NEW ORGANOCATALYZED TRANSFORMATIONS OF AZIRIDINES.

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NEW ORGANOCATALYZED TRANSFORMATIONS OF AZIRIDINES

DOCTORAL THESIS

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Departament de Química Analítica i Química Orgànica

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Els sotasignants Sergio Castillón Miranda, Catedràtic de Química Orgànica del Departament de Química Analítica i Química Orgànica de la Universitat Rovira i Virgili, i Piet W. N. M. van Leeuwen, responsable de grup en l' Institut Català d'Investigació Química (ICIQ).

FEM CONSTAR que aquesta memòria, titulada "*New Organocatalyzed Transformations of Aziridines"*, que presenta Miriam Díaz de los Bernardos Sánchez al grau de Doctor en Química per la Universitat Rovira i Virgili, ha estat realitzada sota la nostra direcció al Departament de Química Analítica i Química Orgànica d'aquesta universitat, així com en d'altres laboratoris universitaris en el marc d'una sèrie de col·laboracions científiques i que, a més, compleix els requeriments per poder optar a la Menció Europea.

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Dr. Piet W. N. M. van Leeuwen

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Miriam.

Dedicada a

Mis padres y
a la memoria de mi abuelo Esteban

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ABREVIATIONS AND ACRONYMS

A

Abs	absorbance
Ac	acetyl
acac	acetylacetonate
aq	aqueous

B

Bn	benzyl
Boc	*tert*-butyl carbonate
bs	broad singlet
Bz	benzoyl

C

Calcd	calculated
Conv.	conversion

D

d	doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N*'-dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DCM	dichloromethane
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethyl sulfoxide

E

El	electrophile
ESI	electrospray ionization
Et	ethyl

F

FCC	flash column chromatography
FT	Fourier transform

G

g	gram(s)
gCOSY	gradient correlation spectroscopy
gHMBC	gradient heteronuclear multiple bond correlation
gHSQC	gradient heteronuclear single quantum coherence

H

h	hour(s)
HPLC	high performance liquid chromatography
Hz	hertz(s)

I

imid	imidazole
^{i}Pr	isopropyl
IR	infrared
I^{t}Bu	1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene

J

J	coupling constant

K

K_{app}	apparent dissociation constant
K_{cat}	constant of proportionality
K_{i}	inhibition constant
K_{m}	Michaelis constant

L

L	litre(s)
LA	Lewis acid
LC/MSD	liquid chromatography/mass spectrometry detector

M

m	meter(s)
m (in NMR)	multiplet
M	molar
m/z	mass under charge
MALDI-TOF	matrix-assisted laser desorption/ionisation time-of-flight
Me	methyl
min	minute(s)

Mp	melting point
MS	mass spectrometry
	N
n	number of repeat units
NHC	*N*-heterocyclic carbene
NIS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect spectroscopy
Nu	nucleophile
	P
P	product
PG	protecting group
Ph	phenyl
ppm	parts per million
	Q
q	quadruplet
	R
Rf	retention factor
ROP	ring-opening polymerization
	S
s	singlet
S	substrate
sat.	saturated
Select.	selectivity
	T
t	time
t (in NMR)	triplet
TBDMS	*tert*-butyldimethylsilyl
Tf	trifluoromethane sulfonyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TOF	time of flight

U

UV	ultra-violet

V

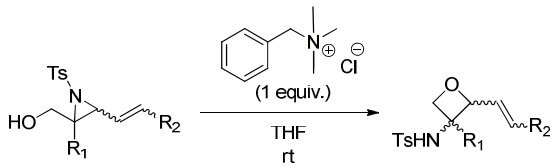
v	reaction rate

SUMMARY

Aziridines are among the most versatile intermediates in organic synthesis. A number of biologically significant molecules contain these strained three-membered rings within their structures. Consequently, there is currently a growing interest of the synthetic community in selective transformations of aziridines.

This thesis aims at the development of new synthetic strategies for efficient aziridine transformations using selective catalysis based on small organic molecules. Thus, new organocatalytic procedures in aziridine ring-opening chemistry, focusing on the development of efficient synthetic applications of these versatile intermediates were envisioned.

Our desire to develop methods that in a simple and easy manner transform starting materials into more complex products, led us to think about the formation of oxetanes from vinyl aziridinols. Oxetanes have received considerable interest in the synthetic community as well as in various fields of chemical industry because they are important heterocycles by virtue of their frequent appearance in a large number of biologically active natural products and pharmaceuticals. After analyzing the current routes for the preparation of oxetanes, an alternative synthetic application of aziridines for the synthesis of oxetanes was also visualized. Thus, the goal described in Chapter 3 was to synthesize vinyl oxetanes from vinyl aziridinols via an alternative aza-Payne-type rearrangement using N-Heterocyclic carbenes. Our preliminary results inspired us to conduct mechanistic studies which resulted eventually in an alternative methodology for the synthesis of vinyl oxetanes. This new procedure is based on a *one-pot formation of vinyl aziridinols to vinyl oxetanes through a consecutive ring-opening/ring-closing reaction promoted by a simple chloride source* (Scheme 1).

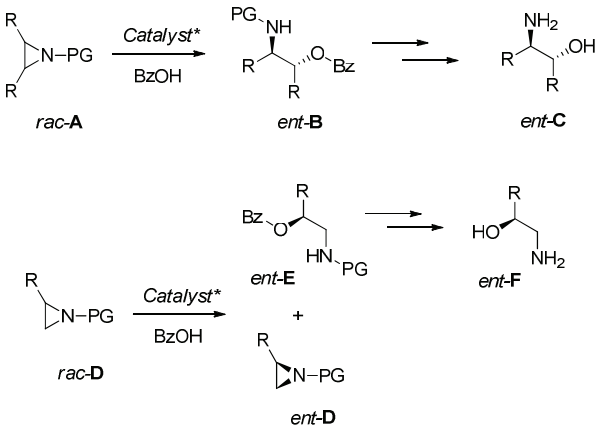


Scheme 1. Regio- and stereoselective synthesis of vinyl oxetanes using tetraalkylammonium halides

The reaction was found to evolve through a set of consecutive reactions in a *one-pot* procedure: a) nucleophilic selective aziridine ring cleavage promoted by a simple chloride source, b) proton transfer with concomitant formation of the alkoxide, and c) intramolecular nucleophilic substitution with concomitant ring closing to form the vinyl oxetane. Good yields for *cis*- and *trans*-aziridinols, trisubstituted vinyl aziridinols, and aryl aziridinols were obtained. The reaction is completely regioelective, since only the formation of vinyl oxetane out of all the possible competing ring-opening/ring closing reactions was observed, and stereoselective, since *cis*-vinyl aziridines led to the *cis*-disubstituted vinyl oxetane rings, and vinyl *trans*-aziridinols led to the *trans*-disubstituted vinyl oxetanes. This methodology was further demonstrated by its successful application to the synthesis of a wide range of vinyl oxetanes.

Several successful studies were reported for the stereoselective synthesis of β-amino alcohols using enantiopure starting materials or chiral auxiliaries. However, no attention has been paid to the organocatalytic asymmetric ring-opening of aziridines using oxygen-nucleophiles in spite of its potential in the synthesis of optically active β-amino alcohols with one or two stereogenic centers in a single step. Therefore, the goal described in Chapter 4 was to develop an organocatalytic approach for the *asymmetric*

desymmetrization of meso-aziridines and the kinetic resolution of terminal aziridines using oxygen-nucleophiles (Scheme 2).

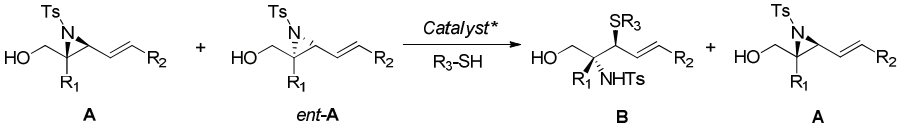


Scheme 2. Desymmetrization of *meso*-aziridines and kinetic resolution of terminal aziridines using oxygen-nucleophiles.

This study was realized in the Max-Planck Institute für Kohlenforschung (Germany) under the supervision of Professor Benjamin List. Several chiral phosphoric acids were tested and (*S*)-TRIP-phosphoric acid was found to be an excellent catalyst due to its superior behaviour in terms of enantioselectivity. A range of *meso*-aziridines protected with *N*-benzoyl groups were applied in their asymmetric desymmetrization and excellent conversions (up to 98%) and enantioselectivities (87 to 99% *ee*) were obtained. The potential utility of (*S*)-TRIP phosphoric acid-catalyzed, asymmetric oxygen-nucleophile ring-opening protocol was further demonstrated by its successful application in the kinetic resolution of racemic terminal aziridines.

It is noteworthy that currently there are no existing catalytic methods for the synthesis of highly enantioenriched vinyl aziridinols (neither via metal catalysis nor organocatalysis). A strategy based on kinetic resolution of

racemic vinyl aziridinols could be particularly interesting. Thus, the research described in Chapter 5 aims to develop a new methodology for the *asymmetric BINOL-derived Brønsted phosphoric acid-catalyzed kinetic resolution of vinyl aziridinols* (Scheme 3).



Scheme 3. General concept for the kinetic resolution of vinyl aziridinols.

Preliminary results showed total conversions and high *ee*'s for all substrates, starting from racemic mixtures. These results non compatible with a kinetic resolution process, prompted us to investigate this process. A mechanistic study by isotopic labeling, allowed us to discard a double isomerization process and to conclude that in fact a kinetic resolution process took place, but that the unreacted aziridine was lost during the work-up. Further experiments in the optimization of this kinetic resolution process are currently under investigation in our laboratory.

CHAPTER 1

GENERAL INTRODUCTION

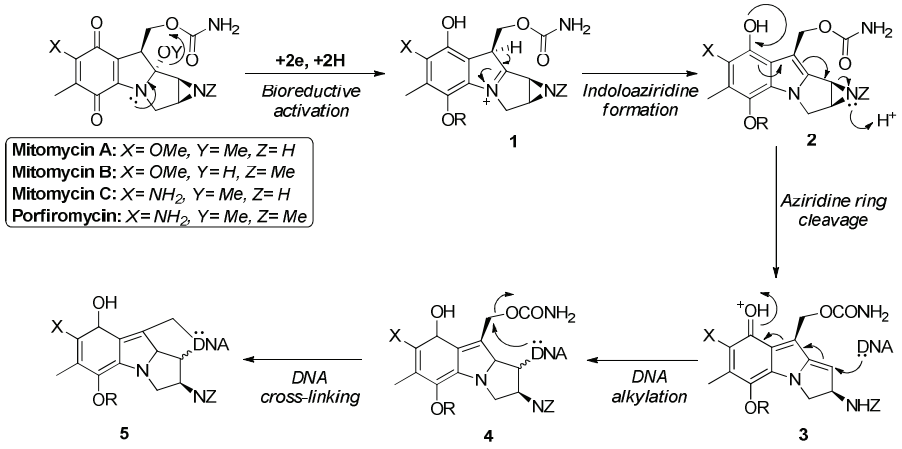
1.1. AZIRIDINES: IMPORTANT BUILDING BLOCKS IN ORGANIC SYNTHESIS

Aziridines, which are three-membered nitrogen containing heterocycles, have created considerable research interest due to their fundamental and practical importance as a class of versatile intermediates in the synthesis of different kinds of amino acids, natural products and biologically active compounds.[1]

Reports on aziridines have always represented an extensive part of the chemical literature. Interest in these heterocycles can be dated back to Gabriel's[2] studies in 1888. For their analogies with epoxides and cyclopropanes and their unique chemical and physical properties, aziridines are valuable compounds in terms of chemical, biological, and pharmacological activities. The high strain energy (27 kcal/mol) associated with their three-membered cyclic structure is at the origin of several characteristics of this class of compounds. Aziridines have attracted considerable attention as starting materials in numerous applications, and many papers and review articles dealing with the synthesis of aziridines[3] as well as their use in synthetic applications have been published since 1995.[4]

The biological activity of aziridines lies in their property as powerful alkylating agents. Aziridines have an inherent *in vivo* potency due to their ability to act as DNA cross-linking agents via nucleophilic ring opening, resulting in biological properties which make them useful as antibiotic and antitumor agents.[5] In these reactions, aziridines are alkylating agents, the toxicity of which is at the origin of their intrinsic *in vivo* potency.[6] If the aziridine ring is incorporated in a larger organic framework, high selectivity can be achieved, as is the case for several aziridine-containing natural products such as mitosanes A-C (Scheme 1.1). Mitosanes are a class of compounds isolated from soil extracts of the bacteria *Streptomyces verticillatus* that exhibit antitumor and antibiotic activity,

which is attributed to the presence of the aziridine ring in their structure. The antitumor activity of these natural products relies on DNA alkylation resulting from the aziridine ring-opening**.** The ring opening process is therefore the key feature.



Scheme 1.1. Mode of action of mitosanes.

These natural products represented one of the first classes of bioactive compounds relying on a bioreductive activation to provide a means for DNA alkylation. Thus, in the first step of the postulated mechanism of action, the natural products are converted from the native quinone form to the hydroquinone **1** (Scheme 1.1). Secondly, formation of indoloaziridine **2** occurs. The aziridine ring is next cleaved and DNA is first alkylated and then cross-linking occurs.

1.2. REACTIVITY OF AZIRIDINES

As previously mentioned, the rich chemistry of aziridines is mostly due to the strain present in their three membered ring, which enables ring

opening under relatively mild conditions. Furthermore, the electronegativity of the heteroatom polarizes the bonds of the ring. Intuitively, due to the diminished electronegativity of nitrogen compared to oxygen, ring-opening reactions of aziridines are less facile than the opening of the corresponding epoxides.

1.2.1. Chemical Bonding and Chemical Properties of Aziridines

The chemical bonding system of the aziridine ring resides in the category of bent bonds, similarly to that of cyclopropane (Figure 1.1). Thus, the atoms involved in the ring present a 60° angle between them, which contrasts with the standard sp^3-hybridization features. To reach such a geometry, the C atoms increase the p-character of the C–C bonds, which consequently shortens the C–H and N–H bonds as their molecular orbitals gain more σ character. The increased σ character of the nitrogen lone pair causes the weaker basicity of aziridines (pK_a = 7.98 for the aziridinium ion) compared to that of acyclic aliphatic amines (pK_a = 10.7 for dimethylammonium ion).[7]

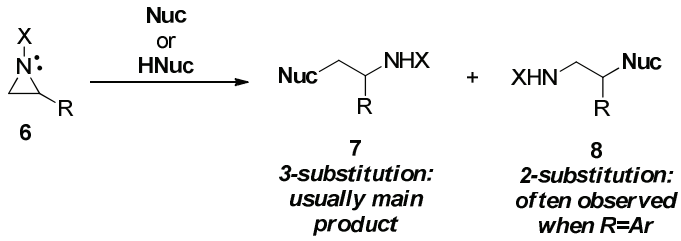
Figure 1.1. Chemical bonding system of *cyclopropane* made of bent bonds.

The chemical reactivity of an aziridine originates from the high strain energy associated with their three-membered cyclic nature. This property facilitates the cleavage of the C–N bonds of the ring under either acidic or basic conditions. Aziridines can undergo ring-opening reactions

with a range of nucleophiles or cycloaddition reactions with dipolarophiles, constituting precious building blocks towards the synthesis of a plethora of chemical compounds.

1.2.2. REGIOSELECTIVITY IN RING-OPENING PROCESSES

Analogously to epoxides, the ring cleavage of aziridines takes place via nucleophilic attack at carbon, under both acidic and basic conditions. When unsymmetrically substituted aziridines such as **6** are used, the two ring opening products **7** and **8** can be formed (Scheme 1.2).



Scheme 1.2. Nucleophilic ring opening of aziridines.

The regioselectivity of the attack obeys the classic rules for nucleophilic substitution reactions; the combination of steric and electronic factors will drive the nucleophile towards one carbon or the other, dictating the final distribution of products. Usually, independently of the nature of the R substituent, the 3-substituted product **7** is obtained (Scheme 1.2). Generally, high regioselectivity could be achieved, making aziridines important intermediates for stereoselective organic synthesis.[8] In ring-opening reactions it is common either to perform the reactions employing Lewis acid catalysts[9] or to employ aziridines with an activating group on the nitrogen atom,[10] thus, in both cases, increasing the ability of the nitrogen atom to function as a leaving group.

1.2.3. EFFECT OF *N*-SUBSTITUENTS ON THE RING OPENING OF AZIRIDINES

According to the nature of the substituent at nitrogen, aziridines can be divided in two main groups:[11] activated **9** and nonactivated aziridines **10** (Figure 1.2). Activated aziridines contain electron withdrawing substituents, which can stabilize, by conjugation, the negative charge formed at the nitrogen in the transition state of a nucleophilic ring opening reaction. The more common substituents are acyl, alkoxycarbonyl and sulphonyl groups. Nonactivated aziridines contain substituents such as H, alkyl or aryl groups at the nitrogen, and ring opening reactions usually occur under more drastic conditions, or in the presence of Brønsted or Lewis acids.

Figure 1.2. Activated and nonactivated aziridines.

Having a basic non-bonded electron pair, the aziridine nitrogen is susceptible to interaction with Lewis acids (**12**), similarly to the analogous epoxides (**11**) (Figure 1.3). Coordination to a Lewis acid enhances the rate of the ring-opening processes. Indeed, the Lewis acid-coordinated aziridine nitrogen would greatly suffer from the strain of the cycle. Nonetheless, Lewis-acid mediated ring-opening reactions of aziridines are not as common as those of epoxides. The reason behind this lies on the requirement for polar activating *N*-substituents to facilitate the ring-opening process of aziridines. In the majority of the cases, these *N*-substituents contain at least one oxygen atom, i.e. carbonyl, sulphonyl, phosphoryl groups, etc. The presence of this oxygen atom impedes the direct interaction

of the aziridine nitrogen with the Lewis acids **13**. As a matter of fact, the acid will coordinate preferentially to the oxygen of the *N*-substituent **14** rather than to the nitrogen itself **13** (Figure 1.3).

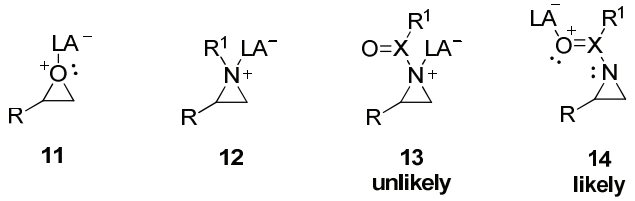
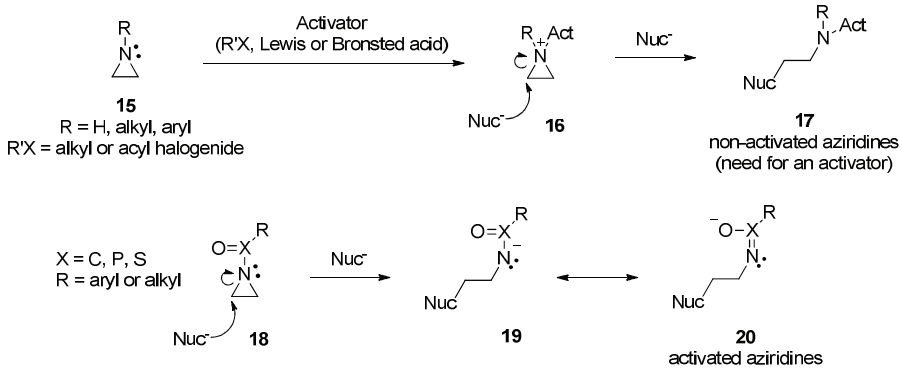


Figure 1.3. General features of Lewis acid coordination to epoxide and aziridines.

Typically, non-activated aziridines contain a basic nitrogen atom. *N*-aryl, *N*-alkyl and N-H aziridines **15** are considered as non-activated aziridines towards the ring opening reaction (Scheme 1.3). Ring-opening of non-activated aziridines usually occurs only after reaction with an activator such as protonation, quaternization or formation of a Lewis acid adduct. In contrast, activated aziridines contain *N*-substituents capable of conjugatively and/or inductively stabilizing the negative charge that develops on the aziridine nitrogen atom as a consequence of the nucleophilic attack (Scheme 1.3).



Scheme 1.3. Nucleophilic ring-opening of non-activated and activated aziridines.

Thus, the role of activating group is often neatly fulfilled by oxygenated substituents such as sulfonyl (**21**), sulfonyl (**22**), phosphonyl (**23**), phosphinyl (**24**) or carbonyl (**25**) functional groups (Figure 1.4).

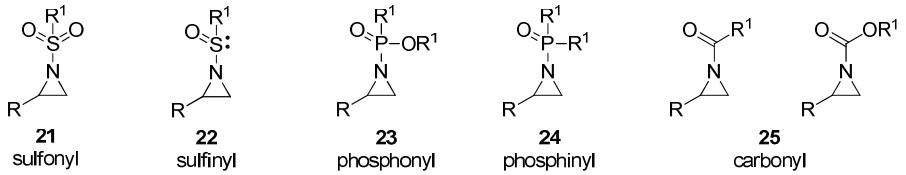
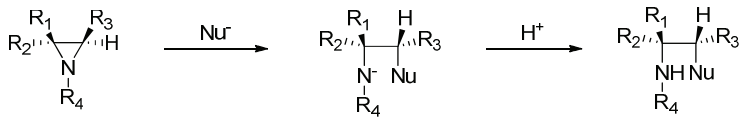


Figure 1.4. Activating *N*-functionalised groups for the ring-opening of aziridines.

