Université de Montréal

Enantiopure 3-Substituted Piperidines via an Aziridinium Ion Ring Expansion

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Cette thèse intitulée :

Enantiopure 3-Substituted Piperidines via an Aziridinium Ion Ring Expansion

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a été évaluée par un jury composé des personnes suivantes :

Prof. Hélène Lebel, président-rapporteur
Prof. André B. Charette, directeur de recherche
Prof. Yvan Guindon, membre du jury

Résumé

Ce mémoire décrit le développement d'une nouvelle méthodologie d'expansion de cycle irréversible à partir de *N*-alkyl-3,4-déhydroprolinols pour former des *N*-alkyl tétrahydropyridines 3-substituées en passant par un intermédiaire aziridinium bicyclique. Cette méthode permet l'introduction d'un vaste éventail de substituants à la position 3 et tolère bien la présence de groupements aux positions 2 et 6, donnant accès à des pipéridines mono-, di- ou trisubstituées avec un excellent diastéréocontrôle. De plus, il est démontré que l'information stéréogénique du 3,4-déhydroprolinol de départ est totalement transférée vers le produit tétrahydropyridine. Additionnellement, une méthodologie fut dévelopée pour la préparation des produits de départ 3,4-déhydroprolinols en forme énantiopure, avec ou sans substituants aux positions 2 et 5, avec un très bon stéréocontrôle.
Le premier chapitre présente un résumé de la littérature sur le sujet, incluant un bref survol des méthodes existantes pour la synthèse de pipéridines 3-substituées, ainsi qu'une vue d'ensemble de la chimie des aziridiniums. L'hypothèse originale ainsi que le raisonnement pour l'entreprise de ce projet y sont également inclus.

Le second chapitre traite de la synthèse des *N*-alkyl-3,4-déhydroprolinols utilisés comme produits de départ pour l'expansion de cycle vers les tétrahydropyridines 3-substituées, incluant deux routes synthétiques différentes pour leur formation. Le premier chemin synthétique utilise la L-*trans*-4-hydroxyproline comme produit de départ, tandis que le deuxième est basé sur une modification de la réaction de Petasis-Mannich suivie par une métathèse de fermeture de cycle, facilitant l'accès aux précurseurs pour l'expansion de cycle.

Le troisième chapitre présente une preuve de concept de la viabilité du projet ainsi que l'optimisation des conditions réactionnelles pour l'expansion de cycle. De plus, il y est démontré que l'information stéréogénique des produits de départs est transférée vers les produits.

Au quatrième chapitre, l'étendue des composés pouvant être synthétisés par cette méthodologie est présentée, ainsi qu'une hypothèse mécanistique expliquant les stéréochimies relatives observées. Une synthèse énantiosélective efficace et divergente de tétrahydropyridines 2,3-disubstituées est également documentée, où les deux substituants furent introduits à partir d'un intermédiaire commun en 3 étapes.

Mots-clés : Pipéridine
Tétrahydropyridine
Aziridinium
Synthèse énantiosélective
Synthèse diastereoselective

Abstract

This thesis describes the development of a novel methodology of irreversible ring expansion from *N*-alkyl-3,4-dehydroprolinols to *N*-alkyl-3-substituted tetrahydropyridines through a bicyclic aziridinium ion intermediate. This method allows a wide variety of substituents at the 3-position, and also permits substitution at the 2- and 6-positions of the tetrahydropyridine giving mono-, di- or tri-substituted piperidines with excellent diasterocontrol. Complete transfer of the stereogenic information of the 3,4-dehydroprolinol to the tetrahydropyridine product is demonstrated. Also, a methodology was developed to prepare the 3,4-dehydroprolinol starting materials in enantiopure form, with the possibility of substitution at the 2- and 5-positions with excellent diasterocontrol.

The first chapter presents the literature background, including a brief summary of methodologies for the synthesis of 3-substituted piperidines, and an overview of aziridinium ion chemistry. Also presented is the original hypothesis of the project, and our reasoning for undertaking this project.

The second chapter describes the synthesis of *N*-alkyl-3,4-dehydroprolinols used as precursors for the ring expansion to 3-substituted tetrahydropyridines, including two different synthetic routes. The first route route converts L-*trans*-4-hydroxyproline to enantioenriched *N*-benzyl-3,4-dehydroprolinol in 6 steps. The second synthetic route was developed using a variant of the Petasis-Mannich reaction and a ring closing metathesis, making the precursors more readily available and simple to synthesize.

The third chapter presents the proof of concept of the viability of the project and optimization studies. Moreover, the transfer of stereogenic information to the resulting product is demonstrated.

The fourth chapter demonstrates the broad scope of the ring expansion and mechanistic insight is given based on the relative configuration of the products. An expedient divergent enantioselective synthesis of a 2,3-disubstituted tetrahydropyridine is also shown, with both substituents being chosen from a common intermediate in 3 steps.

Keywords : Piperidine
Tetrahydropyridine
Aziridinium
Enantioselective synthesis
Diastereoselective synthesis

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List of Schemes

List of abbreviations

α-EWG	α-Electron Withdrawing Group
Ac	acetyl
aliph.	aliphatic
aq.	aqueous
Ar	aryl
arom.	aromatic
Boc	*tert*-butoxycarbonyl
br.	broad
Bu	butyl
ca	*circa,* approximately
cat.	catalytic
conc.	concentrated
COSY	correlation spectroscopy
d	day(s)
δ	chemical shift
DCM	dichloromethane
DEPT	distortionless enhancement by polarization transfer
DMF	dimethyl formamide
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
EDG	electron-donating group
ee	enantiomeric excess
Et	ethyl
equiv	equivalent(s)
EWG	electron-withdrawing group
FTIR	Fourier transform infrared spectroscopy
h	hour(s)

HMQC	heteronuclear multiple quantum coherence
HRMS	high resolution mass spectrometry
Hz	Hertz
i	iso
J	coupling constant
LA	Lewis acid
LG	leaving group
Lit.	literature
M	molar, mol/L
mCPBA	*m*-chloroperbenzoic acid
Me	methyl
min	minute(s)
mp	melting point
MS	molecular sieves
NMR	nuclear magnetic resonance
Ph	phenyl
ppm	parts per million
PM	Petasis-Mannich Reaction
Pr	propyl
quat.	quaternary
RCM	Ring Closing Metathesis
R_f	retention factor
rt	room temperature
sat.	saturated
SFC	supercritical fluid chromatography
temp	temperature
tert, t	tertiary
THF	tetrahydrofuran
TLC	thin layer chromatography
xs.	excess

Acknowledgements

I would like to thank my supervisor, Professor André B. Charette for giving me the opportunity to work in his successful and gifted research group, for his support, and advice. His outstanding dedication to teaching, his knowledge of chemistry and an enthusiasm for chemistry have made my past two years in the group quite enlightening. I am deeply grateful for his confidence, for the freedom and trust to work independently despite the many setbacks that occurred during this project, and for the excellent academic support that I received, anytime I needed it.

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Finally, I would like to thank the special people in my life for their love and support: my family for their encouragement, and most of all my wife Ying-tzy (Sharon) Lin who stood by my side and kept me going with endearing love.

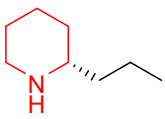
Chapter 1: The Aza-Heterocycles Piperidine and Aziridinium

Introduction

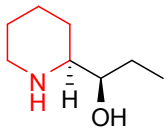
1.1 Overview of Piperidines

Substituted piperidines are widespread in natural products as structural features and are of great interest to organic chemists.[1] The piperidine ring is found in many simple substituted alkaloids with significant biological activity with examples such as Coniine (a poisonous neurotoxin in Poison Hemlock and the Yellow Pitcher plant)[2], Pipecoline[3], Conhydrine (poisonous, in Poison Hemlock)[4], and Sedamine (poisonous, in Wallpepper).[5] They are also present in the more complex bicyclic indolizidines, perhydroquinoline, and quinolizidine alkaloids, as well as in many of the more complex polycyclic alkaloids (Figure 1). These nitrogen derivatives occur in plants as defense mechanisms, such as feeding deterrents against insects.[6] They are also common in the animal kingdom as chemical weapons. For example, the fire ant produces a variety of simple alkaloids such as Solenopsins for venom[7], the lady beetle extrudes small droplets of hemolymph which contains piperidine alkaloids when it is disturbed as a deterent to predators[8], and over 150 piperidine alkaloids such as indolizidines have been isolated from poison dart frog skin alone.[9]

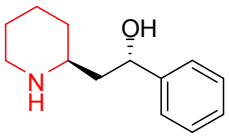
Figure 1: Naturally Occurring Piperidine Containing Alkaloids



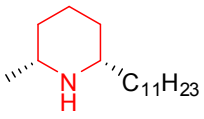
Coniine **1**



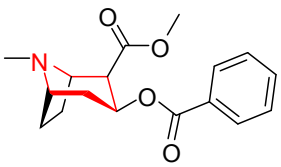
Conhydrine **2**



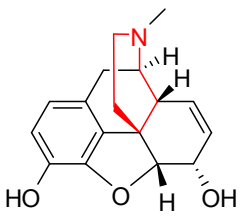
Sedamine **3**



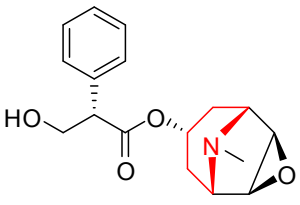
cis-Solepsin A **4**



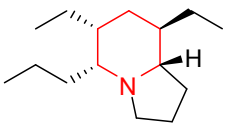
Cocaine **5**



Morphine **6**



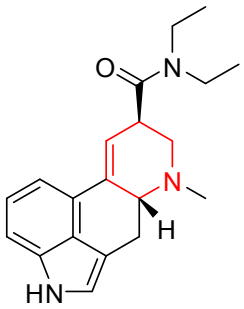
Scopolamine **7**



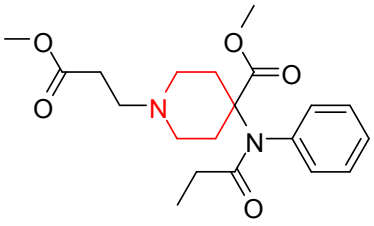
Indolizidine 223A **8**

The piperidine skeletal structure is also common in the pharmaceutical industry as a feature in many drugs. In fact, 23 of the "Top 200 Brand-Name Drugs by Retail Dollars in 2009" contain piperidine fragments.[10] Some examples of bioactive piperidine containing compounds are Lysergic acid diethylamide (LSD, hallucinogenic), Remifentanil (analgesic), and Paroxetine (anti-depressant), as shown in Figure 2.[11] Due to the prevalence of piperidines as natural products and their importance in the pharmaceutical industry their synthesis has garnered much attention, however much of that effort has concentrated on 2- and 2,6-substituted piperidines.[12] The construction of enantiopure 3-substituted and multi-substituted piperidines still remains a significant synthetic challenge.

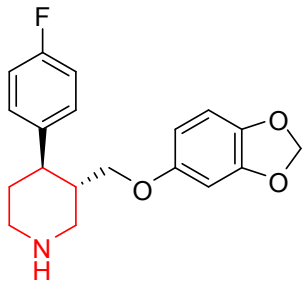
Figure 2: Piperidine Containing Bioactive Compounds



LSD **9**



Remifentanil **10**



Paroxetine **11**

1.2 3-Substituted Piperidine synthesis

1.2.1 Overview of the Methods to Prepare 3-Substituted Piperidines

Given the value of piperidines as structural components in natural products and for the pharmaceutical industry, it is not surprising that an abundance of piperidine methodologies have been developed. However, to obtain enantiopure 3-substituted piperidines there are still few methods, and those that are available suffer from several key drawbacks such as a lack of substrate scope, the reliance on diastereomeric separation, a lack of general conditions or catalyst, limited substitution at other positions of the piperidine, and/or they do not yield enantiopure products.

One methodology for the synthesis of 3-substituted piperidines is the enolate alkylation of oxazolopiperidines.[12m, 13] Though this method leads to enantiopure 3-alkyl piperidines, it requires the diastereomeric separation of the intermediates at two points in the synthesis and leads to the destruction of the chiral auxiliary (Scheme 1). The oxazolopiperidine method has the benefit of not requiring analytical equipment to ascertain the enantiomeric purity of the piperidine product due to the dependence on a chiral auxiliary to give diastereomers.

Another method towards 3-substituted piperidines, that was recently published, is the enantioselective hydrogenation of tetrahydropyridines.[14] This method was reported to give good to excellent enantiomeric excess and yields, though a small scope was reported including only alkyl and aryl substituents, also the nitrogen was protected with a tosyl which can be difficult to remove. A key drawback of this approach was the lack of general conditions, as the authors used a small family of chiral ligands instead of a general ligand. The enantiomeric excess was reported with whichever ligand gave the best result (Scheme 9).

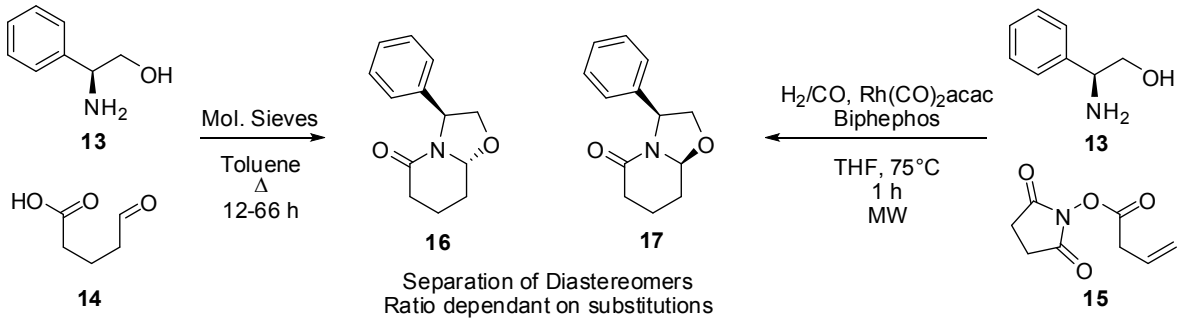
Yet another methodology to obtain 3-substituted piperidines is the use of an aziridinium ion intermediate to perform a ring expansion from *N*-alkyl-2-hydroxymethylpyrrolidine derivatives (Scheme 10).[15] This method depends on the piperidine being the thermodynamically favoured product, with the hydroxyl of the *N*-alkyl-2-hydroxypyrrolidine being converted to a labile group such as a halide or trifluoroacetate. This method maintains the enantiomeric excess of the precursor allowing enantiopure piperidines to be made if enantiopure precursors are used such as proline. However, it also limits the substitution at the 3-position to be labile groups.

1.2.2 3-Substituted Piperidines via Oxazolopiperidines

The use of oxazolopiperidines to obtain 3-substituted piperidines was pioneered by the group of Meyers and refined by the group of Bosch (Schemes 1 and 2).[12m,13] It continues to be a field of interest to these groups and others. By generating a bicyclic oxazolopiperidine it allows functionalization of the piperidine skeleton by taking advantage of the natural

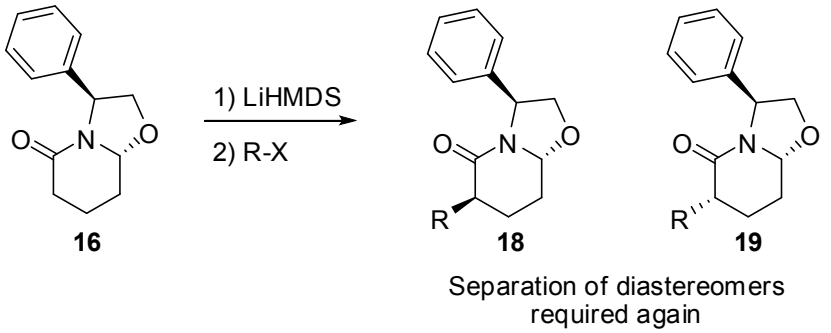
electrophilic and nucleophilic sites with decent diastereoselectivity. The 2- and 6-positions are electrophilic with the 6-position being the more reactive of the two since it contains an aminal. The 3-position when deprotonated can be alkylated with a variety of electrophiles. The chiral auxiliary can be varied to be other 1,2-amino alcohols than phenylglycinol such as valinol or serine.[16] However, typically phenylglycinol is used as an auxiliary since the substituted benzyl is simple to remove by hydrogenation. The total yield of the ring forming step is typically good to excellent (Scheme 1, 70-99%).[12m,16] The ratios between the two diastereomers is often low such as 1:1 or 1:2 but can range up to 1:20 with the ratio of the diastereomers depending on the substitution about the rings.[17] Which diastereomer is formed as the major product is dependant on the substituents of the ring, if present, and the chiral auxiliary employed. Therefore, a detailed NMR analysis to determine not only the ratio between the two diastereomers but also the newly formed stereocenter configuration in relation to the auxiliary stereocenter of the major isomer is required. Interestingly, a new method to prepare the oxazolopiperidine was reported recently, which uses a multicomponent rhodium catalyzed cyclization (Scheme 1) from a readily available precursor (O-succinyl-3-butenoic acid, **15**).[18] This new method to prepare the oxazolopiperidine has moderate diastereoselectivity (50-68% de), and demonstrates the continuing relevance of this approach to 3-substituted piperidines.

Scheme 1: Formation of the Oxazolopiperidine



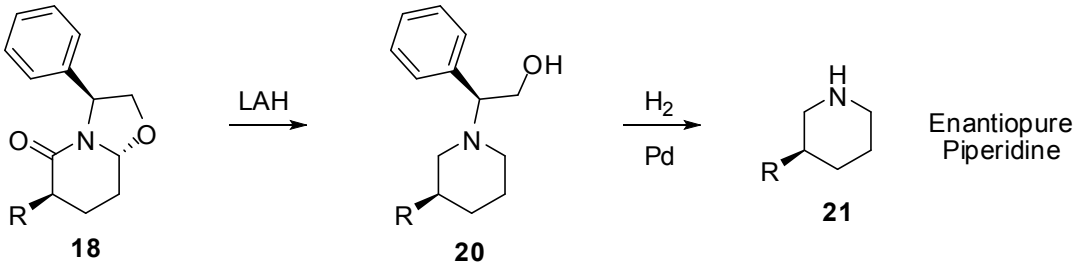
Enolate alkylation of the oxazolopiperidine (Scheme 2) occurs with moderate to good diastereoselectivity with reactive electrophiles such as benzyl bromide (4:1), allyl bromide (9:1), methyl iodide or ethyl iodide (>99:1).[19]

Scheme 2: Enolate Alkylation of the Oxazolopiperidine

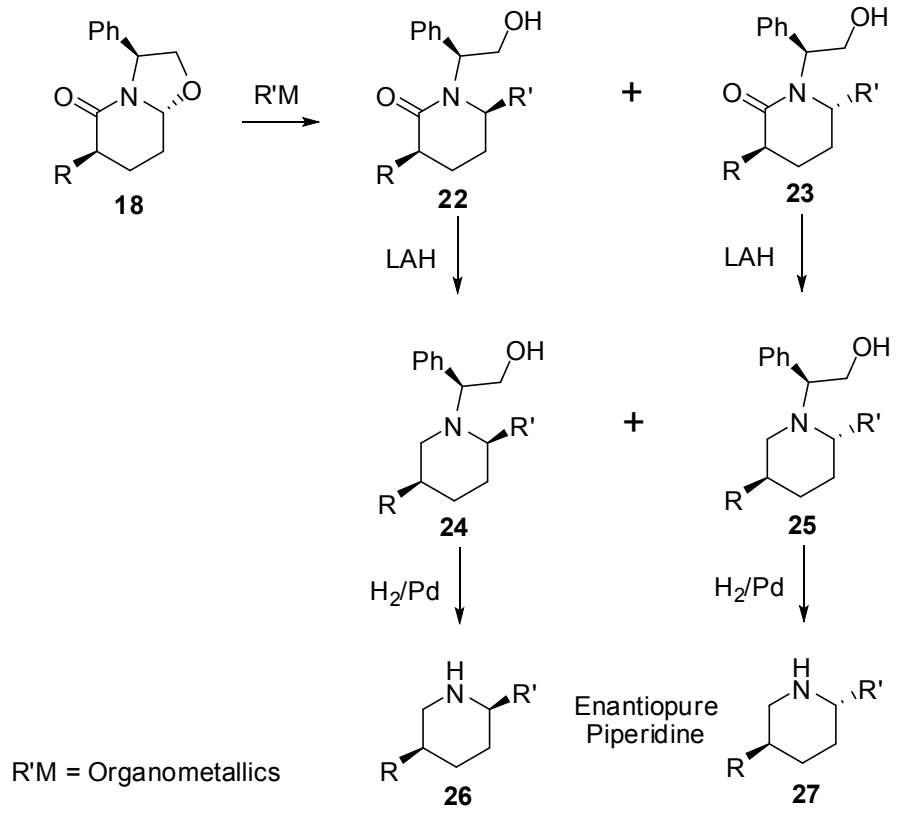


Removal of the chiral auxiliary can be accomplished by a two step procedure: cleavage of the bridging C-O bond of the auxiliary and piperidone with a hydride source, followed by hydrogenolysis of the auxiliary (Scheme 3).[12m, 13] The cleavage of the C-O bond can be done by reduction with lithium aluminum hydride, or displaced with an organometallic to gain substitution at the 6-position of the 2-piperidone (Scheme 4). However, the stereochemical outcome of the new substituent depends on the substituents present, their relative stereochemistry, and the nucleophile employed.

Scheme 3: Cleavage of the Chiral Auxiliary

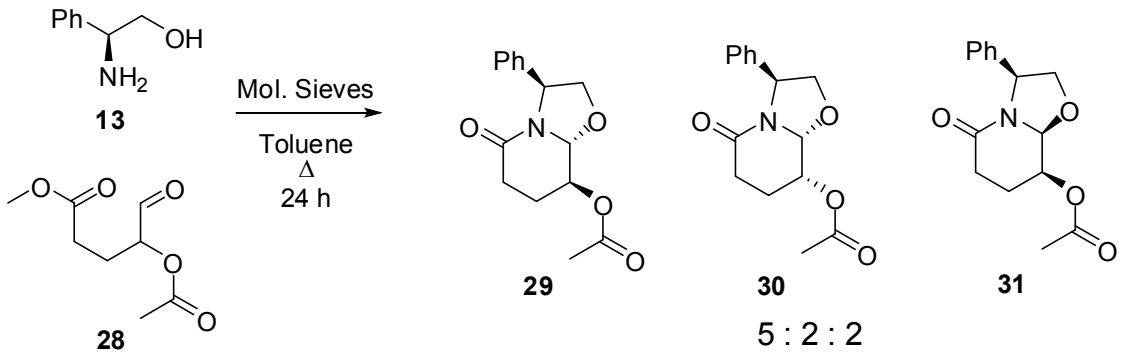


Scheme 4: Displacement of the Chiral Auxiliary Followed by Cleavage



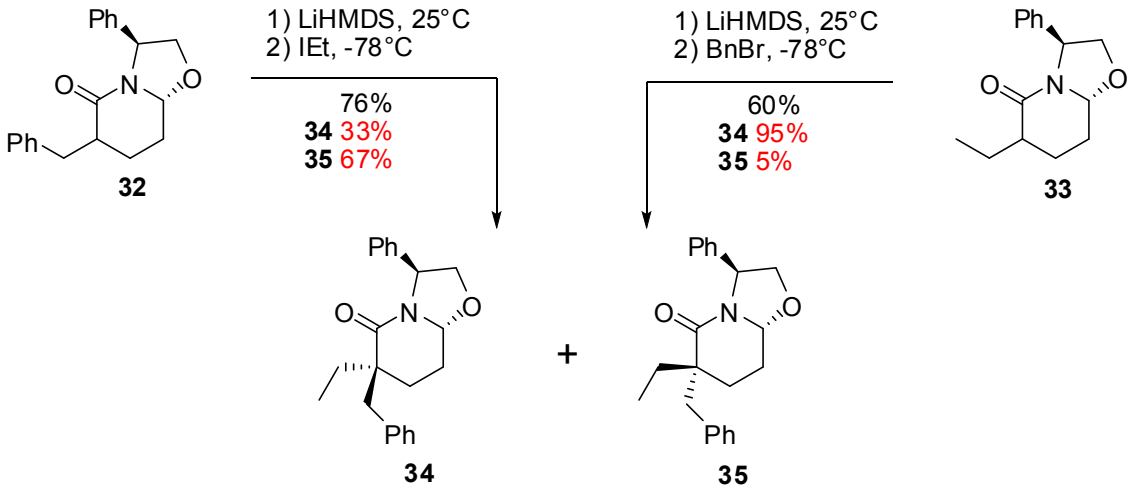
An obvious drawback of the oxazolopiperidine method is the inability to place aryl substituents at the 3-position using enolate alkylation and currently no heteroatom electrophiles have been explored with the enolate. However, this can be overcome to some extent using this chemistry by including the substituent in the 1,5-dicarbonyl precursor as shown in Scheme 5.[17] However, a significant potential drawback of using an achiral substituted 1,5-dicarbonyl precursor is the increase in the number of products and the resulting difficulty of separation (Scheme 5).

Scheme 5: Using Substituted 1,5-Dicarbonyls for Oxazolopiperidine Formation



One significant advantage of the oxazolopiperidine methodology is the ability to generate quaternary centers at the 3-position of the piperidine. The order of alkylation with electrophiles, solvent and counterion do impact the diastereoselectivity, and facial selectivity is determined experimentally (Scheme 6).[19]

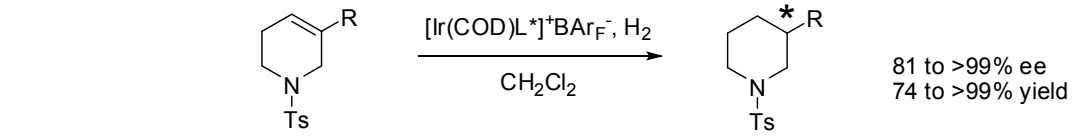
Scheme 6: Double Alkylation to Generate a Quaternary Center at the 3-Position of Piperidine



1.2.3 3-Substituted Piperidines by an Enantioselective Hydrogenation

For 3-alkyl or phenyl substituted piperidines, another approach was introduced recently by Andersson *et al* (Scheme 7).[14] This enantioselective iridium-catalyzed hydrogenation of tetrahydropyridines was reported to give good to excellent enantiomeric excess when the 3-substituent was an alkyl or aryl substituent and good to excellent yields.

Scheme 7: Enantioselective Iridium-Catalyzed Hydrogenation to 3-Substituted Piperidines



R = Me: **46**, >99%
97% ee with **62**

R = *n*-Bu: **47**, >99%
81% ee with **62**

R = Bn: **48**, 97%
92% ee with **62**

R = CH_2OH: **49**, >99%
97% ee with **62**

R = Ph: **50**, >99%
>99% ee with **58**

R = 4-MePh: **51**, >99%
>99% ee with **58**

R = 3-MePh: **52**, 97%
97% ee with **58**

R = 4-MeOPh: **53**, >99%
99% ee with **58**

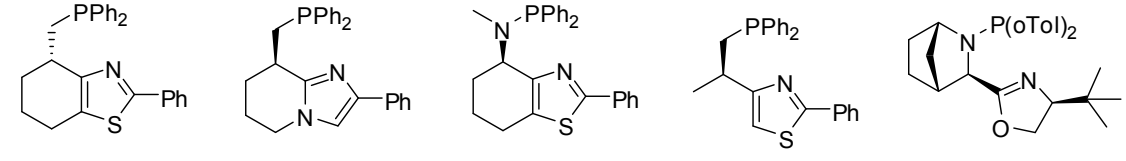
R = 3-MeOPh: **54**, 60%
98% ee with **58**

R = 4-CF_3Ph: **55**, 74%
96% ee with **59**

R = 4-ClPh: **56**, 94%
98% ee with **59**

R = 4-BrPh: **57**, 92%
98% ee with **59**

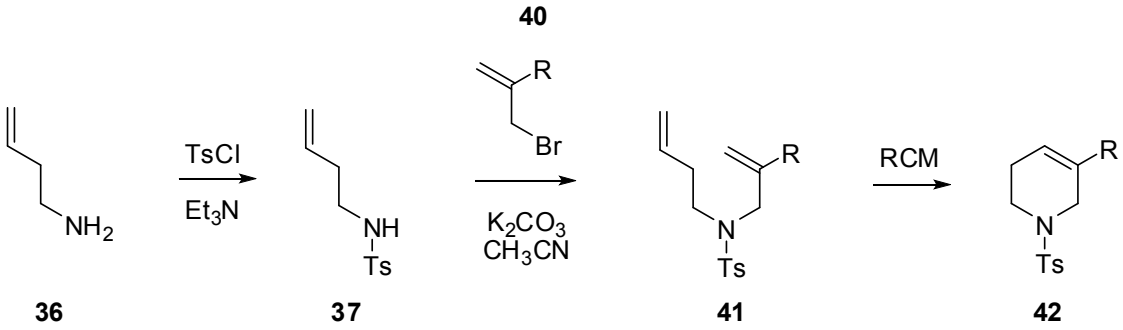
Ligands



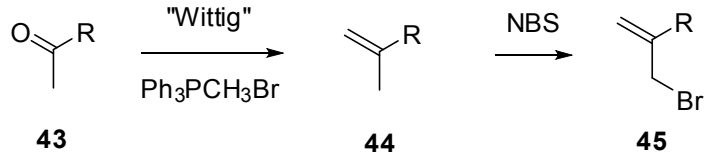
58 **59** **60** **61** **62**

The synthesis of the tetrahydropyridine was accomplished by tosylation of but-3-en-1-amine, alkylation of the sulfonamide with an allylbromide, which can be made in 2 steps if not commercially available, and a ring closing metathesis (Schemes 8 and 9). Overall this gives a 3 step synthesis to the tetrahydropyridine if the allyl bromide is commercially available or a total of 5 linear steps if the allyl bromide must be made from a ketone.

Scheme 8: Formation of the 3-Substituted Tetrahydropyridine



Scheme 9: Formation of the Allyl Bromide for the Tetrahydropyridine Synthesis



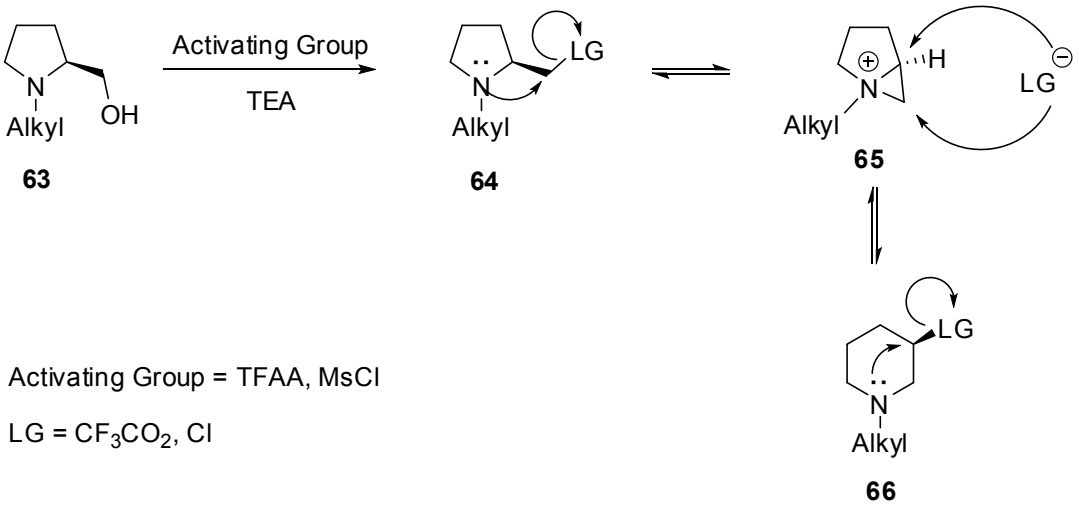
The key drawback of Andersson's methodology was the lack of a general ligand. They screened their reaction using a family of P,N-ligands (**58-62** of Scheme 7) and reported the enantiomeric excess of the piperidine and ligand which had the best result for each specific example. Despite the elegance of this transformation this prevents it from being widely used to obtain a large variety of 3-substituted piperidines as each would have to be screened and optimized with a family of ligands. Also, it is unlikely that these iridium catalysts would be used to generate a specific 3-substituted piperidine in process scale since iridium is one of the rarer elements found on earth and is as such prohibitively expensive.[20]

1.2.4 3-Substituted Piperidines by an Aziridinium Ion Ring Expansion Under Thermodynamic Control

An interesting approach to piperidines was pioneered by the group of Cossy[15] using prolinol, a cheap enantiopure precursor available in either enantiomeric form. They developed the use of an aziridinium ion ring expansion under thermodynamic conditions to obtain 3-substituted piperidines with labile nucleophiles (Scheme 10). Activation of the *N*-

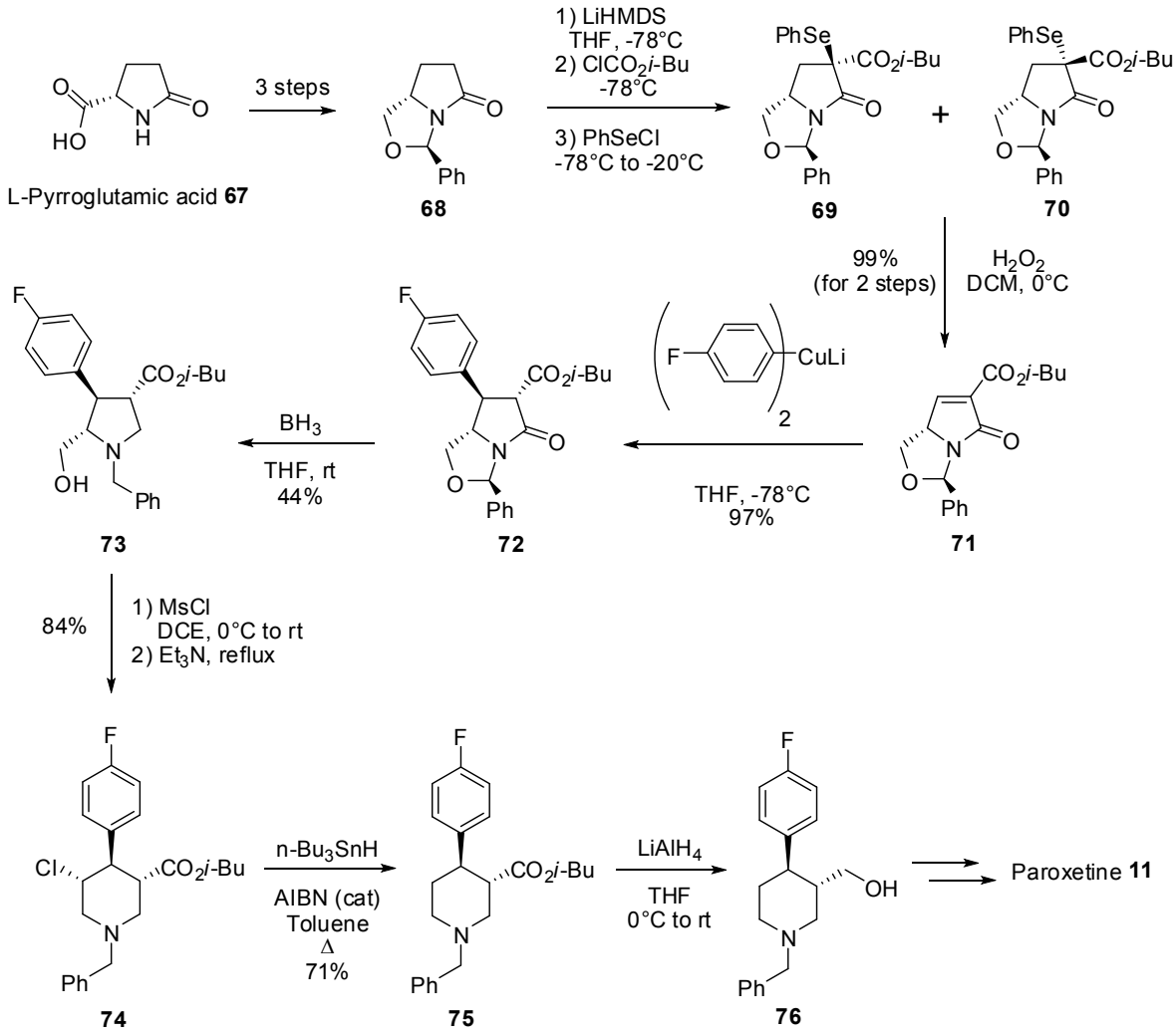
alkyl-prolinol with trifluoroacetic anhydride or mesyl chloride allows the prolinol derivative to exist in equilibrium with the aziridinium ion, that under thermodynamic conditions converts to the piperidine. This ring expansion occurs since the piperidine has a secondary leaving group which is less reactive than the primary leaving group of the pyrrolidine precursor. The leaving group typically used for this transformation by Cossy's group is trifluoroacetate, but they also use chloride (through the use of mesyl chloride). Their method can give enantiopure *N*-alkyl-3-hydroxypiperidines by saponification of the trifluoroacetate, or the *N*-alkyl-3-chloropiperidines. Also, the 3-chloropiperidines can be reacted through a radical pathway with tin hydrides to obtain the reduced piperidine after the ring expansion as demonstrated by their group in a synthesis of Paroxetine (Scheme 11).

Scheme 10: Aziridinium Ion Ring Expansion From Prolinol to a Piperidine



The ring expansion from prolinols has been limited to labile nucleophiles at the 3-position almost exclusively. There is one interesting exception from Cossy where *N*-alkylprolinols were converted into the *N*-alkyl-3-fluoropiperidines with DAST. Here, the bulk of the alkyl group on the nitrogen was shown to have a significant impact on the regioselectivity of the fluoride ion in opening of the aziridinium ion. *N*-trityl substituted substrates gave >99:1 regioselectivity to yield the piperidine. Conversely, other alkyl groups gave little selectivity to either isomer. Interestingly, Cossy demonstrated that the solvent and whether DAST or Deoxofluor was used had little impact on the regioselectivity.[21]

Scheme 11: Synthesis of Paroxetine via an Aziridinium Ion Ring Expansion Followed by Reduction



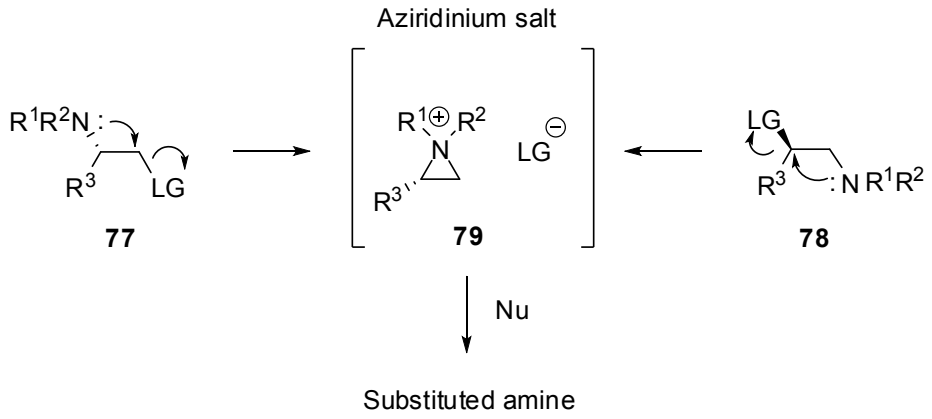
1.3 Aziridinium Ions in Synthesis

1.3.1 Overview of Aziridinium Ions

Aziridines have been used as building blocks in organic synthesis much like their epoxide cousins. However, aziridines have relatively low reactivity often requiring a strong electron withdrawing group on the nitrogen atom, which can be problematic to remove later, and necessitate Lewis acids to activate them sufficiently to react with nucleophiles. Their synthesis and opening have been studied extensively, and the control of regio-selectivity of their opening provides access to amines.[22]

Currently *N,N*-dialkyl aziridinium ions such as **79** are less well studied than aziridines. Aziridinium ions are rarely used as intermediates in organic synthesis, and when used they were often unexpectedly formed.[23] However, they are stronger electrophiles than aziridines so they can be used with a wider variety of nucleophiles and under milder conditions. In synthesis when encountered they are often used as an argument for retention of overall configuration during a displacement of a leaving group by neighboring group participation though these intermediates are rarely isolated.[24] Aziridinium ions have been isolated previously as tetrafluoroborate salts and they proved to be quite stable as a solid though in solution they are typically unstable over several hours even at lower temperatures.[25,26] Recently aziridinium ions have been of interest to a few groups investigating various aspects such as in the formation, isolation and regioselectivity of opening though much work remains to be done.[15a,27,28,29,30]

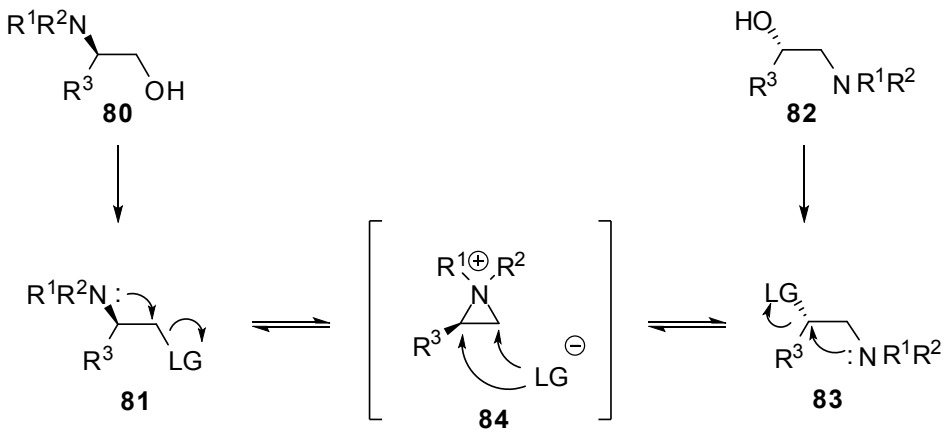
Figure 3: Formation of an Aziridinium Ion



1.3.2 Formation and Thermodynamic Equilibrium of Aziridinium Ions

Aziridinium ions are often prepared from *N,N*-dialkyl-1,2-aminoalcohols by first converting the alcohol into a leaving group, and the aziridinium ion formed intramolecularily by displacing the leaving group through an S_Ni mechanism.[23] Typical leaving groups are chloride, bromide, iodide, trifluoracetate, mesylate, tosylate and triflate though phosphonates have also been reported.[23,25,31,32,33,34] Also, the aziridinium ion (**84**) is not commonly isolated before use, instead the amine latent form is used with an α-leaving group that exists in equilibrium with the aziridinium ion (**81** or **83**).

Scheme 12: Formation of an Aziridinium Ion From *N,N*-Dialkyl-1,2-aminoalcohols



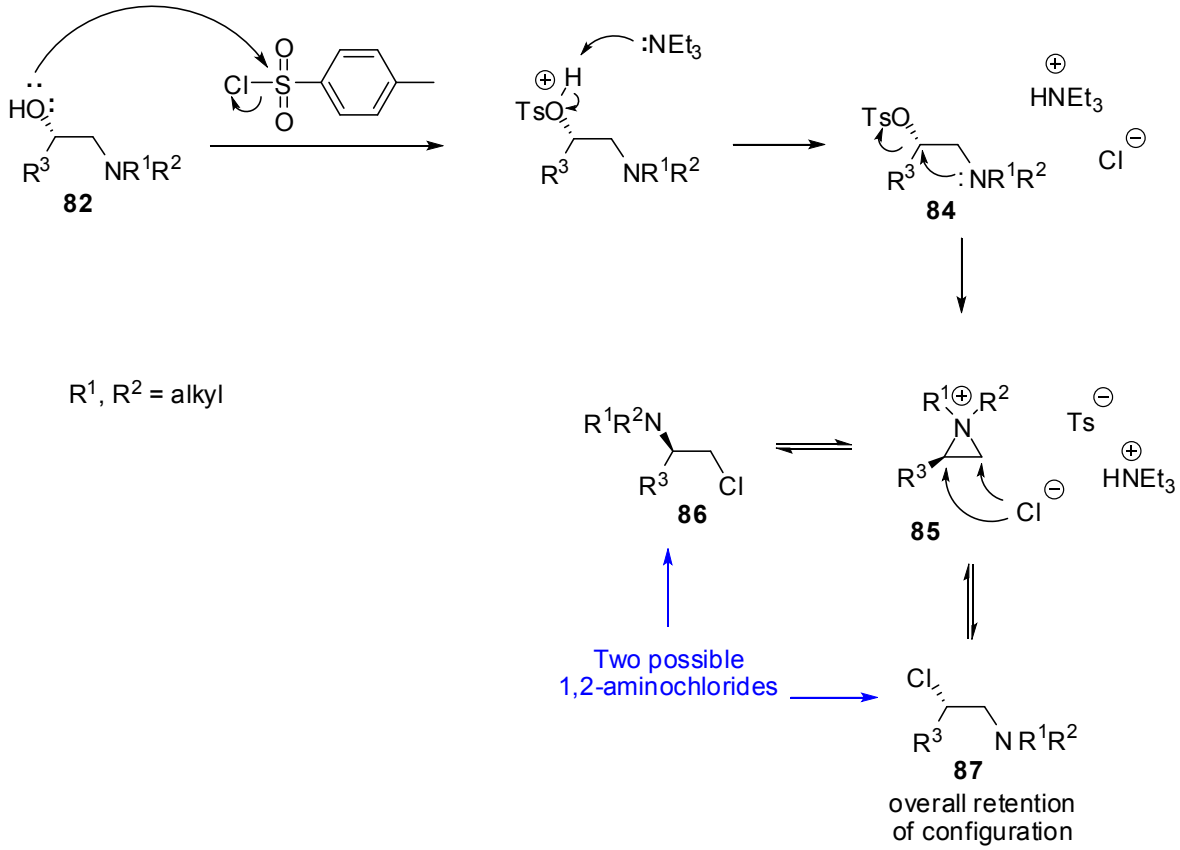
Under Appel reaction conditions with tetrabromomethane the alcohol is converted into triphenylphosphonium oxide, and that oxide is replaced by a bromide.[23] However, the oxide is not displaced by the bromide directly, instead the phosphonium undergoes an S_Ni mechanism to form the aziridinium ion and this is followed by aziridinium ion opening by the bromide for overall retention of configuration. For tosylate and mesylate groups the same can occur if a chloride ion is in solution to form the leaving group (ie: TsCl or MsCl) since it is much more nucleophilic than the sulfonic acids as shown in Scheme 13, and Scheme 11 during the synthesis of Paroxetine.

When the aziridinium salt counterion is a labile nucleophile such as chloride, the aziridinium ion and the tertiary amine exist in equilibrium (Scheme 13, **85-87**). This favours the leaving group to be in the most hindered and least electronically activated position to give the more energetically favoured product (**87**). This can cause a rearrangement from the original 1,2-amino-leaving group compound (reversible with Nu = LG). The two amines (**86** and **87**) that exist in equilibrium with the aziridinium ion are latent forms of the aziridinium ion and can react with nucleophiles through this intermediate.[23]

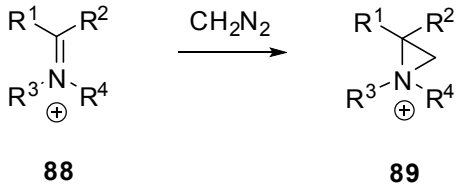
A second method, though less common, is to prepare aziridinium ions through the reaction of diazomethane with iminium cations (Scheme 14).[35] Other diazoalkanes have also been

demonstrated to react with iminium salts to give aziridinium ions.[36] The mechanism of addition probably involves initial attack by the diazoalkane at the highly electrophilic carbimino position of the iminium salt, followed by displacement of the diazo with the tertiary amine. No example of this transformation being done with an asymmetric induction to gain a chiral center was found in the literature.

Scheme 13: Conversion of the Alcohol into a Chloride with Overall Retention of Configuration

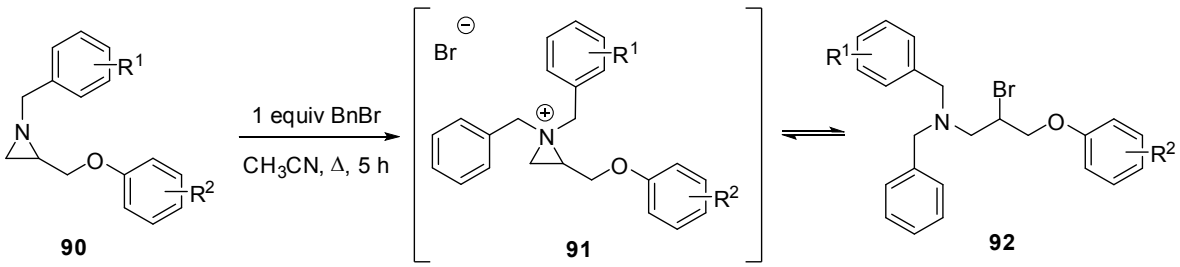


Scheme 14: Conversion of an Iminium Cation to an Aziridinium Ion



Yet another method that is used to form aziridinium ions but is less common is the *N*-alkylation of aziridines (Scheme 15).[27] The aziridine can be produced also from 1,2-aminoalcohols or through [1+2] cyclization with a nitrene and an alkene.[37] Here, benzyl bromide and methyl trifluoromethanesulfonate are common as alkylating agents.[27] As shown in Scheme 15, the aziridine is alkylated to form the aziridinium ion which is then ring opened with bromide to yield the 1,2-aminobromide. The product observed is the thermodynamically favoured one since the halide is less reactive as a secondary leaving group instead of as a primary leaving group.

Scheme 15: Aziridinium Ions via Aziridine Alkylation

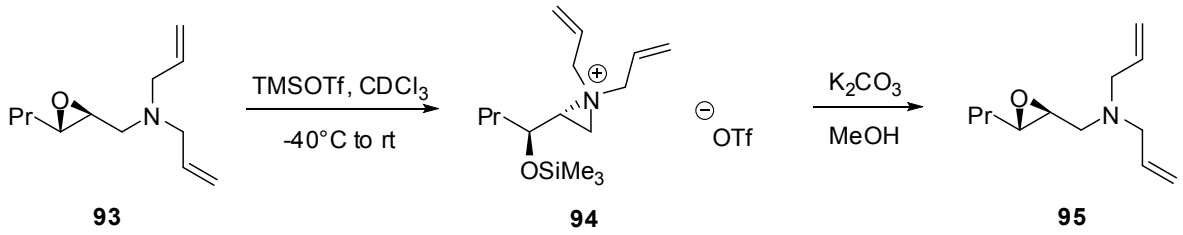


The leaving groups chloride, bromide, iodide, trifluoroacetate, mesylate, and phosphonate have all been demonstrated to not only be leaving groups but also nucleophiles capable of opening the aziridinium ion, so that the aziridinium ion exists in equilibrium with the tertiary amine with an α-leaving group (Scheme 12).[23,25,31,32,33,34] Just recently, it was demonstrated that mesylate is also a reversible leaving group that gives the thermodynamic product.[33] By extension then, tosylate would be expected to be a reversible leaving group also. Interestingly, in a recent publication the authors originally claimed they were able to form and isolate the aziridinium ion as the salt with bromide as a counterion.[38] This was rather surprising since the bromide ion is a good nucleophile and in all previous publications it was cited as a reversible leaving group with the 1,2-aminobromide obtained. The paper has since been withdrawn citing that the aziridinium ion was not in fact the compound isolated with no further details given.

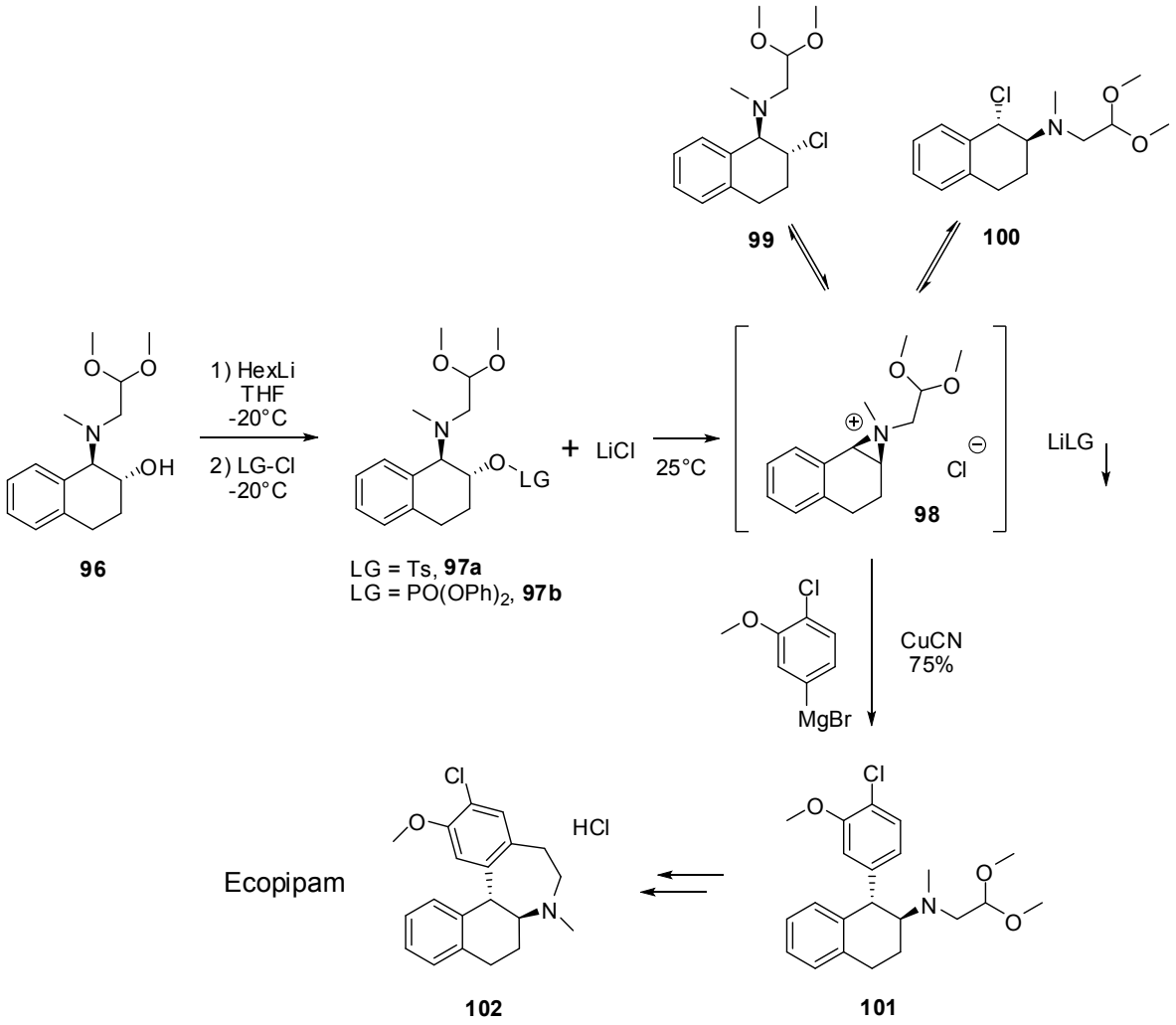
The equilibrium from 1,2-aminohalides to the aziridinium ion can be forced through the use of Ag^{I} salts with 1,2-aminohalides.[26, 39] Through the use of non-nucleophilic counterions such as triflate, tetrafluoroborate, tetraphenylborate, and perchlorate the aziridinium can be

formed and isolated. Also, Rayner has demonstrated that aziridinium ions can be prepared from a 1,2-amino-epoxide by reaction with trimethylsilyltriflate (Scheme 16). Interestingly, if the aziridinium α-silyl ether were deprotected the epoxide reforms.[40]

Scheme 16: An Aziridinium Ion From a 1,2-Aminoepoxide



Scheme 17: Ecopipam Synthesis Using a Latent Aziridinium Ion



The aziridinium ion **94** observed through the use of ^{1}H NMR by Rayner (Scheme 16) was cited as being stable in solution at room temperature for days.[40] However, during the synthesis of Ecopipam the authors noted the aziridinium tetrafluoroborate or triflates were unstable over several hours in solution even at -20 °C.[25] There appears to be no trend for substitution patterns to the stability of aziridinium ions, except that in general they appear to be unstable in solution over prolonged periods of time. For this reason, aziridinium ions are typically not isolated but used as a latent reactive species from the 1,2-aminohalide. For example, the authors of the process scale of Ecopipam synthesis relied on using a 1,2-aminochloride, which exists in equilibrium with the aziridinium ion, reacting with organometallics as their key step in the synthesis.

1.3.3 Ring Opening of Aziridinium Ions with Irreversible Nucleophiles

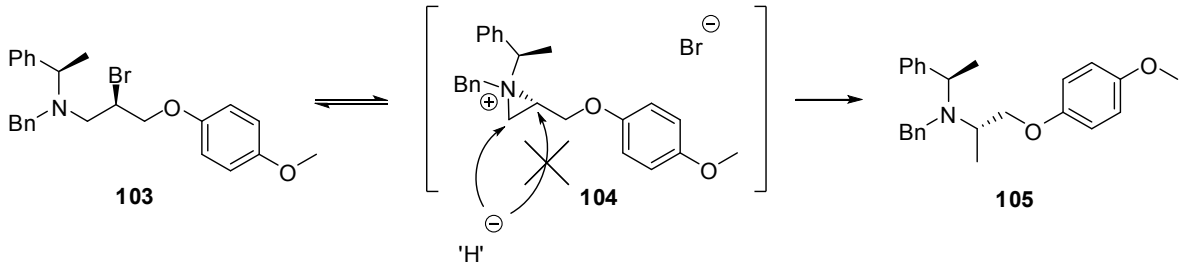
This section covers nucleophiles that are poor leaving groups so as to obtain the kinetic product, and not the thermodynamic product resulting from an equilibrium with the aziridinium ion. The reaction of aziridinium ions with irreversible nucleophiles is directed by the steric demands, electronic factors such as electron withdrawing groups adjacent to the aziridinium ion carbons (α-EWG) and the nature of the nucleophile.[23] Electron withdrawing groups that have been demonstrated in literature to be effective include phenyl, the carbonyl of an ester, and an acrylate. Surprisingly, trifluoromethyl was shown to not direct the addition to the aziridinium ion with a number of nucleophiles.[41] Nucleophiles in this section are separated by atom grouping as it is helpful to compare regioselectivity within the same atom family.

