

CATALYTIC ASYMMETRIC AZIRIDINATIONS AND THEIR APPLICATIONS

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ABSTRACT

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The catalytic asymmetric aziridination of imines and diazo compounds mediated by boroxinate catalysts derived from the VANOL and VAPOL ligands was investigated with chiral imines derived from α -methylbenzyl amine and various aldehydes. The matched case for *cis*-aziridines from ethyl α -diazo acetate involves the (*R*)-imine with the (*S*)-ligand whereas the matched case for *trans*-aziridines from *N*-phenyl α -diazo acetamide involves the (*R*)-imines with the (*R*)-ligand for imines from benzaldehyde and butyraldehyde, and the (*R*)-imines with the (*S*)-ligand for imines derived from the bulkier aliphatic aldehydes, pivaldehyde and cyclohexane carboxaldehyde. Optically pure aziridines could be obtained in good yields and with high diastereoselectivity, which could be converted to α - or β -amino ester derivatives *via* hydrogenolysis.

Extension of our protocol for di-substituted aziridine synthesis to tri-substituted aziridine proved to be challenging. However, it was realized by employing *N*-Boc imines and α -diazo carbonyl compounds in which the diazo carbon was disubstituted. The highly reactive α -diazo esters give only moderate yields, but the more slowly reacting α -diazo-*N*-acyloxazolidinones give much

higher yields. The optimal ligand is VANOL that can provide a catalyst for the stereocomplimentary approaches to tri-substituted aziridines: *trans*-isomers *via* aziridination and *cis*-isomers *via* aziridination/alkylation.

Having established a very efficient catalytic asymmetric synthesis of aziridines, the next logical step would be to develop its potential in organic synthesis. The ring expansion of aziridine-2-carboxylic acids has significant potential for the synthesis of heterocycles and the type of heterocycles proved to be dependent on the structure of the aziridine-2-carboxylic acids. When there is alkyl group on the C2 position and an aromatic group on the C3 position, the reaction of aziridine-2-carboxylic acids with $(\text{COCl})_2$ provides *N*-carboxyanhydrides whereas morpholine-2,3,5-triones are formed if there is an aromatic group on the C3 position with a hydrogen on C2. Curiously, β -lactams are formed in a stereoselective manner when aziridine-2-carboxylic acids with an alkyl group present on the C3 position is treated with $(\text{COCl})_2$. Finally, it proved possible to convert the aziridine-2-carboxylic acids with an aromatic group on the C3 position to β -lactams with a Vilsmeier reagent.

To
my parents and my husband

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CHAPTER ONE

CHIRAL AZIRIDINES IN ORGANIC CHEMISTRY

1.1 Introduction

Aziridines are saturated strained three-membered heterocycles containing a nitrogen atom. They have attracted great interest to chemists for years because of their easy transformation into pharmacologically and biologically active compounds,¹ their appearance as subunits in naturally occurring substances,² their antitumor and antibiotic activities,³ their use as chiral ligands⁴ and auxiliaries⁵ in asymmetric synthesis⁶ and their application as chiral building blocks for the construction of various nitrogen-containing compounds, such as chiral amines, amino acids, amino alcohols, alkaloids, β -lactam antibiotics etc.⁷

Due to approximate 27 kcal/mol high strain energy, aziridines can undergo ring cleavage reaction with a range of nucleophiles or cycloaddition reactions with dipolarphiles. Aziridines, which are extremely important synthetic building blocks, are the nitrogen equivalent to epoxides.⁸ However, they are less widely used in synthesis than their oxygen counterparts, partly because there are fewer efficient methods for aziridinations than epoxidations. This is particularly true when enantioselective methods are considered.

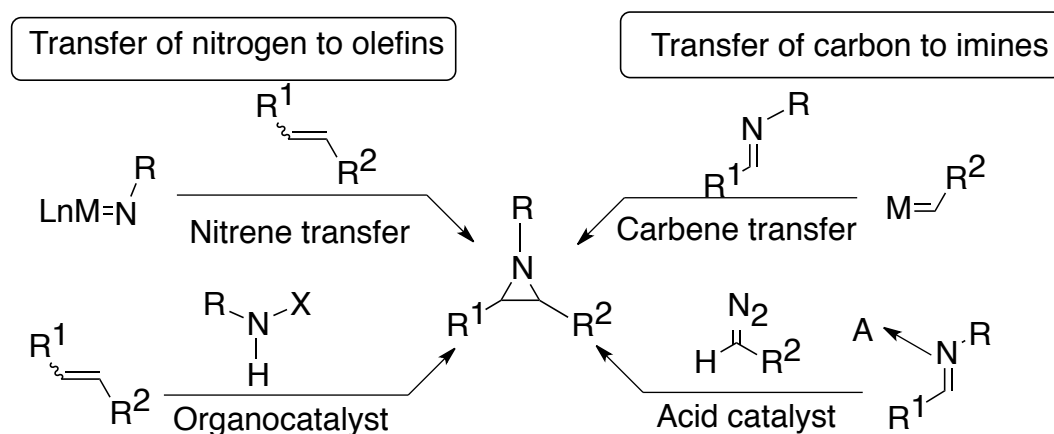
1.2 Main approaches towards the synthesis of chiral aziridines

As most optically active aziridines are prepared from 'chiral pool', asymmetric synthesis of chiral aziridines can be obtained either based on the use of chiral

auxiliaries or by catalytic asymmetric methods. Asymmetric aziridination based on the use of chiral auxiliaries was reviewed by Sweeney in 1997.² On the other hand, asymmetric aziridination based on chiral catalysts was previously reviewed by Müller and Fruit in 2003, covering the literature till the end of 2002.⁹ The asymmetric synthesis of aziridines based on both methods has been reviewed by Pellissier in 2010, covering the literature till the end of 2009.¹⁰

The main approaches to the synthesis of chiral aziridines can be classified as transfer of nitrogen to olefins, transfer of carbon to imines, cyclization reactions, addition across the carbon-nitrogen double bond of azirines, reactions of ylides, aza-Darzens approaches and miscellaneous reactions such as ring contraction.¹⁰ Among those, catalytic asymmetric aziridination reactions have been developed based on two approaches: transfer of nitrogen to olefins and transfer of carbon to imines (Scheme 1.1). Specifically, transfer of nitrogen to olefins could fall into two categories: the metal nitrene transfer to an olefin (metal nitrene approach) and organocatalyst-mediated addition of nitrene surrogate to an activated olefin. As to the transfer of carbon to imines, the aziridine ring could be constructed from transfer of a metal carbene to an imine and the reaction of a diazo compound with an acid-activated imine.

Scheme 1.1 Approaches for catalytic asymmetric aziridination reactions



The publication of successful efforts of finding catalytic asymmetric nitrene transfer methods by using different organometallic catalysts for the enantioselective synthesis of aziridines began in the 1990s. Evans,^{11a} Jacobsen^{11b} and Katsuki,^{11c} and their coworkers reported the catalytic asymmetric aziridination of olefins with [*N*-4-toluenesulfonyl]imino]phenyliodinane as a nitrene source. The second approach involves the chiral organocatalyst-mediated addition of a nitrene surrogate to electron-deficient olefins (α,β -unsaturated carbonyl compounds) and has just appeared in the literature.¹² The asymmetric transfer of a metal carbene to an imine has not been fully developed yet. The only real success with this approach involves the Rh-catalyzed asymmetric generation of aziridine from chiral in situ generated sulfur ylides and imines by diazo decomposition developed by Aggarwal and coworkers.¹³ In this method, however, the stereogenic step does not involve the transfer of carbon to the imine from a metal carbene complex, but rather from a chiral sulfur ylide. The final approach involves the activation of an imine by a chiral Lewis or Brønsted

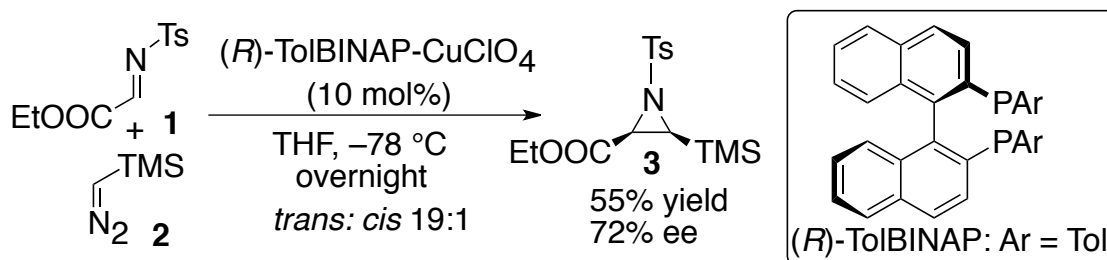
acid towards reaction with a diazo compound. It has been an active field in recent years and the focus of our studies in our research group. The following will provide an overview of catalytic asymmetric reactions of imines with diazo compounds catalyzed by Lewis or Brønsted acids.

1.2.1 Lewis acid catalyzed catalytic asymmetric aziridinations

Since the pioneering work of Brookhart and Templeton^{14a} and of Jørgensen^{14b} and their co-workers who reported that simple non-chiral Lewis acids such as $\text{BF}_3 \cdot \text{OEt}_2$ and $\text{Yb}(\text{OTf})_3$ could catalyze the formation of aziridines from imines and ethyl diazoacetate (EDA), the asymmetric catalytic version has been developed. The reaction of EDA with imines mediated by a Lewis acid is normally selective for *cis*-aziridines.

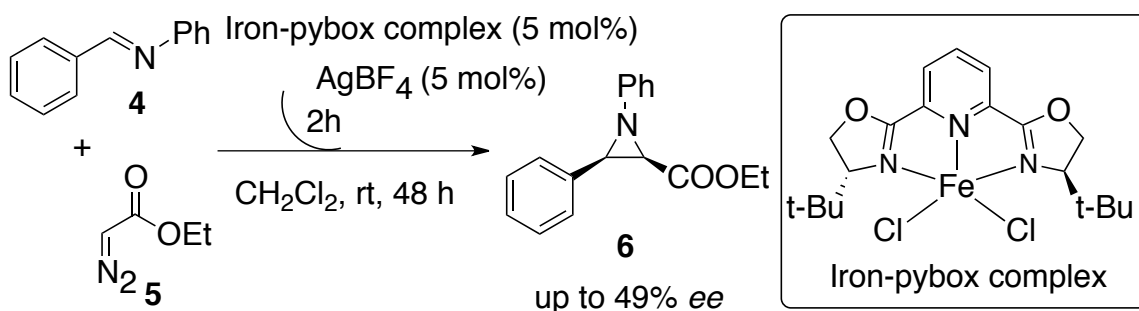
Jørgensen's group reported in 1999 the first catalytic diastereo- and enantio-selective aziridination of imine **1** derived from α -ethyl glyoxylate with trimethylsilyldiazomethane **2** in which the imine is activated by a chiral Lewis acid complex (Scheme 1.2). Chiral Tol-BINAP in combination with CuClO_4 in particular can catalyze the reaction, leading to the *cis*-aziridine **3** with up to 72% ee, the highest asymmetric induction so far obtained in the Lewis acid catalyzed aziridination.

Scheme 1.2 Lewis acid catalyzed aziridination of imine **1** and diazo **2**



In 2004, Hossain et al reported the enantioselective reaction of EDA **5** with *N*-aryl imine **4** catalyzed by iron-pybox complexes as Lewis acids.¹⁵ When AgSbF₆ was used as initiator, the reaction afforded the corresponding *cis*-aziridine **6** in enantioselectivity of up to 49% ee in the presence of iron-pybox depicted in Scheme 1.3. The role of Ag⁺ ion was assumed to create an open site for the coordination of the imine to the Lewis acid.

Scheme 1.3 Lewis acid catalyzed aziridination reaction

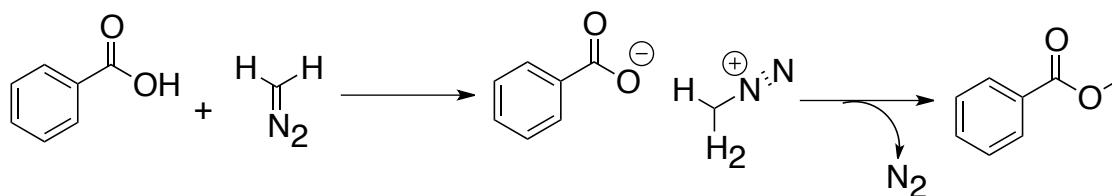


1.2.2 Brønsted acid catalyzed asymmetric aziridinations

Chiral Brønsted acids, such as dicarboxylic acids and phosphoric acid derivatives, have recently been employed as catalysts for the reactions of imines and diazo compounds. A diazo compound is considered to be an unlikely candidate for the development as a donor in transformations promoted or catalyzed by a Brønsted acid. Compared with Lewis acid activation, a Brønsted

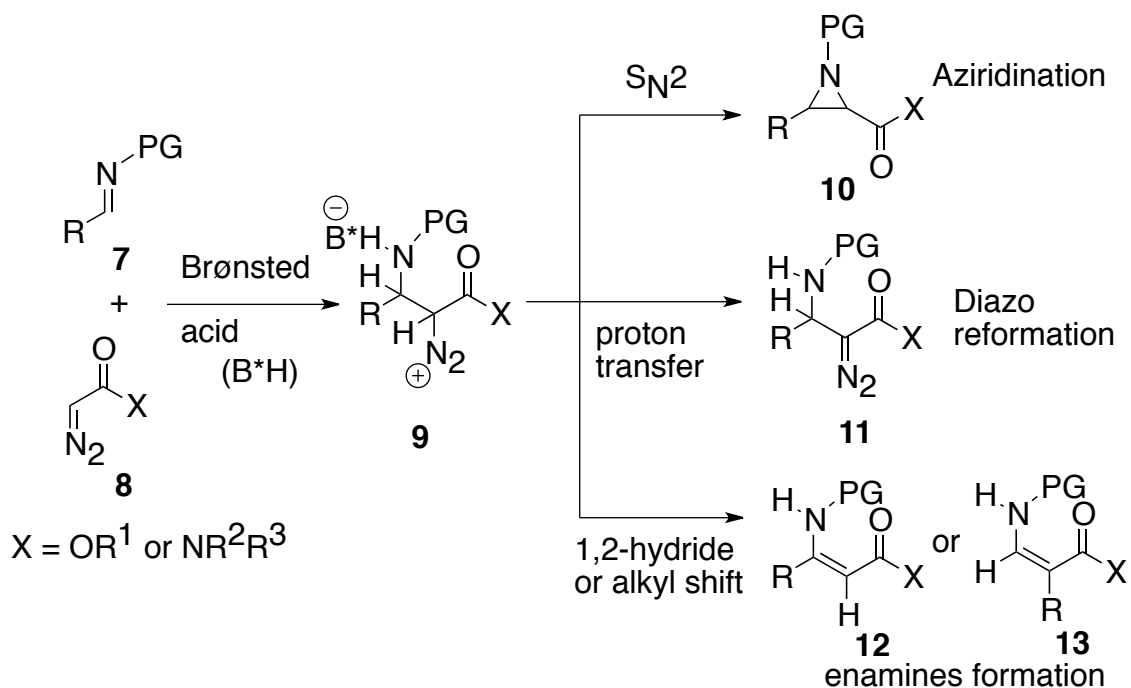
acid activation mode in the formation of aziridines has the additional challenge of avoiding competitive protonative decomposition of a diazo compound that leads to alkylation (Scheme 1.4) or diazo coupling.¹⁶

Scheme 1.4 Protonative decomposition of the diazoalkane.



The mechanism for the reaction of imine **7** and diazo compound **8** involves the addition of the diazo 'ylide' to the catalyst bound imine, thus leading to a discrete diazonium intermediate **9** (Scheme 1.5). Subsequent nucleophilic substitution and loss of N₂ furnishes the aziridine **10**. Use of some catalysts, for reasons that are not clear, leads to proton loss to reform the diazo functionality. A 1,2-shift of an alkyl group or a hydride gives rise to the formation of some enamine by-products **12** and **13**.¹⁶ Aziridine formation will be the focus of the following discussions.

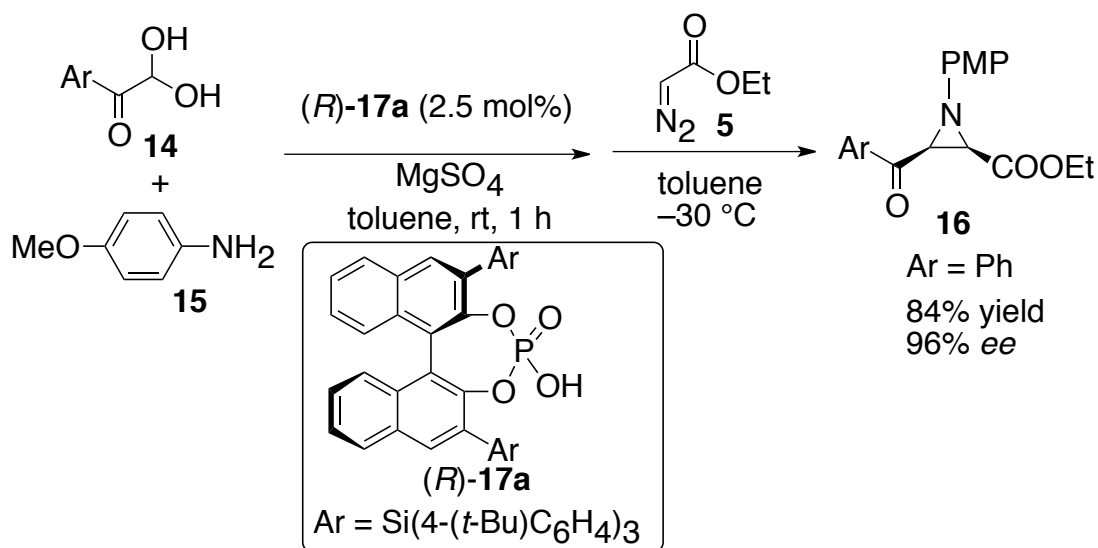
Scheme 1.5 Divergent evolution of a diazonium intermediate to aziridines, α -diazo esters and enamine by-products in the addition of diazo compounds to aldimines



In 2009, Akiyama et al. reported the aziridination reaction using EDA **5** and 4-methoxyphenyl(PMP)-protected imine.¹⁷ The addition of EDA to the electron-deficient aldimine generated in situ from *p*-methoxyaniline **15** and phenyl glyoxal hydrate **14** was catalyzed by a chiral phosphoric acid (*R*)-**17a** and gave aziridine **16** in a good yield with high diastereo- and enantio-selection. It is also interesting to note that the structure of the chiral phosphoric acid affected not only the degree but also the sense of enantioselectivity. Introduction of a bulky substituent to the 4-position of aryl groups in the 3,3'-position of the BINOL ligand significantly improved the enantioselectivity. Optimization of the reaction provided a two-step, one-pot method (Scheme 1.6). Although the reaction shows a good

tolerance towards electron-rich and electron-poor aryl groups of **14**, the substrate is still limited to aryl glyoxal.

Scheme 1.6 Akiyama's one pot procedure

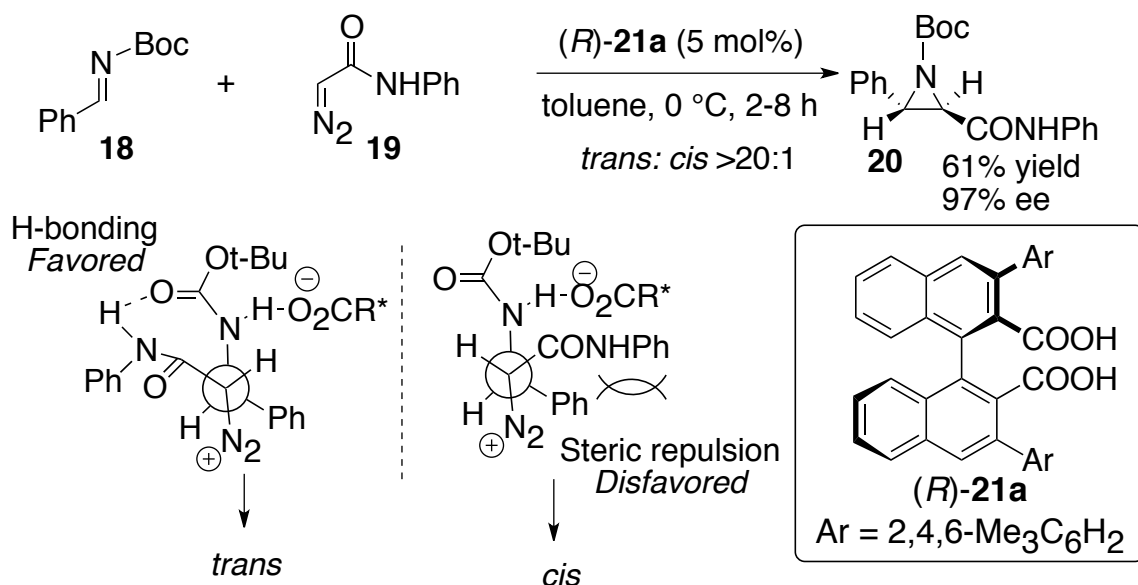


Unlike the proceeding aziridinations, which are *cis*-selective, Maruoka's group reported, in 2008, a *trans*-selective asymmetric aziridination of diazoacetamide **19** and *N*-Boc imine **18** mediated by an axially chiral dicarboxylic acid.¹⁸ 3,3'-dimesityl substituted dicarboxylic acid (R) -**21a** depicted in Scheme 1.7 was identified as the optimal catalyst and provided the corresponding *trans*-aziridine **20** exclusively in 61% yield and 97% ee. A proposed explanation of the *trans* selectivity involves hydrogen bonding between the amide N-H and Boc carbonyl group as indicated in the Newmann projection in Scheme 1.7.

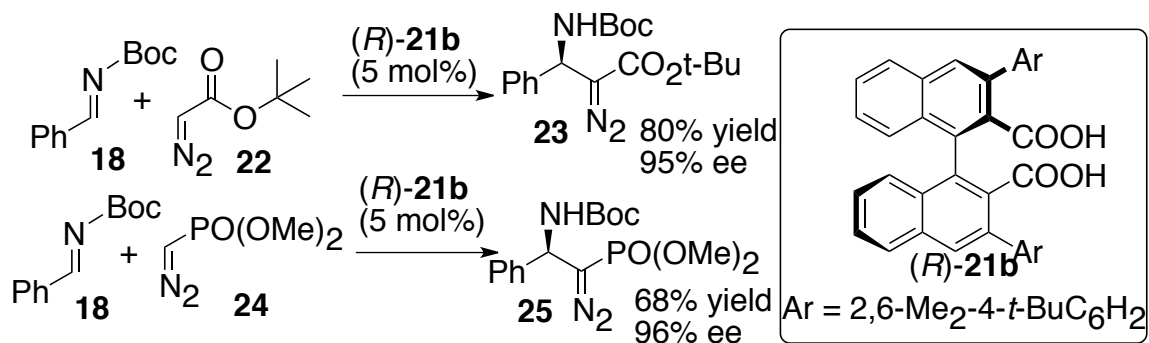
In contrast to this *trans*-aziridination with diazoacetamide **19** with catalyst **21a**, the closely related catalyst **21b** does not give aziridine products with diazoacetates (Scheme 1.8). Instead, this reaction leads to the α -diazo ester **23**.¹⁹ Good enantioselection is observed within a range of electronically varied

aryl aldimines. They further extended this Mannich reaction of *N*-Boc imines to dimethyl diazomethylphosphonate **24**, as a means of creating the optically enriched β -aminophosphonate derivative **25**. Based solely on the general mechanism presented in Scheme 1.5, it is still not clear why the putative diazonium intermediate **9** evolves to the *trans*-aziridine product **10** instead of the diazo compound **11** when a diazoacetamide is used.

Scheme 1.7 Bis(carboxylic acid) catalyzed enantioselective *trans*-aziridination reaction with α -diazoacetamide

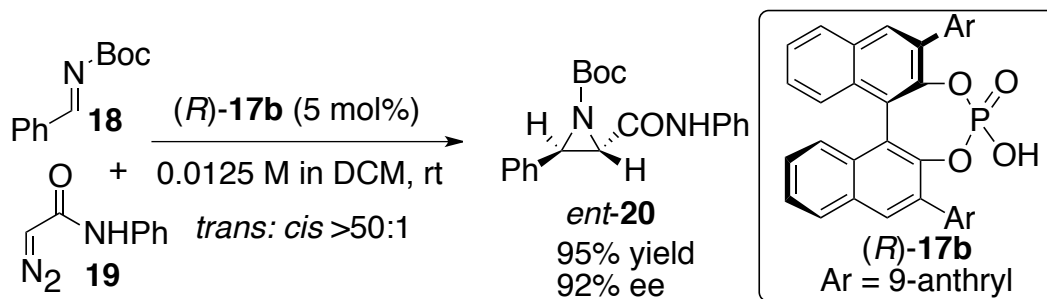


Scheme 1.8 Bis(carboxylic acid) catalyzed enantioselective Mannich additions of α -diazo esters



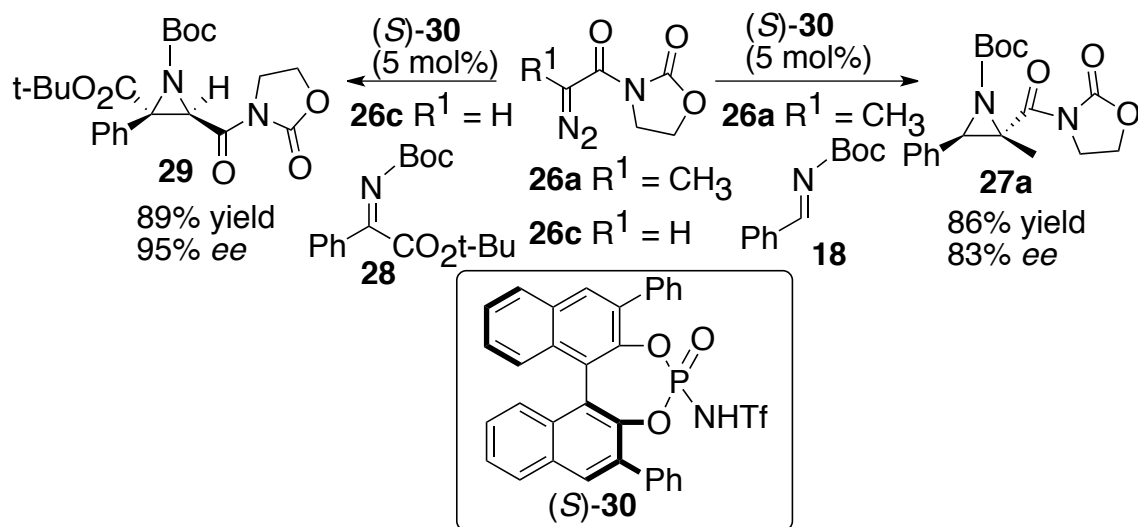
After the report of Maruoka's *trans*-aziridination system, a clean and fast *trans*-aziridination of diazoacetamides with *N*-Boc-imines, catalyzed by chiral phosphoric acid (*R*)-**17b** in dichloromethane (DCM) at room temperature was developed by Zhong's group (Scheme 1.9).²⁰ Excellent yields, diastereoselectivities, chemoselectivities and enantioselectivities were achieved in the reaction. *N*-Cbz protected imines could also be employed in this aziridination reaction, affording *trans*-aziridines in high yield and excellent enantioselectivity.

Scheme 1.9 Phosphoric acid catalyzed *trans*-aziridination system developed by Zhong and coworkers.



The significant extension of the Brønsted acid catalyzed reaction of diazoacetates and imines to give aziridines was the extension of this reaction to trisubstituted aziridines by Maruoka in 2011.²¹ One year after their discovery of the synthesis of trisubstituted aziridines based on a chiral auxiliary,²² Maruoka's group has reported the general procedure for the catalytic asymmetric synthesis of trisubstituted aziridines in the presence of the strong chiral Brønsted acid, *N*-triflyl phosphoramidate (*S*)-**30**.

Scheme 1.10 Maruoka's catalytic asymmetric system for trisubstituted aziridines



Two possible substrate combinations: α -substituted α -diazocarbonyl compound **26a** / aldimine **18** and α -unsaturated α -diazocarbonyl compound **26c** / ketimine **28** serve the goal of providing a catalytic asymmetric synthesis of trisubstituted aziridines as shown in Scheme 1.10. Noteworthy is the observation that in contrast to the Brønsted acid catalyzed asymmetric synthesis of disubstituted aziridines, wherein an axially chiral dicarboxylic acid and an axially chiral monophosphoric acid worked efficiently, the reaction of *N*-Boc imines and α -substituted diazocarbonyls could not be facilitated by these catalysts even at room temperature.

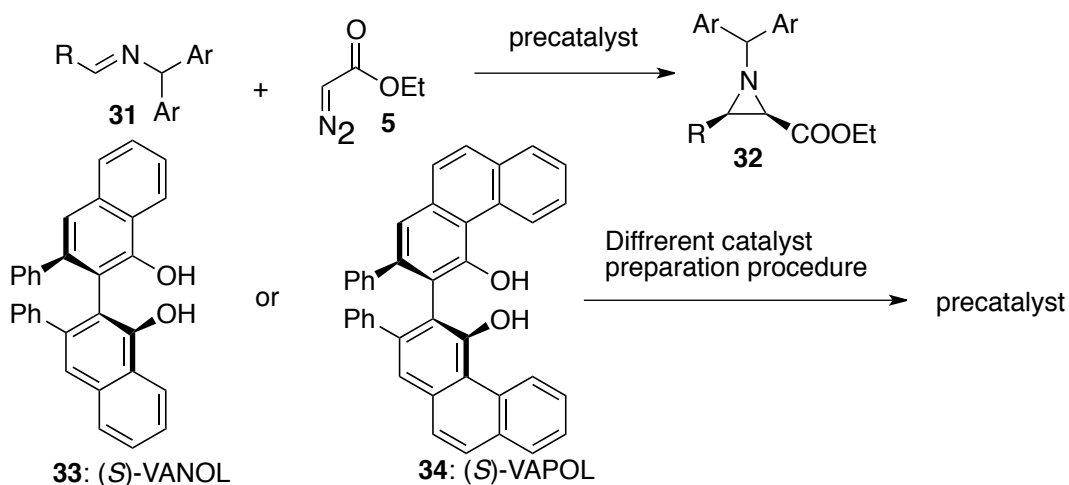
1.2.3 The catalytic asymmetric Wulff aziridination reaction

The research in our group is based on the use of vaulted chiral biaryl ligands, VANOL **33** and VAPOL **34**. Catalysts derived from these ligands have provided some of the most successful contributions to date for the enantioselective aziridination of imines with diazo compounds.¹⁰

1.2.3.1 Protocols for *cis*- and *trans*-aziridination in our group

In 2000, we reported the very first general catalytic asymmetric aziridination that gave good yields and ee's of *cis*-aziridines **32** from the reaction of imine **31** with a benzhydryl group as the *N*-protecting group and EDA **5** with a catalyst prepared from either the VANOL or VAPOL ligand and B(OPh)₃ (Scheme 1.11).²³ The detailed discovery of the original catalytic system can be found in a review.²⁴

Scheme 1.11 Catalytic asymmetric aziridination of aldimines with EDA mediated by VANOL and VAPOL ligands.



The vaulted chiral biaryls, VANOL and VAPOL have both proven to be superior ligands for the reaction. In contrast, the linear chiral biaryls, BINOL and its derivatives give poor to moderate inductions.²⁵

Table 1.1 Averaged ligand and *N*-substituent effects over nine imines with aromatic and aliphatic substituents R

<i>N</i> -substituent	Ligand	Average % yield	Average % ee
Benzhydryl	VAPOL	70	88
	VANOL	77	88
DAM	VAPOL	73	88
	VANOL	78	85
BUDAM	VAPOL	88	95
	VANOL	90	94
MEDAM	VAPOL	92	97
	VANOL	91	96

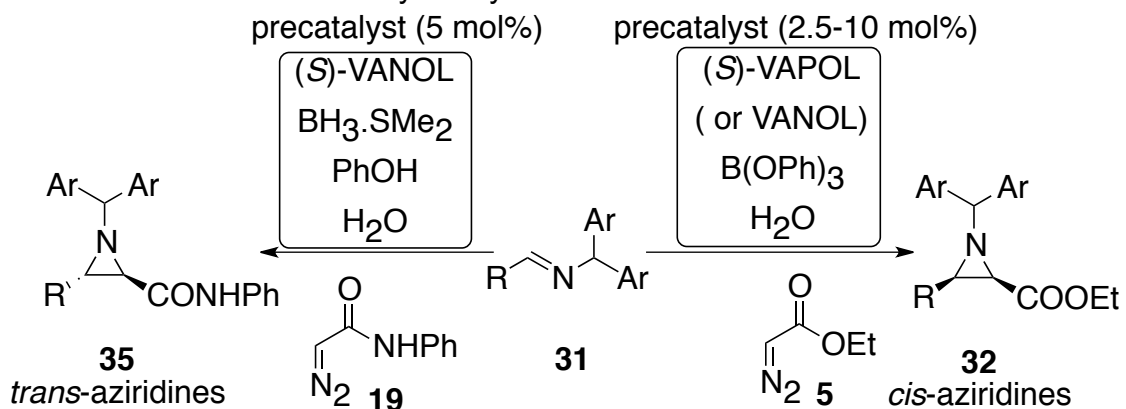
Over the years, we have focused on the optimization of the yields and asymmetric inductions in this reaction. Higher yields and enantioselectivities have been realized by the fine-tuning of the nitrogen substituent of the imine. The catalytic asymmetric AZ reaction with imines derived from the dianisylmethyl (DAM) amine^{26b} is as effective as that with benzyhydryl imines^{26a}. The 3,5-di-*tert*-butyldianisylmethyl (BUDAM) *N*-substituent gives exceptionally high asymmetric inductions in the asymmetric aziridinations for imines from aryl aldehydes.^{26c} Imines derived from tetra-methyldianisylmethyl (MEDAM) amine were found to be superior to the benzyhydryl and BUDAM imines especially for

imines derived from aliphatic aldehydes.^{26d} Comparative data for the VAPOL and VANOL ligands over nine imine substrates with four different nitrogen protecting groups on the imines is listed in Table 1.1. The DAM, BUDAM and MEDAM group have the advantage that they can be cleaved from the aziridines with a strong Brønsted acid without ring opening. Triflic acid can cleave all three under conditions that are milder than that required for cleavage of the benzyhydryl group and this is presumably due to the greater stabilization of the resulting dianisylmethyl cation.^{26b}

This highly efficient asymmetric methodology can be successfully applied to other diazo compounds, such as diazomethyl vinyl ketones^{27a} and functionalized diazomethyl ketones.^{27b}

Inspired by the report on *trans*-aziridination by Maruoka¹⁸, we have shown recently that the chiral catalysts derived from VANOL/VANOL can also give *trans*-aziridines **35** in the reaction of imine **31** and diazoacetamide **19** with high yields and asymmetric inductions. Our protocol thus represents the only universal catalytic asymmetric aziridination reaction where either *cis* or *trans*-aziridines can be prepared from the same imine substrate **31** and the same catalyst (Scheme 1.12).^{28a}

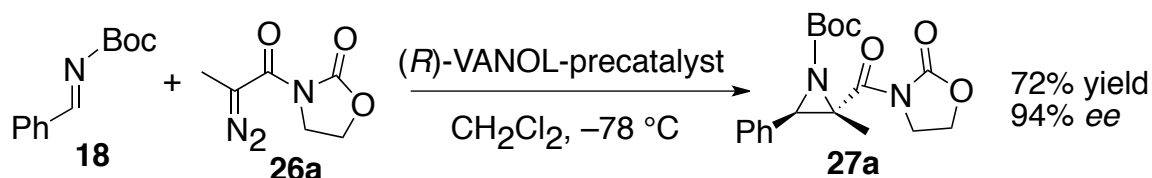
Scheme 1.12 Universal catalytic asymmetric aziridinations.



The origin of the *cis*-selectivity in the reactions of EDA **5** can be understood on the basis of the difference in specific noncovalent interactions in the stereochemistry-determining step. A hydrogen bonding interaction between the amidic hydrogen and an oxygen atom of the chiral counterion in the catalyst has been identified as the key interaction responsible for the *trans*-selectivity.^{28b}

Independently from Maruoka, we found that our VANOL borate precatalyst can catalyze the reaction of *N*-Boc imine **18** and diazo compound **26a** to give trisubstituted aziridines (Scheme 1.13).²⁹ While a strong Brønsted acid (S)-**30** was used as the catalyst by Maruoka in the synthesis of tri-substituted aziridines²¹, we were surprised by the fact that the reaction with the VANOL catalyst afforded a good yield of **27a** even at $-78\text{ }^\circ\text{C}$. This reaction will be the subject of Chapter Three.

Scheme 1.13 Catalytic asymmetric synthesis of trisubstituted aziridines developed in our group.

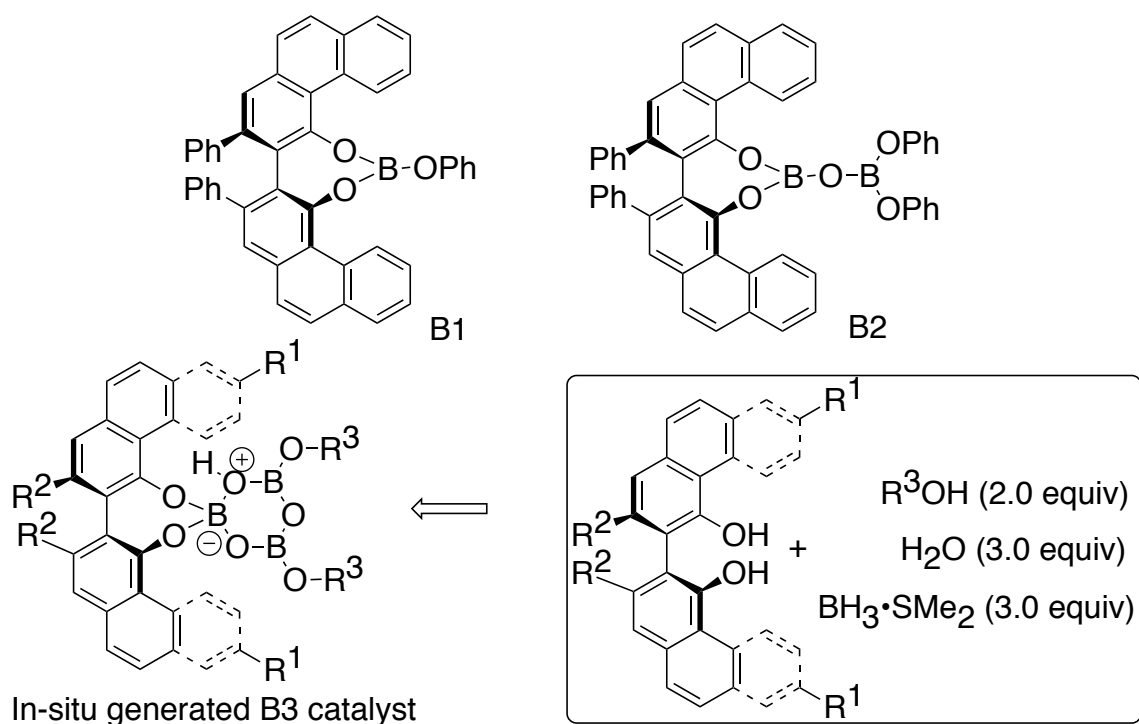


1.2.3.2 Active catalyst and catalytic cycle in the aziridination system

In the course of the development of an asymmetric catalytic method for the synthesis of *cis*-aziridines, we also devoted efforts to the identification of the active catalyst in the system. Mass spectral analysis and the ¹¹B NMR spectrum of the catalyst mixture suggested the presence of two species: one derived from one of one molecule of the ligand and one boron atom (B1) and the second from one molecule of the ligand and two boron atoms (B2). These species have been tentatively identified as those shown in Scheme 1.13.^{26a} Studies with catalysts enriched in either the B1 or B2 species reveal that precatalyst enriched in the B2 species gives higher asymmetric induction and higher rates in the asymmetric aziridination reaction than the precatalyst enriched in the B1 species. It was not until 2009 that we came to know that the catalyst for this system was actually a species derived from one molecule of the ligand and three borons (B3). This was a surprise since the catalyst is a chiral Brønsted acid (B3) and not a chiral Lewis acid as we had long thought.^{30a} The mixture of the B1 and B2 species is converted under reaction conditions to the boroxinate (B3), the actual catalyst in these reactions. More recently, the crystal structures of the catalyst/substrate complex were obtained.^{30b} We have not yet confirmed the existence of the

protonated boroxinate as B3-H species, but instead we have observed ion-pairs in which a basic substrate abstracts the proton and the resulting protonated substrate is hydrogen bonded to the anionic core. These new chiral Brønsted acids are chiral polyborates, which contain a boroxinate core that incorporate the biaryl ligands VANOL and VAPOL and have the general structure shown in Scheme 1.14.

Scheme 1.14 Active catalysts in the catalytic asymmetric aziridination.

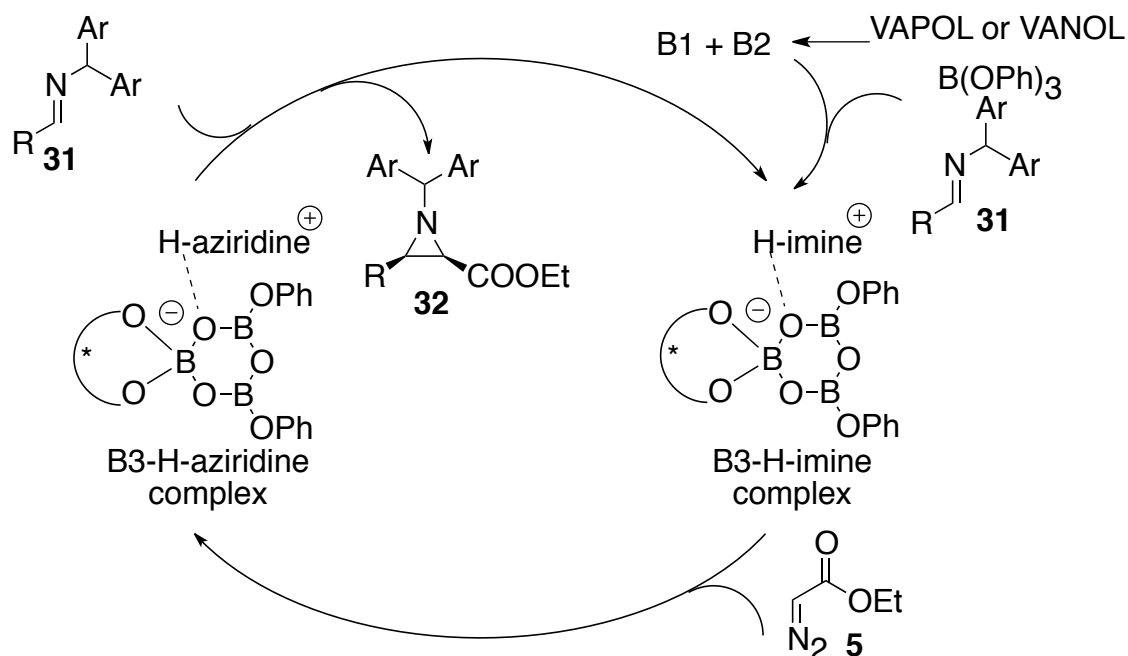


The discovery of this new class of strong chiral Brønsted acids not only provides critical insights into the binding of the substrates with the boroxinate catalyst in the aziridination reaction but also opens up new opportunities in asymmetric catalysis. In the long run, this new class of the catalyst will actually stand out as being one of great diversity. As in the BINOL phosphoric acids and derivatives, diversity can be achieved by preparing the catalysts from substituted

VANOL and VAPOL ligands. Another dimension to diversity could be attained by variation of the alcohol or phenol that makes up the boroxinate core. In addition, the catalyst can be quickly generated from 1.0 equiv of the ligand, 2.0 equiv of alcohol or phenol, 3.0 equiv of H₂O and 3.0 equiv of BH₃•SMe₂. As illuminated by the crystal structure of polyborate-imine complex, the variety and diversity of non-covalent interactions that are involved in the binding of the substrate and the catalyst is particularly appealing in thinking about and designing asymmetric catalyst systems. The fact it has been used in other reactions³¹ will make it more appealing to the scientific community.

The catalytic cycle for the *cis*-aziridination has been proposed^{30b} as that in Scheme 1.14. Several protocols for catalyst preparation allows for the generation of mixtures of B1 and B2, which, along with a basic imine substrate **31**, could be converted to boroxinate B3 with hydrogen bonding to a protonated imine. Once the boroxinate B3 catalyst is assembled, the next step involves the reaction with EDA **5** to give a boroxinate-H-aziridine complex. The loss of aziridine and incorporation of another molecule of imine **31** regenerate the boroxinate-imine complex and continues the catalytic cycle.

Scheme 1.15 Proposed catalytic cycle in the catalytic asymmetric aziridination.



1.3 Conclusion

The understanding of the mechanistic basis of action of the catalyst in the asymmetric aziridination of imines with diazo compounds should widen its employment in organocatalysis. The discovery of chiral boroxinate structures not only provides new insights into molecular recognition between a catalyst and its substrate that would be important in the design of function of catalyst in existing reactions, but also should stimulate new applications of this catalyst in new catalytic asymmetric reactions. Our unique polyborate template for which new applications in enantioselective synthesis of chiral molecular frameworks will undoubtedly emerge in the years to come.

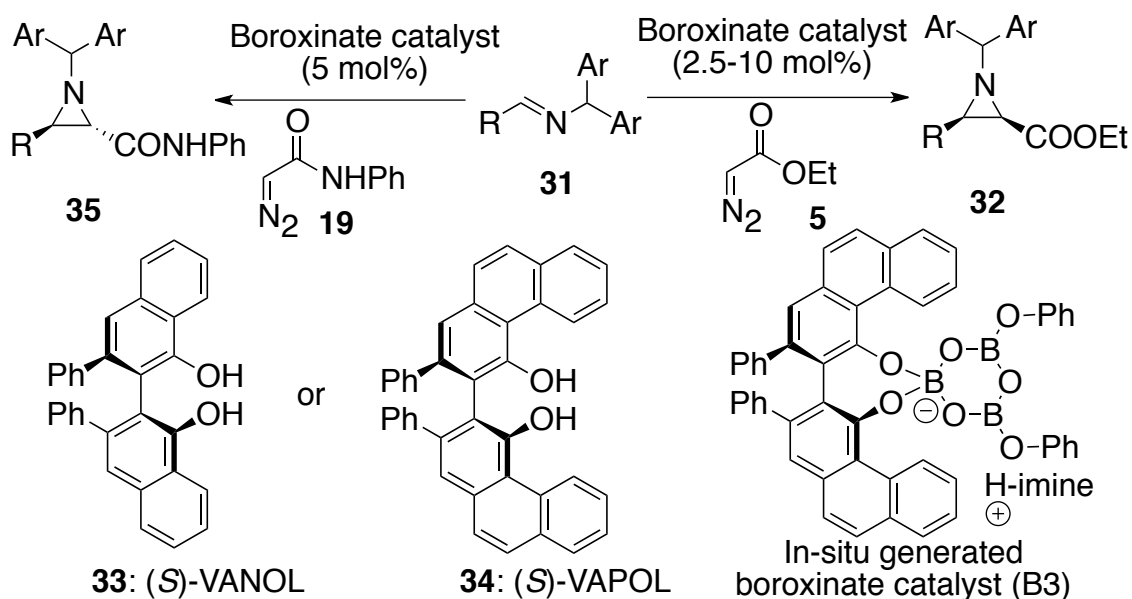
CHAPTER TWO

DOUBLE STEREODIFFERENTIATION IN THE CATALYTIC ASYMMETRIC AZIRIDINATION OF IMINES PREPARED FROM α -CHIRAL AMINES

2.1 Introduction

A general method has been developed in our group for the asymmetric catalytic synthesis of both *cis*- and *trans*-aziridines that involves the reaction of imines and diazo compounds with catalysts prepared from either VANOL or VAPOL ligand and $B(OPh)_3$ or $BH_3 \cdot SMe_2$.^{23, 28} The actual catalyst in the reaction is an ion pair consisting of a boroxinate anion and an iminium cation as shown in Scheme 2.1.³⁰

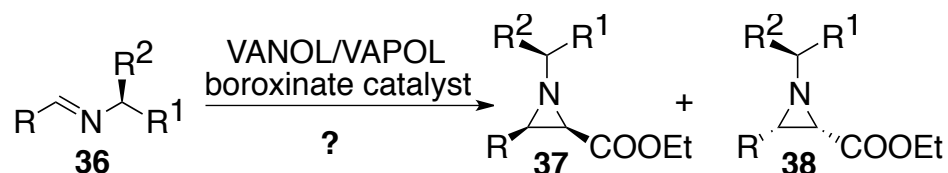
Scheme 2.1 *cis*-Aziridination protocols with VANOL/VAPOL boroxinate catalysts



Over the years we have focused on the identification on the optimal aryl substituents for the diarylmethyl group on the nitrogen in imine **31**.²⁶ Over all of

the imines **31** of the type that we have examined, the optical purity of *cis*-aziridines **32** range from 77-99% ee and that of *trans*-aziridines **35** from 81-98% ee which includes imines derived from electron-rich and electron-poor aromatic aldehydes as well as primary, secondary and tertiary aliphatic aldehydes. Since many reactions gave 98-99% ee, those substrates that give less than ideal asymmetric inductions usually require an upgrade of the optical purity of the product by any number of procedures.^{26a} When a chiral imine **36** prepared from a chiral amine is employed, two diastereomeric aziridines could be formed, for example **37** and **38** in the *cis*-aziridination reaction (Scheme 2.2). Once one diastereomer is separated from the other, the optical purity of this particular diastereomer would be 100% ee. Given a good yield, the strategy may prove to be ideal for many synthetic applications. Therefore, we decided to investigate the aziridination of imines of type **36** prepared from chiral amines.

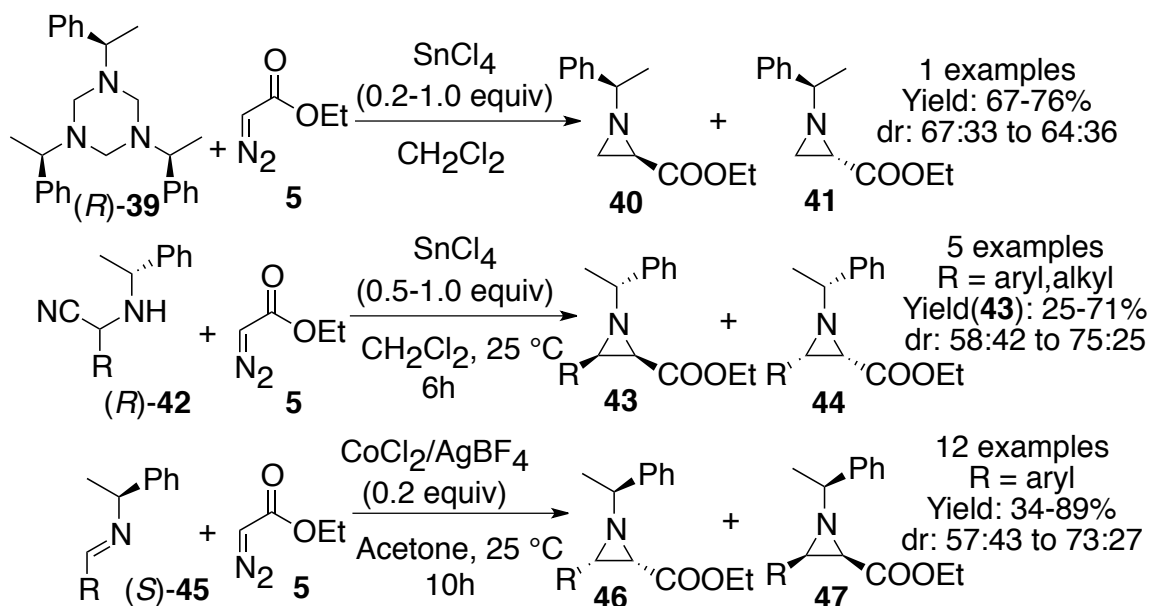
Scheme 2.2 *cis*-Aziridination reactions with a chiral imine as substrate



Although the *cis*-aziridination of chiral imines of type **36** with diazo compounds have not been previously investigated with chiral catalysts, three reports have appeared that describes these reactions with non-chiral Lewis acids as shown in Scheme 2.3. The synthesis of aziridine-2-carboxylates from the reaction of hexahydro-1,3,5-triazine (*R*)-**39** with EDA in the presence of SnCl₄ as a catalyst has been reported.^{32a} An *N*-methylethylamine equivalent could be generated in

situ from hexahydro-1,3,5-triazine prepared from α -methylbenzylamine. The overall yield of the reaction was 67-76% with the diastereomeric ratio ranging from 64:36 to 67:33. Ha and coworkers generated imines (*R*)-**45** in situ during Lewis acid mediated aziridination of α -aminonitriles (*R*)-**42** derived from α -methylbenzylamine with EDA.^{32b} The optimal condition involved the reaction with 0.5-1.0 equivalent of SnCl₄, affording a mixture of diastereomers **43** and **44** in ratios from 58:42 to 75:25 with **43** being the major one. Both aryl and alkyl substituents could be introduced into the aziridine in the 3-position with the yield of the major diastereomer being 25-71%. In another example, Lee and coworkers found that the reaction of chiral imines (*S*)-**45** with 3.0 equivalent EDA gave the diastereomeric aziridines **46** and **47** with dr of 57:43 to 73:27 and an overall yield of 34-89%.^{32c} While a range of imines prepared from aryl aldehydes and the chiral amine afforded good yields of the aziridines, imine from *p*-methoxybenzaldehyde gave no reaction. To summarize, the reaction of imines prepared from aldehydes and α -methylbenzylamine with EDA in the presence of non-chiral Lewis acids give a slight diastereomeric preference for a particular diastereomer. But the degree of stereoinduction is generally low and the yields of aziridine products are not practically useful.

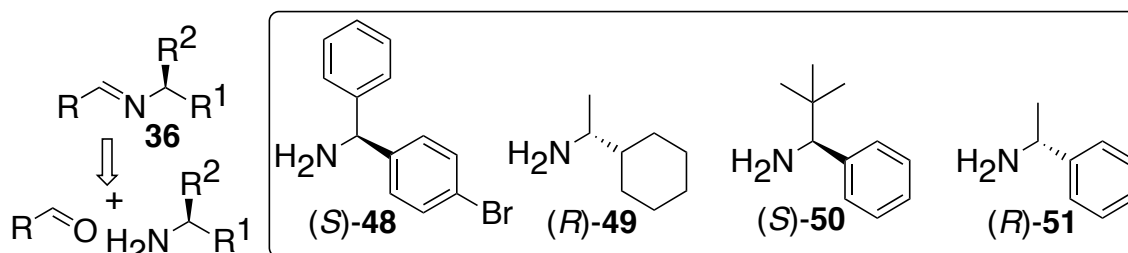
Scheme 2.3 Previous examples of aziridination of chiral imines mediated by non-chiral Lewis acids



2.2 Double stereo-differentiation with chiral imines

The set of amines that we chose to examine in the double stereo-differentiation study are the four amines shown in Scheme 2.4. These were chosen to examine the effect of the competition between the aryl and alkyl groups, between aryl groups of different electron density and between alkyl groups of different sizes. We decided to first screen chiral imines prepared from benzaldehyde and chiral amine **48-51** in the *cis*-aziridination reaction.

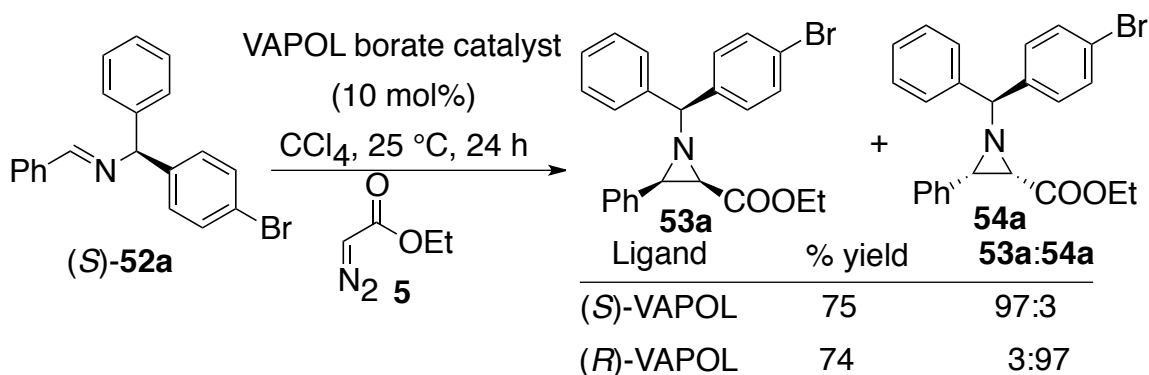
Scheme 2.4 The set of amines chosen in our study



2.2.1 Double stereo-differentiation with the chiral imine (S)-52a

Yu Zhang, our former group member, conducted the reactions of the unsymmetrical chiral benzhydryl imine (S)-**52a** prepared from benzaldehyde and the chiral amine (S)-**48** with EDA.³³ The imine (S)-**52a** was chosen such that the two phenyl rings are nearly sterically identical but electronically distinct. It was observed in the X-ray analysis of a boroxinate-iminium complex (Scheme 2.1) that the binding of the protonated imine **31** in the VAPOL boroxinate catalyst results from several different types of non-covalent interactions of the two phenyl groups with the boroxinate catalyst. This includes a CH- π interaction of one of phenyl rings of MEDAM group to one of the phenyl rings on the back end of the VAPOL ligand.^{30b}

Scheme 2.5 *cis*-Azirdination reactions of the chiral imine (S)-**52a**



With all the efforts that it took to resolve the amine (S)-**48**, it was thus disappointing to find that in the reaction of chiral imine (S)-**52a** with a phenyl and *p*-bromophenyl substituent, aziridine **53a** and **54a** were obtained in a 97:3 mixture in favor of **53a** with the (S)-VAPOL catalyst and in a 3:97 mixture in favor of **54a** with the (R)-VAPOL catalyst (Scheme 2.5). Both enantiomers of the VAPOL-borate catalyst gave a 30:1 mixture of products with no evidence for a

matched/mismatched pair of the substrate. It is clear that the *cis*-aziridination reactions of imine (*S*)-**52a** with chiral benzhydryl substituents were dominated by catalyst control.

2.2.2 Double stereo-differentiation with the chiral imine (*R*)-**55a**

The catalytic aziridination reaction of chiral imine (*R*)-**55a** pits the effects of a cyclohexyl group against a methyl group in the control of diastereoselectivity in competition with VAPOL and VANOL catalyst. As indicated in Table 2.1, these effects turn out to be very small as there is only a slight difference in the selectivity with the (*R*) and (*S*)-isomers of the ligands. With the non-chiral catalyst B(OPh)₃, nearly a 1:1 mixture of **56a** and **57a** was obtained. It was also noted that the reaction of cyclohexylethyl imine (*R*)-**55a** was not complete even after 24 h with the VAPOL catalyst. This is actually consistent with the fact that the aziridination with imine derived from dicyclohexylmethanamine and benzaldehyde is 25 times slower than the corresponding imine derived from benzhydryl amine and benzaldehyde.^{26c}

Table 2.1 Matched and mismatched aziridinations of the cyclohexylethyl imine**(*R*)-55a**^a

entry	ligand	% conv	56a:57a ^b	% yield 56a ^c	% yield 57a ^d	% yield 58a/59a ^d
1	(<i>S</i>)-VAPOL	90	83:17	35	6	3/7
2	(<i>R</i>)-VAPOL	66	20:80	7	28	3/5
3	(<i>S</i>)-VANOL	64	83:17	32	5	2/4
4	(<i>R</i>)-VANOL	100	25:75	15	45	4/9
5	B(OPh) ₃ only	38	56:44	nd	nd	nd

^a Unless otherwise specified all reactions were run at 0.5 M in imine with 1.2 equiv EDA (**5**) and 10 mol% catalyst in toluene at rt for 24 h. The catalyst was prepared from 1.0 equiv of the ligand, 4.0 equiv of B(OPh)₃ and 1.0 equiv of H₂O according to general procedure (Method A) in the experimental section. nd = not determined. ^b Determined from the ¹H NMR spectrum of the crude mixture. ^c Isolated yield after chromatography on silica gel. ^d Yield from ¹H NMR spectrum of the crude mixture and based on the isolated yield of **56a**.

2.2.3 Double stereo-differentiation with the chiral imine (*S*)-60a

The aziridination of the chiral imine **60a** pits a *t*-butyl versus a phenyl group in vying for the diastereoselection in competition with the VAPOL and VANOL derived catalysts. As can be observed from the data in Table 2.2 obtained by Yu Zhang³³, there is a strong matched and mismatched relationship between the chiral imine substrate (*S*)-**60a** and the chiral catalyst. The matched case results from the reaction of (*S*)-**60a** and the catalyst prepared from (*R*)-enantiomer of the

ligand, affording the major diastereomer **62a** in 80-85% yield. No detectable amount of the diastereomers **61a** was formed in the matched reaction. In the mismatched case, the reaction of (S)-**60a** and EDA gave a 69:31 and 52:48 mixtures of **61a** and **62a** with (S)-VAPOL and (S)-VANOL catalysts, respectively. Even the reaction with the non-chiral catalyst B(OPh)₃ gives a strong preference for the matched diastereomers **62a**.

Table 2.2 Matched and mismatched aziridinations of the phenylneopentyl imine (S)-**60a**^a

entry	ligand	61a : 62a ^b	% yield 61a ^c	% yield 62a ^d	% yield 63a / 64a ^d
1	(S)-VAPOL	69:31	56	25	nd
2	(R)-VAPOL	<2:98	<2	80	<2
3	(S)-VANOL	52:48	36	33	11/2
4	(R)-VANOL	<2:98	<2	85	<2
5	B(OPh) ₃ only	8:92	nd	nd	nd

^a Unless otherwise specified all reactions were run at 0.5 M in imine with 1.2 equiv EDA (**5**) and 10 mol% catalyst in CCl₄ at rt for 24 h. The catalyst was prepared from 1.0 equiv of the ligand, 3.0 equiv of B(OPh)₃ according to general procedure. nd = not determined. All the reaction went to completion. All data in this Table comes from the thesis of Yu Zhang.³³ ^b Determined from the ¹H NMR spectrum of the crude mixture. ^c Isolated yield after chromatography on silica gel. ^d Yield from ¹H NMR spectrum of the crude mixture and based on the isolated yield of **62a**.

2.2.4 Double stereo-differentiation with the chiral imine (*R*)-**45a**

The results in Table 2.3 definitely show that there is a synergism between the chiral centers in the imine (*R*)-**45a** and in the catalyst with the matched case from the reaction of (*R*)-**45a** and the (*S*)-enantiomer of the catalyst.

Table 2.3 Matched and mismatched aziridinations of the phenylethyl imine (*R*)-**45a**^a

entry	ligand	time	% con	43a:44a ^b	% yield 43a ^c	% yield 44a ^d	% yield 65a/66a ^d
1	(<i>S</i>)-VAPOL	24	100	96:4	74	3	1/7
2	(<i>R</i>)-VAPOL	24	100	33:67	17	33	7/11
3	(<i>S</i>)-VAPOL	1	87	97:3	51	2	4/6
4	(<i>R</i>)-VAPOL	1	82	41:59	18	26	3/8
5	(<i>S</i>)-VANOL	24	100	>97:3	69	<2	3/3
6	(<i>R</i>)-VANOL	24	100	31:69	22	48	9/15
7	B(OPh) ₃	24	66	75:25	31	10	7/8

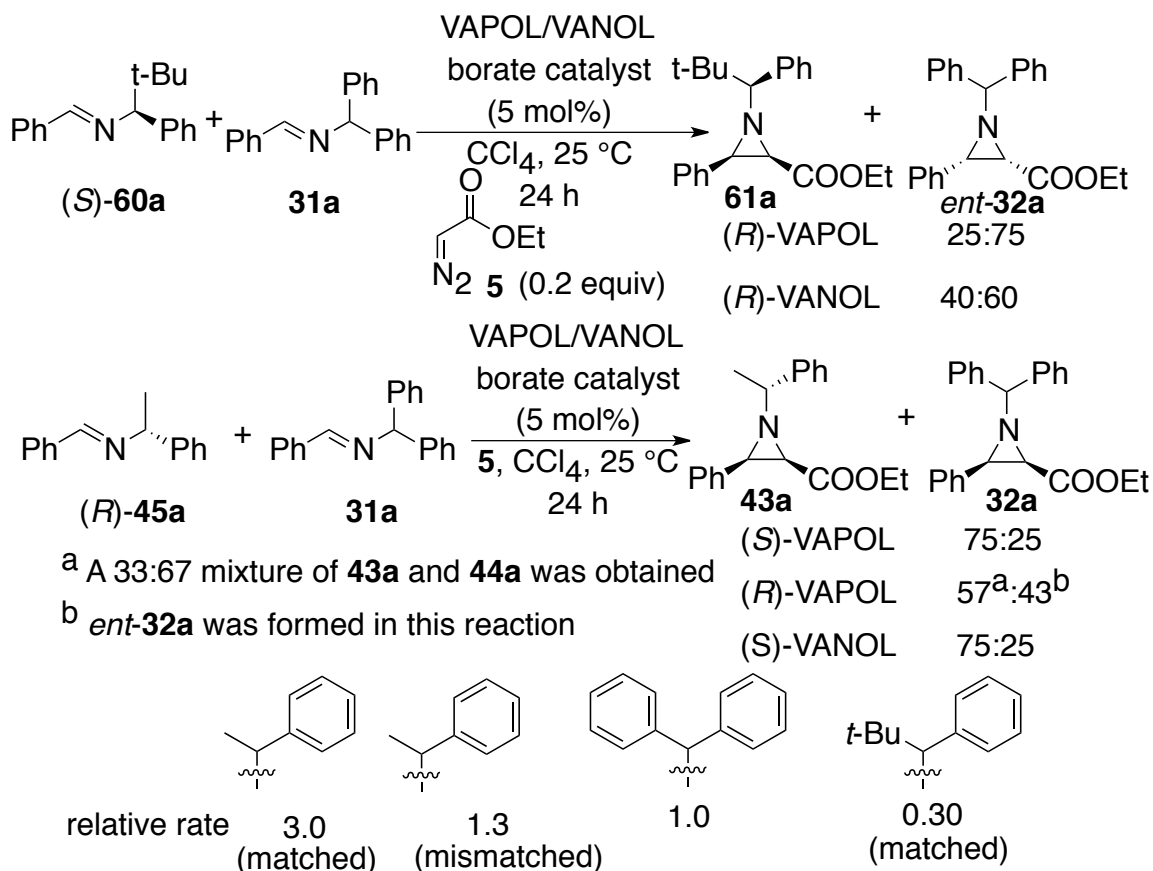
^a Unless otherwise stated all reactions were run at 0.5 M in imine with 1.2 equiv EDA (**5**) and 10 mol% catalyst in toluene at rt for the specified time. The catalyst was prepared from 1.0 equiv of the ligand, 4.0 equiv of B(OPh)₃ and 1.0 equiv H₂O according to the general procedure (Method A). nd = not determined. ^b Determined from the ¹H NMR spectrum of the crude reaction mixture. ^c Isolated yield after chromatography on silica gel. ^d Yield from ¹H NMR spectrum of the crude reaction mixture based on the isolated yield of **43a**.

This is a slightly weaker matched/mismatched pair than seen in the reaction of *t*-butylbenzyl imine (*S*)-**60a**. This is also reflected in the fact that the nonchiral

catalyst B(OPh)₃ gives a 3:1 selectivity of the two diastereomers **43a** and **44a** (92:8 in case of (*R*)-**60a**). The selectivity flips over for the mismatched case with the (*R*)-VAPOL catalyst giving a 33:67 mixture of **43a** and **44a**, but the (*R*)-VANOL catalyst gives nearly a 1:1 mixture of the two. Fewer amounts of the enamines were detected in the matched case than in the mismatched one. No effort was made to determine the minimum reaction time which are definitely less than 24 h since the reaction stopped after 1 h went to 87% and 82% conversion for the VAPOL catalyst.

With the finding that both α -methylbenzylamine and α -*t*-butylbenzylamine have a strong matched and mismatched relationship with the VAPOL and VANOL catalysts, it was then decided to investigate how the rates of these reactions compare with the corresponding benzhydryl imine **31a**. The relative rates of the chiral imines were measured in a pair-wise reaction with equimolar amounts of the two imine substrates ((*S*)-**60a** vs **31a** and (*R*)-**45a** vs **31a**) with 5 mol% catalyst in the presence of a substoichiometric amount (0.2 equivalent) of EDA. It was found that the α -*t*-butylbenzylimine **60a** reacted three times slower than imine **31a** in the matched case with VAPOL, while the α -methylbenzylimine **45a** reacted three times faster. Surprisingly, the α -methylbenzylimine reacted 1.3 times faster than the benzhydryl imine **31a** even in the mismatched case with VAPOL.

Scheme 2.6 The relative rate study of the imines (*S*)-**60a**, (*R*)-**45a** and **31a**



Although the imine (*S*)-**60a** derived from the chiral amine **50** and benzaldehyde furnished a higher diastereoselectivity and yield in the matched reaction, the α -*t*-butylbenzylamine **50** is not commercially available. Given the facts that both enantiomers of *N*- α -methylbenzylamine are commercially available and relatively inexpensive (about the same cost as benzyhydrol amine) and that it has been recognized as a simple, yet powerful chiral adjuvant³⁴, it becomes the amine of choice in our study.

2.3 Substrate scope of *cis*-aziridinations with α -methylbenzyl imines

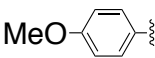
The scope of the aziridination of imines (**R**)-**45** from (**R**)-*N*- α -methylbenzylamine was explored with five additional aromatic aldehydes and three aliphatic aldehydes. The results for imines derived from aromatic aldehydes are shown in Table 2.4. In all these reactions, the *cis:trans* selectivity was >50:1. There is no difference between the VAPOL and VANOL catalyst on the *cis:trans* selectivity. Chiral imine (**R**)-**45b** derived from 4-nitrobenzaldehyde has a relatively higher reaction rate than the rest of the imines. This is reflected in the fact that the reaction of imine (**R**)-**45b** and EDA with only B(OPh)₃ as catalyst went to completion after 24 h. The optimal ligand for imine (**R**)-**45b** is VANOL, giving the major diastereomer *cis*-**43b** in 74% yield and the minor diastereomer *cis*-**44b** in only 3% yield. A similar situation was found with imine (**R**)-**45c**. In this case, (*S*)-VAPOL gave a higher yield with a slightly reduced diastereoselectivity as compared to (*S*)-VANOL. In the matched reaction of imine (**R**)-**45d** and **45e** derived from 4- and 2-tolualdehyde, respectively, >98:2 diastereomeric ratios were observed with both (*S*)-VAPOL and (*S*)-VANOL catalysts. In the case of imine (**R**)-**45f** derived from 4-methoxybenzaldehyde, a strong electron-donating benzaldehyde, we found that the (*S*)-VANOL catalyst was much more efficient than that from (*S*)-VAPOL: the reaction went to completion with excellent diastereoselectivity (98:2) with the (*S*)-VANOL catalyst whereas only 46% conversion was observed with the (*S*)-VAPOL catalyst but still with good diastereo-selection (95:5). This is consistent with the fact that the aziridination reaction of the *N*-benzhydryl imine derived from 4-methoxybenzaldehyde with the VAPOL catalyst is also sluggish, affording 73% conversion after 24 h while that

with the VANOL catalyst went to 100% conversion in the same time period, although the same level of the asymmetric induction was observed for both VAPOL and VANOL catalysts.^{26a} The low reactivity of imine **45f** is also manifested by the fact that no reaction of (S)-**45f** with EDA was observed when 20 mol% CoCl₂/AgBF₄ was used as catalyst.^{32c}

Table 2.4 Matched and mis-matched aziridinations of the phenethyl imine (R)-**45** from aryl aldehydes^a

Reaction scheme showing the aziridination of (R)-**45** with diazo ester **5** using VAPOL/VANOL borate catalyst (10 mol%) in toluene at 25 °C. The reaction yields aziridines **43** and **44** (cis:trans >50:1) and enamine **65** (**66**).

entry	substrate	ligand	% con	43:44 ^b	%yield 43 ^c	%yield 44 ^d	% yield 65/66 ^d
1	(R)-45b	(S)-VAPOL	100	96:4	74	3	1/7
2		(R)-VAPOL	100	33:67	17	33	7/11
3		(S)-VANOL	100	>97:3	69	<2	3/3
4		(R)-VANOL	100	31:69	22	48	9/15
5		B(OPh) ₃ only	100	75:25	31	10	7/8
6	(R)-45c	(S)-VAPOL	100	94:6	82	5	4/4
7		(R)-VAPOL	100	38:62	24	40	13/13
8		(S)-VANOL	100	97:3	77	2	11/9
9		(R)-VANOL	100	31:69	21	46	9/9
10		B(OPh) ₃ only	94	77:23	35	10	11/8
11	(R)-45d	(S)-VAPOL	100	>98:2	71	<1	0/1
12		(R)-VAPOL	100	33:67	19	38	3/7

		Table 2.4	cont'd				
13		(S)-VANOL	100	>98:2	70	<1	3/13
14		(R)-VANOL	100	38:62	21	35	6/8
15		B(OPh) ₃ only	61	80:20	28	7	4/3
16	 Me (R)- 45e	(S)-VAPOL	100	>98:2	62	<1	1/0
17		(R)-VAPOL	100	41:59	23	16	15/0
18		(S)-VANOL	100	>98:2	52	<1	9/6
19		(R)-VANOL	100	44:56	16	13	11/0
20		B(OPh) ₃ only	28	75:25	<21	<7	<15/<2
21	 MeO (R)- 45f	(S)-VAPOL	46	95:5	35	2	3/5
22		(R)-VAPOL	21	47:53	nd	nd	nd
23		(S)-VANOL	100	98:2	63	1	7/23
24		(R)-VANOL	29	44:56	nd	nd	nd
25		B(OPh) ₃ only	8	nd	nd	nd	nd

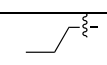
^a Unless otherwise stated all reactions were run at 0.5 M in imine with 1.2 equiv EDA (**5**) and 10 mol% catalyst in toluene at rt for 24 h. The catalyst was prepared from 1.0 equiv of the ligand, 4.0 equiv of B(OPh)₃ and 1.0 equiv H₂O according to general procedure (Method A). nd = not determined. ^b Determined from the ¹H NMR spectrum of the crude reaction mixture. ^c Isolated yield after chromatography on silica gel. ^d Yield from ¹H NMR spectrum of the crude reaction mixture based on the isolated yield of **43**.

The results of the aziridination of imines (*R*)-**45** derived from three aliphatic aldehydes are summarized in Table 2.5. In the reactions of imine (*R*)-**45g** from cyclohexanecarbaldehyde, there is no profound difference in the selectivities seen with the (*R*)- or (*S*)-enantiomers of the ligands. This is also true even with the non-chiral catalyst B(OPh)₃ which gives nearly a 1:1 ratio of the diastereomers **43g** and **44g**. The selectivity imparted by the catalysts is 5:1 in favor of *cis*-**43g** when the (*S*)-enantiomers of the VAPOL and VANOL ligands are

used and 3:1 in favor of *cis*-**44g** when the (*R*)-enantiomers of the VAPOL and VANOL ligands are used. This is so far the weakest matched and mis-matched relationship found between the chiral imines in the series (*R*)-**45** series with either VAPOL or VANOL catalyst. These reactions are dominated by catalyst control rather than by substrate control. Fortunately, the products **43g** and **44g** are easy to separate and obtained in good yields with the (*S*)-catalysts. The optimal ligand for chiral imine (*R*)-**45h** is VANOL, with higher diastereoselectivity and isolated yield than observed with the (*S*)-VAPOL ligand.

Table 2.5 Matched and mis-matched aziridinations of the phenethyl imine (*R*)-**45** from aliphatic aldehydes^a

entry	substrate	ligand	% con	43:44 ^b	% yield 43 ^c	% yield 44 ^d	% yield 65/66 ^d
1		(<i>S</i>)-VAPOL	100	83:17	66	13	0/0
2	 (R)-45g	(<i>R</i>)-VAPOL	100	23:77	14	47	0/0
3		(<i>S</i>)-VANOL	100	83:17	72	14	0/0
4		(<i>R</i>)-VANOL	100	23:77	23	76	0/0
5		B(OPh) ₃ only	53	55:45	17	21	0/0
6	 (R)-45h	(<i>S</i>)-VAPOL	100	91:9	61	6	0/0
7		(<i>R</i>)-VAPOL	31	38:62	13	22	0/0
8		(<i>S</i>)-VANOL	100	93:7	79	6	0/0
9		(<i>R</i>)-VANOL	100	41:59	22	31	0/0

Table 2.5		cont'd					
10		B(OPh) ₃ only	43	58:42	18	13	0/0
11		(S)-VANOL	100	80:20	28	7	0/0
12	(<i>R</i>)- 45i	(<i>R</i>)-VANOL	100	47:53	29	33	0/0

^a Unless otherwise stated all reactions were run at 0.5 M in imine with 1.2 equiv EDA (**5**) and 10 mol% catalyst at rt for 24 h. The catalyst was prepared from 1.0 equiv of the ligand, 4.0 equiv of B(OPh)₃ and 1.0 equiv H₂O according to general procedure (Method A). nd = not determined. ^b Determined from the ¹H NMR spectrum of the crude reaction mixture. ^c Isolated yield after chromatography on silica gel. ^d Yield from ¹H NMR spectrum of the crude reaction mixture and based on the isolated yield of **43**.

The reaction of chiral imine (*R*)-**45h** and EDA with the (*S*)-VANOL catalyst gave moderate yield and the mis-matched reaction with the (*R*)-VANOL catalyst only went to 31% conversion. These results are consistent with the fact that the reaction of *N*-benzhydryl imine from trimethylacetaldehyde with the VANOL catalyst is sluggish and gives a lower yield and asymmetric induction compared with the VANOL catalyst.^{26a} Although imine (*R*)-**45i** prepared from the primary aldehyde *n*-butanal gives a matched and mis-matched relationship with the VANOL catalysts, the major aziridine **43i** from the reaction in the matched case could be isolated in only 28% yield. The low yield might be due to an aldol side product similar to that observed in the aziridination of imines derived from the DAM amine and *n*-butanal.^{26d} It is also interesting to note that no enamine by-products were observed in the reaction of any of the imines derived from aliphatic aldehydes. The low migratory aptitudes of aliphatic groups might be responsible for an absence of the enamine byproducts relative to aromatic groups.^{14a}

Unlike the aziridination reactions of chiral imines (*R*)-**45a-i** and EDA investigated above, in which a >50:1 *cis:trans* selectivity was observed, the reaction of chiral imine (*R*)-**45** from *o*-halobenzaldehydes and EDA afforded all four possible *cis*- and *trans*-diastereomers (Table 2.6). A significant amount of the *trans*-isomers was observed in all the reactions of chiral imine (*R*)-**45j-k**. This is consistent with the fact that the reaction of the *N*-benzhydryl imine derived from *o*-bromobenzaldehyde and EDA with the VAPOL or VANOL catalysts gave a ~2:1 *cis/trans* selectivity.^{26a} For both *cis*- and *trans*-isomers of the aziridines from imine (*R*)-**45j**, there is a strong matched and mismatched relationship between the chiral imine and one of the enantiomers of the ligands. In the matched *cis*-aziridination reaction of imine (*R*)-**45j** and EDA with (*S*)-enantiomer of the catalysts, a 91:9 mixture of *cis*-diastereomers **43j** and **44j** was obtained using (*S*)-VAPOL and a 97:3 mixture was obtained using (*S*)-VANOL. In the mismatched case for the *cis*-diastereomer, nearly a 1:1 mixture of **43j** and **44j** was obtained from (*R*)-enantiomer of both VAPOL and VANOL catalysts. However, the (*R*)-enantiomer of the catalysts provided the matched reaction for *trans*-diastereomers, giving a ~12:1 mixture of *trans*-diastereomers **67j** and **68j**. The reactions of chiral imine (*R*)-**45j** and (*S*)-enantiomer of the catalysts furnished a 2:1 to 1:1 diastereoselectivity of the *trans*-aziridines. It is interesting to note that the matched cases for *cis*-aziridines are the mismatched cases for *trans*-aziridines. A very similar pattern was seen for imine (*R*)-**45k** derived from *o*-iodobenzaldehyde. The origin of formation of substantial amount of *trans*-aziridines from imines (*R*)-**45j-k** that bear an *ortho*-halogen substituent is not

understood at this stage but it is clear that it is not due to just the presence of the *ortho*-substituents since the imine from *o*-tolualdehyde does not give any detectable amount of the *trans*-aziridines. In addition, the bromine atom could be removed from the *trans*-aziridine **67j** with tributyltin hydride without ring opening to give the *trans*-aziridine **67a** in 68% yield (Scheme 2.7). Despite the fact that a significant amount of *trans*-isomers could be obtained in the aziridination reaction and the fact that the halogen could be selectively removed, this does not provide for a practical method for providing access to *trans*-aziridines due to their low isolated yields in the aziridination reaction.

Table 2.6 Matched and mismatched aziridinations of the *o*-bromo- and *o*-iodophenyl imine^a

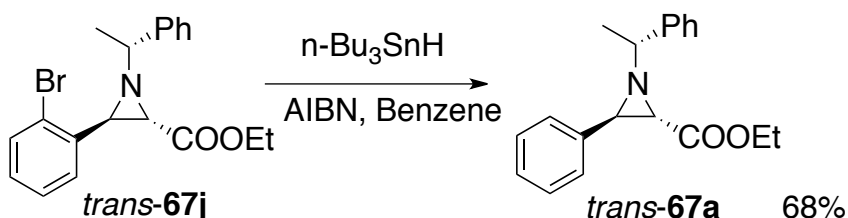
$(R)\text{-45j: X = Br}$ $(R)\text{-45k: X = I}$ VAPOL/VANOL borate catalyst (10 mol%) Toluene, 25 °C, 24 h Ethyl azide (5) Products: 43, 44, 67, 68, and 65/66								
entry	X	ligand	43 / 44	67 / 68	<i>cis</i> / <i>trans</i> ^b	%yield 43 ^c	%yield 67 ^d	% yield 65/66 ^d
1	Br	(<i>S</i>)-VAPOL	91:9	67:33	71:29	48	14	10/16
2	Br	(<i>R</i>)-VAPOL	50:50	93:7	35:65	10	33	15/21
3	Br	(<i>S</i>)-VANOL	97:3	44:56	70:30	43	8	10/12
4	Br	(<i>R</i>)-VANOL	55:45	92:8	36:64	10	30	10/13
5	Br	B(OPh) ₃ only	75:25	88:12	23:77	13	50	13/13

Table 2.6 cont'd

6	I	(S)-VAPOL	94:6	67:33	50:50	21	15	11/17
7	I	(R)-VAPOL	50:50	91:9	26:74	8	40	15/21
8	I	(S)-VAPOL	96:4	67:33	52:48	23	15	10/12
9	I	(R)-VANOL	63:37	91:9	25:75	7	30	10/13
10	I	B(OPh) ₃ only	33:67	85:15	23:77	6	51	11/11

^a Unless otherwise stated all reactions were run at 0.5 M in imine with 1.2 equiv EDA (**5**) and 10 mol% catalyst in toluene at rt for 24 h. The catalyst was prepared from 1.0 equiv of the ligand, 4.0 equiv of B(OPh)₃ and 1.0 equiv H₂O according to general procedure (Method A). nd = not determined. ^b Determined from the ¹H NMR spectrum of the crude reaction mixture. ^c Isolated yield after chromatography on silica gel. ^d Yield from ¹H NMR spectrum of the crude reaction mixture based on the isolated yield of **43**.

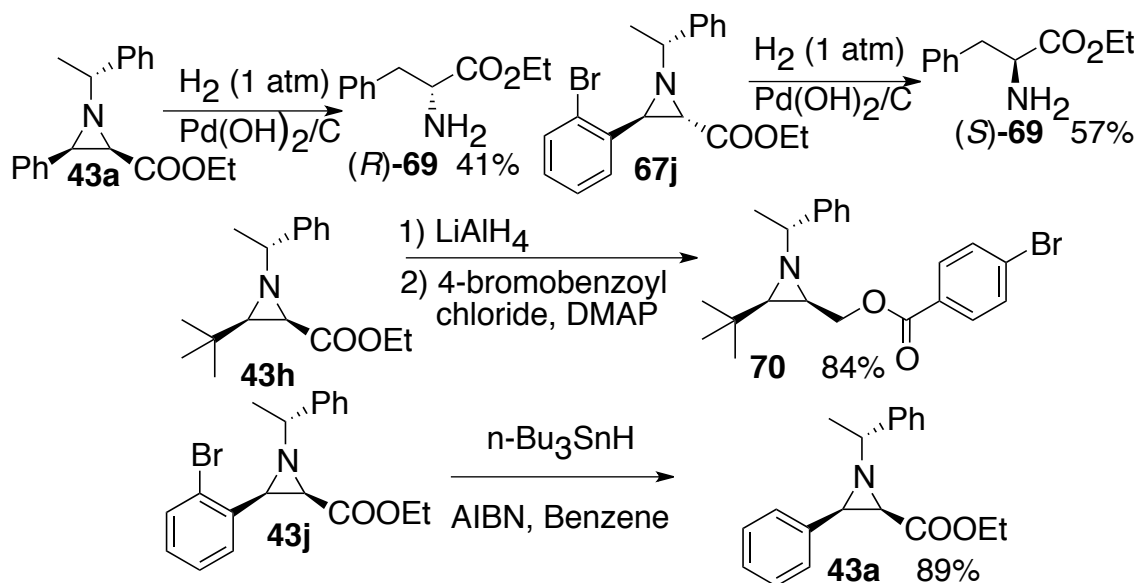
Scheme 2.7 Selective removal of bromine *via* tin hydride reduction



The assignment of the relative stereochemistry of the *cis*-aziridine **43a** was made after comparison of its rotation with that reported in the literature for this compound^{32b} and by its conversion to the (*R*)-enantiomer of phenylalanine ethyl ester **69** and comparison of its optical rotation with that previously reported for this compound (Scheme 2.8).^{23a} The relative stereochemistry for aziridines **43b-f** with aryl substituents on C-3 position was assumed to be the same as that determined for **43a**. The relative stereochemistry of the cyclohexyl aziridine **43g** was assigned by a chemical correlation with the known aziridine **80g**^{26b} as

outlined in Scheme 2.13. The assignment of the relative stereochemistry of *t*-butyl aziridine **43h** was made by its conversion to the *p*-bromobenzoate **70**, which was a solid that gave crystals suitable for X-ray crystallographic analysis. Hydrodebromination of **43j** with tributyltin hydride gives aziridine **43a** in 89% yield which was found to be identical with the major aziridine formed from the matched reaction of chiral imine (*R*)-**43a** and EDA with (*S*)-VAPOL. The assignment of the *trans*-aziridine **67j** was made by its conversion to the (*S*)-enantiomer of phenylalanine ethyl ester **69**.^{23a} In the matched reaction of imine (*R*)-**45j** from *o*-bromobenzaldehyde, the facial selectivity for the imine is the same for both the major *cis* and *trans* diastereomers but that for the diazo compound EDA is changed in the *trans*-aziridine. The relative stereochemistry for *o*-iodophenyl substituted aziridines was assumed to be the same as aziridine **43j** and **67j**.

Scheme 2.8 Determination of the relative stereochemistry of the α -methylbenzyl aziridines



2.4 *trans*-Aziridines from α -methylbenzyl imines and diazoacetamide 19

A substantial proportion of *trans*-aziridine was observed in the reaction of imine (*R*)-**45j-k** and EDA, yet the synthetic utility is limited due to the low isolated yield. A better route to the synthesis of *trans*-aziridines should be the reaction of imine (*R*)-**45** with diazoacetamide **19** since the reaction of imines of the type **31** and diazoacetamide **19** with either the VAPOL or VANOL catalyst gave high *trans/cis* selectivity with good isolated yields for *trans*-aziridines (Scheme 2.1). The question now becomes whether the double differentiation approach that was successful for *cis*-aziridination of chiral imines (*R*)-**45** and EDA could be extended to the *trans*-aziridination by simply changing the diazo compound from EDA to diazoacetamide **19**.

Table 2.7 Matched and mismatched *trans*-aziridinations of imine (*R*)-**45a** with diazoacetamide **19**^a

entry	ligand	71a / 72a ^b	73a / 74a ^b	<i>trans</i> / <i>cis</i> ^b	% yield 71a ^c	%yield 73a ^d	% yield 75/76 ^d
1	(<i>S</i>)-VAPOL	60:40	83:17	79:21	25	9	12/19
2	(<i>R</i>)-VAPOL	91:9	50:50	88:12	71	5	6/6
3	(<i>S</i>)-VANOL	62:32	75:25	68:32	28	16	18/16
4	(<i>R</i>)-VANOL	89:11	67:33	89:11	70	6	8/10

Table 2.7 cont'd							
5 ^e	(<i>R</i>)-VANOL	96:4	67:33	96:4	78	2	3/4
6 ^f	(<i>R</i>)-VANOL	91:9	60:40	91:9	69	4	6/9
7	B(OPh) ₃ only	86:14	75:25	86:14	43	8	4/4

^a Unless otherwise stated all reactions were run at 0.5 M in imine with 1.2 equiv diazoacetamide **19** and 10 mol% catalyst in toluene at rt for a specified time. The catalyst was prepared from 1.0 equiv of the ligand, 3.0 equiv of BH₃•SMe₂, 2.0 equiv of PhOH and 3.0 equiv H₂O according to the general procedure (Method B). nd = not determined. ^b Determined from the ¹H NMR spectrum of the crude reaction mixture. ^c Isolated yield after chromatography on silica gel. ^d Yield from ¹H NMR spectrum of the crude reaction mixture based on the isolated yield of **71a**. ^e The reaction was run at 0 °C. ^f The catalyst was prepared from 1.0 equiv of the ligand 4.0 equiv of B(OPh)₃ and 1.0 equiv of H₂O.

Fortunately, it was found that the aziridination reaction of chiral imine (*R*)-**45a** and diazoacetamide **19** beginning with either the (*R*) or (*S*)-enantiomer of the ligand gave good to high *trans:cis* selectivity ranging from 68:32 to 89:11 at room temperature (Table 2.7). Interestingly, there is a matched relationship found between the chiral imine (*R*)-**45a** and the (*R*)-VAPOL catalyst in the *trans*-aziridination with diazoacetamide **19** while a matched relationship was observed between the same chiral imine and (*S*)-enantiomer of the catalyst in the *cis*-aziridination with EDA. The (*R*)-VAPOL and (*R*)-VANOL catalysts are equally effective, affording ~8:1 *trans:cis* selectivity and isolated yield of the major *trans*-diastereomer **71a** in 70-71%. A higher *trans:cis* selectivity (96:4), a better isolated yield (78%) and reduced amounts of the enamine by-products were obtained in the reaction with the (*R*)-VANOL catalyst at a lower temperature (0 °C) (entry 5). A different catalyst preparation procedure was proven to be equally effective for the reaction (entry 4 vs entry 6). Generally, a reduced amount of

enamine by-products was observed in the matched case than in the mismatched case.

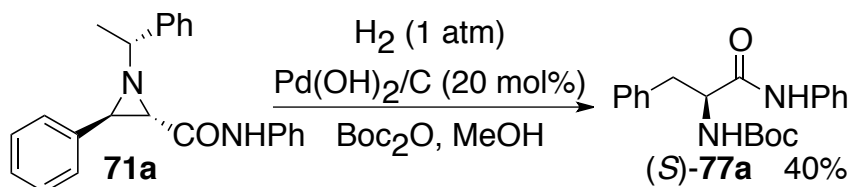
Since the asymmetric inductions for the *trans*-aziridines derived from aliphatic aldehydes and nonchiral amines were not generally as high as they were for those from aromatic aldehydes, we decided to explore the *trans*-aziridination reactions of the imines (*R*)-**45g-i** derived from aliphatic aldehydes. The results for the aziridination reaction of chiral imines from primary, secondary and tertiary aliphatic aldehydes and diazoacetamide **19** are summarized in Table 2.8. Similar to what we found with imine (*R*)-**45a**, there is a strong matched relationship between (*R*)-**45i** and the (*R*)-enantiomer of the ligands with high diastereomeric ratios and good yields. The (*R*)-VAPOL and (*R*)-VANOL catalysts gave equally good profiles with chiral imine (*R*)-**45i**. It is not clear why the *trans*-aziridination of the imine (*R*)-**45i** and diazoacetamide **19** gives the *trans*-aziridine **71i** in excellent yields while the reaction of the same substrate with EDA only gives low yields of *cis*-aziridine **43i** (Table 2.5). It is not surprising to note that matched/mismatched cases were also found with chiral imine (*R*)-**45g** and (*R*)-**45h** but what is so unexpected is to observe that the matched reaction for (*R*)-**45g** or (*R*)-**45h** is with the (*S*)-ligands. A very high diastereomeric ratio (>96:4) for **71g:72g** was observed with good isolated yields for the **71g** in the reaction of (*R*)-**45g** and diazoacetamide **19** with the (*S*)-catalyst. In addition, no detectable amount of the other diastereomer **72g** could be found in these matched reactions. The same situation was found with (*R*)-**45h**. All the *trans*-aziridination reactions with (*R*)-**45h** were sluggish, with 64-87% conversion after 24 h at room temperature. A 97:3

Table 2.8		cont'd				
10		B(OPh) ₃ only	100	91:9	42	4
11		(S)-VAPOL	87	97:3	69	2
12	 (R)- 45h	(R)-VAPOL	70	50:50	30	30
13		(S)-VANOL	81	>97:3	61	<2
14		(R)-VANOL	63	67:33	19	10
15		B(OPh) ₃ only	64	83:17	42	8

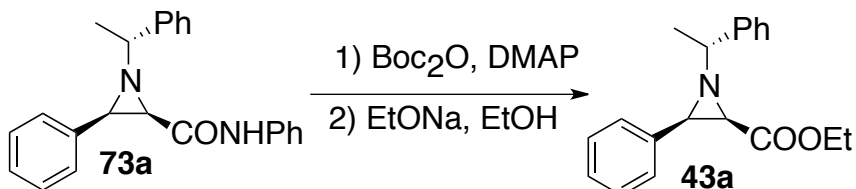
^a Unless otherwise stated all reactions were run at 0.2 M in imine with 1.2 equiv diazoacetamide **19** and 10 mol% catalyst in toluene at rt for 24 h. The catalyst was prepared from 1.0 equiv of the ligand, 3.0 equiv of BH₃•SMe₂, 2.0 equiv of PhOH and 3.0 equiv H₂O according to the general procedure (Method B). nd = not determined. ^b Determined from the ¹H NMR spectrum of the crude reaction mixture. ^c Isolated yield after chromatography on silica gel. ^d Yield from ¹H NMR spectrum of the crude reaction mixture based on the isolated yield of **71**.

The assignment of the relative stereochemistry of *trans*-**71a** was made by conversion to the phenylalanine derivative **77a** of the known optical rotation (Scheme 2.9).^{28a, 35} The relative stereochemistry of the *cis*-aziridine **73a** was determined by its conversion to **43a** (Scheme 2.10). Comparison of **43a** with (2*R*,3*R*)-**43a** obtained from aziridination of (*R*)-**43a** and EDA confirmed its stereochemistry. The stereochemistry of *trans*-**71i** was assumed to be the same as *trans*-**71a** since there are the same matched and mismatched relationships between the chiral imines and the (*R*)-enantiomer of the ligands. The relative stereochemistry of *trans*-**71h** was determined by X-ray analysis which showed *trans*-**71h** and **71a** gave the same relative stereochemistry in the major diastereomers in the matched cases even though the matched case for (*R*)-**45a** is with the (*R*)-catalyst and for (*R*)-**45h** is with the (*S*)-catalyst. The aziridine *trans*-**71g** was assumed to have the same relative stereochemistry as *trans*-**71h**.

Scheme 2.9 Catalytic hydrogenation of **71a** to (S)-**77a**



Scheme 2.10 Conversion of *cis*-aziridine **73a** to **43a**

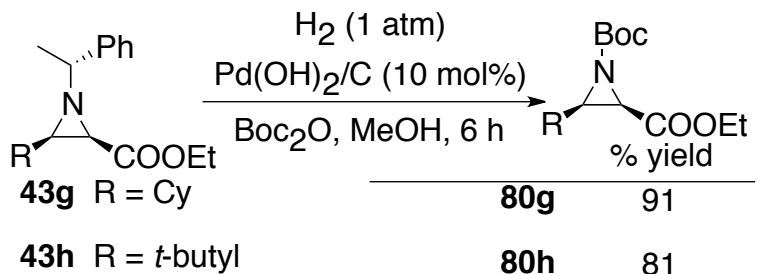


2.5 Synthesis of α - and β -amino acid derivatives

The regio- and stereoselective ring opening reactions of aziridine 2-carboxylate esters serve as valuable methods for access to a structurally diverse array of α and β -amino acids.³⁶ Activation of the aziridine nitrogen by an electron-withdrawing group (acyl, carbamoyl, sulfonyl) or by Brønsted or Lewis acids promotes either C2 cleavage to give β -amino acids or C3 cleavage to give α -amino acids (Scheme 2.11).³⁶ Since ring opening does not affect the stereochemistry at C2 or C3, the aziridine stereochemistry is maintained in the amino acid product. The ring substituents and the reaction conditions determine stereo- and regioselectivity of the ring opening. With C3 aryl or vinyl substituted aziridines, catalytic hydrogenation regiospecifically cleaves the benzylic/vinyl C-N bond in unactivated and sulfonyl-activated aziridine carboxylates.³⁷ In the absence of a C3 benzylic or vinyl aziridine substituent, hydrogenation occurs at C2 for mono- and disubstituted aziridine-2-carboxylates to give β -amino esters.³⁸

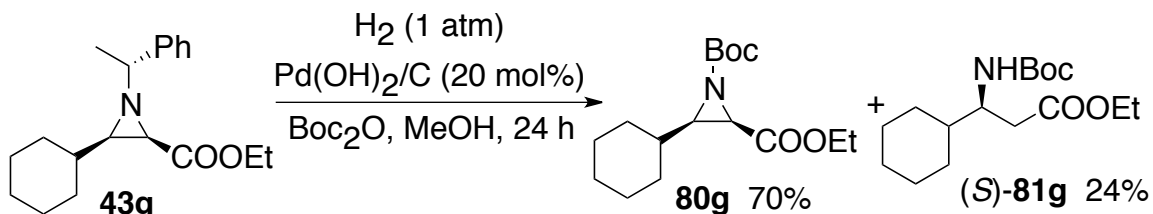
In the cases of the alkyl-substituted *cis*-aziridines **43g-h**, deprotection occurred without reductive ring opening to give the *N*-Boc protected aziridines **80g-h** in high yields (Scheme 2.13).

Scheme 2.13 Hydrogenation of C3-alkyl substituted aziridines



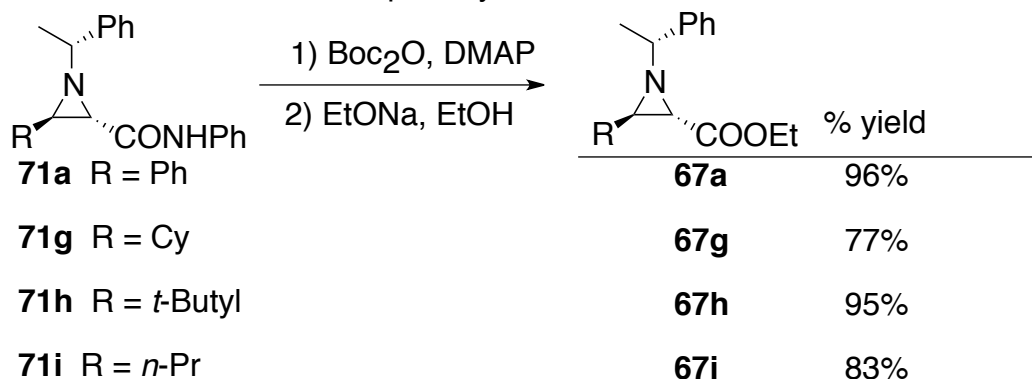
However, hydrogenation of aziridine **43g** with a high catalyst loading and prolonged reaction time did provide some of the C2 cleavage product **81g** in 24% yield along with a 70% yield of the *N*-Boc protected aziridine **80g** (Scheme 2.14). This indicated that debenzoylation of the chiral auxiliary was occurring faster than the reductive ring cleavage which is consistent with previous results.^{38b}

Scheme 2.14 Hydrogenation of **43g** under conditions that give a mixture



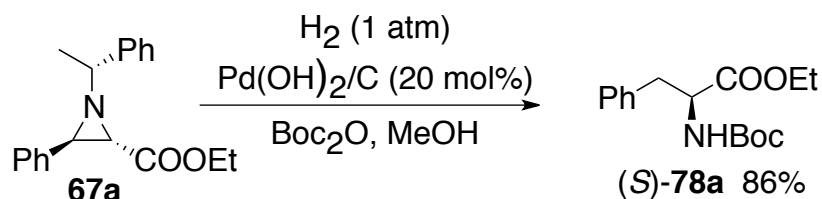
The direct reductive ring opening of the *trans*-aziridine amide **71a** to give the phenylalanine derivative **77a** suffered a low isolated yield (Scheme 2.9). In order to increase the efficiency of this reaction, the amide group was first converted to an ester group.³⁹ The treatment of *trans*-aziridine amides with Boc_2O and DMAP, and subsequent alcoholysis with sodium ethoxide afforded the corresponding *trans*-aziridine esters **67** in good yields as summarized in Scheme 2.15.

Scheme 2.15 Conversion of a primary amide to an ester



When the *trans*-ester **67a** was subjected to catalytic hydrogenation, the C2 cleavage product was formed as anticipated giving the phenylalanine derivative **78a** in a much higher yield (86%) (Scheme 2.16) than was observed for the hydrogenolysis of the corresponding amide (Scheme 2.9).

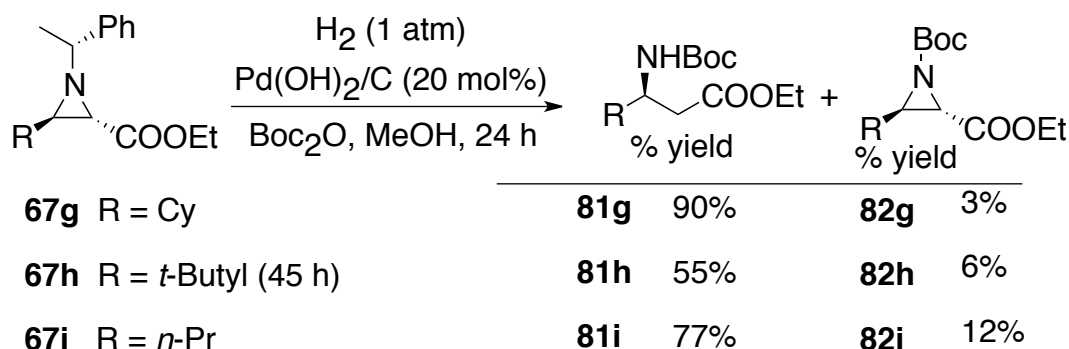
Scheme 2.16 Hydrogenation of *trans*-aziridine ester **67a**



Unlike 3-alkyl substituted *cis*-aziridine esters **43g**, which gave predominantly the non-ring opened *N*-Boc protected aziridines (Scheme 2.14), 3-alkyl substituted *trans*-aziridine esters **67g-i** under the same conditions underwent smooth reductive ring opening to give the β -amino acid esters **81g-i** in a moderate to high yield with only a small amount of *N*-Boc protected *trans*-aziridines **82g-i**. As shown in Scheme 2.17, the yields are highly dependent on the nature of the 3-substituent. In cases of *n*-propyl and cyclohexyl as the 3-substituent, β -amino acid esters **81g** and **82i** were obtained in 77% and 90% yield, respectively. Reductive ring opening of **67h** was sluggish: even after 45 h, the β -amino ester was obtained in only 55% yield. A direct comparison of the

hydrogenation of the *cis* and *trans*-aziridine esters **43g** and **67g** indicated that the reductive ring opening of *trans*-aziridine ester **67g** occurs with a faster reaction rate. This might be due to the better coordination of the C2-N bond of the *trans*-aziridine esters with the heterogeneous catalyst.

