BOROX-ANION INDUCED CATALYTIC ASYMMETRIC REACTIONS AND THEIR SYNTHETIC APPLICATIONS

By

Wenjun Zhao

A DISSERTATION

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

Chemistry—Doctor of Philosophy

2014

ABSTRACT

BOROX-ANION INDUCED CATALYTIC ASYMMETRIC REACTIONS AND THEIR SYNTHETIC APPLICATIONS

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The development of a catalytic asymmetric three-component Ugi reaction is described. The first chiral catalyst for the three-component Ugi reaction was identified as a result of a screen of a large set of different polyborate catalysts (BOROX catalysts). The BOROX catalysts were assembled in situ from a chiral biaryl ligand, an amine, water, $BH_3 \cdot SMe_2$, and an alcohol or phenol. The optimal catalyst system (LAP 78-5-47) provided α-amino amides from an aryl aldehyde, a secondary amine, and an isonitrile with high asymmetric induction. It is considered likely that the BOROX bind to the iminium ion or nitrilium ion as a chiral counter anion catalyst, as suggested by ^{1}H and ^{11}B NMR studies.

The second project involves the application of BOROX-catalyzed aziridination to the synthesis of β-amino esters. A general study is undertaken to examine the scope of the reductive ring-opening of aziridine-2-carboxylates with samarium diiodide. The competition between C-C and C-N bond cleavage is examined as a function of the nature of the N-substituent of the aziridine, the nature of the substituent in the 3-position of the aziridine and on whether the substituent in the 3-position is in a cis- or trans-relationship with the carboxylate in the 2-position. Exclusive formation of the C-N cleavage product is observed for all aziridines with the strongly N-activating p-toluene sulfonate group. Nearly as high a selectivity is observed for the 2-trimethylsilylethyl sulfonate group (SES)

which is easier to remove. The utility of these methods is illustrated in the synthesis of (R)-β^3-DOPA and L-DOPA from the same aziridine, the former by SmI_2 mediated reductive opening at C-2 and the latter by palladium mediated reductive opening at C-3.

Lastly, the BOROX-catalyzed asymmetric aziridination is applied in the studies of total synthesis of one of the “two-headed” sphingoid bases, rhizochalinin C. The synthesis of left head **168** and right head **169** was developed. Late stage coupling of the two head-pieces provided the product with the complete carbon skeleton in high yield. The hydrogenation catalyzed by $Pd(OH)_2$ in the presence of $(Boc)_2O$ successfully removed the two MEDAM groups, reduced the triple bond, removed the Bn group and reductively opened the aziridine ring. The final steps planned for the synthesis involving selective reduction of the carboxylic acid or the ester in the presence of a ketone failed to give any desired product. The synthesis will be further investigated.

To my dearest parents, my husband and my brother

ACKNOWLEDGEMENTS

This dissertation would not have been completed without the support offered to me along the way. I owe my sincere gratitude to all those people who have made this dissertation possible and because of whom my graduate experience has been one that I will cherish forever.

First and foremost, I would like to thank my advisor, Dr. William D. Wulff, for his consistent support, invaluable guidance and encouragement throughout this research work. His direction and patience greatly aided me, especially in my early research endeavors. He has taught me, both consciously and un-consciously, the right attitude toward research. The joy and enthusiasm he has for organic chemistry was contagious and motivational for me. He is always available whenever I need his help. Thank you, Dr. Wulff, for all your help and support, for providing me the opportunity to work on these exciting projects. It is a great experience to do research under your guidance.

I would also like to thank Dr. Robert E. Maleczka Jr., Dr. Babak Borhan and Dr. Aaron L. Odom for serving on my Ph.D. committee. I am grateful for their time, insightful suggestions and constructive feedbacks on my research. Thank them for supporting me in my postdoc application. Special thanks to Dr. Robert E. Maleczka Jr. for passing me information about some potential job opportunities.

I am also grateful to the current and the former lab mates: Dr. Aman Desai, Dr. Li Huang, Dr. Yong Guan, Dr. Hong Ren, Dr. Dima Berbasov, Dr. Anil Gupta, Dr. Munmun Mukherjee, Dr. Nilanjana Majumder, Dr. Wynter Gilson, Dr. Mathew Vetticatt, Xin Zhang, Yubai Zhou, Xiaopeng Yin and Yijing Dai for their friendship and collaboration. In

particular, I would like to thank Dr. Hong Ren and Dr. Li Huang for their great help in both my research and my daily life. I am grateful to Dr. Anil Gupta for his training me during my first several months and Dr. Mathew Vetticatt for his encouragement and valuable advice on my research.

I would like to thank my friends, Yimeng Wang, Li Cui, Jinlan Dong, Li Xie, for all the wonderful moments we have shared together since the very first month of my Ph.D. life. I am also grateful to Ms. Dottie Schmidt for being a caring landlord and friend in the last several months of my Ph.D. life. Special thanks to my naughty pet bunny, doudou, who filled my life with fun and responsibility.

I would like to thank Dr. Daniel Holmes and other NMR staff for their tremendous help in NMR training and problem solving. I am also grateful to Dr. Rui Huang for his help in elemental analysis. Great thanks to Ms. Lijun Chen and Prof. Daniel Jones from the Department of Biochemistry, Michigan State University for their kind help in HRMS training and the service. I would like to thank the Department of Chemistry for offering me teaching assistantships, travel grants and fellowships.

Finally, I would like to thank my father, Guoqi Zhao and my mother, Meiling Yang for their love, support and encouragement over the years. They are always there for me throughout my life. Special thanks to my dear husband, Dr. Chao Wang, whose patience, understanding and unconditional love accompanied and supported me throughout my Ph.D. journey.

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CHAPTER 1

INTRODUCTION AND REVIEWS

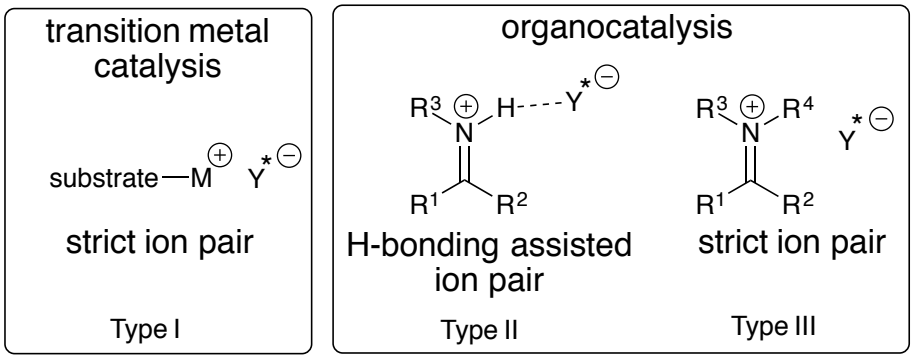
This work has focused on BOROX-anion directed catalysis, including the development of a BOROX-catalyzed asymmetric three-component Ugi reaction and the application of BOROX-catalyzed asymmetric aziridination to the synthesis of *β*-amino acids and total synthesis of "two headed sphingolipids". The catalytic asymmetric three component Ugi reaction is proposed to proceed via a strict ion pair between a fully substituted iminium and the BOROX anion, while the BOROX catalyzed asymmetric aziridination involves a hydrogen-bonding assisted ion pair, and thus is a Brønsted acid catalyzed process.

1.1 Chiral Counteranions Directed Asymmetric Catalysis

The field of asymmetric catalysis has witnessed explosive growth over the last 40 years due to the increasing demands of both industry and academia for enantiomerically enriched molecules. The interactions between chiral catalysts and the substrates, which are key to achieving high levels of asymmetric induction in the products, include covalent bonding as in enamine[1] or iminium[2] catalysis and noncovalent bonding, such as coordinative interactions, hydrogen bonding[3] and ion pairing interactions[4]. Since many organic reactions proceed via ionic intermediates or reagents, an ion paring between a chiral ion and the charged intermediate can be a powerful strategy to achieve highly efficient asymmetric synthesis. The use of a chiral cation through ion-pairing has been effectively applied in reactions involving anionic intermediates via asymmetric phase transfer catalysis since 1984.[5] However, the charge-inverted process,

asymmetric catalysis using chiral anions, has only emerged recently as an important approach for stereochemical control in reactions proceeding via a cationic intermediate.

Figure 1.1 Key activation modes in chiral anion directed asymmetric catalysis

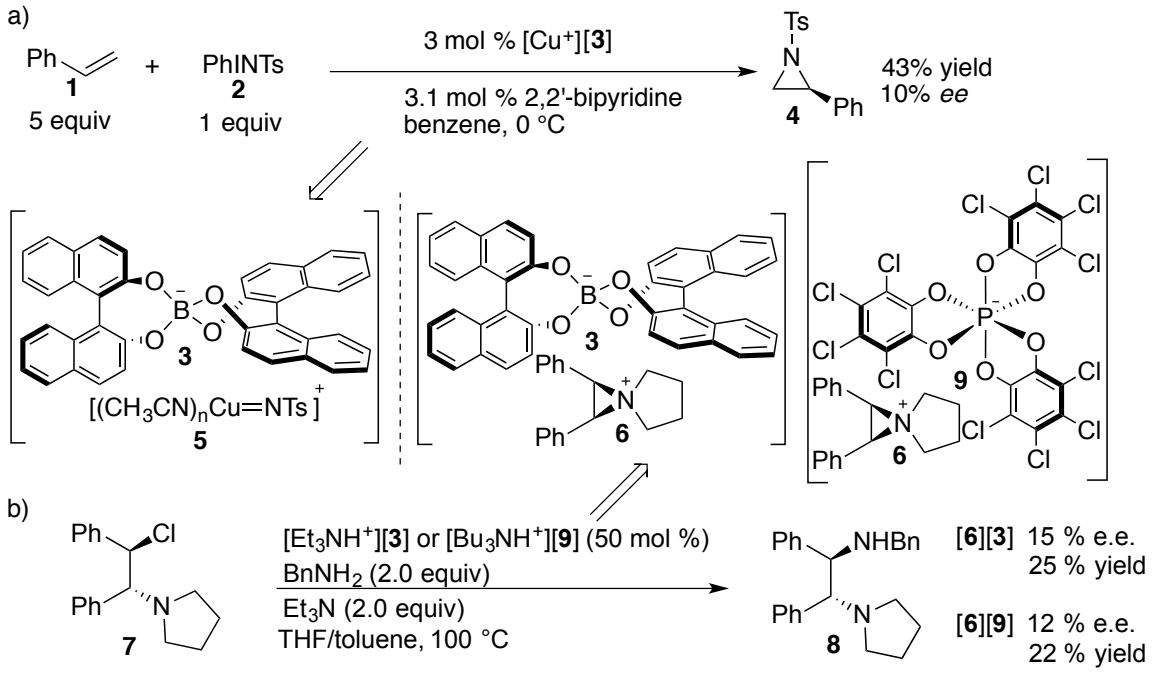


The synthesis, identification and resolution of a number of different chiral anions led to the fast progression of chiral anion-directed catalysis. Typically, there are three types of activation modes in asymmetric counteranion-directed catalysis (ACDC) (Figure 1.1).[6] Type I is the application of ACDC in transition metal catalysis, which involves an ion pairing between a chiral anion and a cationic substrate-metal complex. Type II is the application of ACDC in Brønsted acid catalysis. In this case the key interaction for achieving asymmetric induction is an ion pair between a protonated substrate and the counteranion of the acid catalyst. The ion pair is generated as a result of an initial proton transfer from the strong Brønsted acid catalyst to the basic substrate. Then a non-covalent interaction involving H-bonding is developed between the resulting ion pair of the protonated substrate and the chiral counteranion of the acid catalyst.[6c] If the hydrogen bonding is excluded, as in reactions proceeding via a fully substituted iminium cation where there is no site to accept a hydrogen bonding, it can be

considered as the third category (Figure 1.1, type III). This third type actually can be a very powerful strategy to develop efficient asymmetric organocatalysis.

Different classes of chiral anions have been explored in ACDC. Tetracoordinated borate and hexacoordinated phosphate were selected as suitable candidates in the early attempts of chiral anion directed catalysis due to their non-coordinating nature. In 2000, Arndtsen and co-workers reported the first example of a chiral anion directed transition metal catalysis (type I activation mode) (Scheme 1.1, a)).[7]

Scheme 1.1 Tetracoordinated borate anion directed asymmetric catalysis

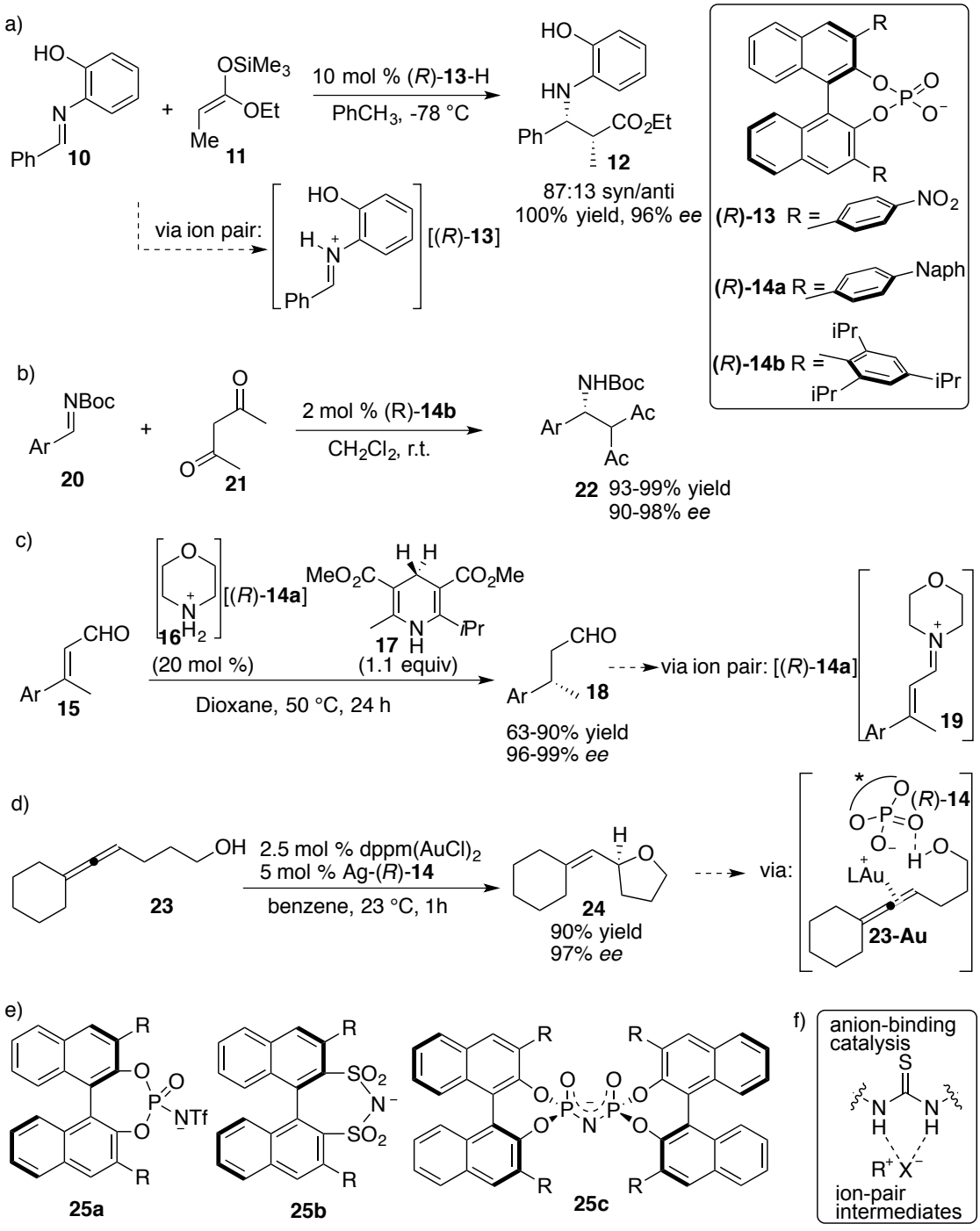


The existence of ion pair [**5**][**3**] was supported by the adverse effect of increasing solvent dielectric constant on the enantioselectivities and also by crystal structure analysis. This spiro-borate anion **3** was later applied to organocatalysis by Nelson and co-workers in an aziridinium ring opening reaction

(type III activation mode) (Scheme 1.1, b)).[8] The NMR chemical shifts and proton splitting information observed in their ^{1}H and ^{13}C NMR studies indicated that there was an ion-paring interaction between the chiral anion **3** and the *meso*-aziridinium cation **6**, but not to a great extent, which was consistent with the low enantioselectivities obtained. Phosphate **9** was also investigated in this work, which gave the same level of enantioselectivity. Despite the low level of asymmetric inductions achieved, the early studies with chiral borate and phosphate anions validated the concept of using chiral counteranions to introduce asymmetric induction, which set the stage for future advances in ACDC.

The more recent developments of ACDC are closely related to Brønsted acid catalysis. The conjugate base of strong chiral Brønsted acid is a widely used class of counteranion in ACDC. The research groups of Akiyama and Terada published their seminal work on chiral monophosphoric acid catalysis in 2004 (Scheme 1.2, a and b, respectively).[9] An ion pairing interaction between the protonated imine **10**-H^{+} and the chiral phosphate anion (*R*)-**13** was proposed by Akiyama and co-workers for their Mannich-type reaction (type II activation mode). Two years later, List and Mayer reported a landmark work involving type III activation mode (Scheme 1.2, c) in ACDC.[6a] The catalyst was generated from an achiral secondary amine and a chiral phosphoric acid. Since hydrogen bonding was not possible in this case due to the full substitution on iminium nitrogen, the asymmetric hydrogenation was achieved via a strict ion pair [**19**][(*R*)-**14a**].

Scheme 1.2 Selected examples of chiral phosphate anion directed asymmetric catalysis and activation mode of anion-binding catalysis



Chiral phosphate anions have also been effectively applied to asymmetric transition metal catalysis. In 2007, the Toste group reported an asymmetric hydroalkoxylation reaction mediated by a dinuclear gold (I) complex, which was the first example of highly enantioselective transition metal catalysis directed by a chiral anion (Scheme 1.2, d).[10] The role of phosphate as a counteranion and not a ligand was revealed by the fact that both of the two available coordination sites on Au^{I} center are occupied by the substrate and one phosphorus atom of the bis-phosphine ligand. The ion pairing was also supported by the strong solvent effect observed. The reaction that was carried out in the less-polar benzene provided the product with very high asymmetric induction, while a significant drop in the enantioselectivity was observed in more-polar solvent, such as nitromethane or acetone. This work demonstrated that high asymmetric inductions can be achieved by ion pairing strategy using chiral counteranions in asymmetric transition metal catalysis, which represents a breakthrough in the application of ACDC in transition metal catalysis.

Successful asymmetric catalysis directed by the conjugate bases of several other chiral strong Brønsted acids have also been reported, such as N-triflyphosphoramidate anions, disulfonimide anions and imidodiphosphate anions (Scheme 1.2, e).[4]

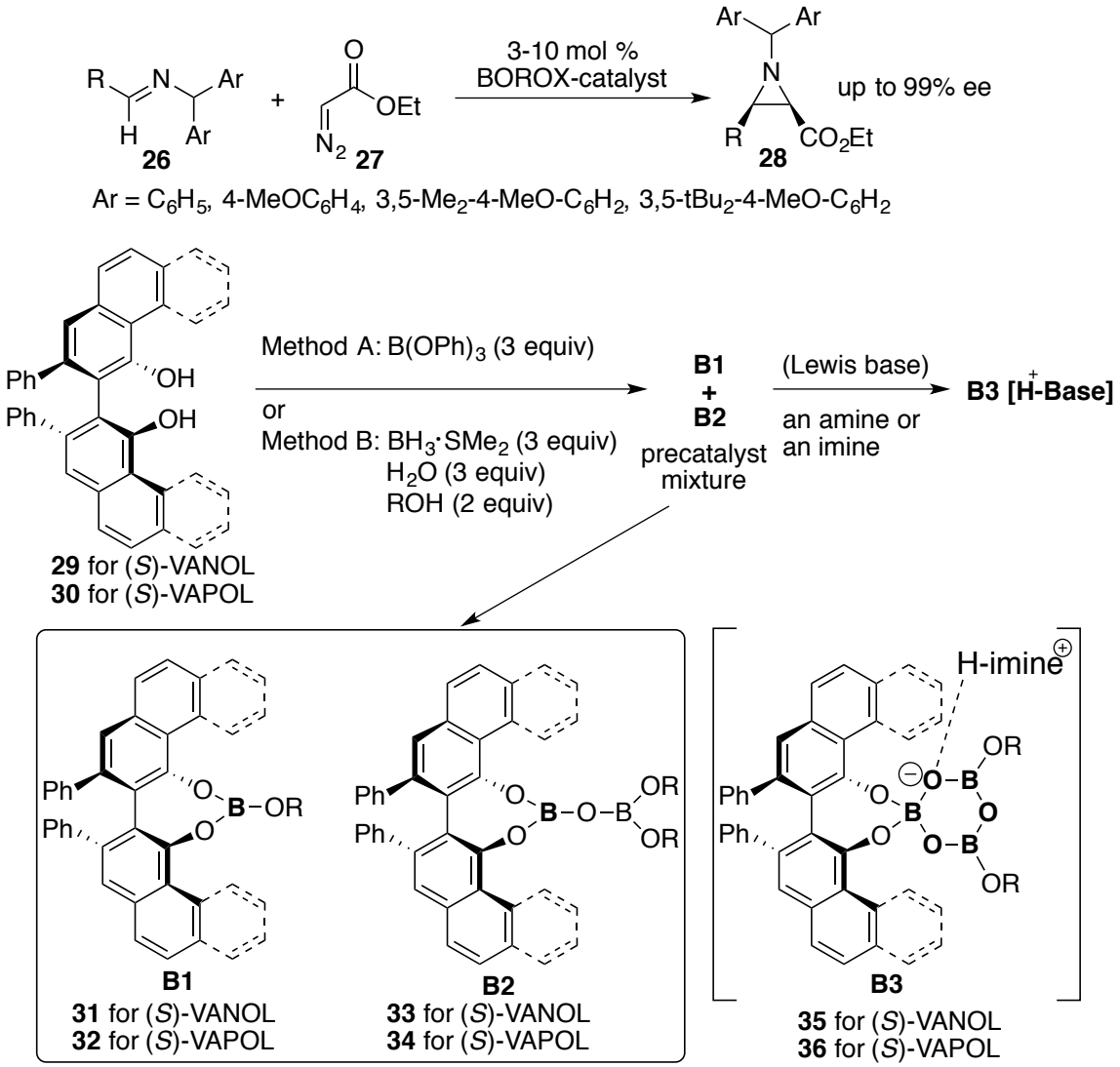
Another class of useful chiral couteranions was identified in anion binding catalysis. Anion binding catalysis can be viewed as a special case of ACDC (type III), where the chiral anion is generated from complexation between a chiral neutral thiourea molecule and an achiral anionic leaving group provided by the

substrate (Scheme 1.2, f). The ion pairing interaction activates the substrate and also provides high enantioselectivity. This strategy has found a variety of applications in asymmetric organocatalysis.[11]

1.2 BOROX Anion Directed Asymmetric Catalysis

In the previous section, the typical types of ACDC and the major classes of chiral anions have been discussed. Tetrahedral spiro-borate is a class of counteranion that was explored in the development of ACDC. Our group has previously developed an anionic chiral poly-borate catalyst for asymmetric reactions that involve iminium ions including aziridination[12], hetero-Diels-Alder reactions[13] and aza-Cope rearrangements[14]. The catalyst structure involves a spiro-borate anion in a boroxinate core and thus we named catalysts of this kind as “BOROX catalysts” (Scheme 1.3, **B3**). There was no report of utility of a boroxine as a catalyst in organic synthesis prior to our work.[15]

Scheme 1.3 Asymmetric aziridination and the formation of BOROX catalysts



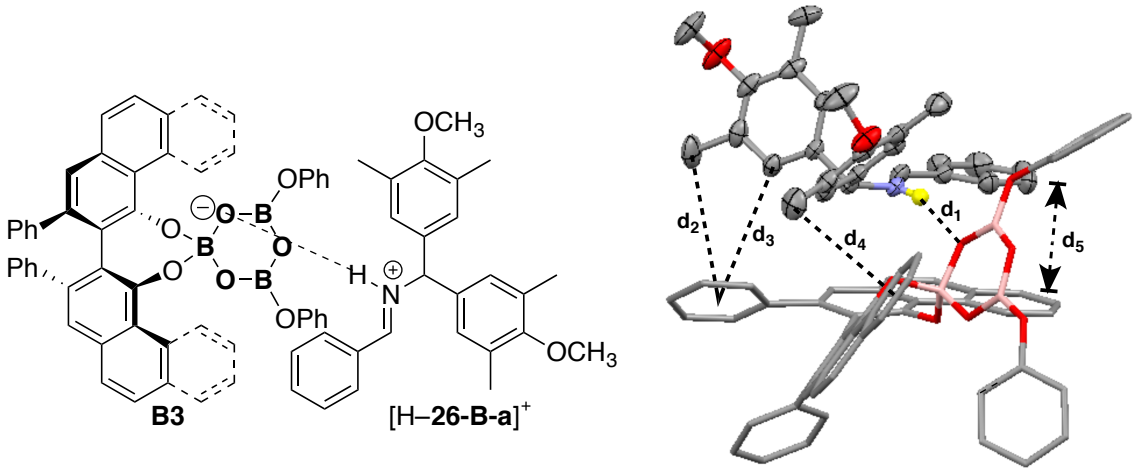
1.2.1 The Identification of BOROX Catalyst in Asymmetric Aziridination

The structure of the BOROX catalyst was identified during our investigation of the catalytic asymmetric aziridination reaction. There are two standard protocols for the preparation of BOROX catalyst (Scheme 1.3). One typical protocol involves reacting the chiral vaulted bisphenol ligand, either VAPOL or VANOL, with commercial $B(OPh)_3$ (Method A). We have also demonstrated that an equally effective mixture can be generated from the ligand,

$BH_3 \cdot SMe_2$, phenols or alcohols and H_2O (Method B). Detailed ^1H and ^{11}B NMR studies and high resolution mass spectroscopy analysis revealed that there were two boron species, tentatively assigned as B1 and B2, in the mixture generated from either of the protocols, with ratios from 10:1 to 1:20 depending on the exact temperature and equivalents of reagents applied.[12p] The fact that the reaction catalyzed by a precatalyst mixture with higher ratio of B2/B1 gave higher asymmetric introduction led us to think of B2 as a Lewis acid catalyst that was responsible for the high enantioselectivities.

Shortly after that, it was found that a mixture of B1 and B2 was converted to a BOROX-involved ion pair when there was a base present.[12n] Under the asymmetric aziridination reaction conditions, the imine was basic enough to induce the formation of the BOROX-substrate ion pair, which consists of a BOROX anion and an iminium cation resulting from protonation of the imine. This is strongly supported by both NMR and X-ray structure analysis (Figure 1.2)[12k]. At that point, we realized that the asymmetric aziridination that we have developed involves BOROX-anion directed Brønsted acid catalysis and not Lewis acid catalysis. The effectiveness of a number of different bases on the formation of the BOROX skeleton was investigated. Besides imines, the assembly of BOROX catalyst can be triggered by primary, secondary, tertiary amines. Ethyl diazoacetate and aldehydes are too weak to induce the formation of a BOROX catalyst. The very week base dimethyl acetamide (pKa ~ –0.5) only led to an 18% yield of the boroxinate.[12e]

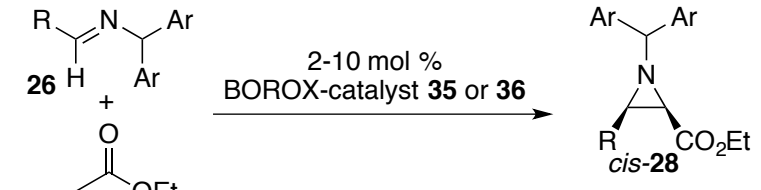
Figure 1.2 X-ray structure of BOROX-iminium ion pair



1.2.2 BOROX-Anion-Directed Asymmetric Aziridination

Our group has put considerable effort into the development of a universal asymmetric aziridination reaction where either *cis*- or *trans*- aziridines can be prepared from the same imine and the same catalyst. The BOROX-catalyzed aziridination can provide *cis*-aziridines in high asymmetric inductions with diazo acetate and benzhydryl imines derived from a broad range of aldehydes including primary, secondary and tertiary aliphatic aldehydes and both electron-rich and electron-poor aromatic aldehydes (Scheme 1.4).[12r, s] Our subsequent studies revealed that certain substituted benzhydryl imine derivertives were even more effective.[12j, 12o, 12q] In addition to diazoacetate, *cis*-aziridines can be made from diazomethyl ketones[12i] and tertiary diazo acetamides[12h, 12j] as well. We have also investigated BOROX-catalyzed asymmetric *cis*-aziridination with chiral imines, where both matched and mis-matched cases were observed.[12d]

Scheme 1.4 The Wulff asymmetric *cis*-aziridination reaction

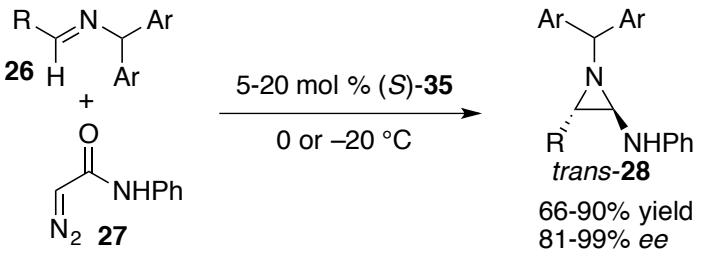


R = aryl or alkyl

Ar		%Yield	%*ee*
C_6H_5	*cis*-**28P**	60-91	90-98
4-$MeOC_6H_4$	*cis*-**28D**	11-92	63-97
3,5-Me_2-4-MeO-C_6H_2	*cis*-**28M**	57-99	78-99
3,5-tBu_2-4-MeO-C_6H_2	*cis*-**28B**	67-98	91-99.8

The diastereoselectivity of the aziridination with the same imine and same BOROX-catalyst is switched to *trans*- if *sec*-diazo acetamides are used (Scheme 1.5).[12l] A companion publication with combined experimental and computational studies revealed that the binding of the diazo acetamide to the BOROX catalyst involves two H-bonding interactions rather than one for a diazo ester, which leads to the switch in diastereoselectivity from *cis*- to *trans*-.[12h]

Scheme 1.5 The Wulff asymmetric *trans*-aziridination reaction

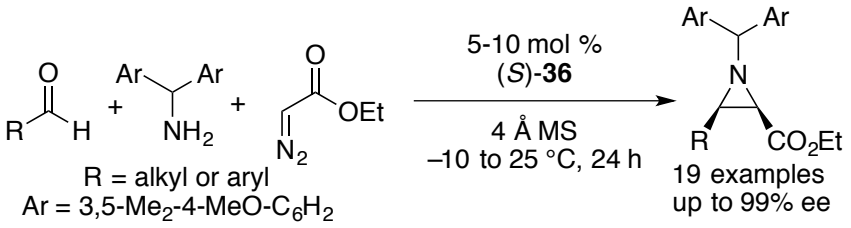


R = aryl and 1°, 2°, 3° alkyl
Ar = 3,5-Me_2-4-MeO-C_6H_2 or 3,5-tBu_2-4-MeO-C_6H_2

More recently, we have developed a multi-component catalytic asymmetric aziridination[12e, 12g] which largely simplifies the traditional reaction procedure and also expands the substrate scope to some unbranched aliphatic aldehydes that fail to give the desired aziridines when the reaction is performed

with pre-formed imines (Scheme 1.6).[16] The multi-component *trans*-aziridination is under investigation and fruitful results have been obtained.[17]

Scheme 1.6 Multicomponent asymmetric cis-aziridination reaction



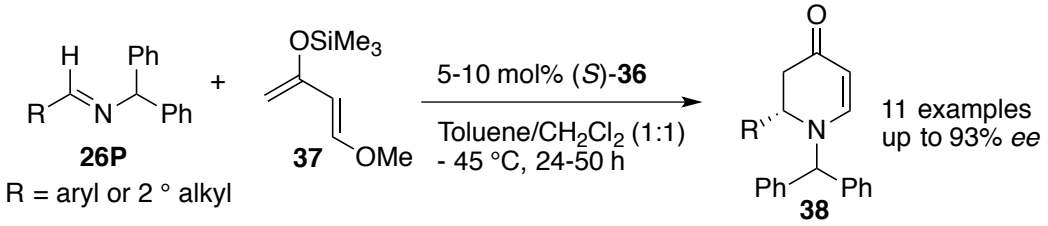
The development of a universal asymmetric aziridination sets the stage for our investigation on its application in organic synthesis. A large part of this dissertation will focus on the application of BOROX-catalyzed asymmetric aziridination to the synthesis of several classes of important functionalized molecules.

1.2.3 BOROX-Anion-Directed Hetero-Diels-Alder Reaction

In addition to aziridination, our group applied the BOROX catalyst to a hetero-Diels-Alder reaction involving benzhydryl imines that were previously identified as suitable substrates for asymmetric aziridination reaction (Scheme 1.7)[13]. The pre-catalyst mixture was prepared from chiral ligand VAPOL and $B(OPh)_3$ (method A). Analogous to aziridination, when this mixture was exposed to imine **26P**, there would be an in situ assembly of the BOROX catalyst. The imine was activated as an iminium cation which was ion-paired with the chiral BOROX anion **B3**. This is another example of BOROX-anion directed Brønsted acid catalysis. It was found that 10-20 equivalents of $B(OPh)_3$ relative to the

chiral ligand VAPOL were required to achieve high yield and high asymmetric induction.

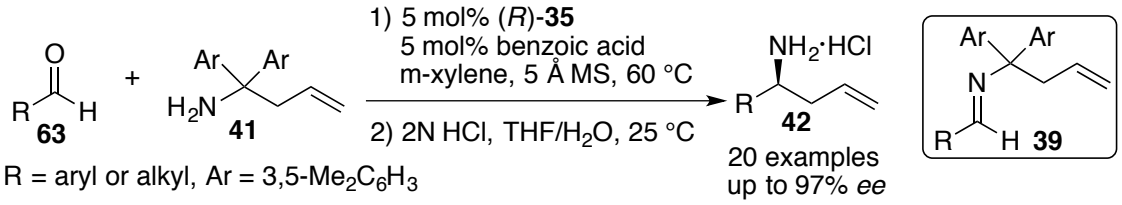
Scheme 1.7 Asymmetric hetero-Diels-Alder reaction



1.2.4 BOROX-Anion-Directed Aza-Cope Rearrangement

In 2011, our group published a catalytic asymmetric aza-Cope rearrangement mediated by a modified BOROX catalyst (Scheme 1.8).[14] The initial attempt of the rearrangement of imine **39** with BOROX (**35**) derived only from VANOL and $B(OPh)_3$ gave very low asymmetric induction, while a significant increase in the enatioselectivity was observed by the addition of benzoic acid as an additive. It is proposed that the benzoate, the conjugate base of benzoic acid, adds to one of the two three coordinated boron in the boroxinate core, which results in a chiral BOROX dianion interacting with the protonated imine [**39**-H]$^+$. After a bit optimization, the reaction can be done in a multicomponent fashion directly from aldehydes **63** and amine **41** on gram-scale, where high yields and inductions up to 97% *ee* can be achieved.

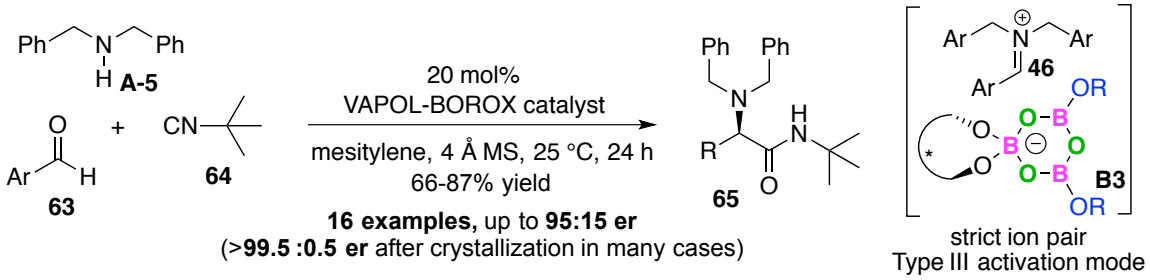
Scheme 1.8 Catalytic asymmetric aza-Cope rearrangement.



1.2.5 BOROX-Anion Directed Three-Component Ugi Reaction

A major part of the work in this thesis has focused on the development of the first catalytic asymmetric three-component Ugi reaction (Scheme 1.9), which provides access to chiral α–amino amides. An effective chiral catalyst has been identified in this work, which is proposed as a BOROX catalyst derived from a VAPOL derivative and a substituted phenol. The reaction proceeds via a strict ion pair between the fully substituted iminium **46** and BOROX anion **B3**, which is different from previous BOROX-anion directed Brønsted acid catalysis involving hydrogen bond assisted ion pair. Most of the substrates, including aryl aldehydes with both electron-withdrawing and electron-donating groups, reacted to give α–amino amides with high enantiomeric ratio.

Scheme 1.9 Catalytic asymmetric three-component Ugi reaction



1.3 Conclusion

Asymmetric counteranion-directed catalysis is a young but fast growing research field. The concept of using chiral anions to introduce asymmetry through ion pairing has led to fruitful results in asymmetric synthesis in the last few years. In this context, our group has identified a new class of chiral borate anions, the BOROX anions, which can be applied to a number of different asymmetric reactions involving cationic intermediates (usually iminiums). The

BOROX catalyst functions as a Brønsted acid in asymmetric aziridination reactions, hetero-Diels-Alder reactions, and aza-Cope rearrangements. We have recently developed a BOROX-catalyzed asymmetric three component Ugi reaction (chapter two), where the BOROX catalyst functions as a pure “chiral anion catalyst” without hydrogen bonding involved.

In addition to the expansion of BOROX catalysts to new chemistry, this dissertation has also focused on the application of the well-developed BOROX-catalyzed asymmetric aziridination reactions to the synthesis of important functionalized molecules (chapter three and chapter four).

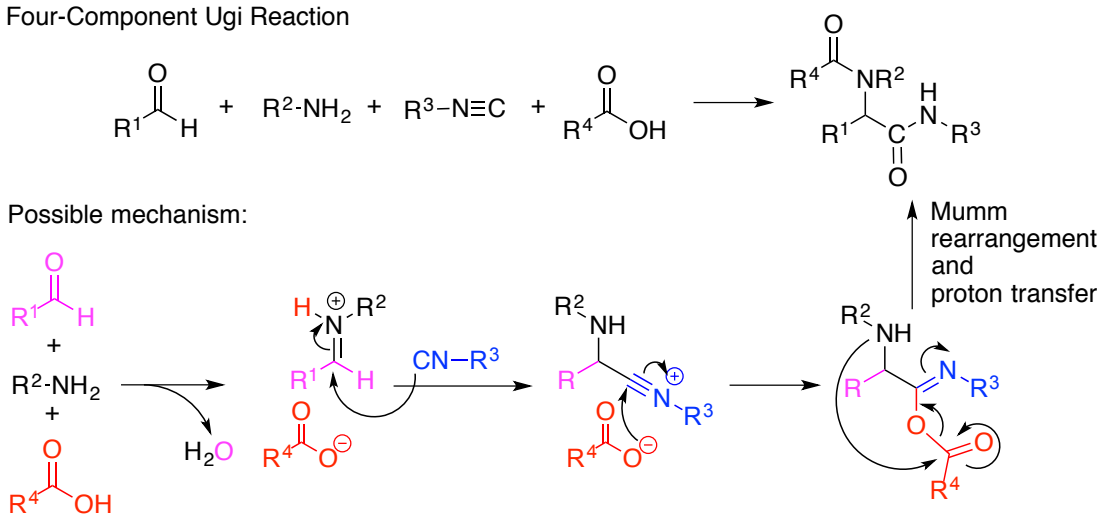
CHAPTER 2

CATALYTIC ASYMMETRIC THREE-COMPONENT UGI REACTION

2.1 Introduction

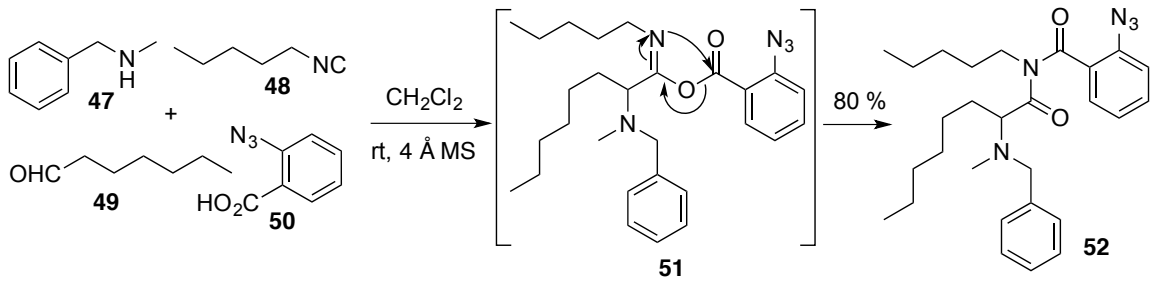
Multicomponent reactions (MCRs) are convergent processes where more than two starting materials react to form a product in a time-saving one-pot procedure thus providing exceptional synthetic efficiency. The MCRs producing α-amino amides from isonitriles have been of interest ever since the first example of this process was discovered by Ugi in 1959 (Scheme 2.1).[18] Since that time, the Ugi reaction has been extensively studied and widely used in organic synthesis[19] presumably due to one of its most salient attractions—the diversity associated with the coupling of many components.[20] The generally accepted mechanism involves an initial formation of an imimium carboxylate ion pair from an aldehyde, an amine and a carboxylic acid, followed by the subsequent nucleophilic addition of an isocyanide to the iminium, interception of the resulting nitrilium by the carboxylate and finally a Mumm rearrangement (Scheme 2.1).[21]

Scheme 2.1 Typical Ugi four component reaction and the proposed mechanism



The four-component Ugi reaction can tolerate variations in the acid component (carboxylic acids, hydrazoic acid, cyanates, thiocyanates, 2° amine salts, water, H_2S, H_2Se) and in the amine component (1° or 2° amines, hydrazines and hydroxyl amines).[19] The Ugi reaction with a 2° amine differs from that with a 1° amine in the acyl migration step (Mumm rearrangement). In 2011, Tron's group developed a four-component Ugi reaction with a 2° amine[22] based on Ugi's procedure with pre-formed enamine (Scheme 2.2).[23] In the case of a 2° amine where the amine nitrogen in the transient O-acyl imidate **51** is not able to capture the acyl group from the caboxylate, the isocyanide nitrogen serves as an acyl group acceptor providing an imide as the product in a non-nucleophilic solvent.

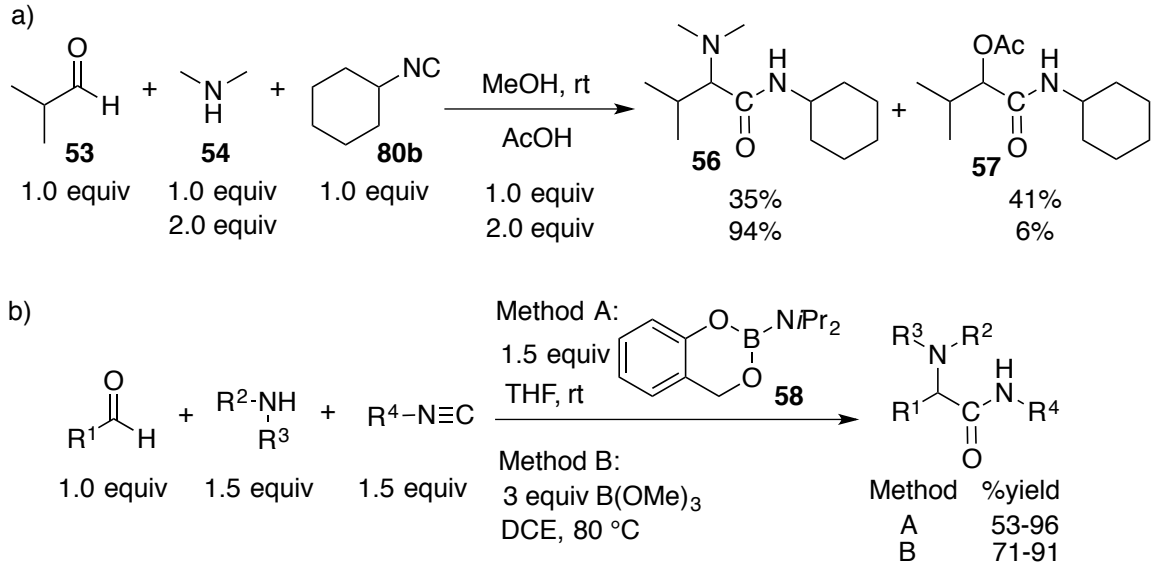
Scheme 2.2 Four-component Ugi reaction with a 2° amine



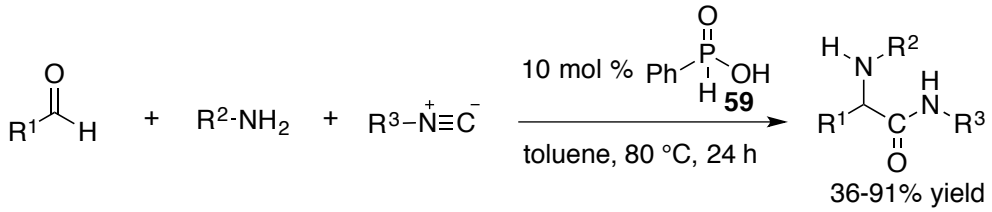
Usually the four-component Ugi reaction can proceed smoothly in the absence of a catalyst with high yield especially in protic solvents due to the activation of the imine by the acid component. A few catalysts have been developed to improve the yields of certain reactions with less reactive substrates, such as aromatic aldehydes.[24] The Ugi reaction can also be effected in the absence of the acid component in a three component fashion where the amine component can be either a 1° [25] or 2° [26] amine. Without the acid component, the

three-component Ugi reaction requires an external activator to ensure sufficient iminium formation for the following transformations. In 1963, McFarland reported a three-component Ugi reaction with the 2° amine **54** mediated by acetic acid (Scheme 2.3, a).[26a] The reaction with only one equivalent acetic acid and one equivalent of amine **54** gave the Ugi product **56** in a low yield along with a significant amount of Passerini product **57**. The yield of **56** was largely improved when the amounts of acetic acid and amine **54** were doubled. In 2007, Suginome and coworkers reported that the aminoborane **58** could serve as an iminium ion generator to facilitate the same type of transformation (Scheme 2.3, b).[26b] A variety of 2° amines, aldehydes and isocyanides were investigated in this work and most of the substrates gave the products in good to excellent yields. They later demonstrated that the same reaction could be effectively promoted by $B(OMe)_3$.[26c] All the examples described above involve an excess amount of the activators, and thus do not involve any turnover. Pan and List were recently the first to report turnover for a three-component Ugi reaction with a 1° amine and the achiral organocatalyst **59** (Scheme 2.4).[25]

Scheme 2.3 Examples of three-component Ugi reaction with 2° amine

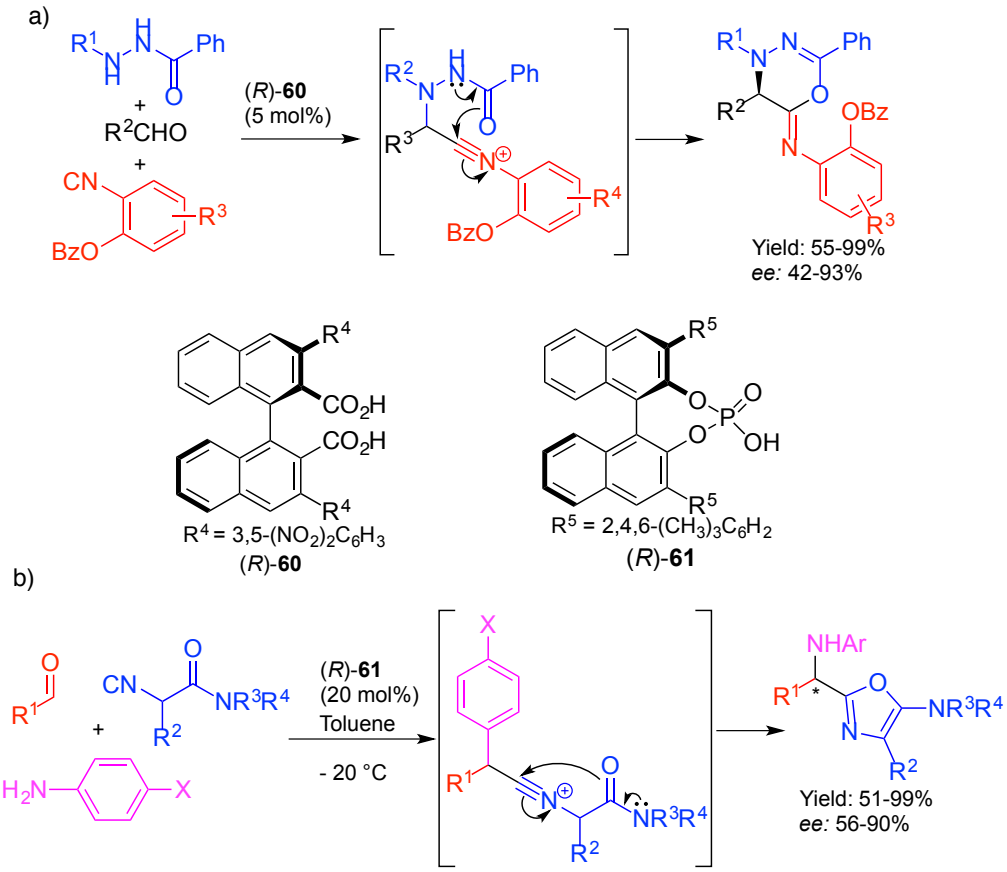


Scheme 2.4 Catalytic three-component Ugi reaction reported by List's group



Unlike the related Passerini reaction,[27] an asymmetric catalyst has yet to be reported for either the three- or four-component Ugi reaction.[19d, 20c, 26b, 28] Asymmetric catalysts have been reported for closely related Ugi-type reactions involving azomethine imines (Scheme 2.5, a)[29] and the formation of oxazoles from α-isocyanoacetamides (Scheme 2.5, b),[30] both of which involve the interception of the nitrilium ion by an amide functional group in an intramolecular fashion.

Scheme 2.5 Catalytic asymmetric Ugi-type reactions

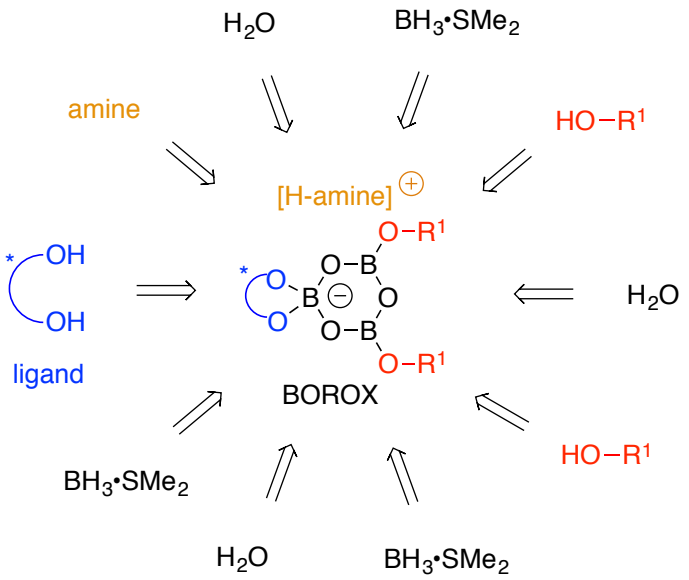


As discussed previously, the Ugi reaction is commonly thought to involve an iminium ion, which is a key intermediate in many of the reactions catalyzed by our asymmetric BOROX catalysts. Therefore, the unsolved problem of an asymmetric catalytic Ugi reaction was an attractive target for the application of the BOROX catalysts, which might provide a new approach to make chiral α-amino amides that are very important synthetic targets.[31] Since the four-component Ugi reaction has a severe background reaction mediated by the acid component, we decided to first investigate the three-component variant.

2.2 Catalyst Diversity of BOROX Catalytic System

The BOROX catalyst is typically assembled in situ from a ligand, $B(OPh)_3$ and an imine (or amine) which would produce the catalyst in Scheme 2.6 with R^1 = Ph. We have also shown that the same BOROX catalyst can be directly assembled by a molecule of an imine (or amine) from the ligand, 3 molecules of $BH_3 \cdot SMe_2$, 3 molecules of water and 2 molecules of phenol as discussed in Chapter 1. This protocol should allow for a facile diversity-oriented generation of an array of BOROX catalysts by incorporation of different ligands and different phenols or alcohols into the boroxinate core during in situ catalyst assembly (Scheme 2.6). This essentially instant access to diversity has enabled the identification of the first effective chiral catalyst for the three-component Ugi reaction.

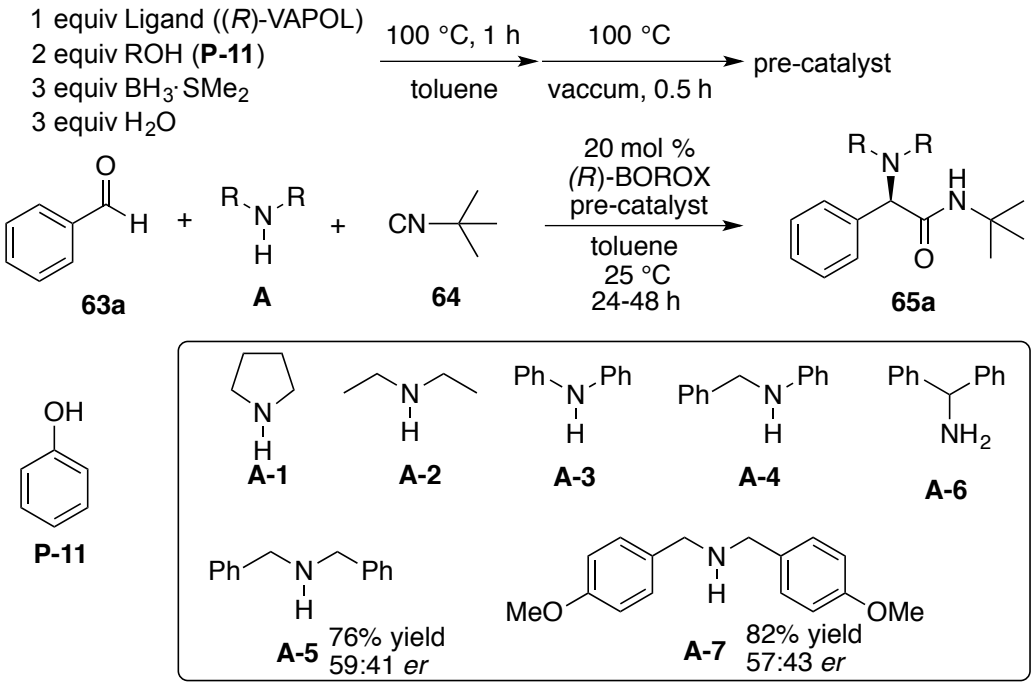
Scheme 2.6 Catalyst diversity via in situ substrate induced assembly



2.3 The Discovery and Initial Optimization of a Catalytic Asymmetric Three-Component Ugi Reaction

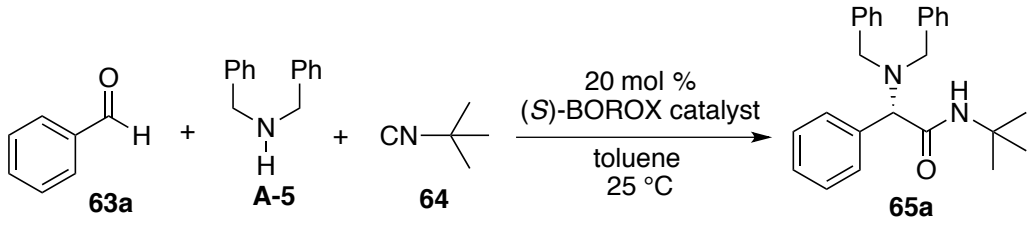
Our former group member Li Huang initiated this project and put a lot of effort into the first stage of the optimization.[32] The first encouraging result obtained by Li was with the VAPOL-BOROX catalyst prepared from PhOH (**P-11**) for the reaction of benzaldehyde **63a** with dibenzylamine **A-5** and t-butyl isonitrile **64** (Scheme 2.7). The reaction gave the α-amino amide **65a** in 76% yield with 41:59 *er*. There was no reaction at all in the same time frame without the catalyst. The 1° amine **A-6** and 2° amines including diethylamine, pyrrolidine and aniline derivatives (**A-1** to **A-4**) produced no detectable amount of product under the same conditions. The *bis*-*p*-methoxybenzylamine **A-7** gave a similar result to that obtained with **A-5**.

Scheme 2.7 Initial screen of amines with benzaldehyde and t-butyl isonitrile

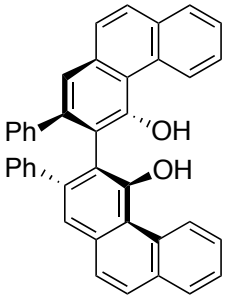


A few chiral ligands were also investigated by Li Huang (Table 2.1). The catalyst from the VANOL ligand **29** gave an even lower selectivity (entry 2). The most effective catalyst among those that are derived from the BINOL ligands **66** to **69** led to the formation of the Ugi product **65a** with 55:45 er, but with a reduced yield compared to the VAPOL catalyst (entries 3-6). The catalyst for each reaction is represented as “LAP X-Y-Z", which means it is generated from the ligand **X**, the amine **A-Y** and the phenol **P-Z**.

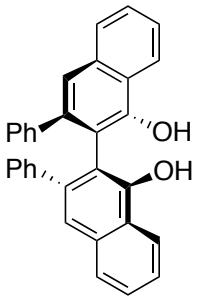
Table 2.1 Screen of VANOL and BINOL ligands



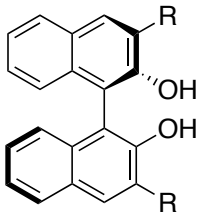
63a **A-5** **64** **65a**



30
(*S*)-VAPOL



29
(*S*)-VANOL



66 R = H (*R*)-BINOL
67 R = Br
68 R = Ph
69 R = $SiPh_3$

Entry	ligand L	amine A	phenol[b] P	catalyst #	time [h]	yield [%][c] **65a**	er[d] **65a**
1	**30**	**A-5**	**P-11**	LAP 30-5-11	24	76	59:41
2	**29**	**A-5**	**P-11**	LAP 29-5-11	36	60	53:47
3	**66**	**A-5**	**P-11**	LAP 66-5-11	40	9[h]	56:44

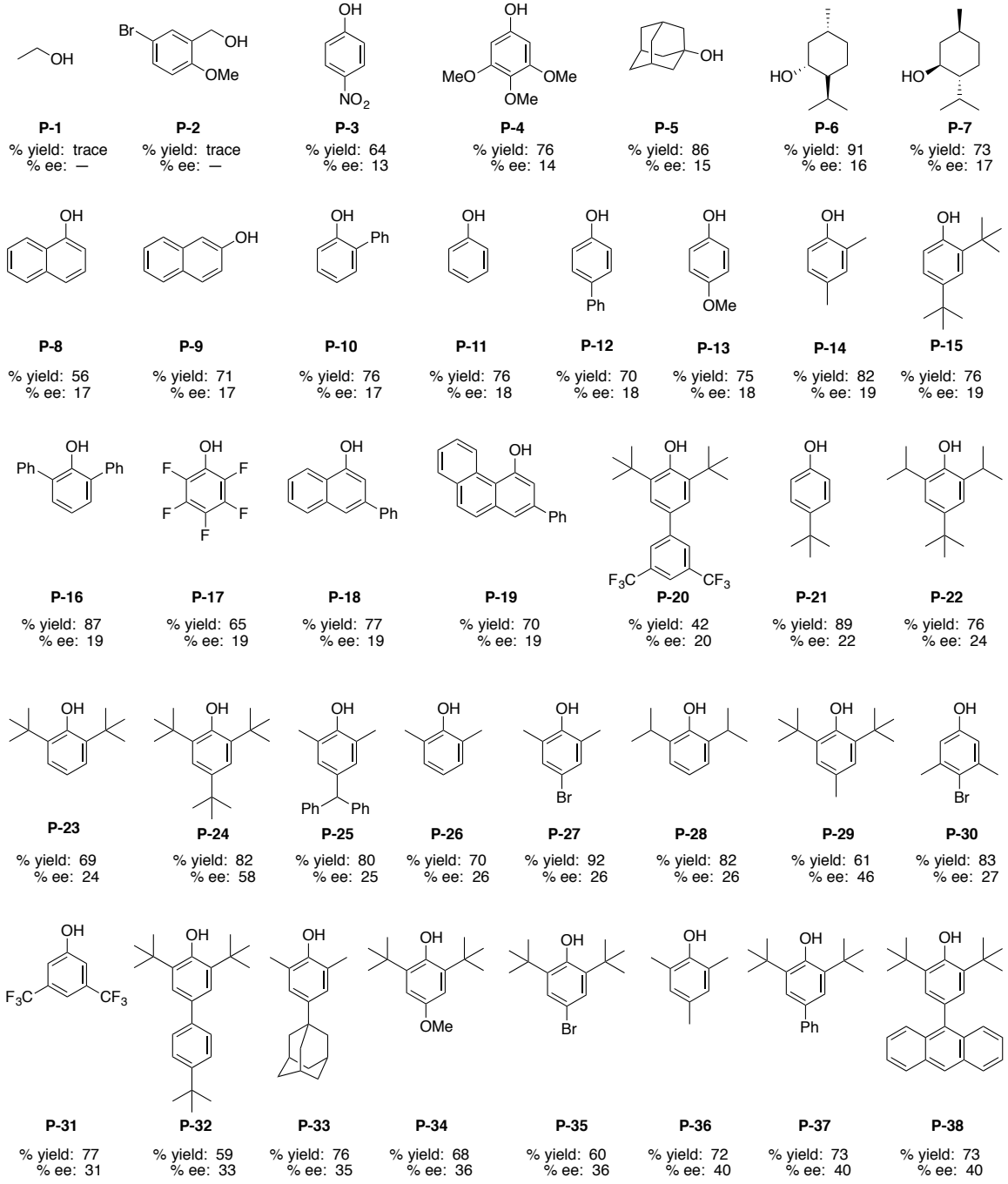
Table 2.1 (cont'd)

4	**67**	**A-5**	**P-11**	LAP 67-5-11	24	37	45:55[f]
5	**68**	**A-5**	**P-11**	LAP 68-5-11	43	30	45:55[f]
6	**69**	**A-5**	**P-11**	LAP 69-5-11	24	trace	—

[a] Unless otherwise specified, all reactions were carried out at 0.2 M in **63** (0.25 mmol) in toluene with 2.0 equiv amine and 1.5 equiv of **64** at RT for the indicated time with 20 mol % of the catalyst. The pre-catalyst was prepared by heating 20 mol % of the (*R*)-ligand, 40 mol % of the phenol or alcohol, 60 mol % H_2O, 60 mol % of $BH_3 \cdot SMe_2$ in toluene at 100 °C for 1 h. After removal of all volatiles, the BOROX catalyst was generated in situ by the addition of the amine at rt and this was followed by the addition of aldehyde and then the isonitrile. [c] Isolated yield after chromatography on silica gel. nd = not detected. [d] Determined by HPLC. [f] Catalyst was generated from (*R*)-ligand. [h] ^1H NMR yield with internal standard.

Additionally, many other alcohol and phenol derivatives were screened by Li Huang for the preparation of different VAPOL-BOROX catalysts, among which the 2,4,6-tri-t-butylphenol **P-24** gave the best result, i.e., 82% yield with 58% *ee* (Figure 2.1). The electronic nature of the phenol does not have a significant effect on the asymmetric induction (**P-3** vs **P-13**). Essentially the same induction was observed with 3° and 2° alcohols as with phenol **P-11**, but the use of ethanol stopped the reaction (**P-5**, **P-6**, **P-1**). Also, the use of either (–)-menthol (**P-6**) or (+)-menthol (**P-7**) gave the product with the same sense of chirality, which indicates that auxiliary chiral centers may not be a useful method for selectivity modification.

Figure 2.1 Screen of different phenols and alcohols



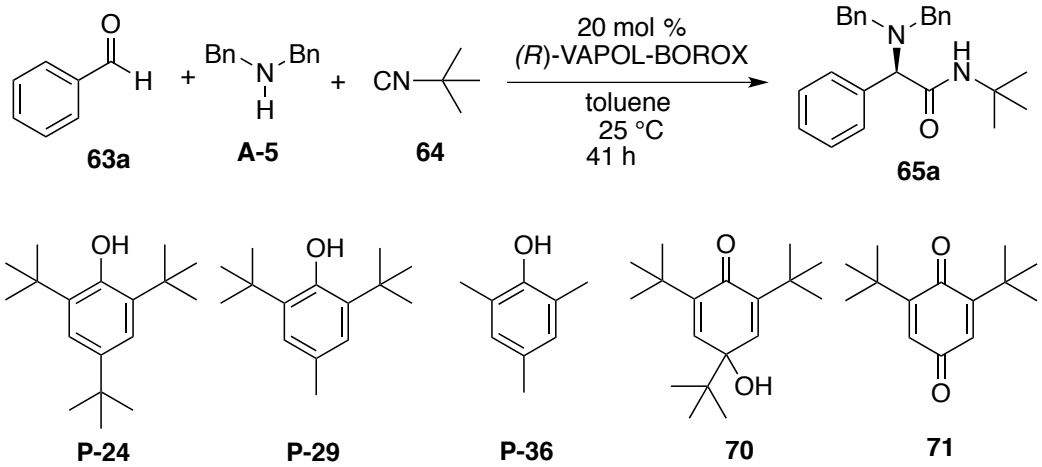
2.4 The Early Impediments to the Further Optimization

At this point, I took over this project to further optimize the asymmetric catalytic three-component Ugi reaction. Firstly, the reactions with several

selected phenols were repeated (Table 2.2). All the phenols were carefully purified before they were used in the experiments. Unexpectedly, the result with the optimal phenol **P-24** could not be reproduced (entry 1, compared to Li's result in Figure 2.1: 58% *ee*). The enantioselectivity varies with different trials. After all of the reaction parameters were systematically probed, evidence showed that the variability of the results could be traced to phenol **P-24**. The phenol sample that was stored for a long time was slightly greenish yellow, with which the product was obtained with 36-49% ee (entry 2); but if it was purified by sublimation or crystallization to give absolutely pure white material, the ee was only 24% (entry 1). Thus, an impurity was assumed to be responsible for the originally observed 58% ee. It was hypothesized that the impurity resulted in a more efficient assembly of the catalyst. With great efforts, two impurities **70** and **71** were isolated and identified from a large quantity of colored phenol sample. Reactions with both **70** and **71** gave better selectivities than pure **P-24** (entry 3-4), but still not close to the original result, 58% *ee*. Reactions with impurity/**P-24** mixtures were also investigated, which gave similar results to those of **P-24** (entry 5-6).

Since the reaction with **P-24** did not produce a desirable result, we turned our attention to phenol **P-29** that gave second highest enantioselectivity (Figure 2.1, 46% *ee*) in the Ugi reaction. Again, the enantioselectivity of reactions with phenol **P-29** could not be reproduced and low asymmetric inductions were observed (Table 2.2, entry 7). Luckily, it was found that phenol **P-36,** which gave the most selective BOROX catalyst among the rest of the phenols, gave very reproducible results. Thus, **P-36** was the choice for further optimization.

Table 2.2 Reactions with selected phenols and impurities from **P-24**



63a **A-5** **64** **65a** **P-24** **P-29** **P-36** **70** **71**

Entry	Phenol or quinone[b]	yield [%][c] **65a**	%*ee*[d] **65a**
1	**P-24** (white)	48	24[e]
2	**P-24** (yellow)	81-88	36-49[f]
3	**70**	68	31
4	**71**	76	34
5	**70/P-24** (1:1)	54	27
6	**71/P-24** (1:15)	65	26
7	**P-29**	50	26[g]
8	**P-36**	87	40[g]

[a] Unless otherwise specified, all reactions were carried out at 0.2 M in **63a** (0.25 mmol) in toluene with 2.0 equiv amine and 1.5 equiv of **64** at RT for the indicated time with 20 mol % of the catalyst. The pre-catalyst was prepared by heating 20 mol % of the (*R*)-ligand, 40 mol % of the phenol or alcohol, 60 mol % H_2O, 60 mol % of $BH_3 \cdot SMe_2$ in toluene at 100 °C for 1 h. After removal of all volatiles, the BOROX catalyst was generated in-situ by the addition of the amine at rt and this was followed by the addition of aldehyde and then the isonitrile. [c] Isolated yield after chromatography on silica gel. nd = not detected.