1.3.3a Hydrogen Nucleophiles

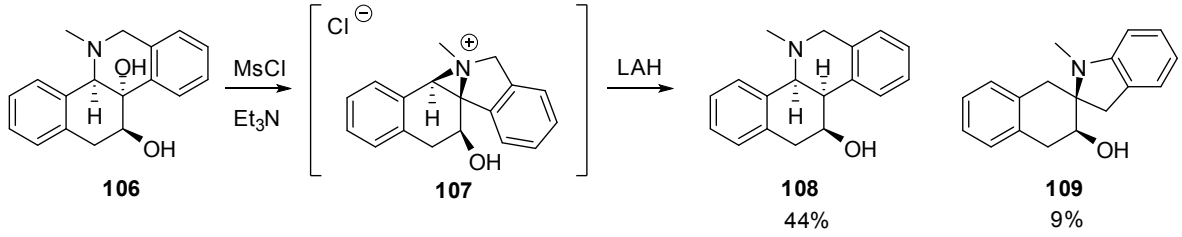
Hydrides have been reported to attack with complete regioselectivity to the least hindered carbon when no α-EWG is present. A variety of reagents including ruthenium hydrides, $NaBH_4$, $NaCNBH_3$, $LiEt_3BH$, $LiBH_4$, and $LiAlH_4$ have been studied (Scheme 18).[29,42] With a single α-EWG, no example in literature was found. However, there was one example where both carbons of the aziridinium ion were benzylic (**107** of Scheme 19) that yielded the bicyclo [4.4.0] decane **108** with moderate selectivity over the spiro [4.5] azecine

109. The stereochemistry of the tertiary center formed from the alcohols, as well as the rearranged product was proposed to be obtained from an aziridinium intermediate.[43]

Scheme 18: Aziridinium Ion Reacting With Hydrides With No α-EWG



Scheme 19: Dibenzylic Aziridinium Ion Opening with LAH

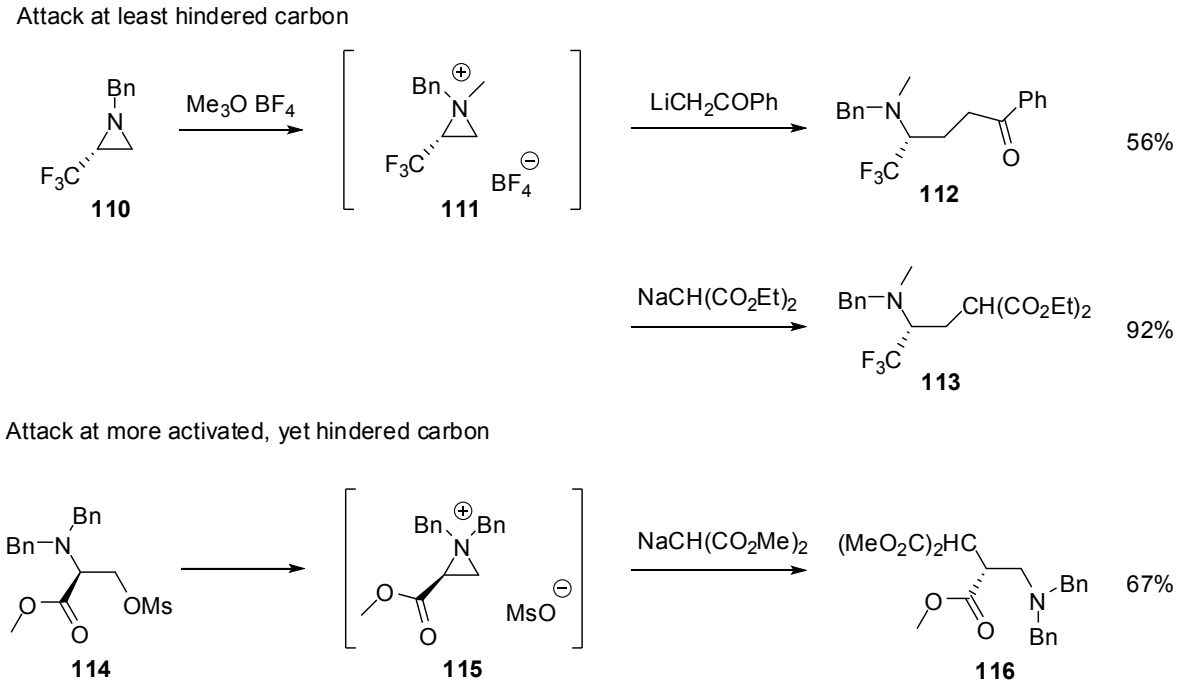


1.3.3b Carbon Nucleophiles

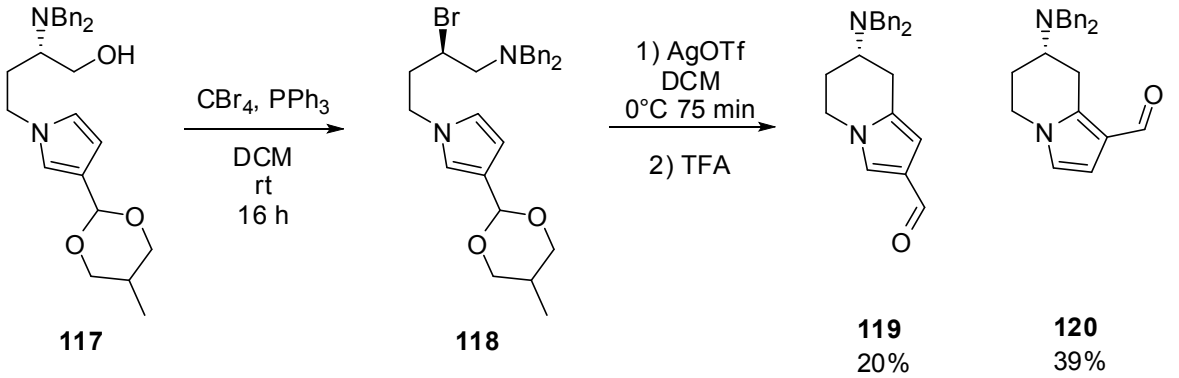
Carbananion nucleophiles in the absence of an α-EWG regioselectively attack the least hindered aziridinium ion carbon. However, the degree of regioselectivity varies depending on the nucleophile, steric demands of the aziridinium ion, and reaction conditions. For example, in the absence of an α activating group adjacent to the aziridinium ion carbon, cyanide attacks the least hindered position with high regioselectivity.[44] With an α-EWG such as an ester or vinyl ester, the cyanide goes regioselectively to the more activated carbon even if it is the more hindered carbon.[29] Malonates and enolates also gave high regioselectivity to the least hindered carbon in the absence of an α activating group to an aziridinium ion carbon. If an activating group was present α to an aziridinium ion carbon, then attack occurred to the activated position.[26,41,45] A trifluoromethyl α to an aziridinium ion carbon has been demonstrated to not be a directing group when malonates and enolates were used as nucleophiles to generate **112** and **113** (Scheme 19).[41] The carbonyl of an ester α to an aziridinium ion carbon has been reported to be an effective directing group causing

regioselective attack to the activated carbon of the aziridinium ion to occur when malonate was employed as a nucleophile for opening of the aziridinium ion **115** (Scheme 20).[46] However, enolate has not been reported as a nucleophile to an aziridinium ion with an α-carbonyl. Likely, with an α-carbonyl the acidity of the aziridinium ion is increased so that the more basic enolate nucleophile may instead deprotonate the aziridinium ion causing its decomposition.

Scheme 20: Aziridinium Ion Reaction with an Enolate and Malonate



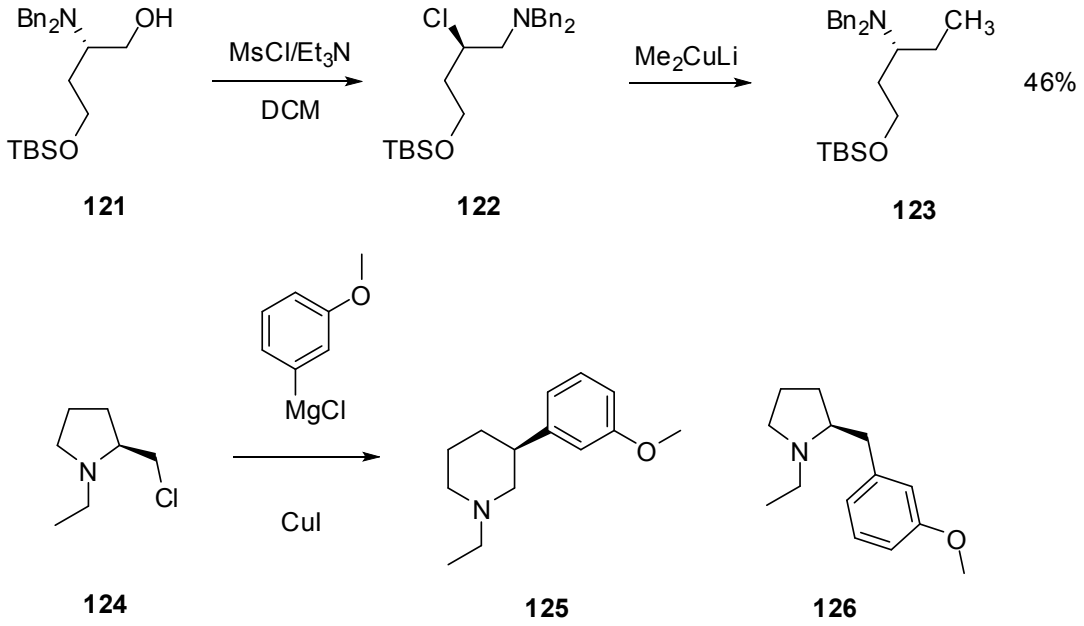
Scheme 21: Intramolecular Aziridinium Ion Opening with Pyrrole



An interesting example of an intramolecular pyrrole alkylation by an aziridinium ion was also found (Scheme 21). Here, the 6-membered rings **119** and **120** were favoured over the 5-membered ring, with the pyrrole selectively attacking the least hindered carbon of the aziridinium ion.[47]

There are few examples with organometallic nucleophiles opening aziridiniums. In the absence of an α-activating group, alkyl cuprates attack the least hindered site with complete regioselectivity whereas aryl cuprates lead to moderate regioselectivity (Scheme 22).[23,44a,48] The only α-activating group examined with organometallics that has been reported is a phenyl during the Ecopipam synthesis, which had a strong effect of directing the attack though the two carbons of the aziridinium ion were equally sterically hindered (Scheme 17).[25]

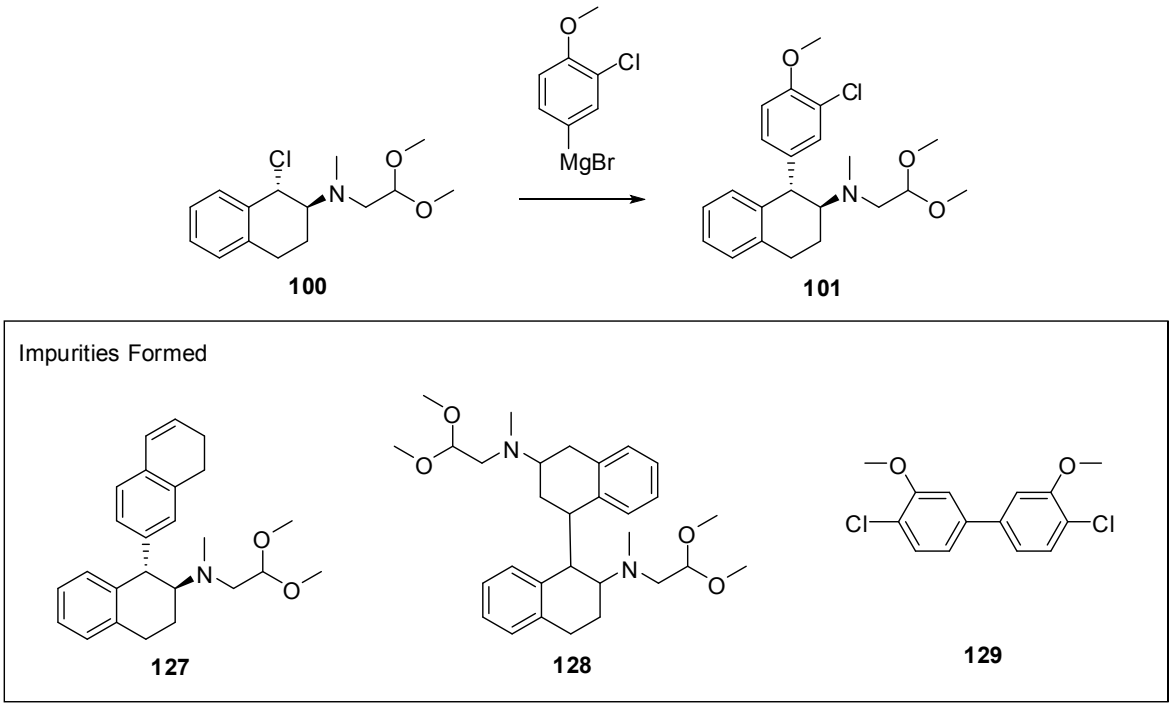
Scheme 22: Aziridinium Ion Reaction With Organocuprates



The mechanism by which organometallics react with aziridinium ions has not been elucidated yet and likely varies depending on which type of organometallic is utilized. During the optimization of the synthesis of Ecopipam the authors noted three impurities (**127**, **128**, and **129**, Figure 4) that could be rationalized as being formed through a single electron transfer mechanism (SET) when they used a Grignard reagent (Figure 5).[25]

However, the authors noted that the addition of catalytic amounts of copper limited the formation of these impurities and the reaction occurred at an accelerated rate. Also, in this publication aryllithiums and arylzinc reagents were noted as being unreactive towards the aziridinium.

Figure 4: Ecopipam Synthesis Impurities Which Support a SET Mechanism With Grignards

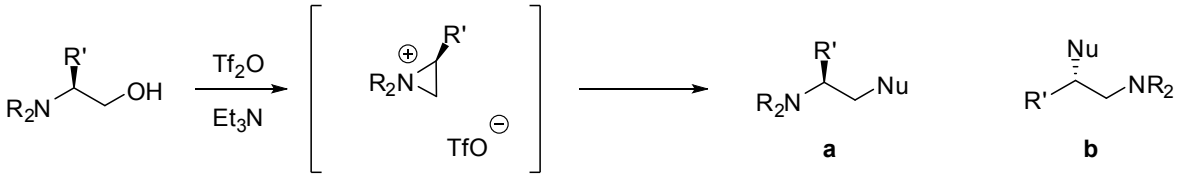


1.3.3c Nitrogen Nucleophiles

Nitrogen nucleophiles in the absence of an α-EWG attack in general at the least hindered position though the degree regioselectivity depends on the nucleophile and steric bulk of the aziridinium ion.[23] For example, Rayner showed a substituted *N*-bis-allyl aziridinium ion system where one carbon of the aziridinium was substituted with a methyl, reacted with morpholine to have moderate regioselectivity (Table 1, **130,** 68:32). However, when *N*-benzyl-valinol was used as a nucleophile an excellent regioselectivity was observed (**132**, >95:5). Increasing the steric bulk of the aziridinium ion before reaction with morpholine by changing the methyl substituent of the aziridinium ion to a benzyl increased regioselectivity (**131** 88:12 vs **130** 68:32). Also, increasing the size of the *N,N*-alkyl groups

of the aziridinium in this system from allyl to benzyl increased the regioselectivity (**131** 88:12 vs **132** 95:5).[32]

Table 1: Steric Bulk Affects Regioselectivity for Nitrogen Nucleophiles



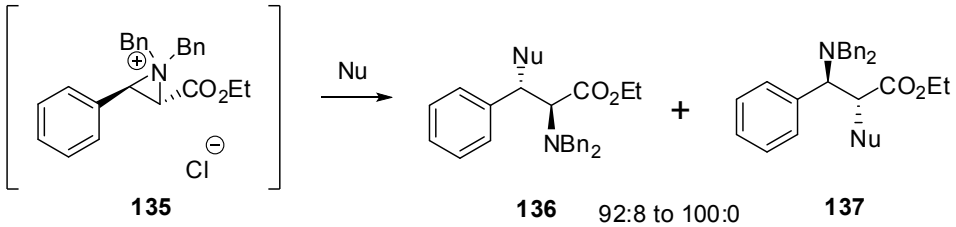
Entry	Product	R	R'	Nu	Ratio (**a**:**b**)
1	**130**	allyl	CH_3	morpholine	68:32
2	**131**	allyl	Bn	morpholine	88:12
3	**132**	Bn	Bn	morpholine	95:5
4	**133**	Bn	CH_3	morpholine	71:29
5	**134**	Bn	CH_3	N-allyl-Valinol	>95:5

Uneyama published an example with an α-trifluoromethyl as the substituent α to the aziridinium ion carbon.[41] In that case, *n*-butylamine and *n*-butylmethylamine reacted to the least hindered position thereby demonstrating that it was not effective as a directing group. The reaction with azide, or phthalimide displayed good regioselectivity, and led to the attack at the least hindered position of an aziridinium ion if no α-EWG is present unless the reaction is done at a high temperature.[23,29]

With α-EWG's such as phenyl, the carbonyl of an ester, or an acrylate then amines, anilines, azide, phthalimide, and imidazole react at the activated, yet more hindered position of the aziridinium ion.[29,46,49] There are three literature examples where two activating groups are present on opposing carbons of the aziridinium ion as α substituents, and the regioselectivity of attack for nucleophiles opening the aziridinium ion examined (Scheme 23).[33,49,50] These examples (**135**, **138**, and **141**) showed nitrogen nucleophiles attack the benzylic aziridinium ion carbon with good selectivity instead of α to the carbonyl or phosphate. This occurs even if it is the more hindered position as can be seen with the spiro aziridinium ion **141** where the nitrogen is the bridgehead (Scheme 23).

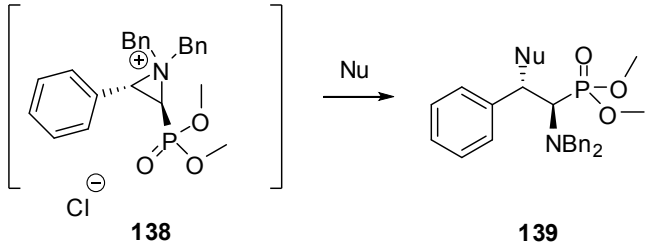
Scheme 23: Regioselectivity of Nitrogen Nucleophiles Towards Activated Aziridinium Ion Carbons

Selective attack at the benzylic carbon



135 **136** 92:8 to 100:0 **137**

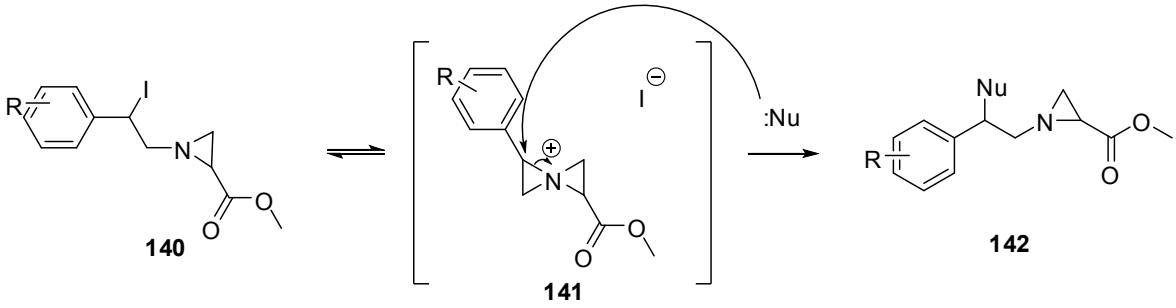
Nu = $BuNH_2$, aniline, piperidine, piperazine, pyrazole



138 **139**

Nu = $BnNH_2$, Bn_2NH

Selective attack at the benzylic carbon despite less hindered carbons available



140 **141** **142**

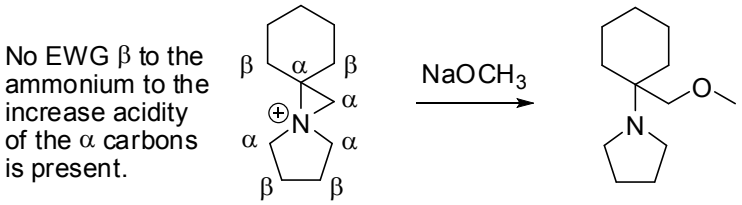
Nu = N_3, allylamine, aniline, benzylamine, *n*-hexylamine, morpholine

1.3.3d Oxygen Nucleophiles

In general, reactions with oxygen nucleophiles have the same regioselectivity as those with nitrogen nucleophiles. They attack the least hindered carbon selectively in the absence of an α-EWG, and with an α-EWG they attack the activated position even if more hindered.[23,29,41,51] However, a key difference between oxygen and nitrogen nucleophiles is that nitrogen nucleophiles are typically added as a neutral species and oxygen nucleophiles

as a salt unless it is an alcohol (ie: KOAc). Neutral oxygen nucleophiles are less reactive than neutral nitrogen nucleophiles but under forcing conditions can react with aziridinium ions, for example when an alcohol nucleophile is used in large excess or as a solvent. Phenols and carboxylic acids are acidic enough that deprotonation of the oxygen nucleophile facilitates their reaction with aziridinium ions without the possibility of the nucleophile acting as a base towards the aziridinium ion. Examples in literature of an alkoxide reacting with an aziridinium ion are rare, and those few examples have no electron deficient groups β to the nitrogen of the aziridinium ion that would increase the acidity of the aziridinium ion such as **143** (Scheme 24).[52] With a trifluoromethyl α to the aziridinium ion carbon the authors used water as a nucleophile to obtain the 1,2-aminoalcohol with selective attack at the least hindered position.[41] Another approach for addition of water is the use of hydrated silica gel as an equivalent of water.[53] There, the authors attempted to isolate the 1,2-aminochloride by column chromatography and found the chloride had instead been displaced by water at the benzylic position.

Scheme 24: Reaction of an Aziridinium Ion



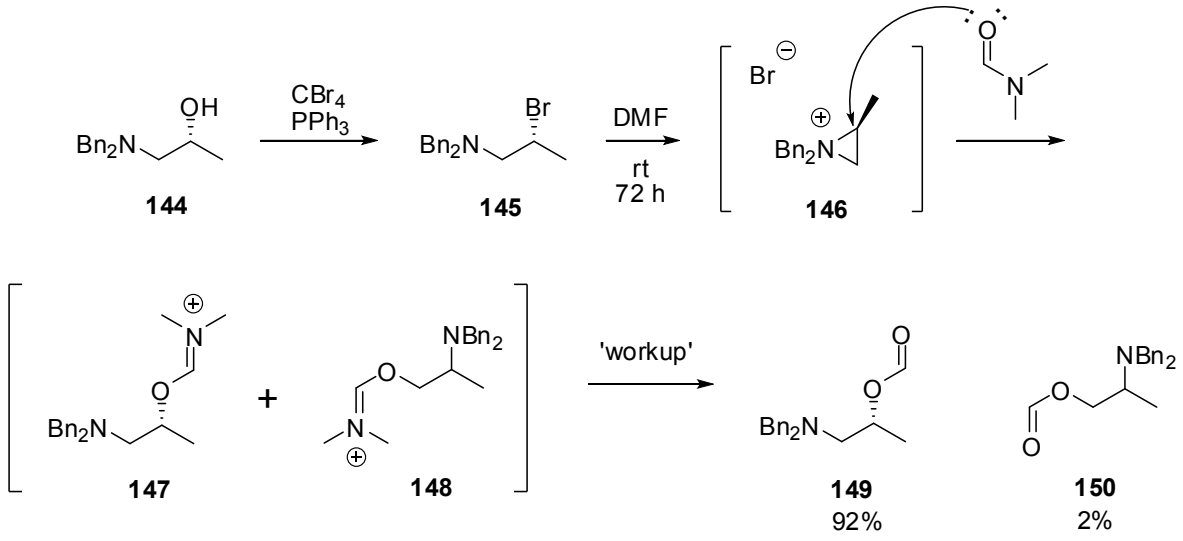
143 **144**

N,N-Dimethylformamide, though not considered as a common oxygen nucleophile, has been reported to react with a 1,2-aminobromide via an aziridinium ion to yield the 1,2-aminoformate. Surprisingly, opposite selectivity of what is normally expected occurred, with the DMF attacking at the more hindered aziridinium ion carbon with high regioselectivity (Scheme 24).[54]

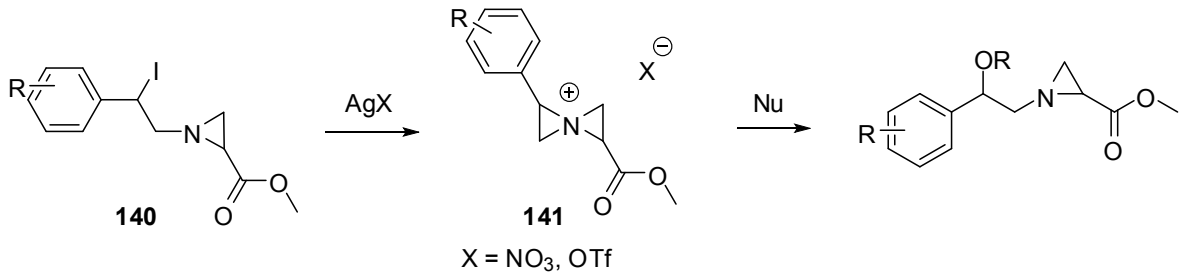
With an α-EWG group such as an ester (or the vinylanalog), oxygen nucleophiles such as acetate, attack the activated and more hindered aziridinium ion carbon selectively over the least hindered one.[29] With the EWG's phenyl and carbonyl present as substituents on the aziridinium carbons, oxygen nucleophiles selectively attacked the activated carbon of the

aziridinium ion (Scheme 26). The latent form of the aziridinium ion, a 1,2-aminoiodide, was unreactive to alcohols but treatment of the 1,2-aminoiodide with silver salts allowed the reaction to proceed. When the authors used silver nitrate they found that the nitrate could act as a nucleophile towards the aziridinium ion which highlighted how electrophilic the aziridinium ion is.[49]

Scheme 25: Reaction of an Aziridinium Ion with DMF



Scheme 26: Regioselectivity of Oxygen Nucleophiles with Activated an Aziridinium Ion Carbon



OR = NO_3, **151**
40%, 4:1 dr

OR = OCH_3, **152**
30%, 5:1 dr

OR = OCH_2CCH, **153**
0%

OR = $OCH_2CH{=}CH_2$, **154**
36%, 1:1 dr

OR = OCH_2CCPh, **155**
20%, 1:1 dr

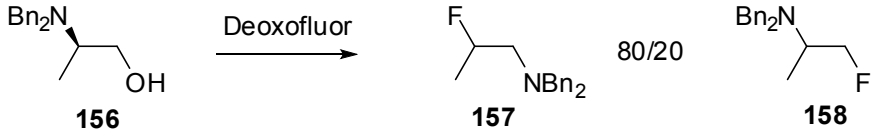
1.3.3e Fluoride as a Nucleophile

Regioselectivity for opening of an aziridinium ion with fluoride appears to depend on the conditions for forming the aziridinium ion. With a pre-formed aziridinium ion, the fluoride selectively attacks the least hindered position as expected. This has been demonstrated to prepare **161** selectively over **162** using TBAF as the source of fluoride with a latent form of the aziridinium ion **159** (Scheme 28).[27]

Reacting a 1,2-aminoalcohol with DAST or Deoxofluor has been proposed to go through an aziridinium ion. However, these reagents gave different results than TBAF. The attack of DAST and Deoxofluor was observed to give the 1,2-aminofluoride in a 4:1 regioselectivity to obtain the fluoride at the more hindered carbon (Scheme 27).[23] Cossy showed that increasing the steric bulk of the groups on the nitrogen of the aziridinium ion favoured attack at the more hindered carbon when DAST or Deoxofluor was used to convert a 1,2-aminoalcohol to the fluorinated analog (Table 2). For the reaction with DAST and Deoxofluor the corresponding rearrangement of the amine had no significant impact by changing the solvent ruling out tight ion pair association being the cause of this unusual regioselectivity. The authors instead suggested that the additional substituents added to the greater partial positive character of that carbon and increased the C-N bond length making it more reactive.[21] However, if this were the case then the same result would be expected no matter how the aziridinium ion was formed which does not appear to be the case.

The carbonyl of an ester α to an aziridinium ion ring carbon has been demonstrated to direct opening of an aziridinium ion when fluoride was used a nucleophile.[27]

Scheme 27: Regioselective Opening with Deoxofluor and a 1,2-Aminoalcohol



156 **157** **158**

Scheme 28: Fluoride as a Nucleophile to Aziridinium Ions

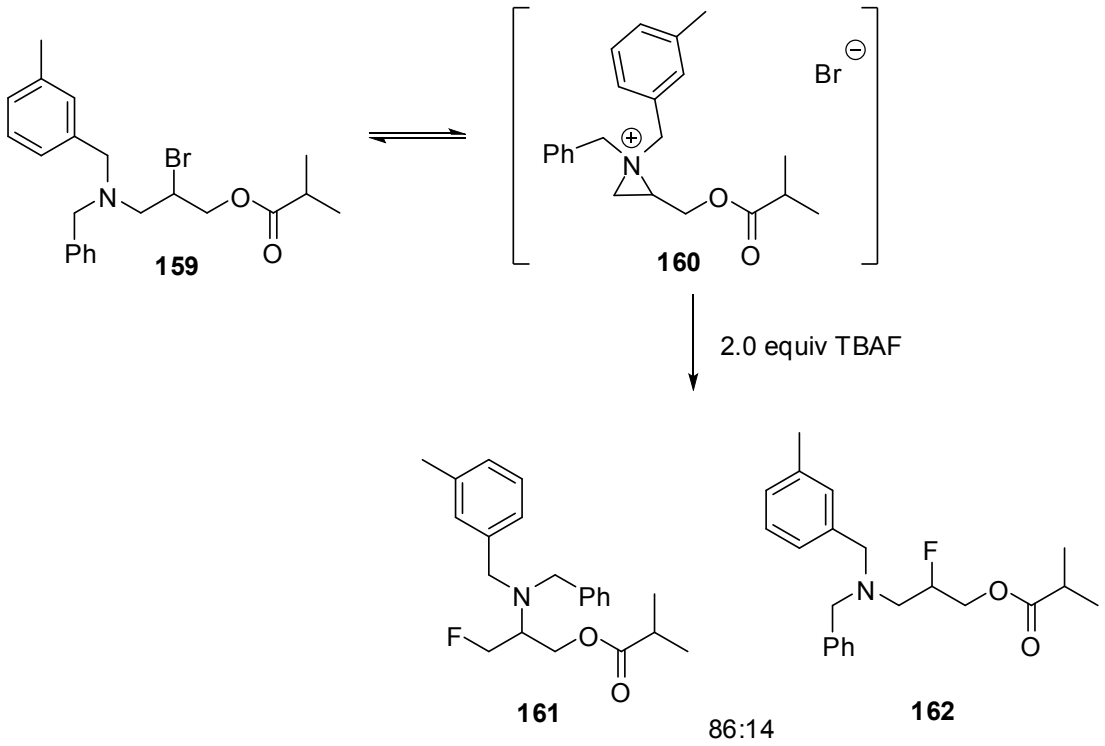
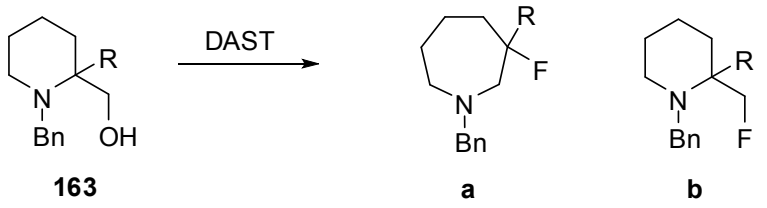


Table 2: Regioselectivity of DAST with 1,2-Aminoalcohols



Entry	Product	R	Ratio (**a**:**b**)	Yield (%)
1	**164**	H	70:30	51:12
2	**165**	Ethyl	100:0	64
3	**166**	Allyl	100:0	76
4	**167**	Phenyl	100:0	76

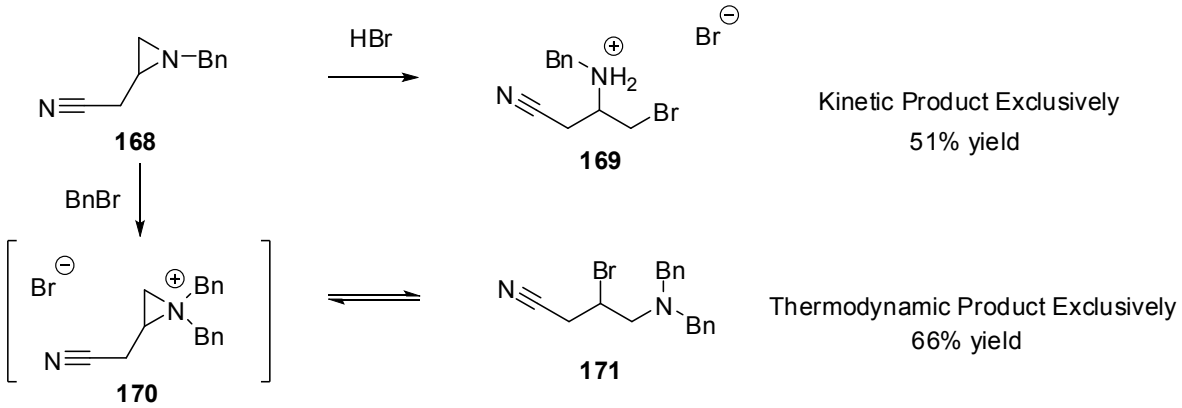
1.3.3f Sulfur as a Nucleophile

Sulfur nucleophiles (thiols, thiophenols, thiolacetate) appear to have regioselectivity that is difficult to predict. Some cases reported that attack occurs at the more hindered position. For example thiocyanate and *n*-propylthiol attack with complete selectivity to the more hindered position.[23] However, in another publication *n*-propylthiol is shown as having complete regioselectivity with attack to the least hindered carbon.[38] The regioselectivity of sulfur nucleophiles in the presence of an activating group however gives predictable regioselectivity with attack at the activated position with the use of a phenyl or carbonyl.[46, 50,55]

1.3.3g Chloride, Bromide and Iodide Nucleophiles

As mentioned in the overview of aziridinium ions the halides from the second row and down (chloride, bromide, and iodide) are nucleophiles for performing ring-opening reactions with aziridinium ions. However, they are also leaving groups which then through a thermodynamic equilibrium can lead to the more energetically favoured product of the two possible 1,2-aminohalides.[23,27] There are a few examples where it appears that the product of the aziridinium ion and a halide other than fluoride give the kinetic product. This can occur when the nitrogen of the ring opening product is protonated by a strong acid to prevent it from reforming the aziridinium ion. A nice comparison of the kinetic product versus a thermodynamic product distribution for bromide was done (**169** and **171**), as shown in Scheme 29.[56]

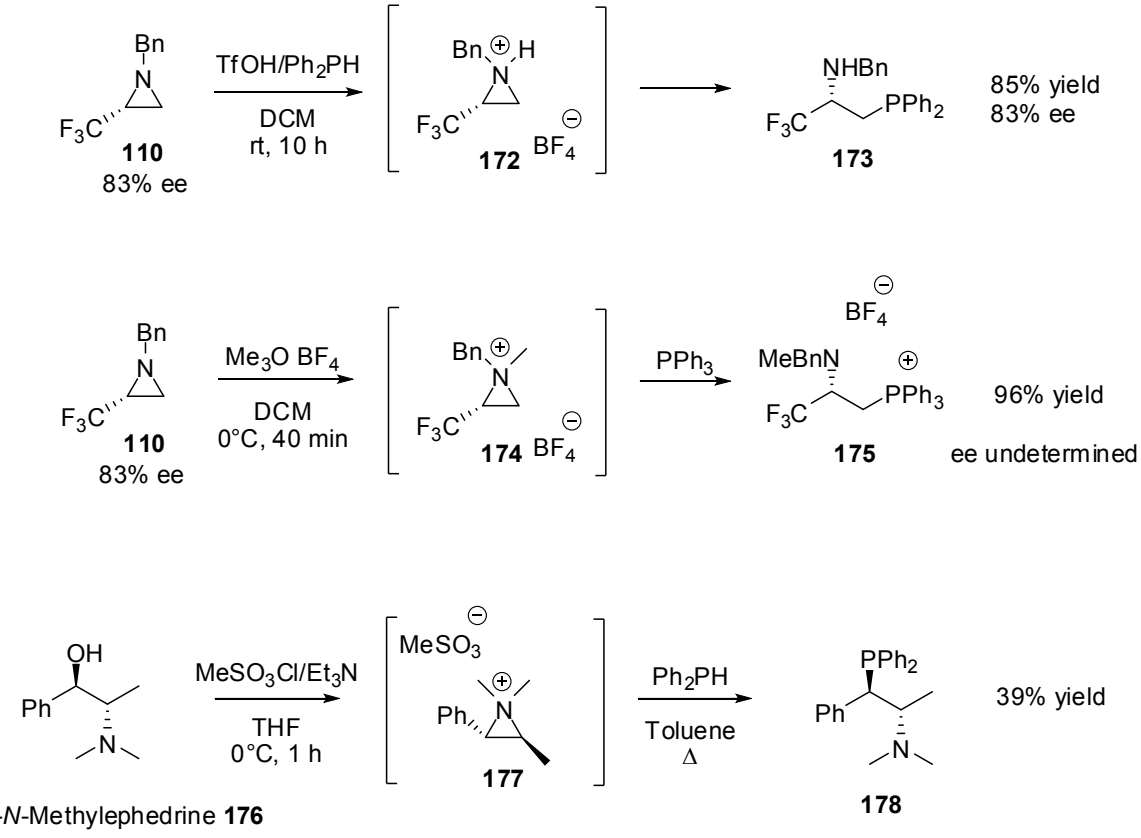
Scheme 29: Kinetic Product and Thermodyamic Products with Bromide



1.3.3h Phosphorous and Selenium Nucleophiles

Examples with phosphorous nucleophiles opening aziridinium ions are quite rare in literature.[41,57] The first example of an aziridinium ion used for this purpose was a protonated aziridine with diphenylphosphine attacking at the least hindered position to give **173** (Scheme 30). The second example showed an *N,N*-dialkylaziridinium ion reacting with triphenylphosphine at the least hindered position selectively to yield **175**. The last example shown has a phenyl as an activating group α to the aziridinium ion carbon. Here, attack of diphenylphosphorane occurred at the activated and more hindered position to give **178**. This last example was used as a method to prepare gram quantities of the enantiopure *P,N*-ligand **178** for asymmetric hydrogenation of ketones.[57]

Scheme 30: Phosphorous Nucleophiles Reacting with Aziridinium Ions



For selenium only one example was found in literature. Phenylselenol attacked the least hindered carbon of the aziridinium ion, giving an excellent yield (97%) and the enantiomeric excess was maintained.[41]

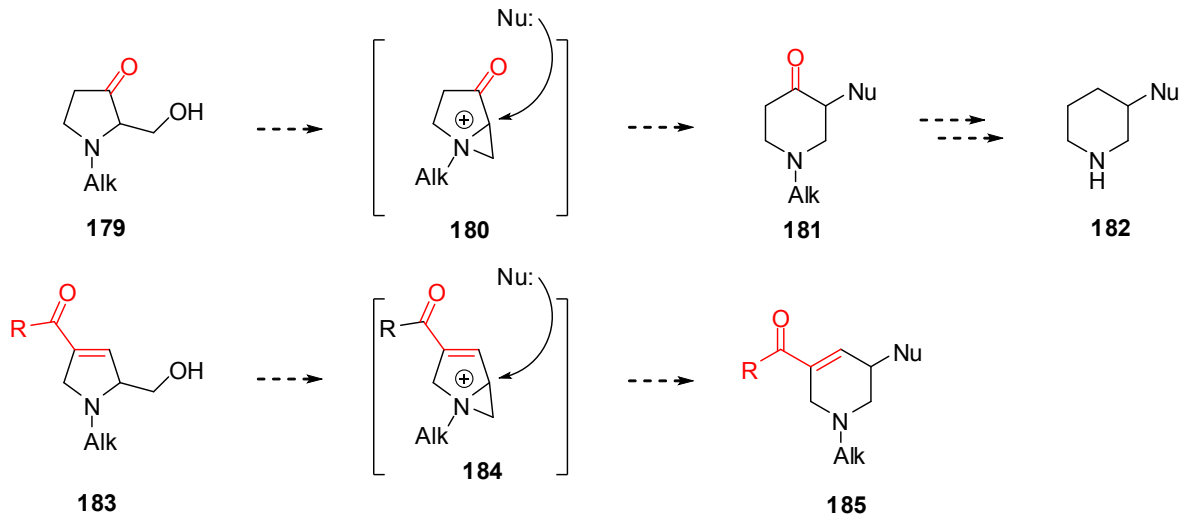
1.4 Hypothesis of the Project

Analysis of the selectivity obtained in reactions with nucleophiles that are poor leaving groups towards aziridinium ions clearly showed a general trend (though with exceptions) the attack occurred at the least hindered position with moderate to excellent selectivity unless an appropriate activating group is employed such as a phenyl or a carbonyl. Cossy's ring expansion from prolinols to piperidines is restricted to labile nucleophiles to obtain the thermodynamic product since they have not employed an activating group in the bicyclic ring system to direct the nucleophile. We believed that with an appropriate activating group the prolinol derivative would ring expand to the piperidine as the kinetic product with a large variety of nucleophiles. Activating groups that have been reported to direct the nucleophiles are carbonyl, the carbonyl vinyl analog, and phenyl.

There are some complications with using a carbonyl in the template to obtain piperidines from 3-oxoprolinols such as **179**; 1) the nucleophiles used with a carbonyl have been mostly limited to heteroatom types, with no organometallics reported. This is likely due to the acidity of the aziridinium ion which has been alluded to in literature[46] 2) the carbonyl would have to be reduced after the ring expansion to obtain the piperidine increasing the length of synthesis after the choice of the nucleophile.

The vinyl analog **183** does not lend itself to this template readily, and if used would require the piperidine product to be substituted at the 5-position by a carbonyl achirally placing a significant restraint on the utility of the method (Scheme 31).

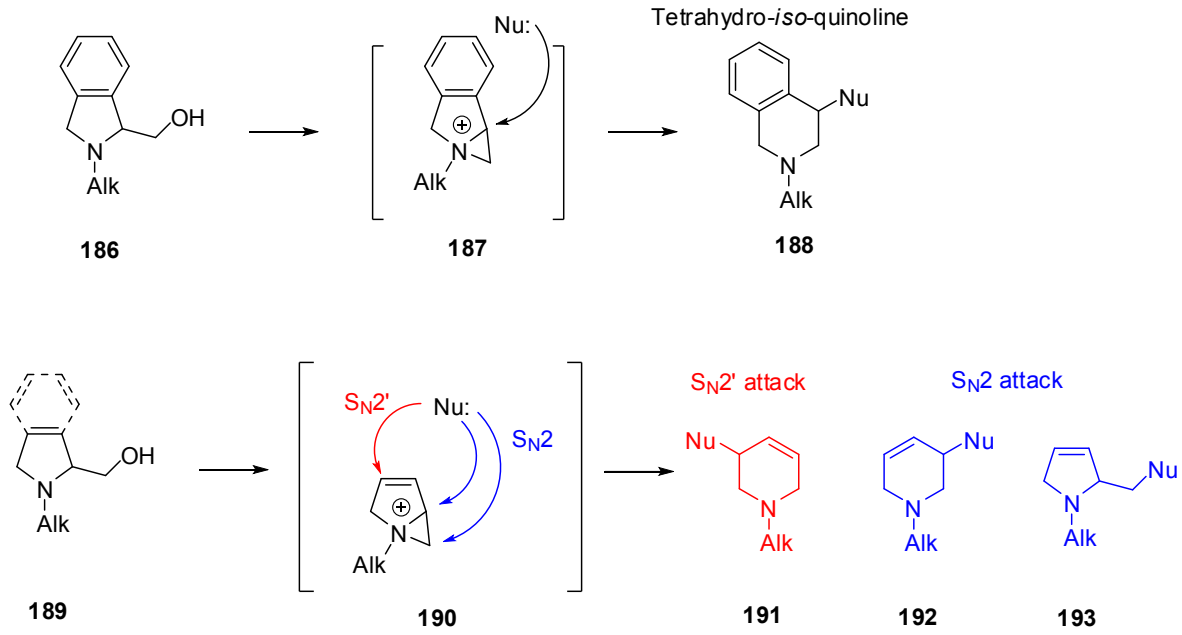
Scheme 31: Hypothesis: Carbonyl in **180** or Vinyl Carbonyl in **184** as a Directing Group



Using a phenyl as an activating group for an aziridinium ion such as **187** would not yield piperidines, but instead *iso*-tetrahydroquinolines and, although they are interesting, they were not the objective of this project. However, conceptually if we remove 4 atoms of the phenyl ring leaving the carbon-carbon double bond we would obtain the tetrahydropyridine **192** (Scheme 32). This could easily be hydrogenated to the desired piperidine while simultaneously removing the protecting group from the piperidine nitrogen. The regioselectivity of nucleophiles towards a vinyl aziridinium ion has not been reported but was believed to react similarily to vinyl epoxides which has been studied extensively.[58]

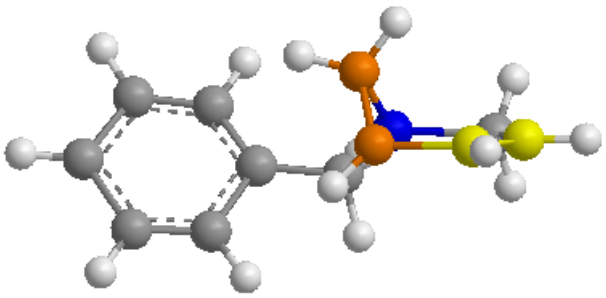
At first glance it appeared that the attack of nucleophiles could not only be at the two aziridinium ion carbons of **190** but also β-to the aziridinium ion through an S_N2' mechanism. However, when one visualizes the intermediate in three dimensions it is apparent that the π system of the alkene and the σ* of the bridging aziridinium ion carbon-nitrogen bond should not have significant orbital overlap (Figure 5). Therefore, S_N2' should not occur due to the conformational constraint of the bicyclic system.

Scheme 32: Hypothesis: Phenyl and Alkene as Directing Groups



In Figure 5, the alkene carbons are shown as yellow and the aziridinium carbons as orange. The σ* of the bridging aziridinium carbon-nitrogen bond points towards the viewers left shoulder, and the alkene π electrons are vertical to demonstrate this lack of orbital overlap. For this project we chose to have the *N*-alkyl group as benzyl, since it can be removed easily (hydrogenation) unlike most other alkyl groups.

Figure 5: Conformation of the *N*-Benzyl-Aziridinium Ion with an Alkene as a Directing Group



We sought to answer whether the alkene was sufficiently strong to direct the nucleophiles to obtain 3-substituted piperidines, and second if in fact 3-substituted piperidines were obtained that they were gained through an S_N2 mechanism.

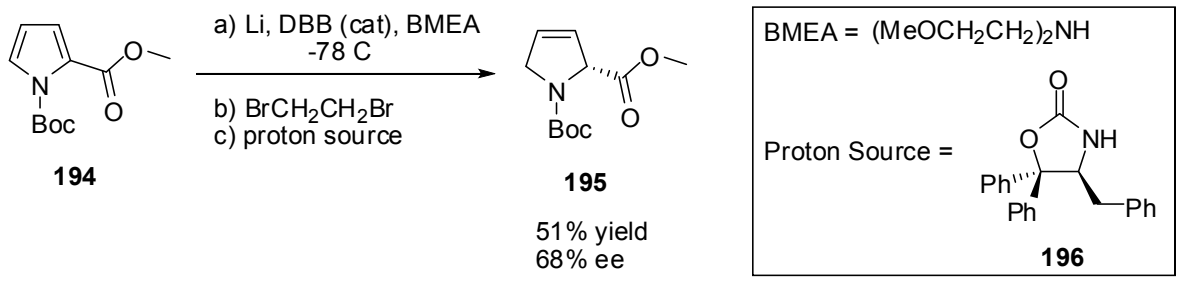
Chapter 2: Synthesis of 3,4-Dehydroprolinols

2.1 Introduction

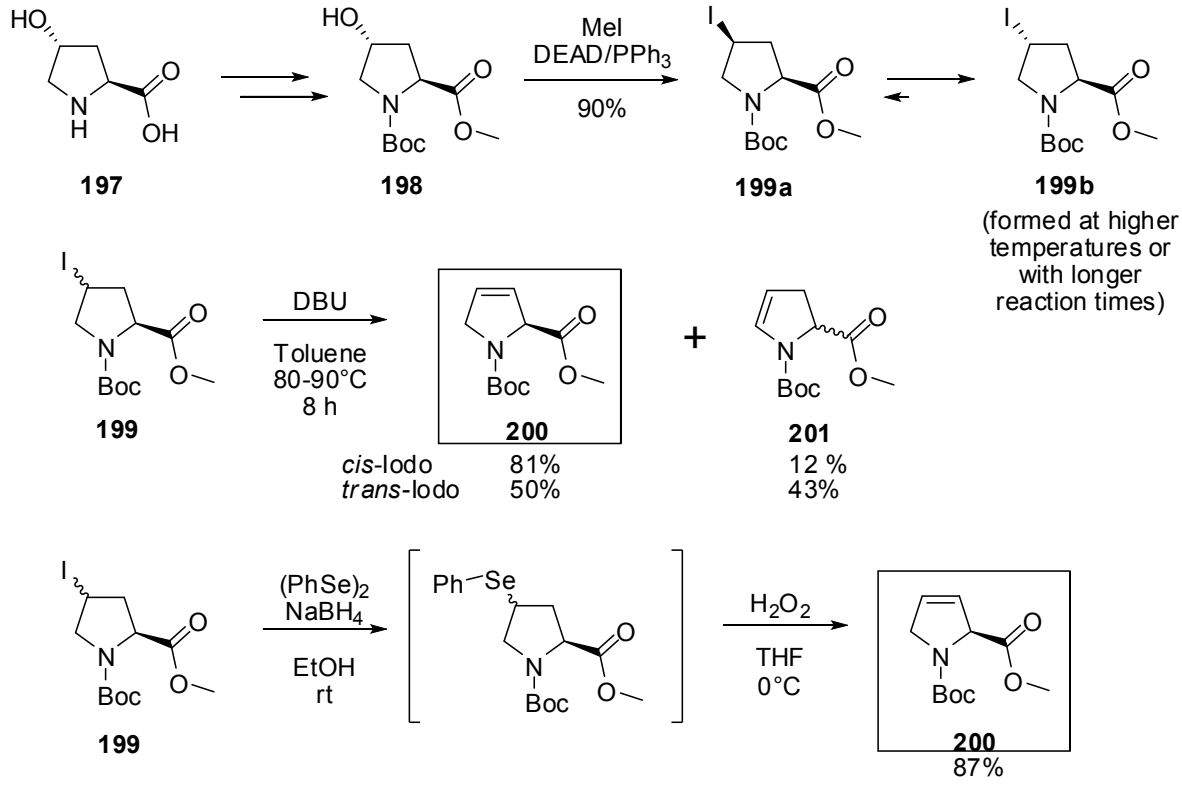
For initial proof of concept, we sought to explore a published concise synthetic route to enantiopure *N*-benzyl-3,4-dehydroprolinols as the precursor to piperidines. Industrially, 3,4-dehydroproline is obtained in enantiopure form on large scale through a partial Birch reduction of the pyrrole followed by a diastereotopic salt resolution of the acid.[59] This method works quite well with an *N*-Boc derivative of an unsubstituted substrate, but we wished to have a general synthetic route to this family of compounds that allows functionalization on the ring diastereoselectively so we did not pursue this avenue. Donohoe has published an interesting enantioselective partial Birch reduction of pyrroles via protonation with the chiral proton source **196** to obtain 3,4-dehydroproline derivatives with moderate enantiomeric excess (Scheme 33).[60] Though this method is interesting, it does not give access to enantiopure materials and has not been shown to give substitution at other points of the dihydropyrrole so it was not investigated here.

A more common and well known synthetic method to prepare 3,4-dehydroproline is from the commercially available and inexpensive 4-hydroxyproline. This is a well established method first published in 1982 (Scheme 34). Though, it is also known to not yield enantiopure products as partial epimerization occurs during the synthesis and it has only been published with an *N*-Boc protecting group.[61] Another key drawback of synthesizing a proline derivative from 4-hydroxyproline is the lack of opportunity to substitute the ring of dihydropyrrole.

Scheme 33: Donohoe's Partial Birch Reduction to 3,4-Dehydroproline

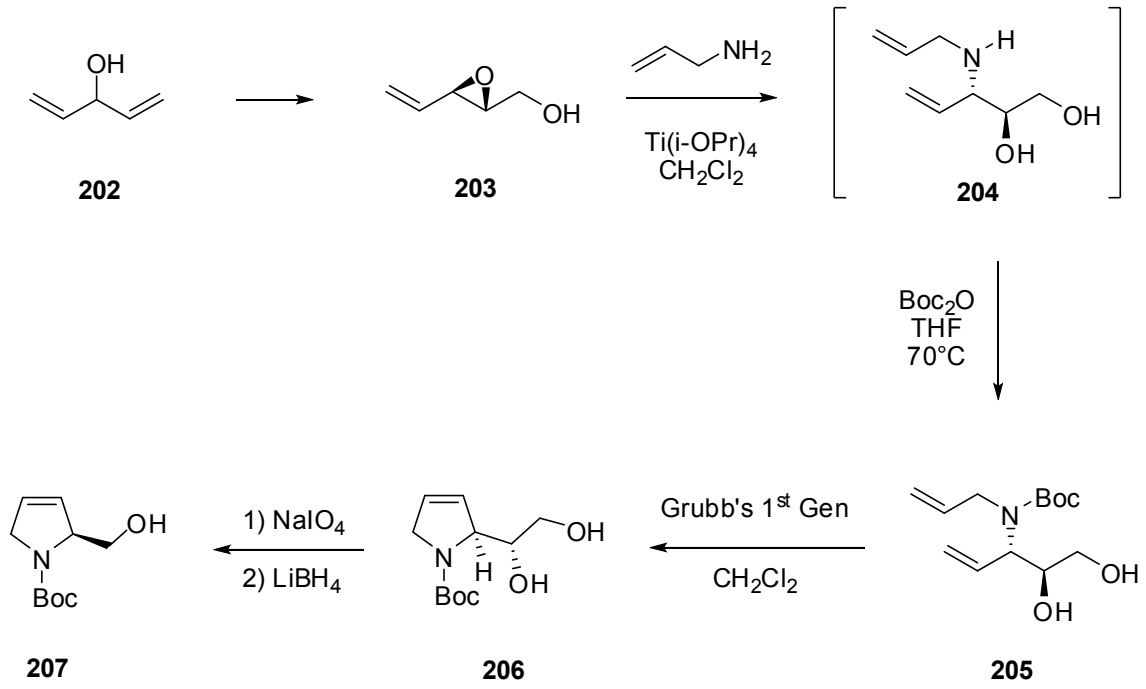


Scheme 34: 4-Hydroxyproline as a Precursor for 3,4-Dehydroproline



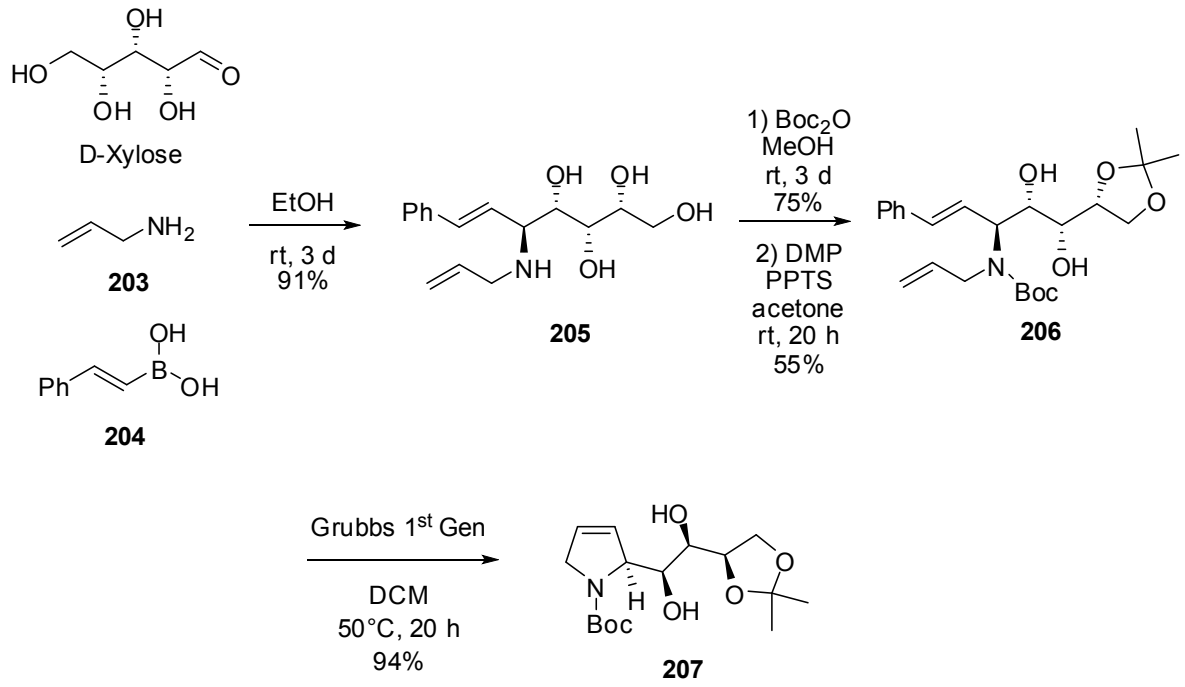
One approach to obtain *N*-Boc-3,4-dehydroprolinol **207** used a Sharpless epoxidation and Payne rearrangement to obtain **203** from **202**. The opening of the epoxide with an amine led to **204**, which after protection underwent a ring-closing-metathesis, followed by Criegee oxidation and *in-situ* reduction to produce **207** (Scheme 35).[62] This is a powerful method that gave an excellent enantiomeric excess (>99%). However, preparing the vinyl epoxide in enantiopure form through an epoxidation is not trivial even with an alcohol anchor. A disadvantage of this method is that the conditions to obtain the desired epoxide with a variety of substituents would likely have to be optimized for each substituent, and they would probably not yield enantiopure products. Also, the opening of the chiral epoxides generated could proceed through an S_N2' mechanism potentially complicating the reaction mixture for analogs with varying substitution. One potential advantage would be the ability to control whether the 1,2-aminoalcohol was *syn* or *anti*, thereby controlling the relative stereochemistry of the 2,3-substituents of the piperidine final product.