Scheme 2.17 Hydrogenation of 3-alkyl substituted *trans*-aziridines to give β -amino acids as the major product



2.6 Conclusion

A significant matched/mismatched relationship has been observed in both *cis*- and *trans*-aziridination reaction of chiral imines derived from chiral α -methylbenzylamine. This double stereo-differentiation study not only provides an excellent approach to *cis*- and *trans*-aziridines but also provides information about the interaction of the substrate and the catalyst. Chromatographic purification allows for easy separation of any minor diastereomers that may have been formed and gives the desired aziridines in good yields and high optical and diastereomeric purity. Reductive ring opening of these aziridines *via* hydrogenation with Pd(OH)₂/C in the presence of Boc₂O allows the efficient synthesis of α - and β -amino acids. The attractive features of this protocol lie in the use of commercially available and inexpensive α -methylbenzylamine, the

high diastereoselectivities and yields observed in both *cis*- and *trans*-aziridination reactions in combination with the perfect optical purity of the final aziridine products.

CHAPTER THREE

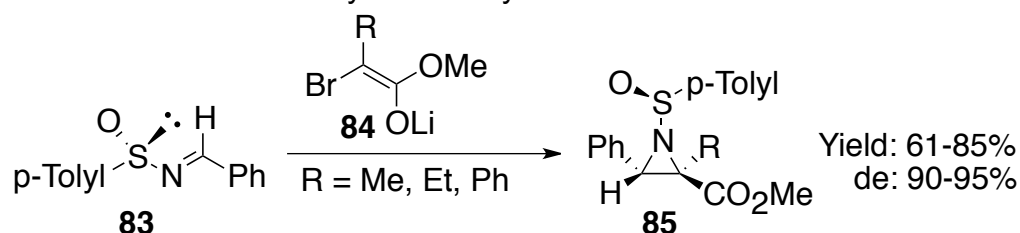
CATALYTIC ASYMMETRIC SYNTHESIS OF TRI-SUBSTITUTED AZIRIDINES

3.1 Introduction

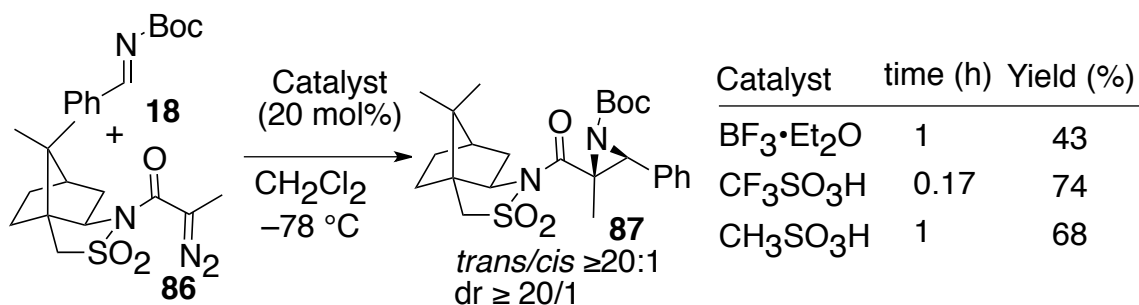
Among the various strategies for the preparation of aziridines demonstrated in Chapter 1, the Brookhart-Templeton aziridination,^{14a} wherein the reaction of aldimines and diazo compounds is catalyzed by a Lewis acid, is considered to be the most elaborated system. Significant advances in the asymmetric catalytic variants of this reaction for the synthesis of *cis*- and *trans*-disubstituted aziridines have been made during the last few years.^{9,10,16,24,28} When it comes to the catalytic asymmetric synthesis of tri-substituted aziridines, neither this method nor any other methodology of making di-substituted aziridines provides a general solution. The successful methods reported to date for the asymmetric synthesis of tri-substituted aziridines in a straightforward manner are based on the use of chiral auxiliaries.⁴⁰ The asymmetric aza-Darzens synthesis of *N*-(*p*-toluenesulfinyl)aziridine-2-carboxylate ester **85** from a chiral sulfinimine **83** has been developed in Davis's group (Scheme 3.1).^{40a,c,d,g} The one-step aza-Darzens reaction of sulfinimine **83** with lithium α -bromoenolate **84** readily affords diversely substituted tri-substituted aziridine carboxylate esters **85** in good yields and excellent diastereoselectivities. In addition, Maruoka's group has established a protocol for the asymmetric synthesis of tri-substituted aziridines by use of a camphor derived chiral auxiliary (Scheme 3.2).^{40i,j} A Brønsted acid-catalyzed

reaction of α -substituted α -diazocarbonyl compound **86** bearing camphorsultam as chiral auxiliary with the *N*-alkoxycarbonyl imine **18** was implemented as an unprecedented means to provide tri-substituted aziridines **87** in a highly stereo-defined manner. In contrast to these methods with chiral auxiliaries, there are only scattered and isolated examples of catalytic asymmetric syntheses of tri-substituted aziridines.⁴¹ A general method for the direct catalytic asymmetric synthesis of tri-substituted aziridines is still lacking.

Scheme 3.1 aza-Darzens asymmetric syntheses of trisubstituted aziridines



Scheme 3.2 Acid-catalyzed aziridination of α -diazocarbonyl compounds and imines



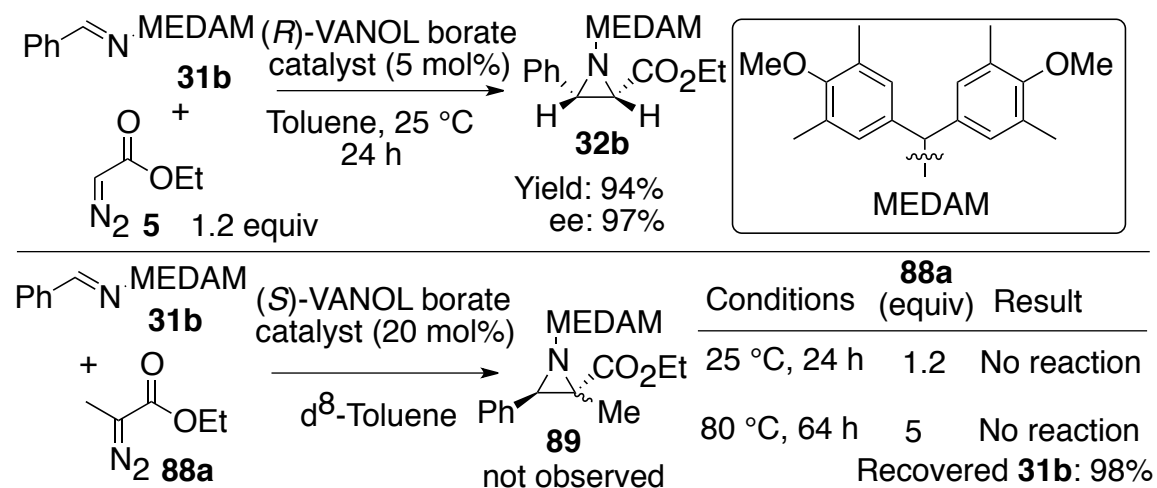
3.2 Catalytic asymmetric aziridination of imine 18 and diazo ester 88

In this context, we set out to investigate the reaction of imine **31b** derived from benzaldehyde and MEDAM amine and ethyl α -diazopropionate **88a** with our precatalyst since this is among the best imine substituent we have identified.^{26d}

The aziridination of MEDAM imine **31b** and EDA is ten times faster and gives much higher yield and asymmetric induction than the corresponding benzhydryl

imine. For example, with 5 mol% VANOL borate catalyst, the reaction of imine **31b** and EDA gives aziridine **32b** in 94% yield and 97% ee after 24 h at room temperature. Unfortunately, the reaction of imine **31b** and α -diazopropionate **88a** was tried in vain. Scheme 3.3 clearly shows the ineffectiveness of the synthesis of tri-substituted aziridine **89** from imine **31b** and ethyl α -diazopropionate **88a**. After 24 h at room temperature, there was no reaction observed for imine **31b** and disubstituted diazo **88a**. Even with 20 mol% catalyst at 80 °C for 64 h with 5 equivalent of imine **31b**, there was no detectable amount of the desired product observed, but rather only a 98% recovery of imine **31b**.

Scheme 3.3 Failed attempts towards a tri-substituted aziridine synthesis



It was thus clear that a much more reactive imine would be required to effect the union with a diazo ester in which the diazo carbon is disubstituted. According to the scale of the electrophilicity of similar reactions in DMSO, *N*-*tert*-butoxycarbonyl-substituted (*N*-Boc) imines would be much more reactive than imine **31b**.⁴² To our delight, the introduction of a Boc group on the imine nitrogen was indeed sufficient enough to induce reactivity even at –78 °C as indicated in

Table 3.1. It was quickly found that the catalyst prepared from the VAPOL ligand gave very low asymmetric induction whereas the one from VANOL under the same conditions gave the tri-substituted aziridine *trans*-**90a** in 83% ee (entry 2 vs entry 3). The yield for the two ligands was about the same but the *trans*:*cis* selectivity was higher for the VANOL catalyst. This striking difference between the two ligands was unexpected, since the two give comparable results for *cis*²⁶ and *trans*-disubstituted²⁸ aziridines. With the VANOL catalyst, the yield and asymmetric induction did not increase or decrease with increased time (entry 3-5). The yield did not depend on the amount of the diazo ester used (entry 6). The asymmetric induction did not change when the temperature was lowered to –100 °C (entry 7). If the catalyst was added as a precooled solution, the asymmetric induction went up to 93% ee with 46% isolated yield (entry 8). Lowering the catalyst loading to 10% or 5% would make the yield and asymmetric induction fall to some extent (entry 9-10). Different catalyst preparation procedures do have an effect on the *trans*:*cis* selectivity and the yield but essentially no effect on the asymmetric induction (entry 8 vs entry 10). Tri-substituted aziridines could also be obtained for diazo compounds **88b** and **88c**, but the more hindered **88d** with an *iso*-propyl group on the diazo carbon failed to give any detectable amount of aziridine under the same reaction conditions.

Table 3.1 Catalytic asymmetric aziridination of α -diazoo esters ^a

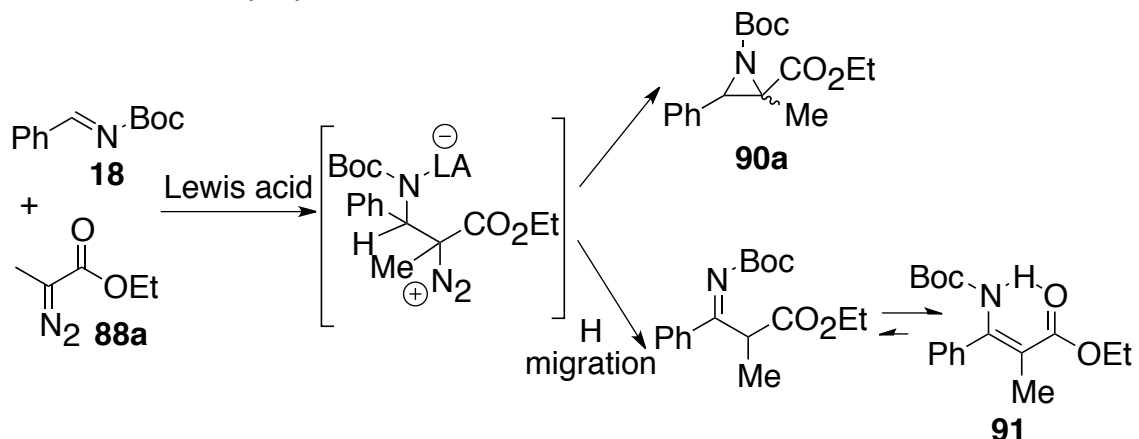
entry	88	R	ligand	mol %	time (min)	<i>trans</i> / <i>cis</i> ^b	%yield <i>trans</i> ^{b,c}	% ee <i>trans</i> ^d	% yield 91 ^b
1 ^e	88a	Me	TfOH	20	15	3:1	42	–	25
2 ^f	88a	Me	(<i>R</i>)-VAPOL	20	60	12:1	49	–5	14
3	88a	Me	(<i>R</i>)-VANOL	20	15	20:1	48	83	13
4	88a	Me	(<i>R</i>)-VANOL	20	60	20:1	48	83	13
5	88a	Me	(<i>R</i>)-VANOL	20	240	20:1	48	84	13
6 ^g	88a	Me	(<i>R</i>)-VANOL	20	15	nd	45	nd	12
7 ^h	88a	Me	(<i>R</i>)-VANOL	20	15	10:1	32	86	9
8 ^{e,f}	88a	Me	(<i>S</i>)-VANOL	20	15	20:1	(46)	–93	12
9 ^f	88a	Me	(<i>R</i>)-VANOL	10	30	25:1	36	84	9
10 ^f	88a	Me	(<i>R</i>)-VANOL	5	30	25:1	34	83	11
11 ^{e,f,i}	88a	Me	(<i>R</i>)-VANOL	20	15	14:1	27	88	23
12 ^f	88b	Et	(<i>S</i>)-VANOL	20	60	16:1	(32)	–82	nd
13 ^f	88c	<i>n</i> -Pr	(<i>S</i>)-VANOL	20	60	5:1	(25)	–70	nd
14 ^f	88d	<i>i</i> -Pr	(<i>S</i>)-VANOL	20	60	–	≤1	–	–

^a Unless otherwise specified, all reactions were performed with a solution of 0.10 mmol of the diazo compound **88** with 2.0 equiv of imine **18** in 0.6 mL CH₂Cl₂ at –78 °C. A solution of the catalyst in 0.4 mL CH₂Cl₂ was then added dropwise over a few minutes and then the solution was allowed to stir for the indicated time after which the reaction was quenched by the addition of 0.5 mL of Et₃N. The catalyst was prepared by heating 1 equiv of the ligand, 3 equiv BH₃•Me₂S, 2 equiv PhOH, and 3.0 equiv of H₂O in toluene at 100 °C for 1 followed by the removal of volatiles at 100 °C for 0.5 h at 0.1 mmHg. The residue was then taken up in the proper amount of CH₂Cl₂ to have the desired catalyst in 0.4 mL. ^b Determined from the ¹H NMR spectrum of the crude reaction mixture with Ph₃CH as internal standard. ^c The yields in parentheses are isolated yields after silica

Table 3.1 cont'd
 gel chromatography.^d Determined by HPLC on purified *trans*-**90**. When *trans*-**90** is not purified, % ee was determined on the reaction mixture that was passed through silica gel. A minus sign indicated that the (2*R*,3*S*)-isomer of *trans*-**90** is formed.^e 3.0 equiv of imine was used.^f The catalyst was added as a solution precooled to -78 °C.^g Reaction was performed with 0.10 mmol imine and 4.0 equiv of diazo ester **88a**.^h Solvent is 3:2 mixture of Et₂O and CH₂Cl₂ (1.0 mL in total) and the temperature was -100 °C.ⁱ Catalyst was prepared as in footnote a except that the ratio of VANOL:PhOH:BH₃•Me₂S was 1:1:1 and no H₂O was used.

As also observed in the synthesis of disubstituted aziridines, enamine products are also formed in this reaction^{14a}, which result from a 1,2-migration of H to the incipient carbocation to yield **92** as the primary product as shown in Scheme 3.4.

Scheme 3.4 The proposed mechanism for the formation of **90a** and **91**



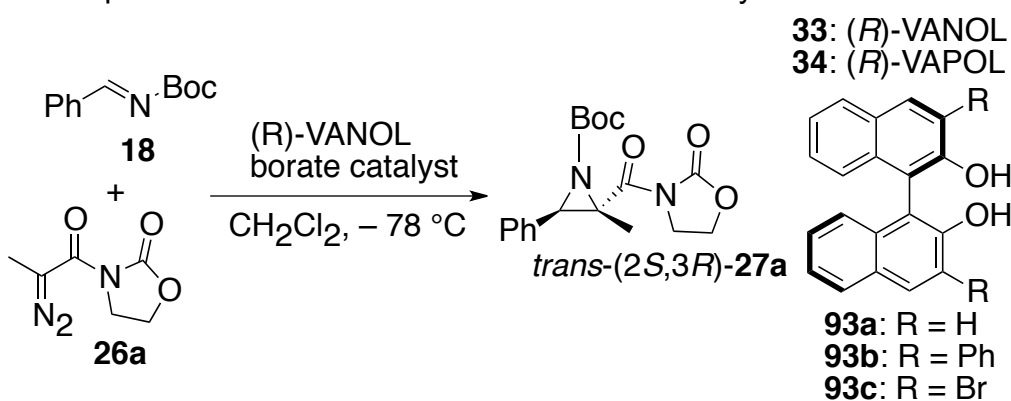
3.3 Catalytic asymmetric synthesis of tri-substituted aziridines from *N*-Boc imines and α -diazo-*N*-acyloxazolidinone **26**

3.3.1 Optimization of the tri-substituted aziridine synthesis from **18** and **26a**

While reactions with diazo ester **88** gave good asymmetric inductions, the yields of the tri-substituted aziridines were moderate. To improve the yields, we turned our attention to the screening of different diazo compounds. As had been demonstrated by Maruoka's group, the nature of the group attached to the

carbonyl carbon of the diazo compound has a drastic influence on the reaction pathway observed in their studies.^{18,19,43} We were thus pleased to find that α -diazo carbonyl compound **26a** having an oxazolidin-2-one unit as the carbonyl substituent reacted with imine **18** in the presence of the VANOL catalyst to give aziridine **27a** in 80% yield and 94% ee with >100:1 selectivity for the *trans*-diastereomer (entry 1, Table 3.2).

Table 3.2 Optimization of the aziridination of α -diazo-*N*-cyclooxazolidinone^a



entry	ligand	mol %	solvent	time (h)	conv % ^b	%yield <i>trans</i> - 27a ^c	%ee <i>trans</i> - 27a ^d
1	(<i>R</i>)- 33	20	CH ₂ Cl ₂	4	100	80	94
2	(<i>R</i>)- 34	20	CH ₂ Cl ₂	4	66	21	−8
3	(<i>R</i>)- 93a	20	CH ₂ Cl ₂	4	92	56	40
4 ^e	(<i>R</i>)- 93a	60	CH ₂ Cl ₂	4	100	65	−16
5	(<i>R</i>)- 93b	20	CH ₂ Cl ₂	4	100	79	53
6	(<i>R</i>)- 93c	20	CH ₂ Cl ₂	4	65	14	0
7	(<i>R</i>)- 33	10	CH ₂ Cl ₂	4	100	78	90
8	(<i>S</i>)- 33	10	toluene	6	96	74	−84
9	(<i>S</i>)- 33	10	THF	8	93	67	−77
10	(<i>S</i>)- 33	10	Et ₂ O	8	100	83	−79

Table 3.2 cont'd

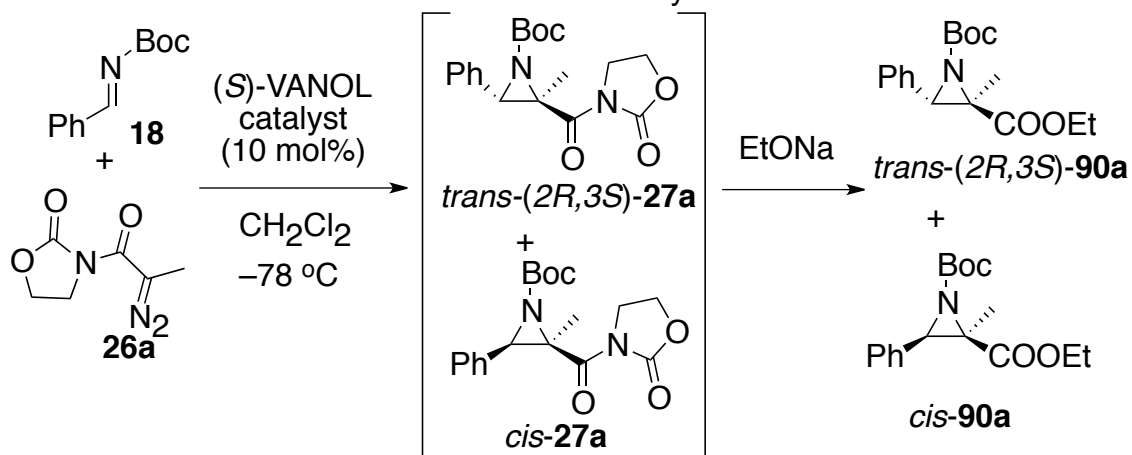
11 ^f	(S)- 33	10	CH ₂ Cl ₂	4	100	78	–94
12 ^{f,g}	(S)- 33	10	CH ₂ Cl ₂	6	98	72	–94
13 ^{f,h}	(S)- 33	10	CH ₂ Cl ₂	6	85	58	–94
14 ^{f,i}	(S)- 33	20	CH ₂ Cl ₂	4	100	80	–95

^a Unless otherwise specified, all reactions were performed with a solution of 0.10 mmol of the diazo compound **26a** with 3.0 equiv of imine **18** in CH₂Cl₂ at –78 °C at 0.2 M in **26a** with 10 mol% catalyst and 0.1 M with 20 mol% catalyst. A solution of the catalyst in a proper amount of CH₂Cl₂ to give the desired concentration was then added dropwise over a few minutes and then the solution was allowed to stir for the indicated time after which the reaction was quenched by the addition of 0.5 mL of Et₃N. The catalyst was prepared as described in Table 3.1. ^b Determined from the ¹H NMR spectrum of the crude reaction mixture with Ph₃CH as internal standard. ^c Isolated yields after silica gel chromatography. ^d Determined by HPLC on purified *trans*-**27a**. A minus sign indicates that the (2*R*,3*S*)-isomer of *trans*-**27a** is formed. ^e Catalyst was prepared by heating 2 equiv BINOL **93a** and 1 equiv BH₃•Me₂S in toluene at 100 °C for 1 h followed by removal volatiles at 100 °C for 0.5 h at 0.1 mm Hg. ^f The catalyst was added as a solution precooled to the reaction temperature. ^g 2.0 equiv imine was used. ^h 1.5 equiv imine was used. ⁱ Catalyst was prepared as indicated in footnote i of Table 3.1.

Ideally, it would be the most desirable to have an authentic sample of the aziridine *cis*-**27a** to determine the *trans*:*cis* selectivity. Unfortunately, we were not able to obtain *cis*-**27a** with the route that was planned, which will be discussed in detail in Chapter 4. Therefore an alternative strategy was taken to determine the *trans*:*cis* selectivity of the reaction of imine **18** and diazo compound **26a** (Scheme 3.5). Specifically, the crude reaction mixture was treated with excess sodium ethoxide to generate a mixture of the *cis*- and *trans*-ester **90a**. Since we have authentic samples of both the *cis* and *trans*-isomer **90a**, it could be determined

that the *trans/cis* selectivity was $\geq 100:1$ by ^1H NMR spectroscopy with the aid of standard solutions varying from 50:1 to 200:1. This in turn suggests that the diastereomeric ratio for *trans*-**27a** and *cis*-**27a** was $\geq 100:1$ as determined by the ^1H NMR spectrum of the crude reaction mixture.

Scheme 3.5 Determination of *trans:cis* selectivity of the reaction of **18** and **26a**



As with diazo ester **88a**, the VAPOL catalyst gave very low and reversed asymmetric induction for the α -diazoacetylloxazolidinone **26a**. The catalyst prepared from the BINOL ligands **93a-c** did not give useful stereoselectivities (entry 3-6). Although the reaction with BINOL **93a** went to completion, the yield was moderate with low induction. The asymmetric induction did increase to 53% when the 3,3'-diphenyl BINOL ligand **93b** was used whereas the 3,3'-dibromo BINOL ligand **93c** gave incomplete reaction with no asymmetric induction. Thus, VANOL is still the ligand of choice for this reaction. Different solvents were also examined (entry 7-10). However, it was found that there was not a strong impact of the solvent upon the reaction, although methylene chloride did give the best asymmetric induction. When the catalyst was added as a precooled solution ($-78\text{ }^\circ\text{C}$), the asymmetric induction increased from 90% to 94% ee (entry 7 vs entry

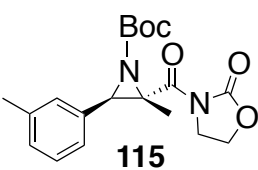
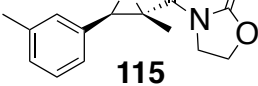
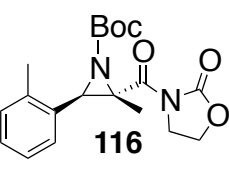
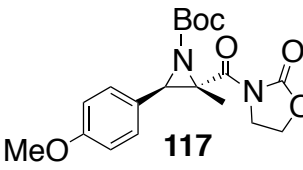
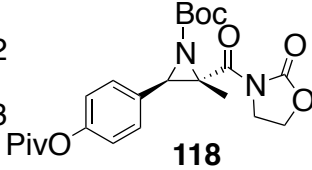
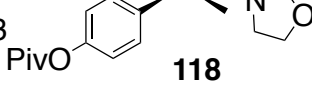
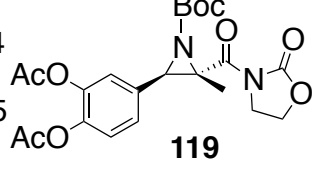
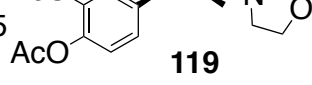
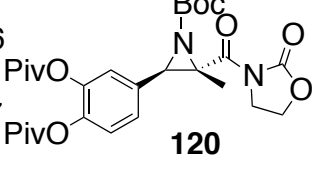
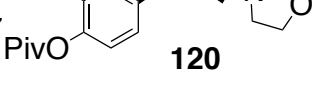
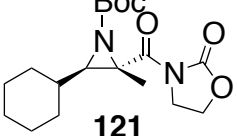
11). The yield for *trans*-**27a** was highly dependent on how much excess imine **18** was employed (entry 11-13). With 2 equivalents of imine **18** instead of 3 equivalents, the *trans*-aziridine **27a** could be obtained with no loss in the asymmetric induction and only a slight decrease in the isolated yield (entries 11 vs 12). Different catalyst preparation procedures within the same protocol gave comparable results in terms of both yields and asymmetric induction (entry 11 vs entry 14). The optimized protocol was identified as that presented in entry 12 of Table 3.2.

3.3.2 Substrate scope for the catalytic asymmetric synthesis of tri-substituted aziridines

With the optimal conditions in hand, the scope of this catalytic asymmetric tri-substituted aziridine synthesis was investigated in detail and the results are summarized in Table 3.3 and 3.4. Irrespective of the substituent pattern and electronic property of the aromatic ring of the *N*-Boc imines, the reaction generally proceeded smoothly and uniformly excellent asymmetric induction was observed for nearly all substrates. The reaction with electron-withdrawing groups are generally faster and *para*-substituents give slightly higher inductions. The asymmetric induction falls off a bit with the *meta*-bromo substituent (entries 13-15, Table 3.3). The reaction of the *para*-methyl aryl imine **100** is slower, requiring 27 hours to go to completion with 10 mol% catalyst, but the asymmetric induction was excellent (96% ee) (entries 16-17, Table 3.3). The *meta*-methyl substituted aryl imine **101** gives good yield with 10 mol% catalyst after 8 hours (entries 18-19, Table 3.3). The *ortho*-methyl substituents is not tolerated and there is

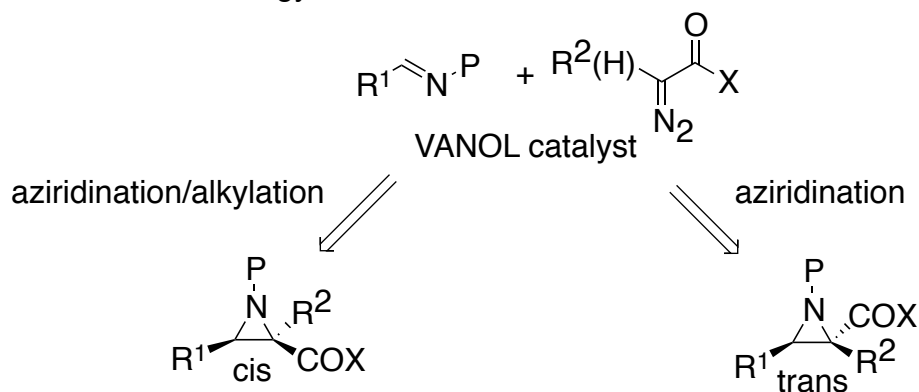
essentially no reaction for imine **102** even with 20 mol% VANOL catalyst after 9 hours. Although *para*-methoxy substituted aryl imine **103** was more reactive than the *ortho*-methyl imine **102**, it only went to 40% conversion in 11 h with 20 mol% catalyst and gave a 15% yield of aziridine. As a surrogate for the *p*-methoxy imine **103**, we were pleased to find that the 4-pivaloyloxybenzaldehyde *N*-Boc imine **104** provided *trans*-aziridine **118** in 69% yield and 98% ee (entry 23, Table 3.3). Even 3,4-dioxycarbonyl substituted aryl imines are tolerated in the reaction. The reaction of the imine prepared from 3,4-diacetoxyl benzaldehyde went smoothly to give the desired *trans*-product **119** in good yield and good asymmetric induction (entry 24-25, Table 3.3). A similar situation was found with the imine from 3,4-dipivaloyoxybenzaldehyde (entry 26-27, Table 3.3). At present, this method is not applicable to the reaction of *N*-Boc imines derived from aliphatic aldehydes: under the reaction conditions, imine **107** gave no reaction at all. Finally, α -ethyl-substituted diazo compound **26b** could also be utilized as well, giving the corresponding *trans*-aziridines in good yields and excellent asymmetric inductions (Table 3.4). The reaction of imine **18** with **26b** was much slower than that with **26a**, and it went to only 70% conversion even after 30 h with 10 mol% catalyst. The asymmetric induction also dropped to 85% ee which is to be compared with 90% ee from the reaction of the same imine and **26a** (entry 12, Table 3.2). Introduction of an electron-withdrawing group bromo substituent into the imine increased not only the rate of the reaction of imine **96** and diazo **26b** but also the asymmetric induction (entry 3-4, Table 3.4).

Table 3.3 cont'd

18		101	(<i>R</i>)-VANOL	20	8	100	83	92
19		101	(<i>S</i>)-VANOL	10	6	84	71	-92
20		102	(<i>R</i>)-VANOL	20	9	--	trace	--
21		103	(<i>R</i>)-VANOL	20	11	40	15	--
22		104	(<i>R</i>)-VANOL	20	1	100	67	98
23		104	(<i>R</i>)-VANOL	10	11	87	69	98
24		105	(<i>R</i>)-VANOL	20	11	100	69	88
25		105	(<i>R</i>)-VANOL	10	11	88	65	88
26		106	(<i>R</i>)-VANOL	20	10	100	63	88
27		106	(<i>R</i>)-VANOL	10	10	85	46	88
28		107	(<i>R</i>)-VANOL	20	8	--	nd	--

^a Unless otherwise specified, all reactions were performed as indicated in footnote a in Table 3.2. ^b Determined from the ¹H NMR spectrum of the crude mixture with Ph₃CH as internal standard. ^c Isolated yields after silica gel chromatography. ^d Determined by HPLC on purified *trans*-aziridine. The absolute configuration was determined for *trans*-**27a** and this was assumed for all the other *trans*-aziridines. A minus sign indicated that the (2*R*,3*S*)-isomer of *trans*-aziridine is formed.

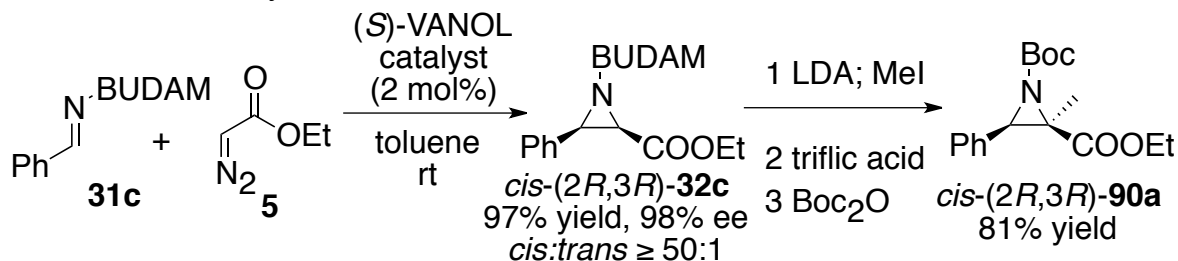
Scheme 3.6 General strategy for access to *cis* and *trans*-tri-substituted aziridines



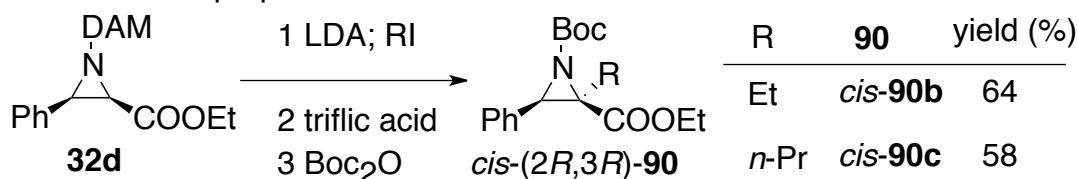
As shown in Scheme 3.7, *trans*-aziridine ester **90a** could be simply obtained from the ethanolysis of aziridine **27a** in high yield. Alternatively, *trans*-**90a** can be obtained directly from the aziridination of imine **18** with the diazo ester **88a** (Table 3.1). The *cis*-isomer of aziridine **90a** could be obtained in three steps starting from the disubstituted aziridine of the *cis*-**32c**. The reaction of the BUDAM imine **31c** and ethyl diazoacetate **5** with the VANOL catalyst provides the *cis*-aziridine **32c** in 97% yield and 98% ee. It has been reported previously that aziridines of the type **29** can be alkylated with methyl iodide with retention of the stereochemistry.⁴⁴ When *cis*-**32c** is thus methylated followed by removal of the BUDAM group with triflic acid and by protection of the nitrogen with Boc anhydride, *cis*-**90a** was furnished in 81% yield over three steps. It is noteworthy that the (*S*)-VANOL catalyst gives different facial selectivities with the imine **31c** and **18**. This indicates that the two aziridinations may occur by different mechanisms. The same chemistry could be applied to the preparation of *cis*-aziridines **90b** and **90c** which were employed as standards to determine the diastereoselectivities for the aziridination reactions of imine **18** and diazo ester **88b** and **88c** shown in Table 3.1 (Scheme 3.8). Thus, with the proper choice of

the catalytic asymmetric method and the proper choice of the chirality of the ligand, all four possible stereoisomers of tri-substituted aziridine-2-carboxylates can be obtained with high diastereoselectivity and optical purity.

Scheme 3.7 The synthesis of *cis* and *trans*-isomers of aziridine **90a**



Scheme 3.8 The preparation of *cis*-**90b** and *cis*-**90c**

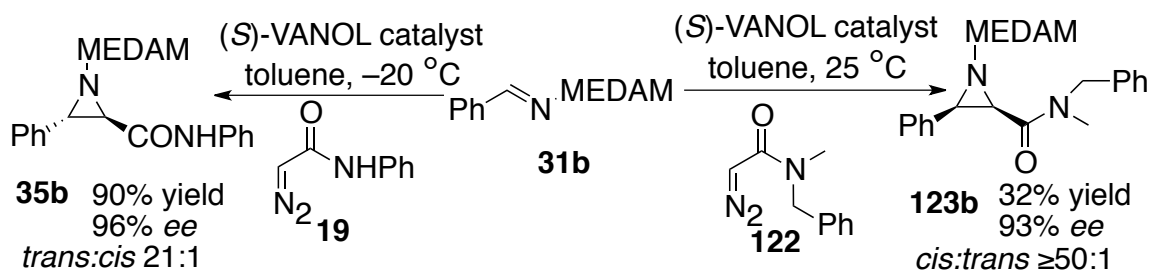


3.5 Attempts towards the direct catalytic asymmetric synthesis of *cis*-tri-substituted aziridines

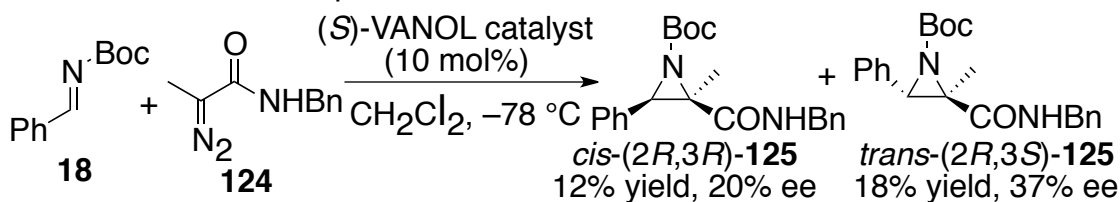
Although we have developed the indirect method to make *cis*-tri-substituted aziridine described above, it would be nice to have a route to *cis*-trisubstituted aziridine in a straightforward and direct manner from the reaction of the imines and diazo compounds. The possibility for direct access to *cis*-tri-substituted aziridines is suggested by previous observations made in our laboratory on control of *cis* and *trans* stereoselectivity in disubstituted aziridine synthesis. The reaction of the imine **31b** with the 3°-diazoacetamide **122** was found to give the *cis*-aziridine **123b** whereas the 2°-diazoacetamide **19** was found to give the *trans*-aziridine **35b** with the same imine **31b** (Scheme 3.9). Thus the question becomes whether a secondary diazoacetamide of the type **124** which has two

substituents on the diazo carbon also reverse the diastereoselectivity to directly give the *cis*-tri-substituted aziridines. When diazo acetamide **124** was subjected to the standard reaction conditions, it was disappointing to find that *trans*-aziridine **125** was still the major product, albeit in a low yield (Scheme 3.10). There is a large change in the level of the diastereoselectivity for the reaction from greater than 100:1 for diazo compound **26a** to 1.5:1 for the diazo compound **124**. The low yield and low asymmetric induction for both the *cis* and *trans*-tri-substituted aziridines **125** will need to be improved in any future investigation of this approach to *cis*-tri-substituted aziridines.

Scheme 3.9 The control of *cis:trans* selectivity by different diazoacetamides in disubstituted aziridine synthesis



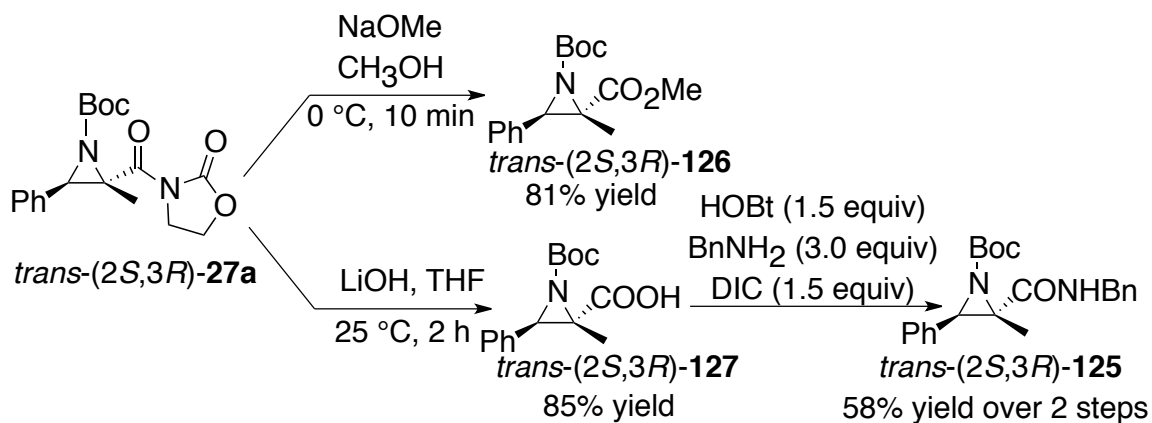
Scheme 3.10 The attempt towards a direct *cis*-tri-substituted aziridination



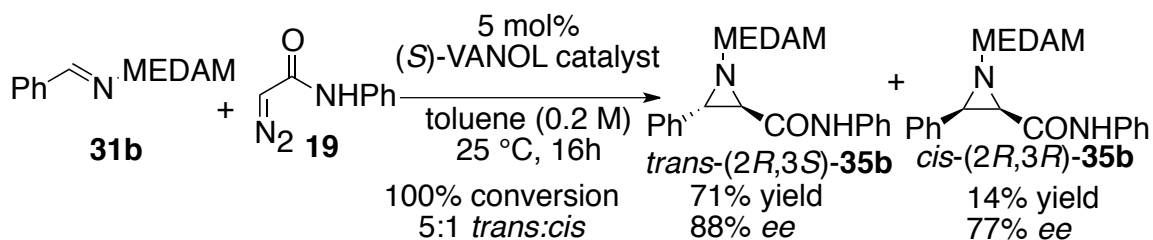
The synthetic utility of the *N*-oxazolidinone function group⁴⁵ of the tri-substituted aziridines is illustrated in the facile conversion of **27a** to the corresponding ester and the acid (Scheme 3.11). The treatment of *trans*-**27a** with methanolic sodium methoxide at $0\text{ }^{\circ}\text{C}$ for 10 min led to the formation of ester *trans*-**126** whose absolute configuration has been reported.⁴¹ⁱ Thus, this

conversion established the absolute configuration of *trans*-**27a**. Acid **127** could be obtained in 85% yield *via* the cleavage of oxazolidinone with LiOH at room temperature for 2 hours. The conversion of the resulting acid **127** to the amide **125** serves to identify the absolute configuration of the *trans*-aziridine **125** obtained from the reaction of the imine **18** and diazoacetamide **124** (Scheme 3.10). It is also interesting to note that the difference in the diastereoselectivity between *cis*- and *trans*-**125** is the result of the change in the facial selectivity to the imine **18** but not to the diazo compound **124**. The same situation was also observed in the catalytic asymmetric synthesis of *cis*- and *trans*-disubstituted aziridine **35b** from imine **31b** and diazoacetamide **19** (Scheme 3.12).

Scheme 3.11 The conversion of oxazolidinone aziridine **90a** to its corresponding ester and acid



Scheme 3.12 The configuration of *cis* and *trans*-aziridine from the reaction of imine **31b** and diazoacetamide **19**

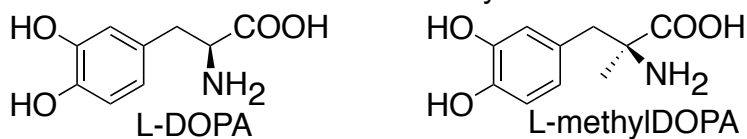


3.6 Synthesis of protected form of L-methylDOPA

There has been a large body of work devoted to the synthesis of α,α -disubstituted amino acids but only a few involve aziridines as intermediates.⁴⁶

The interest in α,α -disubstituted amino acids has been driven by their properties that differ from α -substituted amino acids including biological properties when incorporated into medicinal agents, structural properties as occurring in natural products and solid state properties when incorporated in new materials. One such example is L-DOPA and L-methylDOPA (Figure 3.1).⁴⁷ L-DOPA is used clinically in the treatment of Parkinson's disease, whereas, L-methylDOPA is an antihypertensive agent used in the treatment of high blood pressure, especially gestational hypertension.

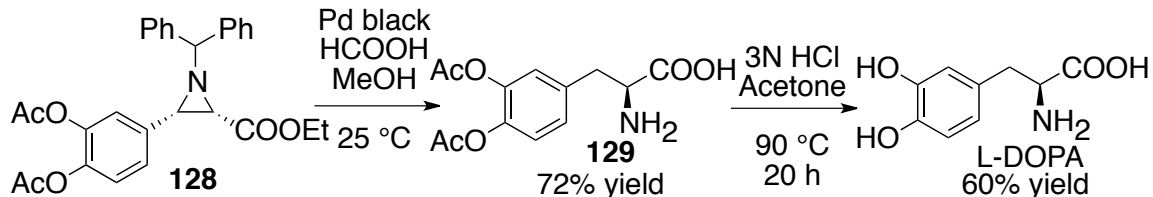
Figure 3.1 The structure of L-DOPA and L-methylDOPA



We have previously reported that the di-substituted aziridine *cis*-(2*S*,3*S*)-**128** can be used to access L-DOPA (Scheme 3.13).^{23b} Ring opening of *cis*-**128** via hydrogenolysis provided α -amino ester **129**, which was then treated with HCl in

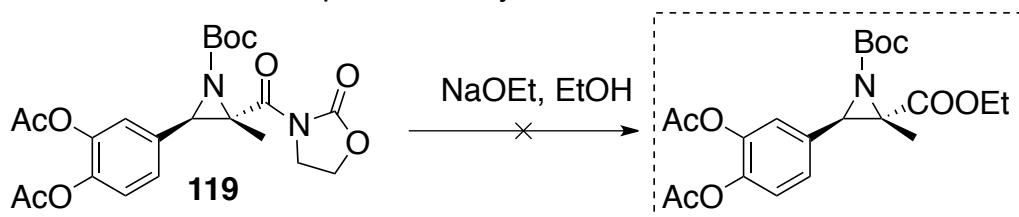
acetone for 20 hours to afford L-DOPA in a moderate yield.

Scheme 3.13 Synthesis of L-DOPA

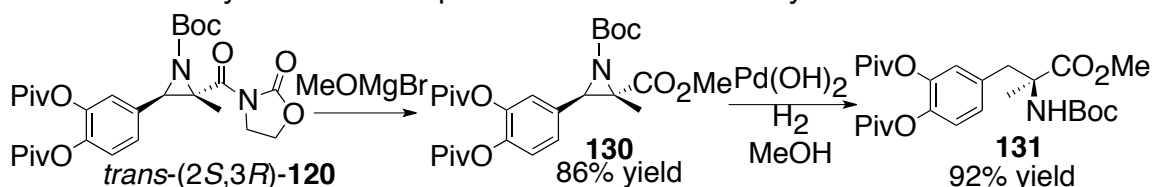


Herein, we show that the tri-substituted *trans*-(2*S*,3*R*)-aziridines described above can provide access to L-methylDOPA. The attempt at the cleavage of the oxazolidinone group from aziridine **119** failed. The treatment of *trans*-aziridine **119** with sodium ethoxide led to a messy crude mixture instead of the desired product as determined from the ^1H NMR spectrum (Scheme 3.14). This is probably due to the presence of the acetyl group that is known to be susceptible to strong basic conditions. The pivaloyloxy group has been proven to be more tolerant towards strong bases. The replacement of acetyl with pivaloyl groups did enable methanolysis of **120** with NaOMe in MeOH to give the methyl ester **130** in 41% yield. It was quickly found that the treatment of aziridine **120** with MeOMgBr^{45} also allows for the cleavage of oxazolidinone and provides a much improved yield of 86% (Scheme 3.15). As expected, catalytic hydrogenation of *trans*-aziridine ester **130** with Pearlman's catalyst provided the ring opening product, α,α -disubstituted amino ester **131** in 92% yield as a protected form of methyl-DOPA.

Scheme 3.14 Failed attempt of ethanolysis of aziridine **119**



Scheme 3.15 Synthesis of the protected form of L-methylDOPA



3.7 Brief study on the nature of the catalyst in the tri-substituted aziridination reaction

3.7.1 Effect of different species on the reaction system

After the development of the catalytic asymmetric tri-substituted aziridination, the next question to be addressed is what is the active catalyst in the reaction.

It has been reported that different catalyst preparation procedures allow for the generation of the B1 and B2 species in different ratios (Chapter 1).^{26a} The reaction was performed with catalysts enriched with either the B1 or B2 species (Table 3.5). With **26a** as the reactant, the enantioselectivity showed essentially no difference from the precatalysts having different B1 and B2 ratios. With **88a** as the reactant, the reaction went with decreased yield and enantioselectivity if the precatalyst with the least amount of B2 was used.

Table 3.5 Catalytic asymmetric aziridination with different catalyst preparation procedures ^a

Entry	B2:B1	Diazo	Time	Yield ^b (%)	ee ^d (%)
1 ^e	1:1.9	26a	4 h	80	94
2	1:0.4	26a	4 h	80	95
3	1:1.9	88a	15 min	46	93
4	1:0.4	88a	15 min	27 ^c	88

^a General procedure was followed as described in Table 3.1 for 20 mol% catalyst loading with a 1:1.9 B2:B1 ratio. The catalyst preparation procedure given in footnote i in Table 3.1 gave a 1:0.4 ratio of B2:B1. ^b Isolated yield after silica gel column chromatography; ^c Determined from ¹H NMR spectra of the crude reaction mixture with Ph₃CH added as internal standard; ^d Determined from chiral HPLC. When the product was not isolated. The crude reaction mixture was flushed through silica gel before HPLC analysis. ^e The catalyst solution was not precooled before addition to the reaction mixture.

It has been previously determined that B1 and B2 species can be assembled into a B3 species (boroxinate) in the presence of a basic component, such as an imine or an amine.³⁰ We were then wondering whether a similar process could be happening with the *N*-Boc imine. *N*-Boc imine **98** (from 4-fluorobenzaldehyde, Table 3.3) was chosen for study because it is a solid and easy to handle. We decided to use VAPOL in this study first because the bay region proton in the

VAPOL ligand is a convenient spectroscopic handle for probing the number of catalyst species that are generated as this proton is significantly deshielded relative to the rest of the aromatic protons. The B1 and B2 derivatives of VAPOL were generated in a ratio of 7:1. There is no profound difference observed in the chemical shift of B1 and B2 before and after the addition of the *N*-Boc imine **98** although the ratio of B2:B1 went up to 13:1 after imine was added. A new peak at ~5.5 ppm in the ^{11}B NMR spectrum was also found after the imine was added to the B1 and B2 mixture. A very similar situation was found with the VANOL derived catalyst where the ratio of B1 and B2 was 1.0:1.5 and did not change before and after imine **98** was added. There was also a new broad peak observed at 6.5 ppm in the ^{11}B NMR spectrum. The new peak in the ^{11}B NMR spectrum could be from a B3 (boroxinate) species or it could result from the imine coordinating B1 and B2 species which are acting as Lewis acids. At this point, it is not known whether the metaborate B1 and pyroborate B2 could function as a mono or bidentate Lewis acid and whether one or another or both could be active catalysts. Further work will be required to determine the structure of the catalyst for this reaction.

3.7.2 Aziridination reaction of imine **18** with different diazo compounds

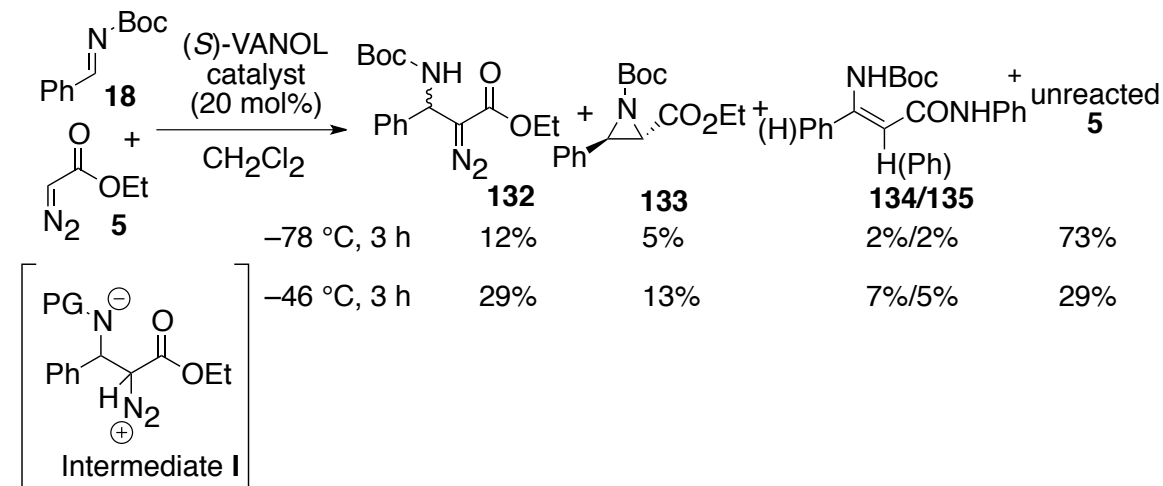
Unlike our *cis*-aziridination protocol, in which the reaction of imines of type **31** and EDA generally gives *cis*-aziridines in high yield and good asymmetric induction (Scheme 3.3), the electron poor *N*-Boc imine **18** reacted with EDA in the presence of our VANOL borate catalyst to afford the Friedel-Crafts adduct **132** in low yield (Scheme 3.16). It was also found that there was no *cis*-aziridine

detected in the reaction and only *trans*-aziridine **133** was observed (5% yield at –78 °C). When the reaction was performed at –46 °C, the Friedel-Crafts adduct **132** was obtained in 29% yield along with *trans*-aziridine **133** in 13% yield. Slightly more enamine products were obtained at –78 °C than at –46 °C. Tentative identification of enamines **134** and **135** was possible on the basis of comparison of their NMR data with similar compounds.^{18a} They showed a doublet (δ = ~10 ppm) assigned as the NH resonance. This low field shift is compatible with the existence of a hydrogen bond to the carbonyl group. In consideration of the electron density of the N attached to Boc group in intermediate **I** (Scheme 3.16) that makes the attack of the N to the α -carbon disfavored, it was not a surprise that the adduct **132** was formed as a major product instead of aziridines. Indeed, this result is consistent with what has been reported by Terada's⁴⁸ and Maruoka's group¹⁹ on the acid catalyzed Friedel-Craft type reaction of diazo esters with *N*-Boc imines. At this point, the reason why the *trans*-aziridine was obtained instead of *cis* remains unknown.

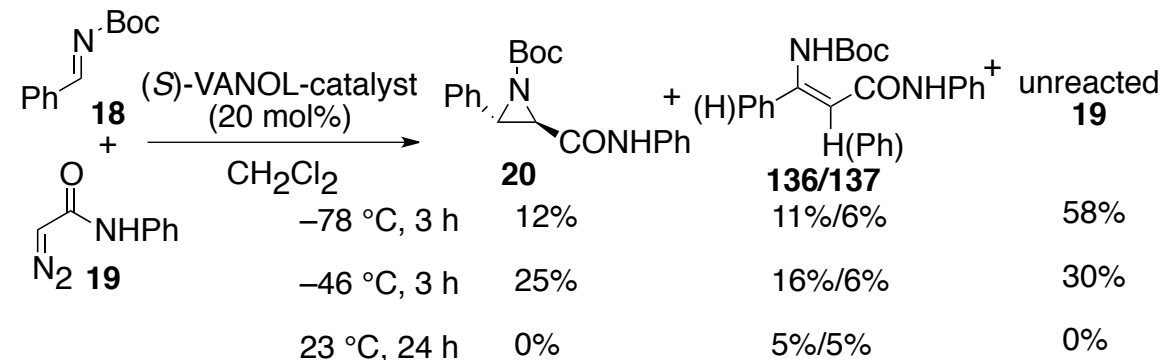
Our *trans*-aziridination protocol involves electron rich *N*-alkyl imines. Thus it was interesting to find that the aziridination also proceeded with *N*-Boc imine **18** and diazoacetamide **19** in the presence of our borate catalyst, albeit in a diminished yield. Scrutiny of the byproducts led to the confirmation of the enamine products **136** and **137** resulting from 1,2-hydride or aryl shift. Again, the identification of the enamines was based on the chemical shift (δ = ~10.5-11.0 ppm) assigned as carbamate NH resonance. Electron deficiency of nitrogen of imine **18** might be responsible for the low yield of *trans*-aziridine **20**. When the

reaction was performed at room temperature, no aziridines could be detected because of its instability in the presence of acids (the catalysts).

Scheme 3.16 The reactions of imine **18** and EDA



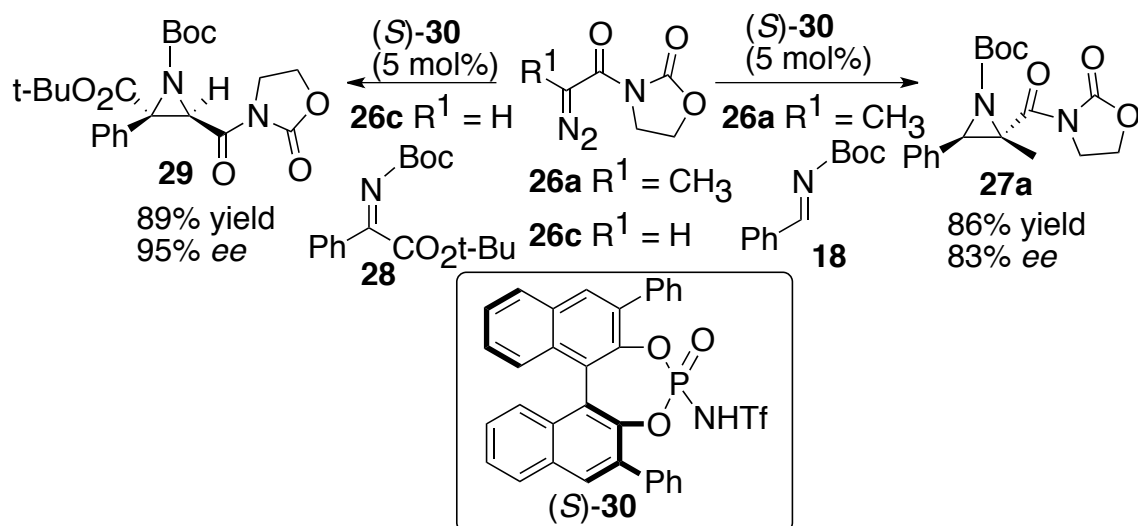
Scheme 3.17 The reactions of imine **18** and diazoacetamide **19**



3.8 Maruoka's system

Two weeks after we published our method for the catalytic asymmetric tri-substituted aziridine synthesis, another acid catalyzed asymmetric method was reported by Maruoka's group.²¹ The right combination of imine, diazo compound and the catalyst was demonstrated to be essential for their reaction (Scheme 3.18).

Scheme 3.18 Catalytic asymmetric synthesis of tri-substituted aziridines developed in Maruoka's group



3.9 Conclusion

With the development of the catalytic asymmetric synthesis of tri-substituted aziridines described herein, it will be of interest not only to investigate its mechanism but also to compare the mechanistic differences in the reactions of electron-rich *N*-alkyl imines giving di-substituted aziridines and electron-poor *N*-Boc imines affording tri-substituted aziridines.

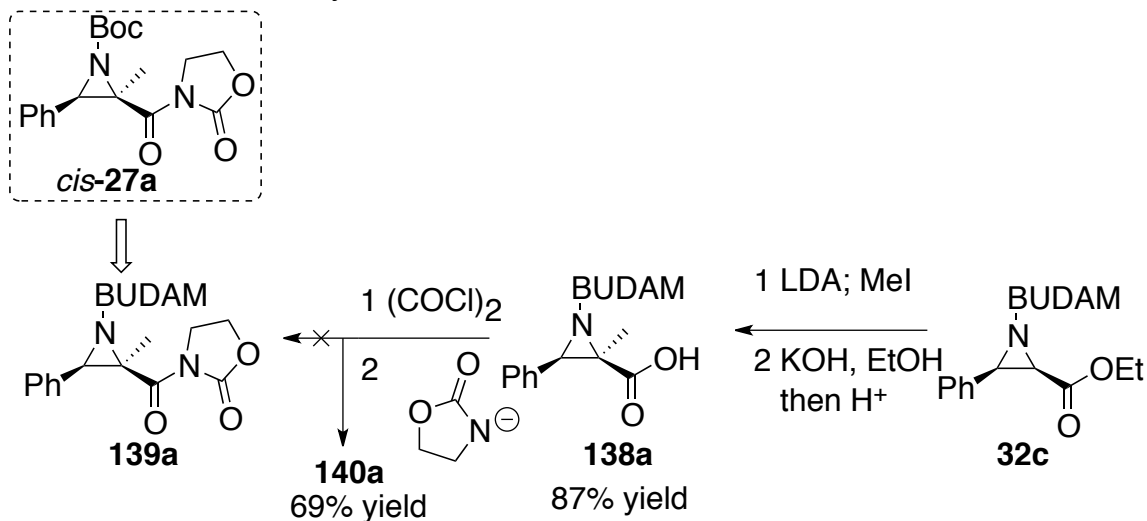
CHAPTER FOUR

RING EXPANSION OF AZIRIDINE-2-CARBOXYLIC ACIDS

4.1 *N*-carboxyanhydride formation

In the course of the catalytic asymmetric synthesis of tri-substituted aziridine, we needed *cis*-**27a** to determine the diastereoselectivity of the reaction of imine **18** and diazo compound **26a** (Scheme 3.5). We first took steps towards the preparation of *cis*-**139a**, a convenient substrate for our planned synthesis of *cis*-**27a** as shown in Scheme 4.1. To this end, the coupling reaction of acyl chloride generated from acid **138a** with oxazolidinone anion was performed, which unfortunately led to another new compound **140a** instead of the desired aziridine **139a**.

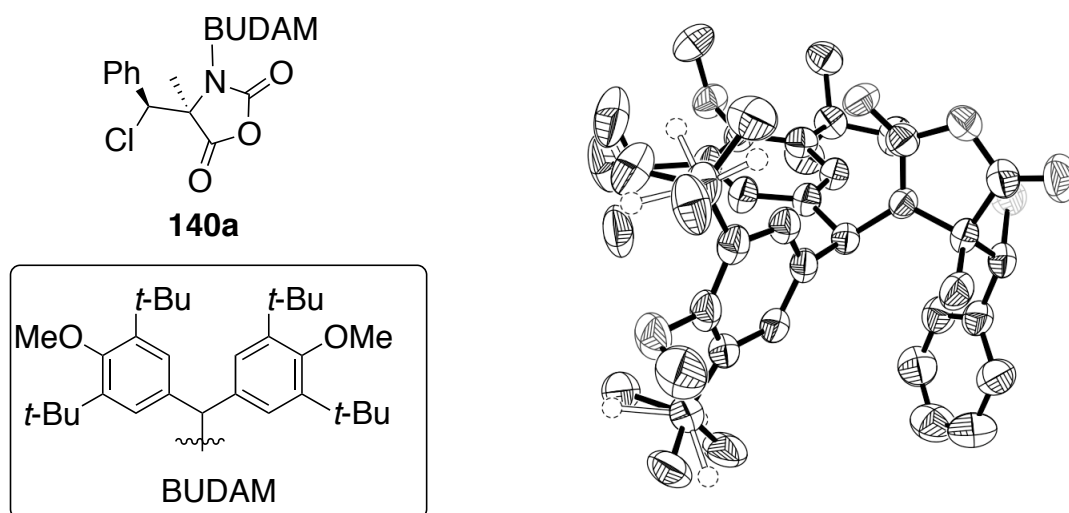
Scheme 4.1 Planned synthesis of *cis*-**27a**



This reaction was examined more closely and it was found that the problem lies in the acyl chloride formation step. The treatment of acid **138a** with oxalyl chloride afforded a single major new product whose ¹³C NMR spectrum

indicated one sp^2 carbon more than expected for aziridine acid **138a**. The infrared spectrum (carbonyl absorbances at 1847, 1784 cm^{-1}) suggested a new CO unit had been incorporated into the new molecule. After several trials, we were pleased to obtain X-ray quality crystals that revealed a five-membered ring consisting of the *N*-carboxyanhydride (NCA) structure (Figure 4.1 and Table 4.1). Notably, only a single diastereomer was isolated in the reaction; no other diastereomers could be detected.

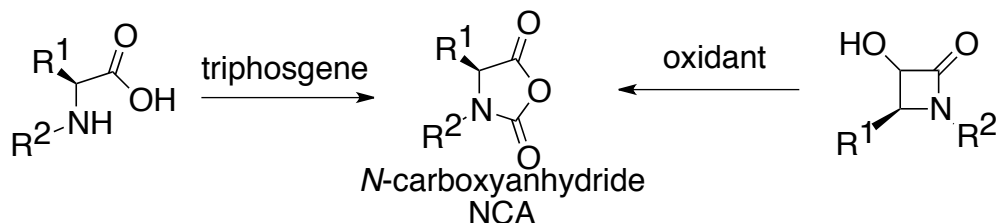
Figure 4.1 ORTEP drawing of NCA **140a**



It is worth noticing that *N*-carboxyanhydrides (NCAs)⁴⁹ have been used extensively as reactive amino acid surrogates in polypeptide synthesis^{50a} and have served more generally as important synthetic intermediates and pharmaceutical building blocks.^{50b-c} Currently, NCAs are largely synthesized in two ways: cyclization of α -amino acids with phosgene or its alternatives⁵¹ and oxidative ring enlargement of 3-hydroxy- β -lactam⁵² (Scheme 4.2). Herein, we

present an unprecedented method for NCA formation from aziridine-2-carboxylic acids.

Scheme 4.2 Two conventional methods for access to NCAs



We then set out to investigate different conditions for this transformation. The reactions of acid **141a** or its sodium salt with oxalyl chloride for 2 hours at room temperature provided the corresponding product **142a** in comparable yields (entries 1-2). Decreasing the reaction time to 1 hour did not change the yield (entry 3).

Table 4.1 Conditions for the formation of NCAs^a

138a, 141a Conditions → 140a, 142a				
entry	Substrate	Conditions	Prod	Yield ^b
1		(COCl) ₂ (2.0 equiv), 23 °C for 2 h		51%
2 ^c	141a	1) NaOH; 2) (COCl) ₂ (2.0 equiv), 23 °C for 2h	142a	56%
3		(COCl) ₂ (2.0 equiv), 0-23 °C for 1 h		54%
4	138a	(COCl) ₂ (2.0 equiv), 0-23 °C for 1 h	140a	69%

^a General procedure: A 25 mL round bottom flask was flame-dried and cooled under N₂. Then the starting material (0.20 mmol, 1.0 equiv) was added to the flask under N₂. The vacuum adapter was quickly replaced with a septum to

Table 4.1 cont'd

which a N₂ balloon was attached *via* a needle. Dry CH₂Cl₂ (2 mL) was added *via* syringe. The flask was then cooled to 0 °C, and then (COCl)₂ (0.040 mL, 0.40 mmol, 2.0 equiv) was added *via* syringe. After it was stirred at 0 °C for 5 min, the ice bath was removed and the resulting mixture was stirred at rt for another 1-2 hour. After the solvent was evaporated, the product was purified by column chromatography.^b Isolated yield after column chromatography.^c To the mixture of acid **141a** (69 mg, 0.20 mmol, 1.0 equiv) in acetone (1 mL) and CH₂Cl₂ (1 mL) was added a solution of NaOH (8 mg, 0.2 mmol, 1 equiv) in H₂O (0.17 mL). The resulting mixture was stirred at rt for 2 h. Then it was evaporated to dryness. And the step was carried out according to the procedure in footnote a.

It was quickly found that this transformation was highly dependent on the structure of the starting acid. When acid **138a** with BUDAM as protecting group on nitrogen was employed, the NCA product **140a** was obtained in 69% yield. The product was found to be stable even to silica gel chromatography. This is actually consistent with the fact that *N*-trityl-NCAs (TNCAs) and the *N*-phenylfluorenyl-NCAs (PFNCAs) are relatively stable (several months at room temperature) and overcome the tendency of NCAs to polymerize.^{51a}

Having identified that a better yield can be obtained from the *N*-BUDAM acid **138a** than the *N*-benzhydryl analog **141a**, we turned our efforts to exploring the substrate scope of the reaction. The results of the reactions of an additional six acids with oxalyl chloride are summarized in Table 4.2. The scope was found to be very broad with C2 methylated aziridine-2-carboxylic acids. The *ortho*- and *para*-substituted aryl groups on the C3 position, as well as aryl electron donating and withdrawing groups were well tolerated (entries 2-6). The reactions produced the corresponding NCAs smoothly in good yields. When it came to the C2 ethylated aziridine carboxylic acid **143c**, the yield of NCA **144c** dropped

significantly (20%). However, only a single diastereomer was observed in all cases.

Table 4.2 Substrate scope for NCA formation^a

Reaction scheme: **138a-f, 143c** $\xrightarrow{(\text{COCl})_2, \text{DCM}}$ **140a-f, 144c**

Entry	Acid	Ar	R	NCA	Yield ^b (%)
1	138a	Ph	H	140a	69
2	138b	4-MeC ₆ H ₄	H	140b	75
3	138c	4-BrC ₆ H ₄	H	140c	71
4	138d	2-MeC ₆ H ₄	H	140d	78
5	138e	2-BrC ₆ H ₄	H	140e	73
6	138f	1-naphthyl	H	140f	79
7	143c	4-BrC ₆ H ₄	CH ₃	144c	20

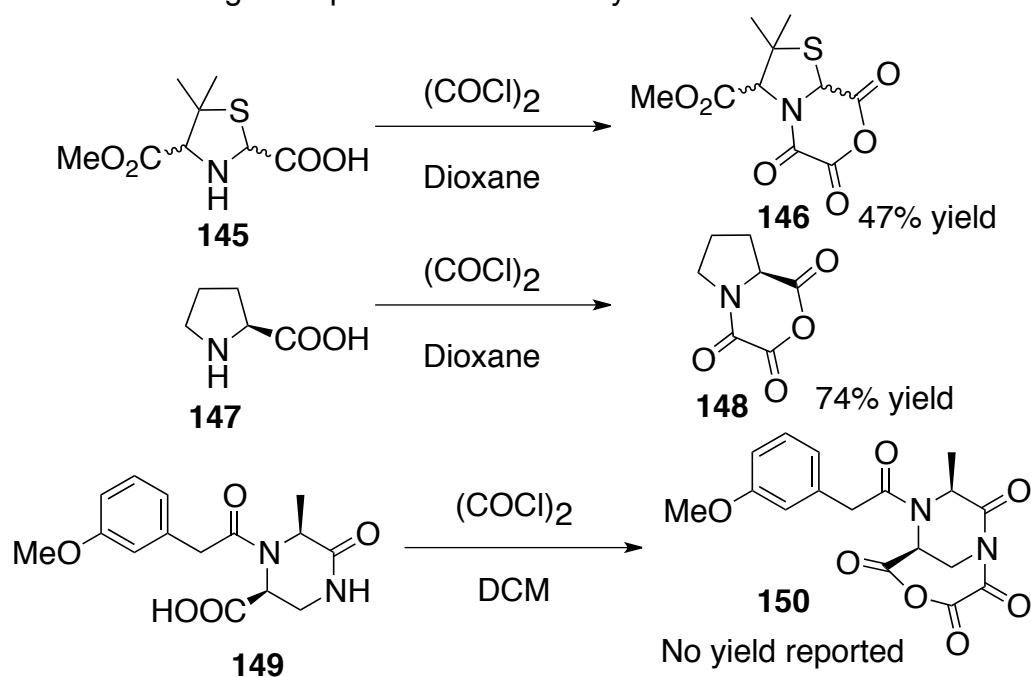
^a General procedure: A 25 mL round bottom flask was flame-dried and cooled under N₂. Then the starting material (0.20 mmol, 1.0 equiv) was added to the flask under N₂. The vacuum adapter was quickly replaced with a septum to which a N₂ balloon was attached *via* a needle. Dry CH₂Cl₂ (2 mL) was added *via* syringe. The flask was then cooled to 0 °C, and then (COCl)₂ (0.040 mL, 0.40 mmol, 2.0 equiv) was added *via* syringe. After the reaction mixture was stirred at 0 °C for 5 min, the ice bath was removed and the resulting mixture was stirred at rt for another 1 hour. After the solvent was evaporated, the product was purified by column chromatography. ^b Isolated yield after column chromatography.

4.2 Formation of morpholine-2,3,5-trione

As is evident from entries 3 and 7 in Table 4.2, the steric effect of substituents at C2 has a dramatic influence on the reaction yield, with the larger ethyl substituent giving a much lower yield than methyl (20% vs 71%). We then became interested in testing the reaction of acid **151a** with a H substituent next

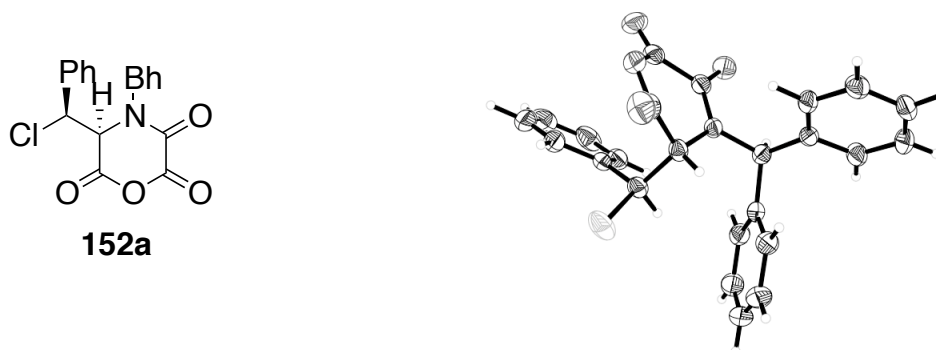
to the acid with oxalyl chloride (Scheme 4.4). Surprisingly, it was found that no NCA structure could be observed at all upon exposure of **151a** to oxalyl chloride. Again, a single isomer of a single product was isolated in 74% yield and found to be unable to survive column chromatography on silica gel. The ^{13}C NMR spectrum showed two sp^2 carbons more than expected for the starting acid **151a**. And the infrared spectrum showed three carbonyl absorbances at 1832, 1782 and 1705 cm^{-1} . This suggests the incorporation of both of the carbonyl groups of oxalyl chloride into the new product. These data prompted the assignment of the structure as the morpholine-2,3,5-trione **152a** (Scheme 4.4). Only three examples of this ring system have been previously reported (Scheme 4.3).⁵³ The reaction of 4-carbomethoxy-5,5-dimethylthiazolidine-2-carboxylic acid **145** and oxalyl chloride led to the *N*-oxalic anhydride **146**.^{53a} The cyclic *N*-oxalic anhydride of L-proline **147** was obtained *via* treatment of the amino acid in dioxane with excess oxalyl chloride. It is noteworthy that when amino acids with primary α -amino groups were treated with oxalyl chloride under conditions successful for L-proline, no anhydride could be isolated.^{53b-c} Another example is that of the *N*-oxalic anhydride **150** which was proposed be formed as an intermediate during the preparation of an aspartic acid side chain.^{53d} The presence of an α - or β -amino acid in the starting material is a common feature of these three examples. The formation of an *N*-oxalic anhydride is unprecedented from aziridine-2-carboxylic acids.

Scheme 4.3 Existing examples of *N*-oxalic anhydrides.



Luckily, we were able to obtain X-ray quality crystals of **152a** that confirmed our assignment. The ORTEP drawing is shown in Figure 4.2.

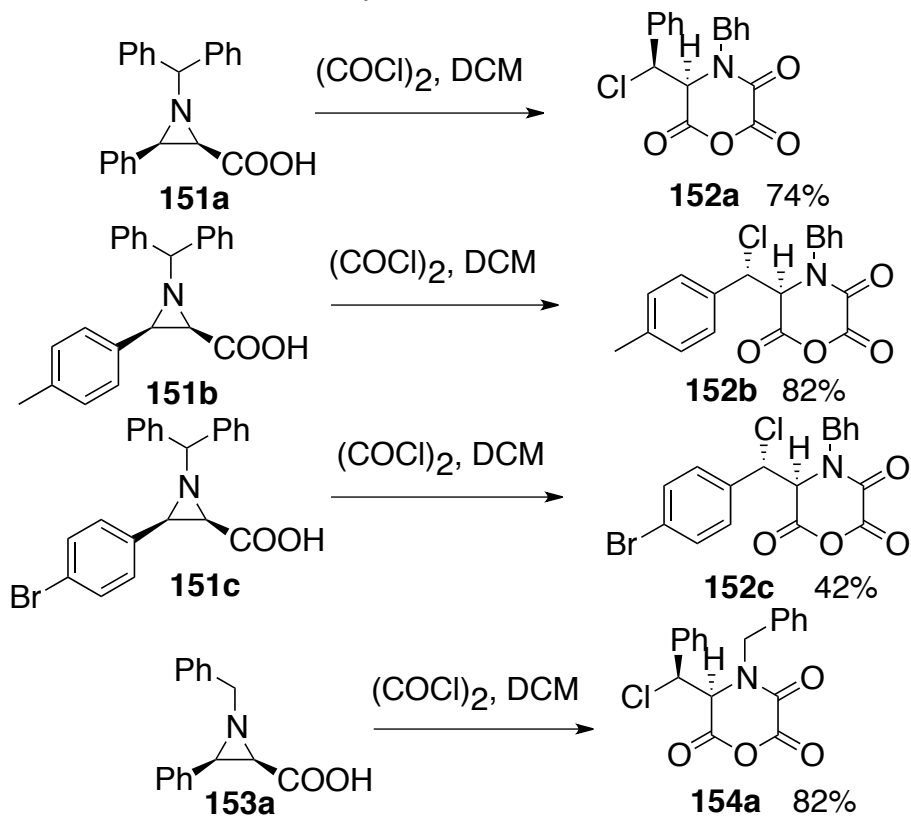
Figure 4.2 ORTEP drawing of morpholine-2,3,5-trione **152a**.



As can be seen from Scheme 4.4, the success of the formation of morpholine-2,3,5-triones is susceptible to structural changes in the starting acids: the protecting group on nitrogen and the substituent on C3. When the *N*-protecting group was changed from benzhydryl to benzyl, the reaction yield increased from

74% to 82% (acid **151a** vs **153a**). It was clear that the presence of an electron-withdrawing group on C3 position (acid **151c**) caused the yield to fall to 42% whereas the electron-donating group (acid **151b**) gave rise to a higher yield.

Scheme 4.4 The formation of morpholine-2,3,5-triones.

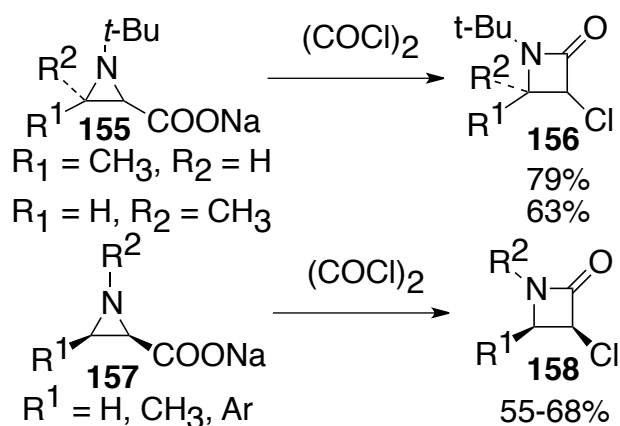


4.3 Rapid access to β -lactams via ring expansion of aziridine-2-carboxylic acids

A substrate with an aliphatic group on the C3-position was also tested in the reaction with oxalyl chloride. To our surprise, the reaction of acid **151g** with oxalyl chloride furnished, in a quantitative yield, *cis*- β -lactam **159g** in high stereoselectivity and as the only detected diastereomer (Table 4.3, entry 1). The relative *cis*-configuration of β -lactam was determined on the basis of the ¹H NMR coupling constant between the hydrogen atoms at the C3 and C4 positions.

Surveying the literature, we found that this transformation is not without precedent. The first example as shown in Scheme 4.5 appeared in 1969. Deyrup and Clough reported that entry into functionally substituted β -lactams can be achieved by ring expansion of the aziridine ring.^{54a,b} For example, reaction of sodium salt **155** with oxalyl chloride yielded β -lactam **156** stereoselectively in good yields. In the only other report of this reaction, Sharma and coworkers expanded the substrate scope of the reaction. A variety of *cis*- α -chloro- β -alkyl/aryl azetidine-2-ones **158** were reported by ring enlargement of *cis*-aziridine-2-carboxylates **157**.^{54c} We have been unable to reproduce the chemistry in this report by Sharma and coworkers and this will be discussed in Scheme 4.6.

Scheme 4.5 Existing examples of lactam formation *via* ring expansion of aziridines.



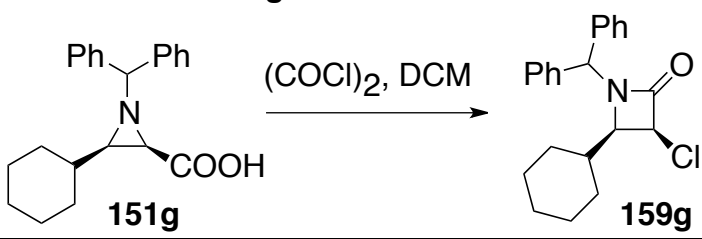
As we have established a catalytic asymmetric method for access to both *cis*- and *trans*-aziridines (see Chapter 1 for details), we were keen to further develop

their potential in synthesis. And the coupling of these methods with ring expansion to β -lactams was particularly attractive.

The β -lactam skeleton is a key structural motif of several classes of antibiotics, such as penicillin, cephalosporin, thienamycin and various monobactams.^{55a} Unfortunately, the longstanding use and abuse of these antibiotics have led to the emergence of bacterial strains resistant to these drugs so that the design and synthesis of new families of β -lactam containing molecules are constantly being pursued. Another aspect underlying the importance of β -lactams in the realm of organic synthesis and medicinal chemistry is their application to the synthesis of other classes of biologically active compounds, especially densely functionalized β -amino acids, *via* the so-called β -lactam synthon methodology (β -LSM).^{55b}

We found that it is unnecessary to employ the sodium salt of the aziridine carboxylic acid as reported by both Deyrup and Clough^{54a,b} and by Sharma and coworkers^{54c}. The acid can be directly converted to 3-chloro-4-alkyl substituted β -lactams in a highly stereoselective manner. The treatment of acid **151g** and oxalyl chloride gave the β -lactam **159g** in an excellent yield whereas the reaction with thionyl chloride furnished the product **159g** in a moderate yield. As expected, the enantiomeric and diastereomeric purity is preserved during this transformation.

Table 4.3 The reaction of acid **151g** with different chlorination reagents^a

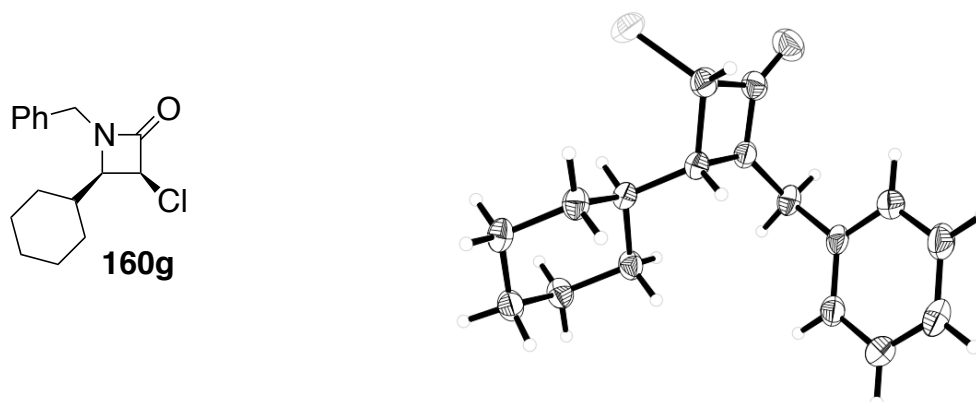


entry	Reagent	Yield (%) ^b
1	(COCl) ₂	100%
2	SOCl ₂	62%

^a General procedure: A 25 mL round bottom flask was flame-dried and cooled under N₂. Then the starting acid (0.10 mmol, 1.0 equiv) was added to the flask under N₂. The vacuum adapter was quickly replaced with a septum to which a N₂ balloon was attached *via* a needle. Dry CH₂Cl₂ (1 mL) was added *via* syringe. The flask was then cooled to 0 °C, and then (COCl)₂ (0.020 mL, 2.0 equiv) or SOCl₂ (0.020 mL, 2.0 equiv) was added *via* syringe. After it was stirred at 0 °C for 5 min, the ice bath was removed and the resulting mixture was stirred at rt for another 1 hour. After the solvent was evaporated, the product was purified by column chromatography. ^b Isolated yield after column chromatography.

We decided to explore the substrate scope of the ring expansion of aziridine-2-carboxylic acids to β -lactams, and the results are summarized in Table 4.4. We were also pleased to find that a range of aziridine-2-carboxylic acids reacted with oxalyl chloride to afford an array of β -lactams not only with generally good yields but also with excellent diastereoselectivity (Table 4.4). The nature of the *N*-protecting group has only a small impact on the yield. Although aziridine carboxylic acids with a benzhydryl protecting group produced the lactam in a quantitative yield (Table 4.3), both the benzyl and MEDAM protected acids **153g** and **161g** gave good yields (entries 1-2, Table 4.4). The *cis*-configuration of the β -lactam was also confirmed by X-ray diffraction analysis of β -lactam **160g**, the ORTEP of which is shown in Figure 4.3.

Figure 4.3 ORTEP drawing of *cis*-lactam **160g**



The reaction of acid **151h** with an isopropyl group on the C3 position under the same conditions gave an excellent yield. Acid **151i** with an *n*-propyl group on the C3 position yielded the β-lactam **159i** in 81% yield. While aziridine with both 1° and 2° aliphatic group on the C3 position gave excellent yields of β-lactam, the presence of a *tert*-butyl group on the C3 position also allowed the transformation, albeit in a low yield (entry 7). The treatment of the tri-substituted aziridine **163** with oxalyl chloride gave the corresponding lactam **164** in 39% yield. When *trans*-acid **153g** was employed, the *trans*-lactam **160g** was formed in 85% yield as the only detectable diastereomers (entry 9).

Table 4.4 Substrate scope of β-lactam formation^a

entry	Substrate	Product	Yield (%) ^b	
1	 153g	 160g	83	

Table 4.4 cont'd

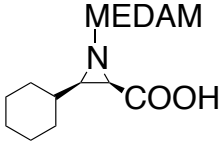
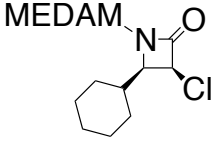
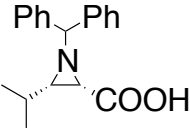
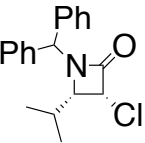
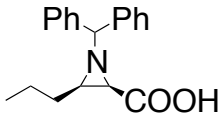
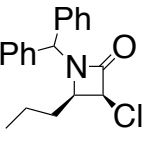
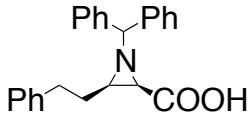
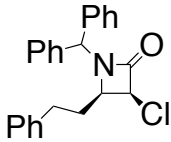
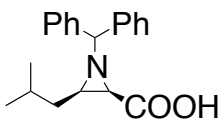
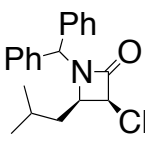
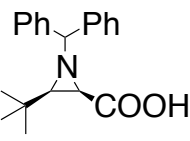
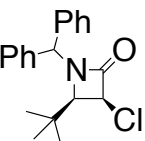
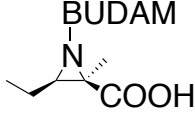
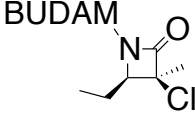
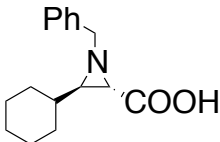
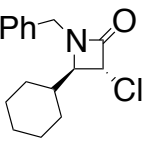
2 ^c		161g		162g	89
3		151h		159h	96
4		151i		159i	81
5		151j		159j	75
6 ^d		151k		159k	75
7 ^e		151l		159l	38
8		163		164	39
9		<i>trans</i> - 153g		<i>trans</i> - 160g	85

Table 4.4 cont'd

^a General procedure: A 25 mL round bottom flask was flame-dried and cooled under N₂. Then the starting acid (0.10 or 0.20 mmol, 1.0 equiv) was added to the flask under N₂. The vacuum adapter was quickly replaced with a septum to which a N₂ balloon was attached *via* needle. Dry CH₂Cl₂ (1 or 2 mL) was added *via* syringe. The flask was then cooled to 0 °C, and then (COCl)₂ (0.020 or 0.040 mL, 2.0 equiv) was added *via* syringe. After the reaction mixture was stirred at 0 °C for 5 min, the ice bath was removed and the resulting mixture was stirred at rt for another 1 hour. After the solvent was evaporated, the product was purified by column chromatography. ^b Isolated yield after column chromatography. ^c After the addition of oxalyl chloride, the reaction mixture was stirred at 0 °C for 10 min, and the reaction was stopped. ^d After it was stirred at 0 °C for 5 min, the reaction mixture was stirred at rt for 30 min. ^e After it was stirred at 0 °C for 5 min, the reaction mixture was stirred at rt for 24 hours.

In order to improve the yield of β -lactam **159I** bearing a *tert*-butyl group on the C3 position, the reaction of aziridine **151I** with oxalyl chloride was further studied under different conditions. It was found that despite the fact that the complete conversion of the starting acid was always observed, there are three species observed in the reaction under all the conditions we investigated. The results are shown in Table 4.5. The ratio of *cis*- and *trans*-**159I** does not change a lot with the reaction time (entries 1-2). An increased excess of oxalyl chloride favored the formation of the acid chloride **165I** and suppressed the formation of *cis*-**155I** (entry 5). Solvent also plays a role in the reaction since the formation of acyl chloride **165I** is dominant in benzene (entry 6).

Table 4.5 The reactions of acid **151I** with oxalyl chloride^a

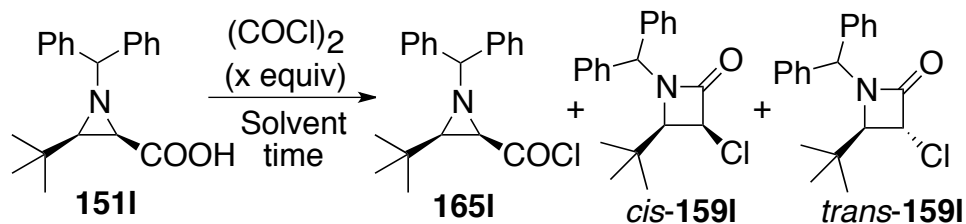


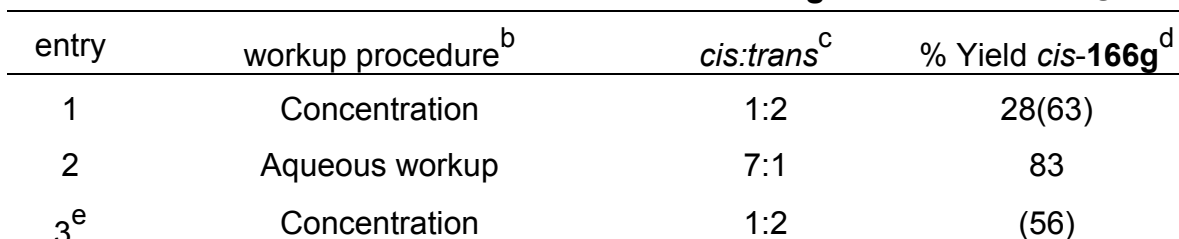
Table 4.5 cont'd

entry	Solvent	Temp (°C)	X	Time (h)	165I/159I	<i>cis</i> - 159I / <i>trans</i> - 159I ^b	Yield of <i>cis</i> - 159I (%) ^c
1	CH ₂ Cl ₂	0-23	2.0	1	49:51	76:24	ND
2	CH ₂ Cl ₂	23	2.0	5	43:57	77:23	ND
3 ^d	CH ₂ Cl ₂	23	2.0	24	55:45	90:10	38
4	CH ₂ Cl ₂	0-23	5.0	1	40:60	66:34	(21)
5	CH ₂ Cl ₂	0-23	10.0	1	75:25	90:10	ND
6	Benzene	23	2.0	1	94:6	83:17	ND

^a General procedure: A 25 mL round bottom flask was flame-dried and cooled under N₂. Then the starting acid (0.10 mmol, 1.0 equiv) was added to the flask under N₂. The vacuum adapter was quickly replaced with a septum to which a N₂ balloon was attached *via* a needle. Dry CH₂Cl₂ (1 mL) was added *via* syringe. Then (COCl)₂ (x equiv) was added *via* syringe at 0 °C or rt, and the resulting mixture was stirred at 0 °C or rt for a specified time. After the solvent was evaporated, the product was purified by column chromatography. ^b Determined from the ¹H NMR spectrum of the crude reaction mixture. ^c Isolated yield. The yield in parentheses refers to the isolated yield of **159I**. ND = not determined. ^d The reaction was quenched by the addition of aqueous *aq* sat NaHCO₃ solution.

Similarly, oxalyl bromide can effect the same transformation. Unlike the reaction with oxalyl chloride, which gave exclusively *cis*-product, the reaction of acid **151g** with oxalyl bromide proceeded with unsatisfactory stereoselectivity, affording **166g** as a 1:2 mixture of *cis:trans* diastereomers. It is possible to improve the *cis:trans* ratio. When the reaction was quenched at 0 °C, the *cis*-lactam **166g** became the dominate diastereomers in the reaction (entry 2). Neither increasing the temperature nor changing the solvent would drive the *cis:trans* ratio to a further extent (entry 3, Table 4.6). It seems that the *cis:trans*

Table 4.6 The reaction of acid **151g** with (COBr)₂^a

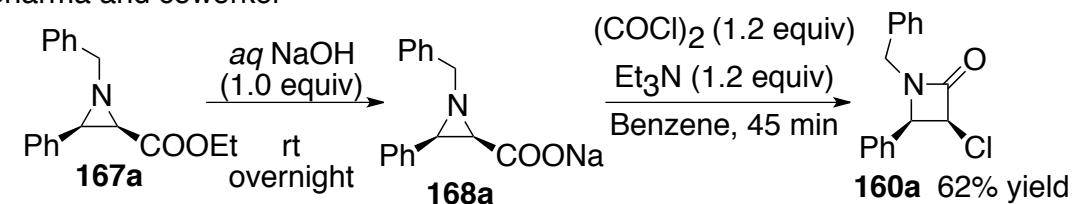


We were not able to obtain the *cis*-lactam **160a** from acid **153a** under conditions identical to those that have been reported by Sharma and coworkers.^{54c} Hydrolysis of ester **167a** with 1.0 equivalent NaOH in H₂O at room temperature only led to the complete recovery of the starting material. It was

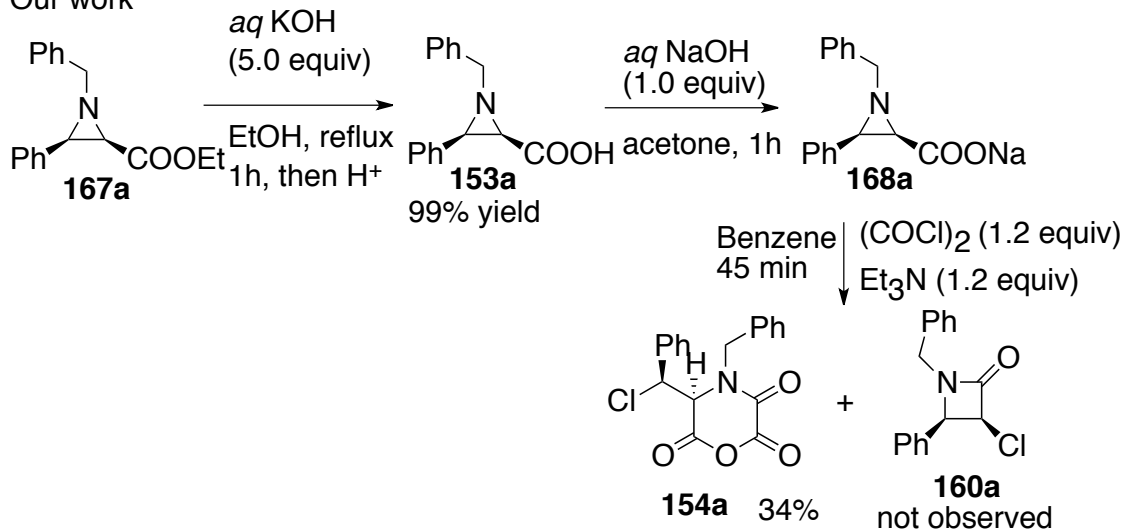
found that the acid **153a** could be obtained in 99% yield after reflux in aqueous KOH solution for 1 hour. The conversion of acid to sodium salt was achieved by treatment with aqueous NaOH at room temperature for 1 hour. Under the reported conditions, β -lactam **160a** could not be observed at all by treatment of sodium salt **168a** with $(\text{COCl})_2$ and Et_3N . Instead, the six-membered ring morpholine-2,3,5-trione **154a** was obtained in 34% yield (Scheme 4.6).

Scheme 4.6 Failed attempts towards the ring expansion

Sharma and coworker



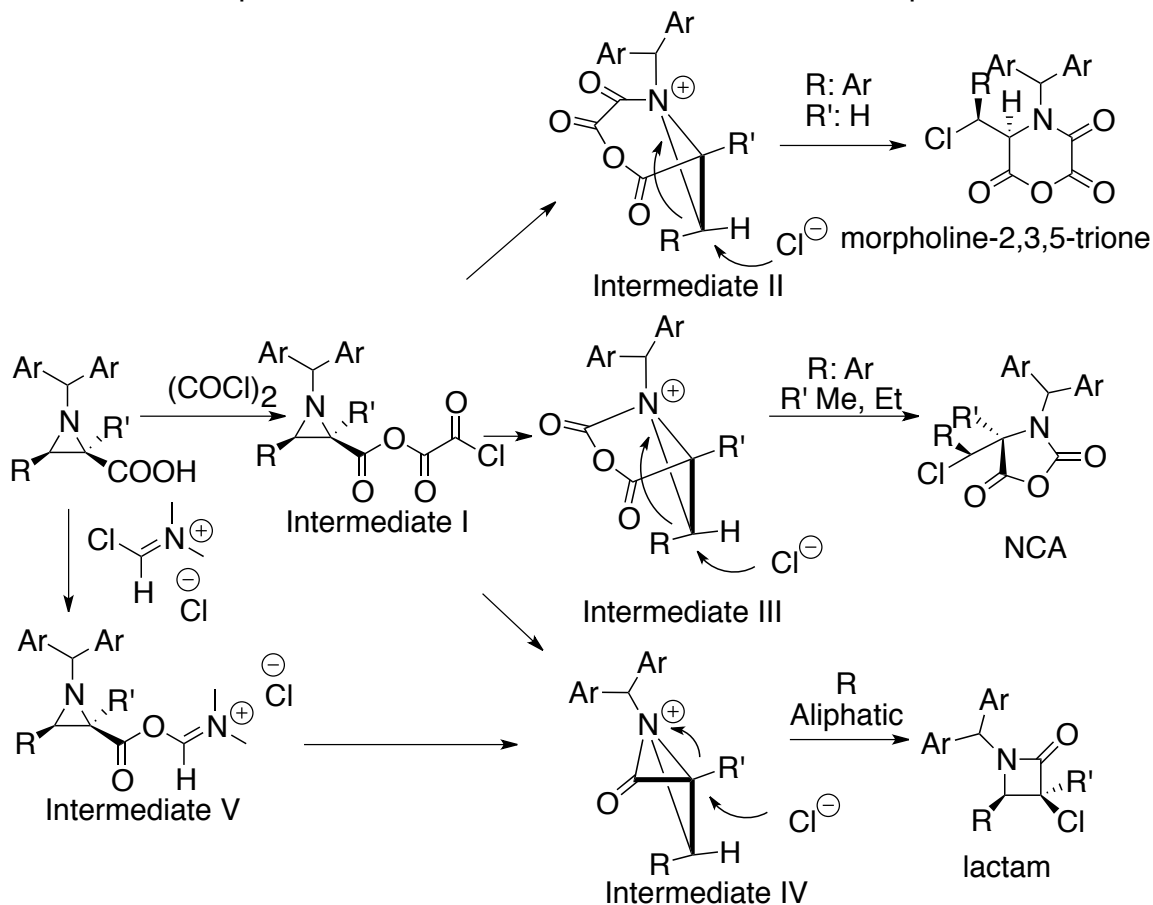
Our work



In the proposed mechanism shown in Scheme 4.7, the treatment of an aziridine-2-carboxylic acid with oxalyl chloride gives intermediate I whose carbonyls will be attacked by aziridine nitrogen to furnish the morpholine trione *via* intermediate II and the NCA *via* intermediate III. As to the formation of β -lactams, it is unlikely that the free carbonium ions are involved in the expansion

process since it is a highly stereospecific process. The proposed bicyclic structure⁵⁴ shown in Scheme 4.7 is indeed in agreement with the observed stereochemistry.

Scheme 4.7 Proposed mechanism for the formation of different products



Based on the mechanism in Scheme 4.7, it is clear that the intermediate I can suffer several different fates and lead to several different products depending on which carbonyl is attacked. It was envisioned that β -lactam formation could be enhanced by removing the options for formation of the other products. This can be simply done by treating the aziridine carboxylic acid with a Vilsmeier reagent which is expected to give intermediate V. This species has a single carbonyl group, the attack on which should lead to a β -lactam. We therefore subjected

acid **151a** with Vilsmeier reagent and were immediately rewarded with success. With 2.3 equivalent Vilsmeier reagent (preformed), *cis*- β -Lactam **155a** was obtained in 57% yield (entry 5, Table 4.7). The equivalents of the Vilsmeier reagent did not have a big effect on the yield of the lactam. Although five equivalents of Vilsmeier reagent increased the yield slightly to 61% (entry 6), we decided to employ 2.3 equivalents in our standard conditions. The Vilsmeier reagent is generated from oxalyl chloride and DMF. This can also be done in-situ as indicated by the data in Table 4.7. There is a competition between the reaction of oxalyl chloride with acid **151a** and the reaction of oxalyl chloride with DMF to give an in-situ generated Vilsmeier reagent. There is no β -lactam if no DMF is added, only a 74% yield of the morpholine-2,3,5-trione (entry 1). With pre-generated Vilsmeier reagent in absence of oxalyl chloride, no morpholine trione is observed and only β -lactam is produced.

Table 4.7 The formation of β -lactam with in-situ or preformed Vilsmeier reagent.

151a Vilsmeier reagent (in-situ generated or preformed) → 159a + 152a					
entry	Formation	(COCl) ₂ (equiv)	DMF (equiv)	% yield 159a ^c	% yield 152a ^c
1	In-situ ^a	2.0	0	0	74
2		2.0	1.0	7.5	11
3		2.0	2.0	5	0
4		2.0	4.0	46	46
5	Preformed ^b	2.3		(57)	0
6		5.0		61	0

Table 4.7 cont'd

^a Procedure for in-situ generated Vilsmeier reagent: A 25 mL round bottom flask was flame-dried and cooled under N₂. Then the starting acid **151a** (0.10 mmol, 1.0 equiv) was added to the flask under N₂. The vacuum adapter was quickly replaced with a septum to which a N₂ balloon was attached *via* a needle. Dry CH₂Cl₂ (1 mL) was added *via* syringe. Dry DMF was added *via* syringe. The flask was then cooled to 0 °C, and then (COCl)₂ (0.020 mL, 2.0 equiv) was added *via* syringe. The reaction mixture was stirred at 0 °C for 15 min. After the solvent was evaporated, the crude reaction mixture was obtained. ^b Procedure for preformed Vilsmeier reagent. A 25 mL round bottom flask was flame-dried and cooled under N₂. Then the starting acid **151a** (0.10 mmol, 1.0 equiv) was added to the flask under N₂. The vacuum adapter was quickly replaced with a septum to which a N₂ balloon was attached *via* a needle. The flask was then cooled to 0 °C, and then Vilsmeier reagent (0.23M in CH₂Cl₂) was added *via* syringe. The reaction mixture was stirred at 0 °C for 15 min. After the solvent was evaporated, the crude reaction mixture was obtained. ^c The yield was determined on the ¹H NMR spectrum of the crude reaction mixture with the aid of triphenylmethane as internal standard. The one in parentheses is the isolated yield.