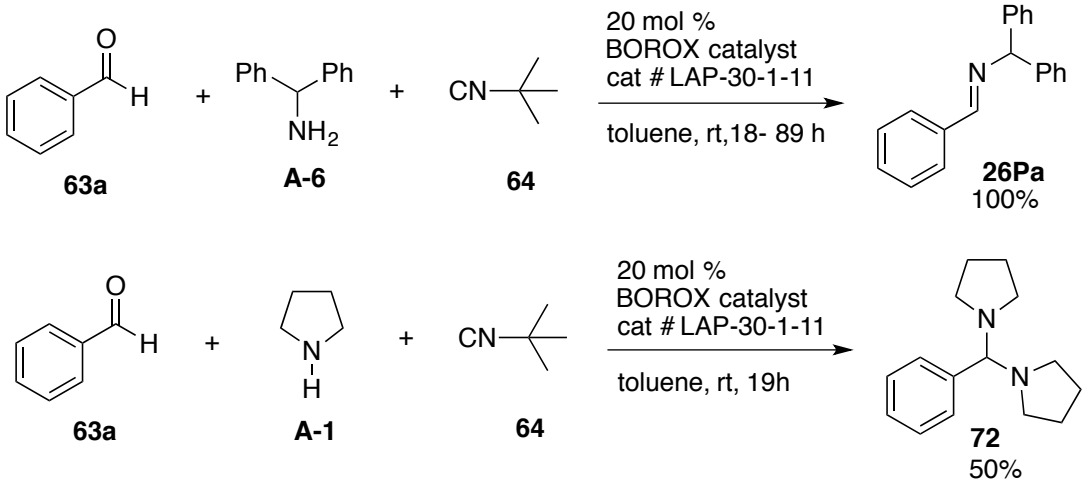
Table 2.2 (cont'd)

[d] Determined by HPLC. [e] Average of six runs. [f] Results from six runs. [g] Average of four runs.

2.5 Revisit of the Ugi Reactions with Amines A-1 and A-6

As shown previously (Scheme 2.7), dibenzylamines were the only class of amines that gave the desired Ugi product. To get some insight about the failures of other amines, the reactions with 1° amine **A-6** and 2° amine **A-1** were re-examined more closely with the BOROX catalyst derived from phenol **P-11** and the VAPOL ligand **30**. It was found that the primary amine **A-6** only led to the formation of imine **26Pa** in quantitative yield (Scheme 2.8), and in the case of amine **A-1**, the only identifiable compound present other than starting materials was the aminal **72** (50%, Scheme 2.8). Heating the mixture containing **72** at 80 °C for 18 h resulted in a complex mixture with **65a** still not detectable.

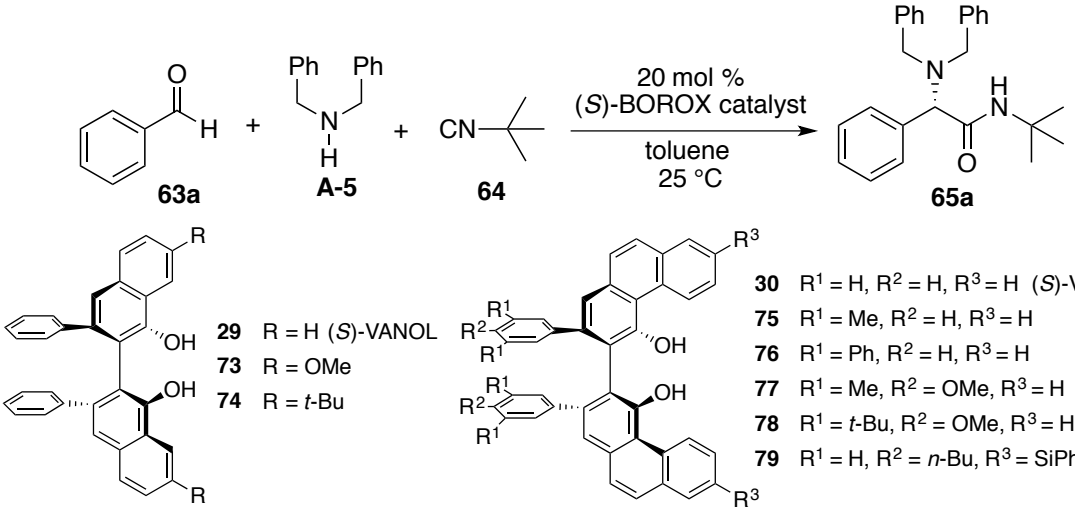
Scheme 2.8 Attempted Ugi reactions with amines **A-1** and **A-6**



2.6 Variation of the Catalysts with Different Chiral Ligands

A series of BOROX catalysts containing 2,4,6-trimethylphenol **P-36** were then generated from a series of newly prepared VANOL and VAPOL ligands. Catalysts prepared from **P-36** and the 7,7'-disubstituted VANOL derivatives **73** and **74** were hardly any more selective (entries 4 and 5) than those from the parent VANOL ligand which gave essentially racemic material (entry 3).[33] The substituted VAPOL ligands **75** to **79**, however, were generally significantly more selective than the parent VAPOL ligand. The optimal BOROX catalyst is obtained from the VAPOL derivative **78** which gave an er of 85:15 (entry 9). The asymmetric synergism between the ligand and phenol components was revealed by the fact that while the substituted VAPOL ligand **78** gave just a skosh of improvement in induction over VAPOL with phenol **P-11** (entries 11 vs 1), a much greater increase in enantioselectivity was observed when **78** was used instead of VAPOL with **P-36** (entries 11 vs 9).

Table 2.3 Synergism in the arrangement of the substituents in the boroxinate core [a]



Entry	ligand	phenol/ alcohol	catalyst #	time [h]	yield [%][b] **65a**	er[c] **65a**
1	**30**	**P-11**	LAP 30-5-11	24	76	59:41
2	**30**	**P-36**	LAP 30-5-36	36	72	70:30
3	**29**	**P-36**	LAP 29-5-36	39	52	49:51[d]
4	**73**	**P-36**	LAP 73-5-36	42	62	54:46
5	**74**	**P-36**	LAP 74-5-36	45	62	52:48
6	**75**	**P-36**	LAP 75-5-36	39	89	74:26
7	**76**	**P-36**	LAP 76-5-36	39	64	35:65[d]
8	**77**	**P-36**	LAP 77-5-36	39	93	74:26
9	**78**	**P-36**	LAP 78-5-36	39	94	15:85[d]
10	**79**	**P-36**	LAP 79-5-36	42	90	71:29
11	**78**	**P-11**	LAP 78-5-11	39	74	62:38[e]
12	**78**	**P-26**	LAP 78-5-26	39	93	78:22[e]

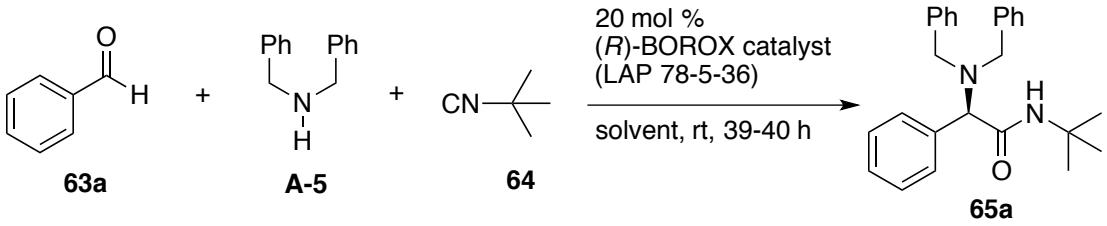
Table 2.3 (cont'd)

[a] Unless otherwise specified, all reactions were carried out at 0.2 M in **63a** (0.25 mmol) in toluene with 2.0 equiv amine and 1.5 equiv of **64** at RT for the indicated time with 20 mol % of the catalyst. The catalyst was made from the (*S*)-enantiomer of the ligand (≥99% ee) according to the procedure in Table 2.1. [b] Isolated yield after chromatography on silica gel. [c] Determined by HPLC. [d] Catalyst generated from (*R*)-ligand. [e] The ligand for this run was 97% ee.

2.7 Study of Solvent Effect on the BOROX Catalyst

At this point a solvent screen was performed on the optimal catalyst prepared from the substituted VAPOL ligand **78** and the 2,4,6-trimethyphenol **P-36** (Table 2.4). The reactions carried out in non-polar solvents gave good aymmetric inductions (entry 1-5). The induction dropped dramatically with polar coordinating solvents such as THF and acetonitrile (entry 6-7) which is consistent with an ion-pair mechanism that will be discussed later. The electrostatic interactions between the anionic BOROX catalyst and cationic intermediate would be expected to decrease in polar solvents, resulting in a loose ion pair and a loss in stereoselectivity. The optimal solvent was found to be mesitylene (Table 2.4, entry 3) and all further optimizations were performed in this solvent.

Table 2.4. Solvent effect on the three-component Ugi reaction.



63a **A-5** **64** **65a**

Entry[a]	Solvent	%Yield[c] **65a**	*er* **65a**
1	toluene	94	85:15
2	m-xylene	92	86:14
3	mesitylene	91	88:12
4[b]	1,3,5-triisopropyl benzene	90	13:87
5	CCl_4	90	86:14
6	THF	77	54:46
7	CH_3CN	26	64:36

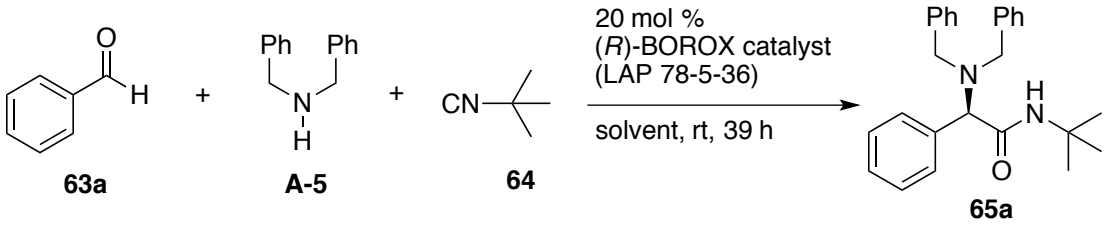
[a] Unless otherwise specified, all reactions were carried out at 0.2 M in **63a** (0.25 mmol) in toluene with 2.0 equiv amine and 1.5 equiv of **64** at RT for the indicated time with 20 mol % of the catalyst. The catalyst was made from phenol **P-36** and the ligand (*R*)-**78** (≥99% ee) according to the procedure in Table 2.1. [b] Catalyst was generated from (*S*)-**78** (97% *ee*). [c] Isolated yield after chromatography on silica gel.

2.8 Effects of Concentration and Amine Stoichiometry on the Three-Component Ugi Reaction

The three-component Ugi reaction operates efficiently with almost no change in the enantioselectivity within the concentration range of 0.1 M to 0.4 M (Table 2.5, entries 2-4). However, a decrease in the concentration from 0.1 M to

0.05 M leads to a drop in both the enantioselectivity and the yield (Table 2.5, entries 1-2). The stoichiometry of the amine does not seem to have a big impact on the reaction with the yields and inductions falling only slightly in the range of 2.0 to 1.02 equivalents (entries 6-8).

Table 2.5 Ugi-3CR with different concentrations and equivalents of amine



63a **A-5** **64** **65a**

Entry[a]	Amine equivalents	Concentration (M)	%Yield[b] **65a**	*er* **65a**
1	2.00	0.05	53	77:23
2	2.00	0.1	89	86:14
3	2.00	0.2	92	87:13
4	2.00	0.4	93	87:13
5	1.20	0.2	86	86:14
6	1.02	0.2	75	84:16

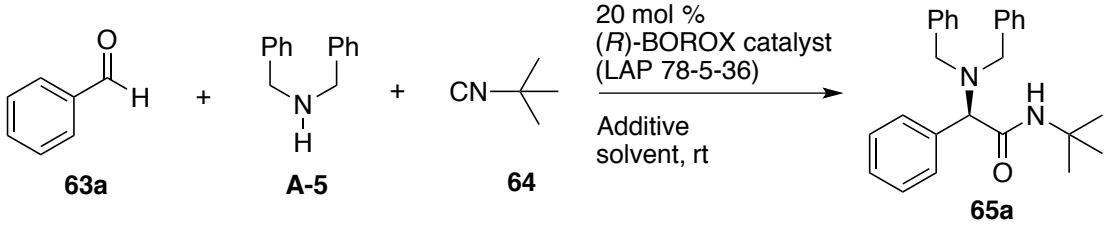
[a] The general procedure described in Table 2.1 was followed with (*S*)-**78** ligand (41.5 mg, 0.0504 mmol, 97% *ee*), phenol **P-36** (14 mg, 0.10 mmol), amine **A-5** (0.05-0.1 mL) and mesitylene (0.45-5.0 mL) as the reaction solvent with a reaction time of 39 h. [b] Isolated yield after chromatography on silica gel.

2.9 Effects of Different Additives in the Catalytic System

We have explored the effects of several different additives, including H_2O, molecular sieves and the salt $Mg(ClO_4)_2$. In one possible mechanism for the three-component Ugi reaction, the hemiaminal formed from the aldehyde and

dibenzylamine (Scheme 2.12, **87**) loses a molecule of H_2O which can trap the nitrilium cation (Scheme 2.12, **86**) to form the product **65**. Thus, we would like to test the effect of free H_2O on the reaction. We also investigated the salt $Mg(ClO_4)_2$ as an additive to the reaction, since our former group member Li Huang found that it improved the asymmetric induction of the same reaction catalyzed by a different BOROX catalyst.[34] The results are shown in Table 2.6 and the reaction progressions for entries 1-6 are plotted in Figures 2.3 and 2.4. Most of the additives tested have either adverse effects or no effects on the reaction. The presence of a small amount of H_2O or $MgClO_4$ was detrimental to both the enantioselectivity and the yield. The reaction with 1.0 equivalent of H_2O gave the product in only 9% yield after 91 hours with hardly any selectivity. It was found that the reaction could be accelerated a bit by the proper amount of 4Å MS (Figure 2.3), with the enantioselectivity almost unchanged (Table 2.6, entries 5-7).

Table 2.6 The effects of different additives on the three-component Ugi reaction



63a + **A-5** + **64** → **65a**

Entry[a]	Solvent	Additive/Amount	Time (h)	%Yield[b] **65a**	*er* **65a**
1	toluene	none	39	94[c]	85:15
2	d_8-toluene	H_2O/100 mol %	91	8.6	59:41

Table 2.6 (cont'd)

3	d_8-toluene	H_2O/50 mol %	91	17.3	61:39
4[d]	d_8-toluene	H_2O/20 mol %	88	78	24:76
5	d_8-toluene	4Å MS/13 mg	18.3	83	85:15
6	d_8-toluene	4Å MS/6 mg	18.3	80	85:15
7	mesitylene	none	39	89[c]	87:13
8	mesitylene	5Å MS/13 mg	39	80[c]	87:13
9	mesitylene	$Mg(ClO_4)_2$/20 mol %	39	15[c]	65:35

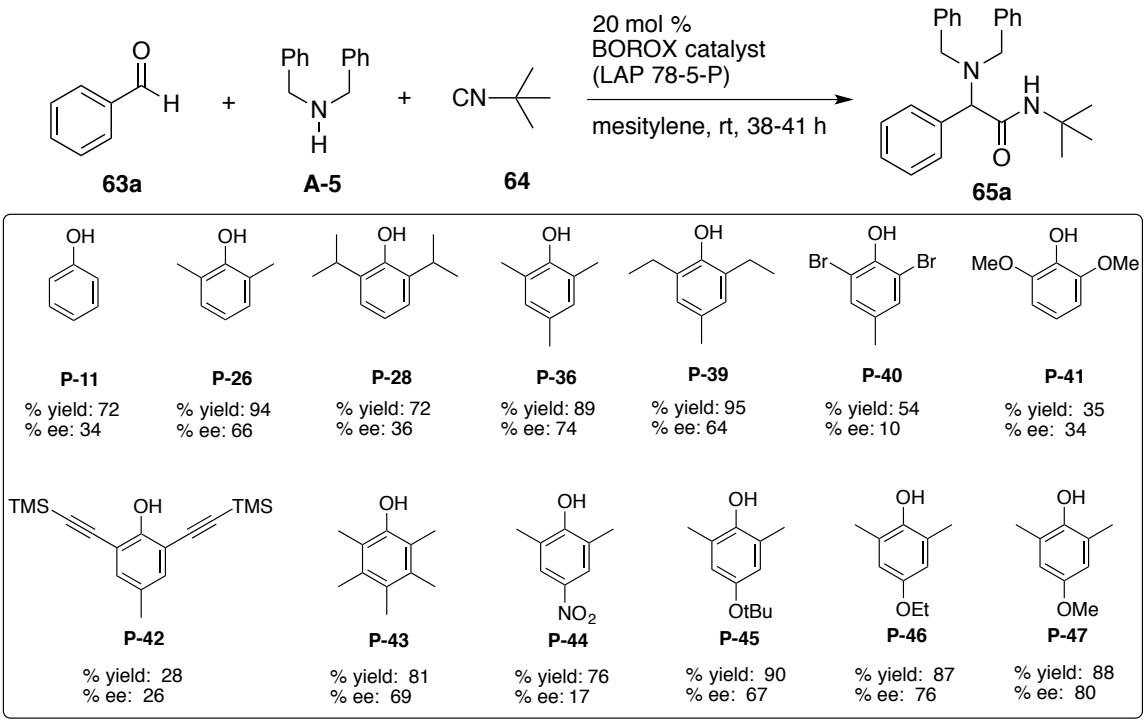
[a] The general procedure described in Table 2.1 was followed with ligand (*R*)-**78** (41.5 mg, 0.0504 mmol, 97% *ee*) and phenol **P-36** (14 mg, 0.10 mmol); The additive was added after the addition of benzaldehyde **63a**. [b] ^{1}H NMR yield with Ph_3CH as an internal standard. [c] Isolated yield after chromatography on silica gel. [d] Catalyst was generated from ligand (*S*)-**78**.

2.10 Variation of the Catalysts by Incorporating Different Alcohols and Phenols

With the identification of the VAPOL derivative **78** as the optimal ligand, a final screen of this ligand and 13 different phenols was performed in mesitylene (Scheme 2.9). The optimal phenol was found to be the 2,6-dimethyl-4-methoxy phenol **P-47** and the resultant catalyst (LAP 78-5-47) gave **65a** with a 90:10 enantiomeric ratio in a total of 88% yield. In contrast to the VAPOL derived catalysts which are insensitive to the electronic nature of the phenol (Figure 2.1, **P-3**, **P-11**, **P-13**), the catalysts derived from the VAPOL derivative **78** are quite sensitive (Scheme 2.9, **P-36**, **P-44**, **P-47**). The induction slightly increased when

the *p*-methyl group in **P-36** was replaced by a methoxyl group (**P-47**) and dramatically dropped when it was replaced with a nitro group (**P-44**). This is consistent with an ion-pair mechanism in which the strength of the electrostatic attraction is important for the asymmetric induction (see Scheme 2.12).

Scheme 2.9 Screen of additional phenol substituents in the boroxinate core with ligand **78**

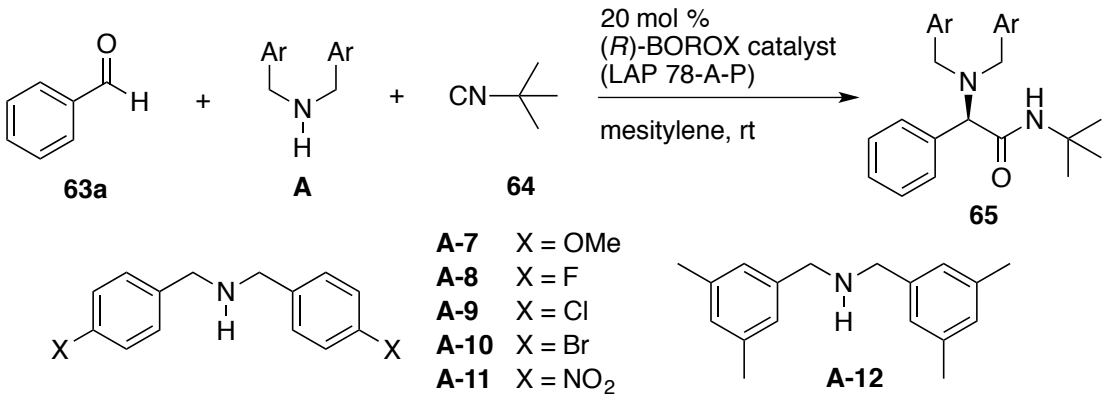


2.11 Study of the Reactivities of Different Dibenzylamine Derivatives.

Based on our experiences with other BOROX-catalyzed systems, the substituent on the amine or imine nitrogen has a great effect on the reaction results. Since dibenzylamines are the only class of amines that work in the three component Ugi reaction, we screened several substituted dibenzylamines (Table 2.7). Most of these dibenzylamines gave high selectivities (87:13 to 90:10 entries 2-5). The *p*-nitro substituted dibenzylamine **A-11** gave a dramatic drop in the

yield and induction (entry 6) and this could be attributed to destabilization of the iminium ion formed from the aldehyde and the amine. A large decrease in both yield and enantioselectivity was also observed when **A-5** was replaced with the 3,5-disubstituted amine **A-12**, which was probably caused by steric effects in the transition state.

Table 2.7 Screen of substituted dibenzyl amines with ligand **78**[a]



Entry	Amine A	Phenol P	catalyst #	time [h]	yield [%][b] **65**	er[c] **65**
1	**A-5**	**P-47**	LAP 78-5-47	38	91	90:10[g,h]
2	**A-7**	**P-47**	LAP 78-7-47	24	91	88:12
3	**A-8**	**P-47**	LAP 78-8-47	24	85	90:10
4	**A-9**	**P-47**	LAP 78-9-47	24	80	88:12
5	**A-10**	**P-47**	LAP 78-10-47	24	79	87:13
6	**A-11**	**P-47**	LAP 78-11-47	24	22	73:27
7	**A-12**	**P-36**	LAP 78-12-36	39	65	39:61[d]
8	**A-5**	**P-36**	LAP 78-5-36	39	89	13:87[d]

Table 2.7 (cont'd)

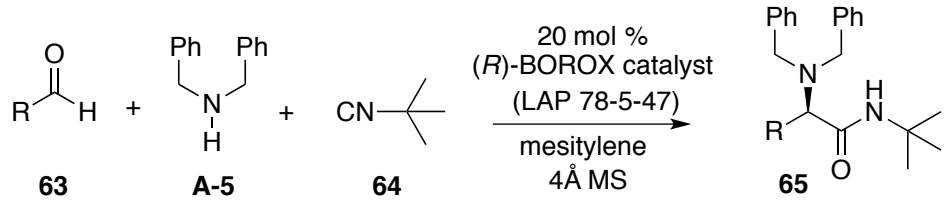
[a] Unless otherwise specified, all reactions were carried out at 0.2 M in **63a** (0.25 mmol) in mesitylene with 2.0 equiv amine and 1.5 equiv of **64** at RT for the indicated time with 20 mol % of the catalyst. Entries 2-6 were carried out in the presence of 4Å molecular sieves. The catalyst was prepared according to the procedure in Table 2.1 with (*R*)-**78** unless otherwise specified. Ligand (*R*)-**78** was >99% ee. [b] Isolated yield after chromatography on silica gel. [c] Determined by HPLC. [d] Catalyst generated from (*S*)-**78**, 97% ee**.** [g] The er was 89:11 when (*S*)-**78** was 97% ee. [h] The yield was 86% after 24 h.

2.12 Substrate Scope of Different Aryl Aldehydes at Both RT and 0 °C

Having established the most effective combination of the all of the parts in the boroxinate catalyst, an evaluation of different aryl aldehydes in the Ugi reaction was undertaken with amine **A-5** and the results are presented in Table 2.8. Most of the substrates reacted to give α-amino amides with enantiomeric ratios of 90:10 to 95:5 including aryl aldehydes with both electron-withdrawing and electron-donating groups. The reaction of cyclohexane carboxaldehyde gave racemic product (47%) and this result will require further examination (not shown in Table 2.8). The reactions in Table 2.8 were performed in the presence of 4 Å molecular sieves, whereas most of the previous reactions in this work were without the sieves. The sieves have essentially no effect on the induction but do seem to accelerate the reaction slightly (Figures 2.3 and 2.4). The rate is slower at 0°C than at 25 °C but the inductions are not substantially different. In many cases the α-amino amide **65** can be crystallized and a few examples are shown where the er can be often enhanced to >99.5:0.5. The ligand **78** can also be recovered from these reactions in high yield (~90%) with no loss in enantiomeric

purity (>99.5:0.5). The reaction can be extended to heterocyclic aldehydes as illustrated by the reaction with pyridine carboxaldehydes. 3-Pyrridyl carboxaldehyde is the most reactive, and the 4-pyrridyl isomer reacts slowly (entries 27 & 28) and the 2-pyrridyl isomer is unreactive (not shown). The reaction with salicylaldehyde **63r** did not provide the desired product **65**. Instead, compound **93** was obtained in 22% yield as a result of an intramolecular interception of the nitrilium cation by the 2-hydroxyl group in **93** (Scheme 2.10).

Table 2.8 Substrate scope of the catalytic asymmetric 3-component Ugi reaction [a]



63 **A-5** **64** **65**

Entry	series	R	time [h]	temp [°C]	yield [%][b] **65**	*er*[c] **65**
1	a	C_6H_5	7	40	87[e]	86:14
2[d]	a	C_6H_5	24	25	86 (71)	90:10 (>99.5:0.5)
3	a	C_6H_5	66	0	75	92:8
4[f]	b	4-$NO_2C_6H_4$	24	25	83	93:7
5[f]	b	4-$NO_2C_6H_4$	66	0	51[e]	92:8
6	c	4-$CF_3C_6H_4$	24	25	85	91:9
7	d	4-BrC_6H_4	24	25	85	93:7
8	d	4-BrC_6H_4	48	0	65[g]	95:5
9[f]	d	4-BrC_6H_4	48	0	75[h,i]	95:5

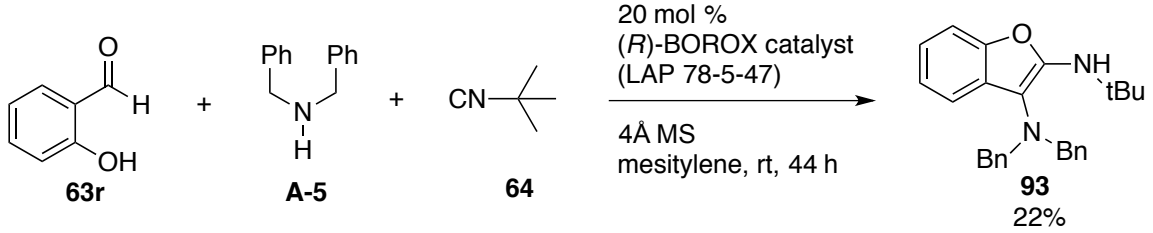
Table 2.8 (cont'd)

10[f]	e	3-BrC_6H_4	22	25	82	93:7
11	e	3-BrC_6H_4	66	0	66[h]	92:8
12	f	3,4-$Cl_2C_6H_3$	24	25	85	94:6
13	f	3,4-$Cl_2C_6H_3$	66	0	54[e]	95:5
14	g	4-FC_6H_4	24	25	87[e]	91:9
15	g	4-FC_6H_4	67	0	62	94:6
16	h	4-$MeO_2CC_6H_4$	24	25	80	93:7
17[f]	h	4-$MeO_2CC_6H_4$	67	0	62	93:7
18	i	4-$AcOC_6H_4$	24	25	86	85:15
19	j	4-$AcNHC_6H_4$	24	25	77 (47)	85:15 (96:4)
20[f]	k	4-MeC_6H_4	24	25	84 (47)	91:9 (>99.5:0.5)
21	k	4-MeC_6H_4	66	0	80[e]	92:8
22	l	2-MeC_6H_4	24	25	76 (56)	78:22 (>99:1)
23	m	4-*t*-BuC_6H_4	24	25	83	84:16
24	n	4-$MeOC_6H_4$	40	25	84[j]	88:12
25	n	4-$MeOC_6H_4$	24	25	70	89:11
26	n	4-$MeOC_6H_4$	24	0	51	92:8
27	o	3-pyridyl	25	25	80 (61)	90:10 (>99:1)
28	p	4-pyridyl	70	25	66	89:11

Table 2.8 (cont'd)

[a] Unless otherwise specified, all reactions were carried out at 0.2 M in **63a** (0.25 mmol) in mesitylene with 2.0 equiv amine and 1.5 equiv of **64** at RT in the presence of 4Å MS for the indicated time with 20 mol % of the catalyst. The catalyst was made from the (*R*)-enantiomer of the ligand (≥99% ee) according to the procedure in Table 1. [b] Isolated yield after chromatography on silica gel. Yield in paranthesis is % recovery of the first crop after crystallization. [c] Determined by HPLC. The er in parentheses is of the first crop. [d] Average of 4 runs. [e] ^{1}H NMR yield with internal standard (Ph_3CH). [f] Average of 2 runs. [g] Yield was 46% after 24 h. [h] Reaction at 0.4 M. [i] Yield was 76% after 66 h. The yield was 60% after 66 h in the absence of 4Å MS. [j] Run in the absence of 4Å MS.

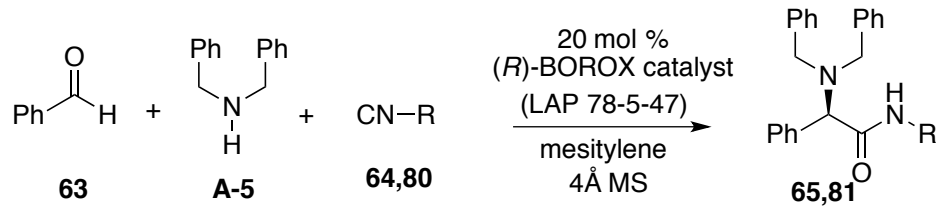
Scheme 2.10 Intramolecular interception of the nitrilium cation



2.13 Substrate Scope of Different Isocyanides at RT

Although *t*-butylisonitrile (**64**) was the optimal isonitrile, a number of other isonitriles (**80a-f**) were effective with inductions ranging from 51:49 to 88:12 under the conditions in Table 2.9. Reactions with tertiary alkyl and aromatic isonitriles gave high asymmetric inductions, although the yields varied in different cases. It seemed that the isonitriles with larger substituents proceeded slower and gave lower yields (entries 1 vs 2, entries 6 vs 7). There was a big drop in the selectivity when a 2° alkyl isonitrile was used (entry 3). Reactions with primary isonitriles gave the product in moderate yields, but with almost no selectivities (entries 4 and 5).

Table 2.9 Ugi-3CR with different isocyanides



63 **A-5** **64,80** **65,81**

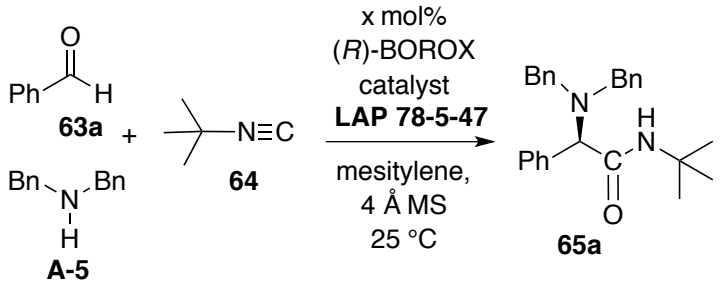
Entry	Isocyanide	R	Time (h)	%Yield[a]	*er*
1	**64**	*t*-Bu	24	86	90:10
2	**80a**	1,1,3,3-tetramethylbutyl	68	55	87:13
3	**80b**	Cy	24	75	67:33
4	**80c**	*n*-Bu	39	48	52:48
5	**80d**	Bn	29	46	51:49
6	**80e**	2,6-diMeC_6H_3	44	29	85:15
7	**80f**	4-$MeOC_6H_4$	24	65	88:12

[a] Isolated yield after chromatography on silica gel.

2.14 Studies of Catalyst Loading

The catalyst loading can be reduced to 10 mol% with no significant drop in yield or induction if molecular sieves are employed (Table 2.10). The er drops from 90:10 to 87:13 when the loading is reduced from 20 to 10 mol%. Both the 90:10 and the 87:13 mixture can be enhanced to an er of >99.5:0.5 by crystallization with 70-71% recovery for the first crop. When there are no molecular sieves present, the changes in catalyst loading has a much larger effect on both reaction rate and enantioselectivity. The yield of **65a** with 5 mol% catalyst was 62% after 73 h (er = 74:26) with sieves and 7% without sieves.

Table 2.10 Effect of molecular sieves on catalyst loading

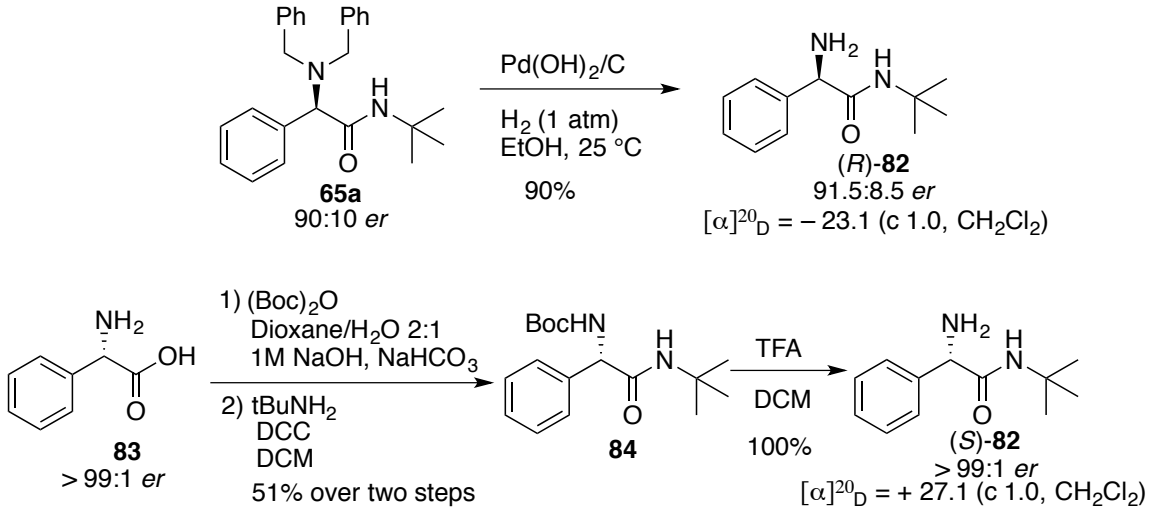


Entry	Cat Loading mol%	Sieves	Time (h)	%Yield **65a**	*er*	% yield **65a** first crop	er **65a** first crop
1	20	yes	23	86	90:10	71	>99.5:0.5
2	10	yes	30	83	87:13	70	>99.5:0.5
3	5	yes	73	62	74:26	–	
4	20	no	38	88	90:10	–	
5	10	no	50	68	71:29	–	
6	5	no	73	7	nd	–	

2.15 Determination of the Absolute Configuration of the Ugi Product 65a

The absolute configuration of the Ugi product **65a** was determined by removal of the benzyl groups to give the α-amino amide (*R*)-**82** whose optical rotation and er were compared to those of an authentic sample prepared from (*S*)-phenyl glycine **83** (Scheme 2.11). The other α-amino amides in Table 2.8 were assumed to be homo-chiral with **65a**.

Scheme 2.11 Determination of absolute stereochemistry of **65a**



2.16 Reaction Progress Monitored by ^{1}H NMR Spectroscopy

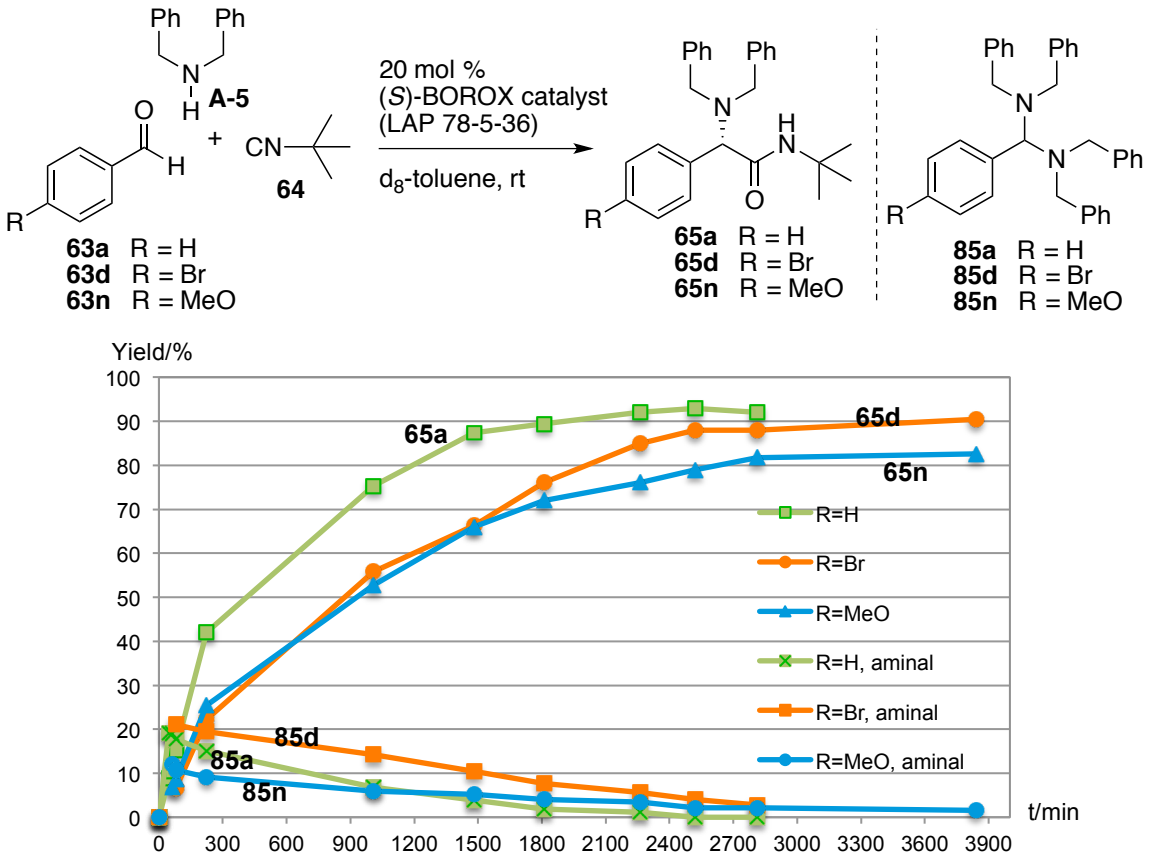
Several sets of Ugi three-component reactions were monitored by ^{1}H NMR spectroscopy to gain more insight into the factors that contribute to the reaction rate and outcome. Reactions with three different aromatic aldehydes and reactions with different amount of added H_2O or 4 Å MS were investigated.

2.16.1 Ugi-3CR with Different Aldehydes.

We first investigated the reaction with benzaldehyde **63a**, and two *p*-substituted benzaldehydes, one electron poor (**63d**) and one electron rich (**63n**). The ^{1}H NMR spectra were taken at certain intervals and the amount of the corresponding product **65** was calculated based on the ^{1}H NMR integration against Ph_3CH as an internal standard (Figure 2.2). Aminal **85** was identified as one of the components in the reaction mixture. It was found that once all the three components were mixed together, there was a 10-20% formation of the aminal **85**, which was slowly converted to the Ugi product as the reaction

proceeded. The reaction with benzaldehyde was slightly faster than its p-substituted analogs.

Figure 2.2 ^{1}H NMR study of the Ugi-3CR with aldehydes **63a**, **63d** and **63n**



2.16.2 Reaction Progress of Ugi-3CR of 63a with Different Amounts of 4Å MS or H_2O as An Additive

Reactions of different amounts of 4Å MS or H_2O were carried out under the same condition as that was shown in Figure 2.2 and monitored by ^{1}H NMR spectroscopy. As shown in Figure 2.3, 4 Å MS does have some effect in bringing the reaction to the ultimate yield in a slightly shorter time (6 and 13 mg 4 Å MS). However, too much sieves will diminish the yield, which is revealed by the reaction with 60 mg 4 Å MS. The sieves have essentially no effect on the

asymmetric induction (see Table 2.6). The results shown in Figure 2.4 reveal that the addition of H_2O will slow down the reaction and diminish the ultimate yield. It was also found that the reactions with H_2O as an additive gave lower asymmetric inductions than those without H_2O (Table 2.6). The formation of aminal **85a** was observed but not plotted for reactions shown in Figure 2.4.

Figure 2.3 ^{1}H NMR study of the Ugi-3CR of **63a** with different amounts of 4Å MS

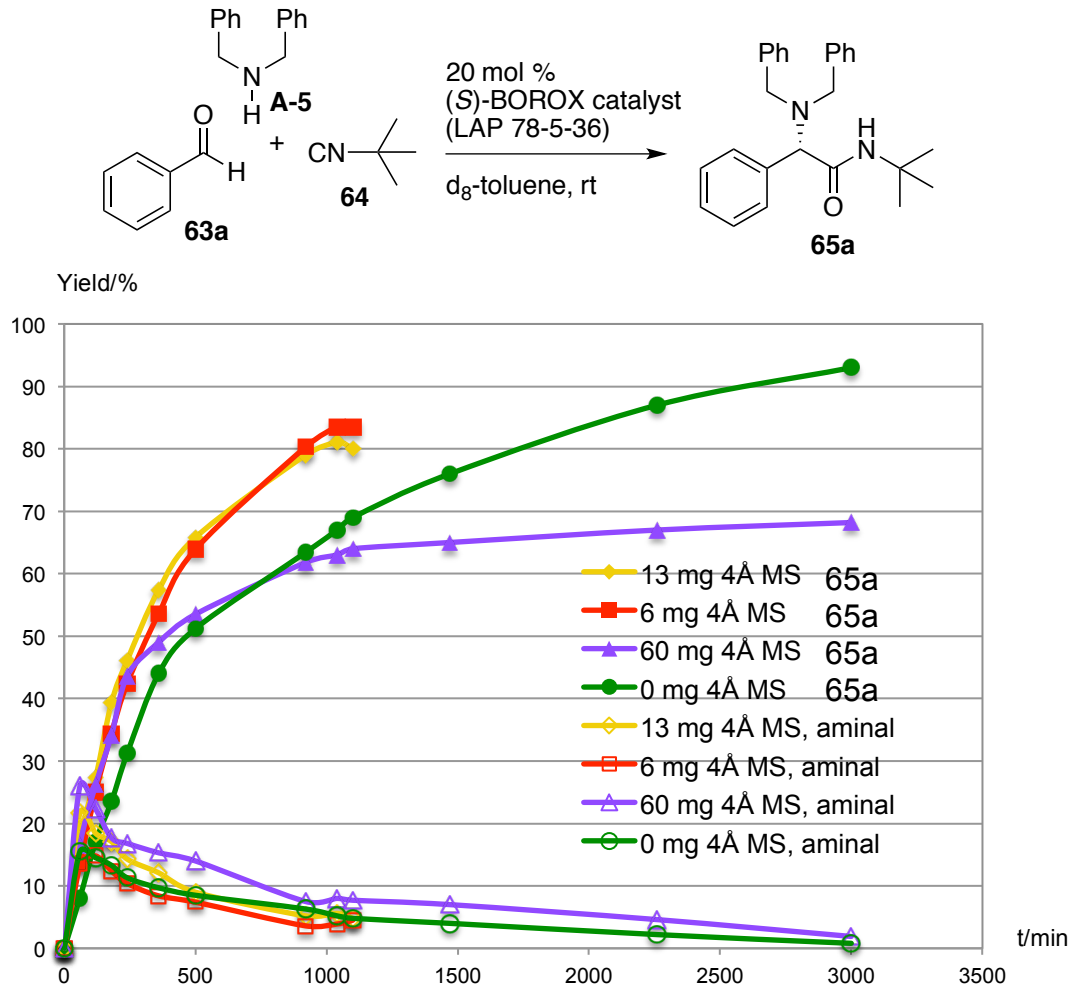
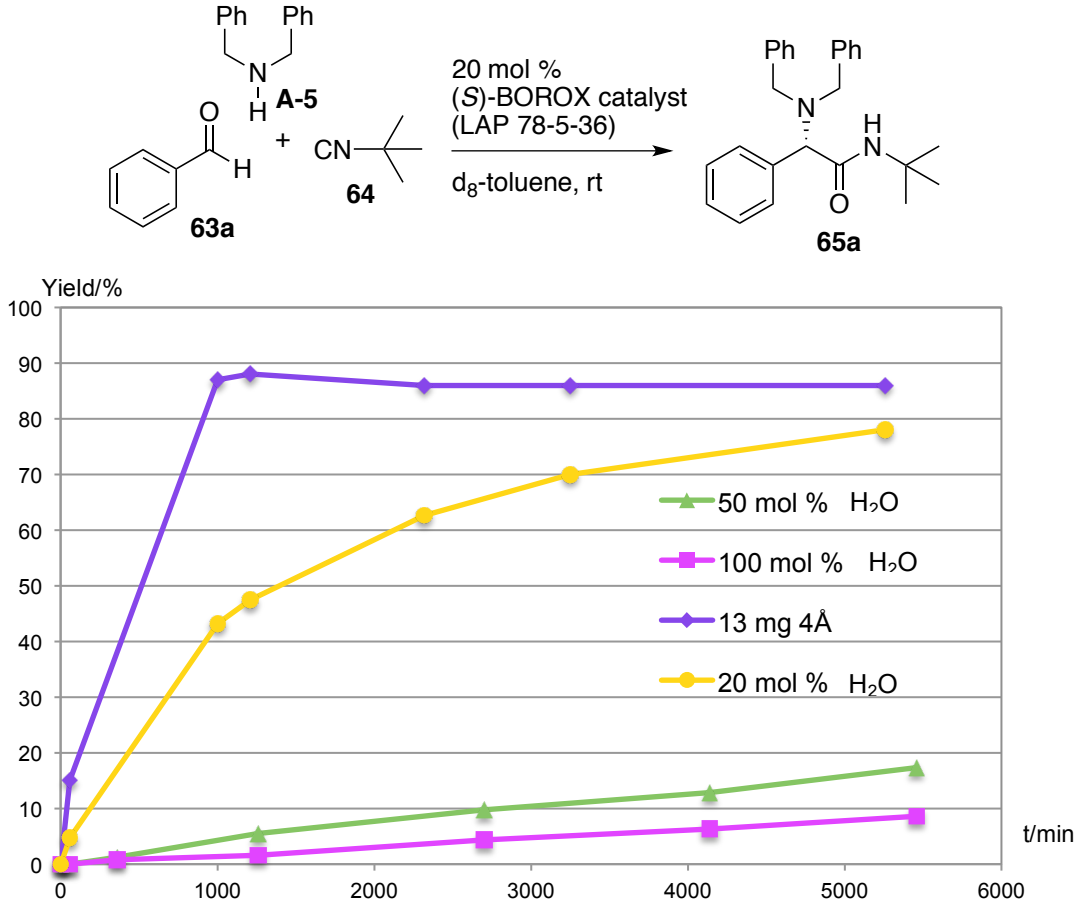


Figure 2.4 ^{1}H NMR study on the formation of 65a from the Ugi-3CR with 4Å MS and H_2O

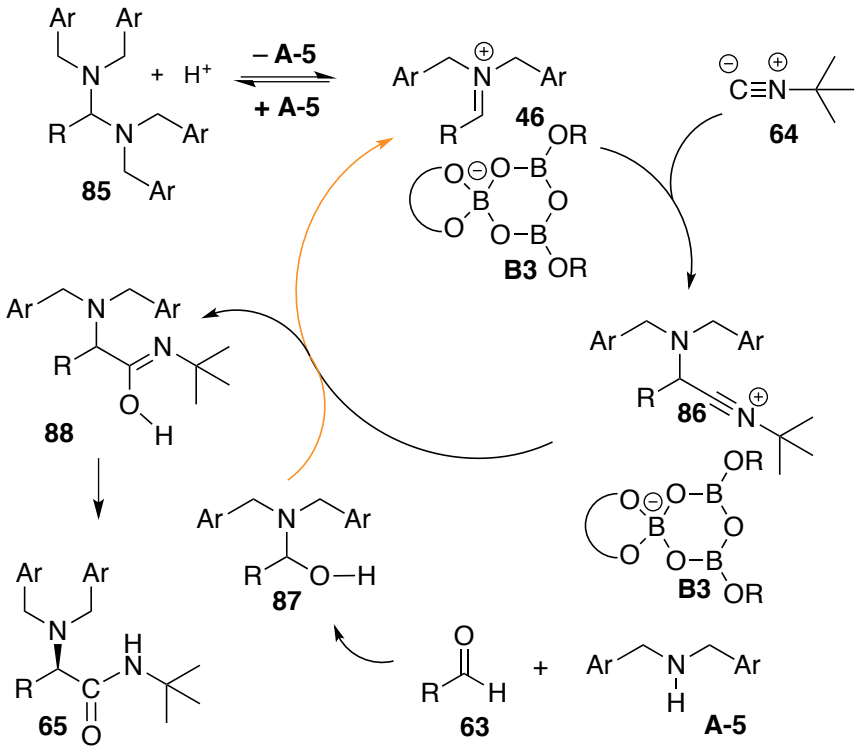


2.17 Proposed Mechanism for the Asymmetric Catalytic Three Component Ugi-3CR

It is considered likely that the catalyst is the boroxinate anion **B3** that exists as an ion pair with the iminium ion **46** and thus this Ugi reaction is an example of "chiral anion catalysis" (Scheme 2.12).[6b] The mechanism can be envisioned to involve the addition of the isonitrile **64** to the iminium cation **46** to give the nitrilium cation **86** which is also ion-paired with the chiral anion catalyst **B3**. We propose that the next step is hydroxyl exchange between the nitrilium cation **86** and the hemi-aminal **87** which would result in the regeneration of the

iminium ion **46** and the formation of the product in the form of the tautomer **88**. It is also possible that the hemi-aminal **87** is protonated and releases H_2O which adds to nitrilium ion **86**. Evidence against the presence of free H_2O in this reaction comes from the fact that the presence of molecular sieves does not greatly affect the rate of the reaction and the addition of H_2O slows down the reaction (see Table 2.6 and Figures 2.3 and 2.4). When the reaction is followed by ^1H NMR spectroscopy it is observed that there is an initial build-up of the aminal **85** (~15% at 10% completion) and then it slowly disappears and is gone at the end of the reaction (**Part 2.16.2**, Figure 2.3).

Scheme 2.12 Proposed mechanism for the catalytic asymmetric Ugi reaction



2.18 NMR Evidence for the Formation of BOROX Anion Catalyst

The involvement of a BOROX catalyst containing a boroxinate core is supported by ^{1}H and ^{11}B NMR studies. A DMAP-BOROX complex has been previously synthesized and fully characterized by our group.[12n] Its structure was elucidated by X-ray diffraction analysis. The most distinctive absorption in the ^{1}H NMR spectrum for this DMAP-BOROX complex is the bay-region (Scheme 2.13, H_b) peak at 10.4 ppm. The ^{11}B NMR spectrum of the complex shows a sharp peak at 5.7 ppm for the tetra-coordinated boron in the structure. Both of these two distinctive absorptions were observed for the catalyst for the Ugi-3CR.

We first investigated the BOROX catalyst formation with 1.0 equivalent of amine **A-5** (Scheme 2.13). After the addition of 1 equiv of the amine **A-5** to the pre-catalyst solution, the ^{1}H NMR spectrum showed a peak around 10.6 ppm (Figure 2.5, b-d) and the ^{11}B NMR spectrum revealed a sharp peak at 5.9 ppm (Figure 2.6, b-d). These results are indicative of the formation of the amine **A-5**-BOROX complex. The absorption for the bay proton of the free ligand (*R*)-**78** in the ^{1}H NMR spectrum appears at 9.6 ppm in d_8-toluene.

Scheme 2.13 Catalyst formation with 1.0 equivalent of dibenzylamine **A-5**

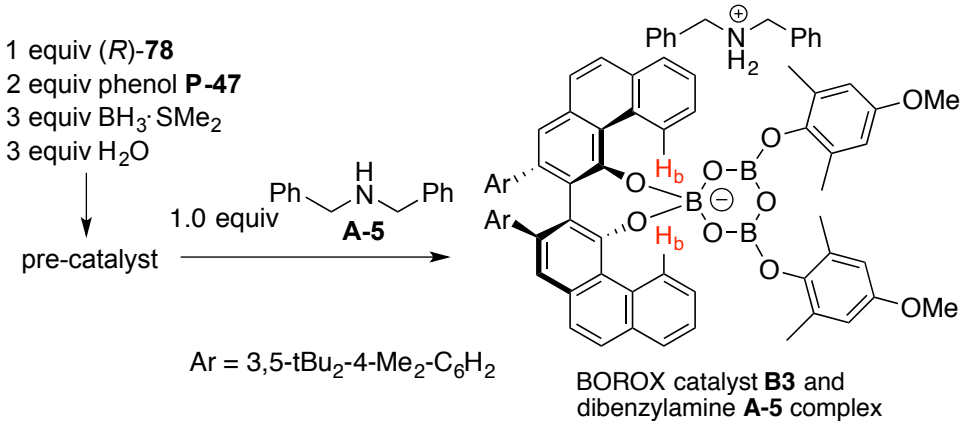
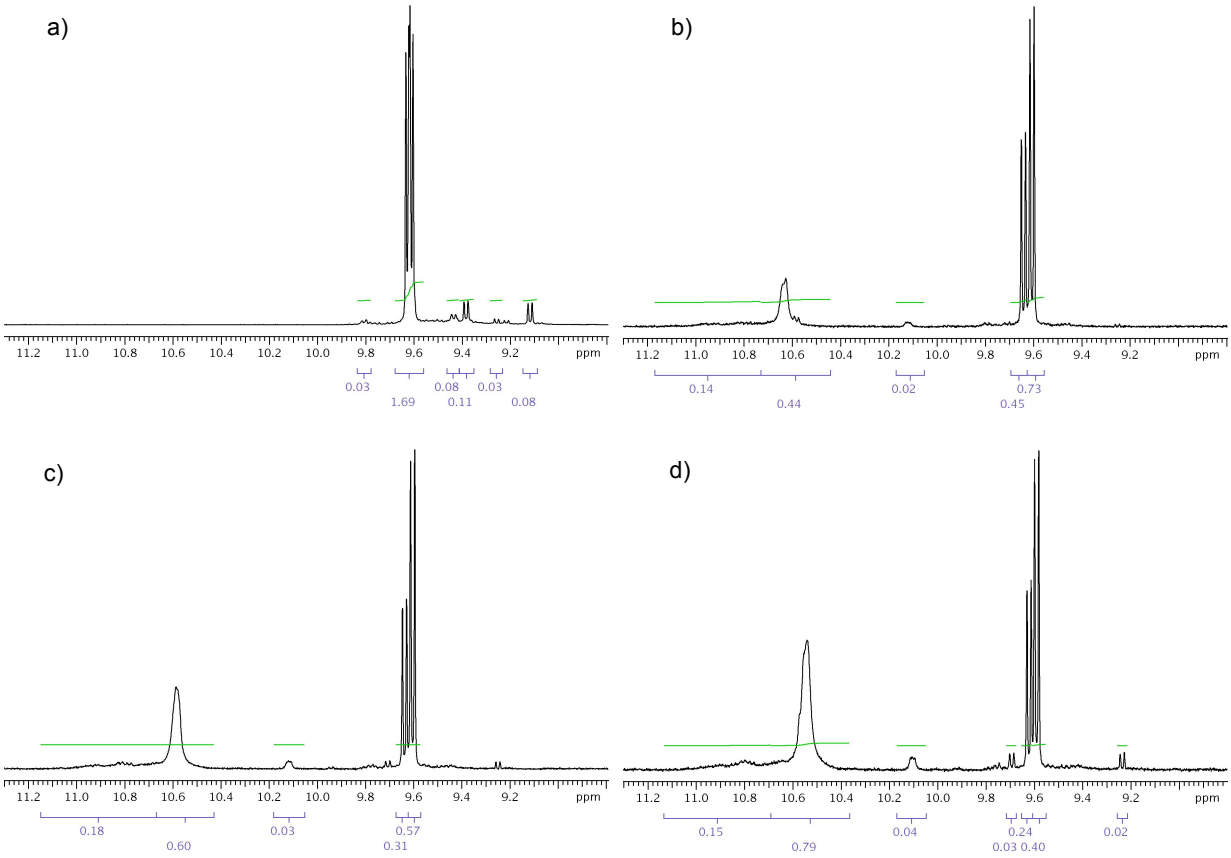


Figure 2.5 ^{1}H NMR spectra in d_8-toluene of the pre-catalyst and catalyst (bay proton region) with 1.0 equivalent amine **A-5**

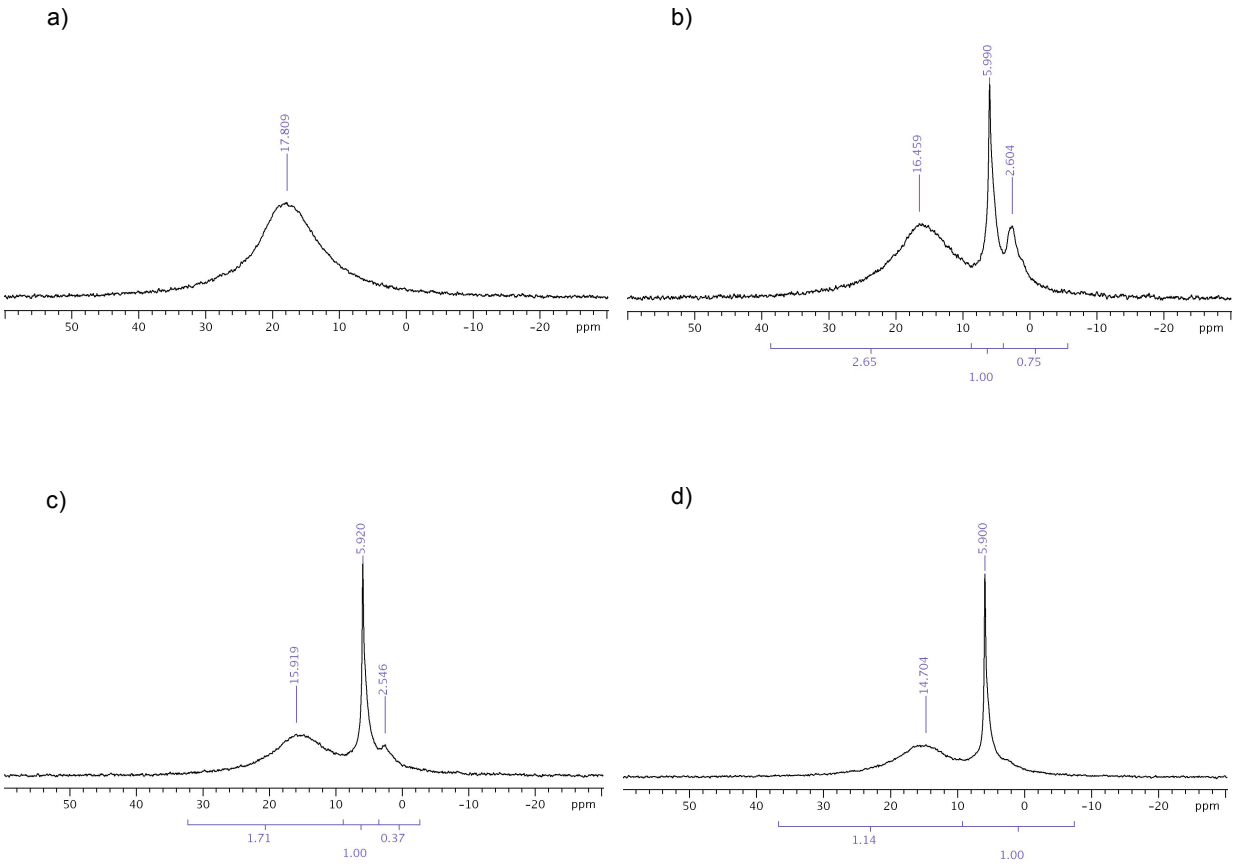


(a) Pre-catalyst; Pre-catalyst formation: a flame-dried 25 mL Schlenk flask equipped with a stir bar was cooled to rt under N_2 and charged with (*R*)-**78** (91.6 mg, 0.111 mmol), **P-47** (35.0 mg, 0.229 mmol), H_2O (5.9 mg, 5.9 µL, 0.33 mmol), dry toluene (3.3 mL) and $BH_3{\cdot}SMe_2$ (2M, 165 µL, 0.33 mmol). The Teflon valve on the Schlenk flask was then closed, and the mixture heated at 100 °C for 1 h. After the flask was cooled to rt, the valve was carefully opened to gradually apply high vacuum (0.1 mm Hg) and the solvent and volatiles were removed. Then the flask was heated at 100 °C under high vacuum for 30 min. The resulting mixture was dissolved in dry d_8-toluene (1.04 mL) after it was cooled to room temperature. To an oven-dried quartz NMR tube filled with nitrogen was added Ph_3CH (10.4 mg, 0.0426 mmol) as an internal standard, the pre-catalyst stock solution (0.49 mL, 0.05 mmol (*R*)-**78**) and 0.21 mL d_8-toluene. The tube was

Figure 2.5 (cont'd)

sealed with a rubber cap. The ^{1}H NMR and ^{11}B NMR spectra of the pre-catalyst were taken at this point. (b) 1 h at rt after the addition of 1 equiv dibenzylamine; (c) 2 h at rt after the addition of dibenzylamine; (d) 6 h at rt after the addition of dibenzylamine (The integrations are based on the methine proton in Ph_3CH, which was set to 1.00.)

Figure 2.6 ^{11}B NMR spectra in d_8-toluene of the pre-catalyst and catalyst with 1.0 equivalent amine **A-5**



(a) Pre-catalyst; (b) 30 min after the addition of 1 equiv dibenzylamine; (c) 2 h after the addition of dibenzylamine; (d) 3.5 h after the addition of dibenzylamine

We then investigated the catalyst formation under the reaction condition where 10 equivalents of amine **A-5** were added (Scheme 2.14). After the addition

of 10 equiv of the amine **A-5** to the pre-catalyst solution, a peak around 10.8 ppm in the ^{1}H NMR spectrum (Figure 2.7, b) and a sharp peak at 5.7 ppm in the ^{11}B NMR spectrum (Figure 2.8, b) were indicative of the formation of the **A-5**-BOROX complex. After the addition of 5 equiv benzaldehyde, three broad absorptions around 10.8 ppm were observed (Figure 2.7, c). This is not surprising since the protonated amine **[A-5]H^{+}**, iminium **46**, protonated hemiaminal **87-H^{+}** and protonated aminal **85-H^{+}** could all pair up with the BOROX anion (Scheme 2.14). These different ion pairs are in equilibrium in the reaction mixture, resulting in slightly different absorptions in the bay-region in ^{1}H NMR spectrum. The addition of isocyanide **64** hardly resulted in any change in both ^{1}H NMR and ^{11}B NMR spectra (Figure 2.6 and 2.7, d).

Scheme 2.14 Catalyst formation with 10.0 equivalent of dibenzylamine **A-5**

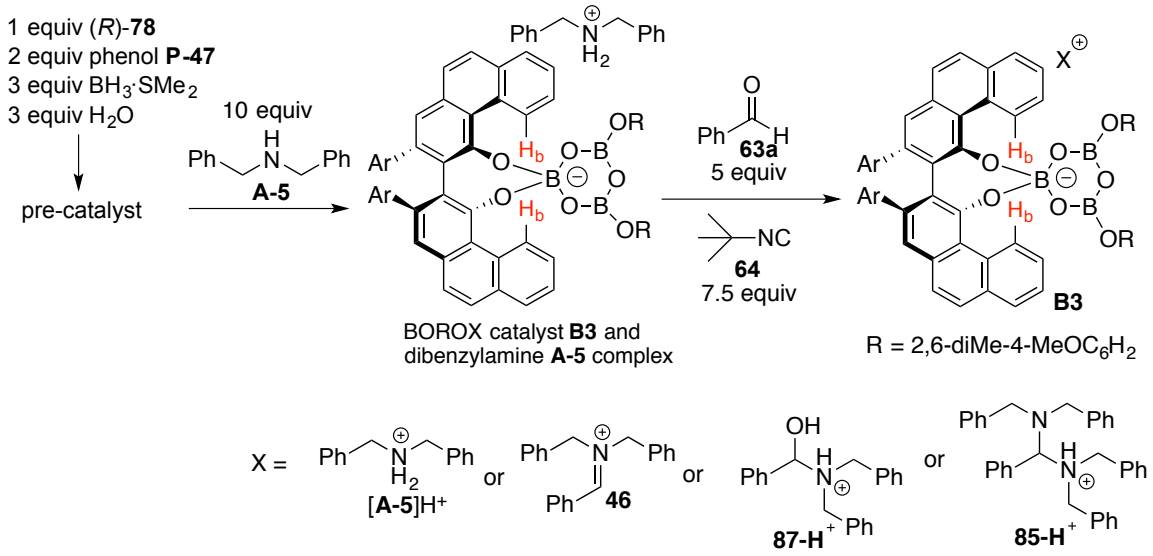
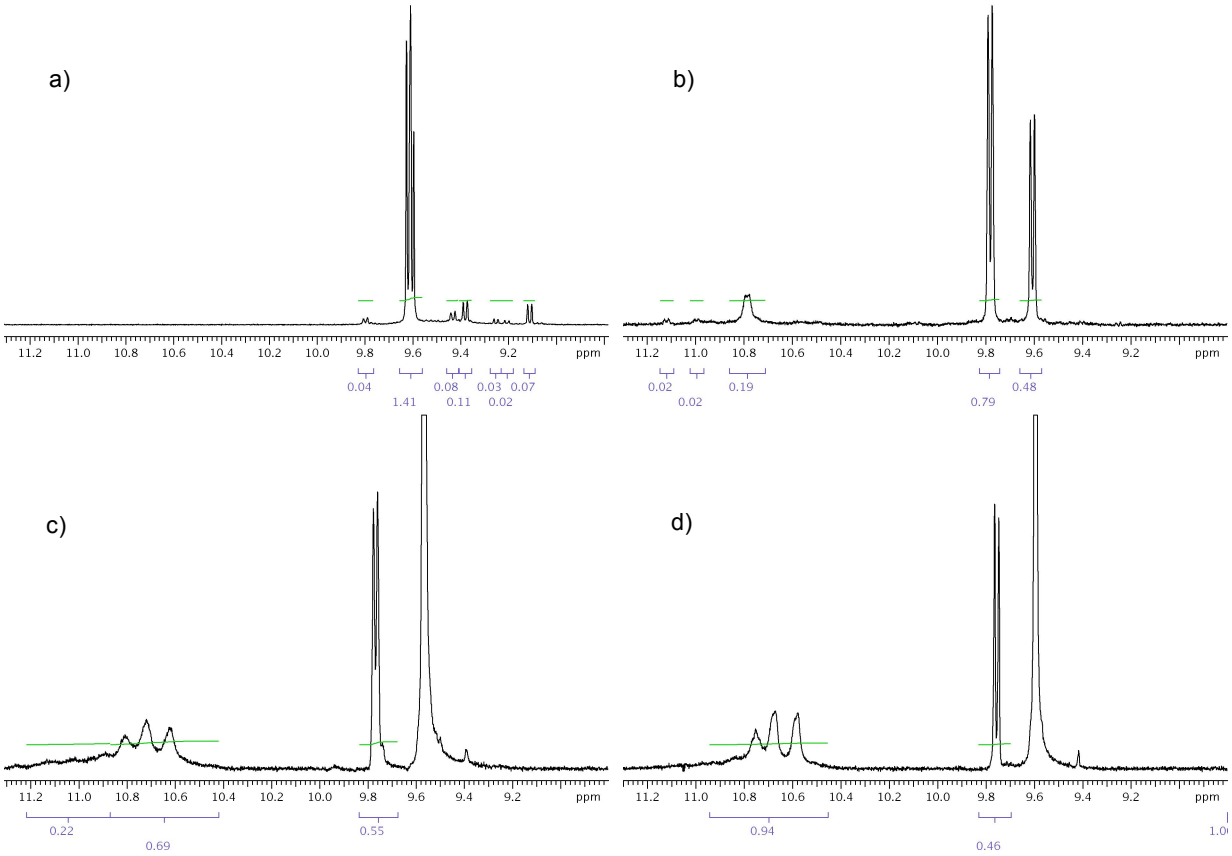
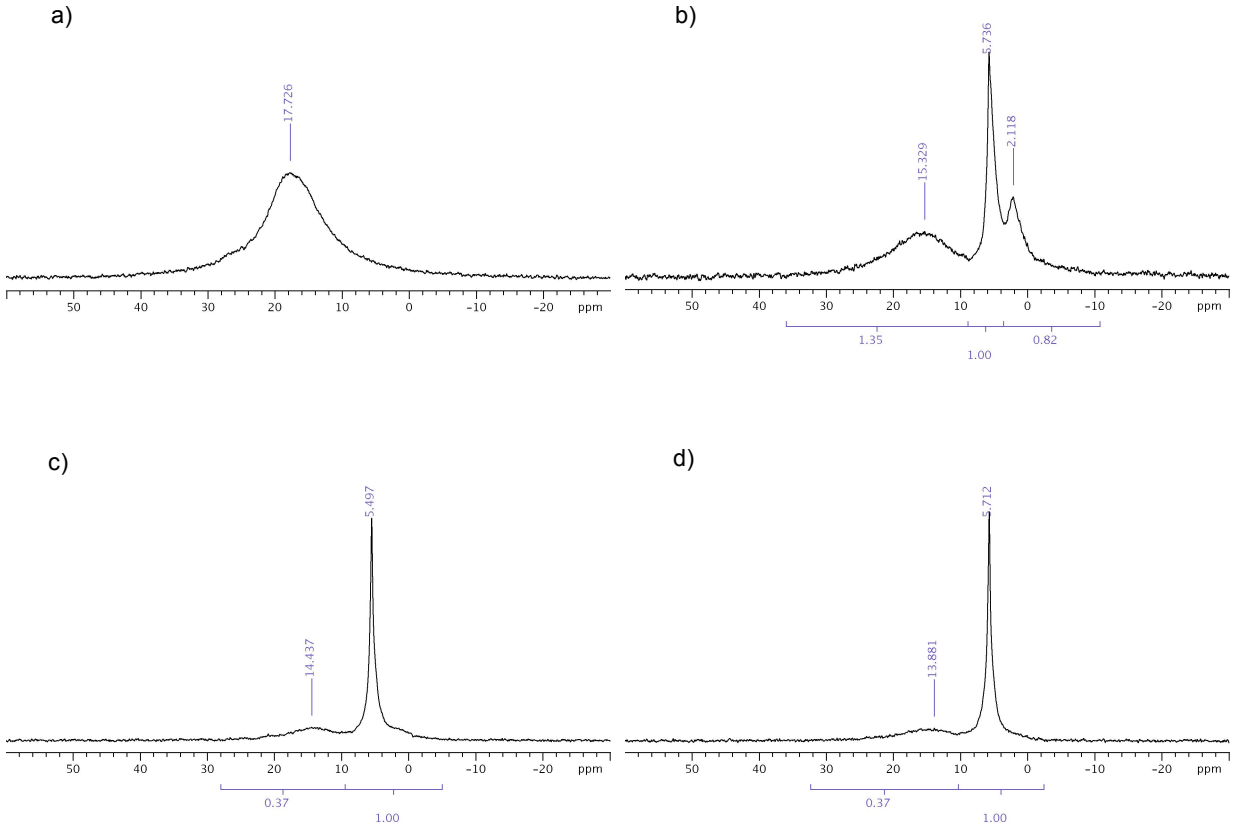


Figure 2.7 ^{1}H NMR spectra in d_8-toluene of the pre-catalyst and catalyst (bay proton region)



(a) Pre-catalyst; Sample preparation: To an oven-dried quartz NMR tube filled with nitrogen was added Ph_3CH (11.7 mg, 0.0479 mmol) as an internal standard, the pre-catalyst stock solution (0.49 mL, 0.05 mmol (*R*)-**78**) (prepared according to the procedure described in Figure 2.5) and 0.21 mL d_8-toluene. The tube was sealed with a rubber cap. The ^{1}H NMR and ^{11}B NMR spectra of the pre-catalyst were taken at this point. The integration of the methine proton in Ph_3CH was set to 1.00. (b) After the addition of 10 equiv dibenzylamine **A-5** at rt; (c) After the addition of 5 equiv benzaldehyde **63a** at rt; (d) After the addition of 7.5 equiv isocyanide **64** at rt.