Scheme 35: 3,4-Dehydroprolinol from a Sharpless Epoxidation



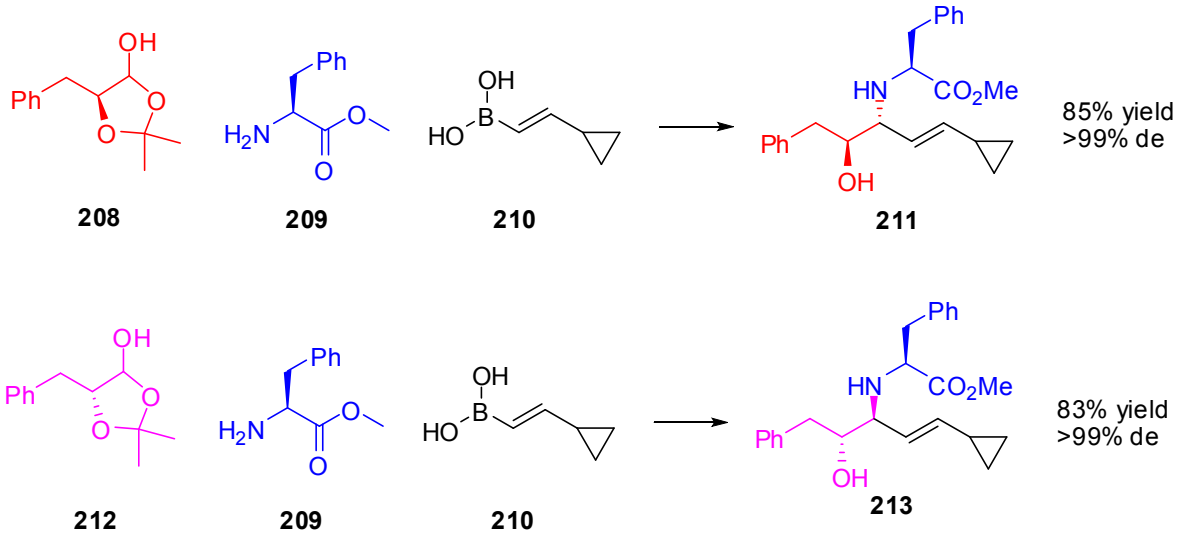
Another methodology to a 3,4-dehydroprolinol derivative is the interesting use of a variant of the Petasis-Mannich reaction (Scheme 36).[63] The authors used D-Xylose as an α-hydroxyaldehyde equivalent, reacting it with an amine and boronic acid to obtain a 1,2-amino alcohol. They then protected the nitrogen, and followed this by a ring-closing-metathesis. It has been demonstrated by Petasis that the 1,2-aminoalcohol, when prepared from an enantiopure α-hydroxyaldehyde, is obtained enantiopure and that it is prepared with >99% diastereoselectivity.[64] Schreiber *et al* demonstrated for this reaction that when a chiral amine was used, the absolute configuration of the amine had no impact on the stereochemical outcome or diastereoselectivity of the new chiral center that is formed during this reaction (Scheme 37). An advantage of this method is that it allows functionalization at the 2 and 5 positions of the 3,4-dehydroprolinol as a single diastereomer in enantiopure form.[65]

Scheme 36: 3,4-Dehydroprolinol from a Petasis-Mannich Condensation

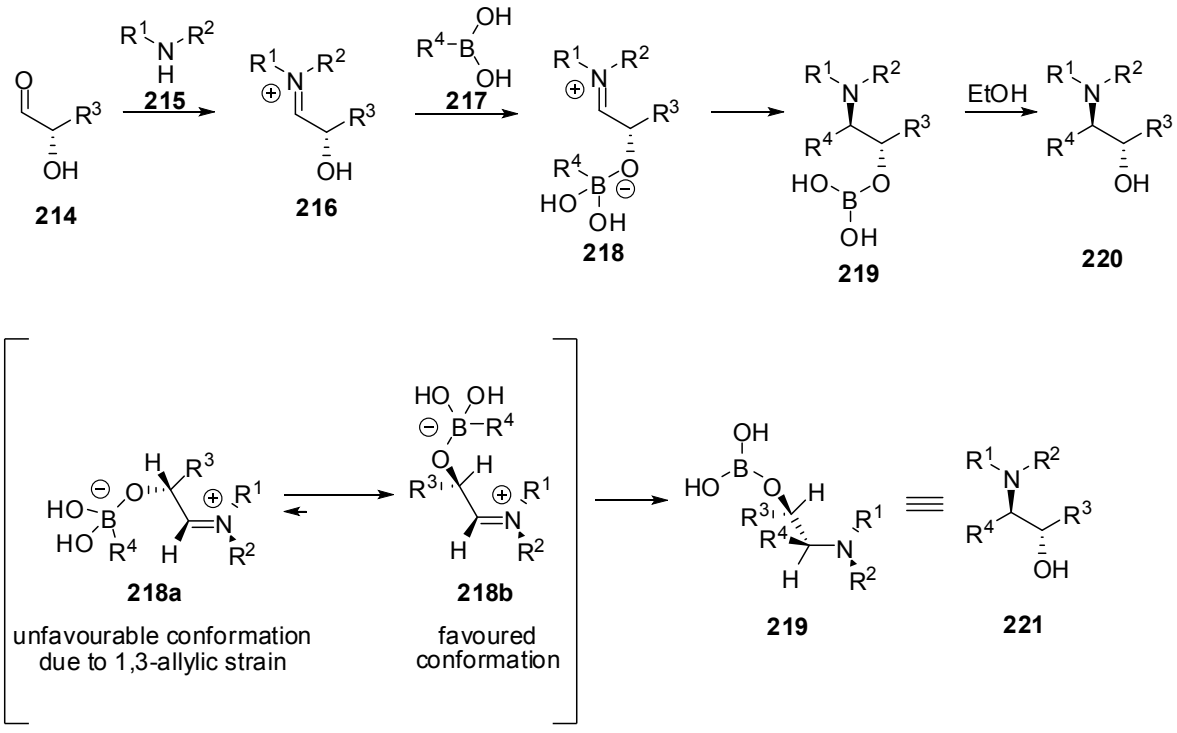


The mechanism of the Petasis-Mannich reaction has been studied for the different variations and is the subject of a recent review. The first step of the reaction has been proposed to be the formation of imine **216**, followed by coordination of the boronic acid or ester **217** by the hydroxyl forming boronate **218**, transfer of the group of the boronic acid or ester to the imine to obtain **219**, and hydrolysis of the resulting intermediate to obtain the 1,2-aminoalcohol **220**. The high diastereoselectivity for this variant has been rationalized to occur from the coordination of the hydroxyl with the boronic acid or ester, and minimization of the 1,3-allylic strain (**218a** vs **218b**) as seen in Scheme 38.[66]

Scheme 37: Stereochemical Outcome of the Petasis-Mannich Reaction



Scheme 38: Proposed Mechanism of the Petasis-Mannich Reaction with α-Hydroxyaldehydes



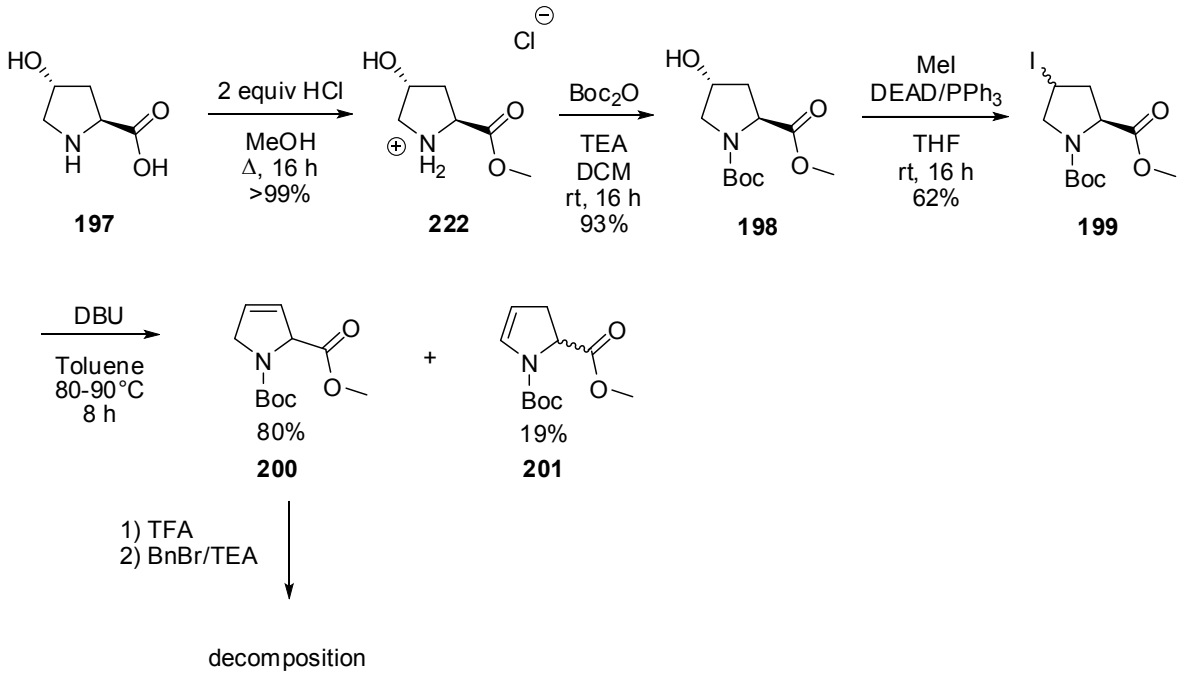
Unfortunately, this elegant variant has been rarely reported in the literature since its introduction in 1998. This is likely due to the α-hydroxyaldehyde and its hemiacetal equivalent being non-trivial to prepare in large amounts in enantiopure form unless a sugar

is employed thereby limiting its usefulness. However, we decided to pursue this avenue since it gives access to enantiopure 3,4-dehydroprolinols with a variety of substituents about the ring with high diastereoselectivity.

2.2 Synthesis of *N*-Benzyl-3,4-Dehydroprolinol from 4-Hydroxyproline

For initial proof of concept we required *N*-benzyl-3,4-dehydroprolinol. For this we decided to prepare it from 3,4-dehydroproline which was made using a modified version of the well established method from 4-hydroxyproline. Initially we followed the original protocol using *N*-Boc as a protecting group, and were successful in preparing the known compound *N*-Boc-3,4-dehydro-methylprolinate **200**.[61a] However, the attempts to deprotect the Boc of **200** and alkylate the nitrogen with a benzyl caused decomposition (Scheme 39).

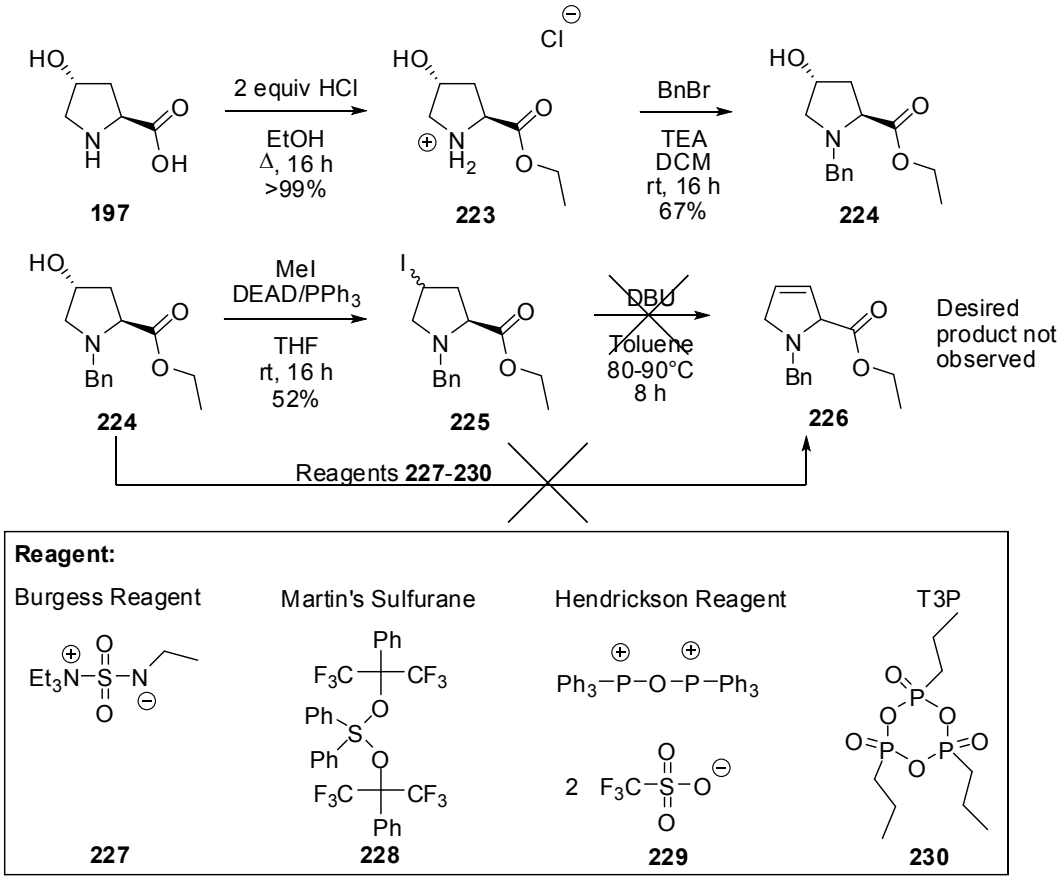
Scheme 39: An Attempt to Prepare *N*-Benzyl-3,4-Dehydroprolinol



The fact that a simple deprotection of **200** and alkylation caused decomposition was surprising. Possibly, it may have been the presence of acid, oxidation of the dihydropyrrole to the pyrrole by air, or a combination of the two or other factors that led to decomposition. Since the purpose of this experiment was simply to prepare a precursor for proof of concept we did not pursue the matter further. We decided to simply alter the protecting group in the

beginning of the synthesis to avoid the complication resulting from Boc cleavage. We first investigated the use of a benzyl as a nitrogen protecting group replacement. Unfortunately, with an *N*-benzyl protecting group the elimination step did not occur during the 3,4-dehydroproline synthesis from 4-hydroxyproline despite a number of conditions for elimination being attempted such as: 1) conversion of the alcohol to an iodide and elimination of that iodide[67] with base, 2) Burgess reagent, 3) Martin's sulfurane, 4) the Hendrickson reagent which typically with secondary alcohols leads to elimination,[68] and 5) T3P, a cyclic phosphate patented for the purpose of conversion of an alcohol to alkene through elimination[69] (Scheme 40).

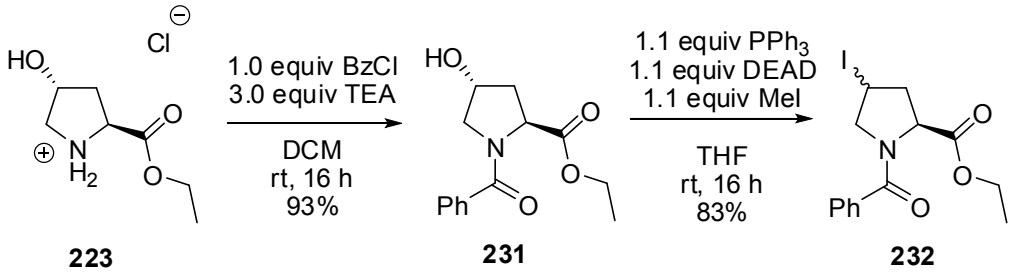
Scheme 40: *N*-Benzyl-3,4-dehydroprolinol From *N*-Benzyl-4-hydroxy-methylprolinate



Since an *N*-alkyl protecting group failed to yield the elimination, but an *N*-carbamate facilitated the elimination, it was decided to attempt the synthesis with an *N*-amide as it should give similar results to the carbamate. The synthesis was repeated using *N*-benzoyl

as the protecting group which could be reduced to the benzyl, in place of Boc as a protecting group. The elimination of the iodide from **232** to the alkene **233** proceeded smoothly (Scheme 42). It was found that the elimination step if done under basic conditions led to complete epimerization of the chiral center to give **233a** (0% ee) as well as **234**. It was also found that if the elimination was done under the essentially neutral conditions using phenylselenide that a small amount of epimerization occurred to give **233b** (94% ee from >99% ee). Though the partial epimerization was unfortunate since it procluded this route as a viable method to an enantiopure precursor, the combination of an enantioenriched and the racemic precursor being obtained from the same advanced intermediate was in fact incredibly useful for proof of concept studies - see Chapters 3 and 4.

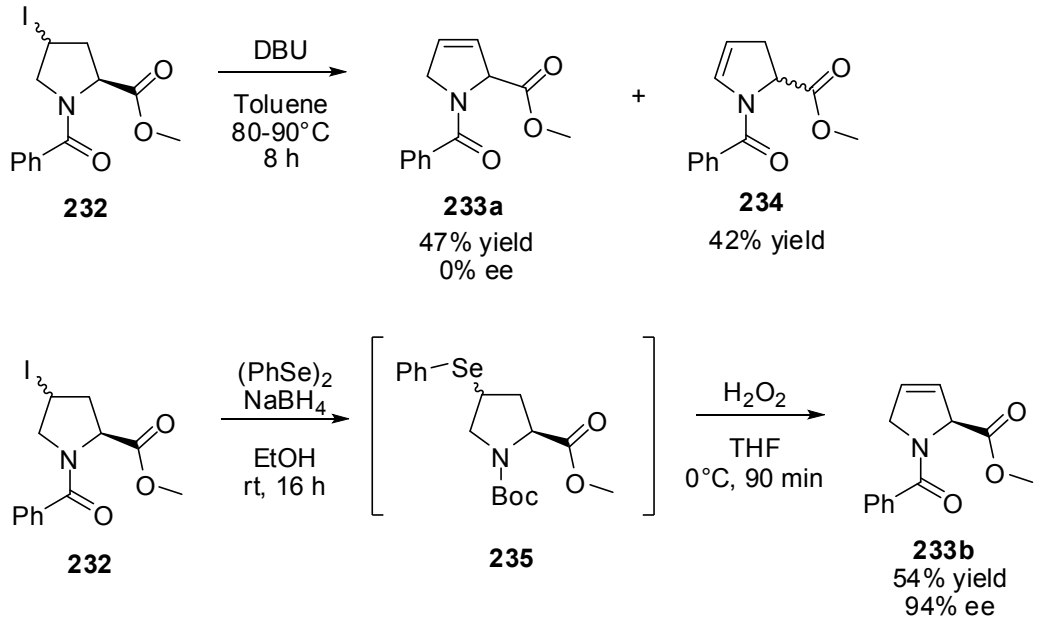
Scheme 41: *N*-Benzoyl-4-iodo-ethylprolinate



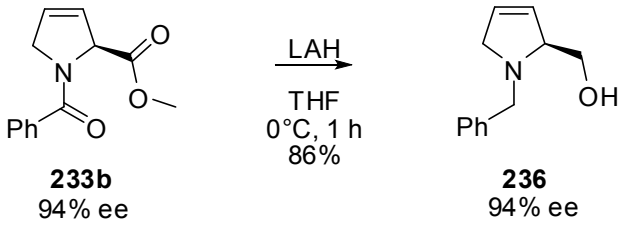
223 **231** **232**

The reduction of the benzoyl could be accomplished with lithium aluminum hydride which had the added benefit of reducing the ester to the desired alcohol simultaneously, thereby limiting the number of synthetic steps required to prepare *N*-benzyl-3,4-dehydroprolinol **236** (Scheme 43).

Scheme 42: Reaction Conditions to Gain Iodine Elimination Causes Epimerization



Scheme 43: Synthesis of *N*-Benzyl-3,4-dehydroprolinol **236**

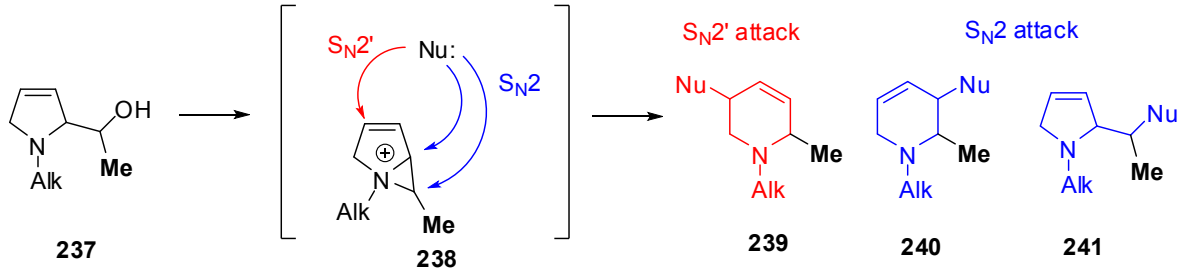


2.3 Synthesis of *N*-Benzyl-3,4-Dehydroprolinols via the Petasis-Mannich Reaction

Initial proof of concept could be accomplished with the *N*-benzyl-3,4-dehydroprolinol **233** available from 4-Hydroxyproline. However, due to the possibility of an S_N2' mechanism the regioselectivity and stereochemistry of the piperidine derivatives prepared through this method would have to be determined. There are few methods to prepare such piperidines, and reference compounds were not available for those piperidines prepared for the initial proof of concept. Therefore, we decided to prepare another dihydropyrrole precursor containing an additional substituent, so that the regioselectivity and relative stereochemistry could be elucidated from products such as **239** and **240**, as seen in Scheme 44. An enantiopure and diastereoselective method to prepare the dihydropyrrole was still required.

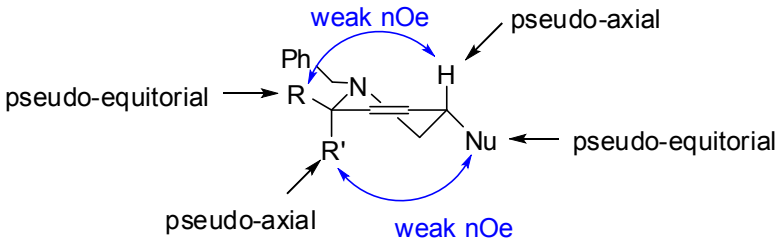
Of the possible routes discussed in section 2.1, the Petasis-Mannich reaction was chosen as it is quite general, could give enantiopure materials, and allow substitution at various points of the dihydropyrrole with high diastereoselectively (>99% de).

Scheme 44: Methyl Tag to Demonstrate the Mechanism of Ring Expansion



The desired substitution pattern was a 2-methyl-3-substituted piperidine for ease of assignment by NMR. With substituents on adjacent carbons it is a simple matter on a cyclic system to assign whether they are *syn* or *anti* – and the relative stereochemistry between the two substituents being conserved would be important for understanding the mechanism. If the substituents were in a 2,5-relationship to one another as in the S_N2' product in Figure 6, their relative stereochemistry would be difficult to ascertain by NMR even in this cyclic system. This is due to a lack of coupling constants between them for assignment and an inability to rely on nOe directly as the 2,5-relationship in a 6-membered ring has weak nOE interactions due to the conformation of the substituents about the ring.

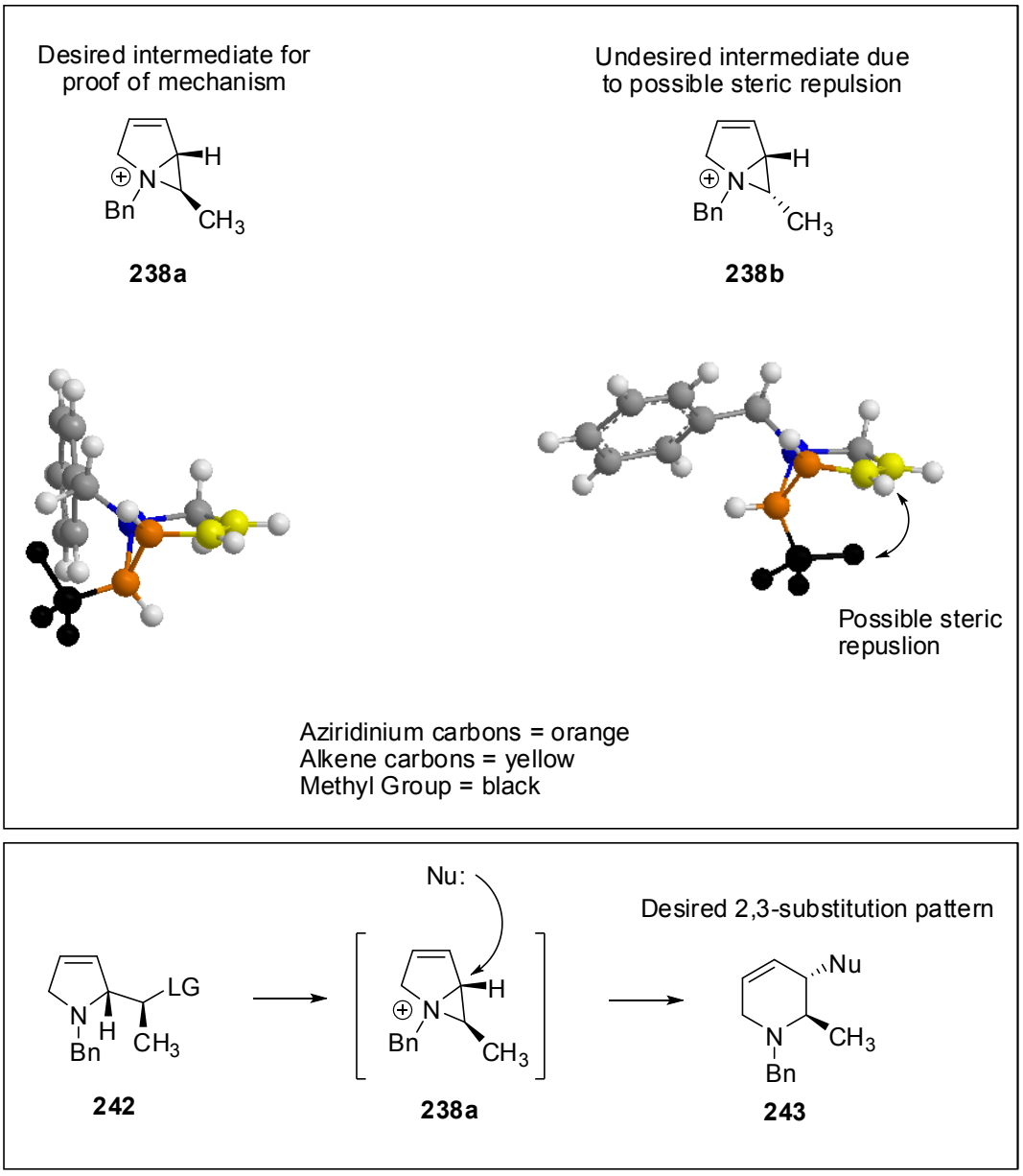
Figure 6: Weak nOe Interactions Between the 2- and 5-Substituents on a 6-Membered Ring



Since the mechanism was expected to be S_N2, to obtain a 2,3-disubstituted piperidine the desired pyrrolidine precursor would be **238a** or its enantiomer as shown in Figure 7. This

diastereomer was desired so as to avoid complications of steric repulsion in the aziridinium ion between the methyl tag (black) and the bicyclic ring system (**238a** vs **238b**).

Figure 7: Desired Diastereomer to Avoid Possible Steric Interactions

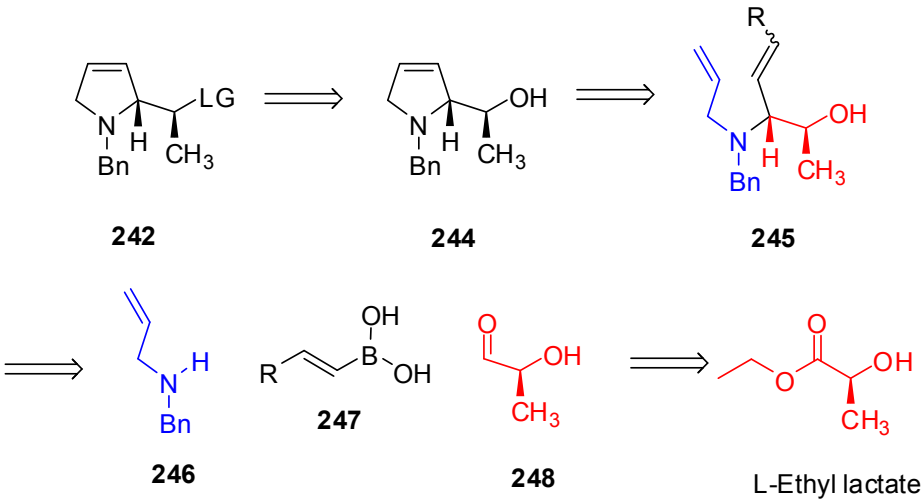


2.4 α-Siloxyetheraldehydes as Prescursors for the Petasis-Mannich Reaction

The Petasis-Mannich reaction was seen as giving the desired (*S*)-1-((*R*)-1-benzyl-2,5-dihydro-1H-pyrrol-2-yl)ethanol diastereomer **242** selectively. A retrosynthetic analysis of the desired diastereomer leads to readily available ethyl lactate which can be obtained in

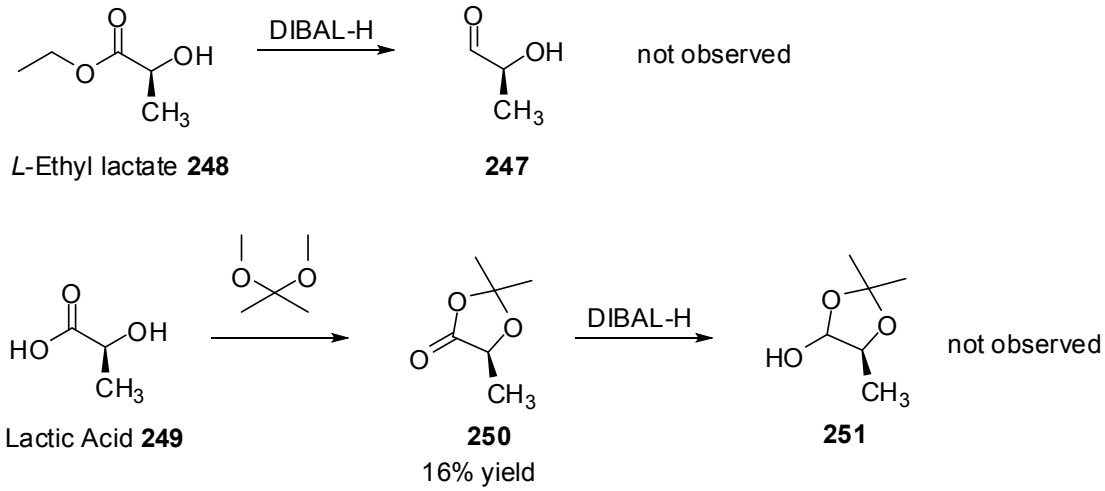
enantiopure form (Scheme 45). As stated in section 2.1, the Petasis-Mannich reaction has been rarely reported due to the difficulty of preparing the α-hydroxyaldehyde in enantiopure form. For this reason Petasis and others have used a ketal equivalent of the α-hydroxyaldehyde[64,65,66]. However, this is also difficult to prepare and suffers from low yields.

Scheme 45: Retrosynthesis of Desired Diastereomer



The DIBAL-H reduction of ethyl lactate was done, but we failed to isolate the α-hydroxyaldehyde **247**. The reported yields to prepare the hemiacetal **251** are quite low also (16% over 2 steps).[70] Attempted isolation of the hemiacetal **251** that has been reported to work with the Petasis-Mannich reaction through a published protocol[70], was also unsuccessful (Scheme 46).

Scheme 46: Attempts to Prepare the α-Hydroxyaldehyde or Latent Equivalent

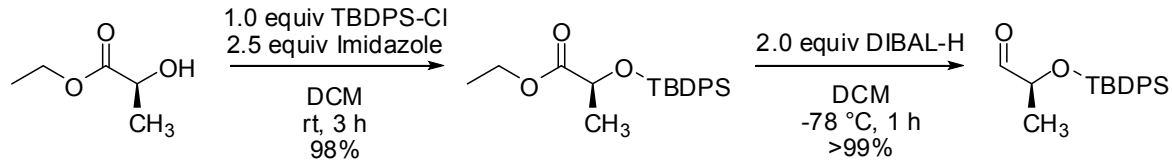


As the dehydroprolinol derivative was desired, and this synthetic route was seen as a powerful concise method that allowed functionalization of the other points, a solution was needed for this apparent drawback of the Petasis-Mannich reaction. α-Siloxy-etheraldehydes are trivial to prepare in large amounts in enantiopure form from the corresponding esters by a reduction with DIBAL-H. However, they have not been previously reported to be a suitable reactant for the Petasis-Mannich reaction. They lack a free hydroxyl for coordination to the boronic acid or ester to facilitate the transfer of the boronate group to the imine. It was hypothesized that an *in-situ* deprotection of the α-siloxyetheraldehyde would free the hydroxyl and then allow it to coordinate the boronic acid or ester. The α-siloxyetheraldehyde **253** was prepared from L-ethyl lactate using a known procedure (Scheme 47).[71] Reaction conditions were tested using the α-siloxyetheraldehyde **253**, amine **246** and (*E*)-styrylboronic acid. For a silyl protecting group, diphenyl-*tert*-butylsilyl was employed since it is UV visible making the isolation of the aldehyde simple.

It was found that when HF in Pyridine was employed for the *in-situ* deprotection during the Petasis-Mannich reaction that the desired product was not obtained. However, using tetrabutylammonium fluoride (TBAF) for the *in-situ* deprotection was successful so a quick optimization was undertaken (Table 3). It was found that additional equivalents of reagents other than TBAF had no significant impact on the isolated yield (entries 1-3,5-6), however

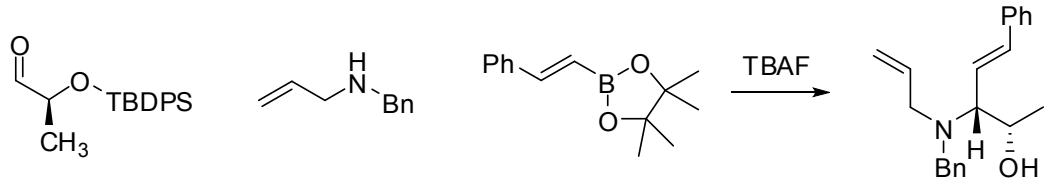
the use of additional TBAF had a dramatic negative impact on the yield (entries 4 and 7). Using one equivalent of each reagent was optimal. Refluxing the reaction mixture was tolerated with no apparent effect on the diastereoselectivity, thereby reducing the reaction time from 3 days to 16 hours. In the optimization study, the pinacol ester was used in place of the equivalent boronic acid since it is quite simple to prepare from inexpensive reagents. With optimal conditions the reaction was repeated using the boronic acid (entry 8) which provided a superior yield when compared to the boronic pinacol ester. Also, it should be noted that the optimized conditions of the Petasis-Mannich reaction using an α-siloxyetheraldehyde with an *in-situ* deprotection gave a comparable yield (entry 8) to the original conditions by Petasis when dibenzylamine was used in place of allylbenzylamine (entry 9).[64]

Scheme 47: Preparation of α-Siloxyetheraldehydes



L-ethyl lactate **248** **252** **253**

Table 3: Optimization for Petasis-Mannich Reaction with α-Siloxyetheraldehydes



253 **246** **254** **255**

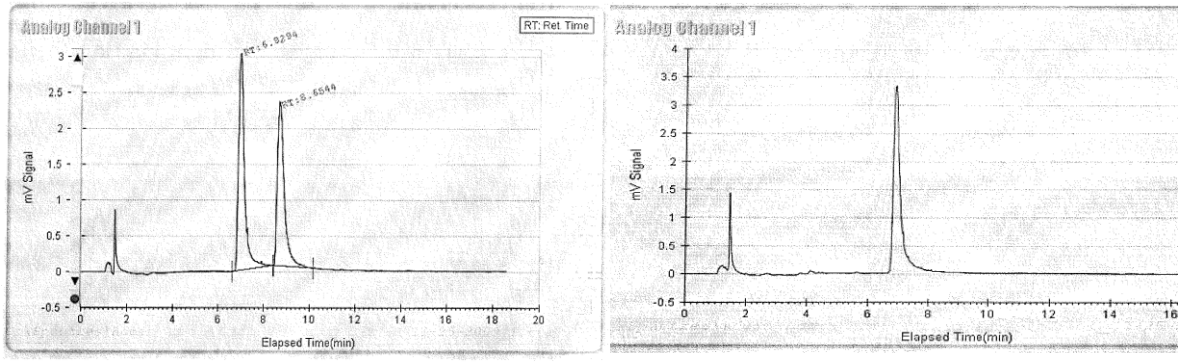
Entry	Aldehyde **253** Equivalents	Amine **246** Equivalents	Boronic ester **254** Equivalents	TBAF Equivalents	**255** Isolated Yield
1	1	1	1	1	64%
2	1	1.2	1.1	1	62%
3	**2**	1.1	1.1	1	59%
4	**2**	1	1	**2**	40%
5	1	**2**	1	1	58%
6	1	1	**2**	1	61%
7	1	1	1	**5**	0%
8	1	1.1	1.1*	1.06	83%*
9	1**	1**	1	0	84%**

* :The boronic acid analog was used in place of the boronic ester

**: Literature value[64]: $HNBn_2$ was used in place of $HN(CH_2CH{=}CH_2)Bn$ and the α-hydroxy-aldehyde was unprotected

The Petasis-Mannich reaction is known to proceed with >99% diastereoselectivity and to maintain the enantiomeric excess of the aldehyde precursor.[64] Since a modification was done to the reaction to make one of the precursors more easily available, the diastereoselectivity and enantiomeric excess of the product had to be confirmed. By ^1H NMR it was apparent both from the reaction mixture and the purified 1,2-aminoalcohol that the diastereoselectivity was >99:1. The scale-up of **255** from the pinacol ester gave a lower yield (40%) than the smaller scale reactions, but the undesired diastereomer was isolated in only a 0.1% yield confirming the diastereoselectivity of >99%. When this reaction was done with dibenzylamine it gave an equivalent yield and the same diastereomer as that prepared by Petasis confirming that the new conditions did not affect the stereochemical outcome. The enantiomeric excess of the 1,2-aminoalcohol **255** was confirmed to be >99% as not even a trace of the enantiomer at 8.65 minutes in the SFC chromatogram was visible, demonstrating that the new conditions did not provoke epimerization of the chiral center (Figure 8).

Figure 8: Petasis-Mannich Product SFC Chromatograms Demonstrating the Enantiomeric Excess

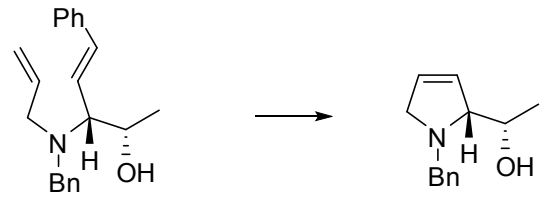


Racemic **255** Enantiopure **255**

2.5 Ring-Closing-Metathesis Optimization to Prepare *N*-Benzyl-3,4-dehydroprolinols

A ring-closing-metathesis optimization was undertaken to convert the 1,2-aminoalcohol **255** to the desired dehydroprolinol **244** (Table 4). The basic nitrogen was a cause of concern as it is well known that such nitrogens can complex the ruthenium of the RCM catalyst and deactivate it. However, it is known that if the nitrogen is properly sterically hindered it will be prevented from complexing the metal center of the catalyst, allowing the reaction to proceed. It is also known that the nitrogen can be deactivated by simple protonation with a strong acid.[72] Various commercially available catalysts were investigated, as well as reaction conditions.

Table 4: Optimization of the Ring-Closing-Metathesis



255 **244**

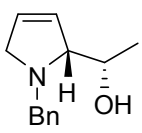
Trial	Catalyst	mol % loading	Concentration (M)	**244** Yield (%) (% brsm)	Solvent, Temperature, and Time
1	Grubbs 1st Gen	4	0.03	47 (52)	DCM reflux, 16h
2	Grubbs 2nd Gen	1	0.03	**70 (79)**	DCM reflux, 16h
3	Hoveyda-Grubbs 1st Gen	1	0.03	34 (47)	DCM reflux, 16h
4	Hoveyda-Grubbs 2nd Gen	1	0.03	58 (58)	DCM reflux, 16h
5	Grubbs 2nd Gen	1	0.1	55 (62)	DCM reflux, 16h
6	Grubbs 2nd Gen	1	0.003	**67 (72)**	DCM reflux, 16h
7	Grubbs 2nd Gen	3	0.003	50 (62)	DCM reflux, 16h

Of the commercially available catalysts investigated (Table 4, entries 1-4), Grubbs' 2nd generation catalyst gave superior results to obtain **244** with a low catalyst loading (entry 2). When Grubbs' 2nd generation catalyst was used with a higher concentration the yield of **244** was adversely affected (entry 5). Doing the reaction at a lower concentration had no significant impact on the yield (entry 6 vs 2). Increasing the catalyst loading had a negative impact on the yield (entry 7). It was observed during the optimization that when the loading of the catalyst was decreased below 1 mol percent, the conversion of **255** to **244** was incomplete even with prolonged reaction times. Therefore, 1 mol % of Grubbs 2nd generation catalyst in refluxing DCM, at 0.03M was seen as the optimal conditions for conversion of the Petasis-Mannich product to the desired *N*-benzyldehydroprolinol **244**.

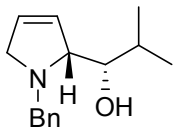
2.6.1 (S)-1-((R)-1-Benzyl-2,5-dihydro-1H-pyrrol-2-yl)-2-methylpropan-1-ol via the Petasis-Mannich reaction and RCM

Now that a viable synthetic route to the desired dehydroprolinol was obtained, variations of the substitution pattern around the dihydropyrrole ring was desired for three reasons; 1) to demonstrate that the synthesis was general, 2) to demonstrate that the other positions could be substituted diastereoselectively in piperidine products, and 3) that changing the substituents of the dihydropyrrole ring had no impact on the regiochemical and stereochemical outcome during the ring expansion. For these reasons, it was decided to prepare analogs where the methyl was replaced by a smaller and larger group - H, and *i*-Pr (Figure 9). Though *N*-benzyl-3,4-dehydroprolinol was previously prepared from 4-hydroxyproline, the Petasis-Mannich reaction was seen as another synthetic route to this desired aminoalcohol since it had not been prepared in enantiopure form from 4-Hydroxyproline. Also, it was deemed necessary to prepare both diastereomers in which the 5-position of the dihydropyrrole was substituted with a bulky group for the goals stated above.

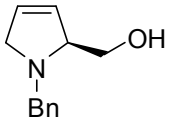
Figure 9: Desired Dehydroprolinols



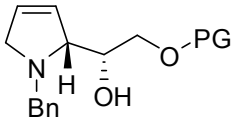
244
previously prepared



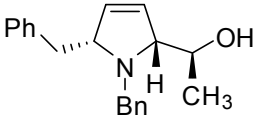
256



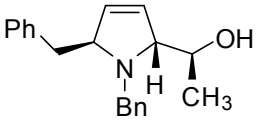
236
enantiopure



257



258

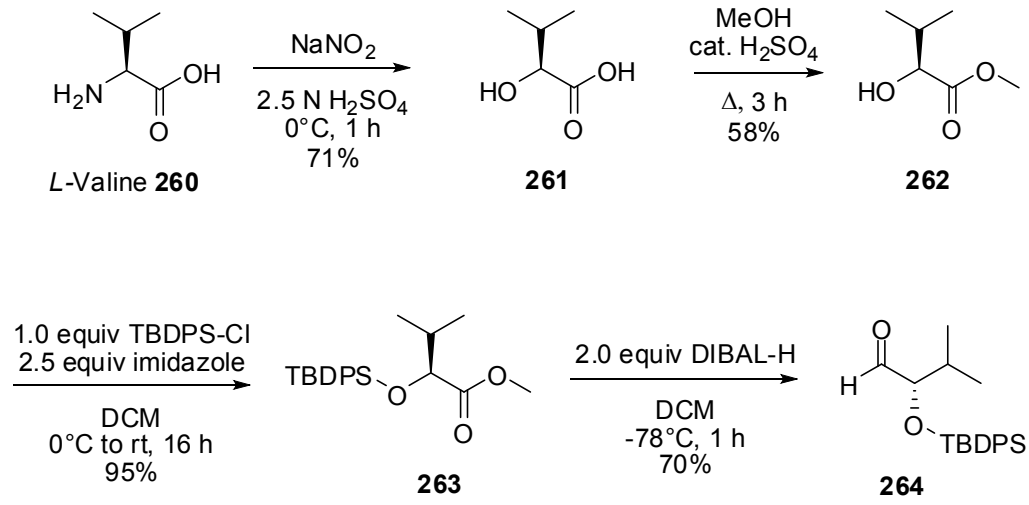


259

Compound **244** had been previously prepared as a single diastereomer and in enantiopure form for the optimization of the Petasis-Mannich reaction and ring-closing-metathesis from

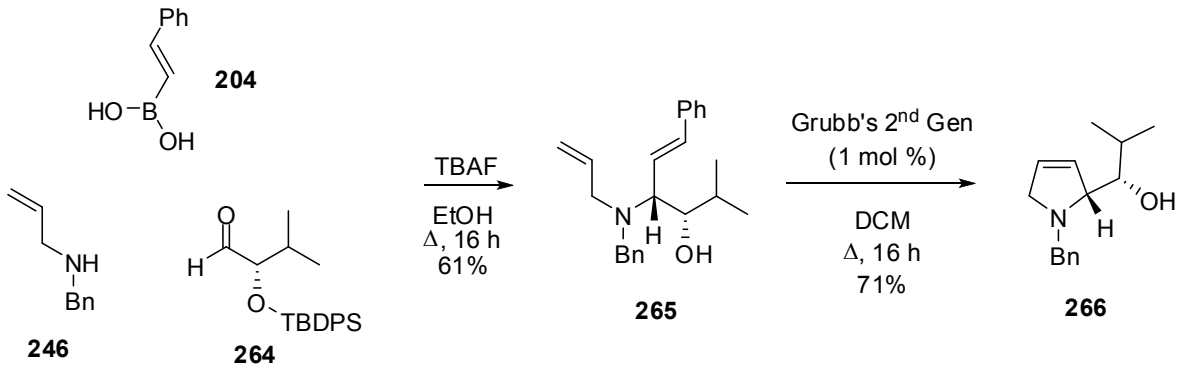
L-ethyl lactate. **256** was prepared in the same manner but from L-valine instead of from ethyl lactate. The synthesis of the desired α-siloxyaldehyde **264** has been previously reported from L-valine and the literature procedure was used (Scheme 48).[73] This was accomplished by first undertaking a diazotization reaction of valine to prepare the α-hydroxyacid with retention of configuration. The retention of configuration is well known to occur with amino acids during diazotization, with the mechanism involving the acid in an S_Ni mechanism before opening with the nucleophile (water) to yield the alcohol.[74] This was followed by esterification, protection of the alcohol with a *tert*-butyldiphenylsilyl, and reduction of the ester to the aldehyde by DIBAL-H to obtain the desired α-siloxyetheraldehyde **264**.

Scheme 48: Preparation of (*S*)-2-(*tert*-Butyldiphenylsilyloxy)-3-methylbutanal



From the prepared aldehyde **264**, the same conditions as for the methyl analog **244** were used to prepare the pyrrolinol, with an *in-situ* deprotection of the silylether for the Petasis-Mannich reaction followed by a ring-closing-metathesis (Scheme 49).

Scheme 49: Preparation of (*S*)-1-((*R*)-1-Benzyl-2,5-dihydro-1H-pyrrol-2-yl)-2-methylpropan-1-ol



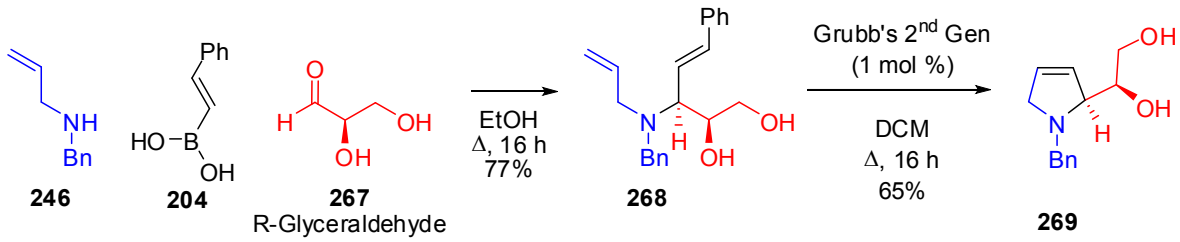
2.6.2 Enantiopure *N*-Benzyl-3,4-dehydroprolinol via the Petasis-Mannich Reaction and RCM

N-Benzyl-3,4-dehydroprolinol **236** had already been prepared from 4-hydroxyproline, however using that synthetic protocol did not yield enantiopure material and only one of the enantiomers is reasonably priced as a commercial product. Therefore, it was decided to use the Petasis-Mannich and RCM protocol to prepare *N*-benzyl-3,4-dehydroprolinol **236**. The use of glyceraldehyde as a reactant for the Petasis-Mannich reaction was published in the original paper by Petasis[64], and it is commercially available in enantiopure form for either enantiomer. As glyceraldehyde is readily available the silylether modification was not necessary for this analog. Commercially available *R*-glyceraldehyde was employed as a reactant to form Petasis-Mannich 1,2-aminoalcohol **268**, followed by a RCM to obtain the pyrrolinol **269** (Scheme 50).

It was also found that the ketal protected glyceraldehyde could be used in place of glyceraldehyde if a prior deprotection of the ketal was done in the reaction solution (ethanol). Glyceraldehyde, while commercially available, is an expensive reagent so being able to use the ketal was useful since it is quite simple to prepare in either two or three steps from inexpensive reagents depending on which enantiomer is desired.[75] It should be noted that the pH of the ethanolic solution after deprotection of the ketal in ethanol was found to

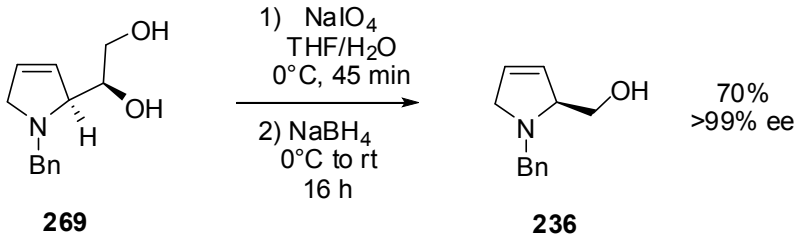
be important for the Petasis-Mannich reaction to occur. To more accurately measure the pH, 95% ethanol was used in place of absolute ethanol. A neutral to slightly basic pH (7.5) was found to be acceptable for the reaction and gave similar yields to when commercially available glyceraldehyde was used, however even slightly acidic (pH 6) conditions prevented the Petasis-Mannich reaction from occurring.

Scheme 50: Preparation of Enantiopure **269**



From **269,** *N*-benzyl-3,4-dehydroprolinol **236** was prepared by a Criegee oxidation followed by reduction in a one-pot procedure (Scheme 51).

Scheme 51: Preparation of Enantiopure *N*-Benzyl-3,4-dehydroprolinol **236**

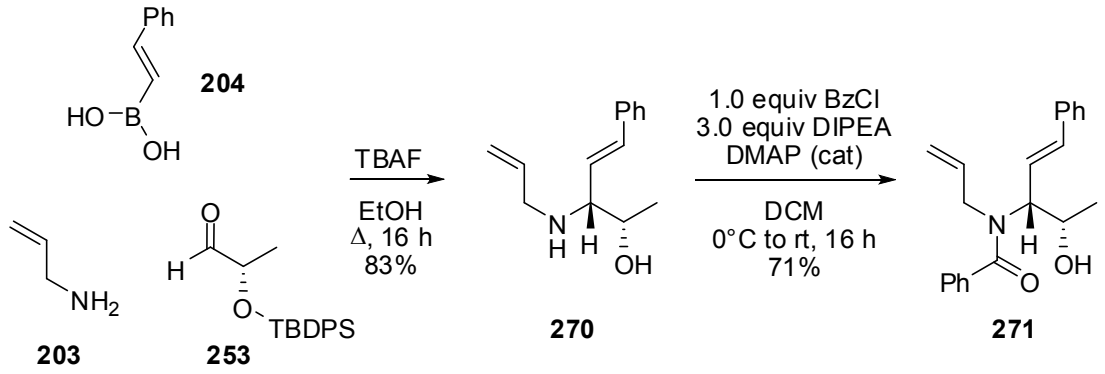


A check of the enantiomeric excess by chiral SFC of the *N*-benzyl-3,4-dehydroprolinol **236** prepared by the Petasis-Mannich reaction showed the presence of only one enantiomer. Therefore, this synthetic route provided **236** in enantiopure form, which could not be accomplished from 4-hydroxyproline. This sequence was also shorter than that from 4-hydroxyproline, and allowed the functionalization at the 5-position of the dihydropyrrole demonstrating that it is a more powerful method to prepare the desired dehydroprolinols.

2.6.3 (*S*)-1-((*S*)-1-Benzyl-2,5-dihydro-1H-pyrrol-2-yl)ethanol

The *syn* 1,2-aminoalcohol diastereomer **244** and its analogs were also desired to give *syn* 2,3-disubstituted piperidines via the aziridinium ion ring expansion. The high diastereoselectivity and ability to obtain enantiopure 1,2-aminoalcohols makes the Petasis-Mannich reaction quite useful for the synthesis of the desired precursors. However, the Petasis-Mannich reaction yields almost exclusively an *anti* 1,2-aminoalcohol. Therefore, in order to obtain the *syn* 1,2-aminoalcohol an inversion of configuration of the alcohol was attempted through the use of Mitsunobu conditions. To prevent the formation of an aziridinium ion intermediate that could cause a rearrangement or overall retention of configuration of the alcohol, the nitrogen was deactivated by acylating it. Benzoyl was used as an *N*-protecting group as it could be reduced to a benzyl after the inversion of the alcohol. Using α-siloxyetheraldehyde precursor **253,** the 1,2-aminoalcohol Petasis-Mannich product **270** was prepared and then the nitrogen protected as the benzoyl amide to yield **271** (Scheme 52).

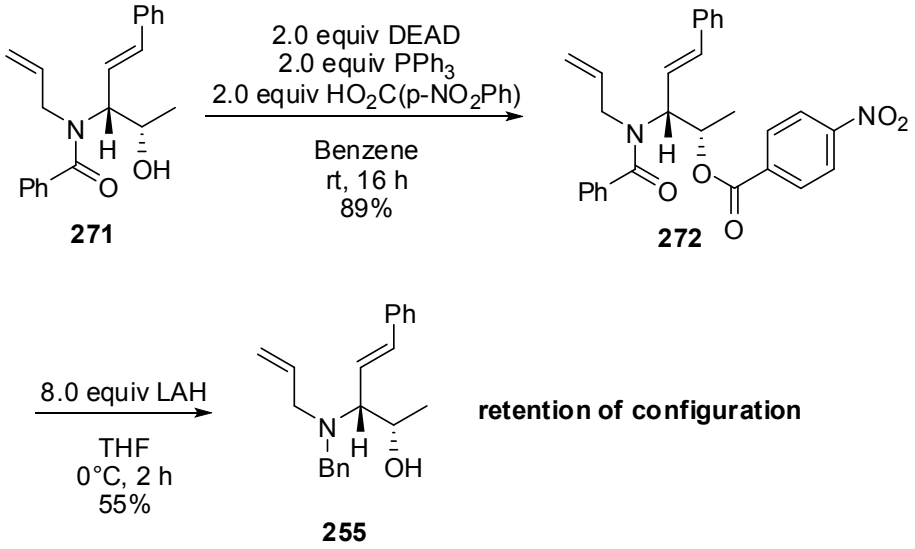
Scheme 52: Preparation of **271**



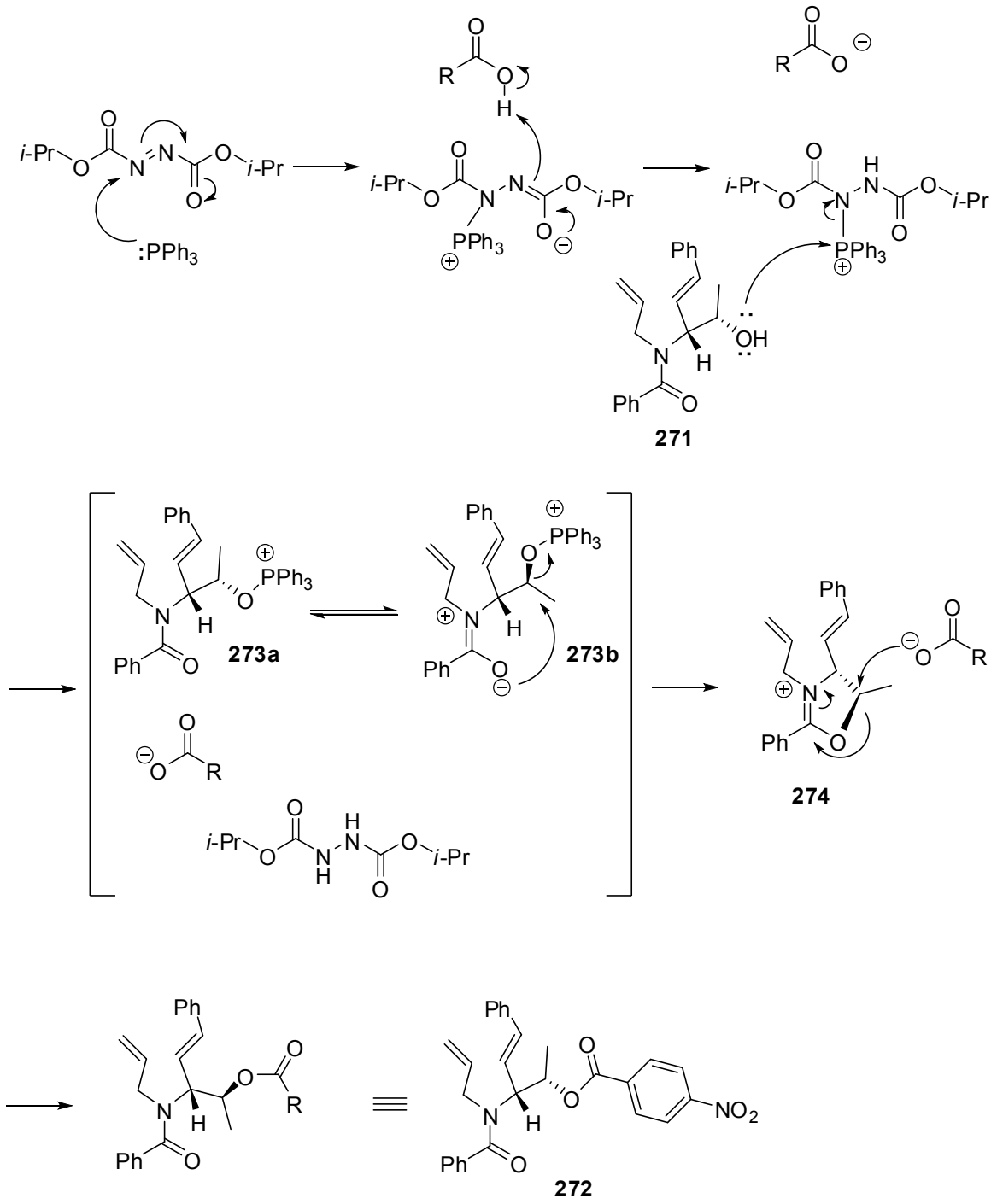
Alcohol **271** was submitted to Mitsunobu reaction conditions. This was then followed by a reduction of the ester and amide with lithium aluminum hydride to obtain 1,2-aminoalcohol **255** (Scheme 53). Comparison of the mitsunobu/reduction product by ^{1}H NMR with **255** and the minor diastereomer isolated from the scale-up of **255** showed that no inversion of configuration of the alcohol had occurred. Likely, the failure to obtain the inverted alcohol was due to the carbonyl of the amide participating in an S_Ni process displacing the

phosphonium oxide followed by attack of the anion of *para*-nitrobenzoic acid (Scheme 54). The desired *syn* 1,2-aminoalcohol was not prepared and this was not pursued further.

Scheme 53: Mitsunobu Gives Retention of Configuration



Scheme 54: Proposed Mitsunobu Mechanism to Have Retention of Configuration

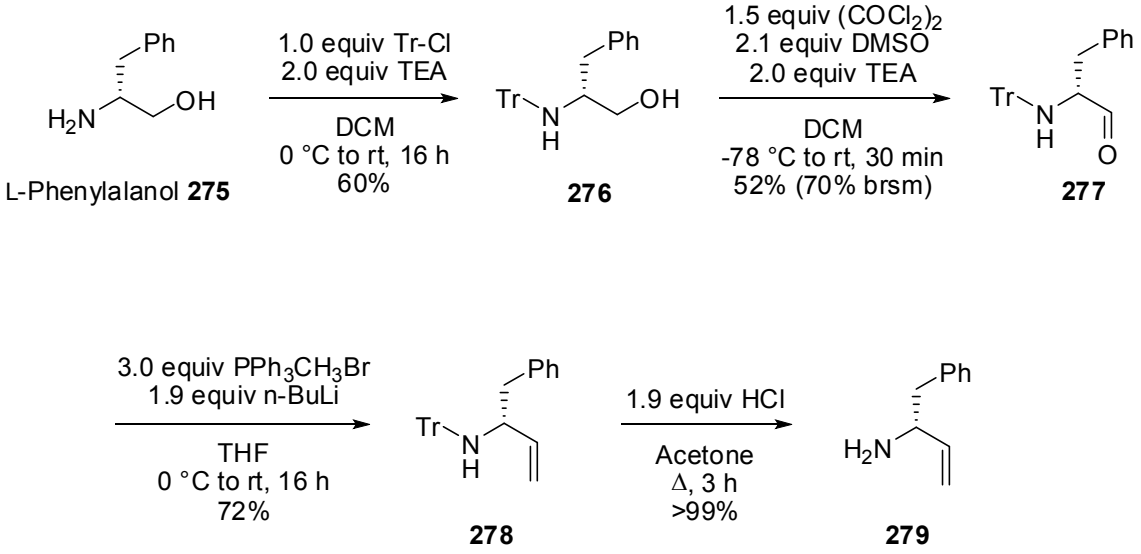


2.6.4 Substituting the 5-position of Dihydropyrroles via the Petasis-Mannich and RCM Protocol

As noted in section 2.1 for the Petasis-Mannich reaction Schreiber *et al* demonstrated that chiral amines can be used with this reaction and that the chirality of that amine had no impact on the stereochemical outcome of the 1,2-aminoalcohol formed or diastereoselectivity of the reaction.[65] Therefore, by using an enantiopure substituted allylamine with an enantiopure α-silyletheraldehyde in this methodology, the 5-substituted dihydropyrrole would accordingly be produced as an enantiopure single diastereomer. There are a variety of methods to prepare chiral allylamines that include: 1) Iridium-catalyzed asymmetric allylation of amines from allyl carbonates,[76] 2) [3,3]-Sigmatropic rearrangement of a chiral allyl cyanate generated from a chiral allylic alcohol (obtained by the catalytic asymmetric addition of diorganozinc reagents to substituted acrolein derivatives),[77] 3) catalytic asymmetric sigmatropic rearrangement of an allyl alcohol,[78] 4) chiron approaches from amino acids to yield enantiopure allylamines,[79] as well as others. An enantiopure allylamine can easily be prepared from an inexpensive amino acid in few steps, and therefore phenylalanine was used as a precursor for the synthesis of tetrahydropyridine derivatives with a benzyl at the 6-position. D-Phenylalanine and L-phenylalanine were esterified, and the nitrogen protected with a trityl group. The ester was then reduced with DIBAL-H to obtain aldehyde **277** which was submitted to a Wittig reaction to produce **278**. Deprotection of the trityl was performed to produce the desired known allylamine **279** (Scheme 55).[79a]

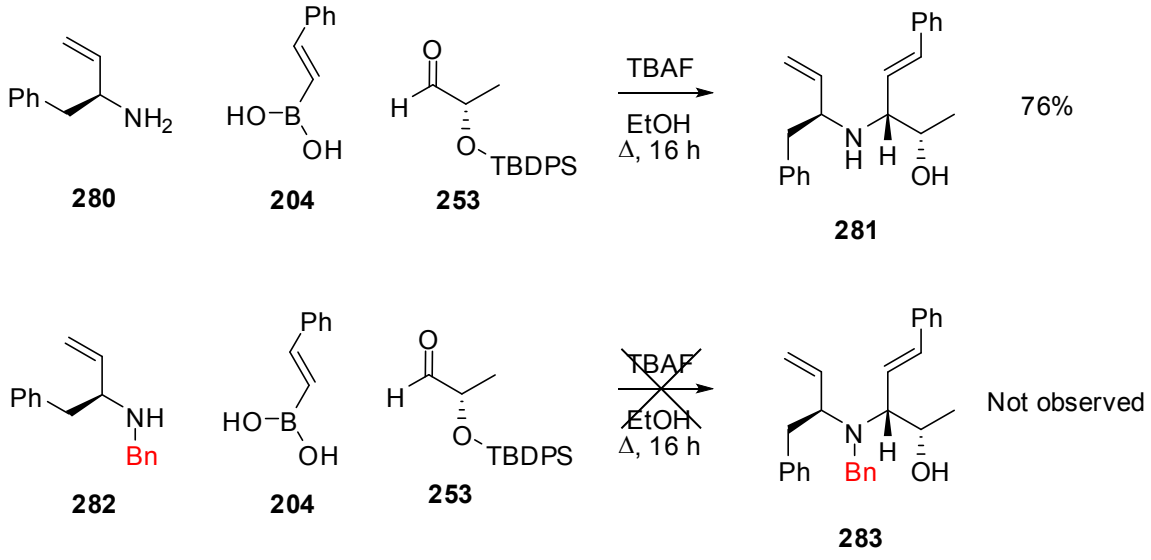
When Boc protected amino-aldehydes derived from amino acids are submitted to the basic conditions of the Wittig reaction, epimerization of the chiral center is observed. The trityl protecting group was used in place of the more common Boc group since the trityl is known to prevent epimerization of the chiral center under the strongly basic reaction conditions of the Wittig reaction. The lack of epimerization is due to the steric hindrance of the trityl group, preventing deprotonation of the α-carbon by bases.[79a]

Scheme 55: Synthesis of Enantiopure Allylamine **279**



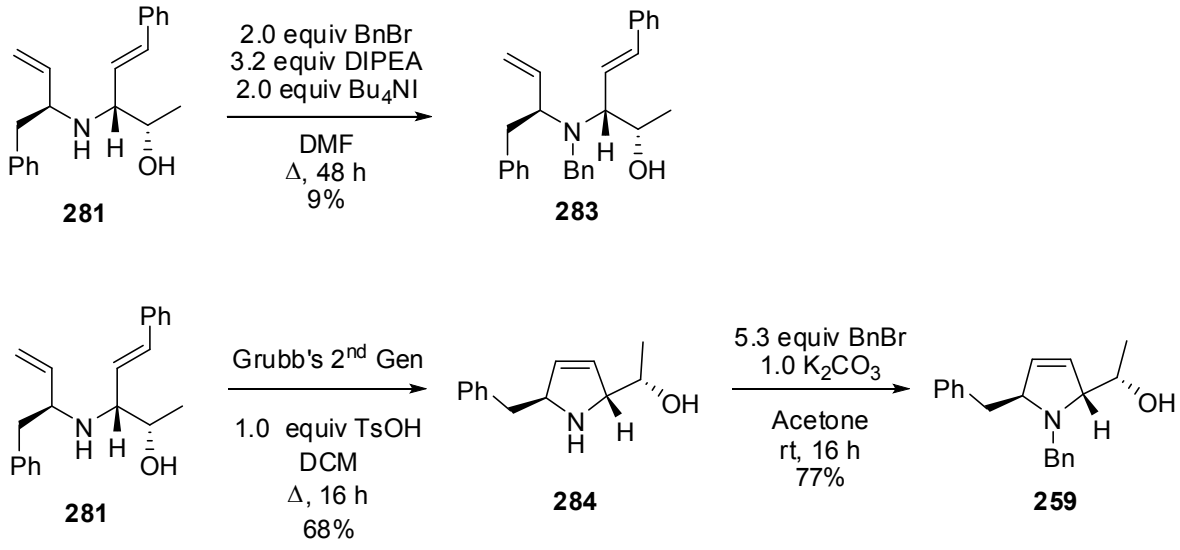
With the enantiopure substituted allylamine **279** and its enantiomer in hand, we were able to synthesize the desired 1,2-aminoalcohols through the Petasis-Mannich reaction. Petasis-Mannich product **281** was smoothly obtained using this procedure (Scheme 56). However, the chiral allyl amine must be primary, as *N*-benzyl analog **282** was unreactive under the same reaction conditions.

