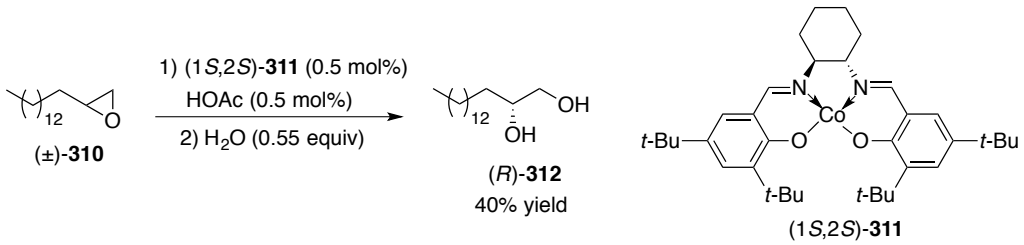
*(S)-2-(tert-butyldimethylsilyloxy)propanal (S)-**104c***: The ester **(*S*)-308c** (437 mg, 2.00 mmol) was reacted according to the third step of the general procedure A with DIBAL-H (4.0 mL, 1 M solution in hexanes, 4.0 mmol, 2.0 equiv) in dry diethyl ether. Purification of the product by silica gel chromatography (20 mm × 300 mm column, 50:1 hexanes/Et_2O as eluent, flash column) afforded pure aldehyde **(*S*)-104c** as colorless liquid in 75% isolated yield (282 mg, 1.50 mmol). Spectral data for **(*S*)-104c**: R_f = 0.54 (6:1 hexanes/EtOAc) ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.09 (s, 3H), 0.11 (s, 3H), 0.92 (s, 9H), 1.28 (d, 3H, *J* = 6.8 Hz), 4.09 (qd, 1H, *J* = 6.8, 1.0 Hz), 9.61 (d, 1H, *J* = 1.0 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ –4.91, –4.82, 18.22, 18.54, 25.69, 73.80, 204.21; $[\alpha]_D^{20}$ +12.3° (c 2.0, $CHCl_3$). Lit[10] $[\alpha]_D^{25}$ +12.1° (c 2.0, $CHCl_3$).



309 (±)-**310** 90% yield

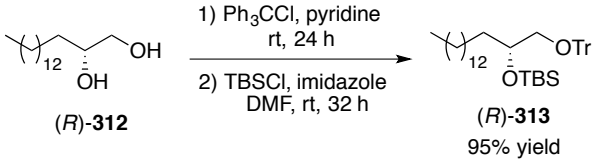
*2-Tetradecyloxirane **310***: To an oven dried 500 mL round bottom flask was added 1-hexadecene **309** (14.3 mL, 50.0 mmol) and freshly distilled dichloromethane (250 mL). The solution was cooled to 0 °C. To this solution was added 3-chloroperoxybenzoic acid (77%, remainder 3-chlorobenzoic acid and water), (15.0 g, 65.0 mmol, 1.30 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 into a 1L round bottom flask 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 separated, dried over $MgSO_4$ and concentrated under reduced pressure to afford crude epoxide **310** as a colorless oil. The epoxide was purified by simple distillation under reduced pressure (bp 93 ºC at 0.1 Hg) to afford **21** as a colorless oil in 90% yield (10.8 g, 44.9 mmol). Spectral data for (±)-**310**: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.88 (t, 3H, J = 7.0 Hz), 1.30-1.33 (m, 26H), 2.46 (dd, 1H, J = 5.1, 2.8 Hz), 2.74 (dd, 1H, J = 5.0, 4.0 Hz), 2.90 (tdd, 1H, J = 5.5, 3.9, 2.7 Hz); ^{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 sp^3 carbon not located). The spectral data matched with those reported for this compound.[11]



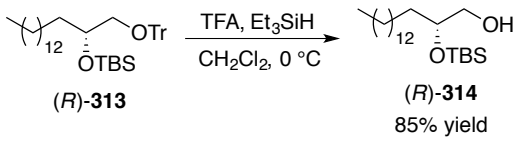
(*R)-hexadecane-1,2-diol (R)-**312***: The hydrolytic kinetic resolution of racemic epoxide **310** was carried out with Jacobsen's protocol.[12] To a 50 mL round bottom flask (1*S*,2*S*)-**312** (151 mg, 0.250 mmol), toluene (1.3 mL), and acetic acid (29 μL, 0.50 mmol, 2.0 equiv to catalyst) were added. 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 2 h. To the reaction flask, (±)-2-tetradecyloxirane **310** (12.0 g, 50.0 mmol) was added in one portion, and the stirred mixture was cooled in an ice-water bath. Water (496 μL, 27.5 mmol, 0.550 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) was 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 **310**. The light reddish white solid (*R*)-**312** was crystallized from EtOAc/hexanes (1:3) mixture. The first crop was collected in 35% yield (4.52 g, 17.6 mmol) of (*R*)-**312** as an off-white flakey solid (mp 83-84 ºC). The mother liquor was concentrated and again crystallized from EtOAc/hexanes (1:3) mixture. The second crop was collected in 5% yield (646 mg, 2.51 mmol) of (*R*)-**312** (mp 83-84 ºC). Spectral data for (*R*)-**312**: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.88 (t, 3H, *J* = 6.7 Hz), 1.30-1.26 (m, 24H), 1.41-1.43 (m, 33m), 1.80 (t, 1H, *J* = 5.7 Hz), 1.94 (d, 1H, *J* = 4.3 Hz), 3.44 (ddd, 1H, *J* = 10.9, 7.5, 5.0 Hz), 3.75-3.63 (m, 33m); ^{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 sp^3 carbon not located); $[\alpha]_D^{20}$ +9.5° (c 1.0 EtOH).



*(R)-tert-butyldimethyl((1-(trityloxy)hexadecan-2-yl)oxy)silane (R)-**313***: 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*)-**312** (1.03 g, 4.00 mmol) and pyridine (22 mL). The mixture was stirred at room temperature until it became 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, 8.40 mmol, 2.10 equiv) at 0 ºC. The reaction mixture was warmed to room temperature and stirred for 24 h under a nitrogen atmosphere. The reaction mixture was concentrated under reduced pressure to

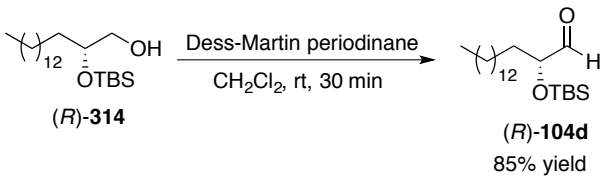
afford a pale yellow solid. The crude trityl ether was dissolved in freshly distilled DMF (10 ml) under a nitrogen atmosphere. To the clear solution was added imidazole (544 mg, 8.00 mmol, 2.00 equiv) and TBSCl (1.21 g, 8.00 mmol, 2.00 equiv). The reaction mixture was stirred at room temperature for 32 h under a nitrogen atmosphere. Upon completion, the reaction mixture was diluted with hexanes (30 mL) and then 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 product by silica gel chromatography with a rubber septum and a nitrogen balloon at the top of the column (30 mm × 300 mm column, 50:1 hexanes/Et_2O as eluent) afforded pure (*R*)-**313** as a colorless liquid in 95 % isolated yield (2.34 g, 3.80 mmol) over two steps from (*R*)-**312**. Spectral data for (*R*)-**313**: R_f = 0.35 (1:40 Et_2O / hexanes) ^{1}H-NMR (300 MHz, $CDCl_3$) δ –0.03 (s, 3H), –0.01 (s, 3H), 0.84-0.89 (m, 125m), 1.18-1.33 (m, 24H), 1.39-1.45 (m, 1H), 1.60-1.67 (m, 1H), 2.96 (dd, 1H, *J* = 9.2, 5.8 Hz), 3.05 (dd, 1H, *J* = 9.2, 5.2 Hz), 3.76 (quintet, 1H, *J* = 5.7 Hz), 7.19-7.32 (m, 9H), 7.46 (dd, 6H, *J* = 8.3, 1.4 Hz); ^{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, 126.82, 127.66, 128.78, 144.31 (three sp^3 carbons not located); IR (thin film) 2926vs, 2855s, 1464s, 1448s, 1257s, 1076s cm^{-1}; HRMS (ESI-TOF) *m/z* 615.4520 [(M^+ + H); calcd for $C_{41}H_{63}O_2Si$: 615.4515]; $[\alpha]_D^{20}$ +9.0° (c 1.0, CH_2Cl_2).



(*R*)-**313** (*R*)-**314**
85% yield

*(R)-2-((tert-butyldimethylsilyl)oxy)hexadecan-1-ol (R)-**314***: To a flame dried 100 mL

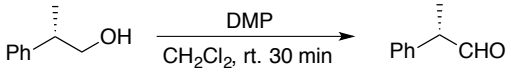
round bottom flask flushed with nitrogen and equipped with a stir bar was added the trityl ether (*R*)-**313** (615 mg, 1.00 mmol) and freshly distilled CH_2Cl_2 (10 mL). The resulting clear solution was cooled to 0 °C. Triethylsilane (186 mg, 1.60 mmol) was added and the solution was stirred for 10 min after which TFA (153 μL, 2.00 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 product 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*)-**314** as a colorless liquid in 85 % isolated yield (317 mg, 0.851 mmol). Spectral data for (*R*)-**314**: R_f = 0.22 (10:1 hexanes / Et_2O); ^{1}H-NMR (300 Hz, $CDCl_3$) δ 0.08 (s, 6H), 0.86-0.91 (m, 125m), 1.30-1.21 (m, 24H), 1.44-1.51 (m, 33m), 1.85 (t, 1H, *J* = 6.3 Hz), 3.40-3.49 (m, 1H), 3.56 (ddd, 1H, *J* = 11.0, 6.3, 3.6 Hz), 3.72 (qd, 1H, *J* = 5.9, 3.6 Hz); ^{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 sp^3 carbons not located); IR (thin film) 3400br, 2926vs, 2855s, 1464s, 1255s, 1109s cm^{-1}; HRMS (ESI-TOF) *m/z* 373.3564 [(M^+ + H); calcd for $C_{22}H_{49}O_2Si$: 373.3578]; $[\square]_D^{20}$ –6.5° (c 1.0, CH_2Cl_2).



(*R*)-**314** (*R*)-**104d**
85% yield

*(R)-2-((tert-butyldimethylsilyl)oxy)hexadecanal (R)-**104d***: Alcohol (*R*)-**314** (410 mg, 1.10

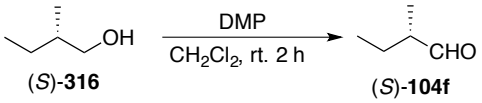
mmol) was reacted according to the general procedure B with Dess-Martin periodinane (560 mg, 1.32 mmol, 1.20 equiv) in CH_2Cl_2 (5.5 mL) for 30 min (until the alcohol was no longer detectable by TLC). Purification of the crude aldehyde by silica gel chromatography (20 mm × 150 mm column, 10:1hexanes/Et_2O as eluent, flash column) afforded pure (*R*)-**104d** as a colorless liquid in 85 % isolated yield (346 mg, 0.935 mmol). Spectral data for (*R*)-**104d**: R_f = 0.12 (10:1 hexanes/Et_2O); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.07 (s, 3H), 0.08 (s, 3H), 0.88 (t, 3H, *J* = 6.8 Hz), 0.92 (s, 9H), 1.22-1.41 (m, 24H), 1.57-1.65 (m, 33m), 3.96 (ddd, 1H, *J* = 6.9, 5.6, 1.5 Hz), 9.59 (d, 1H, *J* = 1.8 Hz); ^{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, 204.32 (two sp^3 carbons not located); IR (thin film) 2928vs, 2855vs, 1738s, 1464s, 1253s cm^{-1}; $[\alpha]_D^{20}$ +18.6° (c 1.0, CH_2Cl_2).



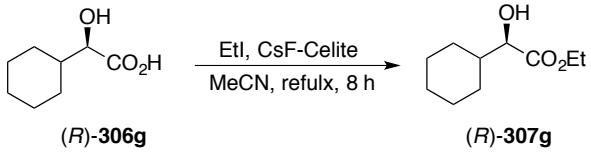
(*S*)-**315** (*S*)-**104e**

*(S)-2-phenyl propanal (S)-**104e***: (*S*)-2-phenyl propanol (*S*)-**315** (150 μL, 1.10 mmol) was reacted according to the general procedure **B** with Dess-Martin periodinane (560 mg, 1.32 mmol, 1.20 equiv) in CH_2Cl_2 (5.5 mL) for 30 min (until the alcohol was no longer detectable by TLC). Purification of the product by silica gel chromatography (20 mm × 150 mm column, 9:1 hexanes/Et_2O as eluent, flash column) afforded pure aldehyde **(*S*)-104e** as a colorless liquid in 70% isolated yield (103 mg, 0.77 mmol). Spectral data for **(*S*)-104e**: R_f= 0.14 (1:1 CH_2Cl_2/hexanes) ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.45 (d, 3H, *J* = 7.1 Hz), 3.64 (qd, 1H, *J* = 7.1, 1.3 Hz), 7.21-7.23 (m, 33m), 7.29-7.32 (m, 1H), 7.37- 7.40 (m, 33m), 9.69 (d, 1H, *J* = 1.5 Hz); ^{13}C-NMR (125 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[13] $[\alpha]_D^{20}$ +314.6° (c 0.45, benzene).

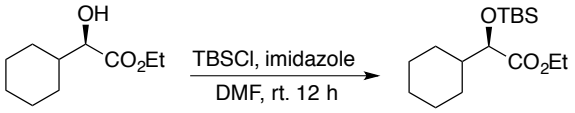


*(S)-2-Methylbutanal (S)-**104f***: (*S*)-2-methylbutan-1-ol (*S*)-**316** (5.4 mL, 50 mmol) was reacted according to general procedure B with Dess-Martin periodinane (25.4 g, 60.0 mmol, 1.20 equiv) in freshly distilled CH_2Cl_2 (100 mL) for 2 h (until the alcohol was no longer detectable by TLC). The crude mixture was treated with bulb-to-bulb distillation under vacuum (0.5 mmHg) to afforded 2.15 g of an oil that was a mixture of the aldehyde (*S*)-**104f** (1.70 g, 19.8 mmol, 40%) and CH_2Cl_2 (5.2 mmol). The aldehyde (*S*)-**104f** was dissolved into dry toluene at a 2 M concentration and stored under nitrogen at –10 °C to be used for the next step without further purification. Spectral data for **(*S*)-104f**: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.94 (t, 3H, *J* = 7.5 Hz), 1.09 (d, 3H, *J* = 7.5 Hz), 1.39-1.47 (m, 1H), 1.71-1.77 (m, 1H), 2.25-2.29 (m, 1H), 9.64 (d, 1H); ^{13}C-NMR (125 Hz, $CDCl_3$) d 11.33, 12.83, 23.48, 47.73, 205.45. These spectral data matched those previously described.[14]



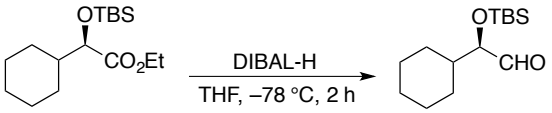
*Ethyl (R)-2-cyclohexyl-2-hydroxyacetate (R)-**307g***: (*R*)-hexahydromandelic acid (*R*)-**306g** (791 mg, 5.00 mmol) was reacted according to the first step of the general procedure A with CsF-Celite (2.60 g) and iodoethane (1.20 mL, 15.0 mL, 3.00 equiv) in dry acetonitrile (120 mL). Purification of the product by silica gel chromatography (30 mm × 300 mm column, 20:1 hexanes/EtOAc, flash column) afforded pure ester (*R*)-**307g** as a

white solid (mp 39–40 °C) in 65% isolated yield (605 mg, 3.25 mmol). Spectral data for (*R*)-**307g**: R_f = 0.34 (20:1 hexanes/EtOAc) ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.17-1.28 (m, 104h), 1.31 (t, 3H, *J* = 7.1 Hz), 1.44-1.45 (m, 1H), 1.64-1.79 (m, 104h), 2.65 (d, 1H, *J* = 6.3 Hz), 4.00 (dd, 1H, *J* = 6.2, 3.5 Hz), 4.25 (qd, 33m, *J* = 7.1, 1.3 Hz); ^{13}C-NMR (125 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 1.5, $CHCl_3$). Lit[16] $[\alpha]_D^{25}$ +17.7° (c 1.5, $CHCl_3$, *S*-isomer).



(*R*)-**307g** (*R*)-**308g**

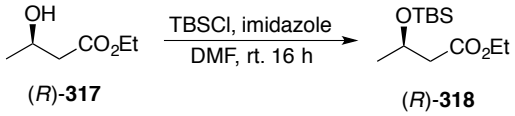
*Ethyl (R)-2-(tert-butyldimethylsilyloxy)-2-cyclohexylacetate (R)-**308g***: The ester (*R*)-**307g** (500 mg, 2.68 mmol) was reacted according to the second step of the general procedure A with imidazole and *tert*-butyldimethylsilylchloride in dry DMF (15 mL). Purification of the product by silica gel chromatography (30 mm × 300 mm column, 100:1 hexanes/EtOAc as eluent, flash column) afforded pure ester **(*R*)-308g** as a colorless liquid in 85% isolated yield (685 mg, 2.28 mmol). Spectral data for **(*R*)-308g**: R_f = 0.68 (20:1 hexanes/EtOAc); ^{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, 3H, *J* = 7.1 Hz), 1.53-1.55 (m, 1H), 1.62-1.74 (m, 104h), 3.93 (d, 1H, *J* = 5.2 Hz), 4.17 (qd, 33m, *J* = 7.1, 2.9 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) 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, 173.41 (one sp^3 carbon not located).



(*R*)-**308g** (*R*)-**104g**

*(R)-2-(tert-butyldimethylsilyloxy)-2-cyclohexylacetaldehyde (R)-**104g***: The ester **(*R*)-308g**

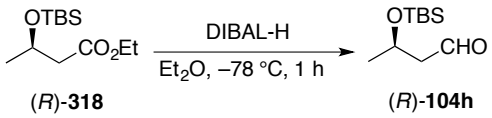
(581 mg, 2.00 mmol) was reacted according to the third step of the general procedure A with DIBAL-H (4.0 mL, 1 M solution in hexanes, 4.0 mmol, 2.0 equiv) in dry diethyl ether. Purification of the product by silica gel chromatography (30 mm × 300 mm column, 20:1 hexanes/Et_2O as eluent, flash column) afforded pure aldehyde **(*R*)-104g** as a colorless liquid in 85% isolated yield (400 mg, 1.70 mmol). Spectral data for **(*R*)-104g**: R_f = 0.31 (20:1 hexanes/EtOAc) ^{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, 104h), 1.61-1.76 (m, 6H), 3.70 (dd, 1H, *J* = 5.1, 2.2 Hz), 9.59 (d, 1H, *J* = 2.2 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) 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 well in agreement with literature reported value.[16]



(*R*)-**317** (*R*)-**318**

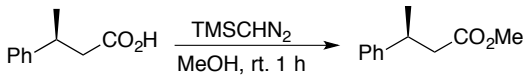
*Ethyl (R)-3-((tert-butyldimethylsilyl)oxy)butanoate (R)-**318**:* Ethyl **(*R*)**-3-hydroxybutanoate (*R*)-**318** (0.90 mL, 7.00 mmol) was reacted according to the second step of the general procedure A with imidazole (724 mg, 10.5 mmol, 1.50 equiv) and *tert*-butyldimethylsilylchloride (1.60 g, 10.5 mmol, 1.50 equiv) in dry DMF (15 mL). Purification of the product by silica gel chromatography (30 mm × 300 mm column, 50:1 hexanes/Et_2O as eluent, flash column) afforded pure ester (*R*)-**318** as a colorless liquid in 85% isolated yield (1.47 g, 5.95 mmol). Spectral data for (*R*)-**318**: R_f = 0.31 (20: hexanes/EtOAc); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.01 (s, 3H), 0.03 (s, 3H), 0.83 (s, 9H), 1.16 (d, 3H, *J* = 6.1 Hz), 1.23 (t, 3H, *J* = 7.1 Hz), 2.43 (dd, 1H, *J* = 14.5, 7.6 Hz), 2.43 (dd, 1H, *J* = 14.5, 7.6 Hz), 4.14-4.05 (m, 33m), 4.28-4.22 (m, 1H); ^{13}C-NMR (125 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[17] $[\alpha]_D^{25}$ –25.5° (c 1.0, CH_2Cl_2).



(*R*)-**318** (*R*)-**104h**

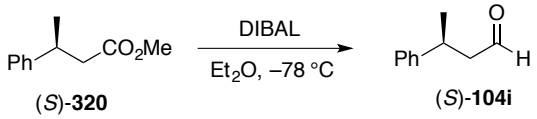
*(R)-3-((tert-butyldimethylsilyl)oxy)butanal (R)-**104h**:* The β-silyloxy ester **(*R*)-318** (487 mg, 2.0 mmol) was reacted according to the third step of the general procedure A with DIBAL-H (4.0 mL, 1 M solution in hexanes, 4.0 mmol, 2.0 equiv) in dry diethyl ether (7 mL) at –78 °C for 1 h. Purification of the product by silica gel chromatography (20 mm × 300 mm column, 25:1 hexanes/Et_2O as eluent, flash column) afforded pure aldehyde **(*R*)-104** as a colorless liquid in 80% isolated yield (320 mg, 1.60 mmol). Spectral data for **(*R*)-104h**: R_f= 0.41 (1:1 CH_2Cl_2/hexanes); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.02 (s, 3H), 0.04 (s, 3H), 0.83 (s, 9H), 1.19 (d, 3H, *J* = 6.2 Hz), 2.38-2.55 (m, 33m), 4.32 (sextet, 1H, *J* = 6.0 Hz), 9.75 (t, 1H, *J* = 2.3 Hz); ^{13}C-NMR (125 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[17] $[\alpha]_D^{25}$ –11.3° (c 1.0, CH_2Cl_2).



(*S*)-**319** (*S*)-**320**

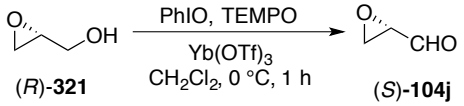
*Methyl (S)-3-phenylbutanoate (S)-**320**:* To a 100 mL flame dried round bottom flask equipped with a stir bar and filled with nitrogen was added (*S*)-3-phenylbutanoic acid (*S*)-**318** (647 mg, 4.00 mmol). Methanol (50 mL) was added to dissolve the acid. The flask was fitted with a rubber septum and a nitrogen balloon. The solution was cooled to 0 °C. To the reaction flask was added (trimethylsilyl)diazomethane (6.0 mL, 2 M in hexanes, 12 mmol, 3.0 equiv) over a period of 2 minutes. The resulting mixture was warmed to room temperature and stirred for 1 h. The reaction mixture was concentrated under

reduced pressure. Purification of the product by silica gel chromatography (20 mm × 150 mm column, 1:1 hexanes/Et_2O as eluent, flash column) afforded pure ester (*S*)-**320** as a colorless liquid in 94% isolated yield (673 mg, 3.76 mmol). Spectral data for (*S*)-**320**: R_f = 0.21 (9:1 hexanes/EtOAc); ^{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, 33m); ^{13}C-NMR (125 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 $[\alpha]_D^{20}$ −44.0° (c 1.0, benzene) (Sigma Aldrich).

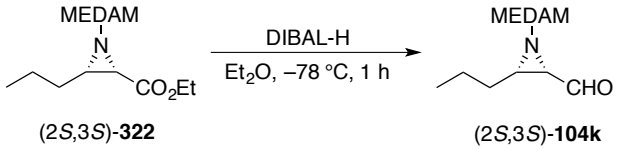


(*S*)-**320** (*S*)-**104i**

*(S)-3-phenylbutanal (S)-**104i**:* The ester (*S*)-**320** (585 mg, 2.00 mmol) was reacted according to the third step of the general procedure A with DIBAL-H (4.0 mL, 1 M solution in hexanes, 4.0 mmol, 2.0 equiv) in dry diethyl ether (10 mL) at –78 °C for 1 h. Purification of the product by silica gel chromatography (30 mm × 300 mm column, 50:1 hexanes//Et_2O as eluent, flash column) afforded pure aldehyde (*S*)-**104i** as a colorless liquid in 75% isolated yield (333 mg, 2.25 mmol). Spectral data for (*S*)-**104i**: R_f = 0.31 (6:1 hexanes/Et_2O); ^{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, 33m), 9.71 (t, *J* = 2.0 Hz, 1H); ^{13}C-NMR (125 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 0.20, Et_2O). Lit[18] $[\alpha]_D^{20}$ –38.0° (c 0.20, Et_2O).



*(S)-oxirane-2-carbaldehyde (S)-**104j***:[19] To a 250 mL flame-dried round bottom flask equipped with a stir bar was added (*R*)-glycidol (*R*)-**321** (2.66 mL, 40.0 mmol) into dry CH_2Cl_2 (150 mL). To the resulting solution was added TEMPO (312 mg, 2.00 mmol, 0.0500 equiv) and PhIO (10.6 g, 48.0 mmol, 1.20 equiv). The suspension was cooled to 0 °C and $Yb(OTf)_3$ (496 mg, 0.800 mmol, 0.0200 equiv) was added. The reaction mixture was stirred at 0 °C for 50 min (until the alcohol was no longer detectable by TLC). The resulting suspension was filtered through a Celite pad and concentrated under reduced pressure at room temperature. The crude mixture was bulb-to-bulb distilled at 0 °C under vacuum (0.05 mmHg). The aldehyde (*S*)-**104j** was collected in the receiving round-bottom flask cooled in liquid nitrogen as a colorless liquid (1.82 g) and was determined to be a mixture of aldehyde (*S*)-**104j** (12.4 mmol), iodobenzene (3.60 mmol) and CH_2Cl_2 (2.23 mmol). The mixture was dissolved in dry toluene to a 2 M concentration and stored under nitrogen at –10 °C to be used for the next step without further purification. Spectral data for (*S*)-**104j**: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 3.02 (dd, *J* = 5.2, 2.5 Hz, 1H), 3.13 (dd, *J* = 5.2, 4.5 Hz, 1H), 3.34 (ddd, *J* = 6.5, 4.5, 2.2 Hz, 1H), 8.94 (d, *J* = 6.5 Hz, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 44.51, 53.02, 198.13; $[\alpha]_D^{20}$ –38.2° (c 1.0, $CHCl_3$) on 99% material.

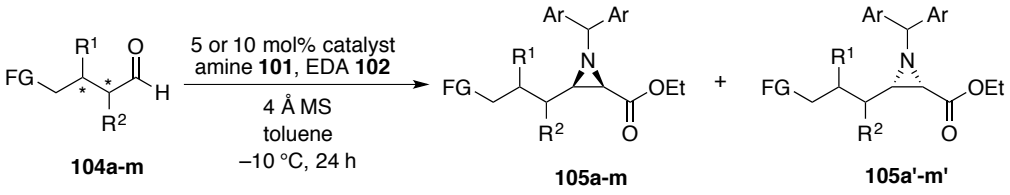


*(2S,3S)-1-bis((4-methoxy-3,5-dimethylphenyl)methyl)-3-propylaziridine-2-carboxaldehyde (2S,3S)-**104k***: The previously reported aziridine 2-carboxylate (2*S*,3*S*)-

322[4] (527 mg, 1.20 mmol) was reacted according to the third step of the general procedure **A** with DIBAL-H (2.40 mL, 1 M solution in hexanes, 2.40 mmol, 1.20 equiv) in dry diethyl ether (4 mL) at –78 °C for 1 h. 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 (2*S*,3*S*)-**104k** as a colorless liquid in 70% isolated yield (332 mg, 0.84 mmol). Spectral data for (2*S*,3*S*)-**104k**: 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, 33m), 2.25 (s, 6H), 2.29 (s, 6H), 3.49 (s, 1H), 3.70 (s, 3H), 3.71 (s, 3H), 7.03 (s, 33m), 7.06 (s, 33m), 9.44 (d, *J* = 5.6 Hz, 1H); ^{13}C-NMR (125 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* 396.2465 [($M+H^+$); calcd. for $C_{2104h34}NO_3$ 396.2460]; $[\alpha]_D^{20}$ – 85.0° (c 1.0, CH_2Cl_2).

6.2.3. Multi-Component *cis*-Aziridination of Chiral Aldehydes 104a-i

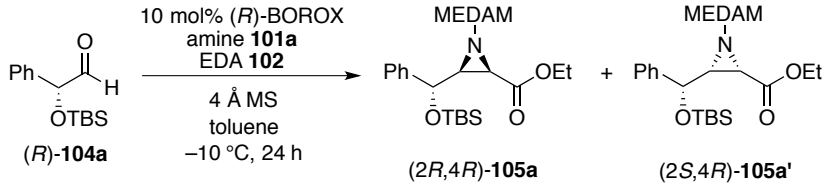
General Procedure for the Multi-Component Aziridination of Chiral Aldehydes



To a 10 mL flame-dried home-made Schlenk flask, prepared from a 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 ligand **68a**, **68b** or **68c** (0.020 mmol), $B(OPh)_3$ (17 mg, 0.060 mmol) and amine **101a** or **101b** (0.200 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 °C) for 0.5 h. The flask was then allowed to cool to room temperature and opened 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 °C and aldehyde (0.22 mmol, 1.1 equiv) was added to the reaction mixture. To this solution was rapidly added ethyl diazoacetate (EDA) **102** (25 μL, 0.24 mmoL, 1.2 equiv). The resulting mixture was stirred for 24 h at –10 °C. The reaction was diluted by addition of hexane (3 mL) at –10 °C before the reaction mixture was filtered through a silica gel plug into 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 a yellow colored viscous oil. Purification of the crude aziridine by neutral alumina chromatography (20 mm × 150 mm column, gravity column) afforded an inseparable disatereomeric mixture of aziridines.

Experimental Details for the Multi-Component Aziridination of Chiral Aldehydes



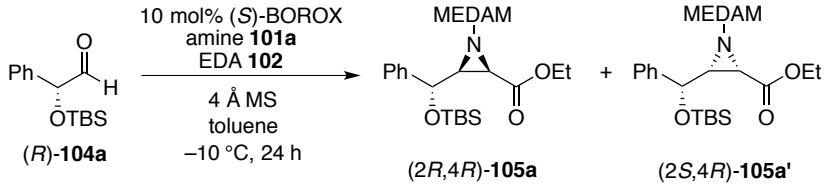
*(2S,3R)-ethyl 1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-((R)-(tert-butyldimethylsilyloxy) (phenyl) methyl)aziridine-2-carboxylate (2S,4R)-**105a'*** (Table 2.5, entry 6): Aldehyde (*R*)-**104a** was reacted according to the general procedure with (*R*)-VAPOL (11 mg, 0.020 mmol) as ligand at –10 °C to afford aziridines (2*S*,4*R*)-**105a'** and

(2*R*,4*R*)-**105a** 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 an inseparable mixture of aziridines **105a** and **105a'** as a white solid (mp 139-140 °C on 99:1 *dr* material) in 90% isolated yield (111 mg, 0.180 mmol). The diastereomeric ratio of (2*S*,4*R*)-**105a'** to (2*R*,4*R*)-**105a** was determined to be 99:1 by HPLC analysis of the crude reaction mixture (PIRKLE COVALENT (R, R) WHELK-O 1 column, 99:1 hexane/2-propanol at 222 nm, flow-rate: 0.7 mL/min), retention times: R_t = 8.49 min (minor diastereomer, (2*R*,4*R*)-**105a**) and R_t = 17.92 min (major diastereomer, (2*S*,4*R*)-**105a'**).

(Table 2.5, entry 8): Aldehyde (*R*)-**104a** was reacted according to the general procedure with (*R*)-VANOL (8.8 mg, 0.020 mmol), as ligand at –10 °C to afford aziridines (2*S*,4*R*)-**105a'** and (2*R*,4*R*)-**105a** 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 an inseparable mixture of aziridines **105a'** and **105a** in a 98:2 ratio as a white solid in 85% isolated yield (105 mg, 0.170 mmol). Single crystals of **105a'** were grown and an X-ray diffraction analysis performed and the results deposited with the CCDC (1495343). The cif can be found in the supporting information as a separate file.

Spectral data for (2*S*,4*R*)-**105a'**: R_f = 0.28 (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, 3H, *J* = 7.1 Hz), 1.99 (d, 1H, *J* = 7.0 Hz), 2.23 (s, 6H), 2.26 (s, 6H), 2.43 (t, 1H, *J* = 7.5 Hz), 3.49 (s, 1H), 3.68 (s, 3H), 3.70 (s, 3H), 4.06 (dq, 1H, *J* = 10.8, 7.1 Hz), 4.14 (dq, 1H, *J* = 10.8, 7.1 Hz), 4.70 (d, 1H, *J* = 7.9 Hz), 7.05 (s, 4H), 7.21-7.28 (m, 104h); ^{13}C-NMR (125 MHz, $CDCl_3$) δ –

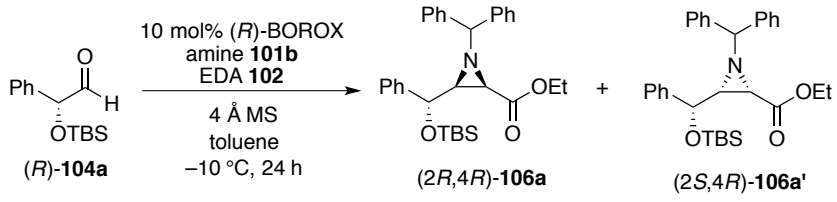
5.12, –5.07, 14.12, 16.17, 16.24, 17.84, 25.55, 41.68, 55.25, 59.40, 59.54, 60.63, 73.40, 77.65, 126.54, 127.23, 127.47, 128.03, 128.63, 130.35, 130.44, 137.97, 138.20, 142.67, 155.64, 156.15, 169.78; IR (thin film) 2955vs, 2928vs, 1742vs, 1483s, 1221s, 1188vs, 1140s cm^{-1}; HRMS (ESI-TOF) *m/z* 618.3631 [($M+H^+$); calcd. for $C_{3105h52}NO_5Si$: 618.3615]; $[\alpha]_D^{20}$ –92.6° (c 1.0, CH_2Cl_2) on 99:1 *dr* material (HPLC).



*(2R,3S)-ethyl 1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-((R)-(tert-butyldimethylsilyloxy)(phenyl) methyl)aziridine-2-carboxylate (2R,4R)-**105a*** (Table 2.5, entry 5): Aldehyde (*R*)-**104a** was reacted according to the general procedure with (*S*)-VAPOL (11 mg, 0.020 mmol) as ligand to afford aziridines (2*R*,4*R*)-**105a** and (2*S*,4*R*)-**105a'** in 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 an inseparable mixture of aziridines **105a** and **105a'** as a white solid (mp 49-50 °C on 98:2 *dr* material) in 90% isolated yield (111 mg, 0.180 mmol). The diastereomeric ratio of (2*R*,4*R*)-**105a** and (2*S*,4*R*)-**105a'** 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, (2*R*,4*R*)-**105a**) and R_t = 18.48 min (minor diastereomer, (2*S*,4*R*)-**105a'**).

(Table 2.5, entry 7): Aldehyde (*R*)-**104a** was reacted according to the general procedure with (*S*)-VANOL (8.8 mg, 0.020 mmol), as ligand at –10 °C to afford aziridines (2*R*,4*R*)-

105a and (2*S*,4*R*)-**105a'** in 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 an inseparable mixture of aziridines **105a** and **105a'** as a white solid in 85% isolated yield (105 mg, 0.170 mmol). Spectral data for (2*R*,4*R*)-**105a**: R_f = 0.28 (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, 1H, *J* = 6.4 Hz), 2.40 (dd, 1H, *J* = 8.2, 6.4 Hz), 3.32 (s, 1H), 3.59 (s, 3H), 3.67 (s, 3H), 4.16 (dq, 1H, *J* = 10.8, 7.2 Hz), 4.29 (dq, 1H, *J* = 10.8, 7.1 Hz), 4.61 (d, *J* = 8.2 Hz, 1H), 6.51 (s, 33m), 6.99 (s, 33m), 7.00-7.01 (m, 3H), 7.11 (dd, 33m, *J* = 6.6, 2.9 Hz); ^{13}C-NMR (150 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 $C_{3105h52}NO_5Si$: 618.3615]; $[\alpha]_D^{20}$ +107.0° (c 1.0, CH_2Cl_2) on 98:2 *dr* material (HPLC).

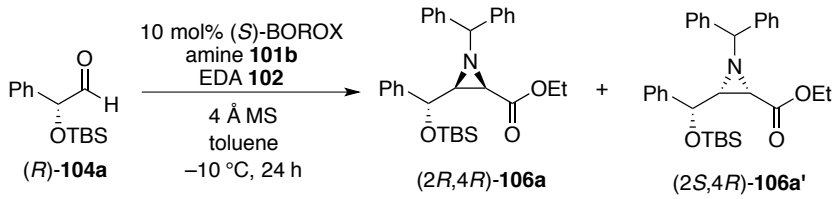


(2S,3R)-ethyl 1-benzhydryl-3-((R)-(tert-butyldimethylsilyloxy)(phenyl)methyl)aziridine-2-carboxylate (2S,4R)-

106a' (Table 2.5, entry 10): Aldehyde (*R*)-**104a** was reacted according to the general procedure with (*R*)-VAPOL (11 mg, 0.020 mmol) as ligand to afford aziridines (2*S*,4*R*)-**106a'** and (2*R*,4*R*)-**106a** 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 an inseparable mixture of aziridines **106a** and **106a'** as a white solid (mp 93-97 °C on 94:6 *dr* material) in 65% isolated yield (65.4 mg, 0.130 mmol). The diastereomeric ratio of (2*S*,4*R*)-**106a'** and (2*R*,4*R*)-**106a** was determined to be 94:6 by HPLC analysis of crude reaction mixture (PIRKLE COVALENT (R, R) WHELK-O 1 column, 99.5:0.5 hexane/2-propanol at 222 nm, flow-rate: 0.7 mL/min), retention times: R_t = 6.43 min (minor diastereomer, (2*R*,4*R*)-**106a**) and R_t = 11.47 min (major diastereomer, (2*S*,4*R*)-**106a'**).

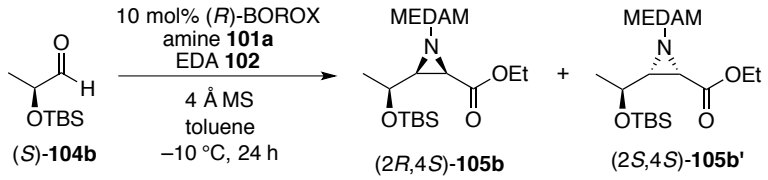
Spectral data for (2*S*,4*R*)-**106a'**: R_f = 0.25 (4:1:0.2 hexanes/CH_2Cl_2/Et_2O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ –0.24 (s, 3H), –0.21 (s, 3H), 0.63 (s, 9H), 1.16 (t, 3H, *J* = 7.1 Hz), 2.09 (d, 1H, *J* = 7.0 Hz), 2.49 (dd, 1H, *J* = 8.0, 7.0 Hz), 3.79 (s, 1H), 4.14-4.07 (m, 33m), 4.74 (d, 1H, *J* = 8.0 Hz), 7.19-7.30 (m, 11H), 7.42-7.45 (m, 4H); ^{13}C-NMR (125 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 94:6 *dr* material (HPLC).



*(2R,3S)-ethyl 1-benzhydryl-3-((R)-(tert-butyldimethylsilyloxy)(phenyl)methyl)aziridine-2-carboxylate (2R,4R)-**7a*** (Table 2.5, entry 9): Aldehyde (*R*)-**104a** was reacted according to the general procedure with (*S*)-VAPOL (11 mg, 0.020 mmol) as ligand to afford

aziridines (2*R*,4*R*)-**106a** and (2*S*,4*R*)-**106a'** in 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 an inseparable mixture of aziridines **106a** and **106a'** as a white solid (mp 126-131 °C on 99:1 *dr* material) in 50% isolated yield (49.7 mg, 0.100 mmol). The diastereomeric ratio of (2*R*,4*R*)-**106a** and (2*S*,4*R*)-**106a'** 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 222 nm, flow-rate: 0.7 mL/min), retention times: R_t = 6.44 min (major diastereomer, (2*R*,4*R*)-**106a**) and R_t = 11.76 min (minor diastereomer, (2*S*,4*R*)-**106a'**).

Spectral data for (2*R*,4*R*)-**106a**: R_f = 0.25 (4:1:0.2 hexanes/CH_2Cl_2/Et_2O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ –0.33 (s, 3H), –0.10 (s, 3H), 0.78 (s, 9H), 1.28 (t, 3H, *J* = 7.2 Hz), 2.35 (d, 1H, , *J* = 6.4 Hz), 2.44 (t, 1H, *J* = 7.2 Hz), 3.58 (s, 1H), 4.12-4.28 (m, 33m), 4.62 (d, 1H, *J* = 7.9 Hz), 6.84-7.13 (m, 10H), 7.24 (t, 3H, *J* = 7.3 Hz), 7.36 (d, 33m, *J* = 7.4 Hz); ^{13}C-NMR (125 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).

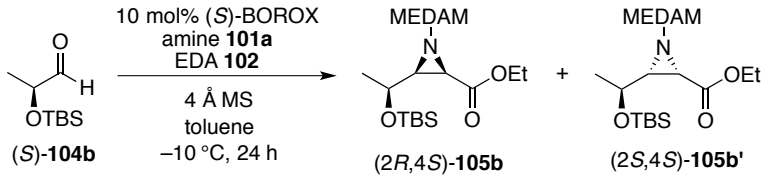


*(2S,3R)-ethyl 1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-((S)-(tert-butyldimethylsilyloxy)ethyl) aziridine-2-carboxylate (2S,4S)-**7b'***: Aldehyde (*S*)-**5b** was reacted according to the general procedure with (*R*)-VAPOL (11 mg, 0.020 mmol) as ligand at –10 °C to afford aziridines (2*S*,4*S*)-**7b'** and (2*R*,4*S*)-**7b** 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 an inseparable mixture of aziridines **7b** and **7b'** as a sticky solid in 87% isolated yield (96.6 mg, 0.174 mmol). The diastereomeric ratio of (2*S*,4*S*)-**7b'** and (2*R*,4*S*)-**7b** 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 222 nm, flow-rate: 0.7 mL/min), retention imes: R_t = 12.36 min (minor diastereomer, (2*R*,4*S*)-**7b**) and R_t = 13.94 min (major diastereomer, (2*S*,4*S*)-**7b'**).

Aldehyde (*R*)-**5b** was reacted according to the general procedure with (*R*)-VANOL (8.8 mg, 0.020 mmol), as ligand at –10 °C to afford aziridines (2*S*,4*S*)-**7b'** and (2*R*,4*S*)-**7b** with a 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 an inseparable mixture of aziridines **7b** and **7b'** as a sticky solid in 82 % isolated yield (91 mg, 0.164 mmol).

Spectral data for (2*S*,4*S*)-**7b'**: R_f = 0.37 (4:1:0.2 hexanes/CH_2Cl_2/Et_2O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ –0.06 (s, 3H), –0.04 (s, 3H), 0.71 (d, 3H, *J* = 6.2 Hz), 0.82 (s, 9H), 1.26 (t, 3H, *J* = 7.1 Hz), 2.06 (dd, 1H, *J* = 8.2, 6.5 Hz), 2.22-2.24 (m, 13H), 3.45 (s, 1H), 3.66

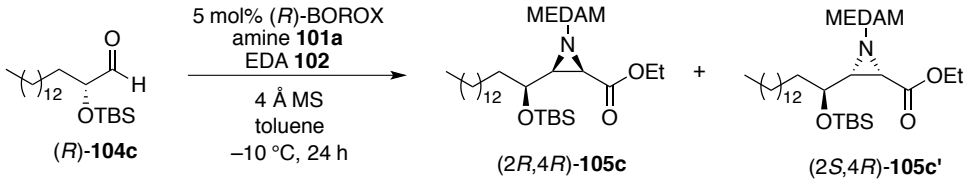
(s, 3H), 3.70 (s, 3H), 3.72- 3.81 (m, 1H), 4.06-4.28 (m, 33m), 6.95 (s, 33m), 7.07 (s, 33m); ^{13}C-NMR (125 MHz, $CDCl_3$) δ – 4.91, –4.34, 14.15, 16.05, 16.16, 17.84, 22.18, 25.70, 43.47, 53.01, 59.59, 59.64, 60.78, 66.12, 127.16, 128.66, 130.43, 130.53, 137.48, 137.76, 155.76, 156.42, 169.50 (one sp^3 carbon not located); IR (thin film) 2957vs, 2930vs, 1744s, 1483s, 1221s, 1194vs cm^{-1}; HRMS (ESI-TOF) *m/z* 556.3470 [$(M+H^+)$; calcd for $C_{333m50}NO_5Si$: 556.3458]; $[\alpha]_D^{20}$ –93.3° (c 0.6, CH_2Cl_2) on 96:4 *dr* material (HPLC).



*(2R,3S)-ethyl 1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-((S)-(tert-butyldimethylsilyloxy)ethyl) aziridine-2-carboxylate (2R,4S)-7**b***: Aldehyde (*S*)-**5b** was reacted according to the general procedure with (*S*)-VAPOL (11 mg, 0.020 mmol) as ligand at –10 °C to afford aziridines (2*R*,4*S*)-**7b** and (2*S*,4*S*)-**7b'** in a 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 an inseparable mixture of aziridines **7b** and **7b'** as a sticky solid in 85% isolated yield (94.1 mg, 0.170 mmol). The diastereomeric ratio of (2*R*,4*S*)-**7b** to (2*S*,4*S*)-**7b'** 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 222 nm, flow-rate: 0.7 mL/min), retention times: R_t = 11.63 min (major diastereomer, (2*R*,4*S*)-**7b**) and R_t = 13.67 min (minor diastereomer, (2*S*,4*S*)-**7b'**).

Spectral data for (2*R*,4*S*)-**7b**: R_f = 0.37 (4:1:0.2 hexanes/CH_2Cl_2/Et_2O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ –0.33 (s, 3H), –0.02 (s, 3H), 0.70 (s, 9H), 1.05 (d, 3H, *J* = 6.3 Hz), 1.27

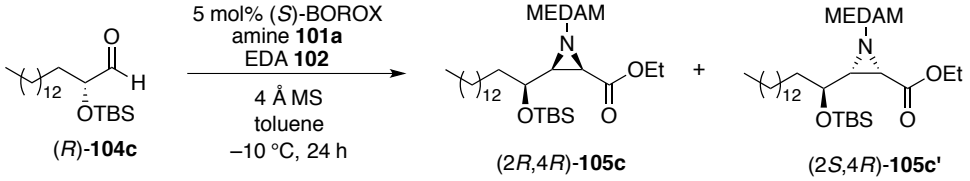
(t, 3H, J = 7.1 Hz), 2.07 (d, 1H, J = 7.1 Hz), 2.14-2.19 (m, 1H), 2.22 (s, 6H), 2.23 (s, 6H), 3.42 (s, 1H), 3.66 (s, 3H), 3.68 (s, 3H), 3.75-3.84 (m, 1H), 4.11-4.26 (m, 33m), 6.96 (s, 33m), 7.04 (s, 33m); ^{13}C-NMR (125 MHz, $CDCl_3$) δ –5.13, –5.00, 14.32, 16.18, 17.93, 21.52, 25.69, 41.53, 54.44, 59.38, 59.57, 60.71, 67.51, 77.78, 127.28, 128.76, 130.35, 130.40, 137.87, 138.15, 155.63, 156.14, 169.80 (one sp^3 carbon not located); IR (thin film) 2928vs, 2956s, 1746s, 1484s, 1221s, 1188vs, 1097s cm^{-1}; HRMS (ESI-TOF) *m/z* 556.3475 [(M+H$^+$); calcd. for $C_{333m50}NO_5Si$: 556.3458]; $[\alpha]_D^{20}$ +69.8° (c 0.6, CH_2Cl_2) on 91:9 *dr* material (HPLC).



(2S,3R)-ethyl 1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-((R)-1-((tertbutyldimethylsilyl)oxy) penta- decyl)aziridine-2-carboxylate ***105c'*** (Table 2 entry 5): Aldehyde (*R*)-**104c** was reacted according to the general procedure with 5 mol% catalyst prepared from (*R*)-VAPOL at –10 °C and 0.2 M to afford aziridine (2*S*,4*R*)-**105c'**. 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 aziridine **105c'** as a colorless oil in 94 % isolated yield (347 mg, 0.470 mmol). The diastereomeric ratio of **105c'** and **105c** was determined to be >99:1 by HPLC analysis of the 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, **105c'**) and R_t = 12.52 min (minor diastereomer, **105c**).

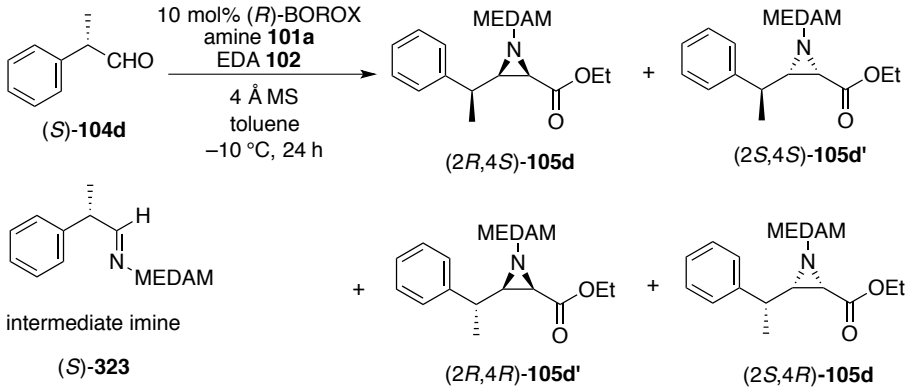
Spectral data for **105c'**: R_f = 0.44 (2:1:0.1 hexanes/CH_2Cl_2/Et_2O); ^{1}H NMR (300 MHz,

$CDCl_3$): δ –0.35 (s, 3H), –0.02 (s, 3H), 0.88 (t, 3H, *J* = 6.7 Hz), 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, 105h), 4.22-4.11 (m, 33m), 6.95 (s, 33m), 7.00 (s, 33m); ^{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, 127.51, 128.86, 130.33, 130.39, 137.81, 138.01, 155.66, 156.11, 170.05 (one sp^3 carbon not located); IR (thin film) 2928vs, 2855vs, 1747s, 1485s, 1221s, 1184vs cm^{-1}; HRMS (ESI-TOF) *m/z* 738.5469 [(M^++H); calcd. for $C_{4104h76}NO_5Si$: 738.5472]; $[\alpha]_D^{20}$ –68.3° (c 1.0, CH_2Cl_2).