The activation is primarily due to inductive effects, exerted by the electron-withdrawing groups that further polarize the C–N bonds of the ring. Resonance effects play a very limited role in the overall activation. The electron-withdrawing *N*-substituents also stabilize the anion produced by nucleophilic attack. The stabilization of sulfonamide, phosphonamide and phosphinamide is again primarily based on an inductive effect.

1.2.4. AZIRIDINE RING-OPENING REACTIONS

Ring opening of aziridines initiated by nucleophiles are in most cases stereoselective, with inversion of configuration at the reacting carbon (Scheme 1.4).

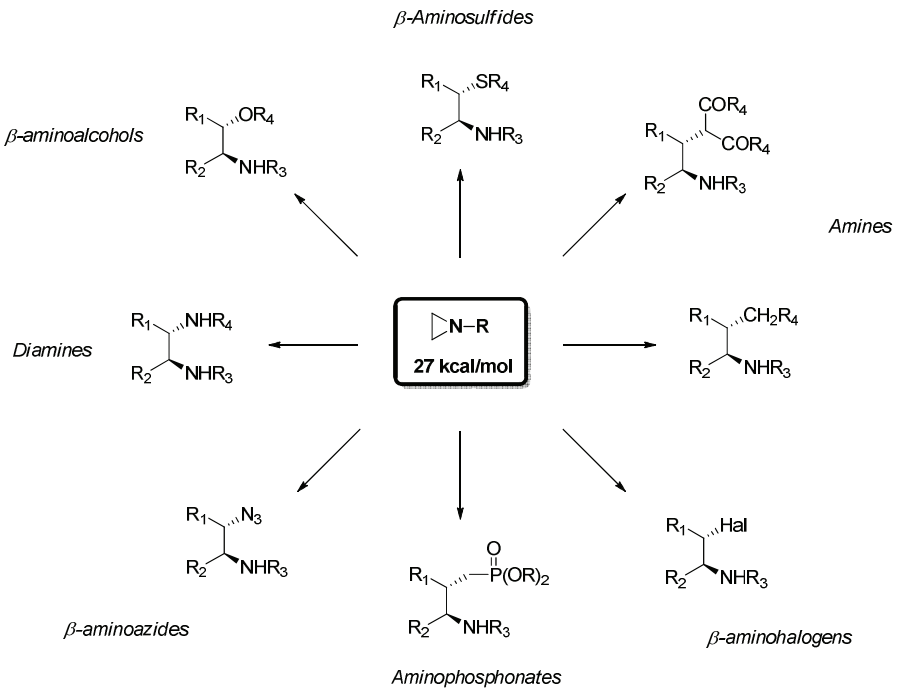


Scheme 1.4. Ring opening of aziridines initiated by nucleophiles.

The nucleophile usually attacks the less substituted carbon, but this regioselectivity can sometimes be modified by using the appropriate

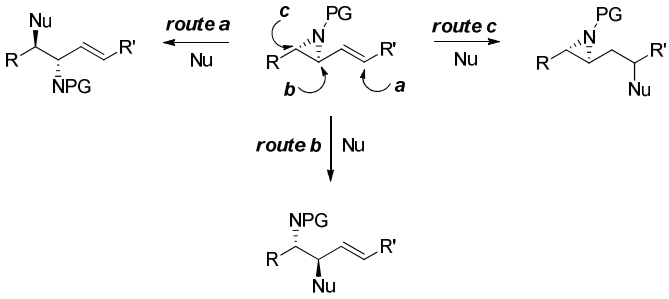
reaction conditions. Activated aziridines undergo direct nucleophilic ring opening under relatively mild conditions. Unactivated aziridines require very strong nucleophiles or very drastic reaction conditions.

Aziridines are well-known carbon electrophiles capable of undergoing reactions with various nucleophiles and several methods have been reported for the regioselective ring opening of aziridines with nucleophiles such as organometallic reagents,[12] silyl based nucleophiles,[13] Wittig reagents,[14] amines,[15] halides,[16] and alkenes.[17] Via these reactions, the ring opening of aziridines allows the construction of several compounds,[18] as outlined in Scheme 1.5. These ranges of compounds are versatile intermediates in the synthesis of different kinds of amino acids, heterocycles and alkaloids.



Scheme 1.5. Overview of ring-opening reactions of aziridines.

Among the distinct types of aziridines, vinyl aziridines strike for their peculiar reactivity. Due to their electrophilic nature, much of their chemistry revolves around the regio- and stereocontrol of the nucleophilic addition reactions. Nucleophilic addition can take place through an S_N2' mechanism (*route c*), which is usually favoured using soft nucleophiles, or through S_N2 attack (*route b*), usually favoured in the case of hard nucleophiles (Scheme 1.6). The vinyl moiety acts as a regiochemical-directing element since it activates the ring, so that attack at C-4 (*route a*) is normally not observed.



Scheme 1.6. Possible routes for the nucleophilic additions to vinyl aziridines.

In the following section, the current state of the art in ring opening of vinyl aziridines will be described.

1.2.5. Ring-Opening Reactions of Vinyl Aziridines

Vinylaziridines are versatile building blocks for the stereoselective synthesis of biologically and synthetically important compounds, thanks to their high reactivity and ability to act as carbon electrophiles. In particular, vinylaziridines can be regio- and stereoselectively opened by various types

of nucleophiles, making them very useful precursors for the synthesis of functionalized amines. Next, an introduction to the reactivity of vinyl aziridines in processes such as ring-opening reactions, isomerizations, cycloadditions and other important transformations of vinyl aziridines are described.

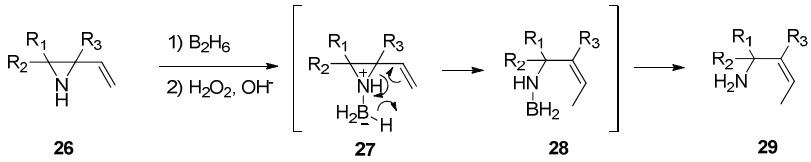
1.2.5.1. RING-OPENING REACTIONS WITH NUCLEOPHILES

Although very few reports on the ring opening of this type of aziridines are available in the literature, all the examples give a straightforward picture regarding their regioselective ring opening, which seems to be independent of the type of nucleophile and electrophile used in these reactions. The observed regioselectivity can be rationalized considering the allylic activation of these compounds (resonance stabilization of the developing carbenium ion at C2).

1.2.5.1.1. HYDRIDE REDUCTION

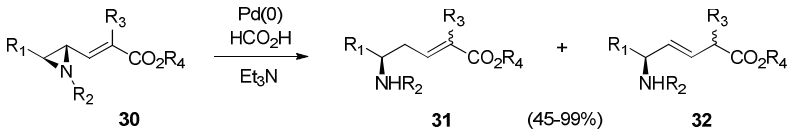
Hydride reduction of both activated and non-activated vinyl aziridines produces allyl amines which are useful building blocks for the synthesis of biologically active products. However, hydrides are less common nucleophiles to undergo/cause ring opening of vinyl aziridines. In the present section, the two only publications about this topic are described.

The first one was developed by *Laurent* and co-workers who developed in 1976 the first hydride reduction of vinylaziridines by diborane.[19] Treatment of *N*-unsubstituted vinylaziridines **26** with B_2H_6 gives allyl amines **39** by S_N2' reduction via cyclic intermediates (Scheme 1.7).



Scheme 1.7. Diborane mediated S_N2' reduction of vinylaziridines.

The second one was published in 1995, in which the palladium-catalyzed reduction of vinyl aziridines **30** with formic acid was reported (Scheme 1.8).[20] Both 1,2-reduction products **31** and 1,4-products **32** were obtained in ratios depending on the reaction conditions, such as the additive, solvent, and catalyst employed.



Scheme 1.8. Palladium(0)-catalyzed reduction with formic acid.

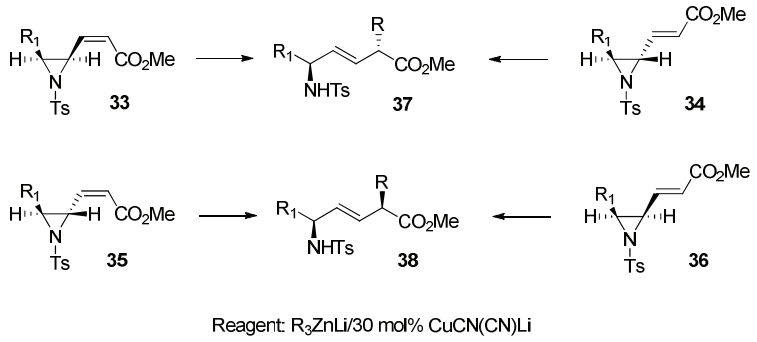
It is interesting to note that, in comparison to the reports of the ring opening of *non*-vinylic aziridines by reductive hydrogenation, much less occurrences of ring opening methods of aziridines by hydride reduction have appeared in recent years.

1.2.5.1.2. ORGANOCOPPER-MEDIATED ALKYLATION

Nucleophilic ring opening of aziridines by organometallic reagents has been known for over three decades.[21] However, the application of the carbanion addition was not significantly accelerated until a more efficient

method developed by *Eis* and *Ganem* in the opening of non-activated aziridines by organocuprates catalyzed by Lewis acid BF_3 was reported.[22] A subsequent report by *Baldwin et al.* on the ring opening of *N*-sulfonated aziridines that did not require catalytic activation further enhanced its broad use.[23]

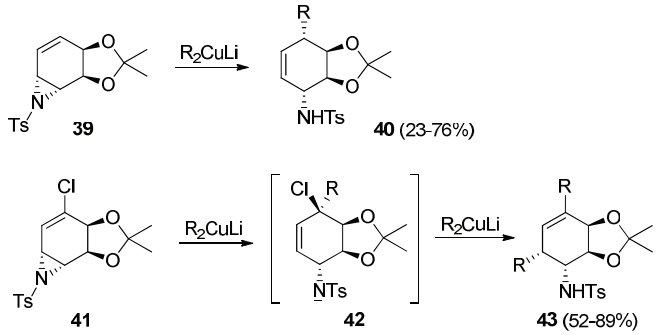
However, it was not until 1994 that two research groups independently reported organocopper-mediated ring-opening reactions of vinylaziridines (Scheme 1.9).[24] The original stereospecific S_N2' alkylation by *Ibuka, Fujii*, *Yamamoto* and coworkers was carried out by treatment of β-aziridinyl-α,β-enoates **33**–**36** with organocyanocuprate species such as RCu(CN)Li or R_3ZnLi/CuCN (cat.) to give the diastereomerically pure (*E*)-alkene dipeptide isosteres **37** or **38** in 82–98 % yields, together with small amounts of S_N2 products (<6 %).



Scheme 1.9. Ibuka's ring-opening reaction of vinyl aziridines **33-36** with organocuprates.

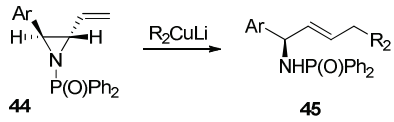
Treatment of cyclic vinylaziridine **39** with organocuprates of the R_2CuLi type proceeds in a highly *syn*-selective manner (Scheme 1.10).[25] The *syn* stereochemistry of the reaction reflects the effect of the acetonide group, which directs the nucleophilic attack to the less hindered face. The formation of the S_N2 products **43** from the cyclic (chlorovinyl)aziridine **41**

can be explained by a *syn*-S_N2' ring-opening reaction of **41** followed by an *anti*-S_N2' reaction of the resulting allyl chloride intermediate **42**.[26]



Scheme 1.10. Ring-opening reactions of cyclic vinyl aziridines.

The organocopper-mediated ring-opening of aziridines possessing terminal vinyl groups was reported by Sweeney and coworkers, demonstrating that the 2,3-*trans*-3-aryl-2-vinylaziridines **44** exclusively gave (*E*)-allyl amines **45** upon treatment with Gilman-type organocopper reagents (Scheme 1.11).[27]

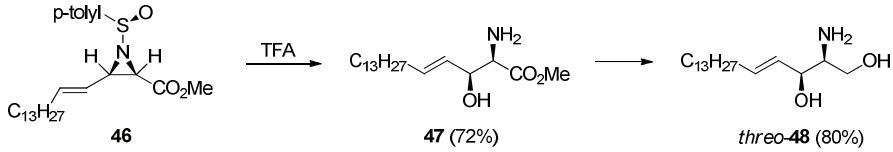


Scheme 1.11. Ring-opening reaction with organocopper reagents to form (*E*)-allyl amines.

After these publications, the nucleophilic addition of carbanions to aziridines has found a significant position in organic synthesis for carbon–carbon bond formation as one of the very prominent methods for organic functional group transformation.

1.2.5.1.3. REACTIONS WITH OXYGEN NUCLEOPHILES

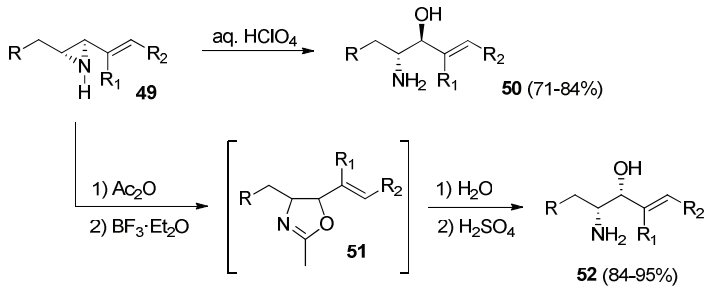
Ring-opening reactions of vinylaziridines with oxygen nucleophiles are generally mediated by acid. This type of reaction is extremely useful for the stereodivergent synthesis of β-amino alcohols. In 1996, *Davis* and coworkers demonstrated a highly stereoselective synthesis of *threo*-sphingosines from the common intermediate *cis*-*N*-sulfinylaziridine **46** (Scheme 1.12).[28] Treatment of **46** in acetone/TFA/H_2O gave the β-hydroxy-α-amino acid ester **47** as a single isomer in 72% yield. Reduction of **50** with $LiBH_4$ gave L-*threo*-sphingosine **48** in 80% yield.



46 **47** (72%) *threo*-**48** (80%)

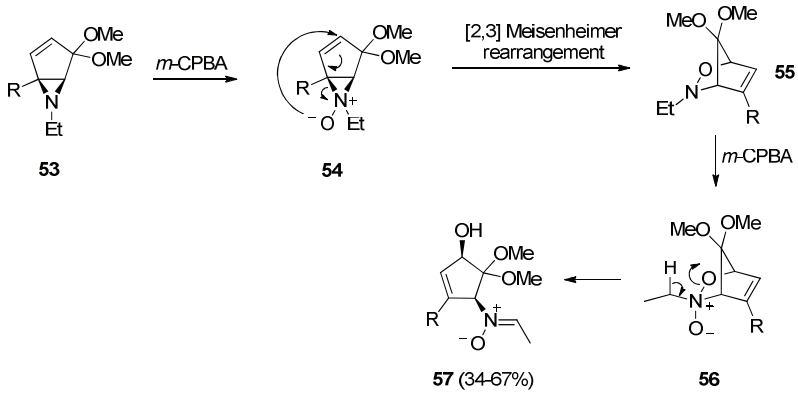
Scheme 1.12. Stereodivergent synthesis of threo-sphingosine **48**.

A stereodivergent synthesis of β-amino alcohols was reported via ring-opening of *N*-unsubstituted aziridines **49** with an acid by *Somfai* and coworkers (Scheme 1.13).[29] Aziridines **49** were regioselectively hydrolyzed into anti-amino alcohols **50** by treatment with $HClO_4$ in THF/H_2O. However, the acetylation of **49** and subsequent rearrangement of the resulting acetates by treatment with $BF_3 \cdot OEt$ gave oxazolines **51** with retention of configuration, and upon hydrolysis and deacetylation, yielded the corresponding *syn*-amino alcohols **52** in a stereospecific manner. This stereodivergent ring-opening reaction is useful for the synthesis of D-*erythro*- and L-*threo*-sphingosines.[30]



Scheme 1.13. Stereodivergent synthesis of *syn*- and *anti*-amino alcohols.

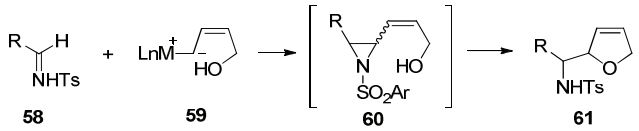
In 2001, an interesting oxidation of vinylaziridines **53** with m-CPBA to yield **57** through [2,3]-Meisenheimer rearrangement of the initial *N*-oxide **54** followed by further oxidation of **55** and ring-cleavage was reported by Penkett and Simpson (Scheme 1.14).[31]



Scheme 1.14. Possible mechanism of the oxidative rearrangement of vinyl aziridines.

The synthesis of the 2,5-dihydrofuran derivatives **61** was also reported by an intramolecular reaction of an oxygen nucleophile (Scheme 1.15). Since the vinylaziridines were generated in situ by treatment of

imines **58** with ylide **59**, this ylide is formally acting as an equivalent of the 2,5-dihydrofuran anion.[32]



Scheme 1.15. Intramolecular reaction of an oxygen nucleophile to give dihydrofurans.

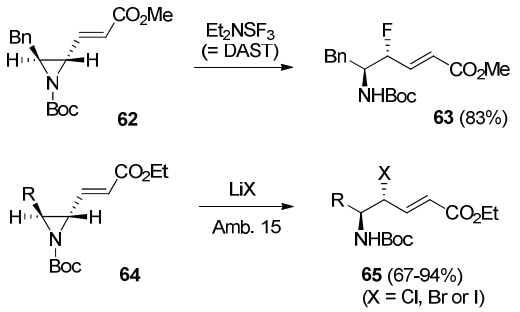
Although structurally identical to epoxides, vinyl aziridines, in general, show lower reactivity toward oxygen containing centered nucleophiles. Therefore, the ring opening of aziridines is largely dependent on the activation at the ring nitrogen either by attaching electron-withdrawing groups and/or on the use of appropriate Lewis acids in oxygen nucleophilic addition.

1.2.5.1.4. REACTIONS WITH HALIDE NUCLEOPHILES

Since a review describing metal halide opening of aziridine rings by *Tighi* and *Bonini*,[33] the development of new methods for nucleophilic ring opening of aziridines by halogen anions has continued in recent years, and the results concern improved reaction conditions, chemical yields and selectivity by applying more efficient catalysts. The new procedures are either complementary or superior to other known methods in the literature. Concerning to halide vinyl aziridine ring-opening methodologies, just the following publications have been reported.

Halide atoms can be stereoselectively introduced by ring-opening of γ-aziridinyl-α,β-enoates (Scheme 1.16). Treatment of **62** with

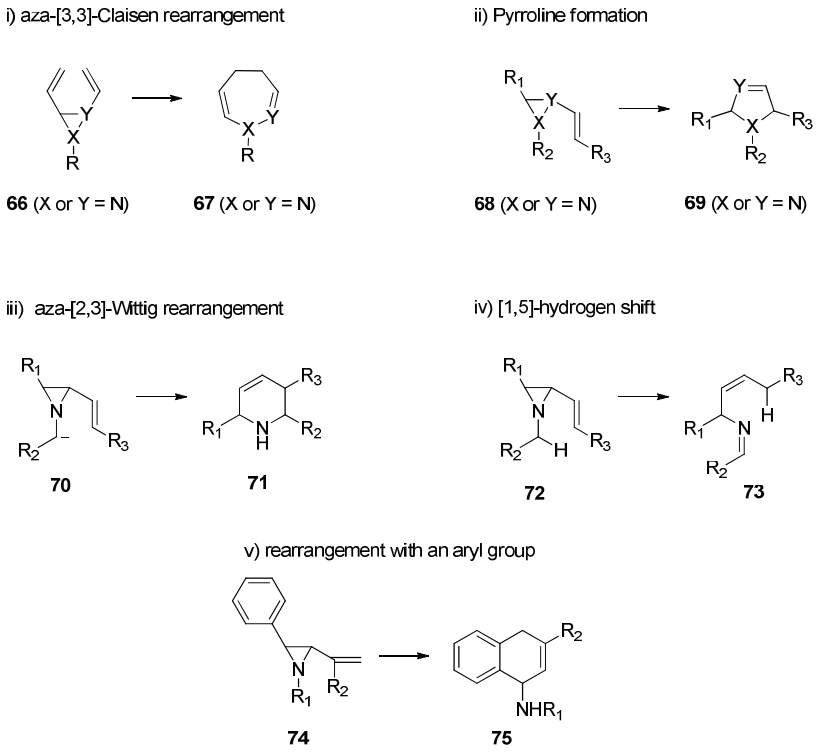
diethylaminosulfur trifluoride (DAST) results in stereospecific ring-opening to yield fluorinated derivative **63**.[34] A related stereoselective conversion of γ-aziridinyl-α,β-enoates **64** into allyl halides **65** by use of lithium halide in the presence of Amberlyst 15 was also reported recently.[35]



Scheme 1.16. Ring-opening reactions with halide nucleophiles.