Figure 2.8 ^{11}B NMR spectra in d_8-toluene of the pre-catalyst and catalyst



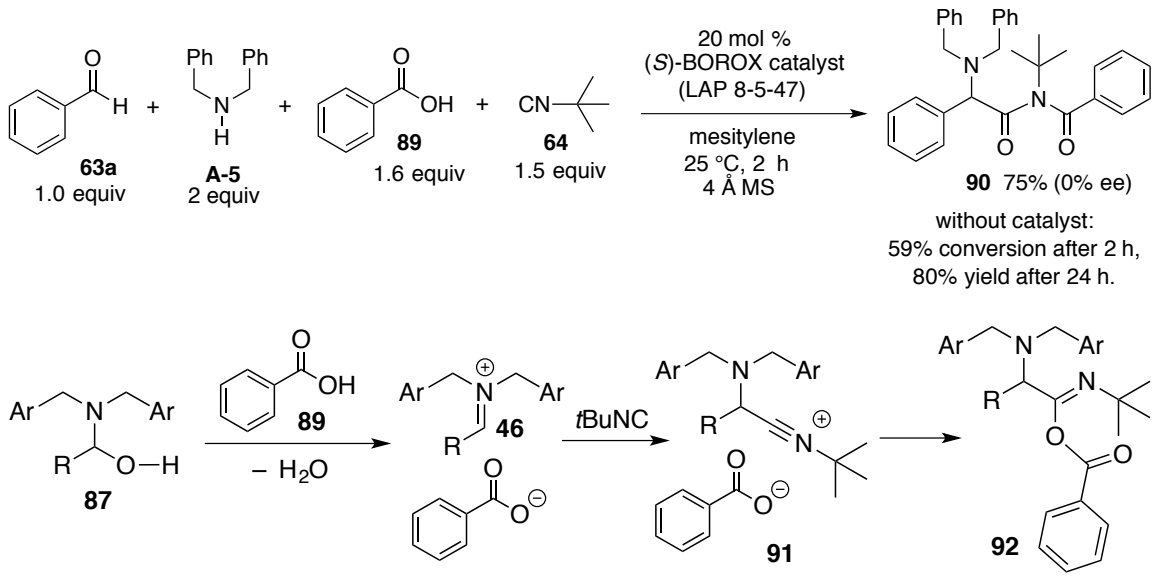
(a) Pre-catalyst; (b) After the addition of 10 equiv dibenzylamine **A-5** at rt; (c) After the addition of 5 equiv benzaldehyde **63a** at rt; (d) After the addition of 7.5 equiv isocyanide **64** at rt.

2.19 Attempted Asymmetric Four-Component Ugi Reaction

Finally, a four-component version of this reaction with the optimal BOROX catalyst (LAP 78-5-47) was performed with benzoic acid **89** (Scheme 2.15). The reaction rate was much faster than that of the three-component version (2 h vs >24 h). The carboxylic acid component is known to accelerate the 4-component Ugi reaction and this was observed in the present case as well where the reaction was complete in 2 h to give the amino imide **90** in 75% yield but the product was racemic. The control experiment without the chiral catalyst still

proceeds but at a slightly slower reaction rate (59% conversion after 2 h). One possible explanation involves the protonation of the hemi-aminal **87** by benzoic acid **89** to give the iminium ion **46** and then upon addition of the isonitrile, the non-chiral ion pair **91**. Subsequent combining of the ions gives **92** and then an O to N acyl migration would produce **90.**

Scheme 2.15 Ugi-4CR with benzoic acid



2.20 Conclusion

A great diversity of BOROX catalysts can be quickly generated and the optimal combination of the ligand, amine and phenol/alcohol components of the catalyst were sought and found for the three-component asymmetric Ugi reaction. The optimal catalyst was found to give high enantioselectivity for α-amino amides from the reaction of a variety of aryl and heteroaryl aldehydes with dibenzyl amine and t-butyl isocyanide. A number of p-substituted dibenzyl amines and some other isonitriles are also effective under the optimal reaction

conditions with benzaldehyde giving the product in high asymmetric induction. The active catalyst is proposed to involve an ion-pair between a chiral boroxinate anion and an achiral iminium ion.

CHAPTER 3

β-AMINO ESTERS FROM THE REDUCTIVE RING OPENING OF AZIRIDINES-2-CARBOXYLATES

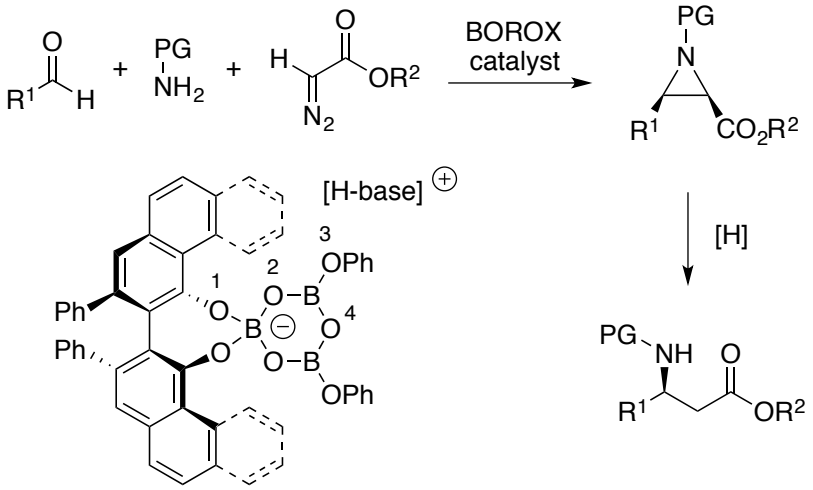
3.1 Introduction

The synthesis of β-amino acids has been a subject of great interest and importance for quite some time[35] but especially since it was discovered that β-peptides derived from β-amino acids have many of the properties of α-peptides but are much more proteolytically stable.[36] There has been a decided uptick in the efforts to develop catalytic asymmetric methods for the synthesis of β-amino acids in the last decade. Some important catalytic asymmetric approaches to β-amino acids include transformations based on the Mannich reaction, hydrogenation of β-aminoacrylic acid derivatives and conjugate addition to α,β-unsaturated carbonyl compounds.[37]

Our interest in this area follows from the experiences we have gained in the development of a method for the catalytic asymmetric synthesis of aziridines as discussed in Chapter 1.[38] We have found that *cis*-aziridine-2-carboxylates can be prepared with a high degree of enantio- and diastereoselection by a three-component coupling of an aldehyde, and amine and ethyl diazoacetate under the aegis of a BOROX catalyst (Scheme 3.1).[12] High yields of aziridine-2-carboxylates can be realized starting with aryl, alkyl or alkynyl aldehydes with a typical selectivity for the *cis*-isomer of ≥50:1. The enantioselection can depend on the nature of the amine substitutent or on the nature of the ligand, and with the right combination a minimum of 96% ee can be obtained with aryl, alkynyl and

primary (1°), secondary (2°) and tertiary (3°) aliphatic aldehydes. The diastereoselection for the aziridine can be switched to trans with the use of a 2° diazoacetamide.[9] The purpose of the present work is to explore the reductive opening of *cis*-aziridine-2-carboxylates with the goal of directing opening at the C-2 position to provide for an efficient and highly stereoselective catalytic asymmetric route to β-amino esters which can be easily hydrolyzed to give β-amino acids.

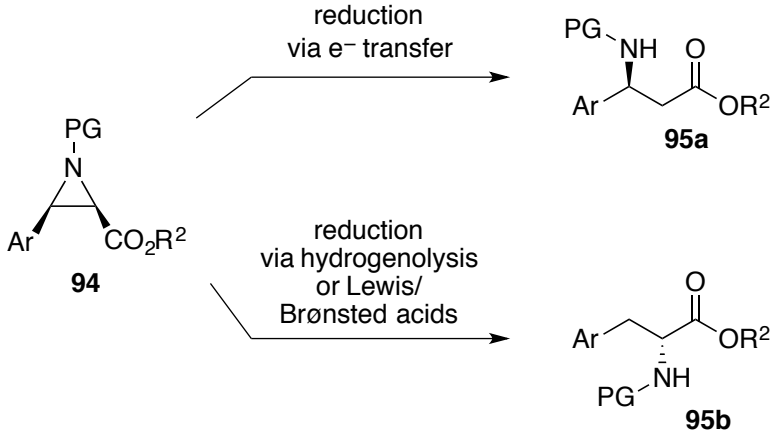
Scheme 3.1 Proposed catalytic asymmetric route to β-amino esters



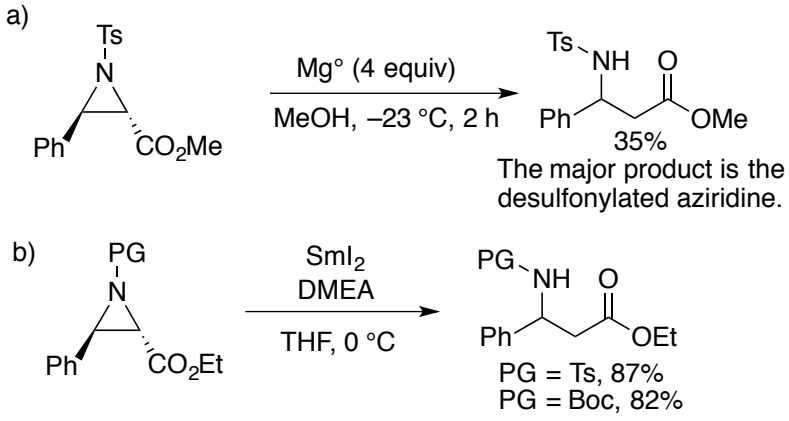
A number of methods are known for the reductive opening of aziridines-2-carboxylates to give β-amino esters, such as hydrogenolysis and processes involving electron transfer.[39,40] The nature of the reducing agent can be quite critical when it comes to aziridines with an aryl group in the 3-position. As illustrated in Scheme 3.2, such aziridines **94** are prone to undergo reductive opening to give α-amino esters **95b** by hydrogenolysis or with Lewis or Brønsted

acid mediated reduction.[39,41] However, this proclivity for reduction can be reversed by using electron transfer reduction methods due to the fact that the electron preferentially adds to the carbonyl function thus directing ring opening to the 2-position resulting in β-amino esters **95a**. This has been reported with samarium diiodide,[42] and magnesium metal (Scheme 3.3).[43]

Scheme 3.2 Ring-opening of aziridine-2-carboxylates with an aryl group at the 3-position under different conditions



Scheme 3.3 Selective ring-opening of aziridine-2-carboxylate at the 2-position with Mg(0) and SmI_2



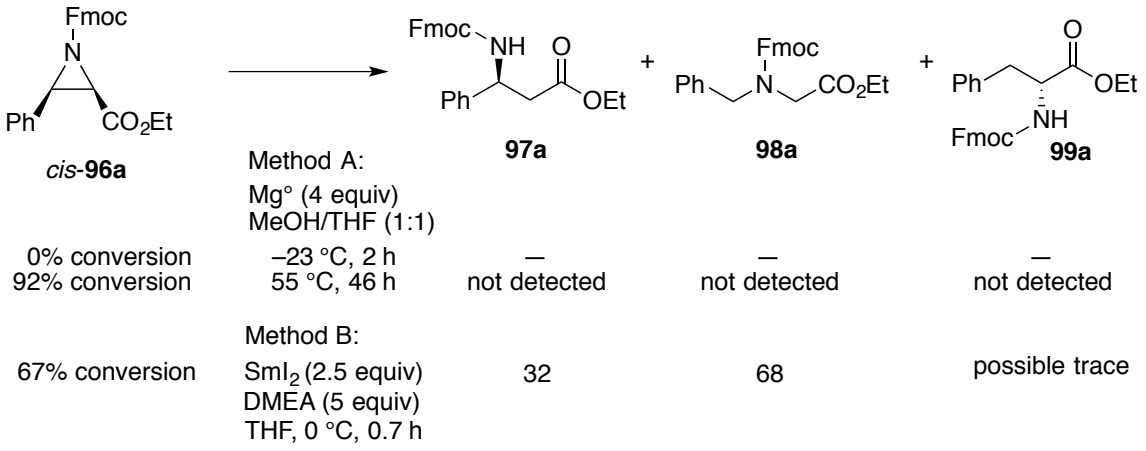
While 3-arylaziridine-2-carboxylates can be reductively opened to β-amino esters with either samarium diiodide or magnesium(0), all examples in the literature are with *trans*-isomers of the aziridine (Scheme 3.3).[42-43] Therefore, since the BOROX catalyst produces very high selectivities for *cis*-aziridines, it became imperative to determine if the same regioselectivities observed in the reductive opening of *trans*-aziridines would translate to *cis*-aziridines.

3.2 Initial Studies of Ring-Opening Reactions with *cis*-Fmoc-Protected Aziridines

We began our studies with Fmoc aziridines since this would be the most desirable N-substituent for the purposes of solid state synthesis of β-peptides. The ring opening reaction with Fmoc aziridine *cis*-**96** that has a phenyl group in the 3-position cis to the ethyl carboxylate was examined by our former group member Zhenjie Lu with magnesium in methanol and with samarium diiodide in the presence of *N*,*N*-dimethylethanol amine (DMEA). The purpose of the DMEA is to sequester the samarium(III) that is formed and prevent it from opening the aziridine as a Lewis acid giving the α-amino ester product **99**.[42c, d] The reduction with magnesium(0) did not occur under the reported conditions (Scheme 3.3 a; Scheme 3.4, method A; Fmoc aziridines were not included in this reported study)[43] and high conversion was only realized after prolonged heating at 55 °C, however, neither the α-cleavage product **97**, the β-cleavage product **99** nor the C-C cleavage product **98** were observed in the crude reaction mixture. This reaction was later repeated during the work of this dissertation and the same results were obtained. The products that were formed were not separated and

identified. The reduction of *cis*-**96** with samarium diiodide was performed with the reported conditions[42c, d] indicated in Scheme 3.4 and the result was that both the α-cleavage product **97** and the C-C cleavage product **98** were formed in substantial amounts.

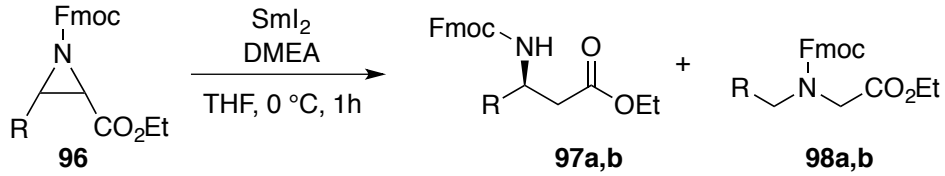
Scheme 3.4 Ring-opening of *cis*-**96a** by Mg(0) and SmI_2



After a bit of optimization, the reductive ring-opening of *cis*-**96a** could be brought to completion with 4 equiv SmI_2 and 8 equiv DMEA in THF in 1 hour at 0 °C (Table 3.1, entry 1).[44] This reaction resulted in the isolation of the α-cleavage product **97a** in 45% yield and the C-C cleavage product **98a** in 46% yield. Upon examining the reductive ring-opening of the corresponding *trans*-aziridine *trans*-**96a** under the optimized conditions, it became clear that there is a big dependence in the product distribution on the stereochemistry of the aziridine. Whereas the *cis*-aziridine **96a** gives a 1 : 1 mixture of **97a** : **98a**, the *trans*-aziridine **96a** gives a 16.7 : 1 mixture of **97a** : **98a** (Table 3.1, entries 1 vs 3). This was not the case with aziridines bearing an alkyl group in the 3-position. Both the *cis*- and *trans*-isomers of the 3-cyclohexyl aziridine **96b** gave exclusive

opening at the α-position and a highly selective formation of the β-amino ester **97b** (Table 3.1, entries 2 vs 4).

Table 3.1 Reductive opening of *cis*- and *trans*-Fmoc aziridines [a]



96 **97a,b** **98a,b**

entry	aziridine	R	**97** : **98** [b]	% yield **97** [c]	% yield **98** [d]
1 [e]	*cis*-**96a**	phenyl	1 : 1	45	46 [c]
2 [e]	*cis*-**96b**	cyclohexyl	>99 : 1	89	< 1
3 [f]	*trans*-**96a**	phenyl	16.7 : 1	82 [d]	5
4 [g]	*trans*-**96b**	cyclohexyl	>99 : 1	73 [d]	< 1

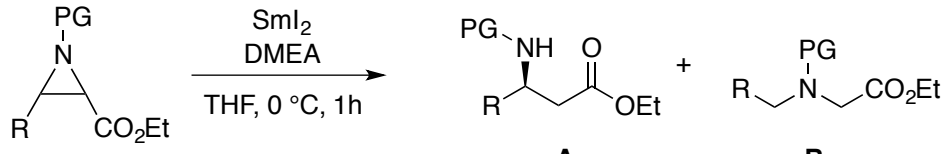
[a] Unless otherwise specified, all reactions were run with 0.2 mmol aziridine in THF (0.07 M) with 4 equiv SmI_2 and 8 equiv DMEA at 0 °C for 1 h and went to completion. [b] Determined from the ^{1}H NMR spectrum of the crude reaction mixture. [c] Isolated yield after silica gel chromatography. [d] Yield from the ^{1}H NMR spectrum of crude reaction mixture with internal standard. [e] Data contributed by Zhenjie Lu. [f] Reaction with 5.5 equiv SmI_2 and 11 equiv DMEA. [g] Reaction with 6 equiv SmI_2 and 12 equiv DMEA.

3.3 SmI_2 Mediated Ring-Opening Reactions with Various *N*-Protected Aziridines

In the search for a more general method for the reductive ring opening of aziridines to β-amino esters, a number of different *N*-protecting groups were examined and the results are presented in Table 3.2. As a carbamate, it was not

surprisingly to find that the profile for the SmI_2 mediated reductive ring opening of the Boc-protected aziridines closely matched that for the Fmoc aziridines with just slightly lower selectivities. Again the ring-opening of phenyl substituted *cis*-aziridine was not selective (1.4:1, Table 3.2, entry 1). The phenyl substituted trans-aziridine **100a** was more selective 6.7:1 (entry 3) and both isomers of the cyclohexyl substituted aziridines **100b** were highly selective (entries 2 and 4). Clearly, the most felicitous *N*-protecting group with regard to selectivity of reductive ring-opening by samarium diiodide is the tosyl group. The profile here is flat with >99:1 selectivity for the β-amino ester with both *cis*- and *trans*-aziridines and with both phenyl and cyclohexyl substituted aziridines, all with very high yields (Table 2, entries 5-8).

Table 3.2 Reductive opening of *cis*- and *trans*-*N*-activated aziridines. [a]



100-103 **A** **B**

entry	PG	aziridine	R	**A** : **B** [b]	% yield **A** [c]	% yield **B** [c]
1	Boc	*cis*-**100a**	phenyl	1.4 : 1	55 (**104a**)	32 (**108a**)
2[e]	Boc	*cis*-**100b**	cyclohexyl	>99 : 1	84 (**104b**)	— (**108b**)
3	Boc	*trans*-**100a**	phenyl	6.7 : 1	85 (**104a**)	10 (**108a**)
4	Boc	*trans*-**100b**	cyclohexyl	>99 : 1	84 (**104b**) [d]	— (**108b**)
5[e]	Ts	*cis*-**101a**	phenyl	>99 : 1	93 (**105a**)	— (**109a**)

Table 3.2 (cont'd)

6	Ts	*cis*-**101b**	cyclohexyl	>99 : 1	97 (**105b**) [f]	— (**109b**)
7	Ts	*trans*-**101a**	phenyl	>99 : 1	88 (**105a**)	— (**109a**)
8	Ts	*trans*-**101b**	cyclohexyl	>99 : 1	95 (**105b**)	— (**109b**)
9	SES	*cis*-**102a**	phenyl	23 : 1	84 (**106a**) [g]	4 (**110a**)
10[e]	Ac	*cis*-**103a**	phenyl	>99 : 1	52 (**107a**) [h]	— (**111a**)

[a] Unless otherwise specified, all reactions were run with 0.2 mmol aziridine in THF (0.07 M) with 6 equiv SmI_2 and 12 equiv DMEA at 0 °C for 1 h and went to completion. [b] Determined from the ^{1}H NMR spectrum of the crude reaction mixture. [c] Isolated yield after silica gel chromatography. [d] Yield from ^{1}H NMR spectrum of crude reaction mixture with internal standard. [e] Data contributed by Zhenjie Lu. [f] Reaction with 5 equiv SmI_2 and 10 equiv DMEA. [g] A small amount (~6%) of SES protected benzylamine was also observed. [h] Reaction with 4 equiv SmI_2 and 8 equiv DMEA. The ring opening product from N-C3 cleavage to give an α-amino ester was obtained in 13 % isolated yield.

The SES group[45] (trimethylsilyl ethyl sulfonyl) is an attractive activating group for an amino function since it is easier to remove than tosyl and very good selectivity for the β-amino ester **106a** is seen with the *cis*-aziridine **102a** (23:1, Table 3.2, entry 9). The slightly lower selectivity for the SES group compared to tosyl (entries 5 vs 9) perhaps could be expected for an alkyl sulfonate compared to an aryl sulfonate (vide infra). Finally, it was found that the *N*-acetyl group is also capable of delivering very high selectivity for the β-amino ester **107a** over the C-C cleavage product in the ring opening of the cis-phenyl aziridine *cis*-**103a**,

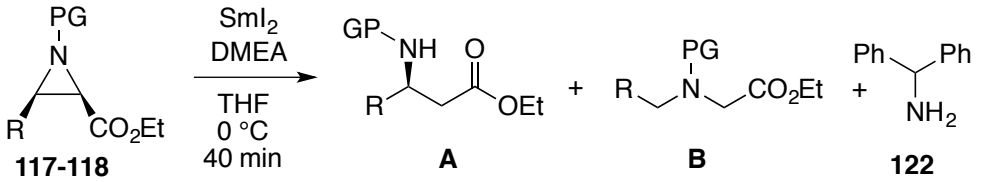
however, the isolated yield of the β-amino ester **107a** was only moderate and the reaction occurs with the formation of 13% of the α-amino ester corresponding to **99** in Scheme 3.4 (Table 2, entry 10). The latter may result from initial electron transfer to the amide carbonyl and then ring opening to a benzyl radical (or anion, vide infra).

3.4 SmI_2 Mediated Ring-Opening Reactions with un-Activated Aziridines

The reductive ring opening of un-activated aziridines by samarium diiodide would be a very useful reaction since this is the class of aziridines for which the BOROX catalysts are most efficient at producing (Scheme 3.1). In previous studies, Kumamoto and coworkers examined the samarium diiodide mediated ring opening of *trans*-aziridine-2-carboxylates with an aryl group in the 3-position and a benzyl group on the aziridine nitrogen and found that β-amino esters could only be obtained in very low yields.[42a] The corresponding *cis*-aziridines were not investigated. Interestingly, this report finds that if the samarium diiodide is generated from samarium metal and iodine instead of methylene iodide, the major outcome is the isomerization of the *trans*-aziridine to a mixture of *cis*- and *trans*-aziridines. There are no other examples of the reductive ring opening of aziridines bearing an alkyl group on the nitrogen with samarium diiodide in which the aziridines have a carbonyl group in the 2-position and either an aryl or alkyl substituent in the 3-position. Thus we decided to probe the first examples of the reductive ring opening of un-activated *cis*-aziridine-2-carboxylates with samarium diiodide (Table 3.3). The samarium diiodide used in these studies was prepared from samarium metal and methylene iodide and no isomerization of the aziridine

was observed. If the substituent in the 3-position is a phenyl group, then the only product that is observed is the C-C cleavage product. Good yields (69-75%) were observed for this product with N-H aziridines as well as with benzhydryl substituents on the aziridine nitrogen (Table 3.3, entries 1-2).

Table 3.3 Reductive opening of *cis*-unactivated aziridines [a]



entry	PG	aziridine	R	**A** : **B** [b]	% yield **A**[c]	% yield **B**[c]
1[f]	H	*cis*-**117a**	phenyl	<1 : 99	—	75 (**120a**)
2[f]	$CHPh_2$	*cis*-**118a**	phenyl	<1 : 99	—	69 (**121a**)
3	$CHPh_2$	*cis*-**118b**	cyclohexyl	>99 : 1	22 (**119b**) [d]	—
4	$CHPh_2$	*cis*-**118b**	cyclohexyl	>99 : 1	22 (**119b**) [e]	—

[a] Unless otherwise specified, all reactions were run with 0.2 mmol aziridine in THF (0.07 M) with 5 equiv SmI_2 and 10 equiv DMEA at 0 °C for 40 min and went to completion. [b] Determined from the ^{1}H NMR spectrum of the crude reaction mixture. [c] Isolated yield after silica gel chromatography. [d] Isolated as a 1:1.4 mixture of **119b** and *cis*-**118b** (22% + 31%). The ^{1}H NMR indicated the formation of the amine **122** in 39% yield. [e] Reaction was run for 2 h at 25 °C. The amine **122** was isolated in 52% yield and the aziridine *cis*-**118b** was isolated in 20% yield. [f] Data contributed by Zhenjie Lu.

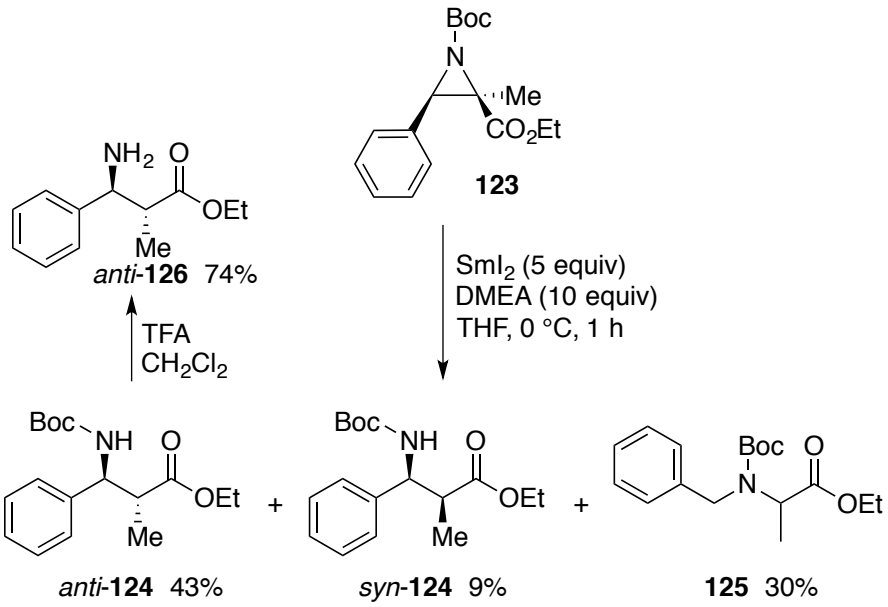
A complete switch in the product distribution was seen with *cis*-azridines bearing a cyclohexyl group in the 3-position. Here the β-amino ester was

generated to the exclusion of the C-C cleavage product, however, the yields were quite low (Table 3.3, entries 3 and 4). These reactions produce a complex mixture of products from which only the β-amino ester **119b**, the starting *cis*-aziridine **118b** and benzhydryl amine **122** could be isolated and characterized. The isolation of **122** suggests that β-cyclohexyl ethyl acrylate should also be formed but it could not be detected in the ^{1}H NMR spectrum of the crude reaction mixture.

3.5 SmI_2 Mediated Ring-Opening Reactions with a Tri-Substituted Aziridine

The reductive process mediated by SmI_2 with a tri-substituted aziridine was also investigated (Scheme 3.5). The reductive ring opening of the stereoisomerically pure tri-substituted aziridine **123**[46] occurred with loss of stereochemical information and the formation of two diastereomers in a ratio of 4.8 : 1. The major diastereomer was identified as the *anti*-isomer of **124** by chemical correlation to the known compound *anti*-**126**. This loss of stereochemistry is to be expected considering the likely mechanism for this reaction (Scheme 3.6, **132** to **133**). The ring opening of **123** also occurred with the formation of the C-C cleavage product **125** in 30% yield. Note that this distribution between C-N and C-C cleavage products is essentially the same as for the cis-di-substituted *N*-Boc aziridine *cis*-**100a** (Table 3.2, entry 1).

Scheme 3.5 Ring-opening of aziridine **123** by SmI_2 and determination of relative stereochemistry of *anti*-**124**

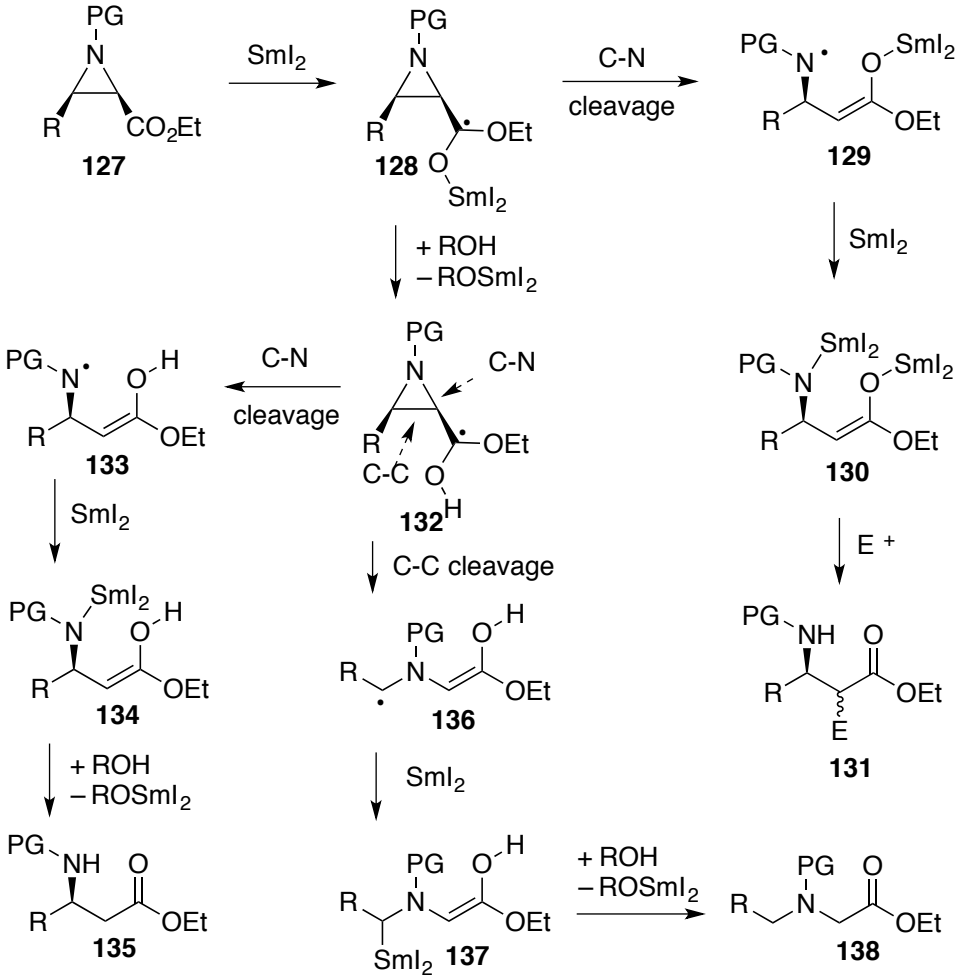


3.6 Mechanistic Rationale for the Selectivity Observed in the SmI_2-Mediated Ring Opening Reactions of Aziridines

The generally accepted mechanism for the reductive ring opening of aziridines by samarium diiodide is illustrated in Scheme 3.6.[42c] After initial reduction to form the ketyl **128** and in the absence of a proton source, the ketyl undergoes a ring opening to give the nitrogen based radical **129** which upon further reduction gives the species **130** containing both a samarium enolate and a samarium amide. The intermediacy of this enolate **130** has been demonstrated and its utility displayed in its alkylation with alkyl halides[42c] and aldol reactions with aldehydes (R' = H) to generate **131**.[42b] Under conditions where a proton source is present, the ketyl **128** is thought to be protonated to give the neutral radical **132** which, depending on the nature of the aziridine, then undergoes a C-N and/or C-C bond scission. Subsequent reduction of the resulting nitrogen or

carbon based radicals **133** and **136** and final protonation would provide the β-amino ester **135** and/or the glycine derivative **138**.

Scheme 3.6 Mechanistic rationale for SmI_2-mediated ring opening process



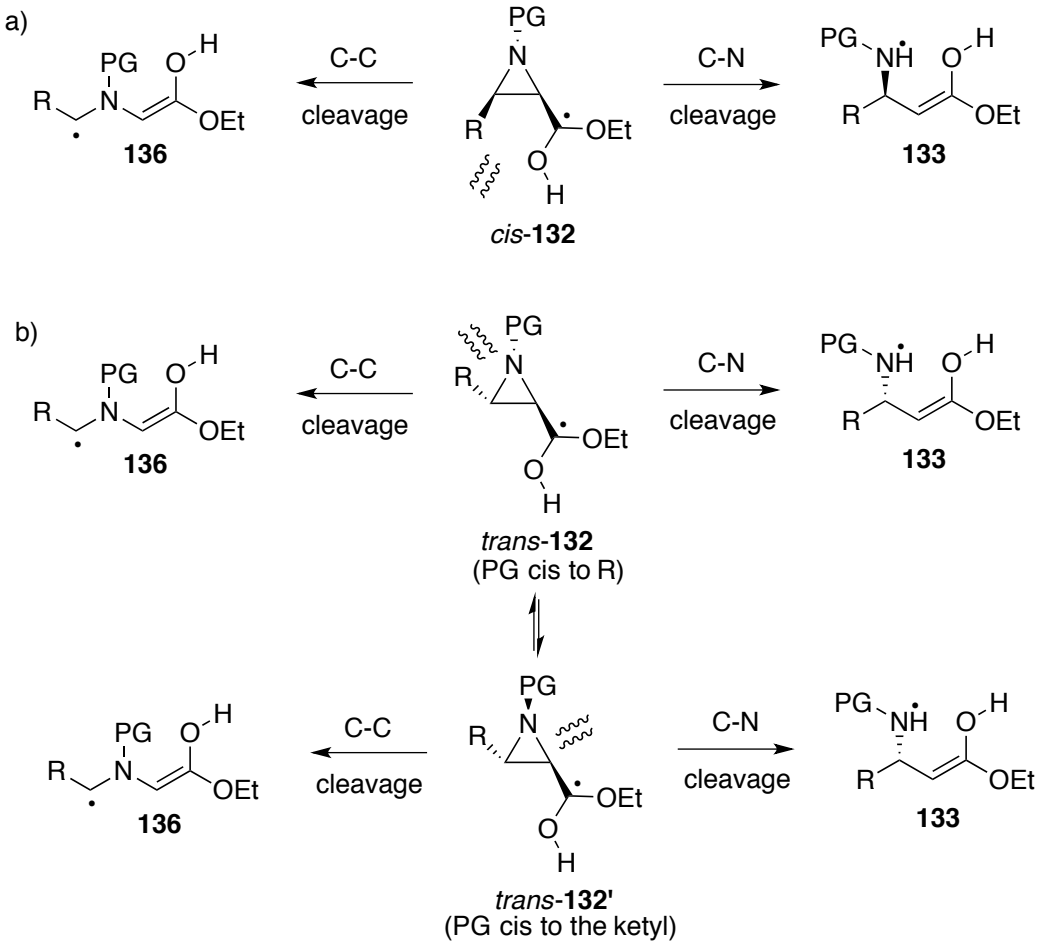
This mechanistic interpretation can be used to account for the observations made in the present work. In all of the examples in Tables 3.1 and 3.2, the aziridines with a cyclohexyl group in the 3-position gives a much higher selectivity for the β-amino ester over the glycine derivative than do aziridines with a phenyl group in the 3-position. This reflects a higher preference for C-C over C-N cleavage for the phenyl aziridines than the cyclohexyl aziridines and this can

be attributed to the greater stability of a benzyl radical compared to an alkyl radical in intermediate **136**. Conversely, the presence of a radical stabilizing group on the nitrogen facilitates the ring opening with C-N bond scission over C-C bond scission. This can be seen in the ring opening reactions of activated aziridines (Tables 3.1 and 3.2) versus un-activated aziridines (Table 3.3). This is illustrated in the comparison of the *N*-tosyl aziridine *cis*-**101a** (Table 3.2, entry 5) versus the *N*-benzhydryl aziridine *cis*-**118a** (Table 3.3, entry 3) and in the comparison of the *N*-tosyl aziridine *cis*-**101a** (Table 3.2, entry 5) versus the *N*-Boc aziridine *cis*-**100a** (Table 3.2, entry 1).

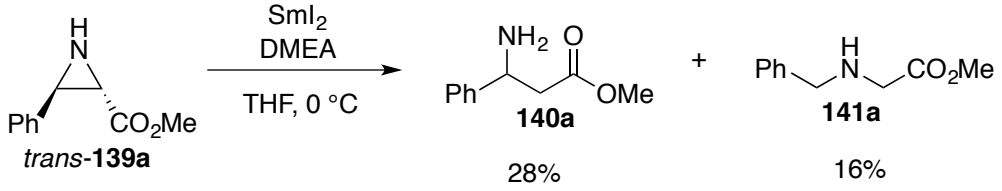
The ratio of C-N versus C-C cleavage is not only a function of the radical stabilizing ability of the substituent on the nitrogen and the substituent on the C-3 position of the aziridine, but also of the stereochemistry of the aziridine. The *cis*-aziridines give a much greater preference for C-C bond cleavage than the *trans*-aziridines. The *N*-Boc aziridine *trans*-**100a** gives a 6.7 : 1 mixture of C-N to C-C cleavage products, whereas, the corresponding *cis*-**100a** gives a much greater propensity for the C-C cleavage product (1.4 : 1, Table 3.2, entries 1 vs 3). The same is also true for the *N*-Fmoc aziridines *cis*-**96a** and *trans*-**96a** (Table 3.1, entries 1 vs 3). The existence of *cis*-**132** in a conformation with the large protecting group (PG) on the nitrogen *trans* to both substituents on C-2 and C-3 (Scheme 3.7, a) is supported by the X-ray crystal structures obtained for several similar aziridines.[47] The greater preference for C-C cleavage products with *cis*-aziridines may be attributed to a relief in steric interactions between the two *cis*-substituents in the transition state where the C-C bond is beginning to lengthen

(Scheme 3.7, *cis*-**132**). This relief in steric interaction would not be realized as the C-C bond begins to lengthen in the *trans*-aziridine. The *trans*-aziridine probably exists in both conformations shown in Scheme 3.7, with PG *cis* to one of the substituents on C-2 and C-3 (Scheme 3.7, b, *trans*-**132** and *trans*-**132'**). In the case of conformer *trans*-**132**, the steric interaction between the PG and the R group can be hardly released by either C-C or N-C cleavage. However, the relief in the steric interaction between the PG and ketyl group in the conformer *trans*-**132'** can be achieved via C-N cleavage, which explains the high selectivity for β-amino ester in the reaction with *trans*-aziridines. It is interesting that C-C cleavage products have been rarely seen in the reductive ring opening of aziridines involving single electron transfer processes and this may be due to the fact that *cis*-aziridines have not been previously evaluated in this reaction. The only example that we are aware of involves an un-activated (N-H) aziridine-2-carboxylate *trans*-**139a** with a phenyl group in the 3-position which gives a 28:16 split between C-N (**140a**) and C-C (**141a**) cleavage products (Scheme 3.8).[42c] This is to be compared with the aziridine *cis*-**117a** which gave exclusively the C-C cleavage product **120a** in 75% yield (Table 3.3, entry 1).

Scheme 3.7 Mechanistic rationale for different selectivities observed for *trans*- and *cis*-aziridines



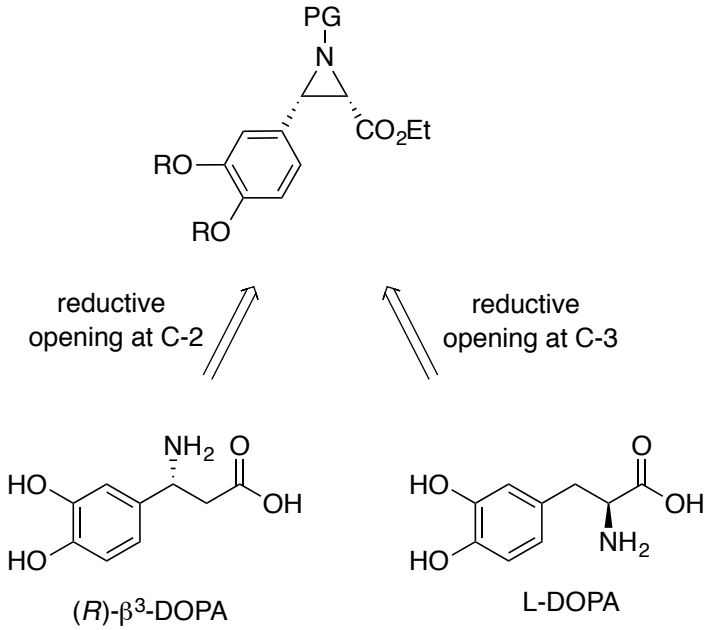
Scheme 3.8 Reported example of a C-C cleavage product from reductive ring opening process



3.7 Syntheses of L-DOPA and (*R*)-β^3-DOPA

The utility of aziridine-2-carboxylates to approach both α- and β-amino acids is illustrated in Scheme 3.9 by the synthesis of L-DOPA and (*R*)-β^3-DOPA, from the same aziridine. L-DOPA is the biological precursor to the catecholamine neurotransmitters, is used in the treatment of Parkinson's disease[48] and is a key compound in the formation of marine adhesive proteins.[49] L-DOPA became the first commercial pharmaceutical agent to be manufactured by a non-proteinaceous asymmetric catalyst which was acknowledged in the 2001 Nobel Prize in chemistry to William S. Knowles.[50] The isomeric (*R*)-β^3-DOPA has been isolated as an iron(III) complex from a dark blue-violet colored mushroom of the species *Cortinarius violaceus*.[51,52] Both natural products could potentially be obtained from the reductive opening of the same aziridine via controlled reductive ring-opening at the C-2 and C-3 positions.

Scheme 3.9 Reported example of C-C cleavage product from reductive ring

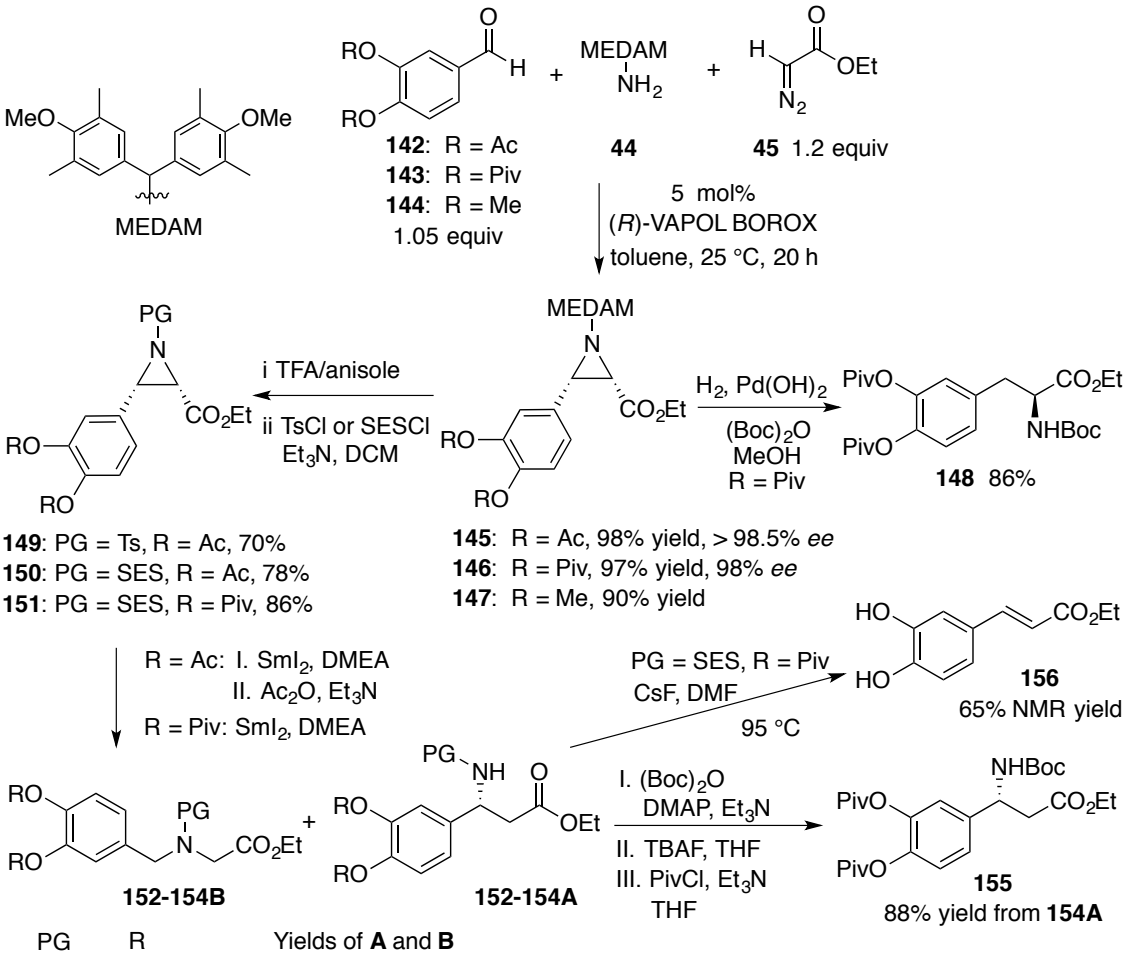


From the synthetic point of view, the *N*-tosyl group is the protecting group of choice for samarium diiodide mediated reductive ring-opening of aziridines if removal of the tosyl group does not cause problems in a later stage. *N*-Tosyl aziridines are completely selective for the C-N cleavage product (>99:1) for both the *cis*- and *trans*-aziridines and with both aryl an alkyl substituents in the 3-position (Table 3.2, entries 5-8). The SES-protecting group can be considered as an alternative to a tosyl sulfonamide which is notorious for its potential in being troublesome during deprotection. The SES-protected aziridine *cis*-**102a** gave excellent selectivity (23:1, Table 3.2) for the β-amino ester and the deprotection of SES is known to proceed under much milder reaction conditions. Thus, we decided to examine both Ts and SES protecting groups.

Our first approach to the synthesis of L-DOPA and (*R*)-β^3-DOPA began with the bis-acetoxy aziridine **145** which was prepared in one step in 98% yield and >98.5% ee from aldehyde **142**, the amine **44** and ethyl diazoacetate **45** by a catalytic asymmetric multicomponent aziridination with 5 mol% VAPOL BOROX catalyst (Scheme 3.10).[12e, 12g] To set the stage for the regio-complimentary reductive ring-opening of the aziridine **145**, the MEDAM group was cleaved with trifluoracetic acid in anisole and the resulting N-H aziridine was not purified but rather directly protected by TsCl or SESCl to give the N-protected aziridines **149** and **150** in 70% and 78% yield, respectively, for the two steps. The samarium diiodide ring-opening of both the tosyl aziridine **149** and SES-aziridine **150** gave complex mixtures due to the cleavage of zero, one or two of the acetoxy groups on the benzene ring. By treating the crude mixtures with acetic anhydride in the

presence of triethylamine, the β-amino esters **152A** and **153A** were isolated in good yields, although an increase in the yield of C-C cleavage product was observed in both cases compared to the corresponding phenyl substituted aziridines *cis*-**101a** and *cis*-**102a** (Table 3.2). This may be due to the electronic effect of the two acetate groups on the benzene ring. Despite the prolonged effort that was taken to investigate the removal of the tosyl group following many of the standard procedures, **152A** could not be deprotected without decomposition.

Scheme 3.10 Syntheses of protected forms of L-DOPA and (*R*)-β^3-DOPA



PG	R	Yields of **A** and **B**			
Ts	Ac	**152B**	8%	**152A**	76%
SES	Ac	**153B**	19%	**153A**	69%
SES	Piv	**154B**	16%	**154A**	74%

Before exploration of SES-deprotection of **153A**, we turned our attention to the acetate cleavage problem in the samarium diiodide ring-opening process. This was solved by replacing the acetate groups with the bulky *tert*-butyl acyloxy (pivaloyl) groups. The catalytic asymmetric multicomponent aziridination worked smoothly with aldehyde **143** and afforded the aziridine **146** in 97% yield and 98% ee. Interestingly the MEDAM group could be removed with trifluoroacetic acid in anisole without cleave of the pivaloyl groups and then directly reacting the N-H aziridine with SESCl gave aziridine **151** in 86% yield. In addition to **146**, we also considered aziridine **147** as a potential candidate for this synthesis. The aziridine **147** was readily prepared from the aldehyde **144** in high yield via the asymmetric aziridination reaction. However, the attempted cleavage of the MEDAM group in **147** with trifluoroacetic acid in anisole only led to decomposition. Formation of β-amino ester **154A** was smoothly achieved (74% yield) from the reductive ring-opening reaction with no detection of cleavage of the pivolyl groups. The first attempt to remove the SES group from the amine function in **154A** following a literature procedure[19] involving heating with CsF in DMF at 95 °C resulted only in the formation of ethyl 3,4-dihydroxycinnamate **156** in 65% yield (NMR yield). This is probably due to a fluoride mediated deprotonation at the α-position of the carbonyl causing an elimination of the SES-amino group. Alternatively **156** could result from a fluoride mediated cleavage of the pivaloyl group followed by a phenoxide assisted elimination of the SES-amino group and a final rearomatization. A similar outcome was also observed for the SES protected β-amino ester **153A**. It has been previously reported that elimination of the SES

group from SES-protected α-amino carbonyl compounds can be a problem during the SES deprotection step.[53] However, there is no example reported for the elimination of the SES-NH_2 group from a β-amino ester during SES deprotection. It is known that *N*-acyl substituted SES groups are much more readily deprotected than simple SES groups.[53] In light of the latter, we carried out the acylation of **154A** by treating it with $(Boc)_2O$ and the crude mixture was treated with TBAF in THF at 25 °C for 1.5 h to afford the desired β-amino ester **155**, the protected form of (*R*)-β^3-DOPA, in 88% isolated yield from **154A**. There was some cleavage of the pivaloyl groups by TBAF and thus a workup with pivaloyl chloride gives **155** as a pure compound. No purification was performed during any of the steps in the conversion of **154A** to **155**. Finally, the reductive ring-opening of aziridine **146** with palladium hydroxide catalyzed hydrogenation in the presence of $(Boc)_2O$ resulted in the formation of the α-amino ester **148**, the protected form of L-DOPA, in 86% isolated yield.

3.8 Conclusion

The reductive ring opening of 3-substituted aziridine-2-carboxylates with samarium diiodide can be controlled to proceed via C-N bond cleavage to give high yields of β–amino esters. The competing C-C bond cleavage gives rise to glycine derivatives. It is necessary to have an activating group on the aziridine nitrogen to achieve selective C-N bond cleavage. Aziridines with non-activating nitrogen substituents (hydrogen or benzhydryl) give exclusively the formation of glycine derivatives when there is a phenyl group in the 3-position and, when there is a cyclohexyl group in the 3-position, low yields of β–amino esters are

observed along with other decomposition products. The selectivity between C-N and C-C bond cleavage directly correlates with the electron-withdrawing power of the activating group on the nitrogen. Sulfonyl groups give higher selectivity than carbamate groups and this is especially noticeable with *cis*-aziridines that have a phenyl group in the 3-position. The lower selectivity with *cis*-aziridines is thought to be due to a steric release during the C-C bond cleavage leading to glycine products. The utility of this methodology is illustrated in the synthesis of a protected form of (*R*)-β^3-DOPA by the reductive opening of aziridine **151** with samarium diiodide to give the β-amino ester **154A**. Furthermore, this synthesis features the targeting of (*R*)-β^3-DOPA and its regioisomer L-DOPA by ring opening of the same aziridine **146**, the former by a reductive opening at the C-2 position and the latter by reductive opening at the C-3 position.

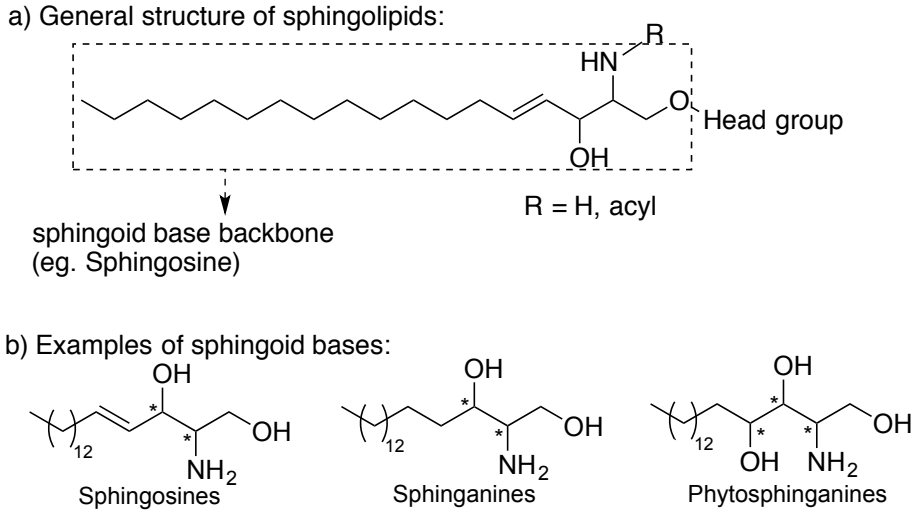
CHAPTER 4

STUDIES ON THE SYNTHESES OF TWO-HEADED SPHINGOID BASES

4.1 Introduction

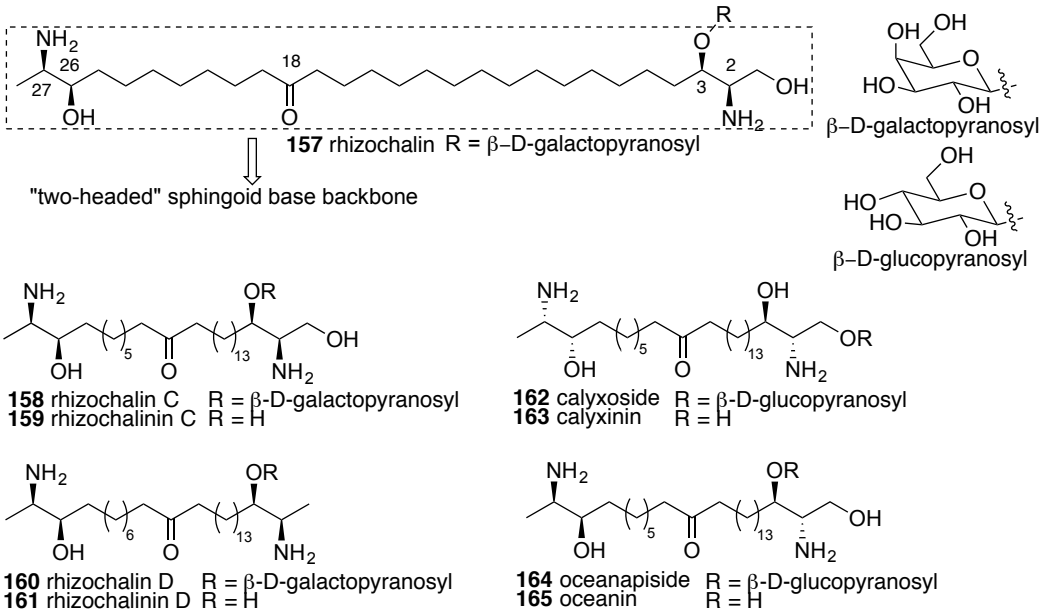
Sphingolipids are important components of eukaryotic cell membranes, which play important roles in various aspects of cell regulation including cell growth, differentiation, cell death, adhesion, neuronal repair and signal transduction.[54] The core structure of a sphingolipid involves a sphingoid base backbone, which is a long-chain (mostly C_{18} chain) amino alcohol (Figure 4.1, a). Usually, the sphingoid base backbone involves a 2-amino-1,3-dihydroxy terminus, where an acyl group can be attached to the amino nitrogen and (or) a head group located on 1-OH, such as hydrogen, phosphate and glycoside. The three most common sphingoid bases found in mammalian cells include sphingosines, sphinganines and phytosphingosines (Figure 4.1, b).[54b]

Figure 4.1 The general structure of sphingolipids and examples of sphingoid bases



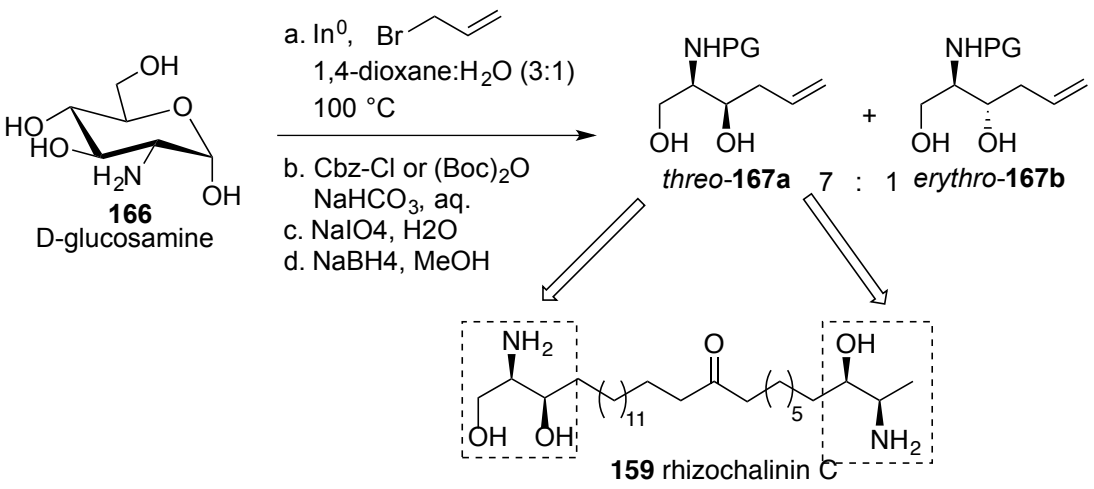
In 1989, Rhizochalin (**157**) was isolated from a marine sponge as the first member of a new series of sphigolipids, whose sphingoid base backbone is a C_{28} chain and has both ends (α and ω terminus) functionalized (Figure 4.2).[55] This special class of sphingolipids derived from the rare bis-α,ω-amino alcohols is called "two headed sphingolipids", as their backbone is a formal "tail to tail" connection of two normal sphingoids. Some other members of this series include rhizochalin C (**158**)[56] and D (**160**)[56], calyxoside (**162**)[57] and oceaninapiside (**164**),[56, 58] with their sphingoid base aglycons being rhizochalinin C (**159**) and D (**161**), calyxinin (**163**) and oceanin (**165**) (Figure 4.2). In addition to their more complex structure, the two-headed sphingolipids were found to have high biological activity, including cytotoxic activity against carcinoma cells,[55] antibacterial activity,[55] antifungal activity,[59,60] selective DNA-damaging activity[57] and inhibition of protein kinase C.[61] More interestingly, Molinski and coworkers discovered that the antifungal activity of the "two headed" sphingoid bases was ten times greater than the normal "one-headed" ones, which might be attributed to interaction with two receptor sites by one bifunctionalized "two-headed" base.[62]

Figure 4.2 The first member of the “two-headed” sphingolipids series



Despite the promising biological properties of the rare “two-headed” sphingolipids, the total synthesis of these sphingolipids or their sphingoid bases has not been explored much. Up till now, there has been only one example of a total synthesis of a two-headed sphingoid base, rhizochalinin C, reported by the Molinski’s group in 2013 (Scheme 4.1).[63] In this synthesis, D-glucosamine was used from the chiral pool to generate the key intermediate *threo*-**167a** in 4 steps starting with an indium-mediated Barbier reaction (dr ~ 7:1). The subsequent protection of the diol, chain elongation by alkene metathesis and further functionalization provided the left half and right half pieces of the targeted molecule. Coupling of the two halves both derived from *threo*-**167a** by Horner-Emmons-Wadsworth reaction and final hydrogenation completed the synthesis of rhizochalinin C (**159**). There have been no examples of an asymmetric synthesis of two-headed sphingoid bases by using a chiral catalyst reported to date.

Scheme 4.1 Total synthesis of rhizochalinin C from a chiral pool



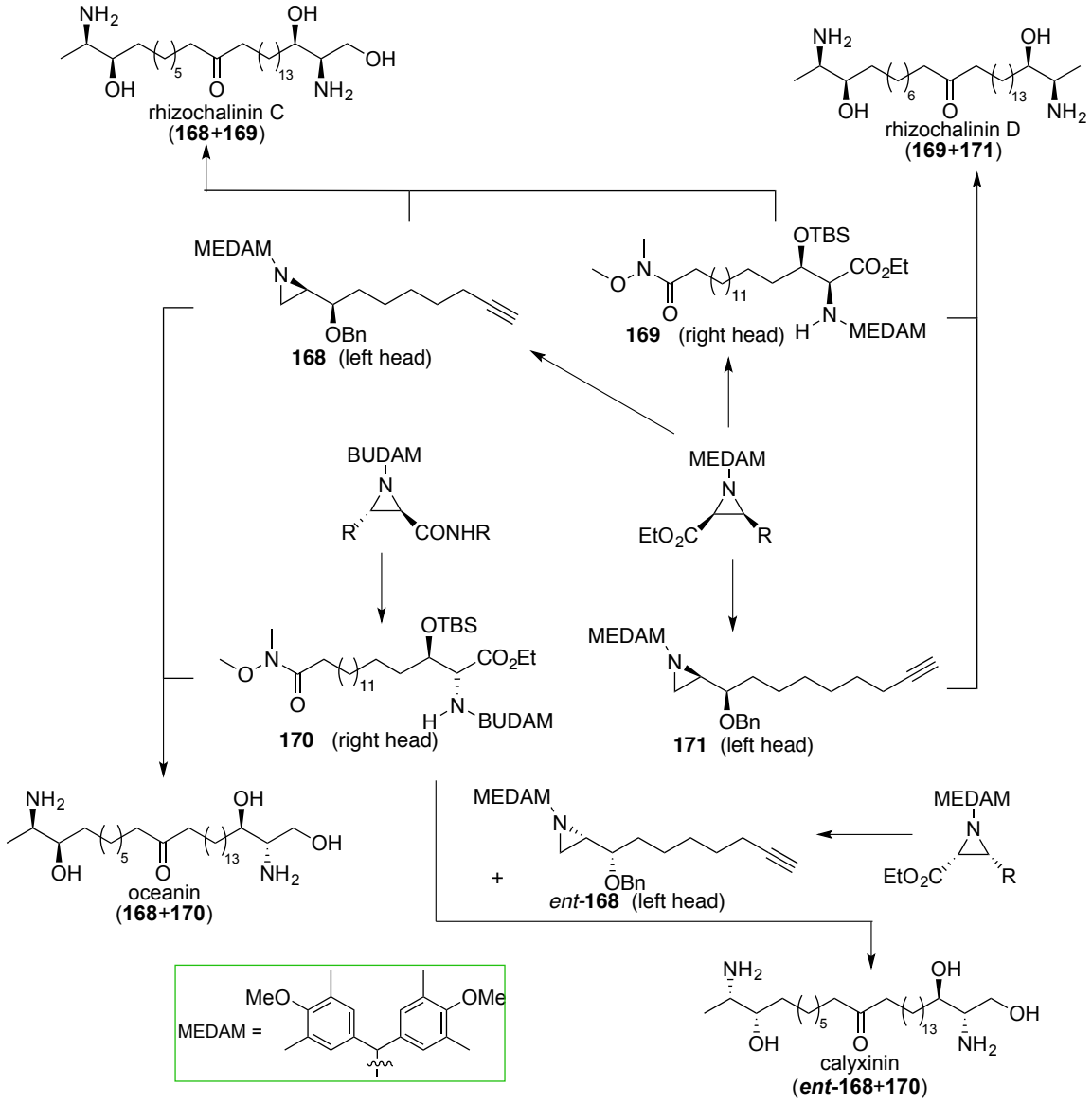
We have previously reported a catalytic asymmetric synthesis of all four diastereomers of the "one-headed" base sphinganines, where the correct stereochemistry of the amino alcohol terminus was accomplished via our catalytic asymmetric aziridination reaction.[12a] Based on these experiences, we became interested in applying the aziridination reaction to the synthesis of four of the "two-headed" sphingoid bases, which are rhizochalinin C (**159**) and D (**161**), calyxinin (**163**) and oceanin (**165**).

Our ultimate goals of this project are twofold: 1) develop a versatile method where the catalytic asymmetric aziridination reaction can be used to provide access to four different marine-derived "two headed" sphingoid bases that are difficult to acquire; 2) confirm the structure and stereochemistry of the corresponding "two-headed" sphingolipids. This chapter will mainly focus on the studies of the synthesis of rhizochalinin C.

4.2 Synthetic Strategy towards the Four Two-Headed Sphingoids

Our strategy to synthesize all four of the targeted “Two-headed” spingolipids involves the initial synthesis of three different “left heads” (**168**, *ent*-**168** and **171**) and two different “right heads” (**169** and **170**) via the asymmetric catalytic aziridination reaction and then convergent late-stage coupling involving proper mix and match of the two “head pieces” (Scheme 4.2). By controlling the stereoselectivity of the aziridination, we can get access to all the requisite stereochemistries at the amino alcohol terminus.