Scheme 56: Synthesis of **281**



Alkylation of the nitrogen of **281** by benzyl bromide required forcing reaction conditions that gave unacceptably low yields (9%), and significant decomposition of the reactant (Scheme 57). The amine **281** was also unreactive towards benzaldehyde for a reductive amination. To side-step this problem, a ring-closing-metathesis on **281** was attempted. However, no reaction initially occurred. It was believed that as the basic nitrogen of the product dihydropyrrole **284** was not significantly sterically hindered once it was formed, and it could therefore complex the catalyst preventing further reaction. Therefore, one equivalent of a strong acid (Tosic acid) was added to quench the basic nitrogens of **281** and **284**, and then **281** was again submitted to RCM conditions. Gratifyingly, the RCM to prepare **284** proceeded smoothly with the nitrogen quenched by an acid. After the RCM, the less sterically hindered nitrogen of the dihydropyrrole of **284** underwent benzylation without difficulty with benzyl bromide at room temperature to produce **259** in a 77% yield.

Scheme 57: Synthesis of **259**



The diastereomer **285** produced in the Petasis-Mannich from D-Phenylalanine was unstable to purification attempts (Scheme 58). Therefore, the crude mixture from the Petasis-Mannich reaction was submitted to an RCM in the presence of a strong acid. The yield of the two-step process to **286** without intermediate purification to produce **285** was lower than its diastereomer **284** (35% for **286** vs 52% for **284**). Once the dihydropyrrole **286** was formed, it was stable to isolation, and alkylation of the nitrogen with benzyl bromide occurred readily to produce **258**.

Scheme 58: Synthesis of **258**

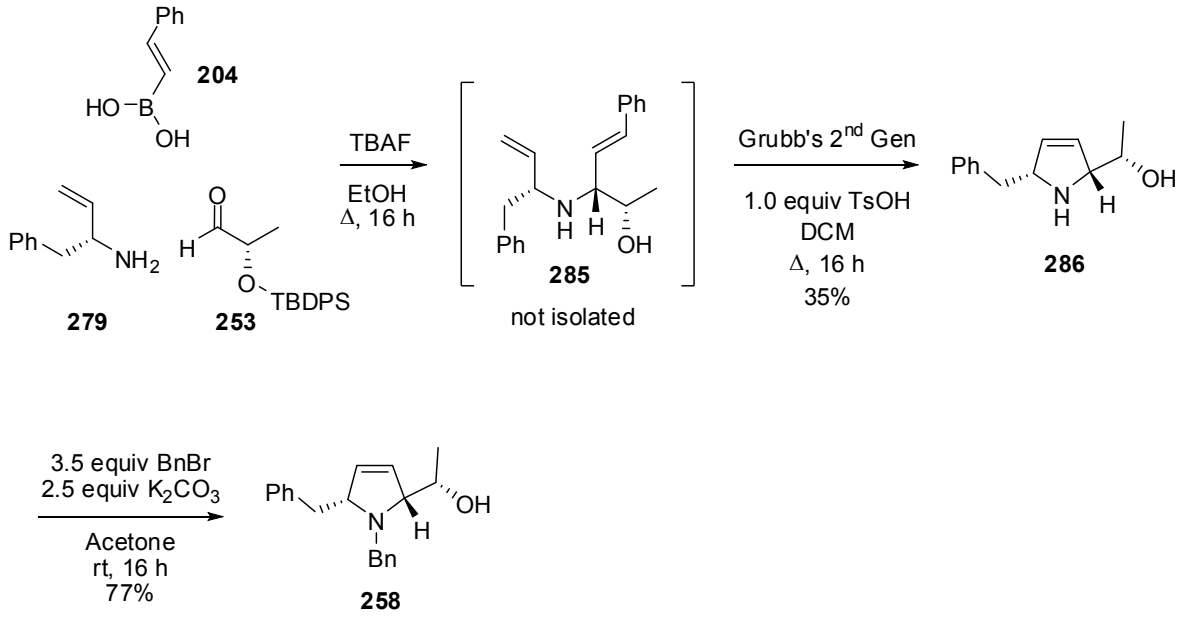
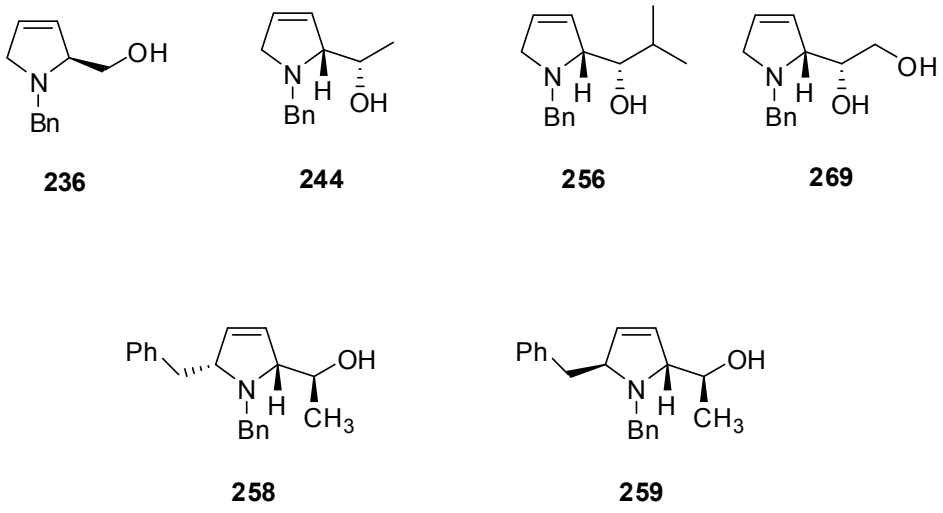


Figure 10: *N*-Benzyl-3,4-Dehydroprolinol Derivatives Prepared in This Chapter

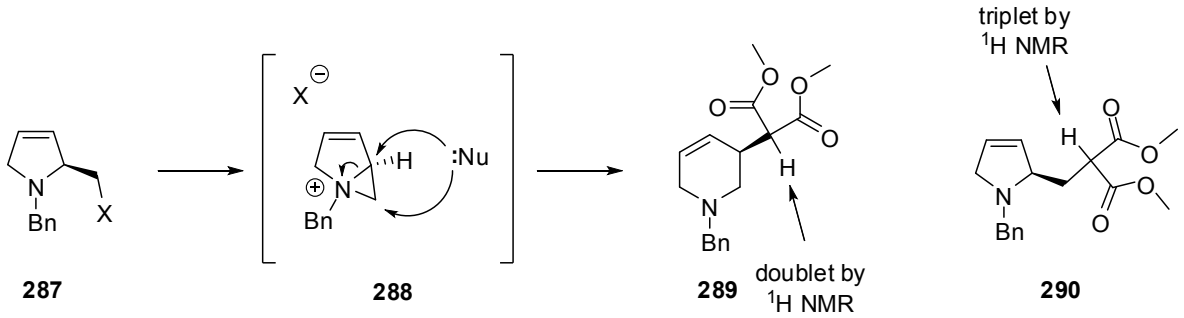


Chapter 3: Proof of Concept for Ring Expansion and Optimization

3.1 Introduction

For initial proof of concept we were first interested in the regioselectivity of the reaction of nucleophiles towards the aziridinium ions to demonstrate that 3-substituted piperidines would be obtained, and that the enantiomeric excess would be maintained during the ring expansion reaction. Therefore, to study the regioselectivity of such a reaction the aziridinium ion would have to be submitted to a representative nucleophile, that would lead to a product simple to analyze by NMR. As we were especially interested in 3-carbon substituted piperidines it was decided that a carbon nucleophile should be used for the proof of concept. As discussed in Chapter 1 section 1.3.2b, aziridinium ion ring opening reactions with malonates are known to be sensitive to electronic factors for their regioselectivity. With malonate as a nucleophile the isomer formed exclusively or the isomer mixture ratio formed could be deduced by ^{1}H NMR experiments. This could be done through the use of the methylene of dimethylmalonate as it is deshielded causing it to be quite downfield for an alkyl (typically ~ 4 ppm). This makes it simple to identify, and the splitting pattern of the dimethylmalonate methylene would reveal whether **289** or **290** was obtained (Scheme 59).

Scheme 59: Dimethylmalonate ^{1}H NMR Coupling Demonstrates Which Isomer is Formed

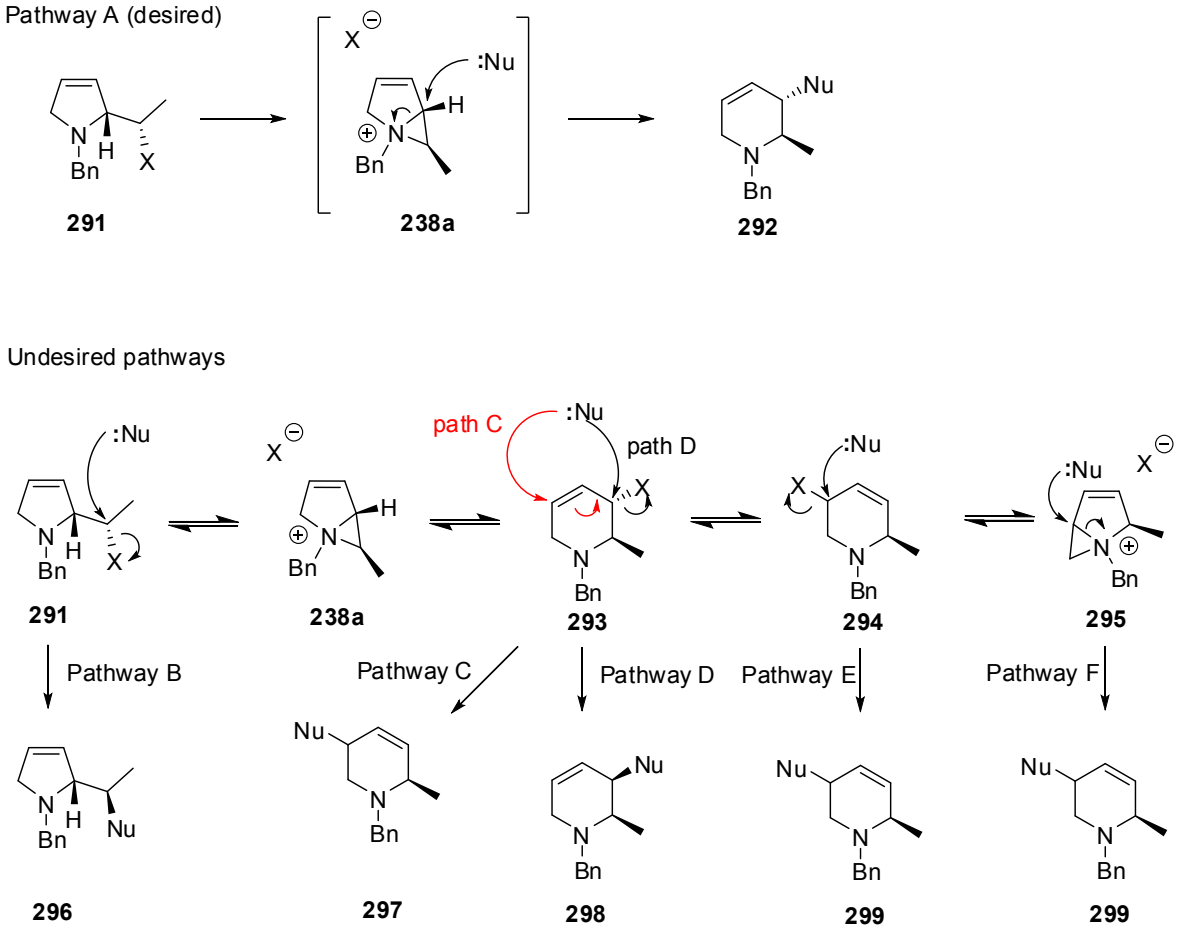


287 **288** **289** **290**

3.2.1 Choice of Leaving Group

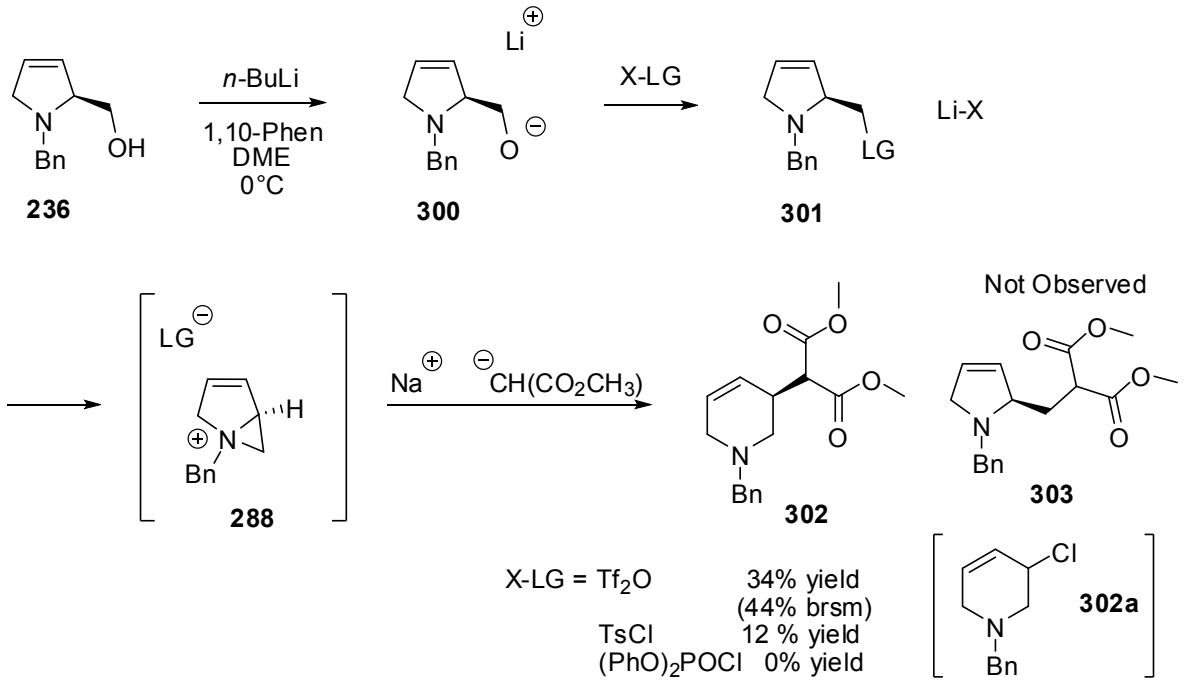
It was believed that the aziridinium ion **238a** should be preformed irreversibly from **291,** before addition of nucleophiles to avoid the possibility of additional mechanisms that would adversely affect the regioselectivity and stereochemical outcome (Scheme 60). This could be accomplished with a leaving group that is an exceptionally poor nucleophile. Side reactions could arise if the aziridinium ion **238a** was formed with a counterion that was nucleophilic thereby resulting in a thermodynamic equilibrium between dihydropyrrole **291** and tetrahydropyridine **293**. Tetrahydropyridine **293** could then undergo allylic rearrangement to yield intermediate **294**, which in turn has similar pathways to react with nucleophiles. Therefore, this ruled out the use of leaving groups that are known to be reversible which include chloride, bromide, iodide, and mesylate.[23,25,31,32,33,34]

Scheme 60: Possible Pathways for Reactions and Rearrangements of Aziridinium Ion **238a**



Ideally, the alcohol of **236** and its analogs could be converted into a leaving group, which would then form the aziridinium ion irreversibly, for further reaction with the nucleophile in a one-pot procedure. The remaining typical leaving groups that are not known to be reversible for formation of aziridinium ions are tosylate, and triflate. As mesylate is a known reversible leaving group, tosylate by extension is also expected to be, as they are quite similar. Reaction of dehydroprolinol **236** and its analogs with activating agents to convert the alcohol to a leaving group generates an acidic proton that would have to be quenched with a base to allow the nitrogen of the prolinol to form an aziridinium ion. Inspiration was taken from the scale-up optimization of Ecopipam where the authors used *n*-hexyllithium to deprotonate the alcohol prior to reaction with the activating reagent. They used the less common *n*-hexyllithium in place of the *n*-butyllithium as it was a large scale process and they wished to avoid the generation of large amounts of butane gas, a potential explosion hazard.[25] For our purposes, *n*-butyllithium would suffice as the scale of the reaction investigated for proof of concept would be rather small. To ensure that the proper amount of base to obtain **300** was used, a titration with *n*-butyllithium and 1,10-phenanthroline as an indicator was performed. The alkoxide solution was then reacted with the activating groups to form species **301** which then could in turn form an aziridinium ion. To this solution of **301** was added the sodium salt of dimethylmalonate. Reaction progression from **300** to **302** was determined by quenching an aliquot with methanol and analysis by LCMS.

Scheme 61: Leaving Group Optimization



Of the three activating agents examined, triflic anhydride gave the best yield with a low conversion of 34% isolated yield (44% based on recovered starting material) in 30 minutes to 3-substituted tetrahydropyridine **302**. We were pleased to find that of the two possible isomers (**302** and **303**) only tetrahydropyridine **302** was observed, albeit in a low yield, showing that the ring expansion occurs regioselectively. This validated our hypothesis that the alkene could act as a directing group for nucleophiles, and that the regioselectivity should be high. The reaction with tosylate **301** produced the desired 3-substituted tetrahydropyridine **302**, albeit only in 12% isolated yield, and also the chloride **302a** (11% isolated yield), but only after a prolonged reaction time of three days. The chloride by-product **302a** was obviously from the aziridinium ion formation with the tosylate followed by opening with the free chloride ion in solution liberated when tosyl chloride was reacted with the alkoxide. The phosphate was unreactive to form aziridinium **288**, even with elevated temperatures for prolonged reaction times, as the methanol adduct was not observed by LCMS.

The chloride by-product **302a** formed in the tosylate trial would be simple to avoid through the use of tosyl anhydride. However, the use of tosylate as a leaving group required

excessively long reaction times which was undesired or elevated temperatures that could decrease the regioselectivity of the addition of the nucleophiles towards the aziridinium ion which was also undesired. Of the two leaving groups that produced the desired tetrahydropyridine, only triflate was deemed to meet the desired criteria. The reaction time with triflate was quick (<30 minutes), and the reaction could be done at lower temperatures increasing the possibility of regioselective attack. Therefore, triflate was seen as the optimal leaving group for conversion of **236** to **302**. Unfortunately, the reaction with triflate did not go to completion as a significant quantity of the alcohol precursor **236** was recovered. We next focused on optimizing the reaction conditions to obtain complete conversion.

3.2.2 Base Optimization

For the initial ring expansion study to find an appropriate leaving group, the alkoxide had been formed using a titration with *n*-butyllithium and 1,10-phenanthroline. However, this was seen as a restrictive factor on the conversion of the alcohol to the tetrahydropyridine as the base was then a limiting reagent. To allow full conversion we wished to be able to employ an excess of reagents in relation to the dehydroprolinol. Therefore, we sought a milder, and non-nucleophilic base than an organometallic that could be added to the solution to quench the acidic proton generated to allow aziridinium ion formation to occur. Alkoxide bases were ruled out as they could potentially react with the triflic anhydride, which left tertiary amine bases for the trial. An inspection of the Bordwell pka table shows a variety of amine bases with a large difference in basicity, as seen in Table 5. For the initial tests to find an appropriate leaving group the solvent had been chosen to be freshly distilled DME. This was because it was compatible with forming an alkoxide from the alcohol and *n*-butyllithium, and also DME was compatible with triflic anhydride. For the amine base optimization study we decided to change the solvent to anhydrous DCM in place of freshly distilled DME as it is commercially available anhydrous, much less expensive than DME, and is also one of the few solvents compatible with triflic anhydride.

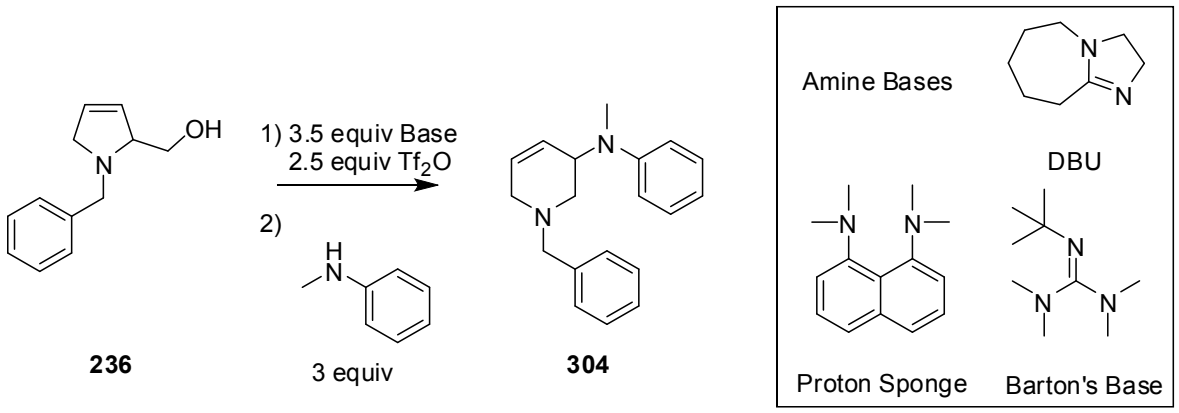
To be certain that yields were consistent, it was deemed necessary to change the nucleophile for the optimization study to one that was not a metal salt (sodium dimethylmalonate), as metal salts typically have a low solubility in organic solvents which

could give variable yields. *N*-Methylaniline was chosen for the optimization study as the nucleophile since it is UV visible and highly organic soluble making isolation of the tetrahydropyridine **304** simple, and by ^{1}H NMR the compound **304** is easily identifiable. The base optimization study was done in DCM at 0.05 M, 0 °C, using 3.5 equivalents of base, 2.0 equivalents of triflic anhydride, with a 5 minute activation period to form the aziridinium, followed by 15 minutes with 3.0 equivalents of *N*-methylaniline (Table 5). Aqueous work-up and purification by silica column was done to obtain an isolated yield of **304**.

The dehydroprolinol **236** was expected to have a pka similar to other tertiary amines such as triethylamine. Logically, the amine base would have to be of approximately equal or greater basicity than the dehydroprolinol nitrogen so that the base would scavenge the acidic proton thereby allowing the dehydroprolinol nitrogen to form the aziridinium ion. Comparison by the bordwell pka scale of the bases was of limited use as the reaction was done in DCM and not in DMSO. The pka of the base and its relative ranking compared to other amine bases in different families depends on the solvent environment of which the base is dissolved as can be seen in Table 5.[80] Unfortunately, no pka data of amine bases in DCM was available when these experiments were carried out.

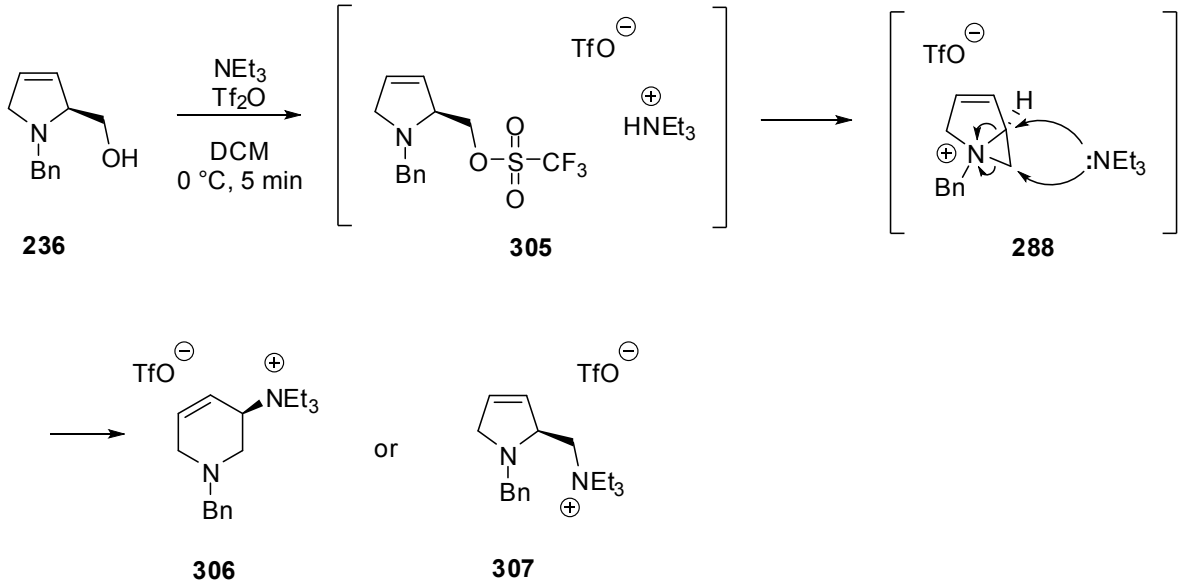
As can be seen in Table 5, the pka of the base had little correlation with the yield and when no base was used the desired reaction with *N*-methylaniline still occurred. The ring expansion occurring in the absence of a base was likely due to the presence of the nucleophile, *N*-methylaniline, acting as a weak base (entry 1). Using pyridine or triethylamine as a base did not yield the desired tetrahydropyridine and the alcohol precursor was not recovered (entries 2 and 4). This was likely due to the amine base acting as a nucleophile towards the aziridinium ion to form quaternary ammonium salts (see Scheme 62 for an example) – though they were not isolated due to their high aqueous solubility they were observed by LCMS from the crude reaction mixture. The sterically hindered bases diisopropylethylamine, DBU, and Barton's base all gave a low to moderate yield of the tetrahydropyridine with no alcohol precursor recovered (entries 5-7). However, the quaternary ammonium salt was observed by LCMS showing a loss of intermediate and yield due to alkylation of those three bases.

Table 5: Base Optimization

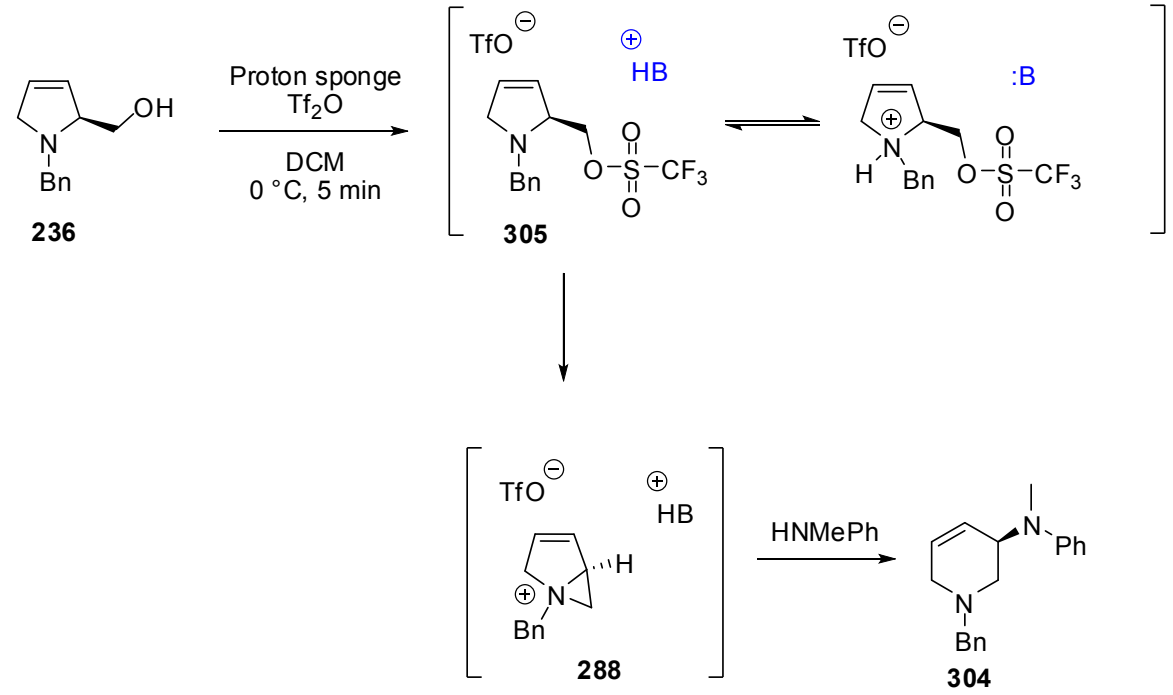


Entry	Base	**304** Isolated Yield (%)	Bordwell pka (DMSO)[80a]	pka (ACN)[80b]	pka (THF)[80c]
1	None	40			
2	Pyridine	0	3.4	12.5	5.5
3	Proton Sponge	**80**	7.5	18.6	11.1
4	Triethylamine	0	9	18.8	12.5
5	Diisopropylethyamine	42	N/A	N/A	N/A
6	DBU	63	12	24.3	16.8
7	Barton's Base	11	14	~26	~18

Scheme 62: Triethylamine Alkylation by the Aziridinium Ion



Scheme 63: Proton Sponge as a Base



Proton sponge gave the best result with an 80% yield and no unreacted alcohol precursor was observed (entry 3). No significant amount of alkylation product of the base was observed by LCMS with proton sponge. Proton sponge is known as a strong amine base

with the high basicity being attributed to the relief of strain between the two dimethylanilines upon protonation. Proton sponge nitrogens are sterically hindered making it a weak nucleophile due to conformational constraint in the molecule which forces the two nitrogen lone pairs to be near each other and unavailable sterically to electrophiles larger than a proton. Though by the Bordwell pka values proton sponge would appear less basic than desired (i.e. less basic than triethylamine) so as to have the ability to deprotonate the dehydroprolinol and allow the formation of the aziridinium ion, the relative basicity of the two amines depends on the solvent environment. Also, as the formation of the aziridinium ion would be irreversible the protonated base could be less basic but simply be in equilibrium with the protonated dehydroprolinol and still facilitate the formation of the aziridinium ion as shown in Scheme 63. If the pka of protonated proton sponge were lower than the pka of the protonated dehydroprolinol it could still allow the formation of the aziridinium ion. As proton sponge is commercially available, gave the highest yield, and no alkylation by the aziridinium ion was observed with it, it was seen as the optimal choice as a base.

As the nucleophile had been altered to *N*-methylaniline the identity of which isomer was obtained with complete regioselectivity had to be demonstrated once again. The identity of the isomer could not be determined by COSY experiments or ^{1}H NMR coupling. The aniline aryl protons, ortho to the nitrogen, are well separated at 6.8 ppm and they were examined for nOe interactions (Figure 11, blue spectra). They have a strong interaction with the *N*-methyl (2.9 ppm), a peak at 4.6 ppm which integrates to one proton, and the *meta* aryl protons as one would expect for the tetrahydropyridine. The signal at 4.6 ppm has COSY interactions with an alkene proton, and a methylene (not shown). Therefore, nOe experiments combined with the ^{1}H NMR chemical shifts and integrations of the peaks, COSY interactions of the signal at 4.6 ppm with the alkene and a methylene points to tetrahydropyridine **304** as being the isomer obtained. Had the product obtained been dihydropyrrole, the aniline aryl protons would have interactions with the methylene which has two protons and not one (Figure 12). Also, the chemical shifts and integrations of the ^{1}H NMR does not match the dihydropyrrole structure but is reasonable for the tetrahydropyridine.

Figure 11: nOe of **304**

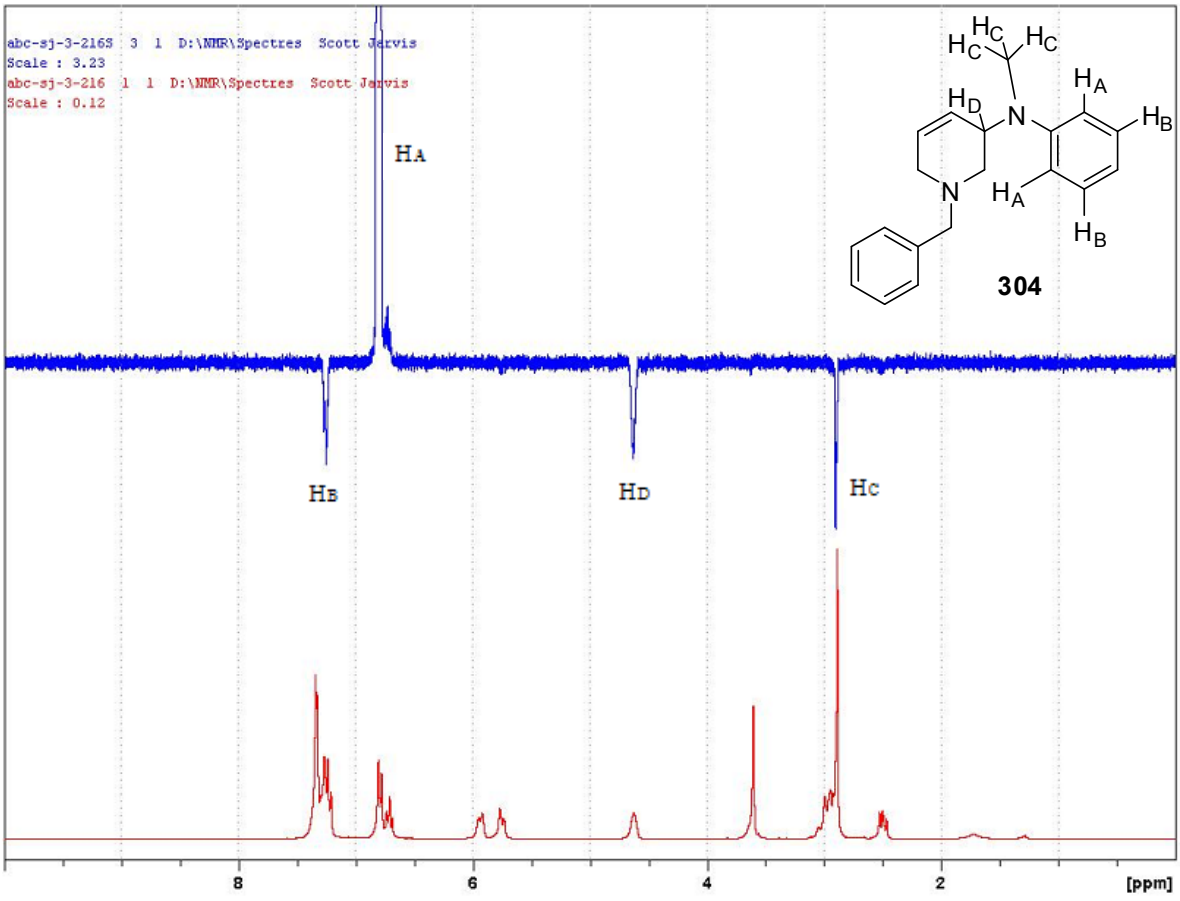
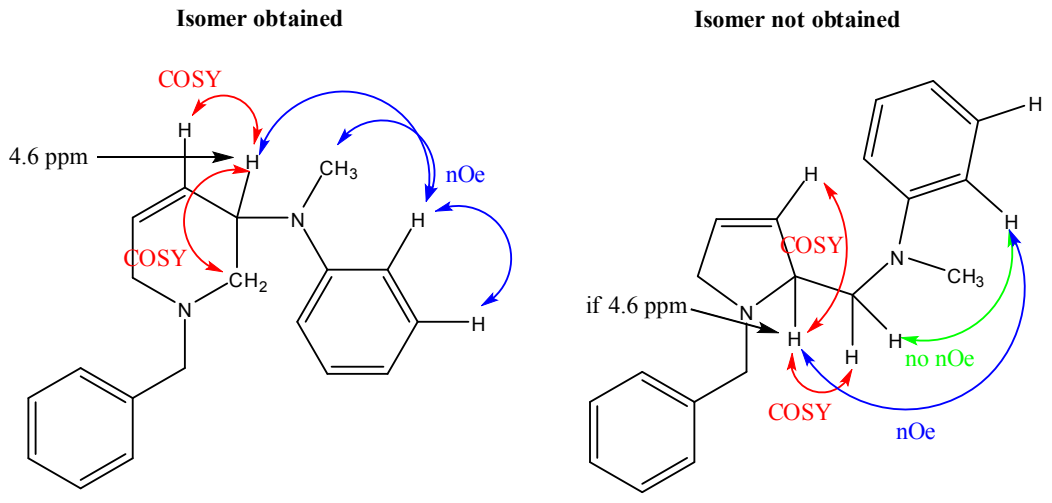


Figure 12: nOe and COSY Interactions of **304**

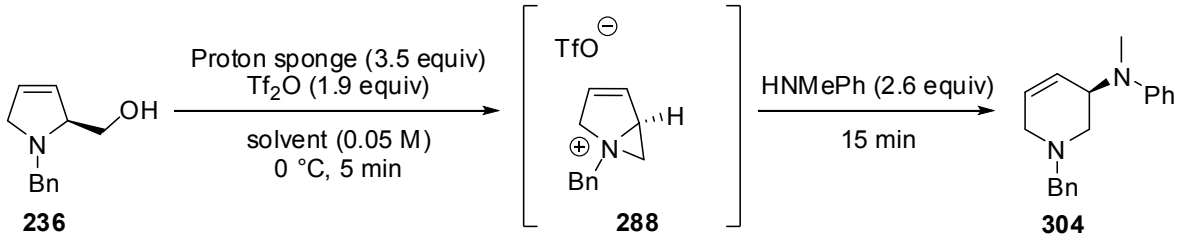


The nOe interactions and COSY clearly point to this isomer as the product obtained.

3.2.3 Reaction Conditions Optimization

The relative pka's between the protonated proton sponge and protonated dehydroprolinol would depend on the solvent environment as seen in section 2.2.2. Therefore, it was expected that the choice of solvent would have a profound effect on the reaction of **236** producing **304**. Furthermore, as the reaction proceeds through charged intermediate **288**, a polar environment that would favor the formation and reaction of such a species would likely be beneficial for the conversion of the dehydroprolinol to the tetrahydopyridine. A stock solution of the dehydroprolinol **236** was prepared in anhydrous toluene, as it does not readily absorb atmospheric moisture, with a measured amount of 1,3,5-trimethoxybenzene which was used as a ^{1}H NMR internal standard. The stock solution was transferred to reaction vessels by volumetric pipette to limit the possibility of errors in comparison between optimization trial results. Accordingly, a variety of solvents that are compatible with triflic anhydride were investigated for their impact on yield for this transformation as seen in Table 6.

Table 6: Solvent Optimization



Entry	Solvent	**304** Yield[a]
1	Acetonitrile	9%
2	Chloroform	9%
3	1,4-Dioxane	5%
4	1,2-Dimethoxyethane	20%
5	Diethyl ether	50%
6	Dichloromethane	62%
7	Toluene	63%

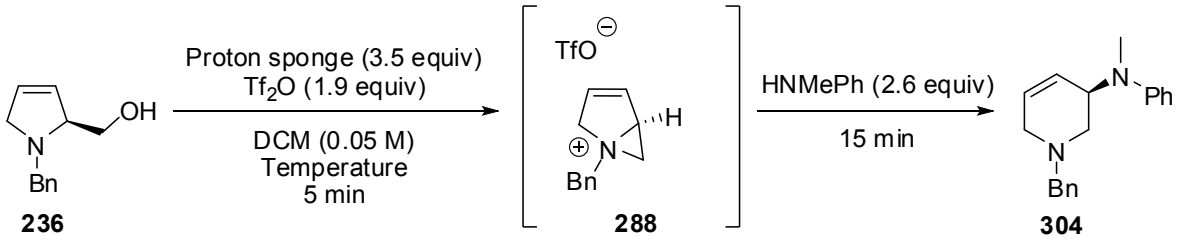
[a] determined by ^{1}H NMR of the crude reaction mixture by comparison to 1,3,5-trimethoxybenzene

Acetonitrile and chloroform gave very poor conversion for the ring expansion at 9% yield by ^{1}H NMR (Table 6, entries 1-2). Ethereal solvents such as 1,2-dimethoxyethane, 1,4-

dioxane, and diethyl ether gave low to moderate yields of the desired tetrahydropyridine (entries 3-5, 5-50%). Of the solvents examined, dichloromethane and toluene gave the best result and were within experimental error of one another, with 62% and 63% yields by ^{1}H NMR respectively (entries 6-7). Dichloromethane was chosen as the optimal solvent over toluene since the dielectric constant is higher (DCM: 8.93 vs Toluene: 2.38).[81] With a higher dielectric constant DCM would be superior in solubolizing polar reagents as compared to toluene.

To determine the optimal temperature at which the ring expansion of **236** producing **304** should be done, a temperature screen was performed (Table 7). It was found that above -10 °C the yields as measured by ^{1}H NMR dropped quite dramatically in a direct correlation with the increased temperature. Below -10 °C, the yields remain consistent with each other within experimental error. This was not surprising as the stability of aziridinium ions in solution has been noted to be limited even at -20 °C over a period of time.[25] The temperature seen as optimal was -15 °C, which is attained with a simple salt and ice bath, thus specialized equipment such as a crysostat would not be necessary.

Table 7: Temperature Optimization

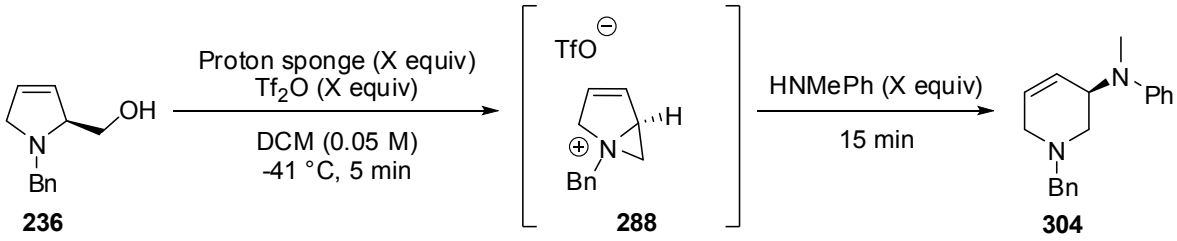


Entry	Bath Temperature (°C)	**304** Yield[a]
1	-84	82%
2	-63	76%
3	-41	81%
4	-18	79%
5	-10	80%
6	0	54%
7	22	9%

[a] determined by ^{1}H NMR of the crude reaction mixture by comparison to 1,3,5-trimethoxybenzene

The minimum amounts of reagents required for the ring expansion of **236** was investigated with three trial sets (Table 8). Firstly, triflic anhydride was examined and it was found that only a small excess (1.1 equivalents) was required (entries 1-4). Secondly, equivalents of Proton Sponge was examined and a stoichiometric amount to small excess of the base (1.0-1.5 equivalents) gave superior results (entries 5-10). The use of a large excess of proton sponge resulted in a decrease in yield (entry 10). Finally, equivalents of the nucleophile were examined (entries 11-16). Though the yields for the nucleophile equivalents trials (entries 11-16) were lower than what would be expected from the previous optimization

Table 8: Reagent Equivalents Optimization



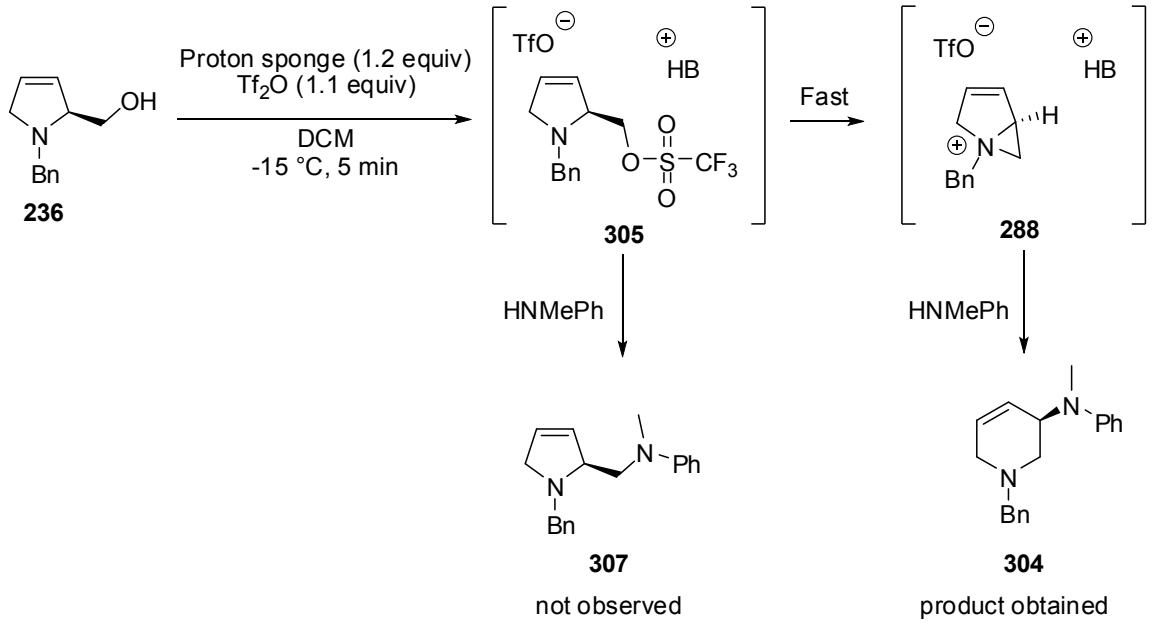
Entry	Triflic anhydride equivalents	Proton Sponge equivalents	*N*-Methylaniline equivalents	**304** Yield[a] (%)
1	**1**	3.5	2.6	76
2	**1.1**	3.5	2.6	84
3	**1.5**	3.5	2.6	84
4	**2**	3.5	2.6	86
5	1.1	**1**	2.6	>99
6	1.1	**1.2**	2.6	>99
7	1.1	**1.5**	2.6	>99
8	1.1	**2**	2.6	90
9	1.1	**3.6**	2.6	84
10	1.1	**10**	2.6	65
11	1.1	1.2	**1**	64
12	1.1	1.2	**1.1**	73
13	1.1	1.2	**1.2**	73
14	1.1	1.2	**1.5**	70
15	1.1	1.2	**2**	70
16	1.1	1.2	**10.4**	65

[a] determined by ^{1}H NMR by comparison to 1,3,5-Trimethyoxybenzene

trials (entries 1-10), the trend was consistent within the data set for that day and considered reliable from a comparison stand-point. Utilizing a large excess of the nucleophile, *N*-methylaniline, was also deemed not necessary as a small excess (1.1 equivalents) gave an equivalent result as using a larger excess.

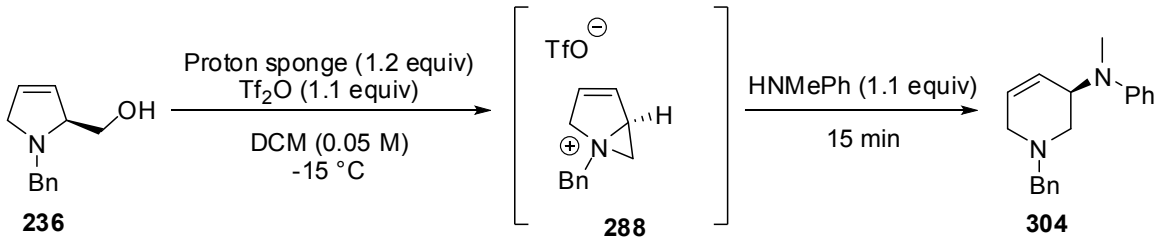
It could be deduced from the early proof of concept experiments and the optimization experiments that formation of the aziridinium ion **288** was fast with triflate as no pyrrolidine isomer by-product was observed. If it were not fast then the nucleophile could react with the alkyl triflate to form the undesired dihydropyrrole in an S_N2 fashion (Scheme 64). However, in order to verify if the formation of the aziridinium ion was complete, and also to discern how stable the intermediate was at this optimal temperature, the timing of the nucleophile addition to the aziridinium ion solution was examined (Table 9).

Scheme 64: Fast Formation of the Aziridinium Ion



A quick examination of Table 9 shows that the formation of **288** under these conditions is fast and almost complete in one minute (entry 1). Also, it is apparent that the aziridinium ion formed is unstable in solution over several hours at -15 °C (entry 6). The highest yield was obtained when the nucleophile addition was done 5 minutes after triflic anhydride addition (entry 2).

Table 9: Delay Period Between Triflic Anhydride Addition and Nucleophile Addition

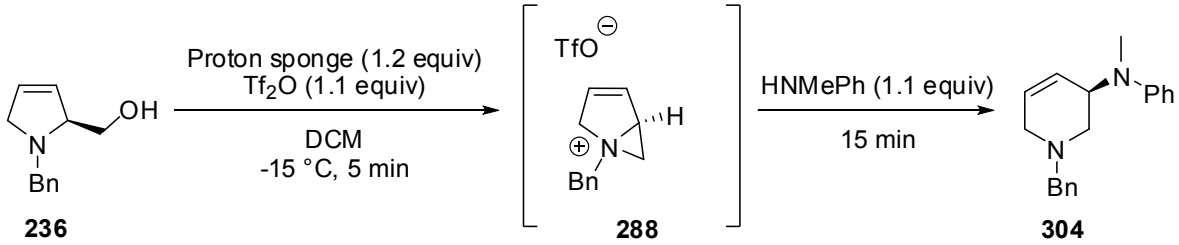


Entry	Activation Time	**304** Yield[a]
1	60 s	78%
2	5 min	86%
3	20 min	83%
4	1 hour	76%
5	2 hours	69%
6	17 hours	42%

[a] determined by ^{1}H NMR of the crude reaction mixture by comparison to 1,3,5-trimethoxybenzene

We next examined the effect of concentration on the yield of the ring expansion reaction. Table 10 shows a clear cut-off in yield as an effect of concentration. It was observed during the optimization trial that solutions with 0.11 M and 0.54 M concentrations were thick suspensions where-as the more dilute trials were solutions. This would explain the lower yields, as in a suspension the reactants would not be dissolved sufficiently to obtain the optimal yield. The optimal concentration was deemed to be 0.05 M (entry 3).

Table 10: Concentration Effect on Yield



Entry	Concentration (M)	**304** Yield[a]
1	0.54	74%
2	0.11	73%
3	0.05	100%
4	0.01	100%

[a] determined by ^{1}H NMR of the crude reaction mixture by comparison to 1,3,5-trimethoxybenzene

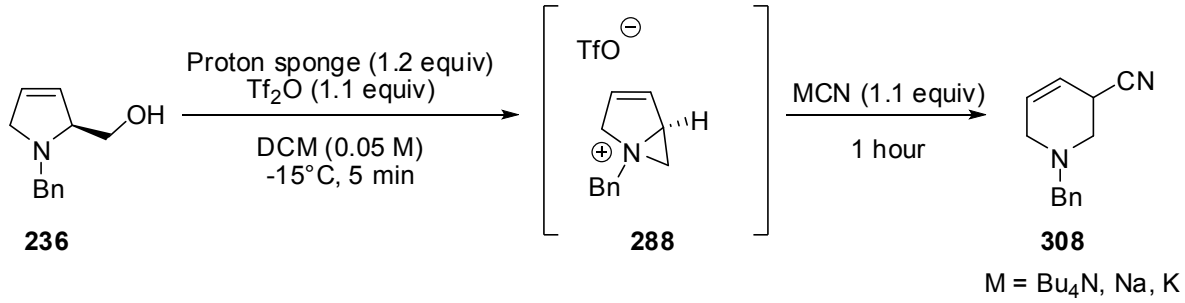
The optimization study to this point had been carried out with a nucleophile that was uncharged and fully soluble in the reaction solution. However, it was also desireable to react nucleophiles that were salts with the aziridinium ion. The effect of co-solvents and solvent modifiers was examined with representative salt nucleophiles (Table 11). Firstly, tetrabutylammonium salts were scrutinized as they are fully soluble in organic solvents. Highly variable yields were obtained when a slight excess of tetrabutylammonium cyanide was used as a nucleophile (entries 1-3). This was hypothesized to be due to the cyanide being basic enough to be protonated by the ammonium salt irreversibly to form cyanide gas consuming the nucleophile in an unproductive pathway. Therefore, an additional equivalent of the cyanide was employed (2.5 equivalents) and yields became quantitative and reproducible (entries 4-5).

The addition of the co-solvent acetonitrile after formation of the aziridinium ion was tolerated with no apparent effect on yield to form **308** (entry 5, Table 11). Acetonitrile had previously been shown to give exceptionally poor yields if used as the reaction solvent in which an aziridinium ion is formed (Table 6). Therefore, solvents other than DCM could be used for the reaction of the aziridinium ion after its formation without a negative impact on the yield.

As sodium salts are more prevalent commercially than tetrabutylammonium salts, sodium cyanide was next used as a representative salt nucleophile (Table 11). This gave a low yield of 48% (entry 6). A small number of co-solvents with sodium cyanide were examined and were found to give no improvement in the yield of **308** (entries 6-9). When DMF was used as a co-solvent the aziridinium ion reacted with DMF instead of the cyanide ion (entry 9). This reactivity of aziridinium ions with DMF has been noted before in literature.[23,54] In the presence of a crown ether, sodium cyanide gave comparable results to the tetrabutylammonium salt (entry 10, quantitative yield), showing that the low yield of the sodium salt was in fact due to its limited solubility. Tetrabutylammonium hexafluorophosphate was also examined as a potential ion exchange reagent to increase the solubility of the sodium salts but it failed to give a significant increase in yields (entry 11). Changing the counterion to potassium in place of sodium had a small beneficial effect on yield (entry 12: K with 59% vs entry 6: Na with 48%). Optimal conditions for salt

nucleophiles were therefore seen as using tetrabutylammonium salts if commercially available, or the sodium salt with the use of the crown ether 15-crown-5.

Table 11: Co-Solvent and Counterion Effect on Yield for Salt Nucleophiles



Trial	Nucleophile	Equivalents	Co-Solvent/Modifier	**308** Yield[a]
1	Bu_4N CN	1.2	DCM	61%
2	Bu_4N CN	1.7	DCM	37%
3	Bu_4N CN	1.2	Acetonitrile	43%
4	Bu_4N CN	2.5	DCM	100%
5	Bu_4N CN	2.5	Acetonitrile	100%
6	NaCN	3	DCM	48%
7	NaCN	3	Acetonitrile	22%
8	NaCN	3	1,2-Dimethoxyethane	<30%
9	NaCN	3	DMF	0%[b]
10	NaCN	3	DCM/15-Crown-5 (2 equiv)	100%
11	NaCN	3.5	DCM/Bu_4N PF_6 (1.1 equiv)	54%
12	KCN	3.2	DCM	59%

[a] determined by ^{1}H NMR of the crude reaction mixture by comparison to 1,3,5-trimethoxybenzene

[b] apparent by ^{1}H NMR of the crude mixture that DMF had reacted with the aziridinium

In summary, the optimal reaction conditions for formation and reaction of aziridinium ion **288** were found to be: 1.1 equivalents of Triflic anhydride; 1.2 equivalents of Proton Sponge; 1.1 equivalents of the nucleophile if neutral or 2.5 equivalents if anionic; 0.05 M in DCM; -15 °C; A 5 minute delay period between the triflic anhydride and nucleophile additions. When anionic nucleophiles were employed, the counterion of the nucleophile was optimal when it was tetrabutylammonium or sodium complexed with 15-crown-5.

Chapter 4: Mechanism of Ring Expansion and Scope

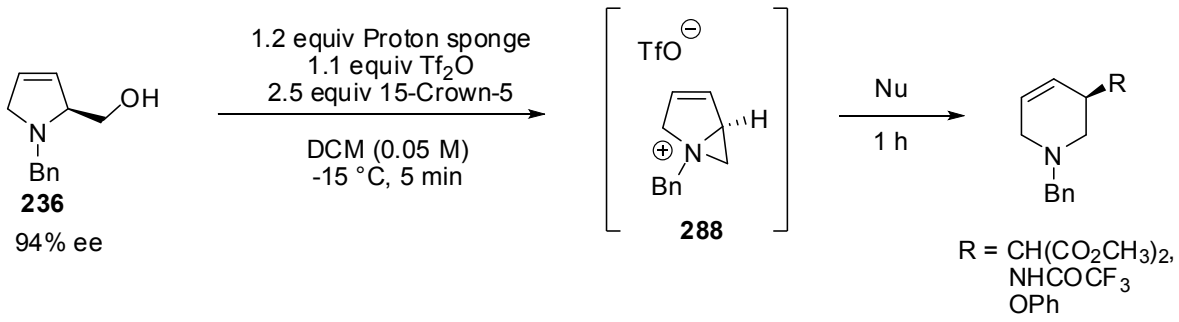
In the previous chapter, we have established optimal reaction conditions for formation and regioselective reaction of aziridinium ion 288 with the nucleophiles malonate, N-methylaniline and cyanide. The scope of this reaction will now be studied with various aziridinium ions and nucleophiles. We need also to establish that the enantiomeric excess of the precursor would be maintained. Furthermore, we need to assign the stereochemical relationship in between the substituents of the dihydropyridine, which will give us insight on the mechanism of this reaction.

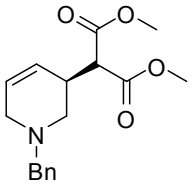
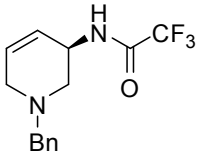
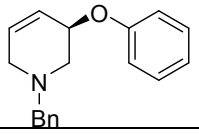
4.1 Enantiomeric Excess Maintained

We have so far developed optimized reaction conditions for the formation and reaction of the bicyclic [3.1.0] aziridinium ion. Furthermore, synthesis from 4-hydroxyproline to both racemic and enantioenriched *N*-benzyl-3,4-dehydroprolinol **236** was now available (section 2.2). The enantiomeric excesses and yields of the ring expansion with three representative nucleophiles were then determined. Nucleophiles were chosen that could be assigned by NMR experiments as the tetrahydropyridine isomer over the dihydropyrrole isomer unambiguously, such as the dimethylmalonate nucleophile used in chapter 3. Nucleophiles with a carbon (dimethylmalonate), nitrogen (trifluoroacetamide) and an oxygen (phenol) as as the reactive atom were used to show that the attack selectively occurred at the bridging aziridinium ion carbon to yield tetrahydropiperidines **309**, **310**, and **311** was general using the optimized conditions (Table 12).