1.2.5.2. Ring Expansion through Isomerization and Cycloadditions Reactions

As previously mentioned, chemistry based on ring opening of vinyl aziridines has been widely studied in organic synthesis. However, it has mainly been centered on ring opening by nucleophiles. In addition, significant efforts have been dedicated to study the participation of vinyl aziridines in [3+2] cycloadditions, isomerization processes and catalytic palladium transformations. This transformation offers significant potential for the synthesis of heterocycles.

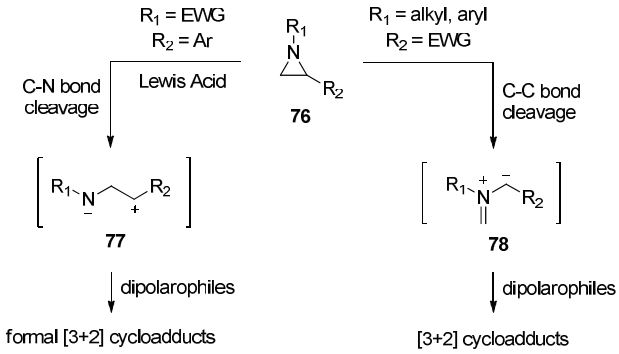


Scheme 1.17. Isomerization of vinyl aziridines

The rapid increase in molecular complexity from simple precursors is a major goal in organic synthesis. Within this context, isomerization of vinylaziridines has been used in organic synthesis. The isomerization reactions reported in the literature are represented in Scheme 1.17: i) azepine formation by aza-[3,3]-Claisen rearrangement of 1,2-divinyl- or 2,3-divinylaziridines **66**,[36] ii) pyrroline formation from **68**,[37] iii) aza-[2,3]-Wittig rearrangement of anionic species **70**,[38] iv) hydrogen shift from **72**, and v) rearrangement of vinylaziridines **74** with an aryl group.[39]

Aziridines **76** undergo electrocyclic ring opening upon irradiation or thermolysis to give azomethine ylides **78**, via C–C bond cleavage, and these

participate in 1,3-dipolar cycloadditions to give five-membered nitrogen heterocycles.[40]



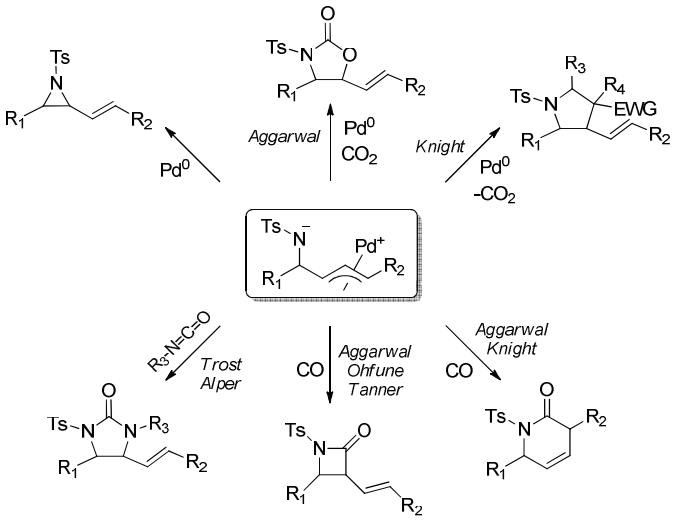
Scheme 1.18. Reactivities of aziridines towards dipolarophiles.

In the presence of Lewis acids, on the other hand, aziridines typically bearing electron-withdrawing N-substituents undergo C–N bond cleavage to afford zwitterionic 1,3-dipoles 77, which react with alkenes, alkynes, ketones, aldehydes, and nitriles to afford formal 1,3-dipolar cycloadducts (Scheme 1.18).[41]

Particularly, vinyl aziridines wearing electron-withdrawing N-substituents undergo Pd-catalyzed C–N bond cleavage to afford the π-allyl palladium intermediate, which react with isocyanates, carbodiimides, isothiocyanates, carbon monoxide affording formal 1,3- or 1,5-dipolar cycloadducts. In the following section, a summary of the main palladium-catalyzed transformation of vinyl aziridines will be described.

1.2.5.2.1. PALLADIUM-CATALYZED INSERTION OF VINYL AZIRIDINES

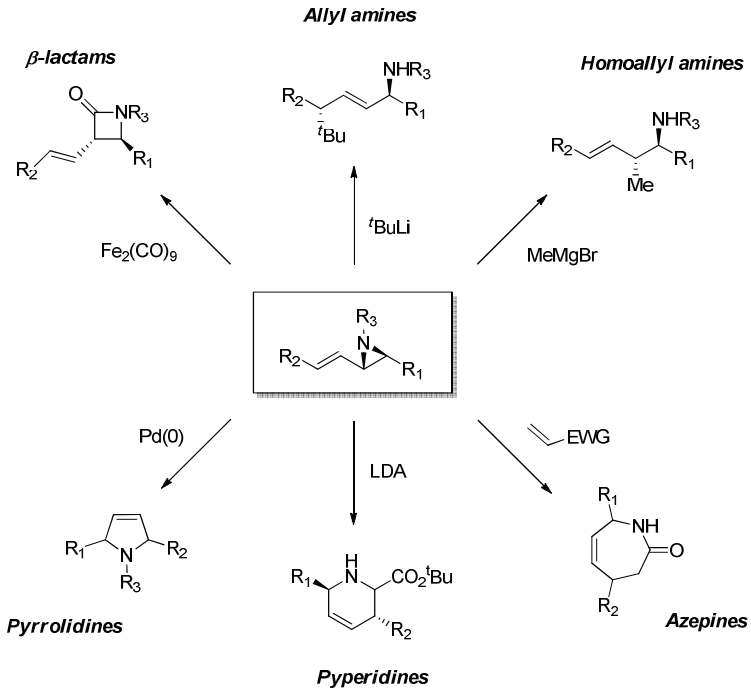
Vinyl aziridines are valuables synthetic intermediates which, as an illustration, undergo a host of very useful palladium-catalyzed transformation (Scheme 1.19).



Scheme 1.19. Pd-catalyzed applications of vinyl aziridines.

In particular, *Aggarwal*,[42] *Somfai*[43] and *Spears*[44] groups showed that vinyl aziridines could be converted into pyrrolidines.[45] Recently, *Aggarwal's* group extended this methodology to singly activated acceptors and demonstrated its utility in a stereocontrolled synthesis of (+)-kainic acid.[46] The Pd-catalyzed reaction of vinyl aziridines with isocyanates, carbodiimides and isothiocyanates is also well established.[47] And recently, *Aggarwal's* group also reported conversion of *trans*-vinyl aziridines into *trans*-vinyl oxazolidinones through a Pd-catalyzed carboxylation process.[48]To summarize, vinylaziridines can be regio- and stereoselectively opened by different nucleophiles making them very useful precursors for the synthesis of functionalized amines. Moreover, appropriately

functionalized vinylaziridines allow an easy access to a wide range of interesting products such as allyl amines,[49] homoallyl amines,[50] β-lactams,[51] pyrrolidines,[52] pyperidines,[53] and azepines (Scheme 1.20).[54]

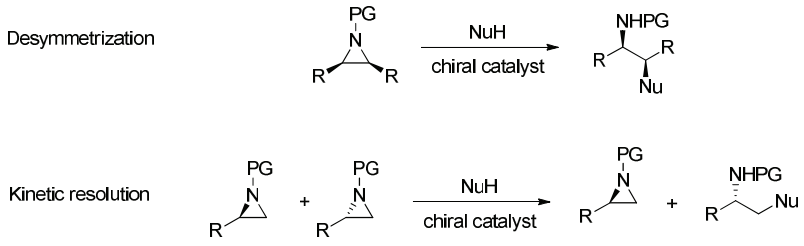


Scheme 1.20. Synthetic application of vinylaziridines.

Although there are several publications dealing with the regio- and stereoselective ring opening of vinyl aziridines by various nucleophiles, the asymmetric organocatalytic version of this transformation has not been published yet and is directly related to the work presented in the *Chapter 5* of this thesis.

1.3. CATALYTIC ASYMMETRIC AZIRIDINE RING-OPENING REACTIONS

The enantioselective ring opening of aziridines has attracted much attention in research due to its potential in the synthesis optically active organic compounds with one or two stereogenic centres in a single step. Some successful studies were reported using enantiopure starting materials or chiral auxiliaries with regard to the development of enantioselective ring opening of aziridines.[55]



Scheme 1.21. Catalytic asymmetric ring-opening of aziridines.

Currently, the catalysed asymmetric aziridine ring-opening reactions may be divided into two categories: a) the desymmetrization of *meso*-aziridines and b) the kinetic resolution of racemic aziridines (Scheme 1.21). Over the past few years, only the desymmetrization of *meso*-aziridines have been the focus of substantial interest, and several advances have been made in the developments of useful catalysts for this process. In contrast, the kinetic resolution method was much less explored, neither through metal- nor organocatalysis.

1.3.1. ENANTIOSELECTIVE NUCLEOPHILIC ADDITION TO *MESO*-AZIRIDINES

Meso compounds possess at least two stereogenic centers and that have a mirror plane bisecting the molecule in a way that leaves the stereocenters with identical substitution, but opposite absolute configuration.[56] Consequently, *meso* molecules are achiral. Thus a molecule possessing an internal plane of symmetry can be desymmetrized by reacting it with a chiral reagent.[57] This strategy is attractive because it can completely convert the *meso* substrates into the desired chiral products, while kinetic resolution reactions of racemic substrates can lead only to a 50% yield, unless racemization of the starting material can be achieved (dynamic kinetic resolution). The following section summarizes the catalytic asymmetric ring opening reactions of meso-aziridines, which are the most appealing methodologies since no chiral starting materials are required.

1.3.1.1. METAL CATALYSED ASYMMETRIC RING-OPENING OF *MESO*-AZIRIDINES

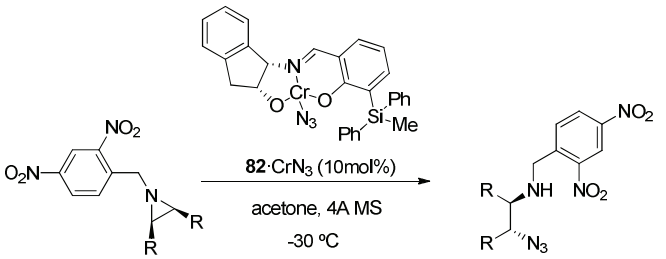
In 1996, *Oguni* and co-workers[58] developed the first desymmetrization of activated *meso*-aziridines with arene thiols promoted by chiral zinc complexes (Scheme 1.22).

79a: R = cyclohexane
79b: R = cyclopentane
79c: R = phenyl

80a: 98% yield; 93% ee
80b: 89% yield; 85% ee
80c: 94% yield; 84% ee

Scheme 1.22. Asymmetric ring opening of *meso*-aziridines with thiols promoted by EtZn-dialkyl tartrate complex.

In the presence of one equimolecular amount of a Et_2Zn-dicyclohexyl L-(+)-tartrate complex, the symmetrical 4-nitrobenzoyl aziridines **79a-c** reacted with 4-*tert*-butyl-benzenethoil to give the ring-opened products *trans* 2-[*N*-(4-nitro-benzoyl)-amino]-1-arylthiolalkanes **80a-c** in 89-98% yield and 84-93% ee. *Jacobsen* and co-workers[59] reported a highly enantioselective desymmetrization of *meso*-aziridines with trimethylsilyl azide ($TMSN_3$) as the nucleophile, using chiral chromium (III) complex **82** as the catalyst (Scheme 1.23). Initially, the best ee value obtained for the desymmetrization of meso-aziridine **81c** was only 70% when the catalytic complex was formed in situ from $CrCl_3$ and the ligands. Azide complex **82**·CrN3 prepared by treatment of the previous complex with $TMSN_3$ significantly improved the enantioselectivity to 87% ee. With the optimized catalyst, a variety of aziridines derived from both cyclic and acyclic alkanes were employed to generate the enantiomerically enriched azido *N*-2,4-dinitrobenzyl amino products **83a-e**, which could be transformed into the corresponding optically active 1,2-diamines under reductive conditions.



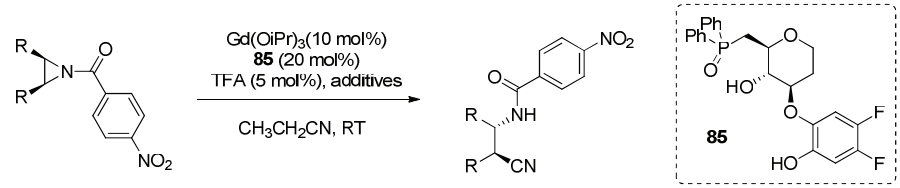
81a: R = cyclohexane
81b: R = cyclohexene
81c: R = cyclopentane
81d: R = tetrahydrofurane
81e: R = methyl

83a: 95% yield; 94% ee
83b: 75% yield; 88% ee
83c: 87% yield; 87% ee
83c: 73% yield; 90% ee
83e: 80% yield; 83% ee

Scheme 1.23. Chromium-catalyzed desymmetrization of meso-aziridines with $TMSN_3$.

In 2001, *Muller* and co-workers developed a ring-opening of *meso*-*N*-sulfonylaziridines with Grignard reagents.[60] It was shown that a chiral copper complex catalyzed the reaction between the *meso*-aziridine and Grignard reagents. Fourteen examples were reported with yields ranging from 28–89% and enantioselectivities from 0–72%.

In 2005, *Shibasaki* and co-workers[61] used a TFA-incorporated chiral Gd complex to catalyze the desymmetrization of *meso*-aziridines with trimethylsilyl cyanide (TMSCN). The active structure of the catalyst was a 2:3 metal/ligand complex which was prepared in situ from $Gd(O^iPr)_3$ and the chiral ligand **85** (Scheme 1.24). A catalytic amount of trifluoroacetic acid (TFA) was needed to stabilize the binuclear Gd complex and enhance the Lewis acidity. Under the catalysis of the TFA-incorporated chiral Gd complex, a wide range of meso *N*-4-nitrobenzoyl aziridines (**84a-i**) reacted with TMSCN to provide β-amino nitriles **86a-i** in good yields with 80–93% ee. These ring-opened products are valuable precursors to chiral β-amino acids.

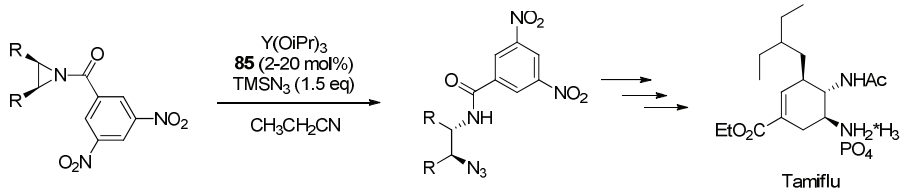


84a: R = cyclohexane
84b: R = cyclohexene
84c: R = cyclopentane
84d: R = tetrahydrofuran
84e: R = *N*-Cbz-pyrrolidine
84f: R = cycloheptane
84g: R = naphthalene
84h: R = methyl
84i: R = phenyl

86a: 94% yield; 87% ee
86b: 85% yield; 82% ee
86c: 81% yield; 93% ee
86d: 92% yield; 88% ee
86e: 89% yield; 84% ee
86f: 92% yield; 80% ee
86g: 91% yield; 83% ee
86h: 93% yield; 85% ee
86i: 93% yield; 85% ee

Scheme 1.24. Gadolinium-catalyzed desymmetrization of meso-aziridines with TMSCN.

This research group also investigated the cooperative bimetallic catalyst catalyzed enantioselective azidolysis of *meso*-aziridines.[62] The previous optimum conditions for the desymmetrization of meso-aziridines with TMSCN were employed to the ring opening with $TMSN_3$ giving only 46% ee. It was found that the *ee* value could be further increased when *N*-3,5-dinitrobenzoyl aziridine **87a** was employed. With the catalyst prepared from $Y(OiPr)_3$ and chiral ligand **85**, a wide range of meso *N*-3,5-dinitrobenzoyl aziridines **87a-j** were opened to give 1,2-azidoamides **88a-j** in high yields with 86–96% ee (Scheme 1.25). This work showed an improvement on Jacobsen's method in terms of enantioselectivity, substrate generality, and catalyst loading. The application of this strategy towards the synthesis of Tamiflu which is an orally active anti-influenza drug highlighted the importance of the recent development of catalytic asymmetric ring opening of aziridines.



87a: R = cyclohexane
87b: R = cyclohexene
87c: R = cyclopentane
87d: R = tetrahydrofuran
87e: R = *N*-Cbz-pyrrolidine
87f: R = cycloheptane
87g: R = naphthalene
87h: R = methyl
87i: R = *n*-propyl
87j: R = phenyl

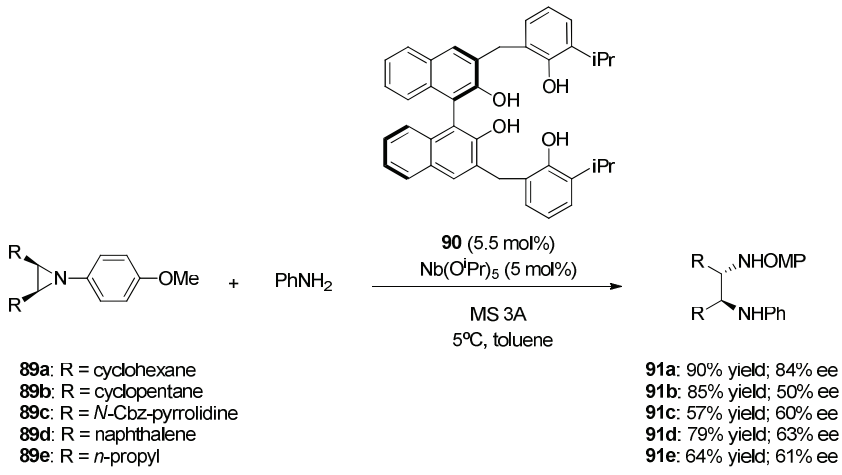
88a: 97% yield; 92% ee
88b: 96% yield; 91% ee
88c: 99% yield; 94% ee
88d: 99% yield; 96% ee
88e: 99% yield; 94% ee
88f: 94% yield; 86% ee
88g: 98% yield; 91% ee
88h: 94% yield; 95% ee
88i: 99% yield; 87% ee
88j: 99% yield; 93% ee

Scheme 1.25. Yttrium-catalyzed desymmetrization of meso-aziridines with $TMSN_3$.

Based on the concept of dual activation, *Shibasaki's* group attempted to develop new catalysts by modifying the structure of the chiral ligands.[63] In order to obtain a higher-order structure of the gadolinium

complex, they designed new ligands (**85-**derivatives) with a smaller distance between the phosphine oxide and the neighbouring hydroxyl group. It was shown that the change of the Lewis base position resulted in significantly higher enantioselectivities (95–99% ee) for the ring-opened products of a wide range of meso-aziridines with TMSCN.

Kobayashi and co-workers[64] were the first to report the desymmetrization of meso *N*-aryl aziridines using anilines as nucleophiles catalyzed by a niobium complex of 2,2′-binaphthol (BINOL) derivative **90** (Scheme 1.26). With *O*-methoxyphenyl (OMP) as the optimum protecting group on the nitrogen atom of aziridine, substrate **89a** derived from cyclohexane reacted with aniline to provide the corresponding 1,2-diamine product **91a** in good yield (90%) and enantioselectivity (84% ee). However, unsatisfactory enantioselectivities (not exceeding 63% ee) were obtained for other cyclic or acyclic aziridines.



Scheme 1.26. Niobium-catalyzed desymmetrization of meso-aziridines with aniline.

More recently, *Nakamura* developed the first enantioselective desymmetrization of aziridines with phosphites using a new class of readily accessible chiral catalysts derived from 9-amino-9-deoxy-epi-cinchona alkaloid in combination with Et_2Zn.[65] This approach gave direct access to both enantiomers of β-aminophosphonates in high yields with high enantioselectivities.

1.3.1.2. ORGANOCATALYTIC ASYMMETRIC RING OPENING OF *MESO*-AZIRIDINES

1.3.1.2.1. ASYMMETRIC ORGANOCATALYSIS: A BRIEF INTRODUCTION

Organocatalysis represents an emerging area of organic methodology and can be defined as a form of catalysis in which small organic molecules act as catalysts. The use of these catalysts is a potential environmentally friendly alternative to metal catalysis.

In an effort to organize the extensive field of organocatalysis, in 2004 *Seayad* and *List*[66] introduced a mechanism-based classification system. Accordingly, organocatalysis can be broadly divided into four major areas: Lewis base catalysis, Lewis acid catalysis, Brønsted base catalysis and Brønsted acid catalysis (Figure 1.5).