The substrate scope for this controlled β-lactam formation was then investigated and the results are shown in Table 4.8. Both electron-donating and electron-withdrawing groups on the *para*-position of the phenyl group on the C3 position of the aziridine-2-carboxylic acid causes a low reaction yield (entries 2-3), as well as the trisubstituted aziridine-2-carboxylic acid **141a** (entry 4). It is clear that the *N*-protecting group has a significant impact on the yield of the reaction. The reaction of the *N*-benzyl protected aziridine acid **153a** gave a 74% yield of β-lactam **160a**. Unfortunately, we still have not been able to prepare ester **167a** in a direct and high enantioselective fashion. The aziridination reaction with *N*-benzyl imine with 10 mol% VAPOL catalyst gave the aziridine **167a** in only 51% yield and 43% ee in CH₂Cl₂ at room temperature at 24 hours.^{26c} From the results shown in entries 1 and 5 in Table 4.8, we then reasoned that aziridine acids with

an *N*- α -methylbenzyl protecting group might be sterically more similar to the benzyl group, hence affording the lactam in a better yield. Indeed, a good yield was obtained when acid **170a** was treated with Vilsmeier reagent (76% yield, entry 6). The presence of the *para*-bromo substituent of the phenyl did not change the yield significantly (entry 7). It was important to find that good reaction yields could be obtained from aziridines with *N*- α -methylbenzyl protecting groups since we have developed an efficient catalytic asymmetric synthesis of *N*- α -methylbenzyl aziridine ester (Chapter 2). As expected from the data in Table 4.3 and 4.4, when an aliphatic group is present on the C3 position of the aziridine acid such as **151g**, Vilsmeier reagent can also effect this transformation in excellent yield (entry 8).

Table 4.8 Substrate scope for the controlled formation of β -lactam^a

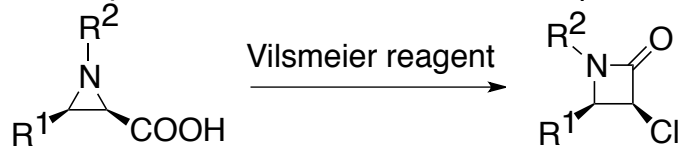
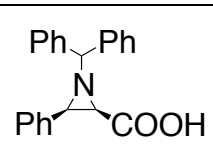
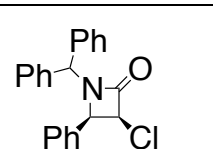
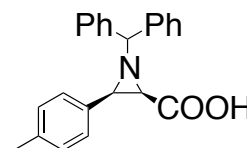
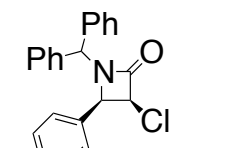
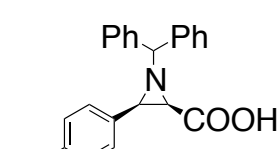
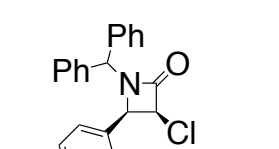
				
entry	Substrate	Product	Yield (%) ^b	
1			159a	57
2 ^c			159b	36
3 ^c			159c	33

Table 4.8 cont'd

4 ^c		141a		169a	22
5		153a		160a	74
6		170a		171a	76
7		170c		171c	69
8 ^c		151g		159g	100

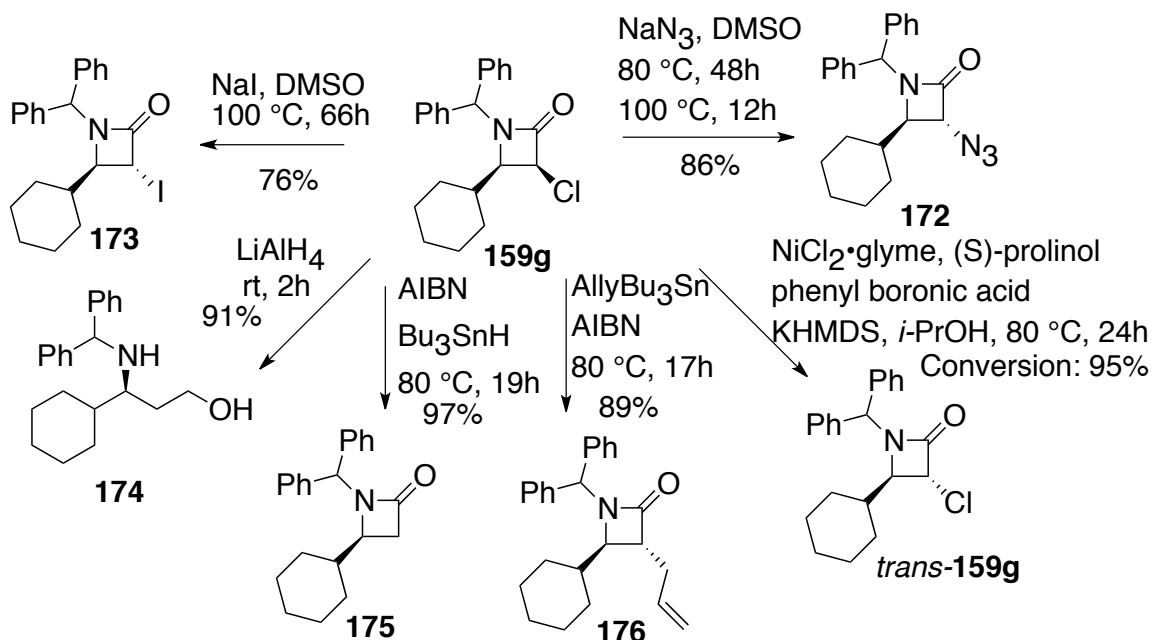
^a General procedure: A 25 mL round bottom flask was flame-dried and cooled under N₂. Then the starting acid (0.10 mmol, 1.0 equiv) was added to the flask under N₂. The vacuum adapter was quickly replaced with a septum to which a N₂ balloon was attached *via* a needle. The flask was placed in the ice bath. A solution of Vilsmeier reagent (0.23M, 1.0 mL, 0.23 mmol, 2.3 equiv) generated from 1:1 ratio of dry DMF (0.1 mL) and oxalyl chloride (0.1 mL) in dry CH₂Cl₂ (5 mL) was added via syringe. The reaction mixture was stirred at 0 °C for 15 min. After the solvent was evaporated, the product was purified by column chromatography. ^b Isolated yield after column chromatography. ^c The reaction mixture was stirred at 0 °C for 1 hour.

The synthetic utility of 3-chloro-β-lactam is illustrated by its facile conversion to a variety of highly functionalized compounds (Scheme 4.8). The nucleophilic substitution of a chlorine atom by an azido group opens a new route for the preparation of β-lactam bearing nitrogen at the same position.⁵⁶ The β-lactam

159g was employed as a test substrate. Treatment of **159g** with excess sodium azide in DMSO gives *trans*-3-azido- β -lactam **172** in 86% yield. It was delightful to find that this substitution reaction underwent a clean inversion by a S_N2 mechanism, furnishing the β -lactam with *trans* stereochemistry. A similar situation was found with the nucleophilic substitution of chloride of β -lactam **159g** with sodium iodide. The *trans*-3-iodo- β -lactam **173** was produced in a high diastereoselective manner. This high inversion of configuration is not surprising since the carbonyl group might be playing a role. Treatment of β -lactam **159g** with $LiAlH_4$ in THF at 0 °C for 2 hours afforded ring-opened product 3-amino alcohol **174** in 91% yield. This transformation proceeded with retention of stereochemistry at C4. The chlorine can be removed from the β -lactam **159g** by means of tin hydride reduction without causing disruption to the β -lactam ring. Treatment of the α -haloazetidinone **159g** in benzene with *n*-Bu₃SnH in the presence of AIBN furnished the 3-unsubstituted azetidinone **175** in an excellent yield. Encouraged by this result, we turned our attention to diastereoselective allylation under free radical conditions.⁵⁷ The reaction of β -lactam **159g** with allyltributyltin in the presence of AIBN upon heating provided the substituted *trans*-lactam **176** as a sole product in 89% yield. Although this radical condition is usually not conducive to high diastereoselectivity^{57b}, we were surprised that the stereoselection was excellent here. This might be due to presence of the stereo-center adjacent to the reacting radical carbon center. Attempted Suzuki coupling

of **159g** with phenylboronic acid under the conditions reported by Fu's group⁵⁸ did not lead to the desired product product, but *trans*-**159g** was obtained instead.

Scheme 4.8 The transformation of β -lactam **159g**

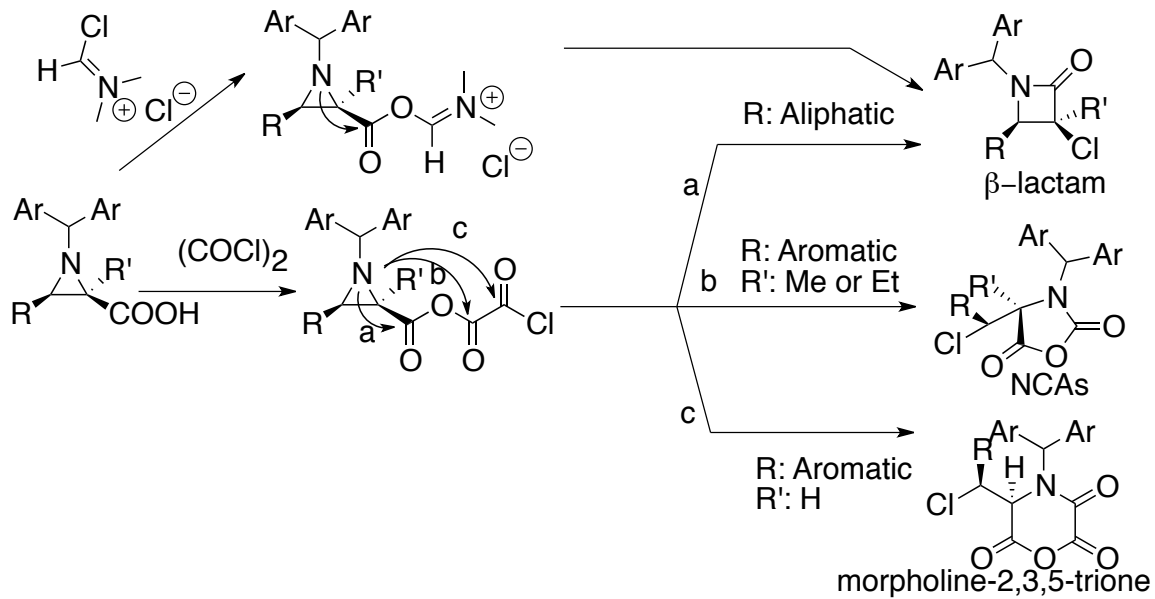


4.4 Conclusion

The rapid increase in molecular complexity from simple precursors is a major goal in organic synthesis.⁵⁹ This chapter has described the diastereoselective conversion of aziridine-2-carboxylic acids to *N*-carboxy anhydride, morpholine-2,3,5-triones or β -lactams — depending on the starting material or reagents as summarized in Scheme 4.10. From consideration of the likely mechanism, a controlled formation of β -lactams was also realized. Hence a variety of β -lactams can be conveniently synthesized from aziridine-2-carboxylic acids in a stereo-specific manner. Since aziridine-2-carboxylic acids are readily available with high enantiomeric purity from our catalytic asymmetric aziridination reaction, this combined methodology has significant potential. The 3-chloro- β -lactam products

are synthetic intermediates with significant utility since they can be converted into various functionalized compounds.

Scheme 4.9 Diastereoselective conversion of aziridine-2-carboxylic acids



CHAPTER FIVE

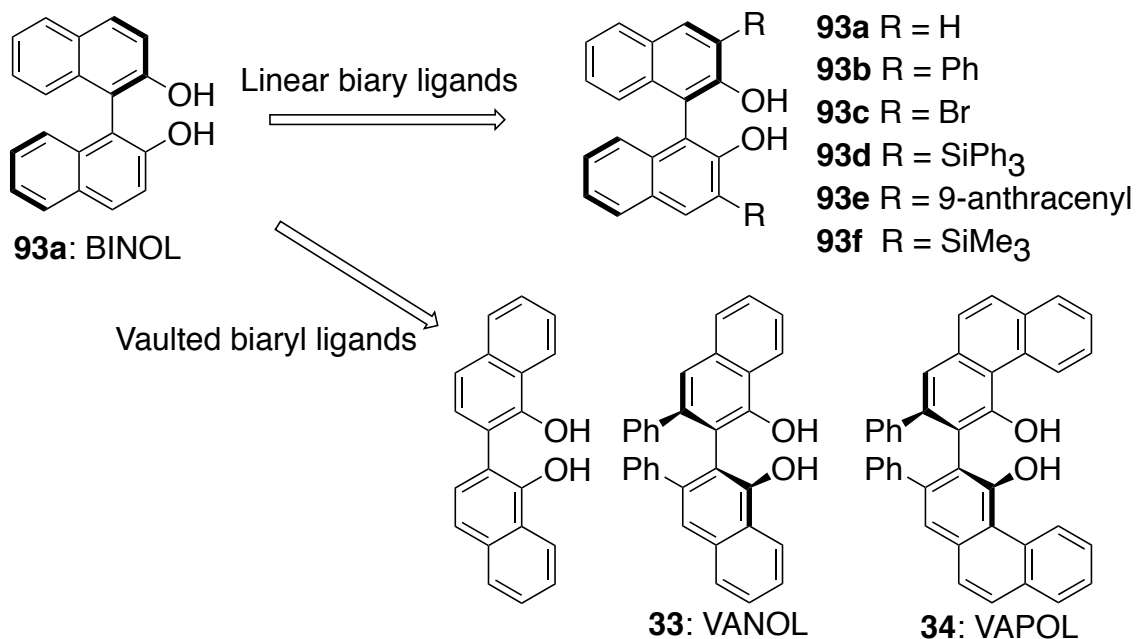
BOROXINATE CATALYSTS BASED ON BINOL DERIVATIVES

5.1 Introduction

BINOL is a classical C₂-symmetric biaryl ligand that has been widely used in asymmetric reactions since 1981.⁶⁰ The biaryl unit is both an important structural feature of many natural products and the conformationally stable backbone of many highly effective chiral catalysts and reagents in asymmetric synthesis. However, BINOL is considered to be an inefficient chiral ligand because its chiral pocket is positioned on the opposite side of the active site. In order to achieve a better-defined chiral pocket around the active site, two general strategies have been applied: introducing substituents at the 3- and 3'-positions^{60a} and re-orientating the chiral pocket towards the active site by changing the naphthalene-naphthalene bond from the 1,1'-positions to the 2,2'-positions. Originated from the latter strategy, a new class of biaryl ligands VANOL and VAPOL⁶¹ has been developed in our group. Based on the orientation of the naphthalene rings, VANOL and VAPOL are termed vaulted biaryl ligands while those BINOL type ligands are called linear biaryl ligands (Scheme 5.1).^{61a} Both types of ligands have found wide applications in asymmetric synthesis. In the course of exploring the application of the vaulted biaryl ligands, we became interested in the borate complexes derived from those ligands that proved to be successful in the

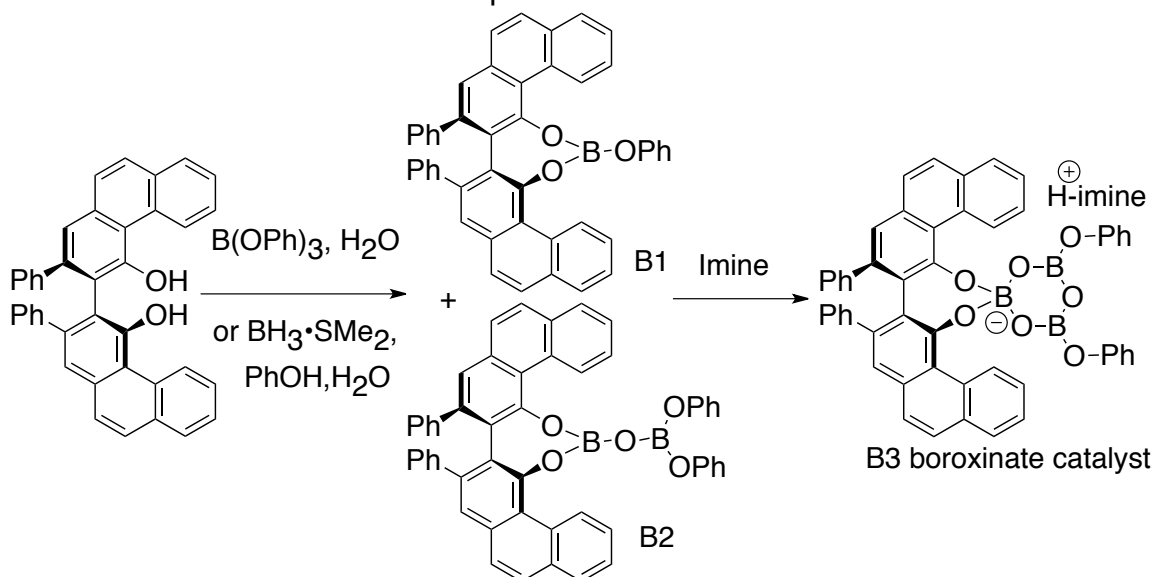
catalytic asymmetric aziridination²⁶, aza-Diels-Alder reactions⁶² and amino allylation of aldehydes³¹.

Scheme 5.1 Linear and vaulted biaryl ligands



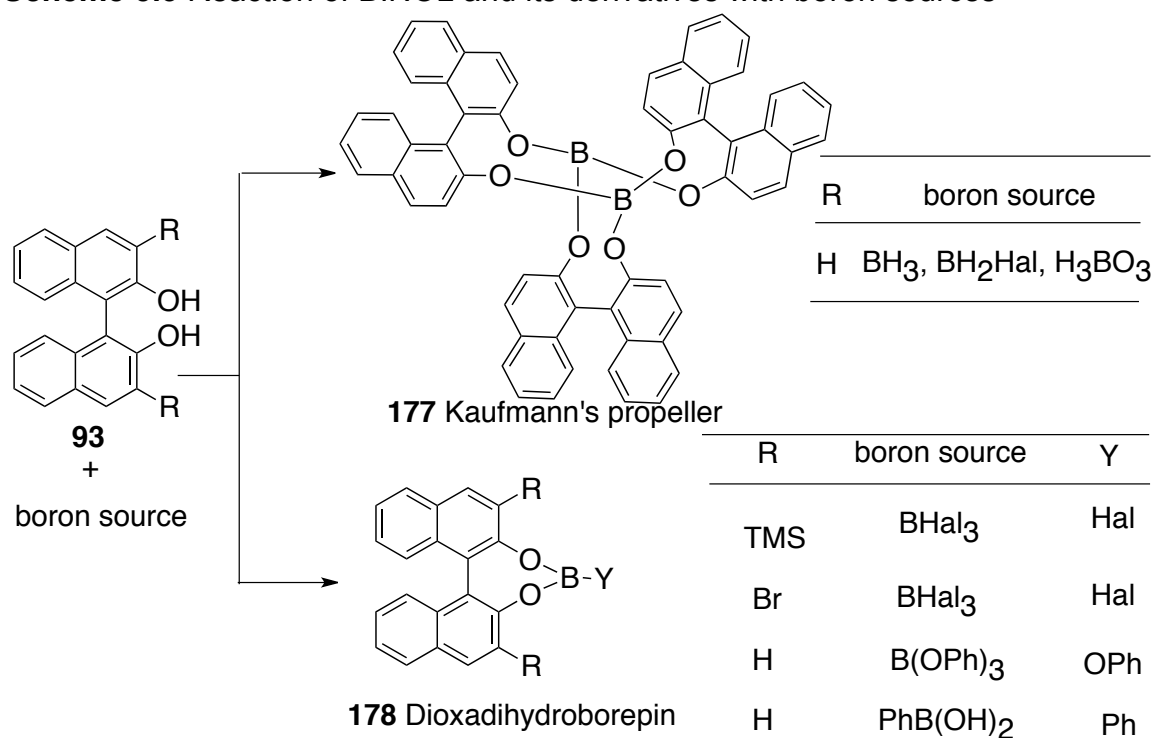
As outlined in Scheme 5.2, we have recently identified the B1 and B2 derivatives of VAPOL in the precatalyst for the aziridination reaction.^{26a} It was later found that the active catalyst for this catalyst is a boroxinate species containing three boron atoms (B3) which is only formed in the presence of the imine substrate.³⁰

Scheme 5.2 The formation of B3 species



It has also been demonstrated that the reaction of biaryl bis-phenols with boron compounds is complicated and dependent on both the boron source and the substitution pattern of the biaryl bis-phenols.⁶³ When BINOL is reacted with borane, hydrohaloboranes or boric acid, the bicyclic homochiral bisborate propeller compound **177** with axially chiral 1,1'-binaphthyl groups as 'blades' is formed exclusively in very good yield.⁶³ Introduction of either a bromo or trimethylsilyl substituent in the 3,3'-positions of BINOL exclusively leads to the formation of the seven membered dioxadihydroborepin system **178** to avoid additional steric strain (Scheme 5.3).⁶³ It was then postulated that the steric hinderance around the active site of the ligands plays the role in which boron species to be favored.⁶³ Previous work in our group suggested that BINOL dioxadihydroborepin **178** with Y = OPh could not be obtained cleanly.⁶⁴

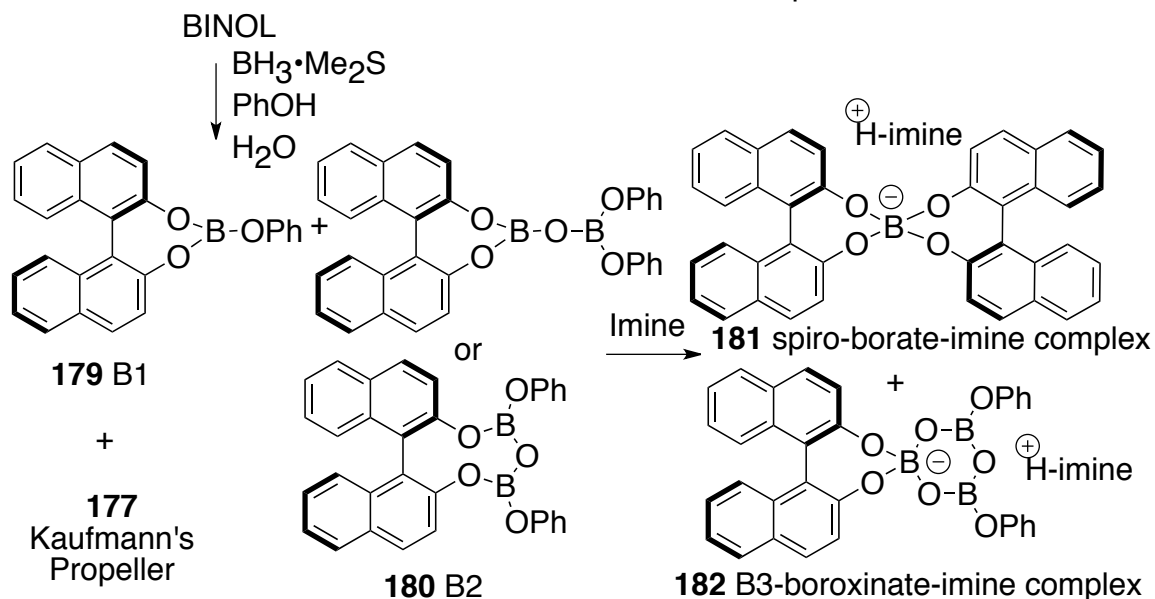
Scheme 5.3 Reaction of BINOL and its derivatives with boron sources



Hu Gang, one of our former group members, devoted his efforts to the identification of the boron complexes formed in the reaction of BINOL with different boron sources under varying conditions.⁶⁴ The optimized procedure to prepare VAPOL B1 was indentified to be from 1:1 ratio of VAPOL and B(OPh)₃ at 80 °C. When this procedure was used with BINOL, it produced a complex mixture in which Kaufmann's propeller **177** and BINOL B2 **180** can be readily observed. However, when 2/3 equivalent of BH₃•SMe₂ based on 1.0 equivalent of BINOL was employed, the reaction gave a nearly exclusively Kaufmann's propeller **177** with a small amount of unreacted BINOL. When an imine was mixed with 2 equivalent BINOL and 1 equivalent of B(OPh)₃ at room temperature, the clean production of the spiro-borate imine complex **181** was

observed to form immediately (Scheme 5.4). The structure of the spiro-borate-imine complex **181** from BINOL has been confirmed by X-ray analysis.⁶⁴

Scheme 5.4 Reaction of BINOL with borane and subsequent transformation



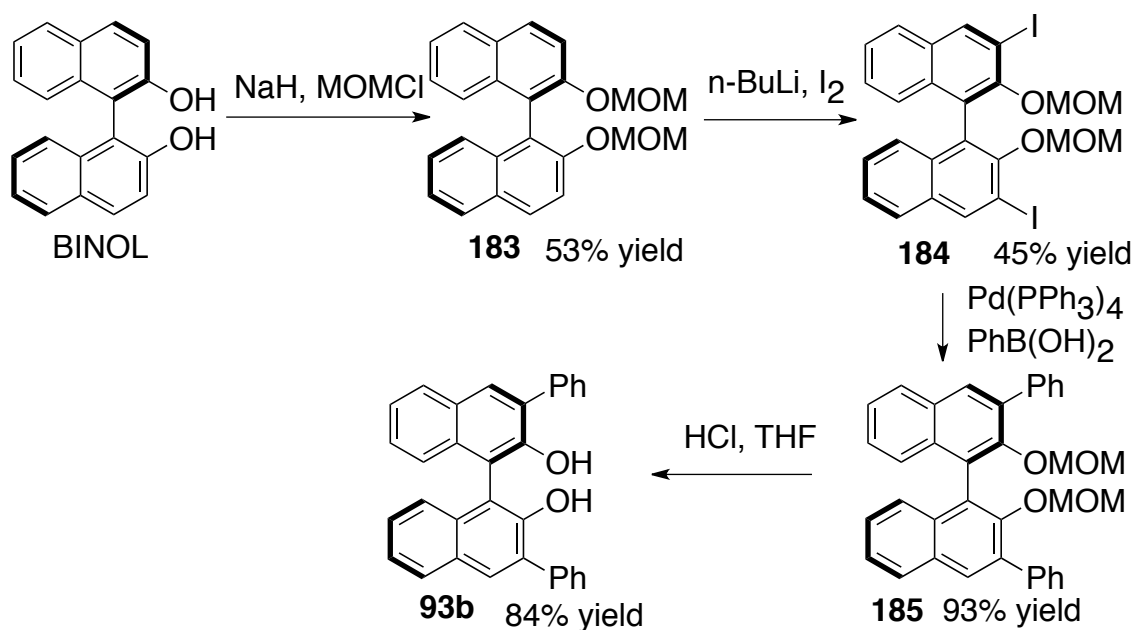
Based on the discovery that in the presence of imine, BINOL and VAPOL borate species self-assemble to a spiro-borate species and a B3 boroxinate structure, respectively, we then became interested in whether borate complexes of the 3,3'-disubstituted derivatives of BINOL would favor the formation of a spiro-borate species or a B3 boroxinate structure upon addition of the imine.

5.2 Preparation of the BINOL derivatives

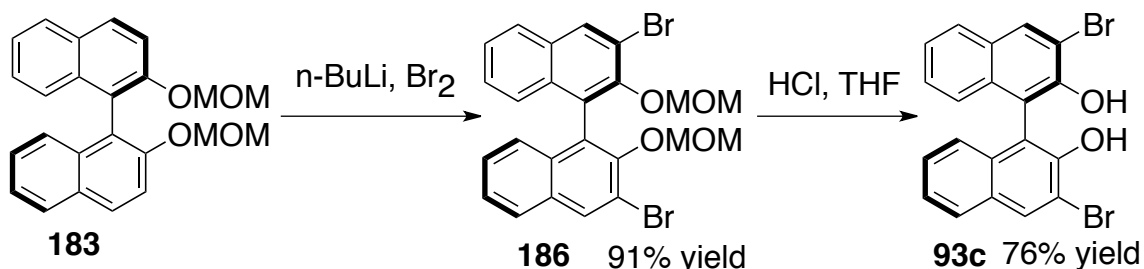
A number of BINOL derivatives with substituents on the 3,3'-positions have been reported.^{60a} The three BINOL analogs **93b-d** were chosen in our study to provide a range of substituents with different sizes. The synthetic routes are outlined in Scheme 5.5, 5.6 and 5.7 and all follow published procedures⁶⁵. In the preparation of **93b**, the BINOL was first protected with MOMCl using NaH as

deprotonation reagent to afford the key intermediate **183** in a high yield. The MOM group serves as both a protecting group and a strong *ortho*-metalation directing group. The treatment of the key intermediate **183** with *n*-BuLi led to an *ortho*-metalated intermediate that can react with a variety of electrophiles: I₂,^{65a} Br₂^{65b} and SiPh₃Cl^{65c} to give **184**, **186** and **187**, respectively. Suzuki coupling of **184** with phenyl boronic acid in the presence of Pd(PPh₃)₄ furnished the 3,3'-diphenyl BINOL derivative **185**.^{65a} Finally, deprotection of the MOM group by *aq* HCl in THF was successfully carried out to give **93b-d** in good isolated yields.

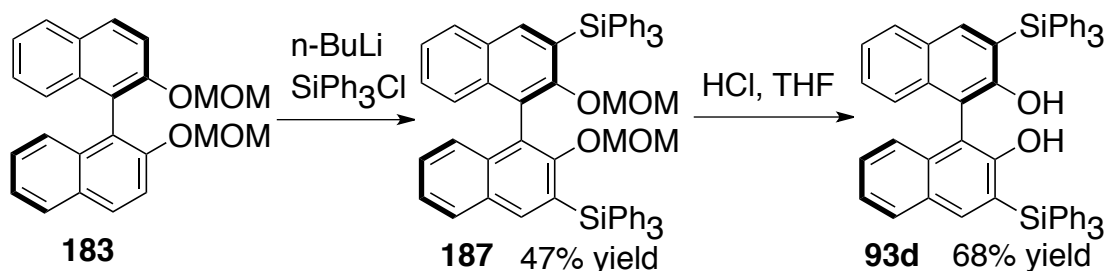
Scheme 5.5 Preparation of BINOL derivative **93b**^{65a}



Scheme 5.6 Preparation of BINOL derivative **93c**^{65b}



Scheme 5.7 Preparation of BINOL derivative **93d**^{65c}



Because oxygen atoms are strong hydrogen bond acceptors, these chiral BINOL derivatives are typically involved in both intramolecular and intermolecular O-H-O hydrogen bonding. Therefore, the investigation of hydrogen bonding in these chiral BINOL derivatives is essential for understanding the role these ligands may play in catalytic process.⁶⁶ While the 3,3'-diphenyl BINOL derivative **93b** is known, its solid state structure has not previously been reported.

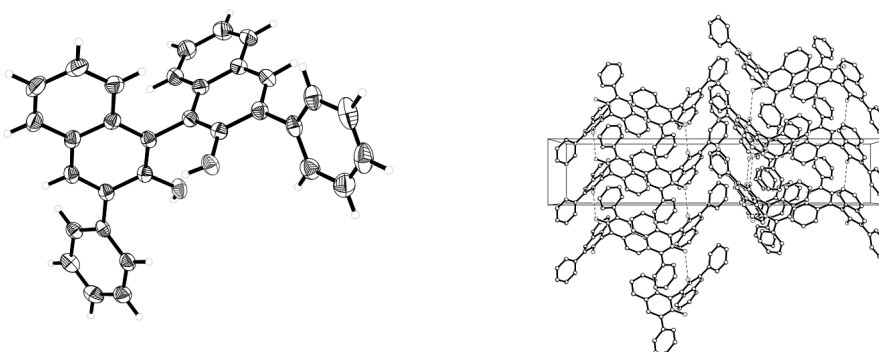
The structure of 3,3'-diphenyl BINOL **93b** in the solid state was studied by X-ray crystallography and the ORTEP diagram is shown in Figure 5.1. The dihedral angle between the naphthalenes of the BINOL derivative **93b** in its solid-state form is 86.99 °. Therefore, this BINOL derivative, along with VAPOL⁶⁷ whose dihedral angle between the phenanthrenes is <90 ° varying from 80.1 to 88.5 °, is described as transoid⁶⁸. In contrast, dihedral angle between the naphthalenes of all of the known solid-state forms of BINOL itself is >90 °. Hence, BINOL itself is

described as cisoid.⁶⁸ As has been reported⁶⁷, the non-solvated forms of VAPOL in the solid state lack the classic hydrogen-bonding that is otherwise common in solid state of BINOL. As can be observed from the crystal packing of **93b** in Figure 5.1, there is indeed intermolecular hydrogen bonding. These structural differences between BINOL derivative **93b** and VAPOL or BINOL might be expected to impact BINOL derivatives's reactivity in catalysis.

Figure 5.1 ORTEP drawing of BINOL derivative **93b** and of its crystal packing

A. ORTEP drawing of **93b**

B. ORTEP drawing of crystal packing of **93b**



5.3 Substrate induced assembly of borate species from BINOL derivatives

By simply mixing $B(OPh)_3$ with imine **197** in $CDCl_3$, a peak at 1.9 ppm in ^{11}B NMR was observed (entry 1, Figure 5.3). It is evident that this is an achiral boron species. Comparing its ^{11}B NMR chemical shift with those of known compounds (Figure 5.2)⁶⁹, species **196** most likely contains a 4-coordinate boroxinate species considering its low chemical shift in the ^{11}B NMR spectrum (Figure 5.3). It was found by another group member Anil K. Gupta that this achiral species has the structure shown in Figure 5.2.^{69f}

Figure 5.2 List of ^{11}B NMR chemical shifts in some known compounds.

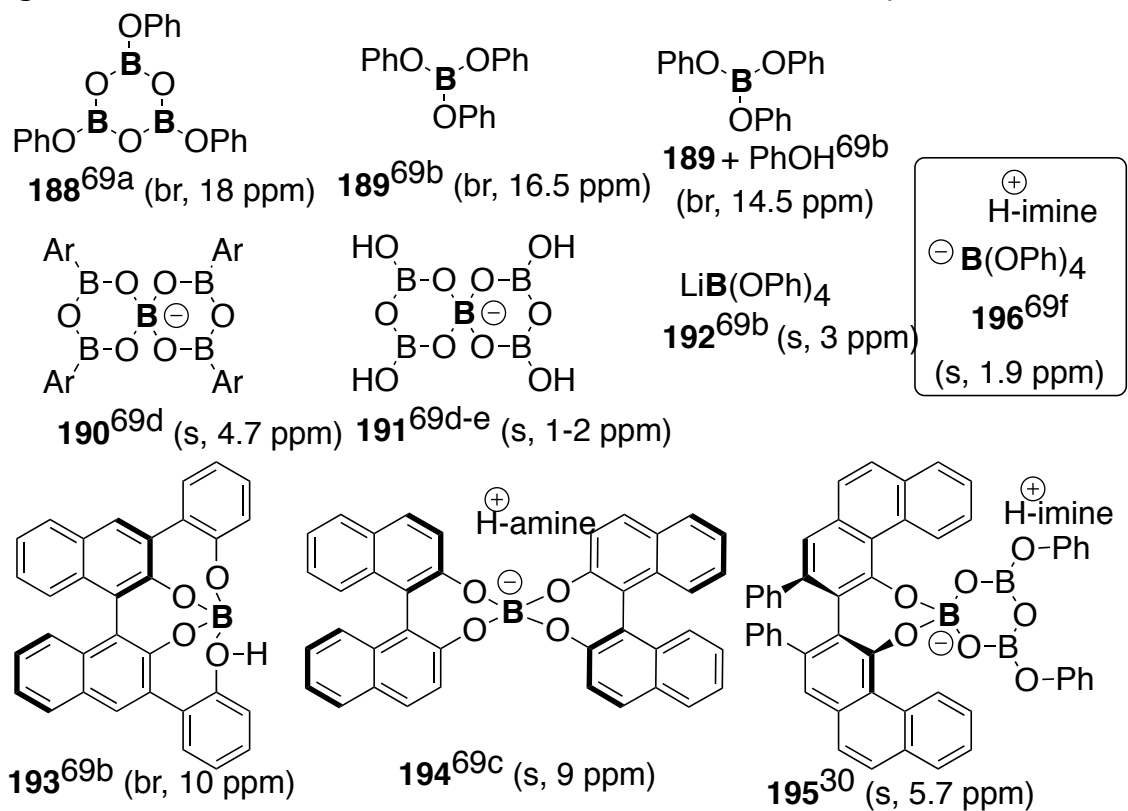


Figure 5.3 Substrate induced assembly of borate species from BINOL and its analogs

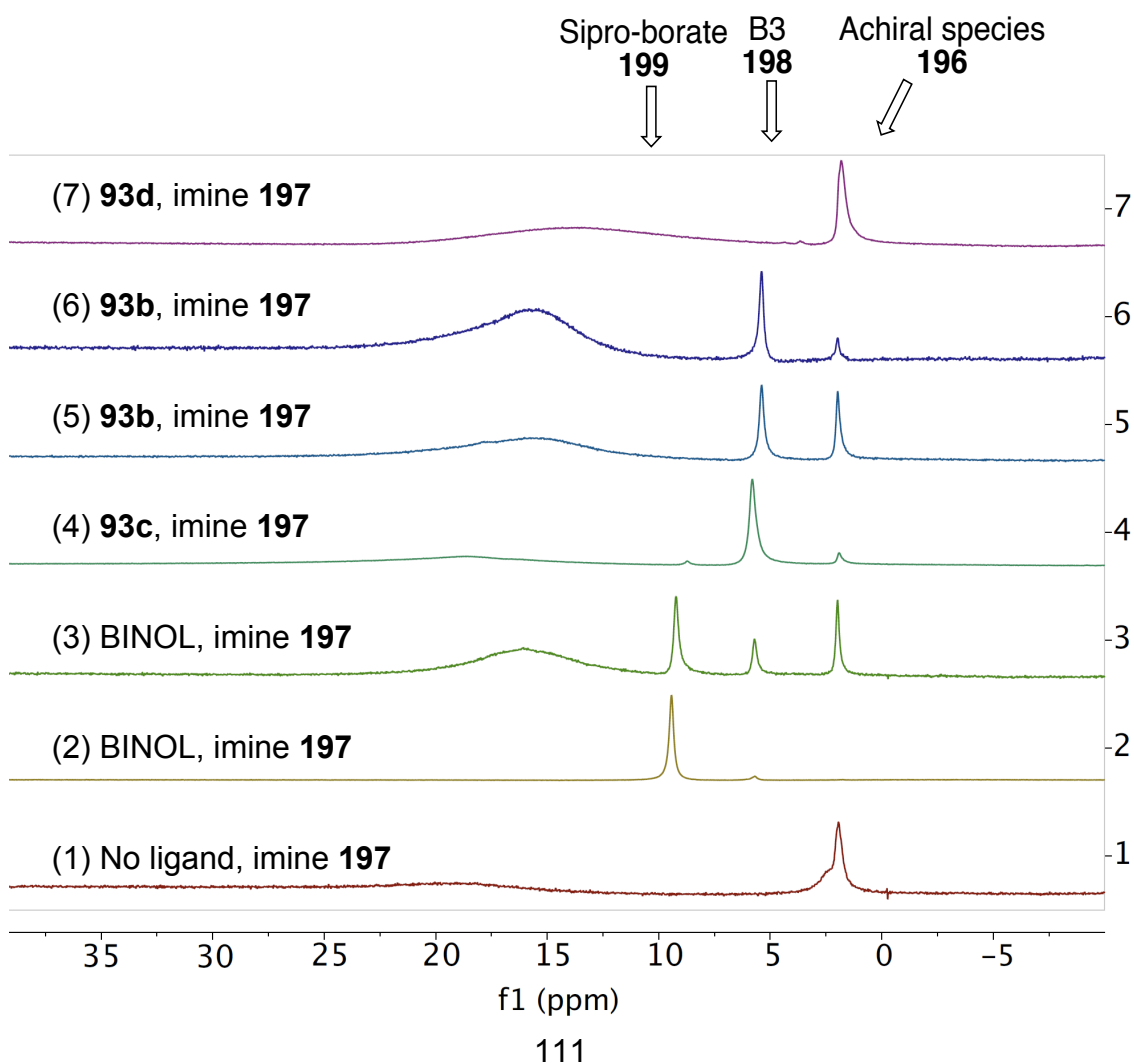
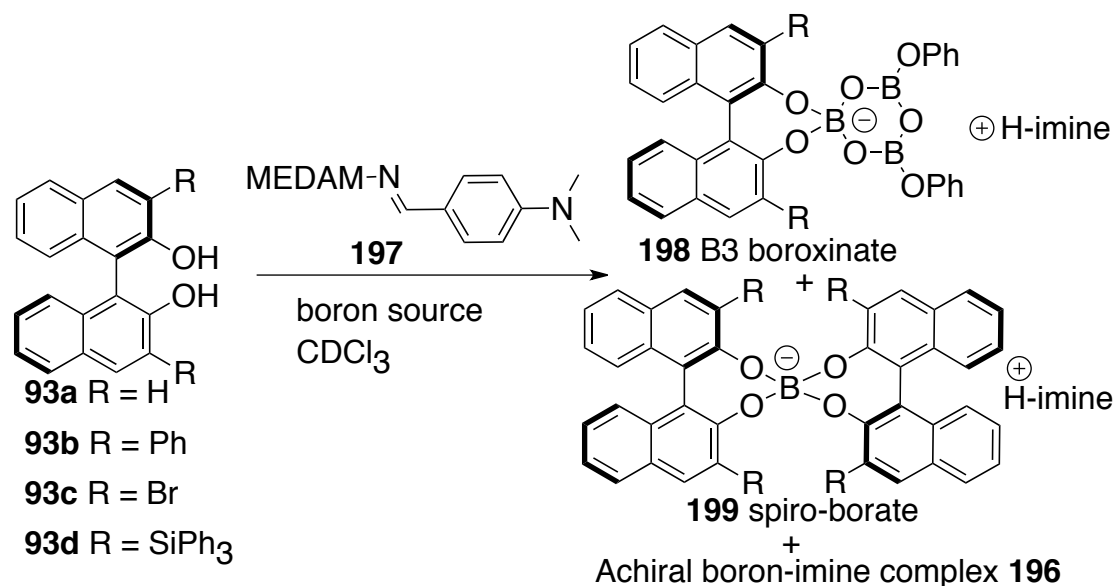


Figure 5.3 cont'd

(1) Imine **197** plus B(OPh)₃ (1:1); (2) Treatment of BINOL, B(OPh)₃ and imine **197** (2:1:1) at room temperature; (3) The catalyst was prepared by the general procedure from BINOL, B(OPh)₃ and H₂O (1:4:1). Then imine **197** was added; (4) The catalyst was prepared by the general procedure from **93c**, B(OPh)₃ and H₂O (1:4:1). Then imine **197** was added; (5) The catalyst was prepared from the general procedure from **93b**, B(OPh)₃ and H₂O (1:4:1). Then imine **197** was added; (6) The catalyst was prepared by the general procedure from **93b**, BH₃•SMe₂, PhOH and H₂O (1:3:2:3). Then imine **197** was added; (7) The catalyst was prepared by the general procedure from **93d**, B(OPh)₃ and H₂O (1:4:1). Then imine **197** was added.

It has been well established that the catalyst prepared from triphenyl borate and the BINOL ligand can have two equivalents of BINOL per boron (a spiro-borate structure).^{64,69c} It was found that the reaction of the BINOL ligand **93a** and triphenyl borate in the presence of imine favored the formation of the spiro-borate iminium species and that the amount of this species would depend on the ratio of the BINOL ligand and triphenyl borate and how the catalyst was prepared. Treatment of BINOL **93a**, B(OPh)₃ and imine **197** in a ratio of 2:1:1 at room temperature generated 94:6 mixture of the spiro-borate iminium species **199a** and the boroxinate B3 iminium species **198a** (entry 2, Figure 5.3). The catalysts in entries 3-7 in Figure 5.3 were prepared from a procedure that involves heating the mixture of the proper BINOL ligand **93a-d**, triphenyl borate and H₂O (1:4:1) in THF at 80 °C for 1 h and then removing the volatiles under high vacuum at 80 °C for 30 min. When the catalyst was prepared from 1:4:1 ratio of BINOL, triphenyl borate and H₂O, the spiro-borate iminium complex **199a** was still the dominant species as a 3:1 mixture with the boroxinate B3-iminium

complex **198a** upon addition of imine **197**. Upon introduction of substituents on the 3,3' position, it was anticipated that the formation of catalysts composed of two equivalents of BINOL derivative per boron should be less favorable. An examination of ligands **93b-d** proved that this is indeed the case. With R being Br, it is apparent that the preference is largely biased to the boroxinate B3-imine complex **198c** with only a small amount of the spiro-borate-imine species **199c** (entry 4); with a sterically bulkier phenyl group, it is observed that the spiro-borate-imine complex **199b** disappears whereas the B3-imine boroxinate **198b** is the only chiral species (entry 5); with the extremely bulky SiPh₃ group, both the spiro-borate-imine **199d** and the B3-imine boroxinate complex **198d** disappear while the achiral boron species **196** has become the only 4-coordinate boron species (entry 7). These observations imply that the nature of the boron species induced by the imine substrate is intrinsically dominated by the steric hindrance imposed in the chiral pocket, indicating a clear trend from the spiro-borate-imine complex **199**, B3-imine boroxinate complex **198** and further to the non-chiral species **196** not containing a BINOL ligand with increasing steric bulkiness of the substituent on the 3,3'-positions. Although the catalyst prepared from BH₃•SMe₂ gave a cleaner ¹¹B NMR spectrum, we decided to use B(OPh)₃ in the other catalyst preparations due to its greater stability (entry 5 vs 6).

5.4 Reactivity of B3 boroxinate based catalysts of BINOL derivatives in the catalytic asymmetric aziridination reaction

The catalytic asymmetric aziridination reactions with catalysts generated from BINOL and BINOL derivatives with different catalyst preparation procedures were examined and the results are shown in Table 5.1. Since as discussed above it was found that the catalyst prepared from 1:4:1 of BINOL, B(OPh)₃ and H₂O generated a mixture of spiro-borate-imine complex and B3-imine boroxinate complex (entry 3, Figure 5.3) upon addition of the imine, it was not surprising that the aziridination reaction with this catalyst gave very low asymmetric induction (entry 2, Table 5.1). When spiro-borate-imine complex was cleanly generated from BINOL (entry 2, Figure 5.3), an increase in the enantioselectivity was noted, but the sign of asymmetric induction was reversed (entry 3, Table 5.1). This indicated that both the spiro-borate-imine complex **199** and the B3-boroxinate-imine complex **198** from BINOL could catalyze the reaction but give different senses of asymmetric induction. The catalyst prepared from the BINOL derivative **93b** gave an increased enantioselectivity. Although different procedures from for catalyst preparation **93b** generated different percentages of the B3-boroxinate-imine complex **198** (entries 5-6, Figure 5.3), we were surprised to find that there is no significant difference seen in either the yield or asymmetric induction (entries 4-5, Table 5.1), indicating that the B3-boroxinate-imine complex is more reactive than achiral species in catalyzing a background reaction. Lowering the temperature from ambient to 0 °C did not give an increase in the enantioselectivity (entry 6). Changing the substrate to imine **31b** provided the corresponding aziridine in a slightly increased enantioselectivity (entry 7).

Table 5.1 Aziridination reactions with different ligands ^a

31a: PG = Benzhydryl
31b: PG = MEDAM

93a R = H
93b R = Ph

entry	Sub ^b	Cat prep ^c	Ligand	T (°C)	<i>cis</i> / <i>trans</i> ^d	%yield <i>cis</i> - 32 ^e	%ee <i>cis</i> - 32 ^f	% yield 200/201 ^d
1	31a	A	(<i>R</i>)-BINOL	23	>50:1	66	13	10/7
2	31a	C	(<i>R</i>)-BINOL	23	17:1	61	20	13/9
3	31a	D	(<i>R</i>)-BINOL	23	8:1	47	-40	24/23
4	31a	A	93b	23	>50:1	88	75	4/5
5	31a	B	93b	23	>50:1	91	78	3/5
6	31a	A	93b	0	>50:1	91	76	1/5
7	31b	A	93b	23	>50:1	88	80	3/4

^a The reaction was run with the imine **31** (0.5 mmol) in dry toluene (1 mL) with 10 mol% catalyst. ^b Substrate **31a** and **31b**. ^c Different catalyst preparation procedure. A: To a flame-dried Schlenk flask filled with N₂ was added the ligand, B(OPh)₃ (1:3) and toluene (1 mL). The flask was sealed and heated at 80 °C for 1 h. Then the volatiles were removed by slightly cracking the Teflon valve. The resulting mixture was heated at 80 °C for 30 min. B: The same as A except that the ligand, BH₃•SMe₂, PhOH and H₂O (1:3:2:3) were used. C: The same as A except that the ligand, B(OPh)₃ and H₂O (1:4:1) were added. ^d Determined from the ¹H NMR spectrum of the crude reaction mixture. ^e Isolated yield from column chromatography. ^f Determined from HPLC on purified *cis*-**32**.

Other BINOL derivatives were also tested in the catalytic asymmetric aziridination reaction and the results are shown in Table 5.2. Interestingly, the aziridination reaction is catalyzed by the achiral species **196** shown in Figure 5.1, giving 100% conversion, >50:1 *cis:trans* ratio and good isolated yield. Ligand **93c**

that gives mostly B3 species afforded moderate enantioselectivity (entry 1). Ligands **93d-e** with more steric bulk at the 3,3'-positions of BINOL produce essentially no asymmetric induction. This is actually consistent with the fact neither the spiro-borate-imine species nor the B3-boroxinate-imine species were generated from ligand **93d** (entry 7, Figure 5.3).

Table 5.2 Aziridination of imine **31a** with catalysts derived from BINOL analog^a

93a R = H

93b R = Ph

93c R = Br

93d R = SiPh₃

93e R = 9-anthracenyl

entry	Ligand	Conv (%) ^b	<i>cis</i> / <i>trans</i> ^b	% Yield <i>cis</i> - 32a ^c	% ee <i>cis</i> - 32a ^d	% Yield 200/201 ^b
1	No	100	>50:1	78	--	8/2
2	93b	100	>50:1	88	76	4/6
3	93c	100	>50:1	89	55	4/3
4	93d	100	>50:1	80	1	2/2
5	93e	80	20:1	65	3	12/8

^a The reaction was run with imine **31a** (0.5 mmol) in dry toluene (1 mL) with 10 mol% catalyst. The catalyst was prepared from the ligand, B(OPh)₃ and H₂O (1:4:1) according to the general procedure C. ^b Determined from the ¹H NMR spectrum of the crude reaction mixture. ^c Isolated yield from column chromatography. ^d Determined by HPLC on the purified *cis*-**32a**.

5.5 Different boron sources in the aziridination reaction

During this study, we also observed that boron sources other than triphenyl borate and borane could also be used to prepare the catalyst. We decide to use VAPOL as our model ligand since it gave high yield and asymmetric induction. When phenylvinyl boronic acid **202** was used to prepare the catalyst, a 12% decrease in enantioselectivity was observed (entry 1 vs 2, Table 5.3). Decreasing the amount of the boronic acid **202** from 30 to 10 mol% did not result in any significant changes in the reaction (entries 3-4). With the catalyst prepared from boric acid, the reaction did not go to completion and the asymmetric induction dropped to 85% (entry 5). We assumed that the solubility of boric acid in toluene might be responsible for the less effective catalyst in this reaction system. Upon addition of PhOH along with boric acid to prepare the catalyst (entry 1 vs 6, Table 5.3), we were delighted to find that the reaction gave essentially the same result as the catalyst derived from triphenyl borate. From a consideration of the cost and stability, boric acid could be an alternative boron source for the aziridination reaction. The NMR spectra of the catalyst used in entries 2 and 5 were studied (see experimental part for the spectra). For the catalysts from entries 2 and 6, the B3-boroxinate-imine complexes could only be observed in a small amount (<5%) upon addition of the imine **197** (Figure 5.3), and a large amount of VAPOL remained unreacted. Therefore, if a B3 boroxinate catalyst is operating in the catalyst prepared from boric acid and phenol as the data shown in entry 6 suggests, then it can be very effective even at low catalyst loadings.

Table 5.3 Aziridination with different boron sources used in the catalyst preparation procedure ^a

entry	Boron source	x (mol%)	Conv (%) ^b	<i>cis</i> / <i>trans</i> ^b	% yield 32a ^c	% ee 32a ^d	% yield 200/201 ^b
1	B(OPh) ₃	30	100	>50:1	83	91	--
2	202	30	100	>50:1	76	79	4/7
3	202	10	100	>50:1	81	80	2/6
4 ^e	202	20	100	>50:1	84	88	3/9
5	B(OH) ₃	30	54	>50:1	25	85	0/0
6 ^f	B(OH) ₃	30	100	>50:1	85	90	3/6

^a The reaction was run with imine **31a** (0.5 mmol) in dry toluene (1 mL) with 10 mol% catalyst. The catalyst preparation procedure: To a flame-dried Schlenk flask filled with N₂ was added the (*R*)-VAPOL (10 mol%), boron source (x mol%) and toluene (1 mL). The flask was sealed and heated at 80 °C for 1 h. Then the volatiles were removed by slightly cracking the Teflon valve. The resulting mixture was heated at 80 °C for 30 min. ^b Determined from the ¹H NMR spectrum of the crude reaction mixture. ^c Isolated from column chromatography. ^d Determined by HPLC on the purified *cis*-**32a**. ^e 10 mol% of B(OPh)₃ was also added to prepare the catalyst. ^f PhOH (30 mol%) was added to prepare the catalyst.

5.6 Conclusion

We have explored the formation and reactivity of borate complexes derived from BINOL and BINOL derivatives. Boroxinate structures represent a new and unique template in asymmetric synthesis. Although the boroxinate catalysts

derived from BINOL analogs only show moderate asymmetric induction in the catalytic asymmetric aziridination reactions, they might prove to be useful in other reactions.

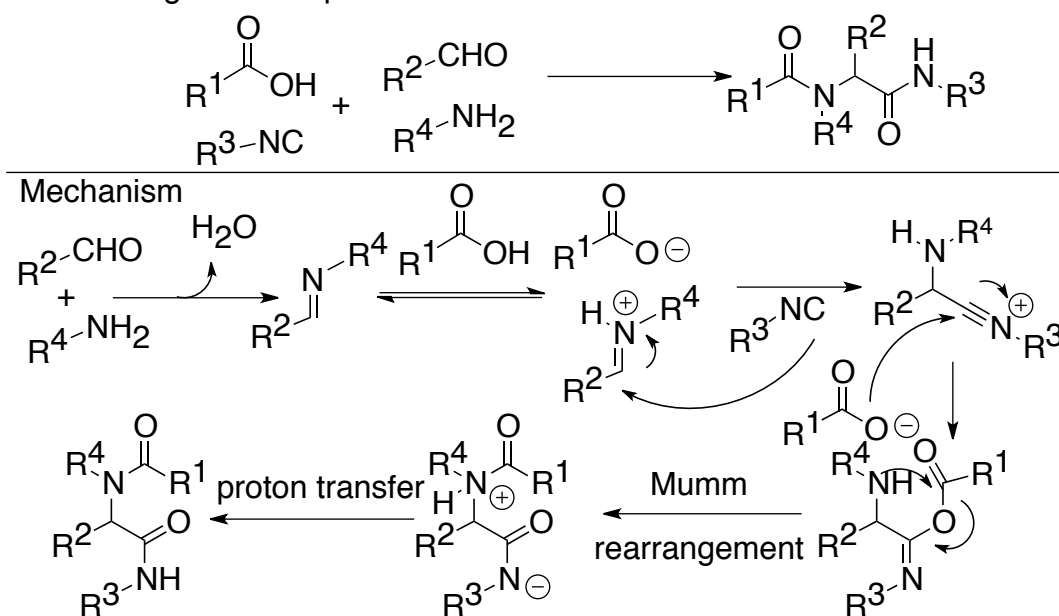
CHAPTER SIX

CATALYTIC ASYMMETRIC 3-COMPONENT UGI REACTION

6.1 Introduction

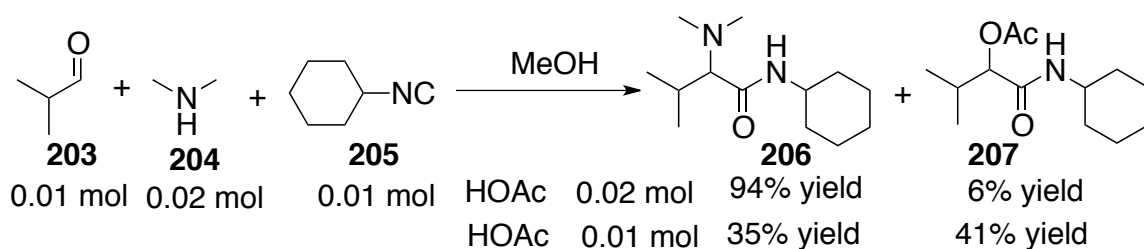
Multicomponent reactions (MCRs) are convergent reactions, in which three or more starting materials react to form a product.⁷⁰ The Ugi four component reaction (Ugi-4CR) is one of the most intensively studied and widely used multicomponent reactions.⁷¹ The reaction involves aldehydes, primary amines, isocyanides and carboxylic acids and affords α -amino amides as the product. From the mechanism shown in Scheme 6.1, the carboxylic acid plays a dual role in the reaction, serving as a Brønsted acid to activate the imine to form an iminium ion intermediate and as a donor to trap a nitrilium ion thus enabling the Mumm rearrangement.

Scheme 6.1 Ugi four-component reaction and its mechanism

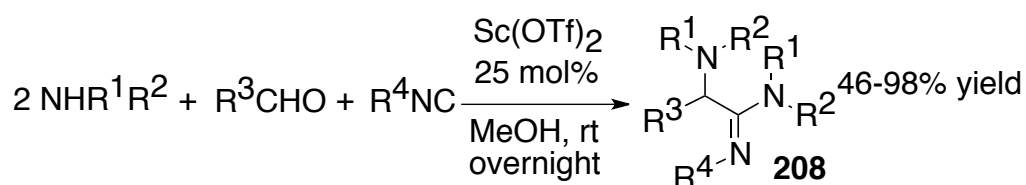


Based on the mechanism in Scheme 6.1, the Ugi reaction can not be carried out with secondary amines. However, the use of secondary amine in the Ugi reaction has been achieved by some groups in a three component (Ugi-3CR) version of the reaction.⁷⁰

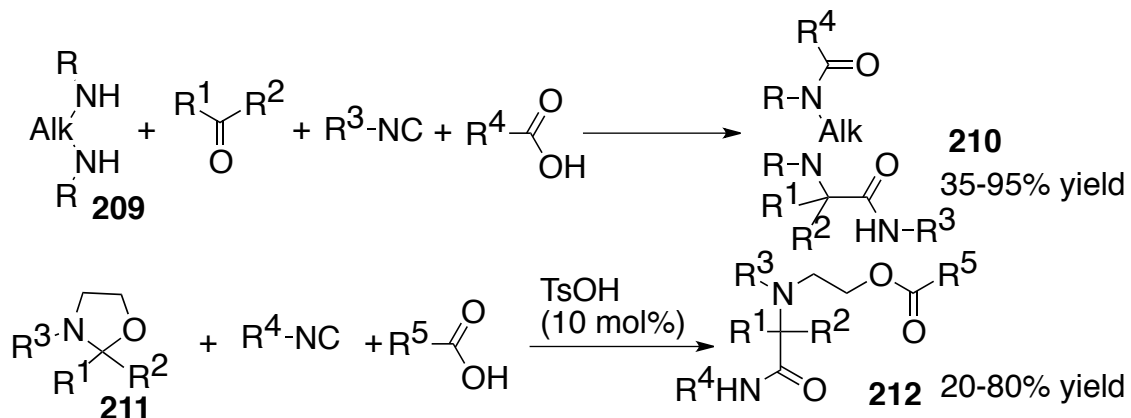
Scheme 6.2 The three component Ugi reaction of aldehyde **203**, dimethylamine **204** and cyclohexyl isocyanide **205** in the presence of acetic acid^{70a}



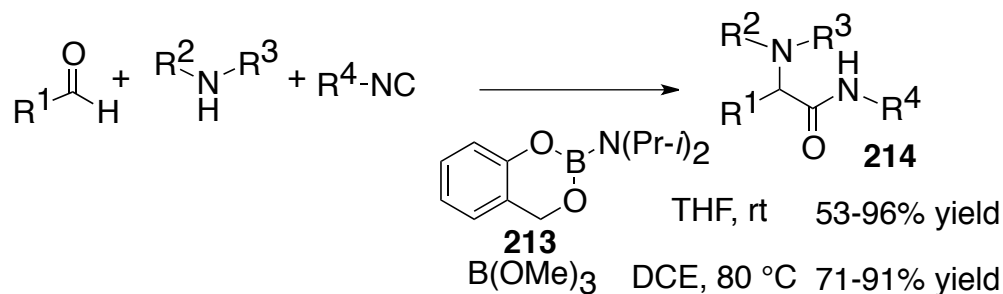
Scheme 6.3 The three component Ugi reaction of aldehydes, secondary amines and isocyanides catalyzed by $\text{Sc}(\text{OTf})_2$ ^{70b}



Scheme 6.4 Other variations of the Ugi reaction with secondary amines^{70c,d}



Scheme 6.5 The three component Ugi reaction of aldehydes, secondary amines and isocyanides in the presence of aminoborane **213** or B(OMe)₃^{70e,f}

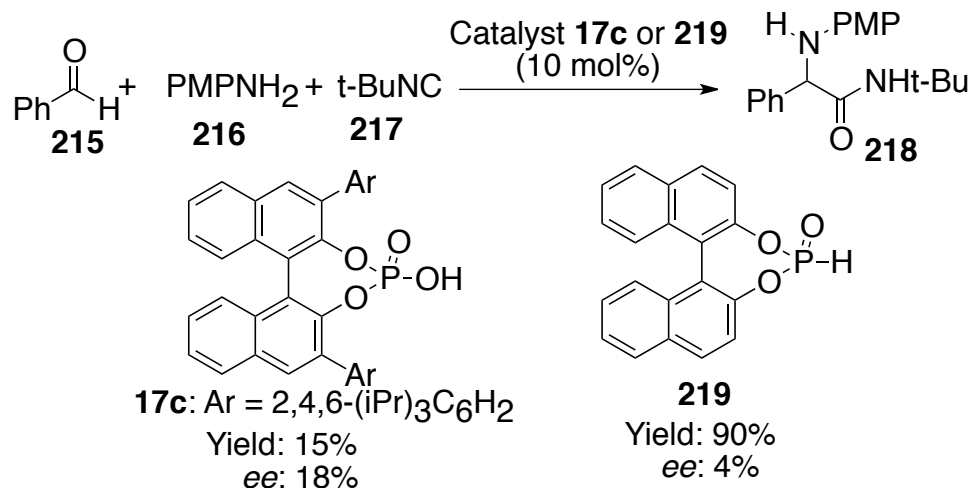


In 1963, McFarland reported a 3-component Ugi reaction in which aldehyde **203**, secondary amine **204** and isocyanide **205** were involved (Scheme 6.2).^{72a} It should be noted that the Passerini product **207** was also detected under these reaction conditions. Although an excellent yield of 2-amino amide **206** could be obtained with 2.0 equivalents of acetic acid, the yield was much lower with 1.0 equivalent of acetic acid and a significant amount of the Passerini product was obtained. A similar reaction could also be achieved with a catalytic amount of the Lewis acid Sc(OTf)₂ (Scheme 6.3).^{72b} In both cases, excess amine (2.0 equiv) has to be used. Secondary amines **209** and **211** that have additional functional groups, such as NHR^{72c} and OH^{72d} groups can also be employed to effect the coupling of these reagents in variants of the Ugi reaction. In fact, the additional OH and NHR group serve as the receptor of the acyl group (Scheme 6.4). In another example, aminoborane **213** has been used as an iminium ion generator in a 3-component Ugi reaction in which a variety of secondary amines have been

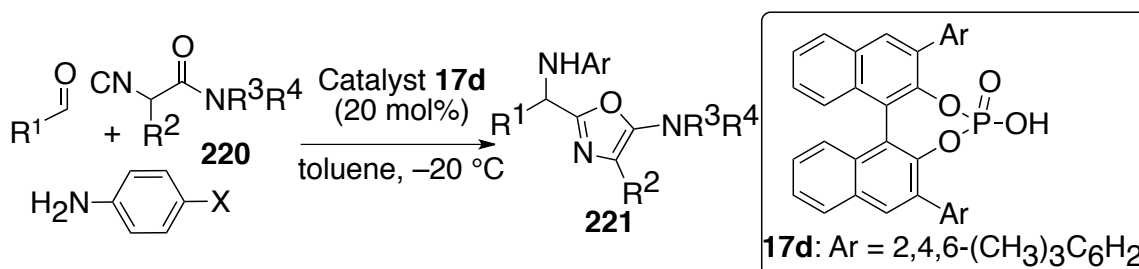
utilized.^{72e} Later on, they found this Ugi reaction can also be mediated by B(OMe)_3 (Scheme 6.5).^{72f}

Although diastereoselective 3- or 4-component Ugi reactions using chiral substrates⁷³ or chiral auxiliaries⁷⁴ have been reported, the progress on the development of a catalytic asymmetric version has been limited. In one example, in the development of a non-asymmetric catalytic version of a 3-component Ugi reaction, a single example with the chiral catalyst **17c** was reported to give an asymmetric induction of 18% ee (Scheme 6.6).⁷⁵ Another example is the three-component reaction of an aldehyde, an aniline and an α -isocyanoacetamide of the type **220** in the presence of a catalytic amount of chiral phosphoric acid **17d** afforded the 5-aminooxazole **221** in excellent yield and moderate to good enantiomeric excess.⁷⁶ The asymmetric induction is strongly substrate-dependent. This three-component coupling is not exactly a Ugi reaction but it is the closest example so far to a catalytic asymmetric Ugi reaction.

Scheme 6.6 Catalytic asymmetric 3-component Ugi reaction reported in List's group⁷⁵



Scheme 6.7 Catalytic asymmetric α -addition of α -isocyanoacetamides to imines⁷⁶



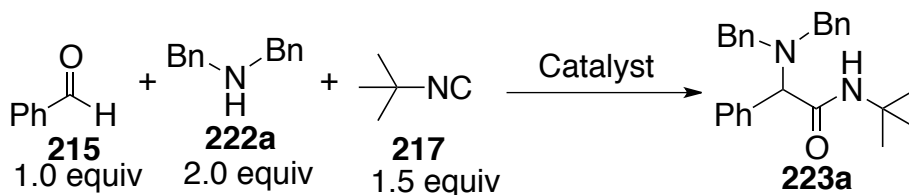
To the best of our knowledge, there is no successful chiral catalyst that has been reported for either the 3- or 4-component Ugi reaction. Given the potential of products in the synthesis of α -amino acids, we decided to put our efforts into developing a catalytic asymmetric Ugi reaction.

6.2 Development of catalytic asymmetric 3-component Ugi reaction

The study was commenced by investigating whether a Ugi-type reaction of benzaldehyde **215**, dibenzylamine **222a** and *t*-butyl isocyanide **217** could be catalyzed by a Brønsted or Lewis acid. As it has been shown by Suginome's

group that a 3-component Ugi reaction could be mediated by B(OMe)₃ (Scheme 6.5),^{72f} it was found that B(OPh)₃ could also be effective in the coupling of benzaldehyde, dibenzylamine and *t*-butyl isocyanide giving a 47% yield of the 2-amino amide **223a** in toluene at 80 °C (entry 2, Table 6.1). A catalytic amount of the strong Brønsted acid, TfOH (20 mol%) can furnish the product **223a** in toluene at room temperature in 45% yield (entry 3). Encouraged by these results with non-chiral Brønsted and Lewis acid, attention was turned to the boroxinate catalyst prepared from VAPOL, B(OPh)₃ and H₂O in the reaction. It was delightful to find that the reaction went smooth in toluene at 80 °C to give the product **223a** in 74% yield and with low but non-negligible enantiomeric excess (entry 4). The additives MgSO₄, 3Å MS and benzoic acid all had a bigger effect on the yield than on the asymmetric induction, whereas, the additive Mg(ClO₄)₂ affected both reaction yield and enantiomeric excess (entries 5-8). The catalyst prepared from VAPOL, BH₃•Me₂S, PhOH and H₂O gave results to those with the catalyst derived from VAPOL, B(OPh)₃ and H₂O (entry 9 vs 4). It was quickly found that the reaction performed at room temperature gave results similar to one at 80 °C (entry 9 vs 10). Lowering the temperature to 0 °C did improve the ee to 23%, however the reaction yield dropped significantly (entry 11). Although the reaction with 10 mol% catalyst gave the same asymmetric induction as the reaction with 20 mol% catalyst, the yield of the reaction dropped from 76% to 61% (entry 10 vs 12).

Table 6.1 The catalytic asymmetric 3-component Ugi reaction ^a



entry	Catalyst ^b	Additive	T °C	Time (h)	% yield 223a ^c	% ee 223a ^d
1 ^e	B(OPh) ₃ (150 mol%)	--	23	30	31 ^f	--
2	B(OPh) ₃ (200 mol%)	--	80	17	47 ^f	--
3	TfOH (20 mol%)	--	23	36	45 ^f	--
4	(S)-VAPOL (20 mol%)	--	80	24	74	17
	B(OPh) ₃ (80 mol%)					
	H ₂ O (20 mol%)					
5	(S)-VAPOL (20 mol%)	MgSO ₄ (4.0 equiv)	80	22	65	19
	B(OPh) ₃ (80 mol%)					
	H ₂ O (20 mol%)					
6	(S)-VAPOL (20 mol%)	3Å MS (150 mg)	80	24	44	19
	B(OPh) ₃ (80 mol%)					
	H ₂ O (20 mol%)					
7	(S)-VAPOL (20 mol%)	Benzoic acid (10 mol%)	80	24	52	17
	B(OPh) ₃ (80 mol%)					
	H ₂ O (20 mol%)					
8	(S)-VAPOL (20 mol%)	Mg(ClO ₄) ₂ (20 mol%)	80	24	44	24
	B(OPh) ₃ (80 mol%)					
	H ₂ O (20 mol%)					
9	(S)-VAPOL (20 mol%)	--	80	24	68	19
	BH ₃ •Me ₂ S (60 mol%)					
	PhOH (40 mol%)					
	H ₂ O (60 mol%)					
10	(S)-VAPOL (20 mol%)	--	23	24	76	18
	BH ₃ •Me ₂ S (60 mol%)					
	PhOH (40 mol%)					
	H ₂ O (60 mol%)					
11	(S)-VAPOL (20 mol%)	--	0	24	21	23
	BH ₃ •Me ₂ S (60 mol%)					
	PhOH (40 mol%)					
	H ₂ O (60 mol%)					

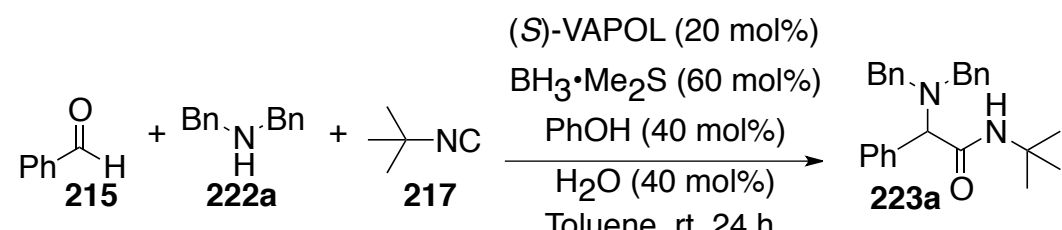
Table 6.1 cont'd

12	(S)-VAPOL (20 mol%) BH ₃ •Me ₂ S (60 mol%) PhOH (40 mol%) H ₂ O (60 mol%)	--	23	24	61	18

^a The reaction was run with benzaldehyde (0.25 mmol, 1.0 equiv), dibenzylamine (0.10 mL, 2.0 equiv) and *t*-butyl isocyanide (45 μ L, 1.5 equiv) in toluene (1 mL). ^b The catalyst was prepared according to the general procedure. ^c Isolated yield after column chromatography. ^d Determined from HPLC on purified **223a**. ^e The reaction was run in THF. ^f The NMR yield was determined from the crude reaction mixture with the aid of triphenylmethane as internal standard.

Although there were no remarkable differences found in the formation of **223a** with different equivalents of the reagents, the reagent ratio of 1:2:1.5 for benzaldehyde, dibenzyl amine and *t*-butyl isocyanide of gave the product **223a** was chosen for continued study of this reaction (Table 6.2).

Table 6.2 Screen of different ratios of the reactants in the catalytic asymmetric 3-CR Ugi reaction^a

					
entry	215 (equiv)	222a (equiv)	217 (equiv)	% yield 223a ^b	% ee 223a ^c
1	1.0	2.0	1.5	76	18
2	1.0	1.0	1.0	60	15
3	3.0	1.0	1.5	79	12

^a The reaction was run with benzaldehyde (0.25 mmol, 1.0 equiv), dibenzylamine (0.10 mL, 2.0 equiv) and *t*-butyl isocyanide (45 μ L, 1.5 equiv) in toluene (1 mL).

Table 6.2 cont'd

The catalyst was prepared from (S)-VAPOL, $\text{BH}_3 \cdot \text{Me}_2\text{S}$, PhOH and H_2O in toluene according to the general procedure.^b Isolated yield after column chromatography.^c Determined from HPLC on purified **223a**.

As has been discussed in Chapter 1 and Chapter 5, the boroxinate catalyst can be prepared from different ligands and different alcohol or phenol derivatives. It was thus decided to investigate the effects of different ligands and alcohol or phenol derivatives. The results of catalysts derived from different ligands are summarized in Table 6.3. It was surprising to find that the catalyst derived from the VANOL ligand gave lower asymmetric induction than the VAPOL catalyst (entry 1 vs 2). This is in striking contrast with the catalytic asymmetric aziridination of imines with EDA in which there is no significant difference seen with VAPOL and VANOL catalysts.²⁶ Although it was previously shown (Chapter 5) that the catalysts derived from BINOL derivatives **93b-d** formed predominantly B3 boroxinate catalyst in the presence of an imine, ligands gave catalysts that were less effective than the VAPOL catalyst.

Table 6.3 The screen of different chiral ligands in the Ugi reaction^a

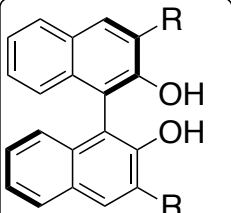
$\text{Ph}-\text{C}(=\text{O})-\text{H}$ 215 1.0 equiv $\text{Bn}-\text{N}(\text{H})-\text{Bn}$ 222a 2.0 equiv $\text{C}(\text{CH}_3)_3-\text{NC}$ 217 1.5 equiv $\xrightarrow[\text{Toluene, rt}]{\begin{array}{l} \text{Ligand (20 mol\%)} \\ \text{BH}_3 \cdot \text{Me}_2\text{S (60 mol\%)} \\ \text{PhOH (40 mol\%)} \\ \text{H}_2\text{O (40 mol\%)} \end{array}}$ $\text{Ph}-\text{CH}(\text{N}(\text{Bn})_2)-\text{C}(=\text{O})-\text{N}(\text{H})-\text{C}(\text{CH}_3)_3$ 223a				
 93b R = Ph 93c R = Br 93d R = SiPh₃				
entry	Ligand	Time (h)	% yield 223a ^b	% ee 223a ^c

Table 6.3 cont'd

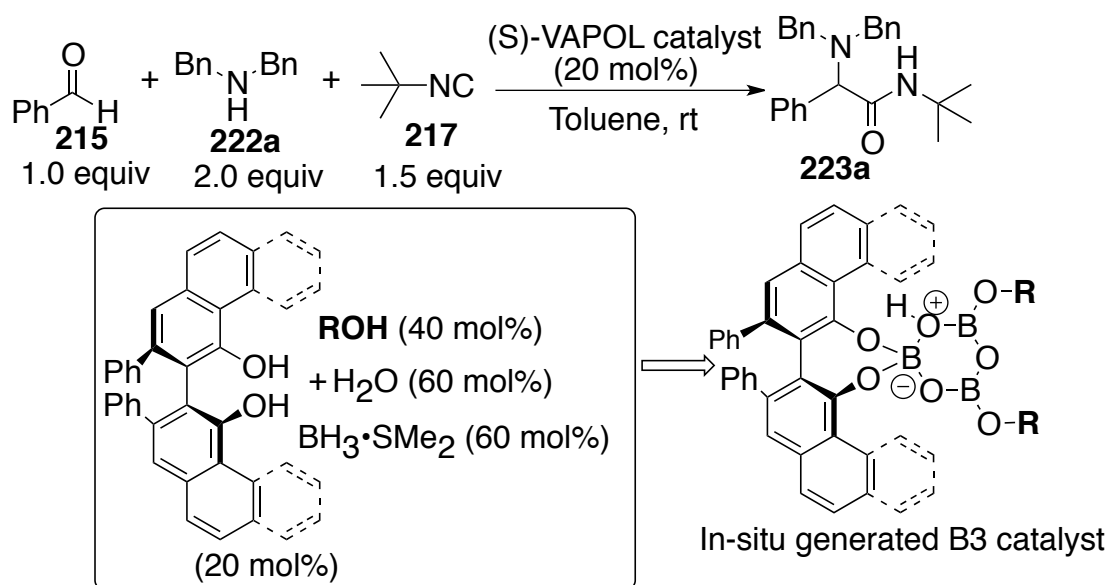
1	(<i>R</i>)-VAPOL	24	76	-18
2	(<i>S</i>)-VANOL	36	60	6
3	(<i>R</i>)- 93b	24	37	-11
4	(<i>R</i>)- 93c	43	30	-11
5	(<i>R</i>)- 93d	24	trace	--

^a The reaction was run with benzaldehyde (0.25 mmol, 1.0 equiv), dibenzylamine (0.10 mL, 2.0 equiv) and *t*-butyl isocyanide (45 μ L, 1.5 equiv) in toluene (1 mL). The catalyst was prepared from chiral ligand (20 mol%), BH₃·Me₂S (60 mol%), PhOH (40 mol%) and H₂O (60 mol%) in toluene according to the general procedure. ^b Isolated yield after column chromatography. ^c Determined from HPLC on purified **223a**. The minus sign means the other enantiomer of **223a** was obtained.

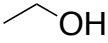
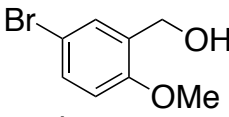
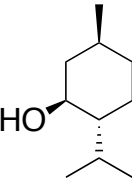
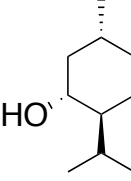
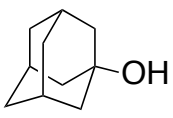
After identifying that VAPOL is the ligand of choice, the optimization effort was then focused on screening different alcohol and phenol derivatives that are incorporated into the boroxinate core of the catalyst and the results are given in Scheme 6.8. Catalysts from primary alcohols, such as ethanol and benzyl alcohol, were found to be ineffective and only give traces of product. The reaction gave good yields and low ee's with catalysts derived from more sterically hindered secondary ((+), (-)-menthol) or tertiary (adamantanol) alcohols. Mono-substituted phenols with strong electron-withdrawing group on the *para*-position diminished the asymmetric induction of the reaction. Phenols with aliphatic groups in the 2- and 6-positions seems to give a slight increase in the asymmetric induction, whereas 2,6-diphenylphenol gave a catalyst that behaved

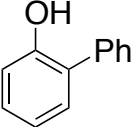
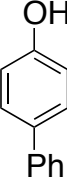
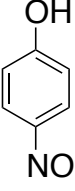
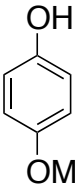
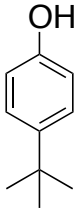
essentially the same as that from phenol. When it came to tri-substituted phenols, there was no clear relationship between the substitution pattern and the asymmetric induction. However, the catalyst derived from 2,4,6-trimethylphenol afforded the α -amino amide **223a** in 72% yield and with 40% ee. Catalysts derived from the phenols with sterically more hindered groups on the *para* position of 2,6-dimethylphenol such as diphenylmethyl and admantyl resulted in a lower ee of the product. The best enantioselectivity came from the catalyst prepared from 2,4,6-tri-*t*-butylphenol, which gave **223a** with 58% ee. Variation of the group in the 4-position of 2,6-di-*t*-butylphenol resulted in a lower ee of the product. VANOL and VAPOL monomers were also examined but gave the same %ee simple phenol.

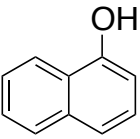
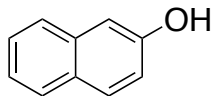
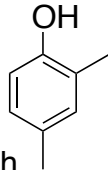
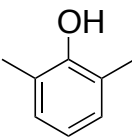
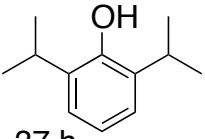
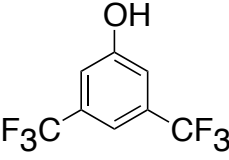
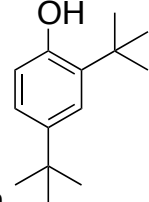
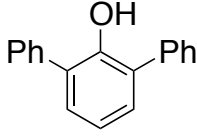
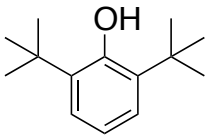
Scheme 6.8 Screen of alcohol and phenol derivatives^a



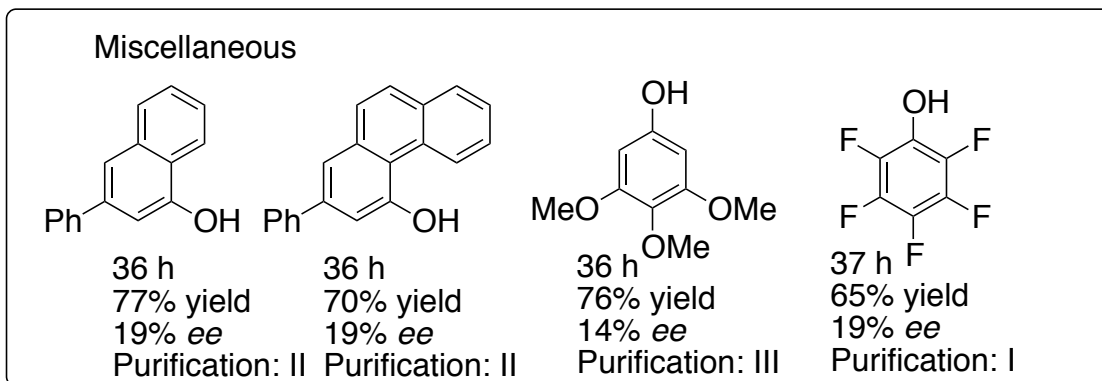
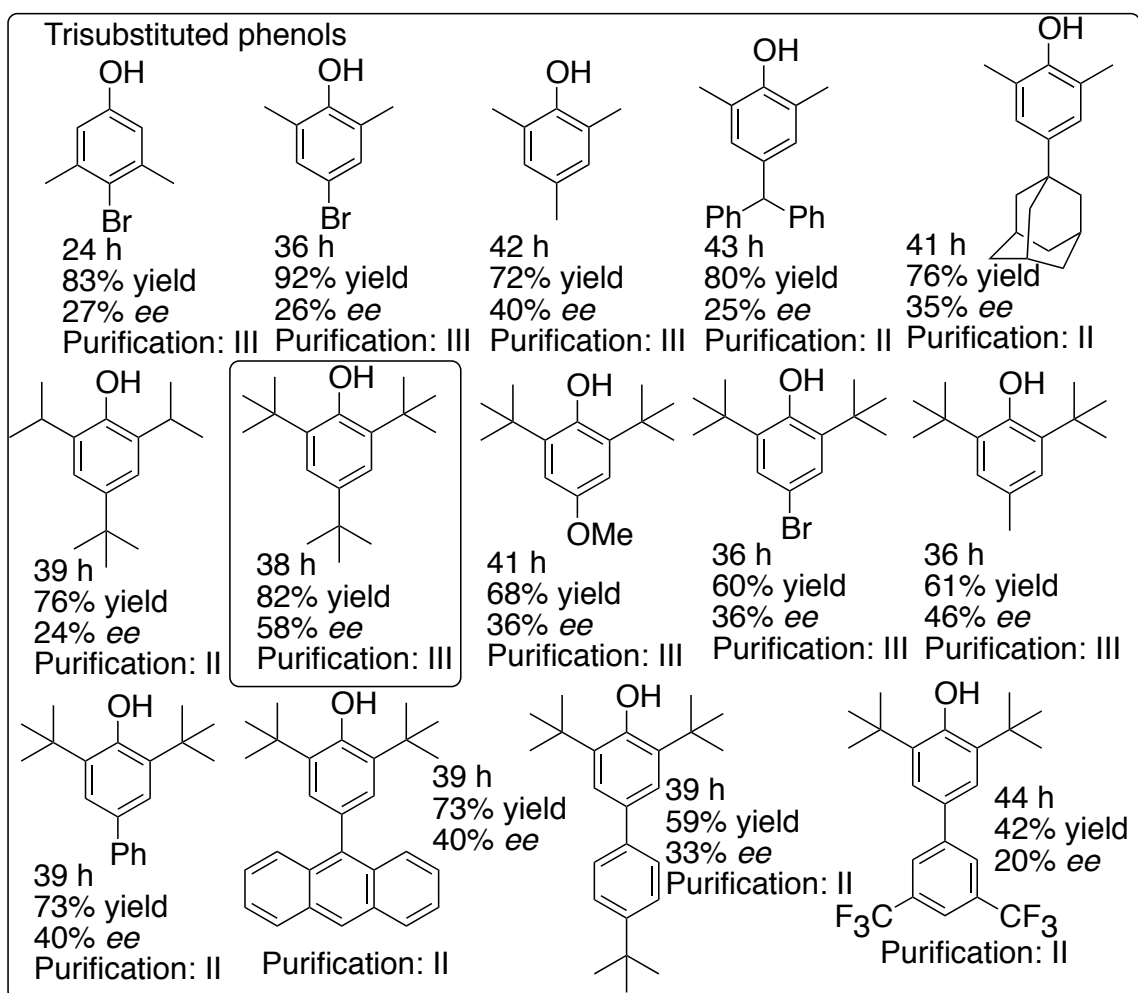
Scheme 6.8 cont'd

Alcohols				
				
trace	trace	(+)-menthol	(-)-menthol	
Purification ^b : I	Purification: II	24 h	24 h	39 h
		73% yield	91% yield	86% yield
		17% ee	16% ee	15% ee
		Purification: III	Purification: III	Purification: III

Monosubstituted phenols				
				
24 h	36 h	36 h	36 h	24 h
76% yield	70% yield	64% yield	75% yield	89% yield
17% ee	18% ee	13% ee	18% ee	22% ee
Purification: III	Purification: III	Purification: III	Purification: III	Purification: III

Disubstituted phenols				
				
24 h	24 h	37 h	39 h	37 h
56% yield	71% yield	82% yield	70% yield	82% yield
17% ee	17% ee	19% ee	26% ee	26% ee
Purification: III	Purification: III	Purification: III	Purification: III	Purification: III
				
37 h	37 h	42 h	37 h	
77% yield	76% yield	87% yield	69% yield	
31% ee	19% ee	19% ee	24% ee	
Purification: I	Purification: III	Purification: III	Purification: III	

Scheme 6.8 cont'd



^a The reaction was run with benzaldehyde (0.25 mmol, 1.0 equiv), dibenzylamine (0.10 mL, 2.0 equiv) and *t*-butyl isocyanide (45 μ L, 1.5 equiv) in toluene (1 mL). The catalyst was prepared from chiral ligand (20 mol%), $\text{BH}_3 \cdot \text{Me}_2\text{S}$ (60 mol%), alcohol or phenol derivatives (40 mol%) and H_2O (60 mol%) in toluene according to the general procedure. Isolated yield after column chromatography. ee was

Scheme 6.8 cont'd

determined from HPLC on purified **223a**.^b Purification means purification method of the alcohol or phenol derivatives. I: used as received; II: Purified by column chromatography on silica gel; III: Purified by sublimation.

With the 2,4,6-tri-*t*-butylphenol and VAPOL derived catalyst identified as giving the best asymmetric induction, a screen of different solvents was undertaken to achieve further optimization. From Table 6.4, it is clear that in polar solvents, such as acetonitrile and ether, the reaction went with a reduced asymmetric induction, with CH₃CN affording the racemic product. In nonpolar solvents, the asymmetric induction improved, with the best 66% ee observed in mesitylene.

Table 6.4 Solvent screening for the 3-component Ugi reaction^a

(<i>S</i>)-VAPOL (20 mol%) BH₃•Me₂S (60 mol%) 2,4,6-tri-<i>t</i>-butylphenol (40 mol%) H₂O (40 mol%)							
entry	Solvent	% yield 223a ^b	% ee 223a ^c	entry	Solvent	% yield 223a ^b	% ee 223a ^c
1	mesitylene	85	66	4	m-xylene	77	57
2	CCl ₄	86	62	5	CH ₃ CN	43	0
3	toluene	82	58	6	Et ₂ O	91	30

^a The reaction was run with benzaldehyde (0.25 mmol, 1.0 equiv), dibenzylamine (0.10 mL, 2.0 equiv) and *t*-butyl isocyanide (45 μL, 1.5 equiv) in the specified solvent (1 mL). The catalyst was prepared from (*R*)-VAPOL (20 mol%), BH₃•Me₂S (60 mol%), PhOH (40 mol%) and H₂O (60 mol%) in toluene according to the general procedure. ^b Isolated yield after column chromatography. ^c Determined from HPLC on purified **223a**.

It was surprising to find that dibenzylamine is the only secondary amine that works in the reaction. There is essentially no reaction with pyrrolidine, diethylamine, phenylbenzylamine and diphenylamine. Fortunately, a series of dibenzylamine derivatives could be employed in the reaction (Table 6.5). When the catalyst was prepared from VAPOL, $\text{BH}_3 \cdot \text{Me}_2\text{S}$, PhOH and H_2O , the asymmetric induction seems to change with the dibenzylamine derivative, with bis-(4-fluorobenzyl)amine giving the highest induction of 27% ee (entry 6). It was then disappointing to observe that with the catalyst prepared from tri-*t*-butylphenol, the reaction of bis-(4-fluorobenzyl)amine provided the same level of asymmetric induction as that of dibenzylamine (Table 6.5, entry 7 vs Table 6.4, entry 3).

Table 6.5 Screen of the dibenzylamine derivatives^a

entry	Ar	Product	T (h)	% yield 223 ^b	% ee 223 ^c
1	Phenyl (222a)	223a	24	76	18
2	2-naphthyl (222b)	223b	48	76	8
3	4-methoxyphenyl (222c)	223c	48	82	15
4	4-bromophenyl (222d)	223d	24	72	19
5	4-chlorophenyl (222e)	223e	24	72	24
6	4-fluorophenyl (222f)	223f	48	68	27
7 ^d	4-fluorophenyl (222f)	223f	39	88	56

^a The reaction was run with benzaldehyde (0.25 mmol, 1.0 equiv), dibenzylamine

Table 6.5 cont'd
(0.10 mL, 2.0 equiv) and *t*-butyl isocyanide (45 μ L, 1.5 equiv) in toluene (1 mL) in the specified time. The catalyst was prepared from (*R*)-VAPOL (20 mol%), $\text{BH}_3\cdot\text{Me}_2\text{S}$ (60 mol%), PhOH (40 mol%) and H_2O (60 mol%) in toluene according to the general procedure.^b Isolated yield after column chromatography.^c Determined from HPLC on the purified material **223**.^d 2,4,6-tri-*t*-butylphenol was used instead of phenol in the preparation of the catalyst.

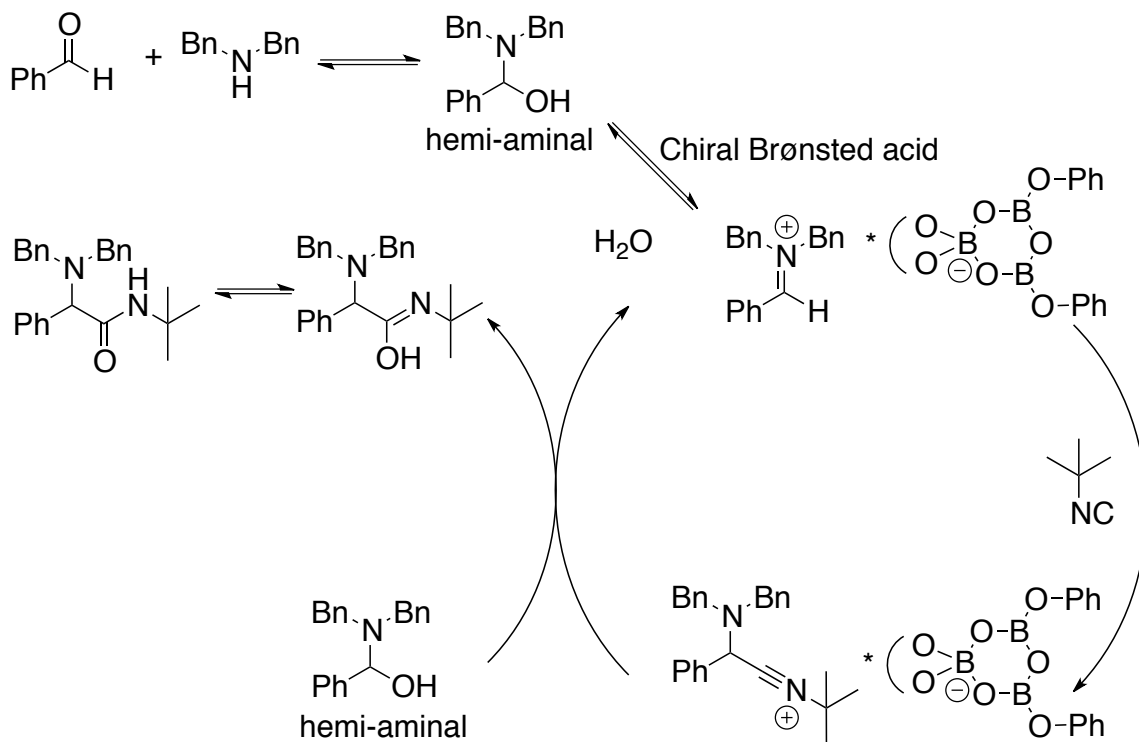
This project has been taken over by Wenjun Zhao, one of our group members. She found that the reaction with the catalyst prepared from the VAPOL and tri-*t*-butylphenol that gave 58% ee in toluene was not reproducible. After a lot of efforts on her part, it was found that the reason appears to be closely related to impurities present in the 2,4,6-tri-*t*-butylphenol and this is now under investigation.

6.3 Proposed mechanism

Although no detailed mechanistic study has been carried out at this point, a catalytic cycle leading to α -amino amides can be proposed (Scheme 6.9).

The reaction of benzaldehyde and dibenzylamine provides an hemiaminal that is in equilibrium with the starting materials. In the presence of the catalyst, the hemi-aminal may form an ion pair consisting of the VAPOL-B3 boroxinate anion and an iminium ion. Subsequent reaction with isocyanide generates the nitrilium ion as an ion pair with the VAPOL-B3 boroxinate anion. Then, abstraction of the hydroxyl group from the hemi-aminal by the nitrilium ion gives a tautomer of the final product. As can be seen from the mechanism in Scheme 6.9, the VAPOL boroxinate catalyst is not acting as a Brønsted acid as in the aziridination reaction but rather as a chiral counter anion catalyst. This is actually consistent with the above observed solvent effect (Table 6.4).

Scheme 6.9 Proposed mechanism for the Ugi-type reaction



6.4 Conclusion

A catalytic asymmetric 3-component Ugi reaction has been described. Although the best enantiomeric excess achieved so far is 66% in our study, it is still by far the best enantioselectivity reported for this reaction. In addition, from consideration of the mechanism, the boroxinate catalyst developed in our group is apparently serving as a chiral counter anion catalyst. This was anticipated as it was expected that it would serve as a chiral Brønsted acid as it does in the aziridination reaction. This new chiral counteranion may very well provide for new options in future catalyst development.

CHAPTER SEVEN

EXPERIMENTAL SECTION

General information: Dichloromethane and acetonitrile were distilled from calcium hydride under nitrogen. Toluene, THF and benzene were distilled from sodium under nitrogen. Hexanes and ethyl acetate were ACS grade and used as purchased. Other reagents were used as purchased from Aldrich. VANOL and VAPOL were prepared according to a literature procedure and were determined to be at least 99% optical purity.⁶¹ Preparation of aziridine ester **32a**^{26a}, **305-307**^{26a}, **312**^{26a}, **317**^{26a}, **32d**^{26b}, **32c**^{26c}, **300-304**^{26c}, **167a**^{26c}, **32b**^{26d} are previously reported. The preparation of **308** and **318** could be found.^{33,77}

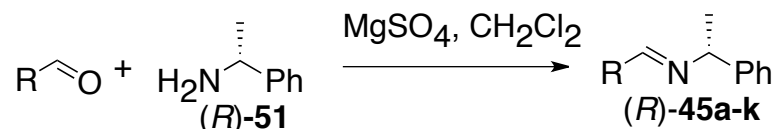
Melting points were determined on a Thomas Hoover capillary melting point apparatus and were uncorrected. IR spectra were taken on a Galaxy series FTIR-3000 spectrometer. ¹H NMR and ¹³C NMR were recorded on a Varian Inova-300 MHz, Varian UnityPlus-500 MHz or Varian Inova-600 MHz instrument in CDCl₃ unless otherwise noted. CDCl₃ was used as the internal standard for both ¹H NMR (δ = 7.24) and ¹³C NMR (δ = 77.0). HR-MS was performed in the department of Biochemistry at Michigan State University. Analytical thin-layer chromatography (TLC) was performed on 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. Column chromatography was performed with silica gel 60 (230 – 450 mesh). HPLC

analyses were carried out using a Varian Prostar 210 Solvent Delivery Module with a Prostar 330 PDA Detector and a Prostar Workstation. Optical rotations were obtained on a Perkin-Elmer 341 polarimeter at a wavelength of 589 nm (sodium D line) using a 1.0-decimeter cell with a total volume of 1.0 mL. Specific rotations are reported in degrees per decimeter at 20 °C.

Although we have not experienced any problems with either the preparation or use of diazo compounds herein, we note that diazo compounds in general are heat sensitive and potentially explosive and should be handled with due care.

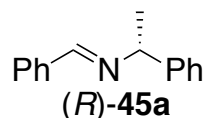
7.1 Experimental for Chapter Two

7.1.1 General procedure for the preparation of aldimines



The mixture of the corresponding aldehyde (1.01-1.20 equiv), *(R)*-**51** (1.00 equiv) and MgSO₄ (4.00 equiv) in dry CH₂Cl₂ (2-4 mL/mmol) was stirred at room temperature for the specified time. After it was filtered over a Celite pad on a sintered glass funnel, the filtrate was concentrated by rotary evaporation to give the crude product.

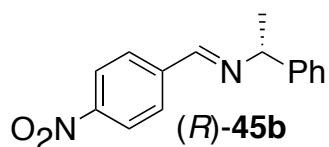
(R)-*N*-Benzyldene-1-methylbenzylamine (**45a**):



The general procedure was followed with 2.76 g benzaldehyde (26.0 mmol, 1.05 equiv), *(R)*-(+)- α -methylbenzylamine **51** (3.00 g, 24.8 mmol, 1.00 equiv), dry CH₂Cl₂ (50 mL) and a reaction time of 6 hours. The crude product was purified

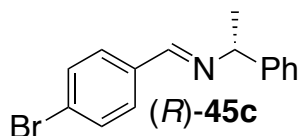
by vacuum distillation (119 °C/6 mmHg) to give the pure imine **45a** (2.658 g, 12.72 mmol, 51%) as a colorless oil. ^1H NMR (300 MHz, CDCl_3) δ 1.44 (d, 3H, J = 6.6 Hz), 4.38 (q, 1H, J = 6.6 Hz), 7.04-7.30 (m, 8H), 7.58-7.66 (m, 2H), 8.20 (s, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 24.89, 69.70, 126.60, 126.79, 128.23, 128.38, 128.49, 130.52, 136.40, 145.18, 159.39.

(R)-*N*-(4-Nitrobenzylidene)-1-methylbenzylamine (**45b**):



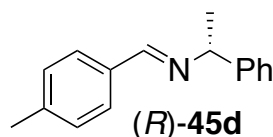
The general procedure was followed with 1.284 g 4-nitrobenzaldehyde (8.500 mmol, 1.030 equiv), *(R)*-**51** (1.00 g, 8.25 mmol, 1.00 equiv), dry CH_2Cl_2 (25 mL) and a reaction time of 24 hours. The crude product was placed at rt under high vacuum (0.1 mmHg) for at least 4 hours to give the imine **45b** (2.09 g, 8.23 mmol, 100%) as a pale yellow oil which was used in the aziridination reaction without further purification. ^1H NMR (300 MHz, CDCl_3) δ 1.50 (d, 3H, J = 5.7 Hz), 4.49 (q, 1H, J = 5.7 Hz), 7.12-7.32 (m, 5H), 7.80-7.84 (m, 2H), 8.12-8.16 (m, 2H), 8.31 (s, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 24.79, 70.08, 123.79, 126.59, 127.15, 128.57, 128.91, 141.87, 144.29, 148.99, 157.05.

(R)-*N*-(4-Bromobenzylidene)-1-methylbenzylamine (**45c**):



The general procedure was followed with 3.084 g 4-bromobenzaldehyde (16.67 mmol, 1.010 equiv), (*R*)-**51** (2.00 g, 16.5 mmol, 1.00 equiv), dry CH₂Cl₂ (50 mL) and a reaction time of 24 hours. The crude product was purified by recrystallization (CH₂Cl₂/hexane 1:10) to afford imine **45c** (3.879 g, 13.47 mmol, 82%) as white crystals; mp 88-89 °C. ¹H NMR (300 MHz, CDCl₃) δ 1.57 (d, 3H, *J* = 6.9 Hz), 4.52 (q, 1H, *J* = 6.9 Hz), 7.10-7.60 (m, 9H), 8.21 (s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 24.80, 69.75, 124.91, 126.60, 126.92, 128.46, 129.67, 131.74, 135.31, 144.92, 158.14; IR (thin film) 2974(w), 2853(w), 1587(m), 831(m) cm⁻¹; Anal calcd for C₁₅H₁₄NBr: C, 62.52; H, 4.90; N, 4.86. Found: C, 62.05; H, 5.02; N, 4.81; [α]_D²⁰ -87.9° (c 1.0, CH₂Cl₂).