The three nucleophiles examined in Table 12 gave a single isomer, and in all cases no trace of dihydropyrrole was observed. Also, all three of them maintained the enantiomeric excess through the ring expansion reaction. These three examples showed that the ring expansion to a tetrahydropyridine occurs selectively, is general and that the enantiomeric excess of the dehydroprolinol precursor would be maintained through this process.

Table 12: Study of Enantiomeric Excess Retention During the Ring Expansion Reaction



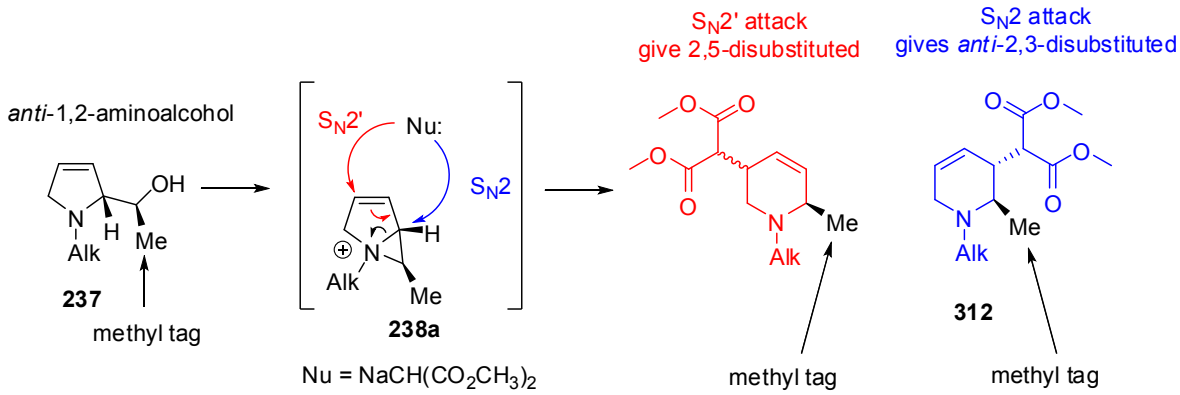
Entry	Compound	Nucleophile	Structure	Isolated Yield (%)	Enantiomeric Excess (%)
1	**309**	$NaCH(CO_2CH_3)_2$		87	94
2	**310**	$NaNHCOCF_3$		69	94
3	**311**	NaOPh		97	94

4.2 Mechanism of Ring Expansion and Scope

In order to assign a mechanism of the ring expansion, the stereochemistry of the products had to be verified. Insight into how the mechanism of nucleophile addition was obtained by comparison of the relative position and stereochemistry of the new substituent to a methyl tag on the tetrahydropyridine product (Scheme 65). If an S_N2' mechanism were to take place then the 2,5-disubstituted-tetrahydropyridine would be obtained. If an S_N2 mechanism were to take place as expected, *anti*-2,3-disubstituted-tetrahydropyridine **312** would be obtained. Also, to be certain that additional substituents or steric bulk would not

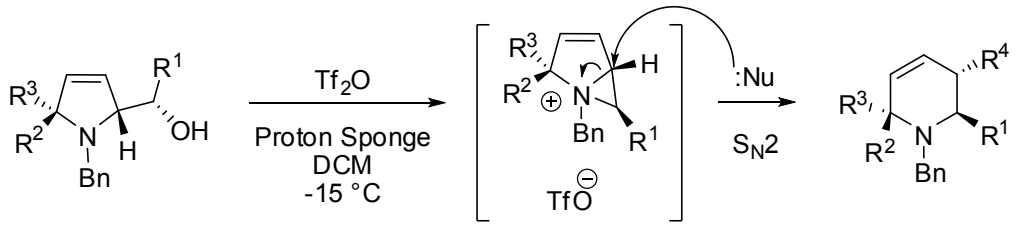
affect the regioselectivity of the nucleophile, the anion of dimethylmalonate was used as a representative nucleophile with aziridinium ions containing various substituents.

Scheme 65: Methyl Tagged Dehydroprolinol for Stereochemical Determination



As can be seen in Tables 13, 14 and 15, the transformation was quite general with a wide scope. The reaction tolerates a large variety of nucleophiles producing tetrahydropyridines in moderate to excellent yields via an S_N2 mechanism for all nucleophiles except organocuprates.

Table 13: Deuterium and Non-Organometallic Carbon Nucleophile Scope of Addition in the Ring Expansion Reaction



313 **314**

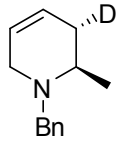
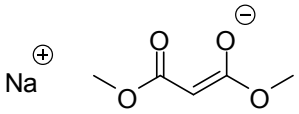
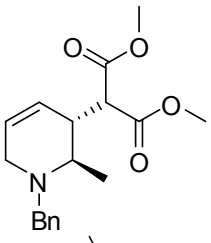
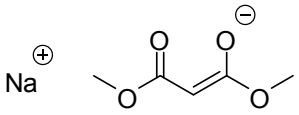
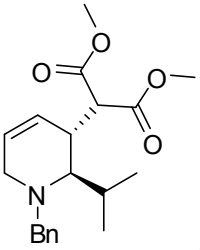
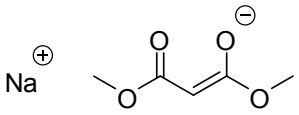
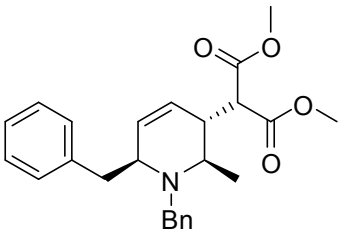
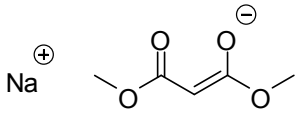
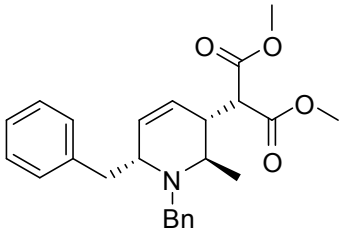
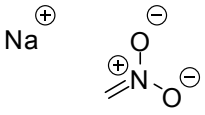
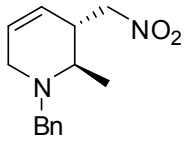
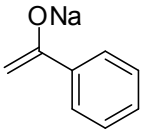
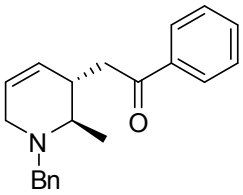
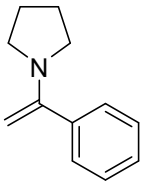
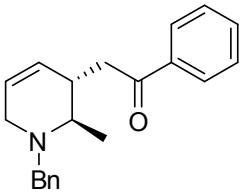
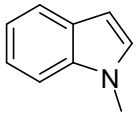
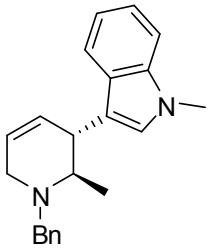
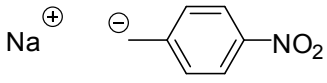
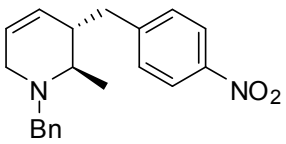
Entry	Nucleophile	Product	Structure	Yield (%)
1	$NaBD_4$	**315**		77
2	Bu_4NCN	**316**		79
3		**312**		71
4		**317**		73
5		**318**		81

Table 13: Continued

Entry	Nucleophile	Product	Structure	Yield (%)
6		**319**		89
7		**320**		0
8		**321**		<40
9		**321**		81
10		**322**		<5
11		**323**		0

Sodium borodeuteride was an effective nucleophile to afford the isotopically labeled tetrahydropyridine **315** in a 77% yield (Table 13, entry 1). Carbon nucleophiles such as cyanide afforded **316** in a 79% yield, malonate gave **312** in a 71% yield (entries 2-3).

Variable substitution patterns on the tetrahydropyridine were well tolerated for the ring expansion (Table 13, entries: 3-6, compounds **312**, **317**, **318**, and **319**) and had no impact

on the mechanism of nucleophile addition for the anion of dimethylmalonate. Unlike dimethylmalonate, when deprotonated nitromethane was used as a nucleophile it gave no ring expansion product – only decomposition products were observed (entry 7, **320**). Though while less reactive, similarities between *N*-methylindole and an enamine exist and indoles can be alkylated by strong electrophiles under forcing conditions at the 3-position selectively.[82] Attempts to alkylate *N*-methylindole with the aziridinium ion were unsuccessful at producing significant quantities of the tetrahydropyridine (entry 10). Only a trace of the product was observed by LCMS when the reaction temperature was allowed to warm to ambient temperature. No report was found in literature of an *N,N*-dialkylaziridinium ion in an alkylation reaction with an indole. However, there is one report of a protonated aziridine doing so at 70 °C, over a 30 minute period[83] – well above the stable temperature of the aziridinium ion established in the optimization. The reaction of deprotonated *p*-nitrotoluene as a nucleophile also failed to yield the tetrahydropyridine ring expansion product **323** (entry 11). This was surprising as the pka of this nucleophile is somewhat acidic on the Bordwell pKa scale (pka 20.4)[80a] and it appeared to fit the criteria. However, as mentioned earlier the pKa is solvent dependant.[80]

nOe experiments were conducted on the representative compound **312** (Figure 13). nOe confirmed that the methyl at the 2-position and dimethylmalonate at the 3-position were *anti* to one another, as expected if the aziridinium was formed in an S_Ni process then opened in an S_N2 process. By nOe the methyl and malonate were determined to be pseudo-axial in solution. This conformation was likely due to gauche interactions between the methyl and the benzyl group, as well as the dimethylmalonate. If the two substituents are placed in a pseudo-axial conformation in the tetrahydropyridine then the C2 and C3 hydrogens are approximately 90^o from one another, and therefore they would be expected to have a negligible coupling constant[84] as was observed.

Figure 13: nOe of **312** to Confirm the Stereochemistry of the New Substituent

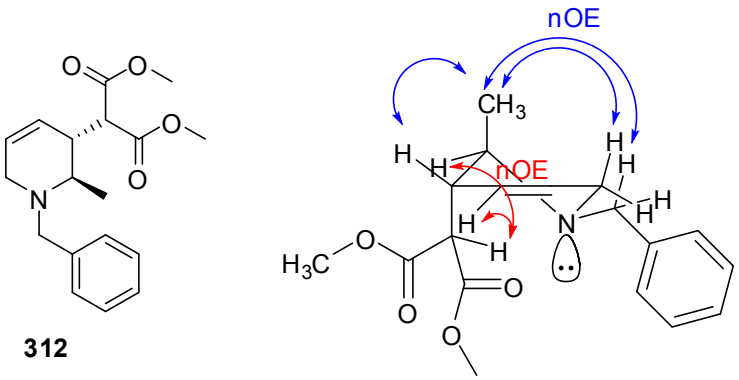
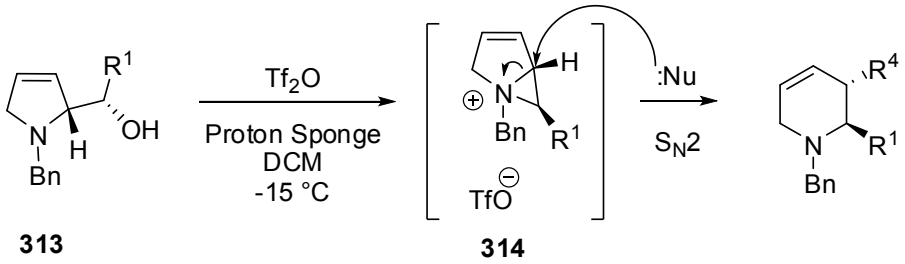


Table 14: Heteroatom Nucleophile Scope of Addition in the Ring Expansion Reaction



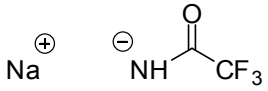
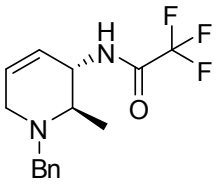
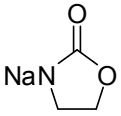
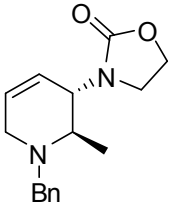
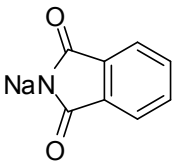
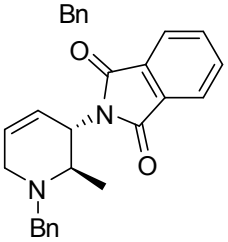
Entry	Nucleophile	Product	Structure	Yield (%)
1		**324**		58
2		**325**		86
3		**326**		70

Table 14: Continued

Entry	Nucleophile	Product	Structure	Yield (%)
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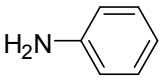
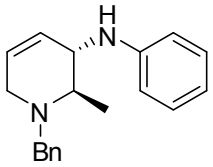
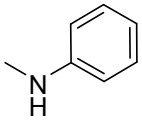
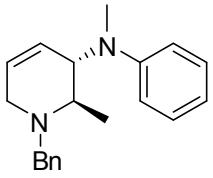
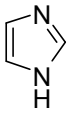
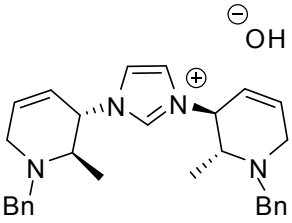
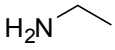
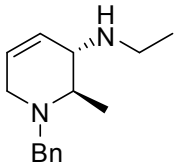
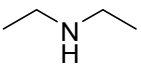
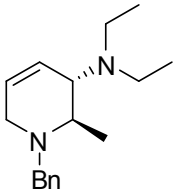
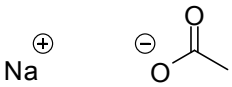
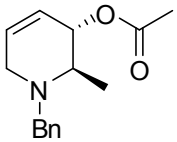
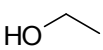
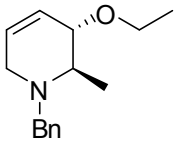
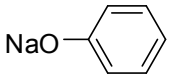
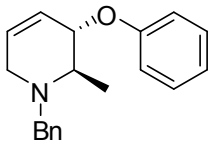
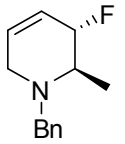
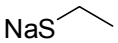
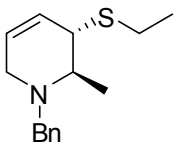
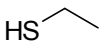
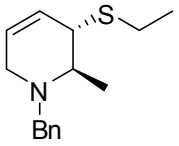
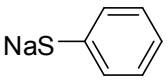
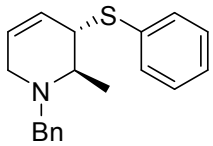
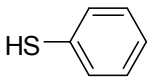
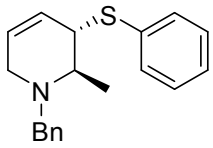
5		**328**		80
6		**329**		93
7		**330**		60
8		**331**		89
9		**332**		87
10		**333**		65
11		**334**		73

Table 14: Continued

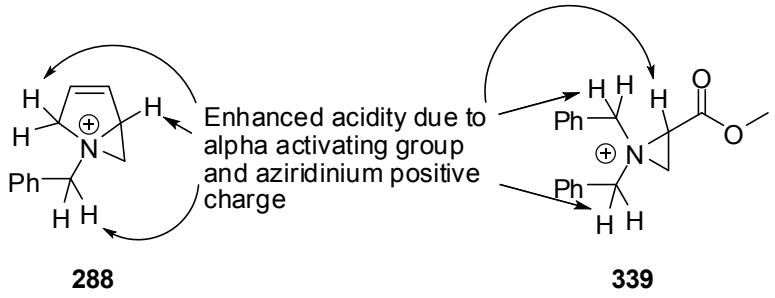
Entry	Nucleophile	Product	Structure	Yield (%)
12		**335**		85
13	Bu_4NF	**336**		57
14		**337**		45
15		**337**		56
16		**338**		70
17		**338**		41

The reaction with heteroatom nucleophiles as shown in Table 14 proceeded through an S_N2 mechanism yielding 2,3-disubstituted tetrahydropyridines. Nitrogen nucleophiles were well accepted and reactions with an amide, carbamate, phthalimide, azide, amines, and anilines gave good to excellent yields (Table 14, entries 1-9, compounds **324-332**). The reaction with oxygen nucleophiles such as an acetate, phenoxide or alcohol also lead to good to excellent yields (entries 10-12, compounds **333-335**). When fluoride was used as a

nucleophile, the reaction proceeded in moderate yield (entry 13, **336**). The reaction with sulfur nucleophiles gave moderate yields (entries 14-17, compounds **337**, **338**), with an alkyl thiol producing a modestly superior yield to the sodium alkyl thiolate. Conversely, the reaction with sodium thiophenolate provided a superior yield compared to thiophenol.

The limit of which nucleophile can be used in the ring expansion appears to be highly related to the acidity of the aziridinium ion which has been alluded to in literature (Figure 14).[46] For example, sodium ethoxide decomposed the aziridinium ion salt but ethanol was a suitable nucleophile (Table 14, entry 11). Likewise, the sodium enolate of acetophenone gave poor yields with significant decomposition (Table 13, entry 8), however the enamine of acetophenone gave an excellent yield which was the first reported example of such a nucleophile reacting with an aziridinium ion (Table 13, entry 9, **321**). Therefore, this limit on acidity can be circumvented to some extent since the aziridinium ion is a very strong electrophile.

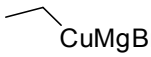
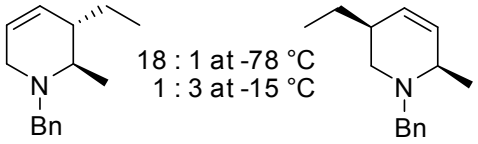
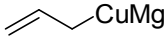
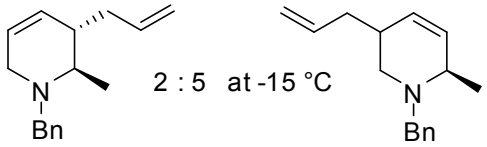
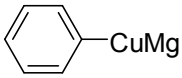
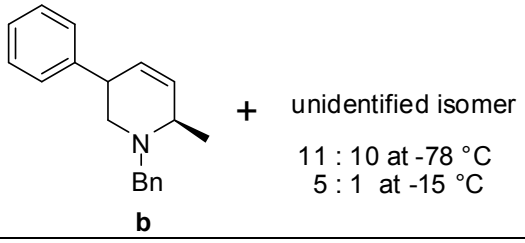
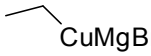
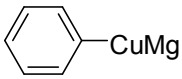
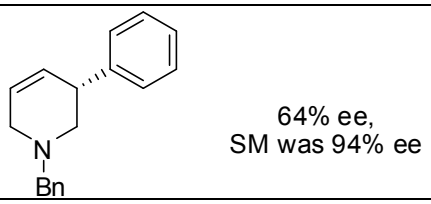
Figure 14: Aziridinium Ion Acidic Protons



4.3 Mechanism of Ring Expansion with Organocuprates

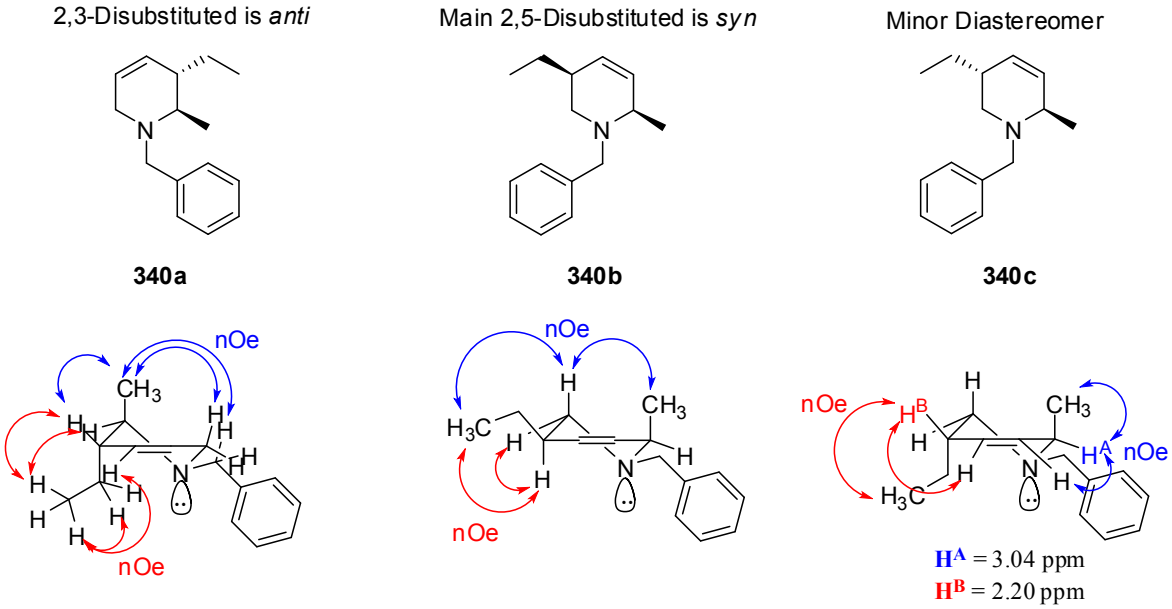
The only nucleophiles that were examined with this system that did not give the 2,3-disubstituted tetrahydropyridine product solely were organocuprates (Table 15, **340**-**344**). They are operating through a different mechanism when reacting with a vinyl aziridinium ion, such as **288**, than other nucleophiles. The lack of the 2,3-disubstituted tetrahydropyridine as the sole product suggests that the aziridinium ion opening and the C-C bond formation occur in separate steps during the ring expansion, instead of in a concerted manner as the other nucleophiles had.

Table 15: Organocuprate Nucleophile Addition in the Ring Expansion Reaction

Entry	Nucleophile	Product	Structure	Yield (%)
1		**340**		78
2		**341**		95
3		**342**		97
4		**343**		73
5		**344**		96

The pKa requirement of the aziridinium ion on the nucleophiles procludes that they are reacting as simple carbanions as they would be too basic and would simply decompose the aziridinium ion much like sodium ethoxide. There has been evidence presented that Grignards can at least partially go through a SET mechanism when reacted with aziridinium ions.[25] However, for cuprates this does not appear to be the case as if it were an allyl radical would be formed and one would expect homocoupling products, which were not observed.

Figure 15: nOe Relationship of Products From an Ethylcuprate and **238a**



nOe experiments on the compound **340a** showed the same *anti* relationship and conformation as compound **312** obtained from a simple carbanion. However **340b**, which was the main product formed at higher temperatures, was established as *syn* by relay nOe between the pseudo-axial hydrogen of the methylene at the 6-position of the piperidine and the methyl and ethyl groups (Figure 15). Also, the minor diastereomer **340c** (by integration <1% by ^{1}H NMR) was formed that was assigned to be the *anti*-2,5-disubstiuted piperidine by nOe and COSY experiments of the mixture.

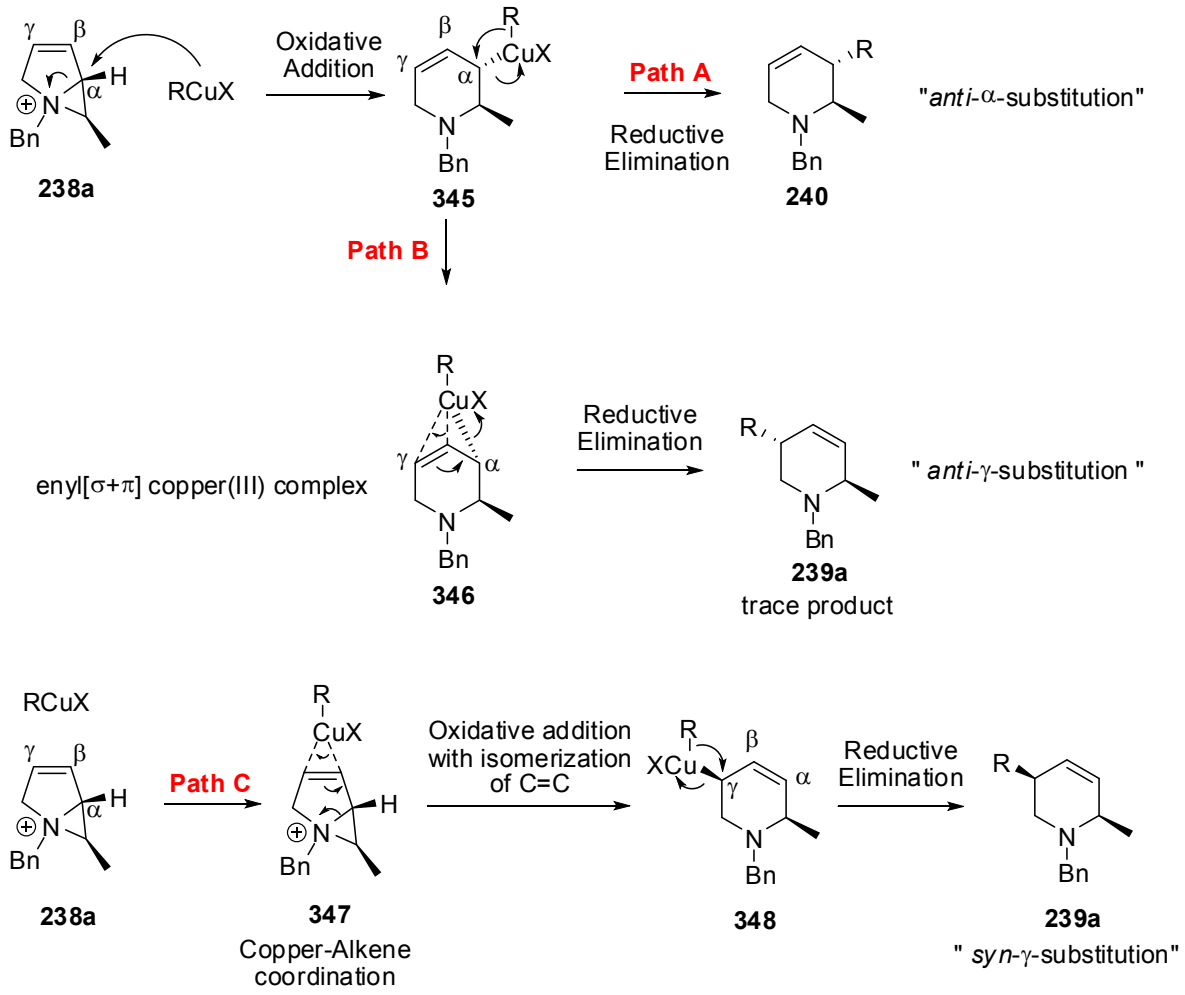
When using ethyl cuprate as a nucleophile, the ratio of the two main products was dependant on temperature. The *anti*-2,3-disubstituted tetrahydropyridine **340a** was favoured at lower temperatures, and the *syn*-2,5-disubstituted tetrahydropyridine **340b** at higher temperatures (Table 14, entry 1). Plausible mechanisms would be as the following (Scheme 66):

Path A would include an oxidative addition of the metal to the aziridinium ion by opening the ring, followed by a reductive elimination resulting in C-C bond formation at the α position to give the 2,3-disubstituted tetrahydropyridine **240** with the two substituents *anti* to one another.

Path B diverges from Path A after the oxidative addition to the cuprate by the aziridinium ion. It leads to the enyl[σ+π] copper(III) complex[85] followed by reductive elimination resulting in C-C bond formation at the γ-position to give **239a**. Path B would place the ethyl at the 5-position *anti* to the methyl at the 2-position.

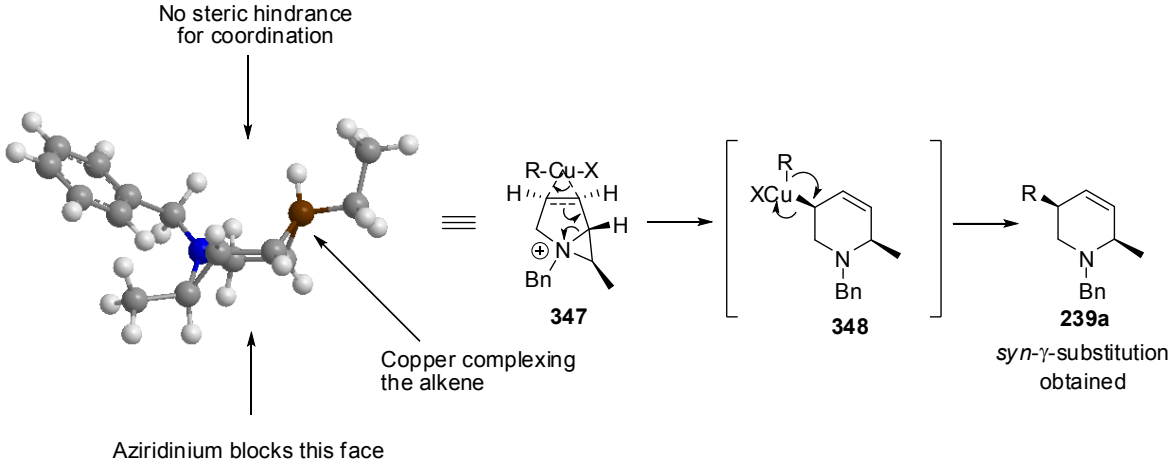
Path C is where the cuprate is involved in a π-complex analogous to the reaction of cuprates with enones.[85] With the greater conformational freedom obtained at higher temperatures, and the bond order of the alkene altered by the copper/alkene complex the bicyclic could adopt the otherwise unfavourable conformation to open the aziridinium ion

Scheme 66: Proposed Mechanism for Organocuprate Addition to the Bicyclic Aziridinium Ion



with an alkene isomerization placing the alkyl copper(III) at the 5-position. The alkyl copper(III) 5-substituted tetrahydropyridine would then undergo a reductive elimination at the γ position to yield the *syn*-2,5-disubstituted tetrahydropyridine. An alkene/copper complex as in Path C would likely give the *syn*-2,5-disubstituted product instead of the *anti* due to steric hindrance of the aziridinium ion blocking one face of the pyrrolidine favouring this face (Figure 16). This pathway would explain the temperature dependence of the product distribution of **340a** to **340b**.

Figure 16: Organocuprate Complexation of the Alkene to Yield the *syn*-γ-Substituted Product



When an allylcuprate was reacted with the methyl tagged aziridinium ion a similar ratio was obtained (Table 14, entry 3, **341**, 2:5 ratio) as the ethylcuprate (**340**, 1:3) favouring 2,5-disubstituted tetrahydropyridine **341b** at -15 °C. A phenylcuprate also favoured 2,5-disubstituted product **342** (entry 4) at -15°C though had a minor unidentified isomer (1:5 ratio of **342**:unknown isomer at -15 °C) but had lower selectivity than the ethylcuprate at a -78°C for 2,3-disubstituted tetrahydropyridine **342a** (10:11 for **342** a:b, 18:1 for **340** a:b).

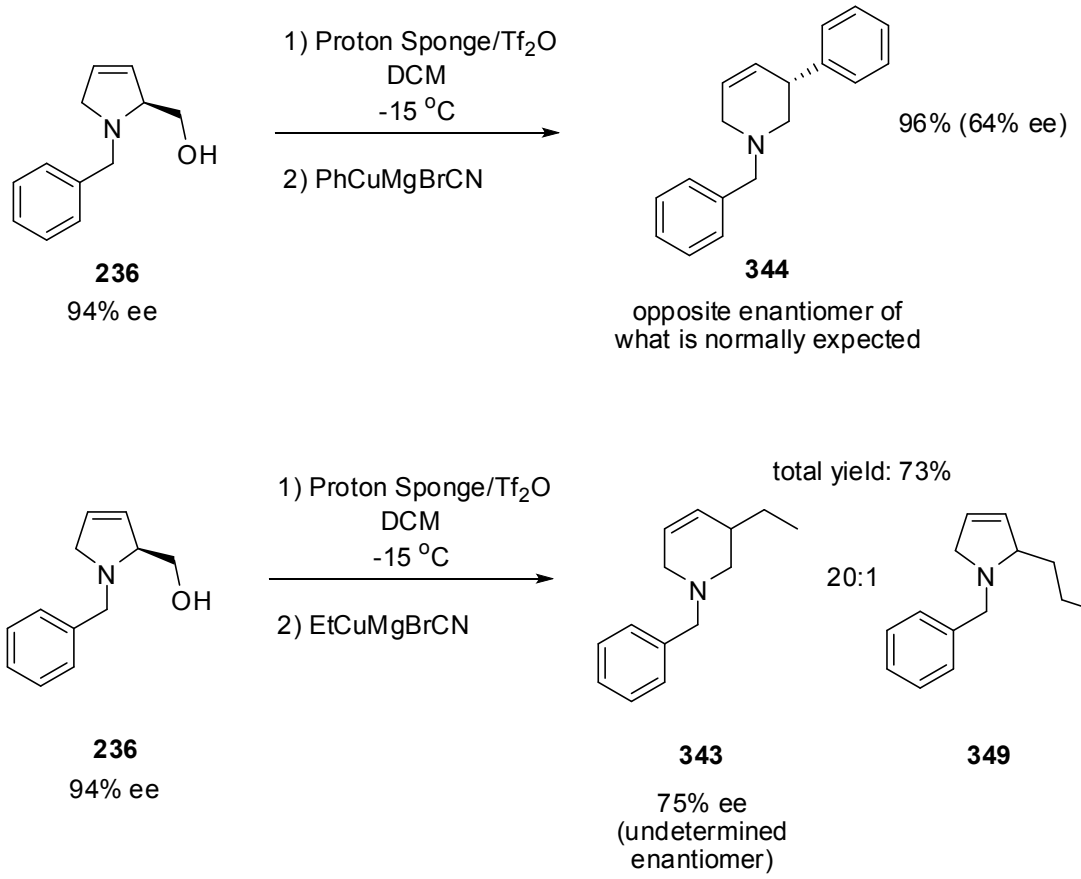
Ethyl analog **340b** relative stereochemistry had been determined by relay nOe interactions using the methylene in the ring at the 6-position of the tetrahydropyridine ring. The two hydrogens of the methylene at this 6-position were diastereotopic and clearly distinguishable from one another. For allyl analog **341b** and phenyl analog **342b** unfortunately, the methylene hydrogens of the 6-position were not clearly distinguishable

so relay nOe was not feasible and the relative stereochemistry of the substituent to the methyl tag could not be assigned.

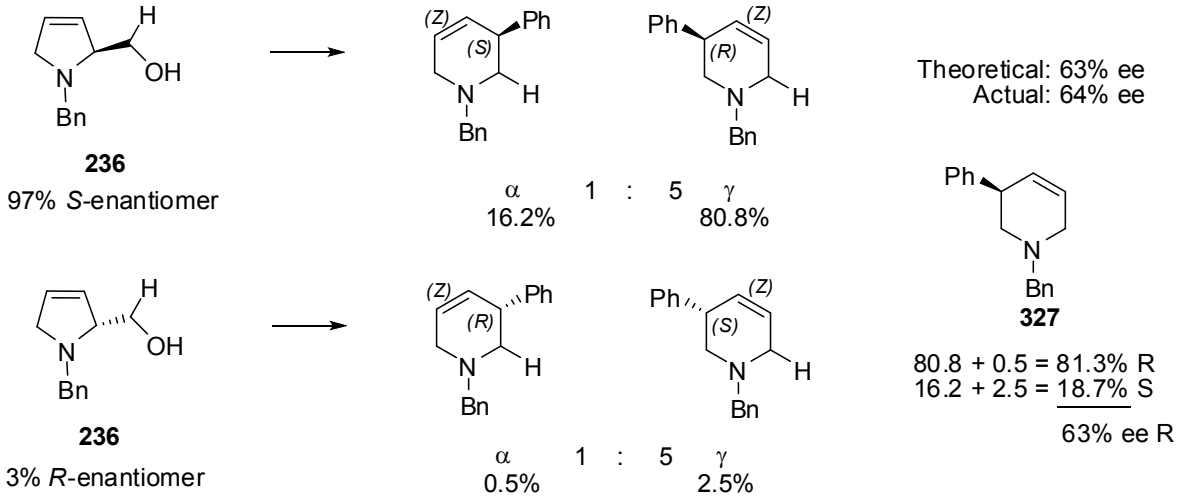
We submitted *N*-benzyl-3,4,-dehydroprolinol **236** obtained from 4-hydroxyproline to the ring expansion reaction conditions with two organocuprates (Table 14, entries 4-5, and Figure 67). The reaction of the aziridinium ion with ethylcuprate proceeded with high regioselectivity to obtain tetrahydropyridine **343** (20:1 **343**:**349**). Phenylcuprate when used as a nucleophile yielded selectively piperidine product **344** with no pyrrole isomer observed. However, the enantiomeric excess was not maintained through the ring expansion for either of the two examples. 3-Phenyl piperidine is a known compound, and comparison of the optical rotation[86] of the hydrogenated analog of **344** showed that the major enantiomer to be the opposite of what is normally expected if the ring expansion would have occurred through an S_N2 mechanism. Chiral SFC showed the enantiomeric excess of **344** to be 64% ee while the precursor **236** had 94% ee. The ethyl analog **343** also had a lowered enantiomeric excess (75% ee) from the precursor **236** (94% ee). Unfortunately, the optical rotation of the reference for the HCl salt of the hydrogenated analog of **327** was too small (3°)[87] to have confidence in enantiomer assignment by this method and was therefore undetermined.

The opposite enantiomer being obtained for the ring expansion from **236** with phenylcuprate to yield **343** is logical if the major reactive pathway for this product to be formed was Path B of Scheme 66. The product ratio for **342** in the ring expansion with the methyl tagged analog and a phenylcuprate was likely 5:1 γ:α substitution (minor unidentified isomer assumed to be α-substitution, though the *anti*-γ-substitution would also give the same result), with the γ product relative stereochemistry undetermined. If the relative stereochemistry of the γ substitution of **342** were *anti* to the methyl tag analog, then in the absence of a methyl tag it would yield the opposite enantiomer expected and be the major product. With the assumption that the methyl tag had no significant impact on the regioselectivity of the new substituent, the ratio of the two possible enantiomers was calculated from 94% ee (Scheme 68). If the γ substitution of the product were *anti* to the methyl tag, this yields a value that approximates the enantiomeric excess obtained experimentally quite well (theoretical: 63% ee, actual: 64% ee). This suggests that in the 2-

Scheme 67: Ring Expansion from *N*-Benzyl-3,4-Dehydroprolinol with Organocuprates



Scheme 68: Approximation of the Enantiomeric Excess of **330** Assuming an *anti* γ Product



methyl-5-phenyl tetrahydropyridine **342** obtained, the two substituents are *anti* to one another but this would require further experiments to conclusively affirm this as the relative stereochemistry.

Ethyl analog **343** also had a reduction in the enantiomeric excess from its precursor (94% ee to 75% ee). However, **340b** was assigned as *syn* by nOe to the methyl so both pathways (α-substitution and γ-substitution) logically should yield the same enantiomer. If the assignment of stereochemistry was incorrect by nOe, and the ratio of the two isomers obtained with methyl analog **340** (3:1 α:γ) were translated to analog **343** with no methyl tag prepared under the same conditions, then the theoretical enantiomeric excess value would still not be in agreement with the experimental enantiomeric excess value. Therefore, it is unlikely that this was the cause of the reduction in enantiomeric excess of **343**. The reduction in enantiomeric excess for the ethyl analog **343** could not be explained with the data available.

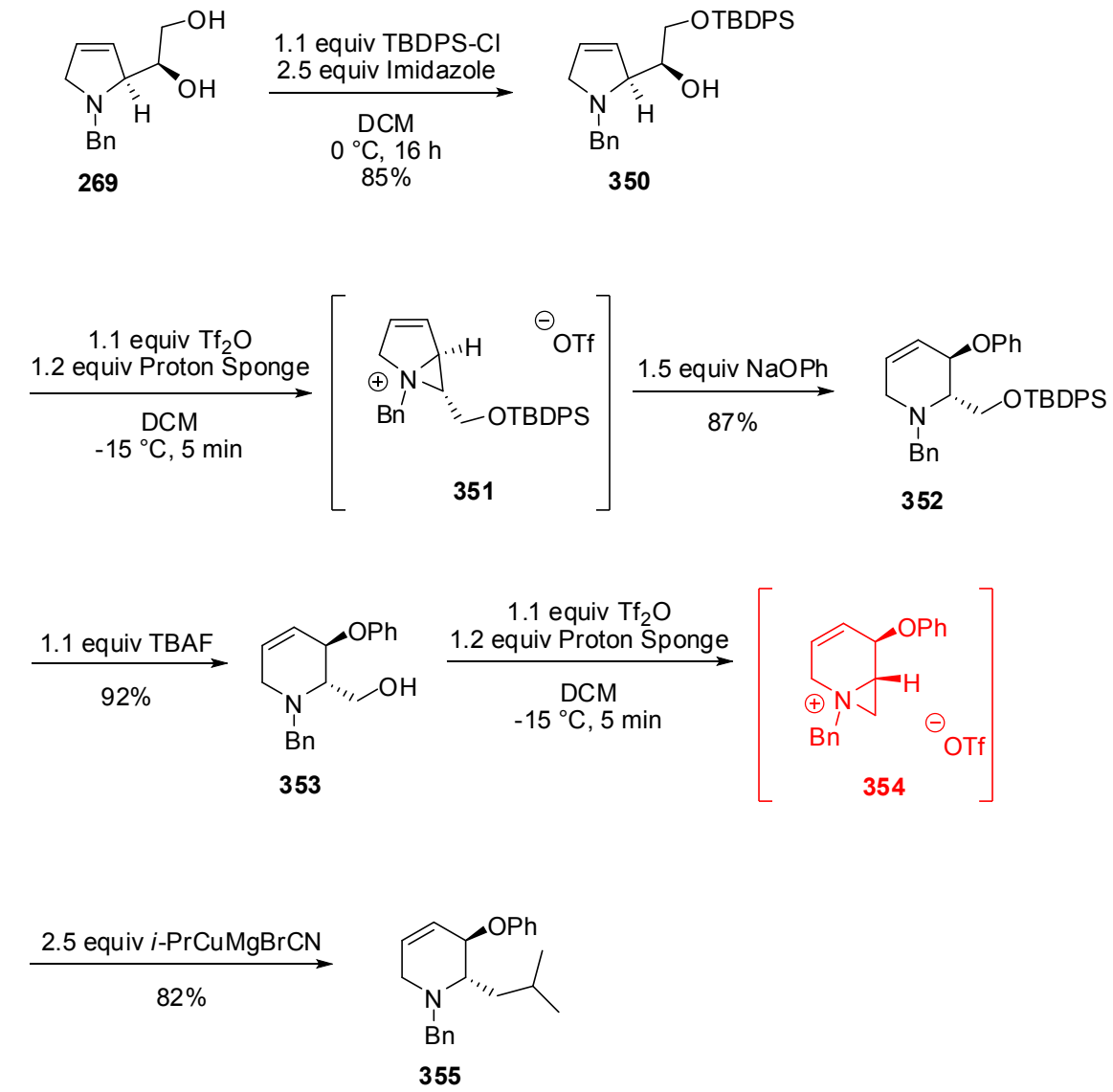
4.4 Divergent Substitution Using an Aziridinium Ion

Substitution at the 2-, 3-, and 6-positions of the tetrahydropyridine has been demonstrated with excellent diastereocontrol using the aziridinium ion ring expansion and Petasis-Mannich reaction to prepare the pyrrolinol precursor in the previous chapters. Also, the alkene is a synthetic handle for further derivatization at the 4- and 5-positions or it can be potentially substituted earlier in the synthesis. However, in using this synthetic route the substitution at the 2-position (or 6-position) required that the substituent be selected in the beginning of the synthesis. We wished to increase the versatility of this methodology even further. We envisioned using a hydroxymethyl to prepare another aziridinium ion to substitute the 2-position at a later stage intermediate (Scheme 69). Since no activating group is present in the bicyclic [4.1.0] aziridinium ion **354** the nucleophiles would regioselectively attack the least hindered position. This would therefore maintain the enantiomeric and diastereomeric purity of this approach while also giving the ability to functionalize different points of the piperidine from a common precursor. Fortunately, the 2-hydroxymethyl tetrahydropyridine **353** and its analogs are readily available in enantiopure form from glyceraldehyde. Potentially, a hydroxymethyl could also be placed at the 6-position of the tetrahydropyridine by using a protected chiral 2-amino-but-3-en-1-

ol as a precursor for the Petasis-Mannich reaction. Chiral 2-amino-but-3-en-1-ols could be made in 2 steps through a catalytic asymmetric method from a racemic vinyloxirane through the use of a sigmatropic allylic rearrangement.[88]

For an example of this divergent approach we selectively protected pyrrolidine diol **269**, obtained from glyceraldehyde to obtain **350** in three steps from commercially available materials (Scheme 69). **350** was ring expanded using sodium phenolate to produce **352** in 87% yield. **352** was then deprotected using TBAF to obtain 2-hydroxymethyl-3-phenolate tetrahydropyridine **353** in a 92% yield. **353** was then converted to an aziridinium ion *in-situ* and reacted with an *iso*-propyl cuprate to produce **355** in an 82% yield. Therefore, **350** was converted to the 2,3-disubstituted tetrahydropyridine **355** with the 2- and 3-substituents both chosen in 3 steps. A similar approach could potentially also be used at the 6-position though the alkene would have to be converted into a non-activating group before the second aziridinium use (e.g.: hydrogenation) so that nucleophiles would be guided by steric demands alone for the second substitution.

Scheme 69: Using a Hydroxymethyl α to the Piperidine Nitrogen for Substitution



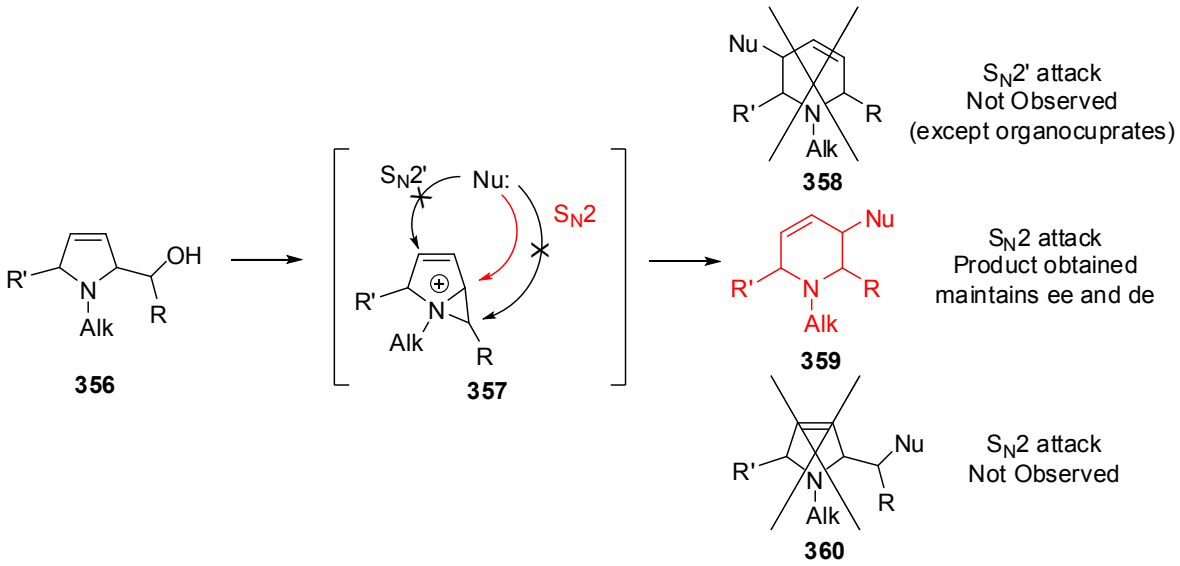
Chapter 5: Conclusions and Future Work

5.1 Summary and Conclusions

A method to prepare enantiopure 3-substituted piperidines has been developed that is flexible, versatile and concise that also allows substitution at the 2- and 6-positions with excellent stereocontrol. This method demonstrated that the alkene is a sufficiently strong activating group so that the aziridinium ion is opened with complete regioselectivity to the desired position to obtain a ring expansion with a large number of nucleophiles.

The aziridinium ion reacted solely with an S_N2 mechanism with all nucleophiles examined with the exception of organocuprates, which have additional mechanistic pathways allowed to them. The mechanism by which nucleophiles react with the bicyclic aziridinium ion was inferred by tagging the template with a methyl group and comparison of the new substituent's relative position and stereochemistry to the methyl tag. Varying the substitution at the 2- or 6-position had no effect on the mechanism of addition of the nucleophiles as expected. Unfortunately, reacting organocuprates with a bicyclic [3.1.0] aziridinium ion did not yield a single product as the regioselectivity was affected by a number of factors such as temperature and the ligands of the organocuprate, which limits their usefulness. However, alkyl organocuprates are promising as the regioselectivity was

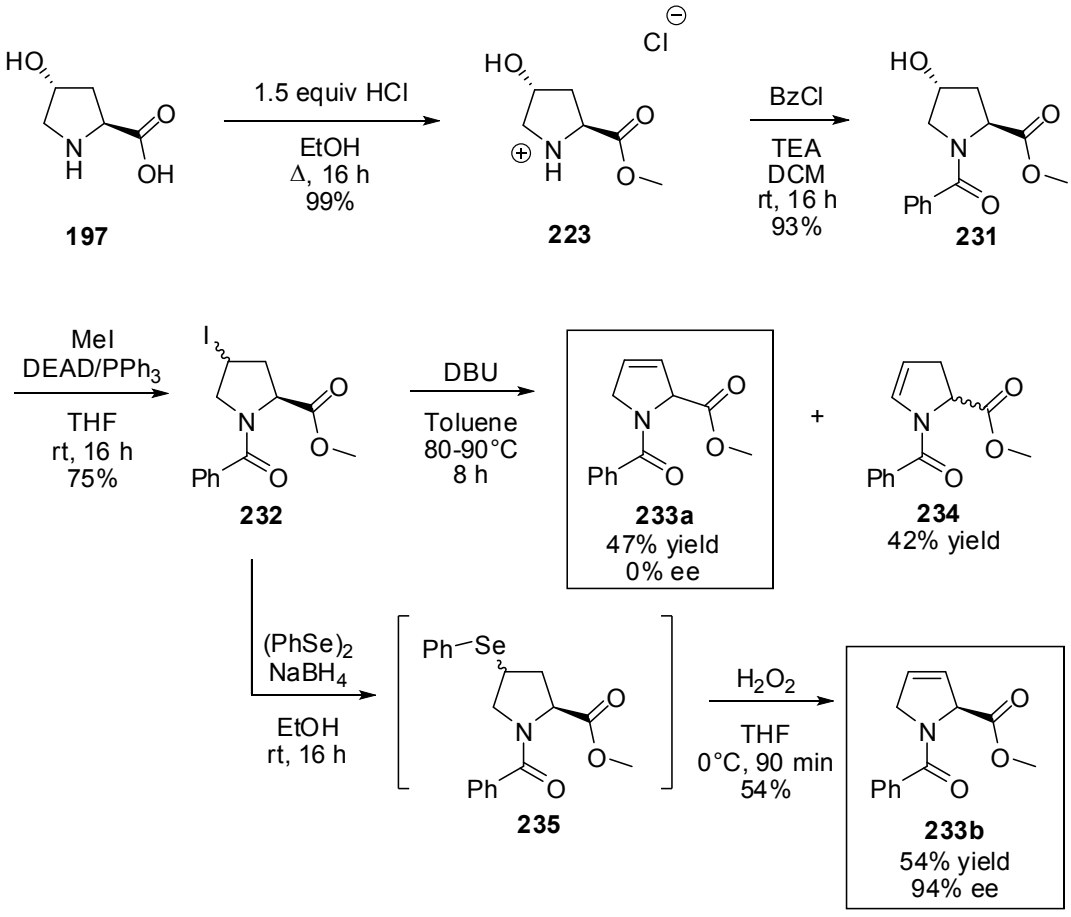
Scheme 70: Ring Expansion of Pyrrolinols to Piperidines



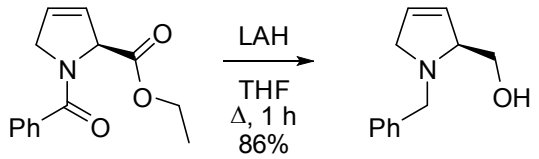
quite high at low temperatures (**340**: -78 °C, 18:1 for a:b). The regioselectivity for other alkyl, alkene, and aryl cuprates requires more study.

Two synthetic routes to *N*-benzyl-3,4-dehydroprolinol **236** were developed, using 4-hydroxyproline or glyceraldehyde as the chiral precursor. The use of 4-hydroxyproline as a precursor to prepare the dehydroprolinol for the ring expansion was not optimal giving enantio-enriched (94% ee) *N*-benzyl-3,4-dehydroprolinol **236**, in 5 steps with an overall yield of 32%. The synthesis of *N*-Benzyl-3,4-dehydroprolinol **236** from glyceraldehyde was accomplished with >99% ee in 3 steps from commercial materials in a 35% overall yield.

Scheme 71: *N*-Benzoyl-3,4-Dehydroprolinate **233** from 4-Hydroxyproline



Scheme 72: *N*-Benzyl-3,4-Dehydroprolinol **236** from **233b**

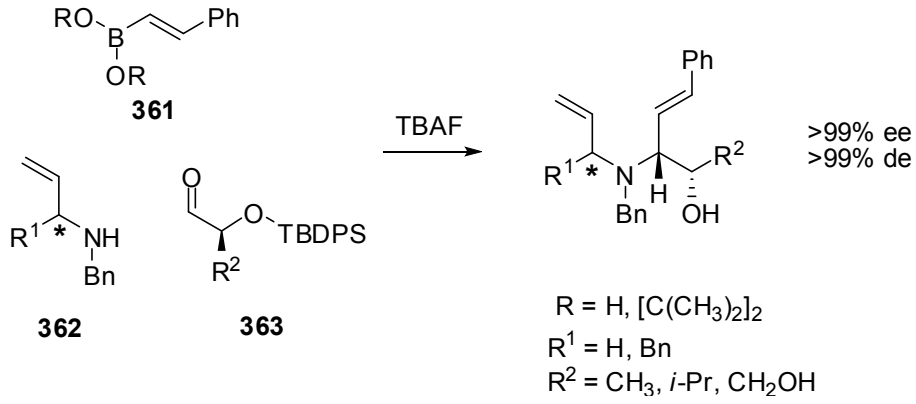


233b
94% ee

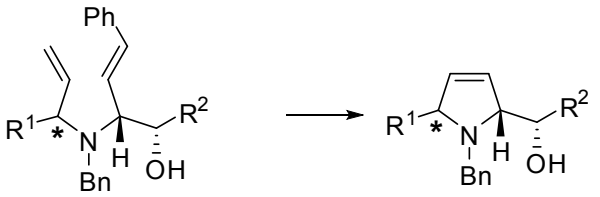
236
94% ee

The Petasis-Mannich reaction was quite powerful, versatile and concise to prepare the desired 1,2-aminoalcohols which were subsequently converted to dehydroprolinols by an RCM reaction. The protecting group modification of the Petasis-Mannich reaction with an *in-situ* deprotection had no impact on the diastereoselectivity, enantiopurity or yield of the reaction but had the advantage of making the precursor synthesis and isolation trivial. The use of the modified version of the Petasis-Mannich reaction added strongly to the versatility of this method of ring expansion, as it allowed diastereoselective synthesis of the substituted pyrrolinol precursors. The enantiomeric purity, length of synthesis, and diastereoselectivity clearly point to the Petasis-Mannich and RCM method as being superior over using 4-hydroxyproline as a precursor for the synthesis of desired pyrrolinols.

Scheme 73: Petasis-Mannich Silyl Protecting Group Modification



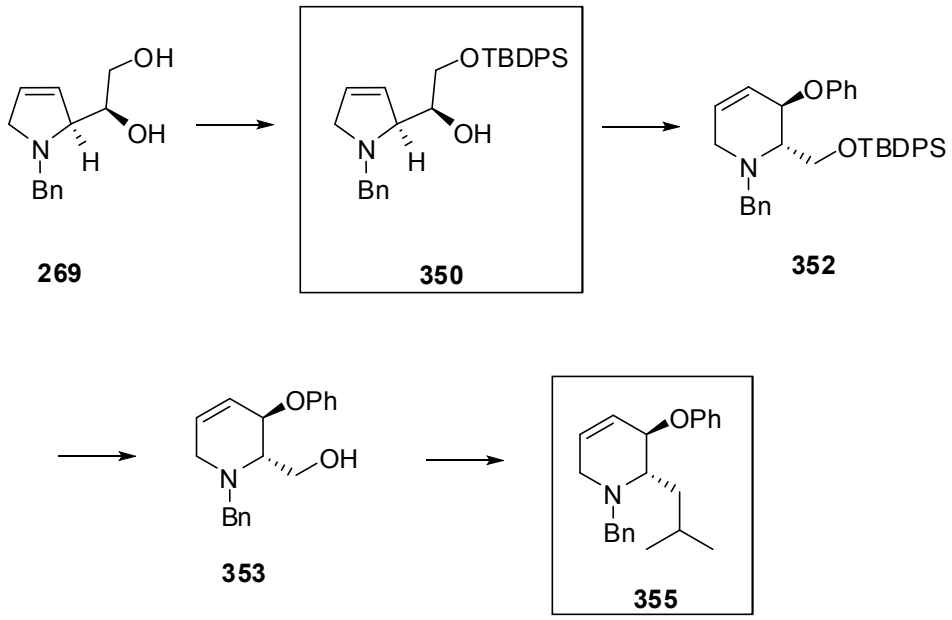
Scheme 74: RCM of the Petasis-Mannich Product to Obtain Pyrrolinols



364 **365**

The use of 2-diol-pyrrolidine **352** prepared from glyceraldehyde in three steps, as a precursor to the ring expansion allowed us to choose the substituents at both the 2- and 3-positions of the tetrahydropyridine from an advanced intermediate (Scheme 75). The 3-substituent was chosen during the ring expansion, and the 2-substituent after the ring expansion through an unactivated aziridinium ion. This demonstrated the ability to substitute various positions on the enantiopure piperidine skeleton with excellent stereocontrol quite well.