Lewis base catalysis encompasses all reactions in which the catalyst donates a pair of electrons to form a covalent bond with the substrate. These catalysts are generally N, C, O, P and S based Lewis bases which can reversibly activate the substrate either as a nucleophile or an electrophile in the form of iminium ions, enamines, acyl ammonium ions, ammonium enolates, and others. After the reactive intermediate has undergone a reaction, the bond between the product and the catalyst is broken, thus allowing that the catalytic cycle can repeat itself. Catalysis mediated by

nucleophilic amines, or aminocatalysis, belongs to this mechanistic class.[67] In Lewis acid catalysis, the catalyst activates neutral or negatively charged substrates by accepting a pair of electrons.

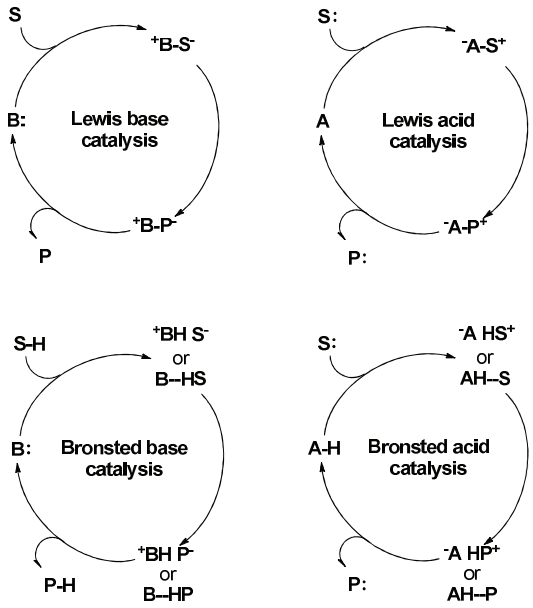


Figure 1.5. Four major areas for asymmetric organocatalysis and their simplified mechanisms (S = substrate, P = product, A = acid, B = base).

The recently introduced organosilicon catalysis[68] and the extensive field of phase-transfer catalysis[69] can be considered examples of such activation. Brønsted base catalysis and Brønsted acid catalysis are conceptually related catalytic modes which involve (partial) deprotonation and protonation, respectively, for the activation of the substrate.

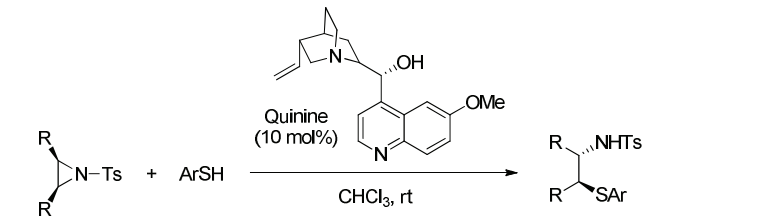
Chiral phosphoric acids have been shown to be excellent catalyst for a wide variety of enantioselective transformations. The most successful reactions involving the use of BINOL phosphates as a powerful Brønsted acid catalyst can be classified as i) Mannich-type Reactions,[70] ii)

Amidations and Imidations,[71] iii) Hydrophosphonylations,[72] iv) Friedel–Crafts-type Reactions,[73] v) Reductions[74] and vi) Cycloadditions Reactions.[75]

Furthermore, in the last few years, *Antilla* and *Lattanzi* reported their seminal works on the desymmetrization of *meso*-aziridines, which belongs to this mechanistic class of catalysis (Section 4.2.2.4). This new area is directly related to the work presented in the *Chapter 4* of this thesis, which deals with the desymmetrization of *meso*-aziridines.

1.3.1.2.2. BIFUNCTIONAL CATALYSTS FOR THE ASYMMETRIC RING OPENING OF *MESO*-AZIRIDINES

Bifunctional catalysts containing both a Lewis base component and a Lewis acid component may catalyze the ring opening of *meso*-aziridines by a dual activation mechanism to orient both the nucleophile and the electrophile, respectively. *Wu* and co-workers[76] demonstrated that the natural Cinchona alkaloids with the tertiary amine and the hydroxyl group could be efficient bifunctional catalysts for the desymmetrization of *meso*-aziridines **92a-e** with arenethiols (Scheme 1.27).



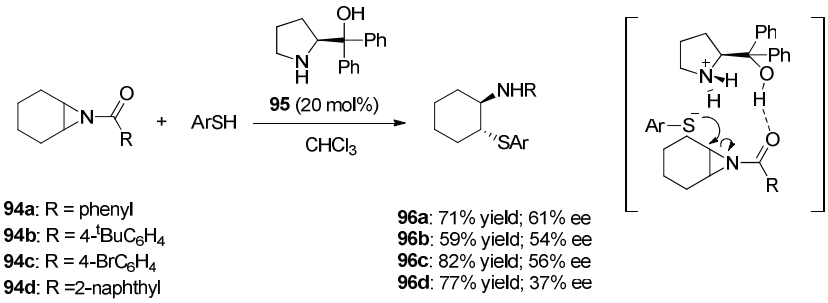
92a: R = cyclohexane
92b: R = cyclohexene
92c: R = cyclopentane
92d: R = tetrahydrofuran
92e: R = *N*-Cbz-pyrrolidine

93a: 52-85% yield; 32-72% ee
93b: 80% yield; 54% ee
93c: 65% yield;36% ee
93d: 72% yield; 52% ee
93e: 87% yield;45% ee

Scheme 1.27. Quinine-catalyzed desymmetrization of *meso*-aziridines with thiols.

Under the catalysis of quinine, *N*-tosyl aziridine derived from cyclohexane were opened with various arenethiols to give the corresponding β-amino thioethers **93a-e** with *ee*s up to 72%. *N*-acyl aziridines were also employed in the reactions with thiophenol, and 45% ee was achieved when *N*-3,5-dinitrobenzoyl aziridine was used.

Lattanzi and *Della Sala*[77] used α,α-diaryl-L-prolinol as bifunctional catalyst for the desymmetrization of *meso N*-acyl aziridines **97a-d** with arenethiols (Scheme 1.28). They proposed that the amino group would deprotonate the thiol to generate the reactive nucleophile, while the hydroxyl group might activate and orient the aziridine by hydrogen bonding. In the presence of 20 mol% α,α-diphenyl-L-prolinol **98**, aziridines bearing 1-naphthyl-substitution on the nitrogen atom reacted with thiophenol to provide the ring-opened product in 71% yield and 61% ee.



94a: R = phenyl
94b: R = 4-^{t}BuC$_6$H$_4$
94c: R = 4-BrC$_6$H$_4$
94d: R =2-naphthyl

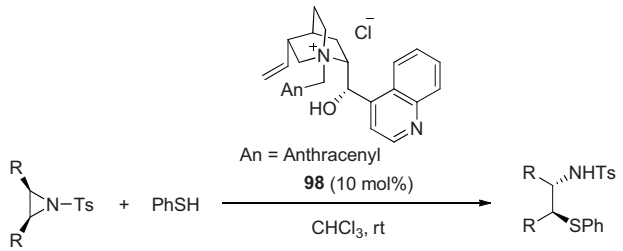
96a: 71% yield; 61% ee
96b: 59% yield; 54% ee
96c: 82% yield; 56% ee
96d: 77% yield; 37% ee

Scheme 1.28. Prolinol-catalyzed desymmetrization of *meso*-aziridines with thiols.

Several additional arenethiols were screened, leading to the formation of the desired products **99a-d** in good yields and moderate enantioselectivities (up to 56% ee).

1.3.1.2.3. PHASE-TRANSFER CATALYZED ASYMMETRIC RING OPENING OF *MESO*-AZIRIDINES

Hou and co-workers[78] reported the use of chiral quaternary ammonium salts **98** derived from cinchona as phase-transfer catalysts in the desymmetrization of *meso N*-tosyl aziridines **97a-c** with thiols (Scheme 1.29). The combination of cinchonine derivatives with the inorganic base $CsOH \cdot H_2O$ gave the best/highest enantioselectivities (40 to 73% ee).

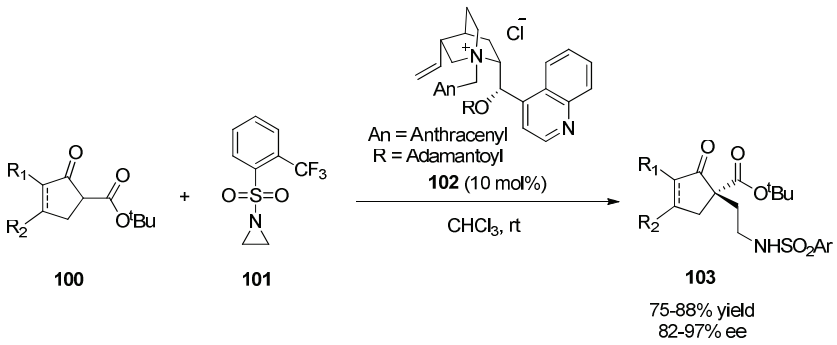


97a: R = cyclohexane
97b: R = cyclohexyl
97c: R = cyclopentyl

99a: 85% yield; 73% ee
99b: 88% yield; 72% ee
99c: 80% yield; 40% ee

Scheme 1.29. Desymmetrization of *meso*-aziridines with thiols under phase-transfer conditions.

Organocatalytic asymmetric ring opening of *meso*-aziridines with less reactive carbon-based pronucleophiles under phase-transfer catalysis have been recently reported by *Dixon et al*. and *Jørgensen et al*. Dixon and co-workers[79] described a highly enantioselective reaction of 1,3-dicarbonyl compounds **100** with *N*-sulfonyl aziridine **101** to generate the products **106** containing the amino ethylene group attached to a stereogenic quaternary carbon (Scheme 1.30).

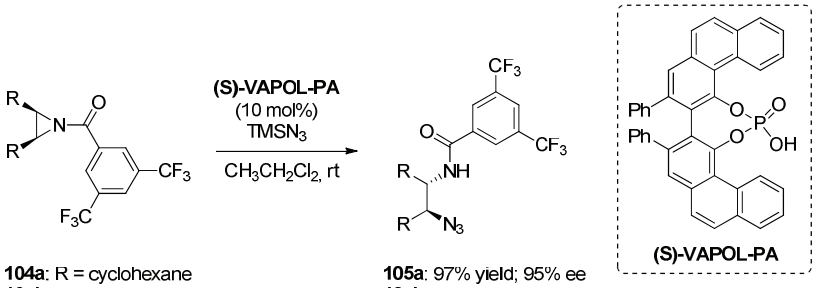


Scheme 1.30. Asymmetric ring opening of unsubstituted aziridine with 1,3-dicarbonyl compounds under phase-transfer conditions.

Using *Cinchona* alkaloid derivatives as the phase-transfer catalyst **102**, 50% aqueous K_2HPO_4 as the base, a range of substituted indanone pronucleophiles provided the ring-opened adducts in high yields and enantioselectivities (91-97% ee). Almost simultanously, *Jørgensen* and co-workers[80] achieved comparable results under similar phase-transfer conditions using unsubstituted *N*-tosyl aziridine as the substrate.

1.3.1.2.4. BRØNSTED ACID CATALYZED ASYMMETRIC RING-OPENING OF *MESO*-AZIRIDINES

Several groups reported the use of phosphoric acids for a large number of enantioselective organocatalytic transformations. With the previous success of phosphoric acid-catalyzed reactions with imines, Antilla and co-workers envisioned the utilization of a chiral phosphoric acid catalyst to open aziridines.[81]



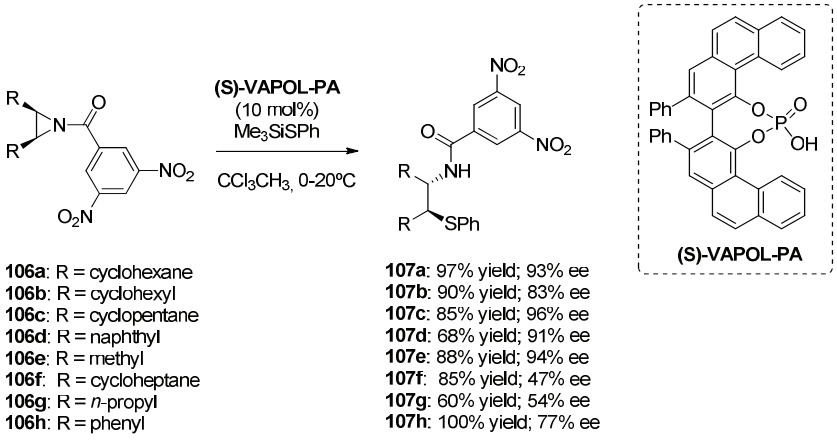
104a: R = cyclohexane
104b: R = cyclohexyl
104c: R = cyclopentane
104d: R = cycloheptane
104e: R = *N*-Cbz-pyrrolidine
104f: R = tetrahydrofuran
104g: R = naphthyl
104h: R = methyl
104i: R = phenyl

105a: 97% yield; 95% ee
105b: 84% yield; 92% ee
105c: 64% yield; 91% ee
105d: 68% yield; 84% ee
105e: 94% yield; 71% ee
105f: 49% yield; 87% ee
105g: 90% yield; 70% ee
105h: 88% yield; 86% ee
105i: 95% yield; 83% ee

Scheme 1.31. Chiral phosphoric acid-catalyzed desymmetrization of meso-aziridines with $TMSN_3$.

Antilla's group reported in 2007 the first phosphoric acid-catalyzed desymmetrization of meso-aziridines.[82] It was also the first example of a phosphoric acid-catalyzed reaction with a non-imine-based electrophile. The reaction between TMS-N_3 and aziridines **104a-i** was catalyzed by VAPOL phosphoric acid (Scheme 1.31). The products **105a-i** were obtained in high yields (49-97% yield) and enantioselectivities (69-95% ee).

Lattanzi and *Della Sala*[83] developed the desymmetrization of *N*-acylaziridines **106a-h** with Me_3SiSPh, catalyzed by (*R*) and (*S*)-VAPOL hydrogen phosphate, producing β-(*N*-acylamino)phenylthioethers **107a-h** in a highly enantioselective and efficient manner (Scheme 1.32).

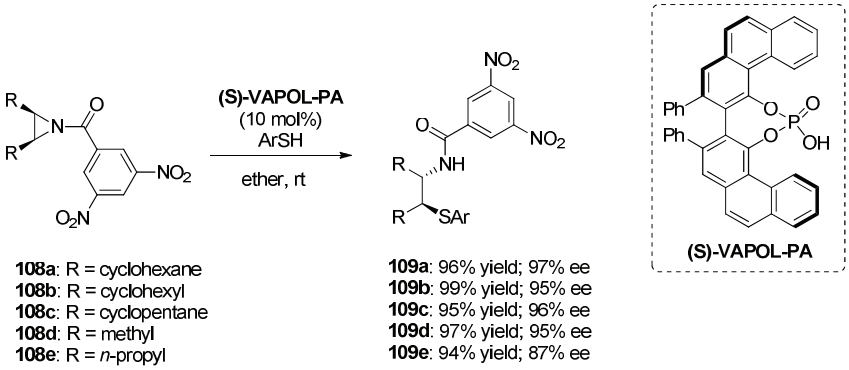


106a: R = cyclohexane
106b: R = cyclohexyl
106c: R = cyclopentane
106d: R = naphthyl
106e: R = methyl
106f: R = cycloheptane
106g: R = *n*-propyl
106h: R = phenyl

107a: 97% yield; 93% ee
107b: 90% yield; 83% ee
107c: 85% yield; 96% ee
107d: 68% yield; 91% ee
107e: 88% yield; 94% ee
107f: 85% yield; 47% ee
107g: 60% yield; 54% ee
107h: 100% yield; 77% ee

Scheme 1.32. Chiral phosphoric acid-catalyzed desymmetrization of meso-aziridines with TMS-SPh.

In 2010, *Antilla's* developed a phosphoric acid-catalyzed highly enantioselective ring opening of *meso N*-acyl aziridines **108a-e** with a series of functionalized aromatic thiol nucleophiles (Scheme 1.33).[84]



108a: R = cyclohexane
108b: R = cyclohexyl
108c: R = cyclopentane
108d: R = methyl
108e: R = *n*-propyl

109a: 96% yield; 97% ee
109b: 99% yield; 95% ee
109c: 95% yield; 96% ee
109d: 97% yield; 95% ee
109e: 94% yield; 87% ee

Scheme 1.33. Chiral phosphoric acid-catalyzed desymmetrization of *meso*-aziridines with thiols.

In this publication they revealed that silylated thiols are not necessary and that unsubstituted thiols can also be used to obtain the products **109a-e** in excellent yield and enantioselectivity.

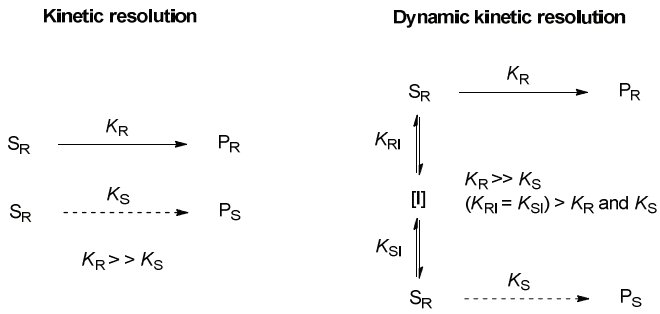
There has been some success using chiral metal complexes as catalysts for the asymmetric ring opening of *meso*-aziridines. Interest in organocatalytic asymmetric ring opening of *meso*-aziridines has increased significantly over the last decade. Chiral phosphoric acid has been identified as the most effective organocatalysts for the desymmetrization of *meso*-aziridines with both silylated nucleophiles and thiols. Chiral phase-transfer catalysts and bifunctional catalysts have also been employed for the desymmetrization of *meso*-aziridines with thiols, providing the ring-opened products with moderate enantioselectivities. However, considering the high utility of the optically active 1,2-difunctionalized products, there remains a need to develop broadly applicable and practical methods with even more readily accessible and more manageable catalysts.

1.3.2. KINETIC RESOLUTION: GENERAL CONCEPT

Asymmetric synthesis consists in the preparation of enantio-enriched compounds in the most efficient and practical manner possible. Additionally, such syntheses should be achieved, when possible, in an atom-economic manner.[85] Driven by the demand to enhance the sustainability of chemical processes, there has been an increased interest in the transformation of racemates into a single enantiomeric product. However, the resolution of racemates is still nowadays one of the principal methods for the production of enantiopure compounds on an industrial scale.[86] Although numerous methods exist which are highly efficient in terms of enantio-discrimination, the maximum theoretical yield of 50% for each enantiomer sets a low ceiling on the productivity of such processes.

One of these strategies is called kinetic resolution (KR), and is based on the difference of reaction rates (k_R, k_S) of the substrate enantiomers (S_R, S_S) during the transformation to produce the enantiomers P_R and P_S

using a chiral catalyst (Scheme 1.34).[87] Due to the fact that two enantiomeric species react simultaneously with enantiomerically pure compounds at different rates (preferably in an irreversible manner), the relative concentrations of S_R/S_S and P_R/P_S vary as the reaction proceeds and, consequently, the enantiomeric composition of *S* and *P* depends on the substrate conversion. The recovery of the product P_R and the unreacted substrate enantiomer S_S constitutes a kinetic resolution. The efficiency of KR is often expressed by the selectivity factor *S* or k_{rel}: $S = k_R/k_S$. Although the maximum theoretical yield based on racemic starting material is only 50%, the most attractive aspect of KR from the point of view of preparative synthesis is that unreacted substrate can be recovered in high ee, simply by carrying the reaction to high enough conversion, even if S (or k_{rel}) is not very high.



Scheme 1.34. Principles of kinetic and dynamic kinetic resolution.

In order to overcome the 50 % yield barrier in KR, considerable effort has been devoted to create processes which afford the product with the same high enantiomeric purity, but in significantly improved chemical yield. A number of strategies have been developed during the past years to allow the conversion of both enantiomers from a racemate into a single stereoisomer.[88] A significant breakthrough was achieved by the development of dynamic kinetic resolution (DKR). The latter combines the

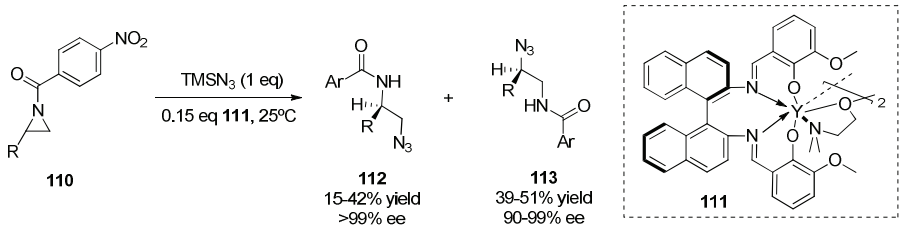
resolution step with an *in situ* racemization of the substrate enantiomers S*R* and S*S* *via* an achiral or prochiral intermediate/transition state (Scheme 1.34). As a consequence, while the concentration of the most reactive enantiomer (S*R*) is depleted during the enantioselective reaction, the equilibrium of S*R*/S*S* is constantly re-adjusted by racemization of the less reactive enantiomer S*S*. To indicate the non-static character of this process, the term "dynamic kinetic resolution" has been coined. In such a process, the kinetic balance of the two reactions (enantioselective transformation of one enantiomer and racemization of the second enantiomer) is of crucial importance for the success of a DKR process. As a rule of thumb, the racemization should occur at an equal or higher rate than the catalytic asymmetric reaction (see Scheme 1.34).