(2R,3R)-ethyl 1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-((R)-1-((tertbutyldimethylsilyl)oxy) penta-decyl)aziridine-2-carboxylate ***105c***: Aldehyde (*R*)-**104c** was reacted according to the general procedure with 5 mol% catalyst prepared from (*S*)-VAPOL at –10 °C and 0.2 M to afford a mixture of aziridines (2*R*,4*R*)-**105c** and (2*S*,4*R*)-**105c'** with a 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 an inseparable mixture of aziridines **105c** and **105c'** as a colorless oil in 88% isolated yield (325 mg, 0.440 mmol). Spectral data for **105c**: R_f = 0.44 (2:1:0.1 hexanes/CH_2Cl_2/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, 3H, *J* = 7.0 Hz), 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),

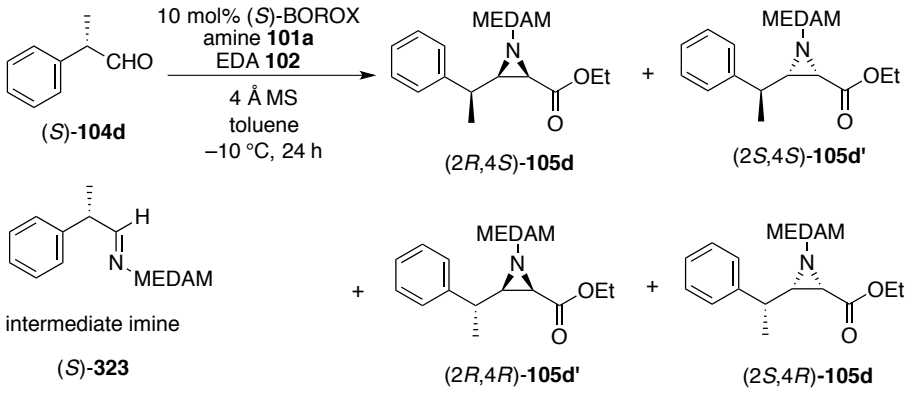
3.71-3.74 (m, 1H), 4.09-4.28 (m, 33m), 6.99 (s, 33m), 7.07 (s, 33m); ^{13}C-NMR (126 MHz, $CDCl_3$): δ –4.65, –4.56, 14.08, 14.14, 16.08, 16.13, 18.00, 22.67, 23.74, 25.77, 25.78, 29.34, 29.58, 29.60, 29.63, 29.65, 29.68, 29.94, 31.91, 35.90, 43.34, 51.96, 59.47, 59.54, 60.74, 69.01, 77.73, 127.01, 128.55, 130.41, 130.50, 137.69, 137.77, 155.71, 156.43, 169.70 (one sp^3 carbon not located); IR (thin film) 2928vs, 2855vs, 1744s, 1483s, 1221s, 1186vs cm^{-1}; HRMS (ESI-TOF) *m/z* 738.5471 [(M^++H); calcd for $C_{4104h76}NO_5Si$: 738.5472]; $[\alpha]_D^{20}$ +36.0° (c 1.0, CH_2Cl_2).



*(2S,3S)-ethyl 1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-((S)-1-phenylethyl)aziridine-2-carboxylate (2S,4S)-**105d'***: Aldehyde (*S*)-**104d** was reacted according to the general procedure with (*R*)-VAPOL (11 mg, 0.020 mmol) as ligand and EDA (83 μL, 0.80 mmol, 4.0 equiv) at –10 °C and at 0.04 M in amine **101a**. 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 an inseparable mixture of aziridines **105d** and **105d'** as a sticky solid in 90% isolated yield (90.3 mg, 0.180 mmol). The stereoisomeric ratio of **105d'**, **105d**, *ent*-**105d'** and *ent*-**105d** 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 226 nm, flow-rate: 0.7 mL/min), retention times: R_t = 14.90 min (*ent*-**105d'**), R_t = 15.79 min (**105d**), R_t =

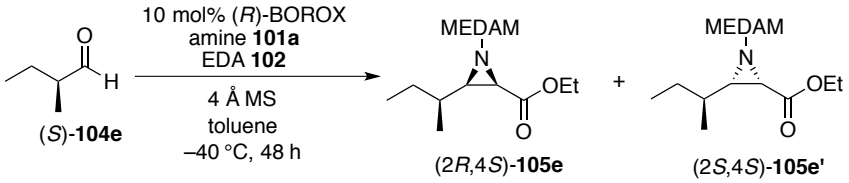
21.82 min (**105d'**) and R_t = 26.25 min (*ent*-**105d**). Analysis of the HPLC data lead to the following results: *dr* = 5:1 (**105d'** + *ent*-**105d'**) : (**105d** + *ent*-**105d**); % *ee* **105d'** 99.9%; % *ee of* **105d** 43%. Although no imine **34d** was detected at the end of the reaction, the % *ee* of intermediate imine (*S*)-**34d** was calculated as 93% from the ratio (**105d'** + **105d**) : (*ent*-**105d'** + *ent*-**105d**). The reaction was repeated at 0.4 M in amine **123a** and gave the following results: 90% yield, *dr* = 3.5:1 (**105d'** + *ent*-**105d'**) : (**105d** + *ent*-**105d**); % *ee* **105d'** 99.5%; % *ee of* **105d** –35%. Although no imine **34d** was detected at the end of the reaction, the % *ee* of intermediate imine (*S*)-**34d** was calculated as 69% from the ratio (**105d'** + **105d**) : (*ent*-**105d'** + *ent*-**105d**).

Spectral data for (2*S*,4*S*)-**105d'**: R_f = 0.31 (4:1:0.2 hexanes/CH_2Cl_2/Et_2O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.15 (d, 3H, *J* = 7.2 Hz), 1.31 (t, 3H, *J* = 7.1 Hz), 2.02 (s, 6H), 2.19 (dd, 1H, *J* = 6.4, 3.1 Hz), 2.22 (s, 6H), 2.26 (d, 1H, *J* = 6.8 Hz), 2.80-2.86 (m, 1H), 3.33 (s, 1H), 3.61 (s, 3H), 3.67 (s, 3H), 4.23-4.30 (m, 33m), 6.63 (s, 33m), 6.96-7.00 (m, 104h), 7.04 (s, 33m); ^{13}C-NMR (125 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 sp^2 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 $C_{333m40}NO_4$: 502.2957]; $[\alpha]_D^{20}$ –73.9° (c 0.6, CH_2Cl_2) on *dr* = 4:1 material (HPLC).



*(2R,3R)-ethyl 1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-((S)-1-phenylethyl)aziridine-2-carboxylate (2R,4S)-**7c***: Aldehyde (*S*)-**104d** was reacted according to the general procedure with (*S*)-VAPOL (11 mg, 0.020 mmol) as ligand and EDA (83 μL, 0.80 mmol, 4.0 equiv) at –10 °C and at 0.04 M in amine **101a.** 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 an inseparable mixture of aziridines **105d** and **105d'** as a sticky solid in 92% isolated yield (91.8 mg, 0.184 mmol). The diastereomeric ratio of **105d'**, **105d**, *ent*-**105d'** and *ent*-**105d** 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 226 nm, flow-rate: 0.7 mL/min). Comparing the HPLC data following results were determined: *dr* = 24:1 (**105d** + *ent*-**105d**):(**105d** + *ent*-**105d'**); % *ee* of **105d** is 99%; % *ee* of *ent*-**105d'** is –80%. Although no imine **34d** was detected at the end of the reaction, the % *ee* intermediate imine (*S*)-**34d** was calculated as 91% *ee* from the ratio (**105d** + **105d'**):(*ent*-**105d** + *ent*-**105d'**). The reaction was repeated at 0.4 M in amine **123a** and gave the following results: 85% yield, *dr* = 11:1 (**105d** + *ent*-**105d**):(**105d** + *ent*-**105d'**); % *ee* of **105d** is 96.4%; % *ee* of *ent*-**105d'** is –86%. Although no imine **34d** was detected at the end of the reaction, the % *ee* intermediate imine (*S*)-**34d** was calculated as 81% *ee* from

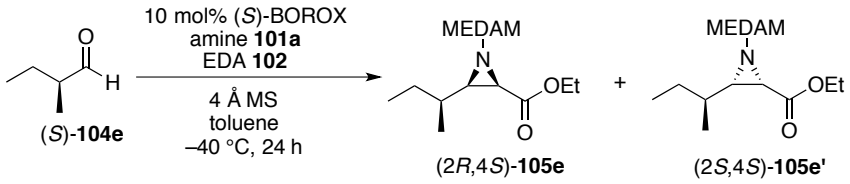
the ratio (**105d** + **105d'**):(*ent*-**105d** + *ent*-**105d'**). Spectral data for (2*R*,4*S*)-**105d**: R_f = 0.31 (4:1:0.2 hexanes/CH_2Cl_2/Et_2O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.90 (d, 3H, *J* = 7.0 Hz), 1.10 (t, 3H, *J* = 7.1 Hz), 2.14 (dd, 1H, *J* = 9.4, 6.8 Hz), 2.20 (d, 1H, *J* = 6.8 Hz), 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, 33m, *J* = 7.1 Hz), 7.07 (s, 33m), 7.10 (dd, 33m, *J* = 8.2, 1.2 Hz), 7.14 (s, 33m), 7.16-7.19 (m, 1H), 7.23-7.27 (m, 33m); ^{13}C-NMR (125 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 $C_{333m40}NO_4$: 502.2957]; $[\alpha]_D^{20}$ +108.9° (c 0.6, CH_2Cl_2) on 23:1 *dr* material (HPLC).



*(2S,3S)-ethyl 1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-((S)-sec-butyl)aziridine-2-carboxylate (2S,4S)-**105e'***: Aldehyde (*S*)-**104e** (1.62 mL, 2 M in toluene, 3.24 mmol, 1.20 equiv) was reacted according to the general procedure with (*R*)-^{t}Bu$_2$VAPOL (145 mg, 0.270 mmol) as ligand and $B(OPh)_3$ (235 mg, 0.810 mmol) at –40 °C for 48 h to afford aziridines (2*S*,4*S*)-**105e'** and (2*R*,4*S*)-**105e** with 96:4 diastereomeric ratio. Purification of the crude aziridine by neutral alumina chromatography (20 mm × 150 mm column, 10:1 hexanes/EtOAc as eluent, gravity column) afforded an inseparable mixture of aziridines **105e'** and **105e** as a viscous liquid in 90% isolated yield (1.10 g, 2.43 mmol). The diastereomeric ratio of (2*S*,4*S*)-**105e'** and (2*R*,4*S*)-**105e** was determined to be

96:4 by ^{1}H-NMR with Ph_3CH as the internal standard.

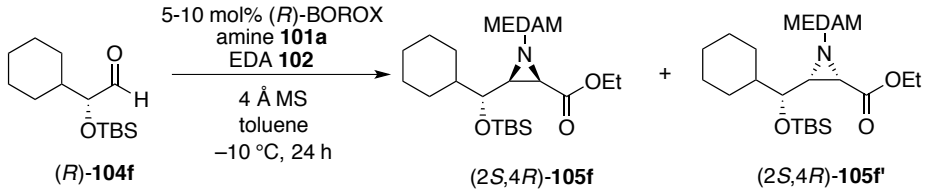
Spectral data for (2*S*,4*S*)-**105e'**: R_f = 0.70 (3:1 hexanes/EtOAc); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.56 (t, 3H, *J* = 5.0 Hz), 0.76 (d, 3H, *J* = 5.0 Hz), 1.03-1.09 (m, 1H), 1.25 (t, 3H, *J* = 5.0 Hz), 1.27 (m, 1H), 1.35-1.42 (m, 1H), 1.71 (dd, 1H, *J* = 10.0, 5.0 Hz), 2.20 (d, 1H, *J* = 5.0 Hz), 2.23 (s, 6H), 2.24 (s, 6H), 3.38 (s, 1H), 3.66 (s, 3H), 3.69 (s, 3H), 4.14-4.27 (m, 33m), 6.98 (s, 33m), 7.11 (s, 33m); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 10.09, 14.35, 15.78, 16.05, 16.18, 26.91, 33.15, 43.61, 52.65, 59.61, 59.65, 60.67, 77.53, 127.29, 128.57, 130.38, 130.47, 137.56, 138.10,155.69, 156.27, 169.76; IR (thin film) 2960vs, 1750s, 1442s, 1275vs, 1260vs, 1038s cm^{-1}; HRMS (ESI-TOF) *m/z* 476.2770 [(M+Na$^+$); calcd. for $C_{28}H_{39}NO_4Na$: 476.2777]; $[\alpha]_D^{20}$ –99.5° (c 0.4, CH_2Cl_2) on 96:4 *dr* material (NMR).



*(2R,3R)-ethyl 1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-((S)-sec-butyl)aziridine-2-carboxylate (2R,4S)-**105e***: Aldehyde (*S*)-**104e** (2.40 mL, 2 M in toluene, 4.80 mmol, 1.20 equiv) was reacted according to the general procedure with (*S*)-^{t}Bu$_2$VAPOL (215 mg, 0.400 mmol) as ligand and $B(OPh)_3$ (348 mg, 1.20 mmol) at –40 °C for 24 h afforded aziridines (2*R*,4*S*)-**105e** and (2*S*,4*S*)-**105e'** with a 96:4 diastereomeric ratio. Purification of the crude aziridines by neutral alumina chromatography (20 mm × 150 mm column, 10:1 hexanes/EtOAc as eluent, gravity column) afforded an inseparable mixture of aziridines **105e** and **105e'** as a viscous liquid in 95% isolated yield (1.72 g, 3.80 mmol). The diastereomeric ratio of (2*R*,4*S*)-**105e** to (2*S*,4*S*)-**105e'** was determined to be 96:4 by

^{1}H-NMR with Ph_3CH as the internal standard.

Spectral data for (2*R*,4*S*)-**105e**: R_f = 0.70 (3:1 hexanes/EtOAc); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.48 (d, 3H, *J* = 5 Hz), 0.78 (t, 3H, *J* = 5.0 Hz), 1.11-1.14 (m, 1H), 1.25 (t, 3H, *J* = 5.0 Hz), 1.26 (m, 1H), 1.39-1.42 (m, 1H), 1.71 (dd, 1H, *J* = 10.0, 5.0 Hz), 2.20 (d, 1H, *J* = 5.0 Hz), 2.23 (s, 6H), 2.24 (s, 6H), 3.37 (s, 1H), 3.66 (s, 3H), 3.69 (s, 3H), 4.16-4.24 (m, 33m), 6.91 (s, 33m), 7.11 (s, 33m); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 11.23, 14.34, 16.08, 16.19, 17.65, 27.46, 33.37, 44.14, 53.08, 59.61, 59.66, 60.66, 77.64, 127.30, 128.60, 130.37, 130.48, 137.66, 138.09, 155.70, 156.27, 169.91; IR (thin film) 2958vs, 1744s, 1438s, 1275vs, 1260vs, 1017s cm^{-1}; HRMS (ESI-TOF) *m/z* 476.2769 [(M+Na$^+$); calcd. for $C_{28}H_{39}NO_4Na$: 476.2777]; $[\alpha]_D^{20}$ +70.1° (c 1.0, CH_2Cl_2) on 96:4 *dr* material (NMR).



*(2S,3R)-ethyl 1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-((R)-(tert-butyldimethylsilyloxy) (cyclohexyl) methyl)aziridine-2-carboxylate (2S,4R)-**105f'***: Aldehyde (*R*)-**104f** was reacted according to the general procedure with 5 mol% catalyst prepared from (*R*)-^{t}Bu$_2$VAPOL (5.5 mg, 0.010 mmol) as ligand and $B(OPh)_3$ (8.7 mg, 0.030 mmol) to afford aziridines (2*S*,4*R*)-**105f'** and (2*R*,4*R*)-**105f** with a 99:1 diastereomeric ratio. Purification of the crude aziridines by neutral alumina chromatography (20 mm × 150 mm column, 4:2:0.1 hexanes/CH_2Cl_2/Et_2O as eluent, gravity column) afforded an inseparable mixture of aziridines **105f'** and **105f** as a white solid (mp 48-50 °C on 99:1 *dr* material) in 93% isolated yield (116 mg, 0.186 mmol).

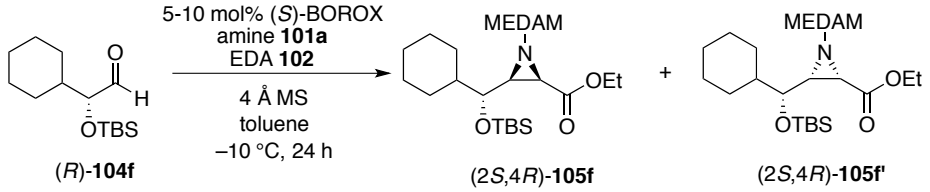
The diastereomeric ratio of (2*S*,4*R*)-**105f'** to (2*R*,4*R*)-**105f** was determined to be 99.9:0.1 by HPLC analysis of the crude reaction mixture (PIRKLE COVALENT (R, R) WHELK-O 1 column, 99.5:0.5 hexane/2-propanol at 222 nm, flow-rate: 0.7 mL/min), retention times: R_t = 10.73 min (minor diastereomer, (2*R*,4*R*)-**105f**) and R_t = 13.51 min (major diastereomer, (2*S*,4*R*)-**105f'**).

Aldehyde (*R*)-**104f** was reacted according to the general procedure with 10 mol% catalyst prepared from (*R*)-VAPOL (5.4 mg, 0.010 mmol) to afford aziridines (2*S*,4*R*)-**105f'** and (2*R*,4*R*)-**105f** with 99:1 diastereomeric ratio. Purification of the crude aziridines by neutral alumina chromatography (20 mm × 150 mm column, 4:2:0.1 hexanes/CH_2Cl_2/Et_2O as eluent, gravity column) afforded an inseparable mixture of aziridines **105f'** and **105f** as a white solid in 85% isolated yield (106 mg, 0.170 mmol).

Aldehyde (*R*)-**104f** was reacted according to the general procedure **b1** with 10 mol% catalyst prepared from (*R*)-VANOL (4.4 mg, 0.010 mmol) to afford aziridines (2*S*,4*R*)-**105f'** and (2*R*,4*R*)-**105f** with 99:1 diastereomeric ratio. Purification of the crude aziridines by neutral alumina chromatography (20 mm × 150 mm column, 4:2:0.1 hexanes/CH_2Cl_2/Et_2O as eluent, gravity column) afforded an inseparable mixture of aziridines **105f'** and **105f** as a white solid in 80% isolated yield (100 mg, 0.160 mmol).

Spectral data for (2*S*,4*R*)-**105f'**: R_f = 0.30 (4:1:0.2 hexanes/CH_2Cl_2/Et_2O); ^{1}H-NMR (500 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, 3H, *J* = 7.1 Hz), 1.55-1.73 (m, 104h), 2.04 (d, 1H, *J* = 6.9 Hz), 2.21-2.25 (m, 13H), 3.52 (dd, 1H, *J* = 8.5, 3.8 Hz), 3.63 (s, 1H), 3.67 (s, 3H), 3.70 (s, 3H), 4.18 (qd, 33m, *J* = 7.1, 1.7 Hz), 6.92 (s, 33m), 6.96 (s, 33m); ^{13}C-NMR (125 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* 624.4073 [(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).

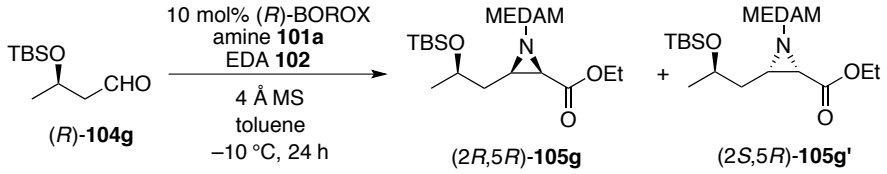


*(2R,3S)-ethyl 1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-((R)-(tert-butyldimethylsilyloxy) (cyclohexyl) methyl)aziridine-2-carboxylate (2R,4R)-**105f***: Aldehyde (*R*)-**104f** was reacted according to the general procedure with 5 mol% catalyst prepared from (*S*)-^{t}Bu$_2$VAPOL (5.5 mg, 0.010 mmol) as ligand and $B(OPh)_3$ (8.7 mg, 0.030 mmol) to afford aziridines (2*R*,4*R*)-**105f** and (2*S*,4*R*)-**105f'** with a 82:18 diastereomeric ratio. Purification of the crude aziridines by neutral alumina chromatography (20 mm × 150 mm column, 4:2:0.1 hexanes/CH_2Cl_2/Et_2O as eluent, gravity column) afforded an inseparable mixture of aziridines **105f** and **105f'** as a white solid (mp 42-45 °C on 82:18 *dr* material) in 75% isolated yield (93.5 mg, 0.150 mmol).

Aldehyde (*R*)-**104f** was reacted according to the general procedure **b1** with 10 mol% catalyst prepared from (*S*)-VAPOL (5.4 mg, 0.010 mmol) to afford aziridines (2*R*,4*R*)-**105f** and (2*S*,4*R*)-**105f'** with 52:48 diastereomeric ratio. Purification of the crude aziridines by neutral alumina chromatography (20 mm × 150 mm column, 4:2:0.1 hexanes/CH_2Cl_2/Et_2O as eluent, gravity column) afforded an inseparable mixture of aziridines **105f** and **105f'** as a white solid in 30% isolated yield (37.0 mg, 0.060 mmol).

Aldehyde (*R*)-**104f** was reacted according to the general procedure with 10 mol%

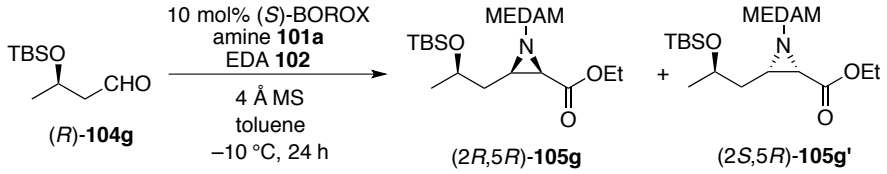
catalyst prepared from (*S*)-VANOL (4.4 mg, 0.010 mmol) to afford aziridines (2*R*,4*R*)-**105f** and (2*S*,4*R*)-**105f'** with 60:40 diastereomeric ratio. Purification of the crude aziridines by neutral alumina chromatography (20 mm × 150 mm column, 4:2:0.1 hexanes/CH_2Cl_2/Et_2O as eluent, gravity column) afforded an inseparable mixture of aziridines **105f** and **105f'** as a white solid in 15% isolated yield (19.1 mg, 0.030 mmol). Spectral data for (2*R*,4*R*)-**105f**: R_f = 0.30 (4:1:0.2 hexanes/CH_2Cl_2/Et_2O); ^{1}H-NMR (600 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, 3H, *J* = 7.1 Hz), 1.57- 1.86 (m, 104h), 2.14 (d, 1H, *J* = 6.4 Hz), 2.21-2.23 (m, 13H), 3.42 (s, 1H), 3.54 (d, 1H, *J* = 8.1 Hz), 3.67 (s, 3H), 3.68 (s, 3H), 4.05-4.31 (m, 33m), 7.03 (s, 4H); ^{13}C-NMR (150 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. IR (thin film) 2929vs, 2854s, 1737s, 1472s, 1250s, 1221s, 1181vs, 1147vs, 1051vs cm^{-1}; HRMS (ESI-TOF) *m/z* 624.4098 [(M+H$^+$); calcd. for $C_{37}H_{58}NO_5Si$: 624.4084; $[\alpha]_D^{20}$ +40.3° (c 1.0, EtOAc) on 82:18 *dr* material (HPLC).



*(2S,3S)-ethyl 1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-((R)-2-(tert-butyldimethylsilyloxy) propyl) aziridine-2-carboxylate (2S,5R)-**105g'***: Aldehyde (*R*)-**104g** was reacted according to the general procedure with (*R*)-VAPOL (11 mg, 0.020 mmol) as ligand to afford aziridines (2*S*,5*R*)-**105g'** and (2*R*,5*R*)-**105g** with a 99:1 diastereomeric ratio. Purification of the crude aziridines by neutral alumina chromatography (20 mm × 150 mm column, 4:2:0.1 hexanes/CH_2Cl_2/Et_2O as eluent, gravity column) afforded an

inseparable mixture of aziridines **105g'** and **105g** as a viscous liquid in 85% isolated yield (97.3 mg, 0.170 mmol). The diastereomeric ratio of (2*S*,5*R*)-**105g'** to (2*R*,5*R*)-**105g** 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 222 nm, flow-rate: 0.7 mL/min), retention times: R_t = 20.83 min (minor diastereomer, (2*R*,5*R*)-**105g**) and R_t = 28.04 min (major diastereomer, (2*S*,5*R*)-**105g'**).

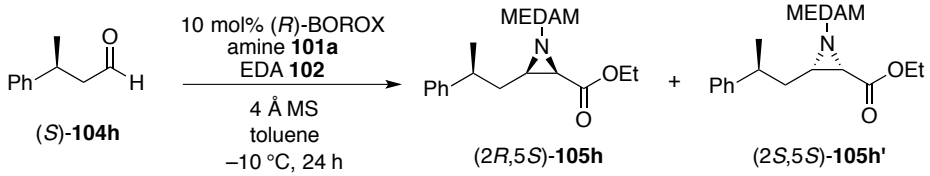
Spectral data for (2*S*,5*R*)-**105g'**: R_f = 0.34 (4:1:0.2 hexanes/CH_2Cl_2/Et_2O); ^{1}H-NMR (300 MHz, $CDCl_3$) δ –0.21 (s, 3H), –0.10 (s, 3H), 0.80 (s, 9H), 1.04 (d, 3H, *J* = 6.2 Hz), 1.24 (t, 3H, *J* = 7.1 Hz), 1.77-1.59 (m, 33m), 2.16-2.24 (m, 14H), 3.43 (s, 1H), 3.68 (s, 6H), 3.70-3.76 (m, 1H), 4.17 (q, 33m, *J* = 7.1 Hz), 7.07 (s, 33m), 7.08 (s, 33m); ^{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).



*(2R,3R)-ethyl 1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-((R)-(tert-butyldimethylsilyloxy) ethyl) aziridine-2-carboxylate (2R,5R)-**105g***: Aldehyde (*R*)-**104g** was reacted according to the general procedure with (*S*)-VAPOL (11 mg, 0.020 mmol) as ligand to afford aziridines (2*R*,5*R*)-**105g** and (2*S*,5*R*)-**105g'** with a 98:2 diastereomeric ratio. Purification of the crude aziridines by neutral alumina chromatography (20 mm ×

150 mm column, 4:2:0.1 hexanes/CH_2Cl_2/Et_2O as eluent, gravity column) afforded an inseparable mixture of aziridines **105g** and **105g'** as a sticky solid in 83% isolated yield (94.0 mg, 0.160 mmol). The diastereomeric ratio of (2*R*,5*R*)-**105g** to (2*S*,5*R*)-**105g'** was determined to be 98:2 by HPLC analysis of the crude reaction mixture (PIRKLE COVALENT (R, R) WHELK-O 1 column, 99.5:0.5 hexane/2-propanol at 222 nm, flow-rate: 0.7 mL/min), retention times: R_t = 20.28 min (major diastereomer, (2*R*,4*S*)-**105g**) and R_t = 29.15 min (minor diastereomer, (2*S*,4*S*)-**105g'**).

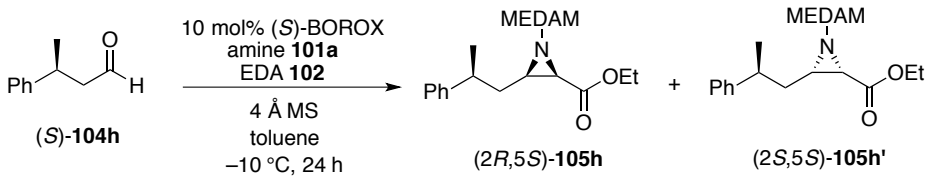
Spectral data for (2*R*,5*R*)-**105g**: R_f = 0.34 (4:1:0.2 hexanes/CH_2Cl_2/Et_2O); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.00 (s, 3H), 0.02 (s, 3H), 0.86 (s, 9H), 0.88 (d, 3H, *J* = 6.1 Hz), 1.26 (t, 3H, *J* = 7.1 Hz), 1.56 (ddd, 1H, *J* = 13.6, 6.7, 6.7 Hz), 1.78 (ddd, 1H, *J* = 13.6, 6.7, 6.7 Hz), 2.07 (q, 1H, *J* = 6.5 Hz), 2.19 (d, 1H, *J* = 6.8 Hz), 2.24 (s, 125m), 3.56 (q, 1H, *J* = 6.3 Hz), 3.68 (s, 3H), 3.68 (s, 3H), 4.25-4.13 (m, 33m), 6.99 (s, 33m), 7.08 (s, 33m); ^{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, 127.36, 128.03, 130.47, 130.50, 137.72, 138.06, 155.77, 156.12, 169.62, (one sp^3 carbon not located); 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 0.6, CH_2Cl_2) on 98:2 *dr* material (HPLC).



*(2S,3S)-ethyl 1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-((S)-2-phenylpropyl)aziridine-2-carboxylate (2S,5S)-**105h'***: Aldehyde (*S*)-**104h** was reacted

according to the general procedure with (*R*)-VAPOL (11 mg, 0.020 mmol) as ligand to afford aziridines (2*S*,5*S*)-**105h'** and (2*R*,5*S*)-**105h** with >99:1 diastereomeric ratio. Purification of the crude aziridines by neutral alumina chromatography (20 mm × 150 mm column, 4:2:0.1 hexanes/CH_2Cl_2/Et_2O as eluent, gravity column) afforded an inseparable mixture of aziridines **105h'** and **105h** as a white solid (mp 101-102 °C on 99:1 *dr* material) in 85% isolated yield (87.8 mg, 0.170 mmol). The diastereomeric ratio of (2*S*,5*S*)-**105h'** to (2*R*,5*S*)-**105h** was determined to be 99.4:0.6 by HPLC analysis of the crude reaction mixture (PIRKLE COVALENT (R, R) WHELK-O 1 column, 99.5:0.5 hexane/2-propanol at 222 nm, flow-rate: 0.7 mL/min), retention times: R_t = 18.49 min (minor diastereomer, (2*R*,5*S*)-**105h**) and R_t = 31.04 min (major diastereomer, (2*S*,5*S*)-**105h'**).

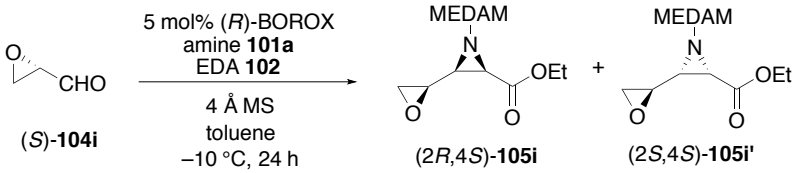
Spectral data for (2*S*,5*S*)-**105h'**: R_f = 0.32 (4:1:0.2 hexanes/CH_2Cl_2/Et_2O); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.02 (d, 3H, *J* = 6.9 Hz), 1.27 (t, 3H, *J* = 7.1 Hz), 1.71-1.81 (m, 1H), 1.85-1.97 (m, 33m), 2.22-2.54 (m, 13H), 2.45-2.55 (m, 1H), 3.40 (s, 1H), 3.68 (s, 3H), 3.69 (s, 3H), 4.20 (qd, 33m, *J* = 7.1, 2.3 Hz), 7.02 (s, 33m), 7.08 (s, 33m), 7.10-7.28 (m, 104h); ^{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 sp^2 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).



*(2R,3R)-ethyl 1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-((S)-2-phenylpropyl)aziridine-2-carboxylate (2R,5S)-**105h***: Aldehyde (*S*)-**104h** was reacted according to the general procedure with (*S*)-VAPOL (11 mg, 0.02 mmol) as ligand to afford aziridines (2*R*,5*S*)-**105h** and (2*S*,5*S*)-**105h'** with a 94:6 diastereomeric ratio. Purification of the crude aziridines by neutral alumina chromatography (20 mm × 150 mm column, 4:2:0.1 hexanes/CH_2Cl_2/Et_2O as eluent, gravity column) afforded an inseparable mixture of aziridines **105h** and **105h'** as a sticky solid in 80% isolated yield (82.4 mg, 0.16 mmol). The diastereomeric ratio of (2*R*,5*S*)-**105h** to (2*S*,5*S*)-**105h'** was determined to be 94:6 by HPLC analysis of crude reaction mixture (PIRKLE COVALENT (R, R) WHELK-O 1 column, 99.5:0.5 hexane/2-propanol at 222 nm, flow-rate: 0.7 mL/min), retention times: R_t = 17.68 min (major diastereomer, (2*R*,5*S*)-**105h**) and R_t = 32.01 min (minor diastereomer, (2*S*,5*S*)-**105h'**).

Spectral data for (2*S*,5*S*)-**105h**: R_f = 0.32 (4:1:0.2 hexanes/CH_2Cl_2/Et_2O); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.14 (d, 3H, *J* = 7.0 Hz), 1.25 (t, 3H, *J* = 7.1 Hz), 1.73-1.83 (m, 33m), 2.07 (d, 1H, *J* = 6.3 Hz), 2.22-2.25 (m, 105h), 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, 33m), 6.68 (dd, 33m, *J* = 7.7, 1.7 Hz), 7.06 (s, 33m), 7.07 (s, 33m), 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, 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 sp^2 and one sp^3 carbon not located); IR (thin film) 2957vs, 2930vs, 1742s, 1483s, 1221s, 1186vs cm^{-1};

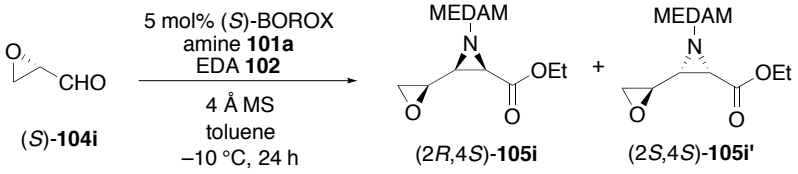
HRMS (ESI-TOF) *m/z* 516.3119 [(M+H$^+$); calcd. for $C_{33}H_{42}NO_4$: 516.3114]; $[\alpha]_D^{20}$ +70.6° (c 1.0, CH_2Cl_2) on 94:6 *dr* material (HPLC).



*(2S,3R)-ethyl 1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-((R)-oxiran-2-yl)aziridine-2-carboxylate (2S,4S)-**105i'***: Aldehyde (*S*)-**104i** (0.15 mL, 2 M in toluene, 0.30 mmol, 1.5 equiv) was reacted according to the general procedure with (*R*)-^{t}Bu$_2$VAPOL (5.5 mg, 0.010 mmol) as ligand and $B(OPh)_3$ (8.7 mg, 0.030 mmol) and EDA (48 μL, 0.40 mmol, 2.0 equiv) to afford aziridines (2*S*,4*R*)-**105i'** and (2*R*,4*R*)-**105i** with an 89:11 diastereomeric ratio. Purification of the crude aziridines by neutral alumina chromatography (20 mm × 150 mm column, 4:1 hexanes/Et_2O as eluent, flash column) afforded an inseparable mixture of aziridines **105i'** and **105i** as a viscous liquid in >99% isolated yield (87.8 mg, 0.200 mmol). The diastereomeric ratio of (2*S*,4*R*)-**105i'** to (2*R*,4*R*)-**105i** was determined to be 89:11 by HPLC analysis of the crude reaction mixture (PIRKLE COVALENT (R, R) WHELK-O 1 column, 85:15 hexane/2-propanol at 222 nm, flow-rate: 0.7 mL/min), retention times: R_t = 21.53 min (major diastereomer, (2*S*,4*R*)-**105i'**) and R_t = 31.19 min (minor diastereomer, (2*R*,4*R*)-**105i**).

Aldehyde (*S*)-**104i** was reacted according to the general procedure with (*R*)-VANOL (4.4 mg, 0.010 mmol) as ligand to afford aziridines (2*S*,4*R*)-**105i'** and (2*R*,4*R*)-**105i** with 88:12 diastereomeric ratio. Purification of the crude aziridines by neutral alumina chromatography (20 mm × 150 mm column, 4:1 hexanes/Et_2O as eluent, flash column) afforded an inseparable mixture of aziridines **105i'** and **105i** as a viscous liquid in >99% isolated yield (88.0 mg, 0.200 mmol).

Spectral data for (2*S*,4*R*)-**105i'**: R_f = 0.30 (1:1 hexanes/Et_2O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.26 (t, 3H, *J* = 7.2 Hz), 1.76 (t, 1H, *J* = 6.8 Hz), 2.22 (s, 125m), 2.34 (dd, 1H, *J* = 5.2, 4.2, 2.2 Hz), 2.37 (d, 1H, *J* = 7.0 Hz), 2.70 (dd, 1H, *J* = 4.2, 5.2 Hz), 3.11 (ddd, 1H, *J* = 2.2 Hz), 3.48 (s, 1H), 3.67 (d, 6H, *J* = 2.0 Hz), 4.20 (dq, 33m, *J* = 2.5, 7.2 Hz), 6.70 (s, 33m), 7.05 (s, 33m); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 14.18, 16.14, 16.18, 42.53, 46.14, 46.31, 48.83, 59.58, 59.61, 76.45, 115.25, 127.31, 127.69, 130.65, 130.69, 137.20, 137.50, 155.99, 156.14, 168.79; IR (thin film) 2937.5vs, 1743vs, 1484vs, 1220vs, 1192s, 1014s cm^{-1}; HRMS (ESI-TOF) *m/z* 462.2282 [(M+Na$^+$); calcd. for $C_{26}H_{33}NO_5Na$: 462.2251]; $[\alpha]_D^{20}$ –59.7° (c 1.0, $CHCl_3$) on 89:11 *dr* material (HPLC).

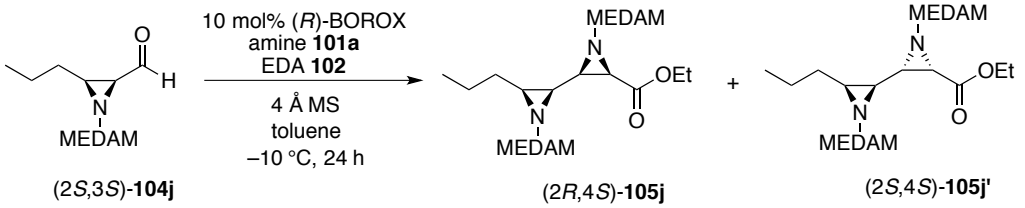


*(2R,3S)-ethyl 1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-((R)-oxiran-2-yl)aziridine-2-carboxylate (2R,4S)-**105i***: Aldehyde (*S*)-**104i** (0.15 mL, 2 M in toluene, 0.30 mmol, 1.5 equiv) was reacted according to the general procedure with (*S*)-^{t}Bu$_2$VAPOL (5.5 mg, 0.010 mmol) as ligand and $B(OPh)_3$ (8.7 mg, 0.030 mmol) and EDA (48 μL, 0.40 mmol, 2.0 equiv) to afford aziridines (2*R*,4*R*)-**105i** and (2*S*,4*R*)-**105i'** with 92:8 diastereomeric ratio. Purification of the crude aziridines by neutral alumina chromatography (20 mm × 150 mm column, 4:1 hexanes/Et_2O as eluent, flash column) afforded an inseparable mixture of aziridines **105i** and **105i'** as a viscous liquid in 96% isolated yield (84.3 mg, 0.192 mmol). The diastereomeric ratio of (2*R*,4*R*)-**105i** to (2*S*,4*R*)-**105i'** was determined to be 92:8 by HPLC analysis of the crude reaction mixture (PIRKLE COVALENT (R, R) WHELK-O 1 column, 85:15 hexane/2-propanol at 222 nm, flow-rate: 0.7 mL/min), retention times: R_t = 22.17 min (minor diastereomer, (2*S*,4*R*)-**105i'**) and R_t = 29.74 min

(major diastereomer, (2*R*,4*R*)-**105i**).

Aldehyde (*S*)-**104i** was reacted according to the general procedure with (*S*)-VANOL (4.4 mg, 0.010 mmol), as ligand to afford aziridines (2*R*,4*S*)-**105i** and (2*S*,4*S*)-**105i'** with 87:13 diastereomeric ratio. Purification of the crude aziridines by neutral alumina chromatography (20 mm × 150 mm column, 4:1 hexanes/Et_2O as eluent, flash column) afforded an inseparable mixture of aziridines **105i** and **105i'** as a viscous liquid in 99% isolated yield (86.6 mg, 0.198 mmol).

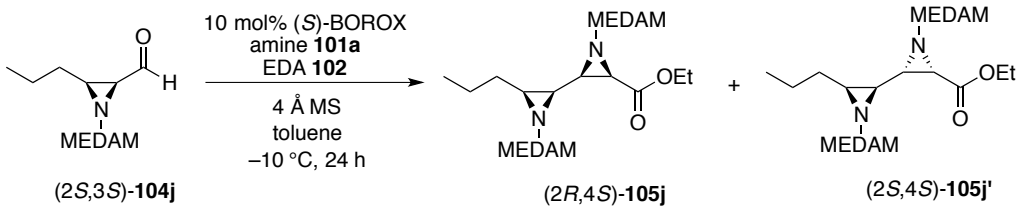
Spectral data for (2*S*,4*R*)-**105i**: R_f = 0.30 (1:1 hexanes/Et_2O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.24 (t, 3H, *J* = 7.0 Hz), 1.77 (t, 1H, *J* = 6.8 Hz), 2.23 (d, 125m, *J* = 5.0 Hz), 2.31 (d, 1H, *J* = 7.0 Hz), 2.53 (dd, 1H, *J* = 4.8, 2.8 Hz), 2.72 (t, 1H, *J* = 4.8 Hz), 3.22 (td, 1H), 3.53 (s, 1H, *J* = 4.8, 2.8 Hz), 3.67 (d, 6H, *J* = 2.0 Hz), 4.18 (q, 33m, *J* = 7.2 Hz), 7.05 (s, 4H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 14.18, 16.15, 16.17, 41.50, 45.14, 46.88, 50.07, 59.34, 61.10, 76.28, 115.24, 127.54, 127.58, 130.57, 130.62, 137.18, 137.40, 155.97, 156.04, 169.07; IR (thin film) 2937vs, 1743vs, 1439vs, 1221vs, 1192vs, 1015s cm^{-1}; HRMS (ESI-TOF) *m/z* 462.2288 [(M+Na^+); calcd. for $C_{26}H_{33}NO_5Na$: 462.2251]; $[\alpha]_D^{20}$ +30.8° (c 1.0, $CHCl_3$) on 92:8 *dr* material (HPLC).



*(2S,2'S,3S,3'S)-ethyl 1,1'-bis(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3'-propyl-[2,2'-biaziridine]-3-carboxylate (2S,4S)-**105j'***: Aldehyde (2*S*,3*S*)-**104j** was reacted according to the general procedure with (*R*)-VAPOL (11 mg, 0.020 mmol) as ligand to afford aziridines (2*S*,4*S*)-**105j'** and (2*R*,4*S*)-**105j** with 99:1 diastereomeric ratio. Purification of

the crude aziridines by neutral alumina chromatography (20 mm × 150 mm column, 4:2:0.1 hexanes/CH_2Cl_2/Et_2O as eluent, gravity column) afforded an inseparable mixture of aziridines **105j'** and **105j** as a white solid (mp 79-82 °C on 99:1 *dr* material) in 80% isolated yield (122 mg, 0.160 mmol). The diastereomeric ratio of (2*S*,4*S*)-**105j'** to (2*R*,4*S*)-**105j** was determined to be 99.5:0.5 by HPLC analysis of the crude reaction mixture (PIRKLE COVALENT (R, R) WHELK-O 1 column, 99.7:0.3 hexane/2-propanol at 222 nm, flow-rate: 0.7 mL/min), retention times: R_t = 16.30 min (minor diastereomer, (2*R*,4*S*)-**105j**) and R_t = 19.75 min (major diastereomer, (2*S*,4*S*)-**105j'**).

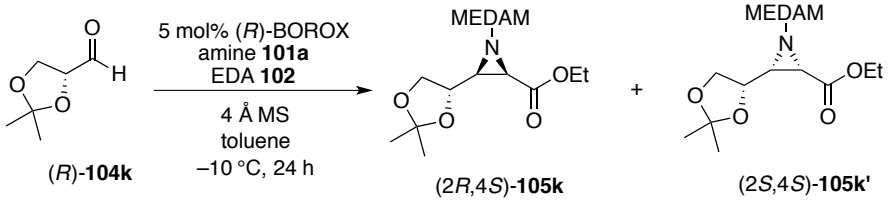
Spectral data for (2*S*,4*S*)-**105j'**: R_f = 0.25 (4:1:0.2 hexanes/CH_2Cl_2/Et_2O); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.49 (t, 33m, *J* = 6.5 Hz), 0.55-0.64 (m, 33m), 0.68-0.77 (m, 33m), 1.00 (t, 3H, *J* = 7.1 Hz), 1.50-1.56 (m, 1H), 1.80 (dd, 1H, *J* = 8.7, 6.7 Hz), 2.01-2.06 (m, 1H), 2.20-2.28 (m, 25H), 3.28 (s, 1H), 3.45 (s, 1H), 3.64 (brs, 6H), 3.66-3.67 (m, 6H), 6.87 (s, 33m), 6.97 (s, 4H), 7.04 (s, 33m); ^{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 sp^2 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).



(2R,2'S,3R,3'S)-ethyl 1,1'-bis(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3'-propyl-[2,2'-

*biaziridine]-3-carboxylate (2R,4S)-**105j***: Aldehyde (2*S*,3*S*)-**104j** was reacted according to the general procedure with (*S*)-VAPOL (11 mg, 0.020 mmol) as ligand to afford aziridines (2*R*,4*S*)-**105j** and (2*S*,4*S*)-**105j'** with a 99:1 diastereomeric ratio. Purification of the crude aziridines by neutral alumina chromatography (20 mm × 150 mm column, 4:2:0.1 hexanes/CH_2Cl_2/Et_2O as eluent, gravity column) afforded an inseparable mixture of aziridines **105j** and **105j'** as a white solid (mp 67-70 °C on >99:1 *dr* material) in 84% isolated yield (129 mg, 0.168 mmol).

Spectral data for (2*R*,4*S*)-**7i**: R_f = 0.25 (4:1:0.2 hexanes/CH_2Cl_2/Et_2O); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.61 (t, 3H, *J* = 7.2 Hz), 0.75-1.02(m, 33m), 1.07-1.28 (m, 5H), 1.50-1.57 (m, 1H), 2.01 (dd, 1H, *J* = 6.5, 5.3 Hz), 2.05 (s, 125m), 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, 33m, *J* = 7.1 Hz), 6.85 (s, 33m), 6.91 (s, 33m), 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, 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 (one sp^2 carbon not located); 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 (HPLC).



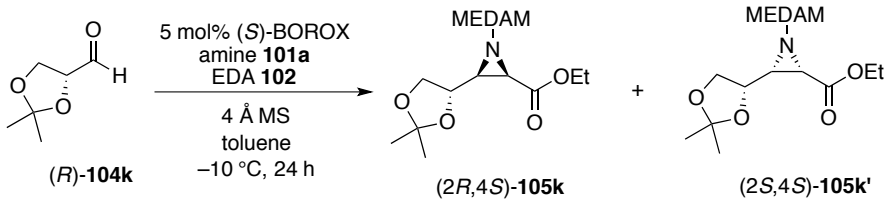
*(2S,3R)-ethyl 1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)aziridine -2-carboxylate (2S,4S)-**105k'***: (*R*)-2,2-dimethyl-1,3-dioxolane-4-

carboxaldehyde **104k** was reacted according to the general procedure with (*R*)-^{t}Bu$_2$VAPOL (5.5 mg, 0.010 mmol) as ligand and B(OPh)$_3$ (8.7 mg, 0.030 mmol) to afford aziridines (2*S*,4*S*)-**105k'** and (2*R*,4*S*)-**105k** with 97:3 diastereomeric ratio. Purification of the crude aziridines by neutral alumina chromatography (20 mm × 150 mm column, 2:1 hexanes/Et$_2$O as eluent, flash column) afforded an inseparable mixture of aziridines **105k'** and **105k** as a viscous liquid in 99% isolated yield (99.0 mg, 0.198 mmol). The diastereomeric ratio of (2*S*,4*S*)-**105k'** to (2*R*,4*S*)-**105k** was determined to be 97:3 by HPLC analysis of the crude reaction mixture (PIRKLE COVALENT (R, R) WHELK-O 1 column, 98:2 hexane/2-propanol at 222 nm, flow-rate: 0.7 mL/min), retention times: R_t = 16.88 min (minor diastereomer, (2*R*,4*S*)-**105k**) and R_t = 31.23 min (major diastereomer, (2*S*,4*S*)-**105k'**).

Aldehyde (*R*)-**104k** was reacted according to the general procedure with (*R*)-VAPOL (5.4 mg, 0.010 mmol) as ligand to afford aziridines (2*S*,4*S*)-**105k'** and (2*R*,4*S*)-**105k** with 94:6 diastereomeric ratio. Purification of the crude aziridines by neutral alumina chromatography (20 mm × 150 mm column, 2:1 hexanes/Et$_2$O as eluent, flash column) afforded an inseparable mixture of aziridines **105k'** and **105k** as a viscous liquid in 90% isolated yield (90.3 mg, 0.18 mmol).