Scheme 75: Choosing the 2- and 3-substituents of the Piperidine from a Common Intermediate



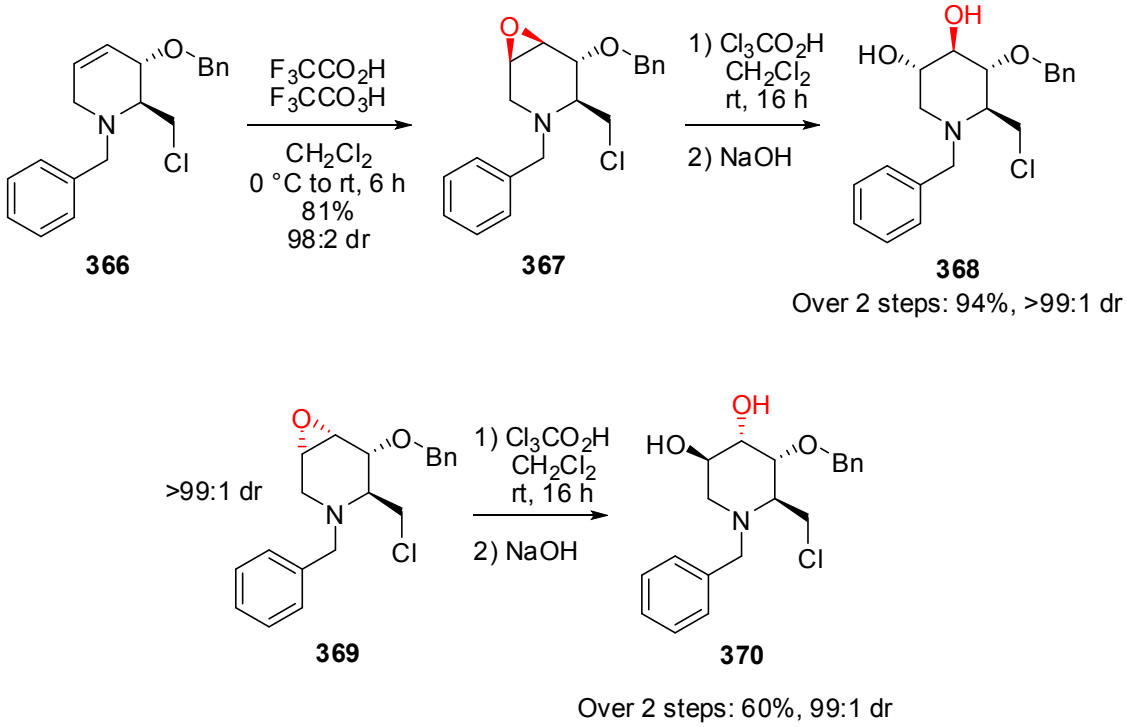
269 **350** **352** **353** **355**

5.2 Future Work

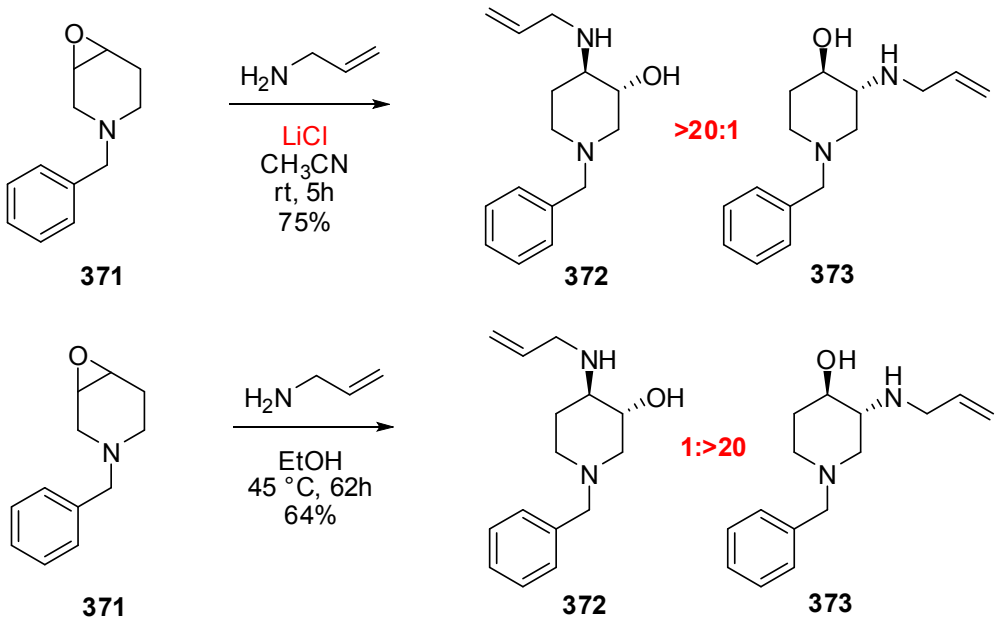
The alkene of the tetrahydropyridine is a potentially useful synthetic handle for further derivatization or substitution. Thus, all 5 carbon sites of the piperidine skeleton could in principle be accessed for substitution by this ring expansion method. For example, epoxidation of the 3,4-tetrahydropyridine has been done with excellent diastereoselectivity on a similar substrate, as shown in Scheme 76.[89] Epoxides such as **367** have been shown to be opened regioselectively by a number of nucleophiles such as hydrides, cuprates, cyanide, amines and acids to gain substitution at the 3- or 4-position of the piperidine.[90]

The conditions for some nucleophiles to obtain epoxide opening at the 3-position or 4-position regioselectively with the same nucleophile has been studied as shown in Scheme 77. This regioselectivity between the two epoxide carbons was due to electrostatic replusion of the amine and epoxide oxygen, or through chelation of the additive by the amine and oxygen depending on whether an additive was employed or not. This allowed the authors to selectively attack each carbon of the epoxide. [90c]

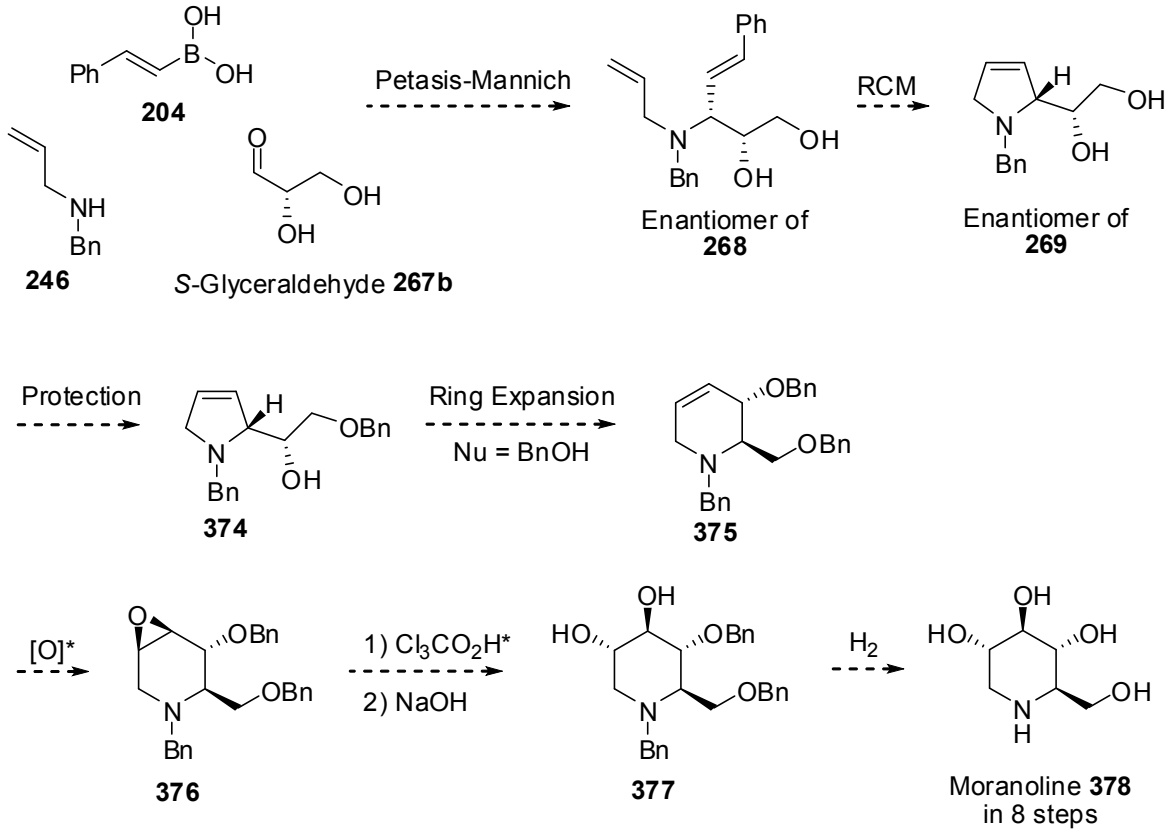
Scheme 76: Epoxidation of an *N*-Benzyl-Tetrahydropyridine and Opening of Such an Epoxide



Scheme 77: Regioselective Opening of the Epoxide



Scheme 78: Proposed Synthesis of Moranoline

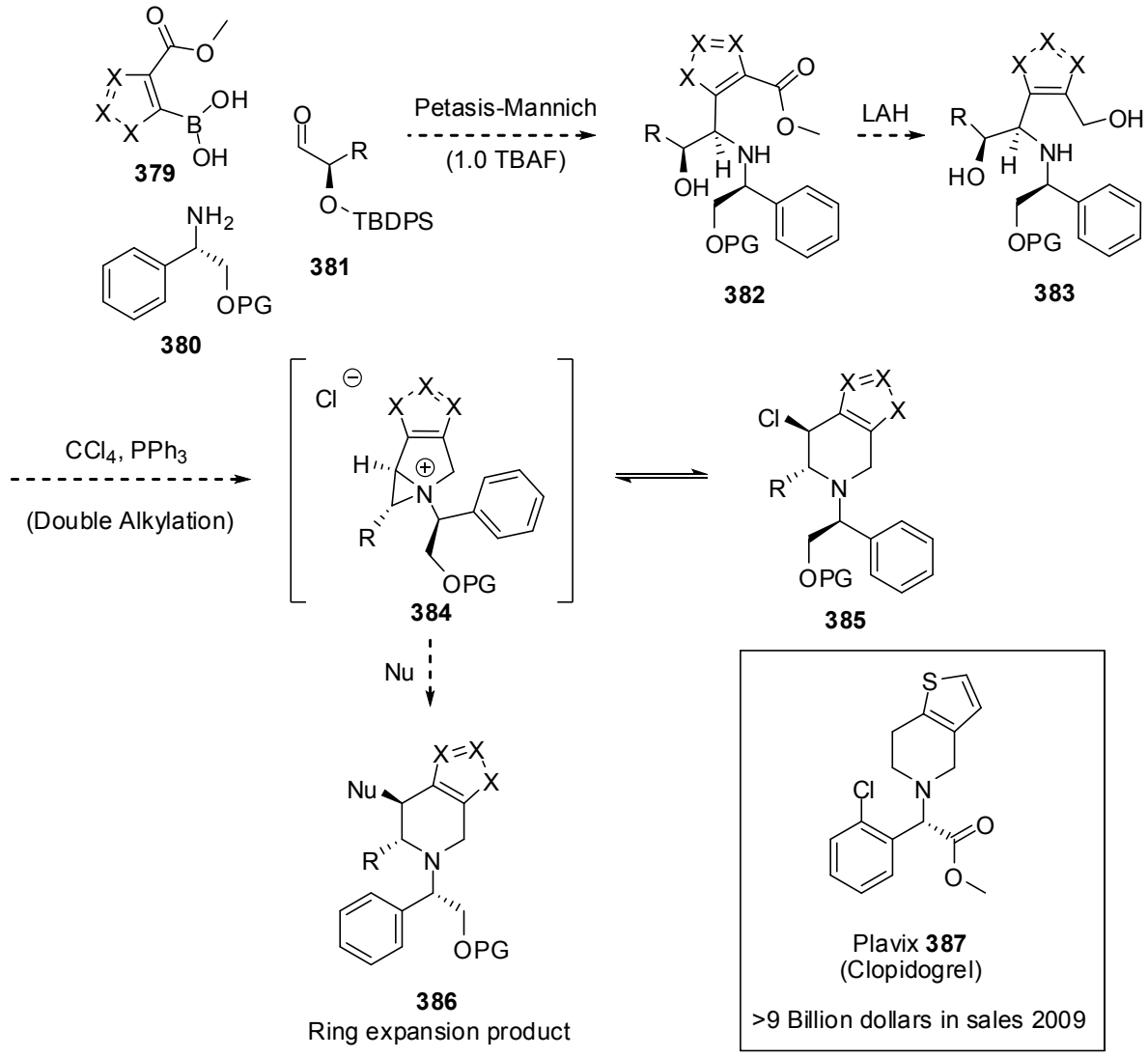


* *Org. Lett.*, **2010**, 136

There are a number of natural products that are potential synthetic targets of this methodology such as the aza-sugars Miglitol, Fagomine, Isofagomine, Castanospermine, Moranoline, and many others.[91] Previously Moranoline has been prepared in racemic form in 10 steps.[89,**Error! Bookmark not defined.**] Moranoline could potentially be prepared in enantiopure form in 8 steps from glyceraldehyde using the ring expansion methodology put forward here as shown in Scheme 78.

A π-allyl cation has been demonstrated to not form from this system with a large number of nucleophiles and this is due to the bridged C-N σ* of the aziridinium ion being orthogonal to the π-system electrons. Therefore, the tagged bicyclic [3.1.0] aziridinium ion gives a unique way to study how cuprates react with allyl leaving groups, separating the various mechanistic pathways that could occur by comparing the regioselectivity and relative stereochemistry of the new substituent to a tag. As discussed in section 4.3 the mechanism of organocuprate addition can be elucidated from the relative stereochemistry of the S_N2 and S_N2' products to a tag. This would require two tags, at the 2- and 6-positions of the tetrahydropyridine to be done quickly. Two tags would be necessary so that all possible products made could have the stereochemistry of the new substituent from the cuprate determined and therefore its mechanism of formation elucidated. Alternatively, the products could have the substituent stereochemistry determined by X-ray crystallography. However, X-ray determination of each analog would be quite laborious and as seen in earlier chapters placing substitution at the 2- and 6-positions is simple.

Scheme 79: Aryl or Heteroaryl as a Directing Group for Ring Expansion

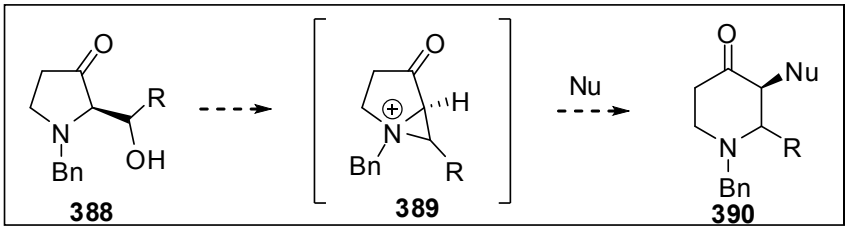


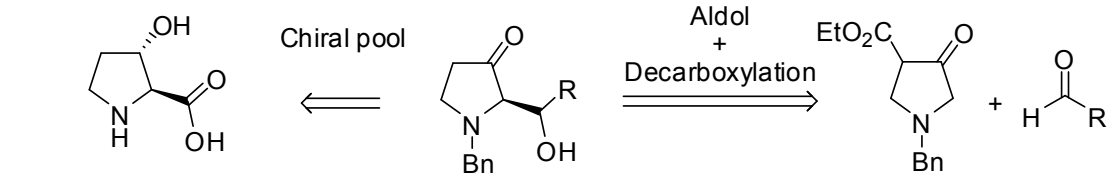
A variety of activating groups with aziridinium ions have not yet been studied. For example, 1-hydroxymethylisoindolines being ring expanded to tetrahydroisoquinolines or homoanalogs for larger rings or heteroaryls with an example shown in Scheme 79. These could be of interest to the pharmaceutical industry, as one could envision producing analogs of Plavix, which was the number 2 selling drug in the world in terms of sales in 2009 (>9$ billion US),[92] quite easily enantiopure with high diastereoselectivity (>99%). The Petasis-Mannich reaction would be incredibly useful in such an endeavor as it could be

used twice. Once for the formation of the phenylglycinol derivative **380**, and then again to form the second 1,2-aminoalcohol **382**.

The preparation of 3-substituted-4-piperidones could be accomplished from the 3-pyrrolidone, as shown in Scheme 80. The precursors are available from the chiral pool such as 3-hydroxyproline **391**, or possibly through an asymmetric method using aldol chemistry. Enolate formation selectivity between the 2 reactive sites of 3-oxo-pyrrolidine has been studied previously, and it is possible to obtain the 3-oxo-prolinol derivative **392** from the β-ketoester **393** though no asymmetric examples have been in found in literature for this template.[93]

Scheme 80: 4-Piperidone Synthesis via Ring Expansion





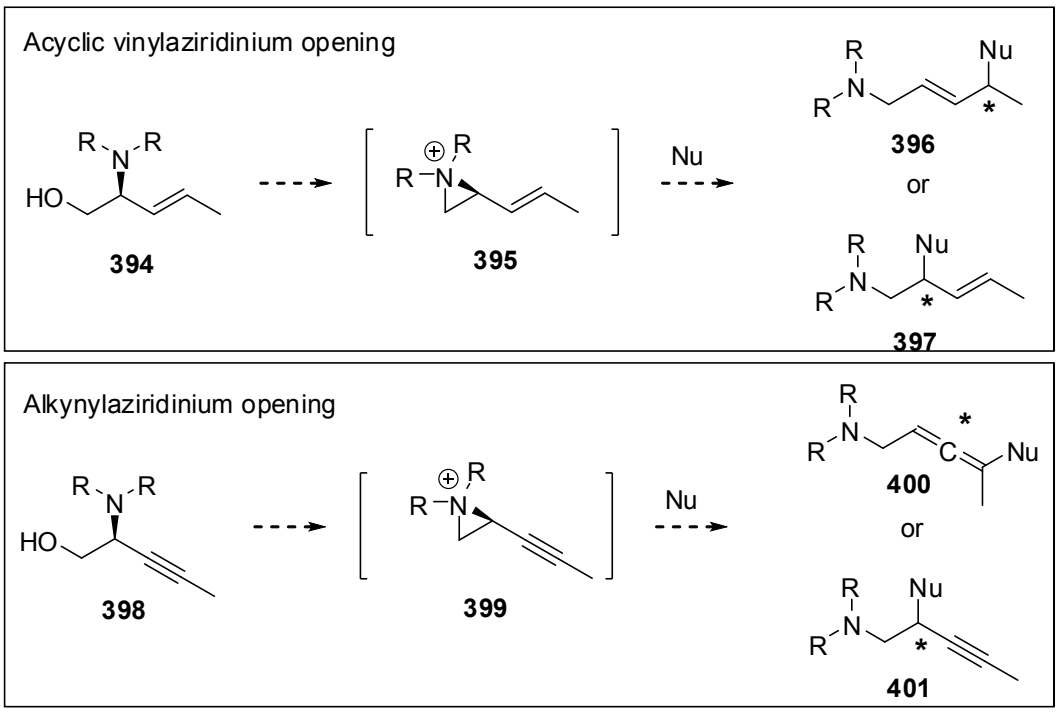
3-Hydroxyproline **391** (commercially available)

392

393

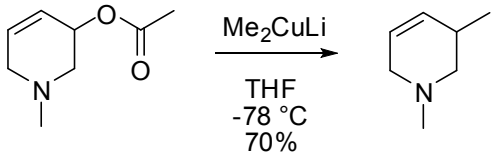
Acyclic vinyl aziridiniums such as **395** or alkynyl aziridiniums such as **399** could be explored to see if the S_N2' product was favoured, and if the stereochemical information was maintained during the rearrangement. Surprisingly, this has not been reported to date despite the similarity of the aziridinium ion to an epoxide.

Scheme 81: Vinyl Aziridinium Ion or Alkynyl Aziridinium Ion Opening



There are a few reports of allyl acetates in a tetrahydropyridine template reacting with carbon nucleophiles such as cuprates[94] (Scheme 82), malonates[95], and nitromethane[96] though this has not yet been reported as a general synthetic method to obtain chiral 3-substituted piperidines.

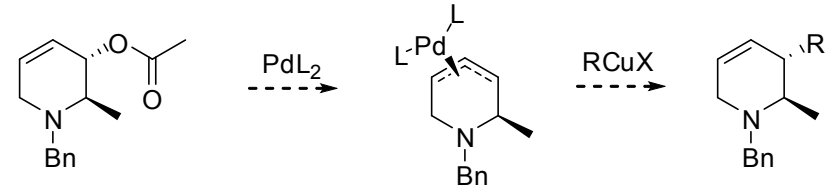
Scheme 82: 3-Substituted Piperidines by an Allylic Sigmatropic Rearrangment



We have demonstrated that **340** can be prepared in enantiopure form easily using the method developed herein. Potentially this product could be used for a sigmatropic allylic rearrangement to prepare 3-substituted piperidines such as **409** (Scheme 83). The methyl tag at the 2-position would be useful for determination of regioselectivity and

stereochemistry of the new substituent, or could be omitted to obtain potentially a simple chiral 3-substituted piperidine.

Scheme 83: Proposed Method to Prepare 3-Substituted Piperidines



Compound **340** **408** **409**

Chapter 6: Experimental

6.1 General information

All non-aqueous reactions were run under an inert atmosphere of argon with rigid exclusion of moisture from reagents and glassware using standard techniques for manipulating air-sensitive compounds.[97] All glassware was stored in the oven and/or was flame-dried prior to use under an inert atmosphere of gas. Analytical thin-layer chromatography (TLC) was performed on precoated, glass-backed silica gel (Merck 60 F254). Visualization of the developed chromatogram was performed by natural fluorescence or fluorescence quenching at 254 nm UV light and/or aqueous cerium molybdate, or aqueous potassium permanganate. Flash column chromatography was performed using 230-400 mesh silica (EM Science or Silicycle) and the indicated solvent system according to standard technique. Melting points were obtained on a Büchi melting point apparatus and are uncorrected. Infrared spectra were taken on a Perkin Elmer Spectrum One FTIR and are reported in reciprocal centimeters (cm^{-1}). Nuclear magnetic resonance spectra (^{1}H, ^{13}C, DEPT 135, COSY, HMQC) were recorded either on a Bruker AV 300, AMX 300, AV 400, ARX 400, or DMX 700 spectrometer. Chemical shifts for ^{1}H NMR spectra are recorded in parts per million from tetramethylsilane with the solvent resonance as the internal standard (chloroform, δ 7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, m_c = centered multiplet and br = broad), coupling constant in Hz, integration, and assignment. Chemical shifts for ^{13}C NMR spectra are recorded in parts per million from tetramethylsilane using the central peak of deuterochloroform (δ 77.00 ppm) as the internal standard. All spectra were obtained with complete proton decoupling. When ambiguous, proton and carbon assignments were established using COSY, HMQC and DEPT 135 experiments.

Where inseparable and/or interconvertible mixtures of diastereomers were obtained, the spectra are reported as observed; where chemical shifts are coincidental, they are reported with an integration of 1 H (assignment *X-H*); where diastereomers display separate chemical shifts, integrations (and assignments) are reported as 1 H^{d1} (assignment *X-H*^{d1}) and 1 H^{d2} (assignment *X-H*^{d2}) for the first and second diastereomer, respectively. The two

diastereomers were arbitrarily assigned as d_1 and d_2 with the following relationship to their chemical shifts:

d_1 = more deshielded diastereomer
d_2 = less deshielded diastereomer

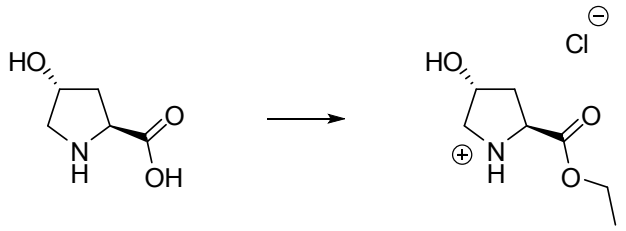
Diastereotopic protons with separate chemical shifts are reported as H_a and H_b; diastereotopic carbons with separate chemical shifts are reported as C_a and C_b. Quaternary carbons identified by DEPT 135 experiments are reported as C_{quat}.

Optical rotations were determined with a Perkin-Elmer 341 polarimeter at 589 nm and 20 °C. Data are reported as follows: $[\alpha]_\lambda^{temp}$, concentration (c in g/100 mL), and solvent. High resolution mass spectra were performed by the Centre régional de spectroscopie de masse de l'Université de Montréal. Analytical supercritical fluid chromatography (SFC) was performed on a Thar Technologies SD-AMDS SFC system equipped with a diode array UV detector recording at 210 nm. Data are reported as follows: (column type, eluent, flow rate, pressure, column temperature: retention time (t_r)).

6.2 Reagents

Unless otherwise stated, commercial reagents were obtained from commercial sources (Sigma-Aldrich, Alfa Aesar or Strem) and used without purification. Anhydrous solvents were obtained either by filtration through drying columns (THF, diethyl ether, CH_2Cl_2, benzene, toluene, hexane) on a GlassContour system (Irvine, CA) or by distillation over calcium hydride (Et_3N, pyridine, diisopropylamine). Molecular sieves were dried at 120 °C for 16 hours and stored in a dessicator.

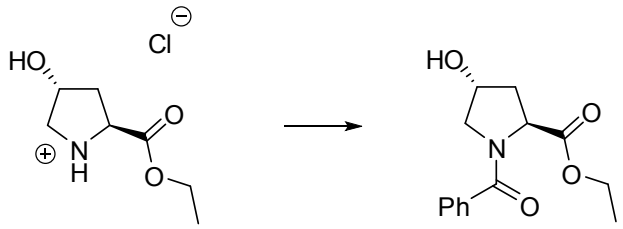
6.3 Synthesis of 236 from *L-trans*-4-Hydroxyproline



L-4-Hydroxyproline **223**

(2S,4R)-ethyl 4-hydroxypyrrolidine-2-carboxylate Hydrochloride (223)

L-trans-4-Hydroxyproline (5.05 g, 38.7 mmol) was suspended in anhydrous ethanol (100mL), and concentrated HCl was added (1.3 mL, 48% by wt, in water, 49 mmol). The suspension was refluxed for 16 hours, becoming a light yellow clear solution. Solvent was removed under reduced pressure yielding a white solid. The white solid was resuspended in diethyl ether (200 mL), stirred vigorously until a fine suspension, then filtered through a sintered glass filter and the filter cake was washed with a minimum of diethyl ether. Solvent was removed under reduced pressure to obtain **223** as a fine white powder (7.55 g, 99%). mp = 150 °C. $[\alpha]^{20}_{D}$ = -33 (c = 0.725, MeOH). IR (film)/cm^{-1} 3360br, 2921, 2848, 1738, 1633, 1244, 1023. ^{1}H NMR (300 MHz, CD_3OD): δ 4.55-4.63 (m, 2H), 4.32 (q, *J* = 7.1 Hz, 2H), 3.46 (dd, *J* = 13.7 Hz, 3.5 Hz, 1H), 3.29-3.35 (m, 1H), 2.43 (dd, *J* = 13.7, 7.8 Hz, 1H), 2.20 (ddd, *J* = 13.7, 10.7, 4.11 Hz, 1H), 1.34 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, CD_3OD): δ 169.7, 70.1, 63.4, 58.9, 54.4, 38.1, 13.8. HRMS Calcd for $C_7H_{13}NO_3$ [M + H]$^+$: 160.09682; Found: 160.09666.

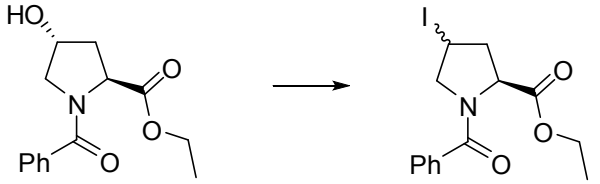


223 **231**

(2S,4R)-ethyl 1-benzoyl-4-hydroxypyrrolidine-2-carboxylate (231)

To a stirred suspension of **223** (7.10 g, 36.3 mmol) in anhydrous DCM (100 mL) was added triethylamine (15 mL, 108 mmol), followed by dropwise addition of benzoyl chloride (4.25 mL, 36.6 mmol). The suspension was stirred for 16 hours. The mixture was diluted with ethyl acetate (300 mL), then washed with 1M HCl (3 x 100 mL), saturated $NaHCO_3$ (3 x

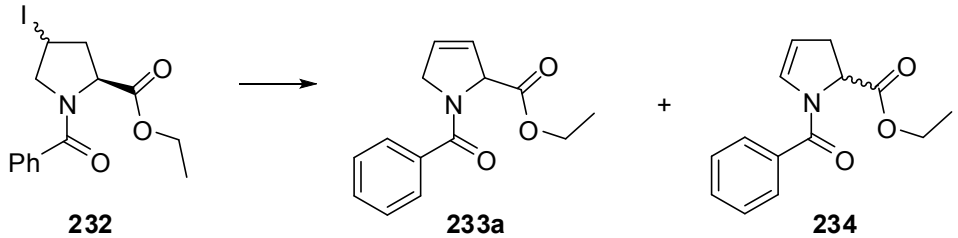
100 mL), brine (100 mL), and dried (Na_2SO_4), filtered and solvent removed under reduced pressure. Purification by flash chromatography (50-100% ethyl acetate/hexane) afforded **231** as a white solid (8.88 g, 93%). *Rf* = 0.52 (EtOAc). mp = 69 °C. $[\alpha]^{20}_D$ = -123 (c = 2.2, $CHCl_3$). IR (film)/cm^{-1} 3384br, 2983, 1738, 1612, 1574, 1423, 1275, 1192, 1083, 1029, 862. ^{1}H NMR (300 MHz, CD_3OD): δ 7.57-7.60 (m, 2H), 7.44-7.52 (m, 3H), 4.73 (t, *J* = 8.9 Hz, 2H), 4.42 (bs, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 3.83 (dd, *J* = 11.5, 4.2 Hz, 1H), 3.44 (d, *J* = 11.4 Hz, 1H), 2.33-2.40 (m, 1H), 2.11 (ddd, *J* = 13.3, 9.5, 4.2 Hz, 1H), 1.31 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, CD_3OD): δ 173.3, 171.8, 136.4, 131.3, 129.0, 127.8, 127.5, 70.4, 61.9, 59.0, 38.0, 13.9. HRMS Calcd for $C_{14}H_{17}NO_4$ $[M + H]^+$: 264.12303; Found: 264.12312.



231 **232**

(S)-ethyl 1-benzoyl-4-iodopyrrolidine-2-carboxylate (232)

To a stirred solution of **231** (3.30 g, 13.5 mmol) in anhydrous THF (40 mL) was added triphenylphosphine (4.20 g, 16.0 mmol), the mixture was chilled with an ice bath, and then diethyldiazodicarboxylate (2.60 mL, 16.5 mmol) was added followed by iodomethane (1.00 mL, 16.0 mmol). The ice bath was removed and the solution stirred for 16 hours at ambient temperature. Solvent was removed under reduced pressure to yield a yellow oil. Purification by flash chromatography (50% diethyl ether/hexane) with TLC visualization by UV afforded **232** as an inseparable mixture of diastereomers as a light yellow oil (7.30 g, 83%). *Rf* = 0.22 (50% diethyl ether/hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54-7.59 (m, 1.7H), 7.37-7.48 (m, 3.51H), 4.86 (t, *J* = 7.3 Hz, 0.57H), 4.69 (t, *J* = 8.7 Hz, 0.29H), 4.54 (t, *J* = 6.3 Hz, 0.16H), 4.44 (t, *J* = 4.8 Hz, 0.76H), 4.26 (q, *J* = 7.0 Hz, 1.75H), 4.08 (dd, *J* = 11.9, 5.1 Hz, 0.68H), 3.92-3.99 (m, 0.1.18H), 3.73-3.83 (m, 1.46H), 2.95-3.03 (m, 0.29H), 2.69 (ddd, *J* = 14.3, 7.9, 5.1 Hz, 0.70H), 2.31-2.51 (m, 1H), 1.84-1.87 (m, 0.92H), 1.32 (t, *J* = 7.1 Hz, 2.92H), 1.07 (t, *J* = 6.9 Hz, 0.45H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.3, 171.4, 170.5, 169.6, 136.2, 136.0, 131.7, 131.4, 131.0, 129.3, 128.4, 128.1, 127.7, 68.8, 62.4, 61.3, 60.5, 59.8, 59.6, 42.3, 42.0, 26.4, 18.2, 15.0, 12.6. HRMS Calcd for $C_{14}H_{16}INO_3$ $[M + H]^+$: 374.02476; Found: 374.02541.



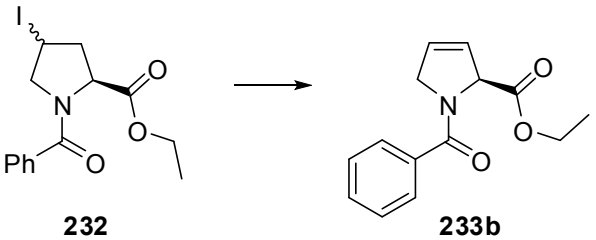
Ethyl 1-benzoyl-2,5-dihydro-1H-pyrrole-2-carboxylate and Ethyl 1-benzoyl-2,3-dihydro-1H-pyrrole-2-carboxylate (233a and 234)

232 (3.30 g, 8.84 mmol) was dissolved in Toluene (100 mL), and 1,8-diazabicyclo[5.4.0]undec-7-ene (1.32 mL, 8.83 mmol) was added to the stirred solution. The mixture was refluxed for 16 hours, then cooled to ambient temperature and filtered washing the filter cake with a minimum of toluene. The filtrate solvent was removed under reduced pressure to obtain an oil. Purification by flash chromatography (20-100% ethyl acetate/hexane) with TLC visualization by UV afforded **233a** and **234** as yellow oils (**233a**: 1.01 g, 47%; **234**: 900 mg, 42%). *Rf* = **233a**: 0.17 (20% ethyl acetate/hexane); **234**: 0.12 (20% ethyl acetate/hexane).

233a: The enantiomeric excess of **233a** was verified by optical rotation and SFC analysis (see **233b**, left SFC trace). $[\alpha]^{20}_{D}$ = 0.0 (c = 0.34, $CHCl_3$). IR (film)/cm^{-1} 2981, 2868, 1742, 1638, 1404, 1335, 1256, 1404, 1029. **233a** was a mixture of rotamers: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.58-7.61 (m, 2H), 7.38-7.47 (m, 3H), 6.12 (bs, 0.38H), 5.90-5.97 (m, 1.84H), 5.75 (bs, 0.37H), 5.47 (bs, 0.87H), 5.12 (bs, 0.33H), 4.58 (bs, 0.70H), 4.43-4.49 (m, 1.01H), 4.20-4.26 (m, 2.89H), 3.90-4.04 (m, 0.79H), 1.33 (t, *J* = 7.1 Hz, 3.00H), 1.08 (t, *J* = 7.1 Hz, 1.12H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.6, 170.5, 136.8, 131.0, 130.8, 130.1, 129.4, 129.3, 127.8, 127.5, 125.9, 125.5, 69.1, 67.4, 62.3, 56.8, 54.8, 15.0, 14.8. HRMS Calcd for $C_{14}H_{15}NO_3$ $[M + H]^+$: 246.11247; Found: 246.11267.

234: $[\alpha]^{20}_{D}$ = -140 (c = 0.725 $CHCl_3$). IR (film)/cm^{-1} 2980, 1742, 1640, 1616, 1402, 1290, 1191, 1107, 1032, 1017, 943, 840. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.58 (d, *J* = 6.7 Hz, 2H), 7.42-7.51 (m, 3H), 6.54 (bs, 2H), 5.13 (bs, 1H), 5.03 (dd, *J* = 11.5, 5.0 Hz, 1H), 4.29 (q, *J* = 7.1 Hz, 2H), 3.07-3.17 (m, 1H), 2.70-2.78 (m, 1H), 1.33 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75

MHz, $CDCl_3$): δ 171.8, 167.9, 135.8, 131.7, 131.5, 129.3, 128.7, 109.7, 62.3, 59.3, 34.6, 15.0. HRMS Calcd for $C_{14}H_{15}NO_3$ $[M + H]^+$: 246.11247; Found: 246.11261.

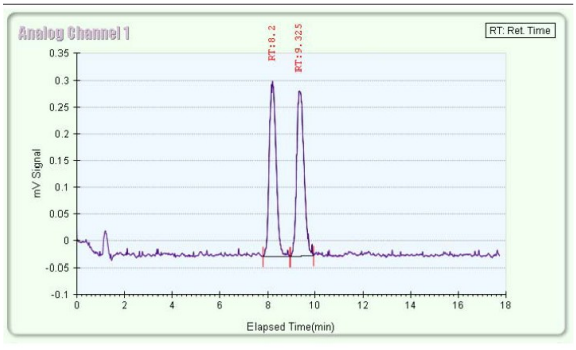


232 **233b**

94%ee

(S)-ethyl 1-benzoyl-2,5-dihydro-1H-pyrrole-2-carboxylate (233b)

To a solution of Diphenyldiselenide (3.34 g, 10.7 mmol) in methanol (100 mL) that was chilled with an ice bath was added sodium borohydride (832 mg, 22.0 mmol). 5 minutes later **232** (7.10, 19.0 mmol) was added to the stirred solution, and the solution was refluxed for 16 hours. The solution was allowed to cool to ambient temperature and then was chilled with an ice bath. Hydrogen peroxide (30% by weight in water, 20 mL) was added dropwise to the stirred cold solution, delayed initiation occurred and an exotherm resulted raising the temperature of the mixture to 40 °C. After 90 minutes the mixture was diluted with ethyl acetate (400 mL) and washed with water (3x100 mL), brine (100mL), and dried (Na_2SO_4). Purification by flash chromatography (20% ethyl acetate/hexane) with TLC visualization by UV afforded **233b** as a yellow oil (2.53 g, 54%). The enantiomeric excess was determined by SFC analysis on a chiral stationary phase (Chiralpak AD-H 25 cm, 5% MeOH, 3mL/min, 40°C, 150bar, 210 nm, t_r (minor) 8.2 min, t_r (major) 9.3 min. *Rf* = **233b**: 0.17 (20% ethyl acetate/hexane). IR, ^{1}H NMR and ^{13}C NMR was identical to **233a**.



Peak Name	Area %	Area	Retention Time
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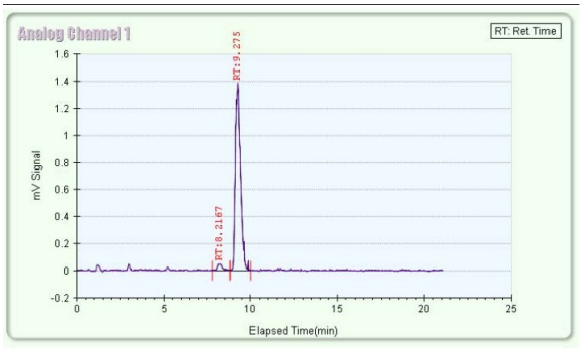
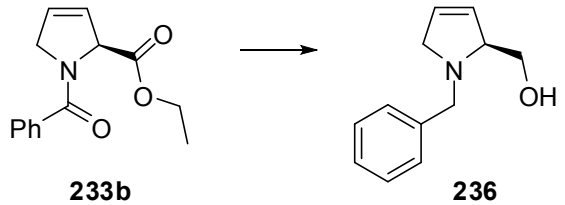
Peak2	50.167	6.6643	9.325 min

233a



Peak Name	Area %	Area	Retention Time
Peak1	3.3576	0.9811	8.2167 min
Peak2	96.6424	28.2384	9.275 min

233b

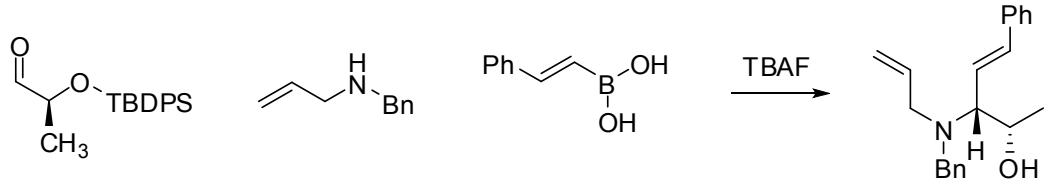


233b **236**

(S)-(1-benzyl-2,5-dihydro-1H-pyrrol-2-yl)methanol (236 from 233b, 94% ee)

Anhydrous THF (100 mL) was brought to reflux, and then lithium aluminum hydride (920 mg, 24.2 mmol) was added (effervescence!) portionwise forming a grey suspension. The suspension was refluxed for 5 minutes, then a solution of **233b** (1.80 g, 7.34 mmol) in a minimum of anhydrous THF was added dropwise. The mixture was refluxed for 1 hour, then quenched by adding $Na_2SO_4 \bullet 10H_2O$ portionwise until effervescence ceased. The hot solution was allowed to cool to ambient temperature, filtered through Celite over a cotton washing the filter cake with ethyl acetate. The filtrate solvent was removed under reduced pressure. Purification by flash chromatography (0-5% methanol/DCM) with TLC visualization by $KMnO_4$ afforded **236** as a yellow oil (1.20 g, 86%). *Rf* = 0.26 (5% MeOH/DCM). IR (film)/cm^{-1} 3385br, 3064, 3027, 2867, 2791, 1494, 1453, 1376, 1347, 1112, 1077, 1028, 910, 734. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26-7.38 (m, 5H), 5.84 (m, 1H), 5.68 (m, 1H), 4.04 (d, *J* = 13.2 Hz, 1H), 3.82 (m, 1H), 3.73 (m, 1H), 3.65 (d, *J* = 13.2 Hz, 1H), 3.57 (d, *J* = 2.5 Hz, 2H), 3.28-3.38 (m, 1H), 2.79 (bs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.2, 130.1, 129.5, 129.3, 129.3, 128.0, 72.3, 62.2, 61.2, 59.2. HRMS Calcd for $C_{12}H_{16}NO$ $[M + H]^+$: 190.12264; Found: 190.12242.

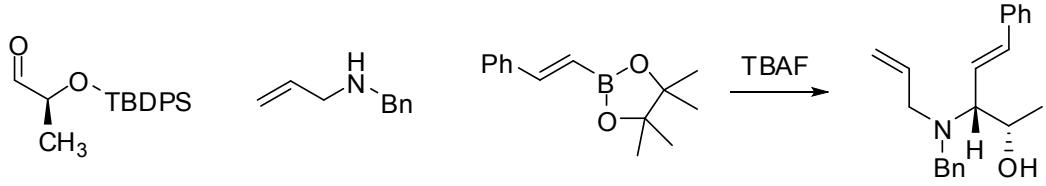
6.4 Synthesis of the 1,2-Aminoalcohols by the Petasis-Mannich Reaction



253 **246** **204** **255**

(2S,3R,E)-3-(allyl(benzyl)amino)-5-phenylpent-4-en-2-ol (255) from the Boronic Acid (204)

(S)-2-(tert-butyldiphenylsilyloxy)propanal **233** (103 mg, 0.330 mmol) was dissolved in anhydrous ethanol (1.4 mL) and a tetrabutylammonium fluoride solution (1.0 M in THF, 350 μL, 0.350 mmol) was added. The mixture was stirred for 5 minutes, then *N*-benzylprop-2-en-1-amine **246** (53.6 mg, 0.364 mmol) and (E)-styrylboronic acid **204** (52.2 mg, 0.353 mmol) were added and the mixture refluxed for 16 hours. Solvent was removed under reduced pressure, the resulting orange oil was dissolved in diethyl ether (20 mL) and washed with water (3x10 mL), brine (10mL) then extracted with 1M HCl (3x20 mL). The combined acid extracts had the pH adjusted to 8 using $NaHCO_3$, and then the aqueous solution was extracted with DCM (3x20 mL). The combined DCM extracts were dried (Na_2SO_4), and solvent removed under reduced pressure. Purification by flash chromatography (0-10% diethyl ether/hexanes) to obtain **255** as a yellow oil (85 mg, 83%). Identical by NMR to that made from the pinacol ester of the boronic acid shown below.



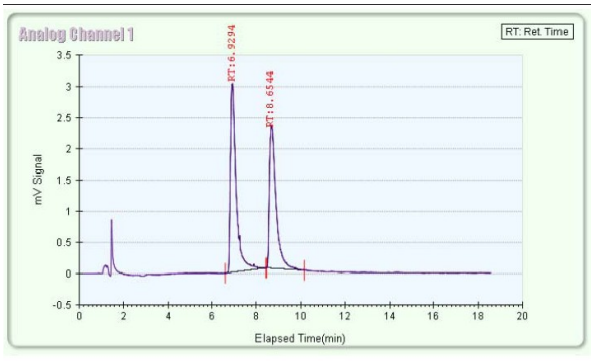
253 **246** **254** **255**

(2S,3R,E)-3-(allyl(benzyl)amino)-5-phenylpent-4-en-2-ol (255) from the Pinacol Boronic Ester (254)

(S)-2-(tert-butyldiphenylsilyloxy)propanal **253** (13.75 g, 44.0 mmol) was dissolved in anhydrous ethanol (220 mL) and a tetrabutylammonium fluoride solution (1.0 M in THF,

44.0 mL, 44.0 mmol) was added. The mixture was stirred for 5 minutes, then N-benzylprop-2-en-1-amine **246** (7.90 g, 53.7 mmol) and (E)-4,4,5,5-tetramethyl-2-styryl-1,3,2-dioxaborolane **254** (11.59 g, 50.4 mmol) were added and the mixture refluxed for 5 hours. Solvent was removed under reduced pressure, then the resulting oil dissolved in diethyl ether (200 mL) and washed with water (3x100 mL), brine (50 mL) and dried (Na_2SO_4). Purification by flash chromatography (0-10% diethyl ether/hexanes) to yield **255** as a yellow oil (8.37 g, 62%, >99% ee) and its diastereomer was isolated (20 mg, 0.1%).

255 : The enantiomeric excess was determined by SFC analysis on a chiral stationary phase (Chiralpak AD-H 25 cm, 10% *i*-PrOH, 3mL/min, 40°C, 150bar, 210 nm, t_r (major) 6.9 min, t_r (minor) 8.7 min. *Rf* = 0.15 (10% diethyl ether/hexanes). $[\alpha]^{20}_D$ = -146 (c = 0.892 $CHCl_3$). IR (film)/cm^{-1} 3438, 3025, 2972, 2928, 2808, 1494, 1449, 1366, 1099, 1071, 971, 912. ^1H NMR (300 MHz, $CDCl_3$): δ 7.26-7.44 (m, 11H), 6.54 (d, *J* = 15.9 Hz, 1H), 6.25 (dd, *J* = 15.9, 9.6 Hz, 1H), 5.82-5.96 (m, 1H), 5.20 (m, 1H), 4.05 (m, 1H), 3.92 (d, *J* = 14.1 Hz, 1H), 3.53 (d, *J* = 14.0 Hz, 1H), 3.34 (dd, *J* = 14.5, 5.2 Hz, 1H), 3.13 (d, *J* = 8.9 Hz, 1H), 3.09 (t, *J* = 7.2 Hz, 1H), 2.36 (s, 1H), 1.25 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.7, 137.4, 136.7, 136.7, 129.5, 129.5, 129.2, 128.7, 127.8, 127.3, 126.1, 118.5, 69.8, 68.0, 55.8, 54.5, 20.8. HRMS Calcd for $C_{21}H_{25}NO$ $[M + H]^+$: 308.20089; Found: 308.20110.



Peak Name	Area %	Area	Retention Time
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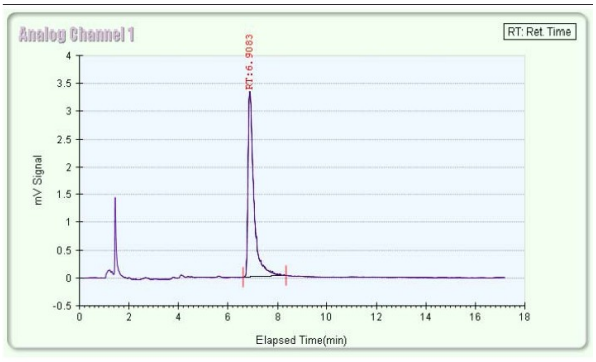
Peak2	45.7743	47.4168	8.6544 min

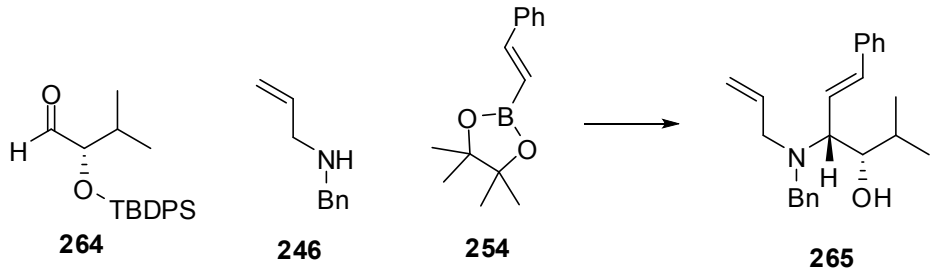
Racemic 255



Peak Name	Area %	Area	Retention Time
Peak1	100	54.537	6.9083 min

Enantiopure 255

Diastereomer of 255 : *Rf* = 0.16 (10% diethyl ether/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27-7.47 (m, 10H), 6.54 (d, *J* = 15.9 Hz, 1H), 6.11 (dd, *J* = 15.9, 9.8 Hz, 1H), 5.81-5.91 (m, 1H), 5.21-5.28 (m, 2H), 4.02 (d, *J* = 13.4 Hz, 1H), 3.85-3.91 (m, 1H), 3.42-3.49 (m, 1H), 3.36 (d, *J* = 13.4 Hz, 1H), 3.03 (t, *J* = 9.7 Hz, 1H), 2.99 (dd, *J* = 13.9, 8.6 Hz, 1H), 1.14 (d, *J* = 6.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.3, 136.9, 136.7, 129.3, 129.1, 129.0, 129.0, 128.4, 127.7, 126.9, 123.8, 118.4, 69.1, 65.5, 54.3, 53.2, 20.1



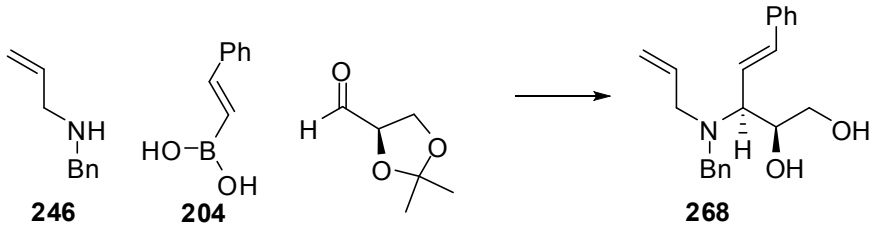
264 **246** **254** **265**

(3S,4R,E)-4-(allyl(benzyl)amino)-2-methyl-6-phenylhex-5-en-3-ol (265)

Aldehyde preparation (known synthesis)[74]: To a solution of (S)-methyl 2-(tert-butyldiphenylsilyloxy)-3-methylbutanoate (1.03 g, 2.78 mmol) in anhydrous DCM (30 mL) that was chilled with a dry ice/acetone bath (-78 °C) was added a solution of DIBAL-H in Toluene (1M, 5.50 mL, 5.50 mmol) dropwise. After the reaction was stirred for 1 hour, the reaction was quenched by adding MeOH (1mL) and the mixture was allowed to warm to rt. A saturated Rochelle salt solution (30 mL) was added, and the mixture stirred at rt until clear (aprox. 1 hour). The solution was extracted with DCM (30 mL), and the organic extract was washed with water (30 mL), brine (30 mL), and dried (Na_2SO_4). Purification by flash chromatography (5% ethyl acetate/hexane) to yield **264** as a colourless oil (70%). *Rf* = 0.2 (5% ethyl acetate/hexanes). $[\alpha]^{20}_{D}$ = -35 (c = 0.2 $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.55-9.56 (m, 1H), 7.65-7.68 (m, 4H), 7.37-7.48 (m, 6H), 3.87-3.89 (m, 1H), 1.98-2.07 (m, 1H), 1.15 (s, 9H), 0.97 (ddd, *J* = 6.9, 5.8, 1.3 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.4, 136.7, 136.7, 134.1, 133.9, 130.8, 130.8, 128.6, 128.6, 83.1, 33.4, 27.9, 20.4, 19.2, 17.9.

Petasis-Mannich Reaction: **264** (663 mg, 1.95 mmol) was dissolved in anhydrous ethanol (10 mL) and a tetrabutylammonium fluoride solution (1.0 M in THF, 1.95 mL, 1.95 mmol) was added. The mixture was stirred for 16 hours, then N-benzylprop-2-en-1-amine (315

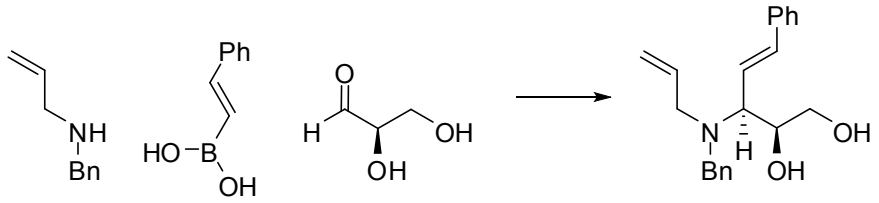
mg, 2.15 mmol) **246** and (E)-4,4,5,5-tetramethyl-2-styryl-1,3,2-dioxaborolane **254** (289 mg, 1.95 mmol) were added and the mixture stirred at rt for 40 hours. Solvent was removed under reduced pressure, then the resulting oil dissolved in diethyl ether (50 mL) and washed with sat. NaHCO3 (3x30 mL), brine (50 mL) and dried (Na_2SO_4). Purification by flash chromatography (Benzene) to yield **265** as a yellow oil (396 mg, 61%). *Rf* = 0.31 (10% ethyl acetate/hexane). $[\alpha]^{20}_D$ = -114 (c = 1.19 $CHCl_3$). IR (film)/cm^{-1} 3444, 3026, 2958, 2870, 1494, 1449, 1365, 1107, 1071, 1051, 1028, 972, 912, 738, 696. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24-7.42 (m, 10H), 6.57 (d, *J* = 16.0 Hz, 1H), 6.25 (dd, *J* = 16.6, 6.8 Hz, 1H), 5.86-5.96 (m, 1H), 5.15-5.21 (m, 2H), 3.87 (d, *J* = 13.9 Hz, 1H), 3.57-3.63 (m, 2H), 3.28-3.35 (m, 2H), 3.16 (dd, *J* = 14.8, 6.8 Hz, 1H), 2.66 (bs, 1H), 1.87-1.96 (m, 1H), 0.93 (d, *J* = 4.0 Hz, 3H), 0.91 (d, *J* = 4.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.6, 137.5, 136.2, 135.8, 129.6, 129.4, 129.2, 128.6, 127.7, 127.3, 126.6, 118.8, 76.4, 66.6, 55.5, 54.2, 30.4, 19.7, 18.4. HRMS Calcd for $C_{23}H_{30}NO$ $[M + H]^+$: 336.23219; Found: 336.23256.



(2S,3S,E)-3-(allyl(benzyl)amino)-5-phenylpent-4-ene-1,2-diol (268) from (R)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde

(R)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde (187 mg, 1.43 mmol) was dissolved in 95% ethanol (30 mL) and with stirring 0.5 M H_2SO_4 (3 mL) was added. After 10 minutes at rt, a check by TLC showed the reaction was complete (10% MeOH/DCM; *Rf* of acetonide = 0.60; *Rf* of deprotected diol = 0.19). The pH of the solution was adjusted to 8 using ethanolic NaOH (Note: pH is important, too basic or acidic and the yields suffer, pH 6 no reaction occurs therefore it is important to use wet EtOH to more accurately measure the pH). *N*-Benzylprop-2-en-1-amine **246** (210 mg, 1.43 mmol) and (E)-styrylboronic acid **204** (210 mg, 1.42 mmol) were added and the mixture refluxed for 16 hours. Solvent was removed under reduced pressure, purification by flash chromatography (0-50% ethyl acetate/hexane) to yield **268** as light yellow oil (122 mg, 77%). *Rf* = 0.43 (50% ethyl acetate/hexanes). $[\alpha]^{20}_D$ = +158 (c = 1.28 $CHCl_3$). IR (film)/cm^{-1} 3346, 3026, 2922, 2812,

1494, 1449, 1071,970, 910. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46 (d, J = 7.3 Hz, 2H), 7.29-7.40 (m, 8H), 6.59 (d, J = 15.8 Hz, 1H), 6.27 (dd, J = 15.8, 9.6 Hz, 1H), 5.82-5.95 (m, 1H), 5.22-5.31 (m, 2H), 3.92-3.99 (m, 2H), 3.77 (dd, J = 11.1, 5.3 Hz, 1H), 3.67 (dd, J = 11.0, 5.8 Hz, 1H), 3.41-3.47 (m, 1H), 3.39 (d, J = 13.4 Hz, 1H), 3.32 (t, J = 9.1 Hz, 1H), 3.01 (dd, J = 13.9, 8.3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.5, 138.2, 137.0, 136.4, 129.8, 129.6, 129.5, 129.0, 128.2, 127.4, 124.1, 119.3, 70.9, 67.0, 66.9, 55.8, 54.5. HRMS Calcd for $C_{21}H_{26}NO_2$ $[M + H]^+$: 324.19581; Found: 324.19588.

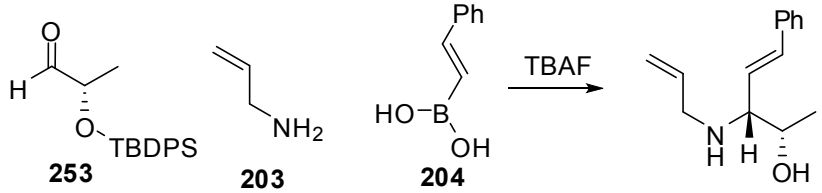


246 **204** **267** **268**

R-Glyceraldehyde

(2S,3S,E)-3-(allyl(benzyl)amino)-5-phenylpent-4-ene-1,2-diol (268) from R-Glyceraldehyde

A solution of (R)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde **267** in water (80%, 450mg, 4.00 mmol) was dissolved in absolute ethanol (50 mL), followed by the addition of *N*-Benzylprop-2-en-1-amine **246** (600 mg, 4.08 mmol) and (E)-styrylboronic acid **204** (600 mg, 4.05 mmol) were added and the mixture stirred at ambient temperature for 40 hours. Solvent was removed under reduced pressure to yield an oily residue. Purification by flash chromatography (0-20% Acetone/DCM) to yield **268** as a light yellow oil (1.00 g, 77%). $[\alpha]^{20}_{D}$ = +157 (c = 1.01 $CHCl_3$). Spectral data were identical to **268** prepared from the acetonide protected glyceraldehyde above.

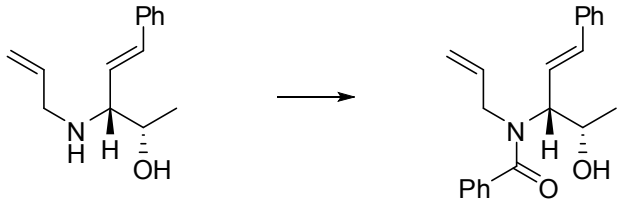


253 **203** **204** **270**

(2S,3R,E)-3-(Allylamino)-5-phenylpent-4-en-2-ol (270)

(S)-2-(tert-butyldiphenylsilyloxy)propanal **253** (1.26 g, 4.03 mmol) was dissolved in anhydrous ethanol (20 mL) and a tetrabutylammonium fluoride solution (1.0 M in THF, 4.0 mL, 4.0 mmol) was added. The mixture was stirred for 5 minutes, then allylamine **203**

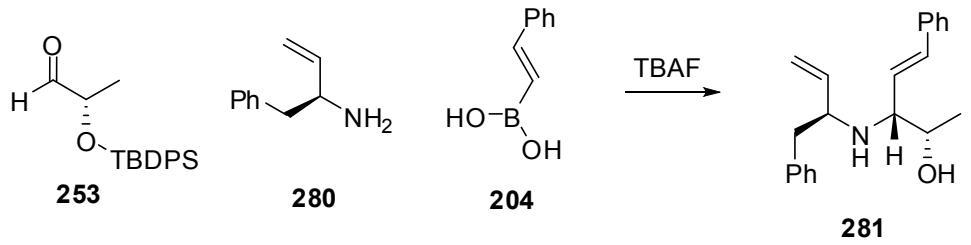
(300 μL, 4.00 mmol) and (E)-4,4,5,5-tetramethyl-2-styryl-1,3,2-dioxaborolane **254** (614 mg, 4.15 mmol) were added and the mixture stirred at rt for 40 hours. Solvent was removed under reduced pressure, then the resulting oil dissolved in diethyl ether (200 mL) and washed with water (3x100 mL), brine (50 mL) and dried (Na_2SO_4). Purification by flash chromatography (100% benzene, then flush with EtOAc) to yield **270** as a yellow solid (720 mg, 83%). $[\alpha]^{20}_D$ = -56 (c = 0.0059 $CHCl_3$). IR (film)/cm^{-1} 3271, 3075, 3026, 2973, 2932, 1641, 1493, 1448, 1416, 1372, 1320, 1073, 967, 911, 743. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23-7.42 (m, 5H), 6.54 (d, *J* = 16.0 Hz, 1H), 6.12 (dd, *J* = 16.0, 8.7 Hz, 1H), 5.85-5.98 (m, 1H), 5.20 (dd, *J* = 17.2, 1.2 Hz, 1H), 5.13 (dd, *J* = 10.2, 0.9 Hz, 1H), 3.87-3.95 (m, 1H), 3.36 (dd, *J* = 14.1, 5.9 Hz, 1H), 3.12-3.26 (m, 2H), 1.16 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.5, 134.5, 129.4, 128.5, 128.4, 127.2, 117.0, 69.2, 66.4, 50.6, 19.5.



270 **271**

(2S,3R,E)-3-(Allylamino)-5-phenylpent-4-en-2-ol (271)

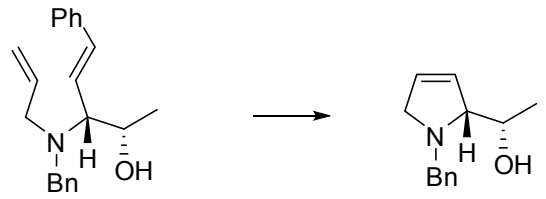
270 (580 mg, 2.67 mmol) was dissolved in anhydrous dichloromethane (20 mL). *N,N*-diisopropylethylamine (1.4 mL, 8.0 mmol), and DMAP (31.5 mg, 0.258 mmol) were added to the stirred solution. The solution was placed in an ice bath under positive pressure of Argon, and then benzoyl chloride (310 μL, 2.67 mmol) was added dropwise. The reaction mixture was allowed to stir for 16 hours during which time it warmed to ambient temperature. The reaction mixture was diluted with ethyl acetate (50 mL) and hexanes (50 mL) and washed with 1M HCl (3x30 mL), a saturated $NaHCO_3$ solution (30 mL), and brine (30 mL). The organic layer was dried using Na_2SO_4, filtered and solvent was removed under reduced pressure. The residue was purified by flash chromatography (0-50% ethyl acetate in hexanes) to yield **271** was a yellow oil (609 mg, 71%). $[\alpha]^{20}_D$ = -53 (c = 0.57 $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31-7.57 (m, 10H), 6.75-6.90 (m, 1H), 6.57 (d, *J* = 17.1 Hz, 1H), 5.77-5.92 (m, 1H), 5.26-5.26 (m, 2H), 4.95-5.15 (m, 1H), 4.43 (s, 1H), 3.98 (d, *J* = 16.4 Hz, 1H), 3.86 (d, *J* = 14.3 Hz, 1H), 3.78 (s, 1H), 1.20-2.31 (m, 3H).