1.3.2.1. KINETIC RESOLUTION OF RACEMIC AZIRIDINES

Existing methods for the synthesis of highly enantioenriched terminal aziridines are often inefficient and limited in range, and require multistep procedures. Given the availability of racemic terminal aziridines from inexpensive terminal olefins, and the absence of effective asymmetric aziridination methods for these substrates, kinetic resolution strategies could be particularly interesting for the preparation of optically active monosubstituted aziridines. However, to the best of our knowledge, only three examples of such a process have been reported to date.

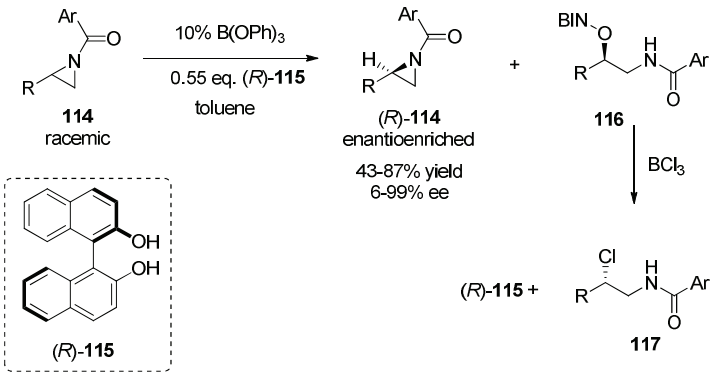
In 2009, *RajanBabu* and co-workers[89] reported the first example of kinetic resolution in which a single chiral small-molecule catalyst induces divergent regioselectivities in the ring-opening reactions of racemic aziridine mixtures **110**. High yields of 1,2-diamine derivatives **112** and **113** can be obtained in nearly enantiomerically pure form (> 97% ee) from

racemic aziridines by this process (Scheme 1.35). Thus, the configurations of the chiral centers in both β-azidoamides are identical. They found that in the presence of $TMSN_3$ the dimeric yttrium-salen complex **111** catalyzed the ring opening reactions of the two enantiomers of **110** with exceptionally high, complementary regioselectivities. Accordingly, the nucleophilic attack occurs at the primary position in (*R*)-**110**, leading to the azidoamide **112** as the exclusive product, whereas (*S*)-**110** gives the product **113**, resulting from exclusive S_N2-inversion at the secondary center.



Scheme 1.35. Regiodivergent kinetic resolution of terminal aziridines.

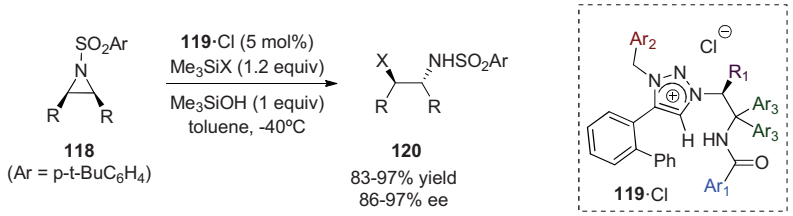
In 2012, *Morgan* and co-workers developed a simple kinetic resolution of *N*-acylaziridines **114** with a broad substrate scope using non-racemic 1,1'-bi-2-naphthol (BINOL, **115**) as the resolution agent.



Scheme 1.36. Kinetic resolution of racemic terminal *N*-acylaziridines.

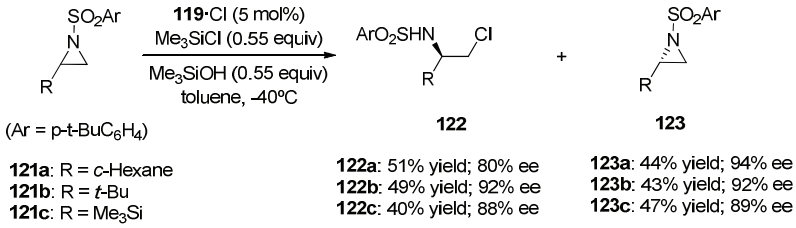
The BINOL-derived byproduct **116** is further processed to recover BINOL and produce an enantiomerically pure 1,2-chloroamide **117** (Scheme 1.36).[90]

Almost at the same time, *Ooi* and co-workers[91] published a chloride and bromide catalysed asymmetric ring openings of *meso*-aziridines **118** with trimethylsilyl halides using modular chiral 1,2,3-triazolium chlorides **119**·Cl as catalysts (Scheme 1.37). Control experiments suggest a reaction pathway involving hypervalent silicate ions as reactive intermediates.



Scheme 1.37. Catalytic asymmetric ring-opening of *meso*-aziridines with halides mediated by chiral 1,2,3-triazolium salts.

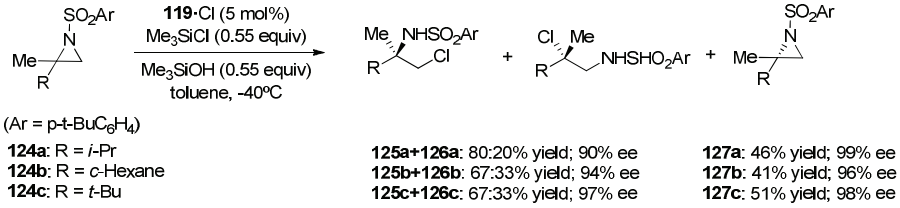
The potential utility of the chiral 1,2,3-triazolium chloride **119**·Cl-catalyzed asymmetric halide ring-opening protocol was further demonstrated by its successful application to the kinetic resolution of racemic terminal aziridines **121** (Scheme 1.38).



Scheme 1.38. Kinetic resolution of terminal aziridines with mediated by chiral 1,2,3-triazolium silicate chloride.

The reaction of the vinylcyclohexane-derived aziridine **121a** with Me_3SiOH in the presence of **119**·Cl gave rise to the ring-opened product **122a** exclusively (51% yield) with 80% ee, and **123a** was recovered in 44% yield with 94% ee. Even higher selectivities were achieved with terminal aziridines bearing sterically demanding *tert*-butyl trimethylsilyl substituents (**123b** and **123c**).

This approach allowed the unprecedented kinetic resolution of 2,2-disubstituted aziridines **124a-c**, with high levels of selectivity. This enables the preparation of the enantiomerically pure products **127a-c**, not readily accessible by conventional methodologies (Scheme 1.39). When **124a** was exposed to reaction conditions similar to those of the kinetic resolution of **121**, a regioisomeric mixture of the chlorinated products was isolated in 48% combined yield (**125a**/**126a** = 80:20) and the enantiomeric excess of the major derivative **127a** was 90% ee. Importantly, substrate**124a** was recovered in 46% yield in an essentially enantiopure form. While the regioselectivity was dependent on the substrate structure, an almost complete discrimination of the two enantiomers of **124** was consistently realized.



Scheme 1.39. Kinetic resolution of terminal 2,2-disubstituted aziridines with chloride mediated by chiral 1,2,3-triazolium silicates.

Although, the interest in organocatalytic asymmetric ring opening of *meso*-aziridines has increased significantly over the last decade, just one

publication reported the organocatalytic kinetic resolution of terminal aziridines. Chiral 1,2,3-triazolium silicate chlorides has been identified as the most effective organocatalysts for the kinetic resolution of terminal aziridines with silylated chlorides. There has been a single success using chiral metal complexes as catalysts for the regiodivergent kinetic resolution of terminal aziridines. However, considering the high utility of both optically active aziridine and their corresponding 1,2-difunctionalized product, remains a need to develop more practical methodologies.

This thesis is focused on the development of new methodologies for i) the regio- and stereoselective synthesis of vinyl oxetanes from vinyl aziridines using tetraalkylammonium salts, ii) the asymmetric Brønsted acid-catalyzed desymmetrization of *meso*-aziridines and kinetic resolution of terminal aziridines, and finally, iii) the kinetic resolution of vinyl aziridines promoted by chiral Brønsted phosphoric acids. The corresponding results will be described in *Chapters 3*, *4* and *5*, respectively. In *Chapter 2*, the objectives of this work will be detailed.

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CHAPTER 2

OBJECTIVES OF THIS PH.D WORK

The final goal of this thesis is the development of new synthetic strategies for efficient aziridine transformations using selective catalysis based on small organic molecules. In this context, the present work aims to develop new organocatalytic procedures in aziridine ring-opening chemistry, focusing on the development of synthetic applications of these versatile intermediates.

The research described in Chapter 3 aims to develop a new synthesis of vinyl oxetanes from vinyl aziridinols using *N*-Heterocyclic carbenes. Therefore, the specific objectives of this chapter are:

- To synthesize a set of new vinyl aziridinols.
- To synthesize a series of novel vinyl oxetanes from vinyl azirirdinols in the presence of NHC-carbenes.
- To investigate the mechanistic aspects of the formation of oxazines during the transformation above mentioned.
- To apply the new synthetic methodology to the synthesis of vinyl oxetanes from vinyl aziridinols in the presence of tetraalkylammonium halides.

The research described in Chapter 4 aims to develop a new methodology for the asymmetric BINOL-derived Brønsted phosphoric acid-catalyzed desymmetrization of *meso*-aziridines and kinetic resolution of terminal aziridines. Therefore, the specific objectives of this chapter are:

- To synthesize a set of *meso*-aziridines and terminal aziridines
- To test the (*S*)-TRIP phosphoric acid catalyst in the desymmetrization of the previously synthesized *meso*-aziridines using benzoic acid as oxygen-nucleophile.

- To test the (*S*)-TRIP phosphoric acid catalyst in the kinetic resolution of the previously synthesized terminal aziridines using benzoic acid as oxygen-nucleophile.

The work presented in this chapter has been developed in the Max-Plank Institute für Kohlenforschung under the supervision of Professor Benjamin List.

The research described in Chapter 5 aims to develop a new methodology for the asymmetric BINOL-derived Brønsted phosphoric acid-catalyzed kinetic resolution of vinyl aziridinols. Therefore, the specific objectives of this chapter are:

- To synthesize a family of BINOL-derived Brønsted phosphoric acids.
- To apply the Brønsted phosphoric acid catalysts previously synthesized in the kinetic resolution of vinyl aziridinols.
- To investigate the mechanistic aspects of the asymmetric vinyl aziridinol ring-opening reaction using isotopic labelling procedures.

CHAPTER 3

REGIO- AND STEREOSELECTIVE SYNTHESIS OF VINYL OXETANES FROM VINYL AZIRIDINOLS USING TETRAALKYLAMMONIUM HALIDES

3.1. INTRODUCTION

3.1.1. OXETANES IN NATURAL PRODUCTS

Several important naturally occurring compounds enclose an oxetane ring, which is intriguing because it is difficult to build an oxetane by standard chemical reactions.[1] Examples include *Taxol* (a potent anti-cancer drug), *Oxetanocin* (anti-AIDS activity) and *Thromboxane A* (Figure 3.1). The marine natural product *Dictyoxetane* (**128**) has been isolated from the brown algae *Dictyota dichotoma* and is structurally related to the class of diterpenoid dolabellanes,[2] which show a wide spectrum of biological activities. A biogenetic pathway has been suggested for *Dictyoxetane* (**128**) from a known dolabellane metabolite supported by the experimental introduction of the oxetanes moiety *in vitro*.[3]

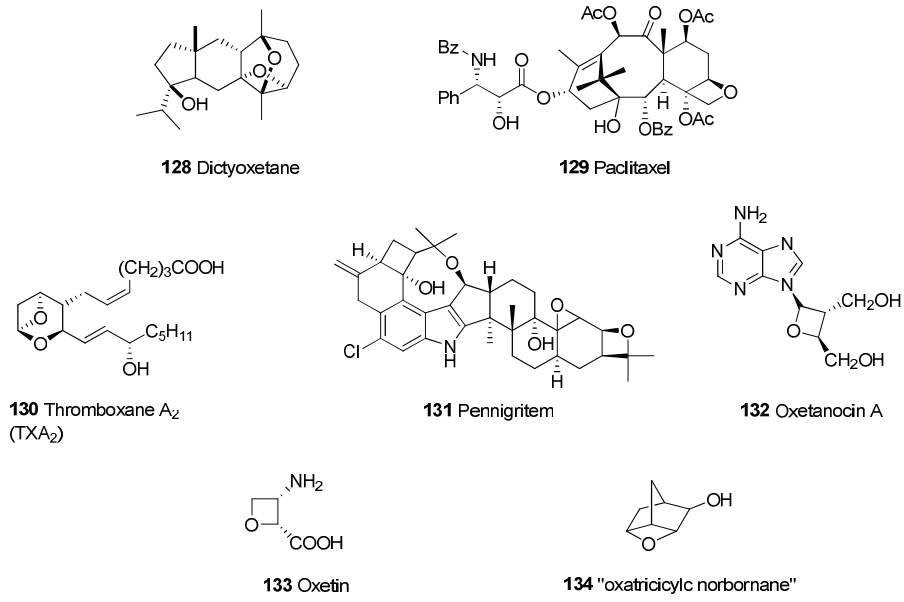


Figure 3.1. Natural products containing an oxetane ring.

A potent anti-cancer drug and naturally occurring oxetane is *Paclitaxel* (Taxol) **129**, a tricyclic diterpene (C_{20}) isolated from the bark of the western yew (*Taxus brevifolia*),[4] a slow-growing tree found in the Pacific Northwest forests. *Paclitaxel* (**129**), considered a prototype for new chemotherapeutic agents,[5] shows high activity against different tumor types like mama or ovarian cancer. The oxetane ring seems to be essential for its biological activity.[6] Another example of a natural product containing an oxetane ring is *Pennigritem* (**131**), a toxin isolated from *Penicillium nigricans* and related to the family of penitrems. Penitrems intercede in amino-acid neurotransmitters-release mechanisms. These toxins induce an excessive release of neurotransmitters into the synaptic cleft and over-stimulate the receptors on the postsynaptic membrane. *Oxetanocin A* (**132**) is a potent antiviral, formally a nucleoside with an oxetanosyl-*N*-glycoside, which has been isolated from a culture filtrate from *Bacillus megaterium.*[7] Naturally occurring *Oxetanocin A* (**132**) and its synthetic derivatives are inhibitors of reverse transcriptases of retrovirus and therefore potential drugs for the treatment of AIDS,[8] cytomegalovirus (CMV),[9] hepatitis B-virus, and herpes simplex-virus (HSV-1 and HSV-2).

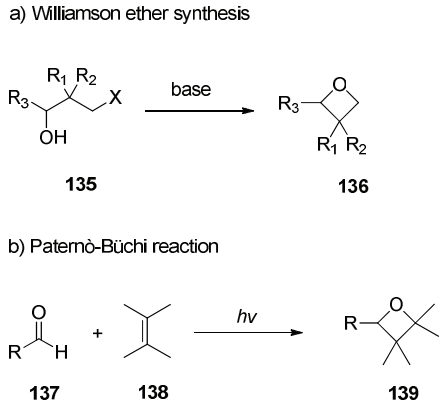
Another naturally occurring oxetane is *Oxetin* (**133**), an amino acid-antimetabolite isolated from the fermentation broth of a *Streptomyces sp.* It can inhibit the growth of *Bacillus subtilis* and *Piricularia oryzae.*[10] Oxetin also exhibits herbicidal activity and is a non-competitive inhibitor of glutamine synthetase. Finally, *Oxatricyciclic Norborane* (**134**) is a potential herbicide and plant growth regulator.[11]

3.1.2. PREPARATION OF OXETANES

There are various strategies for the synthesis of oxetanes, but two general approaches present the widest application (Scheme 3.2).[12] The

intramolecular *Williamson* reaction is the most commonly used reaction for the preparation of oxetanes, which is a ring-closing etherification reaction. Treating a 1,3-halohydrin (**135**) with a base gives the corresponding oxetane (**136**) by deprotonation followed by intramolecular nucleophilic substitution. In general, the slow rate of the reaction often allows competing reactions to take place, namely the conjugate elimination and intramolecular nucleophilic substitution.[13]

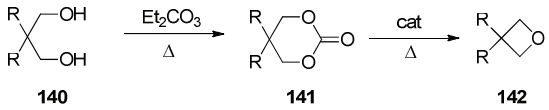
The second method entails a [2+2] cycloaddition, such as the *Paternò-Büchi* reaction. Most carbonyl compounds (**137**) undergo photochemical cyclizations with alkenes (**138**) to give oxetanes (**139**). However, oxetanes that are not substituted in the 2-position cannot be obtained through this reaction.



Scheme 3.2. Main synthetic pathways to obtain oxetanes.

There are less common strategies for the synthesis of oxetanes. An example is the pyrolysis of carbonate esters **141** to obtain 3-substituted oxetanes **142**. The synthesis and subsequent pyrolysis of the carbonate esters of 1,3-diols **140** is the method of choice for the synthesis of 3,3-dialkyloxetanes **142**. The carbonate esters **141** are formed in a simple base

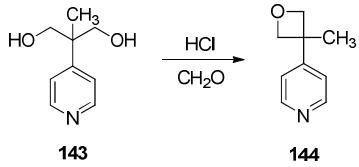
catalyzed transesterification of diethyl carbonate or ethylene carbonate with a 2,2-dialkyl-1,3-diol **140** (Scheme 3.3).[14]



Scheme 3.3. Pyrolisis of carbonate esters **141**.

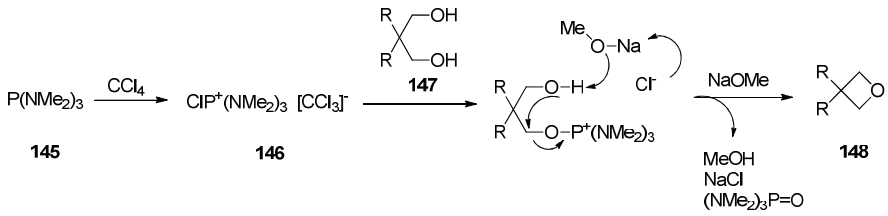
Searles[15] reported the decomposition of 5,5-diethyl-1,3-dioxan-2-one to give 3,3-diethyloxetane at 180–220ºC using copper (II) carbonate-copper (II) hydroxide catalyst, and the same reaction at 350ºC using alumina as the catalyst. The pyrolysis is thought to proceed *via* nucleophilic attack by the catalysts on the carbonyl group, causing an intramolecular Williamson type reaction.

The cyclodehydration of 1,3-diols using strong acids is not a general reaction for the synthesis of oxetanes. However, 2-methyl-2-(4-pyridyl)-1,3-propanediol **143** was converted to 3-methyl-3-(4-pyridyl)oxetanes **144** using hydrochloric acid in the presence of formaldehyde. Formaldehyde was added to suppress the conjugate elimination of formaldehyde and water, which would yield 2-(4-pyridyl)propene (Scheme 3.4).[16]



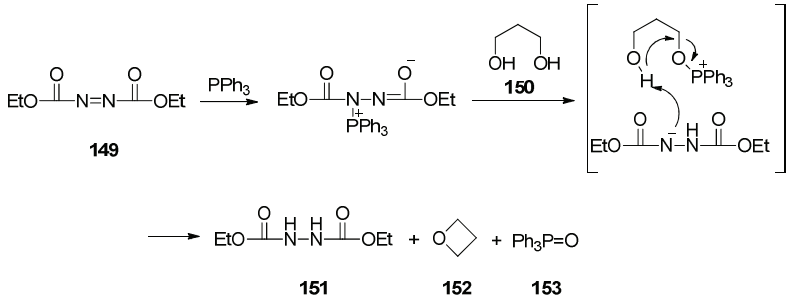
Scheme 3.4. Cyclodehydration of 1,3-diols.

Castro[17] reported yields of 3,3-dialkyloxetanes **148** up to 70% when 2,2-dialkyl-propane-1,3-diols **147** were treated with tris(dimethylamino)phosphine **145** and carbon tetrachloride **146** followed by sodium methoxide (Scheme 3.5).



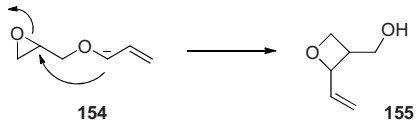
Scheme 3.5. Cyclodehydration of 1,3-diols **147** to give 3,3-dialkyloxetanes **148**.

Following the same direction, the quantitative cyclization of α,ω-diols **1293** was reported by *Carlock*.[18] The diol was added to diethyl azodicarboxylate **149** and triphenyl phosphine, and cyclized instantly at room temperature (Scheme 3.6).



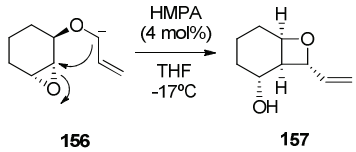
Scheme 3.6. Cyclodehydration of 1,3-diols to give unsubstituted oxetanes.

Another procedure for the synthesis of oxetanes is the deprotonation of allyl glycidyl ethers **154** which has been found to give the 2-vinyloxetanes **155** (Scheme 3.7).