Aldehyde (*R*)-**104k** was reacted according to the general procedure with (*R*)-VANOL (4.4 mg, 0.010 mmol) as ligand to afford aziridines (2*S*,4*S*)-**105k'** and (2*R*,4*S*)-**105k** with 92:8 diastereomeric ratio. Purification of the crude aziridines by neutral alumina chromatography (20 mm × 150 mm column, 2:1 hexanes/Et$_2$O as eluent, flash column) afforded an inseparable mixture of aziridines **105k'** and **105k** as a viscous liquid in 86% isolated yield (85.5 mg, 0.172 mmol).

Spectral data for (2*S*,4*S*)-**105k'**: R_f = 0.27 (2:1 hexanes/Et_2O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.22 (s, 3H), 1.24 (t, 3H, *J* = 7.2 Hz), 1.28 (s, 3H), 2.12 (dd, 1H, *J* = 8.0, 6.5 Hz), 2.24 (d, 125m, *J* = 3.5 Hz), 2.27 (d, 1H, *J* = 6.5 Hz), 3.06 (dd, 1H, *J* = 9.0, 6.5 Hz), 3.58 (s, 1H), 3.66-3.69 (m, 1H), 3.68 (s, 3H), 3.70 (s, 3H), 3.92 (dd, 1H, *J* = 8.0, 6.0 Hz), 4.10-4.23 (m, 3H), 7.05 (s, 33m), 7.09 (s, 33m); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 14.20, 16.05, 16.15, 25.40, 26.63, 41.46, 48.17, 59.54, 59.57, 61.00, 67.02, 75.05, 76.31, 109.46, 127.84, 128.23, 130.18, 130.50, 137.09, 137.34, 156.00, 169.07 (one sp^2 carbon not located); IR (thin film) 2987vs, 2938vs, 1739vs, 1483vs, 1381s, 1220vs, 1149s cm^{-1}; HRMS (ESI-TOF) *m/z* 498.2848 [($M+H^+$); calcd. for $C_{29}H_{40}NO_6$: 498.2856]; $[\alpha]_D^{20}$ – 32.2° (c 1.0, CH_2Cl_2) on 97:3 *dr* material (HPLC).



*(2R,3S)-ethyl 1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)aziridine -2-carboxylate (2R,4S)-**105k***: (*R*)-2,2-dimethyl-1,3-dioxolane-4-carboxaldehyde **104k** was reacted according to the general procedure with (*S*)-^{t}Bu$_2$VAPOL (5.5 mg, 0.010 mmol) as ligand and $B(OPh)_3$ (8.7 mg, 0.030 mmol) to afford aziridines (2*R*,4*S*)-**105k** and (2*S*,4*S*)-**105k'** with 97:3 diastereomeric ratio. Purification of the crude aziridines by neutral alumina chromatography (20 mm × 150 mm column, 2:1 hexanes/Et_2O as eluent, flash column) afforded an inseparable mixture of aziridines **105k** and **105k'** as a viscous liquid in 99% isolated yield (99.1 mg, 0.198 mmol). The diastereomeric ratio of (2*R*,4*S*)-**105k** and (2*S*,4*S*)-**105k'** was determined to be 97:3 by HPLC analysis of the crude reaction mixture (PIRKLE COVALENT (R, R)

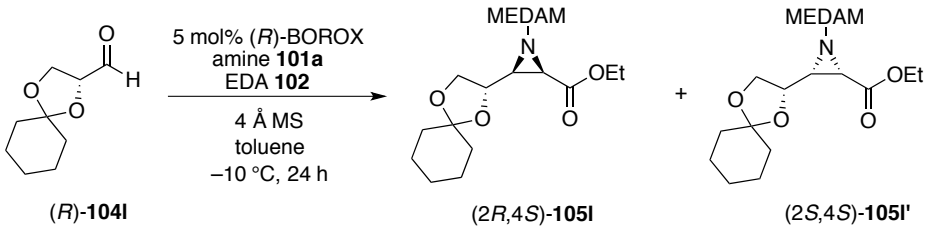
WHELK-O 1 column, 98:2 hexane/2-propanol at 222 nm, flow-rate: 0.7 mL/min), retention times: R_t = 16.64 min (major diastereomer, (2*R*,4*S*)-**105k**) and R_t = 30.26 min (minor diastereomer, (2*S*,4*S*)-**105k'**).

Aldehyde (*R*)-**104k** was reacted according to the general procedure with (*S*)-VAPOL (5.4 mg, 0.010 mmol) as ligand to afford aziridines (R*S*,4*S*)-**105k** and (S*R*,4*S*)-**105k'** with 84:16 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 an inseparable mixture of aziridines **105k** and **105k'** as a viscous liquid in 73% isolated yield (72.8 mg, 0.146 mmol).

Aldehyde (*R*)-**104k** was reacted according to the general procedure with (*S*)-VANOL (4.4 mg, 0.010 mmol) as ligand to afford aziridines (2*R*,4*S*)-**105k** and (2*S*,4*S*)-**105k'** with an 84:16 diastereomeric ratio. Purification of the crude aziridines by neutral alumina chromatography (20 mm × 150 mm column, 2:1 hexanes/Et_2O as eluent, flash column) afforded an inseparable mixture of aziridines **105k** and **105k'** as a viscous liquid in 67% isolated yield (67.0 mg, 0.134 mmol).

Spectral data for (2*R*,4*S*)-**105k**: R_f = 0.27 (2:1 hexanes/Et_2O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.25 (s, 3H), 1.26 (t, 3H, *J* = 7.2 Hz), 1.34 (s, 3H), 2.08 (dd, 1H, *J* = 8,5, 6.5 Hz), 2.24 (d, 125m, *J* = 3.5 Hz), 2.38 (d, 1H, *J* = 6.5 Hz), 3.06 (dd, 1H, *J* = 8.5, 6.5 Hz), 3.48 (s, 1H), 3.67 (s, 3H), 3.68 (s, 3H), 3.80 (dd, 1H, *J* = 8.5, 6.5 Hz), 4.10 (ddd, 1H, *J* = 12.5, 8.0, 6.0 Hz), 4.22 (q, 33m, *J* = 7.0 Hz), 6.97 (s, 33m), 7.06 (s, 33m); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 14.18, 16.08, 16.15, 25.18, 26.66, 42.69, 47.59, 59.55, 59.65, 60.98, 68.07, 73.27, 76.75, 109.27, 127.07, 127.92, 130.65, 130.76, 137.23, 137.74, 155.93, 156.47, 168.88; IR (thin film) 2987vs, 2938vs, 1737vs, 1483vs, 1382s, 1373s, 1220vs,

1148s cm^{-1}; HRMS (ESI-TOF) *m/z* 498.2850 [(M+H^+); calcd. for $C_{29}H_{40}NO_6$: 498.2856]; $[\alpha]_D^{20}$ +62.3° (c 1.0, CH_2Cl_2) on 97:3 *dr* material (HPLC).

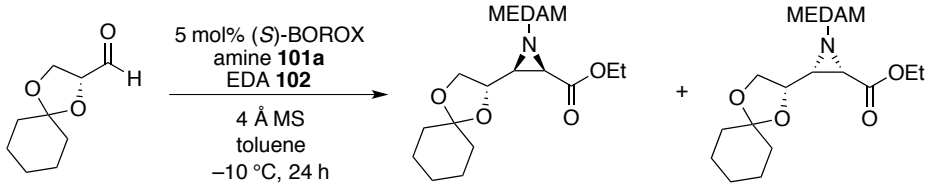


*(2S,3R)-ethyl 1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-((S)-1,4-dioxaspiro[4.5]decan-2-yl)aziridine-2-carboxylate (2S,4S)-**105l'***: (*R*)-1,4-dioxaspiro[4.5]decane-2-carboxaldehyde **104l**[20] (0.15 mL, 2 M in toluene, 0.30 mmol, 1.5 equiv) was reacted according to the general procedure with (*R*)-^{t}Bu$_2$VAPOL (5.5 mg, 0.010 mmol) as ligand, $B(OPh)_3$ (8.7 mg, 0.060 mmol) and EDA (48 μL, 0.40 mmol, 2.0 equiv) to afford aziridines (2*S*,4*S*)-**105l'** and (2*R*,4*S*)-**105l** with 98:2 diastereomeric ratio. Purification of the crude aziridines by neutral alumina chromatography (20 mm × 150 mm column, 4:1 hexanes/Et_2O as eluent, flash column) afforded an inseparable mixture of aziridines **105l'** and **105l** as a viscous liquid in >99% isolated yield (108 mg, 0.200 mmol). The diastereomeric ratio of (2*S*,4*S*)-**7k'** to (2*R*,4*S*)-**7k** was determined to be 98:2 by HPLC analysis of the crude reaction mixture (PIRKLE COVALENT (R, R) WHELK-O 1 column, 95:5 hexane/2-propanol at 222 nm, flow-rate: 0.7 mL/min), retention times: R_t = 13.93 min (minor diastereomer, (2*R*,4*S*)-**105l**) and R_t = 23.99 min (major diastereomer, (2*S*,4*S*)-**105l'**).

Aldehyde (*R*)-**104l** was reacted according to the general procedure with (*R*)-VANOL (4.4 mg, 0.010 mmol), as ligand to afford aziridines (2*S*,4*S*)-**105l'** and (2*R*,4*S*)-**105l** with 97:3 diastereomeric ratio. Purification of the crude aziridines by neutral alumina chromatography (20 mm × 150 mm column, 4:1 hexanes/Et_2O as eluent, flash column)

afforded an inseparable mixture of aziridines **105l'** and **105l** as a viscous liquid in >99% isolated yield (108 mg, 0.200 mmol).

Spectral data for (2*S*,4*S*)-**105l'**: R_f = 0.48 (1:1 hexanes/Et_2O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.22 (t, 3H, *J* = 7.2 Hz), 1.39-1.53 (m, 10H), 2.09 (dd, 1H, *J* = 4.5, 6.5 Hz), 2.22 (s, 125m), 2.24 (d, 1H, *J* = 6.0 Hz), 3.53 (s, 1H), 3.64 (dd, 1H, *J* = 5.5, 7.5 Hz), 3.66 (d, 6H, *J* = 10.0 Hz), 3.90 (dd, 1H, *J* = 7.5, 8.0 Hz), 4.08-4.19 (m, 3H), 7.03 (s, 33m), 7.06 (s, 33m); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 14.22, 16.15, 16.17, 23.66, 23.69, 25.09, 34.87, 36.54, 41.34, 48.39, 59.48, 59.58, 61.05, 66.64, 74.72, 76.50, 110.09, 127.70, 128.18, 130.22, 130.53, 137.14, 137.49, 155.92, 156.00, 169.11; IR (thin film) 2936vs, 2861s, 1743vs, 1484vs, 1448s, 1221vs, 1190vs, 1163s, 1146s, 1040s, 1016s cm^{-1}; HRMS (ESI-TOF) *m/z* 560.3011 [(M+Na^+); calcd. for $C_{333m43}NO_6Na$: 560.2988]; $[\alpha]_D^{20}$ –44.6° (c 1.0, $CHCl_3$) on 98:2 *dr* material (HPLC).

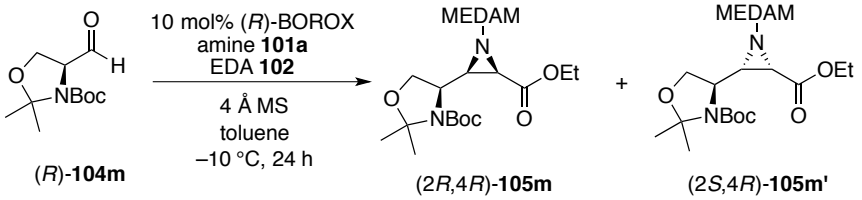


*(2R,3S)-ethyl 1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-((S)-1,4-dioxaspiro[4.5]decan-2-yl)aziridine-2-carboxylate (2R,4S)-**105l***: (*R*)-1,4-dioxaspiro[4.5]decane-2-carboxaldehyde **104l**[20] (0.15 mL, 2 M in toluene, 0.30 mmol, 1.50 equiv) was reacted according to the general procedure with (*S*)-^{t}Bu$_2$VAPOL (5.5 mg, 0.010 mmol) as ligand, $B(OPh)_3$ (8.7 mg, 0.030 mmol) and EDA (48 μL, 0.40 mmol, 2.0 equiv) to afford aziridines (2*R*,4*S*)-**105l** and (2*S*,4*S*)-**105l'** with a 97:3 diastereomeric ratio. Purification of the crude aziridine by neutral alumina chromatography (20 mm ×

150 mm column, 4:1 hexanes/Et_2O as eluent, flash column) afforded an inseparable mixture of aziridines **105l** and **105l'** as a viscous liquid in >99% isolated yield (108 mg, 0.200 mmol). The diastereomeric ratio of (2*R*,4*S*)-**105l** to (2*S*,4*S*)-**105l'** was determined to be 97:3 by HPLC analysis of the crude reaction mixture (PIRKLE COVALENT (R, R) WHELK-O 1 column, 95:5 hexane/2-propanol at 222 nm, flow-rate: 0.7 mL/min), retention times: R_t = 13.91 min (major diastereomer, (2*R*,4*S*)-**105l**) and R_t = 25.94 min (minor diastereomer, (2*S*,4*S*)-**105l'**).

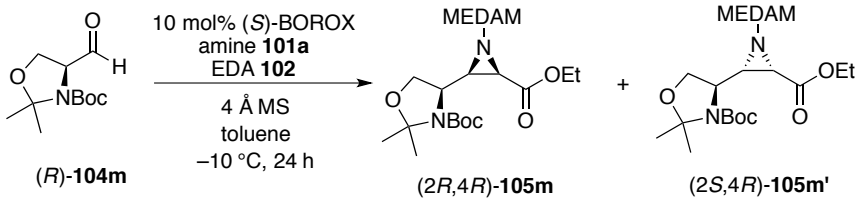
Aldehyde (*R*)-**104l** was reacted according to the general procedure with (*S*)-VANOL (4.4 mg, 0.010 mmol) as ligand to afford aziridines (2*R*,4*S*)-**105l** and (2*S*,4*S*)-**105l'** with 91:9 diastereomeric ratio. Purification of the crude aziridine by neutral alumina chromatography (20 mm × 150 mm column, 4:1 hexanes/Et_2O as eluent, flash column) afforded an inseparable mixture of aziridines **105l** and **105l'** as a viscous liquid in >99% isolated yield (108 mg, 0.200 mmol).

Spectral data for (2*R*,4*S*)-**105l**: R_f = 0.48 (1:1 hexanes/Et_2O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.25 (t, 3H, *J* = 7.0 Hz), 1.41-1.54 (m, 10H), 2.05 (dd, 1H, *J* = 6.5, 8.0 Hz), 2.22 (d, 125m, *J* = 2.5 Hz), 2.37 (d, 1H, *J* = 6.5 Hz), 3.05 (dd, 1H, *J* = 6.0, 8.5 Hz,) 3.45 (s, 1H), 3.66 (d, 6H, *J* = 5.0 Hz), 3.79 (dd, 1H, *J* = 6.2, 8.8 Hz), 4.06 (qd, 1H), 4.17-4.23 (m, 33m, *J* = 2.0, 6.2 Hz), 6.95 (s, 33m), 7.04 (s, 33m); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 14.22, 16.11, 16.17, 23.72, 23.97, 25.08, 34.61, 36.31, 42.74, 47.73, 59.57, 59.66, 60.99, 67.74, 72.88, 76.63, 109.83, 127.07, 127.87, 130.65, 130.75, 137.27, 137.74, 155.88, 156.38, 168.94; IR (thin film) 2936vs, 2861s, 1743vs, 1484vs, 1448s, 1221vs, 1190vs, 1038s, 1100s, 1038s, 1016s cm^{-1}; HRMS (ESI-TOF) *m/z* 560.3021 [($M+Na^+$); calcd. for $C_{333m43}NO_6Na$: 560.2988]; $[\alpha]_D^{20}$ +53.2° (c 1.0, $CHCl_3$) on 97:3 *dr* material (HPLC).



*tert-Butyl (R)-4-((2S,3S)-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-(ethoxycarbonyl)aziridin-2-yl)-2,2-dimethyloxazolidine-3-carboxylate (2S,4R)-**105m'***: (*S*)-3-Boc-2,2-dimethyl oxazolidine-4-carboxaldehyde **104m** was reacted according to the general procedure with (*R*)-VAPOL (11 mg, 0.020 mmol) as ligand to afford aziridines (2*S*,4*R*)-**105m'** and (2*R*,4*R*)-**105m** 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 an inseparable mixture of aziridines **105m'** and **105m** as a viscous liquid in 60% isolated yield (72.0 mg, 0.120 mmol).

Spectral data for (2*S*,4*R*)-**105m'**: R_f = 0.31 (2:1 hexanes/Et_2O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.26-1.28 (m, 5H), 1.36-1.38 (m, 4H), 1.43 (s, 9H), 2.16 (t, 1H, J = 6.8 Hz), 2.26-2.68 (m, 13H), 3.47 (s, 1H), 3.66-3.73 (m, 8H), 3.88-3.91 (m, 1H), 4.18-4.26 (m, 33m), 6.95 (s, 33m), 7.04 (s, 33m); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 14.17 16.27, 16.19, 26.15, 28.40, 28.47, 43.62, 47.02, 59.49, 59.56, 60.91, 63.72, 64.81, 79.60, 105.11, 127.70, 128.20, 130.45, 137.11, 137.16, 137.90, 155.81, 169.21, (one sp^2 carbon not located); IR (thin film) 2989vs, 2938vs, 1756s, 1747s, 1486s, 1220s, 1192vs, 1149s 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 (NMR).



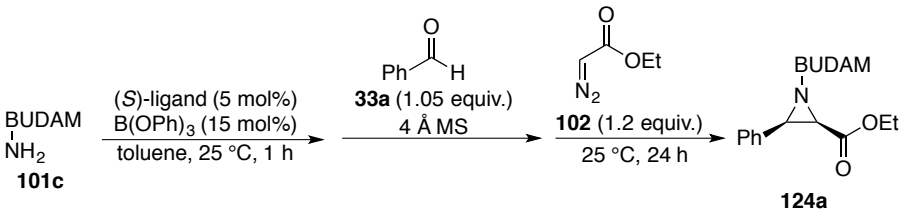
*tert-butyl (R)-4-((2R,3R)-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-(ethoxycarbonyl)aziridin-2-yl)-2,2-dimethyloxazolidine-3-carboxylate (2R,4R)-**105m***: (*S*)-3-Boc-2,2-dimethyloxazolidine-4-carboxaldehyde **104m** was reacted according to the general procedure with (*S*)-VAPOL (10.8 mg, 0.020 mmol) as ligand to afford aziridines (2*R*,4*R*)-**105m** and (2*S*,4*R*)-**105m'** with 99:1 diastereomeric ratio. Purification of the crude aziridines by neutral alumina chromatography (20 mm × 150 mm column, 2:1 hexane/Et_2O as eluent, flash column) afforded an inseparable mixture of aziridines **105m** and **105m'** as a viscous liquid in 70% isolated yield (83.1 mg, 0.140 mmol). The diastereomeric ratio of (2*R*,4*R*)-**105m** to (2*S*,4*R*)-**105m'** was determined to be 99.4:0.6 by HPLC analysis of the crude reaction mixture (PIRKLE COVALENT (R, R) WHELK-O 1 column, 98:2 hexane/2-propanol at 222 nm, flow-rate: 0.7 mL/min), retention times: R_t = 16.26 min (major diastereomer, (2*R*,4*R*)-**105m**) and R_t = 18.98 min (minor diastereomer, (2*S*,4*R*)-**105m'**).

Spectral data for (2*R*,4*R*)-**105m**: R_f = 0.31 (2:1 hexanes/Et_2O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.16-1.29 (m, 9H), 1.41 (s, 9H), 2.15 (d, 1H, *J* = 6.6 Hz), 2.19-2.27 (m, 13H), 3.53 (s, 1H), 3.63 (s, 3H), 3.67 (s, 3H), 3.69-3.72 (m, 1H), 3.93-3.96 (m, 1H), 4.01-4.08(m, 1H), 4.15 (q, 33m, *J* = 7.1 Hz), 6.89 (s, 33m), 7.11 (s, 33m); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 14.15, 16.07, 16.18, 26.17, 28.35, 28.47, 43.51, 47.00, 59.45, 59.55, 60.77, 63.73, 64.85, 79.62, 104.12, 127.65, 128.15, 130.39, 137.11, 137.12, 137.84, 155.81, 168.76, (one sp^2 carbon not located); IR (thin film) 2988vs, 2938vs, 1755s,

1748s, 1486s, 1221s, 1194vs, 1149s 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 (HPLC).

6.3 Experimental Information of Chapter 3

6.3.1 Multi-Component *cis*-Aziridination of Benzaldehyde

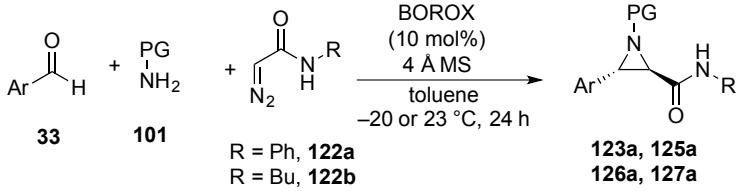


*Ethyl (2R,3R)-1-(bis(3,5-di-tert-butyl-4-methoxyphenyl)methyl)-3-phenylaziridine-2-carboxylate (2R,3R)-**124a*** (Scheme 3.2): Benzaldehyde **33a** (21 μL, 0.21 mmol) was reacted according to the general procedure in 6.2.1 with BUDAM amine **101c** (93.5 mg, 0.200 mmol) and EDA **102** (29 μL, 0.24 mmoL, 1.2 equiv). The pre-catalyst was prepared at room temperature for 1 h. Purification of the crude aziridine by silica gel chromatography (20 mm × 200 mm column, 15:1 hexanes/Et_2O as eluent, flash column) afforded aziridine (2*R*,3*R*)-**124a** as a white foam (mp 155-156 °C on 97% *ee* material) in 91% yield (117 mg, 0.182 mmol); *trans*/*cis* 8:1. The enantiomeric purity of (2*R*,3*R*)-**124a** was determined to be 91% *ee* by HPLC analysis (PIRKLE COVALENT (R, R) WHELK-O 1 column, 99.5:0.5 hexane/2-propanol at 222 nm, flow-rate: 0.7 mL/min): retention times; R_t = 13.25 min (minor enantiomer, *ent*-**124a**) and R_t = 29.14 min (major enantiomer, **124a**). The aziridination of **33a** in the presence of (*S*)-VAPOL BOROX catalyst afforded (2*R*,3*R*)-*ent*-**124a** in 99% *ee* and 85% yield (109 mg, 0.170 mmol); *trans*/*cis* 6:1.

Spectral data for **124a**: R_f= 0.56 (5:1 hexanes/Et_2O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.91

(t, 3H, J = 7.2 Hz), 1.26 (s, 18H), 1.34 (s, 18H), 2.58 (d, 1H, J = 7.0 Hz), 3.10 (d, 1H, J = 6.8 Hz), 3.53 (s, 3H), 3.60 (s, 3H), 3.76 (s, 1H), 3.79-3.91 (m, 33m), 7.12 (t, 1H, J = 7.0 Hz), 7.18 (t, 33m, J = 7.0 Hz), 7.26 (d, 33m, J = 3.0 Hz), 7.36 (d, 33m, J = 3.5 Hz), 7.41 (d, 33m, J = 8.0 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 13.94, 32.02, 32.11, 35.69, 35.76, 46.33, 48.78, 60.51, 63.91, 64.01, 77.22, 125.33, 125.44, 127.23, 127.57, 128.13, 135.29, 136.68, 136.83, 142.96, 143.04, 158.21, 168.28 (one sp^2 carbon not located). These spectral data match those previously reported for this compound.[2]

6.3.2 Multi-Component *trans*-Aziridination of Aromatic Aldehydes



33 **101**

R = Ph, **122a**
R = Bu, **122b**

123a, 125a
126a, 127a

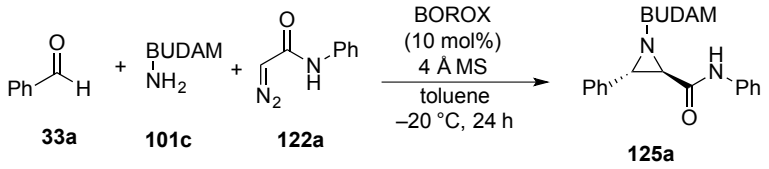
General Procedure A for Multi-Component *trans*-Aziridination of Aromatic Aldehydes

To a 10 mL flame-dried home-made Schlenk flask, prepared from a 10 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 ligand **68a**, **68b** or **68c** (0.020 mmol), $B(OPh)_3$ (17 mg, 0.060 mmol) and amine **101a**, **101b** or **101c** (0.200 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 the mixture was stirred at room temperature for 1 h. To the flask containing the catalyst was added the 4Å Molecular Sieves (60 mg, freshly flame-dried) and aldehyde (0.24 mmol, 1.2 equiv). The reaction mixture was allowed to stirred at room temperature for 20 min that the corresponding imine was formed completely. This solution was then allowed to cool to –

20 °C and rapidly added diazoacetamide **122a** or **122b** (0.28 mmoL, 1.4 equiv). The resulting mixture was stirred for 24 h at –20 °C. The reaction was dilluted by addition of pre-cooled hexane (3 mL) under –20 °C before the reaction mixture was 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 a yellow-colored viscous oil. Purification of the crude aziridine by silica gel chromatography (20 mm × 150 mm column, gravity column) afforded an *trans*-aziridine as a white solid.

General Procedure B for Multi-Component *trans*-Aziridination of Aromatic Aldehydes

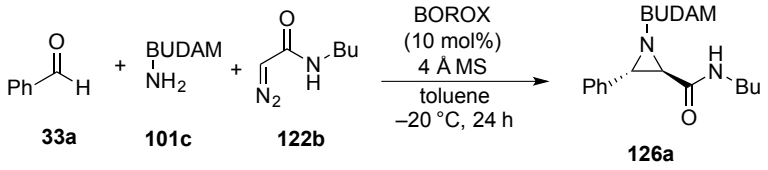
To a 10 mL flame-dried home-made Schlenk flask, prepared from a 10 mL pear-shaped flask that had its 14/20 glass joint replaced with a high vacuum threaded Teflon valve, equipped with a stir bar and filled with argon was added ligand **68a**, **68b** or **68c** (0.020 mmol), $B(OPh)_3$ (17 mg, 0.060 mmol) and amine **101a**, **101b** or **101c** (0.200 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 °C) 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. The following procedure to complete the aziridination was according to the general procedure A. Purification of the crude aziridine by silica gel chromatography (20 mm × 150 mm column, gravity column) afforded an *trans*-aziridine as a white solid.



*(2R,3S)-1-(bis(3,5-di-tert-butyl-4-methoxyphenyl)methyl)-N,3-diphenylaziridine-2-carboxamide (2R,3S)-**125a***: (Table 3.1, entry 10) Benzaldehyde **33a** (24 μL, 0.24 mmol, 1.2 equiv) was reacted according to the General Procedure B of multi-component *trans*-aziridination of aromatic aldehydes with BUDAM amine **101c** (94 mg, 0.20 mmol), (*S*)-VANOL (8.8 mg, 0.020 mmol, 0.10 equiv) and *N*-phenyl diazoacetamide **122a** (45 mg, 0.28 mmol, 1.4 equiv). Purification of the crude aziridine by silica gel chromatography (20 mm × 200 mm column, 12:1 hexanes/Et_2O as eluent, flash column) afforded aziridine (2*R*,3*S*)-**125a** as a white foam (mp 88-90 °C on 92% *ee* material) in 90% yield (124 mg, 0.180 mmol); *trans*/*cis* 18:1. The enantiomeric purity of (2*R*,3*S*)-**125a** was determined to be 92% *ee* by HPLC analysis (PIRKLE COVALENT (R, R) WHELK-O 1 column, 90:10 hexane/2-propanol at 222 nm, flow-rate: 0.7 mL/min): retention times; R_t = 13.56 min (minor enantiomer, *ent*-**125a**) and R_t = 21.43 min (major enantiomer, **125a**). (Table 3.1, entry 11) The aziridination of **33a** in the presence of (*R*)-^{t}Bu$_2$VANOL BOROX catalyst afforded (2*S*,3*R*)-*ent*-**125a** in –40% *ee* and 36% yield (49.6 mg, 0.072 mmol); *trans*/*cis* 2:1. (Table 3.1, entry 12) The aziridination of **33a** according to the General Procedure A of multi-component *trans*-aziridination of aromatic aldehydes in the presence of (*S*)-VANOL BOROX catalyst afforded (2*R*,3*S*)-**125a** in 95% *ee* and 80% yield (110 mg, 0.160 mmol); *trans*/*cis* 18:1.

Spectral data for (2*R*,3*S*)-**125a**: R_f = 0.44 (5:1 hexanes/Et_2O); ^{1}H-NMR (500 MHz, DMSO-*d*6) δ 1.22 (d, 36H, *J* = 5.5 Hz), 2.99 (d, 1H, *J* =2.5 Hz), 3.38 (d, 1H, *J* = 2.5 Hz),

3.41 (s, 3H), 3.53 (s, 3H), 5.23 (s, 1H), 7.02 (t, 1H, J = 7.2 Hz), 7.20 (s, 33m), 7.22-7.26 (m, 3H), 7.31 (s, 33m), 7.32-7.37 (m, 4H), 7.50 (d, 33m, J =8.5 Hz), 10.30 (s, 1H); ^{13}C-NMR (125 MHz, DMSO-*d*6) δ 31.76, 31.78, 35.19, 35.25, 46.26, 46.58, 63.69, 63.89, 65.41, 118.98, 123.44, 125.19, 125.68, 126.06, 127.27, 128.30, 128.56, 137.80, 138.73, 139.01, 142.13, 142.25, 157.31, 157.37, 165.13; These spectral data match those previous reported for this compound.[3]

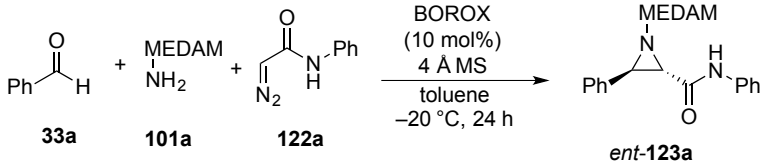


33a **101c** **122b** **126a**

*(2R,3S)-1-(bis(3,5-di-tert-butyl-4-methoxyphenyl)methyl)-N-butyl-3-phenylaziridine-2-carboxamide (2R,3S)-**126a***: (Table 3.1, entry 13) Benzaldehyde **33a** (24 μL, 0.24 mmol, 1.2 equiv) was reacted according to the General Procedure B of multi-component *trans*-aziridination of aromatic aldehydes with BUDAM amine **101c** (94 mg, 0.20 mmol), (*S*)-VANOL (8.8 mg, 0.020 mmol, 0.10 equiv) and *N*-butyl diazoacetamide **122b** (40 mg, 0.28 mmol, 1.4 equiv). Purification of the crude aziridine by silica gel chromatography (20 mm × 200 mm column, 6:1 hexanes/Et_2O as eluent, flash column) afforded aziridine (2*R*,3*S*)-**126a** as a white solid (mp 212-215 °C on 86% *ee* material) in 43% yield (58 mg, 0.086 mmol); *trans*/*cis* 8:1. The enantiomeric purity of (2*R*,3*S*)-**126a** was determined to be 86% *ee* by HPLC analysis (PIRKLE COVALENT (R, R) WHELK-O 1 column, 90:10 hexane/2-propanol at 222 nm, flow-rate: 0.7 mL/min): retention times; R_t = 10.22 min (minor enantiomer, *ent*-**126a**) and R_t = 27.49 min (major enantiomer, **126a**).

Spectral data for (2*R*,3*S*)-**126a**: R_f = 0.38 (2:1 hexanes/Et_2O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.95 (t, 3H, J = 7.2 Hz), 1.32 (s, 18H), 1.38 (s, 18H), 1.40-1.41 (m, 33m), 1.50-

1.53 (m, 33m), 2.96 (d, 1H, *J* =3.0 Hz), 3.20 (dt, 1H, *J* = 8.5, 1.8 Hz), 3.32 (dt, 1H, *J* = 8.7, 1.8 Hz), 3.43 (d, 1H, *J* = 3.0 Hz), 3.59 (s, 1H), 3.64 (s, 3H), 3.66 (s, 3H), 3.80 (s, 1H), 6.87 (d, 33m), 7.07 (d, 33m, *J* =7.5 Hz), 7.19 (s, 33m), 7.22 (d, 33m, *J* = 8.0 Hz), 7.30-7.32 (m, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 13.78, 20.14, 31.73, 32.05, 35.59, 35.69, 38.62, 42.99, 49.62, 64.04, 64.20, 67.74, 125.32, 125.38, 127.79, 128.07, 130.14, 131.86, 136.77, 136.81, 142.61, 143.31, 158.10, 158.35, 170.19; IR (thin film) 3447s, 2960s, 2870s, 1647vs, 1546s, 1455s, 1413vs, 1264s, 1222vs, 1115s, 1014s cm^{-1}; HRMS (ESI-TOF) *m/z* 669.4978 [(M+H$^+$); calcd. for $C_{44}H_{65}N_2O_3$: 669.4995]; $[\alpha]_D^{20}$ –13.6° (c 1.0, CH_2Cl_2) on 86% *ee* material (HPLC).

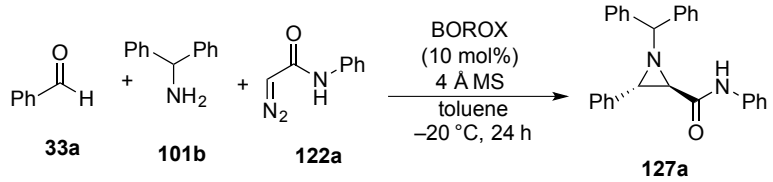


33a **101a** **122a** ***ent*-123a**

*(2S,3R)-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-N,3-diphenylaziridine-2-carboxamide (2S,3R)-ent-**123a***: (Table 3.1, entry 15) Benzaldehyde **33a** (61 μL, 0.60 mmol, 1.2 equiv) was reacted according to the General Procedure B of multi-component *trans*-aziridination of aromatic aldehydes with MEDAM amine **101a** (150 mg, 0.500 mmol), (*R*)-VAPOL (27 mg, 0.050 mmol, 0.10 equiv) and *N*-phenyl diazoacetamide **122a** (112 mg, 0.700 mmol, 1.40 equiv). Purification of the crude aziridine by silica gel chromatography (20 mm × 200 mm column, 6:1 hexanes/EtOAc as eluent, flash column) afforded aziridine (2*S*,3*R*)-*ent*-**123a** as a white foam (mp 86-88 °C on 87% *ee* material) in 57% yield (148 mg, 0.284 mmol). The enantiomeric purity of (2*S*,3*R*)-*ent*-**123a** was determined to be 87% *ee* by HPLC analysis (CHIRALCEL OD-H column, 97:3 hexane/2-propanol at 222 nm, flow-rate: 0.7 mL/min): retention times; R_t = 23.68 min

(major enantiomer, *ent*-**123a**) and R_t = 36.64 min (minor enantiomer, **123a**).

Spectral data for (2*R*,3*S*)-*ent*-**123a**: R_f= 0.57 (2:1 hexanes/EtOAc); ^{1}H-NMR (500 MHz, DMSO-*d*6) δ 2.02 (s, 6H), 2.07 (s, 6H), 2.93 (d, 1H, *J* = 2.8 Hz), 3.35 (d, 1H, *J* = 2.8 Hz), 3.49 (s, 3H), 3.55 (s, 3H), 5.06 (s, 1H), 6.99 (s, 33m), 7.05 (s, 33m), 7.05-7.07 (m, 1H), 7.28-7.31 (m, 3H), 7.33-7.36 (m, 3H), 7.49 (d, 33m, *J* = 7.5 Hz), 10.30 (s, 1H); ^{13}C-NMR (125 MHz, DMSO-*d*6) δ 15.74, 15.93, 45.93, 47.48, 58.97, 59.09, 65.37, 119.22, 123.56, 126.06, 127.26, 127.34, 127.90, 128.35, 128.68, 129.70, 129.73, 138.64, 138.72, 138.88, 138.91, 155.13, 155.26, 164.87; These spectral data match those previous reported for this compound.[3]

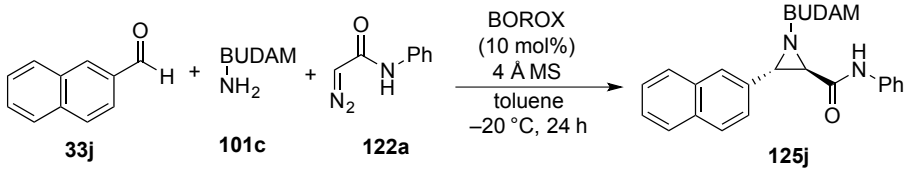


33a **101b** **122a** **127a**

*(2R,3S)-1-benzhydryl-N,3-diphenylaziridine-2-carboxamide (2R,3S)-**127a***: (Table 3.1, entry 19) Benzaldehyde **33a** (24 μL, 0.24 mmol, 1.2 equiv) was reacted according to the General Procedure B of multi-component *trans*-aziridination of aromatic aldehydes with benzhydrylamine **101b** (34 μL, 0.20 mmol), (*S*)-VANOL (8.8 mg, 0.020 mmol, 0.10 equiv) and *N*-phenyl diazoacetamide **122a** (45 mg, 0.28 mmol, 1.4 equiv). Purification of the crude aziridine by silica gel chromatography (20 mm × 200 mm column, 5:1 hexanes/Et_2O as eluent, flash column) afforded aziridine (2*R*,3*S*)-**127a** as a white semi-solid in 62% yield (50 mg, 0.12 mmol). The enantiomeric purity of (2*R*,3*S*)-**127a** was determined to be 69% *ee* by HPLC analysis (PIRKLE COVALENT (R, R) WHELK-O 1 column, 85:15 hexane/2-propanol at 222 nm, flow-rate: 0.7 mL/min): retention times; R_t = 27.41 min (minor enantiomer, *ent*-**127a**) and R_t = 34.78 min (major enantiomer, **127a**).

(Table 3.1, entry 20) The aziridination of **33a** in the presence of (*R*)-VAPOL BOROX catalyst afforded (2*S*,3*R*)-*ent*-**127a** in –75% *ee* and 49% yield (40 mg, 0.098 mmol).

Spectral data for (2*R*,3*S*)-**127a**: R_f = 0.34 (2:1 hexanes/Et_2O); ^{1}H-NMR (500 MHz, DMSO-d^6) δ 2.96 (d, 1H, *J* = 2.5 Hz), 3.43 (d, 1H, *J* = 2.5 Hz), 5.39 (s, 1H), 7.02 (t, 1H, *J* = 7.5 Hz), 7.09-7.16 (m, 2H), 7.20-7.28 (m, 7H), 7.31-7.38 (m, 4H), 7.42-7.45 (m, 6H), 10.26 (s, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 45.96, 47.31, 65.85, 119.33, 123.60, 125.94, 126.78, 127.15, 127.30, 128.13, 128.25, 128.37, 128.66, 138.46, 138.82, 143.65, 143.88, 165.00 (two sp^2 carbon not located); These spectral data match those previous reported for this compound.[3]

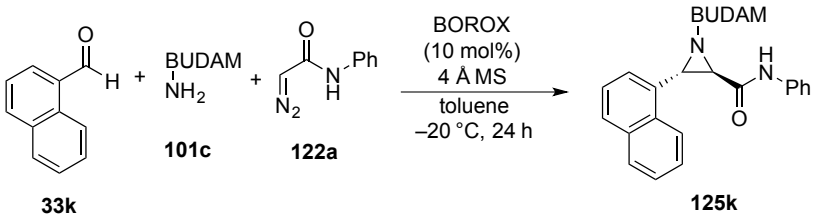


*(2R,3S)-1-(bis(3,5-di-tert-butyl-4-methoxyphenyl)methyl)-3-(naphthalen-2-yl)-N-phenylaziridine-2-carboxamide (2R,3S)-**125j***: To a 10 mL flame-dried home-made Schlenk flask, prepared from a 25 mL pear-shaped flask that had its 14/20 glass joint replaced with a high vacuum threaded Teflon valve, equipped with a stir bar and filled with argon was added (*S*)-VANOL (8.8 mg, 0.020 mmol, 0.10 equiv), $B(OPh)_3$ (17 mg, 0.060 mmol) and BUDAM amine **101c** (94 mg, 0.20 mmol). Under an argon flow through the side arm of the Schlenk flask, dry toluene (0.40 mL) was added. The flask was sealed by closing the Teflon valve, and then placed in an oil bath (80 °C) for 0.5 h. The pre-catalyst was subjected to high vacuum (0.05 mmHg) at 80 °C for 30 min to remove all the volatile substances. 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 dry toluene (1.0 mL) to dissolve all the materials,

followed by the addition of the 4Å Molecular Sieves (60 mg, freshly flame- dried) and 2-Naphthaldehyde **33j** (38 mg, 0.24 mmol, 1.2 equiv). The reaction mixture was allowed to stirred at room temperature for 20 min that the corresponding imine was formed completely. This solution was then allowed to cool to –20 °C and rapidly added *N*-phenyl diazoacetamide **122a** (45 mg, 0.28 mmol, 1.4 equiv). The resulting mixture was stirred for 24 h at –20 °C. The reaction was dilluted by addition of pre-cooled hexane (3 mL) under –20 °C before the reaction mixture was 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 a yellow-colored viscous oil. Purification of the crude aziridine by silica gel chromatography (20 mm × 200 mm column, 8:1 hexanes/Et_2O as eluent, flash column) afforded aziridine (2*R*,3*S*)-**125j** as a white foam (mp 65-68 °C on 92% *ee* material) in 82% yield (121 mg, 0.164 mmol); *trans*/*cis* 62:1. The enantiomeric purity of (2*R*,3*S*)-**125j** was determined to be 92% *ee* by HPLC analysis (PIRKLE COVALENT (R, R) WHELK-O 1 column, 90:10 hexane/2-propanol at 222 nm, flow-rate: 0.7 mL/min): retention times; R_t = 20.65 min (minor enantiomer, *ent*-**125j**) and R_t = 33.34 min (major enantiomer, **125j**).

Spectral data for (2*R*,3*S*)-**125j**: R_f = 0.28 (5:1 hexanes/Et_2O); ^{1}H-NMR (500 MHz, DMSO-d^6) δ 1.16 (s, 18H), 1.23 (s, 18H), 3.11 (d, 1H, *J* = 2.5 Hz), 3.40 (s, 3H), 3.48 (s, 3H), 3.57 (d, 1H, *J* = 2.0 Hz), 5.29 (s, 1H), 7.00 (t, 1H, *J* = 7.5 Hz), 7.22 (s, 2H), 7.24 (t, 2H, *J* = 7.2 Hz), 7.35 (s, 2H), 7.43-7.48 (m, 3H), 7.51 (d, 2H, *J* = 7.5 Hz), 7.81 (d, 1H, *J* = 8.0 Hz), 7.86-7.89 (m, 3H), 10.33 (s, 1H); ^{13}C-NMR (125 MHz, DMSO-d^6) δ 31.77,

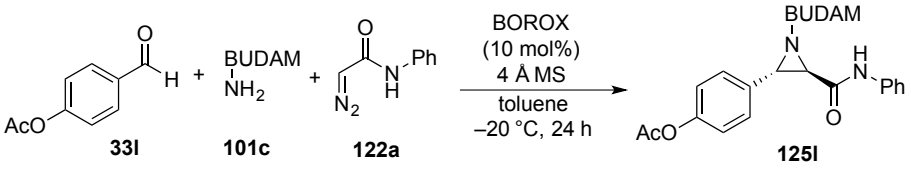
31.80, 35.24, 35.36, 46.65, 47.54, 63.72, 63.88, 65.61, 115.25, 119.04, 123.48, 123.87, 125.28, 125.74, 126.34, 127.39, 128.60, 129.40, 132.46, 132.82, 136.63, 137.83, 138.79, 142.19, 142.32, 157.40, 157.43, 165.18 (one sp^2 carbon not located); IR (thin film) 3439s, 2963s, 1636vs, 1445s, 1413s, 1384s, 1265vs, 1222s, 1115s cm^{-1}; HRMS (ESI-TOF) *m/z* 739.4840 [(M+H$^+$); calcd. for $C_{50}H_{63}N_2O_3$: 739.4839]; $[\alpha]_D^{20}$ +13.9° (c 1.0, CH_2Cl_2) on 92% *ee* material (HPLC).



33k **101c** **122a** **125k**

*(2R,3S)-1-(bis(3,5-di-tert-butyl-4-methoxyphenyl)methyl)-3-(naphthalen-1-yl)-N-phenylaziridine-2-carboxamide (2R,3S)-**125k***: 1-Naphthaldehyde **33k** (38 mg, 0.24 mmol, 1.2 equiv) was reacted according to the General Procedure B of multi-component *trans*-aziridination of aromatic aldehydes with BUDAM amine **101c** (94 mg, 0.20 mmol), (*S*)-VANOL (8.8 mg, 0.020 mmol, 0.10 equiv) and *N*-phenyl diazoacetamide **122a** (45 mg, 0.28 mmol, 1.4 equiv). Purification of the crude aziridine by silica gel chromatography (20 mm × 200 mm column, 8:1 hexanes/Et_2O as eluent, flash column) afforded aziridine (2*R*,3*S*)-**125k** as a white foam (mp 68-71 °C on 87% *ee* material) in 88% yield (130 mg, 0.176 mmol); *trans*/*cis* >99:1. The enantiomeric purity of (2*R*,3*S*)-**125k** was determined to be 87% *ee* by HPLC analysis (PIRKLE COVALENT (R, R) WHELK-O 1 column, 90:10 hexane/2-propanol at 222 nm, flow-rate: 0.7 mL/min): retention times; R_t = 16.25 min (minor enantiomer, *ent*-**125k**) and R_t = 49.74 min (major enantiomer, **125k**).

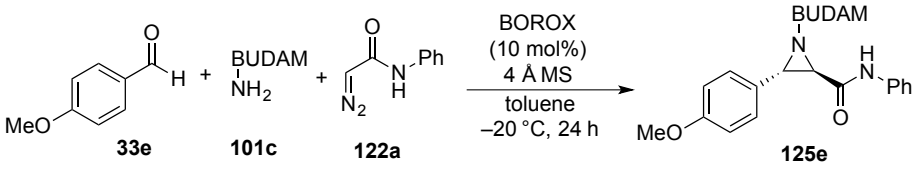
Spectral data for (2*R*,3*S*)-**125k**: R_f = 0.23 (5:1 hexanes/Et_2O); ^{1}H-NMR (500 MHz, DMSO-d^6) δ 1.24 (s, 18H), 1.28 (s, 18H), 3.01 (d, 1H, *J* = 2.5 Hz), 3.36 (s, 3H), 3.52 (s, 3H), 3.98 (d, 1H, *J* = 2.5 Hz), 5.20 (s, 1H), 7.01 (t, 1H, *J* = 7.2 Hz), 7.05-7.11 (m, 1H), 7.24 (t, 2H, *J* = 7.8 Hz), 7.28-7.39 (m, 2H), 7.32 (s, 2H), 7.43-7.56 (m, 2H), 7.52 (s, 2H), 7.65 (d, 2H, *J* = 6.5 Hz), 7.83 (d, 1H, *J* = 8.0 Hz), 7.87-7.96 (m, 1H), 10.20 (s, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 31.82, 31.88, 35.24, 35.37, 44.71, 46.52, 63.67, 63.91, 67.14, 115.25, 119.04, 122.69, 123.26, 123.50, 124.58, 125.51, 125.93, 126.46, 127.61, 128.57, 129.40, 131.12, 133.00, 134.36, 137.72, 138.05, 138.74, 142.22, 142.54, 157.42, 157.62, 165.10; IR (thin film) 3327s, 2960vs, 2869s, 1675vs, 1529vs, 1445vs, 1413s, 1222vs, 1115s, 1013s cm^{-1}; HRMS (ESI-TOF) *m/z* 739.4836 [(M+H$^+$); calcd. for $C_{50}H_{63}N_2O_3$: 739.4839]; +19.6° (c 1.0, CH_2Cl_2) on 87% *ee* material (HPLC).



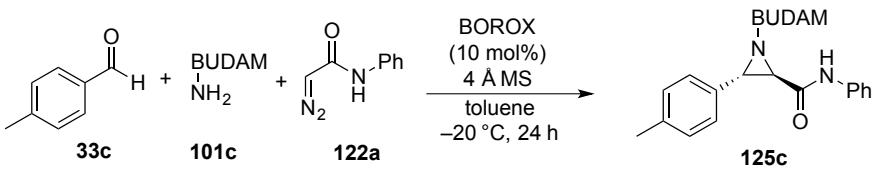
*4-((2S,3R)-1-(bis(3,5-di-tert-butyl-4-methoxyphenyl)methyl)-3-(phenylcarbamoyl)aziridin-2-yl)phenyl acetate (2S,3R)-**125l***: 4-Fomylphenyl acetate **33l** (34 μL, 0.24 mmol, 1.2 equiv) was reacted according to the General Procedure B of multi-component *trans*-aziridination of aromatic aldehydes with BUDAM amine **101c** (94 mg, 0.20 mmol), (*S*)-VANOL (8.8 mg, 0.020 mmol, 0.10 equiv) and *N*-phenyl diazoacetamide **122a** (45 mg, 0.28 mmol, 1.4 equiv). Purification of the crude aziridine by silica gel chromatography (20 mm × 200 mm column, 8:1 hexanes/EtOAc as eluent, flash column) afforded aziridine (2*S*,3*R*)-**125l** as a white foam (mp 106-108 °C on >99% *ee* material) in 82% yield (123 mg, 0.164 mmol); *trans*/*cis* 25:1. The enantiomeric purity of (2*S*,3*R*)-**125l** was determined to be 99.6% *ee* by HPLC analysis (PIRKLE

COVALENT (R, R) WHELK-O 1 column, 90:10 hexane/2-propanol at 222 nm, flow-rate: 0.7 mL/min): retention times; R_t = 34.72 min (minor enantiomer, *ent*-**125l**) and R_t = 38.27 min (major enantiomer, **125l**).