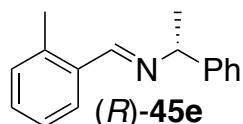
(*R*)-*N*-(4-Tolylbenzylidene)-1-methylbenzylamine (**45d**):



The general procedure was followed with 3.12 g 4-tolualdehyde (26.0 mmol, 1.05 equiv), (*R*)-**51** (3.00 g, 24.8 mmol, 1.00 equiv), dry CH₂Cl₂ (50 mL) and a reaction time of 24 hours. The crude product was purified by recrystallization (CH₂Cl₂/hexane 1:10) to afford imine **45d** (4.14 g, 18.57 mmol, 75%) as white needle-like crystals; mp 97-98 °C. ¹H NMR (300 MHz, CDCl₃) δ 1.58 (d, 3H, *J* = 6.5 Hz), 2.36 (s, 3H), 4.51 (q, 1H, *J* = 6.5 Hz), 7.17-7.45 (m, 7H), 7.64-7.69 (m,

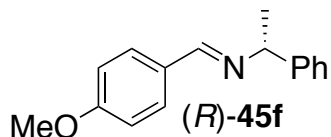
2H), 8.33 (s, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 21.49, 24.85, 69.65, 126.61, 126.74, 128.21, 128.37, 129.22, 133.79, 140.78, 145.31, 159.37; IR (thin film) 2976(m), 1741(s), 1178(s) cm^{-1} ; Anal calcd for $\text{C}_{16}\text{H}_{17}\text{N}$: C, 86.05; H, 7.67; N, 6.27. Found: C, 85.47; H, 7.87; N, 6.22; $[\alpha]_D^{20}$ -92.3° (c 1.0, CH_2Cl_2).

(R)-*N*-(2-Tolylbenzylidene)-1-methylbenzylamine (**45e**):



The general procedure was followed with 3.123 g 2-tolualdehyde (25.99 mmol, 1.05 equiv), *(R)*-**51** (3.00 g, 24.8 mmol, 1.00 equiv), dry CH_2Cl_2 (50 mL) and a reaction time of 24 hours. The crude product was placed at rt under high vacuum (0.1 mmHg) for at least 4 hours to give the imine **45e** (5.53 g, 24.80 mmol, 102%) as a colorless oil which was used in the aziridination reaction without further purification. ^1H NMR (300 MHz, CDCl_3) δ 1.58 (d, 3H, J = 6.6 Hz), 2.48 (s, 3H), 4.45 (q, 1H, J = 6.6 Hz), 7.10-7.44 (m, 8H), 7.83 (d, 1H, J = 3.6 Hz), 8.64-8.70 (s, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 19.44, 25.22, 70.39, 126.09, 126.57, 126.74, 127.86, 128.38, 130.08, 130.73, 134.30, 137.55, 145.38, 158.09.

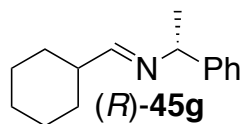
(R)-*N*-(4-Methoxybenzylidene)-1-methylbenzylamine (**45f**):



The general procedure was followed with 3.539 g 4-methoxybenzaldehyde (25.99 mmol, 1.050 equiv), *(R)*-**51** (3.00 g, 24.8 mmol, 1.00 equiv), dry CH_2Cl_2

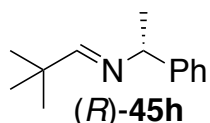
(50 mL) and a reaction time of 120 hours. The crude product was placed at 80 °C under high vacuum (0.1 mmHg) for 24 hours to give the imine **45f** (5.92 g, 24.8 mmol, 100%) as a colorless oil which was used in the aziridination reaction without further purification. ^1H NMR (300 MHz, CDCl_3) δ 1.58 (d, 3H, J = 6.9 Hz), 3.82 (s, 3H), 4.49 (q, 1H, J = 6.6 Hz), 6.86-6.96 (m, 2H), 7.18-7.46 (m, 5H), 7.68-7.76 (m, 2H), 8.29 (s, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 24.87, 55.33, 69.57, 113.89, 126.61, 126.71, 128.36, 129.42, 129.77, 145.44, 158.73, 161.54.

(R)-*N*-(Cyclohexymethylidene)-1-methylbenzylamine (**45g**):



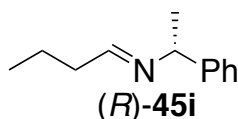
The general procedure was followed with 2.916 g cyclohexanecarboxaldehyde (25.99 mmol, 1.05 equiv), *(R)*-**51** (3.00 g, 24.8 mmol, 1.00 equiv), dry CH_2Cl_2 (50 mL) and a reaction time of 4 hours. The crude product was placed at rt under high vacuum (0.1 mmHg) for at least 4 hours to give the imine **45g** (5.286 g, 24.59 mmol, 99%) as a colorless oil which was used in the aziridination reaction without further purification. ^1H NMR (300 MHz, CDCl_3) δ 1.14-1.38 (m, 5H), 1.50 (d, 3H, J = 4.2 Hz), 1.62-1.90 (m, 5H), 2.16-2.26 (m, 1H), 4.25 (q, 1H, J = 4.2 Hz), 7.18-7.36 (m, 5H), 7.57 (d, 1H, J = 7.0 Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 24.67, 25.33, 25.93, 29.71, 29.73, 43.40, 69.39, 126.42, 126.58, 128.27, 145.22, 167.60 (One sp^3 carbon not located).

(R)-*N*-(*t*-Butylmethylidene)-1-methylbenzylamine (**45h**):



The general procedure was followed with 1.62 g trimethylacetaldehyde (18.2 mmol, 1.10 equiv), (*R*)-**51** (2.00 g, 16.5 mmol, 1.00 equiv), dry CH₂Cl₂ (50 mL) and a reaction time of 25 hours. The crude product was purified by vacuum distillation (98 °C/7 mmHg) to give imine **45h** (1.421 g, 7.52 mmol, 46%) as a colorless oil. ¹H NMR (300 MHz, CDCl₃) δ 1.00 (s, 9H), 1.36 (d, 3H, *J* = 6.6 Hz), 4.18 (q, 1H, *J* = 6.6 Hz), 7.10-7.30 (m, 5H), 7.52 (s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 24.96, 26.98, 36.00, 69.00, 126.40, 126.48, 128.21, 145.60, 170.26.

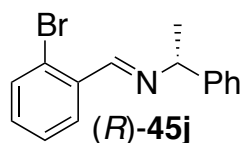
(R)-*N*-(*n*-Propylmethylidene)-1-methylbenzylamine (**45i**):



The general procedure was followed with 86 mg butyraldehyde (1.2 mmol, 1.2 equiv), (*R*)-**51** (121 mg, 1.00 mmol, 1.00 equiv), dry CH₂Cl₂ (10 mL) and a reaction time of 1.5 hours. The crude product was placed at rt under high vacuum (0.1 mmHg) for 5 minutes to give the imine **45i** (180 mg, 1.03 mmol, 103%) as a colorless oil which was used immediately in the aziridination reaction without further purification. ¹H NMR (500 MHz, CDCl₃) δ 0.93 (t, 3H, *J* = 7.5 Hz), 1.48 (d, 3H, *J* = 6.5 Hz), 1.60-1.50 (m, 2H), 2.28-2.20 (m, 2H), 4.25 (q, 1H, *J* = 6.5 Hz), 7.36-7.18 (m, 5H), 7.73 (t, 1H, *J* = 5.0 Hz); ¹³C NMR (75 MHz, CDCl₃) δ

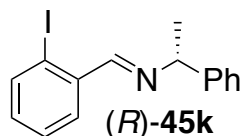
13.78, 19.57, 24.65, 37.79, 69.77, 126.56, 126.78, 128.42, 163.89 (One sp^2 C not located).

(R)-*N*-(2-Bromobenzylidene)-1-methylbenzylamine (**45j**):



The general procedure was followed with 2.36 g 2-bromobenzaldehyde (12.5 mmol, 1.01 equiv), (*R*)-**51** (1.50 g, 12.4 mmol, 1.00 equiv), dry CH_2Cl_2 (50 mL) and a reaction time of 24 hours. The crude product was placed at rt under high vacuum (0.1 mmHg) for at least 4 hours to give the imine **45j** (3.56 g, 12.38 mmol, 100%) as a colorless oil which was used in the aziridination reaction without further purification. ^1H NMR (300 MHz, CDCl_3) δ 1.60 (d, 3H, $J = 6.6$ Hz), 4.64 (q, 1H, $J = 6.6$ Hz), 7.24-7.38 (m, 5H), 7.42-7.47 (m, 2H), 7.52-7.57 (m, 1H), 8.10 (dd, 1H, $J = 9.0, 3.0$ Hz), 8.74 (s, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 24.86, 69.81, 125.01, 126.58, 126.89, 127.53, 128.44, 129.05, 131.69, 132.90, 134.67, 144.84, 158.47.

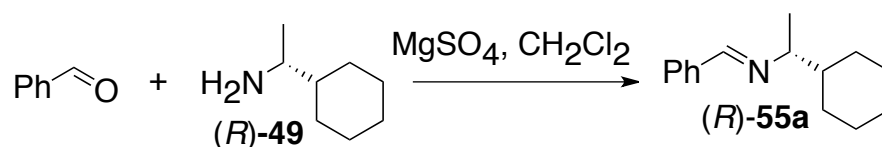
(R)-*N*-(2-Iodobenzylidene)-1-methylbenzylamine (**45k**):



The general procedure was followed with 2.134 g 2-iodobenzaldehyde (9.200 mmol, 1.020 equiv), (*R*)-**51** (1.10 g, 9.02 mmol, 1.00 equiv), dry CH_2Cl_2 (30 mL) and a reaction time of 40 hours. The crude product was placed at rt under high

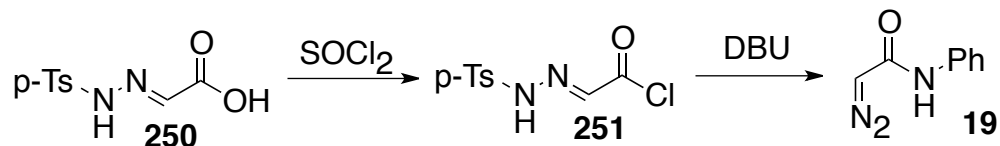
vacuum (0.1 mmHg) for at least 4 hours to give the imine **45k** (3.03 g, 9.04 mmol, 101%) as a yellow oil which was used in the aziridination reaction without further purification; ^1H NMR (300 MHz, CDCl_3) δ 1.50 (d, 3H, J = 6.6 Hz), 4.54 (q, 1H, J = 6.6 Hz), 6.92-7.38 (m, 7H), 7.70-7.76 (m, 1H), 7.92 (dd, 1H, J = 7.8, 1.5 Hz), 8.41 (s, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 24.83, 69.54, 100.07, 126.61, 126.91, 128.35, 128.44, 129.08, 131.91, 137.08, 139.50, 144.79, 162.72.

(R)-*N*-Benzylidene-1-cyclohexylethylamine (**55a**):



The general procedure was followed with benzaldehyde (1.686 g, 15.88 mmol, 1.010 equiv), (*R*)-(-)-1-cyclohexylethylamine **49** (2.00 g, 15.7 mmol, 1.00 equiv), dry CH_2Cl_2 (25 mL) and a reaction time of 20 hours. The crude product was placed under the vacuum (0.1 mmHg) for at least 4 hours before the aziridination reaction to give the imine **55a** (3.377 g, 15.70 mmol, 100%) as a colorless oil. ^1H NMR (300 MHz, CDCl_3) δ 0.82-1.00 (m, 2H), 1.06-1.30 (m, 6H), 1.42-1.52 (m, 1H), 1.60-1.84 (m, 5H), 2.96-3.02 (m, 1H), 7.36-7.40 (m, 3H), 7.69-7.74 (m, 2H), 8.20 (s, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 19.92, 26.21, 26.38, 26.57, 29.81, 29.97, 43.68, 71.99, 128.03, 128.48, 130.22, 136.52, 158.59.

7.1.2 Preparation of diazoacetamide **19**



To a suspension of the acid **250** (17.8 g, 0.0740 mol, 1.00 equiv) in dry benzene (80 mL) was added freshly distilled SOCl_2 (17.5 g, 10.7 mL, 0.147 mol, 2.00 equiv). The resulting mixture was refluxed for 2 hours during which time the solid was gradually dissolved. Then it was cooled to room temperature and filtered through a Celite pad on a sintered glass funnel. After the filtrate was concentrated, warm benzene ($\sim 45^\circ\text{C}$, 30 mL) was added and the solid was broken up into small pieces. The suspension was cooled and filtered. The solid product was washed with cold benzene (2×10 mL). The filtrate was concentrated to give a solid. To the solid was added warm benzene ($\sim 45^\circ\text{C}$, 10 mL), filtered and washed with cold benzene. The combined solids from both crops were heated to dissolve in benzene (25 mL) and petroleum ether (bp $35\text{--}60^\circ\text{C}$, 25 mL) was added. Precipitate came out. After filtration, the product **251** was given as a pale yellow solid (15.56 g, 0.05984 mol, 82%).

A 100 mL round bottom flask was flame dried and cooled to rt under N_2 . It was then charged with acid chloride **251** (3.600 g, 13.85 mmol, 1.000 equiv) and dry CH_2Cl_2 (30 mL). And the vacuum adapter was quickly replaced with a septum in which a N_2 balloon was attached *via* a needle. Then aniline (1.414 g, 1.400 mL, 15.18 mmol, 1.100 equiv) and DBU (4.217 g, 4.200 mL, 2.000 equiv) were added *via* syringe sequentially at 0°C . The resulting mixture was stirred at 0°C for 2

hours during which time the color turned from yellow to dark red. After it was warmed up to rt, aq sat NH_4Cl (30 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 $\times$ 30 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4) and filtered. After concentration, the residue was loaded onto the column (silica gel, 30 $\times$ 270 mm, CH_2Cl_2 :MeOH 50:1). The yellow fractions were collected and concentrated to dryness. After it was put on the high vacuum for 1 hour, the yellow solid was washed with ether (2 $\times$ 50 mL + 25 mL) to afford a yellow crystal solid **19** (1.099 g, 6.819 mmol, 49%). ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 5.48 (s, 1H), 6.95-7.06 (m, 1H), 7.20-7.34 (m, 2H), 7.50-7.52 (m, 2H), 9.69 (s, 1H); ^{13}C NMR (125 MHz, $\text{DMSO}-d_6$) δ 47.97, 118.59, 122.64, 128.72, 139.51, 163.51.

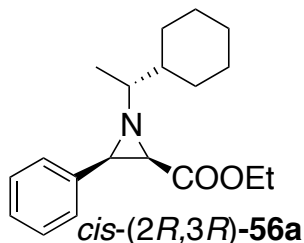
7.1.3 Catalytic asymmetric aziridinations

General Procedure for the Catalytic Asymmetric Aziridination of Aldimines with EDA 5 (Method A): For reactions in Table 2.1, Table 2.3-2.6. A 25 mL pear-shaped single neck flask which had its 14/20 joint replaced by a threaded high vacuum Teflon valve was flame dried (with a stir bar in it), cooled to rt under N_2 and charged with 10 mol% ligand (0.10 mmol, 0.10 equiv) (or no ligand), 40 mol% triphenyl borate (116 mg, 0.400 mmol, 0.400 equiv), H_2O (18 mg, 1.8 μL , 0.10 mmol, 0.10 equiv) and dry toluene (2 mL). The Teflon valve was closed and the flask was heated at 80 $^\circ\text{C}$ for 1 hour. After the flask was cooled to rt, the

toluene was carefully removed by exposing to high vacuum (0.1 mmHg) by slightly cracking the Teflon valve. After the solvent was removed, the Teflon valve was completely opened and the flask was heated at 80 °C under high vacuum for 30 min. The flask was then allowed to cool to rt. The imine substrate (1.0 mmol, 1.0 equiv) and toluene (2 mL) were added. To this stirred solution was rapidly added EDA **5** (124 μ L, 1.20 mmol, 1.20 equiv). The resulting mixture was stirred at rt for 24 h (or 1 h for entries 3 and 4 in Table 2.3). The conversion was determined from the ^1H NMR spectrum of the crude mixture by integration of the aziridine ring methine protons relative to either the imine methine proton or the proton on the imine carbon. The *cis/trans* ratio was determined on the crude mixture by integration of the ring methine protons for each aziridine. The *cis* ($J = 7\text{-}8$ Hz) and *trans* ($J = 2\text{-}3$ Hz) coupling constants were used to differentiate *cis* and *trans* diastereomers. The yield of the noncyclic enamine products were determined from the ^1H NMR spectrum of the crude reaction mixture by integration of the NH proton (9-10 ppm) of the enamine by-product and aziridine methine peak of the desired product. Conversion was 100% unless otherwise stated. In some cases, the minor product from the matched case was isolated and fully characterized. In other cases, it was not but assigned as the minor diastereomer based on the coupling constant (6-7 Hz) of the aziridine methine peak from the ^1H NMR spectrum of the crude reaction mixture. After column chromatography, the corresponding product was obtained.

*General Procedure for the Catalytic Asymmetric Aziridination of Aldimines with Diazoacetamide **19** (Method B):* For reactions in Table 2.7 (entries 1-5) and Table 2.8. A 25 mL pear-shaped single neck flask which had its 14/20 joint replaced by a threaded high vacuum Teflon valve was flame dried (with a stir bar in it), cooled to rt under N₂ and charged with 10 mol% ligand (0.02 mmol, 0.1 equiv) (or no ligand), borane dimethylsulfide in toluene (2M, 30 μ L, 0.060 mmol, 0.30 equiv), sublimed PhOH (5 mg, 0.04 mmol, 0.2 equiv), H₂O (1.08 μ L, 0.0600 mmol, 0.300 equiv) and dry toluene (2 mL). The Teflon valve was closed and the flask was heated at 100 °C for 1 hour. After the flask was cooled to rt, the toluene was carefully removed by exposing to high vacuum (0.1 mmHg) by slightly cracking the Teflon valve. After the solvent was removed, the Teflon valve was completely opened and the flask was heated to 100 °C under high vacuum for 30 min. The flask was then cooled to rt, and the substrate (0.20 mmol, 1.0 equiv) and dry toluene (1 mL) were added to the flask under N₂ flow. To this stirred solution was added diazoacetamide **19** (39 mg, 0.24 mmol, 1.2 equiv) under N₂ flow. Then the Teflon valve was closed and the resulting mixture was stirred at rt for the specified time. The reaction was quenched with *n*-hexane (5 mL) and concentrated. The crude mixture was analyzed by ¹H NMR spectroscopy to determine the conversion and diastereoselectivity. After column chromatography, the corresponding product was obtained.

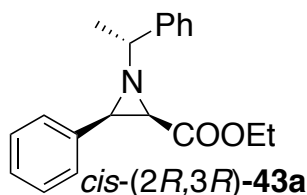
*Synthesis of cis-(2R,3R)-**56a** from aziridination of the cyclohexylethyl chiral imine (R)-**55a** derived from benzaldehyde.*



cis-(2*R*,3*R*)-**56a**: The reaction of imine (*R*)-**55a** (215 mg, 1.00 mmol) and (*S*)-VAPOL (54 mg, 0.10 mmol) was performed according to the General Procedure (Method A). The ^1H NMR spectrum of the crude mixture showed a 90% conversion, >50:1 *cis/trans* ratio, 3%/7% enamine products **58a/59a** and an 83:17 mixture of *cis*-(2*R*,3*R*)-**56a** and *cis*-(2*S*,3*S*)-**57a**. Purification of the products by column chromatography (1st column, silica gel, 40 × 400 mm, hexane:CH₂Cl₂:Et₂O 8:1:1; 2nd column, silica gel, 15 × 150 mm, hexane:EtOAc 19:1) gave *cis*-(2*R*,3*R*)-**56a** (98 mg, 0.35 mmol) in 35% isolated yield as a white solid; mp 47-49 °C; R_f = 0.35 (hexane:EtOAc 9:1). Spectral data for *cis*-(2*R*,3*R*)-**56a**: ^1H NMR (300 MHz, CDCl₃) δ 0.92 (t, 3H, J = 7.2 Hz), 0.97-1.26 (m, 8H), 1.43-1.76 (m, 6H), 1.84-1.95 (m, 1H), 2.36 (d, 1H, J = 6.6 Hz), 2.94 (d, 1H, J = 6.9 Hz), 3.80-4.02 (m, 2H), 7.16-7.30 (m, 3H), 7.36-7.42 (m, 2H); ^{13}C NMR (75 MHz, CDCl₃) δ 13.91, 16.47, 26.43, 26.53, 26.66, 28.94, 30.06, 43.55, 44.53, 49.35, 60.47, 70.50, 127.18, 127.75, 127.90, 135.70, 168.69; IR (thin film) 2980(m), 2924(s), 2853(m), 1734(s), 1201(s), 698(m) cm⁻¹; HRMS (ESI) calcd

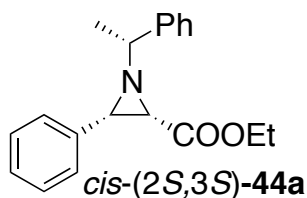
for C₁₉H₂₈NO₂ m/z 302.2120 ([M+H]⁺), meas 302.2117; [α]_D²⁰ -22.3° (c 1.0, CH₂Cl₂).

Synthesis of cis-(2R,3R)-43a and cis-(2S,3S)-44a from aziridination of the phenethyl chiral imine (R)-45a derived from benzaldehyde.



The reaction of imine (*R*)-**45a** (209 mg, 1.00 mmol) and (*S*)-VAPOL (54 mg, 0.10 mmol) was performed according to the General Procedure (Method A). The ¹H NMR spectrum of the crude mixture showed a >50:1 *cis/trans* ratio, 1%/7% of enamine products **65a/66a** and a 96:4 mixture of *cis*-(2*R*,3*R*)-**43a** and *cis*-(2*S*,3*S*)-**44a**. Purification by column chromatography (silica gel, 40 × 400mm, hexane:CH₂Cl₂:Et₂O 8:1:1) gave pure *cis*-(2*R*,3*R*)-**43a** in 74% isolated yield (215 mg, 0.74 mmol) as a pale yellow solid; mp 84-85 °C (Lit^{32b} 87-89 °C); R_f = 0.25 (hexane:CH₂Cl₂:Et₂O 8:1:1). Spectral data for *cis*-(2*R*,3*R*)-**43a**: ¹H NMR (300 MHz, CDCl₃) δ 0.96 (t, 3H, J = 7.2 Hz), 1.54 (d, 3H, J = 6.2 Hz), 2.60 (d, 1H, J = 6.9 Hz), 2.85 (q, 1H, J = 6.6 Hz), 2.95 (d, 1H, J = 6.9 Hz), 3.86-4.04 (m, 2H), 7.10-7.34 (m, 8H), 7.40-7.46 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 13.94, 22.92, 46.03, 47.36, 60.65, 69.80, 126.94, 127.18, 127.28, 127.67, 127.76, 128.39, 135.20, 143.28, 168.26; mass spectrum m/z (% rel intensity) 295(4), 105(100);

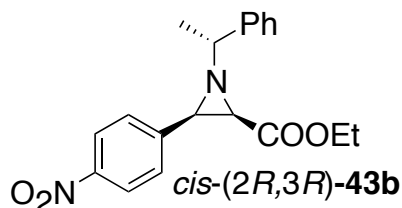
$[\alpha]_D^{20}$ -60.8° (c 1.0, CH_2Cl_2). The major product from this reaction can be assigned as ethyl (2*R*,3*R*)-3-phenyl-1-[(*R*)-1-phenylethyl]aziridine-2-carboxylate by comparison of its optical rotation with that previously reported for this compound.^{32b} This assignment was confirmed by reductive ring opening to (*R*)-phenylalanine ethyl ester **69**.



cis-(2*S*,3*S*)-**44a**: The reaction of imine (*R*)-**45a** (209 mg, 1.00 mmol) and (*R*)-VAPOL (54 mg, 0.10 mmol) was performed according to the General Procedure (Method A). The ^1H NMR spectrum of the crude mixture showed a >50:1 *cis/trans* ratio, 7%/11% of enamine products **65a/66a** and a 33:67 mixture of *cis*-(2*R*,3*R*)-**43a** and *cis*-(2*S*,3*S*)-**44a**. Purification of the products by column chromatography (silica gel, 40 × 400 mm, hexane: CH_2Cl_2 : Et_2O 8:1:1) gave *cis*-(2*R*,3*R*)-**43a** in 17% isolated yield (52 mg, 0.17 mmol) as a pale yellow solid. The fraction containing **44a** was collected and concentrated. It was then further purified by column chromatography (silica gel, 40 × 400 mm, hexane: EtOAc 19:1) to give *cis*-(2*S*,3*S*)-**44a** as a white solid (98 mg, 0.33 mmol) in 33% yield; mp 87-88 °C (Lit^{5b} 64-66 °C); R_f = 0.42 (hexane: CH_2Cl_2 : Et_2O 8:1:1). Spectral data for *cis*-(2*S*,3*S*)-**44a**: ^1H NMR (300 MHz, CDCl_3) δ 0.92 (t, 3H, J = 6.9 Hz), 1.50 (d, 3H, J = 6.6 Hz), 2.49 (d, 1H, J = 6.9 Hz), 2.90 (q, 1H, J = 6.6 Hz), 3.10

(d, 1H, $J = 6.6$ Hz), 3.86-3.94 (m, 2H), 7.20-7.40 (m, 6H), 7.44-7.47 (m, 4H); ^{13}C NMR (75 MHz, CDCl_3) δ 13.89, 23.90, 45.54, 48.02, 60.45, 69.19, 126.67, 127.09, 127.43, 127.89, 127.90, 128.40, 135.52, 143.70, 167.98; IR (thin film) 2963(w), 1738(s), 1201(m) cm^{-1} ; mass spectrum m/z (% rel intensity) 295(2), 190(63), 117(100); Anal calcd for $\text{C}_{19}\text{H}_{21}\text{NO}_2$: C, 77.26; H, 7.17; N, 4.74. Found: C, 76.74; H, 7.20; N, 4.66; $[\alpha]_{\text{D}}^{20} -32.8^\circ$ (c 1.0, CH_2Cl_2).

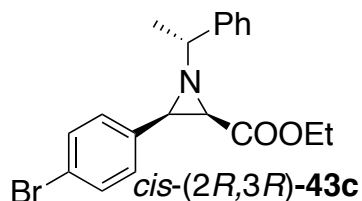
Synthesis of cis-(2R,3R)-43b from aziridination of the phenethyl chiral imine (R)-45b derived from 4-nitrobenzaldehyde.



cis-(2R,3R)-43b: The reaction of imine (R)-45b (254 mg, 1.00 mmol) and (S)-VAPOL (54 mg, 0.10 mmol) was performed according to the General Procedure (Method A). The ^1H NMR spectrum of the crude mixture showed a >50:1 cis/trans ratio, 4%/5% of enamine products and a 94:6 mixture of *cis-(2R,3R)-43b* and *cis-(2S,3S)-44b*. Purification of the major product by column chromatography (1st column, silica gel, 40 × 400 mm, hexane: CH_2Cl_2 : Et_2O 8:1:1; 2nd column, silica gel, 25 × 250 mm, hexane:EtOAc 15:1) gave *cis-(2R,3R)-43b* in 74% isolated yield as a yellow oil (249 mg, 0.732 mmol); $R_f = 0.10$ (hexane: CH_2Cl_2 : Et_2O 8:1:1). Spectral data for *cis-(2R,3R)-43b*: ^1H NMR

(300 MHz, CDCl₃) δ 1.00 (s, 3H, J = 6.6 Hz), 1.48 (d, 3H, J = 6.9 Hz), 2.68 (d, 1H, J = 6.9 Hz), 2.88 (d, 1H, J = 6.9 Hz), 3.00 (d, 1H, J = 6.6 Hz), 3.84-4.02 (m, 2H), 7.12-7.52 (m, 7H), 8.00 (d, 2H, J = 7.5 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 13.91, 22.81, 46.34, 60.89, 69.61, 122.82, 126.67, 127.45, 128.43, 128.65, 142.74, 142.76, 147.05, 167.39 (One sp^3 carbon not located); ¹³C NMR (75 MHz, MeOD) δ 14.35, 22.97, 47.54, 47.66, 62.09, 70.33, 123.81, 128.02, 128.52, 129.51, 129.94, 144.58, 144.71, 148.55, 169.51; IR (thin film) 2978(w), 1747(s), 1520(s), 1346(s) cm⁻¹; HRMS (ESI⁺) calcd for C₁₉H₂₁N₂O₄ m/z 341.1501 ([M+H]⁺), meas 341.1508; [α]_D²⁰ -118.2° (c 1.0, CH₂Cl₂).

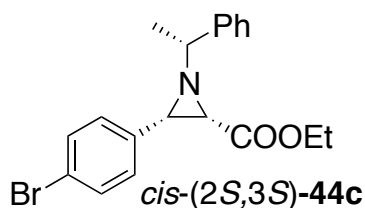
Synthesis of cis-(2R,3R)-43c and cis-(2S,3S)-44c from aziridination of the phenethyl chiral imine (R)-45c derived from 4-bromobenzaldehyde.



cis-(2R,3R)-43c (Table 4, entry 6): The reaction of imine (R)-45c (289 mg, 1.00 mmol) and (S)-VAPOL (54 mg, 0.10 mmol) was performed according to the General Procedure (Method A). The ¹H NMR spectrum of the crude mixture showed a >50:1 cis/trans ratio, 4%/4% of enamine products and a 94:6 mixture of *cis-(2R,3R)-43c* and *cis-(2S,3S)-44c*. Purification of the major product by column chromatography (silica gel, 40 × 400mm, hexane:CH₂Cl₂:Et₂O 8:1:1) gave *cis-(2R,3R)-43c* in 82% isolated yield as a pale colored crystalline solid

(305 mg, 0.820 mmol); mp 80-82 °C; R_f = 0.26 (hexane:CH₂Cl₂:Et₂O 8:1:1).

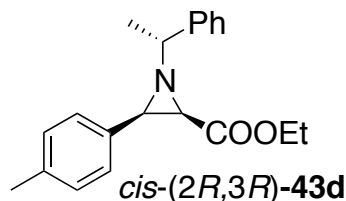
Spectral data for *cis*-(2*R*,3*R*)-**43c**: ¹H NMR (300 MHz, CDCl₃) δ 1.00 (t, 3H, J = 6.9 Hz), 1.50 (d, 3H, J = 6.0 Hz), 2.58 (d, 1H, J = 6.9 Hz), 2.74-2.96 (m, 2H), 3.84-4.06 (m, 2H), 7.04-7.52 (m, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 14.01, 22.89, 46.07, 46.72, 60.81, 69.76, 121.18, 126.83, 127.38, 128.44, 129.53, 130.80, 134.25, 143.10, 160.12; IR (thin film) 2978(m), 1747(s), 1197(s) cm⁻¹; mass spectrum m/z (% rel intensity) 375 M⁺ (0.5, ⁸¹Br), 373 M⁺ (0.5, ⁷⁹Br), 104(100); HRMS (ESI⁺) calcd for C₁₉H₂₁NO₂ ⁷⁹Br m/z 374.0756 ([M+H]⁺), meas 374.0773; $[\alpha]_D^{20}$ -69.8° (c 1.0, CH₂Cl₂).



cis-(2*S*,3*S*)-**44c**: The reaction of imine (*R*)-**45c** (289 mg, 1.00 mmol) and (*R*)-VAPOL (54 mg, 0.10 mmol) was performed according to the General Procedure (Method A). The ¹H NMR spectrum of the crude mixture showed a >50:1 *cis*/*trans* ratio, 13%/13% of enamine products and a 38:62 mixture of *cis*-(2*R*,3*R*)-**43c** and *cis*-(2*S*,3*S*)-**44c**. Purification of the products by column chromatography (silica gel, 40 × 400 mm, hexane:CH₂Cl₂:Et₂O 8:1:1) gave *cis*-(2*R*,3*R*)-**43c** in 24% isolated yield (89 mg, 0.24 mmol) as a pale yellow solid. The fraction containing *cis*-(2*S*,3*S*)-**44c** was collected and concentrated. The aziridine

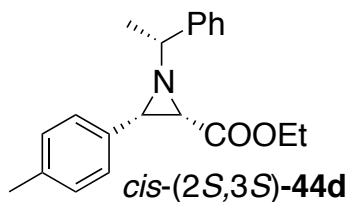
was purified by column chromatography (1st column, silica gel, 40 × 400 mm, hexane:EtOAc 15:1; 2nd column, silica gel, 28 × 280 mm, hexane:EtOAc 15:1) to give *cis*-(2*S*,3*S*)-**44c** as a white crystalline solid (100 mg, 0.267 mmol) in 27% yield; mp 73-74 °C; R_f = 0.33 (hexane:Et₂O:CH₂Cl₂ 8:1:1). Spectral data for *cis*-(2*S*,3*S*)-**44c**: ¹H NMR (300 MHz, CDCl₃) δ 0.96 (t, 3H, J = 6.9 Hz), 1.46 (d, 3H, J = 6.6 Hz), 2.49 (d, 1H, J = 6.9 Hz), 2.90 (q, 1H, J = 6.6 Hz), 3.00 (d, 1H, J = 6.9 Hz), 3.84-3.94 (m, 2H, J = 6.9 Hz), 7.20-7.52 (m, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 13.92, 23.81, 45.59, 47.29, 60.53, 69.05, 121.38, 126.57, 127.13, 128.40, 129.62, 130.95, 134.56, 143.45, 167.58; IR (thin film) 2972(w), 1734(s), 1197(s) cm⁻¹; mass spectrum m/z (% rel intensity) 376 M⁺ (0.1, ⁸¹Br), 374 M⁺ (0.1, ⁷⁹Br), 105(100); HRMS (ESI⁺) calcd for C₁₉H₂₁NO₂⁷⁹Br m/z 374.0756 ([M+H]⁺), meas 374.0746; $[\alpha]_D^{20}$ -61.1° (c 1.0, CH₂Cl₂).

Synthesis of cis-(2*R*,3*R*)-**43d** and *cis*-(2*S*,3*S*)-**44d** from aziridination of the phenethyl chiral imine (*R*)-**45d** derived from 4-tolualdehyde.



cis-(2*R*,3*R*)-**43d**: The reaction of imine (*R*)-**45d** (223 mg, 1.00 mmol) and (*S*)-VAPOL (54 mg, 0.10 mmol) was performed according to the General Procedure (Method A). The ¹H NMR spectrum of the crude mixture showed a >50:1

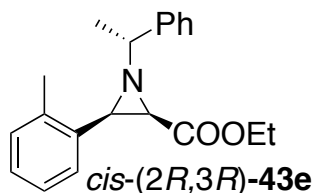
cis/trans ratio, 0%/1% of enamine products and a >98:2 mixture of *cis*-(2*R*,3*R*)-**43d** and *cis*-(2*S*,3*S*)-**44d**. Purification of the major product by column chromatography (silica gel, 40 × 400mm, hexane:CH₂Cl₂:Et₂O 8:1:1) gave *cis*-(2*R*,3*R*)-**43d** in 71% isolated yield (220 mg, 0.710 mmol) as a pale yellow solid; mp 62-64 °C; R_f = 0.28 (hexane:CH₂Cl₂:Et₂O 8:1:1). Spectral data for *cis*-(2*R*,3*R*)-**43d**: ¹H NMR (300 MHz, CDCl₃) δ 1.06 (t, 3H, *J* = 6.9 Hz), 1.58 (d, 3H, *J* = 6.6 Hz), 2.30 (s, 3H), 2.62 (d, 1H, *J* = 6.9 Hz), 2.90 (q, 1H, *J* = 6.6 Hz), 2.98 (d, 1H, *J* = 6.9 Hz), 3.92-4.12 (m, 2H), 7.00-7.10 (m, 2H), 7.20-7.40 (m, 5H), 7.42-7.50 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 13.97, 21.08, 22.88, 45.98, 47.33, 60.60, 69.80, 126.90, 127.21, 127.61, 128.33, 128.37, 132.11, 136.72, 143.30, 168.30; IR (thin film) 2976(m), 1741(s), 1178(s) cm⁻¹; mass spectrum *m/z* (% rel intensity) 309 M⁺ (3), 130(100); HRMS (ESI⁺) calcd for C₂₀H₂₄NO₂ *m/z* 310.1807 ([M+H]⁺), meas 310.1784; [α]_D²⁰ -62.4° (c 1.0, CH₂Cl₂).



cis-(2*S*,3*S*)-**44d**: The reaction of imine (*R*)-**45d** (223 mg, 1.00 mmol) and (*R*)-VAPOL (54 mg, 0.10 mmol) was performed according to the General Procedure (Method A). The ¹H NMR spectrum of the crude mixture showed a >50:1 cis/trans ratio, 3%/7% of enamine products and a 33:67 mixture of *cis*-(2*R*,3*R*)-

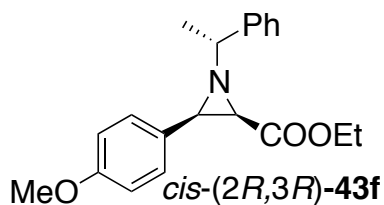
43d and *cis*-(2*S*,3*S*)-**44d**. Purification of the products by column chromatography (silica gel, 40 × 400 mm, hexane:CH₂Cl₂:Et₂O 8:1:1) gave *cis*-(2*R*,3*R*)-**43d** in 19% isolated yield (54 mg, 0.19 mmol) as a pale yellow solid. The fraction containing *cis*-(2*S*,3*S*)-**44d** was collected and concentrated. This isomer was purified by column chromatography (silica gel, 30 × 250 mm, hexane:EtOAc 19:1) to give *cis*-(2*S*,3*S*)-**44d** as a pale solid (100 mg, 0.32 mmol) in 32% yield; mp 48-50 °C; *R_f* = 0.40 (hexane:Et₂O:CH₂Cl₂ 8:1:1). Spectral data for *cis*-(2*S*,3*S*)-**44d**: ¹H NMR (300 MHz, CDCl₃) δ 0.96 (t, 3H, *J* = 6.6 Hz), 1.48 (d, 3H, *J* = 6.6 Hz), 2.15 (s, 3H), 2.46 (d, 1H, *J* = 6.9 Hz), 2.90 (q, 1H, *J* = 6.6 Hz), 3.06 (d, 1H, *J* = 6.9 Hz), 3.80-3.98 (m, 2H), 7.08-7.14 (m, 2H), 7.20-7.40 (m, 5H), 7.46-7.52 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 13.95, 21.19, 23.90, 45.56, 48.01, 60.44, 69.26, 126.67, 127.05, 127.76, 128.38, 128.61, 132.48, 137.07, 143.77, 168.04; IR (thin film) 2974(m), 1749(s), 1194(s) cm⁻¹; mass spectrum *m/z* (% rel intensity) 309 M⁺ (67), 236(100); HRMS (ESI⁺) calcd for C₂₀H₂₄NO₂ *m/z* 310.1807 ([M+H]⁺), meas 310.1819; [α]_D²⁰ -44.3° (c 1.0, CH₂Cl₂).

Synthesis of cis-(2*R*,3*R*)-**43e** from aziridination of the phenethyl chiral imine (*R*)-**44e** derived from 2-tolualdehyde.



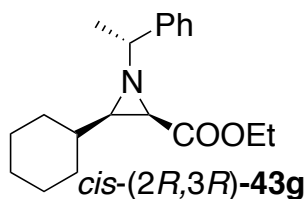
cis-(2*R*,3*R*)-**43e**: The reaction of imine (*R*)-**45e** (223 mg, 1.00 mmol) and (*S*)-VAPOL (54 mg, 0.10 mmol) was performed according to the General Procedure (Method A). The ¹H NMR spectrum of the crude mixture showed a >50:1 *cis*/*trans* ratio, 1%/0% of enamine products and a >98:2 mixture of *cis*-(2*R*,3*R*)-**43e** and *cis*-(2*S*,3*S*)-**44e**. Purification of the major product by column chromatography (silica gel, 40 × 400 mm, hexane:CH₂Cl₂:Et₂O 8:1:1) gave *cis*-(2*R*,3*R*)-**43e** in 62% isolated yield as pale yellow crystals (192 mg, 0.621 mmol); mp 62-64 °C; R_f = 0.25 (hexane:CH₂Cl₂:Et₂O 8:1:1). Spectral data for *cis*-(2*R*,3*R*)-**43e**: ¹H NMR (300 MHz, CDCl₃) δ 0.92 (t, 3H, *J* = 7.2 Hz), 1.50 (d, 3H, *J* = 6.6 Hz), 2.20 (s, 3H), 2.65 (d, 1H, *J* = 6.9 Hz), 2.85 (q, 1H, *J* = 6.3 Hz), 2.95 (d, 1H, *J* = 6.9 Hz), 3.80-4.00 (m, 2H), 6.88-7.32 (m, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 13.80, 18.72, 22.73, 45.21, 46.19, 60.52, 70.12, 125.28, 127.02, 127.13, 127.44, 128.44, 128.54, 129.02, 133.34, 135.89, 143.17, 168.45; IR (thin film) 2966(m), 1743(s), 1192(m) cm⁻¹; mass spectrum *m/z* (% rel intensity) 309 M⁺ (1), 130(100); HRMS (ESI⁺) calcd for C₂₀H₂₄NO₂ *m/z* 310.1807 ([M+H]⁺), meas 310.1784; [α]_D²⁰ -69.2° (c 1.0, CH₂Cl₂).

Synthesis of cis-(2*R*,3*R*)-**43f** from aziridination of the phenethyl chiral imine (*R*)-**45f** derived from 4-methoxybenzaldehyde.



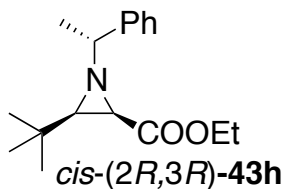
cis-(2*R*,3*R*)-**43f**: The reaction of imine (*R*)-**45f** (239 mg, 1.00 mmol) and (*S*)-VAPOL (54 mg, 0.10 mmol) was performed according to the General Procedure (Method A). The ^1H NMR spectrum of the crude mixture showed a 46% conversion, a >50:1 *cis*/*trans* ratio, 3%/5% of enamine products and a 95:5 mixture of *cis*-(2*R*,3*R*)-**43f** and *cis*-(2*S*,3*S*)-**44f**. Purification of the major product by column chromatography (silica gel, 40 × 400mm, hexane:CH₂Cl₂:Et₂O 8:1:1) gave *cis*-(2*R*,3*R*)-**43f** in 35% isolated yield as a yellow oil (114 mg, 0.351 mmol); R_f = 0.15 (hexane:CH₂Cl₂:Et₂O). Spectral data for *cis*-(2*R*,3*R*)-**43f**: ^1H NMR (300 MHz, CDCl₃) δ 1.00 (t, 3H, J = 6.6 Hz), 1.50 (d, 3H, J = 6.6 Hz), 2.58 (d, 1H, J = 6.6 Hz), 2.85 (q, 1H, J = 6.6 Hz), 2.90 (d, 1H, J = 6.9 Hz), 3.75 (s, 3H), 3.88-4.04 (m, 2H), 6.72-6.80 (m, 2H), 7.16-7.34 (m, 5H), 7.40-7.44 (m, 2H); ^{13}C NMR (75 MHz, CDCl₃) δ 14.03, 22.87, 45.98, 47.08, 55.14, 60.61, 69.79, 113.14, 126.90, 127.22, 127.28, 128.34, 128.83, 143.35, 158.79, 168.36; IR (thin film) 2978(m), 1747(s), 1516(s), 1197(s) cm⁻¹; HRMS (ESI⁺) calcd for C₂₀H₂₄NO₃ m/z 326.1756 ([M+H]⁺), meas 326.1735; $[\alpha]_D^{20}$ -57.3° (c 1.0, CH₂Cl₂).

Synthesis of cis-(2*R*,3*R*)-**43g** from aziridination of the phenethyl chiral imine (*R*)-**45g** derived from cyclohexanecarboxaldehyde.

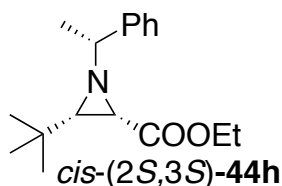


cis-(2*R*,3*R*)-**43g**: The reaction of imine (*R*)-**45g** (215 mg, 1.00 mmol) and (*S*)-VAPOL (54 mg, 0.10 mmol) was performed according to the General Procedure (Method A). The ^1H NMR spectrum of the crude mixture showed a >50:1 *cis*/*trans* ratio, no enamine products and a 83:17 mixture of *cis*-(2*R*,3*R*)-**43g** and *cis*-(2*S*,3*S*)-**44g**. Purification of the major product by column chromatography (silica gel, 40 × 400 mm, hexane:EtOAc 19:1) gave *cis*-(2*R*,3*R*)-**44g** in 66% isolated yield as yellow crystals (198 mg, 0.658 mmol); mp 60-62 °C; R_f = 0.20 (hexane:EtOAc 9:1). Spectral data for *cis*-(2*R*,3*R*)-**44g**: ^1H NMR (300 MHz, CDCl_3) δ 0.46-0.52 (m, 1H), 0.80-1.60 (m, 17H), 2.18 (d, 1H, J = 6.9 Hz), 2.50 (q, 1H, J = 6.3 Hz), 4.12-4.30 (m, 2H), 7.20-7.40 (m, 5H); ^{13}C NMR (75 MHz, CDCl_3) δ 14.27, 21.84, 25.37, 25.49, 26.11, 30.11, 30.79, 36.01, 42.81, 51.49, 60.76, 70.29, 127.45, 127.62, 128.16, 143.01, 170.13; IR (thin film) 2924(m), 1734(s), 1192(m) cm^{-1} ; HRMS (ESI^+) calcd for $\text{C}_{19}\text{H}_{28}\text{NO}_2$ m/z 302.2120 ($[\text{M}+\text{H}]^+$), meas 302.2099; $[\alpha]_D^{20}$ 59.2° (c 1.0, CH_2Cl_2). The relative stereochemistry of **43g** was determined by conversion to **80g** and comparison of its physical properties with those previously reported for this compound.

Synthesis of cis-(2*R*,3*R*)-**43h** and *cis*-(2*S*,3*S*)-**44h** from aziridination of the phenethyl chiral imine (*R*)-**45h** derived from trimethylacetaldehyde.

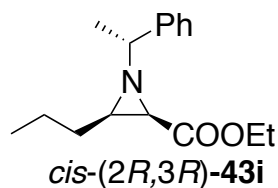


cis-(2*R*,3*R*)-**43h**: The reaction of imine (*R*)-**45h** (189 mg, 1.00 mmol) and (*S*)-VAPOL (54 mg, 0.10 mmol) was performed according to the General Procedure (Method A). The ^1H NMR spectrum of the crude mixture showed a >50:1 *cis*/*trans* ratio, no enamine products and a 91:9 mixture of *cis*-(2*R*,3*R*)-**43h** and *cis*-(2*S*,3*S*)-**44h**. Purification of the major product by column chromatography (1st column, silica gel, 40 × 400 mm, hexane:CH₂Cl₂:Et₂O 8:1:1; 2nd column, silica gel, 25 × 250 mm, hexane:EtOAc 19:1) gave *cis*-(2*R*,3*R*)-**43h** (167 mg, 0.607) in 61% isolated yield as white crystals; mp 58-59 °C; *R*_f = 0.40 (hexane:EtOAc 9:1). The relative stereochemistry of **43h** was determined by conversion to aziridine **70** (see below). Spectral data for *cis*-(2*R*,3*R*)-**43h**: ^1H NMR (300 MHz, CDCl₃) δ 0.60 (s, 9H), 1.26 (t, 3H, *J* = 6.9 Hz), 1.46 (d, 3H, *J* = 6.6 Hz), 1.56 (d, 1H, *J* = 7.5 Hz), 2.06 (d, 1H, *J* = 7.2 Hz), 2.48 (q, 1H, *J* = 6.6 Hz), 4.08-4.30 (m, 2H), 7.20-7.40 (m, 5H); ^{13}C NMR (75 MHz, CDCl₃) δ 14.13, 22.36, 27.41, 31.37, 42.85, 55.78, 60.65, 71.17, 127.28, 127.54, 128.11, 143.94, 170.18; IR (thin film) 2955(m), 1734(s), 1142(w) cm⁻¹; mass spectrum *m/z* (% rel intensity) 274 [*M*-1]⁺ (2), 105(100); HRMS (ESI⁺) calcd for C₁₇H₂₆NO₂ *m/z* 276.1964 ([*M*+H]⁺), meas 276.1958; [α]_D²⁰ 101.5° (c 1.0, CH₂Cl₂).



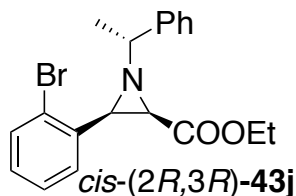
cis-(2*S*,3*S*)-**44h**: The reaction of imine (*R*)-**45h** (189 mg, 1.00 mmol) and (*R*)-VAPOL (54 mg, 0.10 mmol) was performed according to the General Procedure (Method A). The ^1H NMR spectrum of the crude mixture showed a 31% conversion, a >50:1 *cis/trans* ratio and a 38:62 mixture of *cis*-(2*R*,3*R*)-**43h** and *cis*-(2*S*,3*S*)-**44h**. Purification of the products by column chromatography (silica gel, 40 × 400 mm, hexane:EtOAc 19:1) gave *cis*-(2*S*,3*S*)-**44h** in 20% isolated yield (55 mg, 0.20 mmol) as a pale yellow oil; R_f = 0.45 (hexane:EtOAc 9:1). Spectral data for *cis*-(2*S*,3*S*)-**44h**: ^1H NMR (300 MHz, CDCl_3) δ 0.98 (s, 9H), 1.24 (t, 3H, J = 6.9 Hz), 1.42 (d, 3H, J = 6.6 Hz), 1.64 (d, 1H, J = 7.5 Hz), 1.96 (d, 1H, J = 7.2 Hz), 2.58 (q, 1H, J = 6.6 Hz), 3.94-4.20 (m, 2H), 7.18-7.24 (m, 3H), 7.48-7.52 (m, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 14.02, 24.32, 27.79, 31.61, 42.46, 56.84, 60.44, 70.27, 126.80, 126.92, 128.13, 144.19, 169.85; IR (thin film) 2961(s), 1751(s), 1188(s), 758(m), 702(m) cm^{-1} ; HRMS (ESI^+) calcd for $\text{C}_{17}\text{H}_{26}\text{NO}_2$ m/z 276.1964 ($[\text{M}+\text{H}]^+$), meas 276.1945; $[\alpha]_D^{20}$ -10.5° (c 1.0, CH_2Cl_2).

Synthesis of cis-(2*R*,3*R*)-**43i** from aziridination of the phenethyl chiral imine (*R*)-**45i** derived from *n*-butyraldehyde.



cis-(2*R*,3*R*)-**43i**: The reaction of imine (*R*)-**45i** (88 mg, 0.50 mmol) and (*S*)-VANOL (22 mg, 0.05 mmol) was performed according to the General Procedure (Method A). The ^1H NMR spectrum of the crude mixture showed a >50:1 *cis*/*trans* ratio, no enamine products and a 80:20 mixture of *cis*-(2*R*,3*R*)-**43i** and *cis*-(2*S*,3*S*)-**44i**. Purification of the product by column chromatography (1st column, silica gel, 28 × 280 mm, hexane:EtOAc 9:1; 2nd column, silica gel, 28 × 280 mm, benzene:EtOAc 30:1) gave *cis*-(2*R*,3*R*)-**43i** (38 mg, 0.15) in 28% isolated yield as a pale yellow oil; R_f = 0.30 (benzene:EtOAc 30:1). Spectral data for *cis*-(2*R*,3*R*)-**43i**: ^1H NMR (300 MHz, CDCl_3) δ 0.70 (t, 3H, J = 7.5 Hz), 0.94-1.06 (m, 1H), 1.08-1.18 (m, 1H), 1.28 (t, 3H, J = 7.0 Hz), 1.34-1.42 (m, 1H), 1.44 (d, 3H, J = 6.5 Hz), 1.48-1.56 (m, 1H), 1.79 (q, 1H, J = 6.5 Hz), 2.21 (d, 1H, J = 7.0 Hz), 2.57 (q, 1H, J = 6.5 Hz), 4.16-4.28 (m, 2H), 7.22-7.26 (m, 1H), 7.28-7.32 (m, 2H), 7.36-7.40 (m, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 13.57, 14.29, 20.32, 22.54, 29.73, 43.02, 45.97, 60.76, 70.00, 127.11, 127.20, 128.20, 143.53, 169.94; IR (thin film) 2964(m), 1745(s), 1182(s) cm^{-1} ; HRMS (ESI^+) calcd for $\text{C}_{16}\text{H}_{24}\text{NO}_2$ m/z 262.1807 ($[\text{M}+\text{H}]^+$), meas 262.1794; $[\alpha]_D^{20}$ 68.8° (c 1.0, CH_2Cl_2).

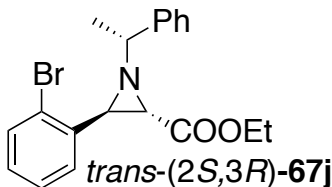
Synthesis of *cis*-(2*R*,3*R*)-**43j** and *trans*-(2*S*,3*R*)-**67j** from aziridination of the phenethyl chiral imine (*R*)-**45j** derived from 2-bromobenzaldehyde.



cis-(2*R*,3*R*)-**24j**: The reaction of imine (*R*)-**45j** (287 mg, 1.00 mmol) and (*S*)-VAPOL (54 mg, 0.10 mmol) was performed according to the General Procedure (Method A). The ^1H NMR spectrum of the crude mixture showed a 71:29 *cis/trans* ratio, 10%/16% enamine products, a 91:9 mixture of *cis*-(2*R*,3*R*)-**43j** and *cis*-(2*S*,3*S*)-**44j** and a 67:33 mixture of *trans*-(2*S*,3*R*)-**67j** and *trans*-(2*R*,3*S*)-**68j**. Purification of the product by column chromatography (silica gel, 40 × 400 mm, hexane:CH₂Cl₂:Et₂O 10:1:1) gave *cis*-(2*R*,3*R*)-**43j** (180 mg, 0.482) in 48% isolated yield as a pale yellow crystalline solid; mp 48-50 °C; R_f = 0.25 (hexane:EtOAc 9:1). The relative stereochemistry of **43j** was confirmed by conversion to aziridine **43a** (see below). Spectral data for *cis*-(2*R*,3*R*)-**43j**: ^1H NMR (300 MHz, CDCl₃) δ 0.96 (t, 3H, J = 6.9 Hz), 1.56 (d, 3H, J = 6.0 Hz), 2.72 (d, 1H, J = 6.6 Hz), 2.90 (q, 1H, J = 6.6 Hz), 3.06 (d, 1H, J = 6.6 Hz), 3.86-4.04 (m, 2H), 7.00-7.50 (m, 9H); ^{13}C NMR (75 MHz, CDCl₃) δ 13.88, 22.67, 45.39, 48.20, 60.71, 69.95, 103.93, 126.69, 127.10, 127.57, 128.50, 128.70, 130.85, 131.52, 134.72, 143.03, 168.17; IR (thin film) 2976(m), 1749(s), 1197(s) cm⁻¹;

HRMS (ESI⁺) calcd for C₁₉H₂₁NO₂⁷⁹Br *m/z* 374.0756 ([M+H]⁺), meas 374.0769;

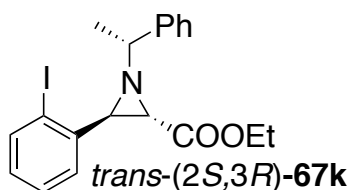
[α]_D²⁰ −41.2° (c 1.0, CH₂Cl₂).



trans-(2*S*,3*R*)-**67j**: The reaction of imine (*R*)-**45j** (1.50 g, 5.23 mmol, 1.00 equiv), (*R*)-VAPOL (282 mg, 0.523 mmol, 0.100 equiv), triphenyl borate (607 mg, 2.09 mmol, 0.400 equiv), H₂O (9.4 mg, 0.52 mmol, 0.10 equiv), EDA (716 mg, 6.28 mmol, 1.20 equiv) in toluene (10 mL) was performed according to the General Procedure (Method A). Purification of the major product by column chromatography (1st column, silica gel, 40 × 400 mm, hexane:CH₂Cl₂:Et₂O 10:1:1; 2nd column, silica gel, 40 × 400 mm, hexane:EtOAc 19:1; 3rd column, silica gel, 40 × 400 mm, hexane:EtOAc 30:1) gave the pure aziridine *trans*-(2*S*,3*R*)-**67j** (613 mg, 1.70 mmol) in 32% isolated yield as a colorless oil; *R*_f = 0.35 (hexane:EtOAc 9:1). The relative stereochemistry of **67j** was confirmed by conversion to (*S*)-phenylalanine ethyl ester **69**. Spectral data for *trans*-(2*S*,3*R*)-**67j**: ¹H NMR (300 MHz, CDCl₃) δ 1.20-1.34 (m, 6H), 2.59 (d, 1H, *J* = 2.7 Hz), 3.42 (d, 1H, *J* = 2.4 Hz), 4.04 (q, 1H, *J* = 6.6 Hz), 4.25 (q, 2H, *J* = 7.2 Hz), 6.90-7.48 (m, 9H); ¹³C NMR (300 MHz, CDCl₃) δ 14.29, 22.85, 43.82, 48.49, 59.59, 61.32, 123.49, 127.30, 128.00, 128.44, 128.67, 131.90, 137.45, 144.19, 168.72

(Two sp^2 carbons not located); ^{13}C NMR (300 MHz, DMSO- d_6) δ 14.12, 22.66, 43.48, 47.55, 59.08, 61.20, 122.74, 127.04, 127.37, 127.63, 127.73, 128.46, 129.37, 131.96, 136.73, 143.82, 167.80; IR (thin film) 2976(w), 1728(s), 1188(s) cm^{-1} ; mass spectrum m/z (% rel intensity) 376 $[\text{M}+1]^+$ (0.20, ^{81}Br), 374 $[\text{M}+1]^+$ (0.20, ^{79}Br), 105(100); HRMS (ESI $^+$) calcd for $\text{C}_{19}\text{H}_{21}\text{NO}_2$ ^{79}Br m/z 374.0756 ($[\text{M}+\text{H}]^+$), meas 374.0764; $[\alpha]_D^{20}$ 39.8° (c 1.0, CH_2Cl_2).

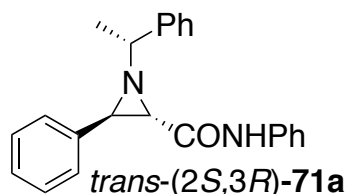
Synthesis of trans-(2S,3R)-67k from aziridination of the phenethyl chiral imine (R)-45k derived from 2-iodobenzaldehyde.



trans-(2S,3R)-67k: The reaction of imine (*R*)-**45k** (335 mg, 1.00 mmol) and (*S*)-VAPOL (54 mg, 0.10 mmol) was performed according to the General Procedure (Method A). The ^1H NMR spectrum of the crude mixture showed a 50:50 *cis/trans* ratio, 11%/17% enamine products, a 94:6 mixture of *cis*-(2*R*,3*R*)-**43k** and *cis*-(2*S*,3*S*)-**44k** and a 67:33 mixture of *trans*-(2*S*,3*R*)-**67k** and *trans*-(2*R*,3*S*)-**68k**. Purification of the major *trans* aziridine by column chromatography (silica gel, 40 × 400 mm, hexane: CH_2Cl_2 : Et_2O 30:1:1) gave *trans*-(2*S*,3*R*)-**67k** (65 mg, 0.15 mmol) in 15% isolated yield as a colorless oil; R_f = 0.35 (hexane:EtOAc 9:1). Spectral data for *trans*-(2*S*,3*R*)-**67k**: ^1H NMR (300 MHz, CDCl_3) δ 1.20-1.40 (m, 6H), 2.75 (d, 1H, J = 2.7 Hz), 3.26 (d, 1H, J = 2.4 Hz), 4.00 (q, 1H, J = 6.6

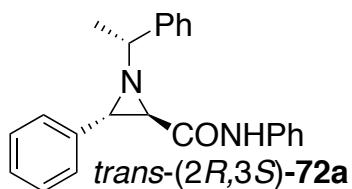
Hz), 4.20-4.30 (m, 2H), 6.76-6.82 (m, 1H), 6.90-7.28 (m, 5H), 7.40-7.48 (m, 2H), 7.58-7.64 (m, 1H); ^{13}C NMR (300 MHz, CDCl_3) δ 14.36, 22.70, 43.96, 53.05, 59.60, 61.31, 98.40, 127.36, 128.05, 128.45, 128.96, 138.30, 140.33, 144.12, 168.70 (Two sp^2 carbons not located); ^{13}C NMR (300 MHz, DMSO-d_6) δ 14.18, 22.55, 43.60, 52.30, 59.03, 61.12, 98.80, 127.10, 127.40, 128.16, 128.45, 129.45, 138.25, 139.69, 143.81, 167.81 (One sp^2 carbon not located); IR (thin film) 2976(w), 1728(s), 1188(s) cm^{-1} ; HRMS (ESI^+) calcd for $\text{C}_{19}\text{H}_{21}\text{NO}_2$ m/z 422.0617 ($[\text{M}+\text{H}]^+$), meas 422.0626; $[\alpha]_D^{20}$ 59.4° (c 1.0, CH_2Cl_2).

Synthesis of trans-(2S,3R)-71a and trans-(2R,3S)-72a from aziridination of the phenethyl chiral imine (R)-45a Derived from benzaldehyde.



trans-(2*S*,3*R*)-**71a**: The General Procedure (Method B) was followed with imine (*R*)-**45a** (42 mg, 0.20 mmol, 1.0 equiv) and (*S*)-VAPOL (11 mg, 0.020 mmol, 0.10 equiv) with a reaction time of 20 hours. Upon workup, the ^1H NMR spectrum of the crude mixture indicated a 79:21 *trans*:*cis* ratio and a 60:40 mixture of *trans*-(2*S*,3*R*)-**71a**/*trans*-(2*R*,3*S*)-**72a** and an 83:17 mixture of *cis*-(2*R*,3*R*)-**73a**/*cis*-(2*S*,3*S*)-**74a**, along with 11% and 19% enamine products **75/76**. The major product was separated by column chromatography (silica gel, 20 × 200 mm, hexane:EtOAc 9:1) and *trans*-(2*S*,3*R*)-**71a** was obtained as a white solid (12 mg,

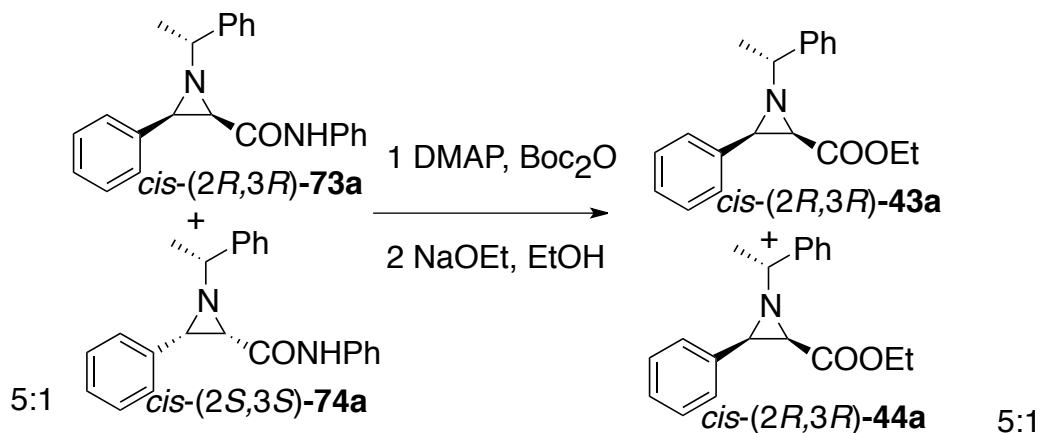
0.05 mmol, 25%); mp 47-49 °C; R_f = 0.30 (hexane:EtOAc 4:1). The relative stereochemistry of **71a** was confirmed by conversion to **77a**. Spectral data for *trans*-(2*S*,3*R*)-**71a**: ^1H NMR (500 MHz, CDCl_3) δ 1.16 (d, 3H, J = 6.0 Hz), 2.90 (s, 1H), 3.06 (d, 1H, J = 6.5 Hz), 3.62 (s, 1H), 7.00-7.80 (m, 15H), 8.60 (brs, 1H); ^1H NMR (500 MHz, DMSO-d_6) δ 1.14 (d, 3H, J = 6.5 Hz), 2.96 (d, 1H, J = 2.5 Hz), 3.26 (d, 1H, J = 2.0 Hz), 4.24 (q, 1H, J = 6.5 Hz), 7.00-7.70 (m, 15H), 10.64 (brs, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 22.96, 42.35, 49.80, 59.21, 119.74, 124.40, 126.98, 127.89, 128.71, 128.90, 129.05, 129.27, 130.35, 131.46, 137.82, 143.98, 168.22; ^{13}C NMR (125 MHz, DMSO-d_6) δ 23.50, 45.66, 46.98, 58.08, 119.25, 123.66, 125.85, 126.64, 126.74, 127.08, 128.16, 128.23, 128.79, 138.78, 138.96, 144.87, 165.24; IR (thin film) 3312(m), 3061(m), 2972(m), 1653(s), 1541(s) cm^{-1} ; HRMS (ESI^+) exact mass calcd for $\text{C}_{23}\text{H}_{22}\text{N}_2\text{ONa}$ m/z 365.1630($[\text{M}+\text{Na}]^+$), meas 365.1661; $[\alpha]_D^{20}$ 72.6° (c 0.5, CH_2Cl_2).



trans-(2*R*,3*S*)-**72a**: The General Procedure (Method B) was followed with imine (*R*)-**45a** (105 mg, 0.500 mmol, 1.00 equiv) and (*S*)-VAPOL (27 mg, 0.050 mmol, 0.10 equiv) in toluene (2 mL) with a reaction time of 22 hours. The reaction mixture was concentrated and the products were purified by column chromatography (1st column, silica gel, 20 × 200 mm, hexane:EtOAc 9:1; 2nd

column, silica gel, 20 × 180 mm, benzene:EtOAc 15:1) to give *trans*-(2*S*,3*R*)-**71a** as a white solid (47 mg, 0.054 mmol, 11%). After the first column, the fraction containing the product *trans*-(2*R*,3*S*)-**72a** was collected and concentrated. This was combined with fractions containing *trans*-(2*R*,3*S*)-**72a** from two different reactions (0.2 mmol) of imine (*R*)-**45a** with (*S*)-VAPOL and (*S*)-VANOL borate catalysts and this aziridine was purified by column chromatography (1st column, silica gel, 20 × 200 mm, benzene:EtOAc 9:1; 2nd column, silica gel, 18 × 180 mm, benzene:EtOAc 15:1) to give *trans*-(2*R*,3*S*)-**72a** as a white foamy solid (32 mg, 0.094 mmol, 11%); mp 130-132 °C; *R*_f = 0.45 (hexane:EtOAc 4:1). Spectral data for *trans*-(2*R*,3*S*)-**72a**: ¹H NMR (500 MHz, CDCl₃) δ 1.50 (d, 3H, *J* = 6.0 Hz), 3.16-2.96 (m, 2H), 3.55 (s, 1H), 6.90-7.80 (m, 15H), 8.80 (brs, 1H); ¹H NMR (600 MHz, DMSO-*d*₆) δ 1.35 (d, 3H, *J* = 7.0 Hz), 2.82 (s, 1H), 3.45 (s, 1H), 4.29 (q, 1H, *J* = 7.2 Hz), 7.00-7.50 (m, 15H), 10.21 (brs, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 23.90, 42.37, 49.01, 58.86, 119.50, 124.23, 126.54, 126.94, 127.82, 128.03, 128.24, 129.03, 130.13, 131.34, 137.50, 143.57, 168.33; IR (thin film) 3300(m), 3060(m), 2970(m), 1653(s), 1539(s) cm⁻¹; HRMS (ESI⁺) calcd for C₂₃H₂₂N₂ONa *m/z* 365.1630 ([*M*+Na]⁺), meas 365.1650; [*α*]_D²⁰ 7.1° (c 1.0, CH₂Cl₂).

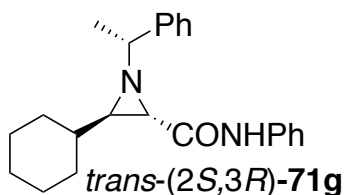
Determination of the relative configuration of cis-(2*R*,3*R*)-**73a** and *cis*-(2*S*,3*S*)-**74a**:



The stereochemistry of *cis*-isomers from the reaction of (*R*)-**45a** and diazoacetamide **19** was determined by the following reaction. The General Procedure (Method B) was followed with imine (*R*)-**45a** (105 mg, 0.500 mmol, 1.00 equiv) and 10 mol% (*S*)-VANOL borate catalyst with a reaction time of 20 hours. After concentration, the *cis* products were purified by column chromatography (silica gel, 18 × 180 mm, hexane:EtOAc 4:1) to give a 5:1 mixture (30 mg, 0.090 mmol, 18%) of *cis*-(2*R*,3*R*)-**73a** and *cis*-(2*S*,3*S*)-**74a** free of *trans*-aziridines. To a solution of the above mixture (30 mg, 0.090 mmol, 1.0 equiv) in a mixture of dry CH_3CN and CH_2Cl_2 (v:v 9:1, 2 mL) were added DMAP (22 mg, 0.18 mmol, 2.0 equiv) and Boc_2O (59 mg, 0.27 mmol, 3.0 equiv). After the mixture was stirred at rt overnight (~12 hours), it was concentrated and the products were purified by column chromatography (silica gel, 15 × 150 mm, hexane:EtOAc 9:1) to give the activated amide intermediates as a pale yellow oil which was dissolved in absolute ethanol (1 mL). To the mixture was added a solution of NaOEt in ethanol (21% by weight, 62 mg, 70 μL , 0.18 mmol, 2.0 equiv) at 0 °C dropwise under N_2 . The resulting mixture was stirred at 0 °C for 1

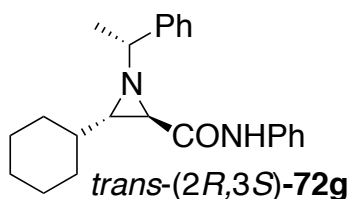
hour under N₂. The reaction was quenched with *aq* sat NH₄Cl (1 mL). Ethanol was removed by rotary evaporation and H₂O (2 mL) was added. The mixture was extracted with CH₂Cl₂ (3 × 10 mL). The organic extracts were combined and dried (Na₂SO₄). This mixture was then filtered and concentrated to give the crude product **73a** and **74a**. The ¹H NMR spectra of this mixture was taken and revealed to be a mixture of *cis*-(2*R*,3*R*)-**73a** and *cis*-(2*S*,3*S*)-**74a** in a ratio of 5:1. The major product was then purified by column chromatography (silica gel, 15 × 150 mm, hexane:EtOAc 15:1) to give the *cis*-(2*R*,3*R*)-**73a** as a white solid (19 mg, 0.078 mmol, 87%) which has spectral data identical to the major product isolated from the reaction of chiral imine (*R*)-**45a** with EDA **5** catalyzed by (*S*)-VAPOL borate.

Synthesis of trans-(2*S*,3*R*)-**71g** and *trans*-(2*R*,3*S*)-**72g** from aziridination of the phenethyl chiral imine (*R*)-**45g** derived from cyclohexanecarboxaldehyde.



trans-(2*S*,3*R*)-**71g**: The General Procedure (Method B) was followed with imine (*R*)-**45g** (44 mg, 0.20 mmol, 1.0 equiv) and (*S*)-VAPOL (11 mg, 0.020 mmol, 0.10 equiv) with a reaction time of 21 hours. Upon workup, the ¹H NMR spectrum of the crude mixture indicated a >96:4 mixture of *trans*-(2*S*,3*R*)-**71g**/*trans*-(2*R*,3*S*)-**72g**. After purification by column chromatography (1st column, silica gel, 20 ×

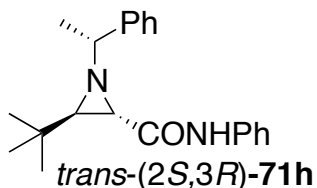
200 mm, hexane:EtOAc 5:1; 2nd column, silica gel, 18 × 180 mm, hexane:acetone 9:1), the product *trans*-(2*S*,3*R*)-**71g** was obtained as a white solid (54 mg, 0.39 mmol, 78%); mp 125-126 °C; R_f = 0.075 (hexane:EtOAc 4:1). Spectral data for *trans*-(2*S*,3*R*)-**71g**: ¹H NMR (600 MHz, CDCl₃) δ 0.40-2.50 (m, 16H), 3.40 (q, 1H, J = 5.4 Hz), 7.00-7.64 (m, 10H), 8.38 (brs, 1H); ¹H NMR (500 MHz, DMSO-*d*₆) δ 0.40-1.90 (m, 14H), 2.02 (dd, 1H, J = 7.0, 2.5 Hz), 2.67 (d, 1H, J = 3.0 Hz), 3.82 (q, 1H, J = 6.0 Hz), 6.90-7.80 (m, 10H), 10.53 (brs, 1H); ¹³C NMR (150 MHz, CDCl₃) δ 24.55, 25.84, 26.07, 26.18, 32.41, 33.32, 34.77, 43.15, 53.74, 59.88, 119.44, 124.02, 126.82, 127.75, 128.95, 129.10, 137.90, 144.33, 168.92; ¹³C NMR (150 MHz, DMSO-*d*₆) δ 22.55, 25.02, 25.22, 25.71, 29.43, 29.69, 36.18, 41.18, 49.68, 58.48, 119.10, 123.38, 126.97, 127.35, 128.07, 128.73, 139.01, 144.86, 166.47; IR (thin film) 3372(m), 2905(m), 1686(s), 1548(m) cm⁻¹; HRMS (ESI⁺) calcd for C₂₃H₂₉N₂O m/z 349.2280 ([M+H]⁺), meas 349.2300; [α]_D²⁰ -98.2° (c 1.0, CH₂Cl₂).



trans-(2*R*,3*S*)-**72g**: The General Procedure (Method B) was followed with imine (*R*)-**45g** (44 mg, 0.20 mmol, 1.0 equiv) and (*R*)-VAPOL (11 mg, 0.020 mmol, 0.10 equiv) with a reaction time of 21 hours. Upon workup, the ¹H NMR spectrum of

the crude mixture indicated a 67:33 mixture of *trans*-(2*S*,3*R*)-**71g** and *trans*-(2*R*,3*S*)-**72g**. After purification by column chromatography (silica gel, 20 × 200 mm, hexane:EtOAc 5:1), the major product *trans*-(2*S*,3*R*)-**71g** was obtained as a white solid (40 mg, 0.12 mmol, 59%). The fraction containing *trans*-(2*R*,3*S*)-**72g** was loaded onto a chromatography column (silica gel, 18 × 180 mm, benzene:EtOAc 30:1) and elution afforded pure *trans*-(2*R*,3*S*)-**72g** as a white solid (14 mg, 0.040 mmol, 20%); mp 163-165 °C; R_f = 0.28 (hexane:EtOAc 4:1). Spectral data for *trans*-(2*R*,3*S*)-**72g**: ^1H NMR (500 MHz, CDCl_3) δ 0.60-1.90 (m, 14H), 2.06 (dd, 1H, J = 8.3, 2.5 Hz), 2.14 (d, 1H, J = 2.5 Hz), 3.44 (q, 1H, J = 6.0 Hz), 7.56-7.62 (m, 10H), 8.60 (brs, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 24.90, 25.31, 25.87, 25.91, 32.00, 32.30, 35.04, 43.61, 52.85, 59.67, 119.28, 123.95, 126.26, 127.20, 128.45, 128.98, 137.70, 144.76, 169.10; IR (thin film) 3328(m), 2930(m), 1683(s), 1621(m) cm^{-1} ; HRMS (ESI^+) calcd for $\text{C}_{23}\text{H}_{29}\text{N}_2\text{O}$ m/z 349.2280 ($[\text{M}+\text{H}]^+$), meas 349.2269; $[\alpha]_D^{20}$ 62.9° (c 1.0, CH_2Cl_2).

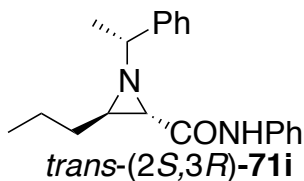
Synthesis of trans-(2*S*,3*R*)-**71h** from aziridination of the phenethyl chiral imine (*R*)-**45h** derived from trimethylacetaldehyde.



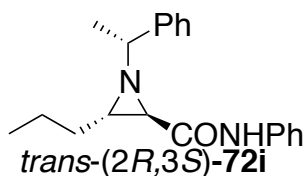
trans-(2*S*,3*R*)-**71h**: The General Procedure (Method B) was followed with imine (*R*)-**45h** (38 mg, 0.20 mmol, 1.0 equiv) and (*S*)-VAPOL (11 mg, 0.020 mmol, 0.10

equiv) with a reaction time of 22 hours. Upon workup, the ^1H NMR spectrum of the crude mixture indicated 87% conversion and a 97:3 mixture of *trans*-(2*S*,3*R*)-**71h**/*trans*-(2*R*,3*S*)-**72h**. After purification by column chromatography (silica gel, 20 × 200 mm, hexane:EtOAc 9:1), *trans*-(2*S*,3*R*)-**71h** was obtained as a white foamy solid (45 mg, 0.14 mmol, 69%); mp 54-56 °C; R_f = 0.20 (hexane:EA 4:1). Spectral data for *trans*-(2*S*,3*R*)-**71h**: ^1H NMR (500 MHz, CDCl_3) δ 0.60 (s, 9H), 1.32 (d, 3H, J = 6.0 Hz), 2.27 (d, 1H, J = 3.0 Hz), 2.48 (d, 1H, J = 3.0 Hz), 3.92 (q, 1H, J = 6.0 Hz), 7.15 (t, 1H, J = 7.5 Hz), 7.20-7.28 (m, 1H), 7.32 (t, 2H, J = 8.0 Hz), 7.38 (t, 2H, J = 8.0 Hz), 7.43 (d, 2H, J = 7.5 Hz), 7.58 (d, 2H, J = 8.0 Hz), 7.78 (brs, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 22.9, 26.6, 30.4, 40.0, 55.3, 59.8, 119.9, 124.6, 127.1, 127.8, 128.1, 129.1, 137.7, 145.1, 166.8; IR (thin film) 3298(m), 2961(m), 1653(s), 1558(s) cm^{-1} ; HRMS (ESI^+) calcd for $\text{C}_{21}\text{H}_{27}\text{N}_2\text{O}$ m/z 323.2123 ($[\text{M}+\text{H}]^+$), meas 323.2107; $[\alpha]_D^{20}$ 94.1° (c 1.0, CH_2Cl_2); Recrystallization from hexane gave crystals suitable for X-ray analysis, which revealed the relative stereochemistry of *trans*-**71h**.

Synthesis of trans-(2*S*,3*R*)-**71i** and *trans*-(2*R*,3*S*)-**72i** from aziridination of the phenethyl chiral imine (*R*)-**45i** derived from *n*-butyraldehyde.

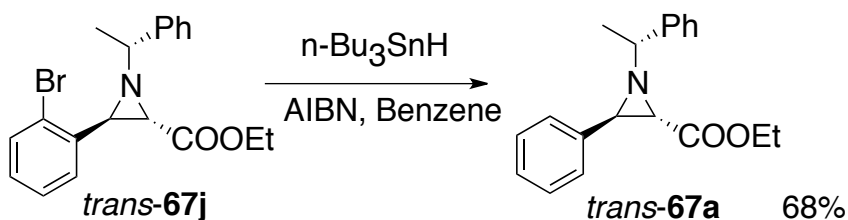


trans-(2*S*,3*R*)-**71i**: The General Procedure (Method B) was followed with imine (*R*)-**45i** (35 mg, 0.20 mmol, 1.0 equiv) and (*S*)-VAPOL (11 mg, 0.020 mmol, 0.10 equiv) with a reaction time of 15 hours. Upon workup, the ^1H NMR spectrum of the crude mixture indicated a 52:48 mixture of *trans*-(2*S*,3*R*)-**71i**/*trans*-(2*R*,3*S*)-**72i**. After purification by column chromatography (1st column, silica gel, 20 × 200 mm, hexane:EtOAc 5:1; 2nd column, silica gel, 18 × 180 mm, hexane:acetone 9:1), the product *trans*-(2*S*,3*R*)-**71i** was obtained as a white solid (9 mg, 0.03 mmol, 15%) after two columns. The fractions containing *trans*-(2*R*,3*S*)-**72i** were collected, concentrated and then the aziridine was purified by a separate column chromatography (silica gel, 18 × 180 mm, benzene:EtOAc 30:1 to 20:1) to give pure *trans*-(2*R*,3*S*)-**72i** as a colorless oil (9 mg, 0.03 mmol, 15%), solidified during storage, mp 57-58 °C; R_f = 0.05 (hexane:EtOAc 5:1); Spectral data for *trans*-(2*S*,3*R*)-**71i**: ^1H NMR (500 MHz, CDCl_3) δ 1.02 (t, 3H, J = 7.5 Hz), 1.46 (d, 3H, J = 6.0 Hz), 1.50-1.70 (m, 3H), 1.90-1.98 (m, 1H), 2.00 (d, 1H, J = 3.0 Hz), 2.32-2.39 (m, 1H), 3.36 (q, 1H, J = 6.5 Hz), 7.04 (t, 1H, J = 7.5 Hz), 7.20-7.40 (m, 7H), 7.46 (d, 2H, J = 7.5 Hz), 8.37 (brs, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 13.96, 21.51, 23.79, 27.82, 44.58, 46.83, 60.13, 119.24, 123.84, 126.62, 127.58, 128.73, 128.92, 137.65, 143.93, 168.52; IR (thin film) 3312(m), 2968(m), 1682(m), 1528(s) cm^{-1} ; HRMS (ESI^+) calcd for $\text{C}_{20}\text{H}_{25}\text{N}_2\text{O}$ m/z 309.1967 ($[\text{M}+\text{H}]^+$), meas 309.1950; $[\alpha]_D^{20}$ -207.3° (c 0.5, CH_2Cl_2).



Spectral data for *trans*-(2*R*,3*S*)-**72i**: R_f = 0.20 (hexane:EtOAc 5:1); ^1H NMR (500 MHz, CDCl_3) δ 0.82 (t, 3H, J = 7.5 Hz), 1.14-1.54 (m, 7H), 2.17 (d, 1H, J = 2.5 Hz), 2.22-2.30 (m, 1H), 3.44 (q, 1H, J = 6.5 Hz), 7.08 (t, 1H, J = 7.5 Hz), 7.20-7.50 (m, 7H), 7.58 (d, 2H, J = 8.0 Hz), 8.61 (brs, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 13.72, 21.27, 24.58, 28.11, 44.90, 46.74, 59.56, 119.34, 124.00, 126.27, 127.14, 128.48, 129.00, 137.63, 144.46, 168.96; IR (thin film) 3310(m), 2963(m), 1683(m), 1525(s) cm^{-1} ; HRMS (ESI^+) calcd for $\text{C}_{20}\text{H}_{25}\text{N}_2\text{O}$ m/z 309.1967 ($[\text{M}+\text{H}]^+$), meas 309.1974; $[\alpha]_D^{20}$ 48.4° (c 0.5, CH_2Cl_2).

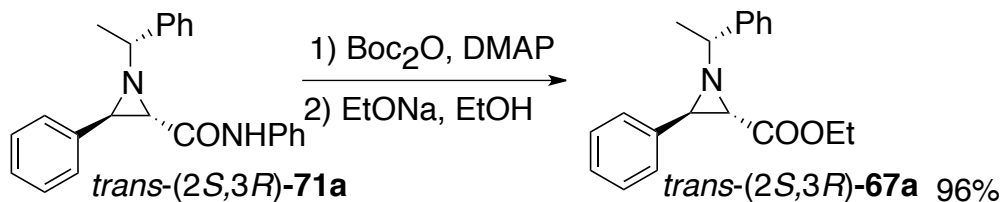
Synthesis of trans-(2*S*,3*R*)-**67a** from *trans*-(2*S*,3*R*)-**67j** via reduction with tin hydride:



To a flame dried 25 mL Schlenk flask was added *trans*-(2*S*,3*R*)-**67j** (120 mg, 0.320 mmol, 1.00 equiv) in dry benzene (2 mL), followed by the addition of Bu_3SnH (280 mg, 0.260 mL, 0.960 mmol, 3.00 equiv) and AIBN (10 mg) under a stream of N_2 . Then the flask was sealed and stirred at 50 °C for 24 h. *aq* sat KF

(10 mL) was added to the mixture to quench the reaction. The aqueous layer was separated and extracted with CH₂Cl₂ (2 × 10 mL). The organic layers were combined, dried (Na₂SO₄), filtered and concentrated. After purification by column chromatography (silica gel, 20 × 200 mm, hexane:EtOAc 9:1), the product *trans*-(2*S*,3*R*)-**67a** (64 mg, 0.22 mmol) was obtained in 68% yield as a colorless oil; *R*_f = 0.63 (hexane:EtOAc 4:1). Spectral data for *trans*-(2*S*,3*R*)-**67a**: ¹H NMR (300 MHz, CDCl₃) δ 1.24-1.34 (m, 6H), 3.08 (d, 1H, *J* = 2.1 Hz), 3.28 (d, 1H, *J* = 2.4 Hz), 4.10-4.40 (m, 3H), 7.20-7.44 (m, 10H); ¹³C NMR (300 MHz, CDCl₃) δ 14.22, 23.50, 44.62, 47.97, 59.36, 61.23, 126.22, 126.91, 127.29, 128.21, 128.26, 138.267, 144.54, 168.88 (One *sp*² carbon not located); IR (thin film) 2976(w), 1728(s), 1188(s) cm⁻¹; HRMS (ESI⁺) calcd for C₁₉H₂₁NO₂ *m/z* 296.1651 ([*M*+*H*]⁺), meas 296.1664; [α]_D²⁰ 55.0° (c 1.0, CH₂Cl₂).

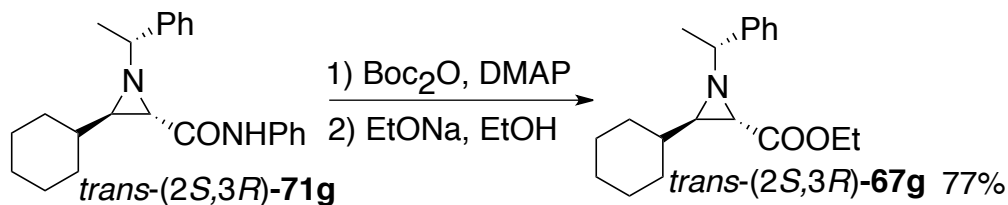
Synthesis of trans-(2*S*,3*R*)-**71a** from *trans*-(2*S*,3*R*)-**67a** via conversion of an amide group to an ester:



To a 25 mL round bottom flask filled with N₂ was added (2*S*,3*R*)-**71a** (146 mg, 0.426 mmol, 1.00 equiv), di-*tert*-butyl dicarbonate (278 mg, 1.28 mmol, 3.00 equiv), 4-dimethylaminopyridine (DMAP, 104 mg, 0.852 mmol, 2.00 equiv) and a

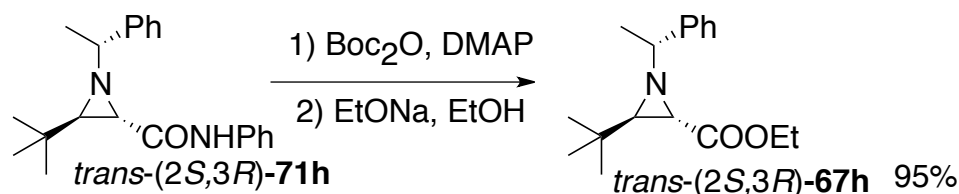
solvent mixture of CH₃CN and CH₂Cl₂ (v:v 9:1, 5 mL). The vacuum adapter was replaced with a rubber septum to which a N₂ balloon was attached *via* a needle. The resulting mixture was stirred at rt overnight (~12 h). After the solution was concentrated, the crude product was purified by column chromatography (silica gel, 18 × 180 mm, hexane:EtOAc 9:1) to give the activated amide intermediate as a foamy solid. This material was introduced into a 25 mL single neck round bottom flask and a N₂ balloon was attached *via* a rubber septum in the neck of the flask. Absolute EtOH (2 mL) was added *via* syringe. The resulting solution was cooled to 0 °C. A solution of NaOEt solution (21wt%, 0.32 mL, 0.85 mmol, 2.0 equiv) was added dropwise *via* syringe at 0 °C. The mixture was stirred at 0 °C for 1 hour, and then *aq* sat NH₄Cl (1 mL), water (1 mL) and CH₂Cl₂ (10 mL) were added. The aqueous layer was separated and extracted with CH₂Cl₂ (2 × 5 mL). The combined organic extracts were dried (Na₂SO₄) and filtered. The filtrate was concentrated and the product was purified by column chromatography (1st column, silica gel, 28 × 200 mm, hexane:EtOAc 15:1; 2nd column, silica gel, 28 × 200 mm, hexane:EtOAc 15:1) and (2*S*,3*R*)-**67a** (120 mg, 0.41 mmol, 96%) was obtained as a colorless oil. The spectral data were identical to the compound prepared by reduction of **67j** with tin hydride described above.

*Synthesis of trans-(2*R*,3*S*)-71g from trans-(2*R*,3*S*)-67g via conversion of an amide group to an ester:*



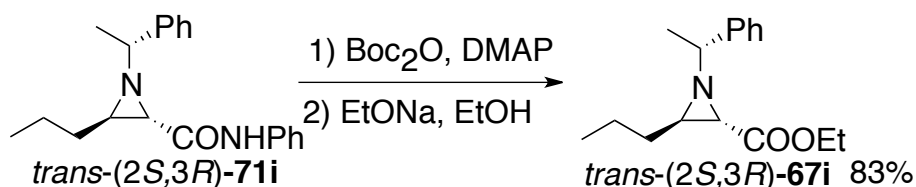
The procedure described above for the synthesis of *trans*-(2*S*,3*R*)-**71g** from *trans*-(2*S*,3*R*)-**67g** was followed. Amide activation proceeded with *trans*-(2*S*,3*R*)-**71g** (100 mg, 0.287 mmol, 1.00 equiv), di-*tert*-butyl dicarbonate (188 mg, 0.860 mmol, 3.00 equiv), 4-dimethylaminopyridine (DMAP, 70 mg, 0.57 mmol, 2.00 equiv). Ester formation was achieved with a solution of NaOEt (21wt%, 0.22 mL, 0.57 mmol, 2.0 equiv). The product was purified by column chromatography (silica gel, 18 × 300 mm, hexane:EtOAc 15:1) which gave *trans*-(2*S*,3*R*)-**67g** (66 mg, 0.22 mmol, 77%) as a colorless oil which solidified as a white solid during storage in the refrigerator; mp 36-37 °C; R_f = 0.45 (hexane:EtOAc 4:1). Spectral data for *trans*-(2*S*,3*R*)-**67g**: ^1H NMR (500 MHz, CDCl_3) δ 0.40-0.56 (m, 1H), 0.80-1.10 (m, 6H), 1.26 (d, 3H, J = 6.5 Hz), 1.31 (t, 3H, J = 7.5 Hz), 1.34-1.64 (m, 4H), 1.99 (dd, 1H, J = 7.5, 3.0 Hz), 2.53 (d, 1H, J = 3.0 Hz), 3.73 (q, 1H, J = 6.5 Hz), 4.14-4.30 (m, 2H), 7.20-7.26 (m, 1H), 7.26-7.32 (t, 2H, J = 8.0 Hz), 7.37 (d, 2H, J = 8.5 Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 14.25, 22.10, 25.49, 25.68, 26.10, 29.85, 30.15, 39.84, 40.59, 52.15, 59.60, 60.99, 127.27, 127.66, 128.24, 144.28, 169.97; IR (thin film) 2926(m), 1720(s), 1190(s) cm^{-1} ; HRMS (ESI^+) calcd for $\text{C}_{19}\text{H}_{28}\text{NO}_2$ m/z 302.2120 ($[\text{M}+\text{H}]^+$), meas 302.2129; $[\alpha]_D^{20}$ 64.6° (c 1.0, CH_2Cl_2).

Synthesis of *trans*-(2*R*,3*S*)-**71h** from *trans*-(2*R*,3*S*)-**67h** via conversion of an amide group to an ester:



The procedure described above for the synthesis of *trans*-(2*S*,3*R*)-**71a** from *trans*-(2*S*,3*R*)-**67a** was followed. Amide activation was performed on *trans*-(2*S*,3*R*)-**71h** (198 mg, 0.615 mmol, 1.00 equiv), di-*tert*-butyl dicarbonate (404 mg, 1.85 mmol, 3.00 equiv) and 4-dimethylaminopyridine (DMAP, 150 mg, 1.23 mmol, 2.00 equiv). Ester formation resulted upon treatment with a NaOEt solution (21wt%, 0.46 mL, 1.2 mmol, 2.0 equiv). The product *trans*-(2*S*,3*R*)-**67h** (160 mg, 0.582 mmol, 95%) was obtained as a colorless oil; $R_f = 0.57$ (hexane:EtOAc 4:1). Spectral data for *trans*-(2*S*,3*R*)-**67h**: ^1H NMR (500 MHz, CDCl_3) δ 0.57 (s, 9H), 1.24 (d, 3H, $J = 6.5$ Hz), 1.32 (t, 3H, $J = 7.5$ Hz), 2.05 (d, 1H, $J = 3.0$ Hz), 2.55 (d, 1H, $J = 3.0$ Hz), 3.75 (q, 1H, $J = 6.5$ Hz), 4.14-4.30 (m, 2H), 7.18-7.23 (m, 1H), 7.26-7.32 (m, 2H), 7.36-7.40 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 14.27, 22.71, 26.45, 30.44, 36.80, 56.58, 60.12, 60.91, 127.15, 127.79, 128.14, 145.05, 170.34; IR (thin film) 2961(m), 1728(s), 1186(s) cm^{-1} ; HRMS (ESI^+) calcd for $\text{C}_{17}\text{H}_{26}\text{NO}_2$ m/z 276.1964 ($[\text{M}+\text{H}]^+$), meas 276.1956; $[\alpha]_D^{20}$ 93.5° (c 1.0, CH_2Cl_2).

Synthesis of *trans*-(2*R*,3*S*)-**71i** from *trans*-(2*R*,3*S*)-**67i** via conversion of an amide group to an ester:



The procedure described above for the synthesis of *trans*-(2*S*,3*R*)-**71a** from *trans*-(2*S*,3*R*)-**67a** was followed. The activated amide was prepared from *trans*-(2*S*,3*R*)-**71i** (170 mg, 0.550 mmol, 1.00 equiv), di-*tert*-butyl dicarbonate (362 mg, 1.66 mmol, 3.00 equiv) and 4-dimethylaminopyridine (DMAP, 134 mg, 1.10 mmol, 2.00 equiv). The ester was prepared by subsequent treatment with a NaOEt solution (21wt%, 0.41 mL, 1.1 mmol, 2.0 equiv). The product was partially purified by column chromatography (silica gel, 18 × 180 mm, hexane:EtOAc 15:1) to give a material that was contaminated with Boc protected aniline (PhNHBoc). This was removed by dissolving the crude product in hexanes and filtering off the white solid. The procedure was repeated several times until no solids could be observed. The pure product *trans*-(2*S*,3*R*)-**67i** (120 mg, 0.460 mmol, 83%) was obtained as a colorless oil; R_f = 0.40 (hexane:EtOAc 4:1).

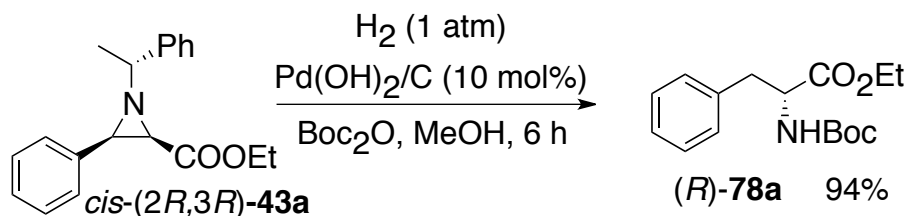
Spectral data for *trans*-(2*S*,3*R*)-**67i**: ^1H NMR (500 MHz, CDCl_3) δ 0.67 (t, 3H, J = 6.0 Hz), 0.82-1.16 (m, 2H), 1.14-1.36 (m, 7H), 1.42 (d, 1H, J = 7.5 Hz), 2.16 (td, 1H, J = 5.0, 2.5 Hz), 2.51 (d, 1H, J = 2.5 Hz), 3.78 (q, 1H, J = 5.5 Hz), 4.18-4.28 (m, 2H), 7.18-7.44 (m, 5H); ^{13}C NMR (125 MHz, CDCl_3) δ 13.57, 14.28, 20.00, 22.68, 34.61, 40.96, 46.52, 59.32, 61.03, 127.13, 127.30, 128.28, 144.57,

169.87; IR (thin film) 2964(m), 1728(s), 1188(s) cm^{-1} ; HRMS (ESI^+) calcd for $\text{C}_{16}\text{H}_{24}\text{NO}_2$ m/z 262.1807 ($[\text{M}+\text{H}]^+$), meas 262.1806; $[\alpha]_{\text{D}}^{20}$ 51.2° (c 1.0, CH_2Cl_2).

7.1.4 Catalytic hydrogenolysis of aziridines

General Procedure for the Synthesis of N-Boc Alanine Derivatives via Hydrogenolysis: To a flame-dried 25 mL round bottom flask filled with N_2 was added the aziridine (0.50 mmol, 1.00 equiv), MeOH (5 mL), Pearlman's catalyst (20% $\text{Pd}(\text{OH})_2$ on carbon, moisture ca 60%, 85 mg, 0.050 mmol, 0.10 equiv) and $(\text{Boc})_2\text{O}$ (220 mg, 1.00 mmol, 2.00 equiv). The flask was equipped with a vacuum transfer adapter connected with vacuum and a H_2 balloon. The valve to vacuum was opened for a few seconds and then switched to the H_2 balloon. This process was repeated for 3 additional times. The suspension was stirred at rt under a H_2 balloon for 6 hours. Then the mixture was filtered through a Celite pad on a sintered glass funnel and washed well with MeOH. The filtrate was concentrated by rotary evaporation, followed by purification of the product by column chromatography on silica gel.

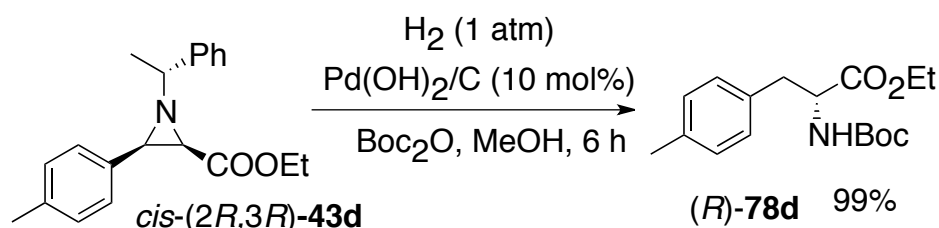
*Synthesis of N-Boc phenylalanine derivative **78a** via reductive ring opening of aziridine **43a**:*



The general procedure for the synthesis of N-Boc alanine derivatives via hydrogenolysis was followed with *cis*-(2*R*,3*R*)-**43a** (149 mg, 0.500 mmol, 1.00 equiv). Purification of the product by column chromatography (silica gel, 20 × 200 mm, hexane:EtOAc 15:1) provided (*R*)-**78a** (140 mg, 0.476 mmol, 94%) as a colorless oil. The optical purity was determined to be >99% ee by HPLC analysis (Chiralpak AS column, 85:15 hexane/2-propanol at 222 nm, flow rate 0.2 mL/min); Retention times: R_t = 25.12 min and R_t = 30.07 min for its enantiomer; R_f = 0.35 (hexane:EtOAc 4:1). Spectral data for (*R*)-**78a**: ^1H NMR (500 MHz, CDCl_3) δ 1.20 (t, 3H, J = 7.0 Hz), 1.30 (s, 9H), 2.84-3.10 (m, 2H), 4.10 (q, 2H, J = 7.0 Hz), 4.50 (q, 1H, J = 12.5, 5.5 Hz), 4.96 (d, 1H, J = 7.0 Hz), 7.10 (d, 2H, J = 6.5 Hz), 7.18-7.28 (m, 3H); ^1H NMR (500 MHz, toluene- d_6) δ 0.90 (t, 3H, J = 7.0 Hz), 1.35 (s, 9H), 2.83 (dd, 1H, J = 13.5, 6.0 Hz), 2.96 (dd, 1H, J = 14.0, 6.0 Hz), 3.60-3.90 (m, 2H), 4.62 (dd, 1H, J = 7.5, 5.0 Hz), 4.96 (d, 1H, J = 6.5 Hz), 6.80-7.20 (m, 5H); ^1H NMR (500 MHz, toluene- d_6 , 80 $^\circ\text{C}$) δ 0.90 (t, 3H, J = 7.0 Hz), 1.35 (s, 9H), 2.83 (dd, 1H, J = 14.0, 6.5 Hz), 2.96 (dd, 1H, J = 13.5, 6.0 Hz), 3.80-3.90 (m, 2H), 4.56 (dd, 1H, J = 7.5, 5.0 Hz), 4.83 (d, 1H, J = 6.5 Hz), 6.80-7.20 (m, 5H); ^{13}C NMR (125 MHz, CDCl_3) δ 14.04, 28.24, 38.34, 54.41, 61.23, 79.77, 126.89, 128.41, 129.30, 136.06, 155.03, 171.81; IR (thin film) 3364(m),

2980(m), 1734(s), 1716(s), 1701(s) cm^{-1} ; mass spectrum m/z (% rel intensity) 237 $[\text{M}-57]^+$ (20), 176(100), 120(88); $[\alpha]_D^{20} -37.6^\circ$ (c 1.0, CH_2Cl_2), $[\alpha]_D^{20} 4.5^\circ$ (c 1.0, MeOH) (Lit: $[\alpha]_D^{20} -3.7^\circ$ (c 1.0, MeOH)).^{28a} The sign of the optical rotation of **78a** in MeOH allows for the assignment of the relative stereochemistry of **43a** as R.

Synthesis of N-Boc 4-methylphenylalanine derivative 43d via reductive ring opening of aziridine 78d:

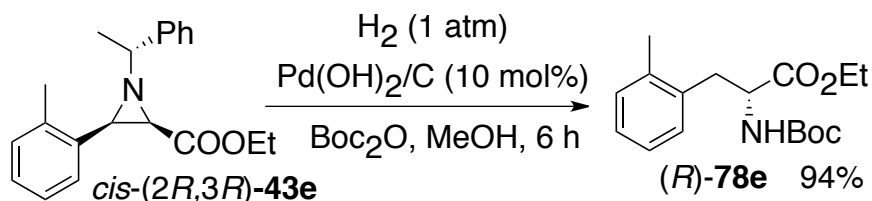


The general procedure for the synthesis of *N*-Boc alanine derivatives via hydrogenolysis was followed with *cis*-(2*R*,3*R*)-**43d** (155 mg, 0.500 mmol, 1.00 equiv). Purification of the product by column chromatography (silica gel, 25 × 200 mm, hexane:EtOAc 15:1) provided (R)-**78d** (154 mg, 0.50 mmol, 99%) as a colorless oil. The optical purity was determined to be >99% ee by HPLC analysis (Chiralcel OD-H column, 99:1 hexane/2-propanol at 222 nm, flow-rate 0.25 mL/min); Retention times $R_t = 26.18$ min and $R_t = 29.45$ min for its enantiomer.