Scheme 4.2 Proposed synthetic approach to the four sphingoid bases

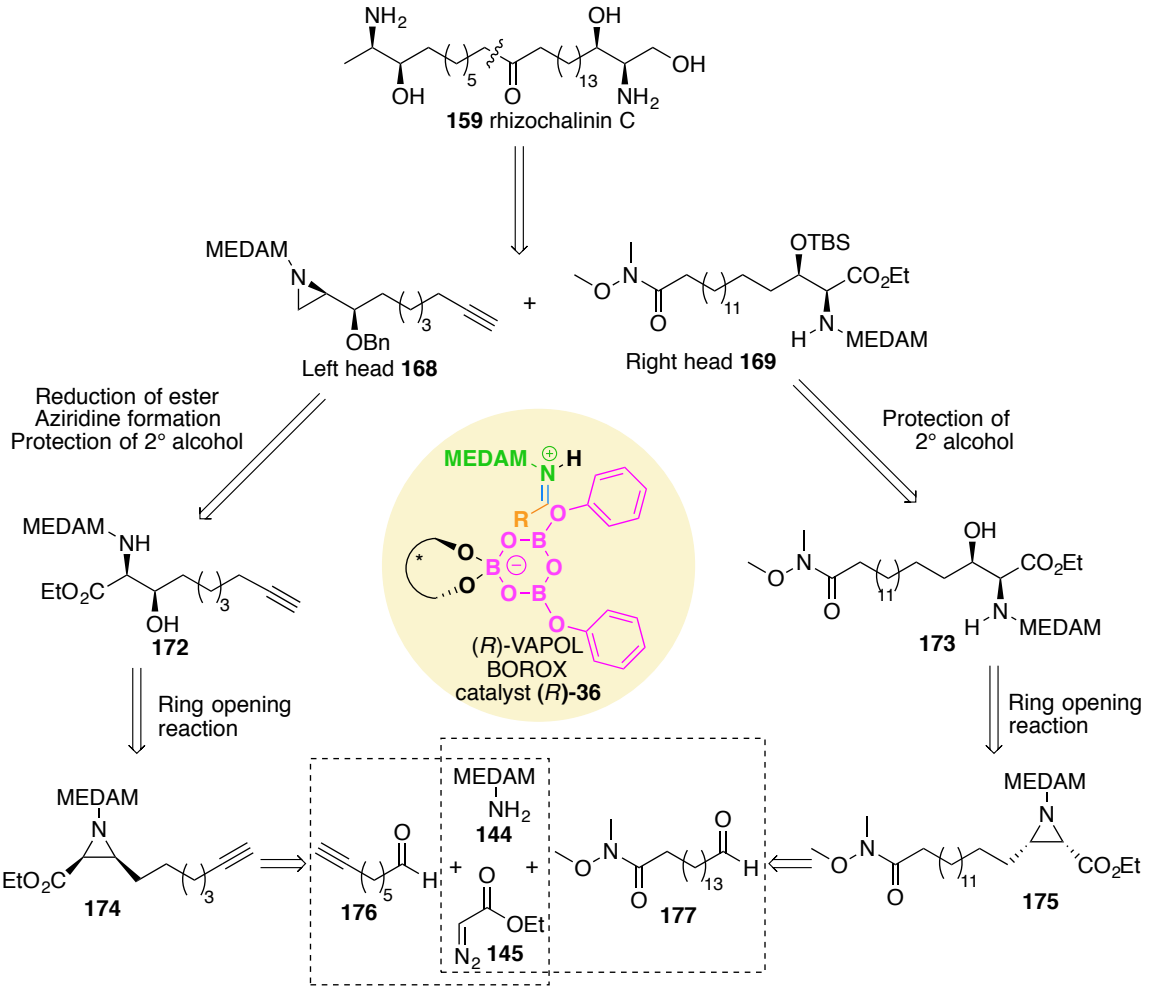


4.3 Retrosynthetic Analysis of Rhizochalinin C

Rhizochalinin C (**159**) was chosen as the first targeted molecule. We envisioned that the skeleton of rhizochalinin C (**159**) could be constructed by a late-stage coupling of left head **168** and right head **169**, which could be derived from compound **172** and **173**, respectively, as shown in Scheme 4.3. The *cis* amino alcohol moiety in **172** and **173** would be achieved via ring an opening

reaction of *cis*-aziridines **174** and **175** by an oxygen nucleophile. Both aziridines could be prepared by the asymmetric aziridination reaction catalyzed by (*R*)-VAPOL-BOROX **36** from corresponding aldehydes **176** and **177**.

Scheme 4.3 Retrosynthetic analysis for rhizochalinin C



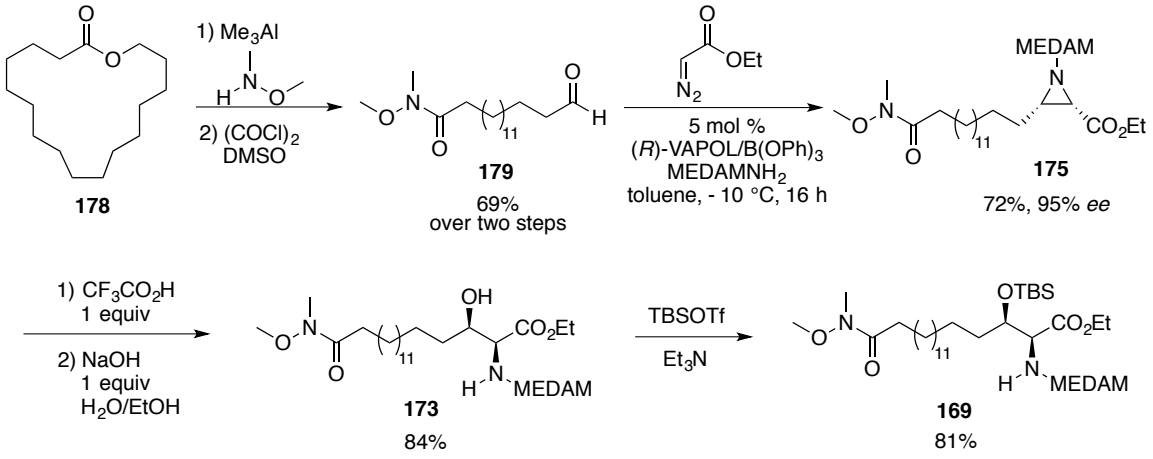
4.4 Synthesis of Right Head 169 and Left Head 168

4.4.1 Synthesis of Right Head 169

The synthesis of right head **169** is shown in Scheme 4.4. Xin Zhang from our group performed the synthesis of **173** from **178**. The aldehyde **179** was prepared from the commercially available lactone **178** by ring opening with

Weinreb's amine and Swern oxidation in 69% yield over two steps. The catalytic asymmetric aziridination of aldehyde **179** afforded the desired aziridine in 72% yield with 95% *ee*, which was then treated with trifluoroacetic acid followed by basic hydrolysis to give the ring opened product **173** in high yield (84%). Protection of **173** was initially attempted with *tert*-butyldimethylsilyl chloride (TBSCl) in the presence of triethylamine, which resulted in low conversion after long reaction time (not shown). The silylated left head **169** was easily obtained in 81% yield by using the more reactive trimethylsilyl trifluoromethanesulfonate (TBSOTf).

Scheme 4.4 Synthesis of right head **169**



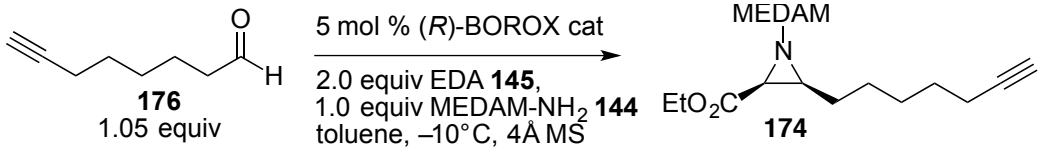
4.4.2 Synthesis of Left Head 168

The synthesis of left head **168** involves several key steps similar to the right head **169**, including asymmetric aziridination, ring opening reaction of the aziridine and protection of the resultant secondary alcohol.

The requisite aziridine **174** was synthesized from aldehyde **176**[64] that can be prepared from the commercially available 3-octyl-1-ol. Initially, the

aziridination was carried out with VAPOL-BOROX catalyst prepared from $B(OPh)_3$ (method A), which provided the aziridine **174** with 95% *ee* in 97% total yield. However, the difficult separation of aziridine **174** and phenol that was generated from the hydrolysis of BOROX catalyst led to only a 24% yield of **174** as a pure fraction and a 73% yield of **174** contaminated with phenol (Table 4.1, entry 1). It was found that if the phenol remained as an impurity in **174**, it would interfere with the next ring-opening reaction (Table 4.2, entry 1). To solve this separation problem, a phenol derivative with a different polarity needs to be used instead of PhOH in the BOROX catalyst and this was prepared by method B. The aziridination with catalyst prepared by method B using p-methoxyphenol afforded the pure product **174** in 91-92% yield with the same asymmetric induction (Table 4.1, entries 2 and 3).

Table 4.1 Catalytic asymmetric aziridination with aldehyde **176**



BOROX catalyst preparation:

Method A: Ligand (5 mol %)
$B(OPh)_3$ (15 mol %)
$MEDAMNH_2$ **144** (100 mol %)
80 °C, toluene, 0.5 h → (*R*)-BOROX catalyst

Method B: Ligand (5 mol %)
$BH_3{\cdot}SMe_2$ (15 mol %)
H_2O (15 mol %)
p-methoxyphenol (10 mol %)
100 °C, toluene, 1h → $MEDAMNH_2$ **144** (100 mol %), rt, 0.5 h → (*R*)-BOROX catalyst

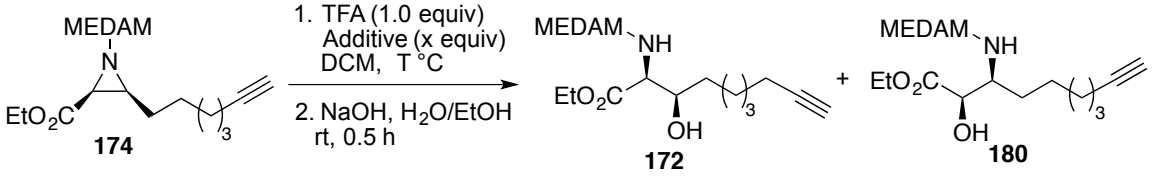
Table 4.1 (cont'd)

entry[a]	Scale (mmol)	method	ligand	time (h)	% *ee*[b] **174**	% yield[c] **174**
1	5	A	(*R*)-VAPOL	16	95	(24+73)[d]
2	10	B	(*R*)-VAPOL	15	95	92
3	2	B	(*S*)-VAPOL	15	–95	91

[a] Unless otherwise specified, all reactions were carried out at 0.5 M in **144** in toluene for the indicated time with 5 mol % the catalyst prepared from method A or B. [b] Determined by HPLC. [c] Isolated yield after silica gel chromatography. [d] 24% pure aziridine was isolated and the other 73% aziridine contained phenol as an impurity (aziridine:phenol = 1:0.43).

Next, the aziridine **174** was subjected to trifluoroacetic acid induced ring opening under the various conditions shown in Table 4.2. The ring opening reaction of **174** in the presence of PhOH was first investigated since it is difficult to separate PhOH from aziridine **174** prepared by method A (Table 4.1). Our group member Yubai Zhou found that the addition of AcOH could improve both the yield and the regioselectivity of the ring opening reaction of a related aziridine. However, both PhOH and AcOH had negative effects on the reaction yield when employed as additives (Table 4.2, entries 1-3 vs 4-5). The reaction at 40 °C gave mixtures of the regioisomers **172** and **180** in ratios that were scale dependent (Table 4.2, entries 4 and 5). When the temperature was lowered to 0°C, the ring opening reaction hardly proceeded determined by TLC after the first step (Table 4.2, entry 7). The reaction carried out at rt gave the product **172** in good yield with a regioselectivity of 16.7:1 (average of two runs) and thus it is the optimal condition for ring opening of **174** (Table 4.2, entry 6).

Table 4.2 Ring opening reaction of aziridine **174**



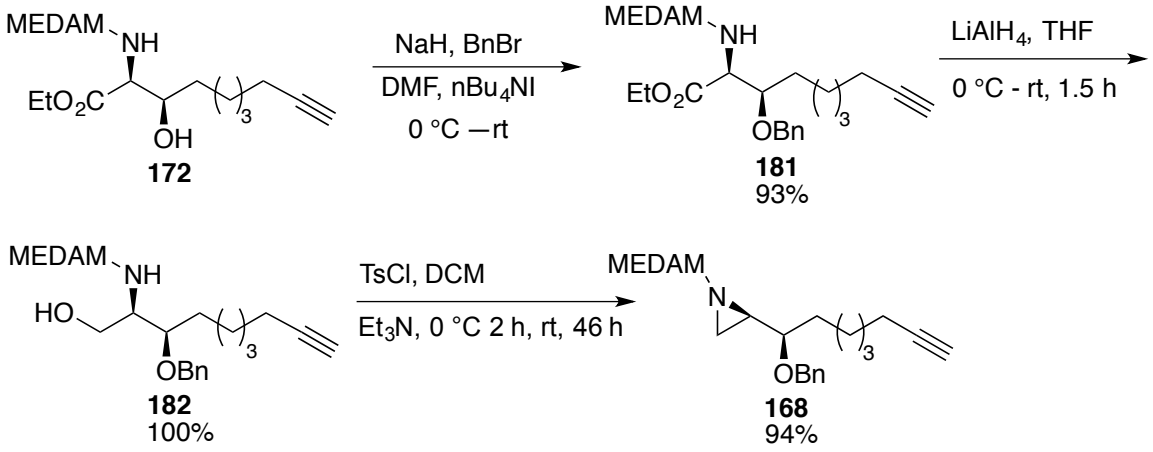
Entry[a]	conc. (M)	temp (°C)	additive	time (h)	ratio of **172**:**180**	% yield[b] **172**
1[d]	0.2	40	PhOH (0.43 equiv)	14	nd	28
2	0.2	40	AcOH (0.5 equiv)	18	nd	44
3	0.2	40	AcOH (1.0 equiv)	18	nd	66
4	0.2	40	–	15	10:1	83[c]
5[e]	0.2	40	–	15	4.5:1	70
6[g]	0.2	rt	–	22	16.7:1	83
7[f]	0.4	0	–	22	nd	nd

[a] Unless otherwise specified, all reactions were carried out with **174** (0.2 mmol) in DCM for the indicated time with x equiv of the additive. [b] Isolated yield of pure **172** after silica gel chromatography. [c] ^{1}H NMR yield determined with Ph_3CH as an internal standard. [d] 22% $(3,5\text{-}Me_2\text{-}4\text{-}MeOC_6H_2)_2CHOPh$ was isolated. [e] Reaction was carried out at 8.6 mmol scale. [f] Little product was formed in the first step as indicated by TLC. [g] Average of two runs at 0.2 mmol and 0.9 mmol scale.

Protection of the 2° alcohol in compound **172** as the benzyl ether afforded compound **181** in 93% yield, which was then reduced by lithium aluminum hydride quantitatively to give compound **182** (Scheme 4.5). Conversion of the 1° alcohol in **182** into a tosylate was immediately followed by an intramolecular S_N2

attack by the adjacent amino group to give an aziridine in the form of the left head **168** in 94% yield (Scheme 4.5).

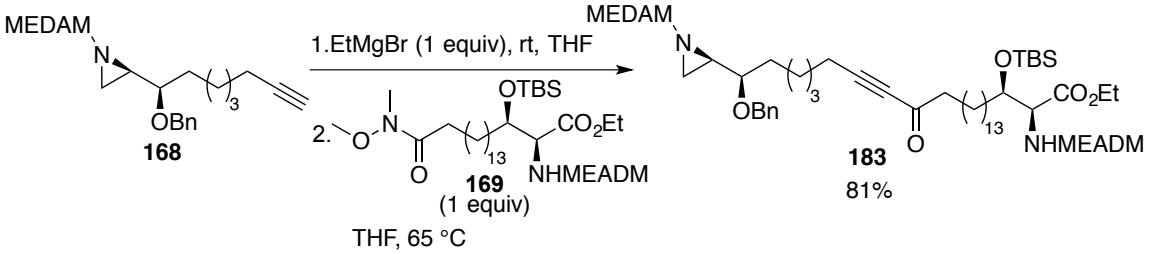
Scheme 4.5 Synthesis of **168** from **172**



4.5 Late-stage Coupling of Left Head 168 and Right Head 169 Followed by Removal of the TBS Group

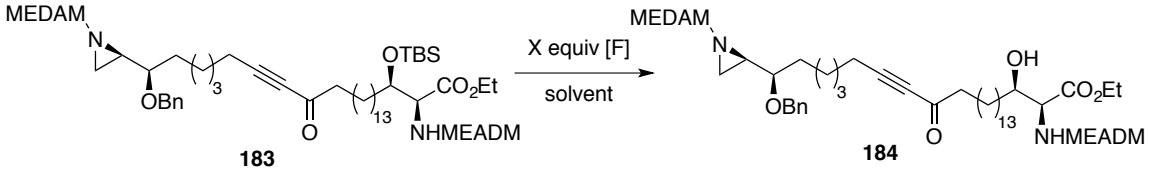
After several different conditions were screened, the coupling reaction of the left head **168** and right head **169** was achieved as shown in Scheme 4.6. Left head **168** was treated with the strong base ethylmagnesium bromide (EtMgBr) to form the corresponding acetylide which was then reacted with the right head **169** to give the desired product **183** in 81% isolated yield.

Scheme 4.6 Coupling of **168** with **169**



Next, different fluoride sources were screened to remove the silyl group in **183** (Table 4.3). Treatment of **183** with 2 equivalent of TBAF only led to complete decomposition (Table 4.3, entry 1), while decreasing the amount of TBAF to 1 equivalent resulted in a very slow reaction with decomposition also observed (Table 4.3, entry 2). The use of the less reactive HF·pyridine failed to provide any desired product. Finally, compound **183** was converted to the mono-protected diol **184** in quantitative yield by treatment with 25% aq HF. It is important to mention that the selective deprotection of the 2° alcohol in the right head provides an entry point to the natural product rhizochalin C via introduction of the carbohydrate unit to the mono-protected diol **184** (Scheme 4.7).

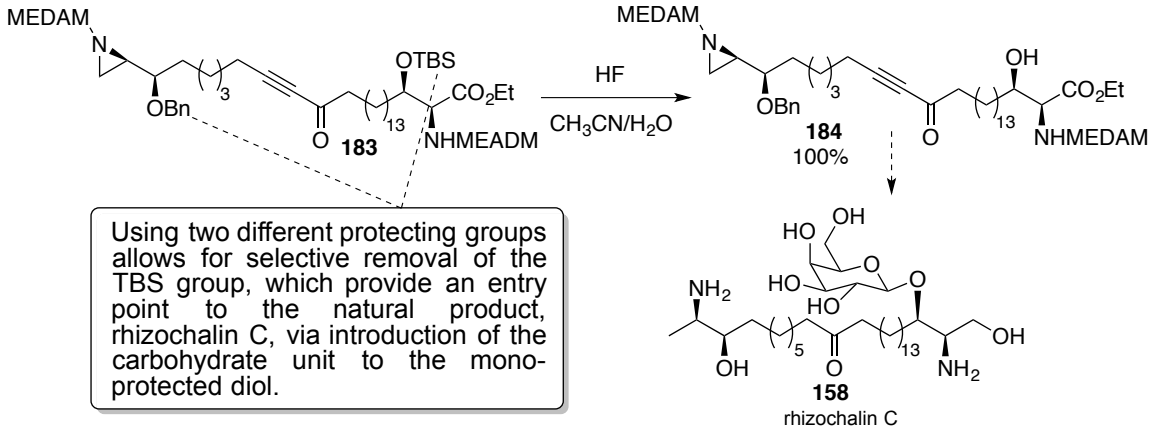
Table 4.3 Removal of TBS group in **183**



Entry	floride source	solvent	equivalent(s)	time (h)	% yield[a] **183**
1	TBAF	THF	2.0	22	trace
2	TBAF	THF	1.0	19	trace
3	HF·Pyr	CH_3CN/CH_2Cl_2	1.0	20	trace
4	aq HF	CH_3CN	1.0	5	90

[a] Isolated yield after silica gel chromatography.

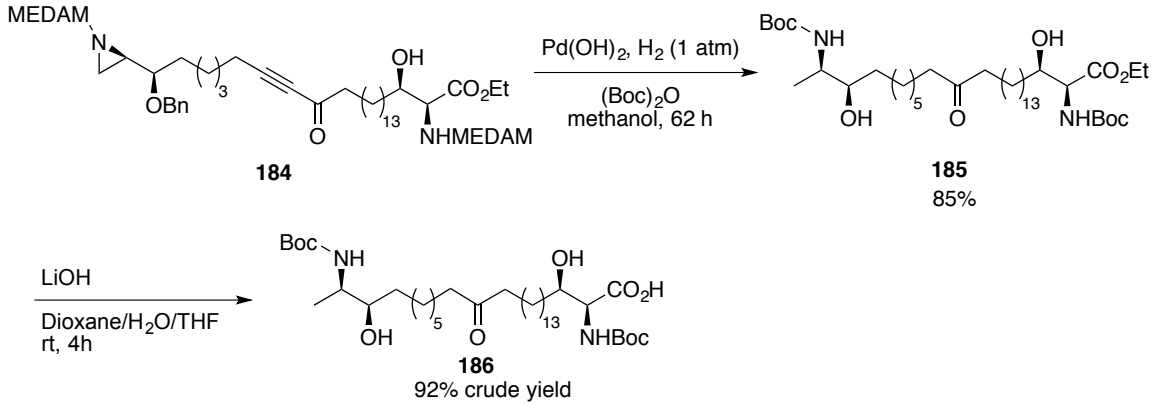
Scheme 4.7 Entry point to rhizochalin C



4.6 Global Deprotection, Alkyne Reduction and Ring Opening of Aziridine 184 by Hydrogenation Followed by Hydrolysis

We next investigated the hydrogenation reaction of **184**. The optimized condition involves $(Boc)_2O$ as an additive to in situ protect the free amino group generated in the reaction. The hydrogenation catalyzed by $Pd(OH)_2$ in the presence of $(Boc)_2O$ successfully reduced the triple bond, removed the Bn group and both MEDAM groups, and reductively opened the aziridine ring to give product **185** in 85% yield. After hydrolysis by LiOH, compound **186** was obtained in 92%.

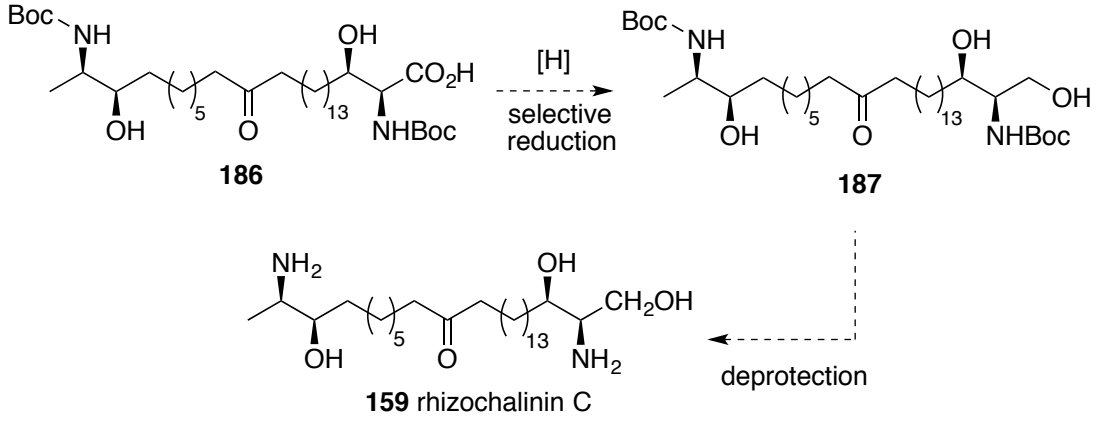
Scheme 4.8 Hydrogenation and hydrolysis



4.7 Attempted Selective Reduction of the Carboxylic Acid in the Presence of a Ketone

The last two steps that we planned for the synthesis of rhizochalinin C include selective reduction of the carboxylic acid in compound **186** to give compound **187** and then removal of the Boc groups. Different conditions reported for such a selective reduction include $BH_3 \cdot THF$[65], $BH_3 \cdot SMe_2$[66] or $BH_3 \cdot THF$ with $B(OMe)_3$ as an additive[67] and all have been examined with **186**, but the reduction of the ketone functional group was always observed at either incomplete or 100% conversion.

Scheme 4.9 Proposed final steps toward the synthesis of rhizochalinin C

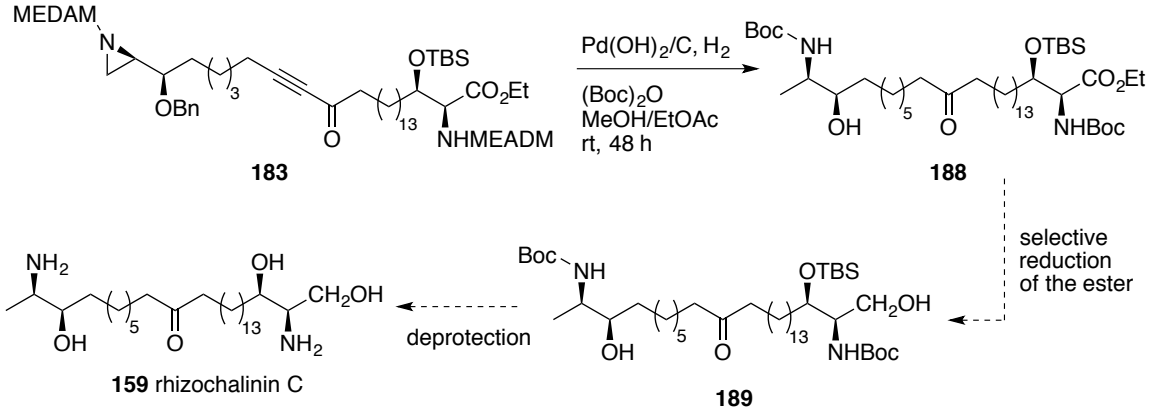


4.8 Attempted Selective Reduction of the Ethyl Ester in the Presence of a Ketone

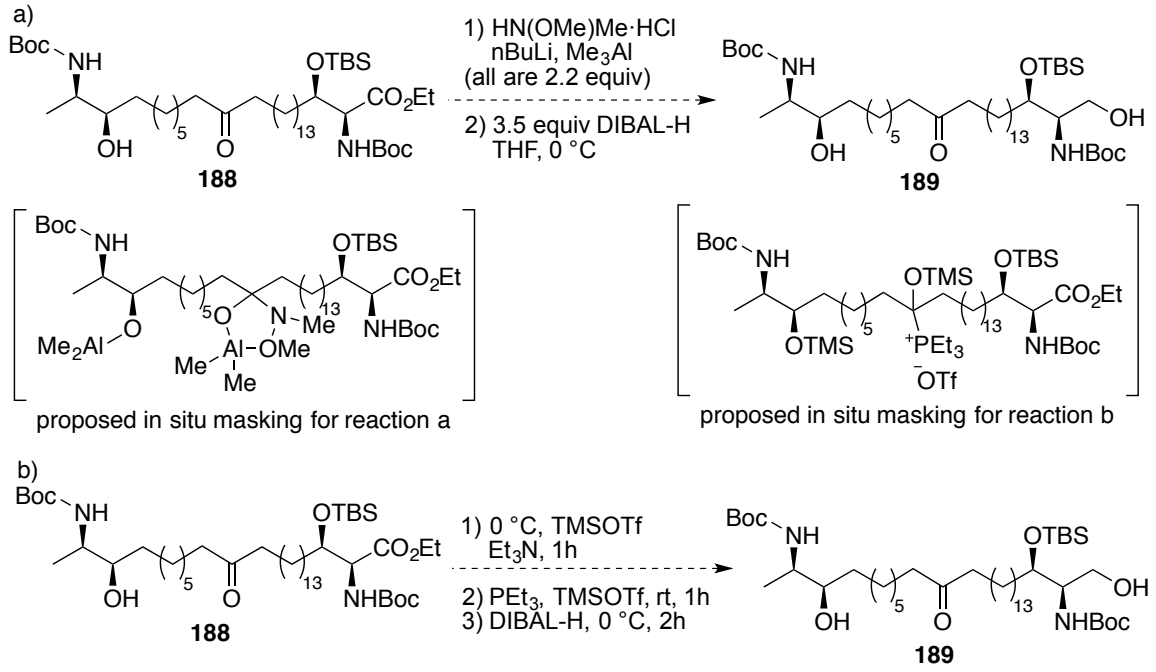
Inspired by two reported examples, which involve in situ masking the more reactive ketones to achieve reactions with the less reactive ester groups, we came up with a modified strategy toward the synthesis of rhizochalinin C as shown in Scheme 4.10. We turned our attention to the selective reduction of compound **188**, which was synthesized by hydrogenation of **183** in high yield

(Scheme 4.9) under the same condition that is shown in Scheme 4.8. The two reported conditions for the selective reduction of an ester group in the presence of a ketone were explored with compound **188**. One involves masking the ketone as an aminal (Scheme 4.11 a) and the other involves masking the ketone as a phosphonium salt (Scheme 4.11 b). Unfortunately, both reactions failed to give the desired product **189**. This new strategy was abandoned at this point.

Scheme 4.10 Modified strategy toward the synthesis of rhizochalinin C



Scheme 4.11 Modified strategy toward the synthesis of rhizochalinin C



4.9 Conclusion

The asymmetric synthesis of one of the four “two headed” sphingoid bases, rhizochalinin C, has been explored. The left head **168** and right head **169** were synthesized via asymmetric aziridination reaction, which highlighted the synthetic utility of the BOROX-catalyzed asymmetric aziridination in building chiral vincinal amino alcohol moieties. Late stage coupling of the two heads afforded the product with the complete carbon skeleton in high yield. The hydrogenation of **184** or **183** catalyzed by $Pd(OH)_2$ in the presence of $(Boc)_2O$ successfully reduced the triple bond, deprotected the 2° alcohol, removed the MEDAM group, and reductively opened the aziridine ring. Finally, the selective reductions of the acid group in **186** and the ester group in **188** in the presence of a ketone functional group were attempted, both of which failed to provide the desired product. It is envisioned that the common strategy involving protection and

deprotection of the ketone will probably remove the obstacle in the final steps toward the targeted molecule, which will be investigated in the future. Once the asymmetric synthesis of rhizochalinin C is developed, the same strategy will be applied to the other three sphingoid bases.

CHAPTER 5

EXPERIMENTAL SECTION

General information: Tetrahydrofuran (THF), diethyl ether and toluene were distilled from sodium under nitrogen. Dichloromethane was distilled from calcium hydride under nitrogen. Hexanes and ethyl acetate were ACS grade and used as purchased. Phenols were sublimed or recrystallized and stored in a dry desiccator. Solid aldehydes were either used as purchased from Aldrich or sublimed before use. Liquid aldehydes were distilled before use. Other reagents were used as purchased from Aldrich. VANOL and VAPOL were prepared according to literature procedures and were determined to be at least 99% optical purity.[1] Preparation of phenols **P-42**[68], **P-43**[69], ligands (*S*)-**73**[12c], (*S*)-**74**[12c], (*S*)-**75**[70], (*S*)-**77**[70], and (*S*)-**79**[70] have been previously reported.

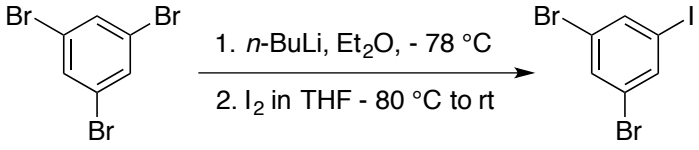
Melting points were determined on a Thomas Hoover capillary melting point apparatus and were uncorrected. IR spectra were taken on a Galaxy series FTIR-3000 spectrometer. ^{1}H NMR and ^{13}C NMR were recorded on a Varian Inova-300 MHz, Varian UnityPlus-500 MHz or Varian Inova-600 MHz instrument in $CDCl_3$ unless otherwise noted. $CHCl_3$ was used as the internal standard for both ^{1}H NMR (δ = 7.24) and ^{13}C 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, by staining with phosphomolybdic acid in ethanol or with the aid of Iodine vapor. 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.

5.1 Experimental Part for Chapter 1

5.1.1 Preparation of Chiral Ligand (*R*)-**76** and (*R*)-**78**

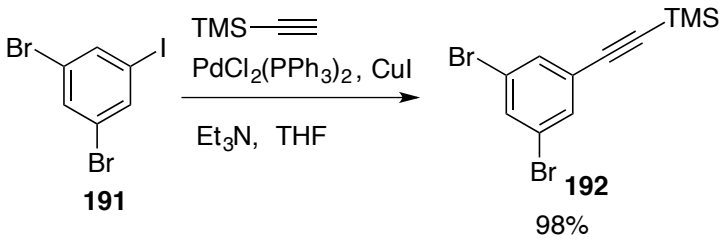
*Preparation of (R)-**76**:*



190 **191**
95% crude yield

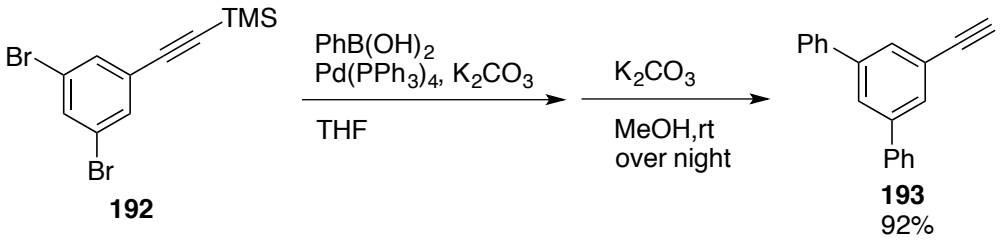
*1,3-dibromo-5-iodobenzene **191**:* The reaction was carried out with an adaptation of a reported procedure.[71] To a flame-dried 1 L round bottom flask was added 1,3,5-tribromobenzene **190** (25.2 g, 80.0 mmol, 1.00 equiv) and dry Et_2O (620 mL). The solution was pre-cooled to – 78°C. Then *n*-BuLi (2.5 M in hexanes, 33 mL, 1.03 equiv) was added via syringe pump in 1.2 h. The reaction mixture was stirred at – 78°C for another 30 min. Then a solution of I_2 (21.3 g in 46 mL THF, 84.0 mmol, 1.05 equiv) was quickly added to the mixture. After it was slowly warmed up to room temperature by removal of the cold bath (about 2 h), a solution of $Na_2S_2O_3$ (8.5 g) in 160 mL H_2O was added to the reaction flask and the resulting mixture was stirred for 20 min. The organic layer was separated

and the aqueous layer was extracted with Et_2O (150 mL × 2). The combined organic layer was washed with H_2O (100 mL × 2) and brine (100 mL), dried over Na_2SO_4, filtered and concentrated to afford a greenish solid (27.6 g, 76.3 mmol) in a crude yield of 95%, which was directly used in the next step without further purification. mp 120-121 °C (Lit.[72] 118 °C). R_f = 0.59 (hexane). Spectral data for **191**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (t, 1H, *J* = 1.8 Hz), 7.78 (d, 2H, *J* = 1.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 94.42, 123.37, 133.64, 138.51. These spectral data match those previously reported for this compound.[72]



1,3-Dibromo-5-(trimethylsilylethynyl)benzene ***192***: To a 250 mL flame-dried round bottom flask filled with nitrogen was added 1,3-dibromo-5-iodobenzene **191** (27.5 g, 76.0 mmol, 1.00 equiv), $PdCl_2(PPh_3)_2$ (801 mg, 1.14 mmol, 1.5 mol %), CuI (218 mg, 1.14 mmol, 1.5 mol %), dry THF (115 mL) and Et_3N (43 mL) under nitrogen. The reaction mixture was stirred at room temperature for 5 min and then trimethylsilyl acetylene (11.3 mL, 79.8 mmol, 1.05 mmol) was added slowly. The reaction mixture was stirred at room temperature for 27 h. After removal of the solvent by rotary evaporation, the residue was treated with $NaHCO_3$ (sat. aq. 450 mL) and Et_2O (450 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (150 mL × 3). The combined organic layer was washed with H_2O (300 mL × 2), dried over Na_2SO_4,

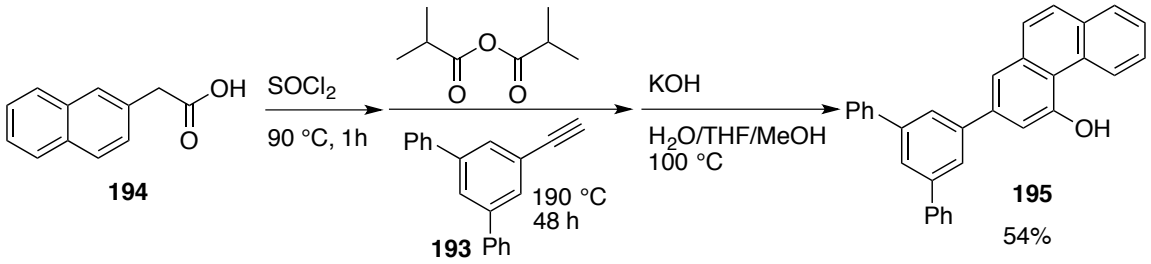
filtered through Celite and concentrated to dryness. The crude product was purified by passing through a short column (50 mm × 150 mm, neutral Al_2O_3, hexanes as eluent) to give **192** as a light orange oil (24.6 g, 74.1 mmol) in 98% yield. R_f = 0.53 (hexane). Spectral data for **192**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.24 (s, 9H), 7.51 (d, 2H, *J* = 1.7 Hz), 7.58 (t, 1H, *J* = 1.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 0.25, 97.55, 101.68, 122.48, 126.51, 133.31, 134.13. These spectral data match those previously reported for this compound.[73]



192 **193** 92%

*1-(Ethynyl)-3,5-diphenylbenzene **193**:* This compound was prepared using a procedure that has been reported for a related compound.[11] To a solution of **192** (4.99 g, 15.0 mmol, 1.00 equiv) in THF (100 mL) were added $Pd(PPh_3)_4$ (2.60 g, 2.25 mmol), K_2CO_3 (20.7 g, 150 mmol) and $PhB(OH)_2$ (5.49 g, 45.0 mmol). After the mixture was stirred at 65 °C under nitrogen for 48 h, it was treated with NH_4Cl (sat. aq. 65 mL) and then subjected to rotary evaporation to remove the organic solvent. Then 30 mL H_2O was added to the residue and it was extracted with Et_2O (100 mL × 3), dried over Na_2SO_4, filtered and concentrated to give an orange residue, which was passed through a short column (silica gel, 30 mm × 150 mm, hexanes) to give a yellow oil. The oil was then dissolved in MeOH (35 mL) and treated with K_2CO_3 (4.81 g, 34.8 mmol). The reaction mixture was stirred at room temperature for 25 h. To the resulting

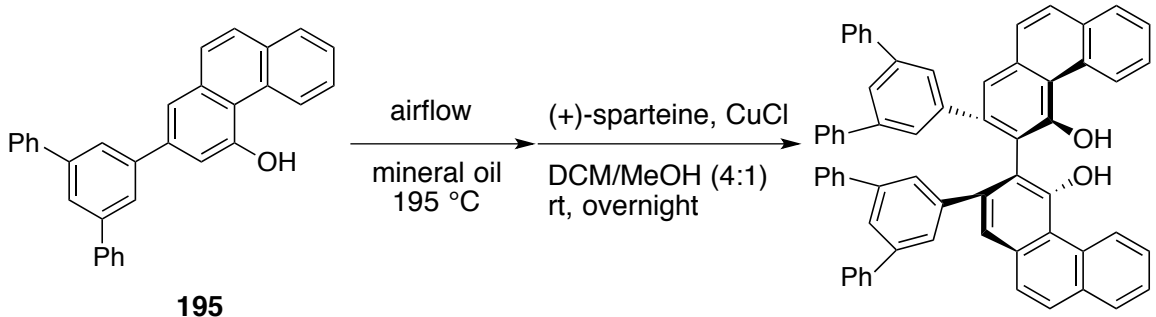
reaction mixture was added H_2O (95 mL) and this mixture was extracted with Et_2O (60 mL × 3). The organic layer was dried over $MgSO_4$, filtered through Celite and concentrated to dryness. Purification of the crude product by column chromatography on silica gel (40 mm × 200 mm, hexanes/EtOAc 10:1) gave **193** as a white solid (2.71 g, 10.7 mmol, 92%). mp 103-105 °C; R_f = 0.41 (1:10 EtOAc/hexanes). Spectral data for **193**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.12 (s, 1H), 7.35-7.40 (m, 2H), 7.42-7.48 (m, 4H), 7.59-7.64 (m, 4H), 7.69 (d, 2H, *J* = 1.7 Hz), 7.77 (t, 1H, *J* = 1.7 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 77.33, 83.58, 122.98, 126.68, 127.19, 127.79, 128.88, 129.66, 140.19, 142.00. IR (thin film) 3291(s), 3036(w), 1591(m), 1497(m) cm^{-1}; HRMS (EI+) calcd for $C_{20}H_{14}$ *m/z* 254.1096 ([M]$^+$), meas 254.1088.



*2-(3,5-diphenylphenyl)phenanthren-4-ol **195**:* A single-neck 100 mL round bottom flask equipped with a condenser was charged with 2-naphthaleneacetic acid **194** (1.44 g, 7.70 mmol, 1.00 equiv) and $SOCl_2$ (2.0 mL, 28 mmol, 3.6 equiv). The top of the condenser was vented to a bubbler and then into a beaker filled with NaOH (sat. aq.) to trap acidic gases. The mixture was heated to reflux for 1 h in a 90 °C oil bath, and then all of the volatiles were carefully removed by swirling it under high vacuum (1 mm Hg) for 1 h with a 2nd liquid N_2 trap to protect the pump. To the flask containing the acyl chloride was added 1-(Ethynyl)-3,5-

diphenylbenzene **193** (2.56 g, 10.1 mmol, 1.3 equiv) and (*i*-PrCO)$_2$O (2.6 mL, 15.7 mmol, 2.0 equiv) under N_2. The mixture was stirred at 190 °C for 48 h with a gentle nitrogen flow across the top of the condenser. The brown reaction mixture was cooled down to below 100 °C (*ca.* 40 °C, oil bath temperature) and THF (4.0 mL), MeOH (7.0 mL) and a solution of KOH (2.6 g, 46 mmol, 6.0 equiv) in 10 mL H_2O were then added slowly. This mixture was stirred at 100 °C overnight. Upon completion, the reaction mixture was subjected to rotary evaporation to remove the organic solvents. Then EtOAc (20 mL) was added to the residue and it was stirred for 10 min at room temperature. The organic layer was separated and the aqueous layer was extracted with EtOAc (15 mL × 3). The combined organic layer was washed with brine (5 mL), dried over $MgSO_4$, filtered through Celite and concentrated to dryness. Purification of the crude product by column chromatography on silica gel (50 mm x 200 mm, CH_2Cl_2/hexanes 1:2 to 1:1 to 2:1) gave the product **195** as a light brown solid, which was recrystallized from CH_2Cl_2/hexane 2:1 (20 mL) to give **195** as an off-white solid (1.40 g, 3.31 mmol) in a yield of 43%. The mother liquor was concentrated to dryness and recrystallized from CH_2Cl_2/hexane 2:1 (3.5 mL) to give a second crop (247 mg, 0.58 mmol) in a yield of 7.6%. This was repeated one more time to give a third crop (118 mg, 0.28 mmol) in a yield of 3.6%. The total yield was 54%. mp 198-199 °C; R_f = 0.25 (1:1 CH_2Cl_2/hexane). Spectral data for **195**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.74 (s, 1H), 7.28 (d, 1H, *J* = 1.8 Hz), 7.39-7.43 (m, 2H), 7.48-7.52 (m, 4H), 7.58-7.62 (m, 1H), 7.65-7.69 (m, 1H), 7.71-7.75 (m, 4H), 7.76 (s, 2H), 7.80-7.83 (m, 2H), 7.88-7.91 (m, 3H), 9.65 (d, 1H, *J* = 8.5 Hz); ^{13}C NMR ($CDCl_3$,

125 MHz) δ 112.31, 118.73, 120.05, 125.19, 125.49, 126.07, 126.70, 127.22, 127.37, 127.63, 128.28, 128.46, 128.53, 128.89, 130.13, 132.63, 135.31, 139.02, 141.05, 141.17, 142.48, 154.69; IR (thin film) 3532(m), 3058(w), 1595(s), 1570(s), 1385(m), 1227(m) cm^{-1}; HRMS (ESI–) *m/z* calculated for $C_{32}H_{21}O$ ($M-H^+$) 421.1592, found 421.1590.



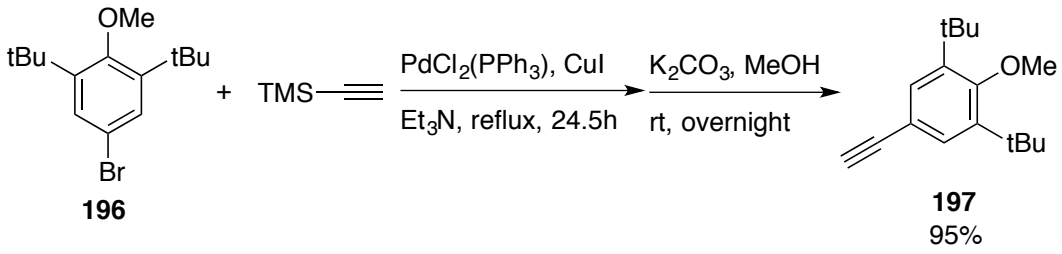
Rac-***76***: To a 50 mL flame-dried three neck round bottom flask equipped with a cooling condenser was added 2-(3,5-diphenylphenyl)phenanthren-4-ol **195** (1.69 g, 4.0 mmol, 1.0 equiv) and mineral oil (5 mL). Airflow was introduced from one side neck via a needle located one inch above the mixture. The airflow rate was about one bubble per second. The mixture was stirred at 195 °C for 12 h. Upon completion, the crude mixture was purified by column chromatography on silica gel (dry loading, 50 mm x 200 mm, CH_2Cl_2/hexanes 1:2 to 1:1 to 2:1) to afford (±)-**76** as an off-white solid (843 mg, 1.00 mmol) in a yield of 50%.

(R)-**76**: To a 25 mL round bottom flask was added (+)-sparteine (170.6 mg, 0.728 mmol, 3.40 equiv), CuCl (36 mg, 0.36 mmol, 1.7 equiv) and MeOH (6.5 mL) under an atmosphere of air. The reaction mixture was stirred for 60 minutes with exposure to air. The flask was then sealed with a septum and

purged with nitrogen, which was introduced by a needle under the surface for 60 minutes. At the same time, to a 100 mL flame-dried round bottom flask was added racemic **76** (180.4 mg, 0.214 mmol, 1.00 equiv) and CH_2Cl_2 (26 mL). The resulting solution was purged with nitrogen for 45 minutes under the surface. The green Cu(II)-(+)-sparteine solution was then transferred via cannula to the solution of racemic **76** under nitrogen and then the combined mixture was stirred at room temperature for 42 h with an nitrogen balloon attached to the flask which was covered with aluminum foil. The reaction was quenched by slow addition of $NaHCO_3$ (sat. aq. 4.2 mL) and H_2O (4.2 mL) and most of the organic solvent was removed under reduced pressure. The residue was then extracted with CH_2Cl_2 (10 mL × 3). The combined organic layer was dried over $MgSO_4$, filtered through Celite and concentrated to dryness. The crude product was purified by column chromatography (silica gel, 25 mm × 200 mm, CH_2Cl_2/hexanes 1:2) to afford *(R)*-**76** as an off-white solid (119 mg, 0.141 mmol) in a yield of 66%. The optical purity was determined to be >99% *ee* by HPLC analysis (Chiralpak AD column, hexanes/2-propanol 90:10, 222 nm, flow 1 mL/min). Retention times: R_t = 6.29 min for (*S*)-**76** (minor enantiomer) and R_t = 11.31 min for (*R*)-**76** (major enantiomer). Mp 203-206 °C; R_f = 0.24 (1:2 CH_2Cl_2/hexane). Spectral data for **76**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.82-6.92 (m, 10H), 6.94-7.02 (m, 8H), 7.04-7.09 (m, 4H), 7.10 (d, 4H, *J* = 1.7 Hz), 7.47 (t, 2H, *J* = 1.7 Hz), 7.64 (s, 2H), 7.71-7.79 (m, 6H), 7.90 (d, 2H, *J* = 8.8 Hz), 8.02-8.06 (m, 2H), 9.88 (dd, 2H, *J* = 8.3, 1.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 116.37, 118.62, 123.48, 124.60, 126.52, 126.65, 126.89, 127.03, 127.07, 127.33, 128.41, 128.48, 129.00, 129.67, 130.19,

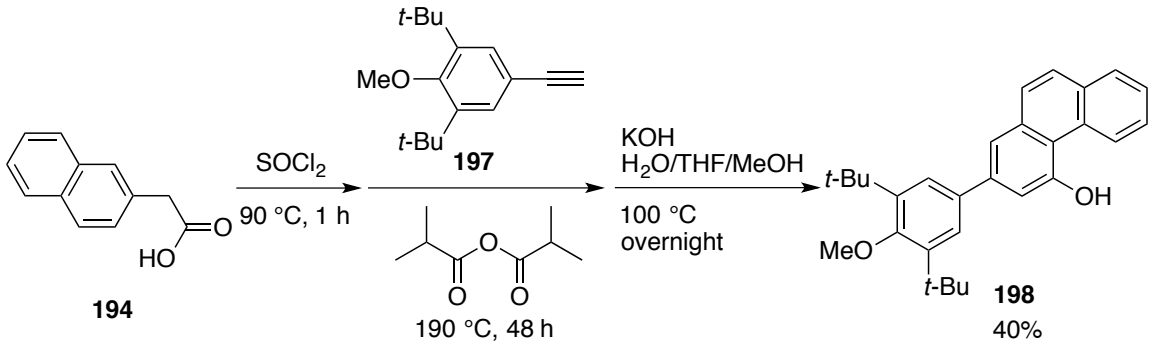
133.00, 135.61, 140.33, 140.46, 141.12, 141.49, 154.08; IR (thin film) 3480(m), 3056(w), 1593(s) cm^{-1}; HRMS (ESI–) *m/z* calculated for $C_{64}H_{41}O_2$ ($M\text{-}H^+$) 841.3107, found 841.3112. $[\alpha]_D^{20}$= +357.5 (c 0.2, EtOAc) on >99% *ee* material.

*Preparation of (R)-**78**:*



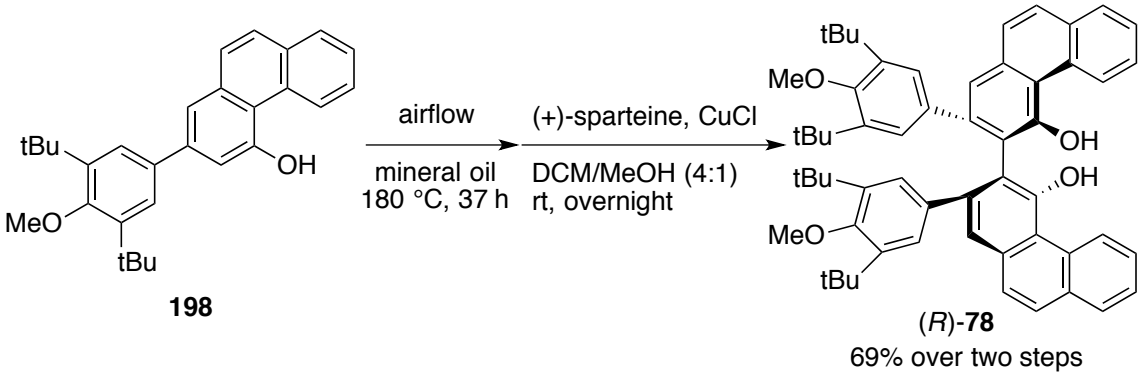
1,3-di-tert-butyl-5-ethynyl-2-methoxybenzene ***197***: The first step was carried out with an adaptation of a procedure reported for a related compound.[74] To a 500 mL round bottom flask filled with nitrogen was added 5-bromo-1,3-di-*tert*-butyl-2-methoxybenzene **196**[12o] (31.5 g, 105 mmol, 1.00 equiv), $Pd(PPh_3)_2Cl_2$ (1.48 g, 2 mol, 2 mol %), CuI (400 mg, 2 mmol, 2 mol %) and dry Et_3N (210 mL) under nitrogen. The flask was then sealed with a septum and purged for 10 minutes with nitrogen, which was introduced by a needle under the surface. Then trimethylsilyl acetylene (26.9 mL, 180 mmol, 1.80 equiv) was added slowly to the flask. After the mixture was refluxed (oil bath: 100 °C) for 24.5 h under nitrogen atmosphere, the solvent was removed by reduced pressure. The residue was dissolved in Et_2O (600 mL) and treated with $NaHCO_3$ (600 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (200 mL × 3). The combined organic layer was washed with H_2O (200 mL), dried over Na_2SO_4, filtered and concentrated to give a black oil. The crude product was roughly purified by passing through a short column (50 mm × 150 mm, neutral Al_2O_3, hexanes as eluent) to give a yellow oil. This oil was then

dissolved in MeOH (300 mL) and treated with K_2CO_3 (43.5 g, 315 mmol). The reaction mixture was stirred at room temperature for 14 h. To the resulting reaction mixture was added H_2O (800 mL) and this mixture was extracted with Et_2O (500 mL × 3). The combined organic layer was dried over Na_2SO_4, filtered and concentrated to dryness. Purification of the crude product by column chromatography on silica gel (50 mm × 200 mm, hexanes) gave **197** as a light yellow oil (24.4 g, 99.8 mmol, 95%). R_f = 0.16 (hexanes). Spectral data for **197**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.40 (s, 18H), 2.98 (s, 1H), 3.66 (s, 3H), 7.37 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 31.90, 35.72, 64.37, 75.49, 84.52, 116.24, 130.60, 144.04, 160.47. These spectral data match those previously reported for this compound.[75]



*2-(3,5-di-tert-butyl-4-methoxyphenyl)phenanthren-4-ol **198***: The procedure for the preparation of 2-(3,5-diphenylphenyl)phenanthren-4-ol **195** was followed with 2-naphthaleneacetic acid **194** (16.8 g, 90.3 mmol, 1.00 equiv), $SOCl_2$ (23.8 mL, 325 mmol, 3.60 equiv), 1,3-di-tert-butyl-5-ethynyl-2-methoxybenzene **197** (24.4g, 99.8 mmol, 1.10 equiv), (*i*-PrCO)$_2$O (30.2 mL, 181 mmol, 2.00 equiv), THF (75 mL), MeOH (75 mL) and a solution of KOH (33.0 g, 588 mmol, 6.50 equiv) in H_2O (130 mL). Purification of the crude product by column

chromatography on silica gel (50 mm x 250 mm, CH_2Cl_2/hexanes 1:3 to 1:1) gave **198** as a light yellow solid (14.84 g, 36.0 mmol) in a yield of 40%. mp 202-203 °C; R_f = 0.21 (1:1 CH_2Cl_2/hexanes). Spectral data for **198**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.50 (s, 18H), 3.75 (s, 3H), 5.69 (s, 1H), 7.18 (d, 1H, *J* = 2.0 Hz), 7.55-7.59 (m, 3H), 7.62-7.67 (m, 2H), 7.74 (d, 2H, *J* = 1.0 Hz), 7.87 (dd, 1H, *J* = 8.0, 1.5 Hz), 9.61 (d, 1H, *J* = 8.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 32.18, 35.99, 64.34, 112.41, 118.21, 119.69, 125.60, 125.86, 126.61, 127.27, 128.24, 128.32, 128.39, 130.26, 132.55, 134.37, 135.30, 139.99, 144.15, 154.52, 159.57; IR (thin film) 3521br m, 2961s, 1420s, 1227s cm^{-1}; HRMS (ESI–) *m/z* calculated for $C_{29}H_{31}O_2$ (M-H$^+$) 411.2324, found 411.2312.



Rac-***78*****:** The general procedure for oxidative phenol-coupling illustrated for **76** was followed with 2-(3,5-di-tert-butyl-4-methoxyphenyl)phenanthren-4-ol **198** (14.3 g, 34.7 mmol) and mineral oil (55 mL). The mixture was stirred at 180 °C for 37 h. After cooling down to room temperature, hexanes (83 mL) were added to the flask and the mixture was stirred until all large chunks had been broken up. The suspension was cooled in a freezer (–20 °C) overnight and then filtered through filter paper. The yellow powder was washed with chilled hexanes and

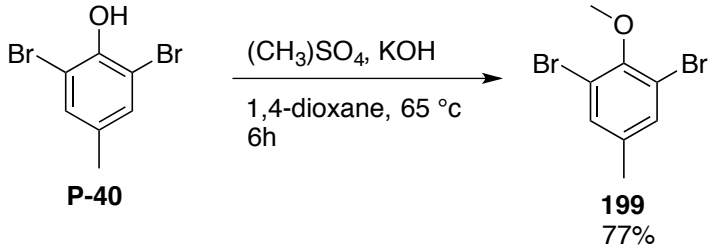
dried under vacuum to afford racemic **78** as an orange solid (10.3 g, 12.5 mmol) in a yield of 72%.

(R)-***78***: Sonification was not employed in this procedure for deracemization. To a 100 mL round bottom flask was added CuCl (1.77 g, 17.9 mmol, 1.70 equiv), (+)-sparteine (8.61 g, 36.8 mmol, 3.5 equiv) and MeOH (60 mL) under an atmosphere of air. The mixture was stirred under air for 45 min. Then the flask was sealed with a septum and purged for 60 min with nitrogen, which was introduced by a needle under the surface of the solution. At the same time, to a flame-dried 1 L round bottom flask was added *rac*-**78** (8.65 g, 10.5 mmol, 1.00 equiv) and dry CH_2Cl_2 (240 mL). The resulting solution was purged with nitrogen for 60 min. The green Cu(II)-(+)-sparteine suspension was then transferred via cannula to the solution of *rac*-**78** under nitrogen and the combined mixture was stirred at room temperature for 16 h with a nitrogen balloon attached to the flask which was covered with aluminum foil. The reaction was quenched by slow addition of 125 mL $NaHCO_3$ (aq. Sat.) and 400 mL H_2O. Most of the organic solvent was removed by rotary evaporation. The residue was then extracted with CH_2Cl_2 (300 mL × 3). Then combined organic layer was dried with Na_2SO_4, filtered and concentrated to dryness. The crude product was purified by column chromatography (silica gel, 55 × 230 mm, hexane: CH_2Cl_2 3:1) to afford *(R)*-**78** as a light pink foamy solid (8.65 g, 10.5 mmol) in 100% isolated yield. The optical purity was determined to be 97.9% *ee* by HPLC analysis (Pirkle D-Phenylglycine column, 75:25 hexane/iPrOH at 254 nm, flow-rate: 2.0 mL/min). Retention times: R_t = 10.75 min (major enantiomer, *(R)*-**78**) and R_t = 21.60 min (minor enantiomer,

(*S*)-**78**). To enhance the optical purity, 13 mL of a mixture of hexane/CH_2Cl_2 (40:3) was added to the product and it was heated until a clear solution was obtained. After the solution was kept at room temperature for 2 h, a fine powder formed which made the solution slightly cloudy. The mixture was filtered through a filter paper and the original flask was rinsed with hexane (5 mL × 2). The rinse was also filtered. The combined filtrate was kept at room temperature for 1 h. It turned cloudy again. The above filtration procedure was repeated until the new filtrate did not turn cloudy after it was kept at room temperature for 1 h. The clear filtrate was concentrated to dryness to afford the product as a light yellow foamy solid (8.30 g, 10.1 mmol) in a yield of 96% with an optical purity of >99% *ee* determined by HPLC analysis (Pirkle D-phenylglycine column, 75:25 hexane/*i*PrOH at 254 nm, flow-rate: 2.0 mL/min). Retention times: R_t = 11.22 min for (*R*)-**78** (major) and R_t = 22.90 min for *(S)*-**78** (minor). mp 150-153 °C; R_f = 0.23 (hexane: CH_2Cl_2 3:1). Spectral data for **78**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.07 (s, 36H), 3.20 (s, 6H), 6.16 (s, 2H), 7.14 (s, 4H), 7.48-7.55 (m, 4H), 7.71-7.79 (m, 6H), 7.82-7.87 (m, 2H), 9.33-9.38 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 31.74, 35.46, 63.78, 116.54, 118.38, 122.27, 125.99, 126.57, 126.80, 127.04, 128.14, 128.59, 129.00, 130.17, 132.54, 133.59, 135.34, 140.81, 142.83, 153.19, 158.84; IR (thin film) 3486(br s), 2961(s), 1412(s), 1225(s), 1115(m) cm^{-1}; HRMS (ESI–) *m/z* calculated for $C_{58}H_{62}O_4$ 822.4648, found 822.4680. $[\alpha]_D^{20}$ = +239.5 (c 1.0, CH_2Cl_2) on >99% *ee* material.

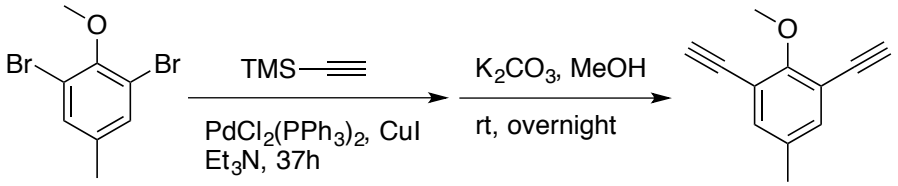
5.1.2 Preparation of Phenols

*Preparation of phenol **P-39**:*



P-40 **199** 77%

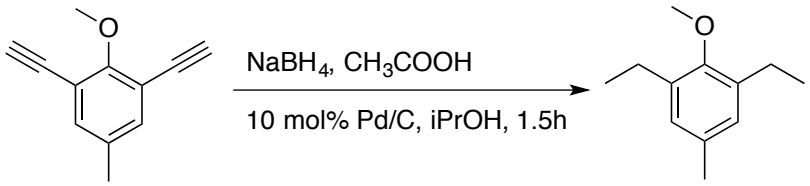
*2,6-Dibromo-4-methylanisole **199***: This compound was prepared using a procedure reported for related compounds.[76] To a solution of 2,6-dibromo-4-methylphenol **P-40** (3.99 g, 15.0 mmol, 1.00 equiv) in 1,4-dioxane (15 mL) at 65 °C was added crushed commercial KOH (3.00 g, 53.5 mmol, 3.57 equiv). Then $(CH_3)_2SO_4$ (1.43 mL, 15.1 mmol, 1.01 equiv) was added slowly to the orange reaction mixture over about 2 h. The resulting mixture was stirred for another 4 h at 65 °C. After it was cooled to rt, the reaction mixture was filtered. The filtrate was concentrated by rotary evaporation and then subjected to vacuum to remove 1,4-dioxane. Purification by column chromatography on silica gel (35 × 160 mm, hexanes as eluent) gave the product **199** as a colorless liquid (3.23 g, 11.5 mmol) in 77% yield. R_f = 0.26 (hexanes). Spectral data for **199**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.25 (t, 3H, *J* = 0.6 Hz), 3.83 (s, 3H), 7.29 (q, 2H, *J* = 0.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.20, 60.59, 117.60, 133.08, 136.53, 151.84. These spectral data match those previously reported for this compound.[77]



199 **200**
94%

1,3-diethynyl-2-methoxy-5-methylbenzene ***200***: The first step was carried out with an adaptation of a procedure reported for a related compound.[74] To a flame-dried 50 mL round bottom flask was added 2,6-dibromo-4-methylanisole **199** (2.24g, 8.00 mmol, 1.00 equiv), $Pd(PPh_3)_2Cl_2$ (225 mg, 0.320 mmol, 0.0400 equiv) and CuI (61 mg, 0.32 mmol, 0.040 equiv) and dry NEt_3 (16 mL). Then the flask was sealed with a septum and purged for 5 min with nitrogen, which was introduced by a needle under the surface of the solution. Then trimethylsilylacetylene (3.90 mL, 27.4 mmol, 3.42 equiv) was added to the flask via syringe. The mixture was refluxed for 37 h under a nitrogen atmosphere. After removal of the solvent, the residue was dissolved in 60 mL Et_2O, followed by the addition of $NaHCO_3$ (sat. aq. 60 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (20 mL x 3). The combined organic layer was washed with 20 mL H_2O, 10 mL brine, dried with Na_2SO_4, filtered and concentrated to give a brown oil. It was roughly purified by passing through a short column (35 mm x 120 mm, neutral Al_2O_3, CH_2Cl_2 as eluent) to give the partially purified product as a yellow liquid, which was dissolved in 45 mL MeOH and treated with K_2CO_3 (6.30g, 45.6 mmol). The reaction mixture was stirred at room temperature overnight to give complete conversion. To the mixture was added 60 mL H_2O and the mixture was extracted with Et_2O (40 mL x 3). The

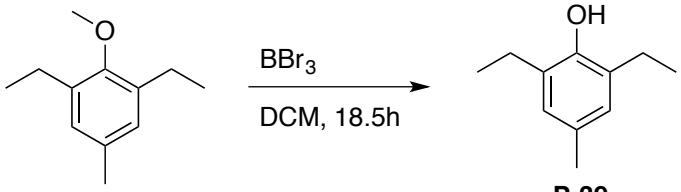
combined organic layer was dried with Na_2SO_4, filtered and concentrated to give the crude product as a light yellow liquid. Purification by silica gel chromatography (30 × 160 mm, hexane: EtOAc 20:1) afforded the product **200** (1.28 g, 7.52 mmol) as a light yellow liquid in 94% overall yield from **199**. R_f = 0.32 (hexane: EtOAc 5:1). Spectral data for **200**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.24 (s, 3H), 3.25 (s, 2H), 4.00 (s, 3H), 7.24 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.20, 61.36, 79.37, 81.42, 115.96, 133.00, 135.19, 161.01. IR (thin film) 3289(w), 2955(w) cm^{-1}; HRMS (EI+) calcd for $C_{12}H_{10}O$ *m/z* 170.0732 ($[M]^+$), meas 170.0744.



200 **201** 80%

1,3-diethyl-2-methoxy-5-methylbenzene ***201***: This compound was prepared using a procedure reported for related compounds.[21] To a 250 mL round bottom flask was added 1,3-diethynyl-2-methoxy-5-methylbenzene **200** (946 mg, 5.56 mmol, 1.00 equiv), Pd/C (594 mg, 10 mol%), iPrOH (55 mL) and acetic acid (1.27 mL, 22.2 mmol, 3.99 equiv). The flask was put into a room temperature water bath before the addition of powdered $NaBH_4$ (1.68 g, 44.5 mmol, 8.00 equiv). Then the water bath was removed. After the reaction mixture was stirred at room temperature open to air for 90 min, 15 mL 0.1 M HCl was carefully added to the pre-cooled mixture at 0 °C. It was stirred until bubbles ceased coming out of solution. Then the pH of the solution was adjusted to 10

with aqueous NaOH. The mixture was filtered through a Celite pad and the Celite pad was washed with Et_2O (20 mL x 3). The filtrate was washed with H_2O (20 mL x 2). The organic layer was separated. The combined aqueous layer was subjected to rotary evaporation to remove iPrOH. Then it was extracted with Et_2O (40 mL x 3). The combined organic layer was dried with Na_2SO_4, filtered and concentrated to give a yellow oil. Purification by column chromatography (35 × 160 mm, hexanes: EtOAc 40:1) gave the product **201** as a colorless oil (798 mg, 4.47 mmol) in 80% yield. R_f = 0.22 (hexanes: EtOAc 40:1). Spectral data for **201**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.23 (t, 6H, *J* = 7.5 Hz), 2.28 (s, 3H), 2.64 (q, 4H, *J* = 7.5 Hz), 3.71 (s, 3H), 6.86 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.03, 20.91, 22.63, 61.19, 127.58, 133.36, 136.60, 153.88. IR (thin film) 2965(s), 2930(s), 1478(m), 1217(m), 1017(m) cm^{-1}; HRMS (EI+) calcd for $C_{12}H_{18}O$ *m/z* 178.1358 ($[M]^+$), meas 178.1361.