Spectral data for (2*S*,3*R*)-**125l**: R_f = 0.30 (5:1 hexanes/EtOAc); ^{1}H-NMR (500 MHz, DMSO-d^6) δ 1.21 (s, 36H), 2.24 (s, 3H), 2.98 (s, 1H), 5.23 (s, 1H), 3.40 (s, 3H), 3.52 (s, 3H), 7.00 (t, 1H, *J* = 7.5 Hz), 7.08 (d, 2H, *J* = 8.0 Hz), 7.18 (s, 2H), 7.24 (t, 2H, *J* = 7.5 Hz), 7.29 (s, 2H), 7.37 (d, 2H, *J* = 8.0 Hz), 7.49 (d, 2H, *J* = 8.0 Hz), 10.30 (s, 1H) (one proton not located); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 20.86, 31.80, 31.84, 35.23, 35.29, 45.79, 47.62, 63.73, 63.93, 65.43, 119.03, 121.80, 123.49, 125.23, 125.72, 127.07, 128.60, 131.12, 136.54, 137.77, 138.76, 142.18, 142.33, 149.76, 157.39, 157.42, 165.12, 169.16; IR (thin film) 3331s, 2960s, 1765vs, 1682vs, 1601vs, 1538s, 1447s, 1413s, 1367s, 1262vs, 1194vs, 1115s, 1013s cm^{-1}; HRMS (ESI-TOF) *m/z* 747.4734 [(M+H$^+$); calcd. for $C_{48}H_{63}N_2O_5$: 747.4737]; $[\alpha]_D^{20}$ +46.6° (c 1.0, CH_2Cl_2) on >99% *ee* material (HPLC).



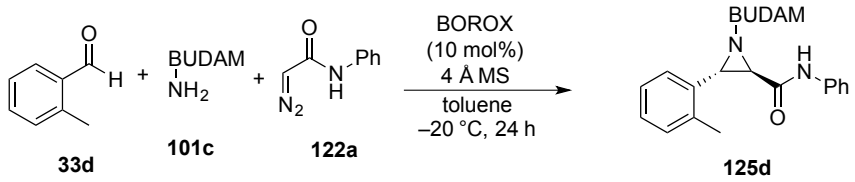
*(2R,3S)-1-(bis(3,5-di-tert-butyl-4-methoxyphenyl)methyl)-3-(4-methoxyphenyl)-N-phenylaziridine-2-carboxamide (2R,3S)-**125e***: 4-anisaldehyde **33e** (29 μL, 0.24 mmol, 1.2 equiv) was reacted according to the General Procedure B of multi-component *trans*-aziridination of aromatic aldehydes with BUDAM amine **101c** (94 mg, 0.20 mmol), (*S*)-VANOL (8.8 mg, 0.020 mmol, 0.10 equiv) and *N*-phenyl diazoacetamide **122a** (45 mg, 0.28 mmol, 1.4 equiv). A 76% of imine and 9% of aziridine (2*R*,3*S*)-**125e** was observed in the ^{1}H NMR spectrum of the crude reaction mixture; *trans*/*cis* 1.3:1.



*(2R,3S)-1-(bis(3,5-di-tert-butyl-4-methoxyphenyl)methyl)-N-phenyl-3-(p-tolyl)aziridine-2-carboxamide (2R,3S)-**125c***: To a 10 mL flame-dried home-made Schlenk flask, prepared from a 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 (*S*)-VANOL (8.8 mg, 0.020 mmol, 0.10 equiv), $B(OPh)_3$ (17 mg, 0.060 mmol) and BUDAM amine **101c** (94 mg, 0.20 mmol). Under an argon flow through the side arm of the Schlenk flask, dry toluene (0.40 mL) was added. The flask was sealed by closing the Teflon valve, and then placed in an oil bath (80 °C) for 0.5 h. The pre-catalyst was subjected to high vacuum (0.05 mmHg) at 80 °C for 30 min to remove all the volatile substances. 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 dry toluene (1.0 mL) to dissolve all the materials, followed by the addition of the 4Å Molecular Sieves (60 mg, freshly flame- dried) and 4-tolualdehyde **33c** (28 μL, 0.24 mmol, 1.2 equiv). The reaction mixture was allowed to stirred at room temperature for 20 min that the corresponding imine was formed completely. This solution was then allowed to cool to –20 °C and rapidly added *N*-phenyl diazoacetamide **122a** (45 mg, 0.28 mmol, 1.4 equiv). The resulting mixture was stirred for 24 h at –20 °C. The reaction was dilluted by addition of pre-cooled hexane (3 mL) under –20 °C before the reaction mixture was 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 a yellow-colored viscous oil. Purification of the crude aziridine by silica gel chromatography (20 mm × 200 mm column, 8:1 hexanes/Et_2O as eluent, flash column) afforded aziridine (2*R*,3*S*)-**125c** as a white foam (mp 82-83 °C on 85% *ee* material) in 73% yield (103 mg, 0.146 mmol); *trans*/*cis* 19:1. The enantiomeric purity of (2*R*,3*S*)-**125c** was determined to be 85% *ee* by HPLC analysis (PIRKLE COVALENT (R, R) WHELK-O 1 column, 90:10 hexane/2-propanol at 222 nm, flow-rate: 0.7 mL/min): retention times; R_t = 14.46 min (minor enantiomer, *ent*-**125c**) and R_t = 34.63 min (major enantiomer, **125c**).

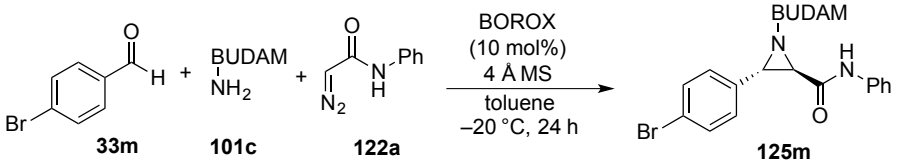
Spectral data for (2*R*,3*S*)-**125c**: R_f = 0.23 (5:1 hexanes/Et_2O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.33 (s, 36H), 2.32 (s, 3H), 3.03 (d, 1H, *J* = 2.8 Hz), 3.58 (d, 1H, *J* = 2.8 Hz), 3.62 (d, 6H, *J* = 7.5 Hz), 6.89 (s, 33m), 6.98 (d, 33m, *J* = 7.8 Hz), 7.03 (d, 33m, *J* = 7.8 Hz), 7.10 (t, 1H, *J* = 7.5 Hz), 7.25 (s, 33m), 7.33 (t, 33m, *J* = 7.8 Hz), 7.54 (d, 33m, *J* = 7.5 Hz), 8.76 (s, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 21.12, 32.02, 35.60, 35.67, 43.34, 49.52, 64.00, 64.21, 67.59, 119.35, 124.12, 125.26, 125.44, 128.34, 128.64, 128.99, 129.97, 136.59, 136.64, 137.44, 137.96, 142.68, 143.39, 143.51, 158.20, 158.45, 168.37 (one sp^3 carbon not located); IR (thin film) 3317s, 2961vs, 2869s, 1668vs, 1602vs, 1533vs, 1446vs, 1413s, 1394s, 1361s, 1222vs, 1115s, 1013s cm^{-1}; HRMS (ESI-TOF) *m/z* 703.4850 [$(M+H^+)$; calcd. for $C_{47}H_{63}N_2O_3$: 703.4839]; $[\alpha]_D^{20}$ +11.9° (c 1.0, CH_2Cl_2) on 85% *ee* material (HPLC).



*(2R,3S)-1-(bis(3,5-di-tert-butyl-4-methoxyphenyl)methyl)-N-phenyl-3-(o-tolyl)aziridine-2-carboxamide (2R,3S)-**125d***: 2-Tolualdehyde **33d** (28 μL, 0.24 mmol, 1.2 equiv) was reacted according to the General Procedure B of multi-component *trans*-aziridination of aromatic aldehydes with BUDAM amine **101c** (94 mg, 0.20 mmol), (*S*)-VANOL (8.8 mg, 0.020 mmol, 0.10 equiv) and *N*-phenyl diazoacetamide **122a** (45 mg, 0.28 mmol, 1.4 equiv). Purification of the crude aziridine by silica gel chromatography (20 mm × 200 mm column, 8:1 hexanes/Et_2O as eluent, flash column) afforded aziridine (2*R*,3*S*)-**125d** as a white foam (mp 72-74 °C on 93% *ee* material) in 85% yield (120 mg, 0.170 mmol); *trans*/*cis* >99:1. The enantiomeric purity of (2*R*,3*S*)-**125d** was determined to be 93% *ee* by HPLC analysis (PIRKLE COVALENT (R, R) WHELK-O 1 column, 90:10 hexane/2-propanol at 222 nm, flow-rate: 0.7 mL/min): retention times; R_t = 34.37 min (minor enantiomer, *ent*-**125d**) and R_t = 43.62 min (major enantiomer, **125d**).

Spectral data for (2*R*,3*S*)-**125d**: R_f = 0.27 (5:1 hexanes/Et_2O); ^{1}H-NMR (500 MHz, DMSO-d^6) δ 1.22 (s, 18H), 1.28 (s, 18H), 2.14 (s, 3H), 2.90 (d, 1H, *J* = 2.0 Hz), 3.34 (s, 3H), 3.45 (d, 1H, *J* = 2.5 Hz), 3.54 (s, 3H), 5.12 (s, 1H), 6.99 (t. 1H, *J* = 7.5 Hz), 7.06-7.18 (m, 2H), 7.22 (t, 2H, *J* = 8.0 Hz), 7.26 (s, 2H), 7.29-7.37 (m, 2H), 7.42 (s, 2H), 7.46 (d, 2H, *J* = 8.0 Hz), 10.19 (s, 1H); ^{13}C-NMR (125 MHz, DMSO-d^6) δ 18.44, 31.78, 31.85, 35.20, 35.34, 63.65, 63.95, 66.60, 115.22, 118.98, 123.39, 125.11, 125.43, 125.73, 126.97, 128.53, 129.61, 135.82, 136.81, 137.75, 138.10, 138.76, 142.13, 142.41, 157.34, 157.53, 165.22; IR (thin film) 3323s, 2960vs, 2869s, 1678vs, 1602vs, 1531vs, 1445vs,

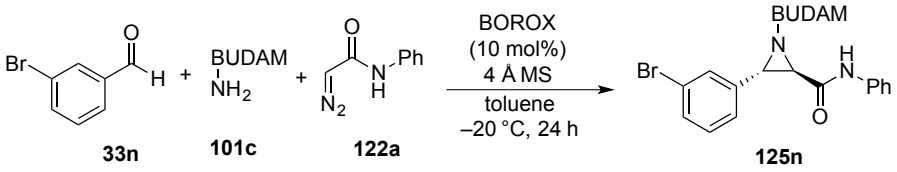
1413vs, 1392s, 1361s, 1221vs, 1115s, 1013s cm^{-1}; HRMS (ESI-TOF) *m/z* 703.4838 [(M+H^+); calcd. for $C_{47}H_{63}N_2O_3$: 703.4839]; $[\alpha]_D^{20}$ +3.0° (c 1.0, CH_2Cl_2) on 92% *ee* material (HPLC).



*(2R,3S)-1-(bis(3,5-di-tert-butyl-4-methoxyphenyl)methyl)-3-(4-bromophenyl)-N-phenylaziridine-2-carboxamide (2R,3S)-**125m***: 4-Bromobenzaldehyde **33m** (44 mg, 0.24 mmol, 1.2 equiv) was reacted according to the General Procedure B of multi-component *trans*-aziridination of aromatic aldehydes with BUDAM amine **101c** (94 mg, 0.20 mmol), (*S*)-VANOL (8.8 mg, 0.020 mmol, 0.10 equiv) and *N*-phenyl diazoacetamide **122a** (45 mg, 0.28 mmol, 1.4 equiv). Purification of the crude aziridine by silica gel chromatography (20 mm × 200 mm column, 8:1 hexanes/Et_2O as eluent, flash column) afforded aziridine (2*R*,3*S*)-**125m** as a white foam (mp 74-76 °C on 96% *ee* material) in 82% yield (126 mg, 0.164 mmol); *trans*/*cis* 23:1. The enantiomeric purity of (2*R*,3*S*)-**125m** was determined to be 96% *ee* by HPLC analysis (PIRKLE COVALENT (R, R) WHELK-O 1 column, 90:10 hexane/2-propanol at 222 nm, flow-rate: 0.7 mL/min): retention times; R_t = 18.83 min (major enantiomer, **125m**) and R_t = 25.16 min (minor enantiomer, *ent*-**125m**).

Spectral data for (2*R*,3*S*)-**125m**: R_f = 0.58 (2:1 hexanes/Et_2O); ^{1}H-NMR (500 MHz, DMSO-d^6) δ 1.21 (s, 36H), 2.98 (d, 1H, *J* = 2.5 Hz), 3.38 (d, 1H, *J* = 2.5 Hz), 3.40 (s, 3H), 3.52 (s, 3H), 5.23 (s, 1H), 7.00 (t, 1H, *J* = 7.2 Hz), 7.17 (s, 2H), 7.23 (t, 2H, *J* = 7.5 Hz), 7.27 (s, 2H), 7.30 (d, 2H, *J* = 7.5 Hz), 7.50 (d, 4H, *J* = 8.0 Hz), 10.32 (s, 1H); ^{13}C-NMR (125 MHz, DMSO-d^6) δ 31.77, 31.79, 35.20, 35.27, 45.55, 47.74, 63.71, 63.92,

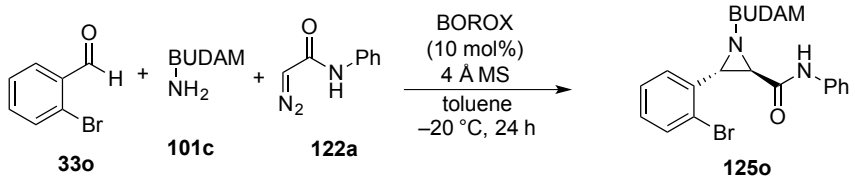
65.38, 115.22, 119.00, 123.50, 125.15, 125.68, 128.29, 128.58, 131.22, 137.63, 137.68, 138.63, 138.72, 142.18, 142.31, 157.38, 157.42, 164.88; IR (thin film) 3313s, 2960vs, 1663vs, 1602s, 1534s, 1489s, 1445s, 1413s, 1393s, 1361s, 1222vs, 1115s, 1011s cm^{-1}; HRMS (ESI-TOF) *m/z* 767.3763 [(M+H^+); calcd. for $C_{46}H_{60}N_2O_3Br$: 767.3787]; $[\alpha]_D^{20}$ +7.2° (c 1.0, CH_2Cl_2) on 96% *ee* material (HPLC).



*(2R,3S)-1-(bis(3,5-di-tert-butyl-4-methoxyphenyl)methyl)-3-(3-bromophenyl)-N-phenylaziridine-2-carboxamide (2R,3S)-**125n***: 3-Bromobenzaldehyde **33n** (28 μL, 0.24 mmol, 1.2 equiv) was reacted according to the General Procedure B of multi-component *trans*-aziridination of aromatic aldehydes with BUDAM amine **101c** (94 mg, 0.20 mmol), (*S*)-VANOL (8.8 mg, 0.020 mmol, 0.10 equiv) and *N*-phenyl diazoacetamide **122a** (45 mg, 0.28 mmol, 1.4 equiv). Purification of the crude aziridine by silica gel chromatography (20 mm × 200 mm column, 8:1 hexanes/Et_2O as eluent, flash column) afforded aziridine (2*R*,3*S*)-**125n** as a white foam (mp 64-67 °C on 95% *ee* material) in 89% yield (137 mg, 0.178 mmol); *trans*/*cis* 27:1. The enantiomeric purity of (2*R*,3*S*)-**125n** was determined to be 95% *ee* by HPLC analysis (PIRKLE COVALENT (R, R) WHELK-O 1 column, 90:10 hexane/2-propanol at 222 nm, flow-rate: 0.7 mL/min): retention times; R_t = 14.48 min (major enantiomer, **125n**) and R_t = 19.11 min (minor enantiomer, *ent*-**125n**).

Spectral data for (2*R*,3*S*)-**125n**: R_f = 0.58 (2:1 hexanes/Et_2O); ^{1}H-NMR (500 MHz, DMSO-d^6) δ 1.22 (d, 36H, *J* = 6.5 Hz), 3.00 (d, 1H, *J* = 2.0 Hz), 3.39 (s, 3H), 3.43 (d, 1H, *J* = 2.0 Hz), 3.52 (s, 3H), 5.24 (s, 1H), 6.99 (t, 1H, *J* = 7.5 Hz), 7.19 (s, 2H), 7.20-

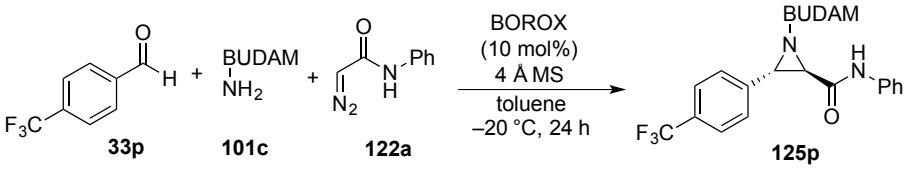
7.29 (m, 3H), 7.31 (s, 2H), 7.35 (d, 1H, J = 7.5 Hz), 7.42 (d, 1H, J = 7.5 Hz), 7.49 (d, 2H, J = 8.0 Hz), 7.54 (s, 1H), 10.28 (s, 1H); ^{13}C-NMR (125 MHz, DMSO-d^6) δ 31.76, 31.80, 35.20, 35.27, 45.30, 47.77, 63.68, 63.89, 65.38, 115.22, 118.97, 121.91, 123.48, 125.14, 125.50, 125.63, 128.55, 129.35, 130.08, 130.45, 137.61, 137.68, 138.70, 141.96, 142.18, 142.37, 157.44, 164.78; IR (thin film) 3316s, 2960vs, 1664vs, 1600vs, 1534vs, 1445vs, 1412vs, 1360s, 1222vs, 1115s, 1013s cm^{-1}; HRMS (ESI-TOF) *m/z* 767.3783 [(M+H$^+$); calcd. for $C_{46}H_{60}N_2O_3Br$: 767.3787]; $[\alpha]_D^{20}$ +5.4° (c 1.0, CH_2Cl_2) on 95% *ee* material (HPLC).



*(2R,3S)-1-(bis(3,5-di-tert-butyl-4-methoxyphenyl)methyl)-3-(2-bromophenyl)-N-phenylaziridine-2-carboxamide (2R,3S)-**125o***: 2-Bromobenzaldehyde **33o** (28 μL, 0.24 mmol, 1.2 equiv) was reacted according to the General Procedure B of multi-component *trans*-aziridination of aromatic aldehydes with BUDAM amine **101c** (94 mg, 0.20 mmol), (*S*)-VANOL (8.8 mg, 0.020 mmol, 0.10 equiv) and *N*-phenyl diazoacetamide **122a** (45 mg, 0.28 mmol, 1.4 equiv). Purification of the crude aziridine by silica gel chromatography (20 mm × 200 mm column, 8:1 hexanes/Et_2O as eluent, flash column) afforded aziridine (2*R*,3*S*)-**125o** as a white foam (mp 170-172 °C on 93% *ee* material) in 86% yield (132 mg, 0.172 mmol); *trans*/*cis* 19:1. The enantiomeric purity of (2*R*,3*S*)-**125o** was determined to be 93% *ee* by HPLC analysis (PIRKLE COVALENT (R, R) WHELK-O 1 column, 90:10 hexane/2-propanol at 222 nm, flow-rate: 0.7 mL/min):

retention times; R_t = 13.14 min (minor enantiomer, *ent*-**125o**) and R_t = 31.61 min (major enantiomer, **125o**).

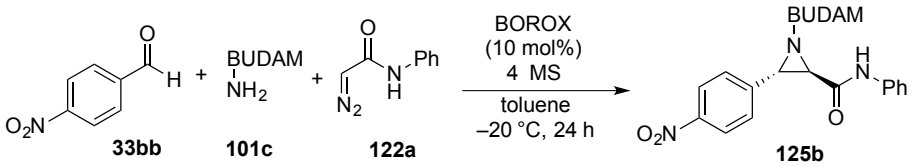
Spectral data for (2*R*,3*S*)-**125o**: R_f = 0.35 (5:1 hexanes/Et_2O); ^{1}H-NMR (500 MHz, DMSO-d^6) δ 1.23 (s, 18H), 1.27 (s, 18H), 2.92 (d, 1H, *J* = 2.5 Hz), 3.36 (s, 3H), 3.53 (s, 3H), 3.64 (d, 1H, *J* = 2.5 Hz), 5.18 (s, 1H), 7.00 (t, 1H, *J* = 7.5 Hz), 7.18 (t, 1H, *J* = 8.0 Hz), 7.22 (t, 2H, *J* = 8.2 Hz), 7.25 (s, 2H), 7.37 (t, 1H, *J* = 7.5 Hz), 7.38 (s, 2H), 7.45 (d, 1H, *J* = 7.5 Hz), 7.47 (d, 2H, *J* = 7.5 Hz), 7.54 (d, 1H, *J* = 8.5 Hz), 10.24 (s, 1H); ^{13}C-NMR (125 MHz, DMSO-d^6) δ 31.77, 31.84, 35.20, 35.33, 46.63, 46.89, 63.65, 63.92, 66.24, 115.22, 118.99, 122.84, 123.48, 125.33, 125.49, 127.44, 127.73, 128.54, 129.36, 132.18, 137.44, 137.77, 138.66, 142.18, 142.47, 157.42, 157.55, 164.56; IR (thin film) 3324s, 2960vs, 1665vs, 1602vs, 1531vs, 1444vs, 1413vs, 1394s, 1361s, 1262s, 1222s, 1115s, 1014s cm^{-1}; HRMS (ESI-TOF) *m/z* 767.3777 [(M+H$^+$); calcd. for $C_{46}H_{60}N_2O_3Br$: 767.3787]; $[\alpha]_D^{20}$ +1.7° (c 1.0, CH_2Cl_2) on 93% *ee* material (HPLC).



(2R,3S)-1-(bis(3,5-di-tert-butyl-4-methoxyphenyl)methyl)-N-phenyl-3-(4-(trifluoromethyl)phenyl)aziridine-2-carboxamide *(2R,3S)-**125p***: 4-Trifluoromethylbenzaldehyde **33p** (33 μL, 0.24 mmol, 1.2 equiv) was reacted according to the General Procedure B of multi-component *trans*-aziridination of aromatic aldehydes with BUDAM amine **101c** (94 mg, 0.20 mmol), (*S*)-VANOL (8.8 mg, 0.020 mmol, 0.10 equiv) and *N*-phenyl diazoacetamide **122a** (45 mg, 0.28 mmol, 1.4 equiv). Purification of the crude aziridine by silica gel chromatography (20 mm × 200 mm column, 8:1 hexanes/Et_2O as eluent, flash column) afforded aziridine (2*R*,3*S*)-**125p** as a white foam

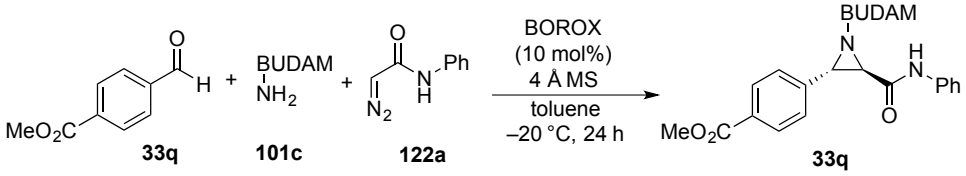
(mp 82-84 °C on 96% *ee* material) in 78% yield (118 mg, 0.156 mmol); *trans*/*cis* 31:1. The enantiomeric purity of (2*R*,3*S*)-**125p** was determined to be 96% *ee* by HPLC analysis (CHIRALCEL OD-H column, 95:5 hexane/2-propanol at 222 nm, flow-rate: 0.7 mL/min): retention times; R_t = 9.11 min (minor enantiomer, *ent*-**125p**) and R_t = 14.56 min (major enantiomer, **125p**).

Spectral data for (2*R*,3*S*)-**125p**: R_f = 0.27 (5:1 hexanes/Et_2O); ^{1}H-NMR (500 MHz, DMSO-d^6) δ 1.18 (s, 18H), 1.21 (s, 18H), 3.08 (d, 1H, *J* = 2.5 Hz), 3.42 (s, 3H), 3.48 (d, 1H, *J* = 2.5 Hz), 3.51 (s, 3H), 5.24 (s, 1H), 7.02 (t, 1H, *J* = 7.2 Hz), 7.16 (s, 2H), 7.24 (s, 2H), 7.26 (t, 2H, *J* = 8.0 Hz), 7.51 (d, 2H, *J* = 8.0 Hz), 7.58 (d, 2H, *J* = 8.5 Hz), 7.71 (d, 2H, *J* = 7.5 Hz), 10.37 (s, 1H); ^{13}C-NMR (125 MHz, DMSO-d^6) δ 31.74, 31.77, 35.21, 35.24, 45.46, 48.05, 63.75, 63.93, 65.26, 115.22, 119.02, 123.58, 125.14, 125.29, 125.73, 126.97, 128.63, 129.38, 137.55, 138.68, 142.25, 142.33, 144.05, 157.38, 157.48, 164.73; IR (thin film) 3319s, 2960vs, 2871s, 1665vs, 1602vs, 1536vs, 1446s, 1413s, 1395s, 1361s, 1325vs, 1223vs, 1168s, 1129s, 1116s, 1067s, 1016s cm^{-1}; HRMS (ESI-TOF) *m/z* 757.4536 [(M+H^+); calcd. for $C_{47}H_{60}F_3N_2O_3$: 757.4556]; $[\alpha]_D^{20}$ +8.5° (c 1.0, CH_2Cl_2) on 96% *ee* material (HPLC).



*(2R,3S)-1-(bis(3,5-di-tert-butyl-4-methoxyphenyl)methyl)-3-(4-nitrophenyl)-N-phenylaziridine-2-carboxamide (2R,3S)-**125b***: 4-nitrobenzaldehyde **33b** (36 mg, 0.24 mmol, 1.2 equiv) was reacted according to the General Procedure B of multi-component *trans*-aziridination of aromatic aldehydes with BUDAM amine **101c** (94 mg, 0.20 mmol), (*S*)-VANOL (8.8 mg, 0.020 mmol, 0.10 equiv) and *N*-phenyl diazoacetamide **122a** (45

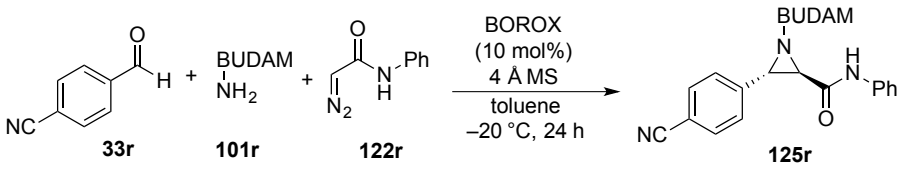
mg, 0.28 mmol, 1.4 equiv). A 52% of imine and 16% of aziridine (2*R*,3*S*)-**125b** was observed in the ^{1}H NMR spectrum of the crude reaction mixture; *trans*/*cis* 29:1.



*Methyl 4-((2S,3R)-1-(bis(3,5-di-tert-butyl-4-methoxyphenyl)methyl)-3-(phenylcarbamoyl)aziridin-2-yl)benzoate (2S,3R)-**125q***: Methyl 4-fomylbenzoate **33q** (39 mg, 0.24 mmol, 1.2 equiv) was reacted according to the General Procedure B of multi-component *trans*-aziridination of aromatic aldehydes with BUDAM amine **101c** (94 mg, 0.20 mmol), (*S*)-VANOL (8.8 mg, 0.020 mmol, 0.10 equiv) and *N*-phenyl diazoacetamide **122a** (45 mg, 0.28 mmol, 1.4 equiv). Purification of the crude aziridine by silica gel chromatography (20 mm × 200 mm column, 5:1 hexanes/Et_2O as eluent, flash column) afforded aziridine (2*S*,3*R*)-**125q** as a white foam (mp 94-95 °C on >99% *ee* material) in 89% yield (133 mg, 0.178 mmol); *trans*/*cis* 42:1. The enantiomeric purity of (2*S*,3*R*)-**125q** was determined to be 99.5% *ee* by HPLC analysis (PIRKLE COVALENT (R, R) WHELK-O 1 column, 90:10 hexane/2-propanol at 222 nm, flow-rate: 0.7 mL/min): retention times; R_t = 32.11 min (minor enantiomer, *ent*-**125q**) and R_t = 39.16 min (major enantiomer, **125q**).

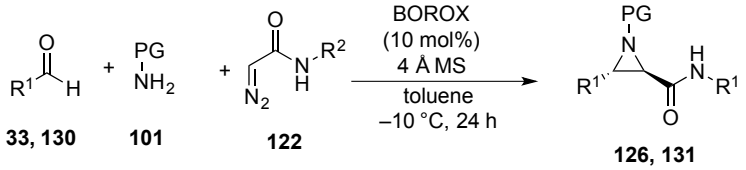
Spectral data for (2*S*,3*R*)-**125q**: R_f = 0.37 (2:1 hexanes/Et_2O); ^{1}H-NMR (500 MHz, $CDCl_3$/DMSO-d^6 1:1, v/v) δ 1.20 (s, 18H), 1.22 (s, 18H), 3.04 (d, 1H, *J* = 2.0 Hz), 3.42 (s, 3H), 3.45 (d, 1H, *J* = 2.5 Hz), 3.52 (s, 3H), 3.82 (s, 3H), 5.23 (s, 1H), 6.97 (t, 1H, *J* = 7.0 Hz), 7.16 (s, 2H), 7.20 (t, 2H, *J* = 7.5 Hz), 7.24 (s, 2H), 7.45 (d, 2H, *J* = 8.0 Hz), 7.51 (d, 2H, *J* = 8.0 Hz), 7.91 (d, 2H, *J* = 8.0 Hz), 10.27 (s, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 30.17, 30.21, 35.58, 35.68, 43.80, 48.92, 52.18, 64.01, 64.29, 68.32, 115.30, 119.46,

120.36, 124.41, 125.06, 125.12, 125.80, 128.98, 129.05, 129.54, 129.98, 142.94, 143.69, 155.87, 158.33, 158.60, 166.50, 167.82; IR (thin film) 3348s, 2960vs, 1725vs, 1688vs, 1602vs, 1543vs, 1445vs, 1413s, 1395s, 1279vs, 1222s, 1115vs, 1016vs cm^{-1}; HRMS (ESI-TOF) *m/z* 747.4731 [(M+H^+); calcd. for $C_{48}H_{63}N_2O_5$: 747.4737]; $[\alpha]_D^{20}$ +49.4° (c 1.0, EtOAc) on >99% *ee* material (HPLC).



*(2R,3S)-1-(bis(3,5-di-tert-butyl-4-methoxyphenyl)methyl)-3-(4-cyanophenyl)-N-phenylaziridine-2-carboxamide (2R,3S)-**125r***: 4-Fomylbenzonitrile **33r** (26 mg, 0.24 mmol, 1.2 equiv) was reacted according to the General Procedure B of multi-component *trans*-aziridination of aromatic aldehydes with BUDAM amine **101c** (94 mg, 0.20 mmol), (*S*)-VANOL (8.8 mg, 0.020 mmol, 0.10 equiv) and *N*-phenyl diazoacetamide **122a** (45 mg, 0.28 mmol, 1.4 equiv). A 66% of imine and 8% of aziridine (2*R*,3*S*)-**125r** was observed in the ^{1}H NMR spectrum of the crude reaction mixture; *trans*/*cis* 13:1.

6.3.3 Multi-Component *trans*-Aziridination of Aliphatic Aldehydes



General procedure A of multi-component *trans*-aziridination of aliphatic aldehydes

To a 10 mL flame-dried home-made Schlenk flask, prepared from a 10 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 ligand **68a**, **68b** or **68c** (0.020 mmol), $B(OPh)_3$ (17 mg, 0.060 mmol) and amine **101a**, **101b** or **101c** (0.200 mmol).

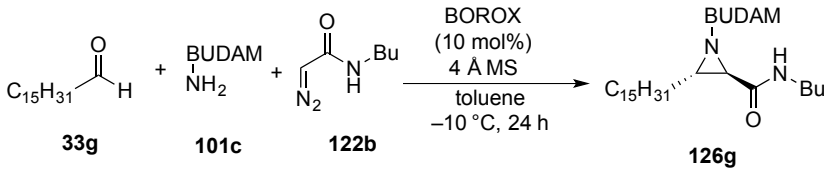
Under an argon flow through the side arm of the Schlenk flask, dry toluene (1.0 mL) was added. The flask was sealed by closing the Teflon valve, and then placed in an oil bath (80 °C) for 0.5 h. The flask was cooled to room temperature, then –10 °C and open to argon through side arm of the Schlenk flask. To the flask containing the catalyst was rapidly added the 4Å Molecular Sieves (60 mg, freshly flame-dried), aldehyde (0.22 mmol, 1.1 equiv) and diazoacetamide **122a**, **122b** (0.24 mmoL, 1.2 equiv). The resulting mixture was stirred for 24 h at –10 °C. The reaction was dilluted by addition of pre-cooled hexane (3 mL) under –10 °C before the reaction mixture was 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 a yellow-colored viscous oil. Purification of the crude aziridine by silica gel chromatography (20 mm × 150 mm column, gravity column) afforded an *trans*-aziridine as a white solid.

General procedure B of multi-component *trans*-aziridination of aliphatic aldehydes

In the general procedure B, the catalyst was stirred with the aldehyde and amine for 20 min at room temperature, before the solution was cooled to –10 °C and the diazoacetamide was added. The rest of the procedure follows the general procedure A.

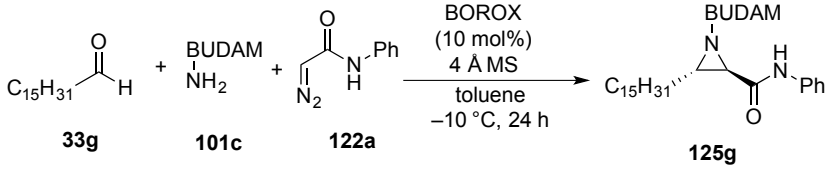
General procedure C of multi-component *trans*-aziridination of aliphatic aldehydes

In the general procedure B, the catalyst was stirred with the aldehyde and amine for 20 h at room temperature, before the solution was cooled to –10 °C and the diazoacetamide was added. The rest of the procedure follows the general procedure A.



(2R,3S)-1-(bis(3,5-di-tert-butyl-4-methoxyphenyl)methyl)-N-butyl-3-pentadecylaziridine-2-carboxamide ***126g***: (Table 3.3, entry 6) Hexadecanal **33g**[21] (53 mg, 0.22 mmol, 1.1 equiv) was reacted according to the General Procedure A of multi-component *trans*-aziridination of aliphatic aldehydes with BUDAM amine **101c** (94 mg, 0.20 mmol), (*S*)-VANOL (8.8 mg, 0.020 mmol, 0.10 equiv) and *N*-butyl diazoacetamide **122b** (34 mg, 0.24 mmol, 1.2 equiv). Purification of the crude aziridine by silica gel chromatography (20 mm × 200 mm column, 6:1 hexanes/Et_2O as eluent, flash column) afforded aziridine (2*R*,3*S*)-**126g** as an off-white solid (mp 78-80 °C on 96% *ee* material) in 85% yield (137 mg, 0.170 mmol); *trans*/*cis* 24:1. The enantiomeric purity of (2*R*,3*S*)-**126g** was determined to be 96% *ee* by HPLC analysis (PIRKLE COVALENT (R, R) WHELK-O 1 column, 95:5 hexane/2-propanol at 222 nm, flow-rate: 0.7 mL/min): retention times; R_t = 9.25 min (minor enantiomer, *ent*-**126g**) and R_t = 19.24 min (major enantiomer, **126g**). (Table 3.3, entry 7) The aziridination of **33g** according to the General Procedure B of multi-component *trans*-aziridination of aliphatic aldehydes in the presence of (*S*)-VANOL BOROX catalyst afforded (2*R*,3*S*)-**126g** in 96% *ee* and 88% yield (141 mg, 0.176 mmol); *trans*/*cis* 21:1. (Table 3.3, entry 10) The aziridination of **33g** in the presence of (*S*)-VAPOL BOROX catalyst afforded (2*R*,3*S*)-**126g** in 91% *ee* and 91% yield (146 mg, 0.182 mmol); *trans*/*cis* 14:1. (Table 3.3, entry 11) The aziridination of **33g** in the presence of (*R*)-^{t}Bu$_2$VANOL BOROX catalyst afforded (2*S*,3*R*)-*ent*-**126g** in –90% *ee* and 71% yield (114 mg, 0.142 mmol); *trans*/*cis* 17:1.

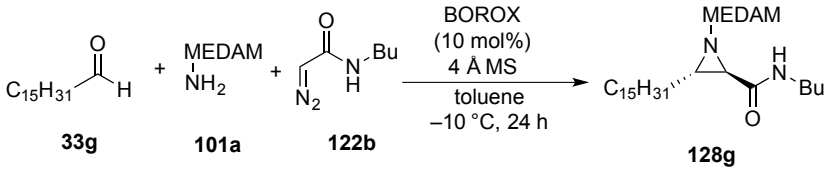
Spectral data for (2*R*,3*S*)-**126g**: R_f = 0.44 (2:1 hexanes/Et_2O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.88 (t, 3H, *J* =6.8 Hz), 0.91 (t, 3H, *J* = 7.2 Hz), 1.13-1.33 (m, 30H), 1.38 (s, 18H), 1.41 (s, 18H), 1.53-1.62 (m, 2H), 2.08 (d, 1H, *J* = 3.0 Hz), 2.18 (td, 1H, *J* = 6.3, 2.8 Hz), 3.10 (m, 1H), 3.21 (m, 1H), 3.65 (d, 6H, *J* = 2.5 Hz), 4.18 (s, 1H), 6.66 (t, 1H, *J* = 5.8 Hz), 7.21 (s, 2H), 7.30 (s, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 13.76, 14.13, 20.08, 22.68, 26.43, 28.22, 29.35, 29.47, 29.48, 29.51, 29.63, 29.66, 29.68, 31.70, 31.92, 32.07, 32.12, 35.68, 35.72, 38.42, 44.98, 47.29, 64.03, 64.16, 68.46, 125.15, 125.33, 137.26, 137.43, 143.06, 143.21, 158.20, 158.29, 170.77 (three sp^3 carbon not located); IR (thin film) 3312vs, 2958vs, 2926s, 2855s, 1652vs, 1540s, 1456s, 1413s, 1264s, 1223s, 1116s, 1014s cm^{-1}; HRMS (ESI-TOF) *m/z* 803.7001 [$(M+H^+)$; calcd. for $C_{53}H_{91}N_2O_3$: 803.7030]; $[\alpha]_D^{20}$ –10.5° (c 1.0, EtOAc) on 96% *ee* material (HPLC).



(2R,3S)-1-(bis(3,5-di-tert-butyl-4-methoxyphenyl)methyl)-3-pentadecyl-N-phenylaziridine-2-carboxamide ***125g***: (Table 3, entry 9) Hexadecanal **33g** (53 mg, 0.22 mmol, 1.1 equiv) was reacted according to the General Procedure B of multi-component *trans*-aziridination of aliphatic aldehydes with BUDAM amine **101c** (94 mg, 0.20 mmol), (*S*)-VANOL (8.8 mg, 0.020 mmol, 0.10 equiv) and *N*-phenyl diazoacetamide **122a** (39 mg, 0.24 mmol, 1.2 equiv). Purification of the crude aziridine by silica gel chromatography (20 mm × 200 mm column, 8:1 hexanes/Et_2O as eluent, flash column) afforded aziridine (2*R*,3*S*)-**125g** as a semi-solid in 78% yield (128 mg, 0.156 mmol); *trans*/*cis* 12:1. The enantiomeric purity of (2*R*,3*S*)-**125g** was determined to be 88% *ee* by HPLC analysis (PIRKLE COVALENT (R, R) WHELK-O 1 column, 98:2 hexane/2-

propanol at 222 nm, flow-rate: 0.7 mL/min): retention times; R_t = 20.53 min (minor enantiomer, *ent*-**125g**) and R_t = 35.84 min (major enantiomer, **125g**). (Table 3.3, entry 8) The aziridination of **33** according to the General Procedure A of multi-component *trans*-aziridination of aliphatic aldehydes in the presence of (*S*)-VANOL BOROX catalyst afforded (2*R*,3*S*)-**125g** in 68% *ee* and 70% yield (115 mg, 0.140 mmol); *trans*/*cis* 6:1.

Spectral data for (2*R*,3*S*)-**125g**: R_f = 0.57 (2:1 hexanes/Et_2O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.88 (t, 3H, *J* = 7.0 Hz), 1.10-1.31 (m, 26H), 1.34 (s, 18H), 1.43 (18H), 1.62-1.67 (m, 2H), 2.20 (d, 1H, *J* = 3.0 Hz), 2.38-2.41 (m, 1H), 3.62 (s, 3H), 3.68 (s, 3H), 4.27 (s, 1H), 7.07 (t, 1H, *J* = 7.8 Hz), 7.27 (s, 2H), 7.30 (t, 2H, *J* = 8.0 Hz), 7.48 (d, 2H, *J* = 8.0 Hz), 8.57 (s, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 14.13, 22.69, 26.44, 28.14, 29.35, 29.41, 29.48, 29.51, 29.63, 29.67, 29.69, 31.92, 32.03, 32.14, 35.68, 35.77, 45.29, 47.54, 64.02, 64.17, 68.38, 119.15, 123.90, 125.15, 125.24, 128.94, 137.00, 137.17, 137.56, 143.22, 143.48, 158.33, 158.44, 168.87 (two sp^3 carbon not located); IR (thin film) 3327vs, 2924vs, 2854s, 1679vs, 1602s, 1528s, 1465s, 1412s, 1221s, 1115s, 1014s cm^{-1}; HRMS (ESI-TOF) *m/z* 823.6707 [(M+H$^+$); calcd. for $C_{55}H_{87}N_2O_3$: 823.6717]; $[\alpha]_D^{20}$ +17.6° (c 1.0, EtOAc) on 88% *ee* material (HPLC).



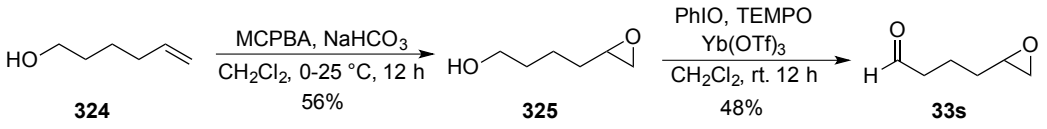
33g **101a** **122b** **128g**

*(2R,3S)-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-N-butyl-3-pentadecylaziridine-2-carboxamide **128g***: (Table 3.3, entry 4) Hexadecanal **33g** (132 mg, 0.220 mmol, 1.10 equiv) was reacted according to the General Procedure A of multi-component *trans*-aziridination of aliphatic aldehydes with MEDAM amine **101a** (150 mg, 0.200 mmol),

(*S*)-VAPOL (22 mg, 0.020 mmol, 0.10 equiv) and *N*-butyl diazoacetamide **122b** (85 mg, 0.24 mmol, 1.2 equiv). Purification of the crude aziridine by silica gel chromatography (20 mm × 200 mm column, 3:1 hexanes/Et_2O as eluent, flash column) afforded aziridine (2*R*,3*S*)-**128g** as an oily liquid in 79% yield (251 mg, 0.395 mmol); *trans*/*cis* 15:1. The enantiomeric purity of (2*R*,3*S*)-**128g** was determined to be 86% *ee* by HPLC analysis (PIRKLE COVALENT (R, R) WHELK-O 1 column, 90:10 hexane/2-propanol at 222 nm, flow-rate: 0.7 mL/min): retention times; R_t = 12.62 min (minor enantiomer, *ent*-**128g**) and R_t = 26.32 min (major enantiomer, **128g**). (Table 3.3, entry 3) The aziridination of **33g** according to the General Procedure A of multi-component *trans*-aziridination of aliphatic aldehydes in the presence of (*S*)-VANOL BOROX catalyst afforded (2*R*,3*S*)-**128g** in 88% *ee* and 67% yield (213 mg, 0.335 mmol); *trans*/*cis* 8:1. (Table 3.3, entry 5) The aziridination of **33g** in the presence of (*R*)-^{t}Bu$_2$VANOL BOROX catalyst afforded (2*S*,3*R*)-*ent*-**128g** in –93% *ee* and 46% yield (146 mg, 0.230 mmol).

Spectral data for (2*R*,3*S*)-**128g**: R_f = 0.46 (1:1 hexanes/Et_2O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.86 (t, 3H, *J* = 6.8 Hz), 0.88 (t, 3H, *J* = 7.0 Hz), 1.14-1.27 (m, 30H), 1.34-1.56 (m, 2H), 2.01 (d, 1H, *J* = 3.0 Hz), 2.20 (s, 6H), 2.21-2.24 (m, 1H), 2.25 (s, 6H), 2.94-3.00 (m, 1H), 3.29-3.36 (m, 1H), 3.64 (s, 3H), 3.67 (s, 3H), 4.08 (s, 1H), 6.61 (dd, 1H, *J* = 7.2, 4.8 Hz), 6.92 (s, 2H), 7.95 (s, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 13.79, 14.11, 16.21, 16.29, 19.90, 22.68, 26.07, 28.11, 29.31, 29.35, 29.46, 29.50, 29.60, 29.64, 29.68, 31.85, 31.90, 38.26, 44.81, 47.33, 59.52, 59.60, 67.55, 126.90, 127.63, 130.52, 130.71, 138.59, 155.77, 156.05, 170.48 (three sp^3 carbon and one sp^2 carbon not located); IR (thin film) 2924vs, 2853s, 1646vs, 1538s, 1483s, 1466s, 1221s, 1137s, 1019s cm^{-1}; HRMS (ESI-

TOF) *m/z* 635.5176 [(M+H$^+$); calcd. for $C_{41}H_{67}N_2O_3$: 635.5152]; $[\alpha]_D^{20}$ +19.1° (c 1.0, CH_2Cl_2) on –93% *ee* material (HPLC).

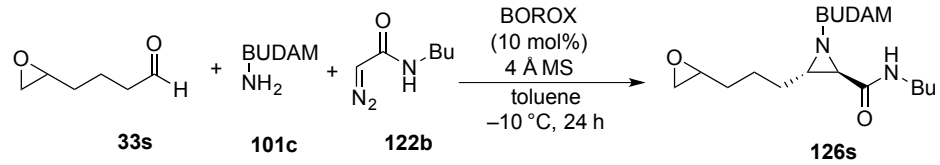


324 **325** **33s**

*4-Oxiranylbutanal **33s***:[22] Hex-5-en-1-ol **324** (1.20 mL, 10.0 mmol) was dissolved in 60 mL of dry CH_2Cl_2 and cooled to 0 °C. *m*-CPBA (77 wt%, 2.69 g, 12.0 mmol, 1.2 equiv) was added in portions, and the resulting mixture was left stirring at 0 °C for 2h, and was then allowed to slowly warm to room temperature. After another 12 h, the mixture was cooled to 0 °C and 10 mL of sat. $Na_2S_2O_3$ was added. The aqueous phase was extracted with CH_2Cl_2 and the combined organic phases were washed with sat. $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4 and concentrated. The crude product (895 mg) contained 22% **324** and 56% **325** as a mixture of both diastereomers, and was used in the next step without further purification. Spectral data for **325**: R_f= 0.31 (2:1 hexanes/Et_2O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.40-1.70 (m, 4H), 2.06 (q, 1H, *J* = 7.0 Hz), 2.46 (dd, 1H, *J* = 5.8, 2.8 Hz), 2.74 (t, 1H, *J* = 4.5 Hz), 2.89-2.92 (m, 1H), 3.62 (d, 1H, *J* = 7.0 Hz), 3.64 (t, 2H, *J* = 6.5 Hz).

To a 50 mL flame-dried round bottom flask equipped with a stir bar was added alcohol **325** (5.25 mmol) into dry CH_2Cl_2 (28 mL). To the resulting solution was added TEMPO (41 mg, 0.26 mmol, 0.050 equiv) and PhIO (1.39 g, 6.30 mmol, 1.20 equiv). The suspension was cooled to 0 °C and $Yb(OTf)_3$ (65 mg, 0.10 mmol, 0.020 equiv) was added. The reaction mixture was stirred at room temperature for 12 h (until the alcohol was no longer detectable by TLC). The resulting suspension was filtered through a Celite pad and concentrated under reduced pressure. Purification of the crude aldehyde by silica

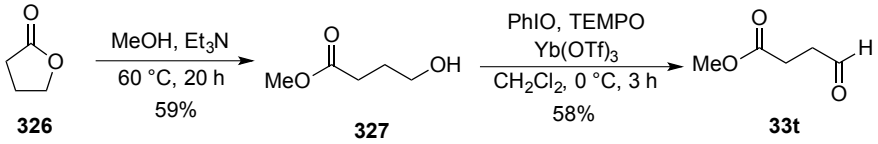
gel chromatography (20 mm × 200 mm column, 3:1 hexanes/Et_2O as eluent, flash column) afforded a mixture of both diastereomers of aldehyde **33s** as a colorless liquid in 48% yield (287 mg, 2.52 mmol). Spectral data for **33s**: R_f= 0.31 (2:1 hexanes/Et_2O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.42-1.52 (m, 1H), 1.61-1.70 (m, 1H), 1.75-1.83 (m, 2H), 2.46 (dd, 1H, *J* = 5.0, 2.5 Hz), 2.51 (td, 2H, *J* = 7.0, 1.2 Hz), 2.74 (dd, 1H, *J* = 5.0, 4.0 Hz), 2.86-2.93 (m, 1H), 9.77 (t, 1H, *J* = 1.5 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 18.55, 31.67, 43.45, 46.80, 51.83, 201.96.