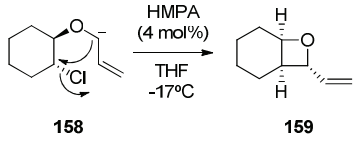
Scheme 3.7. Cyclisation of allyl glycidyl ethers

Still[19] reported an excellent yield of the bicyclic oxetanes **157** on treating the *trans*-epoxy allylic ether **156** with *sec*-butyllithium in tetrahydrofuran containing 4% hexamethylphosphoramide (HMPA) at -17ºC (Scheme 3.8).



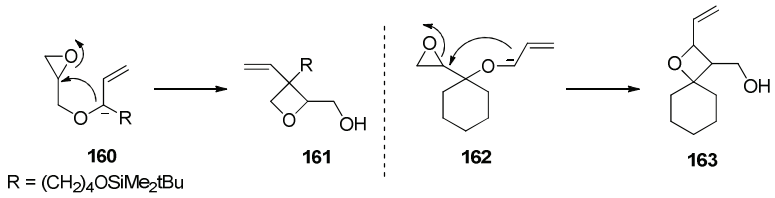
Scheme 3.8. Synthesis of bicyclic oxetane **157**.

Similar results were obtained with *trans*-2-allyloxycyclohexyl chloride **158** which gives good yield of oxetane **159** under the same reaction conditions (Scheme 3.9).



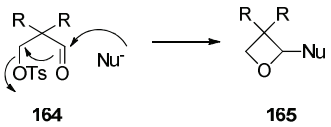
Scheme 3.9. Synthesis of oxetane **159**.

Bird[20] reported good yields of the highly substituted oxetanes **161** and **163** from allyl glycidyl ethers **160** and **162** using similar conditions (Scheme 3.10).



Scheme 3.10. Synthesis of highly substituted oxetanes **161** and **163**.

The cyclisation of carbonyl compounds with good leaving groups in the β-positions has received much attention in the literature. *Nerdel* and co-workers[21] prepared many 2,3,3-trisubstituted systems **165** by the action of a variety of nucleophiles on β-tosyloxyaldehydes **164** (Scheme 3.11).

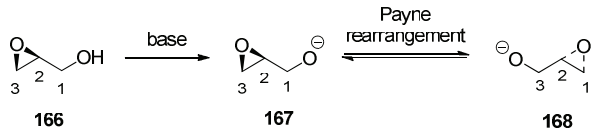


Scheme 3.11. Synthesis of 2,3,3-trisubstituted oxetanes **165**.

Clearly, the importance of oxetanes can be inferred from the significant amount of effort that has led to the development of various methodologies for their synthesis. Our interest in the synthesis of oxetanes stems from our desire to develop methods that convert in a simple and easy manner starting materials into more complex products.

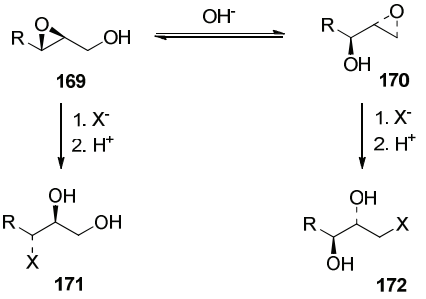
3.1.3. AZA-PAYNE REARRANGEMENT

The Payne rearrangement is a base-mediated isomerization of epoxy alcohols and has been well-utilized in organic synthesis to reveal the latent electrophilicity at C-2 of a 2,3-epoxy-1-ol such as **166** (Scheme 3.12).



Scheme 3.12. Payne rearrangements of 2,3-epoxy-1-ols **166**.

Epoxide migration is reversible, often leading to a mixture of epoxy alcohol isomers. Furthermore, in the presence of hydroxide or other nucleophiles, in situ opening of the equilibrating species may be observed (Scheme 3.13). When such opening is desired, epoxide migration becomes a powerful method for the introduction of functionality into a substrate containing a 2,3-epoxy alcohol moiety. However, when opening is not desired, epoxide migration can become a significant problem.

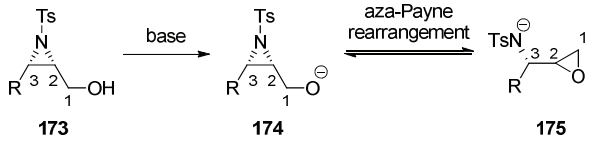


Scheme 3.13. Reversible epoxide migration.

The Payne rearrangement of *trans*-epoxides is not as facile as that of *cis*-epoxides (release of steric strain of *cis*-epoxides is the driving force).[22] However, the presence of an electron-withdrawing atom at C-4 or C-5 of the epoxy alcohol is sufficient for successful tetrahydrofurane formation with 2,3-disubstituted epoxy-1-ols. Certain substrates, mainly

alkyl-disubstituted and trisubstituted 2,3-epoxy-1-ols, do not undergo sufficient Payne rearrangement to allow for successful nucleophilic attack on the less hindered 1,2-epoxy-3-ol.

In contrast to the Payne rearrangement, the aza-Payne rearrangement of activated 2,3-aziridin-1-ols **173** (Scheme 3.14) has not received as much attention, despite its great potential for the synthesis of nitrogen-containing compounds.[23]



173 **174** **175**

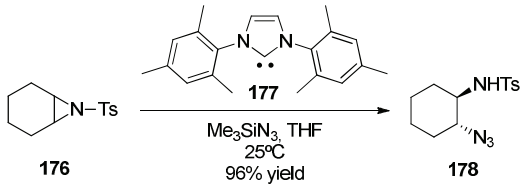
Scheme 3.14. Aza-Payne rearrangement of activated 2,3-aziridin-1-ols **173**.

Ibuka and co-workers have described the aza-Payne rearrangement of a series of *cis*- and *trans*-2,3-disubstituted aziridin-1-ols, as well as the reaction of the resulting epoxy amines with a few selected nucleophiles, including organocuprates and amines.[23] A particularly useful feature of the aza-Payne rearrangement is that, under aprotic conditions, the equilibrium for both *cis*- and *trans*-disubstituted 2,3-aziridin-1-ols lies exclusively toward the epoxy amine. This may result from the greater ability of the activated amine to stabilize the negative charge under the basic reaction conditions and/or the greater thermodynamic stability of the epoxy amine *vs* the aziridinol.[24] The same authors[25] determined that for the aza-Payne rearrangement of 3-methyl-*N*-tosyl-2-aziridinemethanol to yield the corresponding epoxy sulphonamide, bases such as NaH, *tert*-BuOK and KH gave satisfactory results, although DBU, BuLi and LDA were inappropriate for clean and efficient rearrangements.

3.1.4. ORGANOCATALYTIC TRANSFORMATION OF AZIRIDINES PROMOTED BY NHCS

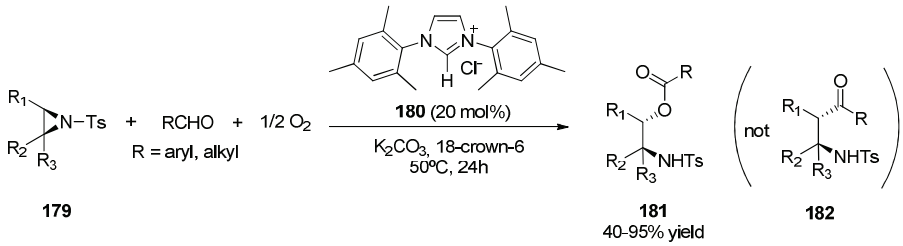
Apart from serving as valuable ligands for transition metals, the use of *N*-Heterocyclic carbenes (NHCs) as potent organocatalysts has attracted considerable attention in recent years. NHCs have been widely used to catalyze organic reactions such as condensations, nucleophilic substitutions, transesterifications and acylation reactions, 1,2-additions, Diels-Alder cycloadditions, and redox processes.[26] In most cases, NHC served as nucleophilic species to initiate the reactions. There have been reports that a hydrogen-bonded intermediate was formed between NHC and alcohol in the transesterification reaction.[27] Most of these synthetic transformations involve initial activation of the diaminocarbene with aldehydes, forming homoenolates.[28]

In the course of studies on the transformations of aziridines, small organic molecules such as phosphines, amines, and nitriles have been utilized as catalysts to effect ring-opening reactions of aziridines.[29] However, there are just a few reports studying the transformation of aziridines catalyzed by NHCs. In 2006, *Wu* et al.[30] described the use of an N-heterocyclic carbene as an efficient catalyst in the desymmetrization of *meso*-aziridines with trimethylsilyl azide ($TMSN_3$) under mild reaction conditions. The advantages of this method include: i) employing easily available *N*-heterocyclic carbene as the catalyst, ii) experimental ease of operation, iii) mild conditions, and iv) good substrate generality. A typical example involves the conversion of aziridine **176** into **178** at room temperature and in 96% yield using the N-heterocyclic carbene **177** (Scheme 3.15).



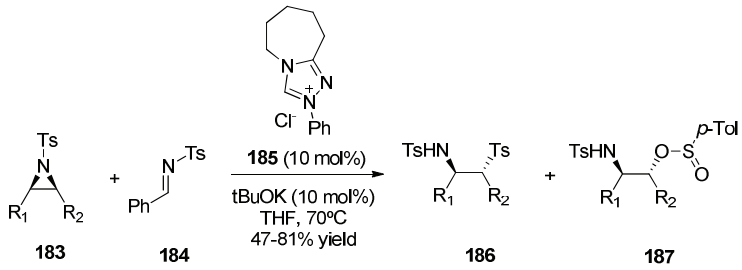
Scheme 3.15. Aziridine ring-opening reaction with $TMSN_3$ in the presence of *N*-heterocyclic carbenes.

Simultaneously, the same authors[31] also described the first highly chemoselective ring-opening reaction of N-tosyl aziridines **179** with aldehydes catalyzed by an N-heterocyclic carbene **180** under aerobic conditions. In this case, unexpected carboxylates of 1,2-amino alcohols **181** from the corresponding aldehydes, rather than the acyl anion ring-opened α-amino ketones **182**, were exclusively obtained (Scheme 3.16).



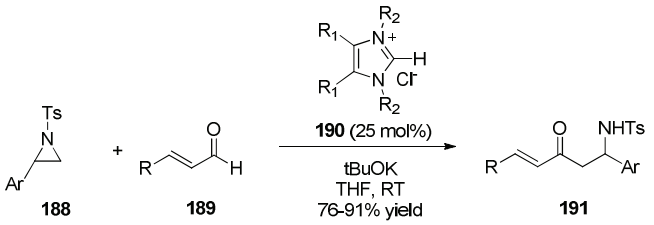
Scheme 3.16. Ring-opening reaction of aziridines with aldehydes catalyzed by carbenes under aerobic conditions.

In 2008, *Dai* and co-workers[32] developed an unexpected tosyl-transfer from the reaction of *N*-tosylimines **184** with aziridines **183** catalyzed by N-heterocyclic carbenes derived from the salt **185** (Scheme 3.17).



Scheme 3.17. Unexpected tosyl-transfer from *N*-tosylimines in the reaction with aziridines catalysed by NHCs.

Finally, in 2010 *Singh* and co-workers[33] developed the first example of NHC catalyzed synthesis of β-amino-α,β-unsaturated ketones **191** via regioselective ring-opening of terminal aziridines **188** with enals **189** (Scheme 3.18).

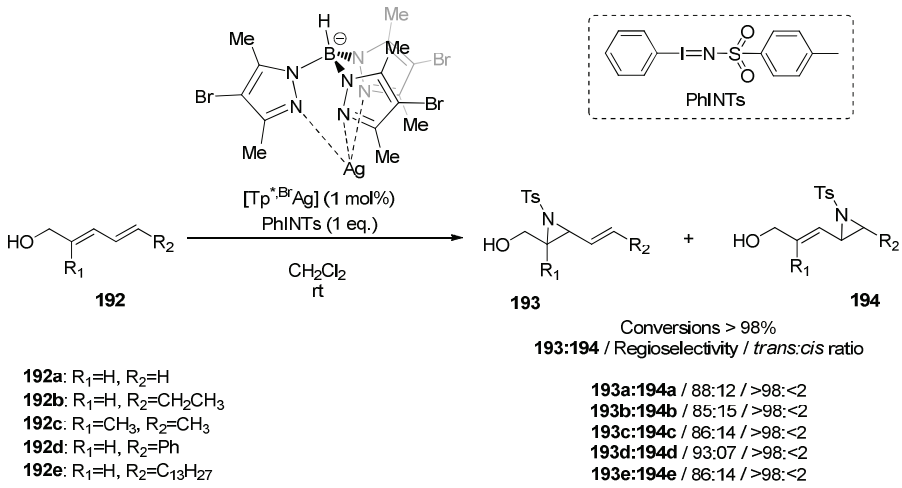


Scheme 3.18. NHC-catalyzed synthesis of β-amino ketones **191**.

3.2. OUTLOOK & CONCEPT

Due to the biological and chemical activities of aziridines, new methods for direct and selective C-N bond formations have been developed.[34] In this context, the nitrogen-atom transfer to alkenes is a particularly appealing strategy for the generation of aziridines due to the availability of olefinic starting materials and the direct nature of such a process. Following the previous works in this field,[35] our group developed an efficient, regioselective and stereospecific method of aziridination of 1,4-

diene-1-ols (**192a-e**) for the production of hydroxymethyl vinyl aziridines (**193a-e**) (Scheme 3.19).[36]

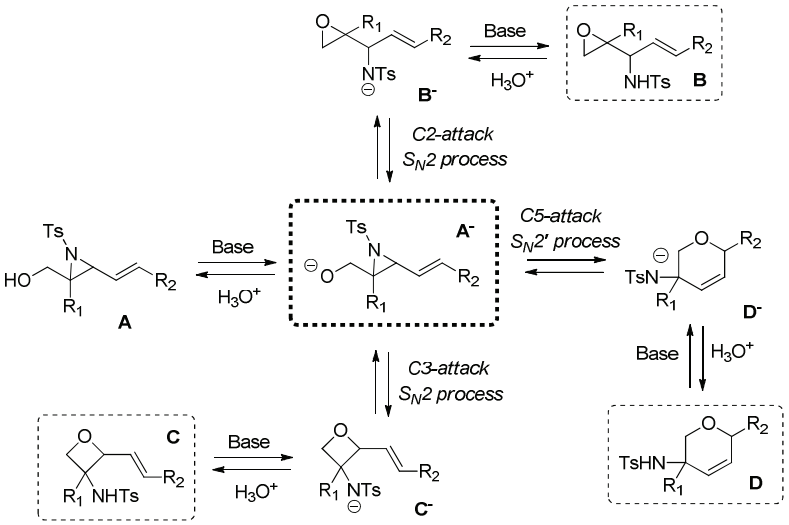


Scheme 3.19. Silver-catalyzed regio- and stereospecific aziridination of dienols.

The key to the success of this methodology was the identification of an efficient catalytic system with the following relevant characteristics: i) [Tp^{*,Br}Ag] resulted to be the more active catalysts providing exclusively *trans* aziridines from *E*-alkenes, and *cis* aziridines from *Z*-alkenes in a stereospecific manner, ii) the regioselectivity was driven by the OH group, the aziridine resulting from aziridination of the double bond close to the OH being mainly obtained, iii) the process is highly regioselective for conjugated dienes (Scheme 3.19) but not for non-conjugated dienes and for homoallylic alcohols.

The establishment of a procedure for the synthesis of *cis*- and *trans*-vinyl aziridin-1-ols[36] together with the successful development of the *Ibuka's* aza-Payne rearrangement of a series of *cis*- and *trans*-disubsituted aziridin-1-ols,[23] encouraged us to explore a Payne-type rearrangement of the

novel hydroxymethyl vinyl aziridines because the vinyl moiety could act as a regiochemical-directing center and as such, new rearrangements could be expected (Scheme 3.20).



Scheme 3.20. General concept for the aza-Payne and related rearrangement of vinyl aziridin-1-ols.

Therefore, it was envisaged that under aza-Payne conditions, hydroxymethyl vinyl aziridines could lead to the preparation of oxygen-heterocycles through a new Payne-type rearrangement. In general terms, the desired Payne-type rearrangement was envisioned to proceed *via* base-deprotonation of the hydroxylic group of the vinyl aziridine **A** to obtain the corresponding anionic product **A**$^-$. Subsequently, a consecutive intramolecular ring-opening/ring-closing reaction at the C2, C3 or C5 center by a nucleophilic attack through a S_N2 or S_N2' process would yield vinyl epoxides **B**, vinyl oxetanes **C** or hydropyranes **D**.

An alternative mechanism for the aza-Payne rearrangement was also visualized. This mechanism could be conceived via catalytic activation of substrate promoted by a Brønsted base catalyst. In this case, the aza-Payne rearrangement starts with the activation of the hydroxyl group of vinyl aziridine **A** by hydrogen bonding to the Brønsted base that concomitantly induces an intramolecular ring-opening attack onto the vinyl aziridine. Such a pathway would provide the oxygen-heterocycle with regeneration of the Brønsted base thus sustaining the catalytic cycle. Since previous reports indicated that hydroxyl groups are prone to activation by NHCs,[37] this type of aza-Payne rearrangement could be promoted by N-Heterocyclic carbenes.

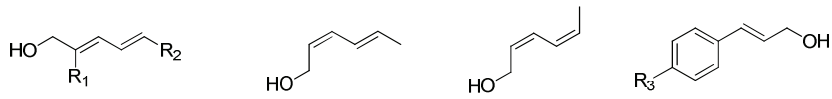
In this context, we decided to study an Aza-type rearrangement of a series of *cis*- and *trans*-vinyl aziridin-1-ols using several bases and NHC carbenes as promoters and in the present chapter, the results and discussion corresponding to the first objective of this thesis will be presented. Further optimization of their synthesis using other promoters is also included.

3.3. RESULTS AND DISCUSSION

As mentioned above, the aza-Payne rearrangement of hydroxymethyl aziridines have received less attention than the Payne rearrangement of hydroxymethyl epoxides. In particular, the aza-Payne rearrangement of hydroxymethyl *vinyl* aziridines did *not* receive any attention. The efficient novel procedure for the synthesis of hydroxymethyl vinyl aziridines developed by our group in 2010, gave us the opportunity to study the aza-Payne rearrangement of a series of *cis*- and *trans*-2,3-disubstituted vinyl aziridin-1-ols.

3.3.1. SYNTHESIS OF VINYL AZIRIDINOLS

To this end a set of diene-1-ols with different substitution at the double bonds as well as different configuration at the double bonds (*Z*:*E*) were prepared in order to be aziridinated (Scheme 3.21).



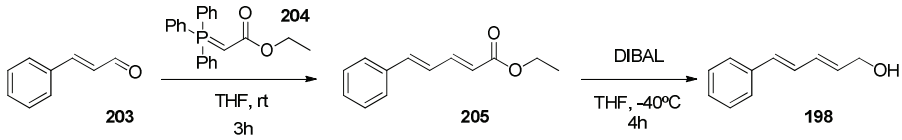
195: R_1=H, R_2=H
196: R_1=CH_3, R_2=H
197: R_1=CH_2CH_3, R_2=CH_3
198: R_1=H, R_2=C_6H_5

199 **200**

201: R_3=H
202: R_3=NO_2

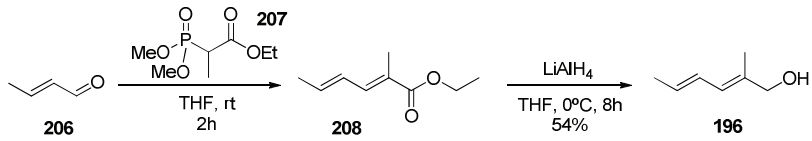
Scheme 3.21. Set of diene-1-ols prepared.

The enols **195** and **201** are commercially available, while dien-1-ol **198** was prepared by a Wittig olefination of cinnamaldehyde **203** with stabilized ylide phosphine **204** giving unsaturated ester **205** in 89% yield. The ester was reduced to 2,4-dienen-1-ol **198** with DIBAL at –40ºC in a 56% yield (Scheme 3.22).[38]



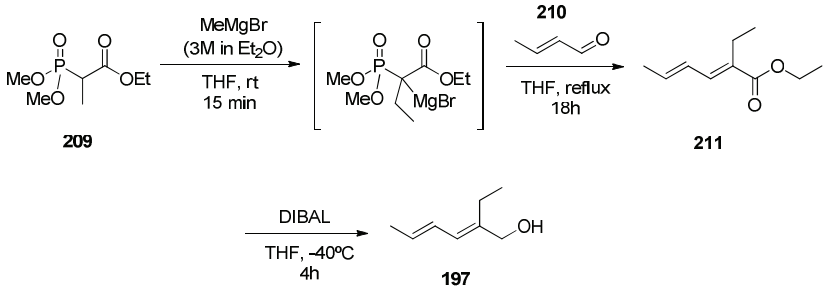
Scheme 3.22. Preparation of dien-1-ol **198**.

Branched dien-1-ol **196** was obtained in 54% yield from the reduction of the corresponding ester **208**, which was prepared by an olefination reaction between crotonaldehyde **206** and methylphosphonate **207** (Scheme 3.23).