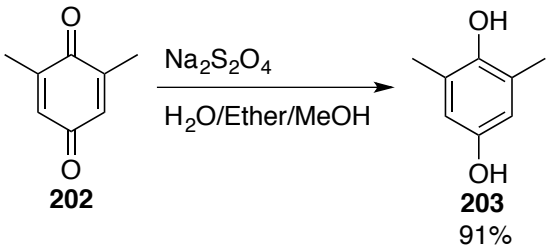


201 **P-39** 71%

2,6-diethyl-4-methylphenol ***P-39***: To a 100 mL round bottom flask was added 1,3-diethyl-2-methoxy-5-methylbenzene **201** (798 mg, 4.47 mmol, 1.00 equiv) and dry CH_2Cl_2 (30 mL). The solution was pre-cooled to 0 °C, followed by the addition of BBr_3 (1M in CH_2Cl_2, 9.0 mL, 9.0 mmol, 2.0 equiv). After the reaction mixture was stirred at room temperature for 18.5 h, 45 mL H_2O was added to the flask. The organic layer was separated. The aqueous layer was

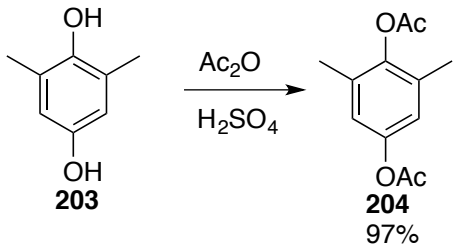
extracted with CH_2Cl_2 (25 mL x 3). The combined organic layer was dried with Na_2SO_4, filtered and concentrated to give a gray brown solid. Purification by column chromatography (25 × 180 mm, hexanes: EtOAc 16:1) gave product **P-39** as white solid (524 mg, 3.19 mmol) in a yield of 71%; mp 47-48 °C; R_f = 0.28 (hexanes: EtOAc 10:1). Spectral data for **P-39**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.22 (t, 6H, *J* = 7.5 Hz), 2.24 (s, 3H), 2.58 (q, 4H, *J* = 7.5 Hz), 4.46 (s, 1H), 6.79 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.07, 20.61, 23.04, 127.28, 128.99, 129.52, 148.87. IR (thin film) 3351(br, s), 2959(w), 1464(m) cm^{-1}; HRMS (ESI–) *m/z* calculated for $C_{11}H_{15}O$ (M-H$^+$) 163.1123, found 163.1120.

*Preparation of phenol **P-45**:*



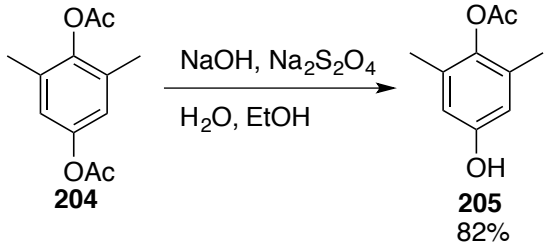
*2,6-Dimethyl-1,4-benzenediol **203***[78]: $Na_2S_2O_4$ (20.9 g, 120 mmol, 4.00 equiv) was dissolved in 145 mL H_2O in a 500 mL round bottom flask filled with nitrogen. A solution of 2,6-dimethylbenzoquinone **202** (4.08 g, 30.0 mmol, 1.00 equiv) in a mixture of 65 mL ether and 40 mL MeOH was poured into the aqueous solution with stirring. Then a balloon filled with nitrogen was attached to the flask through a septum. After the reaction mixture was stirred at room temperature for 1h, the organic layer was separated and the aqueous layer was extracted with ether (60 mL x 4). The combined organic layer was washed with 50 mL H_2O and 25 mL brine, dried over Na_2SO_4, filtered and concentrated to

afford the product as an off-white solid (3.77g, 27.3 mmol) in 91% yield. It was used without further purification; mp 150-151 °C (Lit.[78] 145-148 °C); R_f = 0.11 (hexanes: EtOAc 4:1). Spectral data for **203**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.18 (s, 6H), 4.19 (s, 1H), 4.23 (brs, 1H), 6.46 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.06, 115.00, 124.36, 146.08, 148.62.



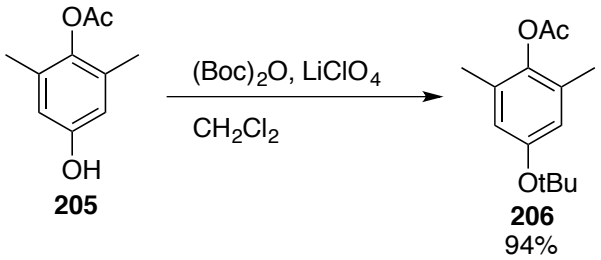
*2,6-Dimethylphenylene-1,4-diacetate **204***: This compound was prepared using a procedure reported for a related compound.[79] To a oven-dried 50 mL round bottom flask filled with nitrogen was added 2,6-dimethyl-1,4-benzenediol **203** (3.77g, 27.2 mmol, 1.00 equiv), acetic anhydride (8.20 mL, 86.7 mmol, 3.19 equiv) and two drops of H_2SO_4 (conc.). After the solution was stirred at room temperature for 1.7 h, it was poured into 100 mL H_2O and the mixture was stirred for 10 min to produce a white precipitate. The mixture was then filtered and the precipitate was washed with H_2O several times and dried under vacuum to give the product **204** as a white solid (5.85 g, 26.3 mmol) in a 97% yield; mp 90-92 °C (Lit.[80] 91-93 °C). R_f = 0.27 (hexanes: EtOAc 3:1). Spectral data for **204**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.12 (s, 6H), 2.25 (s, 3H), 2.31 (s, 3H), 6.78 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.44, 20.42, 21.09, 121.28, 131.42, 145.68, 147.75,

168.70, 169.59. IR (thin film) 1759(s), 1370(m), 1215(s), 1169(s) cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{15}O_4$ *m/z* 223.0970 ($[M+H]^+$), meas 223.0969.



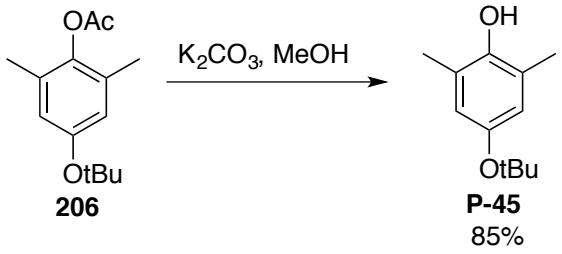
4-hydroxy-2,6-dimethylphenyl acetate ***205***: This compound was prepared using a procedure reported for a related compound.[81] To a 250 mL round bottom flask filled with nitrogen was added 2,6-dimethylphenylene-1,4-diacetate **204** (5.83 g, 26.2 mmol, 1.00 equiv) and EtOH (87 mL). A solution of NaOH (1.05 g, 26.2 mmol, 1.0 equiv) and $Na_2S_2O_4$ (1.15 g, 6.6 mmol, 0.25 equiv) in 8.7 mL H_2O was slowly added to the flask. After the mixture was stirred at room temperature for 40 min, 44 mL 1M HCl was added to the flask. The mixture was subjected to rotary evaporation to remove EtOH, during which the reaction mixture became cloudy. The residue was dissolved in 250 mL EtOAc. The organic layer was separated and washed with NH_4Cl (aq. Sat. 25 mL), dried with Na_2SO_4, filtered and concentrated to give a yellow solid. It was crystallized from hexanes/EtOAc (8:1) to give an additional quantity of the product as white crystals (2.20 g, 12.2 mmol). The mother liquor was purified by column chromatography (silica gel, 40 × 200 mm, hexane:EtOAc 6:1➔5:1➔3:1) to give the product **205** as a white solid (1.65 g, 9.20 mmol). The combined yield was 82%. mp 108-110 °C (Lit.[82] 105-106 °C); R_f = 0.18 (hexanes: EtOAc 3:1). Spectral data for **205**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.04 (s, 6H), 2.31 (s, 3H), 5.78 (brs, 1H), 6.38 (s, 2H); ^{13}C NMR

(125 MHz, $CDCl_3$) δ 16.24, 20.43, 115.16, 130.80, 141.41, 153.19, 170.26. The ^1H NMR data match those previously reported for this compound.[82]



4-(tert-butoxy)-2,6-dimethylphenyl acetate ***206***: This compound was prepared using a procedure reported for a related compound.[83] To a flame-dried 25 mL round bottom flask filled with nitrogen was added 4-hydroxy-2,6-dimethylphenyl acetate **205** (361 mg, 2.00 mmol, 1.00 equiv), $Mg(ClO_4)_2$ (45 mg, 0.20 mmol, 0.10 equiv) and dry CH_2Cl_2 (3 mL), followed by the addition of $(Boc)_2O$ (1.53 g, 7.00 mmol, 3.50 equiv). Then the flask was connected to a condenser with a nitrogen balloon attached on top of the condenser through a septum. The mixture was stirred at 40 °C for 24 h. Then another portion of $(Boc)_2O$ (300 mg, 1.37 mmol) was added to the reaction flask. The reaction mixture was stirred for another 23 h. The solvent was removed by slowly maintaining a nitrogen flow into the flask. The crude product was purified by column chromatography (silica gel, 25 × 200 mm, hexanes➔hexane:EtOAc 5:1) to give the product **206** as a colorless oil (444 mg, 1.88 mmol) in a yield of 94%. R_f = 0.43 (hexanes: EtOAc 5:1). Spectral data for **206**: ^1H NMR (500 MHz, $CDCl_3$) δ 1.31 (s, 9H), 2.08 (s, 6H), 2.29 (s, 3H), 6.66 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.43, 20.41, 28.83, 78.17, 123.77, 130.23, 143.97, 152.57,

168.85. IR (thin film) 2978(s), 1761(s), 1482(s), 1368(s), 1217(s), 1167(s) cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{21}O_3$ *m/z* 237.1491 ($[M+H]^+$), meas 237.1494.

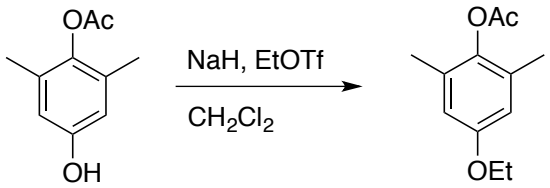


206 **P-45**
85%

4-(tert-butoxy)-2,6-dimethylphenol ***P-45***: This compound was prepared using a procedure reported for a related compound.[84] To a 25 mL round bottom flask filled with nitrogen was added 4-(tert-butoxy)-2,6-dimethylphenyl acetate **206** (444 mg, 1.88 mmol, 1.00 equiv), K_2CO_3 (390 mg, 2.82 mmol, 1.50 equiv) and MeOH (9 mL). After the mixture was stirred at room temperature for 21 h, 15 mL H_2O was added to the reaction flask. The pH of the solution was adjusted to 3-4 with 2N HCl. The mixture was concentrated to about 15 mL and extracted with Et_2O (40 mL × 3). The combined organic layers were dried with Na_2SO_4, filtered and concentrated to afford a yellow solid, which was purified by column chromatography (silica gel, 30 × 200 mm, hexane:EtOAc 5:1) to give the product **P-45** as an off-white solid (351 mg, 1.81 mmol) in a yield of 96%. It was recrystallized from 1 mL hexanes to give the first crop as white needles (270 mg, 1.39 mmol) in a yield of 74%. The second crop (39 mg, 0.20 mmol) was obtained from the residue. The combined yield was 85%. Mp 81-82 °C; R_f = 0.40 (hexanes: EtOAc 3:1). Spectral data for **P-45**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.27 (s, 9H), 2.18 (s, 6H), 4.37 (s, 1H), 6.60 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.07, 28.77, 77.65, 123.06, 124.35, 147.76, 148.22. IR (thin film) 3407(s),

2978(m), 1485(s), 1167(m), 1138(m) cm^{-1}; HRMS (ESI–) *m/z* calculated for $C_{12}H_{17}O_2$ (M-H^+) 193.1229, found 193.1227.

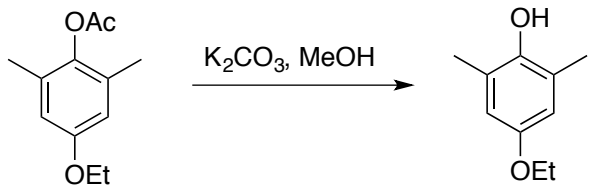
*Preparation of phenol **P-46**:*



205 **207** 90%

*4-(Ethoxy)-2,6-dimethylphenyl acetate **207***: This compound was prepared using a procedure reported for a related compound.[85] To a 100 mL flame dried round bottom flask filled with nitrogen was added the 4-hydroxy-2,6-dimethylphenyl acetate **205** (541 mg, 3.00 mmol, 1.00 equiv) and dry CH_2Cl_2 (15 mL), followed by the addition of NaH (134 mg, 60% in mineral oil, 3.35 mmol. 1.10 equiv) with stirring. At the end of hydrogen evolution, EtOTf (0.47 mL, 3.63 mmol, 1.21 equiv) was added to the reaction flask. After the reaction mixture was stirred at room temperature for 7 h, NH_4Cl (aq. sat. 8 mL) was added to the mixture. The organic layer was separated and the aqueous layer was extracted with EtOAc (10 mL x 3). The combined organic layer was dried over Na_2SO_4, filtered and concentrated to give a yellow oil with some precipitate in it. The crude product was purified by column chromatography (silica gel, 25 × 200 mm, hexane:EtOAc 10:1) to give the product **207** as a colorless oil (562 mg, 2.70 mmol) in a yield of 90%. R_f = 0.37 (hexanes/EtOAc 10:1). Spectral data for **207**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.36 (t, 3H, *J* = 7.0 Hz), 2.10 (s, 6H), 2.30 (s, 3H), 3.96 (q, 2H, *J* = 7.0 Hz), 6.57 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.88, 16.56,

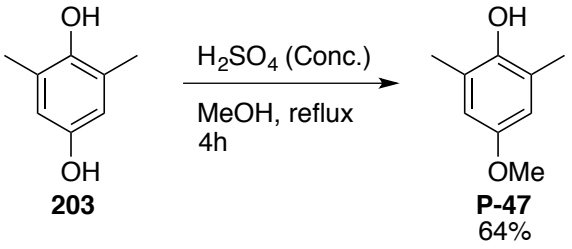
20.43, 63.53, 114.16, 130.87, 141.68, 156.29, 169.26. IR (thin film) 2980(w), 2928(w), 1759(s), 1221(s), 1183(s) cm^{-1}; HRMS (ESI+) calcd for $C_{12}H_{17}O_3$ *m/z* 209.1178 ($[M+H]^+$), meas 209.1180.



207 **P-46** 81%

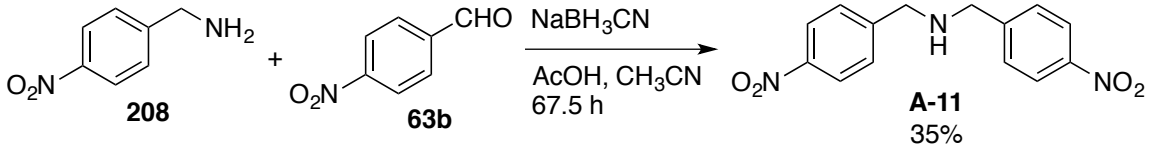
4-Ethoxy-2,6-dimethylphenol ***P-46***: To a 25 mL round bottom flask filled with nitrogen was added the 4-(ethoxy)-2,6-dimethylphenyl acetate **207** (560 mg, 2.69 mmol, 1.00 equiv) and EtOH (6 mL). Then a solution of KOH (377 mg, 6.72 mmol, 2.50 equiv) in H_2O (6 mL) was added to the mixture. After the mixture was stirred at room temperature for 2 h, the pH of the solution was adjusted to ~3 with 2 M HCl. It was then concentrated to approximately 10 mL and extracted with EtOAc (20 mL x 3). The combined organic layer was dried over Na_2SO_4, filtered and concentrated to give a brown oil, which was loaded onto a silica gel column (25 × 200 mm, hexane:EtOAc 10:1) and eluted to afford **P-46** as a light brown solid (364 mg, 2.19 mmol) in a yield of 81%. Mp 43-44 °C; R_f = 0.29 (hexanes: EtOAc 3:1). Spectral data for **P-46**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.36 (t, 3H, *J* = 7.0 Hz), 2.21 (s, 6H), 3.94 (q, 2H, *J* = 7.0 Hz), 4.26 (brs, 1H), 6.54 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.96, 16.24, 63.85, 114.54, 124.05, 146.02, 152.24. IR (thin film) 3449(s), 2978(m), 2923(w), 1491(s), 1196(s), 1059(s) cm^{-1}; HRMS (ESI–) calcd for $C_{10}H_{13}O_2$ *m/z* 165.0916 ($[M-H]^+$), meas 165.0915.

*Preparation of phenol **P-47**:*

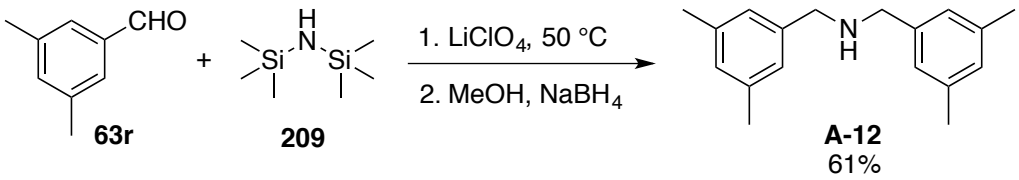


*4-methoxy-2,6-dimethylphenol **P-47**:*[86] To a 100 mL oven dried round bottom flask was added the 2,6-dimethyl-1,4-benzenediol **203** (4.61 g, 33.4 mmol, 1.00 equiv), MeOH (30 mL) and H_2SO_4 (conc., 12 mL). The mixture was refluxed for 4 h (oil bath: 100 °C). The mixture was then cooled to room temperature and poured into a 250 mL beaker containing 100 g ice. After the ice melted, the mixture was extracted with Et_2O (100 mL x 4). The combined organic layer was dried over Na_2SO_4, filtered and concentrated to give a brown oil. The crude product was purified by column chromatography (silica gel, 35 × 200 mm, hexane:EtOAc 8:1 to 6:1 to 5:1) and recrystallization from hexanes (43 mL) to afford white needles (3.24 g, 21.3 mmol) in a yield of 64%. mp 75-76 °C; R_f = 0.45 (hexanes: EtOAc 3:1). Spectral data for **P-47**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.21 (s, 6H), 3.72 (s, 3H), 4.21 (s, 1H), 6.53 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.25, 55.65, 113.77, 124.08, 146.10, 152.99. The ^{1}H NMR data match those previously reported for this compound.[86]

5.1.3 Preparation of Amines A-11 and A-12



*Bis-(4-nitrobenzyl)amine **A-11***: To an oven-dried 25 mL round bottom flask was added 4-nitrobenzaldehyde **63b** (453 mg, 3.00 mmol, 1.00 equiv) and a solution of 4-nitrobenzylamine **208** (456 mg, 3.00 mmol, 1.00 equiv) in CH_3CN (12 mL). After the mixture was stirred at room temperature for 1.5 h, $NaBH_3CN$ (566 mg, 9.00 mmol, 3.00 equiv) was added to the flask. After 20 min, acetic acid (0.86 mL, 15 mmol, 5.0 equiv) was added to the mixture. It was then stirred at room temperature for 67.5 h. The reaction mixture was diluted with CH_2Cl_2 (6 mL), washed with NaOH (1.0 M, 12 mL x 2), dried with Na_2SO_4, filtered and concentrated to dryness. The crude product was purified by column chromatography (silica gel, 30 × 200 mm, hexane/EtOAc 1:1) and recrystallized from hexane/EtOAc (1:1) to give a yellow crystalline solid (302 mg, 1.05 mmol) in a yield of 35%. Mp 90-91 °C (Lit.[87] 90 °C); R_f = 0.13 (hexanes: EtOAc 1:1). Spectral data for **A-11**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.76 (brs, 1H), 3.91 (s, 4H), 7.52 (d, 4H, *J* = 8.5 Hz), 8.18 (d, 4H, *J* = 8.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 52.41, 123.71, 128.61, 147.18, 147.43. The ^{1}H NMR data match previously reported for this compound.[87]



*Bis-(3,5-dimethylbenzyl)amine **A-12***: To a flame dried 25 mL round bottom flask filled with N_2 was added 3,5-dimethylbenzaldehyde **63r** (295 mg, 2.20 mmol, 1.00 equiv), $LiClO_4$ (234 mg, 2.20 mmol, 1.00 equiv) and bis(trimethylsilyl)amine **209** (1.2 mL, 5.73 mmol, 2.60 equiv). The mixture was

stirred at 50 °C for 2 hours. After it was cooled to 0 °C, MeOH (5.5 mL) was added. Then $NaBH_4$ (250 mg, 6.60 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 $NaHCO_3$ (5 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and filtered. The filtrate was concentrated. The crude product was dissolved in CH_2Cl_2 (5 mL) and *aq* HCl (6M, ~ 2.2 mL) was added dropwise until pH ~1. The resulting white precipitate was collected by filtration and suspended in EtOAc (10 mL). Then Na_2CO_3 (aq. sat. ~5 mL) was added. The aqueous layer was separated and extracted with EtOAc (2 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and filtered. The filtrate was concentrated and the product was purified by column chromatography (silica gel, 25 × 200 mm, hexane:EtOAc 3:1). The product **A-12** was obtained as a colorless oil (171 mg, 0.675 mmol, 61%); R_f = 0.19 (Hexane:EtOAc 5:1). Spectral data for **A-12**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.56 (brs, 1H), 2.34 (s, 12H), 3.77 (s, 4H), 6.92 (s, 2H), 6.99 (s, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.21, 53.28, 125.93, 128.46, 137.81, 140.21. The ^{1}H NMR data match previously reported for this compound.[87]

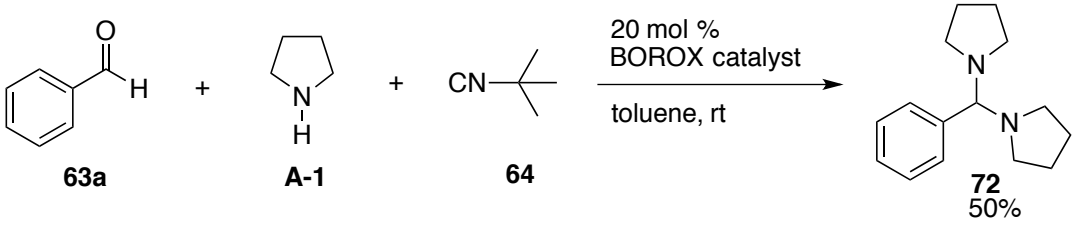
5.1.4 General Procedure A for Optimization of the Ugi-3CR

A 25 mL Schlenk flask equipped with a stir bar was flame dried, cooled to rt under N_2 and charged with 20 mol% ligand (0.050 mmol, 0.20 equiv), 40 mol% phenol (0.10 mmol, 0.40 equiv), dry toluene (1.5 mL), 60 mol% H_2O (27 mg, 2.7 µL, 0.15 mmol, 0.60 equiv), and 60 mol% $BH_3{\cdot}SMe_2$ (2M, 75 µL, 0.15 mmol, 0.60

equiv). The Teflon valve on the Schlenk flask was then closed, and the mixture heated at 100 °C for 1 h. After the flask was cooled to rt, the valve was carefully opened to gradually apply high vacuum (0.1 mm Hg) and the solvent and volatiles were removed. Then the flask was heated at 100 °C under high vacuum for 30 min. Dry reaction solvent (1 mL) was added to dissolve the residue in the flask after it was cooled to room temperature. To the resulting solution was added amine **A** (0.5 mmol, 2.0 equiv) under a N_2 stream, followed by the addition of benzaldehyde **63a** (26 μL, 0.25 mmol, 1.0 equiv) and then *t*-butyl isocyanide **64** (45 μL, 0.38 mmol, 1.5 equiv). The Teflon valve was then closed, and the resulting mixture was stirred at room temperature for a specified time 24-46 h. Upon completion, the reaction mixture was directly loaded onto a silica gel column (20 × 160 mm, hexanes:EtOAc 15:1) to afford the corresponding product **65**. The optical purity was determined by HPLC analysis (Pirkle Covalent (*R*,*R*) WHELK-O1 column or Chiralpak AD column).

5.1.5 Attempted Ugi Reaction with Amines A-1 and A-6 (Scheme 2.8)

*Attempted Ugi reaction with pyrrolidine **A-1**:*

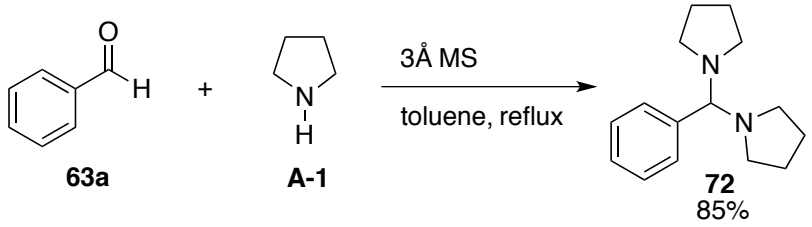


63a **A-1** **64** **72** 50%

The general procedure A described in **Part 5.1.4** was followed with (*S*)-VAPOL ligand (27 mg, 0.050 mmol), phenol **P-11** (9.6 mg, 0.10 mmol), pyrrolidine **A-1** (42 μL, 0.51 mmol, 2.0 equiv) and d_8-toluene (1 mL) as the

reaction solvent. After the reaction mixture was stirred at room temperature for 19 h, the crude NMR spectrum showed that the aminal **72** was formed in 50% yield (average of two runs) with the aid of Ph_3CH as an internal standard. Aminal **72** was the only major species present in the crude reaction mixture other than the starting materials. The assignment of this major species as the aminal **72** was made based on the ^1H NMR data of **72** that was prepared separately as described below.

*Separate preparation of aminal **72** from benzaldehyde **63a** and prolidine **A-1**:*

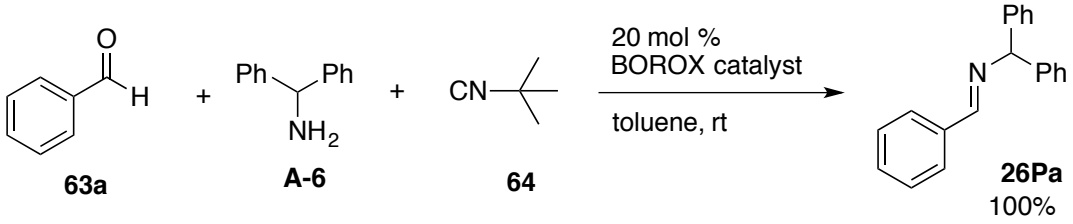


63a **A-1** **72** 85%

α,α-Bis(pyrrolidinyl)toluene **72**: An oven-dried 50 mL round bottom flask charged with 3Å powdered molecular sieves (3.0 g) and equipped with a magnetic stir bar was flame dried under high vacuum and cooled down under nitrogen. To the flask was then added 9.0 mL of dry toluene, pyrrolidine **A-1** (0.82 mL, 10 mmol, 2.0 equiv) and benzaldehyde **63a** (0.51 mL, 5.0 mmol, 1.0 equiv). After the mixture was heated to reflux for 16 h in an 80 °C oil bath, it was cooled to room temperature and filtered through a Celite pad. The pad was washed with dry CH_2Cl_2 (3 mL). The combined filtrate was concentrated to dryness to give **72** as a light yellow oil (980 mg, 4.25 mmol) in 85% yield. The crude product contains a very small amount of benzaldehyde **63a** and pyrrolidine **A-1**. Spectral data for **72**: ^1H NMR (500 MHz, $CDCl_3$) δ 1.60-1.69 (m, 8H), 2.41-2.50 (m, 8H),

3.89 (s, 1H), 7.23-7.33 (m, 5H); ^{1}H NMR (500 MHz, d_8-toluene) δ 1.50-1.64 (m, 8H), 2.43-2.60 (m, 8H), 3.89 (s, 1H), 7.17-7.31 (m, 5H). The ^{1}H NMR data ($CDCl_3$) match those reported for this compound.[88]

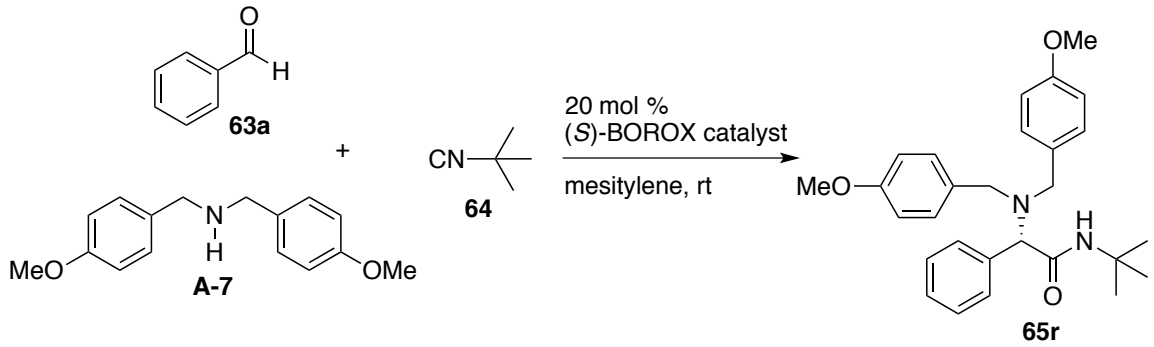
*Attempted Ugi reaction with pyrrolidine **A-6**:*



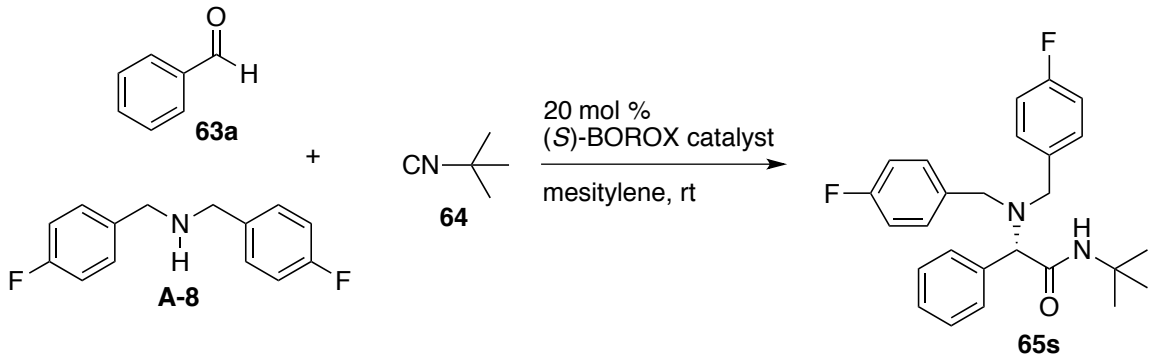
63a **A-6** **64** **26Pa** 100%

The general procedure A described in **Part 5.1.4** was followed with (*S*)-VAPOL ligand (27 mg, 0.050 mmol), phenol **P-11** (9.6 mg, 0.10 mmol), benzhydrylamine **A-6** (88 μL, 0.51 mmol, 2.0 equiv) and toluene (1 mL) as the reaction solvent. The crude NMR spectrum was taken after the reaction mixture had been stirred at room temperature for 18 h and for 89 h. In both cases, the crude NMR spectrum showed 100% formation of imine **4**[12s] with the aid of Ph_3CH as an internal standard.

5.1.6 Ugi Reaction with Amines A-7—A-12 with General Procedure A (Part 5.1.4) and B (Part 5.1.7)



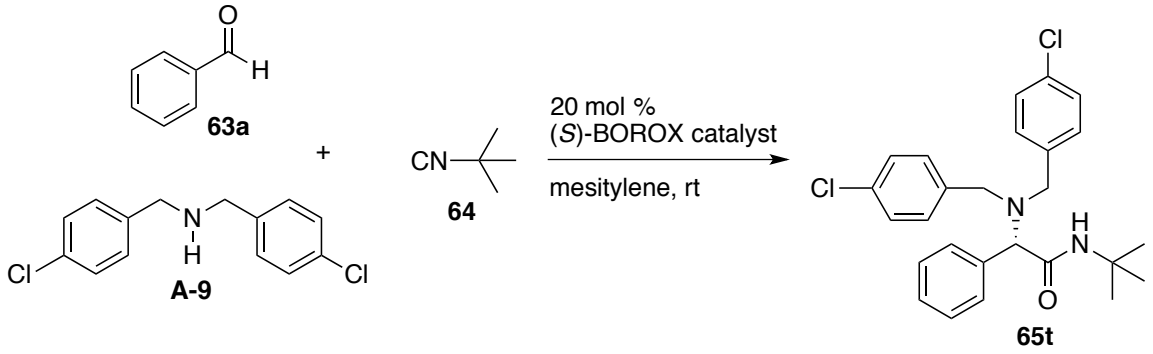
(S)-2-(bis(4-methoxybenzyl)amino)-N-(tert-butyl)-2-phenylacetamide ***65r***: The general procedure A described in **Part 5.1.4** was followed with ligand (*S*)-**78** (41.5 mg, 0.0504 mmol), phenol **P-36** (14 mg, 0.10 mmol), amine **A-7**[32] (98 mg, 0.50 mmol) and mesitylene (1 mL) with a reaction time of 39 h. After purification by column chromatography (silica gel, 20 × 160 mm, hexane:EtOAc 9:1), the product **65r** was obtained as a yellow semi-solid (105 mg, 0.23 mmol, 92%). The optical purity was determined to be 85:15 *er* by HPLC analysis (Chiralpak AD column, hexanes/2-propanol 90:10, 222 nm, flow 1 mL). Retention times: R_t = 7.04 min (major enantiomer) and R_t = 20.04 min (minor enantiomer). A reaction that was run according to general procedure B (described in **Part 5.1.7**) with (*R*)-**78** and phenol **P-47** for 24 h at room temperature afforded the product **65r** in 91% yield with 12:88 er. R_f = 0.30 (hexane:EtOAc 4:1). Spectral data for **65r**: ^{1}H 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 $C_{28}H_{35}N_2O_3$ *m/z* 447.2648 ($[M+H]^+$), meas 447.2631. $[\alpha]_D^{20}$ = +19.8 (c 1.0, CH_2Cl_2) on 85:15 *er* material.



(S)-2-(bis(4-fluorobenzyl)amino)-N-(tert-butyl)-2-phenylacetamide ***65s***:

The general procedure A described in **Part 5.1.4** was followed with ligand (*S*)-**78** (41.5 mg, 0.05 mmol), phenol **P-36** (14 mg, 0.10 mmol), amine **A-8**[32] (119 mg, 0.51 mmol) and mesitylene (1 mL) as the solvent with a reaction time of 39 h. After purification by column chromatography (silica gel, 18 × 200 mm, hexane:EtOAc 15:1), the product **65s** was obtained as a yellow foamy-solid (95.2 mg, 0.225 mmol, 88%). The optical purity was determined to be 86:14 *er* by HPLC analysis (Chiralpak AD column, hexanes/2-propanol 98:2, 222 nm, flow 1 mL). Retention times: R_t = 10.25 min (major enantiomer) and R_t = 27.23 min (minor enantiomer); mp 105-107 °C; A reaction that was run according to general procedure B (described in **Part 5.1.7**) with (*R*)-**78** and phenol **P-47** for 24 h at room temperature afforded the product **65s** in 85% yield with 10:90 er. R_f = 0.40 (hexane:EtOAc 4:1). Spectral data for **65s**: ^{1}H 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

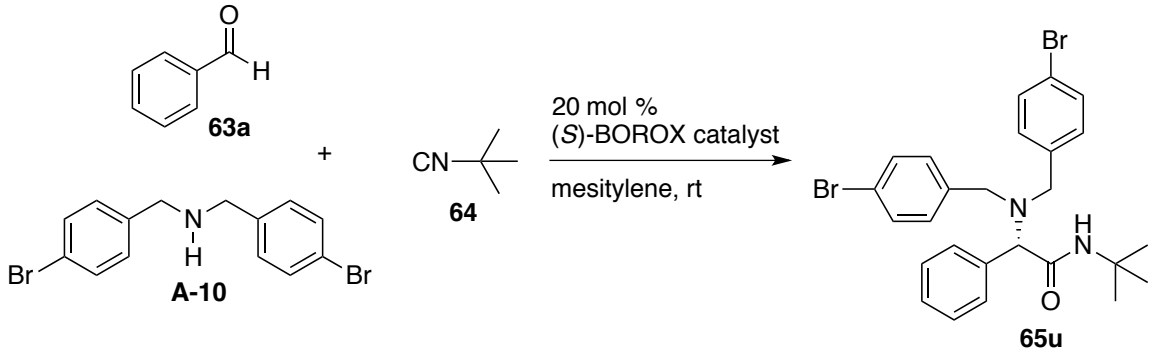
$C_{26}H_{29}F_2N_2O$ *m/z* 423.2248 ($[M+H]^+$), meas 423.2268. $[\alpha]_D^{20}$ = +29.8 (c 1.0, CH_2Cl_2) on 86:14 *er* material.



(S)-2-(bis(4-chlorobenzyl)amino)-N-(tert-butyl)-2-phenylacetamide ***65t***:

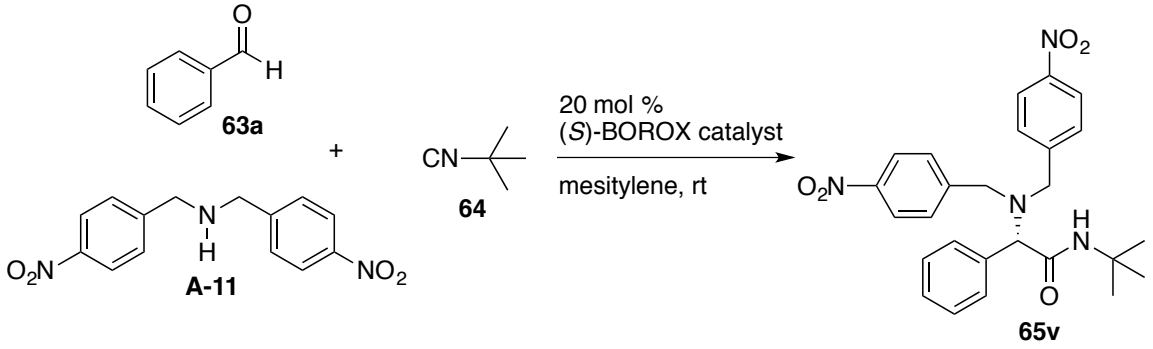
The general procedure A described in **Part 5.1.4** was followed with ligand (*S*)-**78** (41.5 mg, 0.05 mmol), phenol **P-36** (14 mg, 0.10 mmol), amine **A-9**[32] (135 mg, 0.51 mmol) and mesitylene (1 mL) as the solvent with a reaction time of 39 h. After purification by column chromatography (silica gel, 20 × 200 mm, hexane:EtOAc 15:1), the product **65t** was obtained as a white foamy-solid (105 mg, 0.23 mmol, 90%). The optical purity was determined to be 85:15 *er* by HPLC analysis (Chiralpak AD column, hexanes/2-propanol 98:2, 222 nm, flow 1 mL). Retention times: R_t = 9.35 min (major enantiomer) and R_t = 36.82 min (minor enantiomer); mp 105-106 °C, A reaction that was run according to general procedure B (described in **Part 5.1.7**) with (*R*)-**78** and phenol **P-47** for 24 h at room temperature afforded the product **65t** in 80% yield with 12:88 er. R_f = 0.50 (hexane:EtOAc 4:1). Spectral data for **65t**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40 (s, 9H), 3.44 (d, 2H, *J* = 14.2 Hz), 3.78 (d, 2H, *J* = 14.2 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 $C_{26}H_{29}Cl_2N_2O$ *m/z* 455.1657 ($[M+H]^+$), meas 455.1680. $[\alpha]_D^{20}$ = +30.8 (c 1.0, CH_2Cl_2) on 85:15 *er* material.



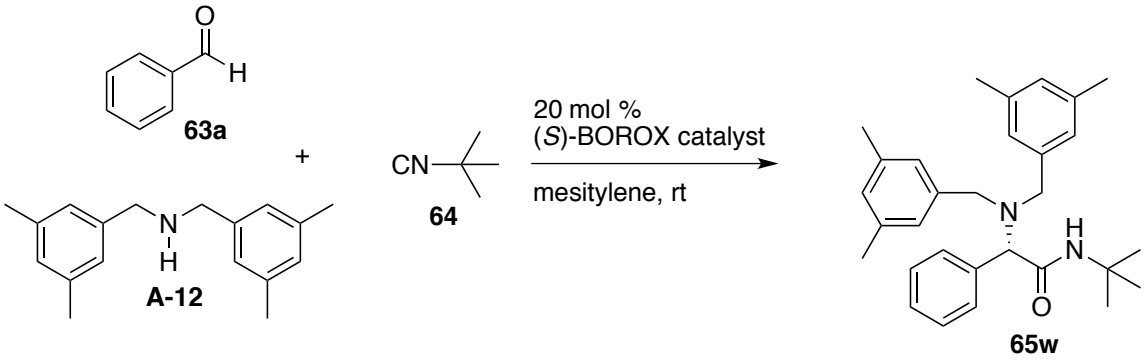
(S)-2-(bis(4-bromobenzyl)amino)-N-(tert-butyl)-2-phenylacetamide ***65u***: The general procedure A described in **Part 5.1.4** was followed with ligand (*S*)-**78** (41.5 mg, 0.05 mmol), phenol **P-36** (14 mg, 0.10 mmol), amine **A-10**[32] (178 mg, 0.50 mmol) and mesitylene (1 mL) as the solvent with a reaction time of 37 h. After purification by column chromatography (silica gel, 20 × 200 mm, hexane:EtOAc 15:1), the product **65u** was obtained as a white foamy-solid (119 mg, 0.219 mmol, 86%). The optical purity was determined to be 83:17 *ee* by HPLC analysis (Chiralpak AD column, hexanes/2-propanol 98:2, 222 nm, flow 1 mL); Retention times: R_t = 9.87 min (major enantiomer) and R_t = 45.29 min (minor enantiomer). Mp 108-109 °C; A reaction that was run according to general procedure B (described in **Part 5.1.7**) with (*R*)-**78** and phenol **P-47** for 24 h at room temperature afforded the product **65u** in 79% yield with 13:87 er. R_f = 0.50 (hexane:EtOAc 4:1); Spectral data for **65u**: ^{1}H 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 $C_{26}H_{29}{}^{79}Br_2N_2O$ *m/z* 543.0647 ($[M+H]^+$), meas 543.0645. $[\alpha]_D^{20}$ = + 27.1 (c 1.0, CH_2Cl_2) on 83:17 *er* material.



(S)-2-(bis(4-nitrobenzyl)amino)-N-(tert-butyl)-2-phenylacetamide ***65v***: The general procedure A described in **Part 5.1.4** was followed with ligand (*S*)-**78** (41.5 mg, 0.05 mmol), phenol **P-36** (14 mg, 0.10 mmol), amine **A-11** (144 mg, 0.50 mmol) and mesitylene (1 mL) as the solvent with a reaction time of 37 h. After purification by column chromatography (silica gel, 20 × 200 mm, hexane:EtOAc 3:1), the product **65v** was obtained as a yellow oil (26 mg, 0.055 mmol, 22%). The optical purity was determined to be 67:33 *er* by HPLC analysis (Pirkle Covalent (*R*,*R*) WHELK-O1 column, hexanes/2-propanol 90:10, 222 nm, flow 1 mL); Retention times: R_t = 51.63 min (major enantiomer) and R_t = 65.73 min (minor enantiomer). A reaction that was run according to general procedure B (described in **5.1.7**) with (*R*)-**78** and phenol **P-47** for 24 h at room temperature

afforded the product **65v** in 22% ^{1}H NMR yield with 27:73 er. R_f = 0.18 (hexane:EtOAc 3:1); Spectral data for **65v**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.37 (s, 9H), 3.73 (d, 2H, *J* = 14.8 Hz), 3.98 (d, 2H, *J* = 14.8 Hz), 4.16 (s, 1H), 5.73 (s, 1H), 7.30-7.40 (m, 5H), 7.47 (d, 4H, *J* = 9.0 Hz), 8.16 (d, 4H, *J* = 9.0 Hz); Unfortunately, the product as obtained was contaminated with some impurities. Thus, a clean ^{13}C NMR could not be obtained. HRMS (ESI) calcd for $C_{26}H_{29}N_4O_5$ *m/z* 477.2138 ($[M+H]^+$), meas 477.2134.



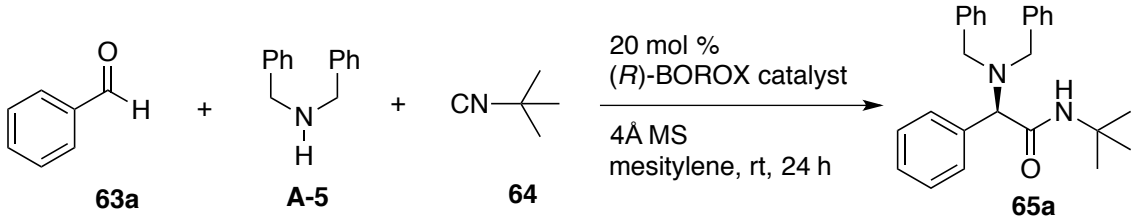
(S)-2-(bis(3,5-dimethylbenzyl)amino)-N-(tert-butyl)-2-phenylacetamide

65w: The general procedure A described in **Part 5.1.4** was followed with ligand (*S*)-**78** (41.5 mg, 0.05 mmol), phenol **P-36** (14 mg, 0.10 mmol), amine **A-12** (130 mg, 0.51 mmol) and mesitylene (1 mL) as the solvent with a reaction time of 39 h. After purification by column chromatography (silica gel, 20 × 200 mm, hexane:EtOAc 15:1), the product **65w** was obtained as a yellow oil (74 mg, 0.167 mmol, 65%). The optical purity was determined to be 61:39 *er* by HPLC analysis (Pirkle Covalent (*R*,*R*) WHELK-O1 column, hexanes/2-propanol 95:5, 222 nm, flow 0.7 mL); Retention times: R_t = 39.43 min (major enantiomer) and R_t = 58.69 min (minor enantiomer). R_f = 0.17 (hexane:EtOAc 10:1); Spectral data for **65w**:

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.42 (s, 9H), 2.31 (s, 12H), 3.14 (d, 2H, *J* = 14.0 Hz), 3.75 (d, 2H, 14.0 Hz), 4.32 (s, 1H), 6.90 (s, 2H), 6.94 (s, 4H), 7.22-7.28 (m, 2H), 7.29-7.34 (m, 1H), 7.35-7.40 (m, 2H), 7.59 (brs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.30, 28.80, 50.78, 54.59, 68.02, 126.49, 127.52, 127.96, 128.80, 130.58, 134.13, 137.92, 138.71, 170.81; IR (thin film) 3343(w), 2963(m), 2919 (m), 1684(s), 1507(s), 1453 (s) cm^{-1}; HRMS (ESI) calcd for $C_{30}H_{39}N_2O$ *m/z* 443.3062 ($[M+H]^+$), meas 443.3058. $[\alpha]_D^{20}$ = + 5.2 (c 1.0, CH_2Cl_2) on 61:39 *er* material.

5.1.7 Formation of α-Amino Amides 65a—65q with General Procedure B

*General procedure B for the catalytic asymmetric Ugi reaction – Illustrated for the synthesis of (R)-N-(tert-butyl)-2-(dibenzylamino)-2-(phenyl)acetamide **65a** (Table 2.8, entry 2):*



63a **A-5** **64** **65a**

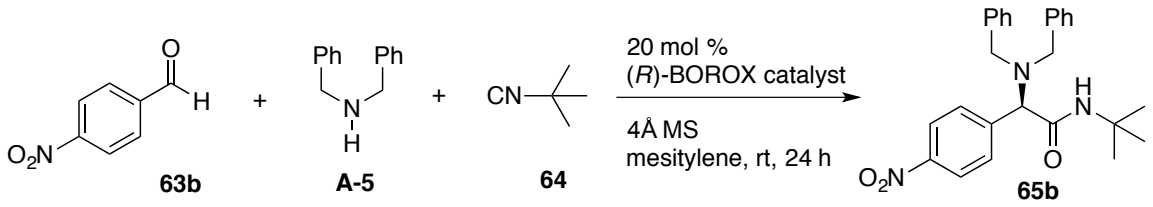
Preparation of catalyst stock solution: A 25 mL Schlenk flask equipped with a stir bar was flame dried, cooled to rt under N_2 and charged with (*R*)-**78** (128 mg, 0.156 mmol), **P-47** (49 mg, 0.32 mmol), H_2O (8.3 mg, 8.3 µL, 0.46 mmol), dry toluene (4.6 mL) and $BH_3{\cdot}SMe_2$ (2M, 232.5 µL, 0.465 mmol). The Teflon valve on the Schlenk flask was then closed, and the mixture heated at 100 °C for 1 h. After the flask was cooled to rt, the valve was carefully opened to gradually apply high vacuum (0.1 mm Hg) and the solvent and volatiles were

removed. Then the flask was heated at 100 °C under high vacuum for 30 min. Dry mesitylene (3.04 mL) was added to dissolve the residue in the flask after it was cooled to room temperature.

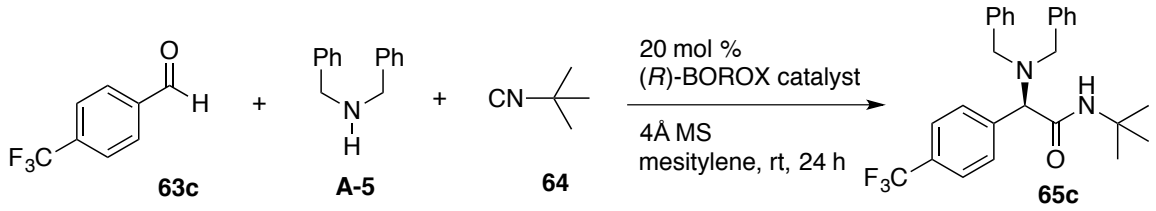
*Catalytic asymmetric Ugi reaction with benzaldehyde **63a**:* A 25 mL Schlenk flask charged with 4Å powdered molecular sieves (13 mg) and equipped with a magnetic stir bar was flame dried under high vacuum and cooled down under nitrogen. To the flask was then added 1.0 mL of the catalyst stock solution (20 mol% catalyst, 0.05 mmol) via a plastic syringe fitted with a metallic needle. To the resulting solution was added dibenzylamine **A-5** (0.10 mL, 0.52 mmol, 2.0 equiv) under a N_2 stream, followed by the addition of benzaldehyde **63a** (26.0 μL, 0.255 mmol, 1.00 equiv) and then *t*-butyl isocyanide (45 μL, 0.39 mmol, 1.5 equiv). The Teflon valve was then closed, and the resulting mixture was stirred at rt for 24 h. Upon completion, 8 μL H_2O was added to the reaction flask. After the mixture was stirred vigorously at room temperature for another 5 min, it was directly loaded onto a silica gel column (20 mm x 160 mm) with a pipette. Purification by column chromatography (1^{st} column, 20 × 160 mm, hexanes:EtOAc 15:1; 2^{nd} column, 20 × 160 mm, hexanes/CH_2Cl_2 1:1 as eluent until all the phenol **P-47** came out, then EtOAc/hexanes 1:5 as eluent) gave product **3a** as a white solid (85 mg, 0.22 mmol) in 86% yield. The optical purity was determined to be 91:9 *er* by HPLC analysis (Pirkle Covalent (*R*,*R*) WHELK-O1 column, hexanes/2-propanol 90:10, 222 nm, flow 1 mL/min). Retention times: R_t = 12.77 min (minor enantiomer) and R_t = 16.45 min (major enantiomer). The product **65a** (85 mg, 0.22 mmol) was recrystallized from hexanes/EtOAc (15:1,

0.8 mL) at room temperature to give colorless crystals of **65a** (60.5 mg, 0.157 mmol) with >99.5:0.5 er and in 71% recovery. A reaction that was run at 40 °C for 7 h afforded the product **65a** in 87% NMR yield with 86:14 er. A reaction that was run at 0 °C for 66 h afforded the product **65a** (74 mg, 0.19 mmol) in 75% isolated yield with 92:8 er. mp 136-137 °C; R_f = 0.40 (hexane: EtOAc 4:1). Spectral data for **65a**: ^{1}H 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 $C_{26}H_{31}N_2O$ *m/z* 387.2431 ([M+H]$^+$), meas 387.2461. $[\alpha]_D^{20}$ = – 34.5° (*c* 1.0, CH_2Cl_2) on >99.5:0.5 *er* material.

*Recovery of the ligand (R)-**78**:* The fractions containing the ligand (*R*)-**78** obtained from the purification of **65a** were combined and concentrated to dryness to give an orange foamy solid (49 mg), the ^{1}H NMR spectrum of which showed that the ligand was contaminated with a small amount of impurities that were not identified. This solid was purified by column chromatography on silica gel (20 × 150 mm, hexanes:EtOAc 30:1) to give *(R)-**78*** as an off-white foamy solid (37 mg, 0.045 mmol) in 90% recovery with > 99% *ee*. If the fractions containing the ligand are allowed to stay at room temperature for several days before purification, a decrease in the *ee* of the recovered *(R)-**78*** can be observed.



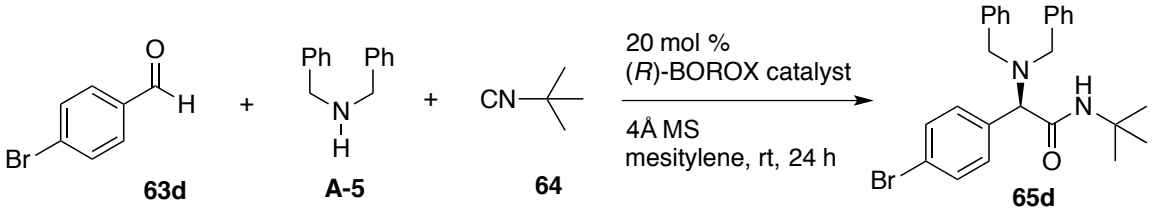
(R)-N-(tert-butyl)-2-(dibenzylamino)-2-(4-nitrophenyl)acetamide ***65b****:* The general procedure B for the catalytic asymmetric Ugi reaction described for **65a** was followed with 4-nitrobenzaldehyde **63b** (38.5 mg, 0.255 mmol, 1.00 equiv) with a reaction time of 24 h. The crude product was purified by column chromatography on silica gel (1st column, 20 × 160 mm, hexanes:EtOAc 15:1**;** 2nd column, 20 × 160 mm EtOAc/hexanes 1:8 as eluent) to afford the product **65b** as a yellow oil (91 mg, 0.21 mmol) in a yield of 83%. The optical purity was determined to be 93:7 *er* by HPLC analysis (Pirkle Covalent (*R*,*R*) WHELK-O1 column, hexanes/2-propanol 90:10, 222 nm, flow 1 mL). Retention times: R_t = 23.87 min (minor enantiomer) and R_t = 31.55 min (major enantiomer); A reaction that was run at 0 °C for 66 h afforded the product **65b** in 51% NMR yield with 92:8 er. R_f = 0.17 (hexane: EtOAc 8:1). Spectral data for **65b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.42 (s, 9H), 3.27 (d, 2H, *J* = 14.0 Hz), 3.85 (d, 2H, *J* = 14.0 Hz), 4.39 (s, 1H), 7.09 (brs, 1H), 7.26-7.41 (m, 10H), 7.46 (d, 2H, *J* = 9.0 Hz), 8.23 (d, 2H, *J* = 9.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.76, 51.29, 54.69, 67.17, 123.12, 127.65, 128.43, 128.75, 131.22, 137.99, 141.91, 147.40, 169.24; IR (thin film) 3351(w), 2969(w), 1680(s), 1520(s), 1348(s) cm^{-1}; HRMS (ESI) calcd for $C_{26}H_{30}N_3O_3$ *m/z* 432.2287 ($[M+H]^+$), meas 432.2283. $[\alpha]_D^{20}$ = – 92.3° (*c* 1.0, CH_2Cl_2) on 93:7 *er* material.



(R)-N-(tert-butyl)-2-(dibenzylamino)-2-(4-trifluoromethylphenyl)acetamide

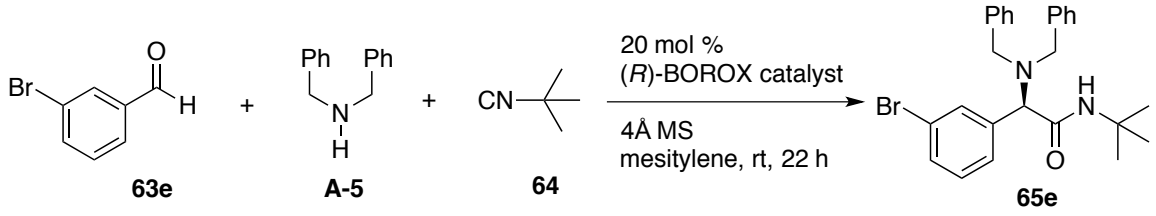
***65c**:* The general procedure B for the catalytic asymmetric Ugi reaction described for **65a** was followed with *4-trifluoromethyl*benzaldehyde **63c** (35 μL, 0.256 mmol, 1.00 equiv) with a reaction time of 24 h. The crude product was purified by column chromatography on silica gel (20 × 160 mm, hexanes:EtOAc 15:1) to give pure product **65c** as an off-white semi-solid (91.6 mg, 0.202 mmol) in a yield of 79% along with fractions containing a mixture of **65c** and phenol **P-47**. This mixture was loaded onto a silica gel column (20 × 160 mm, hexanes:EtOAc 15:1) and eluted to give additional product **65c** (7.40 mg, 0.016 mmol) in a yield of 6%. The combined yield of **65c** was 85%. The optical purity was determined to be 91:9 *er* by HPLC analysis (Pirkle Covalent (*R*,*R*) WHELK-O1 column, hexanes/2-propanol 90:10, 222 nm, flow 1 mL). Retention times: R_t = 9.70 min (minor enantiomer) and R_t = 13.94 min (major enantiomer); R_f = 0.43 (hexanes: EtOAc 3:1). Spectral data for **3c**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.40 (s, 9H), 3.28 (d, 2H, *J* = 14.0 Hz), 3.83 (d, 2H, *J* = 14.0 Hz), 4.34 (s, 1H), 7.10 (brs, 1H), 7.25-7.37 (m, 10H), 7.39 (d, 2H, *J* = 8.0 Hz), 7.63 (d, 2H, *J* = 8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.81, 51.19, 54.69, 67.61, 124.15 (q, *J* = 271.8 Hz), 125.00 (q, *J* = 3.8 Hz), 127.53, 128.52, 128.70, 129.92 (q, *J* = 32.4 Hz), 130.73, 138.35, 138.44, 169.81; IR (thin film) 3343(w), 2969(w), 1682(s), 1325(s) cm^{-1}; HRMS (ESI) calcd

for $C_{27}H_{30}F_3N_2O$ *m/z* 455.2310 ($[M+H]^+$), meas 455.2311. $[\alpha]_D^{20}$ = – 33.8° (*c* 1.0, CH_2Cl_2) on 91:9 *er* material.



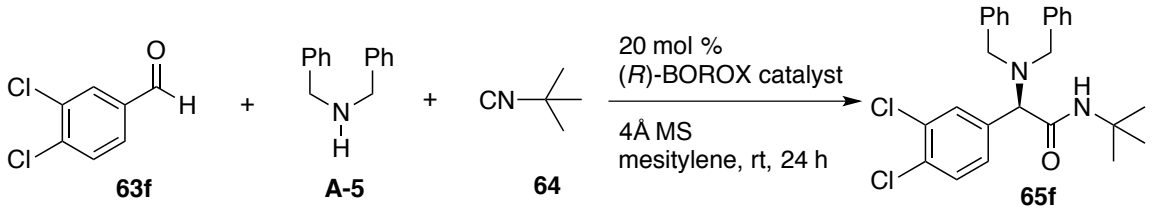
(R)-N-(tert-butyl)-2-(dibenzylamino)-2-(4-bromophenyl)acetamide ***65d****:* The general procedure B for the catalytic asymmetric Ugi reaction described for **65a** was followed with 4-bromobenzaldehyde **63d** (47.1 mg, 0.255 mmol, 1.00 equiv) with a reaction time of 24 h. The crude product was purified on silica gel according to the standard procedure (1st column, 20 × 160 mm, hexanes:EtOAc 15:1; 2nd column, 20 × 160 mm, hexanes/CH_2Cl_2 1:1 as eluent untill all the phenol **P-47** came out, then EtOAc/hexanes 1:5 as eluent) to afford the product **65d** as a colorless oil (100.5 mg, 0.216 mmol) in a yield of 85%. The optical purity was determined to be 93:7 *er* by HPLC analysis (Pirkle Covalent (*R*,*R*) WHELK-O1 column, hexanes/2-propanol 90:10, 222 nm, flow 1 mL). Retention times: R_t = 14.82 min (minor enantiomer) and R_t = 22.53 min (major enantiomer); R_f = 0.14 (hexane: EtOAc 15:1). A reaction that was run at 0 °C for 48 h afforded the product **65d** (77.2 mg, 0.166 mmol) in a yield of 65% with 95:5 er. Spectral data for **65d**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.39 (s, 9H), 3.27 (d, 2H, *J* = 14.0 Hz), 3.80 (d, 2H, *J* = 14.0 Hz), 4.25 (s, 1H), 7.11 (brs, 1H), 7.13-7.17 (m, 2H), 7.24-7.29 (m, 2H), 7.29-7.37 (m, 8H), 7.47-7.52 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.79, 51.07, 54.54, 67.37, 121.85, 127.43, 128.52, 128.64, 131.22, 132.04,

133.29, 138.46, 170.06; IR (thin film) 3345(w), 2967(w), 1684(s), 1507(s), 1453(m), 698(m) cm^{-1}; HRMS (ESI) calcd for $C_{26}H_{30}{}^{79}BrN_2O$ *m/z* 465.1542 ($[M+H]^+$), meas 465.1540. $[\alpha]_D^{20}$ = – 68.3° (*c* 1.0, CH_2Cl_2) on 95:5 *er* material.



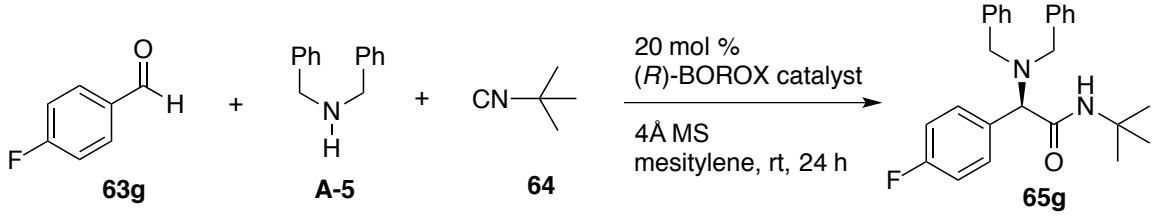
(R)-N-(tert-butyl)-2-(dibenzylamino)-2-(3-bromophenyl)acetamide ***65e****:* The general procedure B for the catalytic asymmetric Ugi reaction described for **65a** was followed with 3-bromobenzaldehyde **63e** (47.2 mg, 0.255 mmol, 1.00 equiv) with a reaction time of 22 h. The crude product was purified on silica gel according to the standard procedure (1st column, 20 × 160 mm, hexanes:EtOAc 15:1; 2nd column, 20 × 180 mm, hexanes/CH_2Cl_2 1:1 as eluent untill all the phenol **P-47** came out, then EtOAc/hexanes 1:5 as eluent) to afford the product **65e** as a colorless oil (98 mg, 0.21 mmol) in a yield of 82%. The optical purity was determined to be 93:7 *er* by HPLC analysis (Pirkle Covalent (*R*,*R*) WHELK-O1 column, hexanes/2-propanol 90:10, 222 nm, flow 1 mL). Retention times: R_t = 13.57 min (minor enantiomer) and R_t = 17.64 min (major enantiomer); A reaction that was run at 0 °C for 66 h at 0.4 M afforded the product **65e** (78.0 mg, 0.168 mmol) in a yield of 66% with 92:8 *er*. R_f = 0.28 (hexane: EtOAc 8:1). Spectral data for **65e**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.41 (s, 9H), 3.30 (d, 2H, *J* = 13.5 Hz), 3.82 (d, 2H, *J* = 13.5 Hz), 4.23 (s, 1H), 7.11 (brs, 1H), 7.20-7.39 (m, 12H), 7.41 (s, 1H), 7.46 (d, 1H, *J* = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.79, 51.09,

54.59, 67.49, 122.23, 127.45, 128.55, 128.65, 129.00, 129.59, 130.83, 133.30, 136.62, 138.41, 169.86; IR (thin film) 3345(w), 2967(w), 1682(s), 1506(s), 1453(s) cm^{-1}; HRMS (ESI) calcd for $C_{26}H_{30}{}^{79}BrN_2O$ *m/z* 465.1542 ($[M+H]^+$), meas 465.1536. $[\alpha]_D^{20}$ = – 43.1° (*c* 1.0, CH_2Cl_2) on 93:7 *er* material.



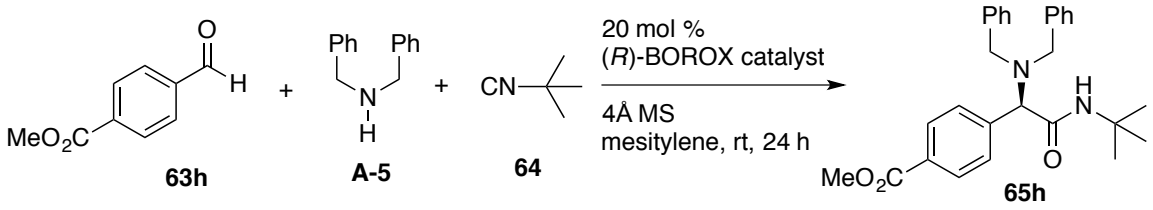
(R)-N-(tert-butyl)-2-(dibenzylamino)-2-(3,4-dichlorolphenyl)acetamide ***65f****:* The general procedure B for the catalytic asymmetric Ugi reaction described for **65a** was followed with 3-bromobenzaldehyde **63f** (44.5 mg, 0.255 mmol, 1.00 equiv) with a reaction time of 24 h. The crude product was purified on silica gel according to the standard procedure (1st column, 20 × 160 mm, hexanes:EtOAc 15:1; 2nd column, 20 × 180 mm, hexanes/CH_2Cl_2 1:1 as eluent untill all the phenol **P-47** came out, then EtOAc/hexanes 1:5 as eluent) to afford the product **65f** as a colorless semi-solid (98.7 mg, 0.217 mmol) in a yield of 85%. The optical purity was determined to be 94:6 *er* by HPLC analysis (Pirkle Covalent (*R*,*R*) WHELK-O1 column, hexanes/2-propanol 90:10, 222 nm, flow 1 mL). Retention times: R_t = 12.31 min (minor enantiomer) and R_t = 17.81 min (major enantiomer); R_f = 0.18 (hexane: EtOAc 10:1). A reaction that was run at 0 °C for 66 h afforded the product **3f** with 95:5 er in a yield of 54% as determined by ^{1}HNMR with the aid of an internal standard (Ph_3CH). Spectral data for **65f**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.39 (s, 9H), 3.28 (d, 2H, *J* = 13.5 Hz), 3.80 (d, 2H, *J* = 13.5 Hz), 4.23 (s, 1H),

7.05 (brs, 1H), 7.11 (dd, 1H, *J* = 8.3 Hz, 1.8 Hz), 7.25-7.39 (m, 11H) 7.43 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.80, 51.19, 54.67, 67.02, 127.56, 128.52, 128.72, 129.71, 129.98, 131.93, 132.25, 132.28, 134.57, 138.25, 169.52; IR (thin film) 3349(w), 2969(w), 1682(s), 1509(s), 733(m), 698(m) cm^{-1}; HRMS (ESI) calcd for $C_{26}H_{29}{}^{35}Cl_2N_2O$ *m/z* 455.1657 ($[M+H]^+$), meas 455.1658. $[\alpha]_D^{20}$ = –65.6° (*c* 1.0, CH_2Cl_2) on 94:6 *er* material.