*(2R,3S)-1-(bis(3,5-di-tert-butyl-4-methoxyphenyl)methyl)-N-butyl-3-(3-oxiranylpropyl)aziridine-2-carboxamide (2R,3S)-**126s***: 4-Oxiranylbutanal **33s** (25 μL, 0.22 mmol, 1.1 equiv) was reacted according to the General Procedure A of multi-component *trans*-aziridination of aliphatic aldehydes with BUDAM amine **101c** (94 mg, 0.20 mmol), (*S*)-VANOL (8.8 mg, 0.020 mmol, 0.10 equiv) and *N*-butyl diazoacetamide **122b** (34 mg, 0.24 mmol, 1.2 equiv). Purification of the crude aziridine by silica gel chromatography (20 mm × 200 mm column, 4:1 hexanes/Et_2O as eluent, flash column) afforded aziridine (2*R*,3*S*)-**126s** as a white foam in 89% yield (121 mg, 0.178 mmol); *trans*/*cis* 8:1. The diastereomeric ratio of (2*R*,3*S*)-**126s** isomers was determined to be 49:49:1:1 by HPLC analysis (PIRKLE COVALENT (R, R) WHELK-O 1 column, 90:10 hexane/2-propanol at 222 nm, flow-rate: 0.7 mL/min): retention times; R_t = 18.47, 18.98 min (minor diastereomer, (2*S*,3*R*)-**126s**) and R_t = 35.33, 36.71 min (major diastereomer, (2*R*,3*S*)-**126s**). The aziridination of **33s** in the presence of (*R*)-^{t}Bu$_2$VANOL BOROX

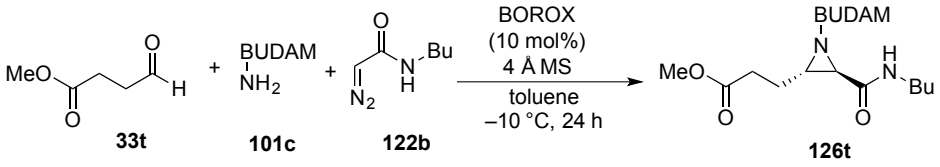
catalyst afforded (2*S*,3*R*)-*ent*-**126s** in 0.5:0.5:49.5:49.5 *dr* and 62% yield (85 mg, 0.12 mmol); *trans*/*cis* 17:1.

Spectral data for (2*R*,3*S*)-**126s**: R_f = 0.32 (2:1 hexanes/Et_2O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.89 (t, 3H, *J* = 7.5 Hz), 1.10-1.48 (m, 8H), 1.35 (s, 18H), 1.38 (s, 18H), 1.59-1.66 (m, 2H), 2.10 (dd, 1H, *J* = 6.8, 2.8 Hz), 2.13-2.21 (m, 1H), 2.31-2.38 (m, 1H), 2.60-2.67 (m, 1H), 2.73 (d, 1H, *J* = 2.5 Hz), 3.03-3.13 (m, 1H), 3.15-3.25 (m, 1H), 3.63 (d, 6H, *J* = 2.0 Hz), 4.15 (s, 1H), 6.62 (t, 1H, *J* = 5.2 Hz), 7.18 (s, 2H), 7.28 (s, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 13.73, 20.04, 24.61, 26.01, 26.02, 32.04, 32.10, 35.66, 35.71, 38.41, 44.98, 46.73, 46.81, 51.82, 51.89, 64.00, 64.14, 68.60, 125.08, 125.26, 137.11, 137.25, 143.16, 143.25, 158.24, 158.31, 170.48; HRMS (ESI-TOF) *m/z* 677.5252 [$(M+H^+)$; calcd. for $C_{43}H_{69}N_2O_4$: 677.5257];



Methyl 4-hydroxybutyrate ***327***:[23] To a solution of γ-butyrolactone **326** (0.76 mL, 10 mmol) in MeOH (50 mL) was added triethylamine (8.4 mL, 60 mmol, 6.0 equiv). The reaction was heated up to 60 °C and stirred for 20 h. The reaction solution was then cooled, dilute with hexanes (50 mL) and concentrated in vacuo. The residual MeOH was removed azeotropically with hexanes (2 × 20 mL). Purification by silica gel chromatography (20 mm × 200 mm column, 6:1 hexanes/EtOAc as eluent, flash column) afforded **327** as a colorless liquid in 59% yield (696 mg, 5.89 mmol). Spectral data for **327**: R_f= 0.60 (2:1 hexanes/EtOAc); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.86 (pent, 2H, *J* = 6.5 Hz), 1.87-1.92 (br, 1H), 2.42 (t, 2H, *J* = 7.0 Hz), 3.65 (s, 3H), 3.66 (t, 2H, *J* = 6.0 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 27.61, 30.74, 51.68, 61.99, 174.40.

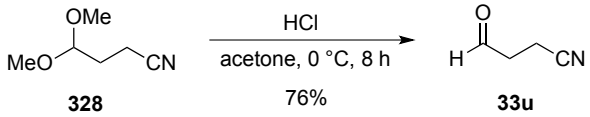
Methyl 4-oxobutyrate ***33t***:[22b] To a 25 mL flame-dried round bottom flask equipped with a stir bar was added alcohol **327** (390 mg, 3.30 mmol) into dry CH_2Cl_2 (28 mL). To the resulting solution was added TEMPO (26 mg, 0.16 mmol, 0.050 equiv) and PhIO (871 mg, 3.96 mmol, 1.20 equiv). The suspension was cooled to 0 °C and $Yb(OTf)_3$ (41 mg, 0.066 mmol, 0.020 equiv) was added. The reaction mixture was stirred at 0 °C for 3 h (until the alcohol was no longer detectable by TLC). The resulting suspension was filtered through a Celite pad and concentrated under reduced pressure. Purification of the crude aldehyde by silica gel chromatography (20 mm × 200 mm column, 2:1 hexanes/Et_2O as eluent, flash column) afforded aldehyde **33t** as a colorless liquid in 58% yield (222 mg, 1.91 mmol). Spectral data for **33t**: R_f = 0.52 (1:2 hexanes/Et_2O); ^{1}H-NMR (500 MHz, $CDCl_3$) 2.60 (t, 2H, *J* = 6.8 Hz), δ 2.77 (t, 2H, *J* = 6.8 Hz), 3.66 (s, 3H), 9.78 (s, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 26.25, 38.47, 51.90, 172.67, 199.95.



Methyl 3-((2S,3R)-1-(bis(3,5-di-tert-butyl-4-methoxyphenyl)methyl)-3-(butylcarbamoyl)aziridin-2-yl)propanoate ***18c***: Methyl 4-Oxobutyrate **33t** (26 μL, 0.22 mmol, 1.1 equiv) was reacted according to the General Procedure A of multi-component *trans*-aziridination of aliphatic aldehydes with BUDAM amine **101c** (94 mg, 0.20 mmol), (*S*)-VANOL (8.8 mg, 0.020 mmol, 0.10 equiv) and *N*-butyl diazoacetamide **122b** (34 mg, 0.24 mmol, 1.2 equiv). Purification of the crude aziridine by silica gel chromatography (20 mm × 200 mm column, 4:1 hexanes/EtOAc as eluent, flash column) afforded aziridine (2*S*,3*R*)-**126t** as a white foam (mp 160-162 °C on 86% *ee* material) in 78% yield (106 mg, 0.156 mmol). The enantiomeric purity of (2*S*,3*R*)-**126t** isomers was determined

to be 86% *ee* by HPLC analysis (PIRKLE COVALENT (R, R) WHELK-O 1 column, 90:10 hexane/2-propanol at 222 nm, flow-rate: 0.7 mL/min): retention times; R_t = 15.72 min (minor enantiomer, *ent*-**126t**) and R_t = 30.32 min (major enantiomer, **126t**). The aziridination of **33t** in the presence of (*R*)-^{t}Bu$_2$VANOL BOROX catalyst afforded (2*R*,3*S*)-*ent*-**126t** in –93% *ee* and 59% yield (80 mg, 0.12 mmol).

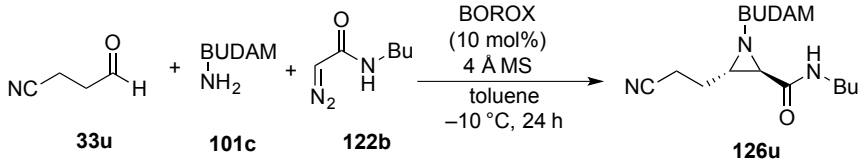
Spectral data for (2*R*,3*S*)-**126t**: R_f = 0.28 (2:1 hexanes/EtOAc); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.89 (t, 3H, *J* = 7.5 Hz), 1.23-1.31 (m, 4H), 1.36 (s, 18H), 1.39 (s, 18H), 1.77-1.84 (m, 1H), 1.86-1.92 (m, 1H), 1.97-2.11 (m, 2H), 2.13 (d, 1H, *J* = 3.0 Hz), 2.20 (td, 1H, *J* =6.2, 2.8 Hz), 3.10 (m, 1H), 3.17 (m, 1H), 3.59 (s, 3H), 3.63 (s, 6H), 4.12 (s, 1H), 6.58 (t, 1H, *J* = 5.5 Hz), 7.20 (s, 2H), 7.30 (s, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 13.74, 20.07, 21.82, 31.67, 32.06, 32.14, 32.20, 35.70, 35.73, 38.47, 44.80, 45.63, 51.60, 64.03, 64.18, 68.73, 136.95, 137.14, 143.34, 143.45, 158.40, 170.17, 172.89 (one sp^2 carbon not located); IR (thin film) 3320s, 2959vs, 2872s, 1740vs, 1656vs, 1534s, 1446s, 1412vs, 1361s, 1265s, 1221vs, 1115s, 1013s cm^{-1}; HRMS (ESI-TOF) *m/z* 679.5049 [(M+H$^+$); calcd. for $C_{42}H_{67}N_2O_5$: 679.5050]; $[\alpha]_D^{20}$ +13.9° (c 1.0, EtOAc) on –93% *ee* material (HPLC).



328 **33u**

4-Oxobutanenitrile ***15d***:[24] A mixture of 4,4-dimethoxybutanenitrile **328** (1.29 g, 10.0 mmol), acetone (50 mL) and 6 N HCl (20 mL) was stirred at 0 °C for 8 h. The mixture was then concentrated to approximately 5 mL and was extracted with $CHCl_3$ (4 × 15 mL). The combined organic phase was dried with Na_2SO_4. The solvent was remove by rotary evaporation to give crude aldehyde **33u** as an oil. Purification of the crude alcohol

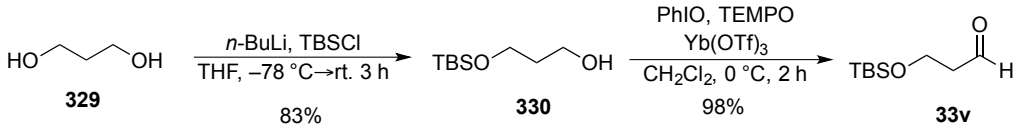
by silica gel chromatography (20 mm × 200 mm column, 2:1 hexanes/EtOAc as eluent, flash column) afforded aldehyde **33u** as a colorless liquid in 76% yield (635 mg, 7.64 mmol). Spectral data for **33u**: R_f = 0.26 (1:1 hexanes/EtOAc); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 2.60 (t, 2H, *J* = 7.0 Hz), 2.88 (t, 2H, *J* = 7.0 Hz), 9.76 (s, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 9.95, 38.87, 118.48, 197.03.



33u **101c** **122b** **126u**

*(2R,3S)-1-(bis(3,5-di-tert-butyl-4-methoxyphenyl)methyl)-N-butyl-3-(2-cyanoethyl)aziridine-2-carboxamide **126u***: 4-Oxobutanenitrile **33u** (20 μL, 0.22 mmol, 1.1 equiv) was reacted according to the General Procedure A of multi-component *trans*-aziridination of aliphatic aldehydes with BUDAM amine **101c** (94 mg, 0.20 mmol), (*S*)-VANOL (8.8 mg, 0.020 mmol, 0.10 equiv) and *N*-butyl diazoacetamide **122b** (34 mg, 0.24 mmol, 1.2 equiv). Purification of the crude aziridine by silica gel chromatography (20 mm × 200 mm column, 3:1 hexanes/EtOAc as eluent, flash column) afforded aziridine (2*R*,3*S*)-**126u** as a white foam (mp 164-167 °C on 60% *ee* material) in 88% yield (114 mg, 0.176 mmol). The enantiomeric purity of (2*R*,3*S*)-**18d** isomers was determined to be 40% *ee* by HPLC analysis (PIRKLE COVALENT (R, R) WHELK-O 1 column, 90:10 hexane/2-propanol at 222 nm, flow-rate: 0.7 mL/min): retention times; R_t = 16.97 min (minor enantiomer, *ent*-**126u**) and R_t = 28.53 min (major enantiomer, **126u**). The aziridination of **33u** in the presence of (*R*)-^{t}Bu$_2$VANOL BOROX catalyst afforded (2*S*,3*R*)-*ent*-**126u** in –60% *ee* and 51% yield (66 mg, 0.10 mmol). The aziridination of **33u** in the presence of (*R*)-VAPOL BOROX catalyst afforded (2*S*,3*R*)-*ent*-**126u** in –47% *ee* and 61% yield (79 mg, 0.12 mmol).

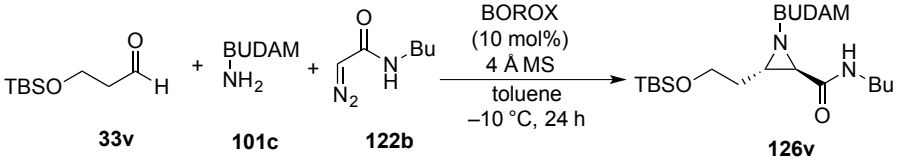
Spectral data for (2*R*,3*S*)-**126u**: R_f = 0.57 (1:1 hexanes/EtOAc); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.89 (t, 3H, *J* = 7.0 Hz), 1.09-1.22 (m, 2H), 1.22-1.32 (m, 2H), 1.36 (s, 18H), 1.40 (s, 18H), 1.75-1.87 (m, 2H), 1.87-1.96 (m, 1H), 2.06-2.13 (m, 1H), 2.20 (d, 1H, *J* = 2.5 Hz), 2.24-2.32 (m, 1H), 3.04-3.24 (m, 2H), 3.64 (d, 6H, *J* = 8.5 Hz), 4.09 (s, 1H), 6.51 (t, 1H, *J* = 5.8 Hz), 7.20 (s, 2H), 7.32 (s, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 13.73, 15.63, 20.04, 22.75, 32.02, 32.09, 32.19, 35.72, 35.81, 38.57, 44.13, 44.95, 64.06, 64.36, 69.35, 118.44, 124.81, 125.02, 125.37, 136.69, 143.56, 144.06, 158.59, 169.41; IR (thin film) 3323s, 2962vs, 2872s, 1645vs, 1550s, 1446s, 1413vs, 1394s, 1360s, 1261s, 1221vs, 1114s, 1014s cm^{-1}; HRMS (ESI-TOF) *m/z* [(M+H$^+$); calcd. for $C_{41}H_{64}N_3O_3$: 646.4948]; $[\alpha]_D^{20}$ –43.4° (c 1.0, EtOAc) on 40% *ee* material (HPLC).



3-(tert-Butyldimethylsilyl)oxypropan-1-ol ***330***:[25] *n*-BuLi (12.5 mL, 1.6 *M* in hexanes, 20.0 mmol) was added in dropwise under 0 °C to a solution of distilled 1,3-propanediol **329** (1.44 mL, 20.0 mmol) in THF (40 mL). A solution of *tert*-butyldimethylsilyl chloride (3.01 g, 20.0 mmol) in THF (2.0 mL) was added after 30 min *via* cannula. The solution was allowed to warm up to room temperature and stirred for 3 h. The reaction was quenched by water (5 mL) and concentrated in vacuo. Extract the residue with CH_2Cl_2 (3 × 30 mL) and wash the combined organic phase with brine (10 mL). The organic phase was dried over $MgSO_4$ and concentrated in vacuo to afford a yellow oil. Purification by silica gel chromatography (20 mm × 200 mm column, 6:1 hexanes/EtOAc as eluent, flash column) afforded alcohol **330** as a colorless liquid in 83% yield (3.16 g, 16.6 mmol). Spectral data for **330**: R_f = 0.61 (2:1 hexanes/Et_2O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.05

(s, 6H), 0.87 (s, 9H), 1.75 (pent, 2H, J = 5.8 Hz), 2.61-2.64 (br, 1H), 3.78 (q, 2H, J = 5.5 Hz), 3.81 (t, 2H, J = 5.8 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ –5.52, 25.85, 34.11, 62.46, 62.48, 62.96.

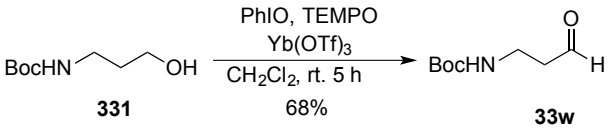
3-(tert-Butyldimethylsilyl)oxypropanal ***15e***:[22b] To a 25 mL flame-dried round bottom flask equipped with a stir bar was added alcohol **330** (390 mg, 5.02 mmol) into dry CH_2Cl_2 (20 mL). To the resulting solution was added TEMPO (39 mg, 0.25 mmol, 0.050 equiv) and PhIO (1.38 mg, 6.26 mmol, 1.20 equiv). The suspension was cooled to 0 °C and $Yb(OTf)_3$ (62 mg, 0.10 mmol, 0.020 equiv) was added. The reaction mixture was stirred at 0 °C for 2 h (until the alcohol was no longer detectable by TLC). The resulting suspension was filtered through a Celite pad and concentrated under reduced pressure. Purification of the crude aldehyde by silica gel chromatography (20 mm × 200 mm column, 15:1 hexanes/EtOAc as eluent, flash column) afforded aldehyde **33v** as a colorless liquid in 98% yield (927 mg, 4.92 mmol). Spectral data for **33v**: R_f = 0.34 (10:1 hexanes/EtOAc); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.04 (s, 6H), 0.86 (s, 9H), 2.57 (td, 2H, J = 6.0, 2.0 Hz), 3.96 (t, 2H, J = 6.0 Hz), 9.78 (t, 1H, J = 2.0 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ –5.43, 18.23, 25.82, 46.58, 57.42, 202.05.



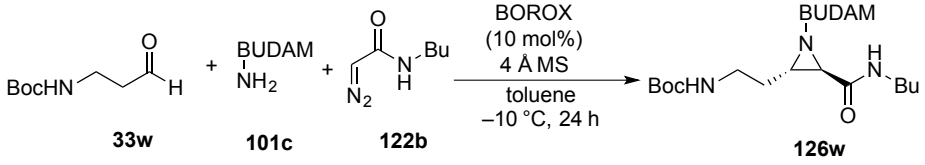
(2R,3S)-1-(bis(3,5-di-tert-butyl-4-methoxyphenyl)methyl)-N-butyl-3-(2-((tert-butyldimethylsilyl)oxy)ethyl)aziridine-2-carboxamide ***126v***: 3-(*tert*-Butyldimethylsilyl)propanal **33v** (51 μL, 0.22 mmol, 1.1 equiv) was reacted according to the General Procedure A of multi-component *trans*-aziridination of aliphatic aldehydes with BUDAM amine **101c** (94 mg, 0.20 mmol), (*S*)-VANOL (8.8 mg, 0.020 mmol, 0.10

equiv) and *N*-butyl diazoacetamide **122b** (34 mg, 0.24 mmol, 1.2 equiv). Purification of the crude aziridine by silica gel chromatography (20 mm × 200 mm column, 4:1 hexanes/Et_2O as eluent, flash column) afforded aziridine (2*R*,3*S*)-**126v** as a white foam (mp 61-62 °C on 96% *ee* material) in 60% yield (90 mg, 0.12 mmol); *trans*/*cis* >99:1. The enantiomeric purity of (2*R*,3*S*)-**126v** isomers was determined to be 96% *ee* by HPLC analysis (PIRKLE COVALENT (R, R) WHELK-O 1 column, 95:5 hexane/2-propanol at 222 nm, flow-rate: 0.7 mL/min): retention times; R_t = 14.09 min (minor enantiomer, *ent*-**126v**) and R_t = 21.85 min (major enantiomer, **126v**). The aziridination of **33v** in the presence of (*R*)-^{t}Bu$_2$VANOL BOROX catalyst afforded (2*S*,3*R*)-*ent*-**126v** in –98% *ee* and 56% yield (84 mg, 0.11 mmol); *trans*/*cis* >99:1.

Spectral data for (2*R*,3*S*)-**126v**: R_f = 0.34 (2:1 hexanes/Et_2O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ –0.07 (s, 6H), 0.81 (s, 9H), 0.89 (t, 3H, *J* = 7.2 Hz), 1.35 (s, 18H), 1.39 (s, 18 H), 1.31-1.42 (m, 4H), 1.81 (q, 2H, *J* = 6.5 Hz), 2.11 (d, 1H, *J* = 3.0 Hz), 2.34 (td, 1H, *J* = 6.4, 2.8 Hz), 3.03-3.10 (m, 1H), 3.20-3.27 (m, 1H), 3.40-3.51 (m, 2H), 3.64 (d, 6H, *J* = 7.0 Hz), 4.14 (s, 1H), 6.65 (t, 1H, *J* = 6.0 Hz), 7.18 (s, 2H), 7.28 (s, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ –5.45, –5.37, 13.75, 20.04, 25.83, 29.68, 31.67, 32.06, 32.09, 35.67, 35.73, 38.40, 44.06, 44.53, 61.43, 64.01, 64.12, 68.54, 125.13, 125.31, 137.13, 137.20, 143.17, 143.24, 158.24, 158.32, 170.52; IR (thin film) 3396s, 2958s, 1653vs, 1412s, 1361s, 1260s, 1221s, 1114s, 1015s cm^{-1}; HRMS (ESI-TOF) *m/z* 751.5803 [(M+H$^+$); calcd. for $C_{46}H_{79}N_2O_4Si$: 751.5809]; $[\alpha]_D^{20}$ –2.6° (c 1.0, EtOAc) on 96% *ee* material (HPLC).



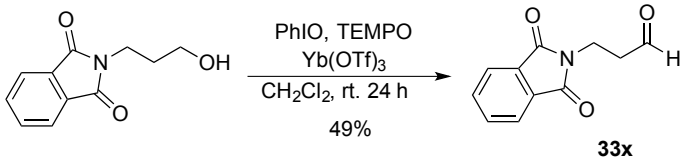
tert-Butyl (3-oxopropyl)carbamate ***33w***:[22b] To a 25 mL flame-dried round bottom flask equipped with a stir bar was added alcohol **331** (0.85 mL, 5.0 mmol) into dry CH_2Cl_2 (20 mL). To the resulting solution was added TEMPO (39 mg, 0.25 mmol, 0.050 equiv) and PhIO (1.32 mg, 6.00 mmol, 1.20 equiv). The suspension was cooled to 0 °C and $Yb(OTf)_3$ (62 mg, 0.10 mmol, 0.020 equiv) was added. The reaction mixture was stirred at room temperature for 5 h (until the alcohol was no longer detectable by TLC). The resulting suspension was filtered through a Celite pad and concentrated under reduced pressure. Purification of the crude aldehyde by silica gel chromatography (20 mm × 200 mm column, 3:1 hexanes/EtOAc as eluent, flash column) afforded aldehyde **33w** as a colorless liquid in 92% yield (797 mg, 4.60 mmol). Spectral data for **33w**: R_f = 0.46 (1:1 hexanes/EtOAc); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.40 (s, 9H), 2.69 (t, 2H, J = 5.8 Hz), 3.40 (q, 2H, J = 6.0 Hz), 4.81-5.07 (br, 1H), 9.79 (s, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 28.01, 33.75, 43.91, 78.91, 155.62, 201.27.



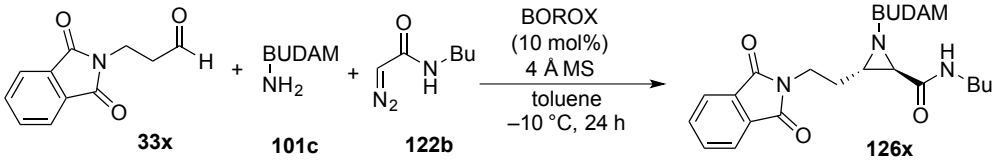
tert-butyl (2-((2S,3R)-1-(bis(3,5-di-tert-butyl-4-methoxyphenyl)methyl)-3-(butylcarbamoyl)aziridin-2-yl)ethyl)carbamate ***126w***: *tert*-Butyl (3-oxopropyl)carbamate **33w** (42 μL, 0.22 mmol, 1.1 equiv) was reacted according to the General Procedure A of multi-component *trans*-aziridination of aliphatic aldehydes with BUDAM amine **101c** (94 mg, 0.20 mmol), (*S*)-VANOL (8.8 mg, 0.020 mmol, 0.10 equiv) and *N*-butyl

diazoacetamide **122b** (34 mg, 0.24 mmol, 1.2 equiv). Purification of the crude aziridine by silica gel chromatography (20 mm × 200 mm column, 3:1 hexanes/EtOAc as eluent, flash column) afforded aziridine (2*S*,3*R*)-**126w** as a white solid (113-115 °C on 88% *ee* material) in 67% yield (99 mg, 0.13 mmol); *trans*/*cis* 25:1. The enantiomeric purity of (2*S*,3*R*)-**126w** isomers was determined to be 85% *ee* by HPLC analysis (PIRKLE COVALENT (R, R) WHELK-O 1 column, 95:5 hexane/2-propanol at 222 nm, flow-rate: 0.7 mL/min): retention times; R_t = 19.10 min (minor enantiomer, *ent*-**126w**) and R_t = 24.78 min (major enantiomer, **126w**). The aziridination of **33w** in the presence of (*R*)-^{t}Bu$_2$VANOL BOROX catalyst afforded (2*R*,3*S*)-*ent*-**126w** in –88% *ee* and 68% yield (100 mg, 0.136 mmol); *trans*/*cis* 10:1.

Spectral data for (2*S*,3*R*)-**126w**: R_f = 0.23 (2:1 hexanes/EtOAc); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.87 (t, 3H, *J* = 7.2 Hz), 1.09-1.20 (m, 4H), 1.35 (s, 18H), 1.38 (d, 9H, *J* = 11.5 Hz), 1.39 (s, 18H), 1.68-1.76 (m, 1H), 1.78-1.88 (m, 1H), 2.13 (d, 1H, *J* = 3.0 Hz), 2.14-2.21 (m, 1H), 2.86-2.95 (m, 1H), 3.06-3.13 (m, 2H), 3.14-3.23 (m, 1H), 3.60 (s, 1H), 3.63 (d, 6H, *J* = 2.5 Hz), 4.13 (s, 1H), 6.58 (t, 1H, *J* = 5.5 Hz), 7.18 (s, 2H), 7.28 (s, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 13.75, 20.08, 28.35, 28.44, 31.67, 32.06, 32.11, 32.21, 35.70, 35.75, 38.47, 44.75, 64.04, 64.20, 68.76, 125.05, 125.26, 126.30, 136.98, 137.05, 143.34, 155.70, 158.34, 158.40, 170.21 (two sp^3 carbon not located); IR (thin film) 3427s, 2961s, 1653vs, 1412s, 1365s, 1261s, 1222s, 1173s, 1115s, 1014s cm^{-1}; HRMS (ESI-TOF) *m/z* 736.5618 [(M+H$^+$); calcd. for $C_{45}H_{74}N_3O_5$: 736.5628]; $[\alpha]_D^{20}$ +15.6° (c 1.0, EtOAc) on –88% *ee* material (HPLC).



N-(3-Oxopropyl)phthalimide ***33x***:[22b] To a 25 mL flame-dried round bottom flask equipped with a stir bar was added alcohol **332** (1.03 g, 5.00 mmol) into dry CH_2Cl_2 (20 mL). To the resulting solution was added TEMPO (39 mg, 0.25 mmol, 0.050 equiv) and PhIO (1.32 mg, 6.00 mmol, 1.20 equiv). The suspension was cooled to 0 °C and $Yb(OTf)_3$ (62 mg, 0.10 mmol, 0.020 equiv) was added. The reaction mixture was stirred at room temperature for 24 h (until the alcohol was no longer detectable by TLC). The resulting suspension was filtered through a Celite pad and concentrated under reduced pressure. Purification of the crude aldehyde by silica gel chromatography (20 mm × 200 mm column, 3:1 hexanes/EtOAc as eluent, flash column) afforded aldehyde **33x** as a white solid (mp 136-138 °C) in 49% yield (498 mg, 2.45 mmol). Spectral data for **33x**: R_f = 0.42 (1:1 hexanes/EtOAc); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 2.85 (td, 2H, *J* = 7.0, 1.2 Hz), 4.01 (t, 2H, *J* = 7.0 Hz), 7.70 (dd, 2H, *J* = 5.8, 3.2 Hz), 7.82 (dd, 2H, *J* = 5.5, 3.5 Hz), 9.79 (t, 1H, *J* = 1.2 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 31.62, 42.32, 123.34, 131.89, 134.10, 167.98, 199.44.



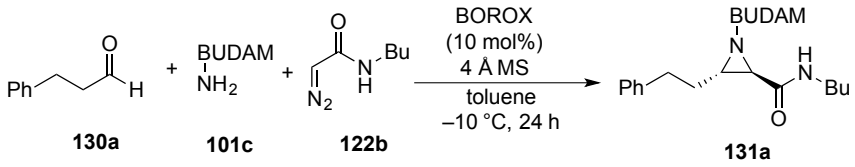
(2R,3S)-1-(bis(3,5-di-tert-butyl-4-methoxyphenyl)methyl)-N-butyl-3-(2-phthalylethyl)aziridine-2-carboxamide ***126x***: *N*-(3-Oxopropyl)phthalimide **33x** (45 mg, 0.22 mmol, 1.1 equiv) was reacted according to the General Procedure A of multi-component *trans*-aziridination of aliphatic aldehydes with BUDAM amine **101c** (94 mg,

0.20 mmol), (*S*)-VANOL (8.8 mg, 0.020 mmol, 0.10 equiv) and *N*-butyl diazoacetamide **122b** (34 mg, 0.24 mmol, 1.2 equiv). Purification of the crude aziridine by silica gel chromatography (20 mm × 200 mm column, 4:1 hexanes/EtOAc as eluent, flash column) afforded aziridine (2*R*,3*S*)-**126x** as a white foam (mp 57-60 °C on 60% *ee* material) in 71% yield (109 mg, 0.142 mmol); *trans*/*cis* 6:1. The enantiomeric purity of (2*R*,3*S*)-**126x** isomers was determined to be 91% *ee* by HPLC analysis (PIRKLE COVALENT (R, R) WHELK-O 1 column, 85:15 hexane/2-propanol at 222 nm, flow-rate: 0.7 mL/min): retention times; R_t = 26.41 min (minor enantiomer, *ent*-**126x**) and R_t = 37.97 min (major enantiomer, **126x**). The aziridination of **33x** in the presence of (*R*)-^{t}Bu$_2$VANOL BOROX catalyst afforded (2*S*,3*R*)-*ent*-**126x** in –60% *ee* and 64% yield (98 mg, 0.13 mmol); *trans*/*cis* 6:1.

Spectral data for (2*R*,3*S*)-**126x**: R_f = 0.62 (1:1 hexanes/EtOAc); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.84 (t, 3H, *J* = 7.8 Hz), 1.18-1.32 (m, 4H), 1.37 (s, 18H), 1.40 (s, 18H), 2.06 (d, 1H, *J* = 3.0 Hz), 2.26-2.32 (m, 1H), 3.00-3.11 (m, 1H), 3.13-3.24 (m, 2H), 3.46-3.54 (m, 1H), 3.61 (d, 6H, *J* = 1.0 Hz), 3.65 (t, 2H, *J* = 7.5 Hz), 4.17 (s, 1H), 6.55 (t, 1H, *J* = 5.8 Hz), 7.18 (s, 2H), 7.32 (s, 2H), 7.68 (dd, 2H, *J* = 5.5, 3.0 Hz), 7.80 (dd, 2H, *J* = 5.0, 3.0 Hz);

^{13}C-NMR (125 MHz, $CDCl_3$) δ 13.78, 20.04, 25.90, 32.06, 32.08, 32.18, 35.69, 35.74, 36.18, 38.44, 44.20, 44.56, 64.01, 64.16, 68.60, 123.11, 123.24, 125.10, 125.21, 125.88, 132.04, 133.83, 133.95, 136.99, 143.20, 143.28, 158.32, 168.16, 169.82;

IR (thin film) 3370s, 2957s, 2926s, 2870s, 1773s, 1717vs, 1451s, 1396s, 1372s, 1273vs, 1224vs, 1115s, 1011s cm^{-1}; HRMS (ESI-TOF) *m/z* 766.5152 [(M+H$^+$); calcd. for $C_{48}H_{68}N_3O_5$: 766.5159]; $[\alpha]_D^{20}$ –5.8° (c 1.0, EtOAc) on 91% *ee* material (HPLC).

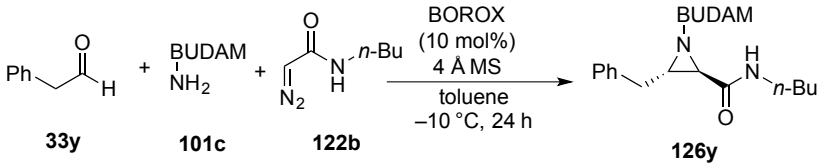


130a **101c** **122b** **131a**

*(2R,3S)-1-(bis(3,5-di-tert-butyl-4-methoxyphenyl)methyl)-N-butyl-3-phenethylaziridine-2-carboxamide **131a***: Hydrocinnamaldehyde **130a** (29 μL, 0.22 mmol, 1.1 equiv) was reacted according to the General Procedure A of multi-component *trans*-aziridination of aliphatic aldehydes with BUDAM amine **101c** (94 mg, 0.20 mmol), (*S*)-VANOL (8.8 mg, 0.020 mmol, 0.10 equiv) and *N*-butyl diazoacetamide **122b** (34 mg, 0.24 mmol, 1.2 equiv). Purification of the crude aziridine by silica gel chromatography (20 mm × 200 mm column, 3:1 hexanes/Et_2O as eluent, flash column) afforded aziridine (2*R*,3*S*)-**131a** as a white foam (mp 114-117 °C on 98% *ee* material) in 87% yield (121 mg, 0.174 mmol); *trans*/*cis* >99:1. The enantiomeric purity of (2*R*,3*S*)-**131a** isomers was determined to be 98% *ee* by HPLC analysis (PIRKLE COVALENT (R, R) WHELK-O 1 column, 90:10 hexane/2-propanol at 222 nm, flow-rate: 0.7 mL/min): retention times; R_t = 10.04 min (minor enantiomer, *ent*-**131a**) and R_t = 18.39 min (major enantiomer, **131a**). The aziridination of **130a** in the presence of (*R*)-^{t}Bu$_2$VANOL BOROX catalyst afforded (2*S*,3*R*)-*ent*-**131a** in –73% *ee* and 77% yield (107 mg, 0.154 mmol); *trans*/*cis* >99:1.

Spectral data for (2*R*,3*S*)-**131a**: R_f = 0.20 (2:1 hexanes/Et_2O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.89 (t, 3H, *J* = 7.5 Hz), 1.23-1.31 (m, 4H), 1.36 (s, 18H), 1.40 (s, 18H), 1.79-1.87 (m, 1H), 1.93-2.00 (m, 1H), 2.13 (d, 1H, *J* = 3.0 Hz), 2.22 (td, 1H, *J* = 6.1, 2.7 Hz), 2.30-2.36 (m, 1H), 2.41-2.47 (m, 1H), 3.06-3.12 (m, 1H), 3.16-3.23 (m, 1H), 3.63 (d, 6H, *J* = 5.5 Hz), 4.19 (s, 1H), 6.62 (t, 1H, *J* = 5.8 Hz), 6.94 (d, 2H, *J* =7.5 Hz), 7.13 (t, 1H, *J* = 7.2 Hz), 7.19-7.22 (m, 2H), 7.20 (s, 2H), 7.34 (s, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 13.58, 20.05, 28.21, 31.66, 32.06, 32.11, 34.35, 35.70, 35.76, 38.46, 44.85, 46.42, 64.03,

64.23, 68.59, 125.11, 125.25, 125.97, 128.24, 128.32, 129.59, 137.17, 137.31, 141.02, 143.31, 158.34, 158.37, 170.57; IR (thin film) 3441s, 2961s, 1645vs, 1412s, 1221s, 1115s, 1014s cm^{-1}; HRMS (ESI-TOF) *m/z* 697.5319 [(M+H^+); calcd. for $C_{46}H_{69}N_2O_3$: 697.5308]; $[\alpha]_D^{20}$ –15.7° (c 1.0, EtOAc) on 98% *ee* material (HPLC).

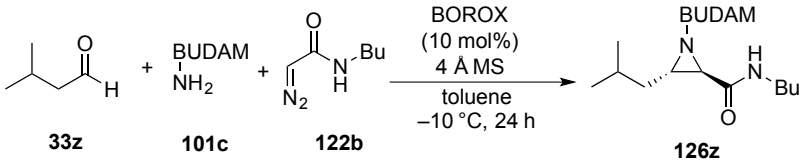


33y **101c** **122b** **126y**

*(2R,3S)-3-benzyl-1-(bis(3,5-di-tert-butyl-4-methoxyphenyl)methyl)-N-butylaziridine-2-carboxamide **126y***: Phenylacetaldehyde **33y**(25 μL, 0.22 mmol, 1.1 equiv) was reacted according to the General Procedure A of multi-component *trans*-aziridination of aliphatic aldehydes with BUDAM amine **101c** (94 mg, 0.20 mmol), (*S*)-VANOL (8.8 mg, 0.020 mmol, 0.10 equiv) and *N*-butyl diazoacetamide **122b** (34 mg, 0.24 mmol, 1.2 equiv). Purification of the crude aziridine by silica gel chromatography (20 mm × 200 mm column, 4:1 hexanes/Et_2O as eluent, flash column) afforded aziridine (2*R*,3*S*)-**126y** as a white foam (mp 82-84 °C on 98% *ee* material) in 71% yield (97 mg, 0.14 mmol); *trans*/*cis* >99:1. The enantiomeric purity of (2*R*,3*S*)-**126y** isomers was determined to be 88% *ee* by HPLC analysis (CHIRALCEL OD-H column, 90:10 hexane/2-propanol at 222 nm, flow-rate: 0.7 mL/min): retention times; R_t = 9.80 min (major enantiomer, **126y**) and R_t = 31.03 min (minor enantiomer, *ent*-**126y**). The aziridination of **33y** in the presence of (*R*)-^{t}Bu$_2$VANOL BOROX catalyst afforded (2*S*,3*R*)-*ent*-**126y** in –96% *ee* and 86% yield (119 mg, 0.174 mmol); *trans*/*cis* >99:1.

Spectral data for (2*R*,3*S*)-**126y**: R_f = 0.30 (2:1 hexanes/Et_2O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.88 (t, 3H, *J* = 7.5 Hz), 1.23-1.30 (m, 2H), 1.37 (s, 36H), 1.34-1.43 (m, 2H),

2.31 (d, 1H, J = 3.0 Hz), 2.45-2.48 (m, 1H), 2.89 (dd, 1H, J = 10.0, 6.0 Hz), 3.00 (dd, 1H, J = 10.0, 6.0 Hz), 3.05-3.12 (m, 1H), 3.14-3.21 (m, 1H), 3.65 (d, 6H, J = 4.5 Hz), 4.29 (s, 1H), 6.61 (t, 1H, J = 5.8 Hz), 6.96 (d, 2H, J = 8.0 Hz), 7.10 (t, 1H, J = 7.2 Hz), 7.15 (t, 2H, J = 7.5 Hz), 7.21 (s, 2H), 7.30 (s, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 13.74, 20.07, 31.66, 32.08, 35.71, 38.45, 45.21, 47.18, 64.04, 64.15, 68.87, 125.19, 125.32, 126.30, 128.38, 128.41, 137.04, 137.09, 138.46, 143.21, 143.34, 158.31, 158.39, 170.21 (three sp^3 carbon not located); IR (thin film) 3323s, 2960vs, 2871s, 1656vs, 1531s, 1454vs, 1412vs, 1394s, 1361s, 1265s, 1221vs, 1115s, 1013s cm^{-1}; HRMS (ESI-TOF) *m/z* 683.5182 [(M+H$^+$); calcd. for $C_{45}H_{67}N_2O_3$: 683.5152]; $[\alpha]_D^{20}$ +9.7° (c 1.0, EtOAc) on – 96% *ee* material (HPLC).

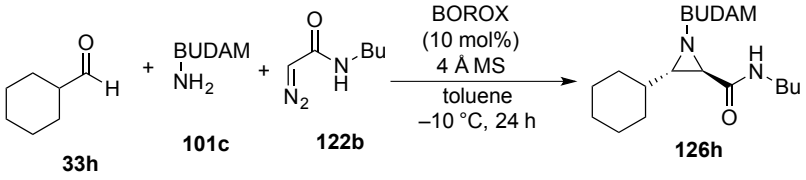


33z **101c** **122b** **126z**

(2R,3S)-1-(bis(3,5-di-tert-butyl-4-methoxyphenyl)methyl)-N-butyl-3-isobutylaziridine-2-carboxamide ***126z***: Isovaleraldehyde **33z** (24 μL, 0.22 mmol, 1.1 equiv) was reacted according to the General Procedure A of multi-component *trans*-aziridination of aliphatic aldehydes with BUDAM amine **101c** (94 mg, 0.20 mmol), (*S*)-VANOL (8.8 mg, 0.020 mmol, 0.10 equiv) and *N*-butyl diazoacetamide **122b** (34 mg, 0.24 mmol, 1.2 equiv). Purification of the crude aziridine by silica gel chromatography (20 mm × 200 mm column, 5:1 hexanes/Et_2O as eluent, flash column) afforded aziridine (2*R*,3*S*)-**126z** as a white foam (mp 136-139 °C on 95% *ee* material) in 88% yield (114 mg, 0.176 mmol); *trans*/*cis* 12:1. The enantiomeric purity of (2*R*,3*S*)-**126z** isomers was determined to be 95% *ee* by HPLC analysis (PIRKLE COVALENT (R, R) WHELK-O 1 column, 95:5 hexane/2-propanol at 222 nm, flow-rate: 0.7 mL/min): retention times; R_t = 9.80 min

(minor enantiomer, *ent*-**126z**) and R_t = 21.43 min (major enantiomer, **126z**). The aziridination of **33z** in the presence of (*R*)-^{t}Bu$_2$VANOL BOROX catalyst afforded (2*S*,3*R*)-*ent*-**126z** in –75% *ee* and 70% yield (91 mg, 0.14 mmol); *trans*/*cis* 19:1.

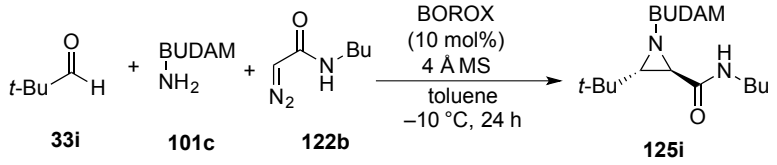
Spectral data for (2*R*,3*S*)-**126z**: R_f = 0.42 (2:1 hexanes/Et_2O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.75 (d, 3H, *J* = 6.5 Hz), 0.86 (d, 3H, *J* = 6.5 Hz), 0.89 (t, 3H, *J* = 7.5 Hz), 1.15-1.47 (m, 7H), 1.36 (s, 18H), 1.39 (s, 18H), 2.08 (d, 1H, *J* = 3.0 Hz), 2.14-2.22 (m, 1H), 3.07-3.13 (m, 1H), 3.16-3.23 (m, 1H), 3.63 (s, 6H), 4.14 (s, 1H), 6.63 (t, 1H, *J* = 5.8 Hz), 7.20 (s, 2H), 7.28 (s, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 13.76, 20.08, 21.90, 23.05, 27.30, 31.71, 32.08, 32.10, 35.02, 35.69, 38.41, 45.34, 45.84, 64.03, 64.16, 68.54, 125.21, 125.34, 137.24, 137.44, 143.06, 143.22, 158.21, 158.30, 170.71; IR (thin film) 3318s, 2958vs, 2870s, 1648vs, 1533vs, 1466vs, 1443vs, 1412vs, 1393s, 1361s, 1265s, 1221vs 1115vs, 1014vs cm^{-1}; HRMS (ESI-TOF) *m/z* [(M+H$^+$); calcd. for $C_{42}H_{69}N_2O_3$: 649.5308]; $[\alpha]_D^{20}$ –14.9° (c 1.0, EtOAc) on 98% *ee* material (HPLC).



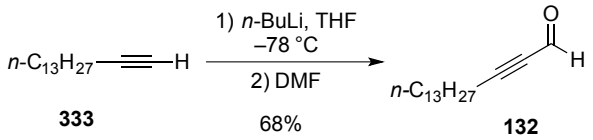
*(2R,3S)-1-(bis(3,5-di-tert-butyl-4-methoxyphenyl)methyl)-N-butyl-3-cyclohexylaziridine-2-carboxamide **126h***: Cyclohexanecarboxaldehyde **33h** (24 μL, 0.22 mmol, 1.1 equiv) was reacted according to the General Procedure A of multi-component *trans*-aziridination of aliphatic aldehydes with BUDAM amine **101c** (94 mg, 0.20 mmol), (*S*)-VANOL (8.8 mg, 0.020 mmol, 0.10 equiv) and *N*-butyl diazoacetamide **122b** (34 mg, 0.24 mmol, 1.2 equiv). Purification of the crude aziridine by silica gel chromatography (20 mm × 200 mm column, 5:1 hexanes/Et_2O as eluent, flash column) afforded aziridine (2*R*,3*S*)-**126h**

as a white foam (mp 174-178 °C on 57% *ee* material) in 45% yield (114 mg, 0.176 mmol); *trans*/*cis* 12:1. The enantiomeric purity of (2*R*,3*S*)-**126h** isomers was determined to be 28% *ee* by HPLC analysis (PIRKLE COVALENT (R, R) WHELK-O 1 column, 95:5 hexane/2-propanol at 222 nm, flow-rate: 0.7 mL/min): retention times; R_t = 10.18 min (minor enantiomer, *ent*-**126h**) and R_t = 20.87 min (major enantiomer, **126h**). The aziridination of **33h** according to the General Procedure A of multi-component *trans*-aziridination of aliphatic aldehydes in the presence of (*R*)-VAPOL BOROX catalyst afforded (2*S*,3*R*)-**126h** in –57% *ee* and 56% yield. The aziridination of **33h** according to the General Procedure B of multi-component *trans*-aziridination of aliphatic aldehydes in the presence of (*S*)-VANOL BOROX catalyst afforded (2*R*,3*S*)-**126h** in 8% *ee* and 61% yield.

Spectral data for (2*R*,3*S*)-**126h**: R_f = 0.36 (2:1 hexanes/Et_2O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.56-0.69 (m, 2H), 0.77-0.93 (m, 2H), 0.90 (t, 3H, *J* = 7.5 Hz), 0.95-1.18 (m, 5H), 1.19-1.46 (m, 2H), 1.36 (s, 18H), 1.39 (s, 18H), 1.50-1.65 (m, 3H), 1.68-1.75 (m, 1H), 1.76-1.83 (m, 1H), 1.90 (dd, 1H, *J* = 4.5, 3.0 Hz), 2.03 (d, 1H, *J* = 3.0 Hz), 3.04-3.13 (m, 1H), 3.15-3.24 (m, 1H), 3.60 (s, 3H), 3.63 (s, 3H), 4.11 (s, 1H), 6.60 (t, 1H, *J* = 5.8 Hz), 7.25 (s, 2H), 7.33 (s, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 13.77, 20.09, 25.79, 25.98, 26.00, 29.68, 31.72, 32.07, 32.13, 35.00, 35.69, 38.40, 44.23, 52.89, 64.00, 64.29, 69.52, 125.05, 125.12, 137.43, 137.68, 143.22, 143.24, 158.29, 158.38, 170.80; IR (thin film) 3423s, 2959s, 2926s, 1647vs, 1448s, 1413s, 1360s, 1221vs, 1115s, 1014s cm^{-1}; HRMS (ESI-TOF) *m/z* 675.5459 [($M+H^+$); calcd. for $C_{44}H_{71}N_2O_3$: 675.5465]; $[\alpha]_D^{20}$ – 2.9° (c 1.0, EtOAc) on 28% *ee* material (HPLC).

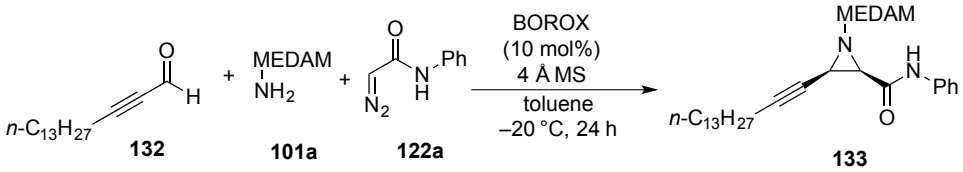


(2R,3S)-1-(bis(3,5-di-tert-butyl-4-methoxyphenyl)methyl)-3-(tert-butyl)-N-butylaziridine-2-carboxamide ***126i***: Pivaldehyde **33i** (24 μL, 0.22 mmol, 1.1 equiv) was reacted according to the General Procedure C of multi-component *trans*-aziridination of aliphatic aldehydes with BUDAM amine **101c** (94 mg, 0.20 mmol), (*S*)-VANOL (8.8 mg, 0.020 mmol, 0.10 equiv) and *N*-butyl diazoacetamide **122b** (34 mg, 0.24 mmol, 1.2 equiv). A 76% of imine and 6% of aziridine (2*R*,3*S*)-**18l** was observed in the ^{1}H-NMR spectrum of the crude reaction mixture.