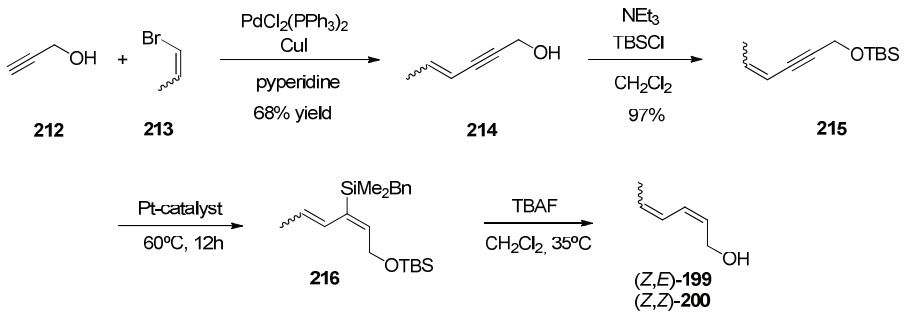
Scheme 3.23. Preparation of dien-1-ol **196**.

Compound **197** was prepared by a Wadsworth-Emmons olefination from the stabilized phosphonate **209** by reaction with methylmagnesium bromide and crotonaldehyde **210** to give the unsaturated ester **211** in a 83% yield. The ester was reduced to **197** with DIBAL at –40ºC in a 64% yield (Scheme 3.24).[39]



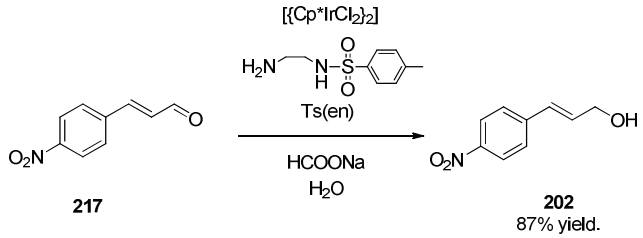
Scheme 3.24. Preparation of dien-1-ol **197**.

Compounds **199** and **200** were prepared from the corresponding *E*- and *Z*-bromopropene **213** and propargyl alcohol **212** by a Sonogashira cross-coupling reaction.[40] Enyne **214** was protected as silyl ether to afford compound **215** in 97% yield.[41] Pt-catalyzed hydrosilylation of compound **215** afforded compound **216** following a reported procedure,[42] and TBAF treatment provided the dienes **199** and **200** in 63% and 56% yield, respectively, over two steps by a protodesilylation and deprotection of silyl ether group (Scheme 3.25).[43]



Scheme 3.25. Preparation of dien-1-ols **199** and **200**.

Compound **202** was prepared by transfer hydrogenation of aldehyde **217** with an iridium catalyst in 87% yield (Scheme 3.26).[44]



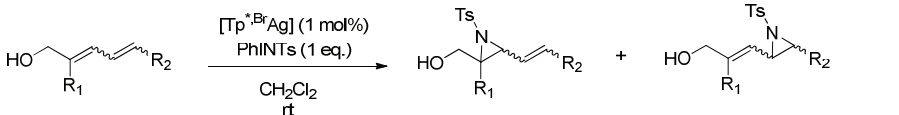
Scheme 3.26. Preparation of dien-1-ol **202**.

The aziridination of dien-1-ols **195-202** was done following the literature procedure reported by our group (Table 3.1).[36] This methodology is based on the nitrene transfer addition to the corresponding 1,4-hexadien-1-ol 18 using 1 equivalent of PhINTs as the nitrene source and 1 mol% of the [Tp^{*,Br}Ag] catalyst, in the presence of dichloromethane (0.02 M) as solvent.

In summary, all the products afforded preferentially the aziridination of the double bond close to the hydroxylic group; the [Tp^{*,Br}Ag] catalyst shows an excellent stereoselectivity providing

exclusively aziridines trans from *E*-alkenes, and aziridines *cis* from *Z*-alkenes, in excellent conversions (up to 98%). Using this methodology hydroxymethyl vinyl aziridines (**195- 200**) were obtained in essentially quantitative yield. However, these aziridines decomposed after column chromatography driving us to explore their reactivity directly in the reaction mixture.

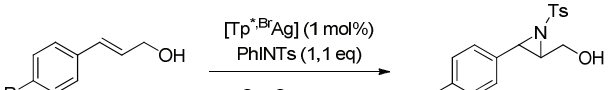
Table 3.1. Aziridination of dien-1-ols **195-202**.[a]



195: (*E*,*E*) R_1=H, R_2=H
196: (*E*,*E*) R_1=CH_3, R_2=H
197: (*E*,*E*) R_1=CH_2CH_3, R_2=H
198: (*E*,*E*) R_1=H, R_2=C_6H_5
199: (*Z*,*E*) R_1=H, R_2=H
200: (*Z*,*Z*) R_1=H, R_2=H

218: (*E*,*E*) R_1=H, R_2=H
220: (*E*,*E*) R_1=CH_3, R_2=H
222: (*E*,*E*) R_1=CH_2CH_3, R_2=H
224: (*E*,*E*) R_1=H, R_2=C_6H_5
226: (*Z*,*E*) R_1=H, R_2=H
228: (*Z*,*Z*) R_1=H, R_2=H

219: (*E*,*E*) R_1=H, R_2=H
221: (*E*,*E*) R_1=CH_3, R_2=H
223: (*E*,*E*) R_1=CH_2CH_3, R_2=H
225: (*E*,*E*) R_1=H, R_2=C_6H_5
227: (*Z*,*E*) R_1=H, R_2=H
229: (*Z*,*Z*) R_1=H, R_2=H



201: R = H
202: R = NO_2

230: R = H
231: R = NO_2

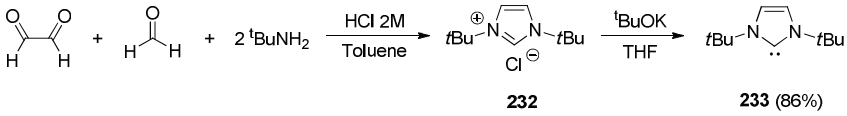
Entry	Diene	Product	Conv (%)[b]	Regioselectivity[b]	*trans*:*cis* ratio (%)[b,c]
1	**195**	**218/219**	>99	90:10	>98:<2[d]
2	**196**	**220/221**	>99	98:2	>98:<2[d]
3	**197**	**222/223**	>99	90:10	>98:<2[d]
4	**198**	**224/225**	>99	87:13	>98:<2[d]
5	**199**	**226/227**	>99	90:10	<2:>98[e]
6	**200**	**228/229**	>99	98:2	<2:>98[e]
7	**201**	**230**	76 (34)[f]	--	>98:<2[d]
8	**202**	**231**	87 (44)[f]	--	>98:<2[d]

[a][cat]:[PhINTs]:[diene] = 1:20:20, referred to 0.0125 mmol of catalyst, 4h, room temperature. $TsNH_2$ accounted for 100% initial PhINTs not converted into aziridines. [b]Determined by ^1H NMR. [c]Ratio *trans:cis* for the major aziridine. [d]*cis* isomer not detected. [e]*trans* isomer not detected. [f]Isolated yield.

3.3.2. PRELIMINARY RESULTS & MECHANISTIC STUDY

Vinyl aziridinol **218** was used as the model substrate for preliminary studies. Initially, the aza-Payne rearrangement of **218** was tested in the presence of different bases such as DBU, K_2CO_3, NaH, KH, KO^{t}Bu, $CsCO_3$ and the free carbene 1,3-di-*tert*-butylimidazol-2-ylidene (I^{t}Bu, **233**).

Carbene **233** was synthesized in two steps using the assembly route to create the imidazole ring starting from glyoxal, formaldehyde and *tert*-butylamine in the presence of hydrochloric acid. The free carbene was generated from precursor **232** by reaction with potassium *tert*-butoxide. Sublimation delivers the stable and pure carbene I^{t}Bu in 86% global yield (Scheme 3.27).[45]



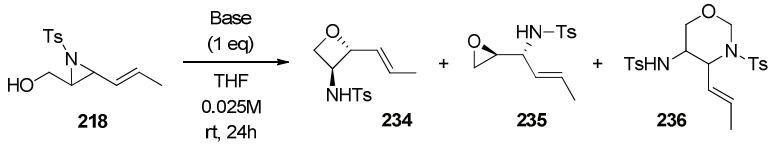
Scheme 3.27. Synthesis of free carbene I^{t}Bu.

The reaction was performed at room temperature using a stoichiometric amount of base. Thus, once vinyl aziridinol **218** was generated in situ, the dichloromethane present in the reaction mixture was evaporated and the resulting mixture was re-dissolved in 4 ml of tetrahydrofuran. Next, the mixture was treated with 1 equivalent of the corresponding base at room temperature. The evolution of the reaction was controlled by ^{1}H-NMR spectroscopy. The results are summarized in Table 3.2.

The attempted rearrangement reaction of vinyl aziridinol **218** with NaH, KO^{t}Bu and KH (Table 3.2, entries 1, 2 and 3) in THF led to the

recovery of the starting material. These results suggest that the rearrangement rates are dependent upon the base concentration used, because *Ibuka*'s rearrangement rates of 3-methyl-*N*-tosyl-2-aziridinemethanol to yield the corresponding epoxy sulphonamide, proceeds completely in the direction of the epoxy sulphonamide using 4 equivalents of base.[46] Interestingly, the treatment of the vinyl aziridinol **218** with I^{t}Bu (1 equiv.) in THF at room temperature provided total conversion after 30 minutes to a complex mixture of products. Unexpectedly, after column chromatography, product **236** was isolated in 10% yield.

Table 3.2. Base screening in the study of the aza-Payne reaction of **218**.[a]



Entry [b]	Base	% Conversion[c]	% Selectivity (234:235:236) [c]
1	NaH	< 2	--
2	*tert*-BuOK	< 2	--
3	KH	< 2	--
4	K_2CO_3	< 2	--
5	$CsCO_3$	< 2	--
6	DBU	< 2	--
7	I^{t}Bu	> 98[d]	0:0:10

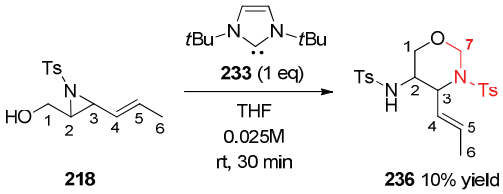
[a]Vinyl aziridine **218** was formed in situ from the corresponding allylic alcohol (0.1 mmol) and PhINTs as a nitrene source (0.11 mmol) in the presence of [Tp*,^{Br}Ag] as catalyst (0.001 mmol) in 5 ml of CH_2Cl_2. [b]General reaction conditions: **218** (0.1 mmol), base (0.1 mmol) in THF (4ml); t = 24h. [c]Determined by ^{1}H-NMR. [d]Product **234** was obtained in 10% isolated yield.

The attempted rearrangement reaction of vinyl aziridinol **218** with NaH, *tert*-BuOK and KH (Table 3.2, entries 1, 2 and 3) in THF led to the recovery of the starting material. These results suggest that the

rearrangement rates are dependent upon the base concentration used, because *Ibuka*'s rearrangement rates of 3-methyl-*N*-tosyl-2-aziridinemethanol to yield the corresponding epoxy sulphonamide, proceeds completely in the direction of the epoxy sulphonamide using 4 equivalents of base.[47] Interestingly, the treatment of the vinyl aziridinol **218** with I^{t}Bu (1 equiv.) in THF at room temperature provided total conversion after 30 minutes to a complex mixture of products. Unexpectedly, after column chromatography, product **236** was isolated in 10% yield.

The formation of **236** was confirmed by its ^{1}H and ^{13}C NMR spectral data (Table 3.3.). The ^{1}H-NMR spectrum of product **236** shows a new doublet signal at 4.88 ppm corresponding to the protons (H-7) of the methylene group directly linked to the oxygen and nitrogen centers, and the presence of two sets of signals in the aromatic region indicates the existence of two tosyl groups. It was also observed that the H-3 and C-3 centers were shifted to higher fields (5.3 and 73.9 ppm, respectively) in comparison to the corresponding vinyl aziridines (3.3 and 48.5 ppm, respectively), which indicates that the C-3 allylic position was also adjacent to the nitrogen atom of the new tosyl amino moiety. All the observations extracted from this table were further confirmed by two-dimensional NMR spectroscopy experiments (COSY, NOESY, HSQC and HMBC) and mass spectroscopy. As represented in Table 3.3, compound **236** presents a new carbon center (C7) and a new *N*-tosyl moiety. As a result of this interesting unexpected incorporation, we decided to study the mechanism of the formation of **236**.

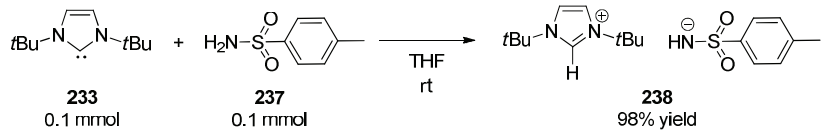
Table 3.3. Characterization of **218** and **236** by ^{1}H and ^{13}C-NMR spectroscopy.[a]



218 **236** 10% yield

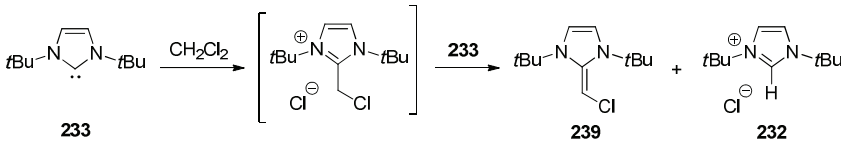
Compound/NMR			1	1'	2	3	4	5	7
218	^{1}H-NMR ($CDCl_3$)	δ	3.99	3.77	3.19	3.3	5.51	5.84	--
		M	dd	dd	ddd	dd	dd	dt	--
		J	12.8 3.2	12.8 6.6	6.6 4.4 3.2	8.8 4.4	15.2 8.8	15.2 6.4	--
	^{13}C-NMR	δ	61.0	61.0	49.6	48.5	129.9	127.7	--
236	^{1}H-NMR ($CDCl_3$)	δ	4.23	3.65	3.25	5.30	5.55	5.29	4.88
		M	dd	dd	m	d	dq	ddq	d
		J	3.2 1.6	12 1.6	--	10.4	15 6.5	15 9.2 1.6	11
	^{13}C-NMR	δ	67.8	67.8	50.8	73.9	124.7	129.9	73.9

The incorporation of the new *N*-tosyl moiety in compound **236** could be due to a slight amount of tosyl amide **237** which remains in the reaction mixture after the formation of vinyl aziridine **218**. To study the possible role of tosyl amide in the formation of **236**, an equimolecular amount of tosyl amide (**237**) and I^{t}Bu (**233**) were mixed in THF (Scheme 3.28). After just a few seconds, the initially homogeneous mixture became heterogeneous due to the formation of a white precipitate. The white precipitate turned out to be the corresponding imidazolium salt **238** resulting from the acid-base reaction between the NHC-**233** (p*K*a = 23)[48] and the tosyl amide **237** (p*K*a = 16.1).[49]



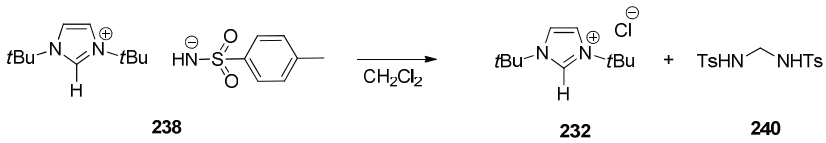
Scheme 3.28. Study of the reactivity of tosyl amide in the presence of I^{t}Bu (**233**).

We hypothesize that the new carbon center **C7** present in compound **236** could originate from the slight amount of methylene chloride that remains in the reaction mixture after the formation of vinyl aziridine **218**. It has been reported that the reaction of the NHC-**233** with methylene chloride proceeds rapidly through cleavage of the C-Cl bond, producing a 2-(chloromethyl)imidazolinium ion (Scheme 3.29).[50] Another free molecule of carbene is sufficiently basic to deprotonate this intermediate and, therein, methyleneimidazolidine **239** is formed altogether with imidazolium salt **232**.



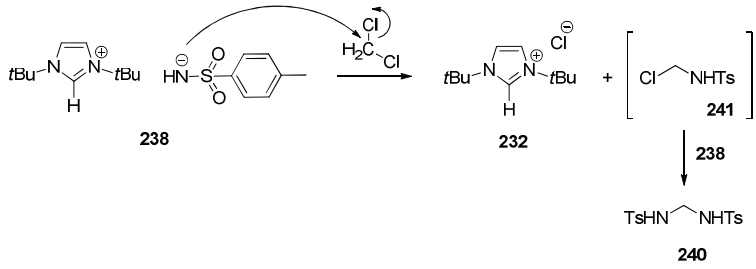
Scheme 3.29. Side-reaction of I^{t}Bu (**233**) with CH_2Cl_2.

In continuation of our study of the role of methylene chloride in the formation of **236**, once the imidazolium salt **238** was formed, the THF present in the reaction mixture was evaporated and the mixture was re-dissolved in methylene chloride (Scheme 3.30). Interestingly, the formation of a new unpolar product **240** and the imidazolium ion **232** was observed, which were both characterized by NMR spectroscopy.



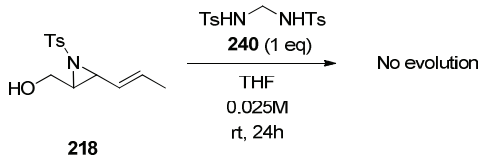
Scheme 3.30. Reactivity study of imidazolium salt **238** with methylene chloride.

Apparently the reaction of the imidazolium anion **238** with methylene chloride proceeds through cleavage of the C-Cl bond *via* a S_N2 process, producing an *N*-chloromethyl-tosyl amide **241**. Another tosylamido anion of the imidazolium salt is again sufficiently nucleophilic to substitute the C-Cl of the *N*-chloromethyl-tosyl amide and in this way *N*,*N*'-methylenebis(4-methylbenzenesulfonamide) **240** is formed together with the imidazolium salt **232** (Scheme 3.31).



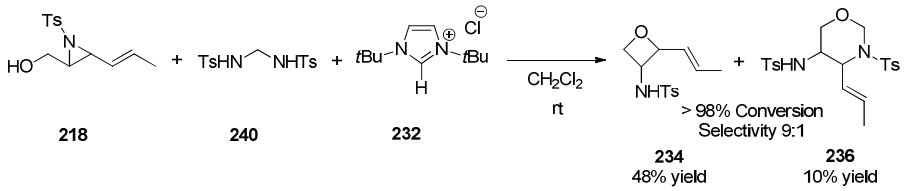
Scheme 3.31. Proposed mechanism for the formation of **240**.

After isolation of *N*,*N*'-methylene-bis(4-methylbenzenesulfonamide) **240** in quantitative yield, hydroxymethyl vinyl aziridine **218** was mixed with one equivalent of **240** in THF at room temperature but no evolution of the reaction was observed and the starting material was recovered (Scheme 3.32).



Scheme 3.32. Reactivity study of hydroxymethyl vinyl aziridine **218** with **240**.

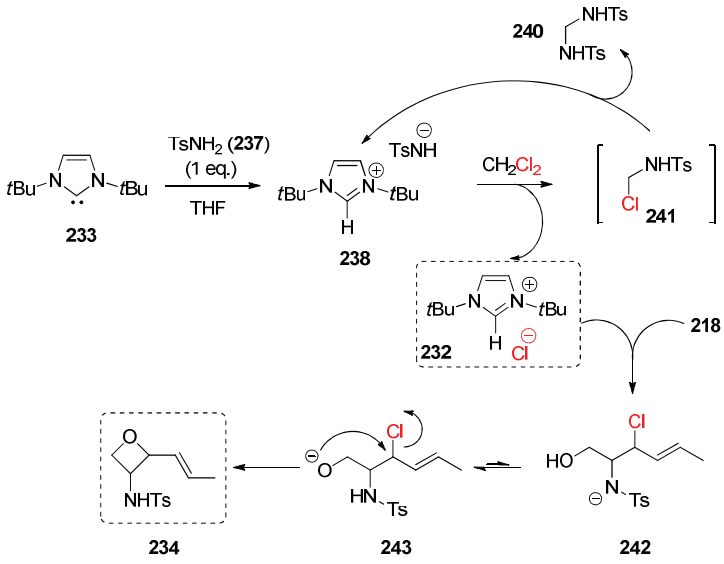
Surprisingly, when vinyl aziridine **218** was added directly in the reaction mixture represented in Scheme 3.30 in methylene chloride at room temperature, the formation of both, vinyl oxetane **234** and vinyl tetrahydro oxazine **236** was observed in a selectivity ratio of 9:1, determined by ^{1}H-NMR of the reaction crude, affording preferentially vinyl oxetane **234** in 48% yield (Scheme 3.33).



Scheme 3.33. Reactivity of vinyl aziridine **218** in the presence of **240** and **232**.