Spectral data for (R)-**78d**: ^1H NMR (500 MHz, CDCl_3) δ 1.20 (t, 3H, $J = 7.5$ Hz), 1.42 (s, 9H), 2.30 (s, 3H), 2.90-3.10 (m, 2H), 4.14 (dd, 2H, $J = 10.5, 7.5$ Hz), 4.50 (dd, 1H, $J = 8.0, 5.0$ Hz), 4.94 (d, 1H, $J = 6.0$ Hz), 6.99 (d, 2H, $J = 7.5$ Hz), 7.06 (d, 2H, $J = 7.5$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 14.00, 20.91, 28.17, 37.71,

54.37, 61.11, 79.58, 129.04, 129.09, 132.80, 136.33, 154.99, 171.80; IR (thin film) 3443(m), 3370(m), 2980(m), 1740(s), 1716(s), 1169(s) cm^{-1} ; mass spectrum m/z (% rel intensity) 307 M^+ (0.1), 251(1), 190(87), 106(48), 57(100); HRMS (ESI^+) calcd for $\text{C}_{17}\text{H}_{26}\text{NO}_4$ m/z 308.1862 ($[\text{M}+\text{H}]^+$), meas 308.1864; $[\alpha]_{\text{D}}^{20} -38.1^\circ$ (c 1.0, CH_2Cl_2).

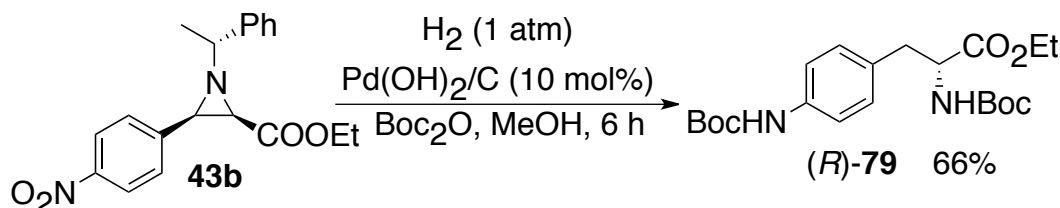
Synthesis of N-Boc 2-methylphenylalanine derivative 78e via reductive ring opening of aziridine 43e:



The general procedure for the synthesis of *N*-Boc alanine derivatives via hydrogenolysis was followed with *cis*-(2*R*,3*R*)-**43e** (155 mg, 0.500 mmol, 1.00 equiv). Purification of the product by column chromatography (silica gel, 20 × 200 mm, hexane:EtOAc 19:1) provided the product (*R*)-**78e** (136 mg, 0.440 mmol, 88%) as a colorless oil; The optical purity was determined to be >99% ee by HPLC analysis (Chiralcel OD-H column, 98:2 hexane/2-propanol at 222 nm, flow-rate 1.0 mL/min); Retention times $R_t = 5.81$ min and $R_t = 6.46$ min for its enantiomer; $R_f = 0.35$ (Hexane:EtOAc 4:1). Spectral data for (*R*)-**78e**: ^1H NMR (300 MHz, CDCl_3) δ 1.15 (t, 3H, $J = 7.2$ Hz), 1.37 (s, 9H), 2.33 (s, 3H), 2.84-3.10 (m, 2H), 4.10-4.22 (m, 2H), 4.52 (dd, 1H, $J = 15.0, 7.5$ Hz), 5.05 (d, 1H, 1H, $J = 7.8$ Hz), 6.97-7.20 (m, 4H); ^{13}C NMR (75 MHz, CDCl_3) δ 13.90, 19.28, 28.17,

36.15, 53.63, 61.14, 79.64, 125.77, 126.91, 129.83, 130.34, 134.50, 136.65, 154.95, 172.25; IR (thin film) 3237(m), 2932(m), 1716(s), 1701(s) cm^{-1} ; mass spectrum m/z (% rel intensity) 307 M^+ (0.3), 251 $[\text{M}-56]^+$ (5), 190(82), 57(100); HRMS (ESI^+) calcd for $\text{C}_{17}\text{H}_{26}\text{NO}_4$ m/z 308.1862 ($[\text{M}+\text{H}]^+$), meas 308.1859; $[\alpha]_{\text{D}}^{20} -16.7^\circ$ (c 1.0, CH_2Cl_2).

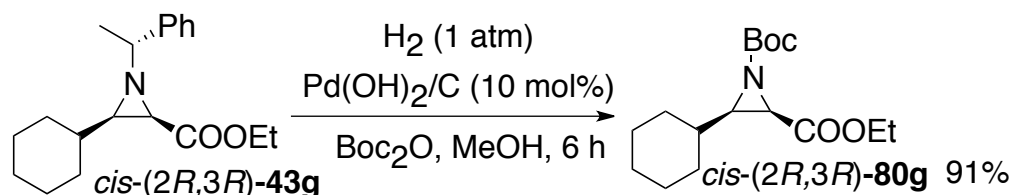
*Synthesis of N-Boc 4-aminophenylalanine derivative **79** via reductive ring opening of aziridine **43b**:*



The general procedure for the synthesis of *N*-Boc alanine derivatives *via* hydrogenolysis was followed with *cis*-(2*R*,3*R*)-**43b** (170 mg, 0.500 mmol, 1.00 equiv) and $(\text{Boc})_2\text{O}$ (440 mg, 2.00 mmol, 4.00 equiv). Purification of the product by column chromatography (silica gel, 25 × 200 mm, hexane:EtOAc 9:1 to 5:1) provided the product (*R*)-**79** (130 mg, 0.330 mmol, 66%) as a white solid; mp 81-83 $^\circ\text{C}$; The optical purity was determined to be >99% ee by HPLC analysis (Chiralpak AS column, 95:5 hexane/2-propanol at 222 nm, flow-rate 1.0 mL/min); Retention times $R_t = 21.68$ min and $R_t = 35.68$ min for its enantiomer; $R_f = 0.20$ (hexane:EtOAc 5:1). Spectral data for (*R*)-**79**: ^1H NMR (300 MHz, CDCl_3) δ 1.22 (t, 3H, $J = 7.0$ Hz), 1.42 (s, 9H), 1.52 (s, 9H), 2.84-3.10 (m, 2H), 4.10-4.22 (q, 2H,

$J = 7.2$ Hz), 4.50 (q, 1H, $J = 7.5$ Hz), 4.93 (d, 1H, $J = 8.1$ Hz), 6.42 (brs, 1H), 7.02 (d, 2H, $J = 7.5$ Hz), 7.24 (d, 2H, $J = 7.5$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 14.12, 28.28, 37.49, 54.41, 61.29, 79.79, 80.46, 118.50, 129.85, 130.47, 137.25, 152.71, 155.08, 171.80 (One sp^3 carbon not located); IR (thin film) 3240(m), 2978(m), 1716(s), 1701(s), 1163(s) cm^{-1} ; mass spectrum m/z (% rel intensity) 408 M^+ (0.05), 352 $[\text{M}-56]^+$ (0.07), 235 $[\text{M}-117]^+$ (8), 106(100); HRMS (ESI^+) calcd for $\text{C}_{21}\text{H}_{32}\text{N}_2\text{O}_6\text{Na}$ m/z 431.2046 ($[\text{M}+\text{Na}]^+$), meas 431.2049; $[\alpha]_{\text{D}}^{20} -34.7^\circ$ (c 1.0, CH_2Cl_2).

Synthesis of *N*-Boc aziridine **80g via hydrogenolysis of aziridine **43g**:**

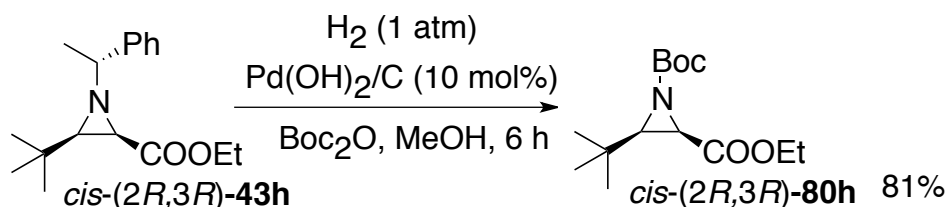


The general procedure for the synthesis of *N*-Boc alanine derivatives via hydrogenolysis was followed with the aziridine *cis*-(2*R*,3*R*)-**43g** (145 mg, 0.500 mmol, 1.00 equiv). Purification of the product by column chromatography (silica gel, 20 $\times$ 200 mm, hexane:EtOAc 19:1) provided the product *cis*-(2*R*,3*R*)-**80g** (135 mg, 0.496 mmol, 91%) as a colorless oil; $R_f = 0.50$ (hexane:EtOAc 9:1).

Spectral data for *cis*-(2*R*,3*R*)-**80g**: ^1H NMR (300 MHz, CDCl_3) δ 0.94-1.80 (m, 22H), 2.03 (d, 1H, $J = 10.5$ Hz), 2.32 (dd, 1H, $J = 9.3, 6.6$ Hz), 3.09 (d, 1H, $J = 6.9$ Hz), 4.14-4.32 (m, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 14.23, 25.28, 25.33,

26.10, 27.82, 29.49, 31.01, 36.31, 39.38, 48.45, 61.34, 81.79, 160.76, 167.77; mass spectrum m/z (% rel intensity) 224 $[M-73]^+$ (1), 124 (56), 57 (100); $[\alpha]_D^{20}$ 23.2 (c 2.0, EtOAc). The optical purity was calculated to be >99% ee based on the optical rotation given in the literature. The sign of the optical rotation of **80g** thus allows for the assignment of the relative stereochemistry of **43g** as 2*R*, 3*R*.^{26b}

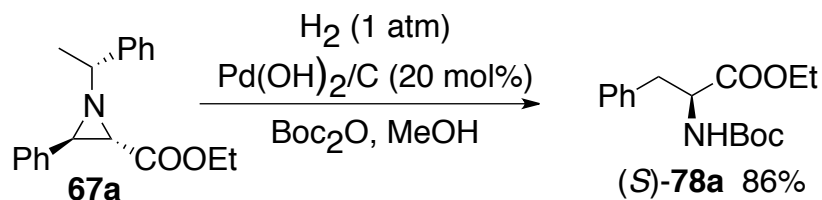
Synthesis of N-Boc aziridine 80h via hydrogenolysis of aziridine 43h:



The general procedure for the synthesis of *N*-Boc alanine derivatives via hydrogenolysis was followed with the aziridine *cis*-(2*R*,3*R*)-**43h** (138 mg, 0.500 mmol, 1.00 equiv). Purification of the product by column chromatography (silica gel, 20 × 200 mm, hexane:EtOAc 19:1) provided *cis*-(2*R*,3*R*)-**80h** (105 mg, 0.41 mmol, 81%) as a colorless oil; R_f = 0.50 (hexane:EtOAc 9:1). Spectral data for *cis*-(2*R*,3*R*)-**80h**: ^1H NMR (500 MHz, CDCl_3) δ 0.98 (s, 9H), 1.25 (t, 3H, J = 7.5 Hz), 1.40 (s, 9H), 2.35 (d, 1H, J = 7.5 Hz), 3.02 (d, 1H, J = 7.5 Hz), 4.12-4.26 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 14.02, 26.82, 27.82, 31.78, 40.40, 52.89, 61.32, 81.68, 161.57, 167.85; IR (thin film, cm^{-1}) 2976(m), 1759(s), 1728(s), 1159(s); mass spectrum m/z (% rel intensity) 198 $[M-73]^+$ (2), 156(44), 82(80),

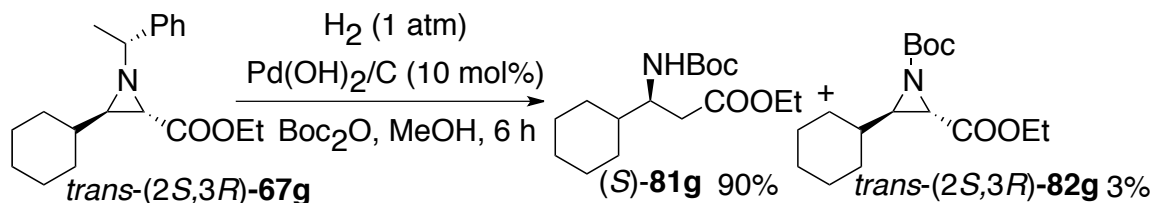
57(100); HRMS (ESI⁺) calcd for C₁₄H₂₅NO₄Na *m/z* 294.1681 ([M+Na]⁺), meas 294.1685; [α]_D²⁰ 70.3° (c 1.0, EtOAc).

Synthesis of N-Boc phenylalanine derivative 78a via reductive ring opening of aziridine 67a:



The general procedure for the synthesis of *N*-Boc alanine derivatives *via* hydrogenolysis was followed with the aziridine (2*S*,3*R*)-**67a** (30 mg, 0.10 mmol, 1.0 equiv), MeOH (2 mL), Pearlman's catalyst (20% Pd(OH)₂ on carbon, moisture *ca* 60%, 36 mg, 0.02 mmol, 0.20 equiv), Boc₂O (64 mg, 0.30 mmol, 3.0 equiv) and a reaction time of 24 h. After purification by column chromatography (silica gel, 18 × 180 mm, hexane:EtOAc 9:1), the product (*S*)-**78a** was obtained as a colorless oil (25 mg, 0.086 mmol, 86%). The spectral data for the product of this reaction was identical with *N*-Boc phenylalanine derivative **78a** prepared from reductive ring opening of aziridine **43a**. The product has the optical rotation [α]_D²⁰ 37.8 (c 1.0, CH₂Cl₂) which indicates an *S* configuration based on the optical rotation for compound (*R*)-**78a** prepared from reductive ring opening of aziridine **43a** (see above).

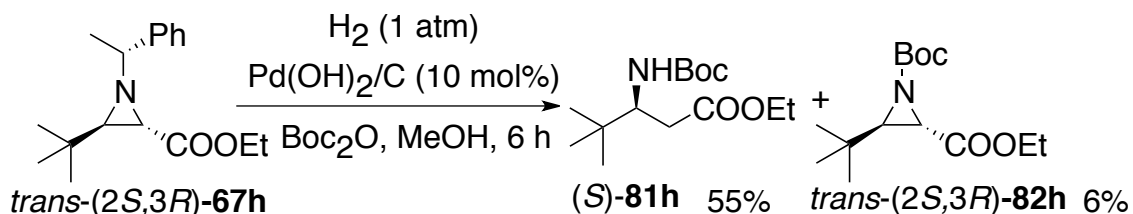
Synthesis of N-Boc alanine derivative 81g via reductive ring opening of aziridine 67g:



The general procedure for the synthesis of *N*-Boc alanine derivatives *via* hydrogenolysis was followed with the aziridine (2*S*,3*R*)-**67g** (31 mg, 0.10 mmol, 1.0 equiv), MeOH (2 mL), Pearlman's catalyst (20% Pd(OH)₂ on carbon, moisture *ca* 60%, 36 mg, 0.02 mmol, 0.20 equiv), Boc₂O (64 mg, 0.30 mmol, 3.0 equiv) and a reaction time of 24 h. The crude reaction mixture was a 13:1 mixture of **81g** and **82g** as determined from the ¹H NMR spectrum. After purification of the major product by column chromatography (silica gel, 18 × 180 mm, hexane:EtOAc 15:1), the pure major product (S)-**81g** was obtained as a colorless oil (27 mg, 0.0903 mmol, 90%) which solidified as a white solid during storage in the refrigerator; mp 43-44 °C; *R_f* = 0.40 (hexane:EtOAc 4:1). Spectral data for (S)-**81g**: ¹H NMR (500 MHz, CDCl₃) δ 0.84-1.02 (m, 2H), 1.04-1.30 (m, 6H), 1.42 (s, 9H), 1.56-1.80 (m, 6H), 2.36-2.54 (m, 2H), 3.66-3.76 (m, 1H), 4.10 (t, 2H, *J* = 7.0 Hz), 4.88 (d, 1H, *J* = 9.5 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 14.15, 26.00, 26.04, 26.20, 28.36, 28.95, 29.74, 37.05, 41.49, 52.23, 60.45, 78.98, 155.50, 172.03; IR (thin film) 3360(m), 2928(s), 1718(s), 1172(s) cm⁻¹; HRMS (ESI⁺) calcd for C₁₆H₃₀NO₄ *m/z* 300.2175 ([M+H]⁺), meas 300.2188; [α]_D²⁰ 11.6° (*c* 1.0, CH₂Cl₂). The structure of the minor product was tentatively assigned as **82g**

based on the following peaks from the ^1H NMR spectrum of the crude mixture in CDCl_3 : 4.14-4.25 (m, 2H), 2.81 (d, 1H, $J = 2.7$ Hz).

*Synthesis of N-Boc alanine derivative **81h** via reductive ring opening of aziridine **67h**:*

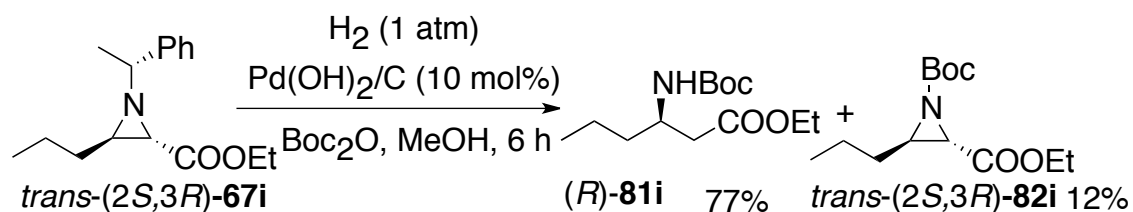


The general procedure for the synthesis of *N*-Boc alanine derivatives via hydrogenolysis was followed with the aziridine (2*S*,3*R*)-**67h** (28 mg, 0.10 mmol, 1.0 equiv), MeOH (2 mL), Pearlman's catalyst (20 % $\text{Pd}(\text{OH})_2$ on carbon, moisture *ca* 60%, 36 mg, 0.02 mmol, 0.20 equiv), Boc_2O (64 mg, 0.30 mmol, 3.0 equiv) and a reaction time of 45 h. The crude reaction mixture was determined to be a 10:1 mixture of **81h** and **82h** by its ^1H NMR spectrum. After purification by column chromatography (silica gel, 18 × 180 mm, hexane:EtOAc 15:1), the pure major product (S)-**81h** was obtained as a colorless oil (15 mg, 0.055 mmol, 55%) which solidified as a white solid during storage in the refrigerator; mp 41-42 °C; $R_f = 0.30$ (hexane:EtOAc 4:1). Spectral data for (S)-**81h**: ^1H NMR (500 MHz, CDCl_3) δ 0.88 (s, 9H), 1.23 (t, 3H, $J = 7.0$ Hz), 1.39 (s, 9H), 2.19 (dd, 1H, $J = 14.0, 10.0$ Hz), 2.55 (dd, 1H, $J = 14.0, 3.5$ Hz), 3.86 (td, 1H, $J = 10.0, 4.0$ Hz), 4.02-4.18 (m, 2H), 4.60 (d, 1H, $J = 9.5$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 14.11,

26.20, 28.32, 34.92, 36.46, 55.98, 60.65, 78.98, 155.47, 172.12; IR (thin film) 3358(m), 2968(s), 1734(s), 1701(s), 1172(s) cm^{-1} ; HRMS (ESI⁺) calcd for $\text{C}_{14}\text{H}_{27}\text{NO}_4\text{Na}$ m/z 296.1838 ($[\text{M}+\text{Na}]^+$), meas 296.1816; $[\alpha]_D^{20}$ 10.5° (c 1.0, CH_2Cl_2). The minor product was tentatively assigned as **82h** based on the following peaks from the ^1H NMR of the crude mixture in CDCl_3 : 0.90 (s, 9H), 2.61 (d, 1H, $J = 2.7$ Hz), 2.85 (d, 1H, $J = 2.7$ Hz).

*Synthesis of N-Boc alanine derivative **81i** via reductive ring opening of aziridine*

67i:

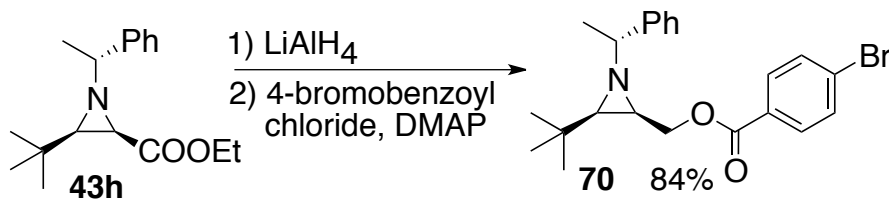


The general procedure for the synthesis of *N*-Boc alanine derivatives via hydrogenolysis was followed with the aziridine (2*S*,3*R*)-**67i** (27 mg, 0.10 mmol, 1.0 equiv), MeOH (2 mL), Pearlman's catalyst (20% $\text{Pd}(\text{OH})_2$ on carbon, moisture *ca* 60%, 36 mg, 0.02 mmol, 0.20 equiv), Boc_2O (64 mg, 0.30 mmol, 3.0 equiv) and a reaction time of 24 h. The crude reaction mixture was determined to be a 5.26:1 mixture of **81i** and **82i** by its the ^1H NMR spectrum. After purification by column chromatography (silica gel, 18 × 180 mm, hexane:EtOAc 15:1), the pure major product was obtained as a colorless oil (20 mg, 0.077 mmol, 77%). Spectral data for (*R*)-**81i**: ^1H NMR (500 MHz, CDCl_3) δ 0.88 (t, 3H, $J = 7.0$ Hz),

1.23 (t, 3H, $J = 7.0$ Hz), 1.26-1.40 (m, 4H), 1.40 (s, 9H), 2.40-2.52 (m, 2H), 3.70-3.92 (m, 1H), 4.10 (t, 2H, $J = 7.0$ Hz), 4.88 (d, 1H, $J = 8.0$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 13.80, 14.17, 19.33, 28.35, 36.79, 39.33, 47.36, 60.44, 79.08, 155.35, 171.75; IR (thin film) 3358(m), 2976(m), 1738(s), 1714(s), 1172(s) cm^{-1} ; HRMS (ESI^+) calcd for $\text{C}_{13}\text{H}_{26}\text{NO}_4$ m/z 260.1862 ($[\text{M}+\text{H}]^+$), meas 260.1857; $[\alpha]_D^{20}$ 23.5° (c 1.0, CH_2Cl_2). The identity of the minor product was tentatively assigned as **82i** based on the following peaks from the ^1H NMR of the crude mixture in CDCl_3 : 0.91 (t, 3H, $J = 6.6$ Hz), 2.61 (td, 1H, $J = 7.5$ 2.4 Hz), 2.72 (d, 1H, $J = 2.4$ Hz), 4.10-4.14 (m, 1H), 4.15-4.22 (m, 1H).

7.1.5 Determination of Stereochemistry.

Determination of the relative configuration for cis-(2R,3R)-43h by conversion to the 4-bromobenzoate 70:



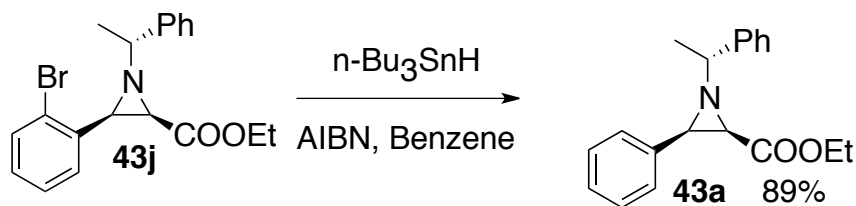
To a flame-dried 25 mL round bottom flask filled with N_2 was added LiAlH_4 (80 mg, 2.0 mmol, 4.0 equiv) and Et_2O (3 mL). Then the vacuum adapter was replaced with a septum to which a N_2 balloon was attached via a needle. The flask was cooled to 0°C . A solution of aziridine *cis*-(2R,3R)-**43h** (138 mg, 0.500 mmol,

1.00 equiv) in Et₂O (2 mL) was added via syringe dropwise to the flask. After it was stirred at 0 °C for 15 min, the ice bath was removed. The mixture was stirred at rt for 6 hours. After cooling to 0 °C, H₂O (0.5 mL) was added slowly to quench the reaction. The resulting suspension was stirred at 0 °C for 30 min. The reaction was filtered through a pad of Celite on a sintered glass funnel and washed well with Et₂O. The filtrate was dried (Na₂SO₄), filtered and concentrated to give the aziridinyl methanol as a white solid (115 mg, 0.493 mmol, 98%); mp 72-73 °C. Spectral data for aziridinyl methanol: ¹H NMR (300 MHz, CDCl₃) δ 0.68 (s, 9H), 1.34 (d, 1H, *J* = 7.2 Hz), 1.47 (d, 3H, *J* = 6.6 Hz), 1.66-1.78 (m, 1H), 2.34 (brs, 1H), 2.46 (q, 1H, *J* = 6.6 Hz), 3.70-3.90 (m, 2H), 7.20-7.40 (m, 5H); ¹³C NMR (125 MHz, CDCl₃) δ 23.11, 28.80, 30.84, 46.17, 54.45, 61.06, 71.53, 127.07, 127.39, 128.10, 144.85; IR (thin film) 3277(m), 2988(s), 1037(s) cm⁻¹; HRMS (ESI⁺) calcd for C₁₅H₂₃NONa *m/z* 256.1677 ([M+H]⁺), meas 256.1671; [α]_D²⁰ 66.1° (c 0.5, CH₂Cl₂).

A mixture of the above aziridinyl methanol (47 mg, 0.20 mmol, 1.0 equiv), 4-bromobenzoyl chloride (97 mg, 0.44 mmol, 2.2 equiv) and DMAP (74 mg, 0.60 mmol, 3.0 equiv) in dry CH₂Cl₂ (1 mL) was stirred at rt for 2 hours. Then the reaction mixture was diluted with CH₂Cl₂ (10 mL). The solution was washed with HCl (2N, 2 × 3 mL) and sat *aq* Na₂CO₃ (2 mL). The organic layer was then dried

(Na₂SO₄), filtered and concentrated to give the crude product which was purified by column chromatography (silica gel, 18 × 180 mm, hexane:EtOAc 15:1) to give the ester **70** as a white solid (71 mg, 0.17 mmol, 86%); mp 66-67 °C. Spectral data for **70**: ¹H NMR (300 MHz, CDCl₃) δ 0.68 (s, 9H), 1.35 (d, 1H, *J* = 7.0 Hz), 1.43 (d, 3H, *J* = 6.5 Hz), 1.74-1.82 (m, 1H), 2.45 (q, 1H, *J* = 6.5 Hz), 4.44 (dd, 1H, *J* = 11.5, 8.5 Hz), 4.56 (dd, 1H, *J* = 11.5, 4.0 Hz), 7.18-7.38 (m, 5H), 7.48-7.52 (m, 2H), 7.92-7.98 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 23.04, 28.74, 30.93, 42.37, 53.86, 65.31, 71.53, 127.15, 127.45, 128.09, 128.14, 129.25, 131.14, 131.79, 144.77, 165.82; IR (thin film) 2961(s), 1751(s), 1188(s), 758(m), 702(m) cm⁻¹; HRMS (ESI⁺) calcd for C₂₂H₂₇NO₂⁷⁹Br *m/z* 416.1225 ([M+H]⁺), meas 416.1194; [α]_D²⁰ -10.6° (c 0.5, CH₂Cl₂). Recrystallization of **70** from hexane gave X-ray quality crystals the X-ray diffraction analysis of which confirmed the relative configuration of *cis*-(2*R*,3*R*)-**43h**.

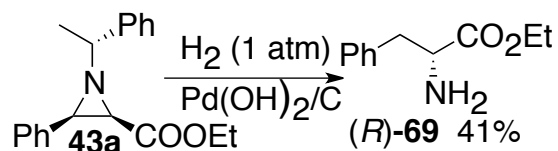
Determination of the relative configuration of cis-(2*R*,3*R*)-**43j** via reduction with tin hydride:



The procedure for the synthesis of *trans*-(2*S*,3*R*)-**67a** from *trans*-(2*S*,3*R*)-**67j** via selective reductive removal of bromine was followed with *cis*-(2*R*,3*R*)-**43j** (110 mg, 0.290 mmol, 1.00 equiv), dry benzene (2 mL), Bu₃SnH (0.26 mL, 0.88 mmol,

3.00 equiv) and AIBN (10 mg) with a reaction time of 15 h at 60 °C. The product was purified by column chromatography (silica gel, 18 × 180 mm, hexane:EtOAc 9:1) to give *cis*-(2*R*,3*R*)-**43a** (77 mg, 0.26 mmol) in 89% yield as a white solid. The spectral data of the reduced product was found to be identical with the major product *cis*-(2*R*,3*R*)-**43a** obtained from the aziridination of (*R*)-**45a** in the matched case with the (*S*)-VAPOL catalyst.

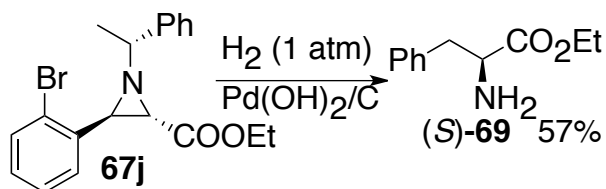
Determination of the relative configuration of cis-(2*R*,3*R*)-**43a** via reductive ring opening:



To a flame dried 100 mL round bottom flask filled with N₂ was added a sample of *cis*-(2*R*,3*R*)-**43a** prepared from imine (*R*)-**45a** (149 mg, 0.500 mmol, 1.00 equiv), Pearlman's catalyst (20% Pd(OH)₂ on carbon, moisture *ca* 60%, 85 mg, 0.050 mmol, 0.10 mmol) and MeOH (30 mL). The flask was equipped with a 3-way valve connected with vacuum and a H₂ balloon. The valve to vacuum was opened for a few seconds and switched to the H₂ balloon. This process was repeated for 3 additional times. The suspension was stirred under a H₂ balloon for 3 hours. Then the mixture was filtered through a Celite pad on a sintered glass funnel and washed well with MeOH. The filtrate was concentrated by rotary evaporation, followed by loading onto a chromatography column (silica gel, 20 × 200 mm, hexane:EtOAc 1:1) and elution to give the product (*R*)-**69** as a pale

yellow oil (39 mg, 0.21 mmol) in 41% isolated yield; $[\alpha]_D^{20} -18.9^\circ$ (c 3.2, EtOH) (Lit^{23a} $[\alpha]_D -23.0^\circ$ (c 3.2, EtOH, 23°C); The product can be assigned as (*R*)-D-phenylalanine ethyl ester). Spectral data for (*R*)-**69**: ¹H NMR (300 MHz, CDCl₃) δ 1.28 (t, 3H, *J* = 7.5 Hz), 1.60 (brs, 2H), 2.90 (dd, 1H, *J* = 13.5, 7.8 Hz), 3.10 (dd, 1H, *J* = 13.5, 5.4 Hz), 3.74 (dd, 1H, *J* = 7.8, 5.4 Hz), 4.20 (q, 2H, *J* = 7.2 Hz), 7.20-7.40 (m, 5H); ¹³C NMR (75 MHz, CDCl₃) δ 14.10, 41.08, 55.79, 60.84, 126.71, 128.45, 129.23, 137.23, 174.97.

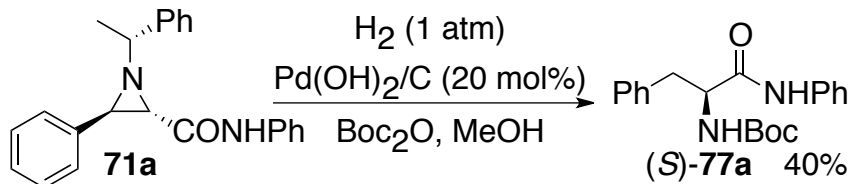
Determination of the relative configuration of trans-(2S,3R)-67j via reductive ring opening:



To a flame dried 100 mL round bottom flask filled with N₂ was added *trans*-(2*S*,3*R*)-**67j** (266 mg, 0.710 mmol, 1.0 equiv), Pearlman's catalyst (20% Pd(OH)₂ on carbon, moisture ca 60%, 85 mg, 0.050 mmol, 0.10 mmol), MeOH (30 mL). The flask was equipped with a 3-way valve connected to vacuum and a H₂ balloon. The valve was opened to vacuum for a few seconds and then switched to the H₂ balloon. This process was repeated for 3 additional times. The suspension was stirred under a H₂ balloon for 5 hours. The mixture was filtered through a Celite pad on a sintered glass funnel, washed well with MeOH and

concentrated. The residue was treated with *aq* sat NaHCO₃ (2 mL) and extracted with Et₂O (2 × 10 mL + 5 mL). The combined organic extracts were dried (Na₂SO₄) and filtered. The filtrate was concentrated by rotary evaporation, followed by loading onto a chromatography column (silica gel, 20 × 200 mm, Hexane:EtOAc 1:1) and elution gave the product **69** (78 mg, 0.36 mmol) as a pale oil in 57% isolated yield. The optical rotation of this material ($[\alpha]_D^{20}$ 19.8° (*c* 3.2, EtOH)) indicated that it is the (*S*)-enantiomer of phenylalanine ethyl ester based on the published optical rotation for this compound.^{23a}

*Determination of the relative configuration of trans-(2*S*,3*R*)-71a via reductive ring opening:*



The general procedure for the synthesis of *N*-Boc alanine derivatives *via* hydrogenolysis was followed with the aziridine *trans*-(2*S*,3*R*)-**71a** (45 mg, 0.13 mmol, 1.0 equiv), MeOH (2 mL), Pearlman's catalyst (20% Pd(OH)₂ on carbon, moisture *ca* 60%, 25 mg, 0.013 mmol, 0.10 equiv), Boc₂O (58 mg, 0.26 mmol, 2.0 equiv) and a reaction time of 6 h. After purification by column chromatography (silica gel, 18 × 180 mm, Hexane:EtOAc 5:1), the product (*S*)-**77a** was obtained as a white solid (17 mg, 0.040 mmol, 40%). Spectral data for (*S*)-**77a**: ¹H NMR (500 MHz, CDCl₃) δ 1.39 (s, 9H), 3.23 (d, 2H, *J* = 6.5 Hz), 4.47

(brs, 1H), 5.20 (brs, 1H), 7.06 (t, 1H, $J = 7.5$ Hz), 7.20-7.38 (m, 9H), 7.82 (brs, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 28.50, 38.59, 56.91, 80.78, 120.27, 124.73, 127.30, 129.04, 129.14, 129.55, 136.87, 137.49, 169.75 (One sp^2 carbon not located); $[\alpha]_{\text{D}}^{20} -22.7^\circ$ (c 1.0, CH_2Cl_2) (Lit: $[\alpha]_{\text{D}}^{25} -37^\circ$ (c 2.0, CH_2Cl_2).^{28a,78}

Rate Competition Study of Chiral α -alkyl benzylimines with VAPOL(VANOL)-borate Catalyst (Scheme 2.6):

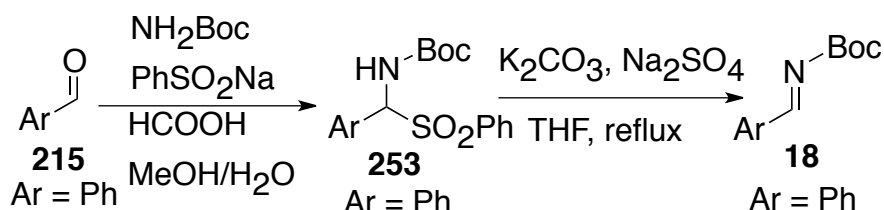
A 25 mL pear-shaped single necked flask which had its 14/20 joint replaced by a threaded high vacuum Teflon valve was flame dried (with a stir bar in it), cooled to rt under N_2 and charged with VAPOL or VANOL (*S* or *R*, 0.05 mmol, 0.05 equiv), 30 mol% triphenyl borate (44 mg, 0.15 mmol, 0.15 equiv) and dry toluene (2 mL). The Teflon valve was closed and the flask was heated at 80°C for 1 hour. After the flask was cooled to rt, the toluene was carefully removed by exposing to high vacuum (0.1 mmHg) by slightly cracking the Teflon valve. After the solvent was removed, the Teflon valve was completely opened and the flask was heated at 80°C under high vacuum for 30 min. The flask was then allowed to cool to rt. The catalyst was dissolved in 4 mL dry CCl_4 and transferred *via* syringe to the flask containing aldimine **31a** (271 mg, 1.00 mmol, 1.00 equiv) and the corresponding chiral imine (*S*)-**60a** (251 mg, 1.00 mmol, 1.00 equiv) or (*R*)-**45a** (209 mg, 1.00 mmol, 1.00 equiv). The resulting light yellow solution was allowed to stir at rt for 5 min, then EDA **5** (21 μL , 0.20 mmol, 0.20 equiv) was added *via* syringe in one portion. The solution was stirred at rt for 24 h. The

reaction was quenched with n-hexane (5 mL) and concentrated to give the crude reaction mixture. The ratio of the two aziridines (**61a** vs. ent-**32a**) or (**43a** vs. **32a**) was determined by the ^1H NMR integration of the crude product by comparing the C-2 and C-3 methine protons from the aziridines. The ratios can be found in Scheme 2.6.

7.2 Experimental Section for Chapter Three

7.2.1 Preparation of *N*-Boc imines

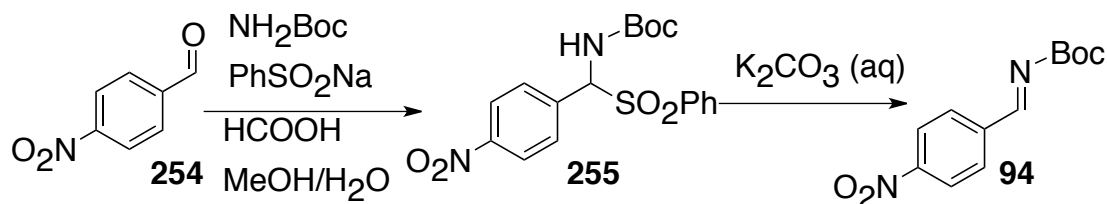
General procedure for the preparation of *N*-Boc imines⁷⁹ – illustrated for the synthesis of imine **18** (*Ar* = *Ph*)



Preparation of α -sulfonyl amine 253: A mixture of benzaldehyde **215** (2.10 mL, 20.0 mmol, 2.00 equiv), *tert*-butyl carbamate (1.17 g, 10.0 mmol, 1.00 equiv), benzenesulfinic acid sodium salt (4.11 g, 25.0 mmol, 2.50 equiv) and formic acid (0.760 mL, 20.0 mmol, 2.00 equiv) in methanol (10 mL) and water (20 mL) was stirred at room temperature for 24 h. The resulting precipitate was filtered and washed well with diethyl ether. After drying under vacuum, the product **253** was obtained as a white solid (2.61 g, 7.50 mmol, 75%); mp 169-170 °C (Lit^{79a} 170 °C); ¹H NMR (CDCl_3 , 300 MHz) δ 1.22 (s, 9H, 3CH₃), 5.75 (d, 1H, *J* = 10.0 Hz), 5.90 (d, 1H, *J* = 10.0 Hz), 7.34-7.47 (m, 5H, Ar-H), 7.47-7.56 (m, 2H, Ar-H), 7.58-7.68 (m, 1H, Ar-H), 7.90 (d, 2H, *J* = 7.2 Hz, Ar-H); ¹³C NMR (CDCl_3 , 125 MHz) δ 27.96, 73.90, 81.16, 128.72, 128.90, 129.00, 129.44, 129.80, 129.91, 133.89, 136.93, 153.46.

Preparation of *N*-Boc imine 18: A 100 mL round bottom flask containing potassium carbonate (4.14 g, 30.0 mmol, 6.00 equiv) and sodium sulfate (4.97 g, 35.0 mmol, 7.00 equiv) was flame dried. After the flask was cooled to room

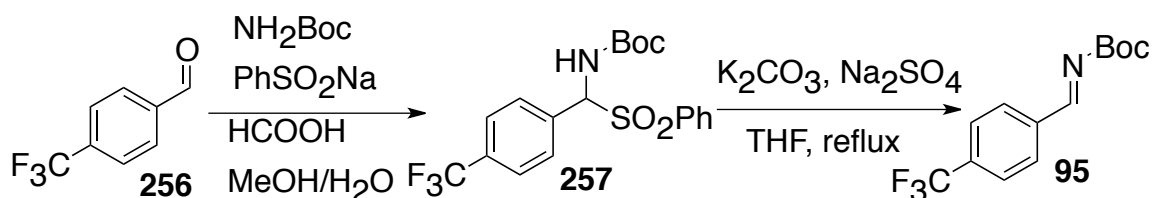
temperature under N₂, sulfonyl amine **253** (1.74 g, 5.00 mmol, 1.00 equiv) was added along with dry THF (20 mL). The mixture was refluxed under N₂ for 18 h. It was then allowed to cool to room temperature, filtered through Celite, and the filtrate was concentrated to give the imine **18** as a colorless oil (1.03 g, 5.00 mmol, 100%) which was used without further purification for the aziridination reaction; ¹H NMR (CDCl₃, 300 MHz) δ 1.58 (s, 9H, 3CH₃), 7.38-7.60 (m, 3H, Ar-H), 7.84-7.94 (m, 2H, Ar-H), 8.85 (s, 1H, CHN); ¹³C NMR (CDCl₃, 125 MHz) δ 27.93, 82.28, 128.85, 130.19, 133.49, 134.10, 162.64, 169.64. The purity of imine **18** by weight was calculated to be ca. 90% based on the ¹H NMR spectrum which revealed the presence of imine **18**, aldehyde **215** and *tert*-butyl carbamate in a ratio of 1:0.09:0.09.



Preparation of α-sulfonyl amine 255: The general procedure was followed with 1.51 g *p*-nitrobenzaldehyde **254** (10.0 mmol) and a reaction time of 4 days to provide the product **255** as a white solid (1.045 g, 2.670 mmol) in 53% yield; mp 172-174 °C; ¹H NMR (CDCl₃, 600 MHz) δ 1.20 (s, 9H, 3CH₃), 5.84 (d, 1H, *J* = 10.2 Hz), 6.04 (d, 1H, *J* = 10.8 Hz), 7.56 (t, 2H, *J* = 8.4 Hz), 7.60-7.70 (m, 3H, Ar-H), 7.92 (d, 2H, *J* = 7.2 Hz, Ar-H), 8.24 (d, 2H, *J* = 7.2 Hz, Ar-H); ¹³C NMR

(CDCl₃, 150 MHz) δ 27.94, 73.03, 81.83, 123.71, 129.32, 129.43, 129.99, 134.48, 136.28, 136.89, 148.67, 153.33.

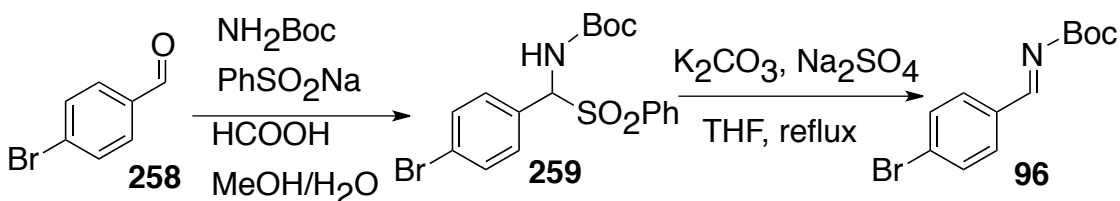
Preparation N-Boc imine 94: To a solution of sulfonyl amine **255** (392 mg, 1.00 mmol, 1.00 equiv) in CH₂Cl₂ (16 mL) was added aq. 1.4 M K₂CO₃ solution (16 mL). The resulting mixture was stirred at rt vigorously for 5 hours. The aqueous layer was separated and extracted with CH₂Cl₂ (2 $\times$ 20 mL). The combined organic extracts were dried (Na₂SO₄), filtered and concentrated to give imine **94** as a white solid (252 mg, 1.00 mmol, 100%). ¹H NMR (CDCl₃, 600 MHz) δ 1.58 (s, 9H, 3CH₃), 8.06 (d, 2H, *J* = 9.5 Hz, Ar-H), 8.30 (d, 2H, *J* = 9.5 Hz, Ar-H), 8.85 (s, 1H, CHN); ¹³C NMR (CDCl₃, 150 MHz) δ 27.88, 83.24, 124.01, 130.64, 139.34, 150.50, 161.74, 166.23.



Preparation of α -sulfonyl amine 257: The general procedure was followed with 1.74 g *p*-trifluoromethylbenzaldehyde **256** (1.50 mL, 10.0 mmol) and a reaction time of 48 hours to provide the product **257** as a white solid (1.17 g, 2.82 mmol) in 56% yield; mp 178-179 °C; ¹H NMR (CDCl₃, 300 MHz) δ 1.20 (s, 9H, 3CH₃), 5.84 (d, 1H, *J* = 8.7 Hz), 5.98 (d, 1H, *J* = 10.5 Hz), 7.50-7.70 (m, 7H, Ar-H), 7.92 (d, 2H, *J* = 7.5 Hz, Ar-H); ¹³C NMR (CDCl₃, 150 MHz) δ 27.74, 73.03, 81.38,

123.50 ($J = 271.2$ Hz), 125.46 ($J = 4.05$ Hz), 129.00, 129.16, 129.24, 131.71 ($J = 33.2$ Hz), 133.66, 134.06, 136.32, 153.15.

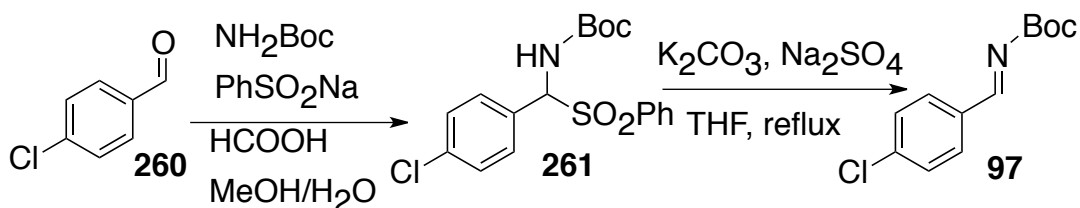
Preparation *N*-Boc imine **95:** The general procedure was followed with sulfonyl amine **257** (830 mg, 2.00 mmol, 1.00 equiv) and a refluxing time of 20 hours. The product **95** was obtained as a white solid (542 mg, 1.98 mmol, 99%). ^1H NMR (CDCl_3 , 300 MHz) δ 1.58 (s, 9H, 3CH₃), 7.77 (d, 2H, $J = 9.5$ Hz, Ar-H), 8.06 (d, 2H, $J = 7.8$ Hz, Ar-H), 8.90 (s, 1H, CHN); ^{13}C NMR (CDCl_3 , 150 MHz) δ 27.89, 82.89, 123.55 ($J = 272.8$ Hz), 125.84 ($J = 4.3$ Hz), 130.19, 134.59 ($J = 29.8$ Hz), 137.14, 162.09, 167.50. The purity of imine **95** by weight was calculated to be ca. 96% based on the ^1H NMR spectrum that revealed the presence of imine **95**, aldehyde **256** and *tert*-butyl carbamate in a ratio of 1:0.04:0.04.



Preparation of α -sulfonyl amine **259:** A mixture of *p*-bromobenzaldehyde **258** (1.11 g, 6.00 mmol, 1.20 equiv), *tert*-butyl carbamate (0.585 g, 5.00 mmol, 1.00 equiv), benzenesulfinic acid sodium salt (2.05 g, 12.5 mmol, 2.50 equiv) and formic acid (0.38 mL, 10.0 mmol, 2.00 equiv) in methanol (5 mL) and water (10 mL) was stirred at room temperature for 3 days. The resulting precipitate was filtered and washed well with diethyl ether. After drying under vacuum, the product **259** was obtained as a white solid (715 mg, 1.70 mmol, 34%); mp 172-173 °C; ^1H NMR (CDCl_3 , 500 MHz) δ 1.20 (s, 9H, 3CH₃), 5.87 (dd, 2H, $J = 10.0$

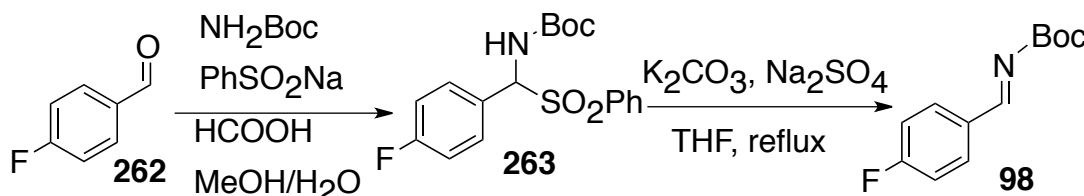
Hz), 7.30 (d, 2H, $J = 8.0$ Hz, Ar-H), 7.52 (m, 4H, Ar-H), 7.64 (t, 1H, $J = 7.0$ Hz, Ar-H), 7.89 (d, 2H, $J = 7.5$ Hz, Ar-H); ^{13}C NMR (CDCl_3 , 150 MHz) δ 27.95, 73.28, 81.40, 124.32, 128.93, 129.11, 129.43, 130.46, 131.91, 134.10, 136.62, 153.42.

Preparation of *N*-Boc imine **96:** Following the general procedure, sulfonyl amine **259** (852 mg, 2.00 mmol, 1.00 equiv) was refluxed with K_2CO_3 and Na_2SO_4 for 24 hours. The product **96** was obtained as a white solid (590 mg, 2.08 mmol, 104%). ^1H NMR (CDCl_3 , 500 MHz) δ 1.58 (s, 9H, 3CH_3), 7.56-7.62 (m, 2H, Ar-H), 7.74-7.78 (m, 2H, Ar-H), 8.80 (s, 1H, CHN). The purity of imine **96** by weight was calculated to be ca. 83% based on the ^1H NMR spectrum that revealed the presence of imine **96** and sulfonyl amine **259** in a ratio of 1:0.14.



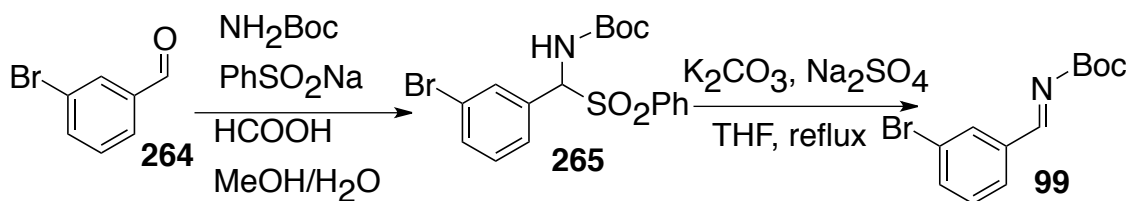
Preparation of α -sulfonyl amine **261:** The general procedure was followed with 1.05 g *p*-chlorobenzaldehyde **260** (10.0 mmol) and a reaction time of 48 hours to provide the product **71** as a white solid (1.15 g, 3.02 mmol) in 61% yield; mp 172-173 $^\circ\text{C}$. ^1H NMR (CDCl_3 , 500 MHz) δ 1.10 (s, 9H, 3CH_3), 5.70 (d, 1H, $J = 11.5$ Hz), 5.88 (d, 1H, $J = 11.0$ Hz), 7.37 (s, 4H, Ar-H), 7.53 (t, 2H, $J = 7.5$ Hz, Ar-H), 7.64 (t, 1H, $J = 7.5$ Hz, Ar-H), 7.89 (d, 2H, $J = 8.0$ Hz, Ar-H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 28.23, 73.43, 81.70, 128.69, 129.26, 129.40, 129.70, 130.44, 134.37, 136.40, 136.92, 153.62.

Preparation N-Boc imine 97: The general procedure was followed with sulfonyl amine **261** (762 mg, 2.00 mmol, 1.00 equiv) and a refluxing time of 24 hours. The product **97** was obtained as a white solid (490 mg, 2.05 mmol, 103%). ^1H NMR (CDCl_3 , 600 MHz) δ 1.58 (s, 9H, 3CH₃), 7.40-7.44 (m, 2H, Ar-H), 7.80-7.85 (m, 2H, Ar-H), 8.80 (s, 1H, CHN); ^{13}C NMR (CDCl_3 , 150 MHz) δ 27.89, 82.50, 129.27, 131.28, 132.54, 139.79, 162.33, 168.22. The purity of imine **97** by weight was calculated to be ca. 91% based on the ^1H NMR spectrum that revealed the presence of imine **97** and sulfonyl amine **261** in a ratio of 1:0.06.



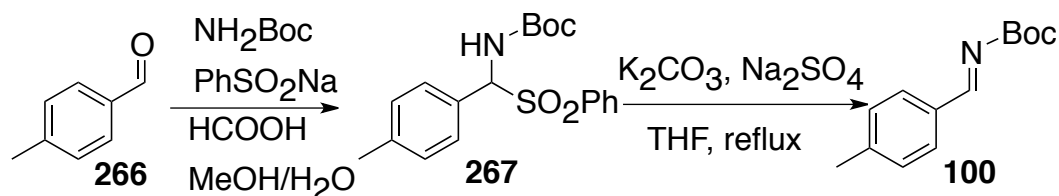
Preparation of α -sulfonyl amine 263: The general procedure was followed with 1.24 g *p*-fluorobenzaldehyde **262** (10.0 mmol) and a reaction time of 48 hours to provide the product **263** as a white solid (1.10 g, 3.01 mmol) in 60% yield; mp 168-170 °C; ^1H NMR (CDCl_3 , 500 MHz) δ 1.20 (s, 9H, 3CH₃), 5.72 (d, 1H, J = 10.0 Hz), 5.89 (d, 1H, J = 10.0 Hz), 7.04-7.12 (m, 2H, Ar-H), 7.42 (dd, 2H, J = 8.0, 5.0 Hz, Ar-H), 7.53 (t, 2H, J = 8.0 Hz, Ar-H), 7.63 (t, 1H, J = 7.0 Hz, Ar-H), 7.89 (d, 2H, J = 8.0 Hz, Ar-H); ^{13}C NMR (CDCl_3 , 150 MHz) δ 27.97, 73.11, 81.36, 115.87 (J = 21.7 Hz), 125.84 (J = 2.8 Hz), 129.10, 129.43, 130.81 (J = 8.0 Hz), 134.05, 136.71, 153.41, 163.61 (J = 248.4 Hz),

Preparation N-Boc imine 98: The general procedure was followed with sulfonyl amine **263** (730 mg, 2.00 mmol, 1.00 equiv) and a refluxing time of 18 hours. The product **98** was obtained as a white solid (450 mg, 2.02 mmol, 101%); ^1H NMR (CDCl_3 , 500 MHz) δ 1.60 (s, 9H, 3CH_3), 7.14 (t, 2H, $J = 8.5$ Hz, Ar-H), 7.88-7.96 (m, 2H, Ar-H), 8.83 (s, 1H, CHN); ^{13}C NMR (CDCl_3 , 150 MHz) δ 27.90, 82.36, 116.21 ($J = 22.1$ Hz), 130.43 ($J = 2.6$ Hz), 132.49 ($J = 9.2$ Hz), 162.41, 166.03 ($J = 254.3$ Hz), 168.28. The purity of imine **98** by weight was calculated to be ca. 95% based on the ^1H NMR spectrum that revealed the presence of imine **98** and sulfonyl amine **263** in a ratio of 1:0.03.



Preparation of α -sulfonyl amine 265: The general procedure was followed with 1.85 g *m*-bromobenzaldehyde **264** (10.0 mmol) and a reaction time of 36 hours to provide the product **265** as a white solid (1.91 g, 4.48 mmol) in 93% yield; mp 172-174 $^\circ\text{C}$; ^1H NMR (CDCl_3 , 500 MHz) δ 1.20 (s, 9H, 3CH_3), 5.75 (d, 1H, $J = 10.0$ Hz), 5.88 (d, 1H, $J = 10.0$ Hz), 7.26 (t, 1H, $J = 7.5$ Hz, Ar-H), 7.38 (d, 1H, $J = 7.5$ Hz, Ar-H), 7.48-7.58 (m, 4H, Ar-H), 7.64 (t, 1H, $J = 7.5$ Hz, Ar-H), 7.89 (d, 2H, $J = 8.0$ Hz, Ar-H); ^{13}C NMR (CDCl_3 , 150 MHz) δ 28.23, 73.42, 81.74, 123.01, 127.96, 129.41, 129.71, 130.44, 132.04, 132.43, 133.20, 134.42, 136.87, 153.61.

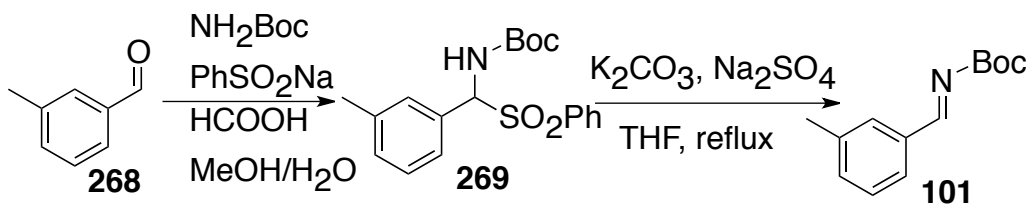
Preparation of *N*-Boc imine **99:** The general procedure was followed with sulfonyl amine **265** (852 mg, 2.00 mmol, 1.00 equiv) and a refluxing time of 16 hours. The product **99** was obtained as a colorless oil (540 mg, 1.90 mmol) in 95% yield. ^1H NMR (CDCl_3 , 500 MHz) δ 1.56 (s, 9H, 3CH₃), 7.33 (t, 1H, J = 8.0 Hz, Ar-H), 7.64-7.68 (m, 1H, Ar-H), 7.76-7.80 (m, 1H, Ar-H), 8.08-8.12 (m, 1H, Ar-H), 8.76 (s, 1H, CHN); ^{13}C NMR (CDCl_3 , 125 MHz) δ 27.90, 82.67, 123.14, 129.02, 130.36, 132.30, 136.01, 136.23, 162.13, 167.81. The purity of imine **99** by weight was calculated to be ca. 92% based on the ^1H NMR spectrum that revealed the presence of imine **99**, aldehyde **264** and *tert*-butyl carbamate in a ratio of 1:0.08:0.08.



Preparation of α -sulfonyl amine **267:** The general procedure was followed with 1.44 g *p*-toluadehyde **266** (12.0 mmol) and a reaction time of 36 hours to provide the product **267** as a white solid (1.63 g, 4.50 mmol) in 75% yield; mp 167-168 °C; ^1H NMR (CDCl_3 , 300 MHz) δ 1.20 (s, 9H, 3CH₃), 2.36 (s, 3H, CH₃), 5.73 (d, 1H, J = 10.0 Hz), 5.87 (d, 1H, J = 10.0 Hz), 7.20 (d, 2H, J = 8.0 Hz, Ar-H), 7.31 (d, 2H, J = 8.0 Hz, Ar-H), 7.46-7.54 (m, 2H, Ar-H), 7.64 (t, 1H, J = 7.5 Hz, Ar-H), 7.89 (d, 2H, J = 8.0 Hz, Ar-H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 21.52, 21.53,

28.26, 74.00, 81.38, 127.06, 129.02, 129.26, 129.73, 134.10, 137.34, 140.25, 153.69 (1 sp^2 C not located).

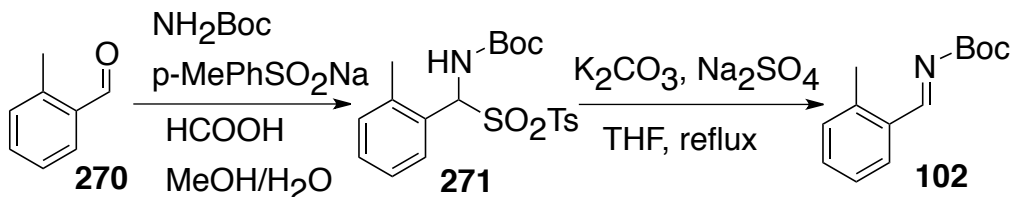
Preparation of *N*-Boc imine **100:** The general procedure was followed with sulfonyl amine **267** (722 mg, 2.0 mmol, 1.0 equiv) and a refluxing time of 18 hours. The product **100** was obtained as colorless oil (442 mg, 2.02 mmol, 101%); ^1H NMR (CDCl_3 , 500 MHz) δ 1.60 (s, 9H, 3CH₃), 2.40 (s, 3H, CH₃), 7.26 (d, 2H, J = 8.0 Hz, Ar-H), 7.80 (d, 2H, J = 8.0 Hz, Ar-H), 8.86 (s, 1H, CHN); ^{13}C NMR (CDCl_3 , 125 MHz) δ 21.79, 27.91, 82.04, 129.62, 130.33, 131.51, 144.53, 162.78, 169.90. Purity of imine **100** by weight was calculated to be ca. 94% based on the ^1H NMR spectrum that revealed the presence of imine **100**, aldehyde **266** and *tert*-butyl carbamate in a ratio of 1:0.06:0.06.



Preparation of α -sulfonyl amine **269:** The general procedure was followed with 1.20 g *m*-tolaldehyde **268** (10.0 mmol) and a reaction time of 24 hours to provide the product **269** as a white solid (1.51 g, 4.17 mmol) in 83% yield; mp 169-170 $^\circ\text{C}$; ^1H NMR (CDCl_3 , 500 MHz) δ 1.22 (s, 9H, 3CH₃), 2.38 (s, 3H, CH₃), 5.73 (d, 1H, J = 10.0 Hz), 5.88 (d, 1H, J = 10.0 Hz), 7.20-7.34 (m, 4H, Ar-H), 7.53 (t, 2H, J = 8.0 Hz, Ar-H), 7.64 (t, 1H, J = 7.0 Hz, Ar-H), 7.92 (d, 2H, J = 8.0 Hz, Ar-H);

^{13}C NMR (CDCl_3 , 125 MHz) δ 21.37, 28.00, 73.89, 81.14, 126.00, 128.64, 129.00, 129.45, 129.54, 129.75, 130.65, 133.86, 137.05, 138.57, 153.41.

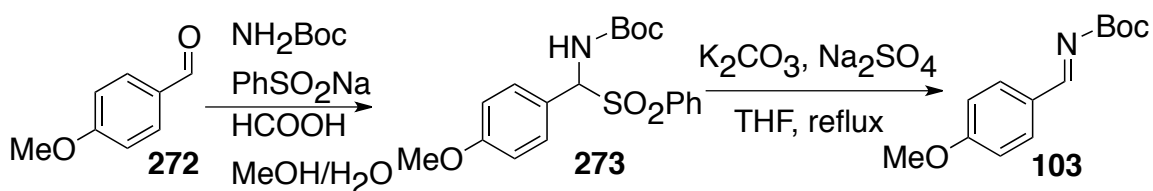
Preparation of *N*-Boc imine **101:** The general procedure was followed with sulfonyl amine **269** (722 mg, 2.00 mmol, 1.00 equiv) and a refluxing time of 24 hours. The product **101** was obtained as a colorless oil (424 mg, 1.96 mmol) in 98% yield; ^1H NMR (CDCl_3 , 300 MHz) δ 1.57 (s, 9H, 3CH₃), 2.37 (s, 3H, CH₃), 7.30-7.38 (m, 2H, Ar-H), 7.60-7.70 (m, 1H, Ar-H), 7.76 (s, 1H, Ar-H), 8.84 (s, 1H, CHN); ^{13}C NMR (CDCl_3 , 150 MHz) δ 21.13, 27.92, 82.18, 127.99, 128.71, 130.17, 134.01, 134.40, 138.71, 162.65, 170.05. The purity of imine **101** by weight was calculated to be ca. 93% based on the ^1H NMR spectrum that revealed the presence of imine **101**, aldehyde **268** and *tert*-butyl carbamate in a ratio of 1:0.06:0.06.



Preparation of α -sulfonyl amine **271:** The general procedure was followed with 1.20 g *o*-toluadehyde **270** (10.0 mmol) and toluene sulfinic acid sodium salt (2.20 g, 12.5 mmol, 2.5 equiv) and a reaction time of 24 hours to provide the product **271** as a white solid (980 mg, 2.71 mmol) in 54% yield; mp 152-154 °C; ^1H NMR (CDCl_3 , 300 MHz) δ 1.30 (s, 9H, 3CH₃), 2.46 (s, 3H, CH₃), 2.47 (s, 3H, CH₃), 5.74 (d, 1H, J = 10.8 Hz), 6.24 (d, 1H, J = 10.5 Hz), 7.22-7.50 (m, 6H, Ar-H), 7.82

(d, 2H, $J = 8.4$ Hz, Ar-H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 19.70, 21.60, 27.99, 69.72, 81.06, 126.45, 127.52, 129.35, 129.62, 129.70, 130.81, 134.35, 138.14, 144.95, 153.57 (1 sp^2 C not located).

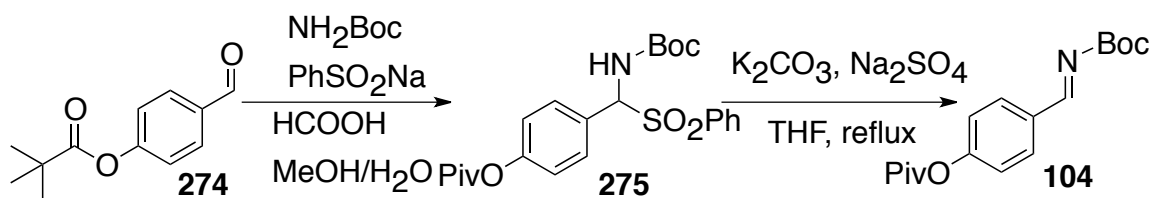
Preparation of *N*-Boc imine **102:** The general procedure was followed with sulfonyl amine **271** (750 mg, 2.00 mmol, 1.00 equiv) and a refluxing time of 24 hours. The product **102** was obtained as a colorless oil (440 mg, 2.00 mmol, 100%). ^1H NMR (CDCl_3 , 500 MHz) δ 1.57 (s, 9H, 3CH₃), 2.57 (s, 3H, CH₃), 7.16-7.30 (m, 2H, Ar-H), 7.36-7.44 (m, 1H, Ar-H), 8.06 (dd, 1H, $J = 7.5$, 1.0 Hz, Ar-H), 9.20 (s, 1H, CHN); ^{13}C NMR (CDCl_3 , 150 MHz) δ 19.23, 27.96, 82.17, 126.37, 128.74, 131.16, 132.04, 133.17, 140.84, 163.01, 167.99. The purity of imine **102** by weight was calculated to be ca. 90% based on the ^1H NMR spectrum that revealed the presence of imine **102**, sulfonyl amine **271**, aldehyde **270** and *tert*-butyl carbamate in a ratio of 1:0.05:0.03:0.03.



Preparation of α -sulfonyl amine **273:** The general procedure was followed with 1.36 g *p*-methoxybenzaldehyde **272** (10.0 mmol, 2.00 equiv) and a reaction time of 36 hours to provide the product **273** as a white solid (1.056 g, 2.801 mmol) in 56% yield; mp 155-156 °C. ^1H NMR (CDCl_3 , 500 MHz) δ 1.20 (s, 9H, 3CH₃), 3.80 (s, 3H, CH₃), 5.67 (d, 1H, $J = 10.5$ Hz), 5.85 (d, 1H, $J = 11.0$ Hz), 6.84-6.96

(m, 2H), 7.34 (d, 2H, $J = 8.5$ Hz), 7.62 (t, 2H, $J = 8.0$ Hz), 7.62 (t, 1H, $J = 7.5$ Hz), 7.89 (d, 2H, $J = 7.5$ Hz, Ar-H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 27.99, 55.36, 73.43, 81.15, 114.24, 121.63, 129.01, 129.42, 130.18, 133.84, 136.99, 160.80 (1 sp^2 C not located).

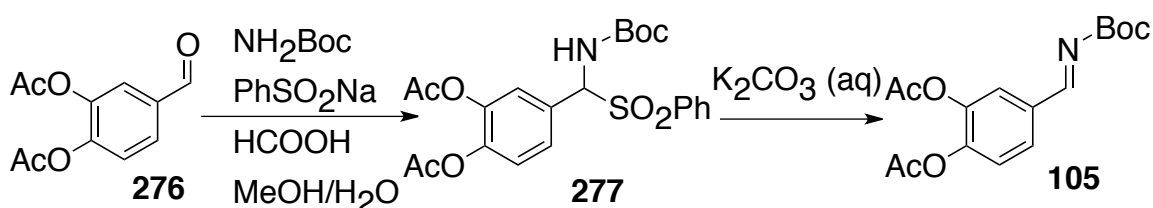
Preparation *N*-Boc imine **103:** The general procedure was followed with sulfonyl amine **273** (754 mg, 2.00 mmol, 1.00 equiv) and a refluxing time of 18 hours. The product **103** was obtained as a white solid (469 mg, 1.00 mmol, 100%). ^1H NMR (CDCl_3 , 300 MHz) δ 1.56 (s, 9H, 3CH₃), 3.86 (s, 3H, CH₃), 6.94 (d, 2H, $J = 8.7$ Hz, Ar-H), 7.86 (d, 2H, $J = 9.0$ Hz, Ar-H), 8.86 (s, 1H, CHN); No ^{13}C NMR was taken. The purity of imine **103** by weight was calculated to be ca. 87% based on the ^1H NMR spectrum that revealed the presence of imine **103**, aldehyde **272** and *tert*-butyl carbamate in a ratio of 1:0.13:0.13.



Preparation of α -sulfonyl amine **275:** The general procedure was followed with 2.47 g *p*-pivaloylbenzaldehyde **274**^{80a} (12.0 mmol) and a reaction time of 22 hours to provide the product **275** as a white solid (1.36 g, 3.03 mmol) in 51% yield; mp 175-176 °C. ^1H NMR (CDCl_3 , 600 MHz) δ 1.25 (s, 9H, 3CH₃), 1.34 (s, 9H, 3CH₃), 5.64 (d, 1H, $J = 10.2$ Hz), 5.89 (d, 1H, $J = 10.2$ Hz), 7.10 (d, 2H, $J = 8.4$ Hz, Ar-H), 7.42 (d, 2H, $J = 8.4$ Hz, Ar-H), 7.52 (t, 2H, $J = 7.8$ Hz, Ar-H), 7.63

(t, 1H, J = 6.6 Hz, Ar-H), 7.88 (d, 2H, J = 7.2 Hz, Ar-H); ^{13}C NMR (CDCl_3 , 150 MHz) δ 27.07, 27.98, 39.12, 73.34, 81.23, 121.92, 127.26, 129.06, 129.45, 130.01, 133.98, 136.75, 152.30, 153.41, 176.61.

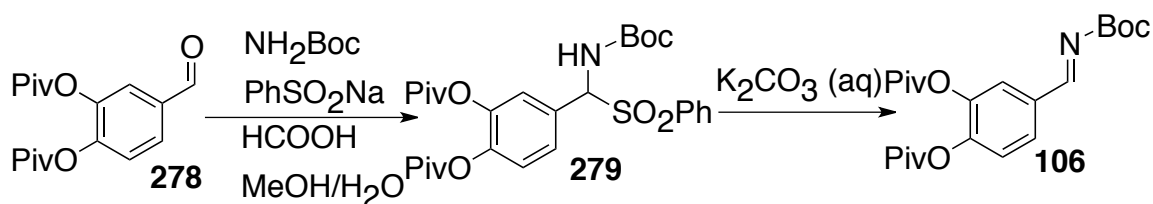
Preparation *N*-Boc imine **104:** The general procedure was followed with sulfonyl amine **275** (762 mg, 2.00 mmol, 1.00 equiv) and a refluxing time of 24 hours. The product **104** was obtained as a white solid (490 mg, 2.05 mmol, 103%). ^1H NMR (CDCl_3 , 300 MHz) δ 1.28 (s, 9H, 3CH₃), 1.48 (s, 9H, 3CH₃), 7.16 (d, 2H, J = 8.4 Hz, Ar-H), 7.98 (d, 2H, J = 8.4 Hz, Ar-H), 8.91 (s, 1H, CHN); ^{13}C NMR (CDCl_3 , 150 MHz) δ 26.84, 27.70, 39.03, 82.13, 121.93, 131.25, 131.32, 155.04, 162.26, 168.52, 176.24. The purity of imine **104** by weight was calculated to be ca. 92% based on the ^1H NMR spectrum that revealed the presence of imine **104**, aldehyde **274** and *tert*-butyl carbamate in a ratio of 1:0.10:0.03.



Preparation of α -sulfonyl amine **277:** The general procedure was followed with 1.16 g 3,4-diacetoxybenzaldehyde **276**^{80b} (4.80 mmol, 1.20 equiv) and a reaction time of 24 hours to provide the product **277** as a white solid (1.04 g, 2.24 mmol) in 56% yield; mp 169-170 °C. ^1H NMR (CDCl_3 , 300 MHz) δ 1.24 (s, 9H, 3CH₃), 2.73, 2.74 (2s, 6H, 2CH₃), 5.64 (d, 1H, J = 10.8 Hz), 5.89 (d, 1H, J = 10.8 Hz), 7.18-7.24 (m, 1H), 7.26-7.34 (m, 2H), 7.46-7.68 (m, 3H), 7.86 (d, 2H, J = 6.6

Hz, Ar-H); ^{13}C NMR (CDCl_3 , 150 MHz) δ 20.54, 20.61, 27.95, 73.02, 81.38, 123.76, 124.00, 127.19, 128.73, 129.10, 129.46, 134.06, 136.50, 142.20, 143.30, 153.33, 167.76, 167.87.

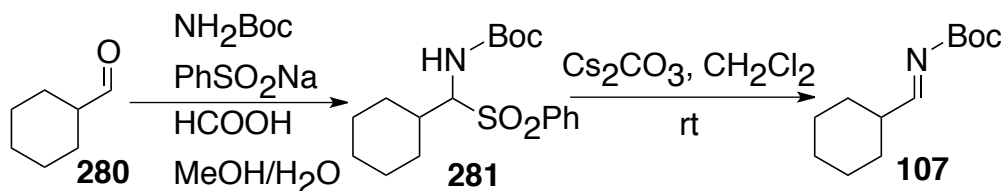
Preparation N-Boc imine 105: To a solution of sulfonyl amine **277** (463 mg, 1.00 mmol, 1.00 equiv) in CH_2Cl_2 (16 mL) was added aq 1.4 M K_2CO_3 solution (16 mL). The resulting mixture was stirred at rt vigorously for 4 hours. The aqueous layer was separated and extracted with CH_2Cl_2 (2×20 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated to give the product **105** as a white solid (330 mg, 1.03 mmol, 103%). ^1H NMR (CDCl_3 , 300 MHz) δ 1.55 (s, 9H, 3 CH_3), 2.27, 2.28 (2s, 6H, 2 CH_3), 7.29 (d, 1H, J = 8.4 Hz, Ar-H), 7.45 (dd, 2H, J = 8.4, 2.1 Hz, Ar-H), 8.78 (s, 1H, CHN); ^{13}C NMR (CDCl_3 , 150 MHz) δ 20.46, 20.61, 27.84, 82.45, 123.93, 124.53, 128.72, 132.65, 142.56, 146.17, 162.08, 167.49, 167.56, 167.80.



Preparation of α -sulfonyl amine 279: The general procedure was followed with 2.34 g 3,4-bis[(pivaloyl)oxy]benzaldehyde **278**^{80c} (7.66 mmol, 1.50 equiv) and a reaction time of 24 hours to provide the product **279** as a white solid (1.40 g, 2.56 mmol) in 52% yield; mp 104-105 °C. ^1H NMR (CDCl_3 , 600 MHz) δ 1.25 (s, 9H,

3CH₃), 1.32, 1.33 (2s, 18H, 6CH₃), 5.67 (d, 1H, *J* = 12.0 Hz), 5.88 (d, 1H, *J* = 13.2 Hz), 7.15 (d, 1H, *J* = 8.4 Hz), 7.20-7.26 (m, 2H), 7.52 (t, 2H, *J* = 7.8 Hz), 7.62 (t, 1H, *J* = 7.2 Hz), 7.86 (d, 2H, *J* = 7.8 Hz); ¹³C NMR (CDCl₃, 150 MHz) δ 27.42, 27.47, 28.24, 39.40, 39.45, 73.40, 81.67, 123.92, 124.15, 127.12, 128.55, 129.33, 129.73, 134.26, 136.79, 142.92, 144.18, 153.62, 175.65, 175.71.

Preparation N-Boc imine 106: To a solution of sulfonyl amine **279** (547 mg, 1.00 mmol, 1.00 equiv) in CH₂Cl₂ (16 mL) was added *aq* 1.4 M K₂CO₃ solution (16 mL). The resulting mixture was stirred at rt vigorously for 4 hours. The aqueous layer was separated and extracted with CH₂Cl₂ (2 × 20 mL). The combined organic extracts were dried (Na₂SO₄), filtered and concentrated to give the product **106** as a semi-solid (410 mg, 1.01 mmol, 101%). ¹H NMR (CDCl₃, 300 MHz) δ 1.33 (s, 18H, 6CH₃), 1.56 (s, 9H, 3CH₃), 7.26 (d, 1H, *J* = 8.4 Hz), 7.70 (dd, 1H, *J* = 8.4, 2.1 Hz), 7.75 (d, 1H, *J* = 2.1 Hz), 8.81 (s, 1H, CHN); ¹³C NMR (CDCl₃, 150 MHz) δ 27.39, 27.46, 28.13, 39.40, 39.54, 82.76, 124.17, 124.55, 129.21, 132.56, 143.38, 147.23, 162.40, 168.30, 175.62, 175.78.



Preparation of α-sulfonyl amine 281⁸¹: *tert*-butyl carbamate (585 mg, 5.00 mmol, 1.00 equiv) was dissolved in THF (5 mL) and H₂O (5 mL). Then benzenesulfinic

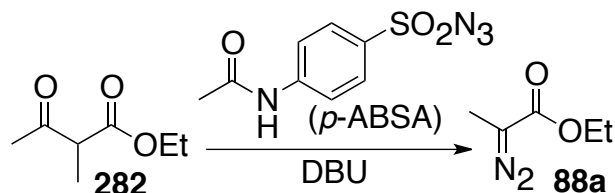
acid sodium salt (821 mg, 5.00 mmol, 1.00 equiv) and cyclohexanecarbaldehyde **280** (606 mg, 0.660 mL, 5.40 mmol, 1.08 equiv) were added, followed by the addition of formic acid (1.5 mL). The resulting mixture was stirred at rt overnight. The precipitate was filtered and washed well with Et₂O. The product **281** was obtained as a white solid (706 mg, 0.400 mmol) in 40% yield; mp 151-152 °C. ¹H NMR (CDCl₃, 300 MHz) δ 1.00-1.44 (m, 14H), 1.62-1.80 (m, 4H), 2.12 (d, 1H, CH), 2.40-2.48 (m, 1H, CH), 4.70 (dd, 1H, *J* = 10.4, 3.6 Hz), 5.12 (d, 1H, *J* = 10.6 Hz), 7.46-7.66 (m, 3H, Ar-H), 7.84-7.92 (m, 2H, Ar-H); ¹³C NMR (CDCl₃, 125 MHz) δ 25.8, 26.0, 26.2, 27.5, 28.2, 30.8, 36.5, 74.5, 80.9, 129.1, 129.2, 133.8, 138.3, 154.2.

Preparation of N-Boc imine 107^{79e}: A 100 mL round bottom flask containing Cs₂CO₃ (2.45 g, 7.50 mmol, 5.00 equiv) was flame-dried and cooled to rt under N₂. Then sulfonyl amine **281** (530 mg, 1.50 mmol, 1.00 equiv) and dry CH₂Cl₂ (15 mL) was added. The resulting mixture was stirred at rt for 11 hours. After it was cooled to 0 °C, hexane (precooled to 0 °C, 15 mL) was added. Then the mixture was washed with water (2 × 5 mL), brine (5 mL) and dried (Na₂SO₄). The solvent was evaporated (water bath temperature was kept under 20 °C) to give imine **107** as a colorless oil (318 mg, 1.50 mmol, 100%). ¹H NMR (CDCl₃, 500 MHz) δ 1.10-1.36 (m, 5H), 1.50 (s, 9H, CH₃), 1.60-1.76 (m, 5H), 2.22-2.34 (m,

1H, CH), 8.14 (brs, 1H, CHN). The ^1H NMR data was identical with those reported in the literature.^{79e}

7.2.2 Preparation of the diazo compounds

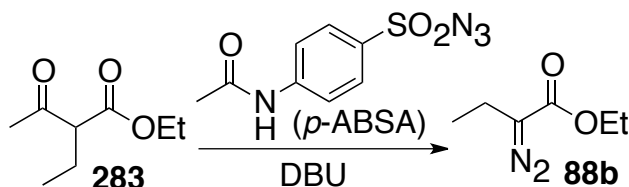
Preparation of ethyl-2-diazopropionate 88a



Diazo compound **88a** was prepared following a modification of a procedure for closely related compounds⁸². To a solution of ethyl 2-methylacetoacetate **282** (0.29 g, 0.29 mL, 2.0 mmol, 1.0 equiv) and *p*-acetamidobenzenesulfonyl azide (*p*-ABSA) (0.72 g, 3.0 mmol, 1.5 equiv) in dry CH_3CN (10 mL) was added DBU (0.46 g, 0.45 mL, 3.0 mmol, 1.5 equiv) dropwise at 0 °C. Then the mixture was stirred at 0 °C for 1 hour and at rt for another hour. To the mixture was added water (5 mL) and EtOAc (10 mL). And the aqueous layer was separated and extracted with EtOAc (2 × 10 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated. The yellow crude product was purified by column chromatography (silica gel, 25 × 200 mm, hexane:EtOAc 15:1) to give the product **88a** as a yellow liquid (volatile) (0.12 g, 0.94 mmol, 47%); R_f = 0.33 (hexane:EtOAc 9:1); ^1H NMR (CDCl_3 , 500 MHz) δ 1.24 (t, 3H, J = 7.0 Hz, CH_3), 1.92 (s, 3H, CH_3), 4.18 (q, 2H, J = 7.0 Hz, CH_2); ^{13}C NMR (CDCl_3 , 150 MHz) δ

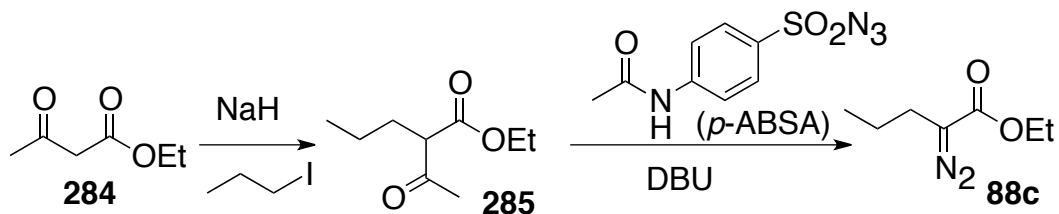
8.38, 14.50, 60.76 (2 sp^2 C not located). The ^1H NMR spectra data of **88a** are identical with those reported previously.⁸³

*Preparation of ethyl-2-diazobutanoate **88b***



Diazo compound **88b** was prepared following the above procedure for **88a** starting from ethyl 2-ethylacetoacetate **283** (0.35 g, 0.36 mL, 2.0 mmol). The product **88b** was obtained as a yellow liquid (234 mg, 1.65 mmol) in 82% yield; $R_f = 0.50$ (hexane:EtOAc 4:1); ^1H NMR (CDCl_3 , 500 MHz) δ 1.12 (t, 3H, $J = 7.5$ Hz, CH_3), 1.25 (t, 3H, $J = 7.0$ Hz, CH_3), 2.32 (q, 2H, $J = 7.5$ Hz, CH_2), 4.20 (q, 2H, $J = 7.0$ Hz, CH_2); ^{13}C NMR (CDCl_3 , 150 MHz) δ 12.17, 14.77, 16.79, 60.92, 165.82 (1 sp^2 C not located); IR 2984(m), 2085(s), 1732(s), 1695(s), 1142(s) cm^{-1} ; HRMS (ESI $^+$) calcd for $\text{C}_6\text{H}_{10}\text{N}_2\text{O}_2\text{Na}$, m/z 165.0640 ($[\text{M}+\text{Na}]^+$), meas 165.0642.

*Preparation of ethyl-2-diazopentanoate **88c***

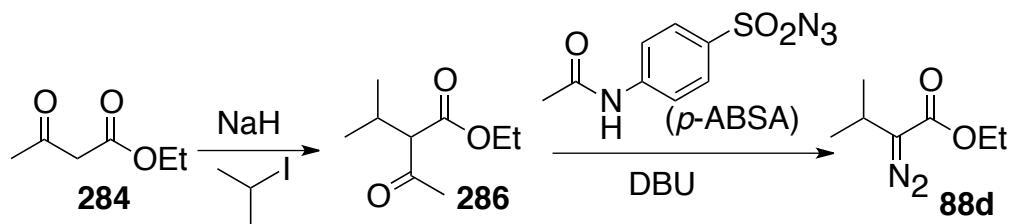


*Synthesis of β -ketoester **285**:* To a suspension of NaH (60% in mineral oil, 0.20 g, 5.0 mmol, 1.0 equiv) in dry THF (5 mL) was added ethyl acetoacetate **284** (0.65 g, 0.64 mL, 5.0 mmol, 1.0 equiv) dropwise. Then the resulting mixture was

stirred at rt for 30 min during which time the colorless suspension became a clear yellow solution. *n*-PrI (0.85 g, 0.50 mL, 5.0 mmol, 1.0 equiv) was added, and the resulting mixture was refluxed for 6 hours. After cooling to rt, aq sat NH₄Cl (5 mL) was added. The aqueous layer was separated and extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were dried (Na₂SO₄), filtered and concentrated. The crude product was purified by column chromatography (silica gel, 18 × 200 mm, hexane:EtOAc 5:1), giving the product **285** as a colorless liquid (730 mg, 4.22 mmol, 84%) which was used in the next step without further purification.

Diazo transfer to give 88c: The diazo transfer step was performed on the crude **285** (346 mg, 2.00 mmol) following the procedure described for **88a**. The product **88c** was obtained as a yellow liquid (249 mg, 1.74 mmol) in 87% yield over 2 steps; *R_f* = 0.63 (hexane:EtOAc 4:1). ¹H NMR (CDCl₃, 300 MHz) δ 1.11 (t, 3H, *J* = 7.5 Hz, CH₃), 1.25 (t, 3H, *J* = 7.0 Hz, CH₃), 1.42-1.60 (m, 2H, CH₂), 2.32 (q, 2H, *J* = 7.5 Hz, CH₂), 4.19 (q, 2H, *J* = 7.0 Hz, CH₂); ¹³C NMR (CDCl₃, 150 MHz) δ 13.46, 14.75, 21.18, 25.22, 60.91 (2 C_{sp2} not located); IR 2984(m), 2085(s), 1732(s) cm⁻¹; HRMS (ESI⁺) calcd for C₇H₁₂N₂O₂Na, *m/z* 179.0796 ([M+Na]⁺), meas 179.0796.

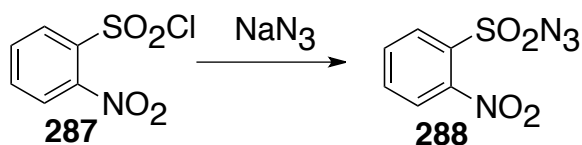
Preparation of ethyl-2-diazo-3-methylbutanoate 88d



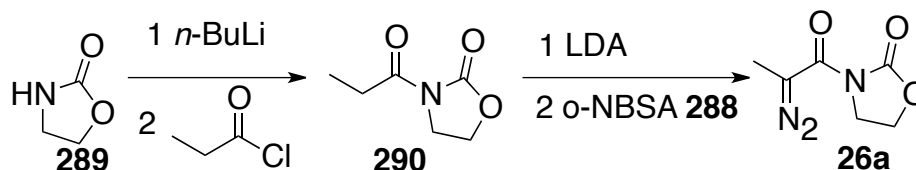
Synthesis of β -ketoester **286:** To a suspension of NaH (60% in mineral oil, 0.20 g, 5.0 mmol, 1.0 equiv) in dry THF (5 mL) was added ethyl acetoacetate **284** (0.65 g, 0.64 mL, 5.0 mmol, 1.0 equiv) dropwise. The mixture was stirred at rt for 15 min during which time the colorless suspension became a clear yellow solution. *i*-PrI (1.75 g, 1.00 mL, 10.0 mmol, 2.00 equiv) was added and the resulting mixture was refluxed for 24 hours. After cooling to rt, aq sat NH_4Cl (5 mL) was added. The aqueous layer was separated and extracted with ether (3 $\times$ 10 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated to give the crude product **286**. This material was subjected to the next step without purification.

The diazo transfer to give **88d:** This reaction was performed on all of the crude **286** following the procedure described above for **88a** on a 5.0 mmol scale. The product was obtained as a yellow liquid (390 mg, 2.50 mmol) in 50% yield over 2 steps; $R_f = 0.63$ (hexane:EtOAc 4:1). ^1H NMR (CDCl_3 , 500 MHz) δ 1.12 (d, 6H, $J = 7.5$ Hz, 2 CH_3), 1.24 (t, 3H, $J = 7.0$ Hz, CH_3), 2.72 (sept, 1H, $J = 7.0$ Hz, CH), 4.19 (q, 2H, $J = 7.0$ Hz, CH_2); ^{13}C NMR (CDCl_3 , 150 MHz) δ 14.50, 20.51, 23.09, 60.55, 165.56 (1 sp_2 C not located). The ^1H NMR spectra data of **88d** are identical with those reported⁸³ for this compound.

*Preparation of α -diazo-*N*-propanyloxazolidine **26a***



The sulfonyl azide **288** was prepared following a literature procedure^{84a}. A solution of *o*-nitrobenzenesulfonyl chloride **287** (443 mg, 2.00 mmol, 1.00 equiv) in a mixture of H_2O and acetone (v:v 1:1, 12 mL) was cooled to 0 °C. Sodium azide (195 mg, 3.00 mmol, 1.50 equiv) was added portionwise at 0 °C. After the addition, the ice bath was removed and the mixture was stirred at rt for 4 h. Acetone was then evaporated, and the aqueous layer was extracted with CH_2Cl_2 (20 mL + 2 $\times$ 10 mL). The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4), filtered and concentrated. The crude product was purified by column chromatography (silica gel, 20 $\times$ 200 mm, hexane:EtOAc 3:1), affording **288** as a pale solid (400 mg, 1.76 mmol, 88%); mp 68-70 °C; R_f = 0.3 (hexane:EtOAc 4:1); ^1H NMR (CDCl_3 , 600 MHz) δ 7.98-8.06 (m, 3H, Ar-H); 8.24 (dd, 1H, J = 7.8, 0.6 Hz, Ar-H); ^{13}C NMR (CDCl_3 , 150 MHz) δ 125.35, 131.69, 132.63, 133.05, 135.70, 147.74. The spectral data for **98** match those previously reported.⁸⁴



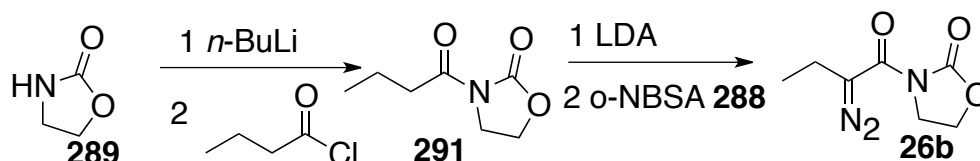
N-acylation of **289**: Compound **290** was prepared by a published procedure⁸⁵. To a flame dried flask was added 2-oxazolidinone **289** (436 mg, 5.00 mmol, 1.00 equiv) and dry THF (10 mL). The mixture was cooled down to – 78 °C under N₂. To the solution of **289** was added *n*-BuLi (2.2 M in Hexane, 2.5 mL, 5.5 mmol, 1.1 equiv) dropwise. The mixture was stirred at – 78 °C for 15 min. Then freshly distilled propionyl chloride (0.51 g, 0.48 mL, 5.5 mmol, 1.1 equiv) was added dropwise. The reaction mixture was stirred at – 78 °C for 2 hours and allowed to warm up to room temperature over 30 min, and then *aq* sat NH₄Cl (5 mL) was added. The aqueous layer was separated and extracted with CH₂Cl₂ (20 mL + 2 × 10 mL). The combined organic extracts were washed with *aq* sat NaHCO₃ (10 mL), dried (MgSO₄), filtered and concentrated. The crude product was purified by column chromatography (silica gel, 25 × 250 mm, hexane:CH₂Cl₂:EtOAc 4:4:1), which gave **100** as a white solid (644 mg, 4.50 mmol, 90%); mp 77-79 °C; (lit⁸, 77-79 °C); *R*_f = 0.45 (hexane:CH₂Cl₂:EtOAc 2:2:1); ¹H NMR (CDCl₃, 500 MHz) δ 1.14 (t, 3H, *J* = 7.5 Hz, CH₃), 2.90 (q, 2H, *J* = 7.5 Hz, CH₂), 3.98 (t, 2H, *J* = 8.0 Hz, CH₂), 4.40 (t, 2H, *J* = 8.0 Hz, CH₂); ¹³C NMR (CDCl₃, 150 MHz) δ 8.24, 28.70, 42.48, 62.02, 153.56, 174.19.

Diazo transfer to give 26a: Diazo **26a** was prepared according to a procedure⁸⁶ reported for the synthesis of (*S*)-(–)-*N*-(α-diazo)acetyl-4-benzyl-2-oxazolidinone.

To a flame dried flask was added dry *i*-Pr₂NH (66 mg, 0.10 mL, 0.65 mmol, 1.3 equiv) and dry THF (1 mL) under N₂. The solution was cooled to –78 °C, and then *n*-BuLi (2.2 M in Hexane, 0.28 mL, 0.60 mmol, 1.2 equiv) was added dropwise *via* syringe. The resulting solution was stirred at the same temperature for 10 min. A solution of acyl-oxazolidinone **290** (72 mg, 0.50 mmol, 1.0 equiv) in dry THF (1 mL) was added dropwise *via* syringe. The flask containing **290** was rinsed with dry THF (1 mL) and this was added dropwise to the reaction mixture. After 30 min, a solution of *o*-nitrobenzenesulfonyl azide **288** (*o*-NBSA) (137 mg, 0.600 mmol, 1.00 equiv) in dry THF (1 mL) was added dropwise *via* syringe. The flask containing **288** was rinsed with dry THF (1 mL) and this was added to the reaction mixture. The resulting reaction mixture was kept at –78 °C for 4.5 h. Then *aq* sat NH₄Cl (2.0 mL) was added *via* syringe dropwise at –78 °C. The mixture was warmed up to rt and the aqueous layer was separated and extracted with CH₂Cl₂ (3 × 10 mL). The combined organic extracts were dried (Na₂SO₄), filtered and concentrated. The product was purified by column chromatography (silica gel, 18 × 180 mm, CH₂Cl₂:MeOH 50:1) to afford **26a** as a yellow oil which solidified in the refrigerator as a yellow solid (43 mg, 0.25 mmol, 50%); *R*_f = 0.40 (CH₂Cl₂:MeOH 20:1); ¹H NMR (CDCl₃, 500 MHz) δ 2.02 (s, 3H, CH₃), 3.98 (t, 2H, *J* = 8.0 Hz, CH₂), 4.40 (t, 2H, *J* = 8.0 Hz, CH₂); ¹³C NMR (CDCl₃, 150 MHz) δ 9.91, 43.69, 57.70, 62.70, 152.90, 165.31; IR 2923(w), 2092(s), 1771(s),

1638(s) cm^{-1} ; HRMS (ESI^+) calcd for $\text{C}_6\text{H}_7\text{N}_3\text{O}_3\text{Na}$, m/z 192.0385 ($[\text{M}+\text{Na}]^+$), meas 192.0386.

*Preparation of α -diazo-*N*-propanyloxazolidine **26b***

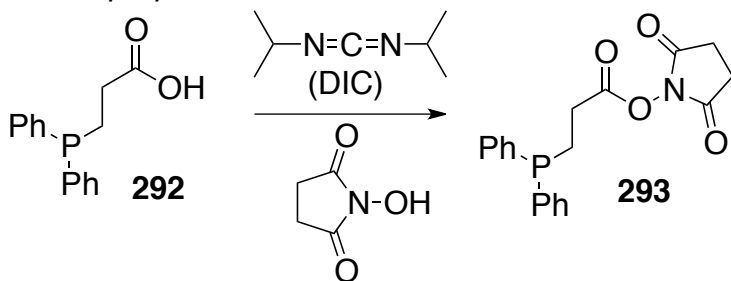


N-acylation of **289**: The preparation of **291** was accomplished using the procedure described above for **290** starting from oxazolidinone **289** (436 mg, 5.00 mmol, 1.00 equiv) and butyryl chloride (639 mg, 0.620 mL, 6.00 mmol, 1.20 equiv). The product **291** was obtained as a white crystalline solid (667 mg, 4.25 mmol) in 85% yield; mp 32-34 °C; R_f = 0.15 (hexane:EtOAc 4:1). ^1H NMR (CDCl_3 , 300 MHz) δ 0.94 (t, 3H, J = 7.2 Hz, CH_3), 1.54-1.72 (m, 2H, CH_2), 2.84 (t, 2H, J = 7.2 Hz, CH_2), 4.96 (t, 2H, J = 8.1 Hz, CH_2), 4.36 (t, 2H, J = 8.1 Hz, CH_2); ^{13}C NMR (CDCl_3 , 125 MHz) δ 13.55, 17.58, 36.82, 42.39, 61.93, 153.48, 173.26; IR 2952(m), 1768(s), 1698(s), 1388(s), 761(m) cm^{-1} ; HRMS (ESI^+) calcd for $\text{C}_7\text{H}_{11}\text{NO}_3$, m/z 157.0739 ($[\text{M}]^+$), meas 157.0732.

*Diazo transfer to give **26b***: The procedure for the preparation of **26a** was used in the preparation of **26b** starting with 157 mg (1.00 mmol) of **291** and gave the product **26b** as a yellow solid (97 mg, 0.52 mmol) in 52% yield; R_f = 0.50 (CH_2Cl_2 :MeOH 20:1). ^1H NMR (CDCl_3 , 500 MHz) δ 1.10 (t, 3H, J = 7.5 Hz, CH_3), 2.42 (q, 2H, J = 7.5 Hz, CH_2), 3.98 (t, 2H, J = 8.0 Hz, CH_2), 4.38 (t, 2H, J =

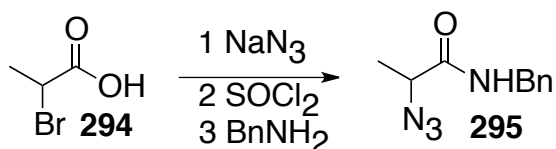
8.0 Hz, CH₂); ¹³C NMR (CDCl₃, 125 MHz) δ 11.32, 17.70, 43.61, 62.64, 152.83, 164.65 (1 sp² C not located); IR 2973(w), 2091(s), 1773(s), 1637(s) cm⁻¹; HRMS (ESI⁺) calcd for C₇H₉N₃O₃Na, *m/z* 206.0542 ([M+Na]⁺), meas 206.0546.

Preparation of 2-diazopropamide 124



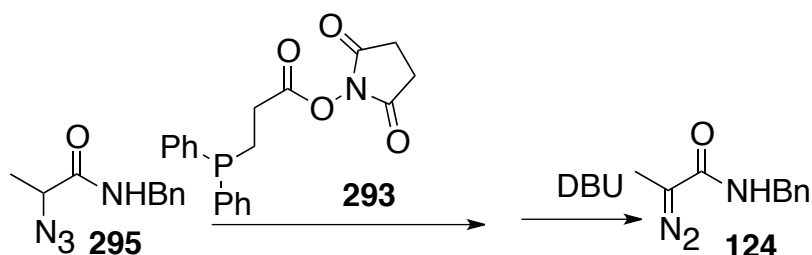
Compound **293** was prepared according to a literature procedure⁸⁷. To a suspension of **292** (532 mg, 2.00 mmol, 1.00 equiv) and *N*-hydroxysuccinimide (460 mg, 4.00 mmol, 2.00 equiv) in dry CH₂Cl₂ (5 mL) was added diisopropylcarbodiimide (DIC) (0.37 mL, 2.4 mmol, 1.2 equiv) dropwise at 0 °C. Then the ice bath was removed and the reaction mixture was stirred at rt overnight under N₂. The resulting mixture was filtered through Celite and the filtrate was concentrated. The crude product was purified by column chromatography (silica gel, 18 × 200 mm, hexane:EtOAc 2:1) giving the pure product **293** as a white solid (655 mg, 0.922 mmol, 92%); mp 101-103 °C; *R*_f = 0.20 (hexane:EtOAc 2:1); ¹H NMR (CDCl₃, 500 MHz) δ 2.38-2.46 (m, 2H, CH₂), 2.62-2.68 (m, 2H, CH₂), 2.70 (s, 4H, 2CH₂), 7.30-7.46 (m, 10H, Ar-H); ¹³C NMR (CDCl₃, 125 MHz, ³¹P coupled, ¹H decoupled) δ 22.57, 22.68, 25.55, 27.64,

27.81, 128.66, 128.71, 129.06, 132.61, 132.75, 136.90, 137.00, 168.33, 168.46, 168.97.



To a suspension of sodium azide (812 mg, 12.5 mmol, 2.50 equiv) in DMSO (15 mL) was added 2-bromopropionic acid **294** (0.45 mL, 5.0 mmol, 1.0 equiv) dropwise. The resulting solution was stirred at rt overnight. Then the mixture was diluted with H_2O (20 mL) and the pH was adjusted to ca. 1 with *conc.* HCl. The reaction mixture was extracted with EtOAc (3 $\times$ 50 mL). The combined organic extracts were washed with brine (3 $\times$ 20 mL). After the organic layer was dried (Na_2SO_4), filtered and concentrated, the azido acid was obtained as a slightly brown colored oil (570 mg, 4.95 mmol, 99%). To a solution of the azido acid (230 mg, 2.00 mmol, 1.00 equiv) in dry benzene (10 mL) was added thionyl chloride (0.30 mL, 4.0 mmol, 2.0 equiv). The resulting solution was refluxed for 2 hours. After cooling to rt, benzylamine (1.10 mL, 10.0 mmol, 5.00 equiv) was added dropwise. After the mixture was stirred at rt for another 1 hour, water (5 mL) was added. The aqueous layer was separated and extracted with Et_2O (3 $\times$ 10 mL). The combined organic extracts were washed with *aq.* HCl (3 M, 3 $\times$ 2 mL), dried (Na_2SO_4) and filtered. After concentration, the crude product was purified by column chromatography (silica gel, 25 $\times$ 250 mm, hexane:EtOAc 3:1), affording the product **295** as a pale yellow oil (exists as a solid only in the refrigerator) (331 mg, 1.62 mmol) in 81% yield; R_f = 0.25 (hexane:EtOAc 3:1). ^1H NMR (CDCl_3 ,

500 MHz) δ 1.54 (d, 3H, J = 7.0 Hz, CH₃), 4.08 (q, 1H, J = 7.0 Hz, CH), 4.40 (d, 2H, J = 5.5 Hz, CH₂), 6.64 (brs, 1H, NH), 7.20-7.34 (m, 5H, Ar-H); ¹³C NMR (CDCl₃, 125 MHz) δ 17.17, 43.47, 59.22, 127.66, 127.72, 128.77, 137.60, 169.64; IR 3302(m), 2109(s), 1654(s), 1539(s) cm⁻¹; HRMS (ESI⁺) calcd for C₁₀H₁₃N₄O, m/z 205.1089 ([M+H]⁺), meas 205.1085.