2-Hexadecynal ***15n***:[11] *n*-BuLi (2.5 *M* in hexanes, 18.8 mL, 30.0 mmol) was added dropwise to a solution of 1-hexadecyne **333** (6.67 g, 30 mmol) in dry Et_2O (25 mL) at –40 °C under nitrogen. After 30 min, dry DMF (3.5 mL, 45 mmol, 1.5 equiv) was added, and then the mixture was allowed to warm up to room temperature, and stirring was continued for 30 min. The mixture was poured into ice water and acidified slightly with concentrated HCl. The mixture was then neutralized with saturated $NaHCO_3$ aq. until a pH between 6 and 7 was reached. The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated. Purification of the crude aldehyde by silica gel chromatography (20 mm × 200 mm column, 2:1 hexanes/CH_2Cl_2 as eluent, flash column) afforded aldehyde **132** as a colorless liquid in 68% yield (4.82 g,

20.4 mmol). Spectral data for (2*R*,3*R*)-**132**: R_f = 0.28 (1:1 hexanes/CH_2Cl_2); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.86 (t, 3H, *J* = 7.0 Hz), 1.19-1.31 (m, 18H), 1.33-1.42 (m, 2H), 1.57 (pent, 2H, *J* = 7.5 Hz), 2.39 (t, 2H, *J* = 7.2 Hz), 9.16 (s, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 14.12, 19.12, 22.68, 27.53, 28.82, 29.00, 29.34, 29.41, 29.57, 29.63, 29.65, 31.90, 81.67, 99.45, 177.30 (one sp^3 carbon not located).



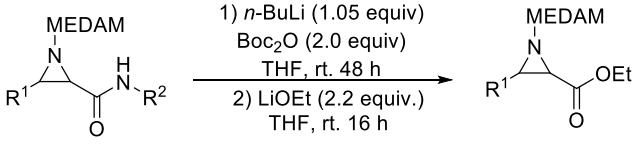
(2R,3R)-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-(pentadec-1-yn-1-yl)-N-phenylaziridine-2-carboxamide ***18n***: 2-Hexadecynal **132** (52 mg, 0.22 mmol, 1.1 equiv) was reacted according to the General Procedure B of multi-component *trans*-aziridination of aromatic aldehydes with MEDAM amine **101a** (60 mg, 0.20 mmol), (*R*)-VANOL (8.8 mg, 0.020 mmol, 0.10 equiv) and *N*-phenyl diazoacetamide **122a** (45 mg, 0.24 mmol, 1.4 equiv). Purification of the crude aziridine by silica gel chromatography (20 mm × 200 mm column, 8:1 hexanes/EtOAc as eluent, flash column) afforded aziridine (2*R*,3*R*)-**133** as an oily liquid in 71% yield (92 mg, 0.14 mmol). The enantiomeric purity of (2*R*,3*R*)-**133** isomers was determined to be 95% *ee* by HPLC analysis (CHIRALCEL AD column, 85:15 hexane/2-propanol at 222 nm, flow-rate: 0.7 mL/min): retention times; R_t = 7.98 min (minor enantiomer, *ent*-**133**) and R_t = 21.54 min (major enantiomer, **133**). The aziridination of **132** in the presence of (*R*)-VANOL BOROX catalyst at 0 °C afforded (2*R*,3*R*)-**133** in 91% *ee* and 92% yield (120 mg, 0.184 mmol).

Spectral data for (2*R*,3*R*)-**133**: R_f = 0.41 (3:1 hexanes/EtOAc); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.86 (t, 3H, *J* = 7.0 Hz), 1.06-1.33 (m, 22H), 2.05 (t, 3H, *J* = 6.8 Hz), 2.22 (s,

6H), 2.28 (s, 6H), 2.50 (d, 1H, J = 6.2 Hz), 2.53 (d, 2H, J = 6.2 Hz), 3.66 (s, 4H), 3.70 (s, 3H), 6.95 (s, 2H), 7.07 (s, 2H), 7.08 (t, 1H, J = 7.2 Hz), 7.30 (t, 2H, J = 7.5 Hz), 7.49 (d, 2H, J = 7.5 Hz), 8.38 (s, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 14.12, 16.27, 16.30, 18.65, 22.68, 28.45, 28.70, 29.07, 29.35, 29.42, 29.65, 29.67, 29.69, 31.91, 35.72, 45.89, 59.57, 59.63, 74.58, 75.38, 84.14, 119.84, 124.21, 127.38, 127.84, 128.88, 130.74, 131.06, 136.69, 136.91, 137.19, 156.06, 156.43, 165.82 (one sp^3 carbon not located); IR (thin film) 3427s, 2924s, 2853s, 1659vs, 1602s, 1529vs, 1444s, 1262s, 1222vs, 1146s, 1096s, 1017s cm^{-1}; HRMS (ESI-TOF) *m/z* [(M+H$^+$); calcd. for $C_{43}H_{59}N_2O_3$: 651.4526]; $[\alpha]_D^{20}$ – 20.4° (c 1.0, EtOAc) on 91% *ee* material (HPLC).

6.3.4 Absolute Stereochemistry of *trans*- and *cis*-Aziridines

General Procedure A of Preparation of Ester from Secondary Amide

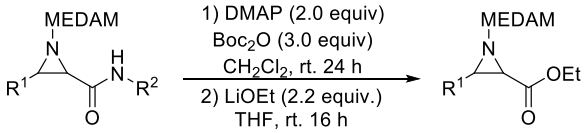


To a flame dried 10 mL round bottom flask flushed with nitrogen was added aziridine (0.20 mmol) and THF (1.2 mL). The reaction flask was placed into the ice-bath for 5 min before the slow addition of *n*-butyllithium (0.14 mL, 1.6 *M* in hexanes, 0.22 mmol, 1.1 equiv) in dropwise. The mixture was stirred at 0 °C for another 10 min until the complete deprotonation of the secondary amide. A solution of Boc_2O (131 mg, 0.600 mmol, 3.00 equiv) in THF (0.8 mL) was added to the reaction mixture. The resulting mixture was stirred for 2 days at room temperature under nitrogen atmosphere. The reaction was quenched by sat. aq. NH_4Cl (2 mL) and brine (4 mL). The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layer was dried by $MgSO_4$ and concentrated under reduced pressure. Purification of the crude product by silica gel

chromatography (20 mm × 200 mm column, 12:1 hexanes/EtOAc as eluent, flash column) afforded *N*-Boc aziridinecarboxylamide, which was used immediately in the next step.

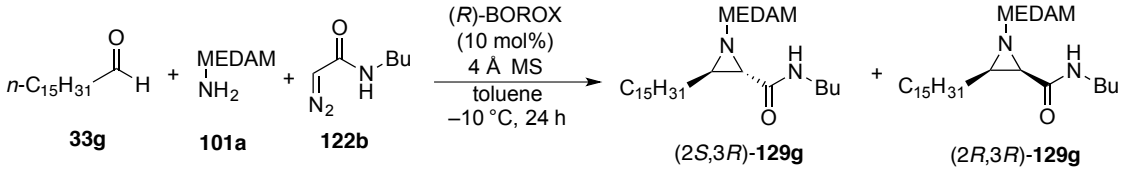
To a flame dried 10 mL round bottom flask flushed with nitrogen was added ethanol (58 μL, 1.0 mmol, 5.0 equiv) and THF (1.2 mL). The reaction flask was placed into the ice-bath for 5 min before the slow addition of *n*-butyllithium (0.28 mL, 1.6 *M* in hexanes, 0.44 mmol, 2.2 equiv) in dropwise. The mixture was stirred at 0 °C for another 10 min until the complete formation of lithium ethoxide. A solution of *N*-Boc aziridinecarboxamide in THF (0.8 mL) was added to the reaction mixture. The resulting mixture was warmed up to room temperature and stirred over night until the *N*-Boc amide was no longer detectable by TLC. The reaction was quenched by sat. aq. NH_4Cl (2 mL) and brine (4 mL). The aqueous layer was extracted with Et_2O (4 × 10 mL). The combined organic layer was dried by $MgSO_4$ and concentrated under reduced pressure. Purification of the crude ester by silica gel chromatography (20 mm × 200 mm column, 9:1 hexanes/EtOAc as eluent, flash column) afforded ethyl aziridinecarboxylate.

General Procedure B of Preparation of Ester from Secondary Amide



To a flame dried 10 mL round bottom flask flushed with nitrogen was added aziridine (0.20 mmol) and dichloromethane (1.0 mL). To the resulting solution was added DMAP (49 mg, 0.40 mmol, 2.0 equiv) and Boc_2O (131 mg, 0.600 mmol, 3.00 equiv). The reaction mixture was stirred for 24 h 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 product by silica gel chromatography (20 mm × 200 mm column, 12:1 hexanes/EtOAc as eluent, flash column) afforded *N*-Boc aziridinecarboxylamide, which was used immediately in the next step. Ethyl aziridinecaboxylate was prepared from *N*-Boc aziridinecarboxylamide according to second step in General Procedure A.

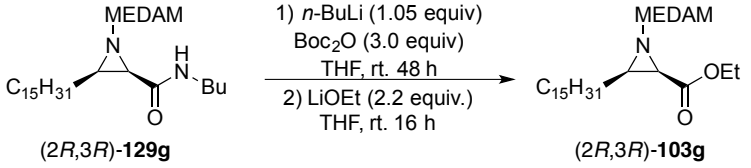


33g **101a** **122b** (2*S*,3*R*)-**129g** (2*R*,3*R*)-**129g**

*(2R,3R)-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-N-butyl-3-pentadecylaziridine-2-carboxamide (2R,3R)-**129g***: Palmitaldehyde **33g** (132 mg, 0.220 mmol, 1.10 equiv) was reacted according to the General Procedure A of multi-component *trans*-aziridination of aliphatic aldehydes with MEDAM amine **101a** (150 mg, 0.200 mmol), (*R*)-^{t}Bu$_2$VANOL (28 mg, 0.020 mmol, 0.10 equiv) and *N*-butyl diazoacetamide **122b** (85 mg, 0.24 mmol, 1.2 equiv). Purification of the crude aziridine by silica gel chromatography (20 mm × 200 mm column, 2:1 hexanes/Et$_2$O as eluent, flash column) afforded aziridine (2*R*,3*R*)-**129g** as an oily liquid in 44% yield (140 mg, 0.220 mmol). The enantiomeric purity of (2*R*,3*R*)-**129g** was determined to be 90% *ee* by HPLC analysis (CHIRARCEL OD-H column, 99:1 hexane/2-propanol at 222 nm, flow-rate: 0.7 mL/min): retention times; R_t = 14.96 min (major enantiomer, *ent*-**129g**) and R_t = 21.33 min (minor enantiomer, *ent*-**129g**).

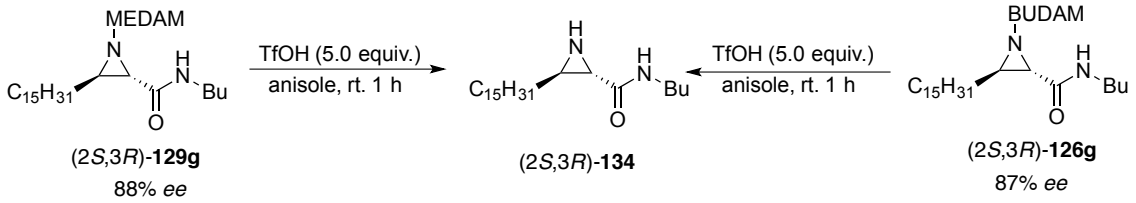
Spectral data for (2*R*,3*R*)-**129g**: R_f = 0.33 (1:1 hexanes/Et$_2$O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.88 (t, 3H, *J* = 7.0 Hz), 0.91 (t, 3H, *J* = 7.5 Hz), 1.13-1.30 (m, 30H), 1.33-1.41 (m, 6H), 1.90 (q, 1H, *J* = 6.8 Hz), 2.25 (d, 13H, *J* = 18.5 Hz), 3.12 (hex, 1H, *J* = 6.5 Hz), 3.33 (hex, 1H, *J* = 7.0 Hz), 3.43 (s, 1H), 3.68 (d, 6H, *J* = 6.0 Hz), 6.65 (t, 1H, *J* = 6.0 Hz),

6.94 (s, 2H), 7.02 (s, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 13.75, 14.10, 16.20, 19.99, 22.67, 27.10, 28.48, 29.30, 29.34, 29.49, 29.64, 29.68, 31.90, 38.45, 45.21, 47.00, 59.54, 59.58, 76.80, 127.50, 127.51, 130.52, 130.72, 137.76, 137.90, 155.99, 156.06, 168.84 (five *sp*^{3} carbon not located); IR (thin film) 2924vs, 2853s, 1646vs, 1538s, 1483s, 1465s, 1221s, 1137s, 1019s cm^{-1}; HRMS (ESI-TOF) *m/z* 635.5178 [(M+H$^+$); calcd. for $C_{41}H_{67}N_2O_3$: 635.5152]; $[\alpha]_D^{20}$ +7.0° (c 1.0, CH_2Cl_2) on 90% *ee* material (HPLC).



*Ethyl (2R,3R)-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-pentadecylaziridine-2-carboxylate (2R,3R)-**103g***: (2*R*,3*R*)-**129g** (88 mg, 0.14 mmol) was reacted according to General Procedure A of preparation of eater from secondary amide with *n*-butyllithium (96 μL, 1.6 *M* in hexanes, 0.15 mmol, 1.1 equiv) and Boc_2O (92 mg, 0.42 mmol, 3.0 equiv). Purification of the crude product by silica gel chromatography (20 mm × 200 mm column, 12:1 hexanes/EtOAc as eluent, flash column) afforded *N*-Boc aziridinecarboxylamide as a colorless oil. The Boc-protected aziridine was then reacted with *n*-butyllithium (0.19 mL, 1.6 *M* in hexanes, 0.31 mmol, 2.2 equiv) and ethanol (41 μL, 0.70 mmol, 5.0 equiv). Purification of the crude ester by silica gel chromatography (20 mm × 200 mm column, 9:1 hexanes/EtOAc as eluent, flash column) afforded aziridine (2*R*,3*R*)-**103g** as a white foam (mp 41-42 °C on 95% *ee* material) in 70% yield (60 mg, 0.098 mmol) over two steps. The optical purity of (2*R*,3*R*)-**103g** 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 226 nm, flow-rate: 0.7 mL/min): retention times; R_t = 24.86 min (major enantiomer, **103g**) and R_t = 42.23 min (minor enantiomer, *ent*-**103g**).

$[\alpha]_D^{20}$ +48.2° (c 1.0, EtOAc) on 95% *ee* material (HPLC); Lit[4] $[\alpha]_D^{20}$ +57.9° (c 1.0, EtOAc) on 95% *ee* (2*R*,3*R*)-isomer.

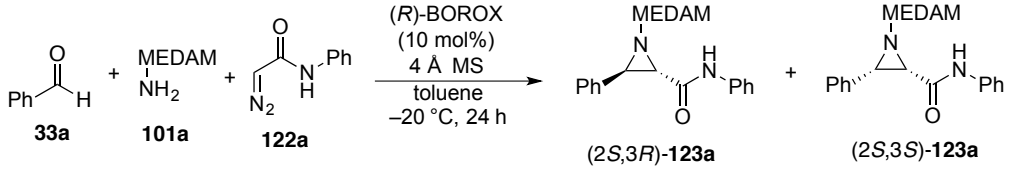


*(2S,3R)-N-butyl-3-pentadecylaziridine-2-carboxamide (2S,3R)-**134***: To a flame dried 10 mL round bottom flask flushed with nitrogen was added (2*S*,3*R*)-**129g** (140 mg, 0.220 mmol) and anisole (2.2 mL). The resulting solution was cooled in the ice-bath for 5 min before the slow addition of trifluoromethanesulfonic acid (97 μL, 1.1 mmol, 5.0 equiv). The reaction mixture was gradually warmed up to room temperature and continually stirred for 1 h. The reaction was quenched by pouring the mixture into sat. aq. Na_2CO_3 (20 mL). The aqueous layer was extracted by EtOAc (4 × 10 mL). The combined organic layer was dried by anhydrous Na_2SO_4 and concentrated by reduced pressure. Purification of the crude aziridine by silica gel chromatography (20 mm × 200 mm column, 1:2 hexanes/EtOAc as eluent, flash column) afforded the deprotected aziridine (2*S*,3*R*)-**134** as a white solid (mp 73-74 °C) in 93% yield (72 mg, 0.20 mmol).

(2*S*,3*R*)-**126g** (161 mg, 0.200 mmol) was reacted according to the general procedure of aziridine nitrogen deprotection with trifluoromethanesulfonic acid (88 μL, 1.1 mmol, 5.0 equiv) in anisole (2.0 mL). Purification of the crude aziridine by silica gel chromatography (20 mm × 200 mm column, 1:2 hexanes/EtOAc as eluent, flash column) afforded aziridine (2*S*,3*R*)-**134** as a white solid in 100% yield (72 mg, 0.20 mmol).

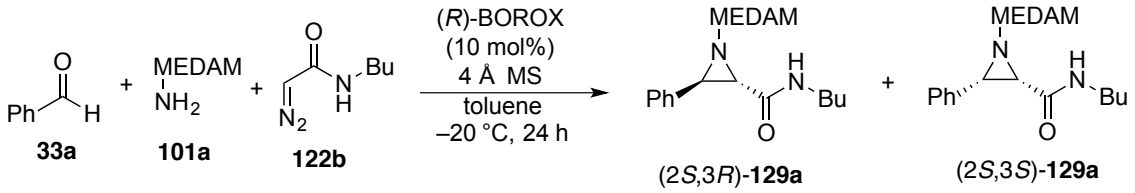
Spectral data for (2*S*,3*R*)-**134**: R_f = 0.24 (1:2 hexanes/EtOAc); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.88 (t, 3H, *J* = 6.8 Hz), 0.92 (t, 3H, *J* = 7.2 Hz), 1.25-1.52 (m, 33H), 2.05 (m,

1H), 2.17 (m, 1H), 3.26 (q, 2H, J = 6.7 Hz), 6.06 (br, 1H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 13.71, 14.11, 20.01, 22.68, 27.31, 29.32, 29.35, 29.54, 29.56, 29.64, 29.66, 29.68, 31.57, 31.91, 37.28, 39.26, 170.68 (five sp^3 carbons not located); IR (thin film) 3288s, 2915vs, 2847s, 1770s, 1759s, 1640s, 1248vs cm^{-1}; HRMS (ESI-TOF) *m/z* 353.3501 [(M+H$^+$); calcd. for $C_{22}H_{45}N_2O$: 353.3532]; $[\alpha]_D^{20}$ +11.9° (c 1.0, EtOAc) on 87% *ee* material.



*(2S,3S)-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-N,3-diphenylaziridine-2-carboxamide (2S,3S)-**123a***: Benzaldehyde **33a** (61 μL, 0.60 mmol, 1.2 equiv) was reacted according to the General Procedure B of multi-component *trans*-aziridination of aromatic aldehydes with MEDAM amine **101a** (150 mg, 0.500 mmol), (*R*)-^{t}Bu$_2$VANOL (28 mg, 0.050 mmol, 0.10 equiv) and *N*-phenyl diazoacetamide **122a** (112 mg, 0.700 mmol, 1.40 equiv). Purification of the crude aziridine by silica gel chromatography (20 mm × 200 mm column, 6:1 hexanes/EtOAc as eluent, flash column) afforded aziridine (2*S*,3*S*)-**123a** as a white foam (mp 67-69 °C on 95% *ee* material) in 75% yield (195 mg, 0.375 mmol). The enantiomeric purity of (2*S*,3*S*)-**123a** was determined to be 95% *ee* by HPLC analysis (CHIRALCEL OD-H column, 97:3 hexane/2-propanol at 222 nm, flow-rate: 0.7 mL/min): retention times; R_t = 10.56 min (minor enantiomer, *ent*-**21a**) and R_t = 25.75 min (major enantiomer, **123a**). The aziridination of **33a** in the presence of (*R*)-VANOL BOROX catalyst afforded (2*S*,3*S*)-**123a** in 73% *ee* and 17% yield (44 mg, 0.085 mmol). Spectral data for (2*S*,3*S*)-**123a**: R_f = 0.35 (2:1 hexanes/EtOAc); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 2.27 (s, 12H), 2.75 (d, 1H, J = 7.2 Hz), 3.30 (d, 1H, J = 7.2 Hz), 3.70 (s, 6H),

3.83 (s, 1H), 7.03 (t, 1H, J = 7.5 Hz), 7.11-7.16 (m, 6H), 7.18-7.32 (m, 7H), 8.10 (s, 1H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 16.23, 16.32, 47.28, 48.72, 59.60, 59.62, 76.69, 120.32, 124.44, 127.47, 127.53, 127.63, 127.70, 128.26, 128.78, 130.90, 131.11, 134.89, 136.61, 137.15, 137.21, 156.25, 156.32, 165.99; These spectral data match those previous reported for this compound.[3] $[\alpha]_D^{20}$ –26.2° (c 1.0, CH_2Cl_2) on 95% *ee* material (HPLC); Lit[3] $[\alpha]_D^{20}$ +4.0° (c 1.0, CH_2Cl_2) on 13% *ee* (2*R*,3*R*)-isomer.

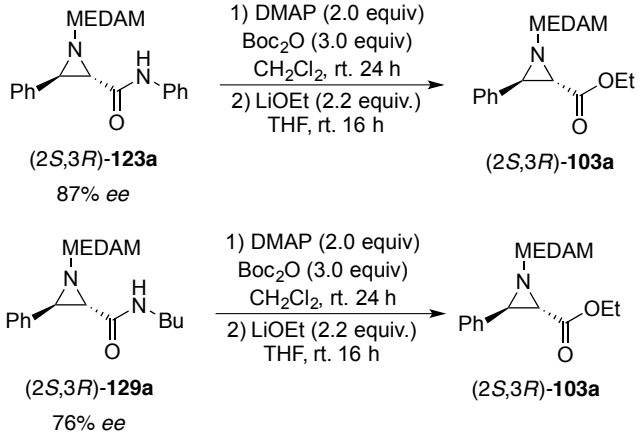


*(2S,3R)-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-N-butyl-3-phenylaziridine-2-carboxamide (2S,3R)-**129a***: Benzaldehyde **33a** (61 μL, 0.60 mmol, 1.2 equiv) was reacted according to the General Procedure B of multi-component *trans*-aziridination of aromatic aldehydes with MEDAM amine **101a** (150 mg, 0.500 mmol), (*R*)-VANOL (22 mg, 0.050 mmol, 0.10 equiv) and *N*-butyl diazoacetamide (99 mg, 0.70 mmol, 1.4 equiv). Purification of the crude aziridine by silica gel chromatography (20 mm × 200 mm column, 6:1 hexanes/EtOAc as eluent, flash column) afforded aziridine (2*S*,3*R*)-**129a** as a white foam (mp 51-52 °C on 76% *ee* material) in 36% yield (90 mg, 0.18 mmol). The enantiomeric purity of (2*S*,3*R*)-**129a** was determined to be 76% *ee* by HPLC analysis (PIRKLE COVALENT (R, R) WHELK-O 1 column, 85:15 hexane/2-propanol at 222 nm, flow-rate: 0.7 mL/min): retention times; R_t = 16.74 min (major enantiomer, **129a**) and R_t = 48.70 min (minor enantiomer, *ent*-**129a**). (Table 1, entry 18) The aziridination of **33a** in the presence of (*R*)-^{t}Bu$_2$VANOL BOROX catalyst afforded (2*S*,3*R*)-**129a** in 89% *ee* and 8% yield (20 mg, 0.040 mmol).

Spectral data for (2*R*,3*S*)-**129a**: R_f = 0.45 (2:1 hexanes/EtOAc); ^{1}H-NMR (500 MHz, DMSO-*d*6) δ 0.78 (t, 3H, *J* = 7.0 Hz), 1.05-1.11 (m, 2H), 1.12-1.19 (m, 2H), 2.05 (s, 6H), 2.17 (s, 6H), 2.71 (s, 1H), 2.79-2.86 (m, 1H), 3.09-3.21 (m, 1H), 3.54 (s, 3H), 3.59 (s, 3H), 5.07 (s, 1H), 7.01 (s, 4H), 7.22-7.37 (m, 5H), 8.24 (t, 1H, *J* = 5.7 Hz); ^{13}C-NMR (125 MHz, DMSO-*d*6) δ 13.61, 15.93, 16.01, 19.34, 30.94, 39.01, 45.18, 46.92, 59.06, 59.08, 64.97, 125.98, 127.07, 127.34, 127.68, 128.28, 128.54, 129.54, 129.66, 139.12, 139.25, 155.05, 155.26, 165.90; These spectral data match those previous reported for this compound.[3] $[\alpha]_D^{20}$ +20.0° (c 1.0, CH_2Cl_2) on 76% *ee* material (HPLC). Lit[3] $[\alpha]_D^{20}$ +39.8° (c 1.0, CH_2Cl_2) on 98% *ee* (2*S*,3*R*)-isomer.

*(2S,3S)-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-N-butyl-3-phenylaziridine-2-carboxamide (2S,3S)-**129a***: Purification of the crude aziridine from the aziridination with (*R*)-^{t}Bu$_2$VANOL BOROX by silica gel chromatography (20 mm × 200 mm column, 2:1 hexanes/EtOAc as eluent, flash column) afforded aziridine (2*S*,3*S*)-**129a** as a white foam (mp 155-157 °C on 91% *ee* material) in 73% yield (183 mg, 0.365 mmol). The enantiomeric purity of (2*S*,3*S*)-**129a** was determined to be 91% *ee* by HPLC analysis (CHIRALCEL OD-H column, 97:3 hexane/2-propanol at 222 nm, flow-rate: 0.7 mL/min): retention times; R_t = 8.70 min (minor enantiomer, *ent*-**129a**) and R_t = 16.43 min (major enantiomer, **129a**). The aziridination of **33a** in the presence of (*R*)-VANOL BOROX catalyst afforded (2*S*,3*S*)-**129a** in 86% *ee* and 50% yield (125 mg, 0.250 mmol). Spectral data for (2*S*,3*S*)-**129a**: R_f = 0.18 (2:1 hexanes/EtOAc); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.77 (t, 3H, *J* = 7.2 Hz), 0.99-1.10 (m, 4H), 2.26 (d, 12H, *J* = 2.5 Hz), 2.61 (d, 1H, *J* = 7.2 Hz), 2.88-2.98 (m, 2H), 3.18 (d, 1H, *J* = 7.2 Hz), 3.69 (d, 6H, *J* = 8.0 Hz), 3.73 (s, 1H), 6.32 (t, 1H, *J* = 6.0 Hz), 7.03 (s, 2H), 7.11 (s, 2H), 7.19-7.25 (m, 5H); ^{13}C-

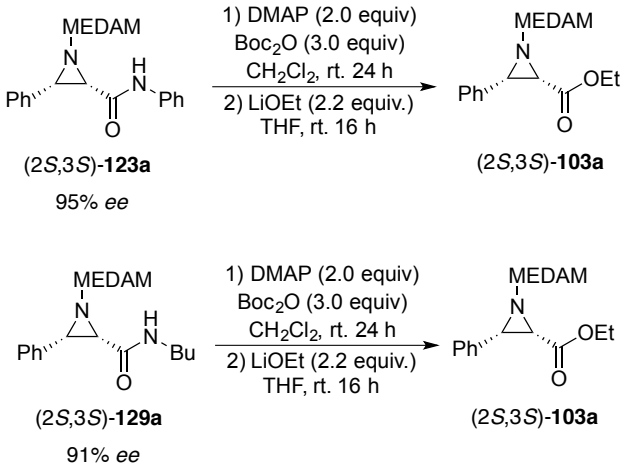
NMR ($CDCl_3$, 125 MHz) δ 13.68, 16.22, 16.25, 31.50, 38.23, 46.90, 48.15, 59.59, 59.61, 76.82, 127.38, 127.46, 127.73, 127.77, 128.05, 130.79, 130.84, 135.27, 137.26, 137.52, 156.16, 156.18, 167.48; IR (thin film) 3350vs, 2954vs, 2870s, 1645vs, 1536vs, 1485s, 1222s, 1147s, 1015s cm^{-1}; HRMS (ESI-TOF) *m/z* 501.3110 [$(M+H^+)$; calcd. for $C_{22}H_{45}N_2O$: 501.3117]; $[\alpha]_D^{20}$ –7.5° (c 1.0, CH_2Cl_2) on 91% *ee* material (HPLC).



*Ethyl (2S,3R)-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-phenylaziridine-2-carboxylate (2S,3R)-**103a***: (2*S*,3*R*)-**123a** (130 mg, 0.250 mmol) was reacted according to General Procedure B of preparation of eater from secondary amide with DMAP (61 mg, 0.50 mmol, 2.0 equiv) and Boc_2O (164 mg, 0.750 mmol, 3.00 equiv). Purification of the crude product by silica gel chromatography (20 mm × 200 mm column, 12:1 hexanes/EtOAc as eluent, flash column) afforded *N*-Boc aziridinecarboxylamide as a colorless oil. The Boc-protected aziridine was then reacted with *n*-butyllithium (0.35 mL, 1.6 *M* in hexanes, 0.55 mmol, 2.2 equiv) and ethanol (73 μL, 1.2 mmol, 5.0 equiv). Purification of the crude ester by silica gel chromatography (20 mm × 200 mm column, 12:1 hexanes/EtOAc as eluent, flash column) afforded aziridine (2*S*,3*R*)-**103a** as a semi-solide in 80% yield (95 mg, 0.20 mmol) over two steps.

(2*S*,3*R*)-**129a** (90 mg, 0.18 mmol) was reacted according to General Procedure B of preparation of eater from secondary amide with DMAP (44 mg, 0.36 mmol, 2.0 equiv) and Boc_2O (118 mg, 0.540 mmol, 3.00 equiv) for 3 days. Purification of the crude product by silica gel chromatography (20 mm × 200 mm column, 12:1 hexanes/EtOAc as eluent, flash column) afforded *N*-Boc aziridinecarboxylamide as a colorless oil. The Boc-protected aziridine was then reacted with *n*-butyllithium (0.25 mL, 1.6 *M* in hexanes, 0.40 mmol, 2.2 equiv) and ethanol (41 μL, 0.90 mmol, 5.0 equiv). Purification of the crude ester by silica gel chromatography (20 mm × 200 mm column, 12:1 hexanes/EtOAc as eluent, flash column) afforded aziridine (2*S*,3*R*)-**103a** as a semi-solide in 60% yield (51 mg, 0.11 mmol) over two steps.

Spectral data for (2*S*,3*R*)-**103a**: R_f = 0.48 (5:1 hexanes/EtOAc); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.04 (t, 3H, *J* = 7.0 Hz), 2.16 (s, 6H), 2.26 (s, 6H), 2.83 (d, 1H, *J* = 2.5 Hz), 3.41 (d, 1H, *J* = 2.5 Hz), 3.64 (s, 3H), 3.68 (s, 3H), 3.95-4.08 (m, 2H), 4.91 (s, 1H), 7.03-7.11 (m, 2H), 7.07 (d, 2H, *J* = 4.0 Hz), 7.23-7.25 (m, 1H), 7.28-7.36 (m, 2H), 7.30 (d, 2H, *J* = 4.0 Hz); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 13.89, 16.15, 16.18, 45.07, 48.70, 59.51, 59.54, 60.92, 67.01, 126.45, 127.36, 127.73, 127.87, 128.22, 130.26, 130.36, 138.31, 138.49, 138.74, 155.68, 155.77, 168.66; These spectral data match those previous reported for this compound.[3] $[\alpha]_D^{20}$ +5.6° (c 1.0, EtOAc) on 87% *ee* material; Lit[3] $[\alpha]_D^{20}$ – 4.4° (c 1.0, EtOAc) on 90% *ee* (2*R*,3*S*)-isomer.



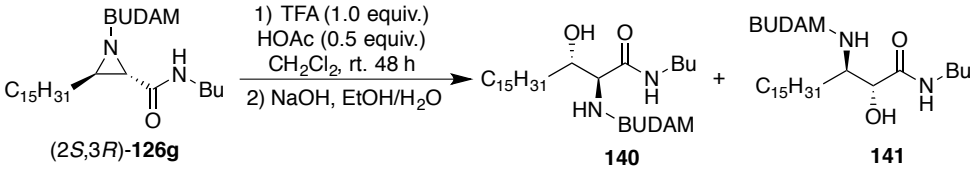
*Ethyl (2S,3S)-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-phenylaziridine-2-carboxylate (2S,3S)-**103a***: (2*S*,3*S*)-**123a** (161 mg, 0.310 mmol) was reacted according to General Procedure B of preparation of eater from secondary amide with DMAP (76 mg, 0.62 mmol, 2.0 equiv) and Boc_2O (203 mg, 0.930 mmol, 3.00 equiv). Purification of the crude product by silica gel chromatography (20 mm × 200 mm column, 12:1 hexanes/EtOAc as eluent, flash column) afforded *N*-Boc aziridinecarboxylamide as a colorless oil. The Boc-protected aziridine was then reacted with *n*-butyllithium (0.43 mL, 1.6 *M* in hexanes, 0.68 mmol, 2.2 equiv) and ethanol (91 μL, 1.6 mmol, 5.0 equiv). Purification of the crude ester by silica gel chromatography (20 mm × 200 mm column, 9:1 hexanes/EtOAc as eluent, flash column) afforded aziridine (2*S*,3*S*)-**103a** as a white foam (mp 105-107 °C) in 67% yield (98 mg, 0.21 mmol) over two steps.

(2*S*,3*S*)-**129a** (190 mg, 0.380 mmol) was reacted according to General Procedure A of preparation of eater from secondary amide with *n*-butyllithium (0.26 mL, 1.6 *M* in hexanes, 0.42 mmol, 1.1 equiv) and Boc_2O (249 mg, 1.14 mmol, 3.00 equiv). Purification of the crude product by silica gel chromatography (20 mm × 200 mm column, 12:1 hexanes/EtOAc as eluent, flash column) afforded *N*-Boc aziridinecarboxylamide as a colorless oil. The Boc-protected aziridine was then reacted with *n*-butyllithium (0.52 mL,

1.6 *M* in hexanes, 0.84 mmol, 2.2 equiv) and ethanol (111 μL, 1.90 mmol, 5.00 equiv). Purification of the crude ester by silica gel chromatography (20 mm × 200 mm column, 9:1 hexanes/EtOAc as eluent, flash column) afforded aziridine (2*S*,3*S*)-**103a** as a white foam in 64% yield (136 mg, 0.290 mmol) over two steps. $[\alpha]_D^{20}$ –26.2° (c 1.0, EtOAc) on 95% *ee* material; Lit[4] $[\alpha]_D^{20}$ +41.3° (c 1.0, EtOAc) on 99% *ee* (2*R*,3*R*)-isomer.

6.3.5 Ring-Opening of *trans*-Aziridines

General Procedure A: Ring-Opening of *trans*-Aziridine Carboxamide 125g

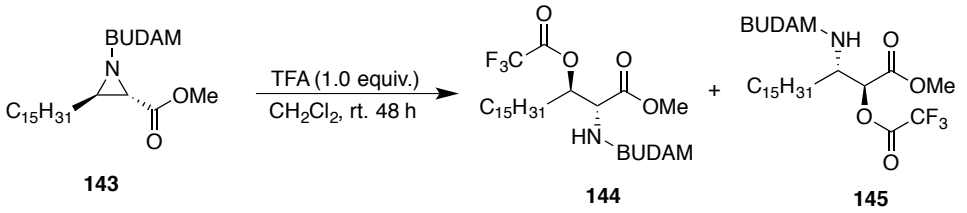


*(2S,3S)-2-((bis(3,5-di-tert-butyl-4-methoxyphenyl)methyl)amino)-N-butyl-3-hydroxyoctadecanamide **140***: (Table 3.7, entry 7) To a 25 mL flame-dried round-bottom flask equipped with a nitrogen balloon was added *trans*-aziridine **126g** (161 mg, 0.200 mmol) and dry CH_2Cl_2 (2 mL). The solution was cooled in the ice bath. Thereafter, trifluoroacetic acid (15 μL, 0.20 mmol) and acetic acid (5.7 μL, 0.10 mmol) was added to the solution. The resulting reaction mixture was stirred at room temperature for 48 h (monitored by TLC). The reaction mixture was concentrated in *vacuo* to afford an oil.

The reaction mixture was dissolved in ethanol (0.8 mL) and a solution of NaOH (8.0 mg, 0.20 mmol) in EtOH/H_2O (0.4/0.2 mL) was added. The mixture was stirred for 30 min and diluted with H_2O (2 mL). The white slurry was extracted by Et_2O and the combined organic layer was dried with Na_2SO_4 and concentrated in *vacuo*. Purification of the crude product by silica gel chromatography (20 mm × 200 mm column, 3:1 hexanes/Et_2O as eluent, flash column) afforded a mixture of regioisomers **140** and **141** in 8:1 ratio as an oil in 86% yield (142 mg, 0.173 mmol) over two steps.

Spectral data for **140**: R_f= 0.20 (2:1 hexanes/Et_2O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.86 (t, 3H, *J* = 7.0 Hz), 0.92 (t, 3H, *J* = 7.2 Hz), 1.16-1.31 (m, 28H), 1.36 (s, 18H), 1.38 (s, 18H), 1.42-1.54 (m, 5H), 2.83-2.90 (m, 1H), 3.02 (d, 1H, *J* = 5.5 Hz), 3.16-3.26 (m, 1H), 3.27-3.36 (m, 2H), 3.65 (d, 6H, *J* = 3.0 Hz), 3.74-3.83 (m, 1H), 4.65 (s, 1H), 6.81 (t, 1H, *J* = 5.8 Hz), 7.15 (s, 2H), 7.20 (s, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 13.74, 14.12, 20.16, 22.68, 26.00, 29.35, 29.59, 29.63, 29.67, 29.68, 30.29, 31.72, 31.91, 32.04, 32.08, 32.10, 3376, 35.72, 35.76, 38.84, 63.92, 64.07, 64.14, 65.60, 72.99, 125.64, 125.70, 126.49, 137.29, 143.28, 143.49, 158.41, 158.54, 173.20 (two sp^3 carbon not located); IR (thin film) 3354s, 2958vs, 2854s, 1655vs, 1529s, 1465s, 1412vs, 1222vs, 1115s, 1014s cm^{-1}; HRMS (ESI-TOF) *m/z* 821.7109 [$(M+H^+)$; calcd. for $C_{53}H_{93}N_2O_4$: 821.7135]; $[\alpha]_D^{20}$ +2.1° (c 1.0, EtOAc) on 94% *ee* material (HPLC).

General Procedure B Ring-Opening of *trans*-Aziridine Carboxylate 143 and 143'

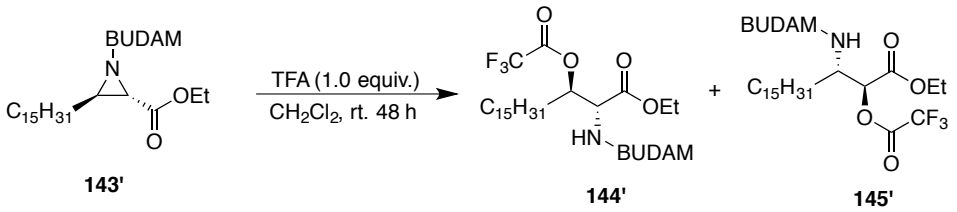


143 **144** **145**

*Methyl (2R,3R)-2-((bis(3,5-di-tert-butyl-4-methoxyphenyl)methyl)amino)-3-(2,2,2-trifluoroacetoxy)octadecanoate **144***: To a 10 mL flame-dried round-bottom flask equipped with a nitrogen balloon was added *trans*-aziridine **143** (207 mg, 0.270 mmol) and dry CH_2Cl_2 (5.4 mL). The solution was cooled in the ice bath. Thereafter, trifluoroacetic acid (21 μL, 0.27 mmol) was added to the solution. The resulting reaction mixture was stirred at room temperature for 48 h (monitored by TLC). The reaction mixture was concentrated in *vacuo* to afford a mixture of regioisomers **144** and **145** in 6:1 ratio as an oily material. Purification of the crude product by silica gel chromatography

(20 mm × 200 mm column, 50:1 hexanes/EtOAc as eluent, flash column) afforded a mixture of regioisomers **144** and **145** as an oil in 61% yield (145 mg, 0.166 mmol) over two steps.

Spectral data for **144**: R_f= 0.80 (10:1 hexanes/EtOAc); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.86 (t, 3H, *J* = 6.8 Hz), 1.16-1.34 (m, 26H), 1.37 (d, 36H, *J* = 7.0 Hz), 1.64-1.76 (m, 1H), 1.93-2.06 (m, 1H), 2.25-2.37 (m, 1H), 3.37 (d, 1H, *J* = 7.0 Hz), 3.65 (d, 6H, *J* = 5.5 Hz), 3.71 (s, 3H), 4.61 (s, 1H), 5.10-5.19 (m, 1H), 7.13 (s, 2H), 7.20 (s, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 14.12, 22.69, 25.08, 27.88, 29.21, 29.34, 29.37, 29.51, 29.60, 29.64, 29.67, 29.68, 29.70, 31.35, 31.93, 32.02, 32.09, 35.74, 35.75, 52.13, 61.55, 64.09, 64.10, 65.60, 79.67, 111.12, 113.39, 115.67, 117.94, 125.51, 126.07, 135.74, 137.34, 143.26, 143.40, 156.37, 156.71, 157.05, 157.38, 158.48, 158.57, 172.59; IR (thin film) 3447s, 2960vs, 2924vs, 2854s, 1739vs, 1457s, 1413s, 1261vs, 1222s, 1202s, 1094s, 1016vs cm^{-1}; HRMS (ESI-TOF) *m/z* 876.6345 [$(M+H^+)$; calcd. for $C_{52}H_{85}F_3NO_6$: 876.6329]; $[\alpha]_D^{20}$ +4.7° (c 1.0, EtOAc) on 96% *ee* material (HPLC).

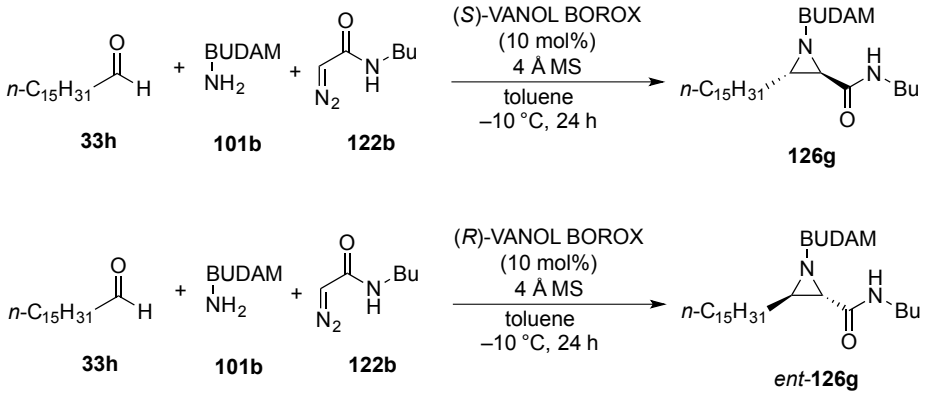


*Ethyl (2R,3R)-2-((bis(3,5-di-tert-butyl-4-methoxyphenyl)methyl)amino)-3-(2,2,2-trifluoroacetoxy)octadecanoate **144'***: The ring-opening of aziridine **143'** (192 mg, 0.250 mmol) followed the general procedure B with trifluoroacetic acid (19 μL, 0.25 mmol) in CH_2Cl_2 (2.50 mL). The resulting reaction mixture was stirred at room temperature for 48 h (monitored by TLC). The reaction mixture was concentrated in *vacuo* to afford a mixture of regioisomers **144'** and **145'** in 5:1 ratio as an oily material. Purification of the

crude product by silica gel chromatography (20 mm × 200 mm column, 50:1 hexanes/EtOAc as eluent, flash column) afforded a mixture of regioisomers **144'** and **145'** as an oil in 49% yield (110 mg, 0.123 mmol) over two steps.

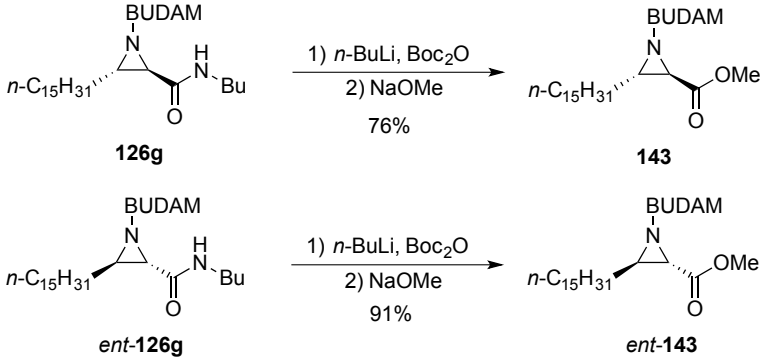
Spectral data for **144'**: R_f = 0.83 (10:1 hexanes/EtOAc); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.86 (t, 3H *J* = 6.8 Hz), 1.16-1.33 (m, 26H), 1.36 (d, 36H, *J* = 9.0 Hz), 1.64-1.75 (m, 1H), 1.92-2.06 (m, 1H), 2.29 (d, 1H, *J* = 10.0 Hz), 3.35 (dd, 1H, *J* = 10.0, 7.0 Hz), 3.65 (d, 6H, *J* = 6.5 Hz), 4.12-4.24 (m, 2H), 4.62 (s, 1H), 5.12-5.20 (m, 1H), 7.12 (s, 2H), 7.20 (s, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 14.12, 14.18, 22.69, 25.08, 27.88, 29.22, 29.33, 29.37, 29.51, 29.60, 29.64, 29.66, 29.68, 29.90, 31.39, 31.93, 32.02, 32.10, 35.74, 35.75, 61.32, 61.56, 64.08, 64.10, 65.51, 79.76, 111.13, 113.40, 115.68, 117.95, 125.51, 126.09, 135.74, 137.39, 143.25, 143.39, 156.35, 156.68, 157.03, 157.36, 158.48, 158.57, 172.04; IR (thin film) 3439s, 2958s, 2925vs, 2854s, 1735vs, 1465s, 1413vs, 1361s, 1261s, 1222s, 1200s, 1115s, 1015s cm^{-1}; HRMS (ESI-TOF) *m/z* 890.6507 [$(M+H^+)$; calcd. for $C_{53}H_{87}F_3NO_6$: 890.6485]; $[\alpha]_D^{20}$ +5.8° (c 1.0, EtOAc) on 96% *ee* material (HPLC).

6.3.6 Synthesis of *erythro*-Sphinganine



*(2R,3S)-1-(bis(3,5-di-tert-butyl-4-methoxyphenyl)methyl)-N-butyl-3-pentadecylaziridine-2-carboxamide **126g***: Palmitaldehyde **33h** (793 mg, 3.30 mmol, 1.10 equiv) was reacted according to the General Procedure A of multi-component *trans*-aziridination of aliphatic

aldehydes with BUDAM amine **101b** (1.40 g, 3.0 mmol), (*S*)-VANOL (132 mg, 0.300 mmol, 0.100 equiv), triphenylborate (261 mg, 0.900 mmol, 0.300 equiv.) and *N*-butyl diazoacetamide (508 mg, 3.60 mmol, 1.20 equiv). Purification of the crude aziridine by silica gel chromatography (20 mm × 200 mm column, 6:1 hexanes/Et_2O as eluent, flash column) afforded aziridine (2*R*,3*S*)-**126g** as an off-white solid in 96% *ee* and 88% yield (2.12 g, 2.64 mmol); *trans*/*cis* 28:1. The aziridination of **126g** in the presence of (*R*)-VANOL BOROX catalyst afforded (2*S*,3*R*)-*ent*-**126g** in 96% *ee* and 86% yield (2.07 g, 2.58 mmol); *trans*/*cis* 30:1.



*Methyl (2R,3S)-1-(bis(3,5-di-tert-butyl-4-methoxyphenyl)methyl)-3-pentadecylaziridine-2-carboxylate (2R,3S)-**143***: *n*-BuLi (1.6 *M* in hexanes, 1.50 mL, 2.40 mmol) was added into the solution of aziridine (2*R*,3*S*)-**126g** (1.92 g, 2.4 mmol) in THF (17 mL) at 0 °C. The resulting solution was stirred for 10 min and a solution of Boc_2O (1.57 g, 7.20 mmol, 3.00 equiv) in THF (7 mL) was added *via* cannula. The reaction mixture was warmed up to room temperature, stirred for 36 h and refluxed for another 8 h to complete the conversion of the starting material. The reaction was cooled down to room temperature and quenched by saturated NH_4Cl aq. (12 mL). The mixture was diluted by Et_2O (20 mL) and the organic phase was separated. The aqueous phase was extracted by Et_2O (3 × 10

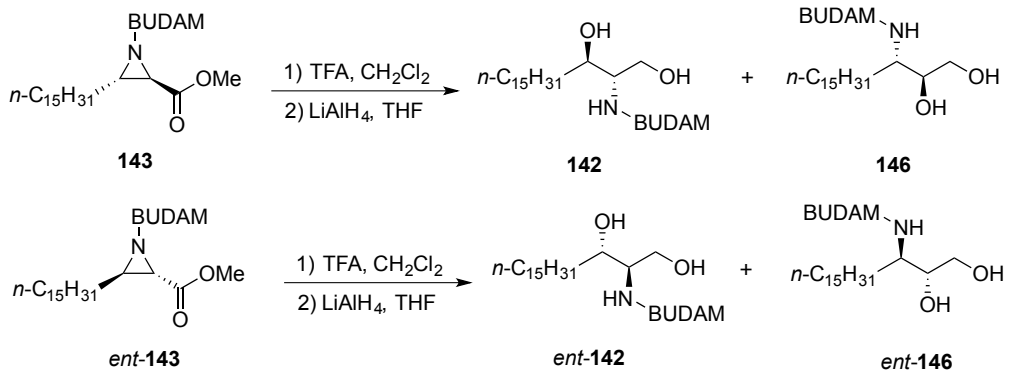
mL). The combined organic phase was dried with Na_2SO_4 and the solvent was removed in vacuo.