(2S,3R,E)-5-phenyl-3-((S)-1-phenylbut-3-en-2-ylamino)pent-4-en-2-ol (281)

(S)-2-(tert-butyldiphenylsilyloxy)propanal **253** (778 mg, 2.49 mmol) was dissolved in anhydrous ethanol (12 mL) and a tetrabutylammonium fluoride solution (1.0 M in THF, 2.40 mL, 2.40 mmol) was added. The mixture was stirred for 5 minutes, then (S)-1-phenylbut-3-en-2-amine **280** (347 mg, 2.36 mmol) and (E)-styrylboronic acid **204** (360 mg, 2.43 mmol) were added and the mixture refluxed for 24 hours. Solvent was removed under reduced pressure, purification by flash chromatography (0-100% ethyl acetate/hexane) to yield **281** as a yellow oil (550 mg, 76%). *Rf* = 0.04 (ethyl acetate). $[\alpha]^{20}_{D}$ = -40 (c = 0.41 $CHCl_3$). IR (film)/cm^{-1} 3060, 3026, 2970, 2926, 1601, 1494, 1453, 1075, 970, 912, 735, 695. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.21-7.35 (m, 10H), 6.20 (d, *J* = 16.1 Hz, 1H), 5.79 (dd, *J* = 16.0, 8.2 Hz, 1H), 5.68 (ddd, *J* = 18.4, 10.3, 8.1 Hz, 1H), 5.11-5.19 (m, 2H), 3.77-3.83 (m, 1H), 3.43 (td, *J* = 8.6, 5.3 Hz, 1H), 3.29 (dd, *J* = 8.1, 3.3 Hz, 1H), 2.88 (dd, *J* = 13.6, 5.2 Hz, 1H), 2.71 (dd, *J* = 13.5, 8.8 Hz, 1H), 1.06 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.8, 139.2, 137.5, 133.4, 130.2, 129.4, 129.3, 128.7, 128.4, 127.4, 127.1, 117.2, 70.1, 63.4, 60.4, 43.6, 19.4. HRMS Calcd for $C_{21}H_{26}NO$ $[M + H]^+$: 308.20089; Found: 308.20113.

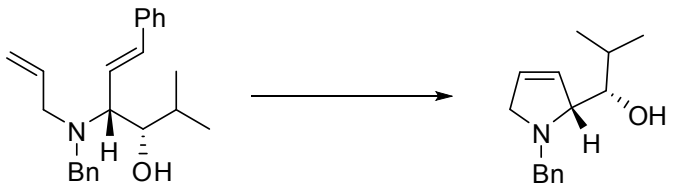
6.5 Synthesis of the 3,4-Dehydroprolinols



255 **244**

(S)-1-((R)-1-benzyl-2,5-dihydro-1H-pyrrol-2-yl)ethanol (244)

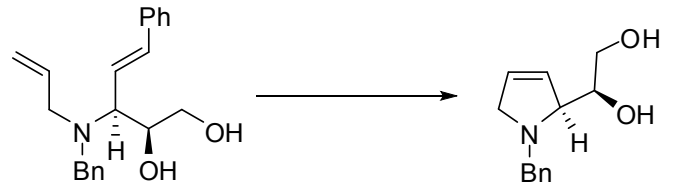
To a refluxing solution of **255** (3.40 g, 11.1 mmol) in anhydrous DCM (350 mL) under positive pressure of Argon was added Grubb's 2nd generation catalyst (85 mg, 0.10 mmol) and the mixture refluxed for 16 hours. Added a second portion of Grubb's 2nd generation catalyst (23.1mg, 0.0272 mmol) and continued to reflux for 24 additional hours. The reaction was allowed to cool to ambient temperature, and quenched with ethyl vinyl ether (1.0 mL). Solvent was removed under reduced pressure, redissolved in diethyl ether (50 mL) and extracted with 1M HCl (3x20 mL). The combined acid extracts had the pH adjusted to 8 using $NaHCO_3$, then extracted with DCM (3x20 mL) and dried (Na_2SO_4). Purification by flash chromatography (10-100% ethyl acetate/hexanes) to obtain **244** as yellow oil (1.57 g, 70%, 79%brsm) along with unreacted **255** (410 mg, 1.33 mmol). *Rf* = 0.31 (50% ethyl acetate/hexanes). $[\alpha]^{20}_D$ = +174 (c = 0.883 $CHCl_3$). IR (film)/cm^{-1} 3439. 2972, 2871, 2791, 1495, 1453, 1364, 1276, 1053, 874. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26-7.38 (m, 5H), 5.87 (d, J = 6.1 Hz, 1H), 5.75 (d, J = 6.1 Hz, 1H), 4.09 (d, J = 13.1 Hz, 1H), 3.60-3.88 (m, 4H), 3.25-3.32 (m, 2H), 1.25 (d, J = 6.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.2, 130.0, 129.3, 129.3, 128.0, 126.7, 76.6, 66.3, 61.2, 59.1, 19.1. HRMS Calcd for $C_{13}H_{18}NO$ $[M + H]^+$: 204.13829; Found: 204.12839.



265 **266**

(S)-1-((R)-1-benzyl-2,5-dihydro-1H-pyrrol-2-yl)-2-methylpropan-1-ol (266)

To a refluxing solution of **265** (322 mg, 0.960 mmol) in anhydrous DCM (50 mL) under positive pressure of Argon was added Grubb's 2nd generation catalyst (10.1 mg, 0.0119 mmol) and the mixture refluxed for 16 hours. The reaction was allowed to cool to ambient temperature, and quenched with ethyl vinyl ether (1.0 mL). Solvent was removed under reduced pressure, purification by flash chromatography (20% ethyl acetate/hexanes) to obtain **266** as yellow oil (157mg, 71%). *Rf* = 0.09 (20% ethyl acetate/hexane). $[\alpha]^{20}_{D}$ = +160 (c = 0.570 $CHCl_3$). IR (film)/cm^{-1} 3429, 3064, 3028, 2957, 2871, 2800, 1495, 1470, 1453, 1407, 1378, 1360, 1324, 1290, 1275, 1155, 1114, 1072, 1030, 979, 910, 864, 734, 699. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25-7.37 (m, 5H), 5.86 (dd, *J* = 6.5, 1.7 Hz, 1H), 5.72-5.74 (m, 1H), 4.08 (d, *J* = 13.1 Hz, 1H), 3.80-3.88 (m, 2H), 3.66-3.73 (m, 1H), 3.59 (d, *J* = 13.1 Hz, 1H), 3.22-3.30 (m, 1H), 3.17 (dd, *J* = 9.5, 3.1 Hz, 1H), 1.66-1.78 (m, 1H), 1.13 (d, *J* = 6.5 Hz, 3H), 0.94 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.0, 130.1, 129.4, 129.3, 128.0, 126.9, 75.7, 73.6, 60.8, 58.8, 32.2, 21.7, 18.9. HRMS Calcd for $C_{15}H_{22}NO$ $[M + H]^+$: 232.16959; Found: 232.16954.

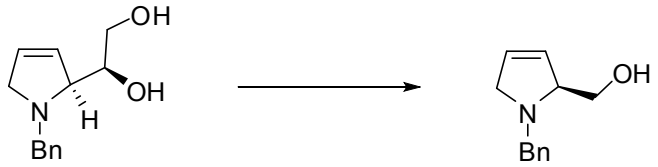


268 **269**

(S)-1-((S)-1-benzyl-2,5-dihydro-1H-pyrrol-2-yl)ethane-1,2-diol (269)

To a refluxing solution of **268** (630 mg, 1.95 mmol) in anhydrous DCM (100 mL) was added Grubb's 2nd generation catalyst (23.3 mg, 0.0274 mmol) and the mixture was refluxed for 16 hours. The catalyst was quenched with ethyl vinyl ether (0.5 mL), cooled to

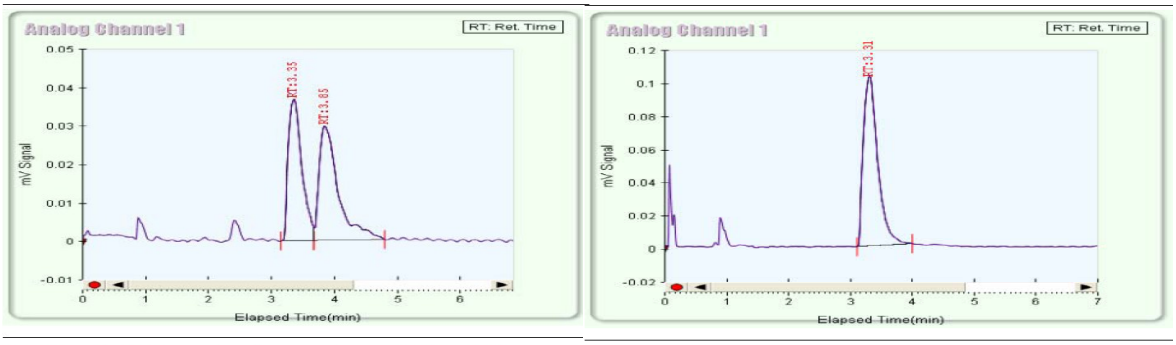
rt and solvent was removed under reduced pressure. Purification by flash chromatography (0-100% acetone/benzene) to yield **269** as an amber oil (300 mg, 70%, 81% brsm) along with unreacted **3c** (86 mg, 0.266 mmol). *Rf* **269** = 0.46 (50% acetone/benzene). *Rf* **268** = 0.83 (50% acetone/benzene). IR (film)/cm^{-1} 3374, 3063, 3027, 2925, 2802, 1495, 1453, 1376, 1074, 1028, 910, 734. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27-7.37 (m, 5H), 5.86 (dd, *J* = 6.1, 1.6 Hz, 1H), 5.70 (dd, *J* = 6.0, 1.7 Hz, 1H), 4.19 (d, *J* = 13.1 Hz, 1H), 3.93 (s, 1H), 3.82 (dd, *J* = 12.0, 5.4 Hz, 1H), 3.72-3.76 (m, 3H), 3.63 (d, *J* = 13.1 Hz, 1H), 3.20-3.29 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.7, 129.8, 129.4, 129.4, 128.1, 127.8, 75.1, 71.9, 64.9, 61.1, 60.8. HRMS Calcd for $C_{13}H_{18}NO_2$ $[M + H]^+$: 220.13321; Found: 220.13344.



269 **236**

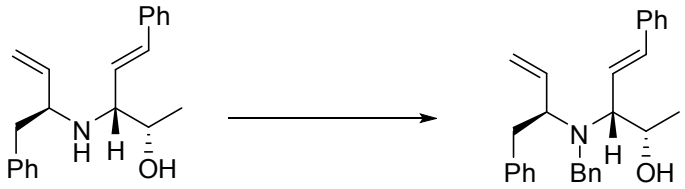
(S)-(1-benzyl-2,5-dihydro-1H-pyrrol-2-yl)methanol (236 from **269, >99% ee)**

To a solution of **269** (100 mg, 0.456 mmol) in ethanol/water (80/20, 5 mL) chilled with an ice bath was added Sodium metaperiodate (99.7 mg, 0.466 mmol) and the reaction progression monitored by TLC (20% acetone/DCM). After 15 minutes the ice bath was removed and the mixture allowed to warm to ambient temperature. After an additional 30 minutes the reaction was complete by TLC, so the mixture was again chilled with an ice bath, and Sodium borohydride (29.5 mg, 0.780 mmol) was added to the stirred cold mixture. The mixture was stirred for 16 hours slowly warming to ambient temperature, then diluted with ethyl acetate and washed with Sat. $NaHCO_3$, Brine and dried (Na_2SO_4). Purification by column chromatography (0-25% acetone/hexanes) to obtain **236** as a light yellow oil (61 mg, 71%, >99% ee). The enantiomeric excess was determined by SFC analysis on a chiral stationary phase (Chiralpak OD-H 25 cm, 4% MeOH, 4mL/min, 45°C, 150bar, 210 nm, t_r (major) 3.3 min, t_r (minor) 3.9 min. *Rf* = 0.25 (25% acetone/hexanes). Spectra were identical to that made from L-*trans*-4-Hydroxyproline (section 6.3).



Peak Name	Peak Number	Area %	Area	Retention Time
	1	46.746	0.5499	3.35 min
	2	53.254	0.6265	3.85 min

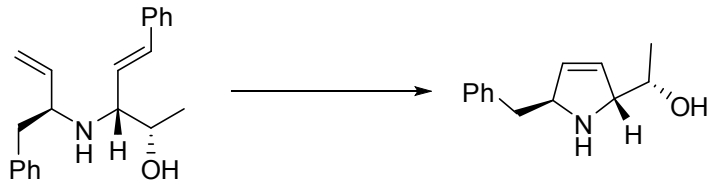
Peak Name	Peak Number	Area %	Area	Retention Time
	1	100	1.6437	3.31 min



281 **283**

((2S,3R,E)-3-(benzyl((S)-1-phenylbut-3-en-2-yl)amino)-5-phenylpent-4-en-2-ol (283)

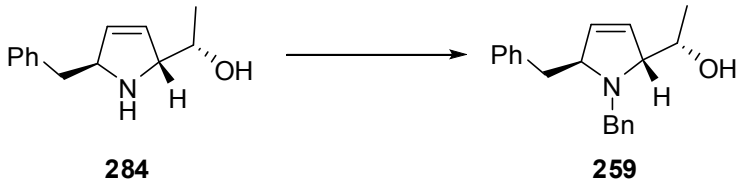
281 (280 mg, 0.911 mmol) was dissolved in acetonitrile (20 mL), then *N,N*-diisopropylethylamine (0.5 mL, 2.87 mmol) and benzyl bromide (210 μL, 1.77 mmol) were added. After stirring at ambient temperature for 16 hours no reaction occurred. Tetrabutylammonium iodide (70.9 mg, 0.192 mmol) was added and the mixture refluxed for 16 hours – no reaction occurred. The solvent was removed under reduced pressure and the oily residue dissolved in *N,N*-dimethylformamide (20 mL). This solution was heated at 100°C for 48 hours. The reaction was incomplete, allowed to cool to ambient temperature. The mixture was diluted with diethyl ether (300 mL) and washed with a Sat. $NaHCO_3$ solution (3x50 mL) and brine (50 mL). The organic layer was dried using Na_2SO_4, filtered and solvent removed under reduced pressure. Purification by flash chromatography (0-100% ethyl acetate/hexanes) to obtain **283** as a yellow oil (36 mg, 9%) along with unreacted **281** (165 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14-7.45 (m, 15H), 6.48 (d, J = 16.0 Hz, 1H), 6.31 (dd, J = 16.0, 9.5 Hz, 1H), 6.00 (ddd, J = 17.3, 10.2, 8.0 Hz, 1H), 5.16 (d, J = 10.5 Hz, 1H), 4.99 (d, J = 17.2 Hz, 1H), 4.06 (d, J = 14.5 Hz, 1H), 3.87 (t, J = 6.2 Hz, 1H), 3.67-3.78 (m, 2H), 3.24 (dd, J = 9.4, 6.0 Hz, 1H), 3.04 (dd, J = 13.7, 6.9 Hz, 1H), 2.89 (dd, J = 13.8, 7.7 Hz, 1H), 1.06 (d, J = 6.3 Hz, 3H).



281 **284**

(S)-1-((2R,5S)-5-benzyl-2,5-dihydro-1H-pyrrol-2-yl)ethanol (284)

To a refluxing solution of **281** (89.0 mg, 0.289 mmol) in anhydrous DCM (50 mL) was added Tosic acid monohydrate (56.3 mg, 0.296 mmol), and 15 minutes later Grubb's 2nd generation catalyst (12.1 mg, 0.0143 mmol) was added. The red mixture was refluxed for 16 hours. The catalyst was quenched by adding ethyl vinyl ether (1.0 mL), and solvent was removed under reduced pressure. Purification by flash chromatography (0-100% ethyl acetate/hexane then 0-10% methanol/ethyl acetate) to yield **284** as an off-white solid (40 mg, 68%). *Rf* = 0.10 (ethyl acetate). mp = 99-110 °C. $[\alpha]^{20}_{D}$ = +326 (c = 0.050 $CHCl_3$). IR (film)/cm^{-1} 3272, 3084, 2847, 1676, 1495, 1454, 1367, 1202, 1140, 1071, 911, 789, 735, 699. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.19-7.34 (m, 5H), 5.90 (d, *J* = 5.9 Hz, 1H), 5.77 (d, *J* = 5.9 Hz, 1H), 4.29 (q, *J* = 6.5 Hz, 1H), 4.11 (s, 1H), 3.62-3.70 (m, 1H), 2.79 (qd, *J* = 13.5, 6.8 Hz, 2H), 2.55 (bs, 2H), 1.16 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.2, 134.8, 130.0, 129.4, 127.7, 127.3, 70.2, 69.5, 67.4, 44.1, 19.3. HRMS Calcd for $C_{13}H_{18}NO$ $[M + H]^+$: 204.13829; Found: 204.13823.

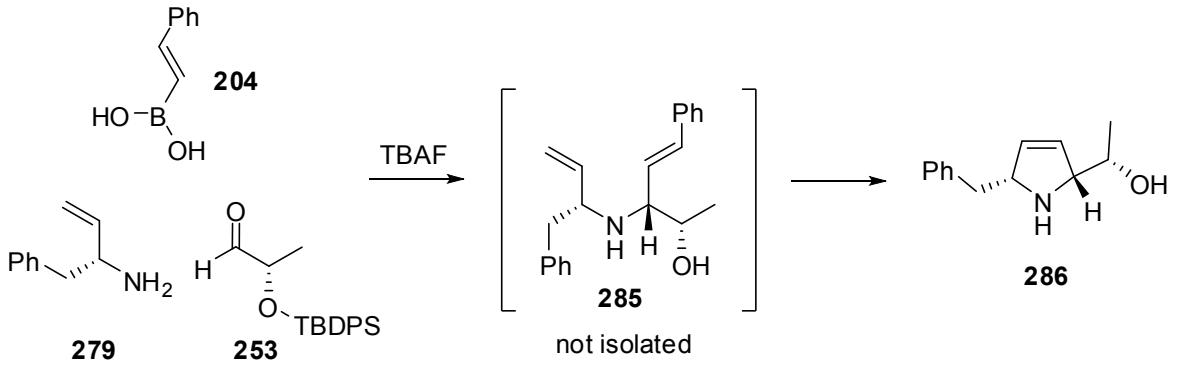


284 **259**

(S)-1-((2R,5S)-1,5-dibenzyl-2,5-dihydro-1H-pyrrol-2-yl)ethanol (259)

To a stirred solution of acetone (10 mL) was added **284** (40 mg, 0.197 mmol), K_2CO_3 (83 mg, 0.600 mmol), and benzyl bromide (125 µL, 1.05 mmol). The mixture was stirred at rt for 16 hours, filtered and solvent removed under reduced pressure. Purification by flash chromatography (10% ethyl acetate/hexane) to yield **259** as a white solid (45 mg, 77%). *Rf* = 0.10 (10% ethyl acetate/hexanes). $[\alpha]^{20}_{D}$ = +240 (c = 0.395 $CHCl_3$). IR (film)/cm^{-1} 3026, 2868, 1494, 1453, 1378, 1289, 1127, 1075, 1053, 909, 734, 700. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31-7.49 (m, 5H), 7.13-7.24 (m, 3H), 6.92 (d, *J* = 7.2 Hz, 2H), 5.75-5.81

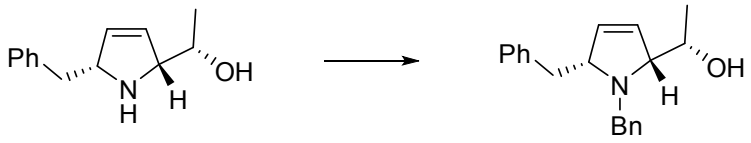
(m, 2H), 3.99-4.14 (m, 3H), 3.91 (q, J = 6.6 Hz, 1H), 3.79 (s, 1H), 3.09-3.16 (m, 2H), 2.39 (t, J = 11.4 Hz, 1H), 1.25 (d, J = 6.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.3, 139.6, 135.6, 129.9, 129.4, 129.1, 128.9, 127.9, 126.8, 126.5, 74.1, 68.5, 65.1, 51.2, 38.6, 19.4. HRMS Calcd for $C_{20}H_{24}NO$ $[M + H]^+$: 294.18524; Found: 294.18535.



(S)-1-((2R,5R)-5-benzyl-2,5-dihydro-1H-pyrrol-2-yl)ethanol (286)

(S)-2-(tert-butyldiphenylsilyloxy)-propanal **253** (556 mg, 1.78 mmol) was dissolved in anhydrous ethanol (20 mL) and a tetrabutylammonium fluoride solution (1.0 M in THF, 1.76 mL, 1.76 mmol) was added. The mixture was stirred for 5 minutes, then (R)-1-phenylbut-3-en-2-amine **279** (290 mg, 1.97 mmol) and (E)-styrylboronic acid **204** (261 mg, 1.76 mmol) were added and the mixture refluxed for 16 hours. Solvent was removed under reduced pressure, and the oily residue was redissolved in anhydrous DCM (100 mL). To the stirred mixture was added Tosic acid monohydrate (710mg, 3.73 mmol). The mixture was refluxed for 30 minutes, then to the refluxing mixture was added Grubb's 2nd generation catalyst (90 mg, 0.106 mmol) and the mixture refluxed for another 16 hours. The reaction was allowed to cool to rt, quenched with ethyl vinyl ether (1.0 mL) and solvent removed under reduced pressure. Purification by flash chromatography (0-20% THF/hexane) to yield **286** as an off-white solid (122 mg, 35%). *Rf* = 0.08 (20% THF/hexanes). mp = 87 °C. $[\alpha]^{20}_D$ = +101 (c = 0.717 $CHCl_3$). IR (film)/cm^{-1} 3286, 3059, 3024, 2974, 2919, 2853, 2810, 1602, 1543, 1495, 1453, 1400, 1374, 1246, 1152, 1088, 996, 951, 909, 734, 701. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.21-7.34 (m, 5H), 5.85 (d, J = 5.8 Hz, 1H), 5.73-5.75 (m, 1H), 4.34-4.38 (m, 1H), 4.09 (s, 1H), 3.53-3.60 (m, 1H), 2.80 (qd, J = 13.1 Hz, 6.0 Hz, 2H), 2.49 (bs, 2H), 1.18 (d, J = 6.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$):

δ 140.0, 134.6, 130.3, 129.1, 127.6, 127.0, 70.9, 68.5, 66.7, 45.2, 19.1. HRMS Calcd for $C_{13}H_{18}NO$ $[M + H]^+$: 204.13829; Found: 204.13831.



286 **258**

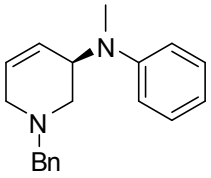
(S)-1-((2R,5R)-1,5-dibenzyl-2,5-dihydro-1H-pyrrol-2-yl)ethanol (258)

To a stirred solution of acetone (10 mL) was added **286** (60 mg, 0.295 mmol), K_2CO_3 (103.5 mg, 0.750 mmol), and benzyl bromide (125 μL, 1.05 mmol). The mixture was stirred at rt for 16 hours, filtered and solvent removed under reduced pressure. Purification by flash chromatography (10% ethyl acetate/hexane) to yield **258** as a yellow oil (40 mg, 69%). *Rf* = 0.11 (10% ethyl acetate/hexanes). $[\alpha]^{20}_D$ = +14 (c = 0.559 $CHCl_3$). IR (film)/cm^{-1} 3456, 3062, 3026, 2972, 2924, 2808, 1602, 1494, 1453, 1325, 1260, 1124, 1076, 1051, 910. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.18-7.39 (m, 8H), 7.09 (d, *J* = 7.2 Hz, 2H), 5.74 (d, *J* = 6.3 Hz, 1H), 5.64 (d, *J* = 6.2 Hz, 1H), 4.01-4.06 (m, 1H), 3.90 (s, 2H), 3.69-3.73 (m, 1H), 3.34 (qd, *J* = 6.4, 2.6 Hz, 1H), 2.79 (bs, 1H), 2.75 (dd, *J* = 13.3, 4.5 Hz, 1H), 2.55 (dd, *J* = 13.2, 7.9 Hz, 1H), 1.09 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.7, 139.2, 133.1, 130.5, 130.1, 129.4, 129.1, 128.2, 127.1, 126.1, 73.7, 66.4, 59.0, 43.5, 25.7, 18.8. HRMS Calcd for $C_{20}H_{24}NO$ $[M + H]^+$: 294.18524; Found: 294.18544.

6.6 General Ring Expansion Protocol

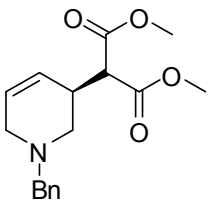
A flask containing the pyrrolinol (1.0 equiv) and proton sponge (1.2 equiv) dissolved in anhydrous DCM under positive pressure of Argon was chilled with a cryostat bath (-15 °C). To this solution was added triflic anhydride (1.1 equiv) via syringe causing the yellow solution to become orange. 5 minutes later the solution containing the nucleophile was cannulated to the aziridinium solution or added as a solid. The mixture was stirred for 1 hour, then allowed to warm to ambient temperature. The solution was diluted with water (20 mL) and extracted with DCM (2x20 mL) and the combined extracts dried (Na_2SO_4). Purification by flash chromatography.

Note: when **236** is referenced as a starting material in this section it was prepared from *L*-4-*trans*-Hydroxproline, and is 94% ee.



(R)-1-benzyl-N-methyl-N-phenyl-1,2,3,6-tetrahydropyridin-3-amine (304)

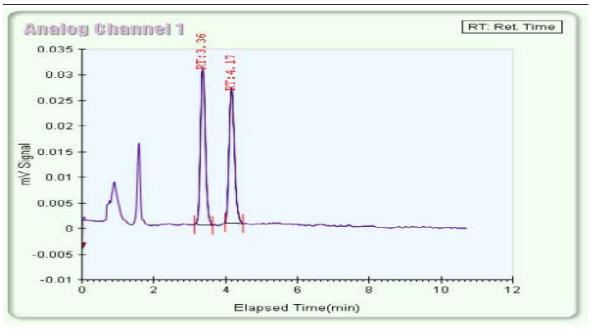
Following the general protocol with **236** and *N*-Methylaniline (1.2 equiv) added in one portion via syringe. Analyzed by ^{1}H NMR by comparison to 1,3,5-Trimethoxybenzene for yield (>99%). *Rf* = 0.06 (chloroform). IR (film)/cm^{-1} 3027, 2928, 2802, 1598, 1503, 1453, 1397, 1358, 1311, 1289, 1219, 1106, 1029, 990, 910, 734, 697. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.21-7.34 (m, 7H), 6.79 (d, *J* = 8.1 Hz, 2H), 6.71 (t, *J* = 7.2 Hz, 1H), 5.90-5.98 (m, 1H), 5.76 (d, *J* = 10.0 Hz, 1H), 4.63 (s, 1H), 3.61 (s, 2H), 2.89-3.05 (m, 6H), 2.50 (dd, *J* = 11.1, 7.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 150.4, 138.8, 130.1, 129.8, 129.4, 129.1, 128.2, 128.0, 117.3, 113.4, 63.6, 54.9, 53.6, 53.0, 34.0. HRMS Calcd for $C_{19}H_{22}N_2$ $[M + H]^+$: 279.18558; Found: 279.18558.



(S)-dimethyl 2-(1-benzyl-1,2,3,6-tetrahydropyridin-3-yl)malonate-dimethyl (309)

Following the general protocol with **236** and the sodium malonate solution prepared by: NaH (2.6 equiv) was dissolved in anhydrous THF, the solution chilled with a cryostat bath (-15 °C) under positive pressure of argon. Then

dimethylmalonate (3.5 equiv) was added dropwise to the stirred solution (effervescence). Purified by flash chromatography ($CHCl_3$) to obtain **309** as a yellow oil (87%, 94% ee). The enantiomeric excess was determined by SFC analysis on a chiral stationary phase and found to be the same as that of the precursor **236** (Chiralpak AD-H 25 cm, 7% MeOH, 5mL/min, 45°C, 150bar, 210 nm, t_r (major) 3.3 min, t_r (minor) 4.2 min. *Rf* = 0.09 (chloroform). IR (film)/cm^{-1} 3031, 2951, 2805, 1752, 1735, 1435, 1335, 1246, 1152, 1027. ^1H NMR (300 MHz, $CDCl_3$): δ 7.23-7.32 (m, 5H), 5.79 (d, J = 10.1 Hz, 1H), 5.63-5.67 (m, 1H), 3.74 (s, 3H), 3.68 (d, J = 10.1 Hz, 1H), 3.58-3.61 (m, 4H), 3.45 (d, J = 13.0 Hz, 1H), 3.12 (dt, J = 16.6, 1.6 Hz, 1H), 2.94-2.97 (m, 1H), 2.86 (dq, J = 16.6, 2.2 Hz, 1H), 2.50 (d, J = 3.9 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.8, 169.7, 139.1, 129.9, 129.2, 129.0, 127.8, 126.2, 63.2, 56.0, 54.0, 53.3, 53.2, 53.1, 37.9. HRMS Calcd for $C_{17}H_{22}NO_4$ $[M + H]^+$: 304.15433; Found: 304.15462.



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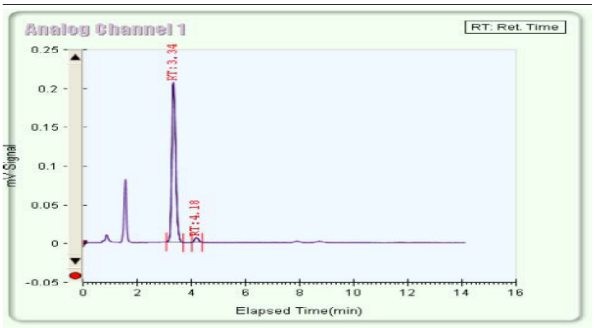
	2	48.5488	0.2677	4.17 min



Peak Name	Peak Number	Area %	Area	Retention Time
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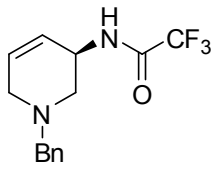
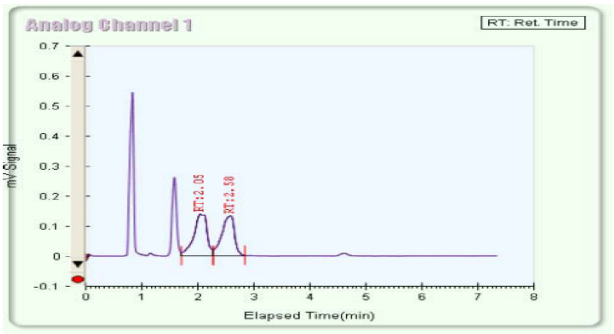
	2	2.8923	0.0608	4.18 min

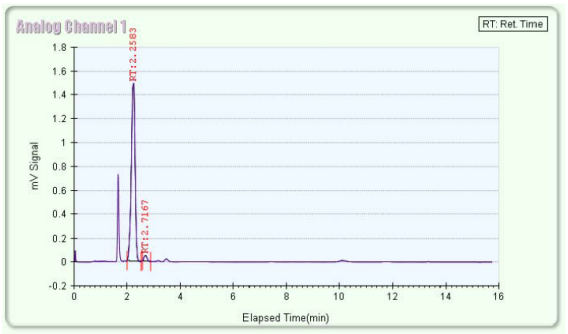


(R)-N-(1-benzyl-1,2,3,6-tetrahydropyridin-3-yl)-2,2,2-trifluoroacetamide (310)

Following the general protocol with **236** and the sodium amide solution prepared by: NaH (2.7 equiv) was dissolved in anhydrous THF, the solution chilled with a cryostat bath (-15 °C) under positive pressure of argon. Then Trifluoroacetamide (3.9 equiv) was added dropwise to the stirred solution (effervescence). Purified by flash chromatography ($CHCl_3$), then once more (20% ethyl acetate/hexane) to obtain **310** as a colourless oil (69%, 94% ee). The enantiomeric excess was determined by SFC analysis on a chiral stationary phase to be the same as the precursor **236** (Chiralpak AD-H 25 cm, 7%

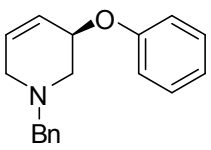
MeOH, 5mL/min, 45°C, 150bar, 210 nm, t_r (major) 2.3 min, t_r (minor) 2.7 min. *Rf* = 0.11 (chloroform). IR (film)/cm^{-1} 3301, 3032, 2922, 2806, 1707, 1526, 1455, 1360, 1276, 1159, 1063, 1028, 871, 737, 699. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27-7.37 (m, 5H), 6.78 (bs, 1H), 5.97 (ddd, *J* = 10.0, 4.1, 1.7 Hz, 1H), 5.77-5.82 (m, 1H), 4.47 (bs, 1H), 3.72 (d, *J* = 13.1 Hz, 1H), 3.52 (d, *J* = 13.0 Hz, 1H), 3.27 (dd, *J* = 17.2, 3.7 Hz, 1H), 2.89 (dq, *J* = 17.0,1.7 Hz, 1H), 2.73 (d, *J* = 11.7 Hz, 1H), 2.49 (dd, *J* = 11.7, 2.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.1, 138.4, 131.8, 129.6, 128.4, 124.3, 118.6, 62.7, 59.3, 54.8, 53.7, 45.7. HRMS Calcd for $C_{14}H_{16}F_3N_2O$ $[M + H]^+$: 285.12092; Found: 285.12112.





Peak Name	Peak Number	Area %	Area	Retention Time
	1	52.3334	2.2522	2.05 min
	2	47.6666	2.0514	2.58 min

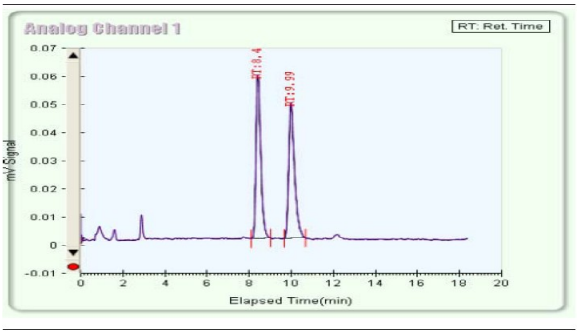
Peak Name	Area %	Area	Retention Time
Peak2	97.5676	14.594	2.2583 min
Peak3	2.4324	0.3638	2.7167 min



(R)-1-benzyl-3-phenoxy-1,2,3,6-tetrahydropyridine (311)

Following the general protocol with **236** and the phenoxide solution prepared by dissolving sodium phenoxide (3.2 equiv) in anhydrous DME (5 mL), the solution chilled with a cryostat bath (-15 °C) under positive pressure of argon. Then the phenoxide solution was added by cannula to the aziridinium solution. Purified by flash chromatography ($CHCl_3$) to obtain **311** as a colourless oil (97%, 94% ee). The enantiomeric excess was determined by SFC analysis on a chiral stationary phase to be the same as the precursor **236** (Chiralpak AD-H 25 cm, 7% MeOH, 5mL/min, 45°C, 150bar, 210 nm, t_r (minor) 8.3 min, t_r (major) 10.0 min. *Rf* = 0.16 (chloroform). IR (film)/cm^{-1} 3709, 3680, 2922, 2865, 2821, 1597, 1585, 1492, 1454, 1398, 1289, 1238, 1173, 1053, 1033, 1017, 752, 735, 691. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25-7.38 (m, 7H), 6.91-6.97 (m, 3H), 5.93-6.01 (m, 2H), 4.92 (s, 1H), 3.71 (d, *J* = 13.2 Hz, 1H), 3.64 (d, *J* = 13.2 Hz, 1H), 3.07 (s, 2H), 2.95 (dd, *J* = 11.4, 4.8 Hz, 1H), 2.70 (dd, *J* = 11.3, 6.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.5, 138.5, 130.7, 130.4, 129.9, 129.1, 128.0, 125.8, 121.7,

116.6, 71.5, 63.1, 54.9, 53.3. HRMS Calcd for $C_{18}H_{20}NO$ $[M + H]^+$: 266.15394; Found: 266.15392.



Peak Name	Peak Number	Area %	Area	Retention Time
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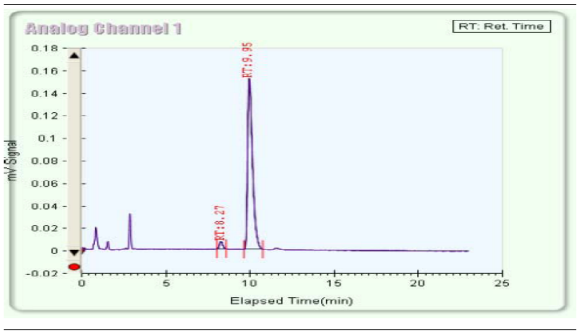

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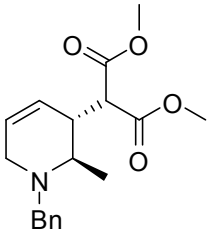
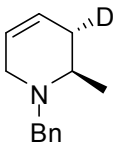


anti-dimethyl 2-(-1-benzyl-2-methyl-1,2,3,6-tetrahydropyridin-3-yl)malonate (312)

Following the general protocol with **244** and the sodium malonate solution prepared by: NaH (2.6 equiv) was dissolved in anhydrous THF, the solution chilled with a cryostat bath (-15 °C) under positive pressure of argon. Then dimethylmalonate (3.5 equiv) was added dropwise to the stirred solution (effervescence). Purified by flash chromatography ($CHCl_3$) to obtain **312** as a yellow oil (71%). *Rf* = 0.11 (chloroform). IR (film)/cm^{-1} 2952, 1732, 1660, 1434, 1261, 1237, 1194, 1148, 1028, 1007, 732, 700. ^1H NMR (300 MHz, $CDCl_3$): δ 7.23-7.33 (m, 5H), 5.78 (d, J = 10.2 Hz, 1H), 5.53-5.59 (m, 1H), 3.85 (d, J = 10.6 Hz, 1H), 3.73 (s, 3H), 3.57 (s, 3H), 3.56 (d, J = 10.6 Hz, 2H), 3.13 (d, J = 17.5 Hz, 1H), 2.89 (dq, J = 17.5, 2.2 Hz, 1H), 2.73 (q, J = 6.4 Hz, 1H), 2.62-2.68 (m, 1H), 0.98 (d, J = 6.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.1, 139.0, 128.9, 128.2, 128.1, 126.9, 123.1, 58.9, 56.1, 52.3, 52.3, 52.3, 52.0, 47.4, 41.9, 8.7. HRMS Calcd for $C_{14}H_{16}N_2$ $[M + H]^+$: 318.16998; Found: 318.17018.



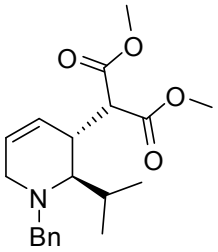
***anti*-1-benzyl-2-methyl-1,2,3,6-tetrahydropyridine-3-deuteride (315)**

Following the general protocol with **244**; $NaBD_4$ (2.5 equiv), and 15-Crown-5 (2.5 equiv), added as a solid and via syringe respectively as the nucleophile. Purified by flash chromatography (5% methanol/$CHCl_3$) to obtain **315** as a yellow oil (77%). *Rf* = 0.59 (5% methanol/chloroform). IR (film)/cm^{-1} 3028, 2962, 2922, 2791,

1659, 1493, 1453, 1368, 1329, 1259, 1145, 1071, 1027, 996, 722, 696, 636. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.22-7.38 (m, 5H), 5.69-5.75 (m, 1H), 5.60-5.65 (m, 1H), 3.82 (d, J = 13.2 Hz, 1H), 3.48 (d, J = 13.1 Hz, 1H), 2.99 (qq, J = 14.4, 2.5 Hz, 2H), 2.91 (t, J = 6.0 Hz, 1H), 1.88 (s, 1H), 1.11 (d, J = 6.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.4, 128.9, 128.2, 126.8, 125.0, 124.0, 70.7, 57.9, 51.0, 48.9, 32.3 (t, J = 19.4 Hz, 1C), 14.5. HRMS Calcd for $C_{13}H_{16}DN$ $[M + H]^+$: 189.14965; Found: 189.14959.

***anti*-1-benzyl-2-methyl-1,2,3,6-tetrahydropyridine-3-carbonitrile (316)**

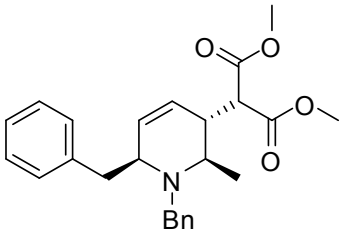
Following the general protocol with **244** and Bu_4NCN (2.5 equiv), added as a solid. Purified by flash chromatography ($CHCl_3$) to obtain **316** as a yellow oil (79%). *Rf* = 0.26 (chloroform). IR (film)/cm^{-1} 3029, 2973, 2928, 2805, 2235, 1494, 1453, 1373, 1361, 1261, 1199, 1147, 1135, 1071, 1002, 770, 733, 698. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25-7.43 (m, 5H), 5.91-5.96 (m, 1H), 5.65-5.71 (m, 1H), 3.76 (d, *J* = 13.3 Hz, 1H), 3.62 (d, *J* = 13.3 Hz, 1H), 3.25-3.33 (m, 1H), 3.13-3.21 (m, 1H), 2.96-3.03 (m, 2H), 1.13 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.2, 129.9, 128.6, 128.4, 127.2, 120.4, 117.7, 57.4, 53.4, 47.5, 33.7, 11.3. HRMS Calcd for $C_{14}H_{16}N_2$ $[M + H]^+$: 213.13862; Found: 213.13860.



***anti*-Dimethyl 2-(1-benzyl-2-isopropyl-1,2,3,6-tetrahydropyridin-3-yl)malonate (317)**

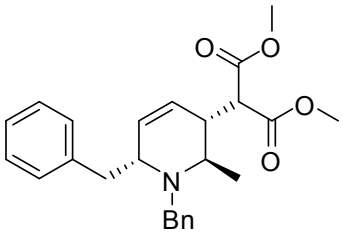
Following the general protocol with **244** and the sodium malonate solution prepared by: NaH (2.6 equiv) was dissolved in anhydrous THF, the solution chilled with a cryostat bath (-15 °C) under positive pressure of argon. Then dimethylmalonate (3.5 equiv) was added dropwise to the stirred solution (effervescence). Purified by flash chromatography ($CHCl_3$), then once more (10% ethyl acetate/hexane) to obtain **317** as a colourless oil (73%). *Rf* = 0.24 (10% ethyl acetate/hexane). IR (film)/cm^{-1} 2953, 1752, 1733, 1453, 1434, 1254, 1193, 1155, 1026, 914. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31-7.36 (m, 4H), 7.23-7.27 (m, 1H), 5.76 (ddd, *J* = 10.2, 3.4, 2.0 Hz, 1H), 5.60-5.66 (m, 1H), 3.91 (d, *J* = 10.8 Hz, 1H), 3.86 (d, *J* = 5.1 Hz, 1H), 3.78 (s, 1H), 3.76 (s, 3H), 3.68 (s, 3H), 3.21 (dq, *J* = 17.7, 2.2 Hz, 1H), 3.11 (d, *J* =

17.6 Hz, 1H), 2.97 (ddd, *J* = 9.4, 5.4, 1.2 Hz, 1H), 2.36 (d, *J* = 7.3 Hz, 1H), 2.09-2.17 (m, 1H), 1.05 (d, *J* = 6.8 Hz, 3H), 0.96 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1, 170.0, 140.9, 129.6, 129.5, 129.1, 127.7, 124.9, 65.6, 61.7, 57.7, 53.2, 53.2, 47.5, 38.5, 28.8, 23.5, 22.3. HRMS Calcd for $C_{20}H_{28}NO_4$ $[M + H]^+$: 346.20128; Found: 346.20157.



Dimethyl 2-((2R,3R,6S)-1,6-dibenzyl-2-methyl-1,2,3,6-tetrahydropyridin-3-yl)malonate (318)

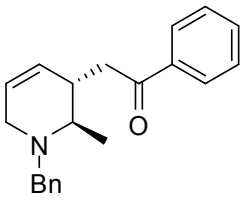
Following the general protocol with **259** and the sodium malonate solution prepared by: NaH (2.6 equiv) was dissolved in anhydrous THF, the solution chilled with a cryostat bath (-15 °C) under positive pressure of argon. Then dimethylmalonate (3.5 equiv) was added dropwise to the stirred solution (effervescence). Purified by flash chromatography ($CHCl_3$) to obtain **318** as a colourless oil (89%). *Rf* = 0.19 (chloroform). $[\alpha]^{20}_D$ = 92.6 (c = 1.50, $CHCl_3$). IR (film)/cm^{-1} 3026, 2952, 1732, 1601, 1494, 1452, 1433, 1262, 1235, 1192, 1150, 1074, 1024, 994, 973, 913, 727, 699. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34-7.41 (m, 5H), 7.23-7.26 (m, 2H), 7.15-7.19 (m, 1H), 7.00 (d, *J* = 8.8 Hz, 2H), 5.66 (dd, *J* = 10.2, 3.3 Hz, 1H), 5.52-5.58 (m, 1H), 4.05 (d, *J* = 13.3 Hz, 1H), 3.84 (d, *J* = 13.2 Hz, 1H), 3.71 (s, 3H), 3.68 (d, *J* = 10.9 Hz, 1H), 3.55 (s, 3H), 3.52 (bs, 1H), 3.29 (dd, *J* = 12.7, 3.5 Hz, 1H), 2.83 (q, *J* = 6.7 Hz, 1H), 2.71 (dd, *J* = 10.6, 5.7 Hz, 1H), 2.45 (t, *J* = 12.0 Hz, 1H), 1.20 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.9, 141.0, 140.1, 131.8, 130.0, 129.9, 129.2, 129.1, 127.8, 126.7, 122.8, 59.9, 56.8, 56.5, 53.2, 53.1, 52.6, 41.9, 38.4, 17.2. HRMS Calcd for $C_{25}H_{30}NO_4$ $[M + H]^+$: 408.21693; Found: 408.21723.



Dimethyl 2-((2R,3R,6R)-1,6-dibenzyl-2-methyl-1,2,3,6-tetrahydropyridin-3-yl)malonate (319)

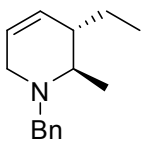
Following the general protocol with **258** and the sodium malonate solution prepared by: NaH (2.6 equiv) was dissolved in anhydrous THF, the solution chilled with a cryostat bath (-15 °C) under positive pressure of argon. Then dimethylmalonate (3.5 equiv) was added dropwise to the stirred solution (effervescence). Purified by flash chromatography ($CHCl_3$)

to obtain **319** as a yellow oil (81%). *Rf* = 0.25 (chloroform). $[\alpha]^{20}_{D}$ = -46.7 (c = 2.25, $CHCl_3$). IR (film)/cm^{-1} 3027, 2950, 2848, 1751, 1735, 1494, 1453, 1434, 1324, 1295, 1265, 1238, 1151, 1027, 910, 733, 700. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.22-7.37 (m, 10H), 5.69 (dd, *J* = 10.1, 1.9 Hz, 1H), 5.59 (dd, *J* = 9.8, 5.4 Hz, 1H), 4.14 (d, *J* = 13.7 Hz, 1H), 3.74 (s, 3H), 3.64 (d, *J* = 10.6 Hz, 1H), 3.46 (d, *J* = 13.7 Hz, 1H), 3.44 (s, 3H), 3.28-3.31 (m, 1H), 3.19 (dd, *J* = 13.6, 3.6 Hz, 1H), 2.70 (dd, *J* = 13.7, 8.8 Hz, 1H), 2.58-2.70 (m, 2H), 1.02 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.8, 169.8, 140.4, 139.6, 132.8, 130.6, 129.5, 129.0, 128.9, 127.5, 127.0, 123.9, 58.7, 56.2, 54.4, 53.2, 53.1, 50.7, 41.9, 41.0, 10.9. HRMS Calcd for $C_{25}H_{30}NO_4$ $[M + H]^+$: 408.21693; Found: 408.21817.

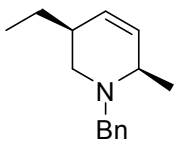


***anti*-2-(-1-benzyl-2-methyl-1,2,3,6-tetrahydropyridin-3-yl)-1-phenylethanone (321)**

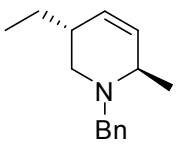
Following the general protocol with **244** and the 1-(1-phenylvinyl)pyrrolidine solution prepared by a previously published method[98] was added in one portion. Purified by flash chromatography ($CHCl_3$) to obtain **321** as a yellow oil (81%). *Rf* = 0.22 (chloroform). IR (film)/cm^{-1} 3027, 2964, 2873, 2751, 1682, 1597, 1580, 1493, 1448, 1358, 1268, 1204, 1132, 1000, 909, 729, 690. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.96-8.00 (m, 2H), 7.54-7.60 (m, 1H), 7.44-7.49 (m, 2H), 7.29-7.33 (m, 2H), 7.13-7.22 (m, 3H), 5.66-5.76 (m, 2H), 3.59 (s, 2H), 3.44 (dd, *J* = 17.3, 8.2 Hz, 1H), 3.07-3.14 (m, 1H), 3.07 (dd, *J* = 17.3, 5.1 Hz, 1H), 2.92 (d, *J* = 17.3 Hz, 1H), 2.78 (q, *J* = 6.6 Hz, 1H), 2.59-2.66 (m, 1H), 1.02 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.6, 139.8, 137.8, 133.2, 128.9, 128.8, 128.5, 128.4, 127.4, 127.1, 125.9, 59.3, 54.6, 47.6, 43.9, 38.5, 9.8. HRMS Calcd for $C_{21}H_{24}NO$ $[M + H]^+$: 306.18524; Found: 306.18534.



324a



324b



324c

324a, 324b, 324c

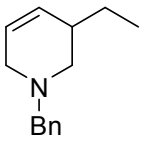
Following the general protocol with **236** and the cuprate solution prepared as follows: a suspension of CuCN (15.3 mg, 0.171 mmol) in anhydrous THF (3 mL) chilled with a dry ice/acetone bath was added an Isopropylmagnesium chloride solution in THF (1.40M, 125 µL, 0.175 mmol). The suspension was allowed to warm to rt, becoming an opaque black suspension, then chilled

with a cryostat bath (-15 °C). The aziridinium solution was cannulated to the cuprate solution since the cuprate solution was too thick to cannulate. Purification by flash chromatography ($CHCl_3$, a second with 10% THF/hexanes was done to separate **324a** from **324b** and **324c** but they did not fully separate) to yield a mixture of **324a**, **324b**, **324c** as a light yellow oil (78% total yield, 30:90:1 ratio of **324a:324b:324c**). Note: when repeated at -78 °C a ratio of 18:1 **324a**:**324b** was obtained. *Rf* = 0.15 ($CHCl_3$), **324a**, **324b**, and **324c** co-elute.

324a: IR (film)/cm^{-1} 3027, 2959, 2929, 2871, 2800, 2750, 1493, 1454, 1368, 1151, 1123, 1072, 1028, 998, 909, 728, 698. ^{1}H NMR (700 MHz, $CDCl_3$): δ 7.41-7.47 (m, 2H), 7.34-7.38 (m, 2H), 7.27-7.30 (m, 1H), 5.75-5.77 (m, 1H), 5.65-5.75 (m, 1H), 3.71 (d, *J* = 13.3 Hz, 1H), 3.63 (d, *J* = 13.3 Hz, 1H), 3.08 (d, *J* = 17.2 Hz, 1H), 2.94 (dq, *J* = 17.1, 2.2 Hz, 1H), 2.81 (qd, *J* = 6.5, 2.0 Hz, 1H), 1.74 (bs, 1H), 1.55-1.66 (m, 2H), 1.02 (d, *J* = 6.6 Hz, 3H), 0.92 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.2, 129.0, 128.5, 128.4, 127.0, 124.6, 58.9, 54.1, 48.2, 44.7, 27.9, 12.3, 11.0. HRMS Calcd for $C_{15}H_{21}N$ $[M + H]^+$: 216.17468; Found: 216.17442.

324b: ^{1}H NMR (700 MHz, $CDCl_3$): δ 7.41-7.47 (m, 2H), 7.34-7.38 (m, 2H), 7.27-7.30 (m, 1H), 5.75-5.77 (m, 1H), 5.62 (ddd, *J* = 10.0, 3.2, 1.9 Hz, 1H), 3.92 (d, *J* = 13.7 Hz, 1H), 3.51 (d, *J* = 13.7 Hz, 1H), 3.18-3.20 (m, 1H), 2.59 (dd, *J* = 11.9, 6.3 Hz, 1H), 2.53 (dd, *J* = 11.9, 4.9 Hz, 1H), 2.09 (bs, 1H), 1.36-1.46 (m, 2H), 1.19 (d, *J* = 6.6 Hz, 3H), 0.88 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 132.0, 129.1, 128.8, 128.2, 128.2, 126.8, 59.3, 55.2, 51.1, 37.0, 27.4, 19.0, 12.4.

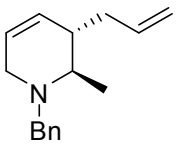
324c: ^{1}H NMR (700 MHz, $CDCl_3$): δ 7.27-7.44 (m, 5H), 5.67-5.70 (m, 1H), 5.55 (dt, *J* = 9.9, 2.2 Hz, 1H), 4.08 (d, *J* = 13.7 Hz, 1H), 3.35 (d, *J* = 13.8 Hz, 1H), 3.04 (s, 1H), 2.90 (dd, *J* = 11.2, 4.9 Hz, 1H), 2.20 (s, 1H), 1.94 (dd, *J* = 11.1, 9.5 Hz, 1H), 1.29 (d, *J* = 6.6 Hz, 3H), 1.26-1.46 (m, 2H), 0.89 (t, *J* = 7.5 Hz, 3H).



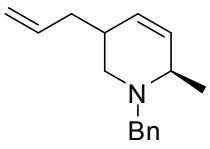
1-benzyl-3-ethyl-1,2,3,6-tetrahydropyridine (325)

The cuprate solution was prepared as follows: a suspension of CuCN (48.5 mg, 0.542 mmol) in anhydrous THF (5 mL) chilled with a dry ice/acetone bath was added an ethylmagnesium chloride solution in ether (1.05 M, 0.500 mL, 0.675mmol). The suspension was allowed to warm to rt, becoming an opaque black suspension, then chilled with a cryostat bath (-15 °C).

To a solution containing **236** (25.8 mg, 0.136 mmol) and proton sponge (37.1 mg, 0.173 mmol) dissolved in anhydrous DCM (5 mL) under positive pressure of Argon was chilled with a cryostat bath (-15 °C). To this solution was added triflic anhydride (25 µL, 0.15 mmol) via syringe causing the yellow solution to become orange. 5 minutes after the triflic anhydride addition the solution containing the aziridinium was cannulated to the cuprate solution. The mixture was stirred for 15 minutes, then allowed to warm to ambient temperature. Purification by flash chromatography ($CHCl_3$) to yield **325** as a light yellow film (20 mg, 73%). *Rf* = 0.05 ($CHCl_3$). IR (film)/cm^{-1} 3027, 2959, 2922, 2859, 2792, 2748, 1664, 1493, 1454, 1362, 1152, 1126, 1028, 978, 909, 861, 728, 698. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24-7.38 (m, 5H), 5.63-5.75 (m, 2H), 3.62 (d, *J* = 13.1 Hz, 1H), 3.57 (d, *J* = 13.1 Hz, 1H), 3.07 (d, *J* = 16.7 Hz, 1H), 2.85 (d, *J* = 16.7 Hz, 1H), 2.77 (dd, *J* = 10.7, 5.0 Hz, 1H), 2.21 (bs, 1H), 2.10 (dd, *J* = 10.8, 7.9 Hz, 1H), 1.28-1.44 (m, 2H), 0.90 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.4, 130.9, 129.9, 129.0, 127.8, 125.6, 63.7, 56.3, 53.9, 38.6, 27.6, 12.3.



326a



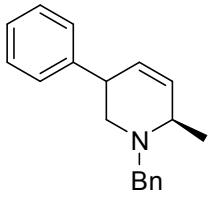
326b

326a and 326b

The cuprate solution was prepared as follows: a suspension of CuCN (93.0 mg, 1.04 mmol) in anhydrous THF (3 mL) chilled with a dry ice/acetone bath was added an allylmagnesium chloride solution in ether (1.14 M, 2.00 mL, 2.28mmol). The suspension was allowed to warm to rt, becoming an opaque black suspension, then chilled with a cryostat bath (-15 °C).

To a solution containing **244** (81.2 mg, 0.399 mmol) and proton sponge (104.6 mg, 0.488 mmol) dissolved in anhydrous DCM (10 mL) under positive pressure of Argon was chilled with a cryostat bath (-15 °C). To this solution was added triflic anhydride (74 µL, 0.440 mmol) via syringe causing the yellow solution to become orange. 5 minutes after the triflic

anhydride addition the solution containing the aziridinium was cannulated to the cuprate solution. The mixture was stirred for 15 minutes, then allowed to warm to ambient temperature. Purification by flash chromatography ($CHCl_3$) to yield **326a** and **326b**, which were an inseparable mixture, as a light yellow oil (86 mg, 95%). *Rf* = 0.05 ($CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24-7.40 (m, 7.1H), 5.67-5.89 (m, 3.4H), 5.60 (ddd, *J* = 10.0, 2.8, 1.7, 1H), 5.03 (dq, *J* = 17.3, 1.8 Hz, 0.57H), 4.89-4.99 (m, 3.03H), 3.91 (d, *J* = 13.6 Hz, 1H), 3.67 (t, *J* = 6.6 Hz, 1H), 3.63 (t, *J* = 13.0 Hz, 0.54H), 3.43 (d, *J* = 13.6 Hz, 1H), 3.04-3.13 (m, 1.32H), 2.78-2.94 (m, 0.81H), 2.57 (dd, *J* = 11.8, 5.6, 1H), 2.46 (dd, *J* = 11.8, 4.6 Hz, 1H), 2.25-2.37 (m, 0.69H), 2.19 (s, 1H), 2.11 (t, *J* = 7.1 Hz, 2.91H), 1.93-2.03 (m, 0.38H), 1.90 (s, 0.31H), 1.56-1.64 (m, 1H), 1.31-1.50 (m, 2.40H), 1.24 (d, *J* = 6.4 Hz, 0.35H), 1.18 (d, *J* = 6.6 Hz, 3H), 0.99 (d, *J* = 6.6 Hz, 1.15H).

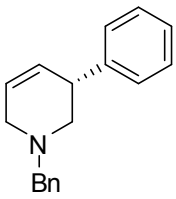


(6R)-1-benzyl-6-methyl-3-phenyl-1,2,3,6-tetrahydropyridine (327)

The cuprate solution was prepared as follows: a suspension of CuCN (100.3 mg, 1.12 mmol) in anhydrous DME (3 mL) chilled with a dry ice/acetone bath was added an phenylmagnesium bromide solution in ether (2.4 M, 0.470 mL, 1.13mmol). The suspension was allowed to warm to rt, becoming an opaque black suspension, then chilled with a cryostat bath (-15 °C).

To a solution containing **244** (86.1 mg, 0.424 mmol) and proton sponge (107.8 mg, 0.503 mmol) dissolved in anhydrous DCM (8 mL) under positive pressure of Argon was chilled with a cryostat bath (-15 °C). To this solution was added triflic anhydride (79 µL, 0.470 mmol) via syringe causing the yellow solution to become orange. 5 minutes after the triflic anhydride addition the solution containing the aziridinium was cannulated to the cuprate solution. The mixture was stirred for 15 minutes, then allowed to warm to ambient temperature. Purification by flash chromatography ($CHCl_3$) to yield **327** and a minor unidentified isomer (5:1) as a light yellow oil (108 mg, 97%). *Rf* = 0.05 ($CHCl_3$).). IR (film)/cm^{-1} 3025, 2968, 2794, 1493, 1452, 1361, 1154, 1027, 910, 734. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20-7.33 (m, 10H), 5.83 (s, 2H), 3.89 (d, *J* = 13.9 Hz, 1H), 3.58 (d, *J* = 13.9 Hz, 1H), 3.48-3.54 (m, 1H), 3.20-3.29 (m, 1H, 2.76 (d, *J* = 6.0 Hz, 2H), 1.24 (d, *J* =

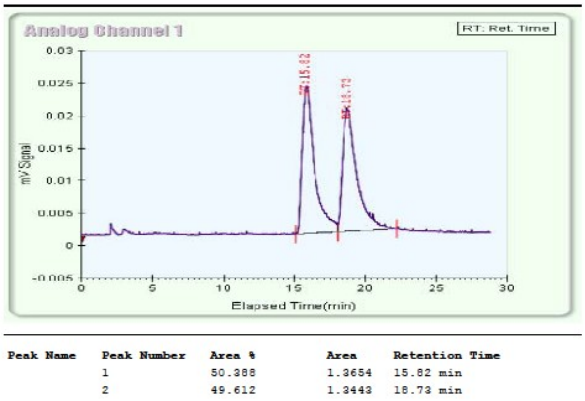
6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.2, 144.1, 139.8, 132.9, 128.8, 128.5, 128.5, 128.4, 127.7, 127.0, 126.6, 58.4, 54.0, 53.7, 41.1, 18.2.