Diazo transfer to give 124: The preparation of **124** followed a procedure⁸⁷ reported for related compounds. To a solution of the azido amide **295** (204 mg, 1.00 mmol, 1.00 equiv) in THF/H₂O (2 mL/300 μ L) was added phosphine **293** (390 mg, 1.10 mmol, 1.10 equiv). The mixture was stirred at rt under N₂ for 6 hours. The solution was diluted with aq sat NaCl (10 mL), and the resulting mixture was extracted with CH₂Cl₂ (3 $\times$ 15 mL). The organic extracts were combined, dried (Na₂SO₄), filtered through Celite and concentrated to give a pale yellow foamy solid. All of the solids were then dissolved in dry CH₂Cl₂ (2 mL) and cooled to 0 °C. Then DBU (274 mg, 0.270 mL, 1.80 mmol, 1.80 equiv) was added dropwise at 0 °C. The resulting yellow solution was stirred at 0 °C for 20 min during which time a precipitate appeared. Then the entire reaction mixture

including the precipitate was quickly loaded without concentration onto a silica gel column (18 × 180 mm) and eluted quickly with hexane:EtOAc:Et₃N 25:25:1 to give the diazo amide **124** as a yellow solid (85 mg, 0.45 mmol, 45%); R_f = 0.43 (hexane:EtOAc 1:2); ¹H NMR (CDCl₃, 600 MHz) δ 1.98 (s, 3H, CH₃), 4.50 (d, 2H, J = 4.5 Hz, CH₂), 5.40 (brs, 1H, NH), 7.22-7.34 (m, 5H, Ar-H); ¹³C NMR (CDCl₃, 150 MHz) δ 8.99, 44.35, 127.75, 128.03, 128.91, 138.71, 166.94 (1 *sp*₂ C not located); IR 3320(m), 2079(s), 1614(s), 1529(s) cm⁻¹; HRMS (ESI⁺) calcd for C₁₀H₁₂N₃O, m/z 190.0980 ([M+H]⁺), meas 190.0972.

7.2.3 Procedures for Asymmetric Catalytic Aziridination Reactions

7.2.3.1 Preparation of racemic aziridines

To the mixture of the proper *N*-Boc imine (0.20 mmol, 2.0 equiv) and diazo compound **26** (0.10 mmol, 1.0 equiv) in CH₂Cl₂ (0.3 mL) at -78 °C under N₂ was added 20 μ L of a BF₃•Et₂O solution (prepared from 100 μ L of neat BF₃•Et₂O in 1 mL of CH₂Cl₂). The reaction mixture was stirred at -78 °C for 10 min to 1 h, and then NEt₃ (0.5 mL) was added at -78 °C. The solvent was evaporated, and the aziridine was purified by column chromatography on silica gel to give the corresponding aziridine in 38-86% yield.

7.2.3.2 Preparation of a catalyst stock solution (0.05 M in CH₂Cl₂)

A 25 mL pear-shaped single necked flask which had its 14/20 joint replaced by a threaded high vacuum Teflon valve was flame dried (with a stir bar in it) and cooled to rt under N₂ and charged with VANOL ((S) or (R), 44 mg, 0.10 mmol, 1.0 equiv), sublimed PhOH (20 mg, 0.20 mmol, 2.0 equiv), dry toluene (1 mL), H₂O (5.4 mg, 5.4 μ L, 0.30 mmol, 3.0 equiv) and BH₃•Me₂S solution (2.0 M in toluene, 150 μ L, 0.300 mmol, 3.00 equiv). The Teflon valve was closed and the flask was heated at 100 °C for 1 hour. After the flask was cooled to rt, the toluene was carefully removed by exposing to high vacuum (0.1 mmHg) by slightly cracking the Teflon valve. After the solvent was removed, the Teflon valve was completely opened and the flask was heated to 100 °C under high vacuum for 30 min. The residue that remained was a white foamy solid, which was cooled to rt before the addition of dry CH₂Cl₂ (2 mL) to make a 0.05 M solution.

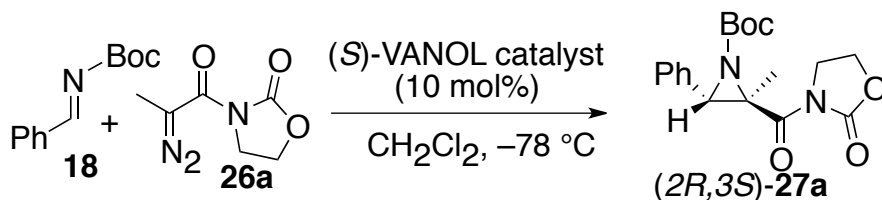
7.2.3.3. General procedure for the asymmetric catalytic aziridination reaction

10 mol% catalyst loading: A 25 mL round bottom flask was flame dried under vacuum and cooled to rt under N₂. The vacuum adapter was replaced with a rubber septum. The septum was removed briefly to allow introduction of the proper imine (0.20 mmol, 2.0 equiv), which was weighed in the flask with the septum. Subsequently, the septum was removed again to allow for the addition of dry stir bar and a pre-weighed amount of the solid diazo compound **26a** or **26b** (0.10 mmol, 1.0 equiv). Dry CH₂Cl₂ (0.3 mL) was then introduced through the septum with a syringe and then a balloon filled with nitrogen was attached *via* a

needle in the septum. After the flask was cooled to $-78\text{ }^{\circ}\text{C}$ under the N_2 balloon, the VANOL catalyst solution (10 mol%, 0.2 mL) that had been precooled to $-78\text{ }^{\circ}\text{C}$ was quickly added. The reaction mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 4-30 h, and then NEt_3 (0.5 mL) was added at $-78\text{ }^{\circ}\text{C}$. The solvent was evaporated and the product was purified by column chromatography on silica gel to give the corresponding aziridine.

20 mol% catalyst loading: A 25 mL round bottom flask was flame dried under vacuum and cooled to rt under N_2 . The vacuum adapter was replaced with a rubber septum. The septum was removed briefly to allow introduction of the proper imine (0.20 mmol, 2.0 equiv), which was weighed in the flask with the septum. Subsequently, the septum was removed again to allow for the addition of dry stir bar and a pre-weighed amount of the solid diazo compound **26a** or **26b** (0.10 mmol, 1.0 equiv). Dry CH_2Cl_2 (0.6 mL) was then introduced through the septum with a syringe and then a balloon filled with nitrogen was attached *via* a needle in the septum. After the flask was cooled to $-78\text{ }^{\circ}\text{C}$ under the N_2 balloon, the VANOL catalyst solution (10 mol%, 0.2 mL) that had been precooled to $-78\text{ }^{\circ}\text{C}$ was quickly added. The reaction mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 4-7 h, and then NEt_3 (0.5 mL) was added at $-78\text{ }^{\circ}\text{C}$. The solvent was evaporated and the product was purified by column chromatography on silica gel to give the corresponding aziridine.

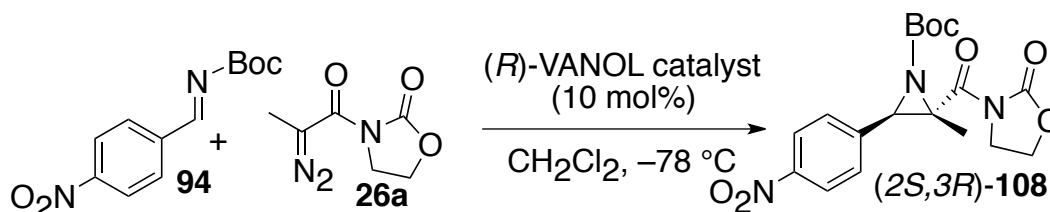
(2*R*,3*S*)-3-[*N*-1-(*t*-butoxycarbonyl)-2-methyl-3-phenylaziridine-2-carbonyl]-1-oxazolidin-2-one **27a**:



The aziridine **27a** was prepared from imine **18** (90% purity by weight, 46 mg, 0.20 mmol, 2.0 equiv), diazo compound **26a** (17 mg, 0.10 mmol, 1.0 equiv) and the (S)-VANOL catalyst solution (10 mol%, 0.2 mL) by the general procedure with a reaction time of 6 hours. The reaction went to 98% conversion. The crude product was purified by column chromatography (silica gel, 18 × 180 mm, hexane:EtOAc:CH₂Cl₂:NEt₃ 3:1:1:0.05) to give the product (2*R*,3*S*)-**27a** as a white foamy solid (26 mg, 0.075 mmol, 76%). The optical purity was determined to be 94% *ee* by HPLC (Chiralpak AS column, 222 nm, 90:10 Hexane/2-PrOH, flow rate: 1 mL/min). Retention time: *t_R* = 11.4 min for (2*R*,3*S*)-**27a** (major) and *t_R* = 23.1 min for (2*S*,3*R*)-**27a** (minor); A second run gave 97% conversion, 68% yield and 93.5% *ee*; mp 47-48 °C; *R_f* = 0.2 (hexane:EtOAc:CH₂Cl₂:NEt₃ 3:1:1:0.05); ¹H NMR (CDCl₃, 600 MHz) δ 1.38 (s, 3H, CH₃), 1.54 (s, 9H, 3CH₃), 3.88 (s, 1H, CH), 3.90-3.96 (m, 1H, CHH), 4.10 (q, 1H, *J* = 8.0 Hz, CHH), 4.38-4.52 (m, 2H, CH₂), 7.25-7.36 (m, 3H, Ar-H), 7.44 (d, 2H, *J* = 7.2 Hz, Ar-H); ¹³C NMR (CDCl₃, 150 MHz) δ 15.42, 27.88, 43.33, 47.70, 52.05, 62.69, 81.70, 127.82, 127.95, 128.39, 133.41, 152.52, 160.10, 170.56; [α]_D²⁰ +30.8° (c 1.0,

CH₂Cl₂) on 94% ee material from (S)-VANOL. The effects of changes in the reaction conditions and the ligands in the catalyst on the formation of **27a** are summarized in Table 3.2.

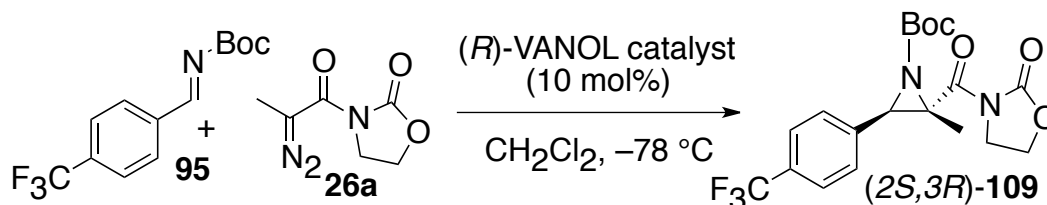
(2*S*,3*R*)-3-[*N*-1-(*t*-butoxycarbonyl)-2-methyl-3-(4-nitrophenyl)aziridine-2-carbonyl]-1-oxazolidin-2-one **108**:



The aziridine **108** was prepared from imine **94** (100% purity by weight, 50 mg, 0.20 mmol, 2.0 equiv), diazo compound **26a** (17 mg, 0.10 mmol, 1.0 equiv) and the (*R*)-VANOL catalyst solution (10 mol%, 0.2 mL) by the general procedure with a reaction time of 6 hours. The crude product was purified by column chromatography (1st column, silica gel, 18 × 180 mm, hexane:EtOAc:CH₂Cl₂:NEt₃ 2:1:1:0.05; 2nd column, silica gel, 18 × 180 mm, CH₂Cl₂:MeOH:NEt₃ 50:1:1) to give the product (2*S*,3*R*)-**108** as a white foamy solid (24 mg, 0.062 mmol, 62%). The optical purity was determined to be 90% ee by HPLC (Chiralpak AS column, 222 nm, 90:10 hexane/2-PrOH, flow rate: 1 mL/min). Retention time: *t_R* = 34.5 min for (2*R*,3*S*)-**108** (minor) and *t_R* = 48.2 min for (2*S*,3*R*)-**108** (major); mp 72-75 °C; *R_f* = 0.3 (hexane:EtOAc:CH₂Cl₂:NEt₃ 2:1:1:0.05); ¹H NMR (CDCl₃, 600 MHz) δ 1.38 (s, 3H, CH₃), 1.56 (s, 9H, 3CH₃), 3.91 (s, 1H, CH), 3.92-3.98 (m, 1H, CHH), 4.08-4.16 (m, 1H, CHH), 4.44-4.54 (m,

2H, CH₂), 7.62 (d, 2H, *J* = 8.4 Hz, Ar-H), 8.18 (d, 2H, *J* = 9.0 Hz, Ar-H); ¹³C NMR (CDCl₃, 150 MHz) δ 15.43, 27.63, 42.97, 46.25, 52.46, 62.62, 82.18, 122.98, 129.27, 140.75, 147.46, 152.44, 159.49, 169.45; IR 2982(w), 1786(s), 1720(s), 1700(m) cm⁻¹; [α]_D²⁰ -43.5° (c 1.0, CH₂Cl₂) on 90% ee material from (*R*)-VANOL; HRMS (ESI⁺) calcd for C₁₈H₂₁N₃O₇Na, *m/z* 414.1277 ([M+Na]⁺), meas 414.1287. The reaction with 20 mol% catalyst loading ((*R*)-VANOL) and a reaction time of 6 hours afforded aziridine **108** in 62% yield and 90% ee.

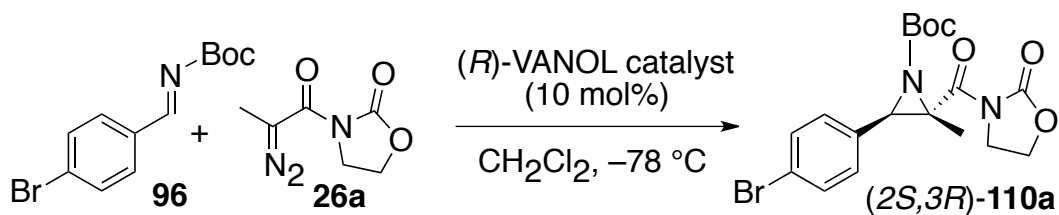
(2*S*,3*R*)-3-[N-1-(*t*-butoxycarbonyl)-2-methyl-3-(4-trifluoromethylphenyl)aziridine-2-carbonyl]-1-oxazolidin-2-one **109**:



The aziridine **109** was prepared from imine **95** (96% purity by weight, 58 mg, 0.20 mmol, 2.0 equiv), diazo compound **26a** (17 mg, 0.10 mmol, 1.0 equiv) and the (*R*)-VANOL catalyst solution (10 mol%, 0.2 mL) by the general procedure with a reaction time of 1 hour. The crude product was purified by column chromatography (1st column, silica gel, 18 × 180 mm, hexane:EtOAc:CH₂Cl₂:NEt₃ 3:1:1:0.05; 2nd column, silica gel, 18 × 180 mm, CH₂Cl₂:MeOH:NEt₃ 100:1:1) to give the product (2*S*,3*R*)-**109** as a white foamy solid (24 mg, 0.058 mmol, 58%). The optical purity was determined to be 95% ee by HPLC (Chiralpak AS column, 222 nm, 90:10 hexane/2-PrOH, flow rate: 1

mL/min); Retention time: t_R = 8.1 min for (2*R*,3*S*)-**109** (minor) and t_R = 13.9 min for (2*S*,3*R*)-**109** (major); mp 122-126 °C; R_f = 0.25 (hexane:EtOAc:CH₂Cl₂:NEt₃ 3:1:1:0.05); ¹H NMR (CDCl₃, 600 MHz) δ 1.36 (s, 3H, CH₃), 1.52 (s, 9H, 3CH₃), 3.89 (s, 1H, CH), 3.90-3.98 (m, 1H, CHH), 4.04-4.16 (m, 1H, CHH), 4.40-4.54 (m, 2H, CH₂), 7.52-7.62 (m, 4H, Ar-H); ¹³C NMR (CDCl₃, 150 MHz) δ 15.55, 27.86, 43.24, 46.85, 52.38, 62.78, 82.11, 124.15 (J = 271.8 Hz), 124.96 (J = 4.5 Hz), 128.85, 130.03 (J = 29.2 Hz), 137.56, 152.61, 159.86, 170.04; IR 2984(w), 1784(s), 1707(s), 1325(m) cm⁻¹; $[\alpha]_D^{20}$ -13.6° (c 1.0, CH₂Cl₂) on 96% ee material from (*R*)-VANOL; HRMS (ESI⁺) calcd for C₁₉H₂₁N₂O₅F₃Na, m/z 437.1300 ([M+Na]⁺), meas 437.1284. The reaction with 20 mol% catalyst loading ((*R*)-VANOL) and a reaction time of 1 hours afforded aziridine **109** in 48% yield and 96% ee.

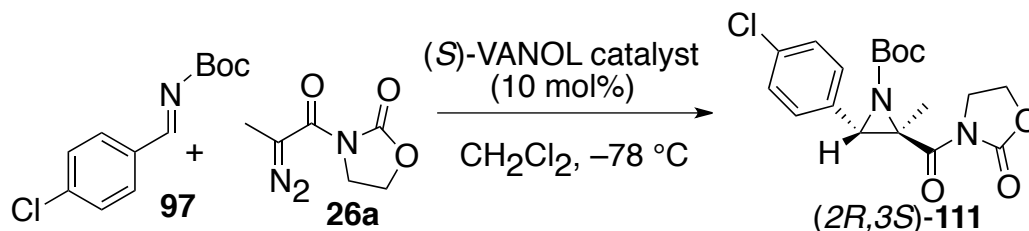
(2*S*,3*R*)-3-[*N*-1-(*t*-butoxycarbonyl)-2-methyl-3-(4-bromophenyl)aziridine-2-carbonyl]-1-oxazolidin-2-one **110a**:



The aziridine **110a** was prepared from imine **96** (83% purity by weight, 69 mg, 0.20 mmol, 2.0 equiv), diazo compound **26a** (17 mg, 0.10 mmol, 1.0 equiv) and the (*R*)-VANOL catalyst solution (10 mol%, 0.2 mL) using the general procedure with a reaction time of 8 hours. The crude aziridine was purified by column

chromatography (silica gel, 18 × 180 mm, hexane:EtOAc:CH₂Cl₂:NEt₃ 3:1:1:0.05) to give the product (2*S*,3*R*)-**110a** as a white foamy solid (33 mg, 0.078 mmol, 78%). The optical purity was determined to be 96% ee by HPLC (Chiralpak AS column, 222 nm, 90:10 hexane/2-PrOH, flow rate: 1 mL/min). Retention time: *t_R* = 11.5 min for (2*R*,3*S*)-**110a** (minor) and *t_R* = 24.1 min for (2*S*,3*R*)-**110a** (major); A second run gave 62% yield and 96% ee; mp 72-74 °C; *R_f* = 0.20 (hexane:EtOAc:CH₂Cl₂:NEt₃ 3:1:1:0.05); ¹H NMR (CDCl₃, 600 MHz) δ 1.34 (s, 3H, CH₃), 1.51 (s, 9H, 3CH₃), 3.80 (s, 1H, CH), 3.90-3.95 (m, 1H, CHH), 4.06-4.13 (m, 1H, CHH), 4.36-4.50 (m, 2H, CH₂), 7.28-7.32 (m, 2H, Ar-H), 7.42-7.46 (m, 2H, Ar-H); ¹³C NMR (CDCl₃, 150 MHz) δ 15.49, 27.87, 43.26, 46.92, 52.16, 62.74, 81.96, 122.00, 130.17, 131.13, 132.52, 152.57, 159.95, 170.23; IR 2980(w), 1789(s), 1720(s), 1160(m) cm⁻¹; [α]_D²⁰ -20.8° (c 1.0, CH₂Cl₂) on 96% ee material obtained from (*R*)-VANOL; HRMS (ESI⁺) calcd for C₁₈H₂₁N₂O₅⁷⁹BrNa, *m/z* 447.0532 ([M+Na]⁺), meas 447.0553. The reaction with 20 mol% catalyst loading ((*S*)-VANOL) and a reaction time of 4 hours afforded aziridine **110a** in 71% yield and 96% ee.

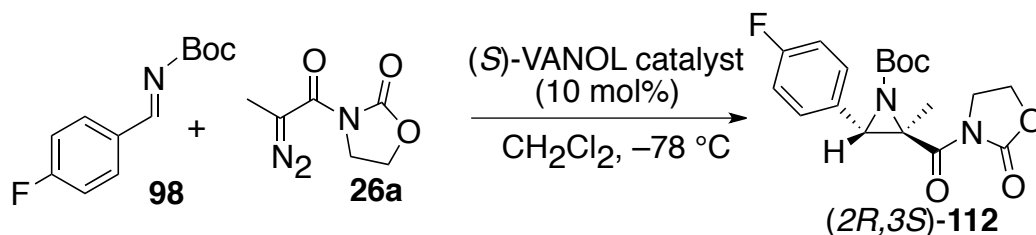
(2*R*,3*S*)-3-[N-1-(*t*-butoxycarbonyl)-2-methyl-3-(4-chlorophenyl)aziridine-2-carbonyl]-1-oxazolidin-2-one **111**:



The aziridine **111** was prepared from imine **97** (91% purity by weight, 53 mg, 0.20 mmol, 2.0 equiv), diazo compound **26a** (17 mg, 0.10 mmol, 1.0 equiv) and (S)-VANOL by the general procedure with a reaction time of 6 hours. The reaction went to 95% conversion. The crude mixture was purified by column chromatography (silica gel, 18 × 180 mm, hexane:EtOAc:CH₂Cl₂:NEt₃ 3:1:1:0.05) to give the product (2R,3S)-**111** as a white foamy solid (30 mg, 0.080 mmol, 80%). The optical purity was determined to be 93% ee by HPLC (Chiralpak AS column, 222 nm, 90:10 Hexane/2-PrOH, flow rate: 1 mL/min); Retention time: t_R = 10.7 min for (2R,3S)-**111** (major) and t_R = 20.1 min for (2S,3R)-**111** (minor). A second run gave **111** in 88% conversion, 68% yield and 93% ee. mp 72-74 °C; R_f = 0.25 (hexane:EtOAc:CH₂Cl₂:NEt₃ 3:1:1:0.05); ¹H NMR (CDCl₃, 600 MHz) δ 1.34 (s, 3H, CH₃), 1.52 (s, 9H, 3CH₃), 3.82 (s, 1H, CH), 3.90-3.96 (m, 1H, CHH), 4.06-4.13 (m, 1H, CHH), 4.36-4.50 (m, 2H, CH₂), 7.26-7.30 (m, 2H, Ar-H), 7.34-7.38 (m, 2H, Ar-H); ¹³C NMR (CDCl₃, 150 MHz) δ 15.69, 28.08, 43.48, 47.08, 52.41, 62.95, 82.15, 128.39, 130.04, 132.20, 133.99, 152.78, 160.18, 170.46; IR 2980(w), 1788(s), 1718(s), 1698(s), 1162(m) cm⁻¹; $[\alpha]_D^{20}$ +19.8° (c 1.0, CH₂Cl₂) on 93% ee material obtained from (S)-VANOL;

HRMS (ESI⁺) calcd for C₁₈H₂₁N₂O₅³⁵ClNa, *m/z* 403.1037 ([M+Na]⁺), meas 403.1053. With 20 mol% catalyst loading ((*S*)-VANOL), the reaction went to 95% completion in 4 hours and gave the aziridine **111** in 71% yield and 93% ee.

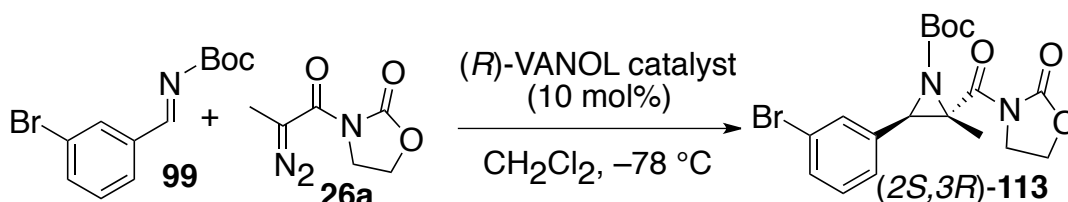
(2*R*,3*S*)-3-[*N*-1-(*t*-butoxycarbonyl)-2-methyl-3-(4-fluorophenyl)aziridine-2-carbonyl]-1-oxazolidin-2-one **112**:



The aziridine **112** was prepared from imine **98** (95% purity by weight, 46 mg, 0.20 mmol, 2.0 equiv), diazo compound **26a** (17 mg, 0.10 mmol, 1.0 equiv) and the (*S*)-VANOL catalyst solution by the general procedure with a reaction time of 8 hours. The reaction went to 81% conversion. The crude aziridine was purified by column chromatography (silica gel, 18 × 180 mm, hexane:EtOAc:CH₂Cl₂:NEt₃ 3:1:1:0.05) to give **112** as a white foamy solid (20 mg, 0.055 mmol, 55%). The optical purity was determined to be 96% ee by HPLC (Chiralpak AS column, 222 nm, 90:10 hexane/2-PrOH, flow rate: 1 mL/min). Retention time: *t_R* = 11.0 min for (2*R*,3*S*)-**112** (major) and *t_R* = 18.7 min for (2*S*,3*R*)-**112** (minor); A second run gave aziridine **112** in 80% conversion, 54% yield and 95% ee. mp 48-50 °C; *R_f* = 0.25 (hexane:EtOAc:CH₂Cl₂:NEt₃ 3:1:1:0.05). ¹H NMR (CDCl₃, 500 MHz) δ 1.35 (s, 3H, CH₃), 1.52 (s, 9H, 3CH₃), 3.82 (s, 1H, CH), 3.88-3.96 (m, 1H, CHH), 4.06-4.14 (m, 1H, CHH), 4.38-4.51 (m, 2H, CH₂), 6.98-7.04 (m, 2H, Ar-H), 7.34-

7.42 (m, 2H, Ar-H); ^{13}C NMR (CDCl_3 , 150 MHz) δ 15.43, 27.86, 43.28, 46.89, 52.15, 62.74, 81.85, 114.91 ($J = 21.6$ Hz), 129.14 ($J = 3.1$ Hz), 130.11 ($J = 8.25$ Hz), 152.59, 160.04, 162.53 ($J = 244.6$ Hz), 170.37; IR 2981(w), 1791(s), 1719(s), 1700(s), 1155(m) cm^{-1} ; $[\alpha]_{\text{D}}^{20} +32.7^\circ$ (c 1.0, CH_2Cl_2) on 96% ee material obtained from (*S*)-VANOL; HRMS (ESI^+) calcd for $\text{C}_{18}\text{H}_{21}\text{N}_2\text{O}_5\text{FNa}$, m/z 387.1332 ($[\text{M}+\text{Na}]^+$), meas m/z 383.1522. The reaction with 20 mol% catalyst loading ((*S*)-VANOL) went to full conversion in 6 hours and gave **112** in 64% yield and 96% ee.

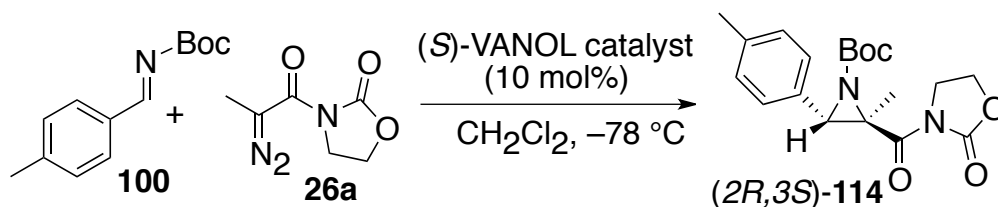
(2*S*,3*R*)-3-[*N*-1-(*t*-butoxycarbonyl)-2-methyl-3-(3-bromophenyl)aziridine-2-carbonyl]-1-oxazolidin-2-one **113**:



The aziridine **113** was prepared from imine **99** (92% purity by weight, 63 mg, 0.20 mmol, 2.0 equiv), diazo compound **26a** (17 mg, 0.10 mmol, 1.0 equiv) and the (*R*)-VANOL catalyst by the general procedure with a reaction time of 4 hours. The aziridine was purified by column chromatography (silica gel, 18 × 180 mm, hexane:EtOAc: CH_2Cl_2 : NEt_3 3:1:1:0.05) to give **113** as a white foamy solid (25 mg, 0.059 mmol, 59%). The optical purity was determined to be 85% ee by HPLC (Chiralpak AS column, 222 nm, 90:10 hexane/2-PrOH, flow rate: 1 mL/min). Retention time: $t_R = 12.6$ min for (2*R*,3*S*)-**113** (minor) and $t_R = 26.4$ min

for (2*S*,3*R*)-**113** (major); A second run gave **113** in 53% yield and 85% ee. mp 50-52 °C; R_f = 0.24 (hexane:EtOAc:CH₂Cl₂:NEt₃ 3:1:1:0.05); ¹H NMR (CDCl₃, 500 MHz) δ 1.37 (s, 3H, CH₃), 1.52 (s, 9H, 3CH₃), 3.82 (s, 1H, CH), 3.90-3.96 (m, 1H, CHH), 4.06-4.14 (m, 1H, CHH), 4.36-4.52 (m, 2H, CH₂), 7.18 (t, 1H, J = 7.5 Hz, Ar-H), 7.36-7.44 (m, 2H, Ar-H), 7.54-7.58 (s, 1H, Ar-H); ¹³C NMR (CDCl₃, 125 MHz) δ 15.52, 27.85, 43.24, 46.70, 52.36, 62.74, 82.03, 122.16, 127.46, 129.57, 130.10, 131.12, 135.83, 152.52, 159.90, 170.11; IR 2976(w), 1783(s), 1709(s), 1688(s), 1162(m) cm⁻¹; $[\alpha]_D^{20}$ -25.3° (c 1.0, CH₂Cl₂) on 85% ee material obtained from (*R*)-VANOL; HRMS (ESI⁺) calcd for C₁₈H₂₁N₂O₅⁷⁹BrNa m/z 447.0532 ([M+Na]⁺), meas 447.0526. The reaction with 20 mol% catalyst loading ((*R*)-VANOL) and a reaction time of 4 hours afforded **113** in 48% yield and 85% ee.

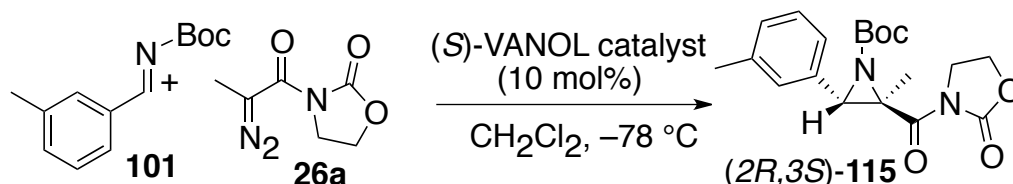
(2*R*,3*S*)-3-[*N*-1-(*t*-butoxycarbonyl)-2-methyl-3-(4-methylphenyl)aziridine-2-carbonyl]-1-oxazolidin-2-one **114**:



The aziridine **114** was prepared from imine **100** (94% purity by weight, 48 mg, 0.20 mmol, 2.0 equiv), diazo compound **26a** (17 mg, 0.10 mmol, 1.0 equiv) and the (*S*)-VANOL catalyst solution (10 mol%, 0.2 mL) by the general procedure with a reaction time of 27 hours. The aziridine was purified by column

chromatography (1st column, silica gel, 18 × 180 mm, hexane:EtOAc:CH₂Cl₂:NEt₃ 3:1:1:0.05; 2nd column, silica gel, 18 × 180 mm, CH₂Cl₂:MeOH:NEt₃ 100:1:1) to give the product **114** as a white foamy solid (30 mg, 0.083 mmol, 83%). The optical purity was determined to be 96% ee by HPLC (Chiralpak AS column, 222 nm, 90:10 Hexane/2-PrOH, flow rate: 1 mL/min). Retention time: t_R = 10.0 min for (2*R*,3*S*)-**114** (major) and t_R = 23.0 min for (2*S*,3*R*)-**114** (minor); A second run gave aziridine **114** in 82% yield and 97% ee. mp 44-46 °C; R_f = 0.23 (hexane:EtOAc:CH₂Cl₂:NEt₃ 3:1:1:0.05). ¹H NMR (CDCl₃, 500 MHz) δ 1.36 (s, 3H, CH₃), 1.50 (s, 9H, 3CH₃), 2.34 (s, 3H, CH₃), 3.84 (s, 1H, CH), 3.89-3.96 (m, 1H, CHH), 4.06-4.14 (m, 1H, CHH), 4.38-4.50 (m, 2H, CH₂), 7.14 (d, 2H, J = 8.0 Hz, Ar-H), 7.30 (d, 2H, J = 8.0 Hz, Ar-H); ¹³C NMR (CDCl₃, 150 MHz) δ 15.38, 21.16, 27.90, 43.34, 47.72, 51.95, 62.67, 81.63, 128.27, 128.69, 130.36, 137.54, 152.50, 160.14, 170.70; IR 2979(w), 1789(s), 1720(s), 1700(s), 1160(m) cm⁻¹; $[\alpha]_D^{20}$ -15.8° (c 1.0, CH₂Cl₂) on 95% ee material obtained from (*R*)-VANOL; HRMS (ESI⁺) calcd for C₁₉H₂₄N₂O₅Na, m/z 383.1583 ([M+Na]⁺), meas 383.1568. With 10 mol% catalyst loading ((*R*)-VANOL) and a reaction time of 9 hours, the reaction went to 60% conversion and gave aziridine **114** in 42% yield and 95% ee. The diazo compound **26a** was recovered in 47% yield. The yield of **114** based on the recovered starting material was 70%.

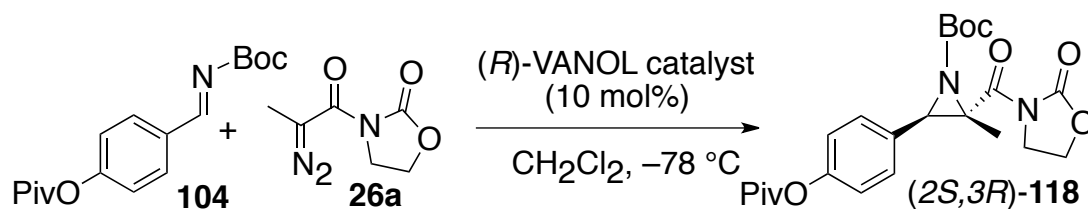
(2*R*,3*S*)-3-[*N*-1-(*t*-butoxycarbonyl)-2-methyl-3-(3-methylphenyl)aziridine-2-carbonyl]-1-oxazolidin-2-one **115**:



The aziridine **115** was prepared from imine **101** (92% purity by weight, 48 mg, 0.20 mmol, 2.0 equiv.), diazo compound **26a** (17 mg, 0.10 mmol, 1.0 equiv) and the (*S*)-VANOL catalyst solution (10 mol%, 0.2 mL) by the general procedure with a reaction time of 8 hours. The reaction went to 84% conversion. The aziridine was purified by column chromatography (silica gel, 18 × 180 mm, Hexane:EtOAc:CH₂Cl₂:NEt₃ 3:1:1:0.05) to give the product as a white foamy solid (26 mg, 0.071 mmol, 71%). The optical purity was determined to be 92% ee by HPLC (Chiralpak AS column, 222 nm, 90:10 Hexane/2-PrOH, flow rate: 1 mL/min). Retention time: *t_R* = 9.6 min for (2*R*,3*S*)-**115** (major) and *t_R* = 20.1 min for (2*S*,3*R*)-**115** (minor); mp 166-167 °C; *R_f* = 0.2 (hexane:EtOAc:CH₂Cl₂:NEt₃ 3:1:1:0.05). ¹H NMR (CDCl₃, 500 MHz) δ 1.42 (s, 3H, CH₃), 1.54 (s, 9H, 3CH₃), 2.36 (s, 3H, CH₃), 3.88 (s, 1H, CH), 3.92-4.00 (m, 1H, CHH), 4.08-4.16 (m, 1H, CHH), 4.42-4.54 (m, 2H, CH₂), 7.08-7.14 (m, 1H, Ar-H), 7.20-7.29 (m, 3H, Ar-H); ¹³C NMR (CDCl₃, 125 MHz) δ 15.43, 21.38, 27.90, 43.36, 47.82, 52.04, 62.67, 81.69, 125.59, 127.87, 128.61, 128.87, 133.32, 137.59, 152.48, 160.17, 170.61; IR 2979(w), 1790(s), 1718(s), 1691(s), 1161(m) cm⁻¹; [α]_D²⁰ -33.8° (c 2.0,

CH₂Cl₂) on 92% ee material obtained from (*R*)-VANOL; HRMS (ESI⁺) calcd for C₁₉H₂₄N₂O₅Na, *m/z* 383.1583 ([M+Na]⁺), meas 383.1568. The reaction with 20 mol% catalyst loading ((*R*)-VANOL) and a reaction time of 6 hours went to full conversion and gave **115** in 83% yield and 92% ee.

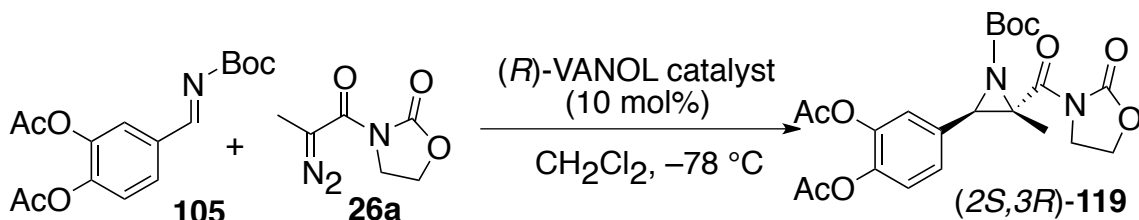
(2*S*,3*R*)-3-[*N*-1-(*t*-butoxycarbonyl)-2-methyl-3-(4-pivaloylphenyl)aziridine-2-carbonyl]-1-oxazolidin-2-one **118**:



The aziridine **118** was prepared from imine **104** (92% purity by weight, 67 mg, 0.20 mmol, 2.0 equiv), diazo compound **26a** (17 mg, 0.10 mmol, 1.0 equiv) and the (*R*)-VANOL catalyst solution (10 mol%, 0.2 mL) by the general procedure with a reaction time of 11 hours. The reaction went to 87% conversion. The crude product was purified by column chromatography (1st column, silica gel, 18 × 180 mm, hexane:EtOAc:CH₂Cl₂:NEt₃ 3:1:1:0.05; 2nd column, silica gel, 18 × 180 mm, CH₂Cl₂:MeOH:NEt₃ 100:1:1) to give the product (2*S*,3*R*)-**118** as a white foamy solid (31 mg, 0.069 mmol, 69%). The optical purity was determined to be 98% ee by HPLC (Chiralpak AS column, 222 nm, 90:10 Hexane/2-PrOH, flow rate: 1 mL/min). Retention time: *t_R* = 11.7 min for (2*R*,3*S*)-**118** (minor) and *t_R* = 20.9 min for (2*S*,3*R*)-**118** (major); mp 58-60 °C; *R_f* = 0.2 (hexane:EtOAc:CH₂Cl₂:NEt₃ 3:1:1:0.05); ¹H NMR (CDCl₃, 600 MHz) δ 1.33 (s,

9H, 3CH₃), 1.36 (s, 3H, CH₃), 1.52 (s, 9H, 3CH₃), 3.86 (s, 1H, CH), 3.90-3.96 (m, 1H, CHH), 4.06-4.14 (m, 1H, CHH), 4.40-4.50 (m, 2H, CH₂), 7.02 (d, 2H, *J* = 8.4 Hz, Ar-H), 7.43 (d, 2H, *J* = 8.4 Hz, Ar-H); ¹³C NMR (CDCl₃, 150 MHz) δ 15.49, 27.11, 27.88, 39.05, 43.32, 47.20, 52.12, 62.70, 81.83, 121.05, 129.43, 130.72, 150.80, 152.51, 160.01, 170.46, 176.92; IR 2978(w), 1790(s), 1730(s), 1718(s) cm⁻¹; [α]_D²⁰ -17.0° (c 1.0, CH₂Cl₂) on 98% ee material from (*R*)-VANOL; HRMS (ESI⁺) calcd for C₂₃H₃₀N₂O₇Na, *m/z* 469.1951 ([M+Na]⁺), meas 469.1941. The reaction with 20 mol% catalyst loading ((*R*)-VANOL) and a reaction time of 1 hours afforded aziridine **118** in 67% yield and 98% ee.

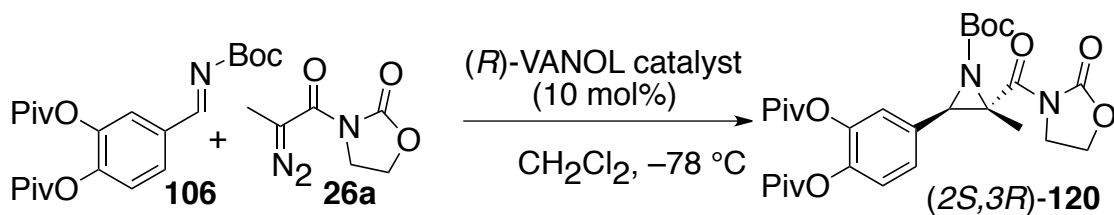
(2*S*,3*R*)-3-[*N*-1-(*t*-butoxycarbonyl)-2-methyl-3-(3,4-diacetoxyphenyl)aziridine-2-carbonyl]-1-oxazolidin-2-one **119**:



The aziridine **119** was prepared from imine **105** (100% purity by weight, 65 mg, 0.20 mmol, 2.0 equiv), diazo compound **26a** (17 mg, 0.10 mmol, 1.0 equiv) and the (*R*)-VANOL catalyst solution (10 mol%, 0.2 mL) by the general procedure with a reaction time of 11 hours. The reaction went to 88% conversion. The crude product was purified by column chromatography (1st column, silica gel, 18 × 180 mm, hexane:EtOAc:CH₂Cl₂:NEt₃ 1:1:1:0.05; 2nd column, silica gel, 18 × 180 mm, hexane:EtOAc:CH₂Cl₂:NEt₃ 1:1:1:0.05) to give the product (2*S*,3*R*)-**119** as

a white foamy solid (30 mg, 0.065 mmol, 65%). The optical purity was determined to be 88% ee by HPLC (Chiralpak AS column, 222 nm, 80:20 hexane/2-PrOH, flow rate: 1 mL/min). Retention time: t_R = 20.54 min for (2*R*,3*S*)-**119** (minor) and t_R = 40.69 min for (2*S*,3*R*)-**119** (major); mp 61-62 °C; R_f = 0.3 (hexane:EtOAc:CH₂Cl₂:NEt₃ 1:1:1:0.05). ¹H NMR (CDCl₃, 500 MHz) δ 1.38 (s, 3H, CH₃), 1.50 (s, 9H, 3CH₃), 2.25 (2s, 6H, 2CH₃), 3.85 (s, 1H, CH), 3.88-3.96 (m, 1H, CHH), 4.04-4.12 (m, 1H, CHH), 4.40-4.50 (m, 2H, CH₂), 7.02 (d, 1H, J = 8.5 Hz, Ar-H), 7.43 (d, 1H, J = 2.0 Hz, Ar-H), 7.34 (dd, 1H, J = 8.5, 2.0 Hz, Ar-H); ¹³C NMR (CDCl₃, 150 MHz) δ 15.88, 20.85, 20.91, 28.06, 43.48, 46.87, 52.67, 62.98, 82.23, 123.27, 123.62, 127.15, 132.68, 141.92, 141.99, 152.80, 160.07, 168.40, 168.43, 170.40; IR 2982(w), 1776(s), 1718(s), 1710(s) cm⁻¹; $[\alpha]_D^{20}$ – 19.0° (c 2.0, CH₂Cl₂) on 88% ee material from (*R*)-VANOL; HRMS (ESI⁺) calcd for C₂₂H₂₆N₂O₉Na, m/z 485.1536 ([M+Na]⁺), meas 485.1509. The reaction with 20 mol% catalyst loading ((*R*)-VANOL) and a reaction time of 11 hours afforded aziridine **119** in 69% yield and 88% ee.

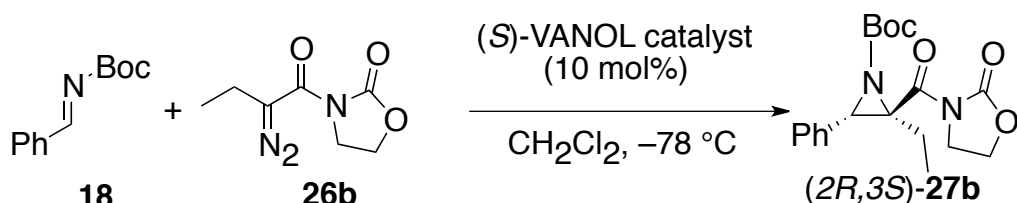
(2*S*,3*R*)-3-{*N*-1-(*t*-butoxycarbonyl)-2-methyl-3-[(3,4-bis(pivaloyl)oxyl]phenyl)aziridine-2-carbonyl}-1-oxazolidin-2-one **120**:



The aziridine **120** was prepared from imine **106** (100% purity by weight, 82 mg, 0.20 mmol, 2.0 equiv), diazo compound **26a** (17 mg, 0.10 mmol, 1.0 equiv) and the (*R*)-VANOL catalyst solution (10 mol%, 0.2 mL) by the general procedure with a reaction time of 10 hours. The reaction went to 85% conversion. The crude product was purified by column chromatography (1st column, silica gel, 18 × 180 mm, hexane:EtOAc:CH₂Cl₂:NEt₃ 3:1:1:0.05) to give the product (2*S*,3*R*)-**120** as a white foamy solid (25 mg, 0.046 mmol, 46%). The optical purity was determined to be 88% ee by HPLC (Chiralpak AS column, 222 nm, 90:10 hexane/2-PrOH, flow rate: 1 mL/min). Retention time: *t_R* = 9.28 min for (2*R*,3*S*)-**120** (minor) and *t_R* = 23.06 min for (2*S*,3*R*)-**120** (major); mp 52-54 °C; *R_f* = 0.2 (hexane:EtOAc:CH₂Cl₂:NEt₃ 3:1:1:0.05). ¹H NMR (CDCl₃, 600 MHz) δ 1.30, 1.31 (2s, 18H, 6CH₃), 1.38 (s, 3H, CH₃), 1.50 (s, 9H, 3CH₃), 3.88 (s, 1H, CH), 3.90-3.96 (m, 1H, CHH), 4.04-4.12 (m, 1H, CHH), 4.38-4.50 (m, 2H, CH₂), 7.08 (d, 1H, *J* = 7.8 Hz, Ar-H), 7.17 (s, 1H, Ar-H), 7.32 (d, 1H, *J* = 8.4 Hz, Ar-H); ¹³C NMR (CDCl₃, 150 MHz) δ 15.55, 27.21, 27.27, 27.86, 39.08, 39.12, 43.29, 46.90, 52.34, 62.67, 82.04, 122.98, 123.12, 126.67, 131.97, 142.16, 142.29, 152.42, 159.92, 170.22, 175.66, 175.77; IR 2978(w), 1786(s), 1761(s), 1722(s) cm⁻¹; [α]_D²⁰ -20.1° (c 1.0, CH₂Cl₂) on 88% ee material from (*R*)-VANOL; HRMS (ESI⁺) calcd for C₂₈H₃₈N₂O₉Na, *m/z* 569.2475 ([M+Na]⁺), meas 569.2455. The

reaction with 20 mol% catalyst loading ((*R*)-VANOL) and a reaction time of 10 hours afforded aziridine **120** in 63% yield and 88% ee.

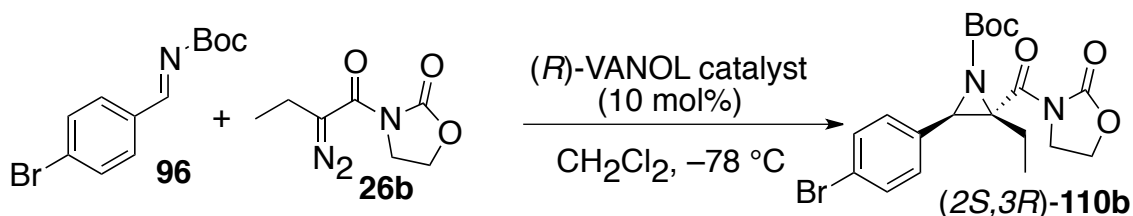
(2*R*,3*S*)-3-[*N*-1-(*t*-butoxycarbonyl)-2-ethyl-3-phenylaziridine-2-carbonyl]-1-oxazolidin-2-one **27b**:



The aziridine **27b** was prepared from imine **18** (90% purity by weight, 46 mg, 0.20 mmol, 2.0 equiv), diazo compound **26b** (19 mg, 0.10 mmol, 1.0 equiv) and the (*S*)-VANOL catalyst solution (10 mol%, 0.2 mL) by the general procedure with a reaction time of 30 hours. The reaction gave 70% conversion. The crude mixture was purified by the column (silica gel, 18 × 180 mm, hexane:EtOAc:CH₂Cl₂:NEt₃ 3:1:1:0.05) to give the product **27b** as a white foamy solid (21 mg, 0.060 mmol, 60%). The optical purity was determined to be 85% ee by HPLC (Chiralpak AS column, 222 nm, 90:10 Hexane/2-PrOH, flow rate: 1 mL/min). Retention time: *t_R* = 10.4 min for (2*R*,3*S*)-**27b** (major) and *t_R* = 17.1 min for (2*S*,3*R*)-**27b** (minor); A second run gave aziridine **27b** in 66% conversion, 50% yield and 85% ee; mp 146-148 °C; *R_f* = 0.30 (hexane:EtOAc:CH₂Cl₂:NEt₃ 3:1:1:0.05). ¹H NMR (CDCl₃, 500 MHz) δ 1.02 (t, 3H, *J* = 7.5 Hz, CH₃), 1.38-1.26 (m, 1H, CHH), 1.54 (s, 9H, 3CH₃), 1.92-1.80 (m, 1H, CHH), 3.84-3.96 (m, 2H, CHH and CH (s, overlap with CHH)), 4.14 (q, 1H, *J* = 9.5 Hz, CHH), 4.36-4.54 (m, 2H, CH₂), 7.22-7.34 (m, 3H, Ar-H), 7.44 (d, 2H, *J* = 7.5 Hz, Ar-H); ¹³C NMR

(CDCl₃, 150 MHz) δ 10.63, 22.42, 27.85, 43.21, 47.80, 57.54, 62.68, 81.35, 127.74, 127.86, 128.42, 133.61, 152.62, 160.15, 170.21; IR 3033(w), 1789(s), 1717(s), 1688(s) cm⁻¹; $[\alpha]_D^{20}$ -49.5° (c 1.0, CH₂Cl₂) on 83% ee material obtained from (*R*)-VANOL; HRMS (ESI⁺) calcd for C₁₉H₂₄N₂O₅Na, *m/z* 383.1583 ([M+Na]⁺), meas 383.1590. The reaction with 20 mol% catalyst loading ((*S*)-VANOL) and a reaction time of 7 hours gave **27b** in 49% conversion, 47% yield and 86% ee. The diazo compound **26b** was recovered in 63% yield. The yield of **27b** based on the recovered starting material was 96%. The reaction with 10 mol% catalyst loading ((*R*)-VANOL) and a reaction time of 9 hours gave **27b** in 35% conversion, 30% yield and 83% ee. The diazo compound **26b** was recovered in 60% yield. The yield of **27b** based on the recovered starting material was 86%.

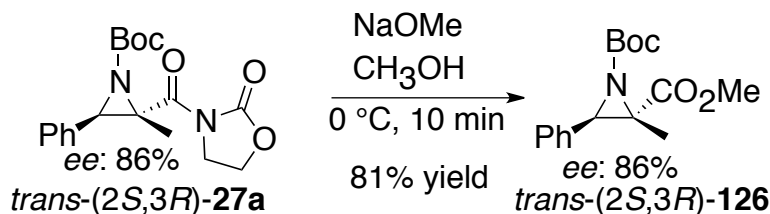
(2*S*,3*R*)-3-[*N*-1-(*t*-butoxycarbonyl)-2-ethyl-3-(4-bromophenyl)aziridine-2-carbonyl]-1-oxazolidin-2-one **110b**:



The aziridine **110b** was prepared from imine **96** (83% purity by weight, 69 mg, 0.20 mmol, 2.0 equiv), diazo compound **26b** (19 mg, 0.10 mmol, 1.0 equiv) and the (*R*)-VANOL catalysts solution (10 mol%, 0.2 mL) by the general procedure with a reaction time of 8 hours. The aziridine was purified by column chromatography (1st column, silica gel, 18 × 180 mm,

hexane:EtOAc:CH₂Cl₂:NEt₃ 3:1:1:0.05; 2nd column, silica gel, 18 × 180 mm, CH₂Cl₂:MeOH:NEt₃ 100:1:1) to give the product as a white foamy solid (30 mg, 0.068 mmol, 68%). The optical purity was determined to be 94% ee by HPLC (Chiralpak AS column, 222 nm, 90:10 Hexane/2-PrOH, flow rate: 1 mL/min). Retention time: *t_R* = 9.6 min for (2*R*,3*S*)-**110b** (minor) and *t_R* = 18.1 min for (2*S*,3*R*)-**110b** (major); A second run gave **110b** in 56% yield and 94% ee. mp 142-144 °C; *R_f* = 0.20 (hexane:EtOAc:CH₂Cl₂:NEt₃ 3:1:1:0.05); ¹H NMR (CDCl₃, 500 MHz) δ 1.04 (t, 3H, *J* = 7.5 Hz, CH₃), 1.20-1.30 (m, 1H, CHH), 1.52 (s, 9H, 3CH₃), 1.80-1.90 (m, 1H, CHH), 3.80 (s, 1H, CH), 3.86-3.94 (m, 1H, CHH), 4.08-4.16 (m, 1H, CHH), 4.38-4.52 (m, 2H, CH₂), 7.30-7.33 (m, 2H, Ar-H), 7.40-7.44 (m, 2H, Ar-H); ¹³C NMR (CDCl₃, 150 MHz) δ 10.62, 22.52, 27.82, 43.14, 47.08, 57.54, 62.71, 81.59, 121.90, 130.18, 131.03, 132.73, 152.67, 159.98, 169.85; IR 2978(w), 1792(s), 1718(s), 1704(s) cm⁻¹; [α]_D²⁰ +53.9° (c 2.0, CH₂Cl₂) on 94% ee material obtained from (S)-VANOL; HRMS (ESI⁺) calcd for C₁₉H₂₃N₂O₅⁷⁹BrNa, *m/z* 461.0688 ([M+Na]⁺), meas 461.0706. The reaction with 20 mol% catalyst loading ((S)-VANOL) and a reaction time of 6 hours gave **110b** in 85% yield and 98% ee.

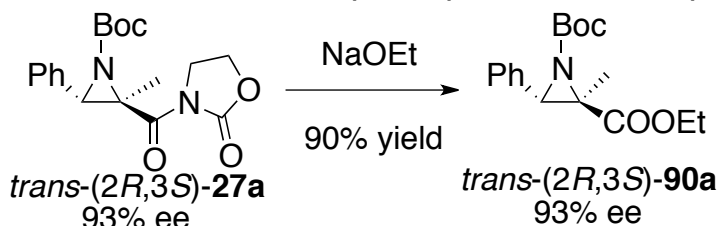
7.2.3.4 Determination of absolute configuration of 27a



To a solution of (2S,3R)-**27a** (86% ee from (*R*)-VANOL, 30 mg, 0.087 mmol, 1.0 equiv) in anhydrous methanol (0.3 mL) and dry CH₂Cl₂ (0.2 mL) at 0 °C was added sodium methoxide in methanol solution (0.5 M, 0.20 mL, 1.2 equiv) dropwise under N₂. The mixture was then stirred at 0 °C for 10 min. H₂O (1 mL) was added and the reaction mixture was neutralized to pH 7 using HCl solution (2 M). Then the reaction mixture was extracted with CH₂Cl₂ (10 mL+ 2 × 5 mL). The combined organic extracts were dried (Na₂SO₄), filtered through Celite and concentrated. The crude product was purified by column chromatography (silica gel, 18 × 150 mm, Hexane:EtOAc 9:1) to give (2S,3R)-**126** (20 mg, 0.070 mmol, 81%) as a colorless oil. The optical purity was determined to be 86% by HPLC analysis (Chiralcel OD-H column, hexane/2-propanol 98:2, 222nm, flow 0.5 mL/min). Retention time: *t_R* = 6.6 min (minor enantiomer) and *t_R* = 7.3 min (major enantiomer); *R_f* = 0.2 (Hexane:EtOAc 9:1); ¹H NMR (CDCl₃, 500 MHz) δ 1.20 (s, 3H, CH₃), 1.40 (s, 9H, 3CH₃), 3.80 (s, 3H, CH₃), 4.10 (s, 1H, CH), 7.25-7.42 (m, 5H, Ar-H); ¹³C NMR (CDCl₃, 125 MHz) δ 13.70, 27.99, 47.21, 49.30, 52.70, 81.61, 127.68, 127.94, 128.24, 134.07, 159.03, 170.03; [α]_D²⁰ +15.1° (c 1.1, CHCl₃). Reported^{22a} for (2*R*,3*S*)-**126** [α]_D²³ −15.5° (c 1.1, CHCl₃). This result

reveals that the (2*S*,3*R*) enantiomer of **27a** is generated from the (*R*)-VANOL catalyst. On this basis the absolute configurations of all aziridines produced from diazo compounds **26a** and **26b** and the (*R*)-VANOL catalyst were assigned the 2*S*,3*R* configuration.

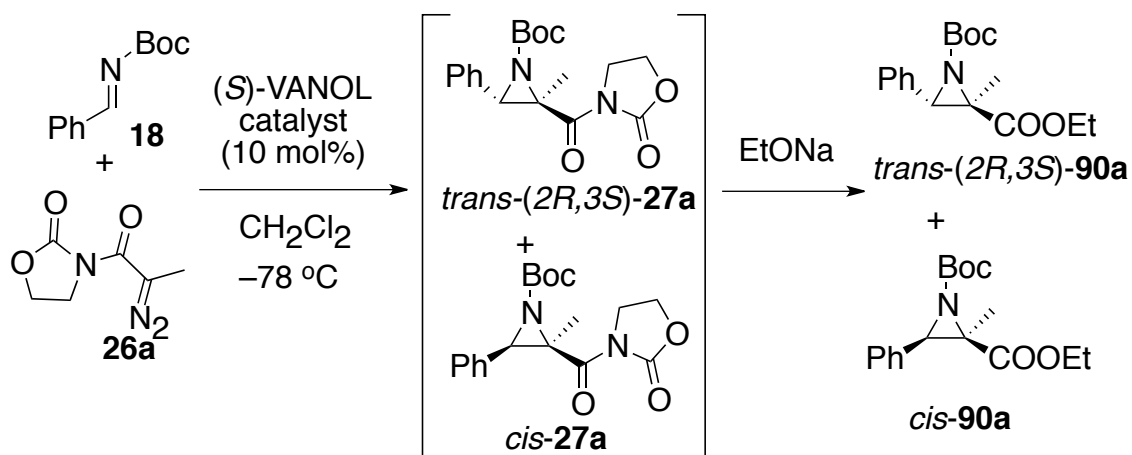
7.2.3.5 Chemical correlation of *trans*-(2*R*,3*S*)-**27a** and *trans*-(2*R*,3*S*)-**90a**



To a solution of *trans*-(2*R*,3*S*)-**27a** (93% ee from (*S*)-VANOL, 48 mg, 0.14 mmol, 1.0 equiv) in absolute ethanol (0.3 mL) and dry CH₂Cl₂ (0.2 mL) at 0 °C was added sodium ethoxide (21 wt% denatured, 61 μL, 0.17 mmol, 1.2 equiv) dropwise under N₂. The mixture was stirred at 0 °C for 10 min, and then aq sat NaHCO₃ (2 mL) and CH₂Cl₂ (10 mL) were added. And the aqueous layer was separated and extracted with CH₂Cl₂ (2 × 5 mL). The combined organic extracts were dried (Na₂SO₄), filtered and concentrated. The product was purified by column chromatography (silica gel, 18 × 200 mm, Hexane:EtOAc 9:1) to give *trans*-(2*R*,3*S*)-**90a** as a pale yellow oil (38 mg, 0.13 mmol, 90%). The optical purity was determined to be 93% ee by HPLC (Chiralcel OD-H column, 222 nm, 98:2 hexane/2-PrOH, flow rate: 0.5 mL/min). Retention time: *t_R* = 5.8 min for (2*R*,3*S*)-**90a** (major) and *t_R* = 6.5 min for (2*S*,3*R*)-**90a** (minor); *R_f* = (hexane:EtOAc 9:1); ¹H NMR (CDCl₃, 500 MHz) δ 1.18 (s, 3H, CH₃), 1.32 (t, 3H,

$J = 7.0$ Hz, CH₃), 1.44 (s, 9H, 3CH₃), 4.08 (s, 1H, CH), 4.12-4.24 (m, 1H, CHH), 4.24-4.36 (m, 1H, CHH), 7.25-7.36 (m, 5H, Ar-H); ¹³C NMR (CDCl₃, 125 MHz) δ 13.66, 14.17, 28.01, 47.22, 49.28, 61.97, 81.54, 127.69, 127.88, 128.21, 134.20, 159.03, 169.57; IR 2980(m), 1738(s), 1158(s), 480(m) cm⁻¹; [α]_D²⁰ -21.0° (c 2.0, CH₂Cl₂); HRMS (ESI⁺) calcd for C₁₇H₂₃NO₄Na, m/z 328.1525 ([M+Na]⁺), meas 328.1577.

7.2.3.6 Determination of diastereoselectivity for the reaction of imine **18** with **26a**



A solution of imine **18** (90% purity by weight, 46 mg, 0.20 mmol, 2.0 equiv) and diazo compound **26a** (17 mg, 0.10 mmol, 1.0 equiv) in dry CH₂Cl₂ (0.3 mL) was cooled to -78 °C under N₂, and then the (S)-VANOL-catalyst solution that had been precooled to -78 °C (10 mol%, 0.2 mL) was quickly added. After it was stirred at -78 °C for 6 hours, NEt₃ (0.5 mL) was added at -78 °C. The mixture was warmed up to rt, H₂O (2 mL) and CH₂Cl₂ (10 mL) were added. And the

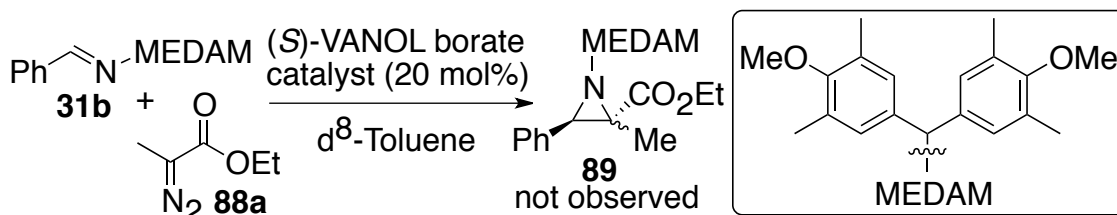
aqueous layer was separated and extracted with CH₂Cl₂ (2 × 5 mL). The combined organic extracts were dried (Na₂SO₄), filtered through Celite and concentrated. The crude product was dissolved in dry CH₂Cl₂ (0.2 mL) and EtOH (0.3 mL), to which EtONa solution (21 wt% denatured, 53 mg, 61 μL, 0.15 mmol, 1.5 equiv) was added dropwise at 0 °C. The resulting mixture was stirred at 0 °C for 10 min. A solution of *aq* sat NaHCO₃ (2 mL) and CH₂Cl₂ (10 mL) were added. The aqueous layer was separated and extracted with CH₂Cl₂ (2 × 5 mL). The combined organic extracts were dried (Na₂SO₄), filtered through Celite and concentrated. The crude product mixture was subjected to ¹H NMR analysis, and *cis-90a* could not be detected.

Detection limit for cis-90a: Pure *trans-90a* (14 mg, 0.046 mmol) was dissolved in CDCl₃ (ca. 0.6 mL). An authentic sample of *cis-90a* (7 mg, 0.02 mmol) prepared as described in Section 7.2.5 was dissolved in CDCl₃ (2 mL). Solutions of *trans-90a* and *cis-90a* were prepared with *trans/cis* ratios of 200:1, 100:1 and 50:1 by the addition of *cis-90a* solution (20 μL, 40 μL and 80 μL respectively) to the solution of *trans-90a*. For the 100:1 sample, *cis-90a* could still be observed from the ¹H NMR. Therefore, the dr was determined to be ≥100:1.

Also notice that the absolute configurations for *cis-27a* and *cis-90a* were not determined. The structures shown in the scheme are assumed to result in a change in the configuration at the 3-position relative to the *trans* isomer.

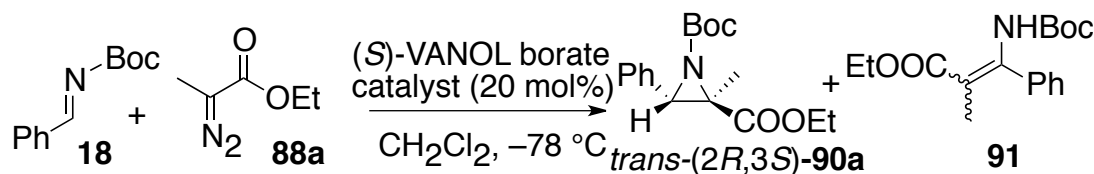
7.2.4 Procedures for Asymmetric Catalytic Aziridination of α -Diazo Esters

7.2.4.1 Reaction of imine **31b** and diazo compound **88a**



A 5 mL vial-shaped single necked flask which had its 14/20 joint replaced by a threaded high vacuum Teflon valve was flame dried (with a stir bar in it) and cooled to rt under N₂ and charged with imine **31b** (39 mg, 0.1 mmol, 1.0 equiv) in d⁸-toluene (0.2 mL). To this was added the (S)-VANOL catalyst solution (prepared as described in Section 7.2.3, d⁸-toluene was used as solvent instead of CH₂Cl₂, 20 mol%, 0.4 mL) at rt, followed by the addition of a solution of diazo compound **88a** (64 mg, 0.5 mmol, 5.0 equiv) in d⁸-toluene (0.4 mL). The Teflon valve was closed and the flask was heated at 80 °C for 64 hours. Analysis of the ¹H NMR spectrum of the crude mixture with the aid of Ph₃CH as internal standard showed that none of desired product **89** could be observed and that imine **31b** (0.098 mmol, 98%) remained essentially unreacted. Only 16% of the initial amount of diazo compound **88a** survived these conditions.

7.2.4.2 Reaction of *N*-Boc imine **18** with diazo compound **88a**



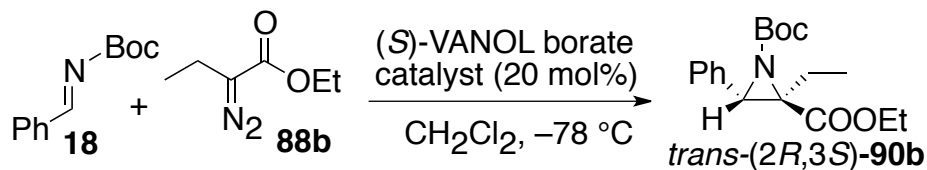
A 25 mL round bottom flask was flame dried under vacuum and cooled to rt under N₂. The vacuum adapter was replaced with a rubber septum. The septum was removed briefly to allow introduction of imine **18** (90% purity by weight, 69 mg, 0.30 mmol, 3.0 equiv) which was weighed in the flask with the septum. Subsequently, the septum was removed again to allow for the addition of dry stir bar. A solution of diazo compound **88a** (12 mg, 0.10 mmol, 1.0 equiv) in dry CH₂Cl₂ (0.6 mL) was then added *via* syringe and a N₂ balloon was attached *via* a needle in the septum. The flask was cooled to –78 °C under N₂ balloon and the (S)-VANOL catalyst solution (see Section 7.2.3, 20 mol%, 0.4 mL) that had been precooled to –78 °C was quickly added. After the reaction mixture was stirred at –78 °C for 15 min, NEt₃ (0.5 mL) was added at –78 °C. The solvent was evaporated and the product was purified by column chromatography (1st column, silica gel, 18 × 180 mm, hexane:EtOAc 15:1; 2nd column, silica gel, 18 × 180 mm, hexane:EtOAc 15:1) to give the product *trans*-(2*R*,3*S*)-**90a** (14 mg, 0.046 mmol, 46%) as a pale yellow oil. The optical purity was determined to be 93% ee by HPLC with *t_R* = 5.8 min for (2*R*,3*S*)-**90a** as the major enantiomer. From the ¹H NMR spectrum of the crude mixture, the yield of **16a** was calculated to be 12% based on the added internal standard triphenylmethane (12 mg, 0.050 mmol, 0.05 equiv). The presence of **91** was confirmed by the comparison with an authentic sample of **16a** obtained as described below. The spectral data of a *trans*-**90a** matched that described above. The aziridine product from this reaction

was shown not to be *cis*-**90a** by comparison of its spectral data with those of an authentic sample of *cis*-**90a** prepared as described in Section 7.2.5. The absolute configuration of *trans*-**90a** was assigned by chemical correlation with *trans*-**27a** (Section 7.2.3.5). This establishes that the (2*R*,3*S*)-enantiomer of **90a** is generated from the (S)-VANOL catalyst. On this basis, the absolute configurations of aziridines **90b** and **90c** from the (S)-VANOL catalyst were assigned as (2*R*,3*S*). The effects of changes in reaction conditions and the ligands in the catalyst on the formation of **90a** can be found in Table 3.1.

Isolation of enamine 91: To a mixture of the imine **18** (69 mg, 0.30 mmol, 1.5 equiv) and ethyl diazo ester **88a** (24 mg, 0.20 mmol, 1.0 equiv) in dry CH₂Cl₂ (1 mL) at –78 °C under N₂ was added triflic acid (2 μL, 20 mol%). The mixture was stirred at –78 °C for 15 min. Then NEt₃ (0.5 mL) was added at –78 °C and the solvent was evaporated. The enamine product was purified by column chromatography (silica gel, 18 × 180 mm, hexane:EtOAc 15:1 to 9:1), affording enamine **91** (12 mg, 0.040 mmol, 20%) as a white solid; mp 90-92 °C; R_f = 0.2 (hexane:EtOAc 4:1); ¹H NMR (CDCl₃, 500 MHz) δ 0.84 (t, 3H, *J* = 7.0 Hz, CH₃), 1.34 (s, 9H, 3CH₃), 2.06 (s, 3H, CH₃), 3.86 (q, 2H, *J* = 7.0 Hz, CH₂), 6.04 (brs, 1H, NH), 7.30 (m, 5H, Ar-H); ¹³C NMR (CDCl₃, 125 MHz) δ 13.42, 16.15, 27.93, 60.34, 81.01, 127.83, 128.31, 128.47, 138.02, 141.44, 152.15, 165.57, 169.94; IR 3328(w), 2979(m), 1715(s), 1698(s), 1162(s) cm^{–1}; HRMS (ESI⁺) calcd for C₁₇H₂₃NO₄Na, *m/z* 328.1525 ([M+Na]⁺), meas 328.1529. The ¹H NMR spectra

of the crude reaction mixture showed a *trans/cis*-**90a** ratio of 5:1 and 37% yield of *trans*-**90a** based on the isolated yield of enamine **91**. In a separate run, Ph₃CH as internal standard was added to the crude reaction mixture and integration allowed the determination that *trans*-**90a** was formed in 42% yield with a *trans/cis* ratio of 3:1 and that enamine **91** was formed in 25% yield.

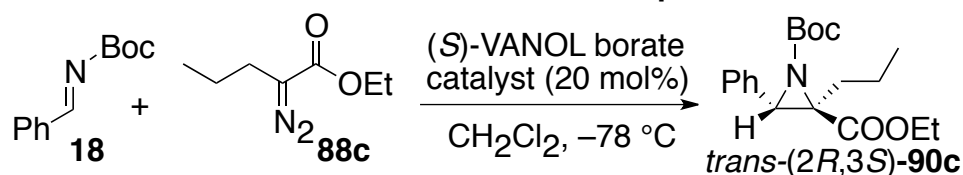
7.2.4.3 Reaction of *N*-Boc imine **18** with diazo compound **88b**



The aziridine *trans*-**90b** was prepared from imine **18** (90% purity by weight, 46 mg, 0.20 mmol, 2.0 equiv), diazo compound **88b** (15 mg, 0.10 mmol, 1.0 equiv) with the (S)-VANOL catalyst solution by the general procedure described for *trans*-(2*R*,3*S*)-**90a** with a reaction time of 1 hour. The product was purified by column chromatography (1st column, 18 × 200 mm, hexane:EtOAc 15:1; 2nd column, 18 × 200 mm, hexane:EtOAc 15:1) to give the aziridine *trans*-(2*R*,3*S*)-**90b** (10 mg, 0.032 mmol, 32%) as a colorless oil. The optical purity was determined to be 82% ee by HPLC (Chiralcel OD-H column, 222 nm, 98:2 Hexane/2-PrOH, flow rate: 0.5 mL/min). Retention time: *t_R* = 5.5 min for (2*R*,3*S*)-**90b** (major) and *t_R* = 6.1 min for (2*S*,3*R*)-**90b** (minor); *R_f* = (hexane:EtOAc 9:1); ¹H NMR (CDCl₃, 500 MHz) δ 0.95 (t, 3H, *J* = 7.5 Hz, CH₃), 1.28-1.20 (m, 1H, CHH), 1.30 (t, 3H, *J* = 7.0 Hz, CH₃), 1.46 (s, 9H, 3CH₃), 1.68-1.56 (m, 1H, CHH), 4.08 (s, 1H, CH), 4.22-4.14 (m, 1H, CHH), 4.36-4.28 (m, 1H, CHH), 7.40-7.20 (m,

5H, Ar-H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 10.24, 14.41, 20.86, 28.22, 50.22, 52.14, 62.03, 81.56, 128.00, 128.07, 128.37, 134.53, 159.32, 169.49; IR 2977(m), 1736(s), 1158(s) cm^{-1} ; $[\alpha]_{\text{D}}^{20} -3.6^\circ$ (c 0.6, CH_2Cl_2) on 82% ee material obtained from (S)-VANOL; HRMS (ESI^+) calcd for $\text{C}_{17}\text{H}_{23}\text{NO}_4\text{Na}$, m/z 342.1681 ($[\text{M}+\text{Na}]^+$), meas 342.1708. The aziridine product was shown not to be *cis*-**17b** by comparison of its spectra with those of an authentic sample of *cis*-**90b** prepared as described in Section 7.2.5.

7.2.4.4 Reaction of *N*-Boc imine **18** with diazo compound **88c**



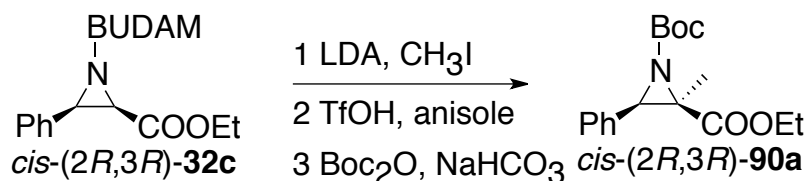
The aziridine **90c** was prepared from imine **18** (90% purity by weight, 46 mg, 0.20 mmol, 2.0 equiv) and diazo compound **88c** (15 mg, 0.10 mmol, 1.0 equiv) with the (S)-VANOL catalyst (20 mol%, 0.4 mL) by the general procedure described for *trans*-(2*R*,3*S*)-**90a** with a reaction time of 1 hour. The product was purified by column chromatography (1st column, silica gel, 18 × 180 mm, hexane:EtOAc 15:1; 2nd column, silica gel, 18 × 180 mm, hexane:EtOAc 15:1) to give the product **90c** (8 mg, 0.025 mmol, 25%) as a colorless oil. The optical purity was determined to be 70% ee by HPLC (Chiralcel OD-H column, 222 nm, 98:2 hexane/2-PrOH, flow rate: 0.5 mL/min). Retention time: t_R = 5.4 min for (2*R*,3*S*)-**90c** (major) and t_R = 6.0 min for (2*S*,3*R*)-**90c** (minor); R_f = 0.50 (hexane:EtOAc 9:1); ^1H NMR (CDCl_3 , 500 MHz) δ 0.80 (t, 3H, J = 7.5 Hz, CH_3),

1.04-1.12 (m, 1H, CHH), 1.30 (t, 3H, $J = 7.0$ Hz, CH₃), 1.40-1.50 (s+m, 11H, 3CH₃ and CH₂), 1.58-1.66 (m, 1H, CHH), 4.03 (s, 1H, CH), 4.22-4.14 (m, 1H, CHH), 4.28-4.36 (m, 1H, CHH), 7.20-7.40 (m, 5H, Ar-H); ¹³C NMR (CDCl₃, 125 MHz) δ 14.07, 14.19, 19.26, 28.01, 29.12, 49.92, 51.12, 61.81, 81.34, 127.74, 127.86, 128.15, 134.30, 159.10, 169.48; IR 2964(m), 1734(s), 1157(s) cm⁻¹; $[\alpha]_D^{20} -18.0^\circ$ (c 0.5, CH₂Cl₂) on 70% ee material obtained from (S)-VANOL; HRMS (ESI⁺) calcd for C₁₉H₂₇NO₄Na, m/z 356.1838 ([M+Na]⁺), meas 356.1825. The aziridine product was shown not to be *cis*-**90c** by comparison of its spectra with those of an authentic sample of *cis*-**90c** prepared as described in Section 7.2.5.

7.2.5 Preparation of the tri-substituted *cis*-aziridines

The optical purity of the starting disubstituted aziridines **32c**^{26c} and **32d**^{26b} were determined to be > 98% ee by chiral HPLC and to have an absolute configuration of 2*R*, 3*R*. The optical purities of the products are assumed to be unchanged as has been previously demonstrated for the alkylation of aziridine-2-carboxylates.⁴⁴

Preparation of *cis*-**90a**



To a solution of dry *i*-Pr₂NH (107 mg, 0.150 mL, 1.05 mmol, 2.10 equiv) in dry THF (5 mL) was added *n*-BuLi (2.3M in hexane, 0.44 mL, 1.0 mmol, 2.0 equiv) at –78 °C. After the mixture was stirred at –78 °C for 5 min, it was stirred at 0 °C for 15 min. After recooling to –78 °C, a solution of *cis*-(2*R*,3*R*)-**32c** (321 mg, 0.500 mmol, 1.00 equiv) in dry THF (5 mL) was added dropwise at –78 °C. The resulting yellow solution was stirred at –78 °C for 30 min. Then methyl iodide (0.21 g, 0.10 mL, 1.5 mmol, 3.0 equiv) was added *via* syringe. The mixture was stirred at this temperature for 1 hour. Then the dry ice-acetone bath was removed and the reaction mixture was allowed to warm up to rt slowly over a period of 1 hour. Then *aq* sat NaHCO₃ (5 mL) was added, and aqueous layer was separated and extracted with ether (3 × 10 mL). The combined organic extracts were dried (Na₂SO₄), filtered through Celite and concentrated. The product was purified by column chromatography (silica gel, 18 × 180 mm, hexane:EtOAc 15:1), affording the alkylated aziridine as a white foamy solid which was subjected to the next step without further purification.

To a solution of all of the above white foamy solids in freshly distilled anisole (5 mL) at 0 °C was added triflic acid (0.38 g, 0.20 mL, 2.5 mmol, 5.0 equiv) dropwise. Then the ice bath was removed and the reaction mixture was stirred at rt for 45 min. The reaction was quenched by the addition of *aq* sat Na₂CO₃ (2 mL). The aqueous layer was separated and extracted with ether (10 mL + 2 × 5 mL). The combined organic extracts were dried (Na₂SO₄), filtered through Celite

and concentrated. The crude N-H aziridine along with anisole (ca. 5 mL) was subjected to the next step without purification.

To all of the crude aziridine was added methanol (2 mL) and NaHCO₃ (252 mg, 3.00 mmol, 6.00 equiv). The mixture was placed in an ultrasound bath for 5 min.

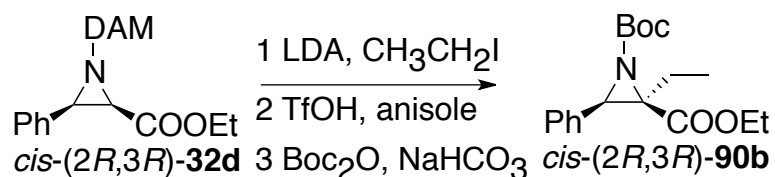
After Boc₂O (438 mg, 2.00 mmol, 4.00 equiv) was added, the mixture was sonicated for 3 hours. After this time, additional portions of NaHCO₃ (252 mg, 3.00 mmol, 6.00 equiv) and Boc₂O (438 mg, 2.00 mmol, 4.00 equiv) were added.

The resulting mixture was sonicated for 2 hours. Then H₂O (2 mL) was added and the mixture was extracted with ether (3 × 10 mL). The combined organic extracts were dried (Na₂SO₄), filtered and concentrated. The product was purified by column chromatography (silica gel, 25 × 250 mm, pure hexane only first to elute anisole and then hexane:EtOAc 9:1), giving the product *cis*-(2*R*,3*R*)-**90a** (142 mg, 0.410 mmol, 81% over three steps) as a colorless oil; *R*_f = 0.48

(hexane:EtOAc 4:1); ¹H NMR (CDCl₃, 500 MHz) δ 0.82 (t, 3H, *J* = 7.0 Hz, CH₃), 1.50 (s, 9H, 3CH₃), 1.70 (s, 3H, CH₃), 3.58 (s, 1H, CH), 3.82-3.96 (m, 2H, CH₂), 7.20-7.31 (m, 3H, Ar-H), 7.32-7.38 (m, 2H, Ar-H); ¹³C NMR (CDCl₃, 125 MHz) δ 13.62, 17.49, 28.00, 49.48, 49.83, 61.13, 82.10, 127.32, 127.79, 127.93, 133.88, 159.23, 167.86; IR 2979(m), 1750(s), 1720(s), 1140(s) cm⁻¹; [α]_D²⁰ +12.0° (c

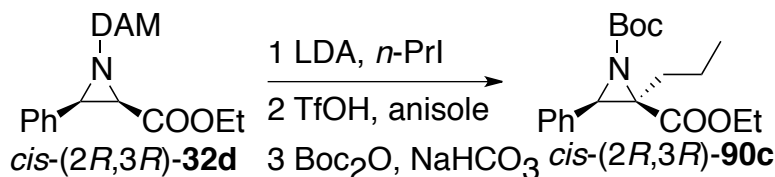
1.0, CH₂Cl₂); HRMS (ESI⁺) calcd for C₁₇H₂₃NO₄Na, *m/z* 328.1525 ([M+Na]⁺), meas 328.1512.

Preparation of *cis*-90b



The *cis*-(2*R*,3*R*)-**90b** was prepared with the procedure described above for *cis*-(2*R*,3*R*)-**90a** except that aziridine *cis*-(2*R*,3*R*)-**32d** (209 mg, 0.500 mmol, 1.00 equiv) was alkylated with iodoethane (0.23 g, 0.12 mL, 1.5 mmol, 3.0 equiv). The product *cis*-(2*R*,3*R*)-**90b** was obtained (101 mg, 0.320 mmol) in 64% yield over three steps as a colorless oil; *R_f* = 0.35 (hexane:EtOAc 4:1); ¹H NMR (CDCl₃, 500 MHz) δ 0.84 (dt, 3H, *J* = 7.5, 2.0 Hz, CH₃), 1.22 (td, 3H, *J* = 7.5, 1.5 Hz, CH₃), 1.52 (s, 9H, 3CH₃), 1.66-1.78 (m, 1H, CHH), 2.20-2.30 (m, 1H, CHH), 3.58 (s, 1H, CH), 3.84-3.96 (m, 2H, CH₂), 7.34-7.20 (m, 5H, Ar-H); ¹³C NMR (CDCl₃, 125 MHz) δ 10.73, 13.70, 25.92, 27.92, 47.54, 54.97, 60.96, 82.06, 127.11, 127.70, 127.96, 134.04, 159.46, 167.25; IR 2978(m), 1720(s), 1152(s) cm⁻¹; [α]_D²⁰ +18.0° (c 1.0, CH₂Cl₂); HRMS (ESI⁺) calcd for C₁₈H₂₅NO₄Na, *m/z* 342.1681 ([M+Na]⁺), meas 342.1672.

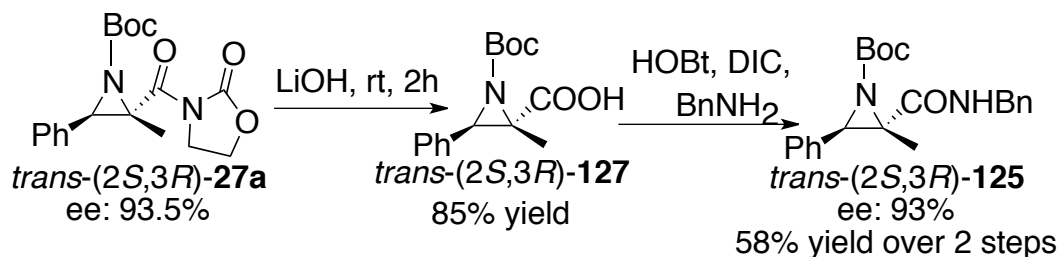
Preparation of *cis*-90c



The *cis*-(2*R*,3*R*)-**90c** was prepared with the procedure described above for *cis*-(2*R*,3*R*)-**90a** except that *cis*-(2*R*,3*R*)-**32d** (209 mg, 0.500 mmol, 1.00 equiv) was alkylated with 1-iodopropane (0.26 g, 0.15 mL, 1.5 mmol, 3.0 equiv). The product *cis*-(2*R*,3*R*)-**90c** (96 mg, 0.29 mmol) was obtained in 58% yield over three steps as a colorless oil; $R_f = 0.50$ (hexane:EtOAc 4:1); ^1H NMR (CDCl_3 , 500 MHz) δ 0.80 (t, 3H, $J = 7.0$ Hz, CH_3), 0.98 (t, 3H, $J = 7.5$ Hz, CH_3), 1.42-1.54 (s+m, 10H, CH and 3 CH_3 overlap), 1.60-1.72 (m, 1H, CHH), 1.80-1.92 (m, 1H, CHH), 2.02-2.12 (m, 1H, CHH), 3.55 (s, 1H, CH), 3.84-3.90 (q, 2H, $J = 7.0$ Hz, CH_2), 7.18-7.32 (m, 5H, Ar-H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 13.64, 14.06, 19.41, 27.89, 34.87, 47.71, 54.18, 60.88, 81.97, 127.05, 127.65, 127.92, 134.09, 159.38, 167.27; IR 2970(m), 1719(s), 1151(s) cm^{-1} ; $[\alpha]_D^{20} +22.8^\circ$ (c 1.0, CH_2Cl_2); HRMS (ESI^+) calcd for $\text{C}_{19}\text{H}_{27}\text{NO}_4\text{Na}$, m/z 356.1838 ($[\text{M}+\text{Na}]^+$), meas 356.1847.

7.2.6 Attempt towards direct asymmetric catalytic access to *cis*-tri-substituted aziridine

Preparation of an authentic sample of aziridine 2-carboxamide *trans*-**125**

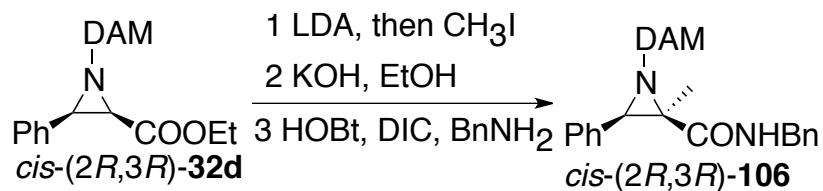


A sample of *trans*-(2*S*,3*R*)-**27a** was prepared with the (*R*)-VANOL catalyst. To a solution of *trans*-(2*S*,3*R*)-**27a** (28 mg, 0.080 mmol, 1.0 equiv) in THF (0.5 mL)

was added a solution of LiOH monohydrate (17 mg, 0.40 mmol, 5.0 equiv) in H₂O (0.3 mL) at room temperature. The mixture was stirred at rt for 2 hours. Then *aq* HCl (6M) was added dropwise to pH ~1-2. The mixture was then extracted with Et₂O (2 × 5 mL). The combined organic extracts were dried (Na₂SO₄), filtered through Celite and concentrated. The aziridine-2-carboxylic acid **127** was obtained as a pale yellow foamy solid, which was subjected to the next step without further purification. The yield of **127** was determined to be 85% by ¹H NMR analysis with the aid of added internal standard triphenylmethane. ¹H NMR (CDCl₃, 500 MHz) δ 1.25 (s, 3H, CH₃), 1.52 (s, 9H, 3CH₃), 4.15 (s, 1H, CH), 6.30 (brs, 1H, NH), 7.12-7.50 (m, 5H, Ar-H), 9.70 (brs, 1H, COOH). A mixture of all of the above acid **127** and 1-hydroxy-benzotriazole (HOBt) monohydrate (19 mg, 0.12 mmol, 1.5 equiv) was suspended in dry CH₂Cl₂ (0.5 mL), and then benzylamine (26 mg, 0.24 mmol, 3.0 equiv) was added. After the mixture was cooled to 0 °C, a solution of diisopropylcarbodiimide (DIC) (15 mg, 0.12 mmol, 1.5 equiv) in dry CH₂Cl₂ (0.3 mL) was added. The resulting mixture was stirred at rt overnight. Without concentration, the entire reaction mixture was loaded onto a silica gel column (18 × 200 mm) and eluted with a 4:1 mixture of Hexane and EtOAc to give the product *trans*-(2*S*,3*R*)-**125** (14.2 mg, 0.0388 mmol) in 49% yield over 2 steps as a white foamy solid with an ee of 93% (Chiralcel OD-H column, 222 nm, 90:10 hexane/2-PrOH, flow rate: 1.0 mL/min). Retention time: *t*_R = 4.3 min for (2*S*,3*R*)-**125** (major) and *t*_R = 11.3 min for

(2*R*,3*S*)-**125** (minor); mp 144-145 °C; R_f = 0.3 (hexane:EtOAc 4:1); ^1H NMR (CDCl_3 , 500 MHz) δ 1.20 (s, 3H, CH_3), 1.42 (s, 9H, 3 CH_3), 4.20 (s, 1H, CH), 4.48 (dd, 1H, J = 14.5, 5.5 Hz, CHH), 4.58 (dd, 1H, J = 14.5, 5.5 Hz, CHH), 6.30 (brs, 1H, NH), 7.38-7.24 (m, 10H, Ar-H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 13.93, 28.03, 44.37, 47.53, 48.44, 81.43, 127.74, 127.92, 128.12, 128.83, 134.63, 137.66, 159.51, 168.00 (2 sp^2 C not located); IR 3372(m), 2998(m), 1726(s), 1720(s), 1161(s) cm^{-1} ; $[\alpha]_D^{20}$ +34.0° (c 1.0, CH_2Cl_2); HRMS (ESI^+) calcd for $\text{C}_{22}\text{H}_{26}\text{N}_2\text{O}_3\text{Na}$, m/z 389.1841 ($[\text{M}+\text{Na}]^+$), meas 389.1857.

Preparation of an authentic sample of aziridine 2-carboxamide cis-125



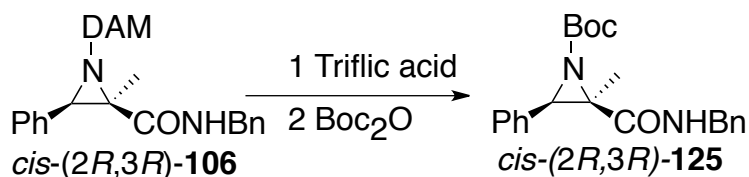
To a solution of dry $i\text{-Pr}_2\text{NH}$ (0.43 g, 0.60 mL, 3.4 mmol, 2.1 equiv) in dry THF (15 mL) was added $n\text{-BuLi}$ (2.5M in hexane, 1.6 mL, 3.2 mmol, 2.0 equiv) at -78°C . After the mixture was stirred at -78°C for 5 min, it was stirred at 0°C for 15 min. After recooling to -78°C , a solution of *cis*-(2*R*,3*R*)-**32d** (836 mg, 2.00 mmol, 1.00 equiv, >98% ee) in dry THF (5 mL) was added dropwise at -78°C . The resulting yellow solution was stirred at -78°C for 30 min. Then methyl iodide (0.85 mg, 0.37 mL, 6.0 mmol, 3.0 equiv.) was added *via* syringe. The reaction mixture was stirred at this temperature for 1 hour. Then the dry ice-acetone bath was removed and the reaction mixture was allowed to warm up to rt slowly over a period of 1 hour. Then sat *aq.* NaHCO_3 (5 mL) was added and the aqueous layer

was separated and extracted with ether (3 × 20 mL). The combined organic extracts were dried (Na₂SO₄), filtered through Celite and concentrated. The crude product was purified by column chromatography (silica gel, 25 × 250 mm, Hexane:EtOAc 5:1), affording the alkylated product as a white foamy solid.

All of the white foamy solids were dissolved in EtOH (5 mL) and then a solution of *aq* KOH (549 mg, 9.8 mmol, 4.9 mmol) in H₂O (5 mL) was added. The resulting mixture was refluxed for 1 hour during which time it became homogeneous. After the reaction mixture was cooled to rt, it was acidified with *aq* HCl (6 M) dropwise to pH ~1-2 and the mixture was extracted with Et₂O (3 × 20 mL). The combined organic extracts were dried (Na₂SO₄), filtered through Celite and concentrated. The crude aziridinene carboxylic acid was purified by column (silica gel, 25 × 100 mm, hexane:acetone 3:1) to give the acid as a white solid (329 mg, 0.82 mmol, 41%).

To a suspension of the above solid acid (101 mg, 0.250 mmol, 1.00 equiv) and 1-hydroxy-benzotriazole (HOBt) monohydrate (58 mg, 0.38 mmol, 1.5 equiv) in CH₂Cl₂ (1.5 mL) was added a solution of benzylamine (81 mg, 0.75 mmol, 3.0 equiv) in CH₂Cl₂ (0.5 mL), followed by the addition of a solution of diisopropylcarbodiimide (DIC) (48 mg, 0.38 mmol, 1.5 equiv) in CH₂Cl₂ (0.5 mL). The resulting mixture was stirred at rt overnight. Without concentration, the entire reaction mixture was loaded onto a silica gel column (18 × 180 mm) eluting with hexane:EtOAc 2:1 to give the product *cis*-(2*R*,3*R*)-**106** (118 mg, 0.24 mmol,

96%) as a white foamy solid; mp 52-56 °C; R_f = 0.25 (hexane:EtOAc 2:1); ^1H NMR (CDCl_3 , 300 MHz) δ 1.68 (s, 3H, CH_3), 3.12 (s, 1H, CH), 3.74 (s, 3H, CH_3), 3.78 (s, 3H, CH_3), 4.05 (dd, 1H, J = 15.5, 6.0 Hz, CHH), 4.23 (dd, 1H, J = 15.0, 6.0 Hz, CHH), 4.43 (s, 1H, CH), 6.76-6.84 (m, 6H), 7.02 (d, 2H, J = 7.5 Hz), 7.12-7.24 (m, 7H), 7.30-7.36 (m, 4H); ^{13}C NMR (CDCl_3 , 150 MHz) δ 12.62, 42.74, 49.70, 53.42, 55.13, 55.15, 69.82, 113.84, 113.86, 126.92, 127.17, 127.20, 127.41, 127.74, 128.10, 128.37, 129.06, 135.23, 135.38, 135.88, 138.01, 158.44, 158.83, 169.85; IR 3379(m), 1666(s), 1512(s), 1248(m) cm^{-1} ; $[\alpha]_D^{23}$ +66.2° (c 1.0, CH_2Cl_2); HRMS (ESI^+) calcd for $\text{C}_{32}\text{H}_{33}\text{N}_2\text{O}_3$, m/z 493.2491 ($[\text{M}+\text{H}]^+$), meas 493.2477.

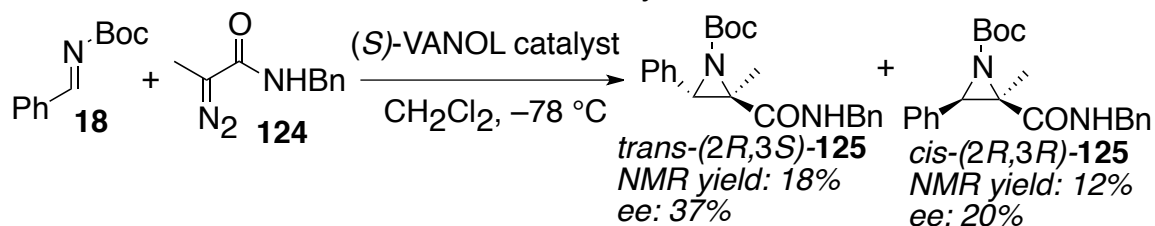


To a solution of *cis*-(2*R*,3*R*)-**106** (118 mg, 0.240 mmol, 1.00 equiv) in freshly distilled anisole (2 mL) at 0 °C was added triflic acid (0.11 mL, 1.2 mmol, 5.0 equiv) dropwise. Then the ice bath was removed and the reaction mixture was stirred at rt for 45 min, and then quenched by the addition of *aq* sat Na_2CO_3 (2 mL). The aqueous layer was separated and extracted with ether (3 x 10 mL). The combined organic extracts were dried (Na_2SO_4), filtered through Celite and concentrated. The crude product along with anisole (ca. 2 mL) was subjected to the next step without purification.

To all of the crude products obtained above was added methanol (2 mL) and NaHCO₃ (61 mg, 0.72 mmol, 3.00 equiv). The mixture was put in an ultrasound bath for 5 min. Then Boc₂O (105 mg, 0.480 mmol, 2.00 equiv) was added and sonicated for 3 hours. After this time, additional portions of NaHCO₃ (61 mg, 0.72 mmol, 3.00 equiv) and Boc₂O (105 mg, 0.480 mmol, 2.00 equiv) were added. The resulting mixture was sonicated for 3 hours and stirred at rt overnight. H₂O (2 mL) was added and the mixture was extracted with ether (3 × 10 mL). The combined organic extracts were dried (Na₂SO₄), filtered and concentrated. The product was purified by column chromatography (1st column, silica gel, 18 × 180 mm, hexane:EtOAc 3:2; 2nd column, silica gel, 18 × 180 mm, benzene:EtOAc 15:1), giving the product *cis*-**125** as a white solid (4.5 mg, 0.012 mmol, 5%). The optical purity of *cis*-**52** was determined to be >98% ee by HPLC (Chiralcel OD-H column, 222 nm, 90:10 hexane/2-PrOH, flow rate: 1.0 mL/min). Retention time: *t_R* = 3.6 min for *cis*-(2*R*,3*R*)-**125** (major) and *t_R* = 11.3 min for *cis*-(2*S*,3*S*)-**125** (minor). *R_f* = 0.20 (hexane:EtOAc 4:1). ¹H NMR (CDCl₃, 300 MHz) δ 1.49 (s, 9H, 3CH₃), 1.71 (s, 3H, CH₃), 3.65 (s, 1H, CH), 3.95 (dd, 1H, *J* = 15.0, 4.5 Hz, CHH), 4.29 (dd, 1H, *J* = 15.0, 7.5 Hz, CHH), 6.55 (brs, 1H, NH), 6.60-6.70 (m, 2H, Ar-H), 7.08-7.18 (m, 3H, Ar-H), 7.22-7.36 (m, 5H, Ar-H); ¹³C NMR (CDCl₃, 150 MHz) δ 16.84, 27.80, 42.86, 50.20, 50.34, 82.16, 126.90, 127.26, 127.29, 127.74,

128.17, 128.20, 133.75, 137.17, 159.11, 167.31; IR 3310(m), 2950(m), 1720(s), 1260(s) cm^{-1} ; $[\alpha]_{\text{D}}^{20} -20.0^\circ$ (c 0.2, CH_2Cl_2); HRMS (ESI^+) calcd for $\text{C}_{22}\text{H}_{26}\text{N}_2\text{O}_3\text{Na}$, m/z 389.1841 ($[\text{M}+\text{Na}]^+$), meas m/z 389.1857.

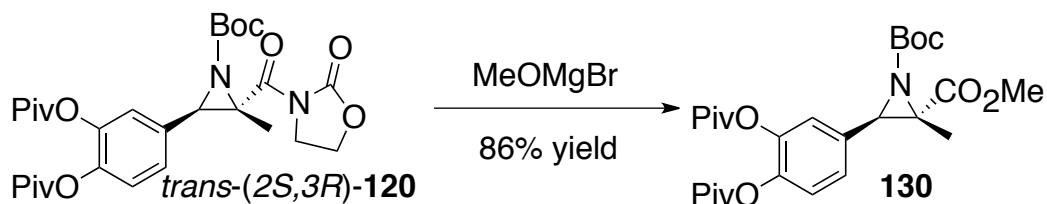
Reaction between imine **18 and the secondary diazoamide **124****



A 25 mL round bottom flask was flame dried under vacuum and cooled to rt under N_2 . The vacuum adapter was replaced with a rubber septum. The septum was removed briefly to allow introduction of imine **18** (90% purity by weight, 69 mg, 0.30 mmol, 3.0 equiv) which was weighed in the flask with the septum. Subsequently, the septum was removed again to allow for the addition of dry stir bar. Dry CH_2Cl_2 (0.2 mL) was then introduced through the septum with a syringe and then a balloon filled with nitrogen was attached *via* a needle in the septum. After the flask was cooled to -78°C , the VANOL catalyst solution (20 mol%, 0.4 mL) was quickly added. Then diazo compound **124** (19 mg, 0.10 mmol, 1.0 equiv) in CH_2Cl_2 (0.4 mL) was added to the reaction mixture *via* syringe at -78°C . The resulting mixture was stirred at -78°C for 1 h, and then NEt_3 (0.5 mL) was added at -78°C . The solvent was evaporated and the product was purified by column chromatography (1st column, 18 × 200 mm, hexane:EtOAc 3:1; 2nd column, 18 × 200 mm, hexane:acetone 4:1) to give the aziridine *trans*-(2*R*,3*S*)-**52**

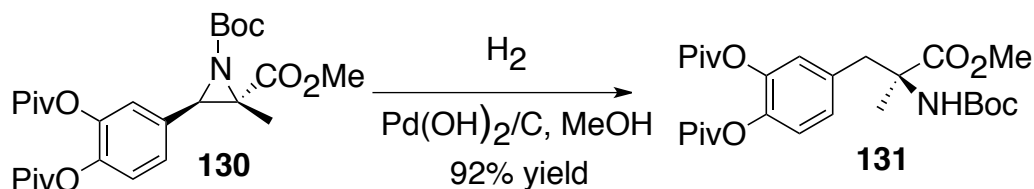
as a white solid (4.5 mg, 0.012 mmol) in 12% isolated yield. The optical purity of *trans*-**125** was determined to be 37% ee by HPLC with *trans*-(2*R*,3*S*)-**125** as the major enantiomer. Unfortunately, due to the low yield, it was not possible to obtain a pure sample of *cis*-**125**. However, a sample of *cis*-**125** was obtained which was contaminated with impurities but free of *trans*-**125**. The optical purity of *cis*-**52** was determined on this sample to be 20% with *cis*-(2*R*,3*R*)-**125** as the major enantiomer. In the ^1H NMR of the crude mixture, there was no diazo compound **124** left. The NMR yields for *trans*-**125** and *cis*-**125** were calculated to be 18% and 12%, respectively based on the internal standard triphenylmethane (12 mg, 0.050 mmol) that was added to the crude mixture.