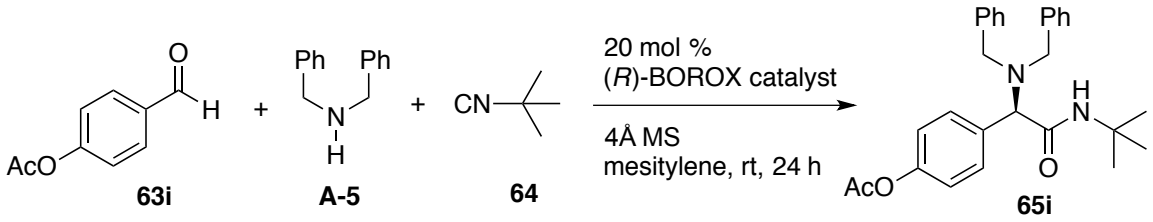
*(R)-N-(tert-butyl)-2-(dibenzylamino)-2-(4-fluorophenyl)acetamide **65g**:* The general procedure B for the catalytic asymmetric Ugi reaction described for **65a** was followed with 4-fluorobenzaldehyde **63g** (31.7 mg, 28 μL, 0.255 mmol, 1.00 equiv) with a reaction time of 24 h. The crude product was purified on silica gel according to the standard procedure (1st column, 20 × 160 mm, hexanes:EtOAc 15:1; 2nd column, 20 × 150 mm, hexanes/CH_2Cl_2 1:1 as eluent untill all the phenol **P-47** came out, then EtOAc/hexanes 1:5 as eluent) to afford the product **65g** as a colorless oil (89.7 mg, 0.22 mmol) in a yield of 87%. The optical purity was determined to be 91:9 *er* by HPLC analysis (Pirkle Covalent (*R*,*R*) WHELK-O1 column, hexanes/2-propanol 90:10, 222 nm, flow 1 mL). Retention times: R_t = 11.97 min (minor enantiomer) and R_t = 15.26 min (major enantiomer); A reaction that was run at 0 °C for 67 h afforded the product **65g** (63.9 mg, 0.158 mmol) in a yield of 62% with 94:6 er. R_f = 0.19 (hexanes: EtOAc 10:1). Spectral data for

65g: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.39 (s, 9H), 3.29 (d, 2H, *J* = 13.8 Hz), 3.80 (d, 2H, *J* = 13.8 Hz), 4.27 (s, 1H), 7.02-7.09 (m, 2H), 7.12 (brs, 1H), 7.21-7.28 (m, 4H), 7.29-7.37 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.77, 51.01, 54.52, 67.22, 114.97 (d, *J* = 21.0 Hz), 127.38, 128.50, 128.60, 129.95 (d, *J* = 3.0 Hz), 131.98 (d, *J* = 7.9 Hz), 138.53, 162.28 (d, *J* = 245.8 Hz), 170.39; IR (thin film) 3345(w), 2967(w), 1682(s), 1509(s), 1227(s) cm^{-1}; HRMS (ESI) calcd for $C_{26}H_{30}FN_2O$ *m/z* 405.2342 ([M+H]$^+$), meas 405.2341. $[\alpha]_D^{20}$ = –21.0 ° (*c* 1.0, CH_2Cl_2) on 94:6 *er* material.



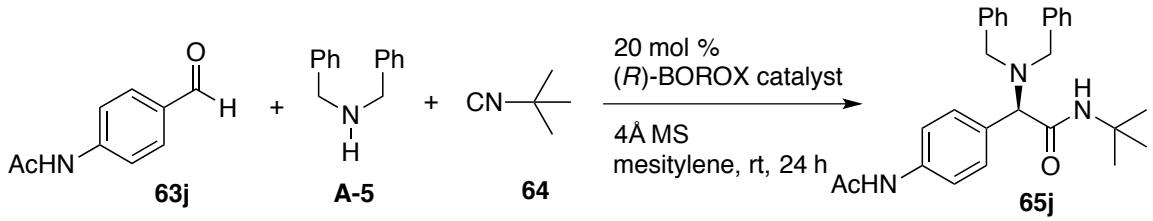
Methyl (R)-4-(2-(tert-butylamino)-1-(dibenzylamino)-2-oxoethyl)benzoate ***65h****:* The general procedure B for the catalytic asymmetric Ugi reaction described for **65a** was followed with methyl-4-formylbenzoate **63h** (42.0 mg, 0.255 mmol, 1.00 equiv) with a reaction time of 24 h. The crude product was purified by column chromatography on silica gel (20 × 160 mm, hexanes:EtOAc 15:1➔7.5:1➔5:1) to afford the product **65h** as a colorless semisolid (90.7 mg, 0.204 mmol) in a yield of 80%. The optical purity was determined to be 93:7 *er* by HPLC analysis (Pirkle Covalent (*R*,*R*) WHELK-O1 column, hexanes/2-propanol 75:25, 222 nm, flow 2 mL). Retention times: R_t = 7.84 min (minor enantiomer) and R_t = 11.73 min (major enantiomer); A reaction that was run at 0 °C for 67 h afforded the product **65h** (70 mg, 0.157 mmol) in a yield of 62% with 93:7 er. R_f =

0.34 (hexanes: EtOAc 3:1). Spectral data for **65h**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.39 (s, 9H), 3.28 (d, 2H, *J* = 13.8 Hz), 3.82 (d, 2H, *J* = 13.8 Hz), 3.91 (s, 3H), 4.33 (s, 1H), 7.07 (brs, 1H), 7.24-7.28 (m, 2H), 7.29-7.38 (m, 10H), 8.02-8.06 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.77, 51.11, 52.12, 54.56, 67.62, 127.45, 128.52, 128.63, 129.30, 129.44, 130.34, 138.35, 139.65, 166.90, 169.95; IR (thin film) 3370(w), 2963(w), 1725(s), 1680(s), 1281(s), 1111(m) cm^{-1}; HRMS (ESI) calcd for $C_{28}H_{33}N_2O_3$ *m/z* 445.2491 ($[M+H]^+$), meas 445.2486. $[\alpha]_D^{20}$ = – 64.3° (*c* 1.0, CH_2Cl_2) on 93:7 *er* material.



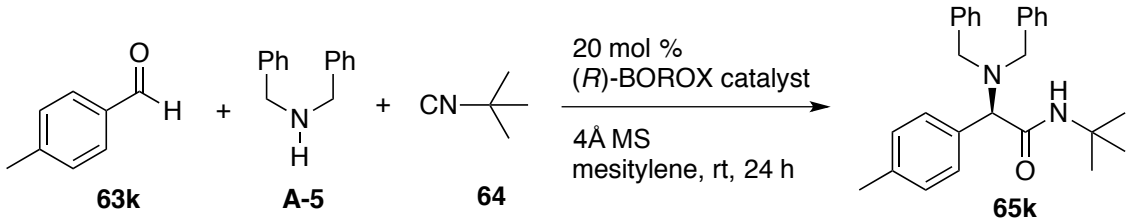
(R)-4-(2-(tert-butylamino)-1-(dibenzylamino)-2-oxoethyl)phenyl acetate ***65i****:* The general procedure B for the catalytic asymmetric Ugi reaction described for **65a** was followed with 4-acetoxybenzaldehyde **63i** (42.0 mg, 0.255 mmol, 1.00 equiv) with a reaction time of 24 h. The crude product was purified by column chromatography on silica gel (1st column, 20 × 160 mm, hexanes:EtOAc 15:1➔7.5:1➔5:1; 2nd column, 2nd column, 20 × 150 mm, hexanes:EtOAc 4:1) to afford the product **65i** as a yellow viscous oil (98.6 mg, 0.22 mmol) in a yield of 86%. The optical purity was determined to be 85:15 *er* by HPLC analysis (Pirkle Covalent (*R*,*R*) WHELK-O1 column, hexanes/2-propanol 75:25, 222 nm, flow 2 mL). Retention times: R_t = 10.49 min (minor enantiomer) and R_t = 13.12 min (major enantiomer); R_f = 0.31 (hexanes: EtOAc 3:1). Spectral data for **65i**: ^{1}H

NMR (500 MHz, $CDCl_3$) δ 1.39 (s, 9H), 2.29 (s, 3H), 3.35 (d, 2H, *J* = 13.8 Hz), 3.81 (d, 2H, *J* = 13.8 Hz), 4.28 (s, 1H), 7.06 (brs, 1H), 7.08-7.12 (m, 2H), 7.23-7.30 (m, 4H), 7.31-7.35 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.17, 28.80, 51.03, 54.50, 67.36, 121.13, 127.33, 128.56, 128.58, 131.30, 131.95, 138.70, 150.20, 169.26, 170.38; IR (thin film) 3374(w), 2965(w), 1763(s), 1680(s), 1505(s), 1202(s) cm^{-1}; HRMS (ESI) calcd for $C_{28}H_{33}N_2O_3$ *m/z* 445.2491 ($[M+H]^+$), meas 445.2490. $[\alpha]_D^{20}$ = – 31.6° (*c* 1.0, CH_2Cl_2) on 85:15 *er* material.



(R)-2-(4-Acetamidophenyl)-N-(tert-butyl)-2-(dibenzylamino)acetamide ***65j****:* The general procedure B for the catalytic asymmetric Ugi reaction described for **65a** was followed with 4-acetaminobenzaldehyde **63j** (41.6 mg, 0.255 mmol, 1.00 equiv) with a reaction time of 24 h. The crude product was purified by column chromatography on silica gel (20 × 160 mm, hexanes:EtOAc 3:1➔1:1) to afford the product **65j** as a white solid (87.0 mg, 0.196 mmol) in a yield of 77%. The optical purity was determined to be 85:15 *er* by HPLC analysis (Pirkle Covalent (*R*,*R*) WHELK-O1 column, hexanes/2-propanol 75:25, 254 nm, flow 2 mL). Retention times: R_t = 15.33 min (minor enantiomer) and R_t = 18.83 min (major enantiomer); The product was extracted with Et_2O to give **65j** as an off-white foamy solid with 96:14 *er* in 47% recovery. This material contains a very small amount of impurities. The precipitate that remained after the extraction was pure

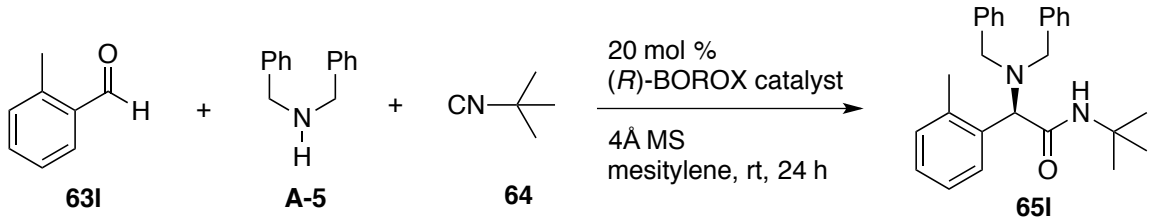
rac-**65j**. R_f = 0.12 (hexanes: EtOAc 1:1). Spectral data for (±)-**65j**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.40 (s, 9H), 2.04(s, 3H), 3.19 (d, 2H, *J* = 13.9 Hz), 3.78 (d, 2H, *J* = 13.9 Hz), 4.23 (s, 1H), 7.05 (d, 2H, *J* = 7.5 Hz), 7.24-7.36 (m, 12H), 7.55 (s, 1H), 8.27 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.20, 28.81, 51.01, 54.60, 67.65, 119.85, 127.38, 128.55, 128.63, 129.14, 130.83, 137.72, 138.57, 168.62, 171.09; IR (thin film) 3312(m), 2969(w), 1663(s), 1514(s) cm^{-1}; HRMS (ESI) calcd for $C_{28}H_{34}N_3O_2$ *m/z* 444.2651 ($[M+H]^+$), meas 444.2654.



63k **A-5** **64** **65k**

(R)-N-(tert-butyl)-2-(dibenzylamino)-2-(4-methyl)acetamide ***65k****:* The general procedure B for the catalytic asymmetric Ugi reaction described for **65a** was followed with p-tolualdehyde **63k** (30.6 mg, 30 μL, 0.255 mmol, 1.00 equiv) with a reaction time of 24 h. The crude product was purified on silica gel according to the standard procedure (1st column, 20 × 160 mm, hexanes:EtOAc 15:1; 2nd column, 20 × 150 mm, hexanes/CH_2Cl_2 1:1 as eluent untill all the phenol **P-47** came out, then EtOAc/hexanes 1:5 as eluent) to afford the product **65k** as a colorless semi-solid (85.7 mg, 0.214 mmol) in a yield of 84%. The optical purity was determined to be 91:9 *er* by HPLC analysis (Pirkle Covalent (*R*,*R*) WHELK-O1 column, hexanes/2-propanol 90:10, 222 nm, flow 1 mL). Retention times: R_t = 15.61 min (minor enantiomer) and R_t = 23.03 min (major enantiomer); R_f = 0.12 (hexanes: EtOAc 10:1). The product **65k** (85.7 mg, 0.214 mmol) was

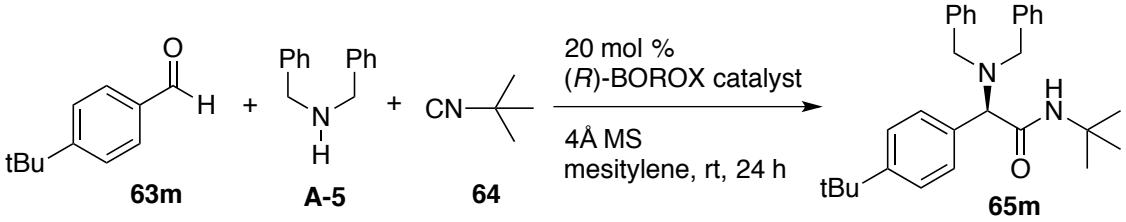
recrystallized from hexanes (0.5 mL) at room temperature to give colorless crystals of **65k** (40.5 mg, 0.101 mmol) with 99.4:0.6 er and in 47% recovery. A reaction that was run at 0 °C for 66 h afforded the product **65k** in 80% NMR yield with 92:8 er. Spectral data for **65k**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.41 (s, 9H), 2.36 (s, 3H), 3.37 (d, 2H, *J* = 14.0 Hz), 3.84 (d, 2H, *J* = 14.0 Hz), 4.28 (s, 1H), 7.09 (brs, 1H), 7.19 (s, 4H), 7.24-7.30 (m, 2H) 7.32-7.37 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.11, 28.79, 50.87, 54.50, 67.92, 127.20, 128.47, 128.59, 128.78, 130.17, 131.48, 137.28, 138.87, 170.79; IR (thin film) 3347(w), 2967(w), 1684(s), 1507(s), 1453(m) cm^{-1}; HRMS (ESI) calcd for $C_{27}H_{33}N_2O$ *m/z* 401.2593 ([M+H]$^+$), meas 401.2587. $[\alpha]_D^{20}$ = – 40.7° (*c* 1.0, CH_2Cl_2) on 91:9 *er* material.



63l **A-5** **64** **65l**

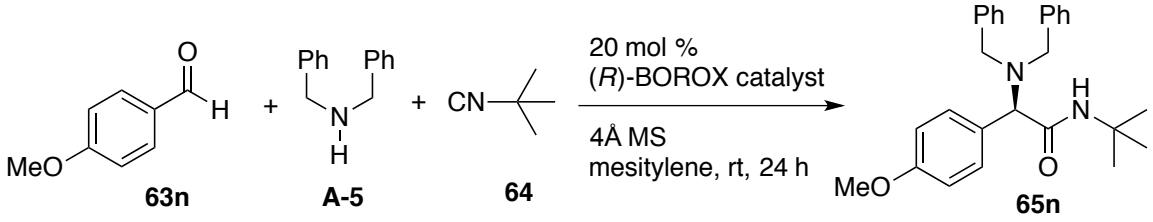
(R)-N-(tert-butyl)-2-(dibenzylamino)-2-(2-methyl)acetamide ***65l:*** The general procedure B for the catalytic asymmetric Ugi reaction described for **65A** was followed with o-tolualdehyde **63l** (30.6 mg, 30 μL, 0.255 mmol, 1.00 equiv) with a reaction time of 24 h. The crude product was purified on silica gel according to the standard procedure (1st column, 20 × 160 mm, hexanes:EtOAc 15:1; 2nd column, 20 × 150 mm, hexanes/CH_2Cl_2 1:1 as eluent until all the phenol **P-47** came out, then EtOAc/hexanes 1:5 as eluent) to afford the product **65l** as a white solid (77.5 mg, 0.193 mmol) in a yield of 76%. The optical purity was determined to be 78:22 *er* by HPLC analysis (Pirkle Covalent (*R*,*R*) WHELK-O1

column, hexanes/2-propanol 90:10, 222 nm, flow 1 mL). Retention times: R_t = 6.91 min (minor enantiomer) and R_t = 13.34 min (major enantiomer). The product (71.4 mg, 0.178 mmol) was recrystallized from 0.9 mL hexanes/EtOAc 20:1 at –10°C to give a white solid (40 mg, 0.010 mmol) with > 99:1 *er* in 56% recovery. mp 104-105 °C. R_f = 0.16 (hexanes: EtOAc 10:1). Spectral data for **65l**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.35 (s, 9H), 2.22 (s, 3H), 3.74 (d, 2H, *J* = 14.0 Hz), 3.83 (d, 2H, *J* = 14.0 Hz), 4.37 (s, 1H), 6.31 (brs, 1H), 7.15 (s, 3H), 7.19-7.25 (m, 6H) 7.26-7.31 (m, 4H), 7.39-7.45 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.87, 28.71, 51.07, 54.53, 65.93, 125.81, 127.03, 127.70, 128.22, 128.75, 129.04, 130.91, 135.52, 138.10, 138.99, 171.66; IR (thin film) 3337(w), 2967(w), 1671(s), 1509(s), 1453(s) cm^{-1}; HRMS (ESI) calcd for $C_{27}H_{33}N_2O$ *m/z* 401.2593 ([M+H]$^+$), meas 401.2589. $[\alpha]_D^{20}$ = –20.1° (*c* 1.0, CH_2Cl_2) on >99:1 *er* material.



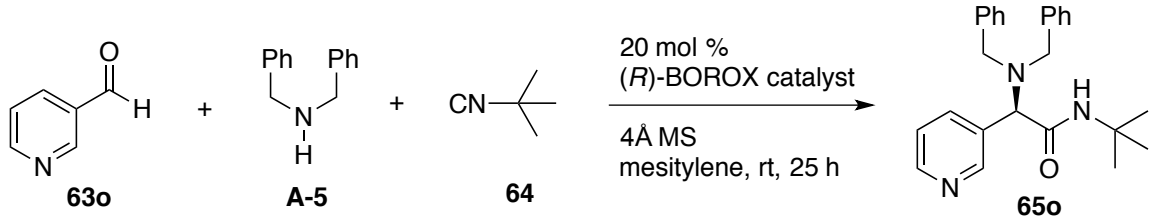
(R)-N-(tert-butyl)-2-(dibenzylamino)-2-(4-tert-butyl)acetamide ***65m****:* The general procedure B for the catalytic asymmetric Ugi reaction described for **65a** was followed with tert-butylbenzaldehyde **65m** (41.3 mg, 42.6 μL, 0.255 mmol, 1.00 equiv) with a reaction time of 24 h. The crude product was purified by column chromatography on silica gel (1st column, 20 × 160 mm, hexanes:EtOAc 15:1; 2nd column, 20 × 150 mm, hexanes/CH_2Cl_2 1:1 as eluent untill all the phenol **P-47** came out, then EtOAc/hexanes 1:5 as eluent) to afford the product **65m** as

a white solid (93.7 mg, 0.212 mmol) in a yield of 83%. The optical purity was determined to be 84:16 *er* by HPLC analysis (Pirkle Covalent (*R*,*R*) WHELK-O1 column, hexanes/2-propanol 90:10, 222 nm, flow 1 mL). Retention times: R_t = 10.99 min (minor enantiomer) and R_t = 16.16 min (major enantiomer); mp 48-51 °C. R_f = 0.52 (hexanes: EtOAc 3:1). Spectral data for **65m**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.31 (s, 9H), 1.39 (s, 9H), 3.37 (d, 2H, *J* = 14.0 Hz), 3.81 (d, 2H, *J* = 14.0 Hz), 4.25 (s, 1H), 7.10 (brs, 1H), 7.17-7.22 (m, 2H) 7.22-7.29 (m, 2H), 7.30-7.40 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.83, 31.33, 34.50, 50.93, 54.64, 67.99, 125.01, 127.21, 128.49, 128.63, 129.96, 131.42, 139.02, 150.41, 170.89; IR (thin film) 3341(w), 2965(s), 1682(s), 1507(s) cm^{-1}; HRMS (ESI) calcd for $C_{30}H_{39}N_2O$ *m/z* 443.3062 ($[M+H]^+$), meas 443.3063. $[\alpha]_D^{20}$ = – 40.9° (*c* 1.0, CH_2Cl_2) on 84:16 *er* material.



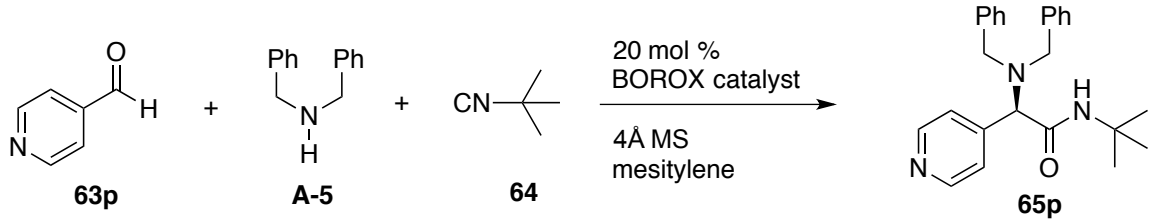
(R)-N-(tert-butyl)-2-(dibenzylamino)-2-(4-methoxy)acetamide ***65n****:* The general procedure B for the catalytic asymmetric Ugi reaction described for **65a** was followed with 4-anisaldehyde **63n** (34.7 mg, 31.0 μL, 0.255 mmol, 1.00 equiv) with a reaction time of 24 h. The crude product was purified by column chromatography on silica gel (20 × 160 mm, hexanes:EtOAc 10:1) to afford the product **65n** as a semi-solid (74.4 mg, 0.179 mmol) in a yield of 70%. The optical purity was determined to be 89:11 *er* by HPLC analysis (Pirkle Covalent (*R*,*R*)

WHELK-O1 column, hexanes/2-propanol 75:25, 222 nm, flow 2 mL). Retention times: R_t = 5.91 min (minor enantiomer) and R_t = 8.80 min (major enantiomer); R_f = 0.34 (hexanes: EtOAc 3:1). A reaction that was run at 0 °C for 66 h afforded the product **65n** (54.2 mg, 0.130 mmol) in a yield of 51% with 92:8 er. Spectral data for **65n**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.39 (s, 9H), 3.32 (d, 2H, *J* = 14.0 Hz), 3.799 (d, 2H, *J* = 14.0 Hz), 3.802 (s, 3H), 4.24 (s, 1H), 6.87-6.93 (m, 2H), 7.11 (brs, 1H), 7.17-7.22 (m, 2H), 7.22-7.28 (m, 2H), 7.30-7.35 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.81, 50.90, 54.54, 55.23, 67.61, 113.54, 126.58, 127.24, 128.52, 128.60, 131.45, 138.89, 159.08, 170.88; IR (thin film) 3355(m), 2963(w), 1680(s), 1510(s), 1248(s) cm^{-1}; HRMS (ESI) calcd for $C_{27}H_{33}N_2O_2$ *m/z* 417.2542 ([M+H]$^+$), meas 417.2548. $[\alpha]_D^{20}$ = – 46.4° (*c* 1.0, CH_2Cl_2) on 92:8 *er* material.



(R)-N-(*tert*-butyl)-2-(dibenzylamino)-2-(pyridin-3-yl)*acetamide* ***65o****:* The general procedure B for the catalytic asymmetric Ugi reaction described for **65a** was followed with 3-pyridinecarboxaldehyde **63o** (27.3 mg, 24.0 μL, 0.255 mmol, 1.00 equiv) with a reaction time of 25 h. The crude product was purified by column chromatography on silica gel (20 × 160 mm, hexanes:EtOAc 15:1➔5:1➔1:1) to afford the product **65o** as a solid (79.0 mg, 0.204 mmol) in a yield of 80%. The optical purity was determined to be 90:10 *er* by HPLC analysis (Chiralpak AD column, hexanes/2-propanol 90:10, 222 nm, flow 1 mL). Retention

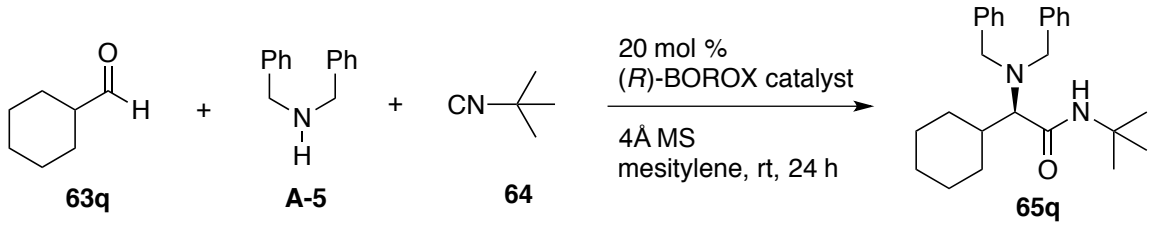
times: R_t = 6.97 min (minor enantiomer) and R_t = 10.93 min (major enantiomer). The product (79.0 mg, 0.204 mmol) was crystallized from a mixture of hexanes/EtOAc (8:1) at room temperature to give 48 mg of **65o** as colorless crystals in >99:1 er and 61% recovery. mp 123-124 °C. R_f = 0.29 (hexanes: EtOAc 1:2). Spectral data for **65o**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.40 (s, 9H), 3.22 (d, 2H, *J* = 13.7 Hz), 3.83 (d, 2H, *J* = 13.7 Hz), 4.34 (s, 1H), 7.21 (brs, 1H), 7.25-7.30 (m, 2H) 7.30-7.38 (m, 9H), 7.65-7.70 (m, 1H), 8.48 (s, 1H), 8.57 (d, 1H, *J* = 4.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.77, 51.17, 54.63, 65.40, 123.12, 127.61, 128.48, 128.76, 129.75, 138.09, 138.43, 148.60, 151.08, 169.46; IR (thin film) 3349(w), 2969(w), 1680(s) cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{30}N_3O$ *m/z* 388.2389 ($[M+H]^+$), meas 388.2384. $[\alpha]_D^{20}$ = –17.1° (*c* 1.0, CH_2Cl_2) on >99:1 *er* material.



63p **A-5** **64** **65p**

(R)-N-(*tert*-butyl)-2-(dibenzylamino)-2-(pyridin-4-yl)*acetamide* ***65p****:* The general procedure B for the catalytic asymmetric Ugi reaction described for **65a** was followed with 4-pyridinecarboxaldehyde **63p** (27.3 mg, 24.0 μL, 0.255 mmol, 1.00 equiv) except that the reaction time is 70 h. The crude product was purified by column chromatography on silica gel (20 × 160 mm, hexanes:EtOAc 3:1➔1:1) to afford the product **65p** as a semi-solid (65.2 mg, 0.168 mmol) in a yield of 66%. The optical purity was determined to be 89:11 *er* by HPLC analysis

(Chiralpak AD column, hexanes/2-propanol 95:5, 222 nm, flow 0.7 mL). Retention times: R_t = 18.38 min (minor enantiomer) and R_t = 22.86 min (major enantiomer). R_f = 0.30 (hexanes/EtOAc 1:2). Spectral data for **65p**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.40 (s, 9H), 3.26 (d, 2H, *J* = 13.8 Hz), 3.82 (d, 2H, *J* = 13.8 Hz), 4.27 (s, 1H), 7.07 (brs, 1H), 7.20-7.22 (m, 2H), 7.25-7.30 (m, 2H), 7.30-7.38 (m, 8H), 8.59-8.64 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.75, 51.24, 54.61, 66.74, 125.41, 127.60, 128.44, 128.73, 138.04, 143.18, 149.42, 169.10; IR (thin film) 3341(w), 3258(w), 3031(w), 2967(w), 1680(s) cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{30}N_3O$ *m/z* 388.2389 ($[M+H]^+$), meas 388.2382. $[\alpha]_D^{20}$ = –11.9° (*c* 1.0, CH_2Cl_2) on >89:11 *er* material.

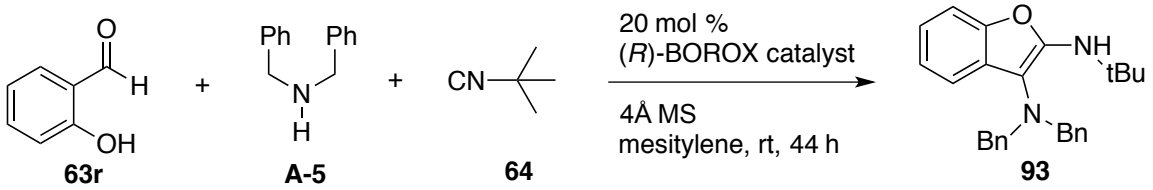


63q **A-5** **64** **65q**

(R)-N-(tert-butyl)-2-cyclohexyl-2-(dibenzylamino)acetamide ***65q****:* The general procedure B for the catalytic asymmetric Ugi reaction described for **65a** was followed with cyclohexanecarboxaldehyde **63q** (28.7 mg, 31.0 μL, 0.256 mmol, 1.00 equiv) with a reaction time of 24 h. The crude product was purified by column chromatography on silica gel (20 × 160 mm, hexanes:EtOAc 15:1) to afford the product **65q** as an off-white solid (45.1 mg, 0.115 mmol) in a yield of 45%. A second run gave **65q** (49.2 mg, 0.125 mmol) in 49% isolated yield. The optical purity was determined to be 50.5:49.5 *er* by HPLC analysis (Pirkle Covalent (*R*,*R*) WHELK-O1 column, hexanes/2-propanol 90:10, 222 nm, flow 1

mL). Retention times: R_t = 4.59 min (minor enantiomer) and R_t = 5.06 min (major enantiomer). mp 97-100 °C. R_f = 0.25 (hexanes/EtOAc 10:1). Spectral data for **65q**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.67-0.79 (m, 1H), 0.80-0.92 (m, 1H), 1.01-1.14 (m, 1H), 1.14-1.31 (m, 2H), 1.37 (s, 9H), 1.53-1.67 (m, 3H), 1.72 (d, 1H, *J* = 13.3 Hz), 1.90-2.01 (m, 1H), 2.27 (d, 1H, *J* = 13.3 Hz), 2.46 (d, 1H, *J* = 10.3 Hz), 3.45 (d, 2H, *J* = 14.5 Hz), 4.06 (d, 2H, *J* = 14.5 Hz), 5.02 (s, 1H), 7.22 (t, 2H, *J* = 7.5 Hz), 7.31 (t, 4H, *J* = 7.5 Hz), 7.40 (d, 4H, *J* = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.97, 26.00, 26.62, 28.98, 29.83, 30.53, 36.14, 51.49, 54.37, 68.75, 126.82, 128.30, 128.37, 140.16, 170.17; IR (thin film) 3430(w), 2926(s), 2851(s), 1676(s), 1503(s), 1453(s) cm^{-1}; HRMS (ESI) calcd for $C_{26}H_{37}N_2O$ *m/z* 393.2906 ([M+H]$^+$), meas 393.2904.

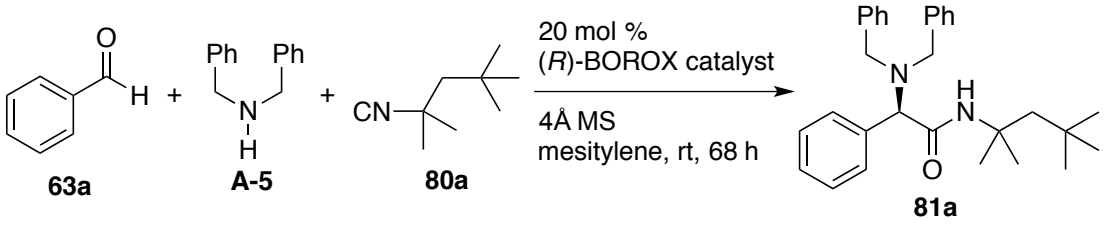
5.1.8 Intramolecular Interception of the Nitrilium Cation



N^3,N^3-dibenzyl-N^2-(tert-butyl)benzofuran-2,3-diamine: The general procedure B for the catalytic asymmetric Ugi reaction described in **Part 5.1.7** was followed with salicylaldehyde **63r** (31.1 mg, 27.0 μL, 0.255 mmol, 1.00 equiv) with a reaction time of 44 h. The crude product was purified by column chromatography on silica gel (20 × 160 mm, hexanes:EtOAc 20:1) to afford the product **93** as a yellow solid (21.5 mg, 0.0559 mmol) in a yield of 22%. The product was assigned as **93** on the basis of its ^{1}H and ^{13}C NMR spectra. A reaction that was run at 0 °C for 66 h afforded the product **93** (20 mg, 0.052

mmol) in a yield of 20%. R_f = 0.24 (hexanes/EtOAc 20:1). Spectral data for **93**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.06 (s, 9H), 3.80 (s, 1H), 4.16 (s, 4H), 6.96-7.02 (m, 1H), 7.12 (t, 1H, *J* = 7.5 Hz), 7.18-7.30 (m, 11H), 7.40-7.44 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.99, 52.33, 58.60, 106.83, 110.38, 117.01, 119.44, 122.08, 127.07, 127.69, 128.21, 129.11, 139.60, 149.26, 155.28.

5.1.9 Formation of α-Amino Amides with Different Isocyanides

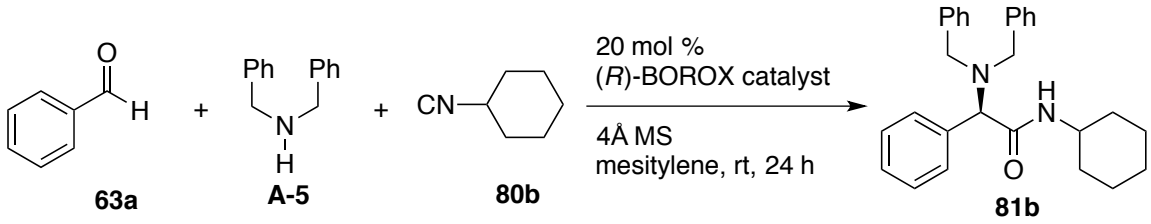


63a **A-5** **80a** **81a**

(R)-2-(dibenzylamino)-2-phenyl-N-(2,4,4-trimethylpentan-2-yl)acetamide

***81a**:* The general procedure B for the catalytic asymmetric Ugi reaction described in **Part 5.1.7** was followed with isocyanide **80a** (67 μL, 0.38 mmol, 1.5 equiv) with a reaction time of 68 h. The crude product was purified by column chromatography on silica gel (20 × 160 mm, hexanes:EtOAc 15:1) to afford the product **81a** as a colorless semi-solid (62.2 mg, 0.141 mmol) in a yield of 55%. The optical purity was determined to be 87:13 *er* by HPLC analysis (Pirkle Covalent (*R*,*R*) WHELK-O1 column, hexanes/2-propanol 90:10, 222 nm, flow 1 mL). Retention times: R_t = 9.78 min (minor enantiomer) and R_t = 11.13 min (major enantiomer); R_f = 0.25 (hexanes: EtOAc 6:1). Spectral data for **81a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.94 (s, 9H), 1.43 (s, 3H), 1.48 (s, 3H), 1.64 (d, 1H, *J* = 15.3 Hz), 1.94 (d, 1H, *J* = 15.3 Hz), 3.25 (d, 2H, *J* = 13.5 Hz), 3.86 (d, 2H, *J* = 13.5 Hz), 4.30 (s, 1H), 7.23-7.42 (m, 16H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.27,

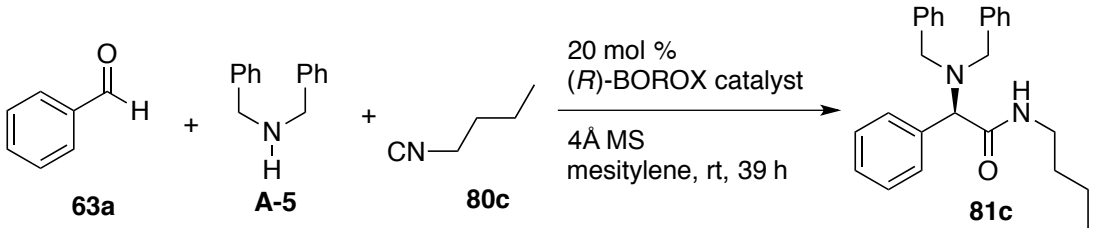
29.38, 31.42, 31.49, 51.28, 54.46, 54.91, 68.02, 127.31, 127.63, 128.02, 128.55, 128.63, 130.63, 133.86, 138.55, 170.28; IR (thin film) 3351(w), 2955(m), 1684(s), 1507(s), 1453(w) cm^{-1}; HRMS (ESI) calcd for $C_{30}H_{39}N_2O$ *m/z* 443.3062 ($[M+H]^+$), meas 443.3060. $[\alpha]_D^{20}$ = – 15.2° (*c* 1.0, CH_2Cl_2) on 87:13 *er* material.



63a **A-5** **80b** **81b**

*(R)-N-cyclohexyl-2-(dibenzylamino)-2-phenylacetamide **81b**:* The general procedure B for the catalytic asymmetric Ugi reaction described in **Part 5.1.7** was followed with isocyanide **80b** (47.5 μL, 0.382 mmol, 1.50 equiv) with a reaction time of 24 h. The crude product was purified by column chromatography on silica gel (20 × 160 mm, hexanes:EtOAc 15:1) to afford the product **81b** as a white solid (78.8 mg, 0.191 mmol) in a yield of 75%. The optical purity was determined to be 67:33 *er* by HPLC analysis (CHIRALCEL OD-H column, hexanes/2-propanol 98:2, 222 nm, flow 1 mL). Retention times: R_t = 8.00 min (minor enantiomer) and R_t = 9.18 min (major enantiomer); mp 129-132 °C. R_f = 0.33 (hexanes: EtOAc 3:1). Spectral data for **81b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.12-1.30 (m, 3H), 1.32-1.46 (m, 2H), 1.57-1.77 (m, 3H), 1.85-2.01 (m, 2H), 3.35 (d, 2H, *J* = 14.0 Hz), 3.82 (d, 2H, *J* = 14.0 Hz), 3.80-3.91 (m, 1H), 4.35 (s, 1H), 7.06 (d, 1H, *J* = 8.4 Hz), 7.23-7.39 (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.67,24.73, 25.55, 33.02, 33.35, 47.81, 54.50, 67.72, 127.26, 127.74, 128.13, 128.52, 128.64, 130.16, 134.71, 138.73, 170.28; IR (thin film) 3318(w), 2930(s),

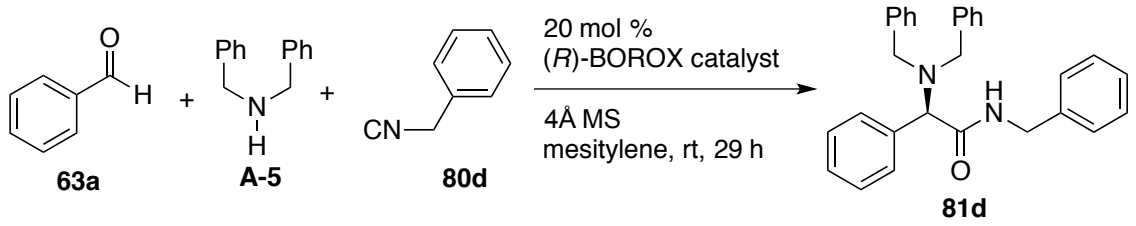
2853(m), 1663(s), 1506(s), 1453(m) cm^{-1}; HRMS (ESI) calcd for $C_{28}H_{33}N_2O$ *m/z* 413.2593 ($[M+H]^+$), meas 413.2591. $[\alpha]_D^{20}$ = – 5.8° (*c* 1.0, CH_2Cl_2) on 67:33 *er* material.



63a **A-5** **80c** **81c**

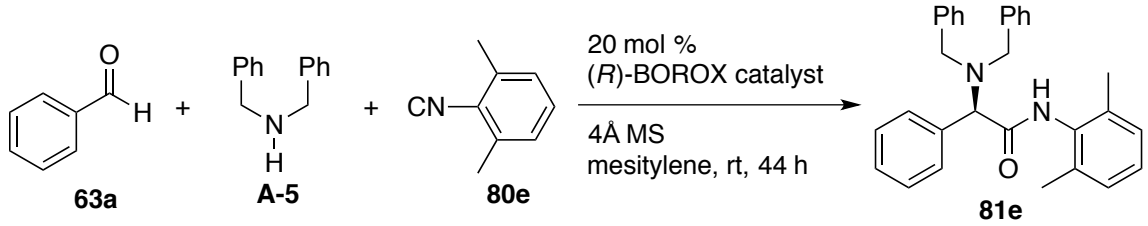
(R)-N-butyl-2-(dibenzylamino)-2-phenylacetamide ***81c****:* The general procedure B for the catalytic asymmetric Ugi reaction described in **Part 5.1.7** was followed with isocyanide **80c** (40 μL, 0.38 mmol, 1.5 equiv) with a reaction time of 39 h. The crude product was purified by column chromatography on silica gel (20 × 160 mm, hexanes:EtOAc 15:1 to 5:1) to afford the product **81c** as an off-white solid (47.3 mg, 0.122 mmol) in a yield of 48%. The optical purity was determined to be 52:48 *er* by HPLC analysis (Pirkle Covalent (*R*,*R*) WHELK-O1 column, hexanes/2-propanol 90:10, 222 nm, flow 1 mL). Retention times: R_t = 30.04 min (major enantiomer) and R_t = 33.40 min (minor enantiomer); mp 83-85 °C. R_f = 0.26 (hexanes: EtOAc 3:1). Spectral data for **81c**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.93 (t, 3H, *J* = 7.3 Hz), 1.31-1.41 (m, 2H), 1.53 (pentet, 2H, *J* = 7.3 Hz), 3.26-3.42 (m, 2H), 3.34 (d, 2H, *J* = 13.5 Hz), 3.84 (d, 2H, *J* = 13.5 Hz), 4.39 (s, 1H), 7.14 (br, t, 1H, *J* = 5.8 Hz), 7.22-7.42 (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.70, 20.08, 31.73, 38.91, 54.48, 67.66, 127.27, 127.76, 128.13, 128.53, 128.58, 130.18, 134.39, 138.62, 171.25; IR (thin film) 3310(m), 2957(m),

2930(m), 1655(s), 1495(m), 1453(m) cm^{-1}; HRMS (ESI) calcd for $C_{26}H_{31}N_2O$ *m/z* 387.2436 ($[M+H]^+$), meas 387.2433.



63a **A-5** **80d** **81d**

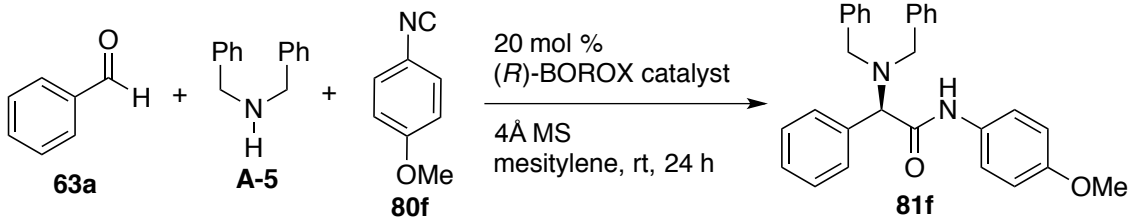
(R)-N-benzyl-2-(dibenzylamino)-2-phenylacetamide ***81d****:* The general procedure B for the catalytic asymmetric Ugi reaction described in **Part 5.1.7** was followed with isocyanide **80d** (47 μL, 0.39 mmol, 1.5 equiv) with a reaction time of 29 h. The crude product was purified by column chromatography on silica gel (20 × 160 mm, hexanes:EtOAc 6:1) to afford the product **81d** as a light yellow solid (49.4 mg, 0.117 mmol) in a yield of 46%. The optical purity was determined to be 51:49 *er* by HPLC analysis (Pirkle Covalent (*R*,*R*) WHELK-O1 column, hexanes/2-propanol 85:15, 222 nm, flow 1 mL). Retention times: R_t = 34.61 min (major enantiomer) and R_t = 39.08 min (minor enantiomer); mp 104-105 °C. R_f = 0.11 (hexanes: EtOAc 6:1). Spectral data for **81d**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.33 (d, 2H, *J* = 14.0 Hz), 3.86 (d, 2H, *J* = 14.0 Hz), 4.48 (s, 1H), 4.51 (dd, 1H, *J* = 14.5 Hz, *J* = 6.0 Hz), 4.61 (dd, 1H, *J* = 14.5 Hz, *J* = 6.0 Hz), 7.24-7.45 (m, 20H), 7.52 (t, 1H, *J* = 5.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 43.47, 54.51, 67.66, 127.29, 127.52, 127.76, 127.88, 128.19, 128.53, 128.68, 128.73, 130.29, 134.06, 138.25, 138.43, 171.31; IR (thin film) 3310(m), 3029(m), 1662(s), 1495(m), 1453(m) cm^{-1}; HRMS (ESI) calcd for $C_{29}H_{29}N_2O$ *m/z* 421.2280 ($[M+H]^+$), meas 421.2278.



63a **A-5** **80e** **81e**

(R)-2-(dibenzylamino)-N-(2,6-dimethylphenyl)-2-phenylacetamide ***81e****:*

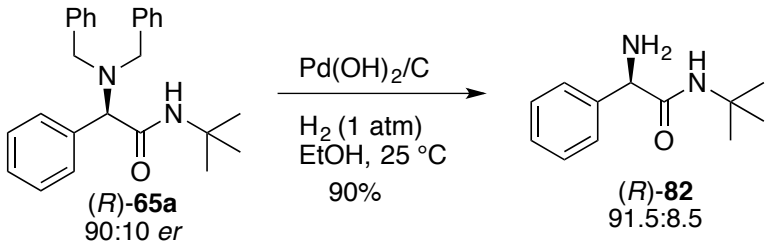
The general procedure B for the catalytic asymmetric Ugi reaction described in **Part 5.1.7** was followed with isocyanide **80e** (50 mg, 0.38 mmol, 1.5 equiv) with a reaction time of 44 h. The crude product was purified by column chromatography on silica gel (20 × 160 mm, hexanes:EtOAc 6:1) to afford a mixture of phenol **P-47** and the product **81e** which contained the product **81e** (32 mg, 0.074 mmol) in a yield of 29%. The optical purity was determined to be 85:15 *er* by HPLC analysis (Pirkle Covalent (*R*,*R*) WHELK-O1 column, hexanes/2-propanol 75:25, 222 nm, flow 2 mL). Retention times: R_t = 4.84 min (major enantiomer) and R_t = 10.60 min (minor enantiomer); R_f = 0.16 (hexanes: EtOAc 6:1). Spectral data for **81e**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.17 (s, 6H), 3.34 (d, 2H, *J* = 14.0 Hz), 4.02 (d, 2H, *J* = 14.0 Hz), 4.67 (s, 1H), 7.05-7.12 (m, 3H), 7.25-7.30 (m, 2H), 7.32-7.45 (m, 13H), 8.83 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.76, 54.59, 67.74, 127.17, 127.54, 128.00, 128.22, 128.29, 128.70, 128.73, 130.68, 133.45, 133.92, 135.38, 138.11, 169.71; HRMS (ESI) calcd for $C_{30}H_{31}N_2O$ *m/z* 435.2436 ($[M+H]^+$), meas 435.2435.



(R)-2-(dibenzylamino)-N-(4-methoxyphenyl)-2-phenylacetamide ***81f****:* The general procedure B for the catalytic asymmetric Ugi reaction described in **Part 5.1.7** was followed with isocyanide **80f** (51 mg, 0.38 mmol, 1.5 equiv) with a reaction time of 24 h. The crude product was purified by column chromatography on silica gel (20 × 160 mm, hexanes:EtOAc 6:1) to afford the product **81f** as a yellow solid (72.2 mg, 0.165 mmol) in a yield of 65%. The optical purity was determined to be 88:12 *er* by HPLC analysis (Pirkle Covalent (*R*,*R*) WHELK-O1 column, hexanes/2-propanol 75:25, 222 nm, flow 2 mL). Retention times: R_t = 14.25 min (major enantiomer) and R_t = 30.58 min (minor enantiomer); mp 54-55 °C. R_f = 0.13 (hexanes: EtOAc 6:1). Spectral data for **81f**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.33 (d, 2H, *J* = 14.0 Hz), 3.79 (s, 3H), 3.95 (d, 2H, *J* = 14.0 Hz), 4.57 (s, 1H), 6.87-6.92 (m, 2H), 7.26-7.46 (m, 15H), 7.50-7.55 (m, 2H), 9.30 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 54.67, 55.48, 68.17, 114.22, 120.83, 127.50, 128.03, 128.24, 128.63, 128.74, 130.59, 131.06, 133.25, 138.21, 156.22, 169.31; IR (thin film) 3322(w), 3029(w), 1682(m), 1514(s), 1246(m) cm^{-1}; HRMS (ESI) calcd for $C_{29}H_{29}N_2O_2$ *m/z* 437.2229 ([M+H]$^+$), meas 437.2227. $[\alpha]_D^{20}$ = + 67.4° (*c* 1.0, CH_2Cl_2) on 88:12 *er* material.

5.1.10 Determination of the Absolute Configuration of the Ugi Product 65a (Scheme 2.10)

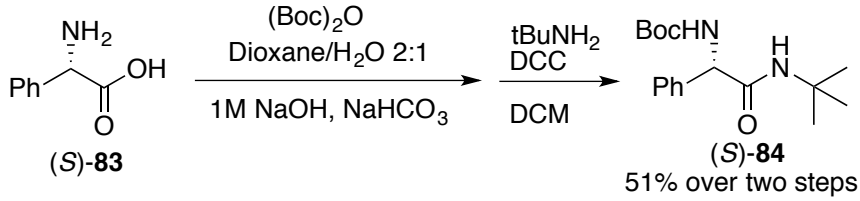
*Removal of the benzyl groups of **65a**:*



*(R)-2-amino-N-(tert-butyl)-2-phenylacetamide **82***: To a flame-dried 25 mL round bottom flask filled with nitrogen was added **65a** (70.0 mg, 0.181 mmol, 90:10 *er*), $Pd(OH)_2$ (20.0 mg, 0.028 mmol) ($Pd(OH)_2$ on carbon 20%, moisture ≤ 50%). The flask was sealed with a rubber septum and a needle connected to a vacuum line was used to apply vacuum in the flask through the septum. The vacuum was applied for a few seconds. Then the vacuum was stopped and a hydrogen balloon was connected to the flask by a needle through the septum. This process was repeated four times. Then 5.0 mL EtOH was added to the flask via a needle through the septum. The suspension was stirred at room temperature under hydrogen for 18 hours and then filtered through a pad of Celite. The filter cake was washed with MeOH (5 mL) and DCM (5 mL × 3). The combined filtrate was concentrated to give a light yellow oil. Purification of the crude product by column chromatography on silica gel (20 mm × 160 mm, CH_2Cl_2/MeOH 20:1) gave the product **82** as a colorless oil (33.4 mg, 0.162 mmol, 90%). The optical purity was determined to be 91.5:8.5 *er* by HPLC analysis (Chiralpak AS column, hexanes/2-propanol 85:15, 222 nm, flow 1 mL). Retention times: R_t = 8.55 min (minor enantiomer) and R_t = 13.56 min (major enantiomer).

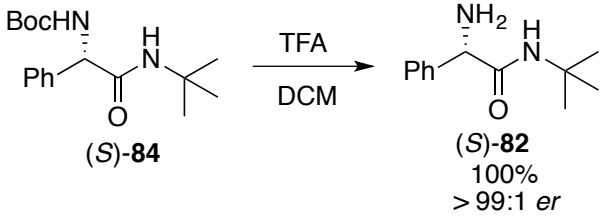
The retention times appear to be dependent on the concentration of the sample. R_f = 0.28 (CH_2Cl_2/MeOH 12:1). Spectral data for **82**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.31 (s, 9H), 1.83 (brs, 2H), 4.36 (s, 1H), 6.92 (brs, 1H), 7.22-7.28 (m, 1H) 7.28-7.36 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.64, 50.69, 60.27, 126.79, 127.76, 128.74, 141.54, 172.04; IR (thin film) 3310(m), 2969(m), 1653(s), 1522(m) cm^{-1}; HRMS (ESI+) calcd for $C_{12}H_{19}N_2O$ *m/z* 207.1497 ([M+H]$^+$), meas 207.1498. $[\alpha]_D^{20}$ = –23.1° (*c* 1.0, CH_2Cl_2) on >91.5:8.5 *er* material.

*Preparation of (S)-2-amino-N-(tert-butyl)-2-phenylacetamide **82** from L-(+)-α-phenylglycine:*



*tert-Butyl (S)-(2-(tert-butylamino)-2-oxo-1-phenylethyl)carbamate **84***: To a 100 mL round bottom flask was added L-(+)-α-phenylglycine **83** (756 mg, 5.00 mmol, 1.00 equiv), a mixture of dioxane/water (2:1, 10 mL) and 1M NaOH (5 mL). After the mixture was cooled in an ice-bath for 5 min, $(Boc)_2O$ (1.64 g, 7.50 mmol, 1.50 equiv) and $NaHCO_3$ (420 mg, 5.00 mmol, 1.00 equiv) were added to the flask. The mixture was stirred at room temperature for 18 h. Then EtOAc (30 mL) was added to the reaction mixture and then it was cooled in an ice bath for 5 min. The pH of the mixture was adjusted to 2-3 with 1M HCl. The organic layer was separated and the aqueous layer was extracted with EtOAc (20 mL x 3). The combined organic layer was dried over Na_2SO_4, filtered and concentrated to dryness. The residue was transferred to a 50 mL round bottom flask and

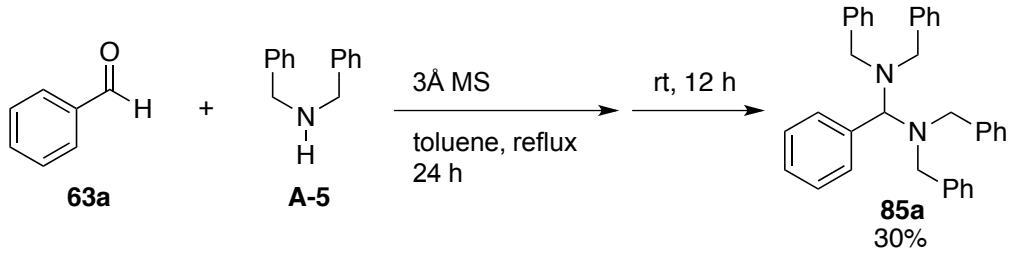
dissolved in CH_2Cl_2 (15 mL). After the solution was cooled to 0 °C, *N,N'*-dicyclohexylcarbodiimide (1.05 g, 5.09 mmol, 1.02 equiv) was added to the flask, followed by the addition of *tert*-butylamine (0.51 mL, 4.9 mmol, 0.98 equiv). The reaction mixture was warmed up to room temperature and stirred for 18 h. Then the white precipitate that formed in the reaction was removed by filtration through a Celite pad. The pad was washed with CH_2Cl_2 (5 mL x 4). The combined filtrate was concentrated and the product was purified by column chromatography on silica gel (30 mm × 160 mm, hexanes/EtOAc 5:1) to give the product **84** as a white solid (774 mg, 2.53 mmol) in a 51% yield over two steps. mp 144-146 °C. R_f = 0.24 (hexanes/EtOAc 3:1). Spectral data for **84**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.26 (s, 9H), 1.38 (s, 9H), 4.99 (brs, 1H), 5.45 (brs, 1H), 5.81 (brs, 1H), 7.25-7.36 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.26, 28.52, 51.64, 58.71, 79.81, 127.12, 128.13, 128.92, 138.95, 155.15, 169.11; IR (thin film) 3360(w), 3283(m), 2975(w), 1692(s), 1645(s), 1364(m) cm^{-1}; HRMS (ESI+) calcd for $C_{17}H_{27}N_2O_3$ *m/z* 307.2022 ($[M+H]^+$), meas 307.2018. $[\alpha]_D^{20}$ = + 102.5° (*c* 1.0, CH_2Cl_2).



*(S)-2-amino-N-(tert-butyl)-2-phenylacetamide **82***: To an oven-dried 10 mL round bottom flask was added tert-butyl (*S*)-(2-(*tert*-butylamino)-2-oxo-1-phenylethyl)carbamate **84** (92.0 mg, 0.300 mmol, 1.00 equiv), dry CH_2Cl_2 (0.80 mL) and trifluoroacetic acid (0.82 mL). After the mixture was stirred at room

temperature for 3 h, it was concentrated and diluted with 1 mL H_2O. The pH of the mixture was adjusted to ~10 with sat. aq. $NaHCO_3$ (*ca*. 35 mL). Then the mixture was extracted with CH_2Cl_2 (30 mL x 3). The combined organic layer was dried over Na_2SO_4, filtered and concentrated to give **82** as a colorless oil (62 mg, 0.30 mmol, 100%). $[\alpha]_D^{20}$ = +27.1° (*c* 1.0, CH_2Cl_2) on >99:1 *er* (by HPLC) material.

5.1.11 Preparation of the Aminal 85a



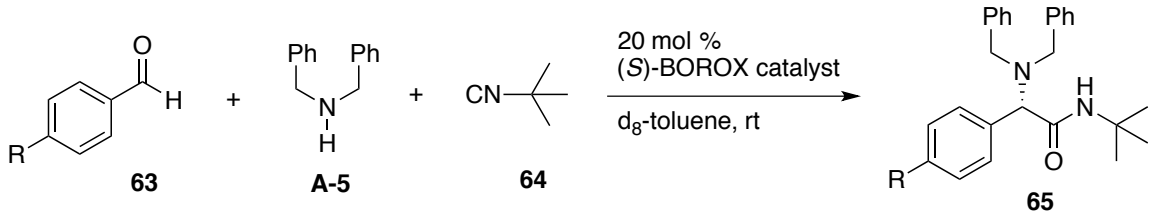
63a **A-5** **85a** 30%

α,α-Bis(N,N-dibenzylamino)toluene ***85a***: An oven-dried 100 mL round bottom flask charged with 3Å powdered molecular sieves (10.0 g) and equipped with a magnetic stir bar was flame dried under high vacuum and cooled down under nitrogen. To the flask was then added 9.0 mL of dry toluene, dibenzylamine **A-5** (0.60 mL, 3.0 mmol, 1.0 equiv) and benzaldehyde **63a** (0.46 mL, 4.5 mmol, 1.5 equiv). After the mixture was heated to reflux for 24 h in an 80 °C oil bath, it was cooled to room temperature and stirred for another 12 h. The mixture was filtered through a Celite pad. The pad was washed with dry CH_2Cl_2 (3 mL). The combined filtrate was concentrated to dryness to give a light yellow viscous oil. After this oil was kept at room temperature for 7 days, a solid separated from the oil, which was filtered off and washed with hexanes to give **85a** as colorless crystals (434 mg, 0.899 mmol) in 30% yield. Mp 142-144 °C (Lit.[33] 138-140 °C); Spectral data for **85a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.54 (d,

4H, *J* = 14.0 Hz), 3.96 (d, 4H, *J* = 14.0 Hz), 4.47 (s, 1H), 7.13-7.22 (m, 20H), 7.30-7.36 (m, 1H), 7.37-7.42 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 52.67, 79.64, 126.53, 127.67, 127.74, 128.04, 129.09, 129.69, 135.09, 139.47; HRMS (ESI) calcd for $C_{35}H_{35}N_2$ *m/z* 483.2800 ($[M+H]^+$), meas 483.2803. The ^{1}H NMR data match those reported for this compound.[33]

5.1.12 ^{1}H NMR Study of the Reaction Progress (Figures 2.2-2.4)

Ugi-3CR with different aldehydes:



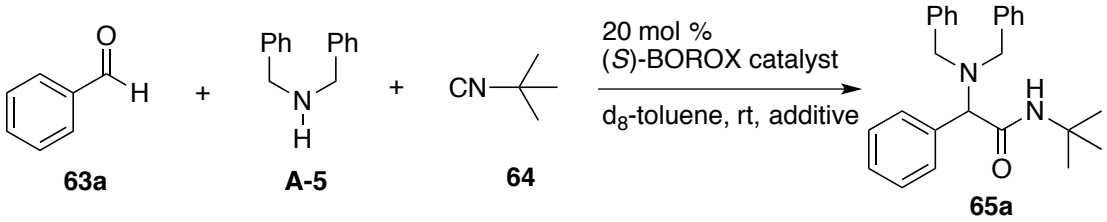
Preparation of pre-catalyst stock solution: A 25 mL Schlenk flask equipped with a stir bar was flame dried, cooled to rt under N_2 and charged with (*S*)-**L-8** (145.3 mg, 0.1765 mmol), **P-36** (49 mg, 0.36 mmol), H_2O (9.5 mg, 9.5 μL, 0.53 mmol), dry toluene (5.3 mL) and $BH_3{\cdot}SMe_2$ (2M, 262.5 μL, 0.525 mmol). The Teflon valve on the Schlenk flask was then closed, and the mixture heated at 100 °C for 1 h. After the flask was cooled to rt, the valve was carefully opened to gradually apply high vacuum (0.1 mm Hg) and the solvent and volatiles were removed. Then the flask was heated at 100 °C under high vacuum for 30 min. Dry d_8-toluene (3.5 mL) was added to dissolve the residue in the flask after it was cooled to room temperature.

*^{1}H NMR study of the Ugi-3CR with aldehyde **63a**, **63d** and **63n**:* A 25 mL Schlenk flask equipped with a magnetic stir bar was flame dried under high vacuum and cooled to 25 °C under nitrogen. To the flask was then added Ph_3CH

as an internal standard and the pre-catalyst stock solution (1.0 mL, 0.050 mmol (*S*)-**78**) via a plastic syringe fitted with a metallic needle. To the resulting solution was added dibenzylamine **A-5** (0.10 mL, 0.52 mmol, 2.0 equiv) under a N_2 stream, followed by the addition of benzaldehyde **63a** (26.0 μL, 0.255 mmol, 1.00 equiv) and then *t*-butyl isocyanide (45 μL, 0.39 mmol, 1.5 equiv). Then to an oven-dried NMR tube filled with nitrogen was added 0.7 mL of the reaction mixture and the tube was sealed with a rubber cap. The ^{1}H NMR spectrum was taken at certain intervals. The NMR yields of **65a** at different time points were determined by comparing the methine proton of Ph_3CH and the methine proton of **65a**.

This procedure was repeated with aldehyde **63d** (47.1 mg, 0.255 mmol, 1.00 equiv) and **63n** (34.7 mg, 31.0 μL, 0.255 mmol, 1.00 equiv). The combined results are presented in Figure 2.2. In each case, there is an intitial build-up of aminal **85** and then it slowly disappears as the product grows in and is gone at the end of the reaction. The rates of the reaction with *para*-methoxylbenzaldehyde **63n** and *para*-bromobenzaldehyde **63d** are essentially the same and both are slower than benzaldehyde **63a**.

Ugi-3CR with different amounts of 4Å MS or H_2O as an additive:

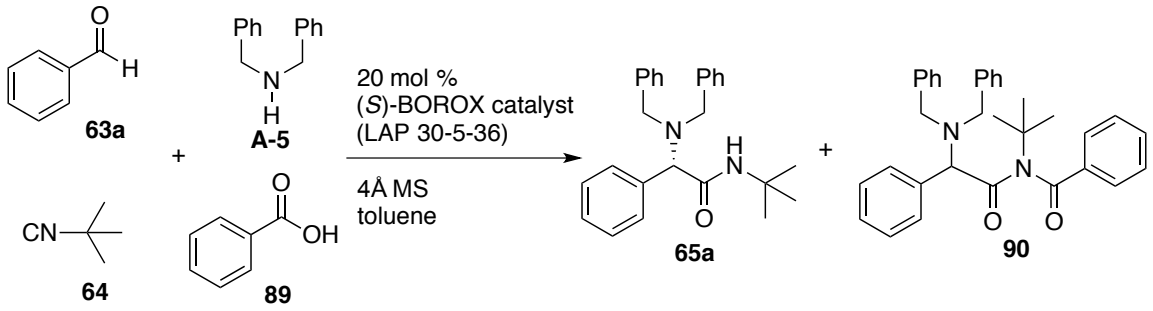


63a **A-5** **64** **65a**

The general procedure A described in **Part 5.1.4** was followed with (*S*)-**78**

ligand (41.5 mg, 0.0504 mmol), phenol **P-36** (14 mg, 0.10 mmol) and 1 mL d_8-toluene as the reaction solvent. A certain amount of 4Å MS was added to the pre-catalyst solution right before the addition of dibenzylamine **A-5**. In the case of H_2O as an additive, it was added right after the addition of benzaldehyde **63a**, followed by the addition of *tert*-butyl isocyanide **64**. The results are shown in Figures 2.3 and 2.4.

5.1.13 Effect of PhCOOH on the Ugi-3CR



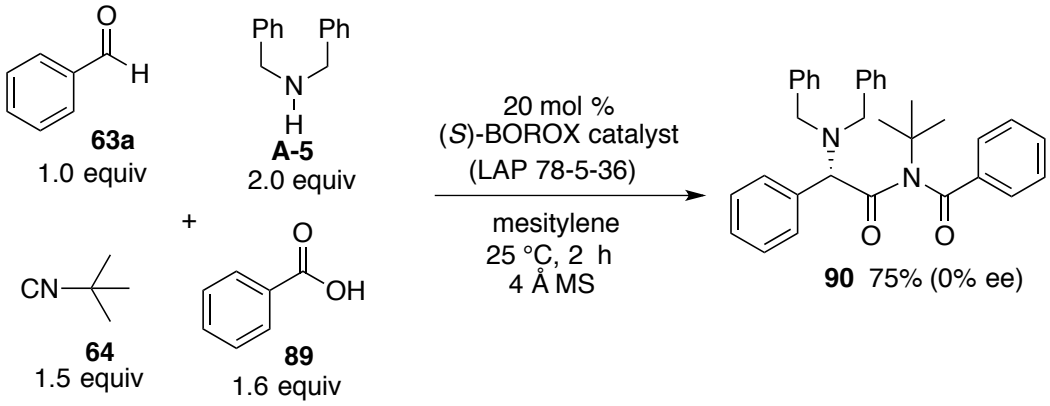
The pre-catalyst was prepared according to the general procedure A described in **Part 5.1.4** with (*S*)-VAPOL ligand (27 mg, 0.050 mmol) and phenol **P-36** (14 mg, 0.10 mmol). Dry toluene (1 mL) was added to the flask to dissolve the pre-catalyst, followed by the addition of dibenzylamine **A-5** (0.10 mL, 0.52 mmol, 2.0 equiv) and a certain amount of benzoic acid **89**. This mixture was stirred at 60 °C for 0.5 h. After it was cooled to room temperature, benzaldehyde **63a** (26.0 µL, 0.255 mmol, 1.00 equiv) and *tert*-butyl isocyanide **64** (45 µL, 0.38 mmol, 1.5 equiv) were added in sequence. The reaction mixture was stirred at room temperature for 36-42 h and the crude product was purified by column chromatography on silica gel (20 x 160 mm, hexanes/EtOAc 15:1). The results are shown in Table 5.1.

Table 5.1 Ugi-3CR with PhCOOH as an additive.

Entry	Time (h)	PhCOOH (mol %)	Ratio of **65a:90**	**65a**[a] %Yield/*er*	**90** %Yield/*er*
1	36	0	1:0	72/70:30	nd
2	39	20	1:0.27	78[b]/65:35	21[b]/nd
3[c]	42	100	1:0.60	60[b]/nd	36[b]/52:48
4[c,d]	42	100	1:0.88	nd	nd

[a] Isolated yield after chromatography on silica gel. [b] NMR yield with the aid of Ph_3CH. [c] 100 mg 4 Å MS was added before the addition of benzaldehyde **3a**. [d] The mixture of pre-catalyst, dibenzylamine and PhCOOH was stirred at rt for 5 min instead of at 60 °C for 0.5 h

5.1.14 Four-Component Ugi Reaction

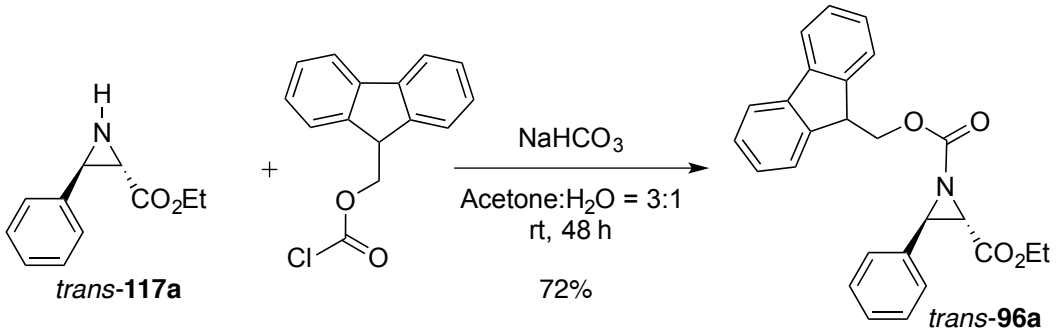


N-(tert-butyl)-N-(2-(dibenzylamino)-2-phenylacetyl)benzamide ***90***: The pre-catalyst was prepared according to the general procedure A (**Part 5.1.4**) with (*S*)-**78** (41.5 mg, 0.050 mmol), **P-36** (14.0 mg, 0.10 mmol), H_2O (2.7 mg, 2.7 µL, 0.15 mmol), dry toluene (1.5 mL) and $BH_3{\cdot}SMe_2$ (2M, 75 µL, 0.15 mmol). After the pre-catalyst was cooled to room temperature, 4 Å MS (250 mg) was added to

the flask, followed by the addition of dry toluene (0.5 mL) to dissolve the pre-catalyst. Then dibenzylamine **A-5** (0.1 mL, 0.5 mmol, 2 equiv) and benzoic acid **89** (50 mg, 0.41 mmol, 1.6 equiv) were added to the solution, followed by addition of another portion of toluene (0.5 mL). After the mixture was stirred for 5 min at room temperature, benzaldehyde **63a** (26.0 μL, 0.255 mmol, 1.00 equiv) and *tert*-butyl isocyanide **64** (45 μL, 0.38 mmol, 1.5 equiv) were added in sequence. After the mixture was stirred at room temperature for 2 h, the crude ^{1}H NMR spectrum showed that the reaction was complete and that the ratio of **90:65a** was about 16:1. Then the reaction mixture was directly loaded onto a silica gel column (20 x 160 mm, hexanes/EtOAc 15:1) to afford a mixture of the product **90** and phenol **P-36**. The yield of product **90** was calculated to be 75% with the aid of Ph_3CH as an internal standard. The optical purity was determined to be 50.1:49.9 *er* by HPLC analysis (Chiralpak AD column, hexanes/2-propanol 98:2, 222 nm, flow 1 mL). Retention times: R_t = 4.91 min and R_t = 12.49 min. Spectral data for **90**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.56 (s, 9H), 3.75 (d, 2H, J = 14.5 Hz), 3.84 (d, 2H, J = 14.5 Hz), 4.18 (s, 1H), 6.92-7.06 (m, 4H), 7.10-7.29 (m, 16H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.61, 54.59, 59.44, 66.95, 126.63, 127.58, 127.98, 128.03, 128.20, 128.49, 129.48, 129.86, 133.47, 135.21, 136.72, 140.22, 171.54, 174.82; HRMS (ESI+) calcd for $C_{33}H_{35}N_2O_2$ *m/z* 491.2699 ($[M+H]^+$), meas 496.2696.