The residue was dissolved in THF (10 mL) and was added to a solution of sodium methoxide (25%wt in MeOH, 0.82 mL, 3.6 mmol). Additional THF (2 mL) was used to rinse the Boc-protected **126g** and combined with the reaction mixture. The reaction was stirred for 16 h at room temperature and was diluted with H_2O (10 mL) and saturated KH_2PO_4 aq. (10 mL). The organic phase was separated and the aqueous phase was extracted by EtOAc (4 × 10 mL). The combined organic phase was dried by Na_2SO_4 and concentrated in vacuo. Purification of the crude aziridine by silica gel chromatography (20 mm × 200 mm column, 25:1 hexanes/Et_2O as eluent, flash column) afforded aziridine **143** as an oil in 76% yield (1.39 g, 1.82 mmol) over two steps.

The Boc-protection and methanolysis of (2*S*,3*R*)-*ent*-**126g** (1.69 g, 2.10 mmol) reacted with *n*-BuLi (1.6 *M* in hexanes, 1.31 mL, 2.10 mmol), Boc_2O (1.37 g, 6.30 mmol, 3.00 equiv) and sodium methoxide (25%wt in MeOH, 1.06 mL, 4.62 mmol, 2.20 equiv), afforded *ent*-**143** in 91% yield (1.46 g, 1.91 mmol) over two steps.

Spectral data for **143**: R_f= 0.66 (10:1 hexanes/Et_2O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.86 (t, 3H, *J* = 6.8 Hz), 1.01-1.31 (m, 28H), 1.37 (d, 36H, *J* = 8.5 Hz), 2.38-2.40 (m, 1H), 2.53 (d, 1H, *J* = 2.5 Hz), 3.44 (s, 3H), 3.60 (s, 3H), 3.64 (s, 3H), 4.65 (s, 1H), 7.17 (s, 2H), 7.26 (s, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 14.13, 22.68, 26.90, 29.25, 29.36, 29.52, 29.56, 29.62, 29.65, 29.68, 31.92, 31.12, 32.42, 35.69, 35.72, 41.42, 48.08, 51.68, 64.06, 64.09, 68.07, 125.88, 126.31, 136.90, 137.55, 142.47, 142.81, 157.97, 158.38, 170.29 (three sp^3 carbon not located); IR (thin film) 3320s, 2959vs, 2872s, 1740vs, 1656vs, 1534s, 1446s, 1413s, 1361s, 1221vs, 1115s, 1013s cm^{-1}; HRMS (ESI-TOF) *m/z*

784.6254 [(M+Na$^+$); calcd. for $C_{50}H_{83}NO_4Na$: 784.6220]; $[\alpha]_D^{20}$ +8.6° (c 1.0, EtOAc) on –96% *ee* material (HPLC).



*(2S,3R)-2-(N-(bis(3,5-di-tert-butyl-4-methoxyphenyl)methyl)amino)octadecane-1,3-diol (2S,3R)-**142*****:** The ring-opening of aziridine **143** (1.52 g, 1.99 mmol) followed the general procedure B in section 6.3.5 with trifluoroacetic acid (152 μL, 1.99 mmol) in CH_2Cl_2 (40 mL). The resulting reaction mixture was stirred at room temperature for 48 h (monitored by TLC). The reaction mixture was concentrated in *vacuo* to afford an oil.

The residue was dissolved in dry THF (4.0 mL). In another flame-dried 100 mL round bottom flask equipped with a nitrogen balloon was containing $LiAlH_4$ (1 *M* in THF, 8.0 mL, 8.0 mmol) in THF (14 mL). The solution of $LiAlH_4$ was cooled in the ice-bath for 5 min. The solution of crude product was then transferred into the solution of $LiAlH_4$ in dropwise. The crude product was rinsed with addition THF (2.0 mL) and the washing was transferred into the solution of $LiAlH_4$ as well. The resulting solution was then stirred at room temperature for 16 h. The reaction mixture was then cooled in the ice-bath and carefully quenched by slow addition of H_2O (10 mL), and then NaOH aq. (1 *M*, 20 mL) and finally H_2O (10 mL). The white slurry was filtered and washed with Et_2O (4 × 10 mL). The organic phase was separated from the filtrate and the aqueous phase was extracted with Et_2O (3 × 20 mL). The combined organic phase was dried by Na_2SO_4 and

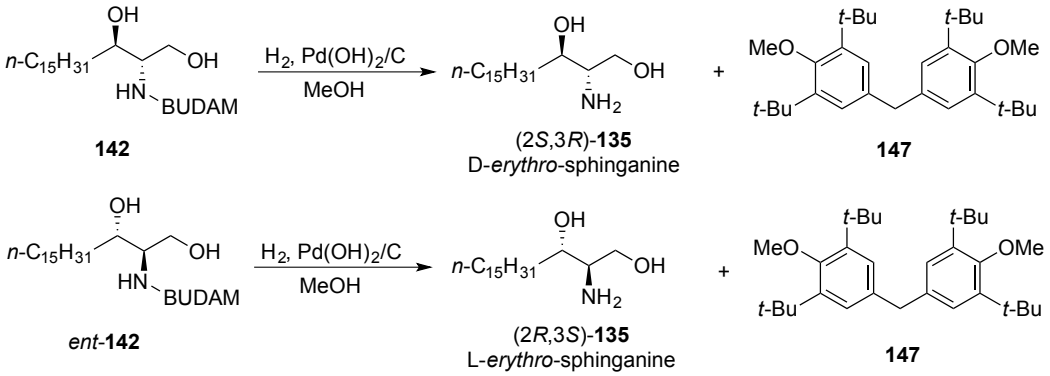
concentrated under reduced pressure to afford a mixture of regioselectivity **142** and **146** with 1.5:1 ratio. Purification of the crude aziridine by silica gel chromatography (20 mm × 200 mm column, 5:1 hexanes/Et_2O as eluent, flash column) afforded compound **142** as an oil in 62% yield (928 mg, 1.23 mmol) and the regioisomer **146** as a semi-solid in 37% (558 mg, 0.740 mmol) over two steps.

The ring-opening and reduction of *ent*-**143** (1.41 g, 1.85 mmol) reacted with TFA (142 μL, 1.85 mmol) and $LiAlH_4$ (1 *M* in THF, 7.4 mL, 7.4 mmol), afforded crude *ent*-**142** in 58% yield (807 mg, 1.07 mmol) and *ent*-**146** in 23% (323 mg, 0.429 mmol) over two steps.

Spectral data for **142**: R_f= 0.41 (2:1 hexanes/Et_2O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.86 (t, 3H, *J* = 6.8 Hz), 1.19-1.30 (m, 28 H), 1.38 (d, 36H, *J* = 3.0 Hz), 2.52 (q, 1H, *J* = 4.2 Hz), 3.65 (d, 6H, *J* = 1.5 Hz), 3.68-3.70 (m, 1H), 3.73 (dd, 2H, *J* = 11.0, 5.0 Hz), 4.83 (s, 1H), 7.20 (d, 4H, *J* = 5.5 Hz) (two OH and one NH not located); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 14.12, 22.68, 26.36, 29.35, 29.60, 29.65, 29.69, 31.91, 32.06, 32.09, 32.10, 33.82, 35.75, 59.18, 60.81, 64.10, 64.56, 72.36, 125.74, 125.75, 137.41, 137.66, 143.20, 143.26, 158.31, 158.35 (six sp^3 carbon not located). IR (thin film) 3340s, 2924s, 2854s, 1465s, 1413s, 1362s, 1261s, 1223vs, 1115s, 1012s cm^{-1}; HRMS (ESI-TOF) *m/z* 752.6556 [($M+H^+$); calcd. for $C_{49}H_{86}NO_4$: 752.6557]; $[\alpha]_D^{20}$ –3.7° (c 1.0, CH) on 96% *ee* material (HPLC).

Spectral data for (2*S*,3*S*)-3-(bis(3,5-di-*tert*-butyl-4-methoxyphenyl)methylamino)octadecane-1,2-diol **146**: R_f= 0.32 (2:1 hexanes/Et_2O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.87 (t, 3H, *J* = 7.0 Hz), 1.17-1.33 (m, 28H), 1.40 (d, 36H, *J* = 4.0 Hz), 1.52-1.66 (m, 1H), 2.67 (q, 1H, *J* = 5.7 Hz), 3.59-3.68 (m, 2H), 3.66 (d, 6H, *J*

= 2.5 Hz), 4.82 (s, 1H), 7.17 (s, 2H), 7.22 (s, 2H) (two OH and one NH not located); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 22.67, 25.72, 29.34, 29.57, 29.60, 29.64, 29.67, 29.88, 30.23, 31.90, 32.05, 32.08, 35.74, 58.28, 64.08, 64.10, 64.60, 65.00, 71.23, 125.56, 125.90, 136.77, 137.63, 143.32, 143.38, 158.39, 158.41 (five sp^3 carbon not located); IR (thin film) 3374s, 2958s, 2925vs, 2854s, 1466s, 1413s, 1362s, 1309s, 1262s, 1224vs, 1115s, 1012s cm^{-1}; HRMS (ESI-TOF) *m/z* 752.6561 [(M+H$^+$); calcd. for $C_{49}H_{86}NO_4$: 752.6557]; $[\alpha]_D^{20}$ +58.4° (c 2.0, $CHCl_3$) on 96% *ee* material (HPLC).



(2S,3R)-2-aminooctadecane-1,3-diol D-erythro-sphinganine ***135***: To a 25 mL flame-dried round-bottom was added BUDAM-protected sphinganine **142** (533 mg, 0.709 mmol), Pearlman's catalyst (20% $Pd(OH)_2$ on carbon, moisture 53%, 530 mg, 0.354 mmol, 0.500 equiv) and MeOH (7.1 mL). The flask was sealed by a septum and applied to freeze-pump-thaw cycling. The reaction mixture was flash-freezed in liquid nitrogen and a vacuum (0.05 mmHg) was applied. The mixture was then disconnected from vacuum line and thawed at room temperature. This process was repeated three times and a hydrogen balloon was placed to the septum. The reaction mixture was stirred at room temperature for 48 h. The solid was filtered and washed with EtOAc (3 × 10 mL). The organic phase was dried with Na_2SO_4 and concentrated. To the residue was added hexanes (10 mL). The white slurry was separated from centrifugation to afford a white

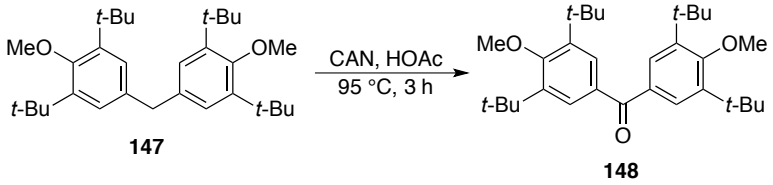
solid. Purification of the crude sphingaine by silica gel chromatography (20 mm × 200 mm column, 8:1:0.1 CH_2Cl_2/MeOH/Et_3N as eluent, flash column) afforded D-*erythro*-sphinganine **135** as a white solid (mp 80-82 °C) in 91% yield (195 mg, 0.645 mmol). The supernatant liquor from centrifugation was concentrated under reduced pressure to afford BUDAM hydrocarbon **147** as a white solid (mp 148-150 °C) in 100% yield (321 mg, 0.709 mmol).

The hydrogenolysis of *ent*-**142** (745 mg, 0.990 mmol) with Pearlman's catalyst (20% $Pd(OH)_2$ on carbon, moisture 53%, 739 mg, 0.495 mmol, 0.500 equiv) afforded L-*erythro*-sphinganine *ent*-**135** in 85% yield (254 mg, 0.842 mmol) and **147** in 100% yield (448 mg, 0.990 mmol).

Spectral data for **135**: R_f = 0.29 (EtOAc); ^{1}H-NMR (500 MHz, d^4-MeOH) δ 0.90 (t, 3H, *J* = 6.8 Hz), 1.22-1.42 (m, 26 H), 1.44-1.59 (m, 3H), 3.20 (dt, 1H, *J* = 8.5, 4.1 Hz), 3.70 (dd, 1H, *J* = 11.5, 8.5 Hz), 3.78 (pent, 1H, *J* = 4.2 Hz), 3.83 (dd, 1H, *J* = 11.2, 4.2 Hz) (one OH and one NH not located); ^{13}C-NMR (125 MHz, d^4-MeOH) δ 14.60, 23.89, 27.18, 30.63, 30.73, 30.85, 30.89, 30.92, 30.95, 33.22, 34.33, 58.59, 59.05, 70.45 (four sp^3 carbon not located); $[\alpha]_D^{20}$ –5.4° (c 1.0, MeOH) on 96% *ee* material (HPLC). For *ent*-**135** $[\alpha]_D^{20}$ +10.8° (c 3.0, MeOH) on 96% *ee* material (HPLC). Lit[21] $[\alpha]_D^{20}$ –1.9° (c 1.0, pyridine, D-*erythro*-sphinganine), $[\alpha]_D^{20}$ +2.1° (c 1.0, pyridine, L-*erythro*-sphinganine).

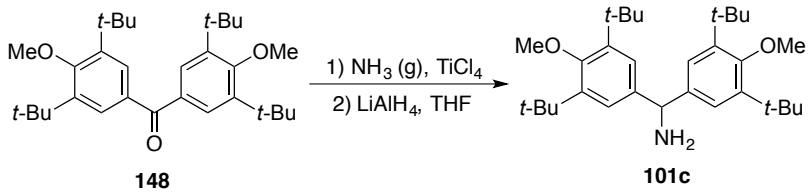
Spectral data for bis(3,5-di-*tert*-butyl-4-methoxyphenyl)methane **147**: R_f = 0.78 (10:1 hexanes/CH_2Cl_2); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.39 (s, 36H), 3.67 (s, 6H), 3.86 (s, 1H), 7.03 (s, 4H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 32.10, 35.67, 41.29, 64.17, 127.04, 134.96, 143.18, 157.57.

6.3.7. Experimental Details of BUDAM Amine 101c Recycling



147 148

*Bis(3,5-di-tert-butyl-4-methoxyphenyl)methanone **148***:[27] A mixture of hydrocarbon **147** (782 mg, 1.73 mol) and CAN (3.79 g, 6.92 mol, 4.00 equiv) in glacial acetic acid (17 mL) was heated to 95 °C. After 3 h, the mixture was poured onto ice and extracted with Et_2O. The combined extracts were neutralized, dried, and reduced to a pale yellow solid (mp 157-158 °C) in 85% yield (685 mg, 1.47 mmol) without further purification. Spectral data for **147**: R_f = 0.64 (10:1 hexanes/Et_2O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.43 (s, 36H), 3.73 (s, 6H), 7.72 (s, 4H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 31.98, 35.92, 64.38, 129.02, 132.29, 143.66, 163.24, 196.23.



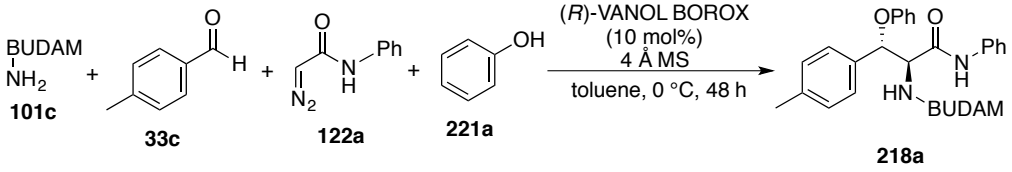
148 101c

*Bis(3,5-di-tert-butyl-4-methoxyphenyl)methanamine BUDAM amine **101c***:[28] To a 10 mL flame-dried round bottom flask was added a solution of ketone **148** (138 mg, 0.300 mmol) in THF (1.5 mL). The resulting mixture was cooled down to 0 °C. Then $TiCl_4$ (53 μL, 0.48 mmol) was quickly added to the cold solution and an orange slurry was formed. The orange slurry then turned dark green after gaseous ammonia was bubbled into the stirred mixture for 5 min. With a continuous supply of gaseous ammonia, the dark green slurry turned orange and NH_3 (g) was kept for another 20 min and then the NH_3 flow was

stopped. The resulting mixture was warmed up to room temperature and then slowly heated to reflux for 24 h. The resulting reaction mixture was cooled down to the room temperature and then placed in the ice bath. A solution of $LiAlH_4$ (2.40 mL, 1 *M* in THF, 2.40 mmol) was added in dropwise at 0 °C to give a dark blue solution. The reaction mixture was then heated to reflux for 12 h until it gave a pale green slurry. The slurry was carefully quenched by conc. ammonium hydroxide at 0 °C and then extracted by Et_2O. The combined organic phase was washed by brine, dried with Na_2SO_4 and concentrated by reduced pressure to afford a yellow oil. Purification of the crude amine by silica gel chromatography (20 mm × 200 mm column, 5:1:0.1 hexanes/EtOAc/Et_3N as eluent, flash column) afforded aziridine **101c** as a white solid (mp 175-178 °C) in 89% yield (125mg g, 0.267 mmol). Spectral data for **147**: R_f = 0.21 (3:1 hexanes/EtOAc); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.42 (s, 36H), 1.77 (s, 2H), 3.69 (s, 6H), 5.10 (s, 1H), 7.28 (s, 4H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 32.09, 35.78, 59.81, 64.12, 125.17, 139.55, 143.14, 158.17. These spectral data match those previous reported for this compound.[2]

6.4 Experimental Information for Chapter 4

6.4.1 *trans*-Aziridination/Ring-Opening Cascade Reaction with Phenol



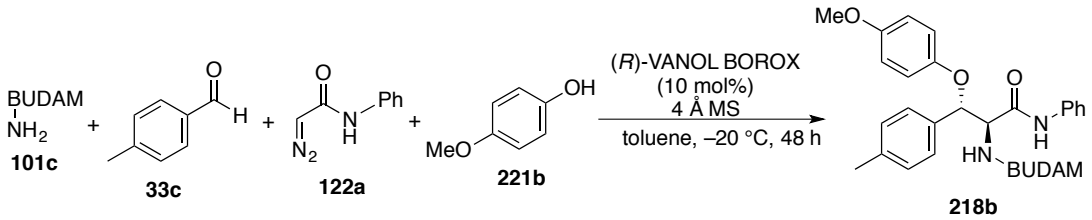
(2S,3S)-2-((bis(3,5-di-tert-butyl-4-methoxyphenyl)methyl)amino)-3-phenoxy-N-phenyl-3-(p-tolyl)propanamide ***218a***: To a 10 mL flame-dried home-made Schlenk flask, prepared from a 10 mL pear-shaped flask that had its 14/20 glass joint replaced with a high vacuum threaded Teflon valve, equipped with a stir bar and filled with argon was added

(*R*)-VANOL **68a** (8.8 mg, 0.020 mmol), $B(OPh)_3$ (17 mg, 0.060 mmol) and BUDAM amine **101c** (94 mg, 0.200 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 the mixture was stirred at 80 °C for 0.5 h. To the flask containing the catalyst was added the 4Å Molecular Sieves (60 mg, freshly flame-dried) and 4-tolualdehyde **33c** (28 μL, 0.24 mmol, 1.2 equiv). The reaction mixture was allowed to stirred at room temperature for 20 min that the corresponding imine was formed completely. This solution was then allowed to cool to 0 °C and rapidly added phenol **221a** (28 mg, 0.3 mmol, 1.5 equiv) *N*-phenyl diazoacetamide **122a** (45 mg, 0.28 mmoL, 1.4 equiv). The resulting mixture was stirred for 48 h at –20 °C. The reaction was dilluted by addition of pre-cooled hexane (3 mL) under 0 °C before the reaction mixture was 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 product as a yellow-colored viscous oil. Purification of the crude aziridine by silica gel chromatography (20 mm × 150 mm column, 15:1 hexanes/Et_2O as eluent, flash column) afforded amino amide **218a** as a white foam (mp 77-79 °C on 94% *ee* material) in 94% yield (149 mg, 0.187 mmol). The enantiomeric purity of **218a** was determined to be 94% *ee* by HPLC analysis (PIRKLE COVALENT (R, R) WHELK-O 1 column, 95:5 hexane/2-propanol at 222 nm, flow-rate: 0.7 mL/min): retention times; R_t = 19.46 min (minor enantiomer, *ent*-**218a**) and R_t = 22.93 min (major enantiomer, **218**). The reaction in the presence of (*R*)-VAPOL BOROX afforded **218a** in 28% *ee* and 26% yield (41 mg, 0.051 mmol). The reaction in the

presence of (*R*)-^{t}Bu$_2$VANOL BOROX afforded **218a** in 26% *ee* and 59% yield (94 mg, 0.12 mmol).

Spectral data for **218a**: R_f= 0.48 (5:1 hexanes/Et_2O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.31 (s, 18H), 1.39 (s, 18H), 2.28 (s, 3H), 2.36 (d, 1H, *J* = 6.5 Hz), 3.60 (s, 3H), 3.69 (s, 3H), 3.98-4.05 (m ,1H), 5.20 (s, 1H), 6.09 (d, 1H, *J* = 3.0 Hz), 6.90 (t, 1H, *J* = 7.2 Hz), 6.94 (d, 2H, *J* = 8.0 Hz), 7.08 (t, 1H, *J* = 7.5 Hz), 7.09 (d, 2H, *J* = 8.0 Hz), 7.13 (s, 2H), 7.18 (s, 2H), 7.21 (t, 2H, *J* = 7.5 Hz), 7.28 (t, 2H, *J* = 8.0 Hz), 7.32 (d, 2H, *J* = 8.0 Hz), 7.40 (d, 2H, *J* = 8.0 Hz), 9.14 (s, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 21.10, 32.02, 32.05, 35.64, 35.80, 64.08, 64.13, 64.35, 66.09, 80.29, 115.70, 119.68, 121.20, 124.25, 126.05, 126.27, 126.27, 126.56, 128.85, 129.41, 129.49, 133.59, 135.59, 135.44, 137.07, 137.32, 137.81, 143.36, 143.50, 157.25, 158.49, 158.68, 169.80; IR (thin film) 3314s, 2961vs, 1688vs, 1600vs, 1519vs, 1494vs, 1442vs, 1412vs, 1393s, 1224vs, 1115s, 1012s cm^{-1}; HRMS (ESI-TOF) *m/z* 797.5275 [(M+H$^+$); calcd. for $C_{53}H_{69}N_2O_4$: 797.5257]; $[\alpha]_D^{20}$ – 61.6° (c 1.0, $CHCl_3$) on 94% *ee* material (HPLC).

6.4.2 *trans*-Aziridination/Ring-Opening Cascade Reaction with 4-Methoxyphenol

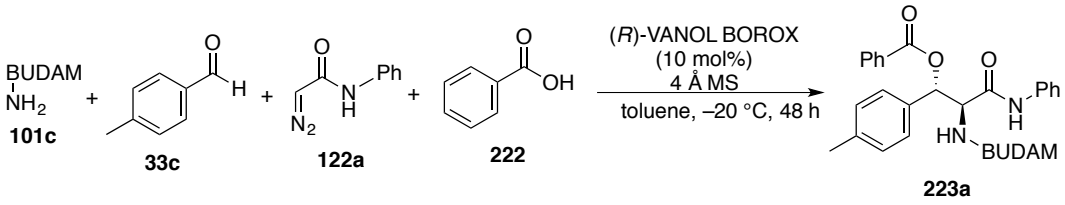


(2S,3S)-2-((bis(3,5-di-tert-butyl-4-methoxyphenyl)methyl)amino)-3-(4-methoxyphenoxy)-N-phenyl-3-(p-tolyl)propanamide ***218b***: To a 10 mL flame-dried home-made Schlenk flask, prepared from a 10 mL pear-shaped flask that had its 14/20 glass joint replaced with a high vacuum threaded Teflon valve, equipped with a stir bar and filled with argon was added (*R*)-VANOL **68a** (8.8 mg, 0.020 mmol), $B(OPh)_3$ (17 mg, 0.060 mmol) and

BUDAM amine **101c** (94 mg, 0.200 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 the mixture was stirred at 80 °C for 0.5 h. The pre-catalyst was subjected to high vacuum (0.05 mmHg) at 80 °C for 30 min to remove all the volatile substances. 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 dry toluene (1.0 mL) to dissolve all the materials, followed by addition of the 4Å Molecular Sieves (60 mg, freshly flame-dried) and 4-tolualdehyde **33c** (28 μL, 0.24 mmol, 1.2 equiv). The reaction mixture was allowed to stirred at room temperature for 20 min that the corresponding imine was formed completely. This solution was then allowed to cool to –20 °C and rapidly added 4-methoxyphenol **221b** (37 mg, 0.3 mmol, 1.5 equiv) *N*-phenyl diazoacetamide **122a** (45 mg, 0.28 mmoL, 1.4 equiv). The resulting mixture was stirred for 48 h at –20 °C. The reaction was dilluted by addition of pre-cooled hexane (3 mL) under –20 °C before the reaction mixture was 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 product as a yellow-colored viscous oil. Purification of the crude aziridine by silica gel chromatography (20 mm × 150 mm column, 10:1 hexanes/Et_2O as eluent, flash column) afforded amino amide **218b** as a white foam (mp 63-64 °C on 93% *ee* material) in 85% yield (141 mg, 0.170 mmol). The enantiomeric purity of **218b** was determined to be 93% *ee* by HPLC analysis (PIRKLE COVALENT (R, R) WHELK-O 1 column, 95:5 hexane/2-propanol at 222 nm, flow-rate: 0.7 mL/min): retention times; R_t =

27.54 min (minor enantiomer, *ent*-**128b**) and R_t = 35.79 min (major enantiomer, **128b**). Spectral data for **218b**: R_f = 0.30 (5:1 hexanes/Et_2O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.30 (s, 18H), 1.38 (s, 18H), 2.28 (s, 3H), 2.31-2.41 (m, 1H), 3.59 (s, 3H), 3.68 (s, 3H), 3.71 (s, 3H), 3.99 (d, 1H, *J* = 3.5 Hz), 5.14 (s, 1H), 5.95 (d, 1H, *J* = 3.5 Hz), 6.74 (d, 2H, *J* = 9.0 Hz), 6.85 (d, 2H, *J* = 8.5 Hz), 7.07 (t, 1H, *J* = 7.5 Hz), 7.09 (d, 2H, *J* = 8.0 Hz), 7.12 (s, 2H), 7.16 (s, 2H), 7.27 (t, 2H, *J* = 7.8 Hz), 7.31 (d, 2H, *J* = 7.5 Hz), 7.38 (d, 2H, *J* = 8.0 Hz), 9.08 (s, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 21.10, 32.00, 32.05, 35.63, 35.79, 55.54, 64.06, 64.12, 64.31, 66.01, 80.97, 114.59, 116.73, 119.68, 124.23, 126.05, 126.25, 126.63, 128.83, 129.34, 133.80, 135.54, 137.02, 137.31, 137.76, 143.32, 143.48, 151.29, 154.04, 158.48, 158.64, 169.94; IR (thin film) 3315s, 2961vs, 2869s, 1685vs, 1601vs, 1506s, 1443s, 1412s, 1394s, 1361s, 1224vs, 1115vs, 1042s, 1012s cm^{-1}; HRMS (ESI-TOF) *m/z* 827.5358 [(M+H$^+$); calcd. for $C_{54}H_{71}N_2O_5$: 827.5363]; $[\alpha]_D^{20}$ –54.5° (c 1.0, $CHCl_3$) on 93% *ee* material (HPLC).

6.4.3 *trans*-Aziridination/Ring-Opening Cascade Reaction with Benzoic Acid



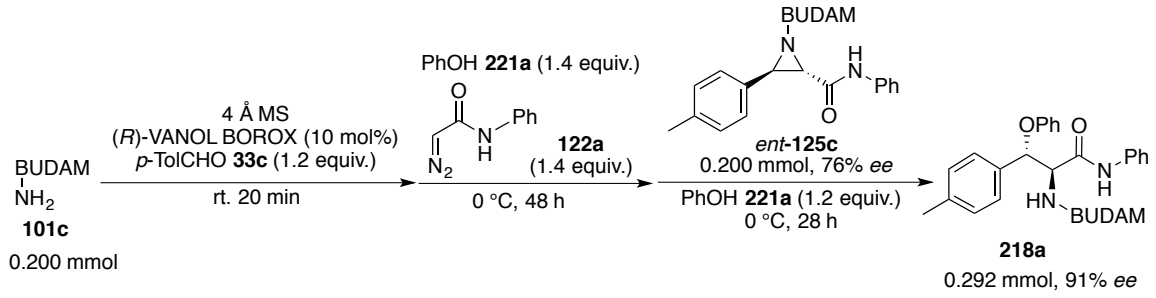
(1S,2S)-2-((bis(3,5-di-tert-butyl-4-methoxyphenyl)methyl)amino)-3-oxo-3-(phenylamino)-1-(p-tolyl)propyl benzoate ***223a***: To a 10 mL flame-dried home-made Schlenk flask, prepared from a 10 mL pear-shaped flask that had its 14/20 glass joint replaced with a high vacuum threaded Teflon valve, equipped with a stir bar and filled with argon was added (*R*)-VANOL **68a** (8.8 mg, 0.020 mmol), $B(OPh)_3$ (17 mg, 0.060 mmol) and BUDAM amine **101c** (94 mg, 0.200 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 the mixture was stirred at 80 °C for 0.5 h. The pre-catalyst was subjected to high vacuum (0.05 mmHg) at 80 °C for 30 min to remove all the volatile substances. 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 dry toluene (1.0 mL) to dissolve all the materials, followed by addition of the 4Å Molecular Sieves (60 mg, freshly flame-dried) and 4-tolualdehyde **33c** (28 μL, 0.24 mmol, 1.2 equiv). The reaction mixture was allowed to stirred at room temperature for 20 min that the corresponding imine was formed completely. This solution was then allowed to cool to –20 °C and rapidly added *N*-phenyl diazoacetamide **122a** (45 mg, 0.28 mmoL, 1.4 equiv). The resulting mixture was stirred for 24 h at –20 °C. Benzoic acid **222** (49 mg, 0.40 mmol, 2.0 equiv) was added and the reaction was kept for another 24 h. The mixture was then dilluted by addition of pre-cooled hexane (3 mL) under –20 °C before the reaction mixture was 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 product as a yellow-colored viscous oil. Purification of the crude aziridine by silica gel chromatography (20 mm × 150 mm column, 10:1 hexanes/Et_2O as eluent, flash column) afforded amino amide **223a** as a white foam (mp 62-64 °C on 68% *ee* material) in 81% yield (133 mg, 0.161 mmol). The enantiomeric purity of **223a** was determined to be 68% *ee* by HPLC analysis (PIRKLE COVALENT (R, R) WHELK-O 1 column, 90:10 hexane/2-propanol at 222 nm, flow-rate: 0.7 mL/min): retention times; R_t = 22.66 min

(minor enantiomer, *ent*-**223a**) and R_t = 39.77 min (major enantiomer, **223a**).

Spectral data for **223a**: R_f= 0.30 (5:1 hexanes/Et_2O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.28 (s, 18H), 1.36 (s, 18H), 2.29 (s, 3H), 2.30-2.36 (m, 1H), 3.60 (s, 3H), 3.67 (s, 3H), 3.91-3.98 (m, 1H), 5.14 (s, 1H), 6.76 (d, 1H, *J* = 3.5 Hz), 7.07 (t, 1H, *J* = 7.0 Hz), 7.08 (s, 2H), 7.12 (d, 2H, *J* = 7.5 Hz), 7.17 (s, 2H), 7.28 (t, 2H, *J* = 7.8 Hz), 7.31 (d, 2H, *J* = 8.0 Hz), 7.42 (d, 2H, *J* = 8.0 Hz), 7.46 (t, 2H, *J* = 7.5 Hz), 7.58 (t, 1H, *J* = 7.5 Hz), 8.14 (d, 2H, *J* = 8.0 Hz), 9.08 (s, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 21.13, 31.96, 32.01, 32.04, 35.63, 35.78, 64.09, 64.14, 64.38, 65.97, 119.66, 124.27, 125.86, 126.02, 126.33, 128.92, 129.54, 129.80, 129.98, 133.31, 133.42, 135.34, 136.82, 137.39, 138.14, 143.58, 143.68, 158.62, 158.78, 165.20, 168.79; IR (thin film) 3316s, 2960vs, 2869s, 1727vs, 1693vs, 1602vs, 1523s, 1444vs, 1412s, 1394s, 1362s, 1314s, 1266vs, 1224vs, 1115s, 1012s cm^{-1}; HRMS (ESI-TOF) *m/z* 825.5200 [(M+H$^+$); calcd. for $C_{54}H_{69}N_2O_5$: 825.5206]; $[\alpha]_D^{20}$ – 30.9° (c 1.0, $CHCl_3$) on 54% *ee* material (HPLC).

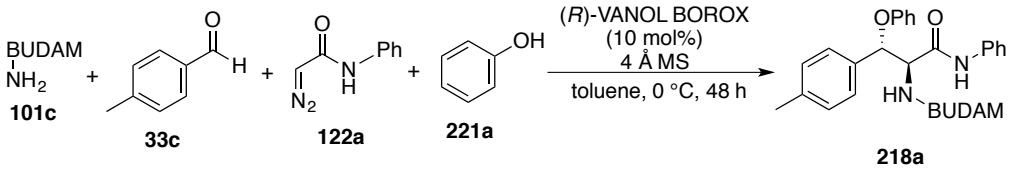
6.4.4 Controlled Experiments



The catalytic *trans*-aziridination/ring-opening reaction was set up by the general procedure in 6.4.1 with BUDAM amine **101c** (94 mg, 0.200 mmol), 4-tolualdehyde **33c** (28 μL, 0.24 mmol, 1.2 equiv), phenol **221a** (28 mg, 0.3 mmol, 1.5 equiv) *N*-phenyl diazoacetamide **122a** (45 mg, 0.28 mmoL, 1.4 equiv). After 48 h, *trans*-aziridine *ent*-**125c** (141 mg, 0.200 mmol, 76% *ee*) obtained from *trans*-azidiridination of 4-

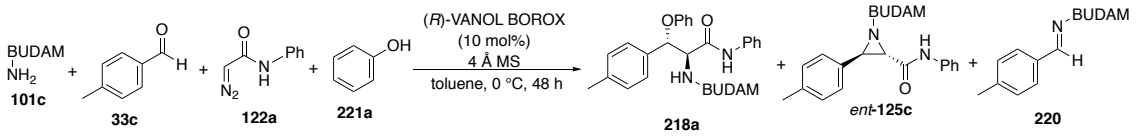
tolualdehyde **33c** was added and the reaction mixture was stirred for another 28 h. Purification of the crude mixture afforded amino amide **218a** (209 mg, 0.292 mmol) in 91% *ee*.

6.4.5 Reaction Monitoring



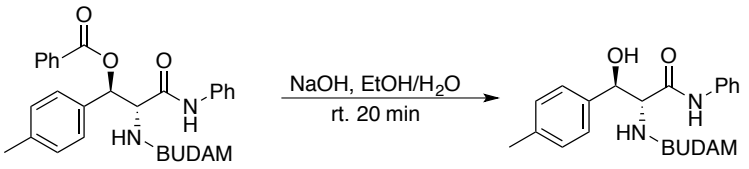
The catalytic *trans*-aziridination/ring-opening reaction was set up by the general procedure in 6.4.1 with BUDAM amine **101c** (94 mg, 0.200 mmol), 4-tolualdehyde **33c** (28 μL, 0.24 mmol, 1.2 equiv), phenol **221a** (28 mg, 0.3 mmol, 1.5 equiv) *N*-phenyl diazoacetamide **122a** (45 mg, 0.28 mmoL, 1.4 equiv). Triphenylmethane (6.4 mg) was added in the reaction mixture as the internal standard. A small portion of reaction mixture was analyzed by ^{1}H-NMR at specific reaction. The yields of each component of the reaction mixture are listed in Table 6.1.

Table 6.1 Reaction tracking



Reaction Time/h	aminophenoxy amide/%	*trans*-azidirine/%	imine/%
0.5	0	25.4	28.4
1	4.2	31.7	8.3
1.5	9.3	29.0	1.7
2	14.4	21.9	0
2.5	19.6	19.6	0
3	22.8	16.1	0
4	27.9	12.5	0
5	30.8	11.6	0
6	32.4	10.2	0
8	35.0	8.1	0
10	36.7	5.8	0
12	38.3	5.5	0
24	47.3	3.3	0
48	62.1	2.9	0

6.4.6 Absolute Stereochemistry of Aminohydroxy Amide



ent-**223a**

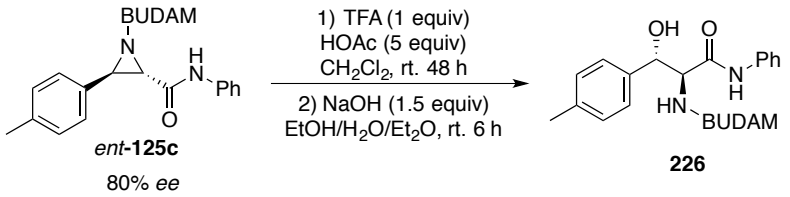
72% *ee*

ent-**226**

*(2S,3S)-2-((bis(3,5-di-tert-butyl-4-methoxyphenyl)methyl)amino)-3-hydroxy-N-phenyl-3-(p-tolyl)propanamide ent-**226***: Aminobenzoyloxy amide *ent*-**223a** (240 mg, 0.29 mmol) was dissolved in ethanol (1.0 mL). NaOH aq. (0.3 mL, 2 *M*) was added and the resulting mixture was stirred at room temperature for 20 min before it was diluted with ethanol (1.5 mL) to dissolved all the suspension. The mixture was extracted with Et_2O and the organic phase was dried with Na_2SO_4 and concentrated to afford an oil. Purification of the crude aminohydroxy amide by silica gel chromatography (20 mm × 150 mm column, 5:1 hexanes/Et_2O as eluent, flash column) afforded amino amide *ent*-**226** as a white foam (mp 80-81 °C on 74% *ee* material) in 79% yield (166 mg, 0.230 mmol). The reaction with aminobenzoyloxy amide **223a** (38 mg, 0.047 mmol, 54% *ee*) afforded amino amide **226** in 98% yield (33 mg, 0.046 mmol).

Spectral data for *ent*-**226**: R_f= 0.31 (2:1 hexanes/Et_2O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.33 (s, 18H), 1.37 (s, 18H), 1.96-2.09 (m, 1H), 2.39 (s, 3H), 3.39 (d, 1H, *J* = 7.5 Hz), 3.61 (s, 3H), 3.66 (s, 3H), 4.07 (s, 1H), 4.54 (s, 1H), 4.89 (d, 1H, *J* = 8.0 Hz), 6.94 (s, 2H), 7.09 (s, 2H), 7.13 (t, 1H, *J* = 7.5 Hz), 7.23 (t, 2H, *J* = 7.0 Hz), 7.31 (d, 2H, *J* 7.5 Hz), 7.32 (d, 2H, *J* = 8.0 Hz), 7.46 (d, 2H, *J* = 8.0 Hz), 9.53 (s, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 21.24, 29.68, 32.01, 35.66, 35.73, 64.00, 64.03, 64.10, 54.77, 76.23, 119.58, 124.54, 125.59, 125.91, 127.09, 129.01, 129.32, 135.42, 136.66, 137.04, 137.35, 138.18, 143.42, 143.51, 158.56, 158.68, 172.42; IR (thin film) 3145s, 2960vs, 2925s,

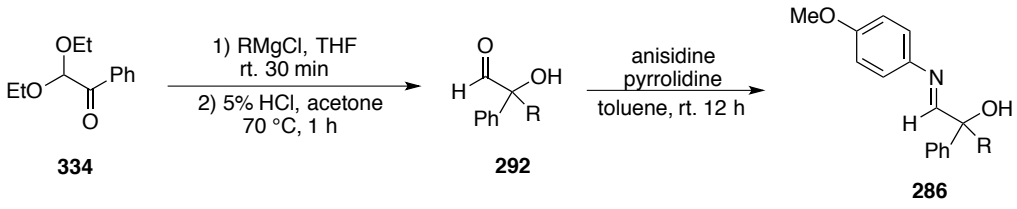
2868s, 1666vs, 1601s, 1527vs, 1444vs, 1412vs, 1361s, 1222vs, 1115s, 1013s cm^{-1}; HRMS (ESI-TOF) *m/z* 721.4940 [(M+H$^+$); calcd. for $C_{47}H_{65}N_2O_4$: 721.4944]; $[\alpha]_D^{20}$ +33.9° (c 1.0, $CHCl_3$) on 74% *ee* material (HPLC); $[\alpha]_D^{20}$ –28.6° (c 1.0, $CHCl_3$) on 52% *ee* material of **126** (HPLC).



*(2S,3S)-2-((bis(3,5-di-tert-butyl-4-methoxyphenyl)methyl)amino)-3-hydroxy-N-phenyl-3-(p-tolyl)propanamide **226***: *trans*-Aziridine *ent*-**125c** (141 mg, 0.200 mmol, 80% *ee*) was reacted according the general procedure of ring-opening **a1** with trifluoroacetic acid (15 μL, 0.20 mmol) and acetic acid (57 μL, 1.0 mmol) in dry CH_2Cl_2 (2 mL). Purification of the crude aminohydroxy amide by silica gel chromatography (20 mm × 150 mm column, 5:1 hexanes/Et_2O as eluent, flash column) afforded amino amide **226** as a white foam in 55% yield (79 mg, 0.11 mmol). $[\alpha]_D^{20}$ –33.6° (c 1.0, $CHCl_3$) on 80% *ee* material of **126** (HPLC).

6.5 Experimental Information for Chapter 5

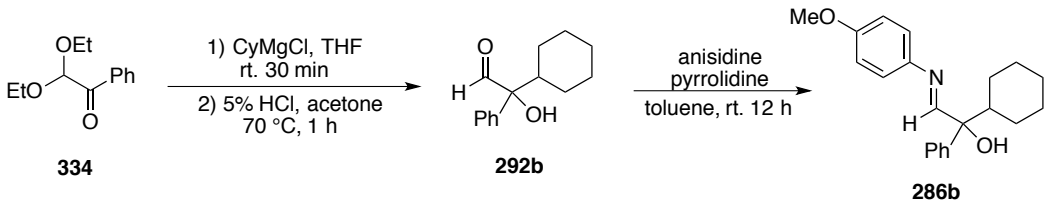
6.5.1 General Procedure for Preparation of α-Iminols 286b-e



To a 25 mL clean and dry Schlenk flask was added a solution of alkylmagnesium chloride (7.5 mmol, 1.5 equiv) in THF. The flask was tightly sealed and the solution was cool down to 0 °C for 10 min. A solution of 2,2-Diethoxyacetopheone **334** (1.01 mL in 2

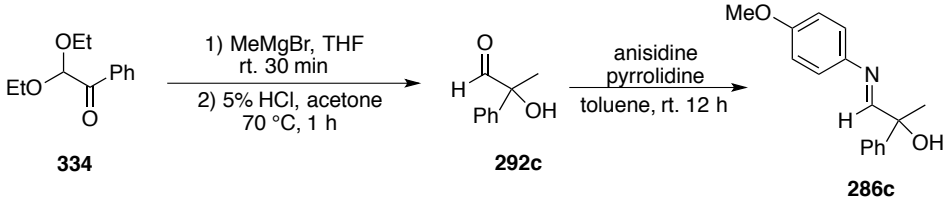
mL THF, 5.00 mmol, 1.00 equiv.) was added in dropwise and slowly via a syringe. The resulting mixture was stirred for another 30 min at room temperature then quenched with 5 mL saturated NH_4Cl solution. The two layers were separated and the aqueous layer was extracted with ether (5 mL × 3). The combined organic layer was concentrated under rotary evaporation and the crude residue was subjected to hydrolysis without purification. The crude acetal intermediate was transferred to a 25 mL Schlenk flask with 0.5 mL 5% HCl (that is 1.7 M HCl) and enough acetone (usually it took 10 mL) to obtain a single layer homogenous solution. Thereafter, the flask was sealed and heated to 70 °C for 1 h. After being cooled to room temperature, the solution was diluted with CH_2Cl_2 (10 mL). The organic layer was separated and washed with $NaHCO_3$ solution and brine, dried over $MgSO_4$ and concentrated by rotary evaporation. The crude residue was purified by silica gel column chromatography with 20:1 hexanes/EtOAc as eluent to afford an α-hydroxyl aldehyde **292** as a white solid without further purification.

To a 20 mL vial was added the α-hydroxyl aldehyde **292** (1.0 equiv), *p*-anisidine (1.1 equiv), pyrrolidine (20 mol%) in toluene. The vial was capped and the mixture was stirred at room temperature for 12 h. Upon completion, the reaction mixture was neutralized with Et_3N and dried over Na_2SO4, then it was concentrated under rotary evaporation to afford crude iminol as an oil. Purification by a short flash column chromatography with hexanes/EtOAc/Et_3N as eluent.



334 **292b** **286b**

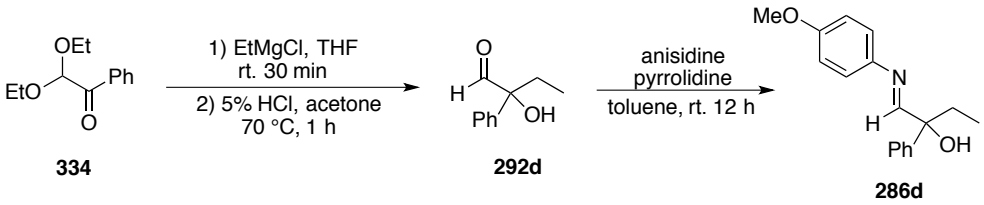
1-Cyclohexyl-2-((4-methoxyphenyl)imino)-1-phenylethan-1-ol ***286b***: Cyclohexylmagnesium chloride (3.8 mL, 2 *M* in THF, 7.5 mmol, 1.5 equiv) was reacted according to the general procedure. Purification by a short flash column chromatography with 15:1:0.1 hexanes/EtOAc/Et_3N as eluent afforded α-iminol **286b** as an off-white solid (mp 103-105 °C) in 47% yield (664 mg, 2.05 mmol) over two steps. Spectral data for **286b**: R_f = 0.45 (5:1 hexanes/Et_2O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.11-1.29 (m, 4H), 1.33-1.42 (m, 2H), 1.54 (d, 1H, *J* = 17.5 Hz), 1.65 (dd, 2H, *J* = 27.2, 6.2 Hz), 1.77 (d, 1H, *J* = 11.0 Hz), 2.02 (tt, 1H, *J* = 12.5, 3.2 Hz), 3.78 (s, 3H), 4.91 (s, 1H), 6.84 (dd, 2H, *J* = 7.0, 2.0 Hz), 7.06 (dd, 2H, *J* = 7.0, 2.0 Hz), 7.24 (t, 1H, *J* = 7.5 Hz), 7.36 (t, 2H, *J* = 7.5 Hz), 7.53 (d, 2H, *J* = 7.0 Hz), 8.08 (s, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 25.85, 26.28, 26.42, 26.56, 26.96, 45.93, 55.48, 79.08, 114.23, 122.30, 125.60, 126.80, 128.38, 141.76, 142.88, 158.44, 164.86; IR (thin film) 3410s, 2930vs, 2852s, 1646s, 1506vs, 1447s, 1388s, 1248vs, 1033s cm^{-1}; HRMS (ESI-TOF) *m/z* 324.1930 [($M+H^+$); calcd. for $C_{21}H_{26}NO_2$: 324.1964].



334 **292c** **286c**

1-((4-Methoxyphenyl)imino)-2-phenylpropan-2-ol ***286c***: Methylmagnesium bromide (10 mL, 3 *M* in THF, 30 mmol, 1.5 equiv) was reacted according to the general procedure. Purification by a short flash column chromatography with 6:1:0.1 hexanes/EtOAc/Et_3N

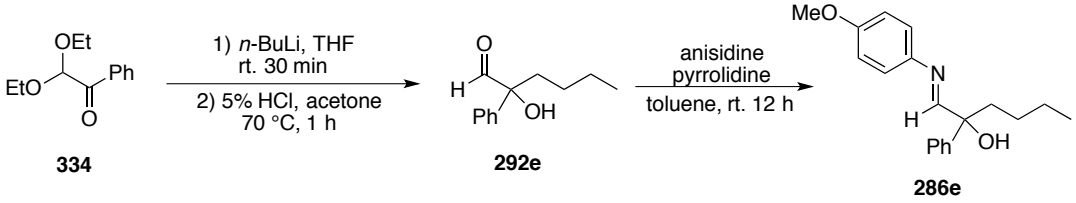
as eluent afforded α-iminol **286c** as a colorless oil in 67% yield (2.63 g, 10.3 mmol) over two steps. Spectral data for **286c**: R_f = 0.37 (2:1 hexane/Et_2O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.74 (s, 3H), 3.78 (s, 3H), 5.20 (d, 1H, *J* = 1.0 Hz), 6.85 (dd, 2H, *J* = 6.2, 2.2 Hz), 7.10 (dd, 2H, *J* = 7.0, 2.2 Hz), 7.26 (t, 1H, *J* = 6.8 Hz), 7.36 (t, 2H, *J* = 7.5 Hz), 7.52 (dd, 2H, *J* = 8.2, 1.2 Hz), 8.01 (d, 1H, *J* = 1.0 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 26.90, 55.45, 74.32, 114.26, 122.39, 125.46, 127.32, 128.52, 141.47, 143.69, 158.56, 164.08; IR (thin film) 3416vs, 2977vs, 2835s, 1646vs, 1603vs, 1581s, 1505vs, 1446vs, 1370s, 1247s, 1106s, 1068s, 1030s cm^{-1}; HRMS (ESI-TOF) *m/z* 256.1337 [($M+H^+$); calcd. for $C_{16}H_{18}NO_2$: 256.1338].