7.2.7 Synthesis of L-methylDOPA derivative



A 5 mL flame-dried round bottom flask filled with N_2 was charged with anhydrous methanol (0.2 mL). The vacuum adapter was replaced with a septum to which a N_2 balloon was attached. MeMgBr (25 mL, 0.069 mmol, 1.5 equiv) was added to form a suspension of MeOMgBr. Another 10 mL flame-dried round bottom flask filled with N_2 was charged with *trans*-(2*S*,3*R*)-**120** (25 mg, 0.046 mmol, 1.0 equiv), dry CH_2Cl_2 (0.2 mL) and anhydrous methanol (0.2 mL). The vacuum adapter was replaced with a septum to which a N_2 balloon was attached. The flask was cooled to 0 °C. Then the suspension of MeOMgBr was transferred via

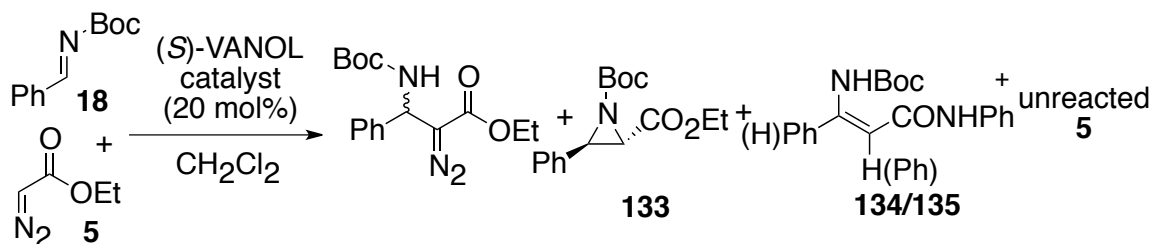
a syringe and added quickly to the solution. The residue in 5 mL flask was rinsed with methanol (0.1 mL) and added to the solution too. The resulting mixture was stirred at 0 °C for 3 min. sat aq NH₄Cl (0.5 mL) and H₂O (0.2 mL) were added to quench the reaction. CH₂Cl₂ (5 mL) was also added. The aqueous layer was separated and extracted with CH₂Cl₂ (2 × 5 mL). The organic layers were combined, dried (Na₂SO₄) and filtered. The filtrate was concentrated and purified by column chromatography (silica gel, 18 × 180 mm, hexane:EtOAc:NEt₃ 4:1:0.05) to give methyl ester **130** as a white foamy solid (19 mg, 0.039 mmol, 86%). ¹H NMR (CDCl₃, 300 MHz) δ 1.21 (s, 3H, CH₃), 1.31,1.32 (2s, 18H, 6CH₃), 1.45 (s, 9H, 3CH₃), 3.77 (s, 3H, CH₃), 4.05 (s, 1H, CHH), 7.06-7.12 (m, 2H, Ar-H), 7.18 (dd, 1H, *J* = 8.4, 2.1 Hz, Ar-H); ¹³C NMR (CDCl₃, 125 MHz) δ 13.64, 27.19, 27.22, 27.97, 39.14, 47.47, 48.47, 48.50, 52.76, 81.89, 122.71, 123.30, 125.47, 132.52, 142.32, 142.44, 158.78, 169.76, 175.71, 175.82; IR 2978(w), 1761(s), 1741(s), 1115(s) cm⁻¹; [α]_D²⁰ +9.5° (c 1.0, CH₂Cl₂); HRMS (ESI⁺) calcd for C₂₆H₃₇NO₈Na, *m/z* 514.2417 ([M+Na]⁺), meas 514.2377.



To a solution was added methyl ester **130** (16 mg, 0.033 mmol, 1.0 equiv) in anhydrous methanol was added Pearlman's catalyst (12 mg, 0.0065 mmol, 0.20

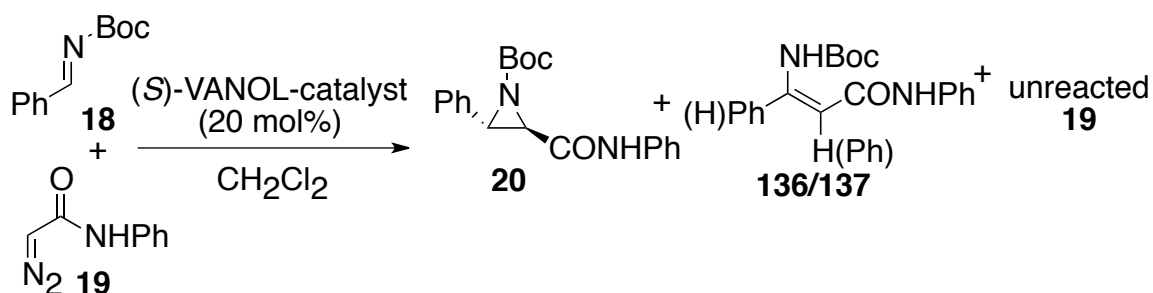
equiv). The flask was evacuated and filled with H₂. This process was repeated for another 3 times. The resulting mixture was stirred at rt under a H₂ balloon for 1 hour. After it was passed through a Celite pad in a short pippet and washed well with MeOH, the filtrate was concentrated to give **131** (15 mg, 0.030 mmol, 92%) as a colorless oil which solidified during storage; mp 50-52 °C; ¹H NMR (CDCl₃, 600 MHz) δ 1.30, 1.31 (2s, 18H, 6CH₃), 1.44 (s, 9H, 3CH₃), 1.51 (brs, 3H, CH₃), 3.21 (d, 1H, *J* = 13.8 Hz), 3.34 (d, 1H, *J* = 13.8 Hz), 5.13 (brs, 1H, NH), 6.83 (s, 1H, Ar-H), 6.90 (d, 1H, *J* = 8.4 Hz, Ar-H), 7.01 (d, 1H, *J* = 7.8 Hz, Ar-H); ¹³C NMR (CDCl₃, 150 MHz) δ 23.95, 27.42, 27.43, 28.58, 39.27, 39.32, 40.66, 52.76, 60.41, 79.69, 123.08, 125.25, 128.00, 135.19, 141.65, 142.28, 154.45, 174.34, 175.86, 176.08; IR 3427(w), 2976(w), 1761(s), 1716(s), 1118(s) cm⁻¹; [α]_D²⁰ +6.8° (c 1.0, CH₂Cl₂); HRMS (ESI⁺) calcd for C₂₆H₃₉NO₈Na, *m/z* 516.2573 ([M+Na]⁺), meas 516.2545.

7.2.8 Reaction between imine **18** and EDA **5** or diazoacetamide **19** with VANOL borate catalyst



A 25 mL round bottom flask was flame dried under vacuum and cooled to rt under N₂. The vacuum adapter was replaced with a rubber septum. The septum

was removed briefly to allow introduction of imine **18** (90% purity by weight, 69 mg, 0.30 mmol, 1.5 equiv) which was weighed in the flask with the septum. Subsequently, the septum was removed again to allow for the addition of dry stir bar. Dry CH₂Cl₂ (0.60 mL) was then introduced through the septum with a syringe and then a balloon filled with nitrogen was attached *via* a needle in the septum. After the flask was cooled to –78 °C or –46 °C, the (S)-VANOL catalyst solution (20 mol%, 0.40 mL) was quickly added. Then diazo compound **5** (32 µL, 0.20 mmol, 1.0 equiv) was added to the reaction mixture *via* syringe at –78 °C. The resulting mixture was stirred at –78 °C or –46 °C for 3 h, and then NEt₃ (0.5 mL) was added at –78 °C. After evaporation, the crude reaction mixture was obtained. The results are shown in Scheme 3.16. The products were not isolated but identified from the crude reaction mixture in comparison with those reported⁸⁸.



A 25 mL round bottom flask was flame dried under vacuum and cooled to rt under N₂. The vacuum adapter was replaced with a rubber septum. The septum was removed briefly to allow introduction of imine **18** (90% purity by weight, 69 mg, 0.30 mmol, 1.5 equiv) and diazoacetamide **19** (33 mg, 0.20 mmol, 1.0 equiv) which were weighed in the flask with the septum. Subsequently, the septum was

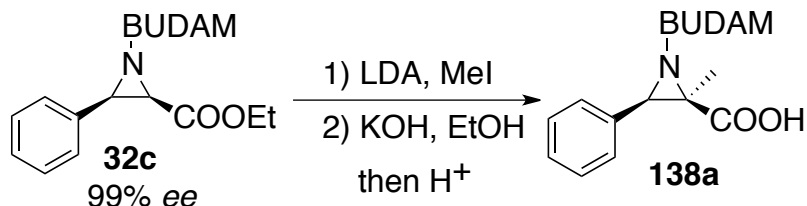
removed again to allow for the addition of dry stir bar. Dry CH_2Cl_2 (0.60 mL) was then introduced through the septum with a syringe and then a balloon filled with nitrogen was attached *via* a needle in the septum. After the flask was cooled to $-78\text{ }^\circ\text{C}$ or $-46\text{ }^\circ\text{C}$, the (S)-VANOL catalyst solution (20 mol%, 0.40 mL) was quickly added. The resulting mixture was stirred at $-78\text{ }^\circ\text{C}$ or $-46\text{ }^\circ\text{C}$ for 3 h, and then NEt_3 (0.5 mL) was added at $-78\text{ }^\circ\text{C}$. After evaporation, the crude reaction mixture was obtained. The results are shown in Scheme 3.16. The products were not isolated but identified from the crude reaction mixture in comparison with those reported¹⁸.

When the reaction was carried at room temperature, the above procedure was followed and the reaction mixture was stirred at rt for 24 h.

7.3 Experimental Section for Chapter Four

7.3.1 Preparation of acids

Preparation of acid **138a**

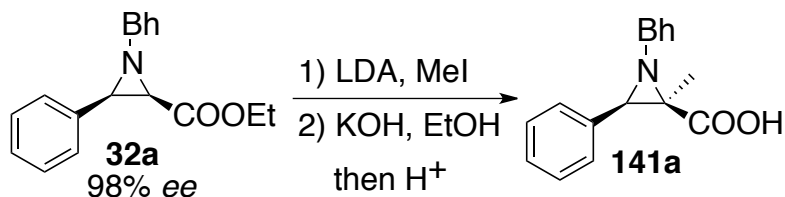


*Alkylation: General procedure for alkylation, illustrated for the acid **138a**.* To a flame-dried 50 mL round bottom flask filled with N₂ was charged with dry *i*-Pr₂NH (0.050 mL, 0.33 mmol, 2.1 equiv) and dry THF (3 mL). The vacuum adapter was quickly replaced with a septum to which a N₂ balloon was attached *via* a needle. The flask was cooled in a dry ice-acetone bath (−78 °C). *n*-BuLi (2.3M, 0.14 mL, 0.32 mmol, 2.0 equiv) was added dropwise *via* syringe. After it was stirred at −78 °C for 5 min, the solution was stirred at 0 °C for 15 min. After the flask was cooled to −78 °C again, a solution of ester **32c** (99% ee, 100 mg, 0.160 mmol, 1.00 equiv) in dry THF (2 mL) was added dropwise. The resulting yellow solution was stirred at −78 °C for 30 min. Then CH₃I (0.030 mL, 0.48 mmol, 3.0 equiv) was added *via* syringe. The resulting mixture was stirred at −78 °C for 1 h, and then dry ice-acetone bath was removed. And the reaction mixture was allowed to warm up to rt slowly over a period of 1 h. Then *aq* sat NaHCO₃ (2 mL) and ether (10 mL) were added. The aqueous layer was separated and extracted with ether (2 × 5 mL). The combined organic extracts were dried (Na₂SO₄) and filtered. The

filtrate was concentrated to afford the methylated ester used directly in the next step.

Hydrolysis: To the mixture of the methylated ester in THF (1 mL) and ethanol (1 mL) was added an aqueous solution of KOH (45 mg, 0.80 mmol, 5.0 equiv) in H₂O (1 mL). The resulting mixture was refluxed overnight (~17 h). After it was cooled to rt, the volatiles were evaporated and *aq* citric acid (2N, 2 mL) was added. The mixture was extracted with ether (10 mL + 2 × 5 mL). The combined organic extracts were dried (Na₂SO₄) and filtered. The filtrate was concentrated and purified by column chromatography (silica gel, 18 × 180 mm, hexane:EtOAc 5:1). The product **138a** was obtained as a white solid (85 mg, 0.14 mmol) in 87% yield over 2 steps; mp 72-74 °C; R_f = 0.30 (hexane:EtOAc 4:1). Spectral data for **138a**: ¹H NMR (500 MHz, CDCl₃) δ 1.36, 1.38 (2s, 36H), 1.63 (s, 3H), 3.24 (s, 1H), 3.638, 3.642 (2s, 6H), 4.31 (s, 1H), 6.96-7.00 (m, 2H), 7.14-7.18 (m, 3H), 7.24 (s, 2H), 7.29 (s, 2H), 10.00 (brs, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 12.14, 32.01, 32.09, 35.80, 35.82, 49.48, 53.65, 64.19, 64.24, 71.06, 125.00, 126.08, 127.28, 128.03, 128.36, 134.54, 135.49, 135.85, 143.83, 143.90, 158.72, 159.15, 170.50; IR (thin film) 2963(s), 1768(m), 1414(m) cm⁻¹; HRMS calcd for C₄₁H₅₈NO₄ (M+H, ESI⁺) *m/z* 628.4366, meas 628.4321; [α]_D²⁰ 23.6 °(c 1.0, Et₂O).

Preparation of acid 141a:

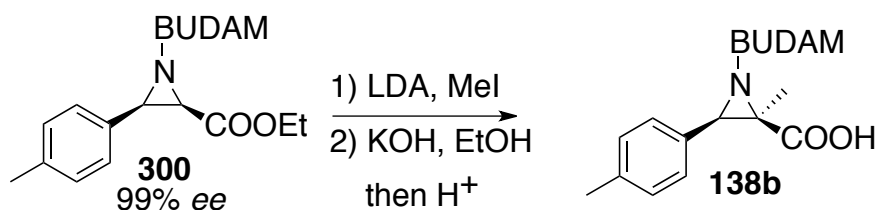


Alkylation: The general procedure for the alkylation was followed with ester **32a** (98% ee, 357 mg, 1.00 mmol, 1.00 equiv), *i*-Pr₂NH (0.30 mL, 2.1 mmol, 2.1 equiv), *n*-BuLi (2.3M, 0.87 mL, 2.0 mmol, 2.0 equiv) and CH₃I (0.20 mL, 3.0 mmol, 3.0 equiv). After workup, the crude product was obtained which was used directly in the next step.

Hydrolysis: To the mixture of the above methylated ester in ethanol (2 mL) was added an aqueous solution of KOH (280 mg, 5.00 mmol, 5.00 equiv) in H₂O (5 mL). The resulting mixture was refluxed overnight (~12 h). After it was cooled to rt, aq citric acid (2N, 5 mL) was added. The resulting precipitate was collected by filtration. The product was obtained as a slightly brown solid (250 mg, 0.730 mmol) in 73% yield over 2 steps; mp 155-156 °C; R_f = 0.10 (hexane:EtOAc 4:1).

Spectral data for acid **141a**: ¹H NMR (500 MHz, DMSO-d₆) δ 1.45 (s, 3H), 3.15 (s, 1H), 4.68 (s, 1H), 7.08-7.44 (m, 11H), 7.56 (d, 2H, *J* = 7.5 Hz), 7.71 (d, 2H, *J* = 7.5 Hz), 12.0 (brs, 1H); ¹³C NMR (125 MHz, DMSO-d₆) δ 13.22, 50.26, 51.56, 68.86, 126.58, 126.63, 126.77, 126.96, 127.17, 127.54, 127.68, 128.19, 128.27, 136.63, 143.92, 144.20, 170.84; IR (thin film) 1720(s), 1265(m) cm⁻¹; HRMS calcd for C₂₃H₂₂NO₂ (M+H, ESI⁺) *m/z* 344.1651, meas 344.1626; [α]_D²⁰ 110.3° (c 0.67, CH₂Cl₂).

Preparation of acid 138b



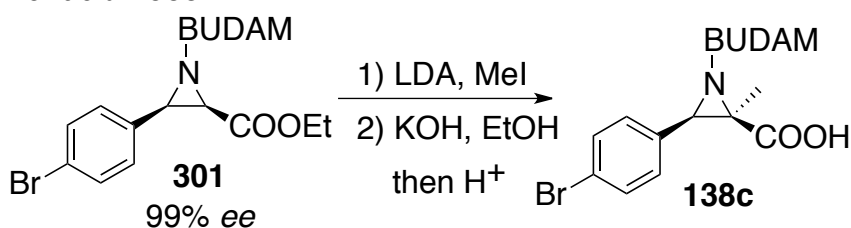
Alkylation: The general procedure for the alkylation was followed with ester **300** (99% ee, 656 mg, 1.00 mmol, 1.00 equiv), *i*-Pr₂NH (0.30 mL, 2.1 mmol, 2.1 equiv), *n*-BuLi (2.5M, 0.84 mL, 2.1 mmol, 2.1 equiv) and CH₃I (0.19 mL, 3.0 mmol, 3.0 equiv). After workup, the crude product was obtained which was used directly in the next step.

Hydrolysis: To the mixture of the crude product in THF (2.5 mL) and ethanol (2.5 mL) was added an aqueous solution of KOH (280 mg, 5.00 mmol, 5.00 equiv) in H₂O (2.5 mL). The resulting mixture was refluxed for 42 h. After it was cooled to rt, the volatiles were evaporated and aq HCl (6N) was added to pH ~2. The mixture was extracted with ether (3 × 10 mL). The combined organic extracts were dried (Na₂SO₄) and filtered. The filtrate was concentrated and purified by column chromatography (silica gel, 25 × 200 mm, hexane:acetone 9:1). The product was obtained as a white solid (602 mg, 0.937 mmol) in 94% yield over 2 steps; mp 82-85 °C; R_f = 0.50 (hexane:EtOAc 4:1). Spectral data for acid **138b**:

¹H NMR (500 MHz, CDCl₃) δ 1.40, 1.41 (2s, 36H), 1.65 (s, 3H), 2.26 (s, 3H), 3.24 (s, 1H), 3.67, 3.68 (2s, 6H), 4.32 (s, 1H), 6.89 (d, 2H, *J* = 8.0 Hz), 6.99 (d, 2H, *J* = 8.0 Hz), 7.28 (s, 2H), 7.34 (s, 2H), 9.50 (brs, 1H); ¹³C NMR (125 MHz,

CDCl₃) δ 12.07, 21.07, 32.02, 32.08, 35.79, 35.80, 49.33, 53.48, 64.17, 64.24, 71.08, 124.99, 126.09, 127.17, 129.02, 131.59, 135.60, 135.92, 137.73, 143.78, 143.85, 158.68, 159.12, 170.66; IR (thin film) 2961(s), 1718(s), 1224(s) cm⁻¹; HRMS calcd for C₄₂H₆₀NO₄ (M+H, ESI⁺) m/z 642.4522, meas 642.4482; $[\alpha]_D^{20}$ 9.3° (c 2.0, CH₂Cl₂).

Preparation of acid 138c

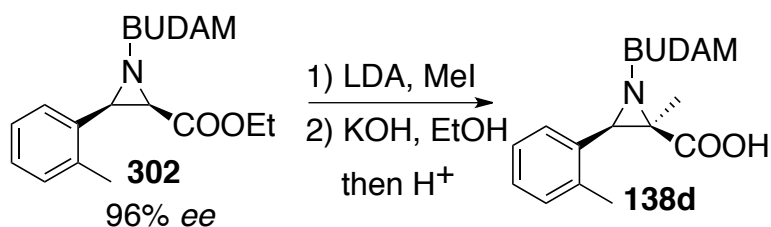


Alkylation: The general procedure for the alkylation was followed with ester **301** (99% ee, 720 mg, 1.00 mmol, 1.00 equiv), *i*-Pr₂NH (0.30 mL, 2.1 mmol, 2.1 equiv), *n*-BuLi (2.5M, 0.84 mL, 2.1 mmol, 2.1 equiv) and CH₃I (0.19 mL, 3.0 mmol, 3.0 equiv). After workup, the crude product was obtained which was used directly in the next step.

Hydrolysis: To the mixture of the crude product in ethanol (2.5 mL) was added an aqueous solution of KOH (280 mg, 5.00 mmol, 5.00 equiv) in H₂O (2.5 mL). The resulting mixture was refluxed for 3 h. After it was cooled to rt, CH₂Cl₂ (5 mL) was added and the mixture was refluxed for 66 hours until it became a homogeneous solution. After it was cooled to rt, the volatiles were removed by rotary evaporation and aq HCl (6N) was added to pH ~2. The mixture was extracted with ether (20 mL + 2 × 10 mL). The combined organic extracts were

dried (Na₂SO₄) and filtered. The filtrate was concentrated and purified by column chromatography (silica gel, 25 × 250 mm, hexane:acetone 9:1). The product **138c** was obtained as a white solid (383 mg, 0.54 mmol) in 54% yield over 2 steps; mp 78-80 °C; R_f = 0.30 (hexane:acetone 9:1). Spectral data for acid **138c**: ¹H NMR (300 MHz, CDCl₃) δ 1.45, 1.47 (2s, 36H), 1.71 (s, 3H), 3.26 (s, 1H), 3.73 (s, 6H), 4.40 (s, 1H), 6.94 (d, 2H, *J* = 8.4 Hz), 7.30-7.40 (m, 6H), 9.60 (brs, 1H); ¹³C NMR (150 MHz, CDCl₃) δ 12.11, 32.01, 32.07, 35.78, 35.80, 49.63, 52.83, 64.17, 64.26, 70.91, 122.08, 124.96, 126.01, 129.04, 131.45, 133.75, 135.29, 135.75, 143.90, 143.92, 158.73, 159.17, 170.14; IR (thin film) 2961(s), 1769(m), 1414(m) cm⁻¹; HRMS calcd for C₄₁H₅₇NO₄⁷⁹Br (M+H, ESI⁺) *m/z* 706.3471, meas 706.3450; [α]_D²⁰ 18.6° (c 1.0, CH₂Cl₂).

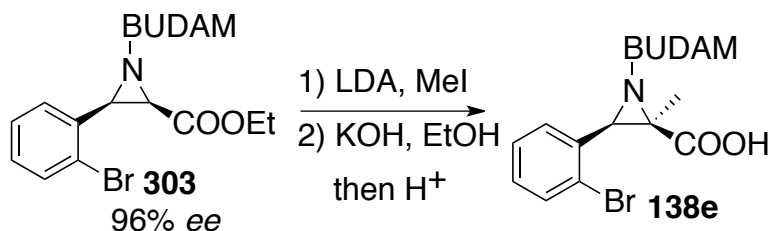
Preparation of acid 138d:



Alkylation: The general procedure for the alkylation was followed with ester **302** (96% ee, 656 mg, 1.00 mmol, 1.00 equiv), *i*-Pr₂NH (0.30 mL, 2.1 mmol, 2.1 equiv), *n*-BuLi (2.5M, 0.84 mL, 2.1 mmol, 2.1 equiv) and CH₃I (0.19 mL, 3.0 mmol, 3.0 equiv). After workup, the crude product was obtained which was used directly in the next step.

Hydrolysis: To the mixture of the crude product in THF (2.5 mL) and ethanol (2.5 mL) was added an aqueous solution of KOH (280 mg, 5.00 mmol, 5.00 equiv) in H₂O (5 mL). The resulting mixture was refluxed for 22 h. After it was cooled to rt, the volatiles were evaporated and aq HCl (6N, 5 mL) was added to pH ~2. The mixture was extracted with ether (20 mL + 2 × 10 mL). The combined organic extracts were dried (Na₂SO₄) and filtered. The filtrate was concentrated and purified by column chromatography (silica gel, 25 × 180 mm, hexane:acetone 9:1). The product **138d** was obtained as a white solid (507 mg, 0.780 mmol) in 78% yield over 2 steps; mp 76-78 °C; R_f = 0.50 (hexane:acetone 4:1). Spectral data for acid **138d**: ¹H NMR (300 MHz, CDCl₃) δ 1.43, 1.46 (2s, 36H), 1.71 (s, 3H), 2.30 (s, 3H), 3.23 (s, 1H), 3.68, 3.71 (2s, 6H), 4.40 (s, 1H), 7.00-7.20 (m, 4H), 7.34 (s, 2H), 7.39 (s, 2H), 9.80 (brs, 1H); ¹³C NMR (150 MHz, CDCl₃) δ 11.91, 18.86, 31.98, 32.08, 35.74, 35.78, 49.09, 53.75, 64.13, 64.15, 71.32, 124.92, 125.49, 126.00, 127.04, 127.93, 129.94, 132.96, 135.56, 135.83, 136.55, 143.72, 143.86, 158.66, 159.07, 170.32; IR (thin film) 2961(s), 1767(s), 1414(m) cm⁻¹; HRMS calcd for C₄₂H₆₀NO₄ (M+H, ESI⁺) *m/z* 642.4522, meas 642.4491; [α]_D²⁰ 31.3° (c 1.0, CH₂Cl₂).

Preparation of acid 138e:

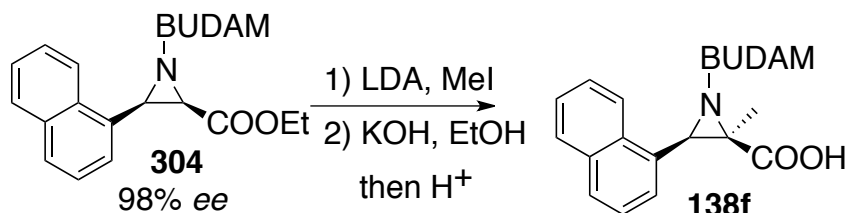


Alkylation: The general procedure for the alkylation was followed with ester **303** (96% ee, 432 mg, 0.600 mmol, 1.00 equiv), *i*-Pr₂NH (0.18 mL, 1.3 mmol, 2.1 equiv), *n*-BuLi (2.3M, 0.51 mL, 1.3 mmol, 2.0 equiv) and CH₃I (0.12 mL, 1.8 mmol, 3.0 equiv). After workup, the crude product was obtained which was used directly in the next step.

Hydrolysis: To the mixture of the crude product in THF (2 mL) and ethanol (2 mL) was added an aqueous solution of KOH (168 mg, 3.00 mmol, 5.00 equiv) in H₂O (2 mL). The resulting mixture was refluxed for 12 h. And another portion of KOH (168 mg, 3.00 mmol, 5.00 equiv) in H₂O (2 mL) was added. The resulting mixture was refluxed for 48 h. After it was cooled to rt, the volatiles were removed by rotary evaporation and aq citric acid (2N, 5 mL) was added. The mixture was extracted with ether (3 × 10 mL). The combined organic extracts were dried (Na₂SO₄) and filtered. The filtrate was concentrated and purified by column chromatography (silica gel, 25 × 200 mm, hexane:acetone 5:1). The product was obtained as a white solid (240 mg, 0.340 mmol) in 57% yield over 2 steps; mp 76-80 °C; R_f = 0.50 (hexane:acetone 5:1). Spectral data for acid **138e**: ¹H NMR (500 MHz, CDCl₃) δ 1.37, 1.40 (2s, 36H), 1.71 (s, 3H), 3.27 (s, 1H), 3.63, 3.67 (2s, 6H), 4.38 (s, 1H), 7.00-7.16 (m, 3H), 7.27, 7.30 (2s, 4H), 7.44-7.50 (dd, 1H, *J* = 7.5, 1.5 Hz), 9.80 (brs, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 12.12, 32.00, 32.10, 35.79, 35.83, 49.88, 55.31, 64.19, 64.21, 71.03, 123.73, 124.98, 125.95, 126.95, 128.91, 129.55, 132.47, 134.44, 135.21, 135.71, 143.86, 143.95, 158.77, 159.12,

169.57; IR (thin film) 2961(s), 1773(m), 1414(m) cm^{-1} ; HRMS calcd for $\text{C}_{41}\text{H}_{57}\text{NO}_4^{79}\text{Br}$ ($\text{M}+\text{H}$, ESI^+) m/z 706.3471, meas 706.3497; $[\alpha]_D^{20}$ 12.0° (c 1.0, CH_2Cl_2).

Preparation of acid 138f:

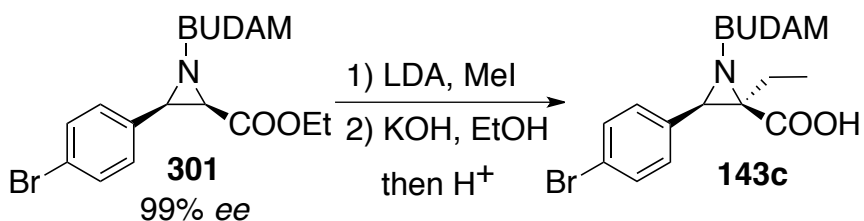


Alkylation: The general procedure for the alkylation was followed with ester **304** (98% ee, 691 mg, 1.00 mmol, 1.00 equiv), $i\text{-Pr}_2\text{NH}$ (0.30 mL, 2.1 mmol, 2.1 equiv), $n\text{-BuLi}$ (2.5M, 0.84 mL, 2.1 mmol, 2.1 equiv) and CH_3I (0.19 mL, 3.0 mmol, 3.0 equiv). After workup, the crude product was obtained which was used directly in the next step.

Hydrolysis: To the mixture of the crude product in ethanol (2.5 mL) was added an aqueous solution of KOH (280 mg, 5.00 mmol, 5.00 equiv) in H_2O (2.5 mL). The resulting mixture was refluxed for 6 h. After it was cooled to rt, the volatiles were removed by rotary evaporation and aq HCl (6N) was added to pH ~2. The mixture was extracted with ether (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and filtered. The filtrate was concentrated and purified by column chromatography (silica gel, 25 × 200 mm, hexane:EtOAc 9:1). The product **138f** was obtained as a white solid (380 mg, 0.560 mmol) in 56% yield over 2 steps; mp 88-91 °C; R_f = 0.45 (hexane:EtOAc 4:1). Spectral data for **138f**:

^1H NMR (500 MHz, CDCl_3) δ 1.37 (s, 18H), 1.41 (s, 18H), 1.83 (s, 3H), 3.27 (s, 1H), 3.65 (s, 3H), 3.67 (s, 3H), 4.46 (s, 1H), 7.12 (d, 1H, $J = 7.0$ Hz), 7.20-7.26 (m, 1H), 7.32, 7.35 (2s, 4H), 7.44-7.54 (m, 2H), 7.70 (d, 1H, $J = 8.5$ Hz), 7.80 (d, 1H, $J = 7.5$ Hz), 7.85 (d, 1H, $J = 7.5$ Hz), 9.80 (brs, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 12.13, 32.02, 32.13, 32.23, 35.81, 35.85, 49.32, 53.18, 64.23, 71.47, 123.18, 124.86, 125.06, 125.15, 126.14, 126.17, 126.72, 128.62, 128.68, 130.76, 131.24, 133.38, 135.40, 135.81, 143.87, 143.98, 158.79, 159.20, 170.14; IR (thin film) 2963(s), 1770(m), 1414(m) cm^{-1} ; HRMS calcd for $\text{C}_{45}\text{H}_{60}\text{NO}_4$ ($\text{M}+\text{H}^+$) m/z 678.4522, meas 678.4510; $[\alpha]_{\text{D}}^{20}$ 9.0° (c 1.0, CH_2Cl_2).

Preparation of acid 143c:

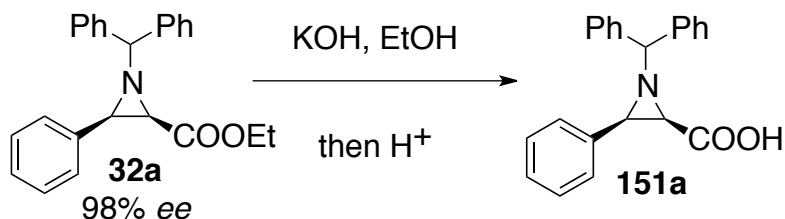


Alkylation: The general procedure for the alkylation was followed with ester **301** (99% ee, 720 mg, 1.00 mmol, 1.00 equiv), $i\text{-Pr}_2\text{NH}$ (0.30 mL, 2.1 mmol, 2.1 equiv), $n\text{-BuLi}$ (2.5M, 0.84 mL, 2.1 mmol, 2.1 equiv) and ethyl iodide (0.24 mL, 3.0 mmol, 3.0 equiv). After workup, the crude product was obtained which was used directly in the next step.

Hydrolysis: To the mixture of the crude product in THF (2.5 mL) and ethanol (2.5 mL) was added an aqueous solution of KOH (280 mg, 5.00 mmol, 5.00 equiv) in H_2O (2.5 mL). The resulting mixture was refluxed for 16 h. After it was cooled to rt, additional THF (2.5 mL) was added and the mixture was refluxed for 48 h.

After it was cooled to rt, the volatiles were removed by rotary evaporation and aq HCl (6N) was added to pH ~2. The mixture was extracted with ether (20 mL + 2 × 10 mL). The combined organic extracts were dried (Na₂SO₄) and filtered. The filtrate was concentrated and purified by column chromatography (silica gel, 25 × 200 mm, hexane:acetone 9:1). The product **143c** was obtained as a white solid (382 mg, 0.530 mmol) in 53% yield over 2 steps; mp 83-87 °C; R_f = 0.50 (hexane:EtOAc 4:1). Spectral data for **143c**: ¹H NMR (500 MHz, CDCl₃) δ 0.80 (t, 3H, *J* = 7.0 Hz), 1.38, 1.40 (2s, 36H), 1.74 (dq, 1H, *J* = 7.5, 7.5 Hz), 2.31 (dq, 1H, *J* = 7.5, 7.5 Hz), 3.14 (s, 1H), 3.64 (s, 3H), 3.67 (s, 3H), 4.35 (s, 1H), 6.79 (d, 2H, *J* = 8.0 Hz), 7.28 (d, 2H, *J* = 8.0 Hz), 7.30 (s, 4H), 9.00 (brs, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 11.27, 20.09, 31.99, 32.07, 35.78, 35.79, 51.42, 54.64, 64.26, 64.30, 70.62, 122.03, 124.97, 126.01, 128.98, 131.44, 133.74, 135.17, 135.79, 143.95, 144.00, 158.83, 159.23, 169.38; IR (thin film) 2961(s), 1710(s), 1224(s) cm⁻¹; HRMS calcd for C₄₂H₅₉NO₄⁷⁹Br (M+H, ESI⁺) *m/z* 720.3627, meas 720.3578; [α]_D²⁰ 6.4° (c 1.0, CH₂Cl₂).

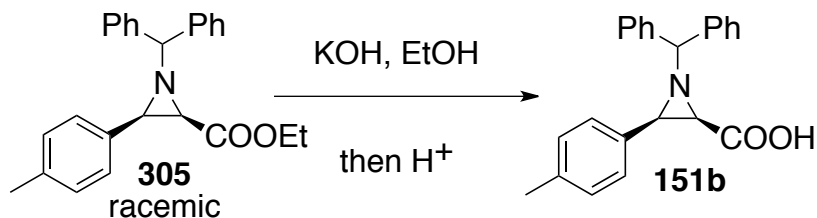
Preparation of acid 151a:



To a 50 mL round bottom flask containing ester **32a** (98% ee, 1.07 g, 3.00 mmol, 1.00 equiv) and ethanol (5 mL) was added an aqueous solution of KOH (840 mg,

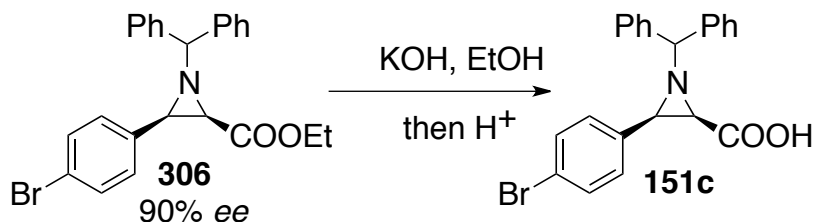
15.0 mmol, 5.00 equiv) in H₂O (5 mL). The resulting suspension was refluxed for 1 h during which time it became a homogeneous solution. After it was cooled to rt, ethanol was removed by rotary evaporation. To the remaining aqueous solution was added *aq* citric acid (2N, 10 mL). The resulting white precipitate was collected by filtration and washed with H₂O and hexane to obtain the pure acid **151a** (976 mg, 2.98 mmol, 99%) as a white solid; mp 143-145 °C; R_f = 0.10 (hexane:EtOAc 4:1). Spectral data for acid **151a**: ¹H NMR (600 MHz, CDCl₃) δ 2.78 (d, 1H, *J* = 7.2 Hz), 3.40 (d, 1H, *J* = 6.6 Hz), 4.04 (s, 1H), 7.20-7.30 (m, 8H), 7.32 (q, 4H, *J* = 7.2 Hz), 7.47 (t, 4H, *J* = 8.4 Hz); ¹H NMR (600 MHz, DMSO-d₆) δ 2.77 (d, 1H, *J* = 7.2 Hz), 3.32 (d, 1H, *J* = 6.6 Hz), 4.17 (s, 1H), 7.14-7.30 (m, 7H), 7.34 (t, 2H, *J* = 7.8 Hz), 7.41 (d, 2H, *J* = 7.8 Hz), 7.49 (d, 2H, *J* = 8.4 Hz), 7.41 (d, 2H, *J* = 7.8 Hz), 12.22 (brs, 1H); ¹³C NMR (150 MHz, DMSO-d₆) δ 46.39, 47.14, 75.34, 126.94, 126.99, 127.05, 127.08, 127.25, 127.59, 127.63, 128.31, 128.34, 135.70, 143.07, 143.20, 168.58; IR (thin film) 1705(s), 1244(m) cm⁻¹; HRMS calcd for C₂₂H₂₀NO₂ (M+H, ESI⁺) *m/z* 330.1494, meas 330.1506; [α]_D²⁰ 19.6° (c 0.5, CH₂Cl₂).

Preparation of acid 151b:



To a 50 mL round bottom flask containing ester **305** (racemic, 250 mg, 0.674 mmol, 1.00 equiv), ethanol (2 mL) and THF (1 mL) was added an aqueous solution of KOH (189 mg, 3.37 mmol, 5.00 equiv) in H₂O (2 mL). The resulting suspension was refluxed for 2 h during which time it became a homogeneous solution. After it was cooled to rt, *aq* citric acid (2N, 5 mL) was added. The resulting white precipitate was collected by filtration and washed with H₂O and hexane to obtain the pure acid **151b** (230 mg, 0.670 mmol, 99%) as a white solid; mp 147-149 °C; R_f = 0.10 (hexane:EtOAc 4:1). Spectral data for acid **151b**: ¹H NMR (500 MHz, DMSO-d₆) δ 2.20 (s, 3H), 2.76 (d, 1H, *J* = 6.5 Hz), 3.32 (d, 1H, *J* = 6.5 Hz), 4.12 (s, 1H), 7.00-7.40 (m, 10H), 7.45 (d, 2H, *J* = 7.5 Hz), 7.57 (d, 2H, *J* = 7.5 Hz), 12.0 (brs, 1H); ¹³C NMR (125 MHz, DMSO-d₆) δ 20.67, 46.33, 47.03, 75.32, 126.92, 127.00, 127.20, 127.48, 128.24, 128.31, 132.64, 136.19, 143.09, 143.21, 168.58 (Two *sp*² carbon not located); IR (thin film) 1705(s), 1244(m) cm⁻¹; HRMS calcd for C₂₃H₂₂NO₂ (M+H, ESI⁺) *m/z* 344.1651, meas 344.1679.

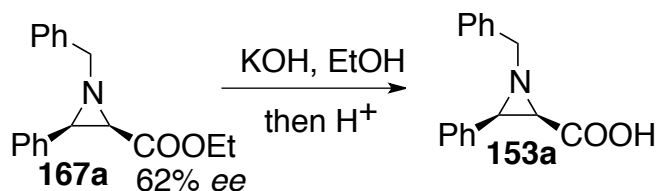
Preparation of acid 151c:



To a suspension of ester **306** (90% ee, 872 mg, 2.00 mmol, 1.00 equiv) in ethanol (5 mL) was added a solution of KOH (560 mg, 10.00 mmol, 5.00 equiv) in

H₂O (5 mL). The resulting mixture was refluxed for 1 h. After it was cooled to rt, aq citric acid (2N, 5 mL) was added. The white precipitate was collected by filtration and washed with H₂O and hexanes. The solid was dissolved in Et₂O (25 mL), dried (Na₂SO₄) and filtered. The filtrate was concentrated to afford the product **151c** as a white solid (810 mg, 1.985 mmol) in 99% yield; mp 140-142 °C; R_f = 0.20 (hexane:EtOAc 4:1). Spectral data for acid **151c**: ¹H NMR (500 MHz, CDCl₃) δ 2.79 (d, 1H, *J* = 7.0 Hz), 3.32 (d, 1H, *J* = 7.0 Hz), 4.03 (s, 1H), 7.17 (d, 2H, *J* = 8.5 Hz), 7.22-7.60 (m, 13H); ¹³C NMR (125 MHz, CDCl₃) δ 45.45, 48.15, 77.23, 122.04, 126.98, 127.40, 127.77, 127.88, 128.75, 128.84, 129.30, 131.45, 133.02, 141.14, 141.55, 169.82; IR (thin film) 1711(s), 1265(m) cm⁻¹; HRMS calcd for C₂₂H₁₉NO₂⁷⁹Br (M+H, ESI⁺) *m/z* 408.0599, meas 408.0576; [α]_D²⁰ 3.5° (c 1.0, CH₂Cl₂).

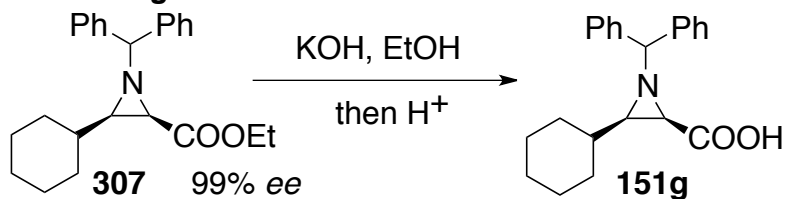
*Preparation of acid **153a**:*



To a suspension of ester **167a** (62% ee, 170 mg, 0.600 mmol, 1.00 equiv) in ethanol (1 mL) was added a solution of KOH (170 mg, 3.00 mmol, 5.00 equiv) in H₂O (2 mL). The resulting mixture was refluxed for 1 h. After it was cooled to rt, aq citric acid (2N, 2 mL) was added. The white precipitate was collected by filtration. The product was obtained as a white solid (150 mg, 0.593 mmol) in

99% yield; mp 123-125 °C; R_f = 0.10 (hexane:EtOAc). Spectral data for **153a**: ^1H NMR (500 MHz, DMSO- d_6) δ 2.74 (d, 1H, J = 6.0 Hz), 3.18 (d, 1H, J = 6.5 Hz), 3.60 (d, 1H, J = 14.0 Hz), 3.81 (d, 1H, J = 14.0 Hz), 7.12-7.48 (m, 10H), 12.20 (brs, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 46.22, 46.74, 62.06, 126.90, 127.03, 127.63, 127.69, 128.23, 135.98, 138.73, 168.78 (One sp^2 C not located); IR (thin film) 1718(s) 1224(s) cm^{-1} ; HRMS calcd for $\text{C}_{16}\text{H}_{16}\text{NO}_2$ ($\text{M}+\text{H}^+$, ESI^+) m/z 254.1181, meas 254.1163; $[\alpha]_D^{20}$ 18.2° (c 1.0, CH_2Cl_2).

*Preparation of acid **151g**:*

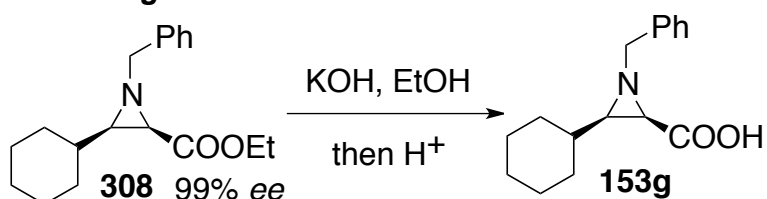


To a suspension of ester **307** (99% ee, 363 mg, 1.00 mmol, 1.00 equiv) in ethanol (3 mL) was added a solution of KOH (280 mg, 5.00 mmol, 5.00 equiv) in H_2O (3 mL). The resulting mixture was refluxed for 1 h. After it was cooled to rt, the volatiles were removed by rotary evaporation. Then aq citric acid (2N, 5 mL) was added. The resulting precipitate was collected by filtration and washed with H_2O , affording the product **151g** as a white solid (306 mg, 0.913 mmol) in 93% yield; mp 151-152 °C; R_f = 0.25 (hexane:EtOAc 4:1). Spectral data for acid **151g**:

^1H NMR (500 MHz, DMSO- d_6) δ 0.46 (q, 1H, J = 10.5 Hz), 0.90-1.10 (m, 5H), 1.16-1.28 (m, 1H), 1.30-1.70 (m, 4H), 1.89 (t, 1H, J = 7.0 Hz), 2.22 (d, 1H, J = 7.0 Hz), 3.80 (s, 1H), 7.16-7.40 (m, 8H), 7.45 (d, 2H, J = 7.5 Hz), 12.40 (brs, 1H);

^{13}C NMR (125 MHz, CDCl_3) δ 24.92, 25.09, 25.63, 29.44, 30.26, 35.60, 42.27, 51.07, 75.77, 126.67, 126.71, 127.96, 128.13, 128.19, 143.08, 143.28, 170.79 (One sp^2 C not located); IR (thin film) 2926(s), 1705(m), 1450(m) cm^{-1} ; HRMS calcd for $\text{C}_{22}\text{H}_{26}\text{NO}_2$ ($\text{M}+\text{H}^+$, ESI^+) m/z 336.1964, meas 336.1950; $[\alpha]_D^{20}$ 75.2° (c 0.5, CH_2Cl_2).

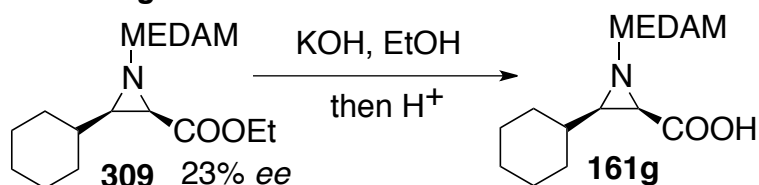
*Preparation of acid **153g**:*



To a mixture of ester **308** (99% ee, 287 mg, 1.00 mmol, 1.00 equiv) in ethanol (2 mL) was added a solution of KOH (280 mg, 5.00 mmol, 5.00 equiv) in H_2O (2 mL). The resulting mixture was refluxed for 2 h. After cooling to rt, aq citric acid (2N, 5 mL) was added. The resulting white precipitate was collected by filtration. The product **153g** was obtained as a white solid (217 mg, 0.838 mmol, 84%); mp 195-196 °C; R_f = 0.05 (hexane:EtOAc 4:1). Spectral data for acid **153g**: ^1H NMR (500 MHz, CDCl_3) δ 0.84-1.24 (m, 6H), 1.50-1.70 (m, 5H), 1.84 (t, 1H, J = 8.0 Hz), 2.45 (d, 1H, J = 7.0 Hz), 3.48 (d, 1H, J = 13.0 Hz), 3.69 (d, 1H, J = 13.0 Hz), 7.10-7.40 (m, 5H), 7.70 (brs, 1H); ^1H NMR (600 MHz, DMSO-d_6) δ 0.80-1.28 (m, 6H), 1.50-1.70 (m, 5H), 1.70-1.80 (m, 1H), 2.24 (d, 1H, J = 7.2 Hz), 3.32 (d, 1H, J = 13.2 Hz), 3.54 (d, 1H, J = 13.2 Hz), 7.20-7.40 (m, 5H), 11.80 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 25.11, 25.19, 25.76, 29.50, 30.74, 35.68, 41.88, 50.76,

62.91, 126.97, 128.08, 128.28, 138.76, 170.91; IR (thin film) 2924(w), 1755(s) cm^{-1} ; HRMS calcd for $\text{C}_{16}\text{H}_{22}\text{NO}_2$ ($\text{M}+\text{H}^+$, ESI^+) m/z 260.1651, meas 260.1667; $[\alpha]_{\text{D}}^{20}$ 52° (c 0.5, DMSO).

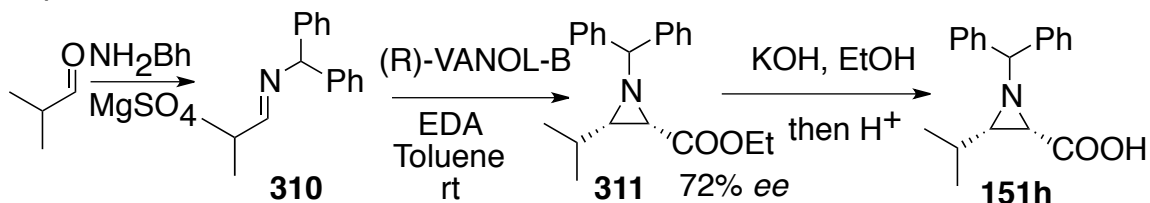
*Preparation of acid **161g**:*



To the mixture of ester **309** (23% ee, 200 mg, 0.420 mmol, 1.00 equiv) in ethanol (2 mL) was added a solution of KOH (117 mg, 2.09 mmol, 5.00 equiv) in H_2O (2 mL). The resulting mixture was refluxed for 1 h. After cooling to rt, aq citric acid (2N, 2 mL) and ether (10 mL) were added. The aqueous layer was separated and extracted with ether (2×10 mL). The combined organic extracts were dried (Na_2SO_4) and filtered. The filtrate was concentrated and purified by column chromatography (silica gel, 28×280 mm, hexane:acetone 4:1 to 3:1) to afford the product **161g** (180 mg, 0.400 mmol) as a white solid in 96% yield; mp 85-90 °C; R_f = 0.30 (hexane:acetone 4:1). Spectral data for **161g**: ^1H NMR (300 MHz, CDCl_3) δ 0.50-0.70 (m, 1H), 0.90-1.70 (m, 10H), 1.88 (dd, 1H, J = 9.3, 6.9 Hz), 2.22, 2.23 (2s, 12H), 2.37 (d, 1H, J = 6.9 Hz), 3.48 (s, 1H), 3.66, 3.67 (2s, 6H), 6.97 (s, 4H), 9.00 (brs, 1H); ^{13}C NMR (150 MHz, CDCl_3) δ 16.11, 16.22, 25.28, 25.34, 25.95, 29.87, 30.97, 37.26, 43.16, 53.15, 59.58, 59.67, 76.72, 127.15, 127.98, 130.70, 131.06, 136.56, 137.12, 156.24, 156.41, 170.75; IR (thin film)

2928(s), 1710(w) cm^{-1} ; HRMS calcd for $\text{C}_{28}\text{H}_{38}\text{NO}_4$ ($\text{M}+\text{H}^+$, ESI^+) m/z 452.2801, meas 452.2791; $[\alpha]_{\text{D}}^{20}$ 10.6° (c 0.5, CH_2Cl_2).

Preparation of 151h:



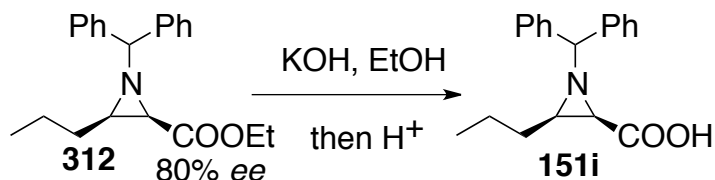
Imine formation: The mixture of *iso*-butylaldehyde (173 mg, 0.220 mL, 2.40 mmol, 1.20 equiv), benzhydrolamine (378 mg, 2.00 mmol, 1.00 equiv), MgSO_4 (960 mg, 8.00 mmol, 4.00 equiv) and dry CH_2Cl_2 (10 mL) was stirred under N_2 for 2 h. After the reaction was filtered over a Celite pad on a sintered glass funnel, the filtrate was concentrated to give the product **310** (450 mg, 1.90 mmol, 95%) as a colorless oil; ^1H NMR (300 MHz, CDCl_3) δ 1.04 (d, 6H, J = 6.9 Hz), 2.40-2.54 (m, 1H), 5.24 (s, 1H), 7.08-7.30 (m, 10H), 7.64 (d, 1H, J = 5.1 Hz); ^{13}C NMR (150 MHz, CDCl_3) δ 19.34, 34.18, 77.74, 126.79, 127.54, 128.32, 143.95, 169.83.

Aziridination: A 25 mL pear-shaped single neck flask which had its 14/20 joint replaced by a threaded high vacuum Teflon valve was flame dried (with a stir bar in it), cooled to rt under N_2 and charged with 5 mol% (*R*)-VANOL (22 mg, 0.050 mmol, 0.050 equiv), 20 mol% triphenyl borate (58 mg, 0.20 mmol, 0.20 equiv), H_2O (9 μL) and dry toluene (1 mL). The Teflon valve was closed and the flask was heated at 80 $^\circ\text{C}$ for 1 hour. After the flask was cooled to rt, the toluene was

carefully removed by exposing to high vacuum (0.1 mmHg) by slightly cracking the Teflon valve. After the solvent was removed, the Teflon valve was completely opened and the flask was heated at 80 °C under high vacuum for 30 min. The flask was then allowed to cool to rt. The solution of imine **310** (237 mg, 1.00 mmol, 1.00 equiv) in toluene (2 mL) was added. And then EDA (0.25 mL, 2.4 mmol, 2.4 equiv) was added *via* syringe in one portion. The solution was stirred at rt for 17 h. The reaction was quenched with hexane (5 mL) and concentrated. After column chromatography (silica gel, 28 × 280 mm, hexane:EtOAc 15:1), ester **311** was obtained as a white solid (230 mg, 0.712 mmol) in 71% yield. The optical purity was determined to be 72% ee by HPLC analysis (Chiralcel OD-H column, 99:1 hexane/2-propanol at 222 nm, flow-rate 1.0 mL/min); Retention times: t_R = 3.24 min (major enantiomer) and t_R = 5.98 min (minor enantiomer); mp 102-104 °C; R_f = 0.40 (hexane:EtOAc 4:1); ^1H NMR (500 MHz, CDCl_3) δ 0.56 (d, 3H, J = 6.0 Hz), 0.85 (d, 3H, J = 7.0 Hz), 1.29 (t, 3H, J = 7.0 Hz), 1.60-1.70 (m, 1H), 1.81 (dd, 1H, J = 9.5, 7.0 Hz), 2.32 (d, 1H, J = 7.0 Hz), 3.68 (s, 1H), 4.14-4.32 (m, 2H), 7.20-7.26 (m, 2H), 7.28-7.36 (m, 4H), 7.38-7.44 (m, 2H), 7.55 (d, 2H, J = 8.0 Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 14.18, 19.53, 20.32, 27.25, 43.58, 53.52, 60.59, 78.01, 126.83, 126.97, 127.43, 128.21, 128.25, 128.29, 142.29, 142.75, 169.48; IR (thin film) 961(m), 1734(s) cm^{-1} ; HRMS calcd for $\text{C}_{21}\text{H}_{26}\text{NO}_2$ ($\text{M}+\text{H}^+$, ESI $^+$) m/z 324.1964, meas 324.1964; $[\alpha]_{\text{D}}^{20}$ -123.5° (c 0.5, CH_2Cl_2).

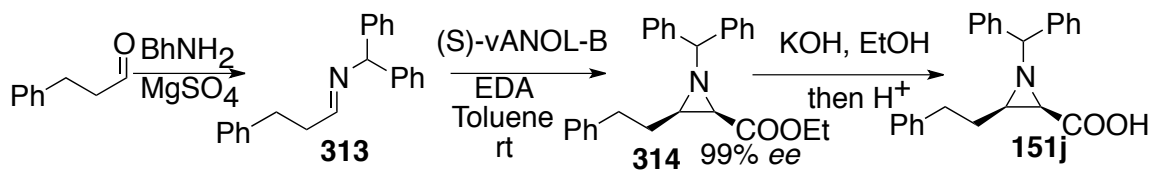
Hydrolysis: To the mixture of ester **311** (100 mg, 0.310 mmol, 1.00 equiv) in ethanol (0.5 mL) was added a solution of KOH (87 mg, 1.6 mmol, 5.0 equiv) in H₂O (1 mL). The resulting mixture was refluxed for 30 min. After cooling to rt, aq citric acid (2N, 2 mL) and ether (10 mL) were added. The aqueous layer was separated and extracted with ether (2 × 5 mL). The combined organic extracts were dried (Na₂SO₄) and filtered. The filtrate was concentrated to give the crude product as a white solid. CH₂Cl₂ (10 mL) was added to the solid and this mixture was filtered and washed well with CH₂Cl₂. The filtrate was concentrated to give the product **151h** as a white foamy solid (80 mg, 0.27 mmol, 88%); mp 84-86 °C; R_f = 0.005 (hexane:EtOAc 4:1). Spectral data for acid **151h**: ¹H NMR (600 MHz, DMSO-d₆) δ 0.41 (d, 3H, *J* = 6.6 Hz), 0.75 (d, 3H, *J* = 7.2 Hz), 1.44-1.56 (m, 1H), 1.84 (dd, 1H, *J* = 9.0, 6.0 Hz), 2.22 (d, 1H, *J* = 6.6 Hz), 3.82 (s, 1H), 7.14-7.54 (m, 10H), 12.40 (brs, 1H); ¹³C NMR (150 MHz, DMSO-d₆) δ 19.30, 20.25, 26.67, 42.59, 52.70, 75.71, 126.70, 127.18, 127.97, 128.12, 128.18, 143.06, 143.32, 170.75 (One *sp*² carbon not located); ¹³C NMR (150 MHz, CDCl₃) δ 19.52, 20.50, 28.15, 43.47, 54.55, 77.48, 126.83, 127.55, 127.84, 127.93, 128.52, 128.74, 141.25, 141.82, 171.03; IR (thin film) 2963(m), 1720(s) cm⁻¹; HRMS calcd for C₁₉H₂₂NO₂ (M+H, ESI⁺) *m/z* 296.1651, meas 296.1640; [α]_D²⁰ -51.1° (c 0.5, CH₂Cl₂).

Preparation of acid 151i:



To the mixture of ester **312** (80% ee, 70 mg, 0.22 mmol, 1.0 equiv) in ethanol (1 mL) was added a solution of KOH (60 mg, 1.54 mmol, 5.00 equiv) in H₂O (1 mL). After the mixture was refluxed for 30 min, THF (1 mL) was added. And the resulting mixture was refluxed for another 30 min. After it was cooled to rt, the volatiles were removed by rotary evaporation and ether (5 mL) was added. The aqueous layer was separated and extracted with ether (2 × 5 mL). The combined organic extracts were dried (Na₂SO₄) and filtered. The filtrate was concentrated and purified by column chromatography (silica gel, 18 × 180 mm, hexane:CH₂Cl₂:EtOAc 2:2:1 to 1:1:1) to obtain the product **151i** (45 mg, 0.15 mmol) as a white foamy solid in 71% yield; mp 50-52 °C; R_f = 0.20 (hexane:CH₂Cl₂:EtOAc 2:2:1). Spectral data for acid **151i**: ¹H NMR (500 MHz, CDCl₃) δ 0.77 (t, 3H, *J* = 7.0 Hz), 1.10-1.28 (m, 2H), 1.38-1.48 (m, 1H), 1.56-1.64 (m, 1H), 2.19 (q, 1H, *J* = 7.0 Hz), 2.48 (d, 1H, *J* = 7.0 Hz), 3.80 (s, 1H), 7.00-8.00 (m, 11H); ¹³C NMR (150 MHz, CDCl₃) δ 13.57, 20.18, 31.45, 43.22, 47.71, 77.02, 127.05, 127.37, 127.65, 127.70, 128.56, 128.81, 141.35, 141.74, 170.61; IR (thin film) 1720(s) cm⁻¹; HRMS calcd for C₁₉H₂₂NO₂ (M+H, ESI⁺) *m/z* 296.1651, meas 296.1626; [α]_D²⁰ 8.9° (c 1.0, CH₂Cl₂).

Preparation of acid 151j:



Imine formation: The mixture of hydrocinnamaldehyde (90% by weight, 328 mg, 2.20 mmol, 1.10 equiv), BhnH₂ (378 mg, 2.00 mmol, 1.00 equiv) and MgSO₄ (960 mg, 8.00 mmol, 4.00 equiv) in CH₂Cl₂ (10 mL) was stirred at rt for 1.5 h. After it was filtered over a Celite pad on a sintered glass funnel, the filtrate was concentrated to give the imine **313** as a colorless oil which was put on the vacuum for 10 sec prior to use.

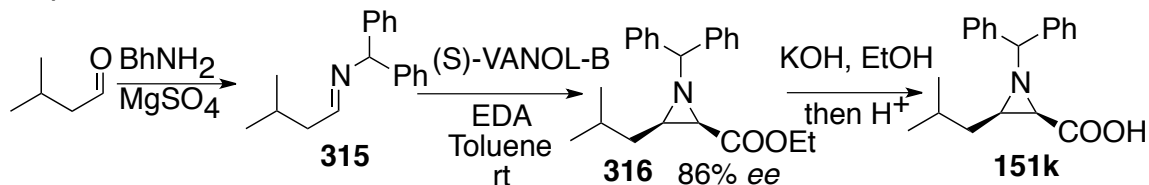
Aziridination: A 25 mL pear-shaped single neck flask which had its 14/20 joint replaced by a threaded high vacuum Teflon valve was flame dried (with a stir bar in it), cooled to rt under N₂ and charged with 5 mol% (S)-VANOL (22 mg, 0.050 mmol, 0.050 equiv), 20 mol% triphenyl borate (58 mg, 0.20 mmol, 0.20 equiv), H₂O (9 μL) and dry toluene (1 mL). The Teflon valve was closed and the flask was heated at 80 °C for 1 hour. After the flask was cooled to rt, the toluene was carefully removed by exposing to high vacuum (0.1 mmHg) by slightly cracking the Teflon value. After the solvent was removed, the Teflon valve was completely opened and the flask was heated at 80 °C under high vacuum for 30 min. The flask was then allowed to cool to rt. The solution of imine **313** (306 mg, 1.00 mmol, 1.00 equiv) in toluene (2 mL) was added. And then EDA (311 μL, 3.00 mmol, 3.00 equiv) was added *via* syringe in one portion. The solution was stirred at rt for 22 h. The reaction was quenched with n-hexane (5 mL) and concentrated

by removing all volatiles. After column chromatography (1st column, silica gel, 28 × 280 mm, hexane:EtOAc 9:1; 2nd column, silica gel, 28 × 280 mm, benzene:EtOAc 50:1), ester **314** was obtained as a white solid (262 mg, 0.680 mmol) in 68% yield. The optical purity was determined to be 78% ee by HPLC analysis (Chiralcel OD-H column, 99:1 hexane/2-propanol at 222 nm, flow-rate 1.0 mL/min); Retention times: t_R = 5.06 min (minor enantiomer) and t_R = 10.16 min (major enantiomer). A single recrystallization of 78% ee material afforded the product (141 mg, 0.366 mmol) with 37% recovery and 99.1% ee; mp 114-115 °C; R_f = 0.50 (hexane:EtOAc 4:1); ^1H NMR (500 MHz, CDCl_3) δ 1.27 (t, 3H, J = 7.5 Hz), 1.82-2.00 (m, 2H), 2.08 (q, 1H, J = 6.5 Hz), 2.28-2.40 (m, 2H), 2.44-2.54 (m, 1H), 3.71 (s, 1H), 4.14-4.26 (m, 2H), 6.98 (d, 2H, J = 7.5 Hz), 7.14-7.40 (m, 9H), 7.49 (d, 2H, J = 8.0 Hz), 7.53 (d, 2H, J = 7.5 Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 14.22, 29.58, 33.22, 43.19, 46.07, 60.72, 77.79, 125.70, 126.98, 127.02, 127.44, 127.83, 128.16, 128.31, 128.33, 128.39, 141.28, 142.40, 142.88, 169.33; IR (thin film) 2918(m), 1734(s) cm^{-1} ; Anal calcd for $\text{C}_{26}\text{H}_{27}\text{NO}_2$: C, 81.01; H, 7.06; N, 3.63. Found: C, 80.86; H, 7.06; N, 3.63; $[\alpha]_D^{20}$ 86.2° (c 0.5, CH_2Cl_2) based on the 99.1% ee material.

Hydrolysis: To a suspension of ester **314** (100 mg, 0.260 mmol, 1.00 equiv) in ethanol (1 mL) was added a solution of KOH (73 mg, 1.3 mmol, 5.0 equiv) in H_2O (2 mL). The resulting mixture was refluxed for 45 min. After cooling to rt, aq citric acid (2N, 2 mL) was added. The resulting precipitate was collected by

filtration. The product was obtained as a white solid (91 mg, 0.26 mmol, 98%); mp 70-72 °C; R_f = 0.13 (hexane:EtOAc 4:1); ^1H NMR (500 MHz, DMSO- d_6) δ 1.72-1.90 (m, 2H), 2.15-2.24 (m, 1H), 2.28-2.38 (m, 1H), 2.38-2.50 (m, 2H), 3.97 (s, 1H), 6.98-7.04 (m, 2H), 7.20-7.60 (m, 13H), 12.50 (brs, 1H); ^{13}C NMR (125 MHz, DMSO- d_6) δ 29.52, 32.71, 42.23, 45.23, 75.42, 125.69, 126.78, 127.14, 127.52, 128.01, 128.02, 128.19, 128.21, 128.30, 128.45, 141.20, 143.49, 170.61; IR (thin film) 1734(s) cm^{-1} ; HRMS calcd for $\text{C}_{24}\text{H}_{24}\text{NO}_2$ ($\text{M}+\text{H}^+$) m/z 358.1807, meas 358.1834; $[\alpha]_D^{20}$ 30.5° (c 0.5, CH_2Cl_2).

Preparation of acid **151k:**



Imine formation: The mixture of iso-pentaldehyde (189 mg, 2.20 mmol, 1.10 equiv), BHNH_2 (378 mg, 2.00 mmol, 1.00 equiv) and MgSO_4 (960 mg, 8.00 mmol, 4.00 equiv) in CH_2Cl_2 (10 mL) was stirred at rt for 2 h. After it was filtered over a Celite pad on a sintered glass funnel, the filtrate was concentrated to give the imine **315** as a colorless oil which was put on the vacuum for 10 sec prior to use.

Aziridination: A 25 mL pear-shaped single neck flask which had its 14/20 joint replaced by a threaded high vacuum Teflon valve was flame dried (with a stir bar in it), cooled to rt under N_2 and charged with 5 mol% (S)-VANOL (22 mg, 0.050 mmol, 0.050 equiv), 20 mol% triphenyl borate (58 mg, 0.20 mmol, 0.20 equiv),

H₂O (9 μ L) and dry toluene (1 mL). The Teflon valve was closed and the flask was heated at 80 °C for 1 hour. After the flask was cooled to rt, the toluene was carefully removed by exposing to high vacuum (0.1 mmHg) by slightly cracking the Teflon valve. After the solvent was removed, the Teflon valve was completely opened and the flask was heated at 80 °C under high vacuum for 30 min. The flask was then allowed to cool to rt. The solution of imine **315** (251 mg, 1.00 mmol, 1.00 equiv) in toluene (2 mL) was added. And then EDA (375 μ L, 3.60 mmol, 3.60 equiv) was added via syringe in one portion. The solution was stirred at rt for 19 h. The reaction was quenched with n-hexane (5 mL) and concentrated by removing all volatiles. After column chromatography (silica gel, 28 $\times$ 280 mm, hexane:acetone 9:1), ester **316** was obtained as a white solid (205 mg, 0.608 mmol) in 61% yield. The optical purity was determined to be 86% ee by HPLC analysis (Chiralcel OD-H column, 99:1 hexane/2-propanol at 222 nm, flow-rate 1.0 mL/min); Retention times: t_R = 3.26 min (minor enantiomer) and t_R = 6.01 min (major enantiomer); mp 105-106 °C; R_f = 0.48 (hexane:acetone 4:1); ¹H NMR (500 MHz, CDCl₃) δ 0.65 (d, 3H, J = 6.5 Hz), 0.76 (d, 3H, J = 7.0 Hz), 1.23 (t, 3H, J = 7.0 Hz), 1.26-1.44 (m, 2H), 1.48-1.56 (m, 1H), 2.06 (q, 1H, J = 6.5 Hz), 2.27 (d, 1H, J = 7.0 Hz), 3.36 (s, 1H), 4.10-4.22 (m, 2H), 7.16-7.30 (m, 6H), 7.36-7.42 (m, 2H), 7.44-7.48 (m, 2H); ¹³C NMR (150 MHz, CDCl₃) δ 14.26, 21.63, 22.93, 26.66, 36.49, 43.43, 45.71, 60.70, 78.06, 126.99, 127.12, 127.36, 127.82, 128.36, 142.51, 142.79, 169.56 (One sp^2 carbon not located); IR (thin film)

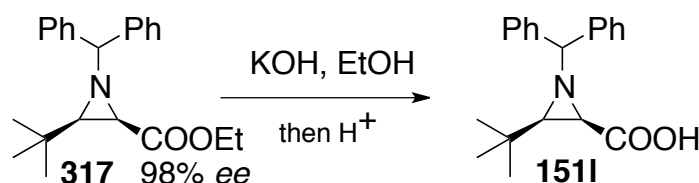
1784(s) cm^{-1} ; HRMS calcd for $\text{C}_{22}\text{H}_{28}\text{NO}_2$ ($\text{M}+\text{H}$, ESI^+) m/z 332.2120, meas 320.2141; $[\alpha]_{\text{D}}^{20}$ 94.7° (c 1.0, CH_2Cl_2).

Hydrolysis: To a mixture of ester **316** (60 mg, 0.18 mmol, 1.0 equiv) in ethanol (1 mL) was added a solution of KOH (50 mg, 0.90 mmol, 5.0 equiv) in H_2O (1 mL).

The resulting mixture was refluxed for 30 min. After the reaction mixture was cooled to rt, aq citric acid (2N, 2 mL) was added. And the mixture was extracted with ether (3×10 mL). The organic extracts were dried (Na_2SO_4) and filtered.

The filtrate was concentrated to give a white viscous foamy solid (50 mg, 0.16 mmol, 91%); mp 124-125 °C; R_f = 0.50 (hexane:acetone 2:1). Spectral data for acid **151k**: ^1H NMR (300 MHz, CDCl_3) δ 0.71 (d, 3H, J = 6.6 Hz), 0.80 (d, 3H, J = 6.6 Hz), 1.16-1.70 (m, 3H), 2.23 (q, 1H, J = 6.7 Hz), 2.49 (d, 1H, J = 7.2 Hz), 3.83 (s, 1H), 7.00-8.00 (m, 11H); ^{13}C NMR (150 MHz, CDCl_3) δ 21.79, 22.76, 26.67, 37.25, 43.32, 46.88, 127.05, 127.24, 127.71, 127.83, 128.62, 128.89, 141.25, 141.59, 169.86; IR (thin film) 1734(s) cm^{-1} ; HRMS calcd for $\text{C}_{20}\text{H}_{24}\text{NO}_2$ ($\text{M}+\text{H}$, ESI^+) m/z 310.1807, meas 310.1811; $[\alpha]_{\text{D}}^{20}$ 26.7° (c 1.0, Et_2O).

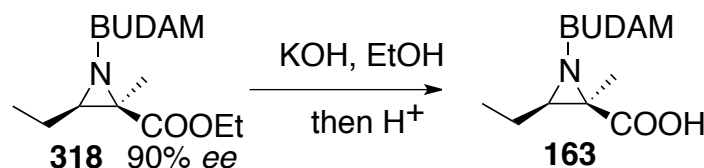
Preparation of acid 151l:



To the mixture of ester **317** (98% ee, 270 mg, 0.800 mmol, 1.00 equiv) in ethanol (4 mL) was added a solution of KOH (224 mg, 4.00 mmol, 5.00 equiv) in H_2O (4

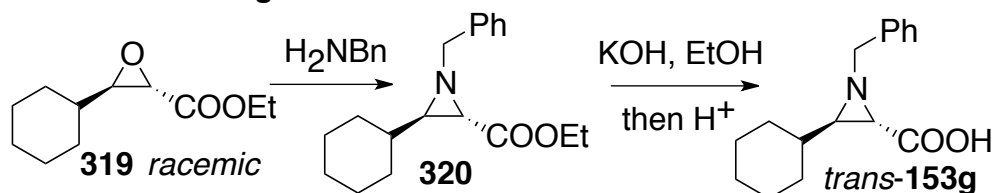
mL). After the mixture was refluxed for 1.5 h, THF (1 mL) was added. The resulting mixture was refluxed for another 1.5 h. After it was cooled to rt, aq citric acid (2N, 5 mL) was added. The resulting white precipitate was collected by filtration. The solid was then dissolved in ether (30 mL) and washed with H₂O (3 × 5 mL). The organic layer was dried (Na₂SO₄) and concentrated to obtain the product **151I** (234 mg, 0.757 mmol, 95%) as a white solid; mp 164-166 °C; R_f = 0.25 (hexane:EtOAc 4:1). Spectral data for acid **151I**: ¹H NMR (500 MHz, CDCl₃) δ 0.80 (s, 9H), 2.00 (d, 1H, *J* = 7.5 Hz), 2.36 (d, 1H, *J* = 8.0 Hz), 3.69 (s, 1H), 7.22-7.28 (m, 3H), 7.30-7.34 (m, 4H), 7.40-7.46 (m, 4H); ¹H NMR (600 MHz, DMSO-d₆) δ 0.66 (s, 9H), 1.81 (d, 1H, *J* = 7.2 Hz), 2.20 (d, 1H, *J* = 7.8 Hz), 3.78 (s, 1H), 7.18-7.22 (m, 2H), 7.26-7.30 (m, 4H), 7.38 (dd, 2H, *J* = 8.4, 1.2 Hz), 7.60 (dd, 2H, *J* = 8.4, 1.2 Hz), 12.40 (s, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 27.57, 31.61, 42.98, 59.16, 78.86, 127.03, 127.60, 127.80, 127.86, 128.55, 128.97, 141.33, 141.81 (The carbonyl peak not located); ¹³C NMR (150 MHz, DMSO-d₆) δ 27.34, 31.29, 42.58, 54.89, 76.94, 126.92, 127.04, 127.98, 128.08, 128.24, 143.14, 143.87, 170.86 (One *sp*² carbon not located); IR (thin film) 2961(s), 1705(s) cm⁻¹; HRMS calcd for C₂₀H₂₄NO₂ (M+H, ESI⁺) *m/z* 310.1807, meas 310.1781; [α]_D²⁰ 30.6° (c 0.5, CH₂Cl₂).

Preparation of acid 163:



To the mixture of ester **318** (90% ee, 800 mg, 1.30 mmol, 1.00 equiv) in THF (2.5 mL) and ethanol (2.5 mL) was added a solution of KOH (364 mg, 6.50 mmol, 5.00 equiv). The resulting mixture was refluxed for 24 h. After cooling to rt, aq HCl (6N) was added to pH ~2. The mixture was extracted with ether (3 × 10 mL). The combined organic extracts were dried (Na₂SO₄) and filtered. The filtrate was concentrated and purified by column chromatography (silica gel, 25 × 200 mm, hexane:acetone 5:1) to give the product **163** (565 mg, 0.976 mmol, 75%) as a white foamy solid; mp 73-76 °C; R_f = 0.25 (hexane:EtOAc). Spectral data for **163**: ¹H NMR (500 MHz, CDCl₃) δ 0.65 (t, 3H, *J* = 7.5 Hz), 1.30-1.52 (m, 38H), 1.54 (s, 3H), 1.96 (t, 1H, *J* = 7.0 Hz), 3.67 (s, 6H), 4.14 (s, 1H), 7.20 (s, 2H), 7.22 (s, 2H), 9.60 (brs, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 10.68, 11.91, 21.97, 31.80, 35.52, 35.54, 48.00, 53.60, 63.89, 63.97, 70.24, 124.78, 125.61, 135.57, 135.67, 143.32, 143.51, 158.37, 158.73, 171.17 (One *sp*³ carbon not located); IR (thin film) 2964(s), 1774(m) cm⁻¹; HRMS calcd for C₃₇H₅₈NO₄ (M+H, ES⁺) *m/z* 580.4366, meas 580.4296; [α]_D²⁰ 33.1° (c 1.0, CH₂Cl₂).

Preparation of acid 149g:



trans-ester formation: A mixture of *trans*-epoxide **319** (*racemic*, 500 mg, 2.50 mmol, 1.00 equiv), NH₄Cl (400 mg, 7.50 mmol, 3.00 equiv) and benzylamine (1.35 mL, 12.5 mmol, 5.00 equiv) in absolute ethanol (5 mL) was refluxed for 8 h. After cooling, the solvent was evaporated and H₂O (10 mL) was added. And the mixture was extracted with ether (3 × 10 mL). The combined organic extracts were dried (Na₂SO₄) and filtered. The filtrate was concentrated and purified by column chromatography (silica gel, 28 × 280 mm, hexane: EtOAc 4:1) to give the ring-opening product (404 mg, 1.32 mmol, 53%). To a solution of the ring-opening product and triphenylphosphine (694 mg, 2.65 mmol, 2.00 equiv) in THF (5 mL) at 0 °C was added diethylazodicarboxylate (DEAD, 0.420 mL, 2.65 mmol, 2.00 equiv) dropwise under N₂. After it was stirred at 0 °C for 1 h, the resulting mixture was stirred at rt for 20 h. The reaction mixture was concentrated and purified by column chromatography (1st column, silica gel, 28 × 280 mm, hexane:EtOAc 9:1; 2nd column, silica gel, 18 × 180 mm, hexane:EtOAc 15:1) afforded the *trans*-aziridine **320** (100 mg, 0.348 mmol) as a colorless oil in 14% over 2 steps; R_f = 0.60 (hexane:EtOAc 4:1); ¹H NMR (500 MHz, CDCl₃) δ 0.86-1.30 (m, 9H), 1.50-1.80 (m, 5H), 2.07 (dd, 1H, *J* = 7.0 , 2.5 Hz), 2.50 (d, 1H, *J* = 3.0 Hz), 3.87 (d, 1H, *J* = 13.5 Hz), 3.92 (d, 1H, *J* = 13.5 Hz), 4.10 (q, 2H, *J* = 7.5 Hz), 7.20-7.4 (m, 1H), 7.26-7.38 (m, 4H); ¹³C NMR (125 MHz, CDCl₃) δ 14.12, 25.62, 25.74, 26.22, 29.93, 30.71, 39.70, 40.71, 52.70, 55.64, 60.89, 126.94,

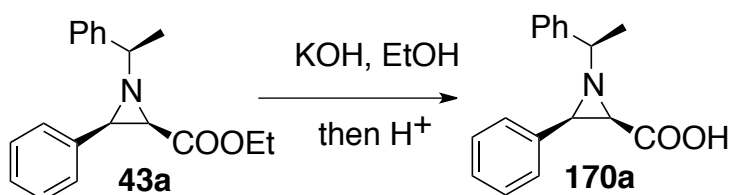
128.24, 128.54, 139.32, 169.77; IR (thin film) 2926(s), 1728(s) cm^{-1} ; HRMS calcd for $\text{C}_{18}\text{H}_{26}\text{NO}_2$ ($\text{M}+\text{H}$, ESI^+) m/z 288.1964, meas 288.1972.

Hydrolysis: To solution of ester **320** (100 mg, 0.348 mmol, 1.00 equiv) in ethanol (1 mL) was added a solution of KOH (97 mg, 1.7 mmol, 5.0 equiv) in H_2O (2 mL).

The resulting mixture was refluxed for 30 min. After cooling, aq citric acid (2N, 2 mL) was added. The resulting white precipitate was collected by filtration. Then the white solid was dissolved in ether (20 mL), dried (Na_2SO_4) and filtered. The filtrate was concentrated to give the product *trans*-**153g** (85 mg, 0.33 mmol, 94%) as a white solid; mp 135-136 $^\circ\text{C}$ (decomposition); R_f = 0.05 (hexane:EtOAc 4:1);

^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 0.80-1.30 (m, 11H), 1.98 (d, 1H, J = 2.5 Hz), 2.37 (d, 1H, J = 2.5 Hz), 3.81 (d, 1H, J = 13.5 Hz), 3.86 (d, 1H, J = 13.0 Hz), 7.20-7.40 (m, 5H), 12.52 (brs, 1H); ^{13}C NMR (125 MHz, $\text{DCMSO}-d_6$) δ 25.14, 25.24, 25.78, 29.36, 30.03, 38.82, 39.77, 51.63, 54.69, 126.79, 128.12, 128.33, 139.60, 170.74; IR (thin film) 2924(s), 1722(s) cm^{-1} ; HRMS calcd for $\text{C}_{16}\text{H}_{22}\text{NO}_2$ ($\text{M}+\text{H}$, ES^+) m/z 260.1651, meas 260.1660.

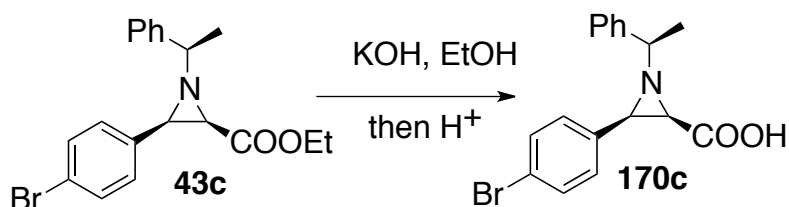
Preparation of acid 170a:



To a suspension of ester **43a** (150 mg, 0.500 mmol, 1.00 equiv) in EtOH (1 mL) was added an aqueous solution KOH (140 mg, 2.50 mmol, 5.00 equiv) in H_2O (1

mL). The resulting mixture was refluxed for 30 min. After it was cooled to rt, aq citric acid (2N, 2 mL) and ether (10 mL) were added. The aqueous layer was separated and extracted with ether (2 × 5 mL). The combined organic extracts were dried (Na₂SO₄) and filtered. The filtrate was concentrated to give the product **170a** a white foamy solid 130 mg (0.487 mmol, 94%). mp 48-50 °C; R_f = 0.10 (hexane:EtOAc 4:1). Spectral data for acid **170a**: ¹H NMR (500 MHz, CDCl₃) δ 1.61 (d, 3H, *J* = 7.0 Hz), 2.80 (d, 1H, *J* = 7.0 Hz), 3.07 (q, 1H, *J* = 6.5 Hz), 3.28 (d, 1H, *J* = 7.0 Hz), 7.20-7.80 (m, 11H); ¹³C NMR (125 MHz, CDCl₃) δ 22.60, 44.88, 47.71, 68.44, 126.95, 127.41, 127.78, 127.92, 128.33, 128.69, 133.96, 142.16, 175.51; IR (thin film) 3400(m), 1775(s) cm⁻¹; HRMS calcd for C₁₇H₁₈NO₂ (M+H, ESI⁺) *m/z* 268.1338, meas 268.1331; [α]_D²⁰ 16.6° (c 1.0, CH₂Cl₂).

Preparation of acid 170c:

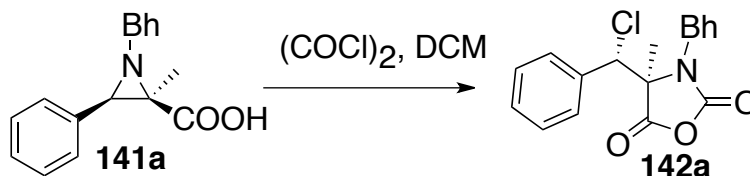


To a suspension of ester **43c** (187 mg, 0.500 mmol, 1.00 equiv) in EtOH (1 mL) was added an aqueous solution KOH (140 mg, 2.50 mmol, 5.00 equiv) in H₂O (2 mL). The resulting mixture was refluxed for 30 min. After it was cooled to rt, aq citric acid (2N, 2 mL) was added, followed by the addition of ether (10 mL). The aqueous layer was separated and extracted with ether (2 × 10 mL). The

combined organic extracts were dried (Na₂SO₄) and filtered. The filtrate was concentrated to give a white foamy solid 175 mg (0.505 mmol, 101%); mp 80-82 °C; R_f = 0.10 (hexane:EtOAc 4:1). Spectral data for acid **170c**: ¹H NMR (500 MHz, CDCl₃) δ 1.55 (d, 3H, *J* = 6.5 Hz), 2.74 (d, 1H, *J* = 7.0 Hz), 2.98 (q, 1H, *J* = 6.5 Hz), 3.12 (d, 1H, *J* = 7.0 Hz), 7.00-7.40 (m, 10H); ¹³C NMR (125 MHz, DMSO-d₆) δ 22.91, 45.71, 46.16, 67.62, 120.13, 126.58, 127.02, 128.30, 129.75, 130.49, 135.51, 143.97, 168.78; IR (thin film) 3408(m), 1770(s) cm⁻¹; HRMS calcd for C₁₇H₁₇NO₂⁷⁹Br (M+H, ESI⁺) *m/z* 346.0443, meas 346.0435; [α]_D²⁰ = 19.4° (c 1.0, CH₂Cl₂).

7.3.2 *N*-carboxy anhydride (NCA) formation

The formation of NCA 142a:



General procedure for N-carboxyanhydride (NCA) formation: Illustrated for the formation of NCA **142a**. A flame-dried 25 mL round bottom flask filled with N₂ was charged with the acid **141a** (69 mg, 0.20 mmol, 1.0 equiv). The vacuum adapter was replaced with a septum to which a N₂ balloon was attached via a needle. Dry CH₂Cl₂ (2.0 mL) was added via syringe. The flask was cooled to 0 °C. And (COCl)₂ (0.040 mL, 0.40 mmol, 2.0 equiv) was added at 0 °C dropwise.

After it was stirred at 0 °C for 5 min and at rt for 1 h, the volatiles were removed. The crude mixture was purified by column (silica gel, 18 × 180 mm, hexane:EtOAc 5:1) to give the product **142a** as a white fomy solid (44 mg, 0.11 mmol) in 54% yield; mp 49-50 °C; R_f = 0.30 (hexane:EtOAc 4:1). Spectral data for NCA **142a**: ^1H NMR (500 MHz, CDCl_3) δ 1.62 (s, 3H), 5.13 (s, 1H), 5.30 (s, 1H), 7.10-7.16 (m, 2H), 7.22-7.48 (m, 13H); ^{13}C NMR (125 MHz, CDCl_3) δ 22.02, 62.73, 65.45, 71.33, 127.63, 127.94, 128.33, 128.44, 128.49, 128.64, 128.76, 129.33, 129.73, 133.11, 137.89, 139.16, 150.23, 170.09; IR (thin film) 1848(s), 1780(s) cm^{-1} ; HRMS calcd for $\text{C}_{24}\text{H}_{21}\text{NO}_3^{35}\text{Cl}$ ($\text{M}+\text{H}^+$, ESI^+) m/z 406.1210, meas 406.1235; $[\alpha]_D^{20}$ 21.3° (c 1.0, CH_2Cl_2).

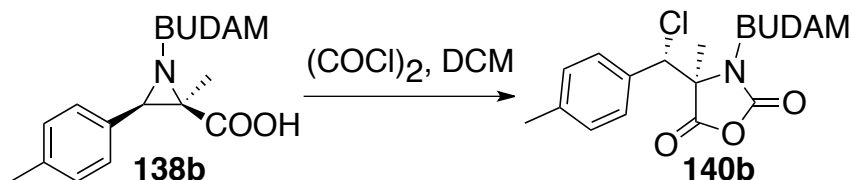
*The formation of NCA **140a**:*



General procedure for NCA formation was followed with acid **138a** (70 mg, 0.11 mmol, 1.0 equiv), $(\text{COCl})_2$ (0.020 mL, 0.23 mmol, 2.0 equiv) and CH_2Cl_2 (2 mL). After column chromatography (1st column, silica gel, 18 × 180 mm, hexane:EtOAc 15:1; 2nd column, silica gel, 18 × 180 mm, benzene:EtOAc 100:1), the product **140a** was obtained as a white solid (54 mg, 0.078 mmol) in 69% yield; mp 41-42 °C; R_f = 0.50 (hexane:EtOAc 4:1). Spectral data for **140a**: ^1H NMR (600 MHz, CDCl_3) δ 1.31 (s, 18H), 1.42 (s, 18H), 1.68 (s, 3H), 3.64 (s, 3H),

3.75 (s, 3H), 5.06 (s, 1H), 5.27 (s, 1H), 6.89 (s, 2H), 7.18-7.26 (m, 6H), 7.35 (t, 1H, $J = 7.2$ Hz); ^{13}C NMR (150 MHz, CDCl_3) δ 22.00, 31.93, 32.10, 35.70, 35.89, 62.61, 64.20, 64.33, 65.21, 71.33, 126.79, 127.34, 128.38, 128.82, 129.48, 132.17, 132.96, 133.44, 143.24, 143.43, 149.70, 158.78, 159.07, 170.39; IR (thin film) 2960(m), 1847(m), 1785(s) cm^{-1} ; HRMS calcd for $\text{C}_{42}\text{H}_{57}\text{NO}_5^{35}\text{Cl}$ (M, ESI^+) m/z 690.3925, meas 690.3954; $[\alpha]_D^{20}$ 5.8° (c 0.5, CH_2Cl_2).

*The formation of NCA **140b**:*

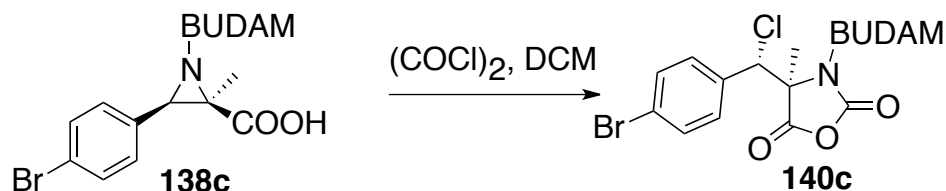


General procedure for NCA formation was followed with acid **138b** (129 mg, 0.200 mmol, 1.00 equiv), $(\text{COCl})_2$ (0.040 mL, 0.40 mmol, 2.0 equiv) and CH_2Cl_2 (2 mL). After column chromatography (silica gel, 18 × 180 mm, benzene:EtOAc 100:1), the product **140b** was obtained as a white foamy solid (106 mg, 0.0150 mmol) in 75% yield; mp 71-78 °C; $R_f = 0.60$ (benzene:EtOAc 100:1). Spectral data for NCA **140b**: ^1H NMR (500 MHz, CDCl_3) δ 1.28 (s, 18H), 1.39 (s, 18H), 1.63 (s, 3H), 2.31 (s, 3H), 3.61 (s, 3H), 3.72 (s, 3H), 5.08 (s, 1H), 5.21 (s, 1H), 6.86 (s, 2H), 7.01 (d, 2H, $J = 8.0$ Hz), 7.04 (d, 2H, $J = 8.5$ Hz), 7.21 (s, 2H); ^{13}C NMR (150 MHz, CDCl_3) δ 20.79, 21.82, 31.66, 31.84, 35.43, 35.62, 62.20, 63.95, 64.07, 64.85, 71.08, 126.58, 127.05, 128.43, 128.78, 130.18, 131.96, 132.69, 139.23, 142.94, 143.14, 149.44, 158.50, 158.79, 170.19; IR (thin film) 2961(m),

1846(m), 1784(s) cm^{-1} ; HRMS calcd for $\text{C}_{43}\text{H}_{59}\text{NO}_5^{35}\text{Cl}$ ($\text{M}+\text{H}$, ESI^+) m/z

704.4082, meas 704.4030; $[\alpha]_{\text{D}}^{20}$ 3.2° (c 1.0, CH_2Cl_2).

*The formation of NCA **140c**:*



General procedure for NCA formation was followed with acid **138c** (141 mg,

0.200 mmol, 1.00 equiv), $(\text{COCl})_2$ (0.040 mL, 0.40 mmol, 2.0 equiv) and CH_2Cl_2

(2 mL). After column chromatography (silica gel, 18 × 180 mm, benzene:EtOAc

100:1), the product **140c** was obtained as a white foamy solid (120 mg, 0.0156

mmol) in 78% yield; mp 78-80 °C; R_f = 0.60 (benzene:EtOAc 100:1). Spectral

data for **140c**: ^1H NMR (300 MHz, CDCl_3) δ 1.29 (s, 18H), 1.40 (s, 18H), 1.73 (s,

3H), 3.62 (s, 3H), 3.73 (s, 3H), 4.99 (s, 1H), 5.15 (s, 1H), 6.88 (s, 2H), 6.94 (d,

2H, J = 8.4 Hz), 7.22 (s, 2H), 7.29 (d, 2H, J = 8.7 Hz); ^{13}C NMR (150 MHz,

CDCl_3) δ 21.74, 31.91, 32.09, 35.71, 35.91, 62.67, 64.18, 64.39, 64.41, 71.24,

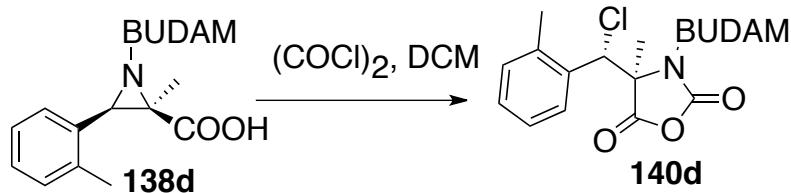
123.72, 126.85, 127.35, 130.38, 131.51, 132.20, 132.40, 132.48, 143.37, 143.57,

149.55, 158.97, 159.09, 169.95; IR (thin film) 2963(m), 1848(m), 1784(s) cm^{-1} ;

HRMS calcd for $\text{C}_{42}\text{H}_{56}\text{NO}_5^{79}\text{Br}^{35}\text{Cl}$ ($\text{M}+\text{H}$, ESI^+) m/z 768.3030, meas

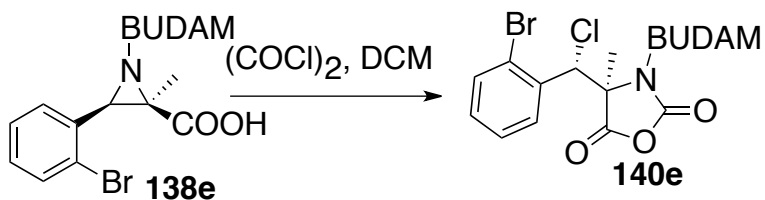
768.2977; $[\alpha]_{\text{D}}^{20}$ -11.3° (c 2.0, CH_2Cl_2).

*The formation of NCA **140d**:*



General procedure for NCA formation was followed with acid **138d** (129 mg, 0.200 mmol, 1.00 equiv), $(\text{COCl})_2$ (0.040 mL, 0.40 mmol, 2.0 equiv) and CH_2Cl_2 (2 mL). After column chromatography (silica gel, 18 × 180 mm, benzene:EtOAc 100:1), the product **140d** was obtained as a white foamy solid (100 mg, 0.0142 mmol) in 71% yield; mp 72-78 °C; R_f = 0.60 (benzene:EtOAc 100:1). Spectral data for **140d**: ^1H NMR (600 MHz, CDCl_3) δ 1.29 (s, 18H), 1.38 (s, 18H), 1.62 (s, 3H), 2.35 (s, 3H), 3.62 (s, 3H), 3.70 (s, 3H), 5.33 (s, 1H), 5.59 (s, 1H), 6.94-7.00 (m, 3H), 7.15 (d, 1H, J = 7.2 Hz), 7.20-7.24 (m, 3H), 7.42 (d, 1H, J = 7.8 Hz); ^{13}C NMR (150 MHz, CDCl_3) δ 20.15, 20.79, 32.16, 32.30, 35.93, 36.70, 62.39, 63.25, 64.40, 64.50, 71.63, 126.55, 126.70, 128.13, 129.40, 129.62, 131.02, 132.37, 132.98, 133.55, 136.33, 143.21, 143.45, 150.13, 158.74, 159.25, 170.81; IR (thin film) 2961(m), 1846(m), 1784(s) cm^{-1} ; HRMS calcd for $\text{C}_{43}\text{H}_{59}\text{NO}_5^{35}\text{Cl}$ ($\text{M}+\text{H}$, ES^+) m/z 704.4082, meas 704.4040; $[\alpha]_D^{20}$ -9.0° (c 1.0, CH_2Cl_2);

*The formation of NCA **140e**:*



General procedure for NCA formation was followed with acid **138e** (71 mg, 0.10 mmol, 1.0 equiv), $(\text{COCl})_2$ (0.020 mL, 0.23 mmol, 2.0 equiv) and CH_2Cl_2 (1 mL).

After column chromatography (silica gel, 18 × 180 mm, benzene:EtOAc 100:1), the product **140e** was obtained as a white foamy solid (56 mg, 0.073 mmol) in 73% yield; mp 75-80 °C; R_f = 0.75 (benzene:EtOAc 100:1). Spectral data for **140e**: ^1H NMR (500 MHz, CDCl_3) δ 1.35 (s, 18H), 1.43 (s, 18H), 1.80 (s, 3H), 3.67 (s, 3H), 3.74 (s, 3H), 5.39 (s, 1H), 5.96 (s, 1H), 7.03 (s, 2H), 7.12-7.18 (m, 1H), 7.22-7.32 (m, 3H), 7.49 (d, 1H, J = 8.0 Hz), 7.61 (d, 1H, J = 8.0 Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 20.23, 31.96, 32.11, 35.74, 35.88, 62.89, 64.20, 64.32, 64.57, 71.17, 124.56, 126.39, 127.80, 127.86, 130.97, 131.07, 132.14, 133.02, 133.06, 134.15, 143.15, 143.22, 149.78, 158.64, 159.04, 169.72; IR (thin film) 2961(m), 1848(m), 1784(s) cm^{-1} ; HRMS calcd for $\text{C}_{42}\text{H}_{56}\text{NO}_5^{79}\text{Br}^{35}\text{Cl}$ ($\text{M}+\text{H}^+$, ESI^+) m/z 768.3030, meas 768.3070; $[\alpha]_D^{20}$ -6.4° (c 0.5, CH_2Cl_2).

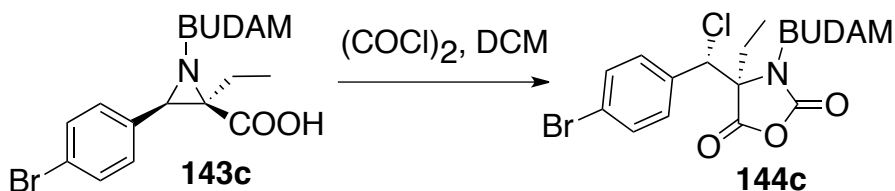
*The formation of NCA **140f**:*



General procedure for NCA formation was followed with acid **138f** (136 mg, 0.200 mmol, 1.00 equiv), $(\text{COCl})_2$ (0.040 mL, 0.40 mmol, 2.0 equiv) and CH_2Cl_2 (2 mL). After column chromatography (silica gel, 18 × 180 mm, benzene:EtOAc 100:1), the product **140f** was obtained as a white foamy solid (118 mg, 0.016 mmol) in 80% yield; mp 89-91 °C; R_f = 0.65 (benzene:EtOAc 50:1). Spectral data for **140f**: ^1H NMR (500 MHz, CDCl_3) δ 1.21 (s, 18H), 1.41 (s, 18H), 1.52 (s, 3H),

3.56 (s, 3H), 3.71 (s, 3H), 5.12 (s, 1H), 6.31 (s, 1H), 6.82 (s, 2H), 7.12 (t, 1H, $J = 8.0$ Hz), 7.26 (s, 2H), 7.52 (t, 1H, $J = 7.0$ Hz), 7.60 (t, 2H, $J = 8.5$ Hz), 7.83 (d, 1H, $J = 8.0$ Hz), 7.89 (d, 1H, $J = 8.5$ Hz), 8.03 (d, 1H, $J = 8.5$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 21.94, 31.88, 32.14, 35.65, 35.91, 61.12, 63.08, 64.13, 64.37, 72.10, 122.34, 124.98, 126.13, 126.44, 127.31, 127.99, 128.73, 129.39, 129.69, 130.27, 131.23, 132.34, 133.16, 133.38, 143.04, 143.06, 150.09, 158.54, 158.94, 171.10; IR (thin film) 2963(m), 1848(m), 1784(s) cm^{-1} ; HRMS calcd for $\text{C}_{46}\text{H}_{59}\text{NO}_5^{35}\text{Cl}$ ($\text{M}+\text{H}^+$, ES^+) m/z 740.4082, meas 740.4075; $[\alpha]_D^{20} -10.3^\circ$ (c 1.0, CH_2Cl_2).

*The formation of NCA **144c**:*

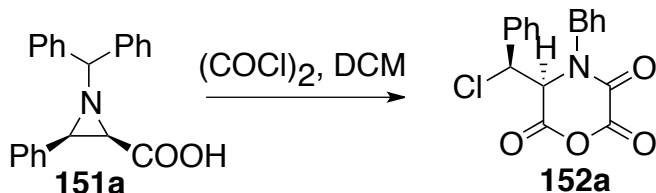


General procedure for NCA formation was followed with acid **143c** (144 mg, 0.200 mmol, 1.00 equiv), $(\text{COCl})_2$ (0.040 mL, 0.40 mmol, 2.0 equiv) and CH_2Cl_2 (2 mL). After column chromatography (1^{st} silica gel, 18×180 mm, benzene:EtOAc 100:1; 2^{nd} silica gel, 18×180 mm, benzene:EtOAc 100:1), the product **144c** was obtained as a white foamy solid (30 mg, 0.038 mmol) in 20% yield; mp $60\text{--}61^\circ\text{C}$; $R_f = 0.725$ (benzene:EtOAc 100:1). Spectral data for **144c**: ^1H NMR (500 MHz, CDCl_3) δ 0.42 (t, 3H, $J = 7.5$ Hz), 1.28 (s, 18H), 1.36 (s, 18H), 1.74 (dq, 1H, $J = 7.5, 7.5$ Hz), 2.02 (dq, 1H, $J = 7.5, 7.5$ Hz), 3.58 (s, 3H),

3.70 (s, 3H), 4.94 (s, 1H), 5.35 (s, 1H), 6.93 (s, 2H), 7.18 (s, 2H), 7.23 (d, 2H, J = 8.5 Hz), 7.40 (d, 2H, J = 8.5 Hz); ^{13}C NMR (150 MHz, CDCl_3) δ 7.73, 27.97, 31.90, 32.11, 35.67, 35.91, 62.87, 64.25, 64.32, 64.72, 76.19, 123.86, 126.19, 128.29, 130.41, 131.55, 131.71, 132.75, 133.12, 143.07, 143.64, 150.01, 158.54, 159.42, 169.60; IR (thin film) 2963(m), 1846(m), 1782(s) cm^{-1} ; HRMS calcd for $\text{C}_{43}\text{H}_{58}\text{NO}_5^{35}\text{Cl}^{79}\text{Br}$ ($\text{M}+\text{H}$, ES^+) m/z 782.3187, meas 782.3253; $[\alpha]_D^{20}$ 9.8° (c 1.0, CH_2Cl_2).

7.3.3 Morpholine-2,3,5-trione formation

*The formation of morpholine-2,3,5-trione **152a**:*

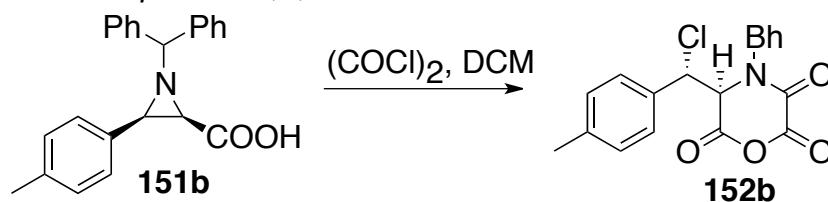


General procedure for the formation of morpholine-2,3,5-trione: Illustrated for the

*formation of **152a**:* To a flame-dried 25 mL round bottom flask filled with N_2 was added acid **151a** (132 mg, 0.400 mmol, 1.00 equiv) and CH_2Cl_2 (4 mL). The vacuum adapter was replaced with a septum to which a N_2 balloon was attached *via* a needle. The flask was cooled in an ice bath. And $(\text{COCl})_2$ (102 mg, 0.0700 mL, 0.800 mmol, 2.00 equiv) was added dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 5 min and the ice bath was removed. After the mixture was stirred at rt for 1 h, the volatiles were removed by rotary evaporation. And a foamy solid was obtained. Hexane was then added and the solid was collected

by filtration and washed with a mixture of CH₂Cl₂ and hexane (v/v 10:1, 2 mL). The product **152a** was obtained as a pale yellow solid (124 mg, 0.296 mmol, 74%). Recrystallization from CH₂Cl₂ and hexane gave X-ray quality crystals; mp 129-131 °C. Spectral data for **152a**: ¹H NMR (300 MHz, CDCl₃) δ 3.77 (d, 1H, *J* = 3.9 Hz), 5.02 (d, 1H, *J* = 3.9 Hz), 6.98-7.10 (m, 4H), 7.15 (s, 1H), 7.28-7.46 (m, 6H), 7.40-7.62 (m, 5H); ¹³C NMR (150 MHz, CDCl₃) δ 58.35, 62.30, 64.51, 126.39, 128.40, 128.82, 129.26, 129.70, 130.08, 130.38, 130.47, 131.01, 131.05, 135.73, 136.27, 148.33, 151.23, 157.65; IR (thin film) 1832(m), 1782(s), 1705(s) cm⁻¹; HRMS calcd for C₂₄H₁₉NO₄³⁵Cl (M+H, ESI⁺) *m/z* 420.1003, meas 420.0970; [α]_D²⁰ -164.5° (c 0.5, CH₂Cl₂).