5.2 Experimental Part for Chapter 3

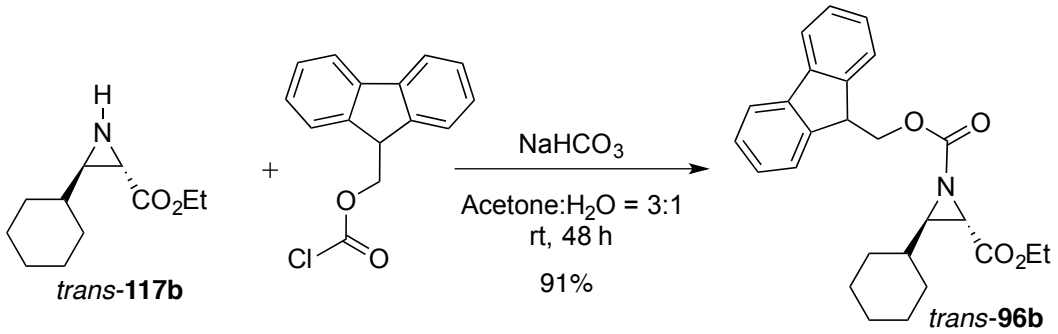
5.2.1 Preparation of Protected Aziridines



Trans-N-9-fluorenylmethyl-carbamate-2-carboxyethyl-3-phenylaziridine

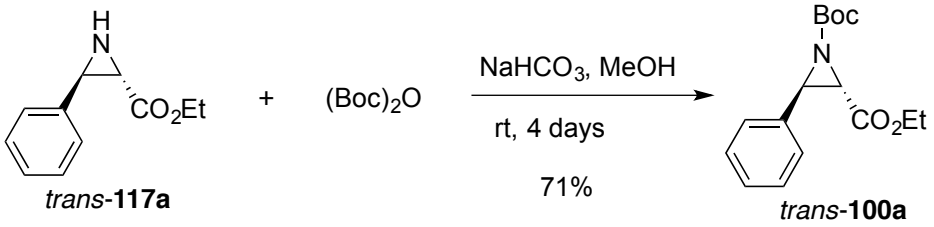
***96a**:* To a 100 mL round bottom flask was added racemc *trans*-2-carboxyethyl-3-phenylaziridine **117a**[89] (0.296 g, 1.5 mmol, 1.0 equiv.), $NaHCO_3$ (0.252 g, 3.0 mmol, 2.0 equiv.), 30 mL of a mixture of acetone and H_2O (3:1). The mixture was stirred at room temperature for 5 min and then 9-fluorenylmethylchloroformate (0.388 g, 1.5 mmol, 1.0 equiv.) was added. Then the reaction mixture was stirred at room temperature for 48 hours. The acetone was removed by rotary evaporation and the aqueous residue was extracted with ethyl acetate (10 mL × 3). The combined organic layer was washed with sat aq NaCl, dried over $MgSO_4$ and concentrated by rotary evaporation to afford a yellow oil. Purification twice by silica gel chromatography (the first column: 18 mm × 250 mm, 4:1:1 hexanes/diethyl ether/CH_2Cl_2 as eluent; the second column: 18 mm × 250 mm, CH_2Cl_2 as eluent) afforded *trans*-**96a** as a colorless oil in 72% isolated yield, which solidified upon standing (white solid, mp 93-95 °C). Spectral data for *trans*-**96a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.25 (t, 3H, *J* = 7.2 Hz), 3.20 (d, 1H, *J* = 2.4 Hz), 3.90 (d, 1H, *J* = 2.4 Hz), 4.18 (q, 2H, *J* = 7.2 Hz), 4.24 (t, 1H, *J* = 7.2 Hz),

4.33 (dd, 1H, *J* = 10.5, 7.8 Hz), 4.48 (dd, 1H, *J* = 10.5, 7.2 Hz), 7.25-7.31 (m, 2H), 7.32-7.42 (m, 7H), 7.55-7.61 (m, 2H), 7.74 (d, 2H, *J* = 7.5 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.05, 44.15, 45.09, 46.80, 62.19, 68.77, 119.96, 119.97, 125.15, 125.28, 126.43, 127.05, 127.06, 127.73, 127.77, 128.57, 128.66, 134.94, 141.25, 141.26, 143.57, 143.68, 159.67, 167.31; IR (thin film) 1744(vs), 1179(s) cm^{-1}; HRMS calcd (MH^+) $C_{26}H_{24}NO_4^+$ 414.1705, found 414.1731.



Trans-N-9-fluorenylmethyl-carbamate-cis-2-carboxyethyl-3-cyclohexylaziridine ***96b****:* This aziridine was prepared according to the procedure described above for *trans*-**96a** starting with racemic *trans*-2-carboxyethyl-3-cyclohexylaziridine *trans*-**117b**[47a] (296 mg, 1.50 mmol). Purification by silica gel chromatography (column: 15 mm × 250 mm, 8:1 hexanes/EtOAc as eluent) afforded *trans*-**96b** as a colorless oil in 91% isolated yield (572 mg, 1.36 mmol). R_f = 0.28 (5:1 hexanes/EtOAc); Spectral data for *trans*-**96b**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.16-1.28 (m, 6H), 1.22 (t, 3H, *J* = 7.2 Hz), 1.62-1.68 (m, 1H), 1.69-1.78 (m, 3H), 1.81 (d, 1H, *J* = 12 Hz), 2.66 (dd, 1H, *J* = 7.2, 2.7 Hz), 2.96 (d, 1H, *J* = 2.7 Hz), 4.08-4.16 (m, 2H), 4.22 (t, 1H, *J* = 6.9 Hz), 4.32 (dd, 1H, *J* = 10.5, 7.5 Hz), 4.46 (dd, 1H, *J* = 10.2, 7.2 Hz), 7.27-7.31 (m, 2H), 7.38 (t, 2H, *J* = 7.5 Hz), 7.60 (t, 2H, 1H, *J* = 7.8 Hz), 7.74 (d, 2H, 1H, *J* = 7.8 Hz); ^{13}C NMR (150 MHz,

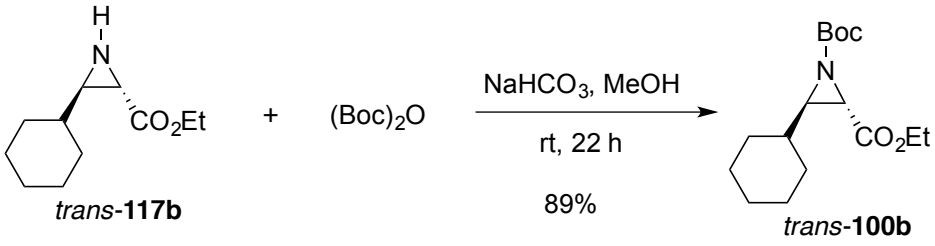
$CDCl_3$) δ 14.03, 25.47, 25.57, 26.05, 29.69, 29.91, 39.18, 39.45, 46.90, 48.96, 61.81, 68.34, 119.90, 119.91, 125.06, 125.19, 127.01, 127.03, 127.66, 127.70, 141.27, 141.29, 143.67, 143.82, 160.23, 168.29; IR (thin film) 2928(s), 2853(w), 1743(vs), 1451(m), 1310(m), 1177(s) cm^{-1}; mass spectrum, *m/z* (% rel intensity) 419 M^+ (0.07), 346 (0.15), 178 (100), 165 (62), 84 (34), 49 (56). HRMS calcd (MH^+) $C_{26}H_{30}NO_4^+$ 420.217, found 420.216.



trans-**117a** *trans*-**100a**

*Trans-N-Boc-2-carboxyethyl-3-phenylaziridine **100a**:* To a 25 mL flame-dried round bottom flask filled with argon was added *trans*-2-carboxyethyl-3-phenylaziridine **117a**[89] (150 mg, 0.784 mmol) and 5 mL MeOH followed by the addition of $NaHCO_3$ (197 mg, 0.450 mmol, 3.00 equiv.). The flask was put in an ultrasonic bath for 5 minutes and then $(Boc)_2O$ (428 mg, 1.96 mmol, 2.50 equiv.) was added. The mixture was left in the ultrasonic-bath for 4 hours with a needle in the rubber septum to release the generated CO_2 gas. After 4 h, a second portion of $NaHCO_3$ and $(Boc)_2O$ was added in equal amounts to the first addition. Then the reaction mixture was stirred for 4 days. The reaction mixture was filtered through Celite and the solid residue was washed with Et_2O. The cloudy filtrate was filtered again through Celite and then concentrated by rotary evaporation to afford the crude product as a colorless liquid. Purification by silica gel chromatography (15 mm × 250 mm, hexanes and then 1:9 ethyl acetate/

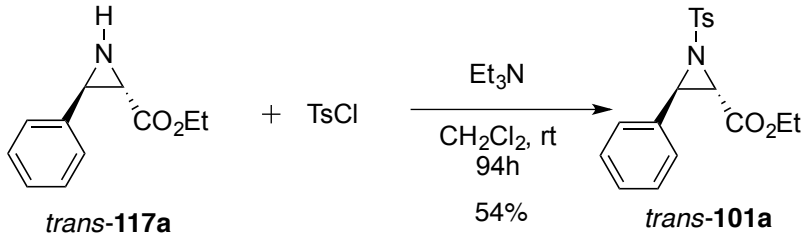
hexanes as eluent) afforded *trans*-**100a** as a colorless oil in 71% isolated yield (163 mg, 0.56 mmol). R_f = 0.36 (hexanes/EtOAc = 4:1); Spectral data for *trans*-**100a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (t, 3H, *J* = 7.0 Hz), 1.44 (s, 9H), 3.07 (d, 1H, *J* = 2.6 Hz), 3.79 (d, 1H, *J* = 2.6 Hz), 4.14-4.36 (m, 2H), 7.24-7.36 (m, 5H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.16, 27.88, 44.02, 44.92, 61.82, 82.04, 126.43, 128.27, 128.48, 135.33, 158.29, 167.40. The ^{1}H and ^{13}C NMR data match those previously reported for this compound.[42c]



trans-**117b** *trans*-**100b**

*Trans-N-Boc-2-carboxyethyl-3-cyclohexylaziridine **100b**:* To a flame-dried 25 mL round bottom flask filled with argon was added racemic *trans*-2-carboxyethyl-3-cyclohexylaziridine **117b**[47a] (198 mg, 1.0 mmol, 1.0 equiv), MeOH (6.5 mL) and $NaHCO_3$ (0.84 g, 10 mmol, 10 equiv.). The flask was put in an ultrasonic bath for 5 min and then $(Boc)_2O$ (1.09 g, 5.00 mmol, 5.00 equiv) was added. The mixture was left in the ultrasonic-bath for 4 hours with a needle in the rubber septum to release the generated CO_2 gas and then it was stirred at room temperature for another 18 h. The reaction mixture was filtered through Celite and the filter cake was washed with diethyl ether. The cloudy filtrate was filtered again through Celite and then concentrated by rotary evaporation to afford the crude product as a light yellow liquid. Purification by silica gel chromatography (15 mm × 250 mm, 45:1 hexanes/EtOAc as eluent until the first fraction came out

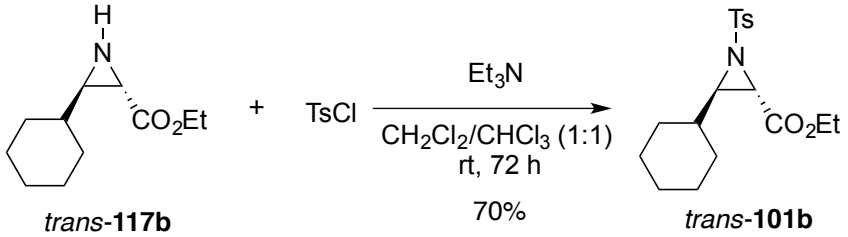
and then 15:1 hexanes/EtOAc as eluent) afforded *trans*-**100b** as a colorless oil in 89% isolated yield (265 mg, 0.89 mmol). R_f = 0.42 (5:1 hexanes/EtOAc); Spectral data for *trans*-**100b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.04-1.25 (m, 6H), 1.28 (t, 3H, *J* = 7.2 Hz), 1.43 (s, 9H), 1.60-1.65 (m, 1H), 1.66-1.76 (m, 3H), 1.80-1.86 (m, 1H), 2.60 (dd, 1H, *J* = 6.8, 3.0 Hz), 2.83 (d, 1H, *J* = 3.0 Hz), 4.11-4.28 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.19, 25.47, 25.60, 26.09, 27.95, 29.71, 30.01, 39.27, 39.45, 48.73, 61.54, 81.47, 159.04, 168.42; IR (thin film) 2980(w), 2930(s), 2855(w), 1744(vs), 1728(s), 1154(s) cm^{-1}; mass spectrum, *m/z* (% rel intensity) 224 (M^+ - 73) (5.6), 196 (21), 124 (85), 95 (73), 57 (100); Anal calcd for $C_{16}H_{27}NO_4$: C, 64.62; H, 9.15; N, 4.71. Found: C, 64.88; H, 9.27; N, 4.72.



trans-**117a** *trans*-**101a**

*Trans-N-Tosyl-2-ethoxycarbonyl-3-phenylaziridine trans-**101a**:* To a flame-dried 50 mL round bottom flask filled with argon was added racemic *trans*-2-carboxyethyl-3-phenylaziridine **117a**[89] (0.335g, 1.75 mmol, 1.0 equiv.) and CH_2Cl_2 (14 mL, freshly distilled). The solution was cooled to 0 °C in an ice-bath followed by the addition of Et_3N (0.7 mL, 5.03 mmol, 2.9 equiv., freshly distilled). After the reaction mixture was stirred for 5 min at 0 °C, TsCl (0.534 g, 2.8 mmol, 1.6 equiv) was added to the mixture at 0 °C. Thereafter, the ice-bath was removed and the mixture was stirred at room temperature for 94 hours. The reaction was quenched by the addition of 26 mL sat aq NH_4Cl and 5 mL H_2O.

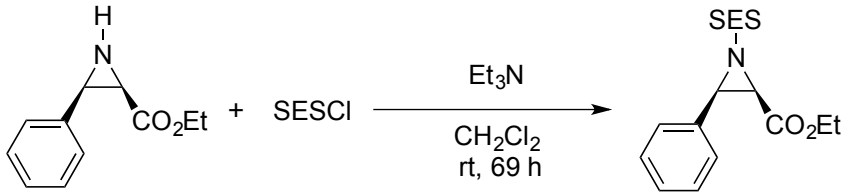
The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (30 mL × 3). The combined organic layer was washed with the following reagents in the indicated sequence: 5 mL H_2O, 10 mL aq citric acid, 5 mL H_2O, 10 mL sat aq $NaHCO_3$ and 20 mL sat aq NaCl. The combined organic layer was dried over $MgSO_4$ and concentrated by rotary evaporation to afford the crude product as an orange oil. Purification by silica gel chromatography (the first column: 15 mm × 250 mm, 40:9 hexanes/EtOAc as eluent; the second column: 15 mm × 250 mm, 16:4:1 hexanes/ CH_2Cl_2/EtOAc as eluent) afforded *trans*-**101a** as a light yellowish oil in 54% yield (0.326 g, 0.94 mmol); R_f = 0.24 (4:1 hexanes/EtOAc); Spectral data for *trans*-**101a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (t, 3H, *J* = 7.0 Hz), 2.39 (s, 3H), 3.49 (d, 1H, *J* = 3.9 Hz), 4.20-4.39 (m, 2H), 4.41 (d, 1H, *J* = 3.9 Hz), 7.19-7.31 (m, 7H), 7.71-7.80 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 13.95, 21.58, 47.08, 47.68, 62.41, 127.32, 127.46, 128.55, 128.86, 129.52, 132.68, 137.17, 144.25, 165.73. The ^{1}H and ^{13}C NMR data match those previously reported for this compound.[42c]



trans-**117b** *trans*-**101b**

*Trans-N-Tosyl-2-ethoxycarbonyl-3-cyclohexylaziridine **101b**:* This aziridine was prepared according the same procedure used for *trans*-**101a**. Racemic *trans*-2-carboxyethyl-3-cyclohexylaziridine **117b**[47a] (197 mg, 1.0 mmol, 1.0 equiv) was reacted with tosyl chloride (0.305 g, 1.6 mmol, 1.6 equiv), Et_3N (freshly

distilled, 0.42 mL, 3.0 mmol, 3.0 equiv) in 1:1(v) $CH_2Cl_2/CHCl_3$ (8 mL) for 72 h. Purification by silica gel chromatography (first column: 15 mm × 250 mm, 10:1 hexanes/EtOAc, second column: 15 mm × 250 mm, 6:1:16 CH_2Cl_2/diethyl ether/hexanes as eluent) and recrystallization from hexanes afforded *trans*-**101b** as white crystals (mp: 71-73 °C) in 70% isolated yield (246 mg, 0.70 mmol). R_f = 0.26 (5:1 hexanes/EtOAc); Spectral data for *trans*-**101b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.00-1.35 (m, 8H), 1.58-1.79 (m, 5H), 1.95 (d, 1H, *J* = 10.5 Hz), 2.41 (s, 3H), 3.02 (dd, 1H, *J* = 9.0, 4.2 Hz), 3.18 (d, 1H, *J* = 4.2 Hz), 4.15 (q, 2H, *J* = 6.9 Hz), 7.24-7.32 (m, 2H), 7.79-7.83 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 13.90, 21.58, 25.19, 25.40, 25.87, 30.59, 31.13, 37.53, 43.71, 53.66, 61.86, 127.52, 129.50, 137.10, 144.20, 166.70. IR (thin film) 2930(s), 2855(m), 1745(s), 1331(s), 1101(s) cm^{-1}; mass spectrum, *m/z* (% rel intensity) 306 (M^+ - 45) (2.3), 278 (3.2), 197 (34), 196 (100), 168 (29), 122 (88), 67 (83); Anal calcd for $C_{18}H_{25}NO_4S$: C, 61.51; H, 7.17; N, 3.99. Found: C, 61.60; H, 7.22; N, 3.96. This compound has been reported as a cis/trans mixture.[90]

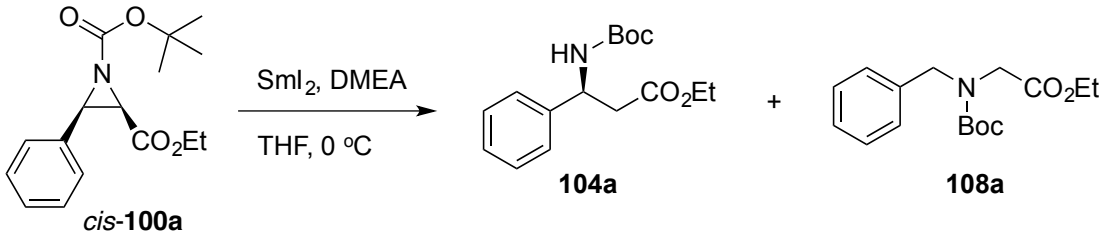


cis-**117a** *cis*-**102a**

*Cis-ethyl (2R, 3R)-3-phenyl-1-((2-(trimethylsilyl)ethyl)sulfonyl)aziridine-2-carboxylate **102a**:* To a 10 mL flame-dried round bottom flask was added 2-(trimethylsilyl)ethanesulfonyl chloride (SESCl, 82.5 μl, 0.639 mmol, 1.28 equiv), Et_3N (0.7 mL, 5 mmol, 10 equiv) and CH_2Cl_2 (2 mL, freshly distilled). The mixture

was pre-cooled in an ice-bath for 5 min. *Cis*-(*2R, 3R*)-2-carboxyethyl-3-phenylaziridine **117a**[12q] (95.6 mg, 0.5 mmol, 1 equiv, 98% *ee*) was dissolved in 0.5 mL CH_2Cl_2 and the solution was added dropwise to the 10 mL round bottom flask containing 2-(trimethylsilyl)ethanesulfonyl chloride. Then the ice-bath was removed and the reaction mixture was stirred at room temperature for 45 hours. Thereafter, another portion of 2-(trimethylsilyl)ethanesulfonyl chloride (160 ml, 1.26 mmol, 2.5 equiv) and Et_3N (0.7 mL, 5 mmol, 10 equiv) was added to the reaction mixture. After the mixture was stirred for 24 hours at room temperature, the reaction was quenched with 2 mL sat aq NH_4Cl and 1 mL H_2O. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (4 mL × 3). The combined organic layer was dried with Na_2SO_4, filtered and concentrated to give a dark brown oil. Purification by silica gel chromatography (15 mm × 180 mm, 9:1 hexanes/EtOAc as eluent) afforded *cis*-**102a** as a light yellow oil in 83 % yield (0.147 g, 0.413 mmol). R_f = 0.19 (9:1 hexanes/EtOAc); Spectral data for *cis*-**102a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.04 (s, 9H), 1.00 (t, 3H, *J* = 7.0 Hz), 1.13-1.24 (m, 2H), 3.16-3.26 (m, 2H), 3.67 (d, 1H, *J* = 7.5 Hz), 3.93-4.05 (m, 2H), 4.07 (d, 1H, *J* = 7.5 Hz), 7.26-7.34 (m, 3H), 7.37-7.41 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -2.05, 9.73, 13.86, 43.67, 44.31, 49.51, 61.63, 127.52, 128.30, 128.66, 131.36, 164.49; IR (thin film) 2955 s, 1755 vs cm^{-1}; HRMS calcd (MH^+) $C_{16}H_{26}NO_4SSi^+$ 356.1352, found 356.1351; $[\alpha]_D^{20}$ = –38.0° (*c* 1.0, CH_2Cl_2) on 98% *ee* material (the optical purity was assumed to be unchanged from **117a**).

5.2.2 Reductive Ring Opening of Aziridines-2-Carboxylates with SmI_2

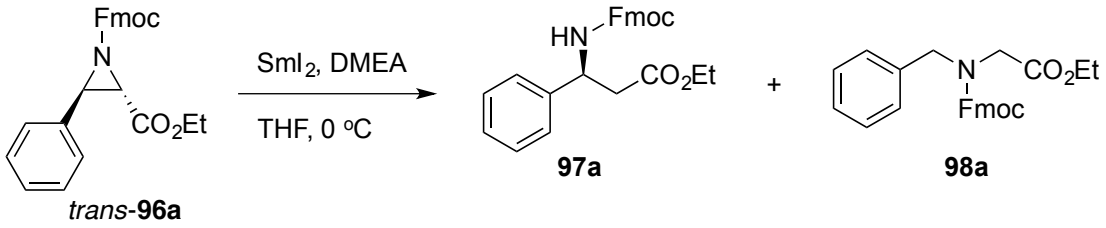


cis-**100a** **104a** **108a**

General procedure for the reductive ring opening of aziridines-2-carboxylates with SmI_2 (*illustrated for cis-**100a***): To a flame-dried 10 mL round bottom flask filled with argon was added Sm (180 mg, 1.20 mmol, 6.00 equiv) and dry THF (1.8 mL, freshly distilled). Thereafter, the vacuum adapter was changed to a rubber septum and the suspension was purged with nitrogen under the surface of the solution for 5 min by a needle through the septum. Another needle was used as an outlet for the nitrogen gas. Then CH_2I_2 (92.5 μL, 1.15 mmol, 5.7 equiv) was added to the reaction flask and the reaction mixture was purged with nitrogen for another 1 min. The needle as an outlet was removed and the one for nitrogen flow was lifted above the surface of the solution. The reaction mixture was stirred at room temperature for 2 hours, resulting in a dark blue slurry. The slurry was then pre-cooled to 0 °C in an ice-bath. To another flame-dried 5 mL round bottom flask filled with nitrogen was added *cis*-(2*R*, 3*R*)-**100a**[12q] (78% ee, 60 mg, 0.2 mmol, 1.0 equiv.), dry THF (1.5 mL, freshly distilled) and *N,N*-dimethylethanolamine (0.24 mL, 2.4 mmol, 12.0 equiv.). The solution was purged with nitrogen under the surface of the solution for 2 min and transferred to the flask containing the SmI_2 slurry dropwise via cannula. Vigorous stirring was maintained during the addition of the aziridine to the SmI_2 slurry. The 5 mL flask was washed with 0.3 mL degassed THF and the rinse was also

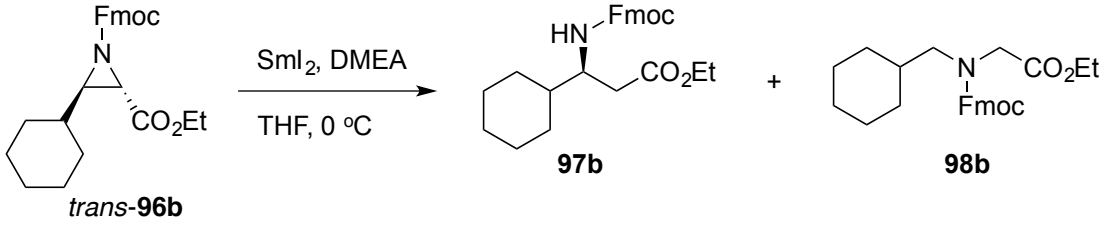
transferred to the reaction flask containing SmI_2. The reaction mixture was stirred at 0 °C for 40 min to 1 h and then quenched by the addition of sat aq $NaHCO_3$ (5 mL) at 0 °C. The organic layer was separated and the aqueous layer was extracted with EtOAc (5 mL × 4). The combined organic layer was dried with Na_2SO_4 and filtered. The solvent was removed by rotary evaporation to give a light yellow solid. The ^1H NMR spectrum of the crude reaction mixture showed that it was a mixture of **104a** and **108a** in a ratio of 1.4:1. Purification by silica gel chromatography (18 × 250 mm, 1:1:4.6 diethyl ether/hexanes/CH_2Cl_2 as eluent) afforded (*S*)-**104a** as a white solid (mp 75-77 °C) in 55% isolated yield (33.6 mg, 0.11 mmol) and **108a** as colorless oil in 32% isolated yield (19.2 mg, 0.065 mmol). The optical purity of (*S*)-**104a** was determined to be 78% ee by HPLC analysis (Chiralcel OD-H column, 98:2 hexanes/iPrOH at 222nm, flow-rate: 1.0 ml/min); retention times: R_t = 6.24 min (minor enantiomer (*R*)-**104a**) and R_t = 7.08 min (major enantiomer (*S*)-**104a**). TLC and Spectral data for (*S*)-**104a**: R_f = 0.24 (5:1 hexanes/EtOAc); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.14 (t, 3H, *J* = 7.1 Hz), 1.40 (s, 9H), 2.70-2.90 (m, 2H), 4.05 (q, 2H, *J* = 7.1Hz), 5.09 (brs, 1H), 5.46 (brs, 1H), 7.19-7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 14.03, 28.31, 41.00, 51.21, 60.63, 79.61, 126.12, 127.43, 128.56, 141.19, 154.99, 170.88; $[\alpha]_D^{20}$ = –31.6 (*c* 1.0, EtOAc) on 78% ee (*S*)-**104a**.[91] TLC and Spectral data for **108a** (mixture of rotamers): R_f = 0.34 (5:1 hexanes/EtOAc); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.219 and 1.224 (2 x t, 3H, *J* = 7.1 Hz), 1.447 and 1.452 (2 x s, 9H), 3.75 and 3.89 (2 x s, 2H), 4.13 and 4.14(2 x q, 2H, *J* = 7.1Hz), 4.49 and 4.52 (2 x s, 2H), 7.18-7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 14.12, 14.21, 28.25, 28.32, 47.71,

48.13 51.04, 51.50, 60.91, 60.96, 80.42, 80.59, 127.37, 127.43, 127.48, 128.12, 128.53, 137.36, 137.60, 155.59, 155.77, 169.90, 169.94.[92]



trans-**96a** **97a** **98a**

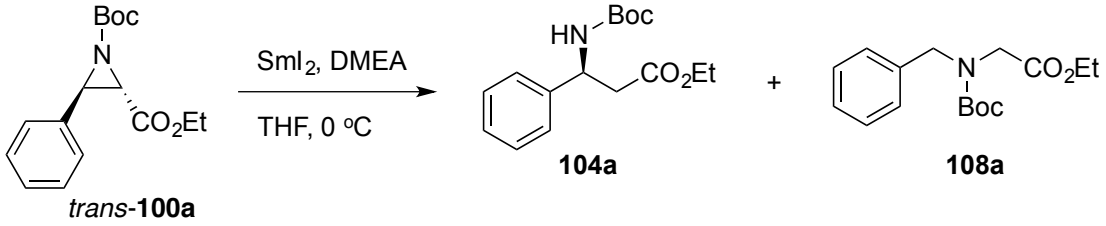
*Reductive ring opening of trans-**96a**:* The reaction was carried out according to the general procedure described above starting with aziridine *trans*-**96a** (racemic, 62.1 mg, 0.15 mmol, 1.0 equiv), SmI_2 (5.5 equiv), *N,N*-dimethylethanolamine (0.17 mL, 1.7 mmol, 11.0 equiv) and dry THF (1.5 mL for SmI_2 and 1.5 mL for aziridine, freshly distilled) at 0 °C for 1 hour. The ^1H NMR spectrum of the crude reaction mixture showed that **97a**[12q] and **98a**[12q] were obtained in a ratio of 16.7:1. The NMR yield of **97a** was determined to be 82% with the aid of Ph_3CH as an internal standard.



trans-**96b** **97b** **98b**

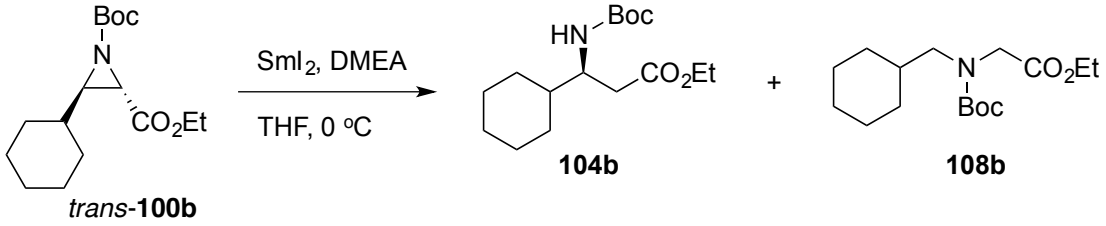
*Reductive ring opening of trans-**96b**:* This reaction was carried out according to the general procedure described above starting with aziridine *trans*-**96b** (racemic, 62.7 mg, 0.15 mmol, 1.0 equiv.), SmI_2 (6.0 equiv.), *N,N*-dimethylethanolamine (0.18 mL, 1.8 mmol, 12.0 equiv.) and dry THF (1.5 mL for SmI_2 and 1.5 mL for aziridine, freshly distilled) at 0 °C for 1 hour. The NMR yield

of **97b**[12q] was determined to be 73% with the aid of Ph_3CH as an internal standard.



trans-**100a** **104a** **108a**

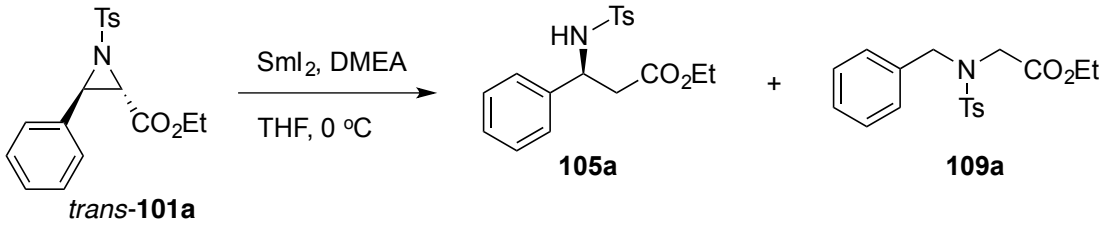
*Reductive ring opening of trans-**100a**:* The reaction was carried out according to the general procedure described above starting with *trans*-**100a** (racemic, 58.3 mg, 0.2 mmol, 1.0 equiv), SmI_2 (6.0 equiv), *N,N*-dimethylethanolamine (0.24 mL, 2.4 mmol, 12.0 equiv) and dry THF (1.8 mL for SmI_2 and 1.8 mL for aziridine, freshly distilled) at 0 °C for 1 hour. The ^1H NMR spectrum of the crude reaction mixture showed that **104a** and **108a** were present in a ratio of 6.7:1. Purification by silica gel chromatography (18 × 250 mm, 1:1:4.6 diethyl ether/hexanes/CH_2Cl_2 as eluent) afforded **104a** as a white solid (mp 75-77 °C) in 85% isolated yield (50.1 mg, 0.17 mmol) and **108a** as colorless oil in 10% isolated yield (5.9 mg, 0.02 mmol). The spectral data for **104a** and **108a** are the same as those obtained in the in the reductive ring-opening of *cis*-**100a**.



trans-**100b** **104b** **108b**

*Reductive ring opening of trans-**100b**:* The reaction was carried out according to the general procedure described above starting with *trans*-**100b**

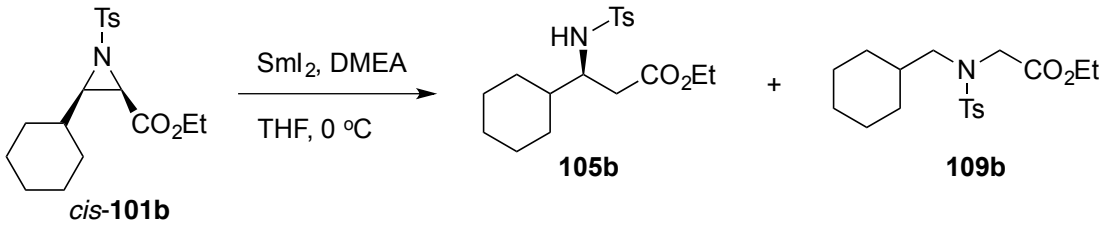
(racemic, 59.5 mg, 0.2 mmol, 1.0 equiv.), SmI_2 (6.0 equiv.), *N,N*-dimethylethanolamine (0.24 mL, 2.4 mmol, 12.0 equiv.) and dry THF (1.8 mL for SmI_2 and 1.8 mL for aziridine, freshly distilled) at 0 °C for 1 hour. The β-amino ester **104b**[12d] was obtained in 84% NMR yield with the aid of Ph_3CH as an internal standard. The ^1H NMR spectrum of the crude reaction mixture showed that the ratio of **104b : 108b** >99:1.



trans-**101a** **105a** **109a**

*Reductive ring opening of trans-**101a**:* The reaction was carried out according to the general procedure described above starting with *trans*-**101a** (racemic, 51.9 mg, 0.15 mmol, 1.0 equiv), SmI_2 (6.0 equiv.), *N,N*-dimethylethanolamine (0.18 mL, 1.8 mmol, 12.0 equiv) and dry THF (1.5 mL for SmI_2 and 1.5 mL for aziridine, freshly distilled) at 0 °C for 1 hour. Purification by silica gel chromatography (18 × 250 mm, 5:1 hexanes/EtOAc as eluent) afforded **105a** as a colorless liquid in 88% isolated yield (45.9 mg, 0.132 mmol). R_f = 0.25 (1:3 EtOAc/Hexanes); Spectral data for **105a**: ^1H NMR ($CDCl_3$, 500 MHz) δ 1.10 (t, 3H, *J* = 7.2Hz), 2.35 (s, 3H), 2.72 (dd, 1H, *J* = 16, 6.0 Hz), 2.81 (dd, 1H, *J* = 16, 6.0 Hz), 3.94-4.05 (m, 2H), 4.70 (q, 1H, *J* = 6.7 Hz), 5.67 (d, 1H, *J* = 7.5 Hz), 7.06-7.11 (m, 2H), 7.12-7.19 (m, 5H), 7.56-7.60 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.97, 21.45, 41.18, 54.31, 60.88, 126.44, 127.11, 127.73, 128.52, 129.44, 137.48, 139.34, 143.22, 170.63. These data match that previously

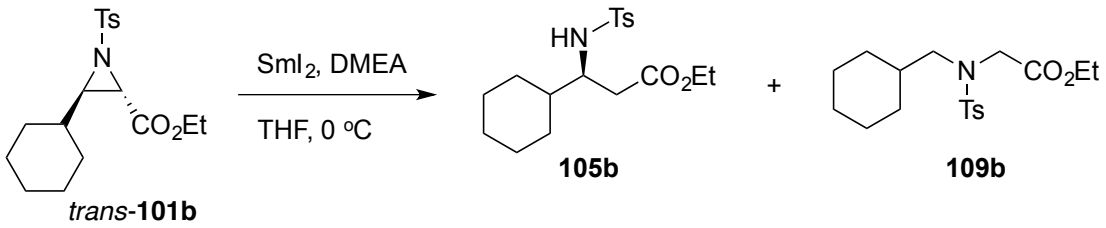
reported for this compound.[42c] The ^{1}H NMR spectrum of the crude reaction mixture showed that the ratio of **105a : 109a** >99:1.



cis-**101b** **105b** **109b**

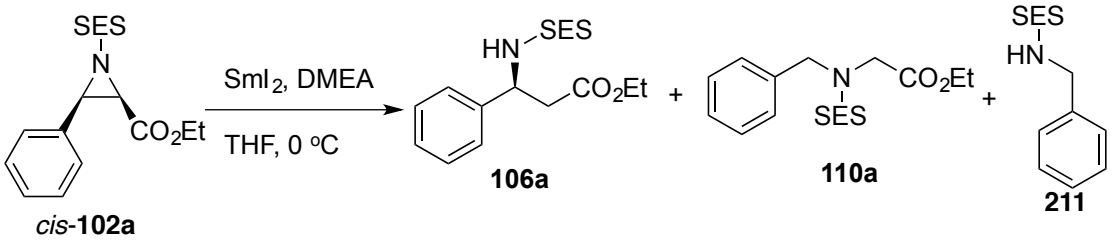
*Reductive ring opening of cis-**101b***: The general procedure for the reductive ring opening described above was followed starting with aziridine (2*R,3R*)-**101b**[12q] (82% ee, 53.4 mg, 0.15 mmol, 1.0 equiv.), SmI_2 (5.0 equiv.), *N,N*-dimethylethanolamine (0.15 mL, 1.5 mmol, 10.0 equiv.) and dry THF (1.5 mL for SmI_2 and 1.5 mL for aziridine, freshly distilled) at 0 °C for 1 hour. Purification by silica gel chromatography (18 × 250 mm, 5:1 hexanes/EtOAc as eluent) afforded (*S*)-**105b** as a colorless oil in 97% isolated yield (52.1 mg, 0.147 mmol); R_f = 0.17 (4:1 hexanes/EtOAc). The optical purity of (*S*)-**105b** was determined to be 84% ee by HPLC analysis (Chiralcel OD-H column, 98:2 hexanes/iPrOH at 222nm, flow-rate: 1.0 ml/min); retention times: R_t = 12.73 min (major enantiomer (*S*)-**105b**) and R_t = 16.94 min (minor enantiomer (*R*)-**105b**). The ^{1}H NMR spectrum of the crude reaction mixture showed that the ratio of **105b : 109b** >99:1 Spectral data for (*S*)-**105b**: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 0.78 (qd, 1H, *J* = 12.0, 3.2 Hz), 0.87 (qd, 1H, *J* = 12.0, 3.2), 1.00-1.17 (m, 3H), 1.18 (t, 3H, *J* = 7.1 Hz), 1.37-1.45 (m, 1H), 1.54-1.61 (m, 2H), 1.63-1.70 (m, 2H), 1.73-1.81 (m, 1H), 2.25 (dd, 1H, *J* = 16.0, 5.6 Hz), 2.37 (dd, 1H, *J* = 16.0, 5.6 Hz), 2.39 (s, 3H), 3.26-3.34 (m, 1H), 4.01 (m, 2H), 5.24 (d, 1H, *J* = 9.3 Hz), 7.26 (d, 2H, *J* = 8.1

Hz), 7.72 (d, 2H, *J* = 8.1 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 14.06, 21.48, 25.87, 25.93, 26.07, 29.10, 29.33, 35.92, 41.24, 55.52, 60.63, 127.02, 129.55, 138.21, 143.15, 171.61. IR (thin film) 3292 m, 2928 vs, 2854 m, 1734 vs, 1718 s, 1456 m, 1324 s, 1161 vs cm^{-1}; mass spectrum, *m/z* (% rel intensity) 354 (MH^+) (6.4), 271 (31), 270 (100), 224 (50), 198 (42), 155 (86), 91 (86), 41 (12); Anal calcd for $C_{18}H_{27}NO_4S$: C, 61.16; H, 7.70; N, 3.96. Found: C, 61.30; H, 8.12; N, 3.88. $[\alpha]_D^{20}$ = –10 (*c* 0.4, EtOAc) on 84% ee (*S*)-**105b**. The reported spectrum data for the compound **3c** (**105b** in this thesis) in this reference does not match our data or the structure of **3c** [93]



trans-**101b**

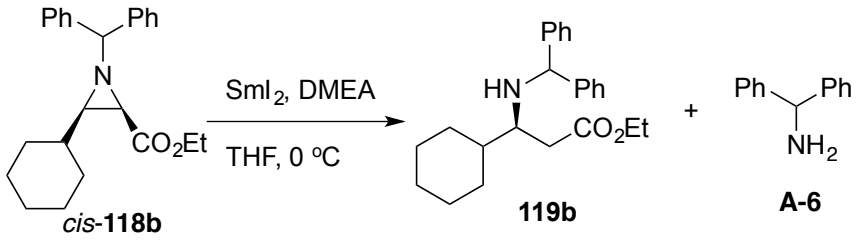
*Reductive ring opening of trans-**101b**:* The reaction was carried out according to the general procedure described above starting with *trans*-**101b** (racemic, 53.3 mg, 0.15 mmol, 1.0 equiv), SmI_2 (6.0 equiv), *N,N*-dimethylethanolamine (0.18 mL, 1.8 mmol, 12.0 equiv) and dry THF (1.5 mL for SmI_2 and 1.5 mL for aziridine, freshly distilled) at 0 °C for 1 hour. Purification by silica gel chromatography (18 × 250 mm, 5:1 hexanes/EtOAc as eluent) afforded **105b** as a colorless oil in 95% isolated yield (51.0 mg, 0.144 mmol). The spectral data of **105b** are the same as the product obtained from the reductive ring-opening of *cis*-**101b**. The ^{1}H NMR spectrum of the crude reaction mixture showed that the ratio of **105b : 109b** >99:1.



cis-**102a** **106a** **110a** **211**

*Reductive ring opening of cis-**102a**:* The general procedure for the reductive ring opening described above was followed with aziridine *cis*-**102a** (53.4 mg, 0.15 mmol, 1.0 equiv), SmI_2 (4.0 equiv), *N,N*-dimethylethanolamine (0.12 mL, 1.2 mmol, 8.0 equiv) and dry THF (2.0 mL for SmI_2 and 1.5 mL for aziridine, freshly distilled) at 0 °C for 1 hour. The ^{1}H NMR spectrum of the crude reaction mixture showed that **106a**, **110a** and **221** were present in a ratio of 23:1:1.6. Purification by silica gel chromatography (18 × 250 mm, 5:1 hexanes/EtOAc as eluent) afforded (*S*)-**106a** as a white solid (mp 60-61 °C) in 84% isolated yield (45.2 mg, 0.126 mmol), **110a** as a colorless oil in 4% isolated yield (2.0 mg, 0.0056 mmol) and **211** as a white solid (mp 91-62 °C, Lit.[94] 98 °C) in 5% yield (2.0 mg, 0.0075 mmol). Spectral data for **106a**: ^{1}H NMR (500 MHz, $CDCl_3$): δ –0.14 (s, 9H), 0.75 (td, 1H, *J* = 14, 4.5 Hz), 0.84 (td, 1H, *J* = 14, 4.0 Hz), 1.17 (t, 3H, *J* = 7 Hz), 2.52 (td, 1H, *J* = 14, 4.5 Hz), 2.63 (td, 1H, *J* = 14, 4.0 Hz), 2.79-2.90 (m, 2H), 4.08 (qd, 2H, *J* = 7.2, 1.5 Hz), 4.81-4.90 (m, 1H), 5.57 (d, 1H, *J* = 8 Hz), 7.24-7.30 (m, 1H), 7.30-7.39 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ -2.17, 10.25, 14.03, 41.91, 49.92, 54.52, 60.96, 126.63, 128.20, 128.87, 140.34, 170.53; IR (thin film) 3277 br s, 2955 w, 1736 s, 1144 s cm^{-1} HRMS calcd (MH^+) $C_{16}H_{28}NO_4SiS^+$ 358.1508, found 358.1509; $[\alpha]_D^{20}$ = –21.7 (*c* 0.87, CH_2Cl_2) on 98% ee (*S*)-**106a**. Spectral data for **110a**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.05

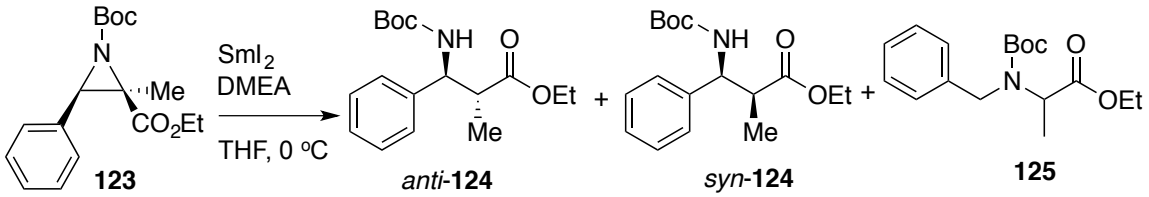
(s, 9H), 1.11-1.16 (m, 2H), 1.24 (t, 3H, *J* = 7.2 Hz), 3.05-3.10 (m, 2H), 3.90 (s, 2H), 4.16 (q, 2H, *J* = 7.2 Hz), 4.53 (s, 2H), 7.27-7.36 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ –1.97, 10.30, 14.15, 46.94, 50.04, 51.76, 61.32, 128.13, 128.51, 128.78, 135.51, 169.64; IR (thin film) 2955 w, 1746 s, 1333 s, 1142 s cm^{-1}; HRMS calcd (MH^+) $C_{16}H_{28}NO_4SiS^+$ 358.1508, found 358.1530. Spectral data for **211**: ^{1}H NMR (500 MHz, $CDCl_3$): δ -0.04 (s, 9H), 0.89-0.96 (m, 2H), 2.76-2.83 (m, 2H), 4.29 (d, 2H, *J* = 10.0 Hz), 4.42 (t, br, 1H, *J* = 10.5 Hz), 7.25-7.38 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ -2.06, 10.57, 47.37, 49.67, 127.98, 128.13, 128.91, 137.11. HRMS calcd (MH^+) $C_{12}H_{22}NO_2SiS^+$ 272.1141, found 272.1164. The ^{1}H and ^{13}C NMR data match those previously reported for this compound.[94]



cis-**118b** **119b** **A-6**

*Reductive ring opening of cis-**118b**:* The general procedure for the reductive ring opening described above was followed with *cis*-**118b**[12r] (44 mg, 0.12 mmol). Purification of the product by silica gel chromatography (18 mm x 300 mm, 1:5 EtOAc/hexanes as eluent) gave a 1:1.4 mixture of the β-amino ester **119b** (22% NMR yield) and unreacted *cis*-**118b** (31% NMR yield). The ^{1}H NMR spectrum of the crude reaction mixture indicated the formation of the amine **A-6** in 39% yield. Extending the reaction time for the ring opening reaction of *cis*-**118b** (42 mg, 0.12 mmol) at room temperature from 40 min to 2 h gave **119b** (8.6 mg, 0.024 mmol) in 22% isolated yield and the amine **A-6** in 52% isolated yield.

The unreacted *cis*-**118b** was isolated with a 20% recovery. Spectral data for **119b**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.90-1.04 (m, 2H), 1.05-1.23 (m, 2H), 1.20 (t, 3H, *J* = 7.1 Hz), 1.45-1.54 (m, 1H), 1.60-1.80 (m, 6H), 2.34 (dd, 1H, *J* = 14.5, 7.0 Hz), 2.47 (dd, 1H, *J* = 14.5, 5.3 Hz), 2.77 (dt, 1H, *J* = 7.0, 5.3 Hz), 4.03-4.14 (m, 2H), 4.94 (s, 1H), 7.15-7.19 (m, 2H), 7.23-7.28 (m, 4H), 7.35-7.41 (m, 4H) (N-H proton not located); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.21, 26.52, 26.59, 26.69, 28.43, 29.53, 36.02, 40.86, 56.78, 60.21, 64.13, 126.89, 126.91, 127.42, 127.55, 128.33, 128.34, 144.24, 144.45, 172.90; HRMS calcd for (MH^+) $C_{24}H_{32}NO_2$ 366.2433, found 366.2431. Spectral data for **A-6**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.84 (bs, 2H), 5.20 (s, 1H), 7.18-7.23 (m, 2H), 7.26-7.32 (m, 4H), 7.33-7.37 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 59.74, 126.88, 126.92, 128.45, 145.58. The ^{1}H and ^{13}C NMR spectral data for **A-6** match those provided by Aldrich for this compound.

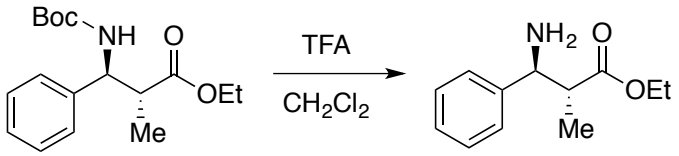


123 *anti*-**124** *syn*-**124** **125**

*Reductive ring opening of **123**:* The general procedure for the reductive ring opening described above was followed with the tri-substituted aziridine **123**[46] (76 mg, 0.25 mmol, 99% *ee*) and 5.0 equiv SmI_2. The ^{1}H NMR spectrum of the crude reaction mixture indicated a mixture of *anti*-**124**, *syn*-**124** and **125** was present in a ratio of 1.28:0.28:1. Purification of the products by silica gel chromatography (18 mm x 200 mm, 1:10 to 1:6 EtOAc/hexanes as eluent) gave

anti-**124** as a white solid (mp 53-55 °C) in 43% isolated yield (32.7 mg, 0.106 mmol), *syn*-**124** as a white solid (mp 89-91 °C) in 9% isolated yield (6.6 mg, 0.021 mmol) and **125** as a colorless oil in 30% isolated yield (23.2 mg, 0.0755 mmol). Spectral data for *anti*-**124**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.09 (t, 3H, *J* = 7.1 Hz), 1.20 (d, 3H, *J* = 7.0 Hz), 1.39 (s, 9H), 2.87 (brt, 1H, *J* = 6.5 Hz), 4.01 (q, 2H, *J* = 7.1 Hz), 4.81 (brs, 1H), 5.81 (brs, 1H), 7.16-7.33 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.00, 15.37, 28.33, 45.27, 56.69, 60.55, 79.39, 126.25, 127.25, 128.40, 141.01, 155.44, 174.92; IR (thin film) 3355 br w, 2978 m, 1721 s, 1171 s cm^{-1}; HRMS calcd (MH^+) $C_{17}H_{26}NO_4^+$ 308.1862, found 308.1860; $[\alpha]_D^{20}$ = – 40.1 (*c* 0.5, CH_2Cl_2) on 99% ee material. Spectral data for *syn*-**124**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.11 (t, 3H, *J* = 7.2 Hz), 1.13 (d, 3H, *J* = 7.2 Hz), 1.39 (s, 9H), 2.87 (brs, 1H), 3.96-4.08 (m, 2H), 4.97 (brs, 1H), 5.27 (brs, 1H), 7.19-7.25 (m, 3H), 7.26-7.31 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 13.11, 13.99, 28.33, 45.43, 56.52, 60.61, 79.59, 126.76, 127.45, 128.40, 140.17, 155.10, 173.70; IR (thin film) 3380 s, 2980 m, 1728 s, 1686 s, 1520 s, 1173 s cm^{-1}; HRMS calcd (MH^+) $C_{17}H_{26}NO_4^+$ 308.1862, found 308.1855; $[\alpha]_D^{20}$ = – 26.0 (*c* 0.5, CH_2Cl_2) on 99% ee material. Spectral data for **125** (compound **125** appeared to be a mixture of two rotamers at room temperature in a ratio of 1.2:1): colorless oil ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.21 (t, 3H, *J* = 7.2 Hz), 1.27-1.50 (m, 12H), 3.82-4.64 (m, 5H), 7.16-7.37 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.10, 15.38, 15.75, 28.29, 49.74, 50.81, 54.83, 55.40, 60.94, 80.42, 80.58, 126.95, 127.18, 127.30, 127.97, 128.29, 128.58, 138.25, 139.20, 155.38, 155.51, 172.08, 172.27. The ^{1}H NMR data match those previously reported for this compound.[95]

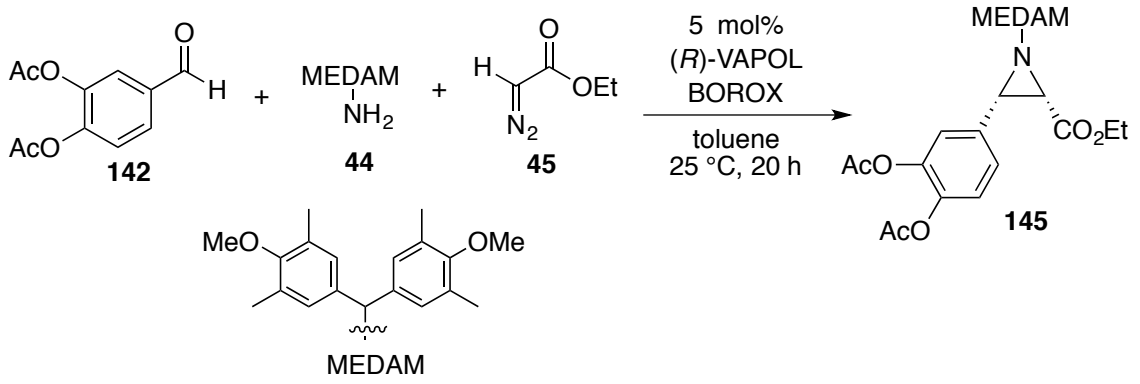
5.2.3 Determination of the Relative Stereochemistry of *anti*-124



anti-**124** *anti*-**126**

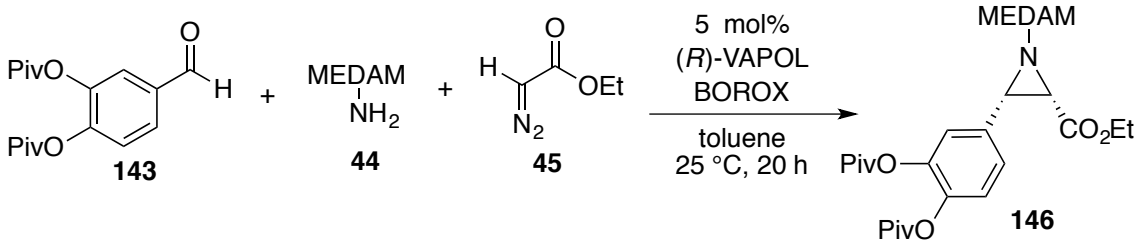
Anti-ethyl 3-amino-2-methyl-3-phenylpropanoate ***126***: To a solution of *anti*-**124** (27 mg, 0.088 mmol, 1.0 equiv) in CH_2Cl_2 (0.24 mL) was added trifluoroacetic acid (0.240 mL, 357 mg, 3.13 mmol, 35.6 equiv). After the reaction mixture was stirred at room temperature under nitrogen overnight, it was concentrated and diluted with 0.3 mL H_2O. The pH of the mixture was adjusted to ~10 with sat aq $NaHCO_3$ (*ca*. 10 mL) and then the mixture was extracted with CH_2Cl_2 (10 mL × 3). The combined organic layer was dried over Na_2SO_4, filtered and concentrated. Purification of the product by silica gel chromatography (18 mm x 150 mm, 1:1 EtOAc/hexanes as eluent) gave ethyl 3-amino-2-methyl-3-phenylpropanoate **126** as a colorless oil in 74% isolated yield (13.5 mg, 0.065 mmol). Spectral data for ethyl 3-amino-2-methyl-3-phenylpropanoate **126**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.93 (d, 3H, *J* = 7.2 Hz), 1.26 (t, 3H, *J* = 7.2 Hz), 1.64 (brs, 2H), 2.60-2.72 (m, 1H), 4.00 (d, 1H, *J* = 9.4 Hz), 4.17 (q, 2H, *J* = 7.2 Hz), 7.21-7.34 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.2, 15.4, 48.1, 59.1, 60.4, 127.0, 127.5, 128.5, 143.6, 175.9. The ^{1}H NMR data match those previously reported for the *anti*-isomer but not those of the *syn*-isomer.[96]

5.2.4 Formation of Aziridines 145-147



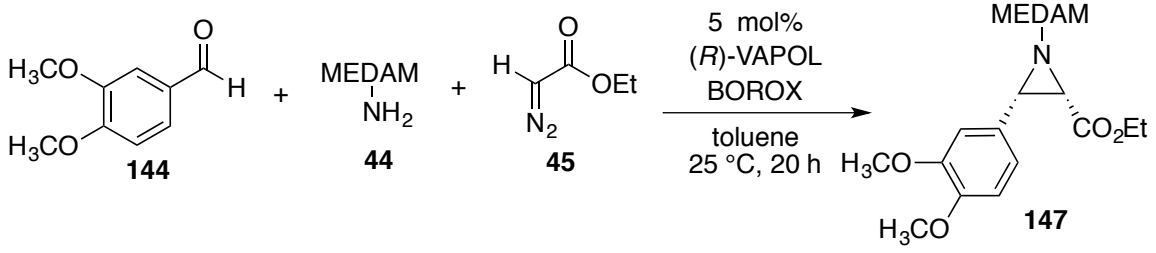
4-((2S,3S)-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-(ethoxycarbonyl)aziridin-2-yl)-1,2-phenylene diacetate ***145***: To a 25 mL flame-dried Schlenk flask equipped with a stir bar and filled with nitrogen was added (*R*)-VAPOL (54 mg, 0.10 mmol), $B(OPh)_3$ (87 mg, 0.30 mmol), amine **44**[12j] (599 mg, 2.00 mmol) and dry toluene (4 mL) to dissolve the reagents. The flask was then sealed and the reaction mixture was stirred at room temperature for 1 h. Thereafter, 4Å powdered Molecular Sieves (600 mg, freshly flame-dried) was added to the reaction flask followed by the addition of the aldehyde **142**[97] (467 mg, 2.10 mmoL, 1.05 equiv). To this solution was rapidly added ethyl diazoacetate (EDA) **45** (0.30 mL, 2.4 mmoL, 1.2 equiv). After the resulting mixture was stirred for 20 h at room temperature, it was dilluted by addition of hexane (12 mL). The reaction mixture was then filtered through a Celite pad into a 100 mL round bottom flask. The reaction flask was rinsed with EtOAc (6 mL × 3) and the rinse was filtered through the same Celite pad. The combined filtrate was then concentrated *in vacuo* followed by exposure to high vacuum (0.05 mm Hg) to afford the crude aziridine as a yellow oil. Purification of the aziridine by

silica gel chromatography (40 mm × 210 mm column, 2:1 hexanes/EtOAc as eluent) afforded pure *cis*-aziridine **145** as a white solid (mp 65-67 °C on >98.5% ee material) in 98 % isolated yield (1.15 g, 1.95 mmol). The optical purity of **145** was determined to be >98.5 % *ee* by HPLC analysis (CHIRALCEL OD-H column, 85:15 hexane/2-propanol at 222 nm, flow-rate: 1 mL/min). Retention times: R_t = 7.18 min (minor enantiomer, *ent*-**145**) and R_t = 8.46 min (major enantiomer, **145**). R_f = 0.19 (1:2 EtOAc/hexane); Spectral data for **145**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.02 (t, 3H, *J* = 7.1 Hz), 2.21 (s, 6H), 2.25 (s, 3H), 2.26 (s, 6H), 2.27 (s, 3H), 2.59 (d, 1H, *J* = 6.8 Hz), 3.09 (d, 1H, *J* = 6.8 Hz), 3.65 (s, 3H), 3.68 (s, 1H), 3.69 (s, 3H), 3.91-4.03 (m, 2H), 7.04-7.10 (m, 3H), 7.17 (s, 2H), 7.24-7.29 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.97, 16.15, 16.22, 20.59, 20.60, 46.39, 47.15, 59.51, 59.57, 60.76, 76.85, 122.60, 122.87, 126.02, 127.27, 127.66, 130.63, 130.76, 134.21, 137.53, 137.59, 141.17, 141.45, 155.90, 156.15, 167.70, 168.01, 168.25; IR (thin film) 2932 m, 1773 vs, 1746 s, 1213 vs cm^{-1}; HRMS calcd (MH^+) $C_{34}H_{40}NO_8^+$ 590.2754, found 590.2769; $[\alpha]_D^{20}$ = – 28.2° (*c* 1.0, CH_2Cl_2) on >98.5% *ee* (by HPLC) material.



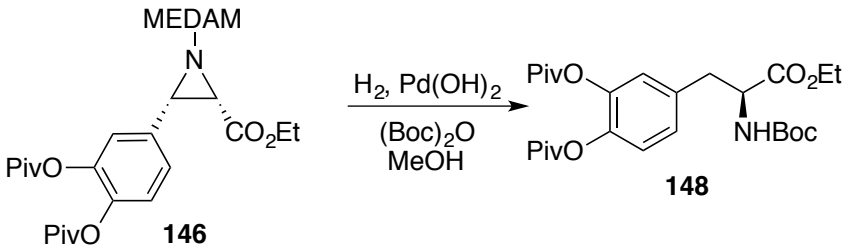
4-((2S,3S)-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-(ethoxycarbonyl)aziridin-2-yl)-1,2-phenylene bis(2,2-dimethylpropanoate) ***146****:* The procedure for the synthesis of aziridine **145** was followed starting with

aldehyde **143**[98] (643 mg, 2.10 mmoL, 1.05 equiv). Purification of the aziridine by silica gel chromatography (40 mm × 210 mm column, 5:1 hexanes/EtOAc as eluent) afforded pure *cis*-aziridine **146** as a white solid (mp 64-66 °C on 98% ee material) in 97 % isolated yield (1.31 g, 1.94 mmol). The optical purity of **146** was determined to be 98 % *ee* by HPLC analysis (Chiralpak AD column, 95:5 hexane/2-propanol at 222 nm, flow- rate: 0.7 mL/min). Retention times: R_t = 8.68 min (minor enantiomer, *ent*-**146**) and R_t = 10.23 min (major enantiomer, **146**). R_f = 0.21 (1:5 EtOAc/hexane); Spectral data for **146**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.04 (t, 3H, *J* = 7.0 Hz), 1.30 (s, 9H), 1.32 (s, 9H), 2.20 (s, 6H), 2.24 (s, 6H), 2.56 (d, 1H, *J* = 6.8 Hz), 3.08 (d, 1H, *J* = 6.8 Hz), 3.64 (s, 3H), 3.66 (s, 1H), 3.68 (s, 3H), 3.90-4.03 (m, 2H), 6.98 (d, 1H, *J* = 8.0 Hz), 7.07 (s, 2H), 7.11 (d, 1H, *J* = 1.5 Hz), 7.16 (s, 2H), 7.25 (dd, 1H, *J* = 8.5, 1.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.04, 16.18, 16.22, 27.18, 27.23, 39.03, 39.06, 46.18, 47.31, 59.51, 59.56, 60.74, 76.88, 122.60, 122.82, 125.63, 127.27, 127.66, 130.62, 130.71, 133.71, 137.55, 137.61, 141.70, 141.88, 155.88, 156.14, 167.82, 175.57, 175.79; IR (thin film) 2977 s, 1761 vs, 1482 s, 1119 vs cm^{-1}; HRMS calcd (MH^+) $C_{40}H_{52}NO_8^+$ 674.3693, found 674.3694; $[\alpha]_D^{20}$ = – 34.2° (*c* 1.0, CH_2Cl_2) on 98% *ee* (by HPLC) material.



*ethyl-(2S,3S)-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-(3,4-dimethoxyphenyl)aziridine-2-carboxylate **147**:* The procedure for the synthesis of aziridine **145** was followed starting with aldehyde **144** (88.0 mg, 0.525 mmoL, 1.05 equiv), amine **44** (150 mg, 0.500 mmol, 1.00 equiv), ethyl diazoacetate (EDA) **45** (0.08 mL, 0.6 mmoL, 1.2 equiv), (*R*)-VAPOL (13.5 mg, 0.0250 mmol) and $B(OPh)_3$ (22 mg, 0.075 mmol). Purification of the aziridine by silica gel chromatography (25 mm × 160 mm column, 3:1 hexanes/EtOAc as eluent) afforded pure *cis*-aziridine **147** as a yellow semi-solid in 90 % isolated yield (240 mg, 0.450 mmol). R_f = 0.17 (1:3 EtOAc/hexane); Spectral data for **147**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.05 (t, 3H, *J* = 7.2 Hz), 2.20 (s, 6H), 2.25 (s, 6H), 2.55 (d, 1H, *J* = 6.8 Hz), 3.09 (d, 1H, *J* = 6.8 Hz), 3.63 (s, 3H), 3.67 (s, 1H), 3.68 (s, 3H), 3.81 (s, 3H), 3.82 (s, 3H), 3.90-4.04 (m, 2H), 6.72 (d, 1H, *J* = 8.2 Hz), 6.83-6.92 (m, 2H), 7.12 (s, 2H), 7.19 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.10, 16.19, 45.94, 48.03, 55.61, 55.77, 59.47, 59.54, 60.54, 76.92, 110.40, 111.06, 115.31, 119.81, 120.05, 127.30, 127.82, 127.84, 129.44, 130.55, 130.58, 137.66, 138.04, 148.07, 148.22, 155.81, 156.02, 168.25, (one sp^3 carbon and one sp^2 carbon not located); IR (thin film) 2940 m, 1746 m, 1518 s, 1223 vs cm^{-1}; HRMS calcd (MH^+) $C_{32}H_{40}NO_6^+$ 534.2856, found 534.2869. $[\alpha]_D^{20}$ = – 24.5° (*c* 1.0, CH_2Cl_2)

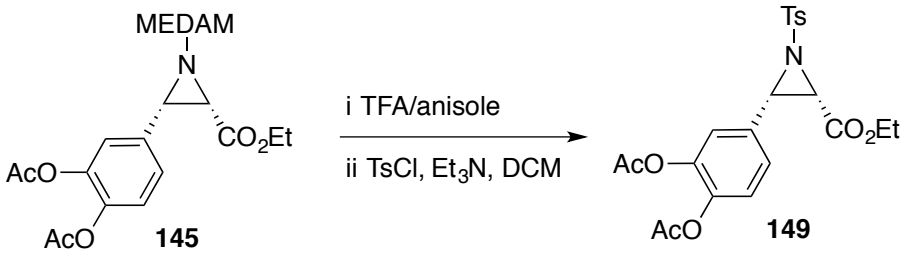
5.2.5 Synthesis of Protected Forms of L-DOPA



(S)-4-(2-((tert-butoxycarbonyl)amino)-3-ethoxy-3-oxopropyl)-1,2-phenylene bis(2,2-dimethylpropanoate) ***148****:* To a oven-dried 25 mL round bottom flask equipped with a stir bar and filled with nitrogen was added aziridine **146** (67.4 mg, 0.100 mmol, 98% *ee*), $Pd(OH)_2$ (28.0 mg, 0.020 mmol, $Pd(OH)_2$ on carbon 20%, moisture ≤ 50%), di-tert-butyl dicarbonate (33 mg, 0.15 mmol) and methanol (10 mL). The flask was sealed with a rubber septum and a needle connected to a vacuum line was used to apply vacuum in the flask through the septum. The vacuum was applied for a few seconds with vigorous stirring of the reaction mixture. Then the vacuum was stopped and a hydrogen balloon was connected to the flask by a needle through the septum. This process was repeated four times. Then the suspension was stirred at room temperature under hydrogen for 17 hours and then filtered through a pad of Celite. The filter cake was washed with EtOAc (5 mL) and DCM (3 mL × 3). The combined filtrate was concentrated to give a light yellow oil. Purification of the crude product by column chromatography on silica gel (20 mm × 160 mm, hexanes/EtOAc 5:1) gave the α-amino ester **148** as a colorless oil (42.2 mg, 0.0855 mmol, 86%). R_f = 0.20 (1:5 EtOAc/hexane); Spectral data for **148**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.20 (t, 3H, *J* = 7.0 Hz), 1.30 (s, 18H), 1.41 (s, 9H), 3.06 (d, 2H, *J* = 6.0 Hz), 4.07-4.18 (m, 2H), 4.50 (dt, 1H, *J* = 7.5, 6.0 Hz), 5.01 (d, 1H, *J* = 7.5 Hz), 6.87 (s, 1H), 6.97 (d, 1H, *J* = 8.2 Hz), 7.02 (d, 1H, *J* = 8.2 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.07, 27.19, 28.27, 37.50, 39.06, 39.09, 54.27, 61.49, 79.90, 123.24, 124.25, 127.05, 134.53, 141.52, 142.31, 155.00, 171.48, 175.63, 175.79, (one sp^3 carbon not located); IR (thin film) 2977 s, 1761 vs, 1482 s, 1119 vs cm^{-1}; HRMS calcd ($M+H^+$)

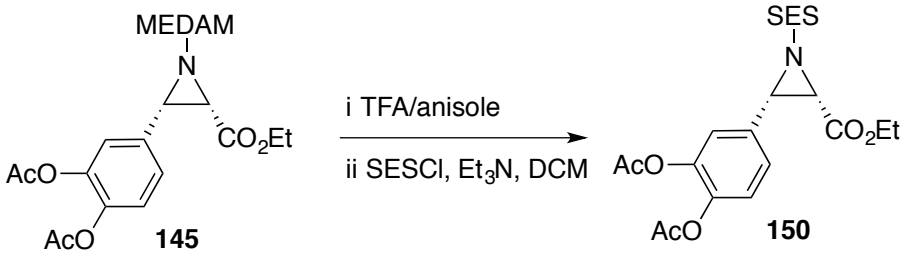
$C_{26}H_{40}NO_8^+$ 494.2754, found 494.2751; $[\alpha]_D^{20}$ = + 27.8° (*c* 1.0, CH_2Cl_2) on 98% *ee* material (The optical purity was assumed to be unchanged from **146**).