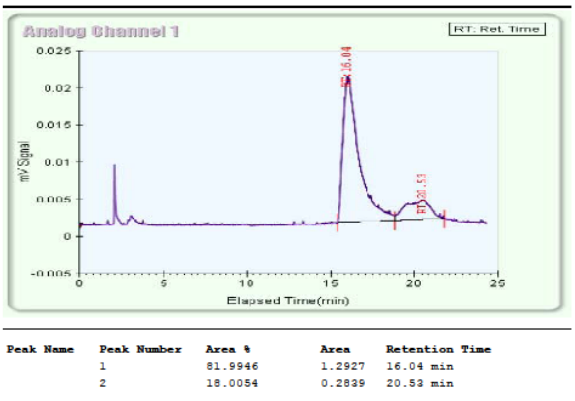
(R)-1-benzyl-3-phenyl-1,2,3,6-tetrahydropyridine (328)

The cuprate solution was prepared as follows: a suspension of CuCN (146.9 mg, 1.64 mmol) in anhydrous THF (5 mL) chilled with a dry ice/acetone bath was added an phenylmagnesium bromide solution in ether (2.50 M, 0.660 mL, 1.65mmol). The suspension was allowed to warm to rt, becoming an opaque black suspension, then chilled with a cryostat bath (-15 °C).

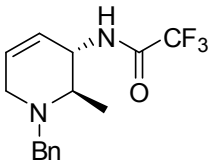
To a solution containing **236** (102.6 mg, 0.542 mmol) and proton sponge (140.4 mg, 0.655 mmol) dissolved in anhydrous DCM (5 mL) under positive pressure of Argon was chilled with a cryostat bath (-15 °C). To this solution was added triflic anhydride (100 μL, 0.594 mmol) via syringe causing the yellow solution to become orange. 5 minutes after the triflic anhydride addition the solution containing the aziridinium was cannulated to the cuprate solution. The mixture was stirred for 15 minutes, then allowed to warm to ambient temperature. Purification by flash chromatography ($CHCl_3$) to yield **328** as a light yellow oil (130 mg, 96%). The DEPT135 NMR clearly showed the product obtained to be the piperidine (43.7ppm peak assigned to the carbon not bound to a heteroatom in ^{13}C NMR has one or three hydrogens on it due to phase). The enantiomeric excess was determined by SFC analysis on a chiral stationary phase to be 64% ee (Chiralpak OD-H 25 cm, 2% *i*-PrOH, 3mL/min, 35°C, 150bar, 210 nm, t_r (major) 21.8 min, t_r (minor) 26.5 min. Hydrogenation of **328** (21.6mg, 0.0866mmol) was done by dissolving **328** in methanol (5 mL), and adding Pd/C (10% by wt Pd, 50% by wt water; 5mg) and H_2 at ambient pressure and temperature (balloon) over 16 hours. The optical rotation was taken of the hydrogenated compound, $[\alpha]^{20}_D$ = -10.6 (c = 0.0094 $CHCl_3$), which showed the major enantiomer was *R* as shown above. *Rf* = 0.08 ($CHCl_3$).). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21-7.34 (m, 10H), 5.80-5.91 (m, 2H), 3.57-3.66 (m, 3H), 3.18 (d, *J* = 16.4 Hz, 1H), 2.88-3.03 (m, 2H), 2.36 (dd, *J* = 11.1, 8.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.6, 139.1, 129.9, 129.5, 129.1, 129.1, 128.9, 127.8, 127.3, 127.1, 63.4, 59.1, 53.4, 43.7.



Racemic **328**

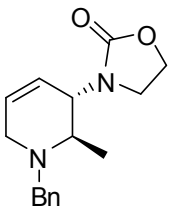


Enantio-enriched **328**



anti-N-((2R,3S)-1-benzyl-2-methyl-1,2,3,6-tetrahydropyridin-3-yl)-2,2,2-trifluoroacetamide (329)

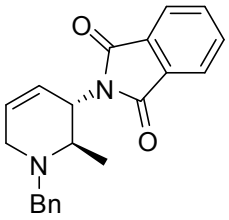
Following the general protocol with **244** and the sodium amide solution prepared by: NaH (2.6 equiv) was dissolved in anhydrous THF, the solution chilled with a cryostat bath (-15 °C) under positive pressure of argon. Then Trifluoroacetamide (3.4 equiv) was added dropwise to the stirred solution (effervescence) followed by 15-Crown-5 (2.5 equiv). Purified by flash chromatography ($CHCl_3$) to obtain **329** as a yellow oil (58%). *Rf* = 0.04 (chloroform). IR (film)/cm^{-1} 3311, 3031, 2971, 2929, 2808, 1719, 1520, 1454, 1374, 1361, 1271, 1201, 1159, 1003, 856. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27-7.37 (m, 5H), 6.87 (bs, 1H), 5.96 (ddd, *J* = 9.8, 4.2, 1.9 Hz, 1H), 5.76-5.79 (m, 1H), 4.18 (t, *J* = 7.0 Hz, 1H), 3.69 (d, *J* = 13.0 Hz, 1H), 3.61 (d, *J* = 13.0 Hz, 1H), 3.22 (ddd, *J* = 17.9, 4.2, 1.9 Hz, 1H), 3.02 (dd, *J* = 17.9, 1.9 Hz, 1H), 2.86 (q, *J* = 6.7 Hz, 1H), 1.00 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.5, 131.0, 128.9, 128.9, 127.8, 122.0, 58.5, 54.5, 49.6, 47.7, 7.6. HRMS Calcd for $C_{15}H_{18}F_3N_2O$ $[M + H]^+$: 299.13657; Found: 299.13697.



anti-3-(-1-benzyl-2-methyl-1,2,3,6-tetrahydropyridin-3-yl)oxazolidin-2-one (330)

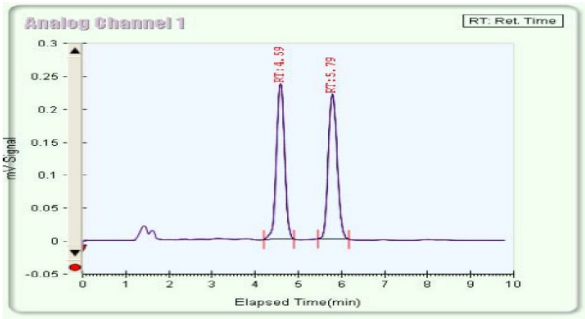
Following the general protocol with **244** and the sodium 2-oxooxazolidin-3-ide solution prepared by: 2-Oxazolidinone (3.0 equiv) was dissolved in anhydrous DME, the solution chilled with a cryostat bath (-15 °C) and the NaHMDS (2.5 equiv) and 15-Crown-5 (2.5 equiv) was added. The sodium 2-oxooxazolidin-3-ide solution

was added by cannula to the stirred aziridinium solution. Purified by flash chromatography ($CHCl_3$) to obtain **330** as white solid (86%). *Rf* = 0.05 (chloroform). mp = 122 °C. IR (film)/cm^{-1} 2970, 2754, 1742, 1426, 1366, 1256, 1139, 1070, 1030, 910, 787, 739, 700. ^1H NMR (300 MHz, $CDCl_3$): δ 7.23-7.37 (m, 5H), 5.99 (d, *J* = 9.9 Hz, 1H), 5.54-5.59 (m, 1H), 4.28 (t, *J* = 8.1 Hz, 2H), 4.14 (m, 1H), 3.94 (dt, *J* = 9.1, 7.9 Hz, 1H), 3.54-3.68 (m, 3H), 3.04-3.12 (m, 2H), 2.88 (dq, *J* = 17.8, 2.3 Hz, 1H), 1.06 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.5, 139.0, 131.4, 129.1, 128.7, 127.5, 120.9, 62.8, 59.2, 57.1, 53.8, 46.9, 43.6, 9.0. HRMS Calcd for $C_{16}H_{21}N_2O_2$ $[M + H]^+$: 273.15975; Found: 273.15976.



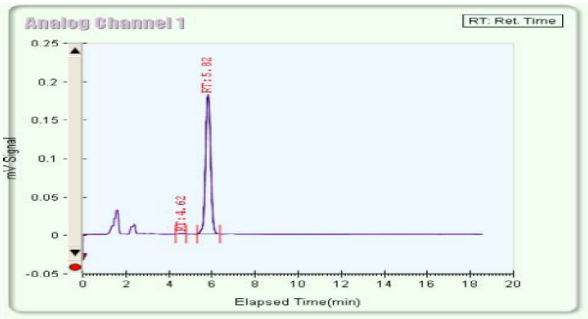
2-((2R,3S)-1-benzyl-2-methyl-1,2,3,6-tetrahydropyridin-3-yl)isoindoline-1,3-dione (331)

Following the general protocol with **244** and the sodium phthalimide solution prepared by: NaHMDS (2.4 equiv) was dissolved in anhydrous THF, the solution chilled with a cryostat bath (-15 °C) under positive pressure of argon. Then phthalimide (2.5 equiv) was added in one portion to the stirred solution followed by 15-Crown-5 (2.5 equiv). Purified by flash chromatography ($CHCl_3$), to obtain **331** as a white solid (70%, >99% ee). The enantiomeric excess was determined by SFC analysis on a chiral stationary phase (Chiralpak AS-H 25 cm, 10% MeOH, 3mL/min, 35°C, 150bar, 220 nm, t_r (minor) 4.6 min, t_r (major) 5.8 min. mp = 72 °C. *Rf* = 0.05 (chloroform). $[\alpha]^{20}_D$ = +124 (c = 0.617, $CHCl_3$). IR (film)/cm^{-1} 3029, 2973, 2925, 2794, 1771, 1708, 1467, 1382, 1329, 1120, 1019, 908, 718. ^1H NMR (300 MHz, $CDCl_3$): δ 7.89 (d, *J* = 3.1 Hz, 1H), 7.87(d, *J* = 3.0 Hz, 1H), 7.77 (d, *J* = 3.1 Hz, 1H), 7.73 (d, *J* = 3.1 Hz, 1H), 7.21-7.37 (m, 5H), 5.90 (ddd, *J* = 10.1, 3.2, 2.8 Hz, 1H), 5.62 (ddd, *J* = 10.1, 2.2, 2.1, 1H), 4.71-4.78 (m, 1H), 3.99 (d, *J* = 13.2 Hz, 1H), 3.52 (d, *J* = 13.2 Hz, 1H), 3.40 (dq, *J* = 8.5, 6.5 Hz, 1H), 3.11-3.14 (m, 2H), 1.19 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.3, 139.3, 134.0, 131.9, 128.7, 128.2, 128.2, 126.9, 124.2, 123.2, 55.2, 55.1, 52.1, 50.5, 15.8. HRMS Calcd for $C_{21}H_{21}N_2O_2$ $[M + H]^+$: 333.15975; Found: 333.16003.



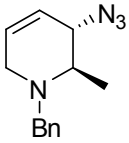
Peak Name	Peak Number	Area %	Area	Retention Time
	1	49.7305	3.0709	4.59 min
	2	50.2695	3.1041	5.79 min

Racemic 331



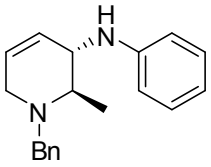
Peak Name	Peak Number	Area %	Area	Retention Time
	1	0.4822	0.0146	4.62 min
	2	99.5178	3.0052	5.82 min

Enantioenriched 331



***anti*-(2R,3S)-3-azido-1-benzyl-2-methyl-1,2,3,6-tetrahydropyridine (332)**

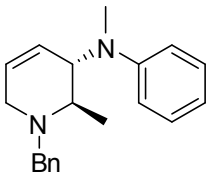
Following the general protocol with **244** and tetrabutylammonium azide (2.6 equiv) added in one portion as a solid. Purified by flash chromatography ($CHCl_3$) to obtain **332** as a yellow oil (75%), note: the azide was unstable forming another isomer visible by ^1H NMR over the course of days. *Rf* = 0.26 (chloroform). IR (film)/cm^{-1} 3033, 2970, 2932, 2875, 2805, 2101, 1494, 1453, 1363, 1221, 1147, 1070, 1026, 1004, 928, 876, 796, 751, 722, 697. ^1H NMR (300 MHz, $CDCl_3$): δ 7.26-7.42 (m, 5H), 6.11 (ddd, *J* = 9.8, 4.2, 2.1 Hz, 1H), 5.72-5.77 (m, 1H), 3.70 (s, 2H), 3.11-3.22 (m, 3H), 2.91 (dq, *J* = 18.0, 2.2 Hz, 1H), 0.99 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.4, 132.5, 129.6, 129.2, 127.9, 120.4, 60.8, 59.6, 57.6, 47.8, 9.6. HRMS Calcd for $C_{13}H_{16}N_4$ $[M + H]^+$: 229.14477; Found: 229.14384.



***anti*-1-benzyl-2-methyl-N-phenyl-1,2,3,6-tetrahydropyridin-3-amine (333)**

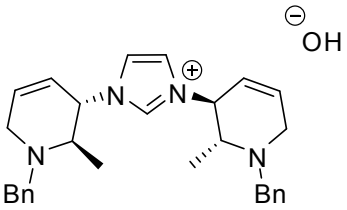
Following the general protocol with **244** and aniline (1.2 equiv) added in one portion via syringe. Purified by flash chromatography ($CHCl_3$), to obtain **333** as a yellow oil (80%). *Rf* = 0.14 (chloroform). IR (film)/cm^{-1} 3377, 3027, 2964, 2924, 2754, 1600, 1498, 1430, 1370, 1313, 1246, 1148, 996. ^1H NMR (300 MHz, $CDCl_3$): δ 7.17-7.30 (m, 7H), 6.73 (t, *J* = 7.3 Hz, 1H), 6.67 (d, *J* = 7.7 Hz, 2H), 5.90-5.95 (m, 1H), 5.84 (ddd, *J* = 9.9, 3.9, 1.7 Hz, 1H), 4.26 (d, *J* = 8.3 Hz, 1H), 3.71 (bs, 1H), 3.66 (s, 2H), 3.07-3.16 (m,

2H), 2.94 (dq, *J* = 17.6, 2.0, 1H), 1.05 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.2, 139.8, 130.1, 129.4, 129.0, 129.0, 127.8, 125.3, 118.4, 114.9, 59.7, 55.7, 54.4, 47.9, 9.5. HRMS Calcd for $C_{19}H_{23}N_2$ $[M + H]^+$: 279.18558; Found: 279.18572.



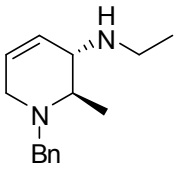
anti-1-benzyl-N,2-dimethyl-N-phenyl-1,2,3,6-tetrahydropyridin-3-amine (334)

Following the general protocol with **244** and *N*-Methylaniline (1.2 equiv) added in one portion via syringe. Purified by flash chromatography ($CHCl_3$) to obtain **334** as a yellow oil (93%). *Rf* = 0.50 (20% diethyl ether/chloroform). IR (film)/cm^{-1} 3026, 2963, 2923, 2802, 1597, 1501, 1452, 1368, 1315, 1136, 1108, 990, 747, 731. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26-7.37 (m, 7H), 6.83 (d, *J* = 8.2 Hz, 2H), 6.76 (t, *J* = 7.2 Hz, 1H), 5.96-6.00 (m, 1H), 5.67-5.72 (m, 1H), 4.17 (bs, 1H), 3.74 (d, *J* = 13.2 Hz, 1H), 3.62 (d, *J* = 13.2 Hz, 1H), 3.08-3.14 (m, 1H), 3.06 (s, 3H), 3.02-3.04 (m, 1H), 2.95 (dq, *J* = 17.4, 2.4 Hz, 1H), 1.17 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 150.7, 140.2, 130.1, 130.0, 129.5, 129.0, 127.7, 125.3, 116.8, 113.4, 60.0, 59.5, 57.9, 48.3, 34.7, 12.2. HRMS Calcd for $C_{20}H_{25}N_2$ $[M + H]^+$: 293.20123; Found: 293.20134.



1,3-bis((2R,3S)-1-benzyl-2-methyl-1,2,3,6-tetrahydro-pyridin-3-yl)-1H-imidazol-3-ium hydroxide (335)

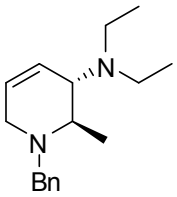
Following the general protocol with **244** and imidazole (1.2 equiv) added in one portion via syringe. Purified by trituration with diethyl ether to obtain **337** as a yellow solid (60%). The mono-alkylated product was present also but not isolated. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.13 (s, 1H), 7.60 (s, 2H), 7.22-7.24 (m, 6H), 7.08-7.10 (m, 4H), 6.27 (dd, *J* = 9.8, 4.1 Hz, 2H), 5.87 (dd, *J* = 9.5, 5.6 Hz, 2H), 4.87 (d, *J* = 5.2 Hz, 2H), 3.62 (d, *J* = 12.9 Hz, 2H), 3.58 (d, *J* = 13.0 Hz, 2H), 3.19-3.28 (m, 2H), 2.95-3.11 (m, 4H), 1.18 (d, *J* = 6.7 Hz, 6H).



(2R,3S)-1-benzyl-N-ethyl-2-methyl-1,2,3,6-tetrahydropyridin-3-amine (336)

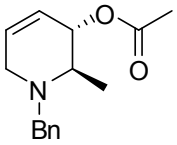
Following the general protocol with **244** and ethylamine (1.2 equiv) added

in one portion via syringe. Purified by flash chromatography ($CHCl_3$) to obtain **337** as a yellow oil (89%). Note: minor impurity of proton sponge present, unable to remove despite multiple column attempts. *Rf* = 0.05 (chloroform). IR (film)/cm^{-1} 3030, 2963, 2928, 2871, 2822, 1577, 1494, 1453, 1369, 1134, 1068, 1028, 998, 909, 731. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.20-7.37 (m, 5H), 5.81-5.88 (m, 1H), 5.72 (ddd, *J* = 10.0, 4.1, 2.0 Hz, 1H), 3.67 (d, *J* = 13.2 Hz, 1H), 3.61 (d, *J* = 13.1 Hz, 1H), 2.98-3.12 (m, 2H), 2.90 (dq, *J* = 17.2, 2.0 Hz, 1H), 2.71-2.76 (m, 1H), 2.53 (q, *J* = 7.1 Hz, 2H), 1.08 (t, *J* = 7.1 Hz, 3H), 0.93 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.7, 129.1, 128.5, 127.3, 127.2, 126.6, 59.1, 58.2, 52.9, 48.0, 41.3, 16.0, 8.7.



***anti*-1-benzyl-*N*,*N*-diethyl-2-methyl-1,2,3,6-tetrahydropyridin-3-amine (337)**

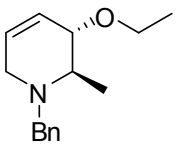
Following the general protocol with **244** and Diethylamine (1.2 equiv) added in one portion via syringe. Purified by flash chromatography ($CHCl_3$) to obtain **337** as a yellow oil (87%). *Rf* = 0.05 (chloroform). IR (film)/cm^{-1} 3028, 2965, 2926, 2870, 2801, 1723, 1661, 1602, 1494, 1453, 1368, 1201, 1135, 1069, 1052, 1028, 996, 909. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24-7.40 (m, 5H), 5.81-5.87 (m, 1H), 5.70-5.74 (m, 1H), 3.77 (d, *J* = 13.1 Hz, 1H), 3.55 (d, *J* = 13.1 Hz, 1H), 3.04 (bs, 1H), 2.84-2.96 (m, 3H), 2.64-2.74 (m, 4H), 1.11 (d, *J* = 6.5 Hz, 3H), 1.07 (t, *J* = 7.2 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.2, 129.8, 129.0, 129.0, 127.7, 125.0, 62.0, 59.5, 55.4, 48.5, 45.7, 45.7, 30.5, 15.1, 12.8. HRMS Calcd for $C_{17}H_{27}N_2$ $[M + H]^+$: 259.21688; Found: 259.21690.



***anti*-1-benzyl-2-methyl-1,2,3,6-tetrahydropyridin-3-yl acetate (338)**

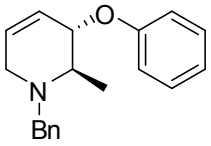
Following the general protocol with **244** and tetrabutylammonium acetate (2.5 equiv) added in one portion as a solid. Purified by flash chromatography ($CHCl_3$) to obtain **338** as a yellow oil (65%). *Rf* = 0.14 (chloroform). IR (film)/cm^{-1} 3029, 2969, 2930, 1728, 1660, 1454, 1370, 1241, 1147, 1024. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (d, *J* = 6.6 Hz, 2H), 7.33 (t, *J* = 7.3 Hz, 2H), 7.26-7.28 (m, 1H), 6.05 (ddd, *J* = 10.0, 3.6, 2.2 Hz, 1H), 5.78-5.82 (m, 1H), 4.96-4.97 (m, 1H), 3.80 (d, *J* = 13.4 Hz, 1H), 3.64 (d, *J* = 13.4 Hz, 1H), 3.21 (d, *J* = 17.0 Hz, 1H), 3.00-3.08 (m, 2H), 2.10 (s, 3H), 1.00 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.1, 139.0, 132.2, 129.0,

128.6, 127.4, 121.8, 72.1, 58.0, 54.4, 47.7, 21.7, 8.7. HRMS Calcd for $C_{15}H_{20}NO_2$ [M + H]$^+$: 246.14886; Found: 246.14875.



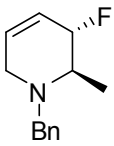
***anti*-1-benzyl-3-ethoxy-2-methyl-1,2,3,6-tetrahydropyridine (339)**

Following the general protocol with **244** and the ethanol (25 equiv) added in one portion via syringe. Purified by flash chromatography ($CHCl_3$), to obtain **339** as a yellow oil (73%). *Rf* = 0.25 (chloroform). IR (film)/cm^{-1} 3030, 2971, 2927, 2870, 1494, 1453, 1371, 1304, 1148, 1092, 1028, 903, 734, 698.. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41 (d, *J* = 7.2 Hz, 2H), 7.22-7.34 (m, 3H), 5.78-5.91 (m, 2H), 3.88 (d, *J* = 13.4 Hz, 1H), 3.42-3.59 (m, 4H), 3.03 (d, *J* = 8.9 Hz, 2H), 2.91-2.99 (m, 1H), 1.22 (t, *J* = 7.0 Hz, 3H), 1.03 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.8, 130.1, 129.2, 128.8, 128.1, 126.8, 123.9, 64.0, 57.6, 54.0, 48.5, 15.7, 10.5. HRMS Calcd for $C_{15}H_{22}NO$ [M + H]$^+$: 232.16959; Found: 232.16939.



***anti*-1-benzyl-2-methyl-3-phenoxy-1,2,3,6-tetrahydropyridine (340)**

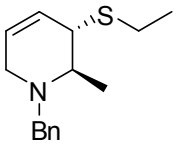
Following the general protocol with **244** and the phenoxide solution prepared by dissolving sodium phenoxide (3.2 equiv) in anhydrous DME (5 mL), the solution chilled with a cryostat bath (-15 °C) under positive pressure of argon. Then the phenoxide solution was added by cannula to the aziridinium solution. Purified by flash chromatography ($CHCl_3$) to obtain **340** as a yellow oil (85%). *Rf* = 0.11 (chloroform). IR (film)/cm^{-1} 3028, 2968, 2924, 2797, 1663, 1596, 1585, 1492, 1453, 1372, 1300, 1236, 1170, 1151, 1029, 909, 753, 734, 693. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39 (d, *J* = 7.1 Hz, 2H), 7.23-7.31 (m, 5H), 6.92-6.97 (m, 3H), 5.92-6.04 (m, 2H), 4.48 (s, 1H), 3.93 (d, *J* = 13.4 Hz, 1H), 3.59 (d, *J* = 13.4 Hz, 1H), 3.08-3.19 (m, 3H), 1.15 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.0, 138.7, 130.5, 129.5, 128.7, 128.2, 126.9, 122.7, 120.7, 115.8, 75.5, 57.6, 54.9, 48.4, 10.9. HRMS Calcd for $C_{19}H_{22}NO$ [M + H]$^+$: 280.16959; Found: 280.16950.



***anti*-1-benzyl-3-fluoro-2-methyl-1,2,3,6-tetrahydropyridine (341)**

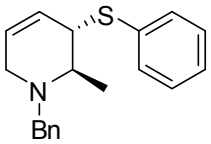
Following the general protocol with **244** and TBAF (1.0M, 2.5 equiv) added dropwise to the stirred aziridinium solution. Purified by flash chromatography ($CHCl_3$) to obtain **341** as a yellow oil (57%). *Rf* = 0.15 (chloroform). IR (film)/cm^{-1} 3031,

2973, 2922, 2803, 1729, 1602, 1494, 1454, 1402, 1371, 1332, 1265, 1149, 1071, 1029, 983, 965, 894, 775, 737, 698. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25-7.42 (m, 5H), 6.03 (dq, *J* = 10.0, 3.2 Hz, 1H), 5.85-5.92 (m, 1H), 4.67 (d, *J*= 49.2 Hz, 1H), 3.91 (d, *J* = 13.3 Hz, 1H), 3.59 (d, *J* = 13.3 Hz, 1H), 3.03-3.15 (m, 3H), 1.09 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.5, 132.3, 128.7, 128.2, 127.0, 122.0/121.8 (C-CF), 90.3/88.1 (C-F), 57.5, 55.8/55.5 (C-CF), 48.2, 10.1. HRMS Calcd for $C_{13}H_{17}FN$ $[M + H]^+$: 206.13395; Found: 206.13376.



***anti*-1-benzyl-3-(ethylthio)-2-methyl-1,2,3,6-tetrahydropyridine (342)**

Following the general protocol with **244** and Ethanethiol (10 equiv) added in one portion via syringe. Purified by flash chromatography ($CHCl_3$) to obtain **342** as a yellow oil (56%). *Rf* = 0.16 (chloroform). IR (film)/cm^{-1} 3029, 2965, 2924, 2869, 2802, 1659, 1494, 1452, 1367, 1261, 1203, 1135, 1067, 1028, 1013, 730. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43 (d, J = 7.3 Hz, 2H), 7.22-7.35 (m, 3H), 5.75-5.77 (m, 2H), 3.75 (d, J = 13.4 Hz, 1H), 3.61 (d, J = 13.4 Hz, 1H), 3.03-3.16 (m, 3H), 2.92-2.99 (m, 1H), 2.50-2.70 (m, 2H), 1.24 (t, J = 7.5 Hz, 3H), 1.06 (d, J = 6.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.8, 129.6, 129.0, 127.7, 127.5, 125.3, 59.1, 57.0, 48.2, 47.8, 26.0, 15.9, 11.6. HRMS Calcd for $C_{15}H_{22}NS$ $[M + H]^+$: 248.14675; Found: 248.14663.

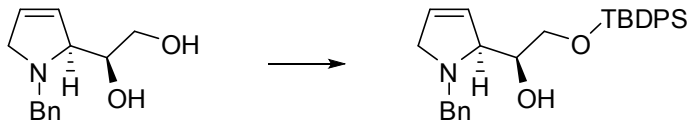


***anti*-1-benzyl-2-methyl-3-(phenylthio)-1,2,3,6-tetrahydropyridine (343)**

Following the general protocol with **244** and the sodium thiophenoxide solution prepared by: NaH (2.7 equiv) was dissolved in anhydrous DME, the solution chilled with a cryostat bath (-15 °C) under positive pressure of argon. Then Thiophenol (4.0 equiv) was added dropwise to the stirred solution (effervescence). Purified by flash chromatography ($CHCl_3$) to obtain **343** as a yellow oil (70%). *Rf* = 0.06 (chloroform). IR (film)/cm^{-1} 3029, 2966, 2923, 2869, 2802, 2751, 1582, 1493, 1478, 1453, 1437, 1360, 1203, 1135, 1066, 1025, 1015, 731. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45 (d, *J* = 7.1 Hz, 2H), 7.30-7.35 (m, 4H), 7.19-7.28 (m, 4H), 5.82-5.86 (m, 2H), 3.76 (d, *J* = 13.4 Hz, 1H), 3.62 (d, *J* = 13.4 Hz, 1H), 3.50-3.54 (m, 1H), 3.17-3.25 (m, 1H), 3.14 (qd, *J* = 6.6, 2.2 Hz, 1H), 2.97-3.05 (m, 1H), 1.03 (d, J = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.6,

137.2, 132.2, 129.7, 129.6, 129.0, 128.6, 127.7, 127.4, 124.4, 59.0, 55.4, 51.9, 48.2, 11.0. HRMS Calcd for $C_{19}H_{22}NS$ $[M + H]^+$: 296.14675; Found: 296.14665.

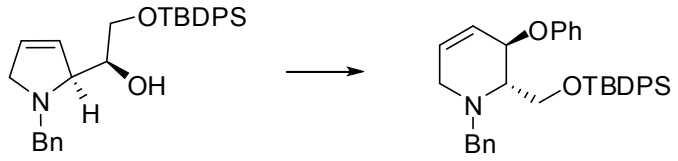
6.7 Divergent Substitution Using an Aziridinium



269 **350**

(S)-1-((S)-1-benzyl-2,5-dihydro-1H-pyrrol-2-yl)-2-(tert-butyldiphenylsilyloxy)-ethanol (350)

To a chilled (ice bath) solution of **269** (300 mg, 1.37 mmol) in anhydrous DCM (100 mL) was added imidazole (237 mg, 3.48 mmol), followed by dropwise addition of tert-butylchlorodiphenylsilane (420 μL, 1.64 mmol). After 2 hours the reaction mixture was diluted with ethyl acetate (200 mL) and washed with Sat. $NaHCO_3$ (2x100 mL), brine (100 mL) and dried (Na_2SO_4). Purification by flash chromatography (0-30% ethyl acetate/hexane) to yield **350** as a colourless oil (527 mg, 84%). *Rf* = 0.60 (30% ethyl acetate/hexane). $[\alpha]^{20}_D$ = -64.8 (c = 0.925 $CHCl_3$). IR (film)/cm^{-1} 3070, 2929, 2857, 1472, 1427, 1112, 911, 737, 701. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66-7.70 (m, 4H), 7.36-7.47 (m, 6H), 7.27-7.33 (5H), 5.81 (d, *J* = 6.2 Hz, 1H), 5.68 (dd, *J* = 6.1, 1.4 Hz, 1H), 4.07 (d, *J* = 13.2 Hz, 1H), 3.88-3.95 (m, 2H), 3.68-3.77 (m, 3H), 3.64 (d, *J* = 13.4 Hz, 1H), 3.22-3.31 (m, 1H), 1.09 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.2, 136.4, 136.4, 134.2, 134.2, 130.6, 129.8, 129.4, 129.2, 128.6, 127.9, 129.5, 73.2, 71.7, 66.1, 61.1, 59.5, 27.7, 20.1. HRMS Calcd for $C_{29}H_{36}NO_2Si$ $[M + H]^+$: 458.25098; Found: 458.25218.



350 **352**

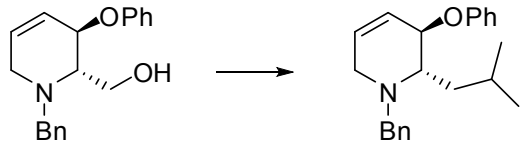
(2S,3R)-1-benzyl-2-((tert-butyldiphenylsilyloxy)methyl)-3-phenoxy-1,2,3,6-tetrahydropyridine (352)

A flask containing Sodium phenoxide (290.0 mg, 1.70 mmol) in THF (5 mL) and a stir bar under positive pressure of Argon was chilled with a cryostat bath to -15°C and 15-Crown-5 (280 μL, 1.41 mmol) was added to solubolize the compound. A sealed (septum) flask containing **350** (260 mg, 0.568 mmol), proton sponge (147.4 mg, 0.688 mmol) and a stir bar was purged with Argon, and then anhydrous DCM (12 mL) was added via syringe. The reaction vessel was chilled with a cryostat bath to -15°C white under positive pressure of Argon. Triflic anhydride (105 μL, 0.624 mmol) was added to the stirred, clear colourless solution – within 1 minute the solution changed to an orange suspension. 5 minutes after the Tf_2O addition the sodium phenoxide solution was added by cannula causing the mixture to become a yellow solution. The mixture was stirred cold for 1 hour, then allowed to warm to rt during which time the colour did not change. Purified by flash chromatography (5% diethyl ether/hexane) to obtain **352** as a yellow oil (264 mg, 87%). *Rf* = 0.11 (5% diethyl ether/hexane). $[\alpha]^{20}_D$ = -7.3 (c = 0.500 $CHCl_3$). IR (film)/cm^{-1} 3028, 2929, 2856, 1596, 1586, 1492, 1471, 1427, 1390, 1361, 1290, 1229, 1105, 1028, 1005, 822, 752, 736, 698. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66 (d, *J* = 7.1Hz, 2H), 7.62 (d, *J* = 7.2 Hz, 2H), 7.19-7.45 (m, 13H), 7.07 (d, *J* = 8.2 Hz, 2H), 6.94 (t, *J* = 7.3, 1H), 5.93-6.01 (m, 2H), 5.02 (s, 1H), 3.99 (dd, *J* = 10.3, 4.3 Hz, 1H), 3.88 (d, *J* = 13.7 Hz, 1H), 3.29 (dd, *J* = 10.2, 8.0 Hz, 1H), 3.72 (d, *J* = 13.7 Hz, 1H), 3.31-3.36 (m, 1H), 3.12 (d, *J* = 10.9 Hz, 1H), 3.02 (d, *J* = 10.9 Hz, 1H), 1.08 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.7,136.5, 136.4, 131.7, 130.6, 130.6, 130.3, 129.4, 129.0, 128.6, 128.6, 127.7, 123.4, 121.4, 116.7, 70.9, 61.6, 60.6, 59.3, 27.7, 20.0. HRMS Calcd for $C_{35}H_{40}NO_2Si$ $[M + H]^+$: 534.28228; Found: 534.28461.

352 **353**

((2S,3R)-1-benzyl-3-phenoxy-1,2,3,6-tetrahydropyridin-2-yl)methanol (353)

To a stirred solution of **352** (145 mg, 0.272 mmol) in anhydrous THF (2 mL) was added TBAF (1.0 M, 0.30 mL, 0.30 mmol), monitoring the reaction by TLC (10% acetone/DCM). After 30 minutes the solution was diluted with ethyl acetate (20 mL), washed with Sat. $NaHCO_3$ (3x20 mL), brine (20 mL) and dried (Na_2SO_4). Purification by flash chromatography (0-10% acetone/DCM) to obtain **353** as a white solid (74 mg, 92%). *Rf* = 0.29 (10% acetone/DCM). mp = 67 °C. $[\alpha]^{20}_D$ = -32 (c = 2.5 $CHCl_3$). IR (film)/cm^{-1} 3412, 3030, 2927, 1596, 1493, 1454, 1401, 1290, 1232, 1172, 1076, 1028, 1002, 910, 753, 736, 694. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25-7.36 (m, 7H), 6.94-7.00 (m, 3H), 6.05 (d, *J* = 10.1 Hz, 1H), 5.95 (d, *J* = 10.3 Hz, 1H), 4.58 (s, 1H), 3.98 (q, *J* = 10.2 Hz, 2H), 3.80 (dd, *J* = 10.8, 5.6 Hz, 1H), 3.70 (dd, *J* = 10.8, 8.4 Hz, 1H), 3.25-3.32 (m, 2H), 3.12 (d, *J* = 18.4 Hz, 1H), 2.11 (bs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.4, 139.9, 130.5, 130.1, 129.6, 129.2, 128.1, 124.3, 122.0, 116.4, 69.6, 62.3, 59.9, 58.6, 46.9. HRMS Calcd for $C_{19}H_{22}NO_2$ $[M + H]^+$: 296.16451; Found: 296.16454.



353 **355**

(2S,3R)-1-benzyl-2-isobutyl-3-phenoxy-1,2,3,6-tetrahydropyridine (355)

The cuprate solution was prepared as follows: a suspension of CuCN (15.3 mg, 0.171 mmol) in anhydrous THF (3 mL) chilled with a dry ice/acetone bath was added an isopropyl-magnesium chloride solution in THF (1.40M, 125 µL, 0.175 mmol). The suspension was allowed to warm to rt, becoming an opaque black suspension, then chilled with a cryostat bath (-15 °C). To a solution containing **353** (20 mg, 0.068 mmol) and proton sponge (20.4 mg, 0.0952 mmol) dissolved in anhydrous DCM (5 mL) under positive

pressure of Argon was chilled with a cryostat bath (-15 °C). To this solution was added triflic anhydride (14 μL, 0.083 mmol) via syringe causing the yellow solution to become orange. 5 minutes after the triflic anhydride addition the solution containing the aziridinium was cannulated to the cuprate solution. The mixture was stirred for 15 minutes, then allowed to warm to ambient temperature. Purification by flash chromatography (10% ethyl acetate/hexane) to yield **355** as a light yellow film (18 mg, 82%). *Rf* = 0.55 (10% ethyl acetate/hexane). IR (film)/cm^{-1} 2922, 2851, 1711, 1597, 1493, 1456, 1260, 1236, 1076, 1027, 911, 798, 734. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39 (d, *J* = 7.2 Hz, 2H), 7.18-7.30 (m, 5H), 6.92-6.96 (m, 3H), 6.00 (bs, 2H), 4.48 (s, 1H), 3.86 (d, *J* = 13.7 Hz, 1H), 3.79 (d, *J* = 13.7 Hz, 1H), 3.08-3.23 (m, 2H), 1.71-1.82 (m, 1H), 1.47-1.56 (m, 1H), 0.93 (d, *J* = 6.5 Hz, 3H), 0.86 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.8, 140.5, 131.8, 130.3, 129.5, 129.0, 127.6, 123.7, 121.6, 116.8, 73.6, 57.9, 57.9, 47.7, 35.9, 30.6, 26.1, 23.7. HRMS Calcd for $C_{22}H_{28}NO$ $[M + H]^+$: 322.21654; Found: 322.21687.

Appendix I References

[1] For reviews see (a) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701. (b) Escolano, C.; Amat, M.; Bosch, J. *Chem.; Eur. J.,* **2006**, 12, 8198. (c) Cossy, J. *Chem. Rec*. **2005**, *5*, 70.

[2] Charette, A. B.; Grenon, M.; Lemire, A.; Pourashraf, M.; Martel, J. *J. Am. Chem. Soc.* **2001**, *123*, 11829.

[3] Bois, F.; Gardette, D.; Gramain, J.-C. *Tetrahedron Lett.* **2000**, *41*, 8769.

[4] Kandula, S. V.; Kumar, P. *Tetrahedron Lett.* **2003**, *44*, 1957.

[5] Felpin, F.-X.; Lebreton, J. *J. Org. Chem.* **2002**, *67*, 9192.

[6] Vonnie D. C.; Shields . Erin J.; Rodgers N. S.; Arnold D. W. *Naturwissenschaften*, **2006**, 93, 3, 127-130.

[7] (a) Fodor, G. B.; Colasanti, B. *In Alkaloids*: *Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, **1985**; 3, 1-90. (b) Strunz, G. M.; Findlay, J. A. *In The Alkaloids*; Brossi, A., Ed.; Academic Press: London, **1985**; 26, 89-183.
(c) Schneider, M. J. In *Alkaloids*: *Chemical and Biological Perspectiv*es; Pelletier, S. W., Ed.; Pergamon: Oxford, UK, **1996**; 10, 155-299.

[8] Kubizna, P.; Spánik, I.; Kozísek, J.; Szolcsányi, P. *Tetrahedron* **2010**, *66*, 2351.

[9] Daly, J. W.; Spande, T. F.; Garraffo, H. M. *J. Nat. Prod.* **2005**, *68*, 1556.

[10] http://www.drugs.com/top200_units.html

[11] (a) Linton, Harriet B.; Langs, Robert J., *Arch. Gen. Psychiat.*, **1962**, 6, 352–68. (b) Weale, N.K.; Rogers, C. A.; Cooper, R.; Nolan, J.; Wolf, A. R., *Br J Anaesth,* **2004**, 92, 2, 187–94. (c) Katzman, M. A., *CNS Drugs*, **2009**, 23, 2, 103–20.

[12] (a) Beng, T. K.; Gawley, R. E. *J. Am. Chem. Soc.* **2010**, *132*, 12216. (b) Lovick, H. M.; Michael, F. E. *J. Am. Chem. Soc.* **2010**, *132*, 1249. (c) Lemonnier, G. R.; Charette, A. B. *J. Org. Chem.* **2010**, *75*, 7465. (d) Wurz, R. P.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 12234. (e) Barbe, G.; St-Onge, M.; Charette, A. B. *Org. Lett.* **2008**, *10*, 5497. (f) Legault, C. Y.; Charette, A. B. *J. Am. Chem. Soc.* **2005**, *127*, 8966. (g) Pattenden, L. C.; Wybrow, R. A. J.; Smith, S. A.; Harrity, J. P. A. *Org. Lett.* **2006**, *8*, 3089. (h) Kobayashi, T.; Hasegawa, F.; Tanaka, K.; Katsumura, S. *Org. Lett.* **2006**, *8*, 3813. (i) Goodenough, K. M.; Moran, W. J.; Raubo, P.; Harrity, J. P. A. *J. Org. Chem.* **2005**, *70*, 207. (j) Poupon, E.; Francois, D.; Kunesch, N.; Husson, H. P. *J. Org. Chem.* **2004**, *69*, 3836. (k) Goodenough, K. M.; Moran, W. J.; Raubo, P.; Harrity, J. P. A. *J. Org. Chem.* **2004**, *70*, 207. For reviews see: (l) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701. (m) Escolano, C.; Amat, M.; Bosch, J. *Chem.; Eur. J.,* **2006**, 12, 8198. (n) Cossy, J. *Chem. Rec*. **2005**, *5*, 70.

[13] (a) Munchhof, M. J.; Meyers, A. I. *J. Am. Chem. Soc.* **1995**, *117*, 5399. (b) Amat, M.; Lozano, O.; Escolano, C.; Molins, E.; Bosch, J. *J. Org. Chem.* **2007**, *72*, 4431. (c) Amat, M.; Llor, N.; Hidalgo, J.; Escolano, C.; Bosch, J. *J. Org. Chem.* **2003**, *68*, 1919. (d) Amat, M.; Brunaccini, E.; Checa, B. a.; Pérez, M.; Llor, N. R.; Bosch, J. *Org. Lett.* **2009**, *11*, 4370. (e) Nakamura, Y.; Burke, A. M.; Kotani, S.; Ziller, J. W.; Rychnovsky, S. D. *Org. Lett.* **2009**, *12*, 72. (f) Gnecco, D.; Lumbreras, A. M.; Teran, J. L.; Galindo, A.; Juarez, J. R.; Orea, M. L.; Castro, A.; Enriquez, R. G.; Reynolds, W. F. *Heterocycles* **2009**, *78*, 2589

[14] Verendel, J. J.; Zhou, T. G.; Li, J. Q.; Paptchikhine, A.; Lebedev, O.; Andersson, P. G. *J. Am. Chem. Soc.* **2010**, *132*, 8880.

[15] (a) Metro, T. X.; Pardo, D. G.; Cossy, J. *J. Org. Chem.* **2007**, *72*, 6556. (b) Cossy, J.; Dumas, C.; Pardo, D. G. *Eur. J. Org. Chem.* **1999**, 1693. (c) Cossy, J.; Mirguet, O.; Pardo,

D. G. *Synlett* **2001**, 1575. (d) Cossy, J.; Dumas, C.; Michel, P.; Pardo, D. G. *Tetrahedron Lett.* **1995**, *36*, 549.
[16] Salvadori, J.; Airiau, E.; Girard, N.; Mann, A.; Taddei, M. *Tetrahedron* **2010**, *66*, 3749.
[17] Amat, M.; Bassas, O.; Llor, N.; Canto, M.; Perez, M.; Molins, E.; Bosch, J. *Chem.; Eur. J.,* **2006**, *12*, 7872.
[18] Airiau, E.; Girard, N.; Mann, A.; Salvadori, J.; Taddei, M. *Org. Lett.* **2009**, *11*, 5314.
[19] Amat, M.; Lozano, O.; Escolano, C.; Molins, E.; Bosch, J. *J. Org. Chem,* **2007**, *72*, 4431.
[20] Renner, H.; Schlamp, G.; Kleinwächter, I.; Drost, E.; Lüschow, H. M.; Tews, P.; Panster, P.; Diehl, M.; Lang, J.; Kreuzer, T.; Knödler, A.; Starz, K. A.; Dermann, K.; Rothaut, J.; Drieselman, R. **2002**. "Platinum group metals and compounds". *Ullmann's Encyclopedia of Industrial Chemistry*. Wiley.
[21] Déchamps, I.; Gomez Pardo, D.; Cossy, J. *Eur. J. Org. Chem.* **2007**, *2007*, 4224.
[22] (a) Sweeney, J. B. *Chem. Soc. Rev.,* **2002**, 31, 247–258. (b) Hu, X. E. *Tetrahedron*, **2004**, 60, 2701–2743. (c) Singh, G. S.; D'Hooghe, M.; De Kimpe, N. *Chem. Rev*., **2007**, 107, 2080–2135.
[23] Metro, T. X.; Duthion, B.; Pardo, D. G.; Cossy, J. *Chem. Soc. Rev.* **2010**, *39*, 89.
[24] Madin, A.; O'Donnell, C. J.; Oh, T.; Old, D. W.; Overman, L. E.; Sharp, M. J. *J. Am. Chem. Soc.* **2005**, *127*, 18054.
[25] Andrews, D. R.; Dahanukar, V. H.; Eckert, J. M.; Gala, D.; Lucas, B. S.; Schumacher, D. P.; Zavialov, I. A. *Tetrahedron Lett.* **2002**, *43*, 6121.
[26] Graham, M. A.; Wadsworth, A. H.; Thornton-Pett, M.; Rayner, C. M. *Chem. Commun.* **2001**, 966.
[27] D'Hooghe, M.; Catak, S.; Stanković, S.; Waroquier, M.; Kim, Y.; Ha, H. J.; Van Speybroeck, V.; De Kimpe, N. *Eur. J. Org. Chem.* **2010**, *2010*, 4920.
[28] Chong, H. S.; Song, H. A.; Dadwal, M.; Sun, X.; Sin, I.; Chen, Y. W. *J. Org. Chem.* **2010**, *75*, 219.
[29] Kim, Y.; Ha, H. J.; Yun, S. Y.; Lee, W. K. *Chem. Commun.* **2008**, 4363.
[30] Durrat, F.; Sanchez, M. V.; Couty, F.; Evano, G.; Marrot, J. *Eur. J. Org. Chem.* **2008**, 3286.
[31] Davies, S. G.; Nicholson, R. L.; Price, P. D.; Roberts, P. M.; Russell, A. J.; Savory, E. D.; Smith, A. D.; Thomson, J. E. *Tetrahedron: Asymmetry* **2009**, *20*, 758.
[32] McKay, C.; Wilson, R. J.; Rayner, C. M. *Chem. Commun.* **2004**, 1080.
[33] Piotrowska, D. G.; Wróblewski, A. E. *Tetrahedron* **2009**, *65*, 4310.
[34] Steiger, A.; Pyun, H. J.; Coates, R. M. *J. Org. Chem.* **1992**, *57*, 3444.
[35] (a) Guan, H.; Saddoughi, S. A.; Shaw, A. P.; Norton, J. R. *Organometallics* **2005**, *24*, 6358. (b) Crist, D. R.; Leonard, N. J. *Angew. Chem., Int. Edit.* **1969**, *8*, 962.
[36] (a) Leonard, N. J.; Jann, K. *J. Am. Chem. Soc.* **1960**, *82*, 6418. (b) Leonard, N. J.; Jann, K. *J. Am. Chem. Soc.* **1962**, *84*, 4806.
[37] (a) Poelert, Martin A.; Hof, Robert P.; Peper, Nathalie C. M. W.; Kellogg, Richard M. *Heterocycles*, **1994** , 37, 1 461 – 476. (b) Huard, K.; Lebel, H. *Chem. Eur. J.* **2008**, *14*, 6222-6230.
[38] Song, H. A.; Dadwal, M.; Lee, Y.; Mick, E.; Chong, H. S. *Angew. Chem., Int. Edit.* **2009**, *48*, 1328.
[39] (a) Carter, C.; Fletcher, S.; Nelson, A. *Tetrahedron: Asymmetry*, **2003** , 14, 14 1995 - 2004 (b) Davies, S. G.; Nicholson, R. L.; Price, P. D.; Roberts, P. M.; Russell, A. J.;

Savory, E. D.; Smith, A. D.; Thomson, J. E. *Tetrahedron: Asymmetry*, **2009** , 20, 6-8 758 – 772
(d) Verhelst, S. H. L.; Martinez, B. P.; Timmer, M. S. M.; Lodder, G.; Marel, G. A.; Overkleeft, H. S.; Boom, J. H. *J. Org. Chem.* **2003**, 68, 25, 9598
[40] Liu, Q.; P. Marchington, A.; Boden, N.; M. Rayner, C. *J. Chem. Soc., Perkin Trans. 1* **1997**, 511.
[41] Katagiri, T.; Takahashi, M.; Fujiwara, Y.; Ihara, H.; Uneyama, K. *J. Org. Chem.* **1999**, *64*, 7323.
[42] (a) Guan, H.; Saddoughi, S. A.; Shaw, A. P.; Norton, J. R. *Organometallics* **2005**, *24*, 6358. (b) Yun, S. Y.; Catak, S.; Lee, W. K.; Dahooghe, M.; De Kimpe, N.; Van Speybroeck, V.; Waroquier, M.; Kim, Y.; Ha, H.-J. *Chem. Commun.* **2009**, 2508.
[43] Harigaya, Y.; Yotsumoto, K.; Takamatsu, S.; Yamaguchi, H.; Onda, M. *Chem. & Pharm. Bull.* **1981** , 29, 9 2557 - 2564
[44] (a) Gmeiner, P.; Junge, D.; Kaertner, A. *J. Org. Chem.* **1994**, *59*, 6766. (b) Madin, A.; O'Donnell, C. J.; Oh, T.; Old, D. W.; Overman, L. E.; Sharp, M. J. *J. Am. Chem. Soc.* **2005**, *127*, 18054.
[45] Von Rücker, G.; Neugebauer, M.; Zhong, D. *Arch. Pharm.* **1992**, *325*, 47.
[46] Couturier, C.; Blanchet, A.; Schlama, T.; Zhu, J. P. *Org. Lett.* **2006**, *8*, 2183.
[47] Lehmann, T.; Hübner, H.; Gmeiner, P. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2863.
[48] Thorberg, S.-O.; Gawell, L.; Csöregh, I.; Nilsson, J. L. G. *Tetrahedron* **1985**, *41*, 129.
[49] Yang, X.; Yudin, A. K. *Synlett* **2007**, *2007*, 2912.
[50] Chuang, T. H.; Sharpless, K. B. *Org. Lett.* **2000**, *2*, 3555.
[51] Bassindale, A. R.; Kyle, P. A.; Soobramanien, M. C.; Taylor, P. G. *J. Chem. Soc., Perkin Trans. 1: Org. and Bio-Org. Chem*. **2000**, 3, 439.
[52] Crist, D. R.; Leonard, N. J. *Angew. Chem., Int. Edit.***1969**, *8*, 962.
[53] Piotrowska, D. G.; Wróblewski, A. E. *Tetrahedron* **2003**, *59*, 8405.
[54] Dakanali, M.; Tsikalas, G. K.; Krautscheid, H.; Katerinopoulos, H. E. *Tetrahedron Lett.* **2008**, *49*, 1648.
[55] Dieter, R. K.; Deo, N.; Lagu, B.; Dieter, J. W. *J. Org. Chem.* **1992**, *57*, 1663.
[56] Catak, S.; D'hooghe, M.; Verstraelen, T.; Hemelsoet, K.; Van Nieuwenhove, A.; Ha, H.-J.; Waroquier, M.; De Kimpe, N.; Van Speybroeck, V. *J. Org. Chem.* **2010**, *75*, 4530.
[57] Dahlenburg, L.; Götz, R. *Eur. J. Inorg. Chem.* **2004**, *2004*, 888.
[58] For selected examples see: (a) Equey, O.; Vrancken, E.; Alexakis, A., *Eur. J. Org. Chem*. **2004**, 10, 2151-2159. (b) Fagnou, K.; Lautens, M., *Org. Lett*. **2000**, 2, 2319-2321.
[59] (a) US Patent Application No. 6,166,222 (issued Dec. 26th, 2000) (b) US Patent Application No. 4,111,951 (issued Sept. 5th, 1978) (c) US Patent Application No. 4,066,658 (issued Jan. 3rd, 1978)
[60] Donohoe, T. J.; Thomas, R. E. *Chem. Rec.* **2007**, *7*, 180. (b) Donohoe, T. J.; Freestone, G. C.; Headley, C. E.; Rigby, C. L.; Cousins, R. P. C.; Bhalay, G. *Org. Lett.* **2004**, *6*, 3055.
[61] (a) Dormoy, J. R. *Synthesis* **1982**, 753 (b) Arakawa, Y.; Ohnishi, M.; Yoshimura, N.; Yoshifuji, S. *Chem. & Pharm. Bull.* **2003**, *51*, 1015.
[62] Murruzzu, C.; Riera, A. *Tetrahedron-Asymmetry* **2007**, *18*, 149.
[63] Ritthiwigrom, T.; Pyne, S. G. *Org. Lett.* **2008**, *10*, 2769.
[64] Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1998**, *120*, 11798.
[65] Kumagai, N.; Muncipinto, G.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 3635.

[66] Candeias, N. R.; Montalbano, F.; Cal, P. M. S. D.; Gois, P. M. P. *Chem. Rev.* **2010**, *110*, 6169.
[67] This is a known compound, see Heindl, C.; Hübner, H.; Gmeiner, P. *Tetrahedron: Asymmetry* **2003**, *14*, 3153.
[68] Elson, K. E.; Jenkins, I. D.; Loughlin, W. A. *Org. & Biomol. Chem.* **2003**, 1, 2958.
[69] Meudt, A.; Scherer, S.; Böhm, C. WO 2005123632, **2005**; *Chem. Abstr.* **2005**, *144*, 69544.
[70] Matsui, T.; Kondo, T.; Nakatani, S.; Omawari, N.; Sakai, M.; Mori, H.; Ogata, A.; Kato, J.; Ohno, H.; Obata, T.; Nakai, H.; Toda, M. *Bioorg. & Med. Chem.* **2003** , 11, 18, 3937 - 3944
[71] Crimmins, M. T.; Jacobs, D. L. *Org. Lett.* **2009**, *11*, 2695.
[72] Fu, G. C.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 9856.
[73] Palomo, C.; Aizpurua, J. M.; Urchegui, R.; Garcia, J. M. *J. Org. Chem*. **1993**, 58, 7 1646 - 1648
[74] (a) Izumiya, N.; Nagamtsu, A. *Bull. Chem. Soc. Jpn*. **1952**, *52*, 265. (b) Souers, A. J.; Schu¨rer, S.; Kwack, H.; Virgilio, A. A.; Ellman, J. A. *Synthesis* **1999**, *4*, 583. (c) Shin, I.; Lee, M.; Lee, J.; Jung, M.; Lee, W.; Yoon, J. *J. Org. Chem*., **2000**, *65*, 7667.
[75] (a) Hubschwerlen, C.; Specklin, J. L.; Higelin, J. In *Organic Syntheses, Vol 72*; John Wiley & Sons Inc: New York, **1995**; Vol. 72, p 1. (b) Schmid, C. R.; Bryant, J. D. In *Organic Syntheses, Vol 72*; John Wiley & Sons Inc: New York, **1995**; Vol. 72, p 6.
[76] Shekhar, S.; Trantow, B.; Leitner, A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 11770.
[77] Ichikawa, Y.; Ito, T.; Isobe, M. *Chem.; Eur. J.,* **2005**, *11*, 1949.
[78] Xin, Z.-q.; Fischer, D. F.; Peters, R. *Synlett* **2008**, *2008*, 1495.
[79] (a) Albeck, A.; Persky, R. *J. Org. Chem.* **1994**, *59*, 653. (b) Concellón, J. M.; Baragaña, B.; Riego, E. *Tetrahedron Lett.* **2000**, *41*, 4361.
[80] (a) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456. (b) Kaljurand, I.; Kütt, A.; Sooväli, L.; Rodima, T.; Mäemets, V.; Leito, I.; Koppel, I. A. *J. Org. Chem.* **2005**, *70*, 1019. (c) Rodima, T.; Kaljurand, I.; Pihl, A.; Mäemets, V.; Leito, I.; Koppel, I. A. *J. Org. Chem.,* **2002**, *67*, 1873.
[81] Lide, D. R., *CRC Handbook of Chemistry and Physics*, 87th edition, CRC Press, Boca Raton, Fl, **2006**.
[82] Joule, J. A.; Mills, K., *Heterocyclic Chemistry*, 4th Edition, p331, Oxford, UK, Blackwell Science, **2001**.
[83] Crist, D. R.; Leonard, N. J. *Angew. Chem., Int. Edit.,* **1969**, *8*, 962.
[84] Friebolin, H., *Basic One- and Two-Dimensional NMR Spectroscopy*, 3rd Revised Edition, p90, Weinhem, Wiley-VCH, **1998**.
[85] For the study of copper-allyl complexes see (a) Nakamura, E.; Mori, S. *Angew. Chem. Int. Ed. Eng*. **2000**, 39, 3750-3771. (b) Yoshikai, N.; Zhang, S. L.; Nakamura, B. *J. Am. Chem. Soc.* **2008**, *130*, 12862 and references therein.
[86] Amat, M.; Cantó, M.; Llor, N.; Escolano, C.; Molins, E.; Espinosa, E.; Bosch, J. *J. Org. Chem.* **2002**, *67*, 5343.
[87] Pedrosa, R.; Andrés, C.; Duque-Soladana, J. P.; Rosón, C. D. *Tetrahedron: Asymmetry* **2000**, *11*, 2809.
[88] Trost, B. M.; Lemoine, R. C. *Tetrahedron Lett.* **1996**, *37*, 9161.
[89] Bagal, S. K.; Davies, S. G.; Lee, J. A.; Roberts, P. M.; Russell, A. J.; Scott, P. M.; Thomson, J. E. *Org. Lett.* **2010**, *12*, 136.

[90] For selected examples see (a) Guilloteau-Bertin, B.; Compère, D.; Gil, L.; Marazano, C.; Das, Bhupesh C. *Eur. J. Org. Chem.* **2000**, *2000*, 1391. (b) Gijsen, H. J. M.; De Cleyn, M. J. A.; Love, C. J.; Surkyn, M.; Van Brandt, S. F. A.; Verdonck, M. G. C.; Moens, L.; Cuypers, J.; Bosmans, J. P. R. M. A. *Tetrahedron* **2008**, *64*, 2456. (c) Tokuda, O.; Aikawa, T.; Ikemoto, T.; Kurimoto, I. *Tetrahedron Lett.* **2010**, *51*, 2832.

[91] For examples of azasugars see : Pearson, M. S. M.; Mathé-Allainmat, M.; Fargeas, V.; Lebreton, J. *Eur. J. Org. Chem.* **2005**, *2005*, 2159.

[92] http://www.drugs.com/top200_units.html

[93] (a) Giles, M.; Hadley, M. S.; Gallagher, T. *J. Chem. Soc., Chem. Commun.* **1990**, 1047. (b) Garst, M. E.; Bonfiglio, J. N.; Grudoski, D. A.; Marks, J. *J. Org. Chem.* **1980**, *45*, 2307.

[94] (a) Niida, A.; Mizumoto, M.; Narumi, T.; Inokuchi, E.; Oishi, S.; Ohno, H.; Otaka, A.; Kitaura, K.; Fujii, N. *J. Org. Chem.* **2006**, *71*, 4118. (b) Sançon, J.; Sweeney, J. B. *Synlett* **2010**, *2010*, 664.

[95] Evans, D. A.; Campos, K. R.; Tedrow, J. S.; Michael, F. E.; Gagné, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 7905.

[96] Uozumi, Y.; Suzuka, T. *J. Org. Chem.* **2006**, *71*, 8644.

[97] Shriver, D.F.; Drezdzon, M.A. *The manipulation of air-sensitive compounds*; 2nd Edition; Wiley: New York, **1986**.

[98] Zhao, W. J.; Yan, M.; Huang, D.; Ji, S. J., *Tetrahedron*, **2005**, 5585.