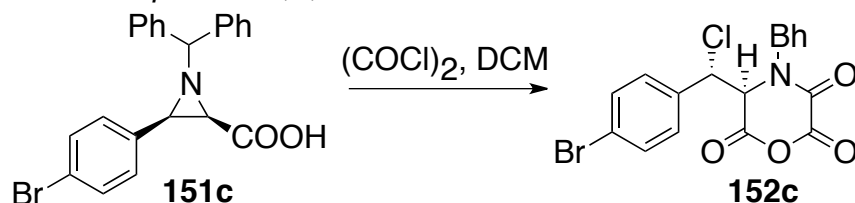
*The formation of morpholine-2,3,5-trione **152b**:*



The general procedure for the formation of morpholine-2,3,5-trione was followed with acid **151b** (35 mg, 0.10 mmol, 0.10 equiv), (COCl)₂ (0.030 mL, 0.30 mmol, 3.0 equiv) and CH₂Cl₂ (1 mL). The product **152b** was obtained as a yellow solid. The NMR yield was 82% with the aid of triphenylmethane. Spectral data for **152b**: ¹H NMR (600 MHz, CDCl₃) δ 2.34 (s, 3H), 3.73 (d, 1H, *J* = 4.0 Hz), 5.00 (d, 1H, *J* = 3.5 Hz), 6.90 (d, 2H, *J* = 7.8 Hz), 7.03 (d, 2H, *J* = 7.5 Hz), 7.10-7.60

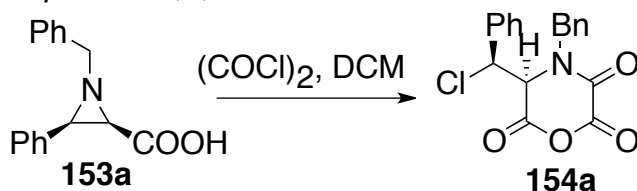
(m, 11H); IR (thin film) 1832(s), 1782(s), 1703(s) cm^{-1} . Unfortunately, it was contaminated with some impurities. A clean ^{13}C NMR was not obtained.

*The formation of morpholine-2,3,5-trione **152c**:*



The general procedure for the formation of morpholine-2,3,5-trione was followed with acid **151c** (82 mg, 0.20 mmol, 1.0 equiv), $(\text{COCl})_2$ (0.040 mL, 0.40 mmol, 2.0 equiv) and CH_2Cl_2 (2 mL). The product **152c** was obtained as a yellow solid (42 mg, 0.084 mmol, 42%); mp 120-122 $^\circ\text{C}$. Spectral data for **152c**: ^1H NMR (600 MHz, CDCl_3) δ 3.74 (d, 1H, $J = 4.2$ Hz), 5.00 (d, 1H, $J = 3.6$ Hz), 6.90 (d, 2H, $J = 7.8$ Hz), 7.03 (d, 2H, $J = 7.8$ Hz), 7.13 (s, 1H), 7.32-7.42 (m, 4H), 7.46-7.60 (m, 6H); ^{13}C NMR (150 MHz, CDCl_3) δ 58.01, 62.64, 64.57, 125.91, 126.62, 128.71, 129.53, 130.36, 130.48, 130.60, 130.70, 133.15, 135.72, 136.47, 148.81, 151.36, 157.60 (One sp^2 carbon not located); IR (thin film) 1832(m), 1784(s), 1708(s) cm^{-1} ; HRMS calcd for $\text{C}_{24}\text{H}_{18}\text{NO}_4$ $^{79}\text{Br}^{35}\text{Cl}$ ($\text{M}+\text{H}^+$) m/z 498.0108, meas 498.0150; $[\alpha]_D^{20} -90.3^\circ$ (c 0.5, CH_2Cl_2).

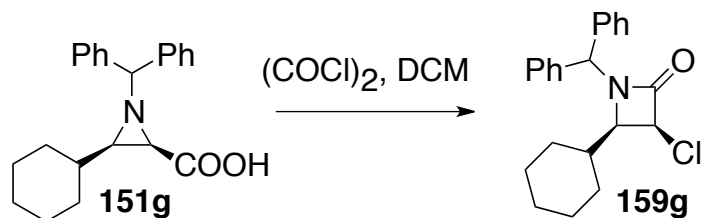
*The formation of morpholine-2,3,5-trione **154a**:*



The procedure for the formation of morpholine-2,3,5-trione was followed with acid **153a** (28 mg, 0.10 mmol, 0.10 equiv), (COCl)₂ (0.020 mL, 0.20 mmol, 2.0 equiv) and CH₂Cl₂ (1 mL). The product **154a** was obtained as a yellow solid. The NMR yield was 91% with the aid of triphenylmethane. Spectral data for **154a**: ¹H NMR (500 MHz, CDCl₃) δ 3.21 (d, 1H, *J* = 15.0 Hz), 4.77 (d, 1H, *J* = 3.0 Hz), 5.18 (d, 1H, *J* = 15.0 Hz), 5.39 (d, 1H, *J* = 2.5 Hz), 6.80-7.60 (m, 10H); IR (thin film) 1830(s), 1780(s), 1701(s) cm⁻¹. Unfortunately, the product was contaminated with some impurities. Thus, a clean ¹³C NMR could not be obtained.

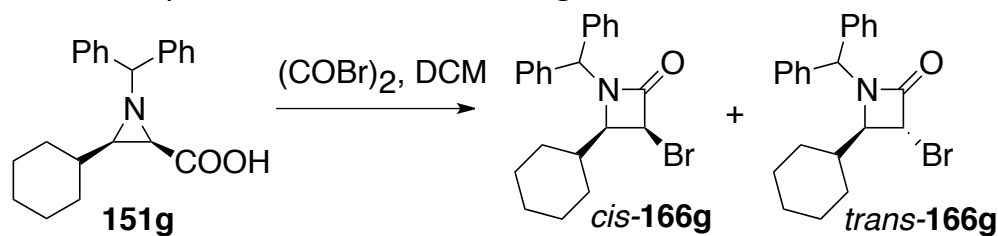
7.3.4 β-lactam formation with (COCl)₂

The formation of β-lactam 159g:



was placed under high vacuum (0.1 mmHg) to give the product **159g** (70 mg, 0.198 mmol, 99%) as a white foamy solid; The optical purity was determined to be >99% ee by HPLC analysis (Chiralpak AS column, 90:10 hexane/2-propanol at 222 nm, flow-rate 1.0 mL/min); Retention times: t_R = 9.57 min and t_R = 32.35 min (its enantiomer); mp 113-114 °C; R_f = 0.50 (hexane:EtOAc 4:1). Spectral data for **159g**: ^1H NMR (500 MHz, CDCl_3) δ 0.84-0.98 (m, 1H), 1.02-1.36 (m, 4H), 1.62-1.94 (m, 6H), 3.57 (dd, 1H, J = 8.5, 5.0 Hz), 4.80 (d, 1H, J = 5.0 Hz), 5.62 (s, 1H), 7.26-7.46 (m, 10H); ^{13}C NMR (125 MHz, CDCl_3) δ 25.55, 25.80, 26.23, 29.94, 30.01, 38.96, 58.69, 62.94, 64.88, 127.92, 128.21, 128.39, 128.55, 128.70, 128.88, 138.28, 139.25, 165.08; IR (thin film) 2927(m), 1764(s) cm^{-1} ; HRMS calcd for $\text{C}_{22}\text{H}_{25}\text{NO}^{35}\text{Cl}$ ($\text{M}+\text{H}^+$, ESI^+) m/z 354.1625, meas 336.1638; $[\alpha]_D^{20}$ -96.6° (c 1.0, CH_2Cl_2).

The formation of β -lactam cis- and trans-166g:



A flame-dried 25 mL round bottom flask filled with N_2 was charged with acid **151g** (67 mg, 0.20 mmol, 1.0 equiv). The vacuum adapter was replaced with a septum to which a N_2 balloon was attached *via* a needle. Dry CH_2Cl_2 (2 mL) was added *via* syringe. The flask was cooled to 0 °C. And $(\text{COBr})_2$ (0.040 mL, 0.40

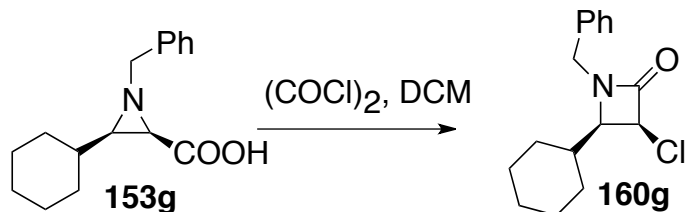
mmol, 2.0 equiv) was added dropwise at 0 °C. After it was stirred at 0 °C for 15 min, the reaction mixture was concentrated. ^1H NMR of the crude mixture showed a 2:1 *trans*:*cis* ratio. The crude product was purified by column chromatography (1st column, silica gel, 18 × 180 mm, hexane:EtOAc 5:1; 2nd column, silica gel, 18 × 180 mm, hexane:EtOAc 15:1). The pure *trans*-**166g** (22 mg, 0.055 mmol) was obtained as a colorless oil in 28% yield. And the overall yield for *cis* and *trans*-isomers after column chromatography was 94%.

A flame-dried 25 mL round bottom flask filled with N₂ was charged with acid **151g** (34 mg, 0.10 mmol, 1.0 equiv). The vacuum adapter was replaced with a septum to which a N₂ balloon was attached *via* a needle. Dry CH₂Cl₂ (1 mL) was added *via* syringe. The flask was cooled to 0 °C. And (COBr)₂ was added dropwise at 0 °C. After the reaction mixture was stirred at 0 °C for 15 min, *aq* sat NaHCO₃ (1 mL) was added at 0 °C *via* syringe along with CH₂Cl₂ (10 mL). Aqueous layer was separated and extracted with CH₂Cl₂ (2 × 5 mL). The combined organic extracts were dried (Na₂SO₄) and filtered. The filtrate was concentrated and ^1H NMR of this crude mixture showed a 7:1 *cis*:*trans* ratio. The crude product was purified by column chromatography (silica gel, 18 × 180 mm, hexane:EtOAc 9:1). The pure *cis*-**166g** (100:1 *cis*:*trans* ratio by ^1H NMR, 33 mg, 0.083 mmol) was obtained as a colorless oil in 83% yield. Overall yield after column chromatography for *cis* and *trans* isomers was 95%.

Spectral data for *cis*-**166g**: solidified in the refrigerator, mp 83-85 °C; R_f = 0.35 (hexane:EtOAc 4:1); ^1H NMR (600 MHz, CDCl_3) δ 0.86 (qd, 1H, J = 11.4, 3.0 Hz), 1.02-1.32 (m, 4H), 1.62-1.74 (m, 3H), 1.78-1.90 (m, 3H), 3.48 (dd, 1H, J = 9.0, 5.4 Hz), 4.86 (d, 1H, J = 5.4 Hz), 5.61 (s, 1H), 7.20-7.40 (m, 10H); ^{13}C NMR (150 MHz, CDCl_3) δ 25.21, 25.52, 25.98, 29.84, 30.01, 40.02, 47.94, 61.30, 64.78, 127.70, 127.99, 128.187, 128.36, 128.48, 128.66, 138.04, 139.04, 165.00; IR (thin film) $1765(\text{s})\text{ cm}^{-1}$; HRMS calcd for $\text{C}_{22}\text{H}_{25}\text{NO}^{79}\text{Br}$ ($\text{M}+\text{H}$, ESI^+) m/z 398.1120, meas 398.1125; $[\alpha]_{\text{D}}^{20} -33.9^\circ$ (c 0.5, CH_2Cl_2).

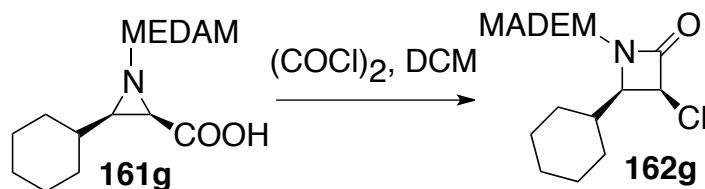
Spectral data for *trans*-**166g**: R_f = 0.35 (hexane:EtOAc 4:1); ^1H NMR (500 MHz, CDCl_3) δ 0.60-1.80 (m, 11H), 3.72 (dd, 1H, J = 5.0, 2.0 Hz), 4.51 (d, 1H, J = 2.0 Hz), 5.78 (s, 1H), 7.20-7.60 (m, 10H); ^{13}C NMR (125 MHz, CDCl_3) δ 25.36, 25.76, 26.03, 26.47, 29.31, 38.86, 43.53, 62.25, 69.23, 127.81, 128.02, 128.05, 128.36, 128.59, 128.69, 138.09, 138.17, 163.76; IR (thin film) $1765(\text{s})$, $1265(\text{m})\text{ cm}^{-1}$; HRMS calcd for $\text{C}_{22}\text{H}_{25}\text{NO}^{79}\text{Br}$ ($\text{M}+\text{H}$, ESI^+) m/z 398.1120, meas 398.1117; $[\alpha]_{\text{D}}^{20} -8.3^\circ$ (c 1.0, CH_2Cl_2);

The formation of β -lactam 160g:



The general procedure for β -lactam formation with $(\text{COCl})_2$ was followed with acid **153g** (52 mg, 0.20 mmol, 1.0 equiv), $(\text{COCl})_2$ (0.040 mL, 0.40 mmol, 2.0 equiv) and CH_2Cl_2 (2 mL). The crude product was purified by column chromatography (silica gel, 18 $\times$ 180 mm, hexane:EtOAc 5:1). The product **160g** was obtained as a white crystalline solid (46 mg, 0.17 mmol) in 83% yield; mp 118-119 $^\circ\text{C}$ from hexane and benzene; R_f = 0.40 (hexane:EtOAc 4:1). Spectral data for **160g**: ^1H NMR (500 MHz, CDCl_3) δ 0.80 (qd, 1H, J = 11.0, 3.5 Hz), 0.98 (qd, 1H, J = 12.0, 3.5 Hz), 1.10 (qt, 1H, J = 13.0, 3.5 Hz), 1.18-1.32 (m, 2H), 1.62-1.80 (m, 6H), 3.33 (dd, 1H, J = 9.0, 5.0 Hz), 4.08 (d, 1H, J = 15.0 Hz), 4.81 (d, 1H, J = 5.0 Hz), 4.86 (d, 1H, J = 15.0 Hz), 7.18-7.22 (m, 2H), 7.26-7.36 (m, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 25.29, 25.54, 25.95, 29.78, 29.80, 38.63, 47.06, 58.93, 61.18, 127.95, 128.20, 128.90, 135.06, 165.44; IR (thin film) 2924(m), 1755(s) cm^{-1} ; HRMS calcd for $\text{C}_{16}\text{H}_{21}\text{NO}^{35}\text{Cl}$ ($\text{M}+\text{H}^+$, ESI^+) m/z 278.1312, meas 278.1313; $[\alpha]_D^{20}$ -20.3° (c 0.5, CH_2Cl_2).

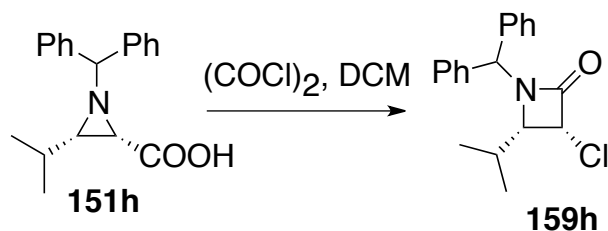
The formation of β -lactam 162g:



A flame-dried 25 mL round bottom flask filled with N_2 was charged with acid **161g** (45 mg, 0.10 mmol, 1.0 equiv). The vacuum adapter was replaced with a septum to which a N_2 balloon was attached *via* a needle. Dry CH_2Cl_2 (1 mL) was

added *via* syringe. The flask was cooled to 0 °C. And (COCl)₂ (0.020 mL, 0.20 mmol, 2.0 equiv) was added dropwise at 0 °C. After it was stirred at 0 °C for 10 min, the reaction mixture was concentrated. The crude product was purified by column chromatography (silica gel, 18 × 180 mm, hexane:EtOAc 5:1) to afford the product as a white solid (42 mg, 0.090 mmol) in 89% yield; mp 58-60 °C; R_f = 0.30 (hexane:EtOAc 4:1). Spectral data for **162g**: ¹H NMR (500 MHz, CDCl₃) δ 0.89 (qd, 1H, *J* = 12.0, 2.0 Hz), 1.00-1.30 (m, 4H), 1.60-1.90 (m, 6H), 2.23, 2.24 (2s, 12H), 3.52 (dd, 1H, *J* = 8.5, 5.5 Hz), 3.69, 3.70 (2s, 6H), 4.78 (d, 1H, *J* = 5.5 Hz), 5.37 (s, 1H), 6.87, 6.88 (2s, 4H); ¹³C NMR (150 MHz, CDCl₃) δ 16.24, 16.29, 25.41, 25.70, 26.06, 29.68, 29.71, 38.79, 58.34, 59.62, 62.40, 63.85, 128.45, 128.64, 130.73, 130.99, 133.42, 134.48, 156.30, 156.53, 164.85 (One *sp*³ carbon not located); IR (thin film) 2928(s), 1765(w) cm⁻¹; HRMS calcd for C₂₈H₃₇NO₃³⁵Cl (M+H, ESI⁺) *m/z* 470.2462, meas 470.2459; [α]_D²⁰ 10.6° (c 0.5, CH₂Cl₂).

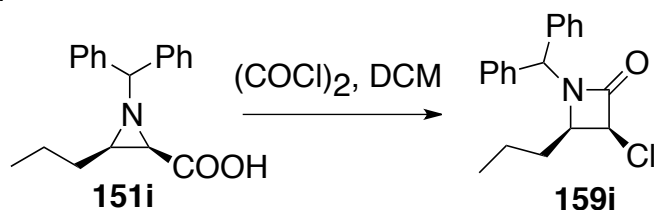
The formation of β-lactam 159h:



The general procedure for β-lactam formation with (COCl)₂ was followed with acid **151h** (30 mg, 0.10 mmol, 1.0 equiv), (COCl)₂ (0.020 mL, 0.20 mmol, 2.0

equiv) and CH₂Cl₂ (1 mL). The crude product was purified by column chromatography (silica gel, 18 × 180 mm, hexane:EtOAc 5:1). The product **159h** was obtained as a white solid (30 mg, 0.096 mmol) in 96% yield; mp 110-112 °C; R_f = 0.35 (hexane:EtOAc 4:1). Spectral data for **159h**: ¹H NMR (600 MHz, CDCl₃) δ 0.95 (d, 3H, *J* = 6.6 Hz), 0.99 (d, 3H, *J* = 7.2 Hz), 2.08-2.18 (m, 1H), 3.56 (dd, 1H, *J* = 9.0, 5.4 Hz), 4.82 (d, 1H, *J* = 5.4 Hz), 5.62 (s, 1H), 7.24-7.40 (m, 10H); ¹³C NMR (150 MHz, CDCl₃) δ 19.55, 19.71, 29.36, 58.49, 64.25, 64.31, 127.78, 128.00, 128.23, 128.29, 128.55, 128.66, 138.09, 138.89, 164.69; IR (thin film) 1759(s) cm⁻¹; HRMS calcd for C₁₉H₂₁NO³⁵Cl (M+H, ESI⁺) *m/z* 314.1312, meas 314.1299; [α]_D²⁰ 66.9° (c 0.5, CH₂Cl₂).

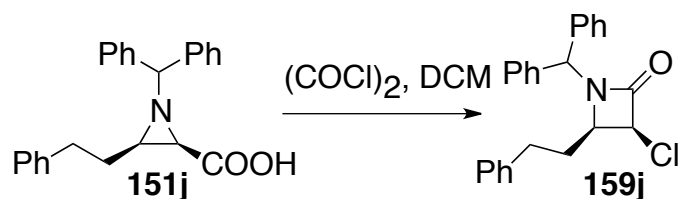
The formation of β-lactam 159i:



The general procedure for β-lactam formation with (COCl)₂ was followed with acid **151i** (30 mg, 0.10 mmol, 1.0 equiv), (COCl)₂ (0.020 mL, 0.20 mmol, 2.0 equiv) and CH₂Cl₂ (1 mL). The crude product was purified by column chromatography (silica gel, 18 × 180 mm, hexane:EtOAc 5:1). The product **159i** was obtained as a colorless oil (25 mg, 0.080 mmol) in 81% yield; R_f = 0.30 (hexane:EtOAc 4:1). Spectral data for **159i**: ¹H NMR (500 MHz, CDCl₃) δ 0.83

(t, 3H, $J = 7.0$ Hz), 1.04-1.18 (m, 1H), 1.26-1.40 (m, 1H), 1.44-1.54 (m, 1H), 1.70-1.82 (m, 1H), 3.64-3.74 (m, 1H), 4.88 (d, 1H, $J = 5.0$ Hz), 5.96 (s, 1H), 7.18-7.42 (m, 10H); ^{13}C NMR (150 MHz, CDCl_3) δ 13.69, 18.98, 31.57, 57.71, 59.15, 61.04, 127.83, 127.85, 128.13, 128.58, 128.69, 128.77, 137.60, 138.57, 164.07; IR (thin film) $1765(\text{s})\text{ cm}^{-1}$; HRMS calcd for $\text{C}_{19}\text{H}_{21}\text{NO}^{35}\text{Cl}$ ($\text{M}+\text{H}^+$) m/z 314.1312, meas 314.1313; $[\alpha]_{\text{D}}^{20} -28.5^\circ$ (c 1.0, CH_2Cl_2).

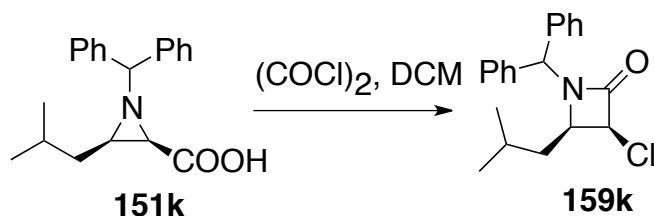
*The formation of β -lactam **159j**:*



The general procedure for β -lactam formation with $(\text{COCl})_2$ was followed with acid **151j** (36 mg, 0.10 mmol, 1.0 equiv), $(\text{COCl})_2$ (0.020 mL, 0.20 mmol, 2.0 equiv) and CH_2Cl_2 (1 mL). The crude product was purified by column chromatography (silica gel, 18×180 mm, hexane:EtOAc 5:1). The product **159j** was obtained as a white solid (27 mg, 0.072 mmol) in 72% yield; mp $93\text{--}94^\circ\text{C}$; $R_f = 0.13$ (hexane:EtOAc 4:1). Spectral data for **159j**: ^1H NMR (300 MHz, CDCl_3) δ 1.72-1.88 (m, 1H), 2.00-2.16 (m, 1H), 2.28-2.44 (m, 1H), 2.58-2.72 (m, 1H), 3.64-3.76 (m, 1H), 4.90 (d, 1H, $J = 5.1$ Hz), 5.94 (s, 1H), 6.94-7.02 (m, 2H), 7.20-7.40 (m, 13H); ^{13}C NMR (125 MHz, CDCl_3) δ 31.12, 31.72, 57.03, 58.96, 60.92, 126.20, 127.78, 127.87, 128.18, 128.23, 128.50, 128.64, 128.66, 128.81, 137.33, 138.39, 140.31, 163.94; IR (thin film) $1765(\text{s})\text{ cm}^{-1}$; HRMS calcd for

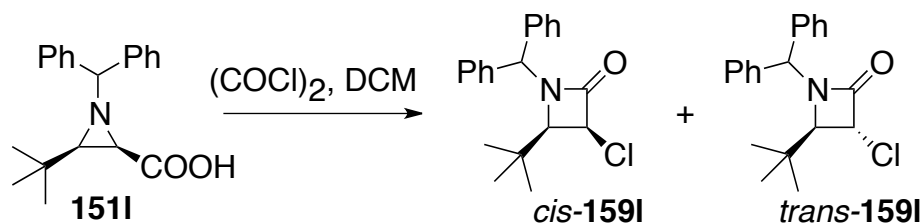
$\text{C}_{24}\text{H}_{23}\text{NO}^{35}\text{Cl}$ (M+H, ESI^+) m/z 376.1468, meas 376.1441; $[\alpha]_D^{20}$ -50.8° (c 1.0, CH_2Cl_2).

*The formation of β -lactam **159k**:*



The general procedure for β -lactam formation with $(\text{COCl})_2$ was followed with acid **151k** (31 mg, 0.10 mmol, 1.0 equiv), $(\text{COCl})_2$ (0.02 mL, 0.20 mmol, 2.0 equiv) and CH_2Cl_2 (1 mL) with a reaction time to be 30 min at rt. The crude product was purified by column chromatography (silica gel, 18×180 mm, hexane:EtOAc 5:1). The product **159k** was obtained as a pale yellow solid (24 mg, 0.074 mmol) in 75% yield; solidified in the refrigerator, mp $72\text{--}73^\circ\text{C}$; R_f = 0.25 (hexane:EtOAc 4:1). Spectral data for **159k**: ^1H NMR (300 MHz, CDCl_3) δ 0.68 (d, 3H, J = 6.3 Hz), 0.81 (d, 3H, J = 6.6 Hz), 1.22–1.34 (m, 1H), 1.40–1.56 (m, 1H), 1.72–1.82 (m, 1H), 3.66–3.76 (m, 1H), 4.86 (d, 1H, J = 4.8 Hz), 5.96 (s, 1H), 7.14–7.20 (m, 10H); ^{13}C NMR (125 MHz, CDCl_3) δ 21.64, 23.04, 25.06, 37.97, 56.27, 59.40, 60.90, 127.77, 127.81, 128.21, 128.60, 128.77, 128.85, 137.50, 138.55, 164.19; IR (thin film) $1767(\text{s})\text{ cm}^{-1}$; HRMS calcd for $\text{C}_{20}\text{H}_{23}\text{NO}^{35}\text{Cl}$ (M+H, ESI^+) m/z 328.1468, meas 328.1475; $[\alpha]_D^{20}$ -10.4° (c 1.0, CH_2Cl_2).

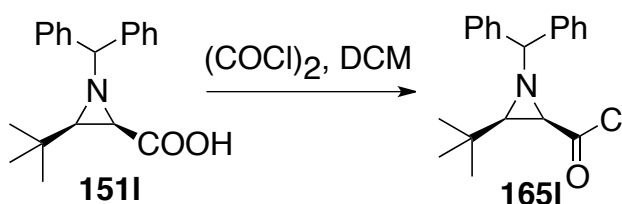
The formation of β -lactam **159I**:



A flame-dried 25 mL round bottom flask filled with N₂ was charged with acid **151I** (62 mg, 0.20 mmol, 1.0 equiv). The vacuum adapter was replaced with a septum to which a N₂ balloon was attached *via* a needle. Dry CH₂Cl₂ (2 mL) was added *via* syringe. The flask was cooled to 0 °C. And (COCl)₂ (0.040 mL, 0.40 mmol, 2.0 equiv) was added dropwise at 0 °C. After it was stirred at 0 °C for 5 min and rt for 5 h, the reaction mixture was concentrated and kept at rt for 3 months. The crude product was purified by column chromatography (silica gel, 18 × 180 mm, hexane:EtOAc 9:1). The pure *cis*-**159I** (40 mg, 0.12 mmol) was obtained as a white solid in 62% yield. And the pure *trans*-**159I** (10 mg, 0.031 mmol) was obtained as a white solid in 15% yield.

Spectral data for *cis*-**159I**: mp 136-138 °C; R_f = 0.33 (hexane:EtOAc 4:1); ¹H NMR (600 MHz, CDCl₃) δ 1.12 (s, 9H), 3.74 (d, 1H, *J* = 6.0 Hz), 4.82 (d, 1H, *J* = 5.4 Hz), 5.48 (s, 1H), 7.18-7.44 (m, 10H); ¹³C NMR (150 MHz, CDCl₃) δ 26.84, 34.10, 57.58, 65.60, 67.63, 127.73, 128.03, 128.15, 128.41, 128.53, 128.72, 138.24, 138.87, 164.69; IR (thin film) 1763(s) cm⁻¹; HRMS calcd for C₂₀H₂₃NO³⁵Cl (M+H, ESI⁺) *m/z* 328.1468, meas 328.1476; [α]_D²⁰ -89.5° (c 0.5, CH₂Cl₂);

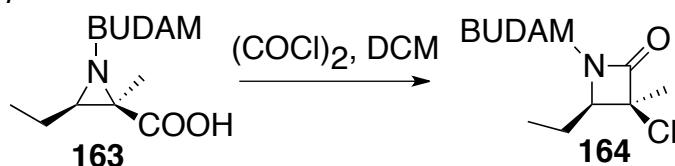
Spectral data for *trans*-**159I**: mp 101-103 °C; R_f = 0.40 (hexane:EtOAc 4:1); ^1H NMR (600 MHz, CDCl_3) δ 0.98 (s, 9H), 3.51 (d, 1H, J = 2.4 Hz), 4.41 (d, 1H, J = 2.4 Hz), 5.44 (s, 1H), 7.24-7.38 (m, 10H); ^{13}C NMR (150 MHz, CDCl_3) δ 26.08, 33.11, 56.30, 65.44, 73.80, 127.86, 127.91, 127.98, 128.54, 128.59, 128.79, 138.29, 138.41, 163.77; IR (thin film) 2963(m), 1768 (s) cm^{-1} ; HRMS calcd for $\text{C}_{20}\text{H}_{23}\text{NO}^{35}\text{Cl}$ ($\text{M}+\text{H}$, ESI^+) m/z 328.1468, meas 328.1453; $[\alpha]_D^{20}$ -15.4° (c 1.0, CH_2Cl_2).



A flame-dried 25 mL round bottom flask filled with N_2 was charged with acid **151I** (93 mg, 0.30 mmol, 1.0 equiv). The vacuum adapter was replaced with a septum to which a N_2 balloon was attached *via* a needle. Dry CH_2Cl_2 (3 mL) was added *via* syringe. The flask was cooled to 0 °C. And $(\text{COCl})_2$ (0.15 mL, 1.5 mmol, 5.0 equiv) was added dropwise at 0 °C. After it was stirred at 0 °C for 5 min and rt for 1 h, the reaction mixture was concentrated. The crude product was purified by column chromatography (silica gel, 18 × 180 mm, hexane:EtOAc 9:1) to obtain the product **165I** (20 mg, 0.033 mmol) as a white solid in 22% yield; mp 85-86 °C; R_f = 0.70 (hexane:EtOAc 4:1). Spectral data for **165I**: ^1H NMR (600 MHz, CDCl_3) δ 0.78 (s, 9H), 2.07 (d, 1H, J = 7.0 Hz), 2.67 (d, 1H, J = 7.0 Hz), 3.66 (s, 1H),

7.20-7.42 (m, 8H), 7.57 (d, 2H, $J = 7.5$ Hz); ^{13}C NMR (150 MHz, CDCl_3) δ 27.77, 32.83, 52.33, 60.27, 79.18, 127.20, 127.55, 127.98, 128.25, 128.72, 128.81, 141.93, 142.66, 170.36; IR (thin film) $1790(\text{s})\text{ cm}^{-1}$; Anal calcd for $\text{C}_{20}\text{H}_{22}\text{NOCl}$: C, 73.27; H, 6.76; N, 4.27. Found: C, 72.84; H, 6.71; N, 4.18. $[\alpha]_D^{20}$ 139.2° (c 0.5, CH_2Cl_2).

*The formation of β -lactam **164**:*

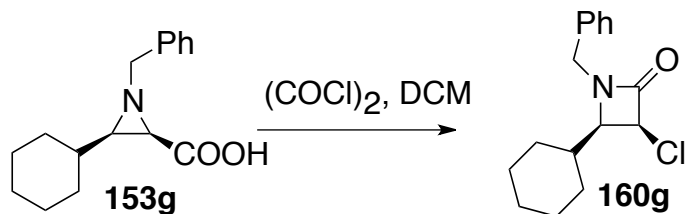


The general procedure for β -lactam formation with $(\text{COCl})_2$ was followed with acid **163** (58 mg, 0.20 mmol, 1.0 equiv), $(\text{COCl})_2$ (0.040 mL, 0.40 mmol, 2.0 equiv) and CH_2Cl_2 (2 mL). The crude product was purified by column chromatography (silica gel, 18×180 mm, hexane:EtOAc 15:1). The product **164** was obtained as a white foamy solid (23 mg, 0.39 mmol) in 39% yield; mp $73\text{--}76^\circ\text{C}$; $R_f = 0.30$ (hexane:EtOAc 4:1). Spectral data for **164**: ^1H NMR (300 MHz, CDCl_3) δ 0.74 (t, 3H, $J = 7.2$ Hz), 1.26-1.50 (m, 37H), 1.64-1.80 (m, 4H), 3.10 (dd, 1H, $J = 10.2, 3.3$ Hz), 3.65, 3.66 (2s, 6H), 5.94 (s, 1H), 7.00 (s, 2H), 7.06 (s, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 10.35, 24.13, 24.41, 32.05, 32.08, 35.79, 35.85, 59.59, 64.26, 64.28, 67.11, 71.60, 125.98, 127.23, 131.51, 132.41, 143.34, 143.74, 158.79, 158.94, 166.94; IR (thin film) $2964(\text{s}), 1770(\text{s})\text{ cm}^{-1}$;

HRMS calcd for $C_{37}H_{57}NO_3^{35}Cl$ ($M+H$, ESI^+) m/z 598.4027, meas 598.4039;

$[\alpha]_D^{20} -7.1^\circ$ (c 0.5, CH_2Cl_2).

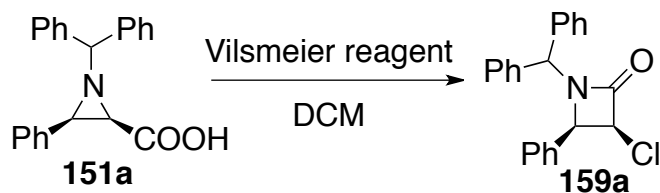
*The formation of β -lactam **trans-160g**:*



The general procedure for β -lactam formation with $(COCl)_2$ was followed with *trans*-acid **153g** (50 mg, 0.193 mmol, 1.0 equiv), $(COCl)_2$ (0.04 mL, 0.40 mmol, 2.0 equiv) and CH_2Cl_2 (2 mL). The crude product was purified by column chromatography (silica gel, 18 $\times$ 180 mm, hexane:EtOAc 5:1). The product *trans*-**160g** was obtained as a colorless oil (45 mg, 0.162 mmol) in 85% yield; R_f = 0.33 (hexane:EtOAc 4:1). Spectral data for *trans*-**160g**: ^1H NMR (500 MHz, $CDCl_3$) δ 0.88-1.26 (m, 5H), 1.48-1.78 (m, 6H), 3.33 (d, 1H, J = 6.0, 2.0 Hz), 4.06 (d, 1H, J = 15.5 Hz), 4.74 (d, 1H, J = 2.0 Hz), 4.80 (d, 1H, J = 15.0 Hz), 7.20-7.40 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.46, 25.55, 25.96, 27.52, 29.45, 39.17, 45.82, 57.22, 67.73, 127.95, 128.10, 128.89, 134.86, 164.15; IR (thin film) 2928(m), 1770(s) cm^{-1} ; HRMS calcd for $C_{16}H_{21}NO^{35}Cl$ ($M+H$, ESI^+) m/z 278.1312, meas 278.1316.

7.3.5 β -lactam formation with Vilsmeier reagent

The formation of β -lactam 159a:

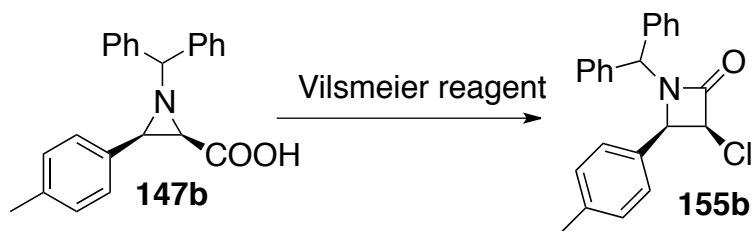


Vilsmeier reagent preparation: To a flame-dried 50 mL round bottom flask filled with N₂ was added dry DMF (0.10 mL, 1.2 mmol, 1.0 equiv). The vacuum adapter was replaced with a septum to which a N₂ balloon was attached *via* a needle. Dry CH₂Cl₂ (5 mL) was added *via* syringe. Then (COCl)₂ (0.10 mL, 1.2 mmol, 1.0 equiv) was added dropwise at rt. The resulting solution was stirred at rt for at least 5 min prior to use. The concentration of Vilsmeier reagent is 0.23M in CH₂Cl₂.

*General procedure for β -lactam formation with Vilsmeier reagent: illustrated for β -lactam **159a**:* To a flame-dried 25 mL round bottom flask filled with N₂ was added acid **151a** (33 mg, 0.10 mmol, 1.0 equiv). The vacuum adapter was replaced with a septum to which a N₂ balloon was attached *via* a needle. The flask was cooled to 0 °C. Vilsmeier reagent (0.23M, 1 mL, 0.23 mmol, 2.3 equiv) was added to the flask *via* syringe all at once at 0 °C. After it was stirred at 0 °C for 15 min, the reaction mixture was concentrated. The crude product was purified by column chromatography (silica gel, 18 × 180 mm, hexane:EtOAc 5:1), affording the product **159a** (20 mg, 0.057 mmol, 57%) as a white solid; mp 107-108 °C; R_f = 0.20 (hexane:EtOAc 4:1). Spectral data for **159a**: ¹H NMR (300 MHz, CDCl₃) δ 4.95 (d, 1H, *J* = 5.0 Hz), 5.13 (d, 1H, *J* = 5.0 Hz), 5.65 (s, 1H), 7.20-7.46 (m,

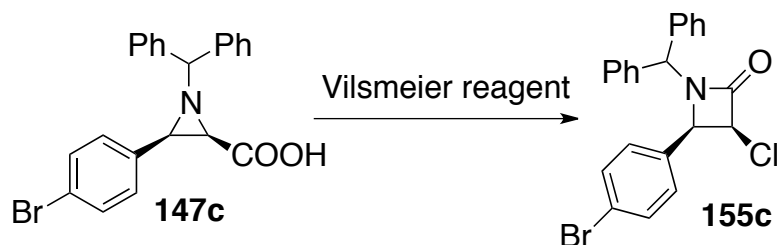
15H); ^{13}C NMR (125 MHz, CDCl_3) δ 60.28, 61.86, 62.89, 127.92, 127.96, 128.17, 128.26, 128.41, 128.56, 128.61, 128.64, 128.91, 133.14, 137.52, 138.22, 164.31; IR (thin film) $1767(\text{s})\text{ cm}^{-1}$; HRMS calcd for $\text{C}_{22}\text{H}_{19}\text{NO}^{35}\text{Cl}$ ($\text{M}+\text{H}$, ES^+) m/z 348.1155, meas 348.1161; $[\alpha]_{\text{D}}^{20} -59.2^\circ$ (c 1.0, CH_2Cl_2).

*The formation of β -lactam **159b**:*



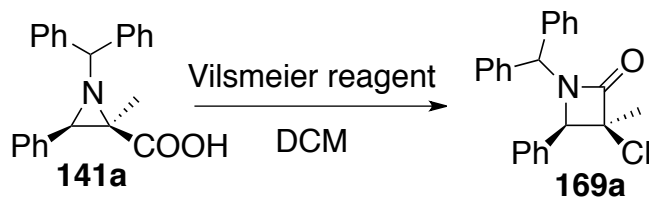
General procedure for β -lactam formation with Vilsmeier reagent was followed with acid **151b** (35 mg, 0.10 mmol, 1.0 equiv), Vilsmeier reagent (0.23M, 1 mL, 0.23 mmol, 2.3 equiv) with a reaction time of 1 h at 0°C . After the column chromatography (silica gel, 18×180 mm, hexane:EtOAc 5:1), the product was obtained as a pale yellow oil (13 mg, 0.036 mmol, 36%); Solidified in refrigerator, mp $65\text{--}67^\circ\text{C}$; $R_f = 0.30$ (hexane:EtOAc 4:1). Spectral data for **159b**: ^1H NMR (600 MHz, CDCl_3) δ 2.30 (s, 3H), 4.89 (d, 1H, $J = 5.4$ Hz), 5.08 (d, 1H, $J = 5.0$ Hz), 5.58 (s, 1H), 7.05 (d, 2H, $J = 8.4$ Hz), 7.10 (d, 2H, $J = 7.8$ Hz), 7.20–7.46 (m, 10H); ^{13}C NMR (150 MHz, CDCl_3) δ 21.22, 60.40, 61.76, 62.96, 127.36, 127.87, 127.95, 128.19, 128.54, 128.62, 128.65, 128.94, 130.05, 137.55, 138.45, 138.88, 164.34; IR (thin film) $1767(\text{s})\text{ cm}^{-1}$; HRMS calcd for $\text{C}_{23}\text{H}_{21}\text{NO}^{35}\text{Cl}$ ($\text{M}+\text{H}$, ESI^+) m/z 362.1312, meas 362.1303.

*The formation of β -lactam **159c**:*



The general procedure for β -lactam formation with Vilsmeier reagent was followed with acid **151c** (41 mg, 0.10 mmol, 1.0 equiv) and Vilsmeier reagent (0.23M, 1.0 mL, 0.23 mmol, 1.0 equiv). The crude product was purified by column chromatography (silica gel, 18 $\times$ 180 mm, hexane:EtOAc 5:1), affording the product **159c** (14 mg, 0.033 mmol, 33%) as a white foamy solid; mp 48-50 $^{\circ}\text{C}$; R_f = 0.30 (hexane:EtOAc 4:1). Spectral data for **159c**: ^1H NMR (600 MHz, CDCl_3) δ 4.89 (d, 1H, J = 5.4 Hz), 5.12 (d, 1H, J = 4.8 Hz), 5.68 (s, 1H), 6.96-7.01 (m, 2H), 7.14-7.18 (m, 2H), 7.20-7.26 (m, 5H), 7.28-7.34 (m, 3H), 7.36-7.40 (m, 2H); ^{13}C NMR (150 MHz, CDCl_3) δ 60.06, 61.41, 62.78, 123.04, 128.04, 128.10, 128.31, 128.34, 128.67, 130.25, 131.35, 132.37, 137.33, 137.95, 164.12 (One sp^2 carbon not located); IR (thin film) 1767(s) cm^{-1} ; HRMS calcd for $\text{C}_{22}\text{H}_{18}\text{NO}^{35}\text{Cl}^{79}\text{Br}$ ($\text{M}+\text{H}^+$, ESI^+) m/z 426.0260, meas 426.0274; $[\alpha]_D^{20}$ -85.0° (c 1.0, CH_2Cl_2).

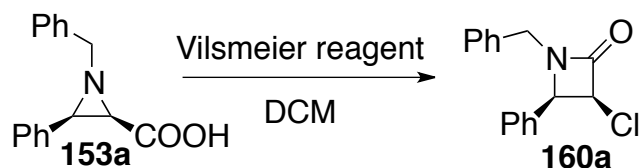
The formation of β -lactam 169a:



The general procedure for β -lactam formation with Vilsmeier reagent was followed with acid **141a** (34 mg, 0.10 mmol, 1.0 equiv), Vilsmeier reagent (0.23M,

2.0 mL, 0.46 mmol, 4.6 equiv). The crude product was purified by column chromatography (silica gel, 18 × 180 mm, hexane:EtOAc 5:1), affording the product **169a** (8 mg, 0.022 mmol, 22%) as a white solid; mp 130-132 °C; R_f = 0.50 (hexane:EtOAc 4:1). Spectral data for **169a**: ^1H NMR (500 MHz, CDCl_3) δ 1.84 (s, 3H), 4.57 (s, 1H), 5.53 (s, 1H), 7.15-7.40 (m, 15H); ^{13}C NMR (125 MHz, CDCl_3) δ 24.38, 62.80, 69.72, 72.91, 127.93, 127.94, 128.17, 128.25, 128.30, 128.50, 128.55, 128.72, 128.88, 134.19, 137.64, 138.63, 167.28; IR (thin film) 1767(s) cm^{-1} ; HRMS calcd for $\text{C}_{23}\text{H}_{21}\text{NO}^{35}\text{Cl}$ ($\text{M}+\text{H}$, ESI^+) m/z 362.1312, meas 362.1299; $[\alpha]_D^{20}$ -9.6° (c 1.0, CH_2Cl_2).

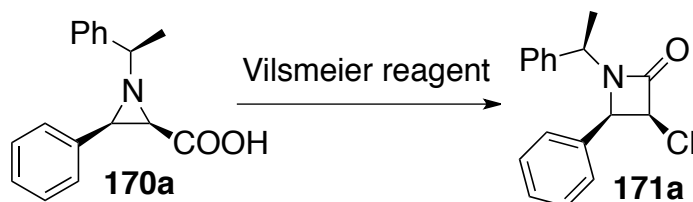
*The formation of β -lactam **160a**:*



The general procedure for β -lactam formation with Vilsmeier reagent was followed with acid **153a** (26 mg, 0.10 mmol, 1.0 equiv), Vilsmeier reagent (0.23 M, 1.0 mL, 0.23 mmol, 1.0 equiv). The crude product was purified by column chromatography (silica gel, 18 × 180 mm, hexane:EtOAc 5:1), affording the product **160a** (20 mg, 0.074 mmol, 74%) as a viscous oil; R_f = 0.35 (hexane:EtOAc 4:1). Spectral data for **160a**: ^1H NMR (300 MHz, CDCl_3) δ 3.90 (d, 1H, J = 14.5 Hz), 4.78 (d, 1H, J = 5.0 Hz), 4.90 (d, 1H, J = 14.5 Hz), 5.07 (d, 1H, J = 5.0 Hz), 7.10-7.24 (m, 4H), 7.31 (d, 3H, J = 5.0 Hz), 7.42 (d, 3H, J = 5.5 Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 44.96, 60.26, 61.15, 128.13, 128.25, 128.55,

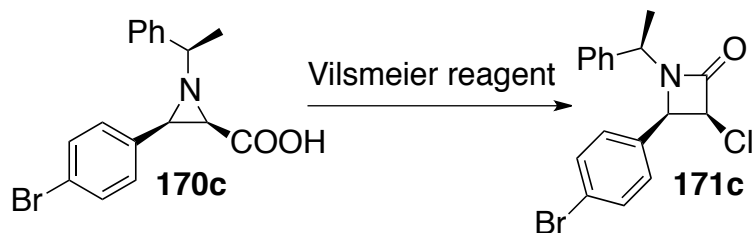
128.62, 128.93, 129.14, 132.69, 134.34, 163.99; IR (thin film) 2922(m), 1770(s) cm^{-1} ; $[\alpha]_{\text{D}}^{20} -56.0^\circ$ (c 1.0, CH_2Cl_2). Spectral data matches previously reported data.⁸⁹

*The formation of β -lactam **171a**:*



The general procedure for β -lactam formation with Vilsmeier reagent was followed with acid **170a** (27 mg, 0.10 mmol, 1.0 equiv) and Vilsmeier reagent (0.23M, 1.0 mL, 0.23 mmol, 2.3 equiv). The crude product was purified by column chromatography (silica gel, 18 $\times$ 180 mm, hexane:EtOAc 5:1), affording the product **171a** (22 mg, 0.077 mmol, 77%) as a white foamy solid; mp 95-96 $^\circ\text{C}$; R_f = 0.30 (hexane:EtOAc 4:1). Spectral data for **171a**: ^1H NMR (500 MHz, CDCl_3) δ 1.43 (d, 3H, J = 7.0 Hz), 4.69 (d, 1H, J = 5.0 Hz), 4.98 (d, 1H, J = 5.0 Hz), 5.07 (q, 1H, J = 7.0 Hz), 7.20-7.40 (m, 10H); ^{13}C NMR (125 MHz, CDCl_3) δ 19.08, 53.04, 60.29, 60.42, 127.28, 128.15, 128.72, 128.81, 129.08, 134.21, 138.99, 164.22 (One sp^2 carbon not located); IR (thin film) 1761(s) cm^{-1} ; HRMS calcd for $\text{C}_{17}\text{H}_{17}\text{NO}^{35}\text{Cl}$ ($\text{M}+\text{H}$, ESI^+) m/z 286.0999, meas 286.0975; $[\alpha]_{\text{D}}^{20} -84.5^\circ$ (c 1.0, CH_2Cl_2).

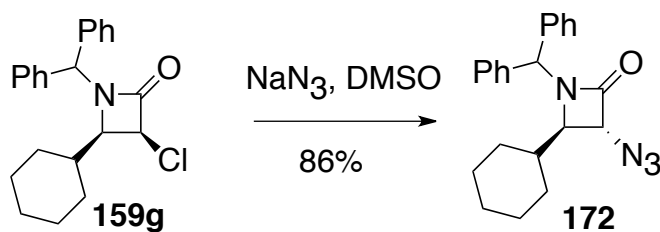
*The formation of β -lactam **171c**:*



The general procedure for β -lactam formation with Vilsmeier reagent was followed with acid **170c** (35 mg, 0.10 mmol, 1.0 equiv) and Vilsmeier reagent (0.23M, 1.0 mL, 0.23 mmol, 2.3 equiv). The crude product was purified by column chromatography (silica gel, 18 $\times$ 180 mm, hexane:EtOAc 5:1), affording the product **171c** (25 mg, 0.069 mmol, 69%) as a white foamy solid; mp 102-103 $^{\circ}\text{C}$; R_f = 0.20 (hexane:EtOAc 4:1). Spectral data for **171c**: ^1H NMR (500 MHz, CDCl_3) δ 1.41 (d, 3H, J = 7.5 Hz), 4.60 (d, 1H, J = 5.0 Hz), 4.94 (d, 1H, J = 5.0 Hz), 5.01 (q, 1H, J = 7.0 Hz), 7.08-7.14 (m, 2H), 7.16-7.20 (m, 2H), 7.28-7.34 (m, 3H), 7.46-7.50 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 19.08, 53.18, 59.86, 60.10, 123.22, 127.25, 128.27, 128.88, 130.31, 131.40, 133.36, 138.77, 164.00; IR (thin film) 1767(s) cm^{-1} ; HRMS calcd for $\text{C}_{17}\text{H}_{16}\text{NO}^{35}\text{Cl}^{79}\text{Br}$ ($\text{M}+\text{H}^+$, ESI^+) m/z 364.0104, meas 364.0078; $[\alpha]_{\text{D}}^{20}$ -116.3° (c 1.0, CH_2Cl_2).

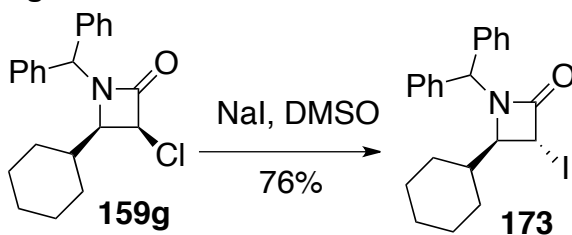
7.3.6 Transformation of **159g**

*Transformation of **159g** with NaN_3 :*



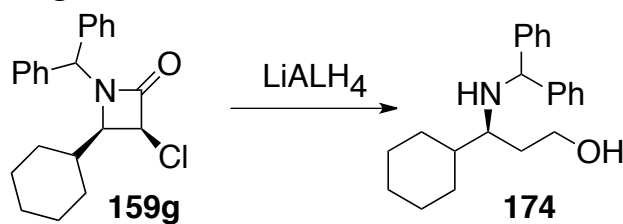
To a flame-dried test tube sized Schlenck flask filled with N₂ were added the lactam **159g** (36 mg, 0.10 mmol, 1.0 equiv), NaN₃ (66 mg, 1.0 mmol, 10 equiv) and DMSO-d₆ (0.20 mL). The resulting mixture was stirred at 80 °C for 48 h and 100 °C for 12 h. H₂O (2 mL) was added. Then the mixture was extracted with ether (3 × 5 mL). The combined organic extracts were washed with H₂O (2 × 1 mL), dried (Na₂SO₄) and filtered. The filtrate was concentrated and purified by column chromatography (silica gel, 18 × 150 mm, hexane:EtOAc 5:1) to afford the product **172** (31 mg, 0.086 mmol) as a white solid in 86% yield; mp 105-107 °C; R_f = 0.50 (hexane:EtOAc 4:1). Spectral data for **172**: ¹H NMR (300 MHz, CDCl₃) δ 0.78-1.40 (m, 6H), 1.46-1.76 (m, 5H), 3.42 (dd, 1H, *J* = 5.4, 2.4 Hz), 4.31 (d, 1H, *J* = 2.1 Hz), 5.73 (s, 1H), 7.20-7.40 (m, 10H); ¹³C NMR (125 MHz, CDCl₃) δ 25.48, 25.77, 26.06, 26.89, 29.53, 37.91, 62.36, 64.80, 65.39, 127.84, 128.04, 128.16, 128.33, 128.59, 128.72, 138.08, 138.24, 164.36; IR (thin film) 2928(m), 2106(s) 1765(s) cm⁻¹; HRMS calcd for C₂₂H₂₅N₄O (M+H, ESI⁺) *m/z* 361.2028, meas 361.2041; [α]_D²⁰ 74.4° (c 0.5, CH₂Cl₂).

Transformation of 159g with NaI:



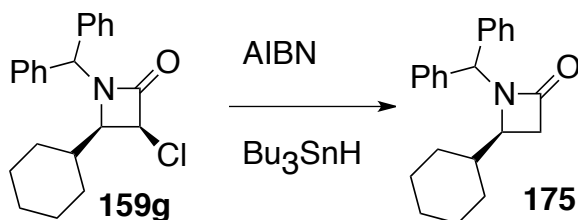
To a flame-dried test tube sized Schlenck flask filled with N₂ were added the lactam **159g** (36 mg, 0.10 mmol, 1.0 equiv), NaI (150 mg, 1.00 mmol, 10.0 equiv) and DMSO-d₆ (0.40 mL). The resulting mixture was stirred at 100 °C for 66 h. After cooling to rt, H₂O (2 mL) and ether (10 mL) were added. The aqueous layer was separated and extracted with ether (2 × 5 mL). The combined organic extracts were dried (Na₂SO₄) and filtered. The filtrate was concentrated and purified by column chromatography (silica gel, 18 × 180 mm, hexane:EtOAc 5:1) to afford the product **172** (34 mg, 0.076 mmol) as a viscous oil in 76% yield; R_f = 0.50 (hexane:EtOAc 4:1). Spectral data for **172**: ¹H NMR (300 MHz, CDCl₃) δ 0.78-1.30 (m, 6H), 1.42-1.70 (m, 5H), 3.78 (dd, 1H, *J* = 5.1, 2.1 Hz), 4.60 (d, 1H, *J* = 1.8 Hz), 5.75 (s, 1H), 7.20-7.40 (m, 10H); ¹³C NMR (125 MHz, CDCl₃) δ 15.65, 25.33, 25.80, 26.07, 26.32, 29.34, 39.82, 62.22, 70.05, 127.76, 128.02, 128.19, 128.36, 128.55, 128.64, 138.21, 138.36, 164.89; IR (thin film) 2926(m), 1759(s) 1265(s) cm⁻¹; HRMS calcd for C₂₂H₂₅NOI (M+H, ESI⁺) *m/z* 446.0981, meas 446.0948; [α]_D²⁰ -12.8° (c 1.0, CH₂Cl₂).

Transformation of 159g with LiAlH₄:



To a flame-dried 25 mL round bottom flask filled with N₂ was added LiAlH₄ (20 mg, 0.50 mmol, 5.0 equiv). The vacuum adapter was quickly replaced with a septum to which a N₂ balloon was attached *via* a needle. Then dry THF (0.5 mL) was added. And it was cooled to 0 °C. A solution of 4-chlorolactam **159g** (36 mg, 0.10 mmol, 1.0 equiv) in THF (0.5 mL) was added dropwise *via* syringe. After it was stirred at 0 °C for 5 min, the ice bath was removed. After the reaction mixture was stirred at rt for 2 h, H₂O (0.1 mL) was added carefully at 0 °C. After it was stirred at 0 °C for 15 min, the mixture was filtered through a Celite pad and Na₂SO₄ on a sintered glass funnel. The filtrate was concentrated and purified by column chromatography (silica gel, 18 × 180 mm, hexane:EtOAc 3:1) to give the product **174** as a white solid (29 mg, 0.090 mmol, 90%). mp 92-94 °C; R_f = 0.30 (hexane:EtOAc 3:1). Spectral data for **174**: ¹H NMR (600 MHz, CDCl₃) δ 0.44-0.54 (m, 1H), 0.90-1.20 (m, 5H), 1.28 (d, 1H, *J* = 12.6 Hz), 1.42-1.64 (m, 6H), 1.79 (q, 1H, *J* = 6.0 Hz), 3.52-3.60 (m+s, 2H), 3.67-3.74 (m, 1H), 7.16-7.30 (m, 6H), 7.37 (d, 2H, *J* = 7.2 Hz), 7.43 (d, 2H, *J* = 7.2 Hz); ¹³C NMR (150 MHz, CDCl₃) δ 25.62, 25.74, 26.19, 30.92, 31.42, 36.93, 44.68, 50.58, 60.66, 78.90, 127.07, 127.17, 127.25, 127.95, 128.23, 128.59, 143.15, 143.55; IR (thin film) 3400(m), 2926(s) cm⁻¹; HRMS calcd for C₂₂H₃₀NO (M+H, ESI⁺) *m/z* 324.2327, meas 324.2303; [α]_D²⁰ 4.0° (c 1.0, CH₂Cl₂).

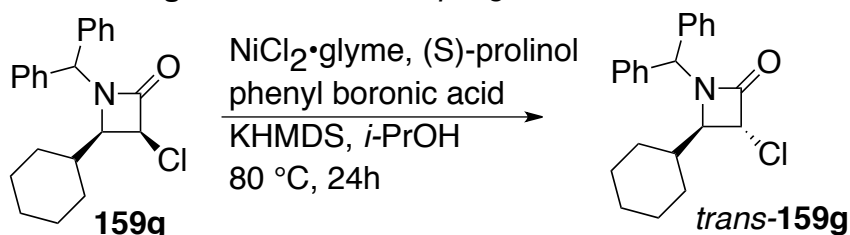
The transformation of 159g with Bu₃SnH:



To a flame-dried Schlenk flask filled with N_2 was added 4-chlorolactam **159g** (36 mg, 0.10 mmol, 1.0 equiv), AIBN (10 mg), and dry benzene (1 mL). And tributyltin hydride (119 mg, 0.100 mL, 0.400 mmol, 4.00 equiv) was quickly added under a N_2 stream. Then the Schlenk flask was sealed and the reaction was stirred at 80 °C for 19 h. After it was cooled to rt, aq sat KF (3 mL) and CH_2Cl_2 (10 mL) were added. The aqueous layer was separated and extracted with CH_2Cl_2 (2 × 5 mL). The combined organic extracts were dried (Na_2SO_4) and filtered. The filtrate was concentrated and purified by column chromatography (silica gel, 18 × 180 mm, hexane:EtOAc 5:1) to obtain the product **175** as a white solid (31 mg, 0.097 mmol, 97%). mp 74-76 °C; R_f = 0.50 (hexane:EtOAc 4:1). Spectral data for **175**: ^1H NMR (500 MHz, CDCl_3) δ 0.78-1.12 (m, 5H), 1.22-1.32 (m, 1H), 1.46-1.68 (m, 5H), 2.69 (dd, 1H, J = 2.5, 15.0 Hz), 2.85 (dd, 1H, J = 5.5, 15.0 Hz), 3.55 (td, 1H, J = 5.5, 2.5 Hz), 5.78 (s, 1H), 7.22-7.38 (m, 10H); ^{13}C NMR (150 MHz, CDCl_3) δ 25.52, 25.90, 26.23, 26.37, 29.76, 38.21, 39.34, 57.07, 62.19, 127.47, 127.65, 128.17, 128.43, 128.49, 139.01, 139.30, 167.72 (One sp^2 C not located); IR (thin film) 2924(m), 1749(s) cm^{-1} ; HRMS calcd for $\text{C}_{22}\text{H}_{26}\text{NO}$ ($\text{M}+\text{H}$, ESI^+) m/z 320.2014, meas 320.2007; $[\alpha]_D^{20}$ -82.8° (c 1.0, CH_2Cl_2).

339

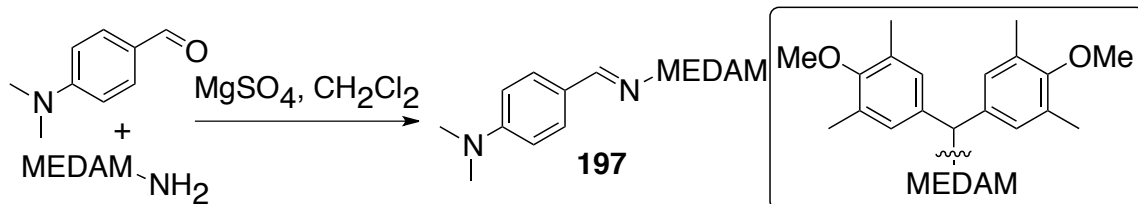
Transformation of **159g** under Suzuki coupling condition:



To a flame-dried test-tube size Schlenk flask filled with N_2 was added (S)-prolinol (5 mg, 0.048 mmol, 0.48 equiv), $\text{NiCl}_2 \cdot \text{glyme}$ (5 mg, 0.024 mmol, 0.24 equiv), phenylboronic acid (24 mg, 0.20 mmol, 2.0 equiv), KHMDS (40 mg, 0.20 mmol, 2.0 equiv) and *i*-PrOH (0.5 mL). Then the mixture was stirred at rt for 5 min. The starting material **159g** (36 mg, 0.10 mmol, 1.0 equiv) was added. Then the Teflon valve was closed and the flask was heated at 80 °C for 24 h. ^1H NMR spectrum of the crude reaction mixture indicated a 95% conversion. The *trans*-**159g** was identified according to the ^1H NMR spectrum of the crude reaction mixture: 3.60 (dd, 1H, $J = 5.0, 2.0$ Hz), 4.49 (d, 1H, $J = 1.5$ Hz), 5.77 (s, 1H).

7.4 Experimental Section for Chapter Five

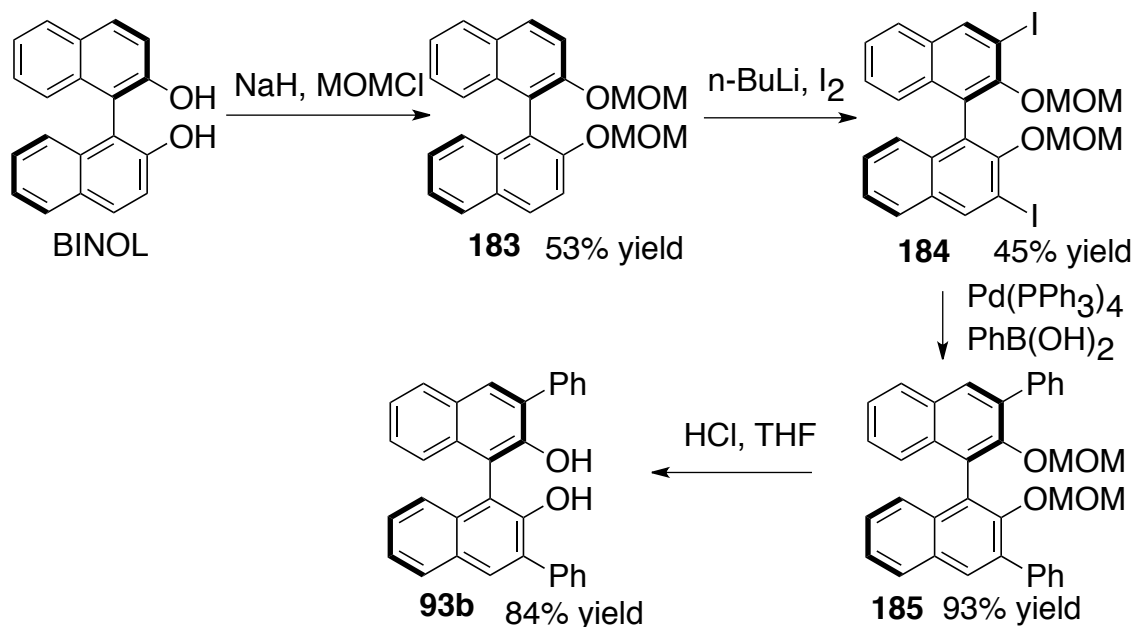
7.4.1 Preparation of imine **197**



The mixture of 4-dimethylaminobenzaldehyde (261 mg, 1.75 mmol, 1.03 equiv), MEDAM amine (510 mg, 1.70 mmol, 1.00 equiv) and MgSO₄ (1.5 g, 8.5 mmol, 5.0 equiv) in dry CH₂Cl₂ (5 mL) was stirred under a N₂ balloon for 1 week. After it was filtered, the filtrate was concentrated to give the crude product which was recrystallized from EtOAc and hexane to give the product **197** as pale yellow crystals (550 mg, 1.28 mmol, 75%); mp 167-169 °C; ¹H NMR (500 MHz, CDCl₃) δ 2.25 (s, 12H), 3.00 (s, 6H), 3.70 (s, 6H), 5.32 (s, 1H), 6.70 (d, 2H, *J* = 9.0 Hz), 7.00 (s, 4H), 7.70 (d, 2H, *J* = 9.0 Hz), 8.24 (s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 16.21, 40.26, 59.59, 77.30, 111.83, 125.37, 128.16, 129.93, 130.44, 134.00, 152.36, 155.96, 160.09.

7.4.2 Preparation of the BINOL derivative **93b-d**

*Preparation of (R)-3,3'-diphenyl-2,2'-dihydroxy-1,1'-binaphthyl **93b***



To a flame dried flask filled with N₂ was added NaH (60% suspension in mineral oil, 500 mg, 12.5 mmol, 2.50 equiv) and dry THF (5 mL). The vacuum adapter was quickly replaced with a septum to which a N₂ balloon was attached *via* a needle. And a solution of (*R*)-BINOL (1.44 g, 5.00 mmol, 1.00 equiv) in THF (5 mL) was added at 0 °C. It was stirred at 0 °C for 1 hour. Then the ice bath was removed and the mixture was stirred at room temperature for 15 min. After it was cooled to 0 °C, MOMCl (1.006 g, 1.000 mL, 12.50 mmol, 2.500 equiv) was added dropwise. The resulting mixture was stirred at room temperature for another 3 hours. Then *aq* sat NH₄Cl (5 mL) was added and THF was removed *via* rotavap. The aqueous layer was extracted with CH₂Cl₂ (3 × 20 mL). The combined organic extracts were washed with brine (10 mL), dried (MgSO₄), filtered and concentrated. The crude product was purified by column chromatography (silica gel, 30 × 300 mm, hexane:EtOAc 9:1) to give a solid which was recrystallized in

CH₂Cl₂:hexane (1:10) to provide the product **183** as a colorless crystalline solid 992 mg, 53%.

To a flame-dried flask filled with N₂ was added **183** (374 mg, 1.00 mmol, 1.00 equiv) and dry THF (2 mL). The vacuum adapter was quickly replaced with a septum to which a N₂ balloon was attached via a needle. After it was cooled to 0 °C, *n*-BuLi (2.47 M in Hexane, 1.30 mL, 3.00 mmol, 3.00 equiv) was added dropwise. After it was stirred at 0 °C for 10 min, the ice bath was removed and the mixture was stirred at room temperature for 1 hour. Then it was cooled to 0 °C again and a solution of I₂ (762 mg, 3.00 mmol, 3.00 equiv) in dry THF (5 mL) was added dropwise *via* syringe. It was stirred at room temperature overnight (~13 hours). Water (5 mL) and EtOAc (20 mL) were added. The aqueous layer was separated and extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed successively with *aq* 5% Na₂S₂O₃ (2 × 10 mL), water (5 mL) and brine (5 mL) and concentrated. The crude product was purified by column chromatography (1st column, silica gel, 25 × 300 mm, hexane:EtOAc 15:1; 2nd column, silica gel, 25 × 200 mm, hexane:EtOAc 15:1), affording the product **184** as white foamy solid 280 mg, 45%.

The mixture of the starting material **184** (275 mg, 0.440 mmol, 1.00 equiv) and Pd(PPh₃)₄ (101 mg, 0.0880 mmol, 0.200 equiv) in DME (2 mL) was stirred at room temperature for 10 min under N₂. Then PhB(OH)₂ (188 mg, 1.54 mmol,

3.50 equiv) was added in one portion, followed by the addition of aq Na₂CO₃ (2 M, 1.1 mL, 2.2 mmol, 5.0 equiv). The resulting mixture was kept refluxing for 15 hours under a N₂ balloon. After it was cooled to room temperature, the aqueous layer was separated and extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried (MgSO₄) and filtered. The filtrate was concentrated to give the dark crude product which was purified by column chromatography (silica gel, hexane:EtOAc 15:1, 25 × 200 mm), affording the product **185** as a white foamy solid, 216 mg, 93%.

The mixture of the starting material **185** (215 mg, 0.41 mmol, 1.0 equiv) in THF (1 mL) and MeOH (1 mL) and con HCl (0.5 mL) was stirred at room temperature overnight. Then it was extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried (MgSO₄) and filtered. The filtrate was concentrated and purified by column chromatography (silica gel, hexane:EtOAc 15:1, 20 × 200 mm), giving the product **93b** as white crystals 150 mg, 84%. mp 199-200 °C (Lit^{65a}: 200-202 °C).

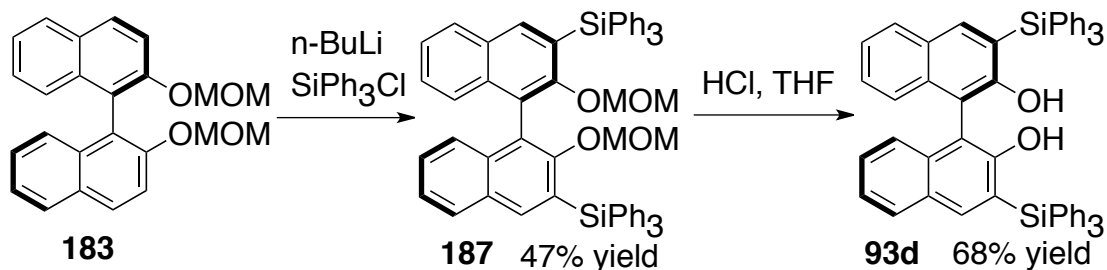
Spectral data for **93b**: ¹H NMR (500 MHz, CDCl₃) δ 5.30 (s, 2H), 7.16-7.54 (m, 12H), 7.82 (d, 4H, *J* = 7.5 Hz), 7.90 (d, 2H, *J* = 8.0 Hz), 8.00 (s, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 112.304, 124.23, 124.30, 127.32, 127.74, 128.42, 128.46, 129.40, 129.57, 130.61, 131.38, 132.86, 137.40, 150.08; MS (EI) 439 (M+1, 39), 438 (M, 100), 191 (83); [α]_D²⁰ 106.2° (c 1.0, THF).

345

The mixture of the starting material **186** (455 mg, 0.865 mmol, 1.00 equiv) in THF (1 mL) and MeOH (1 mL) and *con* HCl (0.9 mL) was stirred at room temperature overnight. Then EtOAc (20 mL) was added. The aqueous layer was separated and extracted with EtOAc (2 × 10 mL). The combined organic extracts were dried (MgSO₄) and filtered. The filtrate was concentrated and purified by column chromatography (silica gel, 20 × 200 mm, hexane:EtOAc 15:1), giving the product as a white solid **93c** (287 mg, 0.657 mmol, 76%); mp > 250 °C (Lit^{65a}: 256-257 °C).

Spectral data for **93c**: ¹H NMR (500 MHz, CDCl₃) δ 5.54 (s, 2H), 7.12 (d, 2H, *J* = 8.5 Hz), 7.24-7.42 (m, 4H), 7.82 (d, 2H, *J* = 8 Hz), 8.25 (s, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 112.22, 114.57, 124.60, 124.86, 127.39, 127.58, 129.70, 132.73, 132.75, 147.98; MS (EI) 444 (M, 39), 442 (M-2, 20), 446 (M+2, 20); [α]_D²⁰ 98.6° (c 1.0, THF).

Preparation of (*R*)-3,3'-ditriphenylsilyl-2,2'-dihydroxy-1,1'-binaphthyl **93d**



To a stirred solution of (*R*)-**183** (1.87 g, 5.00 mmol, 1.00 equiv) in dry Et₂O (50 mL) was added *n*-BuLi (2.47M in hexane, 6.10 mL, 15.0 mmol, 3.00 equiv) dropwise at room temperature over 10 min. Then it was stirred at room temperature for 1.5 hours. After it was cooled to 0 °C, dry THF (10 mL) was

added and the mixture was stirred for another 15 min. Then a solution of Ph_3SiCl (4.41 g, 15.0 mmol, 3.00 equiv) in dry THF (10 mL) was added. The ice bath was removed after 10 min and the mixture was stirred at room temperature for 38 hours. Then it was quenched by *aq* sat NH_4Cl (20 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (50 mL + 2 × 25 mL). The combined organic extracts were washed with brine, dried (MgSO_4) and filtered. The filtrate was concentrated and purified by column (1st column, silica gel, 30 × 300 mm, CH_2Cl_2 : Et_2O :pentane 1:1:20; 2nd column, silica gel, 20 × 200 mm, CH_2Cl_2 : Et_2O :pentane 1:1:20), giving the product **187** as a white solid (2.089 g, 2.350 mmol, 47%).

The mixture of the starting material **187** (2.089 g, 2.350 mmol, 1.000 equiv) in dioxane (20 mL) and *con* HCl (0.4 mL) was kept at 70 °C for 12 hours. Another portion of *con* HCl (0.5 mL) was added and it was stirred at 70 °C for another 11 hours. Then the reaction was cooled to 0 °C and *aq* sat NaHCO_3 (20 mL) was added. The reaction mixture was extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with water (2 × 20 mL), brine (20 mL), dried (MgSO_4) and filtered. The filtrate was concentrated to give the crude product as a brownish white solid. Triturating with CH_2Cl_2 : Et_2O (v/v 1:10) provided the product **93d** as a white solid 1.287 g, 68%, in which it contains some dioxane. ^1H NMR showed a 96% purity by weight; mp 161-163 °C.

Spectral data for **93d**: ^1H NMR (CDCl_3 , 500 MHz) δ 5.26 (s, 2H), 7.22-7.44 (m, 24H), 7.63 (d, 12 H, J = 8.0 Hz), 7.70 (d, 2H, J = 8.0 Hz), 7.90 (s, 2H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 110.67, 123.65, 123.85, 123.91, 127.81, 128.17, 129.04, 129.22, 129.50, 134.28, 134.76, 136.30, 142.08, 156.51; $[\alpha]_{\text{D}}^{20}$ 110.9 $^\circ\text{C}$ (c 1.2, CHCl_3) (Lit^{65c}: $[\alpha]_{\text{D}}^{20}$ 102.7 $^\circ\text{C}$ (c 1.2, CHCl_3)).

7.4.3 Catalytic asymmetric aziridination reaction

7.4.3.1 General procedure

Catalyst preparation procedure A: To a flame-dried Schlenk flask filled with N_2 was added the ligand (BINOL or BINOL derivative) (0.050 mmol, 0.10 equiv) $\text{B}(\text{OPh})_3$ (44 mg, 0.15 mmol, 0.30 equiv) and dry toluene (1 mL) were added. The Teflon valve was closed and the mixture was heated at 80 $^\circ\text{C}$ for 1 hour. Then the solvent was removed under high vacuum by slightly cracking the Teflon valve. Then the Teflon valve was completely open and the residue was kept at 80 $^\circ\text{C}$ for another 30 min. After it was cooled to room temperature, the corresponding imine (0.50 mmol, 1.0 equiv) and toluene (dry, 1 mL) were added, followed by the addition of EDA (63 μL , 0.60 mmol, 1.2 equiv). The resulting mixture was stirred at the specified temperature for 24 hours. Then hexane was added and the volatiles were removed. The residue was purified by column chromatography to give the corresponding product.

Catalyst preparation procedure B: The catalyst preparation procedure A was followed except that ligand (0.050 mmol, 0.10 equiv), $\text{BH}_3\cdot\text{SMe}_2$ (2M, 75 μL ,

0.15 mmol, 0.30 equiv), PhOH (10 mg, 0.10 mmol, 0.20 equiv), H₂O (2.7 μ L, 0.15 mmol, 0.30 equiv) in dry toluene (1 mL) were added.

Catalyst preparation procedure C: The catalyst preparation procedure A was followed except that ligand (0.050 mmol, 0.10 equiv), B(OPh)₃ (58 mg, 0.20 mmol, 0.40 equiv), H₂O (0.9 μ L, 0.05 mmol, 0.10 equiv) in dry toluene (1 mL) were added.

Catalyst preparation procedure D: The catalyst was prepared from BINOL (57 mg, 0.20 mmol, 0.20 equiv) and B(OPh)₃ (29 mg, 0.10 mmol, 0.10 equiv) at room temperature in CH₂Cl₂ (1 mL). Then imine **31** (271 mg, 1.00 mmol, 1.00 equiv) was added, followed by the addition of EDA (120 μ L, 1.20 mmol, 1.20 equiv). Then the reaction was stirred at room temperature for 24 h. Hexane (5 mL) was added. After concentration, the crude product was purified by column chromatography.

The spectroscopic data for the products **32a** and **32b** were reported in the literature.^{26a,d}

7.4.3.2 Aziridination reaction of 31a and EDA with the catalyst prepared from (*R*)-93b (entry 5, Table 5.1)

The reaction of imine **31a** (136 mg, 0.500 mmol, 0.500 equiv) with EDA was performed according to the general procedure: catalyst preparation procedure A with BINOL derivative (*R*)-**93b** (22 mg, 0.050 mmol, 0.10 equiv). The crude product was purified by the column (silica gel, 35 $\times$ 320 mm, hexane:EtOAc 19:1)

to give the product **32a** as a white solid (158 mg, 0.440 mmol, 88%). The optical purity was determined to be 76% ee by HPLC analysis (Chiralcel OD-H column, hexane/2-propanol 90:10, 222 nm, 0.7 mL/min). Retention times: t_R = 4.67 min (major enantiomer) and t_R = 9.36 (minor enantiomer). As has been reported, the major enantiomer is (2*S*, 3*S*)-**32a**.

Spectral data for (2*S*,3*S*)-**32a**: ^1H NMR (300 MHz, CDCl_3) δ 1.00 (t, 3H, J = 7.2 Hz), 2.70 (d, 1H, J = 6.6 Hz), 3.20 (d, 1H, J = 6.9 Hz), 3.88-4.02 (m, 3H), 7.68-7.14 (m, 15H); ^{13}C NMR (75 MHz, CDCl_3) δ 167.72, 142.50, 142.36, 135.00, 128.48, 127.77, 127.75, 127.51, 127.39, 127.31, 127.18, 77.68, 60.56, 48.01, 46.36, 13.93, 46.36, 48.01, 60.56, 77.68, 127.18, 127.31, 127.39, 127.51, 127.75, 127.77, 128.48, 135.00, 142.36, 142.50, 167.72; $[\alpha]_D^{23}$ -30.1° (c 1.0, CH_2Cl_2) based on 76% ee material.

7.4.4 ^{11}B NMR shown in Figure 5.3 was prepared according to the following procedure:

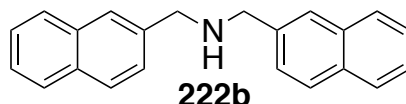
To a flame-dried Schlenk flask filled with N_2 were added BINOL derivative (0.050 mmol, 1.0 equiv), $\text{B}(\text{OPh})_3$ (58 mg, 0.20 mmol, 4.0 equiv), H_2O (0.90 μL , 0.050 mmol, 1.0 equiv) and THF (dry, 2 mL) under a N_2 stream. The Teflon valve was then closed and the reaction mixture was kept at 80 $^\circ\text{C}$ for 1 hour. Then the solvent was removed under high vacuum by slightly cracking the Teflon valve. The valve was completely open and the residue was kept at 80 $^\circ\text{C}$ for another 30

min. After it was cooled to room temperature under N₂, CDCl₃ (0.5-1.0 mL) was added and the solution was transferred to the NMR tube (flame dried and cooled to room temperature prior to use). ¹H NMR and ¹¹B NMR were taken for the borate species. Then imine **197** (22 mg, 0.050 mmol, 1.0 equiv) was quickly added to the NMR tube and shaken to dissolve. ¹H NMR and ¹¹B NMR were also taken again.

7.5 Experimental Section for Chapter Six

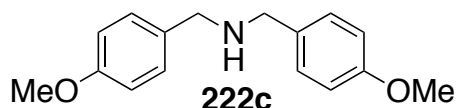
7.5.1 Preparation of different dibenzylamines

bis-(2-naphthylmethyl)amine **222b**:



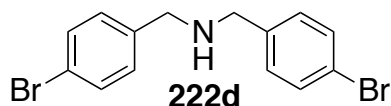
To a flame-dried 25 mL round bottom flask filled with N₂ was added NH₄Cl (535 mg, 10.0 mmol, 2.00 equiv), absolute ethanol (10 mL), dry NEt₃ (1.40 mL, 10.0 mL, 2.00 equiv) and 2-naphthyl aldehyde (781 mg, 5.00 mmol, 1.00 equiv). Then the vacuum adapter was quickly replaced with a septum to which a N₂ balloon was attached *via* a needle. Then Ti(O-*i*-Pr)₄ (3.00 mL, 10.0 mmol, 2.00 equiv) was added dropwise via syringe. The resulting mixture was stirred at rt for 6 hours. NaBH₄ (285 mg, 7.50 mmol, 1.50 equiv) was added in one portion. The reaction mixture was stirred at rt for another 3 hours. After it was poured into *aq* ammonia (2M, 5 mL), the mixture was filtered and washed well with EtOAc (20 mL). The aqueous layer was separated and extracted with EtOAc (2 × 10 mL). The combined organic extracts were dried (MgSO₄) and filtered. After the column chromatography (silica gel, 25 × 200 mm, hexane:EtOAc 4:1 to 2:1), the product **222b** was obtained as a white solid (147 mg, 0.495 mmol, 20%); mp 76-77 °C (Lit:^{90a} 82-83 °C); R_f = 0.20 (hexane:EtOAc 1:1). Spectral data for **222b**: ¹H NMR (500 MHz, CDCl₃) δ 1.75 (brs, 1H), 4.24 (s, 4H), 7.50-7.60 (m, 6H), 7.82-8.04 (m, 8H); ¹³C NMR (125 MHz, CDCl₃) δ 53.11, 125.45, 125.90, 126.42, 126.52, 127.58, 127.62, 127.99, 132.61, 133.37, 137.69.

bis-(4-methoxybenzyl)amine **222c**:



The procedure for the preparation of **222b** was followed with NH₄Cl (214 mg, 4.00 mmol, 2.00 equiv), absolute ethanol (4 mL), dry NEt₃ (0.56 mL, 4.0 mmol, 2.0 equiv), 4-methoxybenzaldehyde (272 mg, 0.250 mL, 2.00 mmol, 1.00 equiv), Ti(O-*i*-Pr)₄ (1.14 g, 1.20 mL, 4.00 mmol, 2.00 equiv) and NaBH₄ (114 mg, 3.00 mmol, 1.50 equiv). The filtrate was concentrated and purified by column chromatography (silica gel, 25 × 200 mm, hexane:EtOAc 4:1 to 1:1). The product **222c** was obtained as a pale yellow oil (177 mg, 0.689 mmol, 69%); R_f = 0.05 (hexane:EtOAc 1:1). Spectral data for **222c**: ¹H NMR (500 MHz, CDCl₃) δ 1.70 (brs, 1H), 3.72 (s, 4H), 3.78 (s, 6H), 6.87 (d, 4H, *J* = 8.5 Hz), 7.25 (d, 4H, *J* = 8.5 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 52.05, 54.80, 113.35, 128.90, 132.14, 158.21; MS (EI) 257.1 (10.88), 121.0 (100). ¹H NMR data match previously reported data.^{90b}

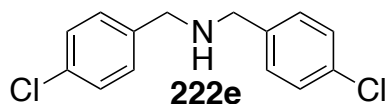
bis-(4-bromobenzyl)amine **222d**:



To a flame dried 50 mL round bottom flask filled with N₂ was added 4-bromobenzaldehyde (925 mg, 5.00 mmol, 1.0 equiv), LiClO₄ (532 mg, 5.00 mmol, 1.00 equiv) and hexamethyldisilazane (HMDS, 2.20 mL, 10.0 mmol, 2.00 equiv). The mixture was stirred at 60 °C for 2 hours. After it was cooled to 0 °C,

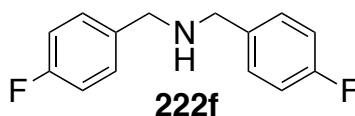
MeOH (10 mL) was added. Then NaBH₄ (568 mg, 15.0 mmol, 3.00 equiv) was added in three portions. After it was stirred at 0 °C for 10 min, the reaction mixture was stirred at rt overnight. Then the volatiles were removed, and *aq* sat NaHCO₃ (10 mL) was added. The aqueous layer was extracted with CH₂Cl₂ (3 × 20 mL). The combined organic extracts were washed with brine, dried (MgSO₄) and filtered. The filtrate was concentrated. The crude product was dissolved in CH₂Cl₂ (10 mL) and *aq* HCl (6M, ~5 mL) was added dropwise until pH ~1. The resulting white precipitate was collected by filtration and suspended in EtOAc (20 mL). *aq* sat Na₂CO₃ (~10 mL) was added. The aqueous layer was separated and extracted with EtOAc (2 × 20 mL). The combined organic extracts were dried (MgSO₄) and filtered. The filtrate was concentrated and purified by column chromatography (silica gel, 25 × 200 mm, Hexane:EtOAc 3:1). The product **222d** was obtained as a colorless oil (536 mg, 1.51 mmol, 60%); R_f = 0.30 (hexane:EtOAc). Spectral data for **222d**: ¹H NMR (500 MHz, CDCl₃) δ 1.60 (brs, 1H), 3.70 (s, 4H), 7.20 (d, 4H, *J* = 8.0 Hz), 7.43 (d, 4H, *J* = 8.0 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 52.27, 120.69, 129.73, 131.40, 139.07. ¹H NMR data match previously reported data.^{90c}

bis-(4-chlorobenzyl)amine **222e**:



The procedure for the preparation of **222d** was followed with 4-chlorobenzaldehyde (703 mg, 5.00 mmol, 1.00 equiv). The product **222e** was obtained as a colorless oil (410 mg, 1.54 mmol, 61.7%); $R_f = 0.30$ (Hexane:EtOAc 1:1). Spectral data for **222e**: ^1H NMR (500 MHz, CDCl_3) δ 1.60 (brs, 1H), 3.70 (s, 4H), 7.20-7.40 (m, 8H); ^{13}C NMR (125 MHz, CDCl_3) δ 52.36, 128.58, 129.50, 132.72, 138.67. ^1H NMR data match previously reported data.^{90c}

bis-(4-fluorobenzyl)amine **222f**:



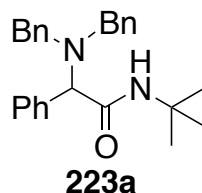
The procedure for the preparation of **222d** was followed with 4-fluorobenzaldehyde (620 mg, 5.00 mmol, 1.00 equiv). The filtrate was concentrated and purified by column chromatography (silica gel, 25 × 200 mm, Hexane:EtOAc 3:1), affording the product **222f** as a colorless oil (400 mg, 1.72 mmol, 69%); $R_f = 0.30$ (hexane:EtOAc 1:1). Spectral data for **222f**: ^1H NMR (500 MHz, CDCl_3) δ 1.60 (brs, 1H), 3.72 (s, 4H), 6.96-7.14 (m, 4H), 7.26-7.50 (m, 4H); ^{13}C NMR (125 MHz, CDCl_3) δ 52.34, 115.14 ($J = 21.1$ Hz), 129.60 ($J = 7.8$ Hz), 135.91 ($J = 3.1$ Hz), 161.92 ($J = 243.0$ Hz). ^1H NMR data match previously reported data.^{90b}

7.5.2 Catalytic asymmetric Ugi-type reaction

General procedure for the catalytic asymmetric Ugi-type reaction

A 25 mL pear-shaped single neck flask which had its 14/20 joint replaced by a threaded high vacuum Teflon valve was flame dried (with a stir bar in it), cooled to rt under N₂ and charged with 20 mol% ligand (0.050 mmol, 0.20 equiv), 40 mol% PhOH (9 mg, 0.10 mmol, 0.40 equiv), 60 mol% H₂O (27 mg, 2.7 μ L, 0.15 mmol, 0.60 equiv), dry toluene (2 mL) and 60 mol% BH₃•Me₂S (2M, 75 μ L, 0.15 mmol, 0.60 equiv). The Teflon valve was closed and the flask was heated at 100 °C for 1 hour. After the flask was cooled to rt, the toluene was carefully removed by exposing to high vacuum (0.1 mmHg) by slightly cracking the Teflon valve. After the solvent was removed, the Teflon valve was completely opened and the flask was heated at 100 °C under high vacuum for 30 min. The flask was then allowed to cool to rt. Then a solution of dibenzylamine or its derivative (0.50 mmol, 2.00 equiv) in specified solvent (0.5 mL) was added under a N₂ stream, followed by the addition of a solution of benzaldehyde (27 mg, 0.25 mmol, 1.0 equiv) in specified solvent (0.5 mL). *t*-butyl isocyanide (45 μ L, 0.37 mmol, 1.5 equiv) was added under N₂. The Teflon valve was then closed, and the resulting mixture was stirred at rt for a specified time (24-46 h). After the reaction, the entire solution was loaded onto the silica gel column to obtain the corresponding product. The absolute stereochemistry for the products was not determined.

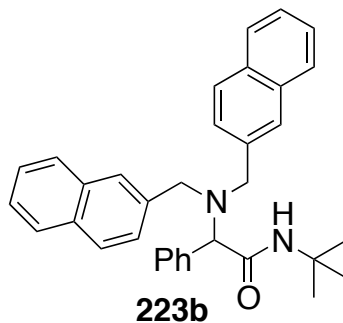
N-(*tert*-butyl)-2-(dibenzylamino)-2-phenylacetamide **223a** (Table 6.4, entry 1):



The general procedure for the catalytic asymmetric Ugi-type reaction was followed with (S)-VAPOL (27 mg, 0.050 mmol, 0.20 equiv), 2,4,6-tri-*t*-butylphenol (27 mg, 0.10 mmol, 0.40 equiv) and mesitylene (1 mL) as the solvent with a reaction time of 36 h at rt. After the column (silica gel, 18 × 250 mm, hexane:EtOAc 19:1), the product was obtained as a pale yellow solid (85 mg, 0.021 mmol, 85%). The optical purity was determined to be 66% ee by HPLC analysis (Chiralpak AD column, hexanes/2-propanol 98:2, 222 nm, flow 1 mL). Retention times: t_R = 12.73 min (major enantiomer) and t_R = 23.70 min (minor enantiomer); mp 112-114 °C; R_f = 0.40 (hexane: EtOAc 4:1). Spectral data for **223a**: ^1H NMR (500 MHz, CDCl_3) δ 1.38 (s, 9H), 3.33 (d, 2H, J = 14.0 Hz), 3.81 (d, 2H, J = 14.0 Hz), 4.28 (s, 1H), 7.10 (brs, 1H), 7.20-7.42 (m, 15H); ^{13}C NMR (125 MHz, CDCl_3) δ 28.81, 50.97, 54.55, 68.14, 127.27, 127.67, 128.09, 128.53, 128.61, 130.31, 134.55, 138.79, 170.65; MS (EI) 386 (M, 0.23), 314 (M-72, 1.30), 286 (M-100, 89.80), 91 (M-295, 100); IR (thin film) 3343(w), 2966(w), 1684(s) cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{31}\text{N}_2\text{O}$ m/z 387.2436 ($[\text{M}+\text{H}]^+$), meas 387.2461.

2-(bis(naphthalen-2-ylmethyl)amino)-N-(tert-butyl)-2-phenylacetamide **223b**

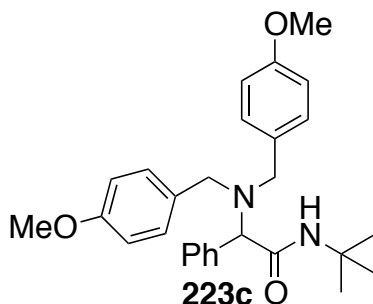
(Table 6.5, entry 2):



The general procedure for the catalytic asymmetric Ugi-type reaction was followed with (*R*)-VAPOL (27 mg, 0.050 mmol, 0.20 equiv), phenol (10 mg, 0.10 mmol, 0.40 equiv), bis-(naphthalene-2-ylmethyl)amine **222b** (188 mg, 0.500 mmol, 2.00 equiv) and toluene (1 mL) as the solvent with a reaction time of 36 h at rt. After the column (1st column, silica gel, 20 × 200 mm, hexane:EtOAc 9:1; 2nd column, silica gel, 18 × 200 mm, hexane:EtOAc 15:1), the product was obtained as a yellow semi-solid (92 mg, 0.19 mmol, 76%). The optical purity was determined to be 8% ee by HPLC analysis (Chiralcel OD-H column, hexanes/2-propanol 98:2, 222 nm, flow 1 mL). Retention times: t_R = 12.73 min (minor enantiomer) and t_R = 23.70 min (major enantiomer); R_f = 0.25 (hexane:EtOAc). Spectral data for **223b**: ^1H NMR (500 MHz, CDCl_3) δ 1.40 (s, 9H), 3.60 (d, 2H, J = 14.0 Hz), 4.05 (d, 2H, J = 14.0 Hz), 4.39 (s, 1H), 7.10 (brs, 1H), 7.32-7.60 (m, 11H), 7.74-7.92 (m, 8H); ^{13}C NMR (125 MHz, CDCl_3) δ 28.84, 51.05, 54.77, 68.10, 125.78, 126.18, 126.56, 127.58, 127.63, 127.65, 127.75, 128.16, 128.32, 130.30, 132.80, 133.33, 134.74, 136.35, 170.64; IR (thin film) 3343(w), 2966(w),

1680(s), 1508(s) cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{34}\text{H}_{35}\text{N}_2\text{O}$ m/z 487.2749 ($[\text{M}+\text{H}]^+$), meas 487.2788.

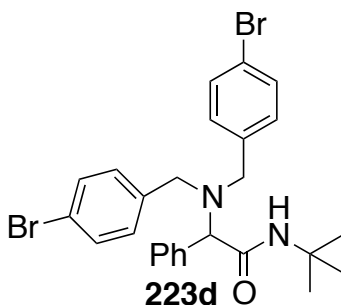
2-(bis(4-methoxybenzyl)amino)-N-(tert-butyl)-2-phenylacetamide **223c** (Table 6.5, entry 3):



The general procedure for the catalytic asymmetric Ugi-type reaction was followed with (*R*)-VAPOL (27 mg, 0.050 mmol, 0.20 equiv), phenol (10 mg, 0.10 mmol, 0.40 equiv), bis-(4-methoxybenzyl)amine **222c** (129 mg, 0.500 mmol, 2.00 equiv) and toluene (1 mL) as the solvent with a reaction time of 48 h at rt. After the column (silica gel, 20 × 200 mm, hexane:EtOAc 9:1), the product was obtained as a yellow semi-solid (90 mg, 0.021 mmol, 82%). The optical purity was determined to be 15% ee by HPLC analysis (Chiralpak AD column, hexanes/2-propanol 90:10, 222 nm, flow 1 mL). Retention times: t_R = 6.90 min (minor enantiomer) and t_R = 19.59 min (major enantiomer). R_f = 0.30 (hexane:EtOAc 4:1). Spectral data for **223c**: ^1H NMR (500 MHz, CDCl_3) δ 1.40 (s, 9H), 3.26 (d, 2H, J = 13.5 Hz), 3.76 (s, 6H), 3.81 (d, 2H, J = 13.5 Hz), 4.30 (s, 1H), 6.90 (d, 4H, J = 9.0 Hz), 7.18 (brs, 1H), 7.25 (d, 4H, J = 8.5 Hz), 7.28-7.42 (m, 5H); ^{13}C NMR (125 MHz, CDCl_3) δ 28.78, 50.84, 53.58, 55.20, 67.95,

113.87, 127.55, 128.00, 129.69, 130.29, 130.68, 134.60, 158.78, 170.77; MS (EI) 346 (M-100, 32.94), 121 (100); IR (thin film) 3348(w), 2963(w), 1680(s), 1512(s) cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{28}\text{H}_{35}\text{N}_2\text{O}_3$ m/z 447.2648 ($[\text{M}+\text{H}]^+$), meas 447.2631.

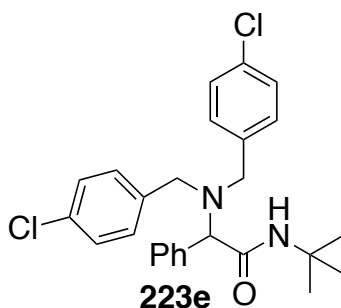
2-(bis(4-fluorobenzyl)amino)-N-(tert-butyl)-2-phenylacetamide **223d** (Table 6.5, entry 4):



The general procedure for the catalytic asymmetric Ugi-type reaction was followed with (*R*)-VAPOL (27 mg, 0.050 mmol, 0.20 equiv), phenol (10 mg, 0.10 mmol, 0.40 equiv), bis-(4-bromobenzyl)amine **222d** (178 mg, 0.500 mmol, 2.00 equiv) and toluene (1 mL) as the solvent with a reaction time of 36 h at rt. After the column (1st column, silica gel, 20 × 200 mm, hexane:EtOAc 15:1; 2nd column, silica gel, 18 × 150 mm, hexane:EtOAc 15:1), the product was obtained as a white foamy-solid (93 mg, 0.0 mmol, 72%). The optical purity was determined to be 27% ee by HPLC analysis (Chiralpak AD column, hexanes/2-propanol 98:2, 222 nm, flow 1 mL); Retention times: t_R = 9.77 min (minor enantiomer) and t_R = 45.91 min (major enantiomer). mp 108-109 °C; R_f = 0.50 (hexane:EtOAc 4:1); Spectral data for **223d**: ^1H NMR (500 MHz, CDCl_3) δ 1.40

(s, 9H), 3.41 (d, 2H, $J = 14.5$ Hz), 3.74 (d, 2H, 14.0 Hz), 4.20 (s, 1H), 6.50 (brs, 1H), 7.14-7.24 (m, 4H), 7.26-7.40 (m, 5H), 7.42-7.52 (m, 4H); ^{13}C NMR (125 MHz, CDCl_3) δ 28.50, 50.94, 53.61, 67.98, 120.79, 127.66, 128.04, 129.48, 129.94, 131.33, 134.77, 137.51, 179.10; IR (thin film) 3337(w), 2966(w), 1669(s), 1487(s) cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{29}\text{N}_2\text{O}^{79}\text{Br}_2$ m/z 543.0647 ($[\text{M}+\text{H}]^+$), meas 543.0645.

2-(bis(4-chlorobenzyl)amino)-N-(tert-butyl)-2-phenylacetamide **223e** (Table 6.5, entry 5):

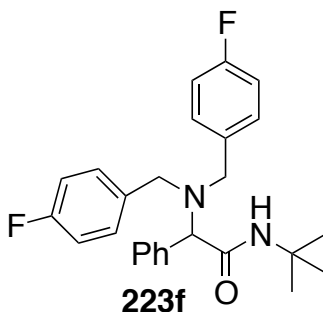


The general procedure for the catalytic asymmetric Ugi-type reaction was followed with (*R*)-VAPOL (27 mg, 0.050 mmol, 0.20 equiv), phenol (10 mg, 0.10 mmol, 0.40 equiv), bis-(4-chlorobenzyl)amine **222e** (133 mg, 0.500 mmol, 2.00 equiv) and toluene (1 mL) as the solvent with a reaction time of 24 h at rt. After the column (1st column, silica gel, 20 × 200 mm, hexane:EtOAc 15:1; 2nd column, silica gel, 18 × 150 mm, 15:1), the product was obtained as a white foamy-solid (83 mg, 0.018 mmol, 73%). The optical purity was determined to be 23% ee by HPLC analysis (Chiralpak AD column, hexanes/2-propanol 98:2, 222 nm, flow 1 mL). Retention times: $t_R = 9.76$ min (minor enantiomer) and $t_R =$

45.91 min (major enantiomer); mp 105-106 °C, R_f = 0.50 (hexane:EtOAc 4:1).

Spectral data for **223e**: ^1H NMR (300 MHz, CDCl_3) δ 1.40 (s, 9H), 3.44 (d, 2H, J = 14.1 Hz), 3.78 (d, 2H, J = 14.1 Hz), 4.23 (s, 1H), 6.60 (brs, 1H), 7.22-7.46 (m, 13H); ^{13}C NMR (125 MHz, CDCl_3) δ 28.75, 51.17, 53.77, 68.16, 127.90, 128.28, 128.64, 129.78, 129.82, 132.96, 134.91, 137.20, 170.41; IR (thin film) 3337(w), 2966(w), 1668(s), 1491(s) cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{29}\text{N}_2\text{O}^{35}\text{Cl}_2$ m/z 455.1657 ($[\text{M}+\text{H}]^+$), meas 455.1680.

2-(bis(4-fluorobenzyl)amino)-N-(tert-butyl)-2-phenylacetamide **223f** (Table 6.5, entry 5):



The general procedure for the catalytic asymmetric Ugi-type reaction was followed with (*R*)-VAPOL (27 mg, 0.050 mmol, 0.20 equiv), phenol (10 mg, 0.10 mmol, 0.40 equiv), bis-(4-chlorobenzyl)amine **222f** (117 mg, 0.500 mmol, 2.00 equiv) and toluene (1 mL) as the solvent with a reaction time of 36 h at rt. After the column (silica gel, 18 × 250 mm, hexane:EtOAc 15:1), the product **223f** was obtained as a yellow foamy-solid (78 mg, 0.018 mmol, 72%). The optical purity was determined to be 27% ee by HPLC analysis (Chiralpak AD column, hexanes/2-propanol 98:2, 222 nm, flow 1 mL). Retention times: t_R = 9.71 min

(minor enantiomer) and $t_R = 25.12$ min (major enantiomer); mp 105-107 °C; $R_f = 0.40$ (hexane:EtOAc). Spectral data for **223f**: ^1H NMR (500 MHz, CDCl_3) δ 1.38 (s, 9H), 3.38 (d, 2H, $J = 14.0$ Hz), 3.74 (d, 2H, $J = 14.0$ Hz), 4.20 (s, 1H), 6.66 (brs, 1H), 6.96-7.20 (m, 4H), 7.20-7.38 (m, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 28.79, 51.12, 53.70, 68.28, 115.34 ($J = 21.13$ Hz), 127.85, 128.26, 129.90, 130.06 ($J = 7.75$ Hz), 134.46 ($J = 3.3$ Hz), 135.03, 162.03 ($J = 244.6$ Hz), 170.50; IR (thin film) 3339(w), 2968(w), 1684(s), 1508(s) cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{29}\text{N}_2\text{OF}_2$ m/z 423.2248 ($[\text{M}+\text{H}]^+$), meas 423.2268.

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