5.2.6 Formation of Aziridines 149-151



4-((2S,3S)-3-(ethoxycarbonyl)-1-tosylaziridin-2-yl)-1,2-phenylene diacetate ***149****:* To a flame-dried 100 mL round bottom flask equipped with a stir bar and filled with nitrogen was added aziridine **145** (467 mg, 0.792 mmol) and anisole (4.1 mL) at room temperature. The resulting solution was cooled to 0 °C in an ice-bath and trifluoroacetic acid (4.1 mL) was rapidly added. The ice-bath was then removed and the reaction mixture was stirred for 40 minutes at room temperature. The reaction mixture was quenched by careful addition of saturated aq Na_2CO_3 (30 mL) and H_2O (10 mL) followed by addition of Et_2O (30 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (30 mL × 3). The combined organic layer was dried with Na_2SO_4, filtered and concentrated *in vacuo* followed by exposure to high vacuum (0.05 mm Hg) for 4 h to give a yellow oil, to which was added 6.5 mL $CH_2Cl_2/CHCl_3$ (1:1) and Et_3N (0.33 mL, 2.4 mmol). The resulting solution was cooled to 0 °C followed by the addition of tosyl chloride (228 mg, 1.20 mmol). The mixture was then stirred at 0 °C for 15 h. Thereafter, another portion of tosyl chloride (228 mg, 1.20 mmol) and Et_3N (0.33 mL, 2.4 mmol) was added to the reaction mixture at room

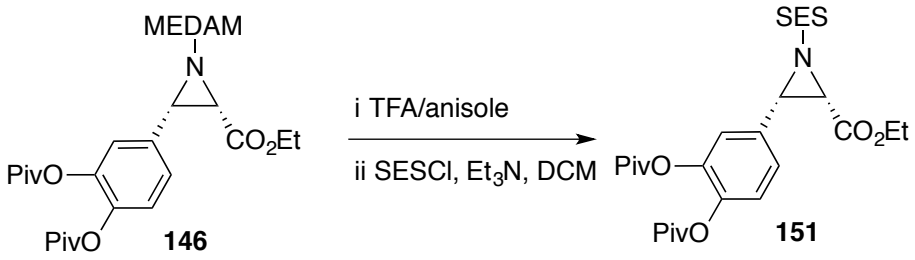
temperature. After the mixture was stirred for 26 hours at room temperature, the reaction was quenched with 12 mL sat aq NH_4Cl and 2.5 mL H_2O. The aqueous layer was extracted with CH_2Cl_2 (15 mL × 3) and the combined organic layer was dried with Na_2SO_4, filtered and concentrated to give a dark brown oil. Purification by silica gel chromatography (25 mm × 160 mm, 2:1 hexanes/EtOAc as eluent) afforded *cis*-**149** as a light yellow oil in 70 % yield (258 mg, 0.559 mmol). R_f = 0.14 (1:2 EtOAc/hexane); Spectral data for **149**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.96 (t, 3H, *J* = 7.1 Hz), 2.236 (s, 3H), 2.240 (s, 3H), 2.43 (s, 3H), 3.66 (d, 1H, *J* = 7.5 Hz), 3.89-4.02 (m, 2H), 4.03 (d, 1H, *J* = 7.5 Hz), 7.07 (d, 1H, *J* = 8.3 Hz), 7.13 (d, 1H, *J* = 2.0 Hz), 7.17 (dd, 1H, *J* = 8.3, 2.0 Hz), 7.34 (d, 2H, *J* = 8.0 Hz), 7.88 (d, 2H, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.71, 20.55, 20.60, 21.71, 43.40, 44.32, 61.86, 122.72, 123.28, 125.81, 128.12, 129.94, 129.97, 133.71, 141.83, 142.27, 145.39, 164.13, 167.85, 168.01; IR (thin film) 2986 w, 1773 vs, 1734 m, 1210 vs, 1165 s cm^{-1}; HRMS calcd (MH^+) $C_{22}H_{24}NO_8S^+$ 462.1223, found 462.1234; $[\alpha]_D^{20}$ = + 15.6° (*c* 1.0, CH_2Cl_2) on >98.5% *ee* material (The optical purity was assumed to be unchanged from **145**).



*4-((2S,3S)-3-(ethoxycarbonyl)-1-((2-(trimethylsilyl)ethyl)sulfonyl)aziridin-2-yl)-1,2-phenylene diacetate **150**:* To a flame-dried 100 mL round bottom flask equipped with a stir bar and filled with nitrogen was added aziridine **145** (366 mg,

0.621 mmol) and anisole (3.1 mL) at room temperature. The resulting solution was cooled to 0 °C in an ice-bath and trifluoroacetic acid (3.1 mL) was rapidly added. The ice-bath was then removed and the reaction mixture was stirred for 40 minutes at room temperature. The reaction mixture was quenched by careful addition of saturated aq Na_2CO_3 (25 mL) and H_2O (10 mL) followed by addition of Et_2O (30 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (30 mL × 3). The combined organic layer was dried with Na_2SO_4, filtered and concentrated *in vacuo* followed by exposure to high vacuum (0.05 mm Hg) for 4 h to give a yellow oil, which was then dissolved in a mixture of CH_2Cl_2 (2 mL) and Et_3N (0.9 mL). After the solution was cooled to 0 °C in an ice-bath, 2-(trimethylsilyl)ethanesulfonyl chloride (0.12 mL, 0.93 mmol) was added dropwise to the reaction mixture at 0 °C. Then the ice-bath was then removed and the reaction mixture was stirred at room temperature for 17 hours. Thereafter, another portion of 2-(trimethylsilyl)ethanesulfonyl chloride (0.12 ml, 0.93 mmol) and Et_3N (0.9 ml) was added to the reaction mixture at room temperature. After the mixture was stirred for 23 hours at room temperature, the reaction was quenched with 2.5 mL sat aq NH_4Cl and 1 mL H_2O. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (4 mL × 3). The combined organic layer was dried with Na_2SO_4, filtered and concentrated to give a dark brown oil. Purification by silica gel chromatography (25 mm × 160 mm, 3:1 hexanes/EtOAc as eluent) afforded *cis*-**150** as a light yellow oil in 78% yield (0.228 g, 0.483 mmol). R_f = 0.20 (1:3 EtOAc/hexane); Spectral data for **150**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.05 (s, 9H), 1.03 (t, 3H, *J* = 7.0 Hz), 1.12-1.20 (m,

2H), 2.26 (s, 6H), 3.16-3.24 (m, 2H), 3.66 (d, 1H, *J* = 7.5 Hz), 3.97-4.09 (m, 2H), 4.02 (d, 1H, *J* = 7.5 Hz), 7.15 (d, 1H, *J* = 8.2 Hz), 7.25 (d, 1H, *J* = 1.9 Hz), 7.30 (dd, 1H, *J* = 8.2 Hz, *J* = 1.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ –2.06, 9.53, 13.81, 20.57, 20.62, 43.50, 43.60, 49.51, 61.99, 122.79, 123.42, 125.84, 130.06, 141.98, 142.42, 164.21, 167.87, 168.00; IR (thin film) 2955 m, 1777 s, 1208 s, 1177 s cm^{-1}; HRMS calcd (MH^+) $C_{20}H_{30}NO_8SiS^+$ 472.1461, found 472.1449; $[\alpha]_D^{20}$ = +27.5° (*c* 1.0, CH_2Cl_2) on >98.5% *ee* material (The optical purity was assumed to be unchanged from **145**).

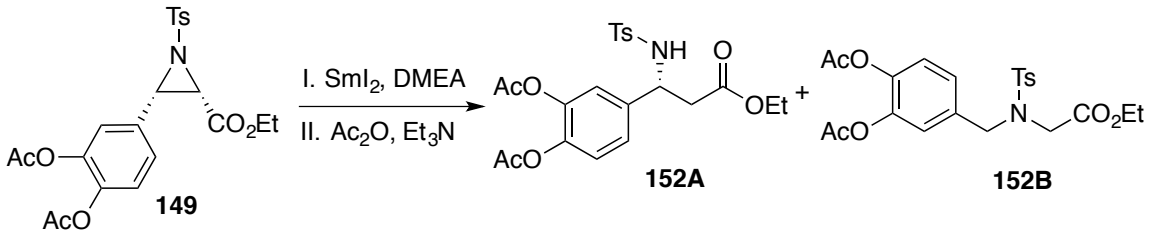


4-((2S,3S)-3-(ethoxycarbonyl)-1-((2-(trimethylsilyl)ethyl)sulfonyl)aziridin-2-yl)-1,2-phenylene bis(2,2-dimethylpropanoate) ***151****:* To a flame-dried 100 mL round bottom flask equipped with a stir bar and filled with nitrogen was added aziridine **146** (674 mg, 1.00 mmol) and anisole (8.9 mL) at room temperature. The resulting solution was cooled to 0 °C in an ice-bath and trifluoroacetic acid (8.9 mL) was rapidly added. The ice-bath was removed and the reaction mixture was stirred for 30 minutes at room temperature. The reaction mixture was quenched by careful addition of saturated aq Na_2CO_3 (68 mL) and H_2O (35 mL) followed by addition of Et_2O (50 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (100 mL × 3). The combined organic layer was dried with Na_2SO_4, filtered and concentrated *in vacuo* followed by

exposure to high vacuum (0.05 mm Hg) for 4 h to give a yellow oil, which was then dissolved in a mixture of CH_2Cl_2 (3.5 mL) and Et_3N (1.5 mL). After the solution was cooled to 0 °C, 2-(trimethylsilyl)ethanesulfonyl chloride (0.20 mL, 1.5 mmol) was added dropwise to the reaction mixture at 0 °C. Then the ice-bath was removed and the reaction mixture was stirred at room temperature for 14 hours. Thereafter, another portion of 2-(trimethylsilyl)ethanesulfonyl chloride (0.20 mL, 1.5 mmol) and Et_3N (1.5 mL) was added to the reaction mixture at room temperature. After the mixture was stirred for 22 hours at room temperature, the reaction was quenched with 4 mL sat aq NH_4Cl and 1.5 mL H_2O. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (6 mL × 3). The combined organic layer was dried with Na_2SO_4, filtered and concentrated to give a dark brown oil. Purification by silica gel chromatography (25 mm × 160 mm, 5:1 hexanes/EtOAc as eluent) afforded *cis*-**151** as a light yellow oil in 86 % yield (0.475 g, 0.855 mmol). R_f = 0.20 (1:5 EtOAc/hexane); Spectral data for **151**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.05 (s, 9H), 1.06 (t, 3H, *J* = 7.1 Hz), 1.11-1.21 (m, 2H), 1.31 (s, 9H), 1.32 (s, 9H), 3.17-3.26 (m, 2H), 3.66 (d, 1H, *J* = 7.5 Hz), 3.98-4.07 (m, 2H), 4.02 (d, 1H, *J* = 7.5 Hz), 7.09 (d, 1H, *J* = 8.3 Hz), 7.18 (d, 1H, *J* = 1.8 Hz), 7.27 (dd, 1H, *J* = 8.3 Hz, *J* = 1.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ –2.13, 9.50, 13.81, 27.10, 27.14, 39.03, 39.06, 43.23, 43.70, 49.39, 61.87, 122.68, 123.32, 125.36, 129.54, 142.40, 142.89, 164.18, 175.37, 175.55; IR (thin film) 2977 m, 1761 vs, 1117 s cm^{-1}; HRMS calcd (M+NH_4^+) $C_{26}H_{45}N_2O_8SiS^+$ 573.2666, found 573.2675; $[\alpha]_D^{20}$ = +

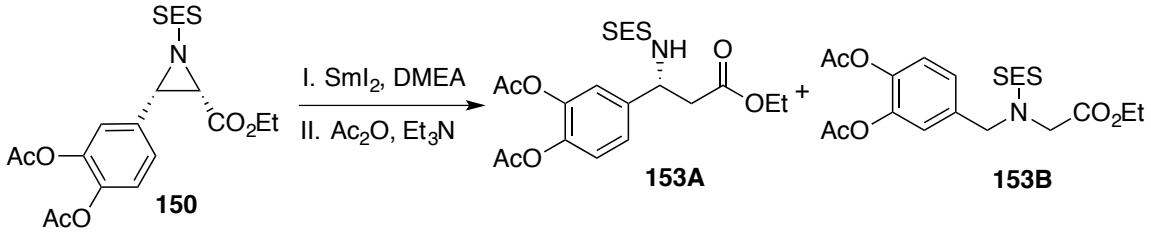
26.9° (*c* 1.0, CH_2Cl_2) on 98% *ee* material (The optical purity was assumed to be unchanged from **146**).

5.2.7 Reductive Ring Opening of Aziridines 149-151



*Reductive ring opening of **149**:* The general procedure for the reductive ring opening described in **Part 6.2.2** was followed with aziridine **149** (228 mg, 0.494 mmol), 2.5 equiv SmI_2 and 5 equiv DMEA. The ^{1}H NMR spectrum of the crude reaction mixture indicated a complex mixture of several products due to partial cleavage of the acetate group on the benzene ring. To this mixture was added Ac_2O (0.2 mL) and Et_3N (0.16 mL). After the reaction was stirred at room temperature for 30 minutes, it was quenched by the addition of EtOH (0.1 mL) and H_2O (2.5 mL). The resulting mixture was extracted with EtOAc (3 mL × 3). The combined organic layer was dried with Na_2SO_4, filtered and concentrated to give a yellow oil. Purification by silica gel chromatography (20 mm × 160 mm, 1:1.5 EtOAc/hexanes as eluent) gave **152A** as a colorless oil in 76% isolated yield (173 mg, 0.373 mmol) and **152B** as a light yellow oil in 8% isolated yield (17.5 mg, 0.0377 mmol). Spectral data for **152A** (R_f = 0.23 (1:1.5 EtOAc/hexane)): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.11 (t, 3H, *J* = 7.1 Hz), 2.22 (s, 6H), 2.33 (s, 3H), 2.68 (dd, 1H, *J* = 16.2, 6.2 Hz), 2.75 (dd, 1H, *J* = 16.2, 6.4 Hz), 3.99 (q, 2H, *J* = 7.1 Hz), 4.70 (dt, 1H, *J* = 7.5, 6.2 Hz), 5.97 (d, 1H, *J* = 7.8 Hz),

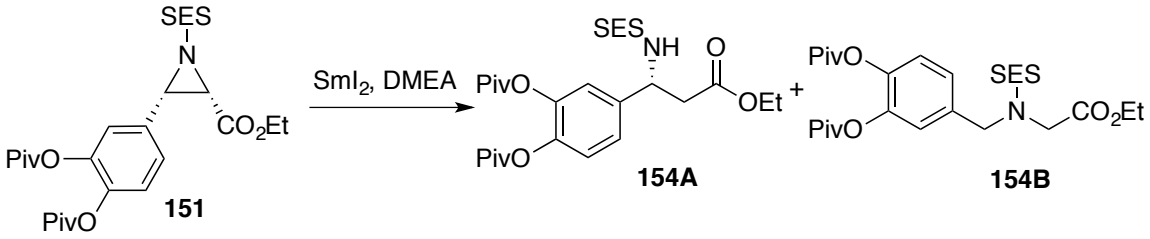
6.90-6.98 (m, 3H), 7.14 (d, 2H, *J* = 8.0 Hz), 7.54 (d, 2H, *J* = 8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.88, 20.51, 20.56, 21.37, 40.96, 53.57, 61.04, 121.79, 123.28, 124.47, 126.93, 129.50, 137.07, 138.01, 141.38, 141.82, 143.39, 167.82, 167.90, 170.40; IR (thin film) 3279 m, 2984 w, 2930 w, 1773 s, 1734 s, 1211 s, 1161 s cm^{-1}; HRMS calcd (MH^+) $C_{22}H_{26}NO_8S^+$ 464.1379, found 464.1381; $[\alpha]_D^{20}$ = + 45.2° (*c* 1.0, CH_2Cl_2) on >98% *ee* material (The optical purity was assumed to be unchanged from **145**). Spectral data for **152B** (R_f = 0.38 (1:1.5 EtOAc/hexane)): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.13 (t, 3H, *J* = 7.1 Hz), 2.26 (s, 6H), 2.42 (s, 3H), 3.93 (s, 2H), 3.99 (q, 2H, *J* = 7.1 Hz), 4.46 (s, 2H), 7.09 (s, 1H), 7.12 (s, 2H), 7.30 (d, 2H, *J* = 8.2 Hz), 7.73 (d, 2H, *J* = 8.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.96, 20.60, 20.65, 21.57, 46.78, 50.48, 61.24, 123.49, 123.64, 126.51, 127.44, 129.60, 134.05, 136.68, 141.88, 142.23, 143.64, 168.06, 168.16, 168.57; IR (thin film) 2984 w, 2934 w, 1773 vs, 1213 s cm^{-1}; HRMS calcd (MH^+) $C_{22}H_{26}NO_8S^+$ 464.1379, found 464.1381.



*Reductive ring opening of **150**:* The general procedure for the reductive ring opening described above was followed with aziridine **150** (236 mg, 0.500 mmol), 4 equiv SmI_2 and 8 equiv DMEA. The ^{1}H NMR spectrum of the crude reaction mixture indicated a complex mixture of several products due to partial cleavage of the acetate group on the benzene ring. To this mixture was added

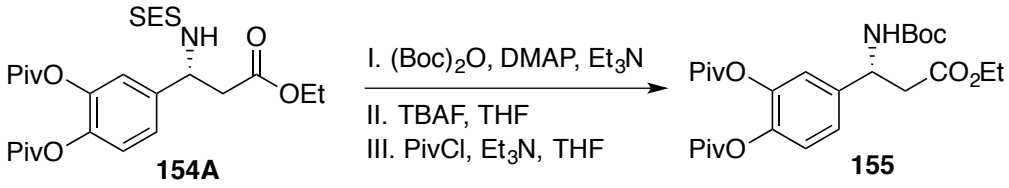
Ac_2O (0.63 mL) and Et_3N (0.5 mL). After the reaction was stirred at room temperature for 40 minutes, it was quenched by the addition of EtOH (0.32 mL) and H_2O (9 mL). The resulting mixture was extracted with EtOAc (10 mL × 3). The combined organic layer was dried with Na_2SO_4, filtered and concentrated to give a yellow oil. Purification by silica gel chromatography (20 mm × 160 mm, 1:2 EtOAc/hexanes as eluent) gave **153A** as a colorless oil in 69% isolated yield (164 mg, 0.346 mmol) and **153B** as a light yellow oil in 19% isolated yield (45 mg, 0.095 mmol). Spectral data for **153A** (R_f = 0.21 (1:2 EtOAc/hexane)): ^{1}H NMR (500 MHz, $CDCl_3$) δ -0.09 (s, 9H), 0.78-0.93 (m, 2H), 1.19 (t, 3H, *J* = 7.1 Hz), 2.26 (s, 6H), 2.59-2.78 (m, 2H), 2.80-2.89 (m, 2H), 4.06-4.13 (m, 2H), 4.87 (dt, 1H, *J* = 8.1, 6.4 Hz), 5.70 (d, 1H, *J* = 8.1 Hz), 7.16 (d, 1H, *J* = 8.7 Hz), 7.19-7.28 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ –2.23, 10.18, 13.97, 20.575, 20.584, 41.57, 50.11, 53.57, 61.15, 121.89, 123.71, 124.60, 139.08, 141.73, 142.23, 167.85, 167.97, 170.48; IR (thin film) 3283 m, 2955 m, 1773 vs, 1734 vs, 1211 s, 1143 s cm^{-1}; HRMS calcd (M+NH_4^+) $C_{20}H_{35}N_2O_8SiS^+$ 491.1883, found 491.1894; $[\alpha]_D^{20}$ = +27.0° (*c* 1.0, CH_2Cl_2) on >98.5% *ee* material (The optical purity was assumed to be unchanged from **145**). Spectral data for **153B** (R_f = 0.27 (1:2 EtOAc/hexane)): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.04 (s, 9H), 1.08-1.16 (m, 2H), 1.24 (t, 3H, *J* = 7.1 Hz), 2.26 (s, 6H), 3.04-3.11 (m, 2H), 3.93 (s, 2H), 4.15 (q, 2H, *J* = 7.1 Hz), 4.52 (s, 2H), 7.12-7.21 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -2.02, 10.19, 14.08, 20.59, 20.63, 46.82, 50.00, 50.91, 61.43, 123.24, 123.68, 126.28, 134.44, 141.87, 142.29, 168.07, 168.15, 169.51; IR (thin film) 2955 w, 2930 w,

1773 s, 1742 s, 1211 s cm^{-1}; HRMS calcd ($M+NH_4^+$) $C_{20}H_{35}N_2O_8SiS^+$ 491.1883, found 491.1897.



*Reductive ring opening of **151**:* The general procedure for the reductive ring opening described above was followed with aziridine **151** (111 mg, 0.200 mmol, 98% *ee*) and 4.0 equiv SmI_2. The ^1H NMR spectrum of the crude reaction mixture indicated a mixture of C-N cleavage product **154A** and C-C cleavage product **154B** was obtained with a ratio of 4.3:1. Purification by silica gel chromatography (20 mm × 160 mm, 1:3 EtOAc/hexanes as eluent) gave **154A** as a yellow oil in 74% isolated yield (81.8 mg, 0.147 mmol) and **154B** as a light yellow oil in 16% isolated yield (18.2 mg, 0.0326 mmol). Spectral data for **154A** (R_f = 0.25 (1:3 EtOAc/hexane)): ^1H NMR (500 MHz, $CDCl_3$) δ – 0.11 (s, 9H), 0.75-0.90 (m, 2H), 1.18 (t, 3H, *J* = 7.2 Hz), 1.29 (s, 9H), 1.30 (s, 9H), 2.55-2.75 (m, 2H), 2.82 (d, 2H, *J* = 6.5 Hz), 4.07 (q, 2H, *J* = 7.1 Hz), 4.84 (dt, 1H, *J* = 8.0, 6.5 Hz), 5.70 (d, 1H, *J* = 8.0 Hz), 7.09 (d, 1H, *J* = 8.4 Hz), 7.13 (d, 1H, *J* = 2.0 Hz), 7.19 (dd, 1H, *J* = 8.4, 2.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ –2.25, 10.15, 13.98, 27.11, 27.13, 39.05, 39.06, 41.65, 50.04, 53.67, 61.07, 121.83, 123.66, 124.30, 138.65, 142.22, 142.64, 170.40, 175.38, 175.47; IR (thin film) 3283 m, 2977 s, 1763 vs, 1736 s, 1117 s cm^{-1}; HRMS calcd ($M+NH_4^+$) $C_{26}H_{47}N_2O_8SiS^+$ 575.2822, found 575.2842; $[\alpha]_D^{20}$ = +26.0° (*c* 1.0, CH_2Cl_2) on 98% *ee* material

(The optical purity was assumed to be unchanged from **146**). Spectral data for **154B** (R_f = 0.39 (1:3 EtOAc/hexane)): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.04 (s, 9H), 1.09-1.16 (m, 2H), 1.24 (t, 3H, *J* = 7.1 Hz), 1.31 (s, 18H), 3.04-3.13 (m, 2H), 3.92 (s, 2H), 4.15 (q, 2H, *J* = 7.1 Hz), 4.52 (s, 2H), 7.06-7.11 (m, 2H), 7.17 (dd, 1H, *J* = 8.4, 1.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ –2.01, 10.20, 14.08, 27.18, 27.21, 39.10, 39.13, 46.73, 49.95, 50.88, 61.39, 123.35, 123.68, 126.12, 133.87, 142.43, 142.75, 169.54, 175.68, 175.81; IR (thin film) 2977 s, 1761 vs, 1507 m, 1337 m, 1256 m, 1117 vs cm^{-1}; HRMS calcd (M+NH_4^+) $C_{26}H_{47}N_2O_8SiS^+$ 575.2822, found 575.2834.

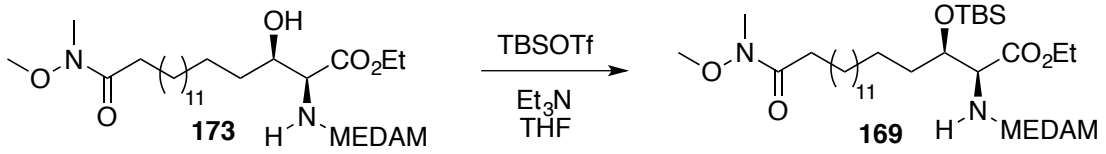


(R)-4-(1-((tert-butoxycarbonyl)amino)-3-ethoxy-3-oxopropyl)-1,2-phenylene bis(2,2-dimethylpropanoate) ***155****:* To a oven-dried 10 mL Schlenk flask equipped with a stir bar and filled with nitrogen was added **154A** (38 mg, 0.068 mmol, 1.0 equiv), 4-dimethylaminopyridine (0.9 mg, 0.007 mmol, 0.1 equiv), Et_3N (19 μL, 14 mg, 0.14 mmol, 2.0 equiv) and CH_2Cl_2 (0.32 mL). The flask was sealed and the reaction mixture was stirred for 2 h at room temperature and then at 40 °C for 15 h. After the reaction mixture was cooled to room temperature, 0.5 mL of 1 N HCl was added to the flask followed by the addition of EtOAc (5 mL). The organic layer was separated, washed with brine (0.3 mL × 2), dried with Na_2SO_4 and concentrated to give a yellow oil, which was then

dissolved in THF (0.65 mL) in a 10 mL Schlenk flask filled with nitrogen. To this solution was added TBAF (0.31 mL, 1 M in THF, 0.31 mmol) dropwise at room temperature. After the reaction mixture was stirred at room temperature under nitrogen for 1.5 h, it was concentrated by rotary evaporation and then high vacuum (0.5 mm Hg) to give a bright yellow oil. This oil was dissolved in a mixture of THF (0.2 mL) and Et_3N (0.2 mL). Then trimethylacetyl chloride (0.05 mL, 0.4 mmol) was added to the solution at room temperature. After the resulting reaction mixture was stirred for 15 minutes at room temperature under nitrogen, it was quenched by the addition of EtOH (0.1 mL) and H_2O (1.5 mL). The resulting mixture was extracted with EtOAc (2 mL × 3). The combined organic layer was dried with Na_2SO_4, filtered and concentrated to afford a yellow oil. Purification by silica gel chromatography (20 mm × 120 mm, 1:3 EtOAc/hexanes as eluent) gave **155** as a light yellow oil in 88% isolated yield (29.5 mg, 0.0598 mmol). R_f = 0.27 (1:3 EtOAc/hexane); Spectral data for **155**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.16 (t, 3H, *J* = 7.2 Hz), 1.30 (s, 9H), 1.31 (s, 9H), 1.39 (brs, 9H), 2.62-2.92 (m, 2H), 4.06 (q, 2H, *J* = 7.2 Hz), 5.06 (brs, 1H), 5.47 (d, 1H, *J* = 7.5 Hz), 7.03 (d, 1H, *J* = 1.6 Hz), 7.06 (d, 1H, *J* = 8.4 Hz), 7.14 (dd, 1H, *J* = 8.4 Hz, *J* = 1.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.04, 27.20, 27.22, 28.30, 39.10, 39.12, 40.72, 50.62, 60.86, 79.83, 121.37, 123.46, 124.04, 139.73, 141.80, 142.50, 154.89, 170.69, 175.61, 175.80; IR (thin film) 3387 m, 2978 s, 2936 m, 2874 w, 1761 vs, 1739s, 1723 s, 1713 s, 1256 s, 1119 vs cm^{-1}; HRMS calcd (MH^+) $C_{26}H_{40}NO_8^+$ 494.2754, found 494.2758; $[\alpha]_D^{20}$ = + 23.6° (*c* 1.0, CH_2Cl_2) on 98% *ee* material (The optical purity was assumed to be unchanged from **146**).

5.3 Experimental Part for Chapter 4

5.3.1 Preparation of Left Head 169

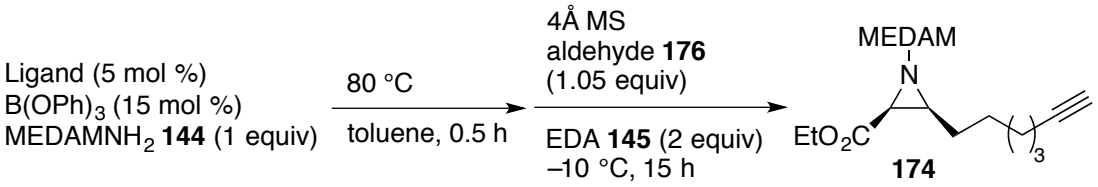


*Compound **169**:* To an oven dried 100 mL round bottom flask filled with nitrogen was added compound **173** (2.35 g, 3.36 mmol, 1.00 equiv) and dry THF (30 mL) followed by the addition of Et_3N (0.90 mL, 6.5 mmol, 1.9 equiv). After the solution was cooled to 0 °C, trimethylsilyl trifluoromethanesulfonate (TBSOTf, 0.80 mL, 3.5 mmol, 1.0 equiv) was added to the reaction flask and the resulting mixture was stirred at 0 °C under nitrogen for 1.5 h. The reaction mixture was then concerntrated by rotary evaporator. The product was purified by column chromatography (silica gel, 40 × 180 mm, hexane:EtOAc 3:1) to afford the product **169** as a colorless oil (2.22 g, 2.73 mmol) in 81% yield. R_f = 0.19 (hexane:EtOAc 3:1). Spectral data for **169**: ^{1}H NMR (500 MHz, $CDCl_3$) δ -0.10 (s, 3H), -0.02 (s, 3H), 0.81 (s, 9H), 0.95-1.43 (m, 29H), 1.55-1.65 (m, 2H), 1.90-2.00 (m, 1H), 2.22 (s, 12H), 2.39 (t, 2H, *J* = 7.4 Hz), 3.08 (d, 1H, *J* = 2.1 Hz), 3.16 (s, 3H), 3.65 (s, 3H), 3.656 (s, 3H), 3.661 (s, 3H), 3.85-3.92 (m, 1H), 4.10-4.20 (m, 2H), 4.63 (s, 1H), 7.00 (s, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -5.07, -4.29, 14.30, 16.18, 16.20, 17.95, 24.64, 25.75, 25.83, 29.44, 29.46, 29.52, 29.63, 29.66, 29.68, 29.74, 29.86, 31.88, 34.08, 59.53, 59.56, 60.41, 61.16, 61.78, 63.97, 74.48, 127.38, 128.12, 130.38, 130.51, 138.16, 140.34, 155.68, 155.85, 174.13, (one sp^2 carbon and two sp^3 carbons not located); IR (thin film) 2926(vs), 2855(s), 1740(m), 1670(m), 1458(m), 1221(m), 1152(m), 1017(m) cm^{-1}; HRMS

calcd for $C_{47}H_{81}N_2O_7Si$ (M+H, ESI^+) *m/z* 813.5813, meas 813.5804; $[\alpha]_D^{20}$ = –15.5° (*c* 1.0, CH_2Cl_2) on 95% *ee* material.

5.3.2 Procedures for Catalytic Azymmetric Aziridination of Aldehyde 176 (Table 4.1)

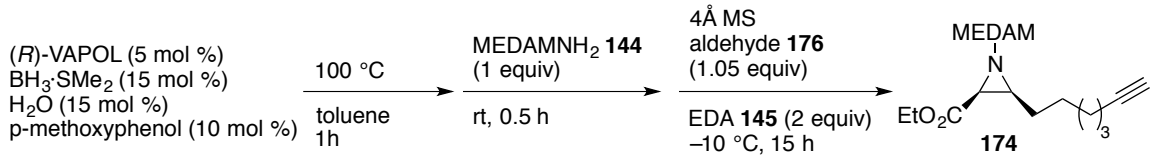
Method A:



To a 50 mL flame-dried Schlenck flask equipped with a stir bar and filled with N_2 was added (*R*)-VAPOL (135 mg, 0.251 mmol), $B(OPh)_3$ (218 mg, 0.751 mmol) and amine **144** (1.5 g, 5.0 mmol). Dry toluene (10 mL) was added under an N_2 atmosphere to dissolve the reagents and the flask was sealed. After the reaction mixture was stirred at 80 °C for 0.5 h, it was first cooled to rt and 4Å Molecular Sieves (1.5 g, freshly flame-dried) were added to the flask. After the reaction mixture was cooled to – 10 °C, the aldehyde **176**[64] (652 mg, 5.25 mmol) was added followed by the addition of ethyl diazoacetate (EDA) **145** (1.3 mL, 10 mmol). The resulting mixture was stirred for 16 h at – 10 °C. The reaction was dilluted by addition of hexane (15 mL). The reaction mixture was then filtered through a Celite pad to a 100 mL round bottom flask. The reaction flask was rinsed with EtOAc (6 mL × 3) and the rinse was filtered through the same Celite pad. The resulting solution was then concentrated in vacuo followed by exposure to high vacuum (0.05 mm Hg) for 1 h to afford the crude aziridine **174** as a viscous yellow oil. The product was purified by column chromatography (silica

gel, 40 × 210 mm, hexane:EtOAc 9:1) to afford the pure product **174** as a light yellow oil (0.600 g, 1.22 mmol, 24%) and a mixture of product **174** and PhOH (1.8 g, **174** : PhOH = 1 : 0.43). The optical purity of **174** was determined to be 95% *ee* by HPLC analysis (Chiralcel OD-H column, 99:1 hexane/2-propanol at 222 nm, flow-rate 0.7 mL/min); Retention times: R_t = 5.70 min (minor enantiomer, *ent*-**174**) and R_t = 7.15 min (major enantiomer, **174**). R_f = 0.34 (hexane:EtOAc 3:1). Spectral data for **174**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.93-1.04 (m, 1H), 1.06-1.16 (m, 1H), 1.17-1.28 (m, 5H), 1.29-1.38 (m, 2H), 1.40-1.55 (m, 2H), 1.88 (t, 1H, *J* = 2.6 Hz), 1.94 (q, 1H, *J* = 6.6 Hz), 2.04 (td, 2H, *J* = 7.2 Hz, *J* = 2.2 Hz), 2.19 (d, 1H, *J* = 6.8 Hz), 2.215 (s, 6H), 2.220 (s, 6H), 3.38 (s, 1H), 3.657 (s, 3H), 3.665 (s, 3H), 4.10-4.25 (m, 2H), 6.99 (s, 2H), 7.07 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.35, 16.14, 16.18, 18.16, 26.69, 27.72, 28.15, 28.38, 43.56, 46.77, 59.59, 59.62, 60.72, 68.12, 77.33, 84.49, 127.32, 128.10, 130.47, 130.50, 137.68, 138.14, 155.76, 156.12, 169.63; IR (thin film) 3289(w), 2934(s), 2861(m), 1744(s), 1719(m), 1483(s), 1221(s), 1184(s), 1144(m), 1015(m) cm^{-1}; HRMS calcd for $C_{31}H_{42}NO_4$ (M+H, ESI$^+$) *m/z* 492.3114, meas 492.3108; $[\alpha]_D^{20}$ = –85.5° (*c* 1.0, CH_2Cl_2) on 95% *ee* material.

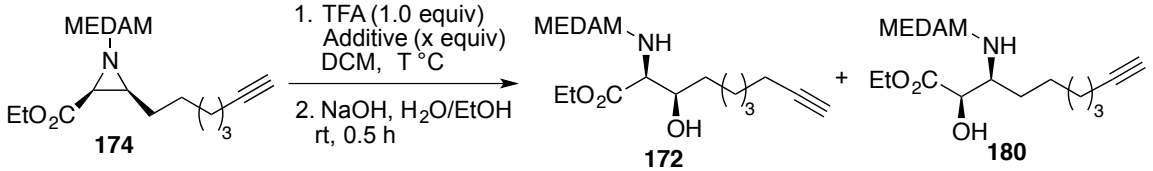
Method B:



A 50 mL Schlenk flask equipped with a stir bar was flame dried, cooled to rt under N_2 and charged with (*R*)-VAPOL (270 mg, 0.501 mmol), p-

methoxylphenol (125 mg, 1.01 mmol), dry toluene (10 mL), H_2O (27 mg, 27.0 µL, 1.50 mmol), and $BH_3 \cdot SMe_2$ (2M, 0.75 mL, 1.5 mmol). The Teflon valve on the Schlenk flask was then closed, and the mixture heated at 100 °C for 1 h. After the flask was cooled to rt, amine **144** (10 mmol, 1.0 equiv) and dry toluene (10 mL) was added to the mixture under a N_2 stream and the resulting mixture was stirred at rt for 30 min. After the mixture was cooled to – 10 °C, 4Å Molecular Sieves (3.0 g, freshly flame-dried) and the aldehyde **176** (1.30 g, 10.5 mmol) were added to the flask followed by the addition of ethyl diazoacetate (EDA) **145** (85%, 2.6 mL, 20 mmol). The Teflon valve was then closed, and the resulting mixture was stirred at room temperature for 15 h. Upon completion, the reaction was dilluted by addition of hexane (25 mL). The reaction mixture was then filtered through a Celite pad to a 250 mL round bottom flask. The reaction flask was rinsed with EtOAc (10 mL × 3) and the rinse was filtered through the same Celite pad. The resulting solution was then concentrated in vacuo followed by exposure to high vacuum (0.05 mm Hg) for 1 h to afford the crude aziridine **174** as a viscous yellow oil. The product was purified by column chromatography (silica gel, 40 × 250 mm, hexane:EtOAc 9:1) to afford compound **174** as a light yellow oil (4.5 g, 9.2 mmol, 92%, 95% *ee*).

5.3.3 Procedure for Ring Opening Reaction of Aziridine 174 (Table 4.1, illustrated for entry 5)

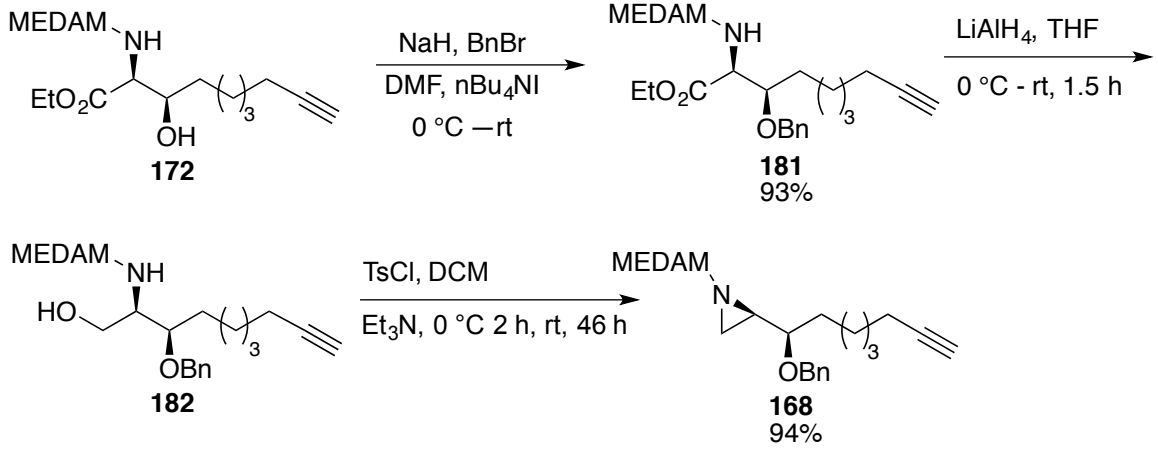


To an oven-dried 100 mL Schlenk flask flask filled with nitrogen was added the aziridine **174** (4.24 g, 8.63 mmol, 1.00 equiv), dry DCM (40 mL) and trifluoroacetic acid (TFA) (0.69 mL, 9.01 mmol, 1.04 equiv). The Teflon valve on the Schlenk flask was then closed, and the mixture was stirred at 40 °C for 15 h. Then the reaction mixture was concentrated by rotary evaporator. To the residue was added a solution of NaOH (345 mg, 8.63 mmol, 1.00 equiv) in EtOH/H_2O (v/v 15:2). After the resulting mixture was stirred at rt for 30 min, it was concentrated under reduced pressure and dissolved in a mixture of H_2O (5 mL) and ethyl acetate (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (10 mL x 2). The combined organic layer was dried with Na_2SO_4, filtered and concentrated. The crude ^{1}H NMR showed that the ratio of the isomers **172** and **180** is 4.5:1. Purification by column chromatography (35 × 180 mm, hexanes:EtOAc 4:1) gave the desired product **172** as a colorless oil (3.08 g, 6.04 mmol) in 70% yield, R_f = 0.20 (hexane:EtOAc 3:1), and its isomer **180** as a colorless oil (440 mg, 0.863 mmol) in 10 yield, R_f = 0.32 (hexane:EtOAc 3:1). Spectral data for **172**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.21-1.31 (m, 1H), 1.26 (t, 3H, *J* = 7.1 Hz), 1.33-1.55 (m, 7H), 1.91 (brt, 1H, *J* = 2.6 Hz), 2.15 (td, 2H, *J* = 7.0 Hz, 2.6 Hz), 2.225 (s, 6H), 2.233 (s, 6H), 3.04 (d, 1H, *J* = 6.1 Hz), 3.11 (brs, 1H), 3.57-3.65 (m, 1H), 3.65 (s, 3H), 3.67 (s, 3H), 4.17 (q, 2H, *J* = 7.1 Hz), 4.56 (s, 1H), 6.94 (s, 2H), 6.98 (s, 2H), one proton not located (N-H or O-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.23, 16.10, 16.19, 18.23, 25.01, 28.28, 28.58, 33.51, 59.45, 59.48, 60.84, 63.58, 64.69, 68.14, 72.18, 84.43, 127.30, 127.73, 130.62, 130.70, 137.22, 139.10, 155.91, 155.95, 173.91; IR (thin

film) 3484(w), 3291(w), 2938(vs), 2861(m), 1730(s), 1483(s), 1221(s), 1142(s), 1017(s) cm^{-1}; HRMS calcd for $C_{31}H_{44}NO_5$ (M+H, ESI^+) *m/z* 510.3219, meas 510.3206; $[\alpha]_D^{20}$ = –28.3° (*c* 1.0, CH_2Cl_2) on 95% *ee* material. Spectral data for **180**: ^1H NMR (500 MHz, $CDCl_3$) δ 1.13 (t, 3H, *J* = 7.1 Hz), 1.20-1.50 (m, 7H), 1.60-1.72 (m, 1H), 1.91 (brt, 1H, *J* = 2.5 Hz), 2.12 (td, 2H, *J* = 6.8 Hz, 2.5 Hz), 2.24 (2s, 12H), 3.677 (s, 3H), 3.682 (s, 3H), 3.88-4.01 (m, 2H), 4.07-4.16 (m, 1H), 4.60 (d, 1H, *J* = 9.0 Hz), 5.19 (s, 1H), 6.85 (s, 2H), 6.87 (s, 2H), two protons not located (N-H and O-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.80, 16.16, 16.19, 18.16, 24.67, 28.03, 28.31, 30.92, 54.63, 59.48, 59.57, 61.91, 68.32, 75.82, 81.08, 84.22, 127.10, 127.52, 130.67, 130.76, 136.36, 136.90, 156.29, 156.46, 169.20; IR (thin film) 3434(w), 3291(w), 2940(s), 2863(w), 1734(vs), 1221(s), 1171(s) 1017(m) cm^{-1}; HRMS calcd for $C_{31}H_{44}NO_5$ (M+H, ESI^+) *m/z* 510.3219, meas 510.3209; $[\alpha]_D^{20}$ = – 24.2° (*c* 1.0, CH_2Cl_2) on 95% *ee* material.

The reaction carried out at rt afforded the product **180** in 83% isolated yield. The diastereoselectivity (**172**:**180**) is 17:1 indicated by ^1H NMR spectrum.

5.3.4 Procedure for Converting Compound 172 to Left Head 168



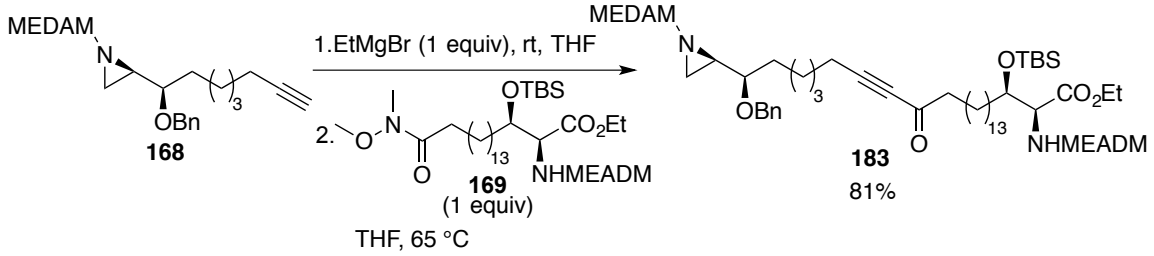
*Compound **181***: To a flame-dried 100 mL round bottom flask filled with nitrogen was added compound **172** (2.27 g, 4.44 mmol, 1.00 equiv), dry DMF (13 mL), tetra-*n*-butylammonium iodide (*n*Bu_4NI) (333 mg, 0.900 mmol, 0.200 equiv) and benzyl bromide (BnBr) (0.90 mL, 7.6 mmol, 1.7 equiv). After the mixture was stirred at 0 °C for 10 min, NaH (198 mg, 60% dispersion in mineral oil, 4.89 mmol, 1.10 equiv) was added to the flask. The resulting suspension was stirred at 0 °C for 2 h which became viscous gel-like mixture. Then it was warmed up to rt and stirred at rt for 15 h. After the reaction mixture was cooled to 0 °C, H_2O (50 mL) was slowly added to the mixture. It was then extracted with DCM (50 mL x 3). The combined organic layer was dried with Na_2SO_4, filtered and concentrated. Purification by column chromatography (35 × 200 mm, hexanes:EtOAc 9:1) gave the desired product **181** as a colorless oil (2.48 g, 4.13 mmol) in 93% yield. R_f = 0.29 (hexane:EtOAc 9:1). Spectral data for **181**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.05-1.31 (m, 5H), 1.35-1.53 (m, 4H), 1.67-1.88 (m, 2H), 1.93 (t, 1H, *J* = 2.6 Hz), 2.16 (td, 2H, *J* = 7.0 Hz, 2.6 Hz), 2.223 (s, 6H), 2.225 (s, 6H), 2.29-2.39 (m, 1H), 3.18 (d, 1H, *J* = 2.5 Hz), 3.64-3.70 (m, 1H), 3.65 (s, 3H), 3.67 (s, 3H), 4.06-4.19 (m, 2H), 4.41 (d, 1H, *J* = 11.6 Hz), 4.47 (d, 1H, *J* = 11.6 Hz), 4.63 (s, 1H), 7.026 (s, 2H), 7.034 (s, 2H), 7.21-7.32 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.29, 16.19, 16.27, 18.36, 25.39, 28.42, 28.83, 30.79, 59.54, 59.58, 60.63, 61.00, 64.63, 68.23, 72.03, 80.66, 84.51, 127.44, 127.57, 127.84, 127.95, 128.23, 130.49, 130.57, 138.17, 138.27, 139.98, 155.82, 155.89, 174.07; IR (thin film) 3293(w), 2938(s), 2861(m), 1736(s), 1483(m) 1456(m), 1221(m), 1144(m),

1017(m) cm^{-1}; HRMS calcd for $C_{38}H_{50}NO_5$ (M+H, ESI^+) *m/z* 600.3689, meas 600.3696; $[\alpha]_D^{20}$ = – 24.6° (*c* 1.0, CH_2Cl_2) on 95% *ee* material.

*Compound **168***: To an ovendried 25 mL round bottom flask filled with nitrogen was added $LiAlH_4$ (115 mg, 3.02 mmol, 1.60 equiv) and THF (7 mL). After the suspension was cooled to 0 °C, a solution of compound **181** (1.13 g, 1.89 mmol, 1.00 equiv) in THF (5 mL) was added dropwise into the reaction flask at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and then rt for 1 h. It was quenched by addition of H_2O (0.115 mL), followed by addition of aq NaOH (15%, 0.115 mL) and then another two portions of H_2O (0.35 mL x 2). After the mixture was vigorously stirred at rt for 30 min, it became a white emulsion, which was filtered through a Celite pad. The Celite pad was washed with ethyl acetate several times until TLC indicated there was no product in the rinse. The combined organic solution was concentrated to give the crude product **182** as an opaque oil which was then dissolved in DCM (9.5 mL) in an oven-dried 50 mL round bottom flask. After the solution was cooled to 0 °C, Et_3N (290 μL, 2.08 mmol, 1.10 equiv) and tosyl chloride (396 mg, 2.08 mmol, 1.10 equiv) were added to the reaction flask. The reaction mixture was stirred at 0 °C for 5 h and then rt for 24 h, which was then added another portion of Et_3N (1.77 mL, 12.7 mmol, 6.72 equiv) and tosyl chloride (540 mg, 2.83 mmol, 1.50 equiv). After the mixture was stirred for another 24 h at rt, it was quenched by the addition of $NaHCO_3$ (28 mL). The organic layer was separated and the aqueous layer was extracted with DCM (30 mL x 3). The combined organic layer was dried with Na_2SO_4, filtered and concentrated. Purification by column chromatography (35 ×

180 mm, hexanes:EtOAc 9:1) gave the desired product **168** as a colorless oil (956 mg, 1.77 mmol) in 94% yield. R_f = 0.24 (hexane:EtOAc 9:1). Spectral data for **168**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.20-1.58 (m, 9H), 1.68 (d, 1H, *J* = 3.6 Hz), 1.79 (td, 1H, *J* = 6.8 Hz, 3.5 Hz), 1.90 (t, 1H, *J* = 2.6 Hz), 2.12 (td, 2H, *J* = 7.2 Hz, 2.7 Hz), 2.17 (s, 6H), 2.25 (s, 6H), 3.00-3.06 (m, 1H), 3.25 (s, 1H), 3.53 (s, 3H), 3.68 (s, 3H), 4.08 (d, 1H, *J* = 12.0 Hz), 4.12 (d, 1H, *J* = 12.0 Hz), 6.99-7.05 (m, 4H), 7.07 (s, 2H), 7.15-7.25 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.17, 16.20, 16.22, 16.24, 18.31, 25.10, 28.35, 28.63, 30.58, 33.26, 44.58, 59.41, 59.45, 59.57, 59.62, 68.10, 70.91, 78.21, 78.22, 80.69, 84.64, 127.06, 127.34, 127.40, 128.01, 128.48, 130.42, 130.54, 138.55, 138.64, 139.15, 155.63, 156.15; IR (thin film) 3293(w), 2938(vs), 2861(m), 1483(s), 1221(s), 1144(s), 1017(s) cm^{-1}; HRMS calcd for $C_{36}H_{46}NO_3$ (M+H, ESI^+) *m/z* 540.3478, meas 540.3484; $[\alpha]_D^{20}$ = –16.7° (*c* 1.0, CH_2Cl_2) on 95% *ee* material.

5.3.5 Procedure for Coupling Reaction of Left Head 168 and Right Head 169

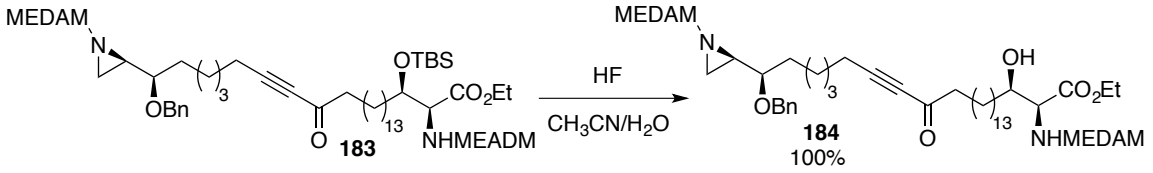


*Compound **183***: The reaction was carried out with an adaptation of a procedure reported for a similar transformation.[99] To a solution of compound **168** (236 mg, 0.437 mmol, 1.00 equiv) in THF (1.2 mL) was added ethylmagnesium bromide (3 M in diethyl ether, 145 μL, 0.435 mmol, 1.00 equiv) dropwise at 0 °C. After this solution was stirred at 0 °C for 20 min, it was transferred via a syringe

to a solution of compound **169** (355 mg, 0.437 mmol, 1.00 equiv) in THF (0.65 mL) at 0 °C. The mixture was then heated up to 65 °C and stirred for 5 h. After it was cooled to rt, the mixture was treated with aq NaH_2PO_4 (1 M, 2.2 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (4 mL x 3). The combined organic layer was dried with Na_2SO_4, filtered and concentrated. Purification by column chromatography (25 × 160 mm, hexanes:EtOAc 5:1) gave the desired product **183** as a colorless oil (460 mg, 0.356 mmol) in 81% yield. R_f = 0.20 (hexane:EtOAc 5:1). Spectral data for **183**: ^{1}H NMR (500 MHz, $CDCl_3$) δ -0.09 (s, 3H), 0.00 (s, 3H), 0.82 (s, 9H), 0.98-1.67 (m, 38H), 1.69 (d, 1H, *J* = 3.7 Hz), 1.79 (td, 1H, *J* = 6.8 Hz, 3.7 Hz), 1.92-2.02 (m, 1H), 2.17 (s, 6H), 2.23 (2s, 12H), 2.26 (s, 6H), 2.29 (t, 2H, *J* = 7.2 Hz), 2.49 (t, 2H, *J* = 7.2 Hz), 3.00-3.07 (m, 1H), 3.09 (s, 1H), 3.26 (s, 1H), 3.53 (s, 3H), 3.66 (s, 3H), 3.67 (s, 3H), 3.69 (s, 3H), 3.87-3.93 (m, 1H), 4.09 (s, 2H), 4.12-4.20 (m, 2H), 4.65 (s, 1H), 6.99-7.05 (m, 8H), 7.08 (s, 2H), 7.16-7.25 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -5.08, -4.29, 14.29, 16.17, 16.19, 16.21, 17.94, 18.83, 24.06, 25.02, 25.74, 25.82, 27.61, 28.74, 28.96, 29.35, 29.46, 29.60, 29.65, 29.67, 29.73, 29.86, 30.56, 33.19, 34.07, 44.49, 45.51, 59.39, 59.52, 59.53, 59.56, 60.40, 61.76, 63.95, 70.89, 74.47, 78.20, 80.60, 80.88, 93.96, 127.07, 127.31, 127.36, 127.37, 127.99, 128.10, 128.47, 130.36, 130.40, 130.50, 130.52, 138.15, 138.52, 138.58, 139.10, 140.33, 155.63, 155.67, 155.83, 156.14, 174.12, 188.49, (2 sp^3 carbons not located); IR (thin film) 2928(s), 2855(s), 2213(w), 1740(m), 1674(m), 1483(m), 1221(m), 1144(m), 1017(m) cm^{-1}; HRMS calcd for

$C_{81}H_{119}N_2O_9Si$ (M+H, ESI^+) *m/z* 1291.8685, meas 1291.8682; $[\alpha]_D^{20}$ = – 16.8° (*c* 1.0, CH_2Cl_2).

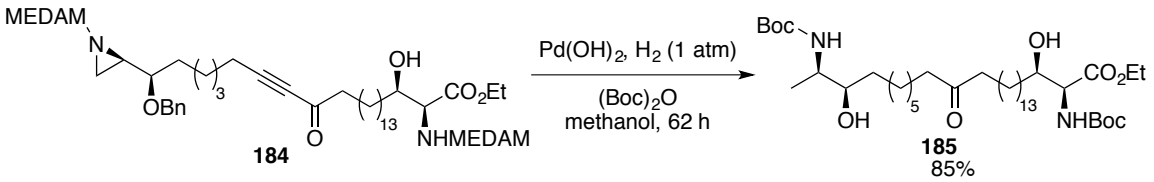
5.3.6 Procedure for Removal of TBS Group in 183



*Compound **184***: The reaction was carried out with an adaptation of a procedure reported for a similar transformation.[100] To a 50 mL Teflon round bottom flask was added a solution of compound **183** (180 mg, 0.139 mmol) in acetonitrile (18 mL) followed by the addition of aqueous HF (25%, 0.73 mL). After the reaction mixture was stirred at rt for 5 h, it was quenched with careful addition of aq $NaHCO_3$ (30 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (40 mL x 3). The combined organic layer was dried with Na_2SO_4, filtered and concentrated. Purification by column chromatography (25 × 160 mm, hexanes:EtOAc 3:1) gave the desired product **184** as a colorless oil (164 mg, 0.139 mmol) in 100% yield. R_f = 0.18 (hexane:EtOAc 3:1). Spectral data for **184**: ^1H NMR (500 MHz, $CDCl_3$) δ 1.18-1.66 (m, 39H), 1.67 (d, 1H, *J* = 3.5 Hz), 1.78 (td, 1H, *J* = 6.8 Hz, 3.5 Hz), 2.16 (s, 6H), 2.22 (s, 6H), 2.23(s, 6H), 2.25 (s, 6H), 2.28 (t, 2H, *J* = 7.1 Hz), 2.48 (t, 2H, *J* = 7.5 Hz), 2.97-3.09 (m, 3H), 3.25 (s, 1H), 3.52 (s, 3H), 3.57-3.63 (m, 1H), 3.65 (s, 3H), 3.67 (s, 3H), 3.68 (s, 3H), 4.08 (s, 2H), 4.17 (q, 2H, *J* = 7.2 Hz), 4.55 (s, 1H), 6.94 (s, 2H), 6.97 (s, 2H), 6.99-7.04 (m, 4H), 7.06 (s, 2H), 7.15-7.24 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.33, 16.19, 16.20, 16.24, 16.28, 18.87,

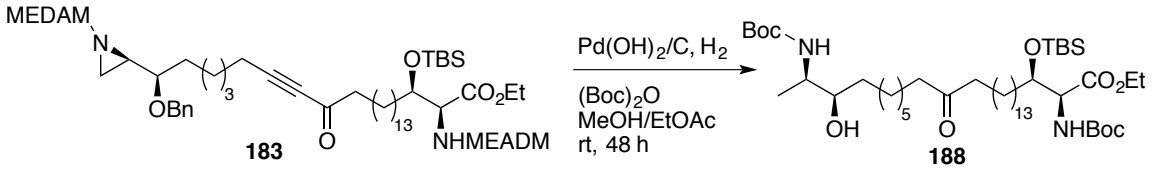
24.10, 25.06, 25.63, 27.65, 28.78, 28.99, 29.36, 29.47, 29.60, 29.62, 29.63, 29.64, 29.67, 30.59, 33.22, 33.76, 44.52, 45.54, 59.44, 59.58, 59.59, 59.61, 60.92, 63.69, 64.75, 70.92, 72.41, 76.75, 78.23, 80.64, 80.91, 94.02, 127.10, 127.34, 127.39, 127.41, 127.81, 128.03, 128.50, 130.44, 130.56, 130.71, 130.81, 137.29, 138.55, 138.61, 139.13, 139.21, 155.66, 155.99, 156.03, 156.18, 174.08, 188.56 (one sp^3 carbons not located); IR (thin film) 3474 (vw), 2926(vs), 2855(s), 1734(m), 1670(m), 1483(m), 1221(s) cm^{-1}; HRMS calcd for $C_{75}H_{105}N_2O_9$ (M+H, ESI^+) *m/z* 1177.7820, meas 1177.7784; $[\alpha]_D^{20}$ = – 14.3° (*c* 1.0, CH_2Cl_2).

5.3.7 Preparation of 185 and 188 by Hydrogenation



*Compound **185***: To a oven-dried 50 mL round bottom flask equipped with a stir bar and filled with nitrogen was added compound **184** (77 mg, 0.065 mmol, 1.0 equiv), $Pd(OH)_2$ ($Pd(OH)_2$ on carbon 20%, moisture ≤ 50%, 28.0 mg, 0.020 mmol, 0.30 equiv), di-tert-butyl dicarbonate (72 mg, 0.33 mmol, 5.0 equiv) and methanol (6.5 mL). The flask was sealed with a rubber septum and a needle connected to a vacuum line was used to apply vacuum in the flask through the septum. The vacuum was applied for a few seconds with vigorous stirring of the reaction mixture. Then the vacuum was stopped and a hydrogen balloon was connected to the flask by a needle through the septum. This process was repeated four times. Then the suspension was stirred at room temperature under hydrogen for 62 hours and then filtered through a pad of Celite. The filter cake

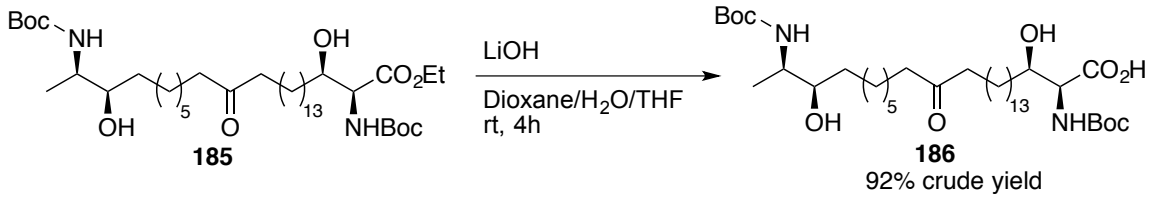
was washed with EtOAc (5 mL × 3). The combined filtrate was concentrated to give a colorless oil. Purification by column chromatography on silica gel (20 mm × 160 mm, hexanes/EtOAc 4:2.5) gave compound **185** as a colorless oil (40.3 mg, 0.0553 mmol, 85%). R_f = 0.30 (1:1.5 EtOAc/hexane); Spectral data for **185**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.13 (d, 3H, *J* = 6.8 Hz), 1.18-1.34 (m, 31H), 1.35-1.57 (m, 28H), 2.21 (brs, 2H), 2.34 (t, 4H, *J* = 7.3 Hz), 3.39-3.48 (m, 1H), 3.60 (brs, 1H), 3.99-4.09 (m, 1H), 4.19 (q, 2H, *J* = 7.1 Hz), 4.25 (d, 1H, *J* = 9.0 Hz), 4.59-4.80 (m, 1H), 5.30 (d, 1H, *J* = 9.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.08, 18.21, 23.70, 23.78, 25.47, 25.53, 28.21, 28.31, 29.07, 29.15, 29.22, 29.30, 29.32, 29.35, 29.39, 29.40, 29.48, 29.52, 33.72, 33.99, 42.67, 42.73, 50.09, 57.59, 61.40, 71.97, 74.67, 79.14, 79.75, 156.05, 156.16, 171.75, 211.82. (three sp^3 carbons not located); IR (thin film) 3440(m, br), 2928(s), 2855(s), 1717(s), 1507(m), 1368(m), 1167(m) cm^{-1}; HRMS calcd for $C_{40}H_{77}N_2O_9$ (M+H, ESI^+) *m/z* 729.5629, meas 729.5626; $[\alpha]_D^{20}$ = + 3.9° (*c* 1.0, CH_2Cl_2).



*Compound **188***: The reaction was carried out according to the procedure described above for hydrogenation of **184** with compound **183** (527 mg, 0.408 mmol, 1.00 equiv), $Pd(OH)_2$ ($Pd(OH)_2$ on carbon 20%, moisture ≤ 50%, 115 mg, 0.0819 mmol, 0.200 equiv), di-tert-butyl dicarbonate (356 mg, 1.63 mmol, 4.0 equiv), methanol (25 mL) and ethyl acetate (15 mL). Purification by column chromatography (30 × 180 mm, hexanes:EtOAc 3:1) gave the desired product

188 as a colorless oil (300 mg, 0.356 mmol) in 87% yield. R_f = 0.45 (hexane:EtOAc 3:1). Spectral data for **188**: ^{1}H NMR (500 MHz, $CDCl_3$) δ –0.10 (s, 3H), –0.03 (s, 3H), 0.77 (s, 9H), 1.09 (d, 3H, *J* = 6.8 Hz), 1.12-1.27 (m, 32H), 1.32-1.54 (m, 27H), 2.30 (t, 4H, *J* = 7.4 Hz), 2.64 (brs, 1H), 3.39 (brs, 1H), 3.56 (brs, 1H), 4.00-4.17 (m, 3H), 4.21 (d, 1H, *J* = 9.9 Hz), 4.73-4.85 (m, 1H), 5.06 (d, 1H, *J* = 9.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ -5.24, -4.35, 13.98, 17.80, 18.28, 23.66, 23.75, 25.22, 25.44, 25.54, 25.61, 28.13, 28.21, 28.27, 29.03, 29.14, 29.18, 29.29, 29.31, 29.36, 29.41, 29.43, 29.49, 29.52, 34.05, 34.43, 42.63, 42.70, 50.01, 56.72, 61.13, 72.89, 74.58, 78.98, 79.56, 156.03, 156.07, 171.61, 211.64; IR (thin film) 3447(w), 2928(s), 2855(m), 1717(s), 1499(m), 1169(m) cm^{-1}; HRMS calcd for $C_{46}H_{91}N_2O_9Si$ (M+H, ESI$^+$) *m/z* 843.6494, meas 843.6503; $[\alpha]_D^{20}$ = – 1.6° (*c* 1.0, CH_2Cl_2).

5.3.8 Preparation of 186 by Hydrolysis of 185



*Compound **186***: To a 10 mL round bottom flask equipped with a stir bar was added compound **185** (40 mg, 0.055 mmol, 1.0 equiv), a mixture of dioxane/THF/H_2O (2:2:1, 0.5 mL) and a solution of LiOH (1.4 M, 0.10 mL, 0.14 mmol, 2.5 equiv). After the mixture was stirred at rt for 4 h, it was acidified with aq HCl (0.5 M) to pH ~5 and extracted with ethyl acetate (1 mL x 3). The combined organic layer was dried with Na_2SO_4, filtered and concentrated to give the cude product **186** as a semi-solid in 92% yield. Spectral data for **186**: ^{1}H

NMR (500 MHz, $CDCl_3$) δ 1.13 (d, 3H, *J* = 6.9 Hz), 1.16-1.33 (m, 30H), 1.41 (brs, 20H), 1.46-1.57 (m, 6H), 2.35 (t, 4H, *J* = 7.5 Hz), 3.44 (brs, 1H), 3.60 (brs, 1H), 4.03-4.19 (m, 1H), 4.26 (d, 1H, *J* = 8.5 Hz), 4.80 (brs, 1H), 5.24 (brs, 2H), 5.60 (d, 1H, *J* = 8.5 Hz), one proton not located (COOH); Unfortunately, a clean ^{13}C NMR could not be obtained; IR (thin film) 3370(m, br), 2926(s), 2855(m), 1715(s), 1169(m) cm^{-1}; HRMS calcd for $C_{38}H_{73}N_2O_9$ (M+H, ESI^+) *m/z* 701.5316, meas 701.5325; $[\alpha]_D^{20}$ = + 6.1° (*c* 1.0, CH_2Cl_2).

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