334 **292d** **286d**

*1-((4-methoxyphenyl)imino)-2-phenylbutan-2-ol **286d***: Ethylmagnesium bromide (10 mL, 3 *M* in THF, 30 mmol, 1.5 equiv) was reacted according to the general procedure. Purification by a short flash column chromatography with 6:1:0.1 hexanes/EtOAc/Et_3N as eluent afforded α-iminol **286d** (2.78 g, 10.3 mmol) as an off-white solid (mp 66-68 °C) in 53% yield over two steps. Spectral data for **286d**: R_f = 0.48 (2:1 hexane/Et_2O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.93 (t, 3H, *J* = 7.5 Hz), 2.00-2.14 (m, 2H), 3.78 (s, 3H), 5.06 (s, 1H), 6.85 (d, 2H, *J* = 8.5 Hz), 7.09 (d, 2H, *J* = 8.5 Hz), 7.27 (t, 1H, *J* = 7.2 Hz), 7.38 (t, 2H, *J* = 8.0 Hz), 7.55 (d, 2H, *J* = 8.5 Hz), 8.04 (d, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 7.53, 32.71, 55.43, 76.97, 114.23, 122.32, 125.53, 127.07, 128.45, 141.63, 143.00, 158.49, 164.17; IR (thin film) 3418vs, 2966s, 2935s, 1645vs, 1603s, 1505s, 1463s,

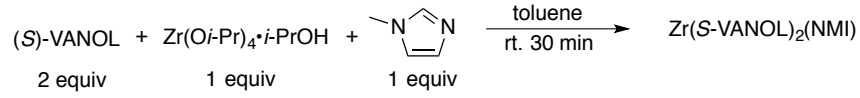
1447s, 1247vs, 1033s cm^{-1}; HRMS (ESI-TOF) *m/z* 270.1496 [$(M+H^+)$; calcd. for $C_{17}H_{20}NO_2$: 270.1494].



1-((4-methoxyphenyl)imino)-2-phenylhexan-2-ol ***286e***: *n*-BuLi (1.88 mL, 2 *M* in THF, 3.75 mmol, 1.50 equiv) was reacted according to the general procedure. Purification by a short flash column chromatography with 9:1:0.1 hexanes/EtOAc/Et_3N as eluent afforded α-iminol **286e** (461 mg, 1.55 mmol) as an off-white solid (mp 55-58 °C) in 65% yield over two steps. Spectral data for **286e**: R_f= 0.59 (2:1 hexane/Et_2O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.86 (t, 3H, *J* = 7.0 Hz), 1.22-1.40 (m, 4H), 1.91-2.01 (m, 1H), 2.02-2.13 (m, 1H), 3.78 (s, 3H), 5.07 (s, 1H), 6.84 (d, 2H, *J* = 8.5 Hz), 7.08 (d, 2H, *J* = 8.5 Hz), 7.25 (t, 1H, *J* = 7.0 Hz), 7.36 (t, 2H, *J* = 7.8 Hz), 7.53 (d, 2H, *J* = 7.0 Hz), 8.04 (d, 1H, *J* = 1.0 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 14.02, 23.00, 25.33, 39.79, 55.48, 76.78, 114.26, 122.36, 125.48, 127.07, 128.48, 141.64, 143.26, 158.52, 164.26; IR (thin film) 3412s, 2955s, 2870s, 1645vs, 1603s, 1506vs, 1465s, 1447s, 1390s, 1291s, 1247vs, 1033s cm^{-1}; HRMS (ESI-TOF) *m/z* 298.1806 [$(M+H^+)$; calcd. for $C_{19}H_{24}NO_2$: 298.1807].

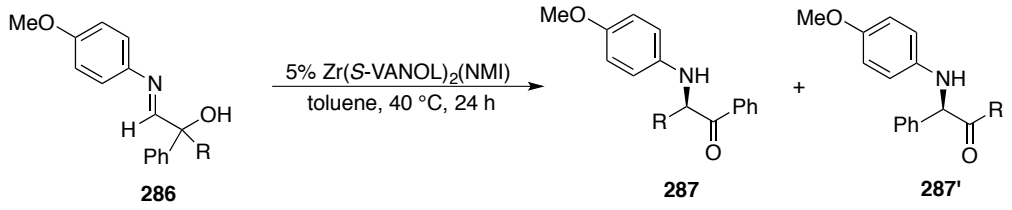
6.5.2 Kinetic resolution of α-Iminols

General Procedure of Zirconium-Catalyzed α-Iminol Rearrangement[29]



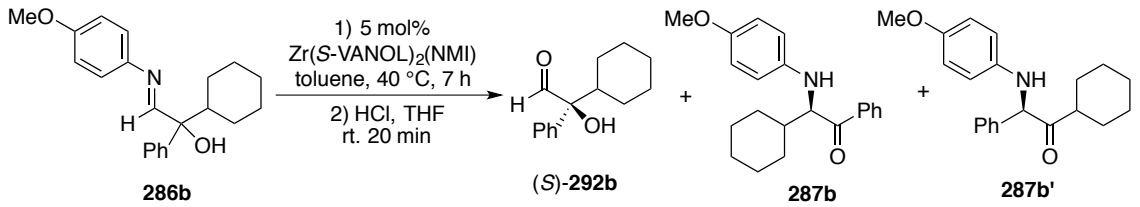
Preparation of zirconium complex catalyst solution: (*R*)-VANOL (44 mg, 0.10 mmol, 2.0 equiv), zirconium(IV) isopropoxide isopropanol complex (19 mg, 0.050 mmol, 1.0 equiv)

and toluene (1.0 mL) were mixed at room temperature in a 4 mL vial, then N-methylimidazole (4.0 μL, 0.050 mmol, 1.0 equiv) was added via a syringe. Soon after addition of *N*-methylimidazole, a white solid precipitate started to form. The resulting slurry was stirred at room temperature under air for 30 min before being used in the following asymmetric catalytic rearrangement of α-iminols. This catalyst solution can be stored in toluene for extended periods, with no compromise to the yield or ee of the rearranged product. The solution of zirconium complex catalyst with a different ligand could all be prepared by this method with an appropriate ligand.



286 **287** **287'**

α-Iminol rearrangement: To a 20 mL clean and dry Schlenk flask under air was added appropriate α-iminol **286** (0.20 mmol) and dry toluene (0.30 mL). The Zr(*S*-VANOL)$_2$(NMI) complex catalyst solution (0.05 *M* in toluene, 0.20 mL, 0.010 mmol, 5.0 mol%, this white slurry was vigorously swirled and agitated while being drawn by a syringe). The Schlenk flask was sealed and applied to freeze-pump-thaw cycling three times. After the reaction mixture was warmed to room temperature and then heated up to 40 °C for 24 h. Upon completion, the solution was cooled to room temperature and diluted with hexanes (1.0 mL). The white precipitate was filtered and the crude product purified by flash column chromatography on silica gel.

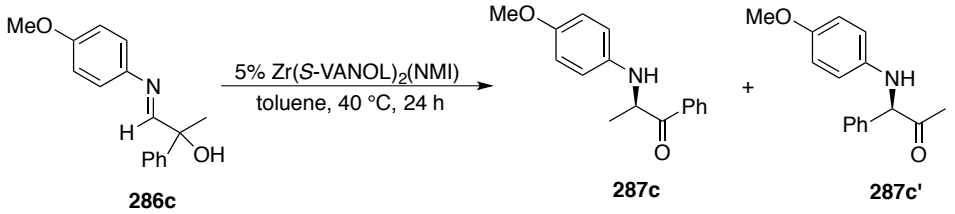


286b (*S*)-**292b** **287b** **287b'**

*(S)-2-cyclohexyl-2-hydroxy-2-phenylacetaldehyde (S)-**292b***: α-Iminol **286b** (65 mg, 0.20 mmol) was reacted according to general procedure. The reaction was monitored by the ^{1}H-NMR spectrum of a small portion from the mixture with an internal standard and quenched at the 49% conversion of substrate. Amino ketone **287b** was detected in 39% yield and amino ketone **287b'** was detected in 7.5% by the ^{1}H-NMR spectrum of crude reaction mixture. The residue was concentrated in high *vavuo* and dissolved in THF (1.0 mL). Diluted HCl (0.20 mL, 1 *M*) was added and the resulting solution was stirred at room temperature for 20 min. The reaction mixture was neutralized by saturated Na_2CO_3 and then extracted by Et_2O (5 mL × 3). The combined organic phase was dried with Na_2SO_4 and concentrated to afford a yellow oil. Purification by silica gel chromatography (20 mm × 150 mm column, 15:1 hexanes/Et_2O as eluent, flash column) afforded α-hydroxyaldehyde (*S*)-**292b** as a white solid (mp 59-60 °C on 60% *ee* material) in 37% yield (16 mg, 0.074 mmol). The enantiomeric purity of **223a** was determined to be 60% *ee* by HPLC analysis (CHIRALCEL AS column, 99:1 hexane/2-propanol at 280 nm, flow-rate: 0.5 mL/min): retention times; R_t = 13.46 min (minor enantiomer, (*R*)-**292b**) and R_t = 27.17 min (major enantiomer, (*S*)-**292b**).

Spectral data for (*S*)-**292b**: R_f= 0.41 (5:1 hexanes/Et_2O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.12-1.18 (m, 3H), 1.25-1.41 (m, 4H), 1.63-1.70 (m, 2H), 1.76-1.79 (m, 1H), 2.17-2.21 (m, 1H), 3.70 (d, 1H, *J* = 1.0 Hz), 7.29 (t, 1H, *J* = 7.5 Hz), 7.39 (t, 2H, *J* = 7.8 Hz), 7.49 (d, 2H, *J* = 8.0 Hz), 9.62 (d, 1H, *J* = 1.5 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 24.98,

26.10, 26.16, 26.37, 26.76, 43.45, 84.35, 125.85, 127.60, 128.75, 138.04, 201.14; IR (thin film) 3421s, 2921vs, 2854vs, 1716vs, 1445s, 1328s, 1191s, 1133s, 1073s cm^{-1}; HRMS (ESI-TOF) *m/z* 219.1384 [(M+H^+); calcd. for $C_{14}H_{19}O_2$: 219.1385]; $[\alpha]_D^{20}$ +64.1° (c 1.0, EtOAc) on 63% *ee* material (HPLC).

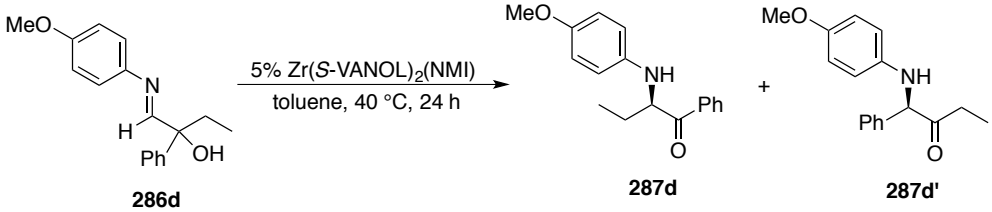


286c **287c** **287c'**

*(R)-2-((4-methoxyphenyl)amino)-1-phenylpropan-1-one **287c***: α-Iminol **286c** (51 mg, 0.20 mmol) was reacted according to general procedure to afford a mixture of amino ketone regioisomers **287c** and **287c'**. Purification by silica gel chromatography (20 mm × 150 mm column, 3:1 hexanes/Et_2O as eluent, flash column) afforded amino ketone **287c** as a yellow oil in 33% yield (17 mg, 0.066 mmol). The enantiomeric purity of **287c** was determined to be 98.5:1.5 *er* by HPLC analysis (CHIRALCEL AS column, 80:20 hexane/2-propanol at 240 nm, flow-rate: 0.5 mL/min): retention times; R_t = 32.24 min (minor enantiomer, *ent*-**287c**) and R_t = 45.41 min (major enantiomer, **287c**). The reaction with zirconium-Cy_2VANOL complex catalyst afforded amino ketone **287c** in 99:1 *er* and 30% yield (15 mg, 0.060 mmol). Spectral data for **287c**: R_f= 0.41 (1:1 hexane/Et_2O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.44 (d, 3H, *J* = 6.5 Hz), 3.71 (s, 3H), 4.08-4.69 (br, 1H), 5.04 (q, 1H, *J* = 6.8 Hz), 6.63 (d, 2H, *J* = 9.0 Hz), 6.75 (d, 2H, *J* = 9.0 Hz), 7.49 (t, 2H, *J* = 7.5 Hz), 7.59 (t, 1H, *J* = 8.0 Hz), 7.98 (d, 2H, *J* = 8.0 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 19.66, 54.45, 55.70, 114.93, 115.18, 128.38, 128.83, 133.56, 134.79, 140.77, 152.48, 201.24; IR (thin film) 3368s, 2930vs, 2833s, 1686vs, 1596s, 1513s, 1448s,

1239vs, 1166s, 1035s cm^{-1}; HRMS (ESI-TOF) *m/z* 256.1338 [($M+H^+$); calcd. for $C_{16}H_{18}NO_2$: 256.1338]; $[\alpha]_D^{20}$ +32.9° (c 1.0, EtOAc) on 97% *ee* material (HPLC).

(R)-1-((4-methoxyphenyl)amino)-1-phenylpropan-2-one ***287c'***: Purification by silica gel chromatography (20 mm × 150 mm column, 3:1 hexanes/Et_2O as eluent, flash column) afforded amino ketone **287c'** as an off-white solid (mp 93-95 °C on 91% *ee* material) in 48% yield (25 mg, 0.096 mmol). The enantiomeric purity of **287c** was determined to be 75.5:24.5 *er* by HPLC analysis (CHIRALCEL AS column, 85:15 hexane/2-propanol at 240 nm, flow-rate: 0.5 mL/min): retention times; R_t = 25.52 min (major enantiomer, **287c'**) and R_t = 41.34 min (minor enantiomer, *ent*-**287c'**). The reaction with zirconium-Cy_2VANOL complex catalyst afforded amino ketone **287c** in 65.5:34.5 *er* and 51% yield (26 mg, 0.10 mmol). Spectral data for **287c'**: R_f = 0.48 (1:1 hexane/Et_2O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 2.10 (s, 3H), 3.67 (s, 3H), 4.92 (s, 1H), 5.14 (s, 1H), 6.48 (d, *J* = 9.0 Hz), 6.67 (d, *J* = 8.5 Hz), 7.29 (t, 1H, *J* = 7.5 Hz), 7.36 (t, 2H, *J* = 7.5 Hz), 7.43 (d, 2H, *J* = 7.5 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 26.71, 55.67, 69.04, 114.40, 114.78, 127.80, 128.32, 129.19, 138.28, 140.28, 152.10, 204.35; IR (thin film) 3372s, 2961s, 2834s, 1686vs, 1603s, 1512vs, 1448s, 1245vs, 1171s, 1106s, 1034s cm^{-1}; HRMS (ESI-TOF) *m/z* 256.1343 [($M+H^+$); calcd. for $C_{16}H_{18}NO_2$: 256.1338]; $[\alpha]_D^{20}$ –58.3° (c 1.0, EtOAc) on 51% *ee* material (HPLC).



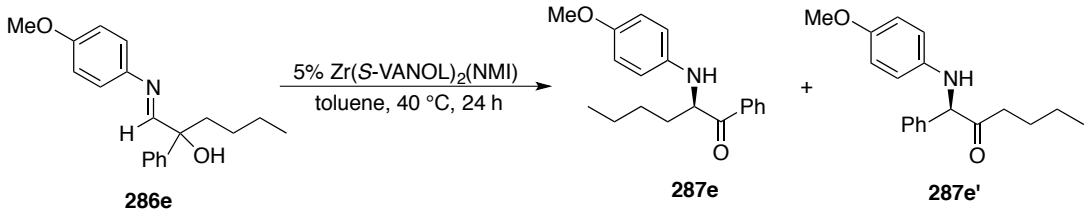
286d **287d** **287d'**

(R)-2-((4-methoxyphenyl)amino)-1-phenylbutan-1-one ***287d***: α-Iminol **286d** (54 mg, 0.20 mmol) was reacted according to general procedure to afford a mixture of amino ketone

regioisomers **287d** and **287d'**. Purification by silica gel chromatography (20 mm × 150 mm column, 6:1 hexanes/Et_2O as eluent, flash column) afforded amino ketone **287d** as a yellow oil in 48% yield (26 mg, 0.096 mmol). The enantiomeric purity of **287d** was determined to be 96.5:3.5 *er* by HPLC analysis (CHIRALCEL OD column, 90:10 hexane/2-propanol at 240 nm, flow-rate: 0.5 mL/min): retention times; R_t = 18.02 min (minor enantiomer, *ent*-**287d**) and R_t = 21.94 min (major enantiomer, **287d**). The reaction with zirconium-Cy_2VANOL complex catalyst afforded amino ketone **287d** in 96:4 *er* and 33% yield (18 mg, 0.066 mmol). Spectral data for **287d**: R_f= 0.32 (2:1 hexane/Et_2O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.91 (t, 3H, *J* = 7.5 Hz), 1.66-1.73 (m, 1H), 1.97-2.04 (m, 1H), 3.71 (s, 3H), 4.40 (s, 1H), 4.91-4.99 (m, 1H), 6.65 (d, 2H, *J* = 9.0 Hz), 6.74 (d, 2H, *J* = 9.0 Hz), 7.48 (t, 2H, *J* = 7.8 Hz), 7.58 (t, 1H, *J* = 7.2 Hz), 7.97 (d, 2H, *J* = 7.0 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 9.42, 26.08, 55.72, 60.01, 114.91, 115.24, 128.28, 128.80, 133.47, 135.34, 141.28, 152.41, 201.02; IR (thin film) 3404s, 2965s, 1684vs, 1512vs, 1448s, 1382s, 1241vs, 1040s cm^{-1}; HRMS (ESI-TOF) *m/z* 270.1495 [($M+H^+$); calcd. for $C_{17}H_{20}NO_2$: 270.1494]; $[\alpha]_D^{20}$ +2.2° (c 1.0, CH_2Cl_2) on 93% *ee* material (HPLC).

(R)-1-((4-methoxyphenyl)amino)-1-phenylbutan-2-one ***287d'***: Purification by silica gel chromatography (20 mm × 150 mm column, 6:1 hexanes/Et_2O as eluent, flash column) afforded amino ketone **287d'** as an off-white solid (mp 51-53 °C on 94% *ee* material) in 47% yield (25 mg, 0.094 mmol). The enantiomeric purity of **287d'** was determined to be 97:3 *er* by HPLC analysis (CHIRALCEL OD column, 90:10 hexane/2-propanol at 240 nm, flow-rate: 0.5 mL/min): retention times; R_t = 17.65 min (major enantiomer, **287d'**) and R_t = 21.43 min (minor enantiomer, *ent*-**287d'**). The reaction with zirconium-Cy_2VANOL complex catalyst afforded amino ketone **287d** in 90:10 *er* and 35% yield (19

mg, 0.070 mmol). Spectral data for **287d'**: R_f = 0.40 (2:1 hexane/Et_2O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.96 (t, 3H, *J* = 7.5 Hz), 2.38-2.48 (m, 2H), 3.66 (s, 3H), 4.92 (d, 1H, *J* = 3.5 Hz), 5.17 (s, 1H), 6.48 (d, 2H, *J* = 9.0 Hz), 6.66 (d, 2H, *J* = 8.5 Hz), 7.28 (t, 1H, *J* = 7.2 Hz), 7.34 (t, 2H, *J* = 7.5 Hz), 7.42 (d, 2H, *J* = 7.0 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 7.90, 32.54, 55.72, 68.37, 114.46, 114.81, 127.84, 128.27, 129.16, 138.62, 140.42, 152.10, 207.35; IR (thin film) 3423s, 1653vs, 1512vs, 1244vs, 1179s, 1108s, 1034s cm^{-1}; HRMS (ESI-TOF) *m/z* 270.1498 [($M+H^+$); calcd. for $C_{17}H_{20}NO_2$: 270.1494]; $[\alpha]_D^{20}$ – 127.7° (c 0.93, EtOAc) on 94% *ee* material (HPLC).

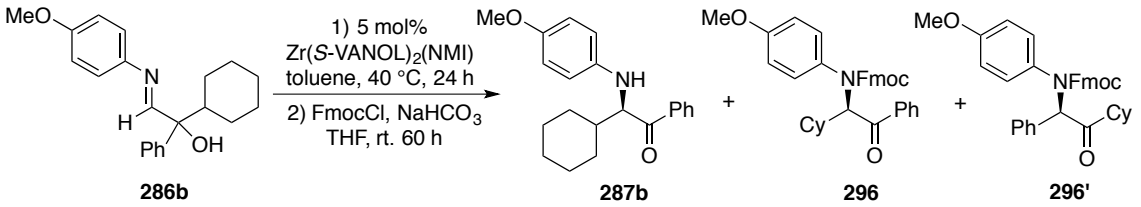


286e **287e** **287e'**

*(R)-2-((4-methoxyphenyl)amino)-1-phenylhexan-1-one **287e***: α-Iminol **286e** (59 mg, 0.20 mmol) was reacted according to general procedure to afford a mixture of amino ketone regioisomers **287e** and **287e'**. Purification by silica gel chromatography (20 mm × 150 mm column, 8:1 hexanes/Et_2O as eluent, flash column) afforded amino ketone **287e** as a yellow oil in 46% yield (27 mg, 0.092 mmol). The enantiomeric purity of **287e** was determined to be 96.5:3.5 *er* by HPLC analysis (CHIRALCEL OD column, 90:10 hexane/2-propanol at 240 nm, flow-rate: 0.5 mL/min): retention times; R_t = 16.60 min (minor enantiomer, *ent*-**287e**) and R_t = 20.39 min (major enantiomer, **287e**). Spectral data for **287e**: R_f = 0.32 (3:1 hexane/Et_2O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.83 (t, 3H, *J* = 7.0 Hz), 1.18-1.49 (m, 4H), 1.55-1.67 (m, 1H), 1.86-1.98 (m, 1H), 3.70 (s, 3H), 4.44 (s, 1H), 4.95 (dd, 1H, *J* = 7.8, 4.8 Hz), 6.63 (d, 2H, *J* = 9.0 Hz), 6.73 (d, 2H, *J* = 9.0 Hz), 7.48 (t, 2H, *J* = 7.5 Hz), 7.58 (t, 1H, *J* = 7.2 Hz), 7.97 (d, 2H, *J* = 7.5 Hz); ^{13}C-NMR (125 MHz,

$CDCl_3$) δ 13.88, 22.62, 27.56, 33.14, 55.71, 59.26, 114.90, 115.31, 128.26, 128.82, 133.46, 135.36, 141.48, 152.48, 201.41; IR (thin film) 3387s, 2957s, 2931s, 2871s, 1685vs, 1603s, 1513vs, 1465s, 1448s, 1244vs, 1178s, 1036s cm^{-1}; HRMS (ESI-TOF) *m/z* 298.1807 [($M+H^+$); calcd. for $C_{19}H_{24}NO_2$: 298.1807]; $[\alpha]_D^{20}$ +1.6° (c 0.93, EtOAc) on 93% *ee* material (HPLC).

(R)-1-((4-methoxyphenyl)amino)-1-phenylhexan-2-one ***287e'***: Purification by silica gel chromatography (20 mm × 150 mm column, 8:1 hexanes/Et_2O as eluent, flash column) afforded amino ketone **287e'** as a colorless oil in 46% yield (27 mg, 0.092 mmol). The enantiomeric purity of **287e'** was determined to be 98:2 *er* by HPLC analysis (CHIRALCEL OD column, 90:10 hexane/2-propanol at 240 nm, flow-rate: 0.5 mL/min): retention times; R_t = 17.06 min (major enantiomer, **287e'**) and R_t = 22.54 min (minor enantiomer, *ent*-**287e'**). Spectral data for **287e'**: R_f = 0.41 (3:1 hexane/Et_2O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.77 (t, 3H, *J* = 7.8 Hz), 1.08-1.20 (m, 2H), 1.35-1.53 (m, 2H), 2.31-2.47 (m, 2H), 3.66 (s, 3H), 4.91 (s, 1H), 5.18 (s, 1H), 6.48 (d, 2H, *J* = 8.5 Hz), 6.66 (d, 2H, *J* = 9.0 Hz), 7.27 (t, 1H, *J* = 7.2 Hz), 7.34 (t, 2H, *J* = 7.5 Hz), 7.41 (d, 2H, *J* = 7.0 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 13.67, 22.04, 25.89, 38.85, 55.70, 68.52, 114.41, 114.78, 127.88, 128.23, 129.10, 138.38, 140.37, 152.04, 206.74; IR (thin film) 3390s, 2957vs, 2932s, 2872s, 1714vs, 1513s, 1464s, 1444s, 1242vs, 1179s, 1037s cm^{-1}; HRMS (ESI-TOF) *m/z* 298.1809 [($M+H^+$); calcd. for $C_{19}H_{24}NO_2$: 298.1807]; $[\alpha]_D^{20}$ –84.6° (c 0.93, EtOAc) on 96% *ee* material (HPLC).



286b **287b** **296** **296'**

*(R)-2-cyclohexyl-2-((4-methoxyphenyl)amino)-1-phenylethan-1-one **287b***: α-Iminol **286b** (65 mg, 0.20 mmol) was reacted according to general procedure. Amino ketone **287b** was detected in 53% yield and amino ketone **287b'** was detected in 44% yield by the crude ^{1}H-NMR spectrum. Purification by silica gel chromatography (20 mm × 150 mm column, 5:1 hexanes/Et_2O as eluent, flash column) afforded a mixture of amino ketones **287b** and **287b'** as a yellow oil. The enantiomeric purity of **287b** was determined to be 94:6 *er* by HPLC analysis (CHIRALCEL OD column, 99:1 hexane/2-propanol at 240 nm, flow-rate: 0.5 mL/min): retention times; R_t = 26.76 min (minor enantiomer, *ent*-**287b**) and R_t = 39.73 min (major enantiomer, **287b**). The enantiomeric purity of **287b'** was determined to be 99:1 *er* by HPLC analysis (CHIRALCEL OD column, 99:1 hexane/2-propanol at 240 nm, flow-rate: 0.5 mL/min): retention times; R_t = 31.10 min (major enantiomer, **287b'**) and R_t = 44.25 min (minor enantiomer, *ent*-**287b'**). The reaction with zirconium-Cy_2VANOL complex catalyst afforded amino ketones **287b** and **287b'** both in 99.5:0.5 *er* and 42% yield.

To a 4 mL vial was added the mixture of amino ketones **287b** and **287b'**, FmocCl (103 mg, 0.400 mmol, 2.00 equiv) and $NaHCO_3$ (50 mg, 0.60 mmol, 3.0 equiv) in THF (1.0 mL). The resulting mixture was stirred for 60 h at room temperature, filtered to remove the precipitate and concentrated. A mixture of *N*-Fmoc amino ketone regioismers **296** and **296'** with unconverted amino ketone **287b** was detected in the residue. Purification by

silica gel chromatography (20 mm × 150 mm column, 5:1 hexanes/Et_2O as eluent, flash column) afforded amino ketone **287b** as a yellow oil in 9% yield (5.8 mg, 0.018 mmol).

Spectral data for **287b**: R_f = 0.44 (2:1 hexanes/Et_2O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.07-1.15 (m, 3H), 1.17-1.28 (m, 2H), 1.37 (qd, 1H, *J* = 12.3, 3.6 Hz), 1.50-1.65 (m, 2H), 1.69-1.82 (m, 3H), 3.69 (s, 3H), 4.37 (s, 1H), 4.75 (d, 1H, *J* = 4.5 Hz), 6.65 (d, 2H, *J* = 9.0 Hz), 6.71 (d, 2H, *J* = 9.0 Hz), 7.46 (t, 2H, *J* = 8.0 Hz), 7.57 (t, 1H, *J* = 7.5 Hz), 7.93 (dd, 2H, *J* = 8.2, 1.2 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 26.01, 26.13, 26.38, 27.66, 30.89, 41.81, 55.72, 64.72, 128.27, 128.79, 133.39, 136.12, 142.44, 152.51, 201.83; IR (thin film) 3371s, 2928vs, 2852s, 1681s, 1512vs, 1448s, 1242vs, 1037s cm^{-1}; HRMS (ESI-TOF) *m/z* 324.1932 [($M+H^+$); calcd. for $C_{21}H_{26}NO_2$: 324.1964]; $[\alpha]_D^{20}$ –65.0° (c 1.2, EtOAc) on 99% *ee* material (HPLC).

*(9H-fluoren-9-yl)methyl (R)-(1-cyclohexyl-2-oxo-2-phenylethyl)(4-methoxyphenyl)carbamate **296***: Purification by silica gel chromatography (20 mm × 150 mm column, 2.5:1 benzene/$CHCl_3$ as eluent, flash column) afforded amino ketone **296** as an off-white solid (mp 75-77 °C on 88% *ee* material) in 36% yield (40 mg, 0.073 mmol). The enantiomeric purity of **296** was determined to be 94:6 *er* by HPLC analysis (CHIRALCEL OD column, 85:15 hexane/2-propanol at 240 nm, flow-rate: 0.7 mL/min): retention times; R_t = 21.06 min (minor enantiomer, *ent*-**296**) and R_t = 23.93 min (major enantiomer, **296**).

Spectral data for **296**: R_f = 0.40 (1:1 benzene/$CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.86-0.93 (m, 1H), 1.09-1.38 (m, 4H), 1.56-1.77 (m, 3H), 1.80-1.90 (m, 1H), 1.98-2.05 (m, 2H), 3.81 (s, 3H), 3.95 (t, 1H, *J* = 7.2 Hz), 4.24 (dd, 1H, *J* = 10.5, 7.5 Hz), 4.39 (dd, 1H, *J* = 10.5, 7.5 Hz), 5.76 (d, 1H, *J* = 10.5 Hz), 6.73 (d, 2H, *J* = 9.0 Hz), 6.78 (d, 2H, *J* =

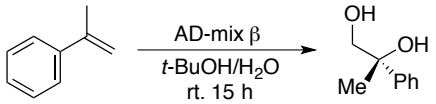
9.5 Hz), 7.00 (d, 1H, *J* = 8.0 Hz), 7.04 (d, 1H, *J* = 7.0 Hz), 7.10 (dt, 2H, *J* = 10.3, 7.6 Hz), 7.29 (t, 2H, *J* = 7.2 Hz), 7.48 (t, 2H, *J* = 7.8 Hz), 7.58 (t, 1H, *J* = 7.2 Hz), 7.64 (d, 2H, *J* = 8.0 Hz), 8.08 (d, 2H, *J* = 7.5 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 25.71, 25.82, 26.47, 29.54, 30.11, 36.56, 46.91, 55.36, 63.90, 67.82, 113.96, 119.75, 119.77, 125.09, 125.20, 126.77, 126.78, 127.50, 128.32, 128.60, 128.89, 130.31, 133.42, 136.80, 141.17, 141.15, 143.50, 143.60, 156.41, 158.94, 196.36; IR (thin film) 2929.2s, 1685s, 1647vs, 1511s, 1449s, 1396s, 1290s, 1248s cm^{-1}; HRMS (ESI-TOF) *m/z* 546.2647 [($M+H^+$); calcd. for $C_{36}H_{36}NO_4$: 546.2644]; $[\alpha]_D^{20}$ +47.0° (c 1.0, EtOAc) on 88% *ee* material (HPLC).

(9H-fluoren-9-yl)methyl (R)-(2-cyclohexyl-2-oxo-1-phenylethyl)(4-methoxyphenyl)carbamate ***296'***: Purification by silica gel chromatography (20 mm × 150 mm column, 2.5:1 benzene/$CHCl_3$ as eluent, flash column) afforded amino ketone **296'** as an off-white solid (mp 70-71 on 90% *ee* material) in 46% yield (37 mg, 0.067 mmol). The enantiomeric purity of **296'** was determined to be 95:5 *er* by HPLC analysis (CHIRALCEL OD column, 85:15 hexane/2-propanol at 240 nm, flow-rate: 0.7 mL/min): retention times; R_t = 40.60 min (minor enantiomer, *ent*-**296'**) and R_t = 44.35 min (major enantiomer, **296'**).

Spectral data for **296'**: R_f = 0.25 (1:1 benzene/$CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.81-0.88 (m, 3H), 1.06-1.76 (m, 6H), 2.13 (d, 1H, *J* = 13.0 Hz), 2.32-2.45 (m, 1H), 3.74 (s, 3H), 4.00 (t, 1H, *J* = 7.8 Hz), 4.17 (t, 1H, *J* = 9.2 Hz), 4.35 (t, 1H, *J* = 9.0 Hz), 6.16 (s, 1H), 6.66 (d, 2H, *J* = 8.0 Hz), 6.94 (d, 2H, *J* = 6.5 Hz), 6.98-7.06 (m, 3H), 7.07 (t, 1H, *J* = 7.2 Hz), 7.12-7.19 (m, 4H), 7.27-7.32 (m, 3H), 7.65 (t, 2H, *J* = 6.0 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 25.18, 25.70, 25.84, 27.95, 29.90, 46.83, 48.38, 55.32, 67.75, 69.72, 113.35, 119.71, 119.74, 125.27, 125.44, 126.72, 126.81, 127.44, 127.50, 128.32, 128.51,

131.03, 131.97, 132.49, 141.10, 141.17, 143.56, 143.82, 156.13, 158.46, 210.45; IR (thin film) 2930s, 1682s, 1646vs, 1511s, 1450s, 1396s, 1247s cm^{-1}; HRMS (ESI-TOF) *m/z* 546.2647 [$(M+H^+)$; calcd. for $C_{36}H_{36}NO_4$: 546.2644]; $[\alpha]_D^{20}$ –43.4° (c 1.0, EtOAc) on 90% *ee* material (HPLC).

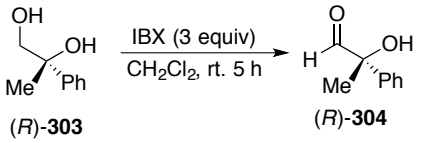
6.5.3 Preparation of Enantiometic Pure α-Iminol (*R*)-286c



302 (*R*)-**303**

*(R)-2-phenylpropane-1,2-diol (R)-**303***:[30] To a 250 mL round-bottomed flask, AD-mix β (14.0 g, 10 mmol), *tert*-butyl alcohol (50 mL) and water (50 mL). Stirring a t room temperature produced two clear phases; the lower aqueous phase appears bright yellow. The mixture was cooled to 0 °C where upon some of the dissolved salts precipitated. α-Methylstyrene was added at once, and the heterogeneous slurry was stirred vigorously at 0 °C for 12 h (progress was monitored by TLC or GLC). While the mixture was stirred at 0 °C, Na_2SO_3 (1.5 g) was added and the mixture was allowed to warm to room temperature with stirring for 30 min. CH_2Cl_2 (10 mL) was added to the reaction mixture, and after separation of the layers, the aqueous phase was further extracted with the CH_2Cl_2 (5 mL × 3). The combined organic extracts were dried over $MgSO_4$ and concentrated to give the diol (*R*)-**303** and the ligand. This crude product was purified by silica gel chromatography (2:1 hexanes/EtOAc as eluent, flash column) to afford the 1,2-diol (*R*)-**303** as a colorless liquid in 40% yield (603 mg, 3.96 mmol). The enantiomeric purity of (*R*)-**303** was determined to be 97% *ee* by HPLC analysis (CHIRALCEL AS column, 95:5 hexane/2-propanol at 240 nm, flow-rate: 0.5 mL/min): retention times; R_t = 7.76 min (minor enantiomer, (*S*)-**303**) and R_t = 10.43 min (major enantiomer, (*R*)-**303**).

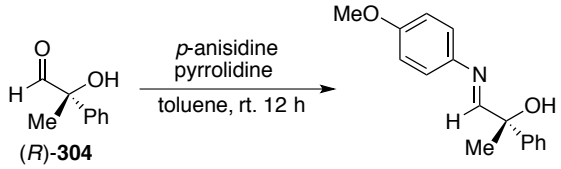
Spectral data for (*R*)-**303**: R_f= 0.27 (1:1 hexane/EtOAc); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.51 (s, 3H), 1.88-1.91 (br, 1H), 2.63 (s, 1H), 3.61 (dd, 1H, *J* = 11.2, 8.2 Hz), 3.77 (dd, 1H, *J* = 10.8, 4.8 Hz), 7.26 (t, 1H, *J* = 7.0 Hz), 7.35 (t, 2H, *J* = 7.5 Hz), 7.43 (d, 2H, *J* = 8.0 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 26.00, 71.06, 74.81, 125.04, 127.18, 128.42, 144.90; $[\alpha]_D^{20}$ –3.2° (c 1.0, EtOH) on 97% *ee* material (HPLC).



(*R*)-**303** (*R*)-**304**

*(R)-2-hydroxy-2-phenylpropanal (R)-**304***:[31] To a solution of 1,2-diol (*R*)-**303** (484 mg, 3.18 mmol) in CH_2Cl_2 (16 mL) was added IBX (2.67 g, 9.54 mmol, 3.00 equiv). After stirring at 40 °C for 8 h, the reaction mixture was filtered off under reduced pressure and the filtrate was concentrated in *vacuo*. The residue was purified by silica chromatography (5:1 hexanes/EtOAc as eluent, flash column) to give hydroxyl aldehyde (*R*)-**304** as a colorless oil in 66% yield (315 mg, 2.10 mmol).

Spectral data for (*R*)-**304**: R_f= 0.53 (2:1 hexane/EtOAc); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.69 (s, 3H), 3.84 (s, 1H), 7.32 (t, 1H, *J* = 7.2 Hz), 7.39 (t, 2H, *J* = 7.0 Hz), 7.45 (d, 2H, *J* = 7.5 Hz), 9.54 (d, 1H, *J* = 1.0 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 23.8, 78.9, 125.5, 128.1, 128.8, 139.4, 200.1; $[\alpha]_D^{20}$ –152.3° (c 0.5, $CHCl_3$) on 97% *ee* material (HPLC).

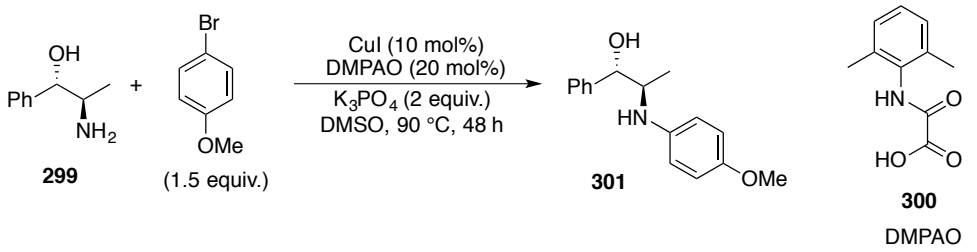


(*R*)-**304** (*R*)-**286c**

*(R)-1-((4-methoxyphenyl)imino)-2-phenylpropan-2-ol (R)-**286c***: Hydroxy aldehyde (*R*)-**304** (310 mg, 2.06 mmol) was reacted with *p*-anisidine (279 mg, 2.27 mmol, 1.10 equiv) and pyrrolidine (34 μL, 0.41 mmol, 20 mol%) in toluene (6.0 mL) according to the

second step of general procedure in section 6.5.1. Purification by a short flash column chromatography with 6:1:0.1 hexanes/EtOAc/Et_3N as eluent afforded α-iminol (*R*)-**286c** as an off-white solid (mp 61-65 °C on 95% *ee* material) in 71% yield (373 mg, 1.46 mmol). The enantiomeric purity of (*R*)-**286c** was determined to be 95% *ee* by HPLC analysis (CHIRALCEL AS column, 95:5 hexane/2-propanol at 240 nm, flow-rate: 0.5 mL/min): retention times; R_t = 25.57 min (minor enantiomer, (*S*)-**286c**) and R_t = 34.84 min (major enantiomer, (*R*)-**286c**). $[\alpha]_D^{20}$ –63.8° (c 1.0, EtOAc) on 95% *ee* material (HPLC).

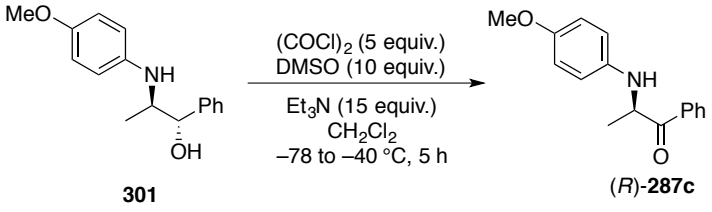
6.5.4 Preparation of Enantiometic Pure Amino ketones (*R*)-287c and (*R*)-287c'



(1S,2R)-2-((4-methoxyphenyl)amino)-1-phenylpropan-1-ol ***301***: The ligand 2-(*N*-(2,6-dimethylphenyl)amino)-2-oxoacetic acid **300** was prepared according to the procedure reported in the literature.[31] An oven-dried Schlenk tube was charged with CuI (19 mg, 0.10 mmol), DMPAO (39 mg, 0.20 mmol), (+)-norephedrine **299** (151 mg, 1.00 mmol), 4-bromoanisole (188 μL, 1.50 mmol) and K_3PO_4 (425 mg, 2.00 mmol) in DMSO (1.0 mL). After the tube was evacuated and backfilled with argon, the reaction mixture was stirred at 90 °C for 48 h. When amino alcohol **299** was consumed, water was added and the mixture was extracted with EtOAc. The organic layer was dried over Na_2SO_4 and evaporated. The residue was purified by silica gel chromatography (5:1 hexanes/EtOAc

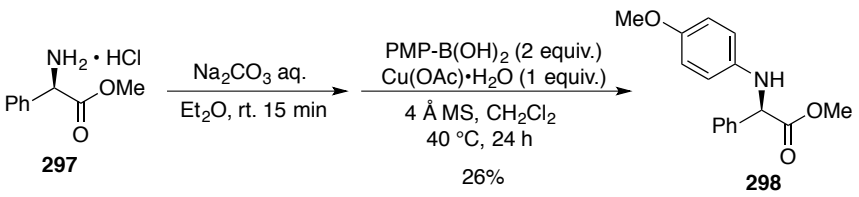
as eluent, flash column) to give the desired product **301** as an off-white solid (mp 62-63 °C on 99% *ee* material) in 59% yield (151 mg, 0.587 mmol).

Spectral data for **301**: R_f= 0.44 (2:1 hexane/EtOAc); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.97 (d, 3H, *J* = 7.0 Hz), 2.50 (s, 1H), 3.35-3.47 (br, 1H), 3.60-3.70 (m, 1H), 3.74 (s, 3H), 4.94 (d, 2H, *J* = 2.5 Hz), 6.68 (d, 2H, *J* = 8.5 Hz), 6.79 (d, 2H, *J* = 9.5 Hz), 7.27 (hex, 1H, *J* = 4.3 Hz), 7.36 (d, 4H, *J* = 4.5 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 14.20, 55.67, 55.75, 74.12, 114.96, 115.84, 125.93, 127.34, 128.27, 141.04, 141.40, 152.68; $[\alpha]_D^{20}$ –74.5° (c 1.0, CH_2Cl_2) on >99% *ee* material (HPLC).



301 (*R*)-**287c**

(R)-2-((4-methoxyphenyl)amino)-1-phenylpropan-1-one ***287c***: To a solution of oxalyl chloride (126 μL, 1.46 mmol, 5.00 equiv) and 3 Å MS in CH_2Cl_2 (0.30 mL) at –78 °C under N_2 was added dropwise a solution of DMSO (210 μL, 2.93 mmol, 10.0 equiv) in CH_2Cl_2 (0.30 mL). After 15 min a solution of the alcohol **301** (76 mg, 0.30 mmol) in CH_2Cl_2 (0.90 mL) was slowly added dropwise. The resulting solution was warmed up to –40 °C and stirred for 30 min. Et_3N (0.61 mL, 4.4 mmol, 15 equiv) was then added dropwise at –78 °C. The reaction was stirred 30 min and then slowly allowed to warm to room temperature. Saturated $NaHCO_3$ aq. was added and the mixture was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and evaporated. The residue was purified by silica gel chromatography (6:1 hexanes/EtOAc as eluent, flash column) to give the desired product (*R*)-**287c** as a yellow oil in 100% yield (75 mg, 0.29 mmol). $[\alpha]_D^{20}$ +39.4° (c 1.0, EtOAc) on >99% *ee* material (HPLC).

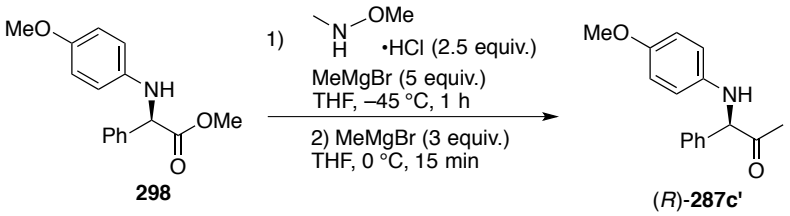


Methyl (R)-2-((4-methoxyphenyl)amino)-2-phenylacetate ***298***:[32] To a solution of (*R*)-2-phenylglycine methyl ester hydrochloride **297** (2.02 g, 10.0 mmol) in Et_2O was added Na_2CO_3 aq. (5.0 mL, 2 *M*, 15 mmol) with vigorous stirring for 15 min. The organic layer was separated and the aqueous layer was extracted with Et_2O. The combined organic phase was dried over $MgSO_4$ and concentrated in *vacuo* to afford a colorless liquid as the free amino ester.

A slurry of (*R*)-2-phenylglycine methyl ester, 4-methoxyphenylboronic acid (4.56 g, 30 mmol) and anhydrous $Cu(OAc)_2$ (2.00 g, 10.0 mmol) [addition of a tertiary amine such as triethylamine or pyridine (2-3 equiv) is likely to increase the yield] in CH_2Cl_2 (50 mL) was stirred at room temperature for 24-48 h. The progress of the reaction was monitored by TLC. The products were isolated by direct flash column chromatography of the crude reaction mixture with pre-absorption on silica gel with 4:1 hexanes/Et_2O as the eluent. The coupling product **298** was obtained as a yellowish liquid in 26% yield (714 mg, 2.63 mmol).

Spectral data for **298**: R_f = 0.59 (1:1 hexane/Et_2O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 3.69 (s, 3H), 3.71 (s, 3H), 4.60-4.72 (br, 1H), 5.01 (s, 1H), 6.52 (d, 2H, *J* = 9.0 Hz), 6.71 (d, 2H, *J* = 9.5 Hz), 7.29 (t, 1H, *J* = 7.5 Hz), 7.34 (t, 2H, *J* = 7.2 Hz), 7.47 (d, 2H, *J* = 7.0 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 52.70, 52.63, 61.58, 114.70, 114.78, 127.23, 128.23, 128.82, 137.72, 140.12, 152.44, 172.52; IR (thin film) 3387s, 2952s, 2835s, 1736vs, 1606s, 1513vs, 1505vs, 1450s, 1245vs, 1177s, 1033s, 1013s cm^{-1}; HRMS (ESI-TOF) *m/z*

272.1287 [(M+H$^+$); calcd. for $C_{16}H_{18}NO_3$: 272.1291]; $[\alpha]_D^{20}$ –3.0° (c 1.0, CH_2Cl_2) on >99% *ee* material (HPLC).



(R)-1-((4-methoxyphenyl)amino)-1-phenylpropan-2-one ***287c'***:[29] To a 25 mL flame dried Schleck flask was added *N*,*O*-dimethylhydroxyamine hydrochloride (200 mg, 2.06 mmol, 2.50 equiv) and THF (4.0 mL) at –45 °C for 5 min in N_2 atmosphere. Methylmagnesium bromide (1.37 mL, 3 *M*, 4.11 mmol, 5.00 equiv) was added in dropwise and the resulting solution was stirred at the same temperature for another 10 min. A solution of amino ester **298** (223 mg, 0.822 mmol) in THF (1.60 mL) was added in dropwise and the mixture was stirred at the same temperature for another 1 h before being quenched by saturated NH_4Cl aq. The reaction mixture was warmed up to room temperature and extracted with EtOAc. The combined organic phase was dried over Na_2SO_4 and purified by chromatography with a short column on silica gel, 2:1 hexanes/EtOAc as the eluent to remove the excess *N*,*O*-dimethylhydroxyamine hydrochloride. The crude Weireb amide was afforded as a pale yellow solid and used in the next step without further purification.

To a 25 mL flame dried Schleck flask was added the Weireb amide (159 mg, 0.529 mmol) in THF (2.50 mL). The solution was cool down to 0 °C for 5 min and methylmagnesium bromide (0.53 mL, 3 *M*, 1.59 mmol, 3.00 equiv) was added in dropwise. The resulting solution was stirred at 0 °C for 15 min before being quenched by saturated NH_4Cl aq. The reaction mixture was warmed up to room temperature and extracted with EtOAc. The combined organic phase was dried over Na_2SO_4. Purification

by a silica gel column chromatography with 5:1 hexanes/Et_2OAc as eluent afforded amino ketone (*R*)-**287c'** as a white solid in 41% yield (86 mg, 0.36 mmol). The enantiomeric purity of (*R*)-**287c'** was determined to be 91% *ee* by HPLC analysis (CHIRALCEL AS column, 80:20 hexane/2-propanol at 240 nm, flow-rate: 0.5 mL/min): retention times; R_t = 26.65 min (minor enantiomer, (*S*)-**287c'**) and R_t = 37.28 min (major enantiomer, (*R*)-**287c'**). $[\alpha]_D^{20}$ –194.3° (c 1.0, EtOAc) on 91% *ee* material (HPLC).

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