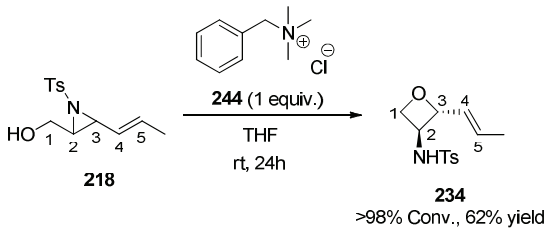
Since, vinyl aziridine **218** do not react with compound **240**, the following mechanism was proposed for the formation of vinyl oxetane **234** from vinyl aziridinol **218** in the presence of NHC-**233** (Scheme 3.34). The formation of the imidazolium salt **238**, as a result of the acid-base reaction between NHC-**233** and tosyl amide **237**, led to a mixture of **232** and **240** after reaction with methylene chloride (Scheme 3.31). We speculated that the presence of the chloride anion present in the imidazolium salt **232** would led to the formation of the vinyl oxetane **234**; the free chloride anion is expected to act as nucleophile in a ring-opening reaction of the vinyl aziridine **218** through a S_N2 type process. Next, the corresponding aza-anion

242 of *N*-tosyl-3-chloride-2-aziridinemethanol is expected to undergo acid-base proton exchange to the corresponding oxa-anion **243**, which will give the formation of vinyl oxetane sulfonamide **234** through an intramolecular nucleophilic substitution.



Scheme 3.34. Proposed mechanism for the synthesis of vinyl oxetane **234**.

With the purpose to confirm the role of the chloride anion in the formation of vinyl oxetane **234** an equimolecular mixture of benzyltrimethylammonium chloride (**244**) and vinyl aziridine **218** was prepared in THF at room temperature. After 24h, the desired vinyl oxetane was formed with full conversion in 62% yield (Scheme 3.35). The formation of the vinyl oxetane **234** was confirmed by its ^{1}H and ^{13}C NMR spectral data. The ^{1}H- and ^{13}C-NMR spectrum of the product **234** showed that the chemical shifts of H-3 and C-3 centers were shifted to higher fields (4.5 and 69.9 ppm, respectively) in comparison with the initial vinyl aziridines (3.3 and 48.5 ppm, respectively), which indicates that the C-3 vinylic position was adjacent to an oxygen atom, and the only one is the hydroxyl moiety presents in the vinyl aziridine-1-ol.

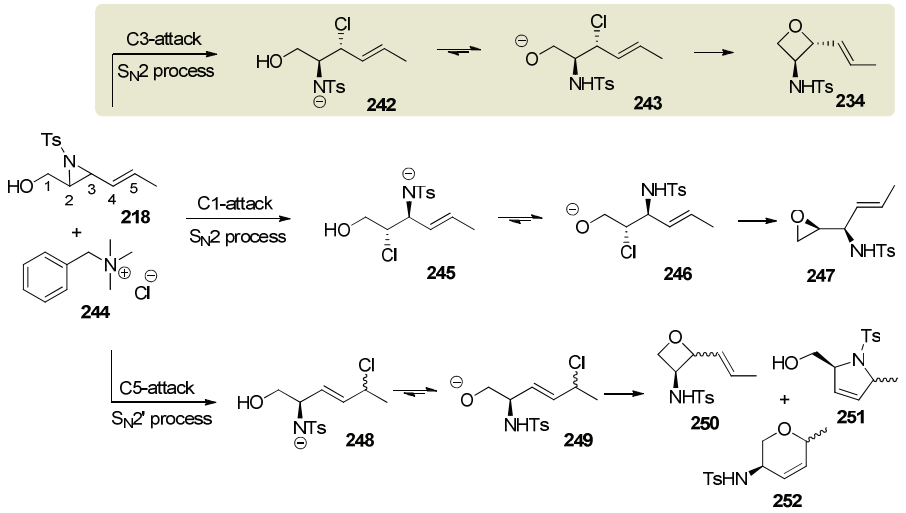


Scheme 3.35. Reaction of vinyl aziridine **218** in the presence of benzyltrimethylammonium chloride (**244**).

All the observations extracted from the ^{1}H- and ^{13}C-NMR spectrums were further established by two dimensional NMR spectroscopy experiments (COSY, NOESY, HSQC and HMBC) and mass spectroscopy.

After this result, it seems clear that the chloride anion is responsible for the conversion of vinyl aziridinol **218** to the vinyl oxetane **234**. The reaction is expected to proceed through a consecutive one-pot ring-opening/ring-closing reaction promoted by the chloride source. It is important to note that several competing ring-opening reactions of the vinyl aziridinol **218** at C2, C5 or C2 by the chloride anion prior the ring-closing could occur and as such, several products could then be obtained, depending on the relative nucleophilicities of the oxygen and nitrogen anions to form oxetanes **250**, epoxides **247**, pyrrolidines **251** and hydropyranes **252** (Scheme 3.36). However, only the formation of vinyl oxetane **234** was observed.

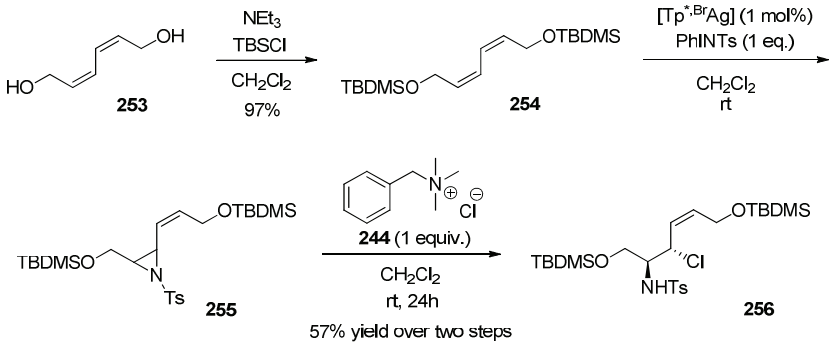
Several factors and experiments were crucial to explain the exclusive formation of vinyl oxetane **234** via a potential sequence of events (C3-S_N2 chloride ring-opening; hydrogen transfer from the oxa-anion to the aza-anion; ring-closure).



Scheme 3.36. Possible competing ring-opening/ring-closing reactions of vinyl aziridinol **218** in the presence of a chloride source **244**.

First, tetraalkylammonium halides have earlier been reported to ring-open aziridines in the presence of β-cyclodextrin[51] and ammonium-12-molybdophosphate,[52] and ring-opening by fluoride ion with TBAF has also been reported.[53] In particular, *Ghorai et al.*[54] reported that tetraalkylammonium halides act as an efficient reagent for the regioselective ring-opening of (*R*)-2-phenyl-*N*-sulfonylaziridines by halides without racemization of the corresponding products through a S_N2-type process. In order to confirm that the conversion of vinyl aziridinol **218** to vinyl oxetanes **234** occurs via a β-haloamide intermediate formation after a regioselective S_N2-type ring-opening process, the following study was conducted (Scheme 3.37). (2*Z*,4*Z*)-2,4-hexadiene-1,6-diol (**253**) was protected as a *tert*-butyldimethylsilyl ether to afford compound **254** in 97% yield. Compound **254** was treated under the standard aziridination conditions and the *cis,cis*-vinyl aziridine **255** was obtained with total conversion and up to 98% stereoselectivity. The solvent of the aziridine reaction mixture was evaporated and re-dissolved in THF. Then, 1

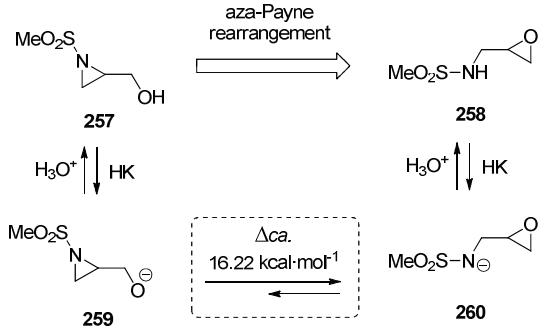
equivalent of benzyltrimethylammonium chloride (**244**) was added at room temperature. After 24h, the regioselective ring-opening reaction gave the desired β-haloamide product **256** resulting from a S_N2-type process, with full conversion in 57% of yield over two reaction steps.



253 **254** **255** **256**

Scheme 3.37. Experimental study to confirm the proposed β-haloamide intermediate.

Second, the corresponding aza-anion **242** (Scheme 3.36) is expected to undergo acid-base proton exchange to the corresponding oxa-anion **243** as was determined by *Ibuka*'s group in 1995.[55]



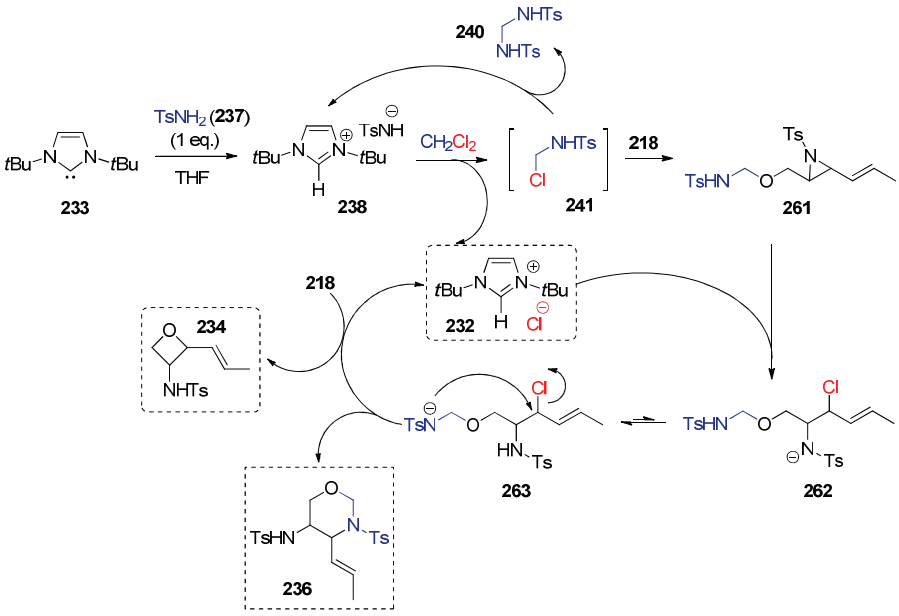
257 **258** **259** **260**

Scheme 3.38. Theoretical study of the aza-Payne isomerization phenomenom.

They determined that the oxa-anion species **259** of an *N*-mesyl-2-hydroxymethyl aziridine **257** was more stable than the aza-anion **260** of the corresponding epoxy sulfonamide **258** in aprotic solvents (Scheme 3.38). Consequently, the vinyl oxetane sulfonamide **234** could be formed after the intramolecular nucleophilic substitution.

And *third*, the reaction is expected to proceed through a ring-opening and subsequently ring-closing reaction both *via* S_N2 type process and as such, with retention of configuration at the C3 center. Therefore, starting from a *trans*-aziridine the *trans*-oxetane would be obtained. Our results showed that the *trans*-aziridinol **218**, led to the corresponding *trans*-disubstituted oxetane ring **234**. The relative stereochemistries were verified by NOE experiments of the *trans*-oxetane **234** that didn't showed enhancement of the H-2 proton when H-3 was irradiated (See *Section 5.3.3* of this chapter).

With these results in hand, we were encouraged to propose an integrated mechanism for the formation of the oxazine **236** and the oxetane **234** (Scheme 3.39). As mentioned above, imidazolium tosyl amide **238** (see Scheme 3.34) reacts with methylene chloride *via* an S_N2 type process, producing *N*-chloromethyl-tosyl amide **241**. The carbon center of this intermediate (**241**) is expected to be sufficiently electrophilic to undergo the nucleophilic attack of the hydroxyl group of **218** through an S_N2 type process, giving the corresponding hemiacetal product **261**. Simultaneously, another free amide anion of **238** is again sufficiently nucleophilic to form *N*,*N*'-methylenebis(4-methylbenzenesulfonamide) **240** together with imidazolium salt **232**.



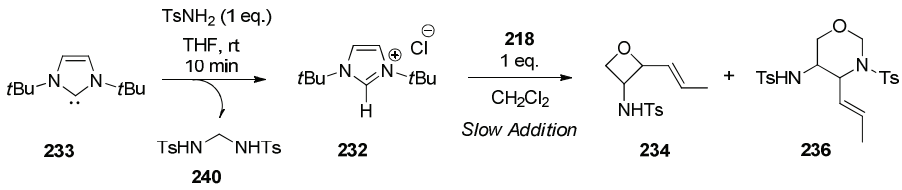
Scheme 3.39. Proposed mechanism for the formation of **236**.

Next, the chloride anion of **232** is expected to act as a nucleophile in the ring-opening reaction of the vinyl aziridine containing the hemiacetal moiety **261** through a S_N2 type process. Subsequently, the corresponding aza-anion **262** is expected to undergo acid-base proton exchange to the corresponding aza-anion **263**. Finally, the aza-anionic species **263** would suffer an intramolecular nucleophilic substitution reaction leading to the formation of vinyl oxazine **236**.

Due to the fact that 2-(chloromethyl) tosyl amide **241** undergoes a fast transformation to **240**, attempts to isolate the oxazine were always accompanied by the formation of vinyl oxetane **234** induced by the chloride salt **232**. Next, aiming to suppress the formation of the vinyl oxetane **234**, we speculated that the slow addition of a solution of vinyl aziridinol **218** in dichloromethane to a solution of the imidazolium salt **238** would decrease the formation of **240** and thus, the formation of the intermediate **261** would

be favored and as such, the formation of the oxazine **236,** which would confirm the mechanism proposed in Scheme 3.39. Results are summarized in Table 3.4.

Table 3.4. Study of the formation of **236**.



Entry [b]	Temperature	Time	% Conversion [c]	% Selectivity (234: 236) [c]	% Yield (234: 236)
1	rt	60 min	> 98%	9:1	57:0
2	-78ºC to rt	90 min	> 98%	9:1	62:0
3	-78ºC	90 min	> 98%	4:6	21: 46

[a]Vinyl aziridine **218** was formed in situ from the corresponding allylic alcohol (0.1 mmol) and PhINTs as a nitrene source (0.11 mmol) in the presence of [Tp*,^{Br}Ag] as catalyst (0.001 mmol) in 5 ml of CH_2Cl_2. [b]General reaction conditions: **233** (0.1 mmol), $TsNH_2$ (0.1 mmol) in THF (4ml); t = 24h. Vinyl aziridine **218** (0.1 mmol) was slowly added to the previously solution. [c]Determined by ^{1}H-NMR. [d]Product **236** was obtained in 10% isolated yield.

When the solution of vinyl aziridinol **218** in dichloromethane was slowly added to the solution of the imidazolium chloride salt **232** at room temperature or from –78 ºC to room temperature full conversion was observed in a selectivity ratio of 1:9 towards the formation of the vinyl oxetane **234** (Table 3.4, entries 1 and 2). However, when the slow addition was done keeping the temperature at –78 ºC, full conversion was also observed but in a selectivity ratio of 6 to 4 towards the formation of the oxazine **236** (Table 3.4, entry 3). Therefore, these results are in agreement with the proposed mechanism described in Scheme 3.39 to the formation of vinyl oxetane **234** and the oxazine **236**.

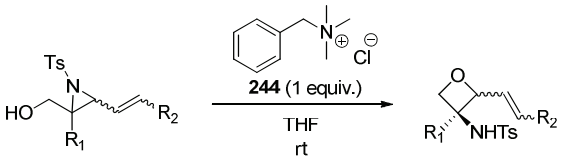
In summary, the mechanistic studies developed for exploring the formation of the unexpected product **236** led us to the discovery of an alternative methodology for the synthesis of vinyl oxetanes. This new procedure is based on a *one-pot* conversion of vinyl aziridinols to vinyl oxetanes through a consecutive ring-opening/ring-closing reaction promoted by a simple chloride source. Aminovinyl tetrahydroxazines can also be isolated using a slightly modified protocol.

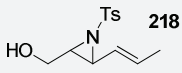
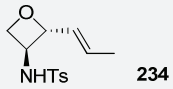
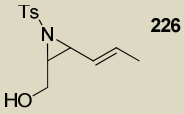
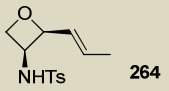
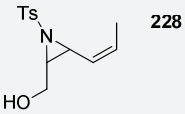
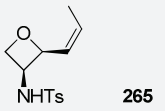
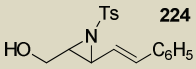
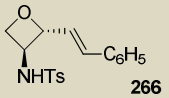
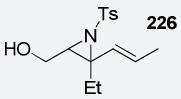
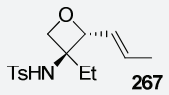
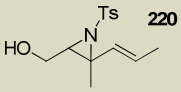
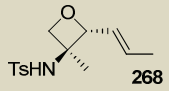
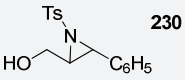
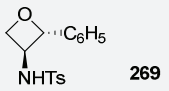
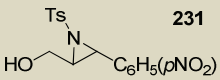
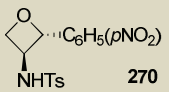
3.3.3. SUBSTRATE SCOPE

In order to utilize vinyl aziridinols for the one-pot synthesis of vinyl oxetanes, a closer inspection of the one-pot ring-opening/ring-closing reaction promoted by a simple chloride source for a variety of substituted aziridines was necessary. The synthesis of the desired vinyl aziridinols was described in a previous section (*Section 4.1.1*) of this chapter.

The one-pot reaction with **9** using 1 equivalent of benzyl trimethyl ammonium chloride (**244**) as the chloride source, previously dried, in THF was reproduced. The reaction was stirred at room temperature overnight, and vinyl oxetane **234** was obtained in 61% yield over two steps (Table 3.5, entry 1). Next, the general reaction conditions used above were adopted for the one-pot conversion of diene-1-ols to vinyl oxetanes *via* vinyl aziridines (Table 3.5). The *cis*-substituted aziridinol gave similar yields than the corresponding *trans* analogues (Table 3.5, entries 2 and 3). Trisubstituted vinyl aziridinol **220** proceeds under the reaction conditions to give vinyl oxetane **268** with full conversion and good yield (Table 3.5, entry 6), in contrast trisubstituted vinyl aziridinol **222** did not provide the desired vinyl oxetane, which seems to indicate a strong influence of the steric hindrance of substituents in the reaction course (Table 3.5, entry 5).

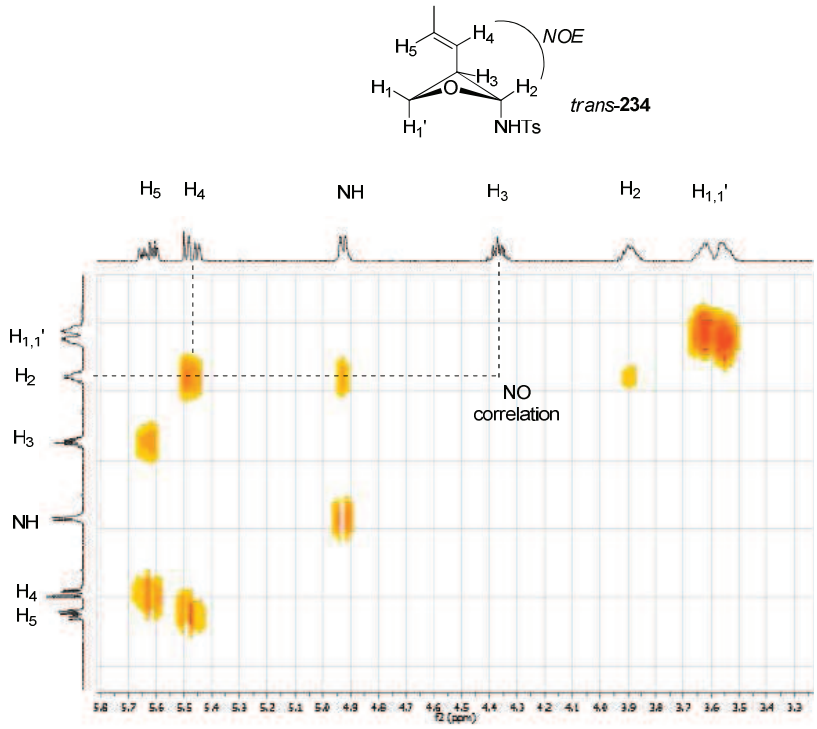
Table 3.5. Reaction scope of vinyl aziridinols.



Entry	Substrate[a]	Product[b]	Time	Conv.[c]/Yield[d] (%)
1	 **218**	 **234**	12h	> 98 (61)
2	 **226**	 **264**	10h	> 98 (60)
3	 **228**	 **265**	3h	> 98 (60)
4	 **224**	 **266**	24h	> 98 (complex mixture)
5	 **226**	 **267**	24h	< 2
6	 **220**	 **268**	7h	> 98 (70)
7	 **230**	 **269**	26h	> 98 (79)[e]
8	 **231**	 **270**	24h	> 98 (76)[e]

[a]Vinyl aziridines were formed in situ from the corresponding allylic alcohol (0.1 mmol) and PhINTs as a nitrene source (0.11 mmol) in the presence of [Tp*,^{Br}Ag] as catalyst (0.001 mmol) in 5 ml of CH_2Cl_2. [b]General reaction conditions: vinyl aziridinol (0.1 mmol), $BnMe_3N^+Cl^-$ (0.1 mmol) in THF (4ml). [c]Determined by ^{1}H-NMR. [d]Isolated yield. [e]Isolated yield over one reaction step (benzyl aziridines **228** and **229** were previously purified).

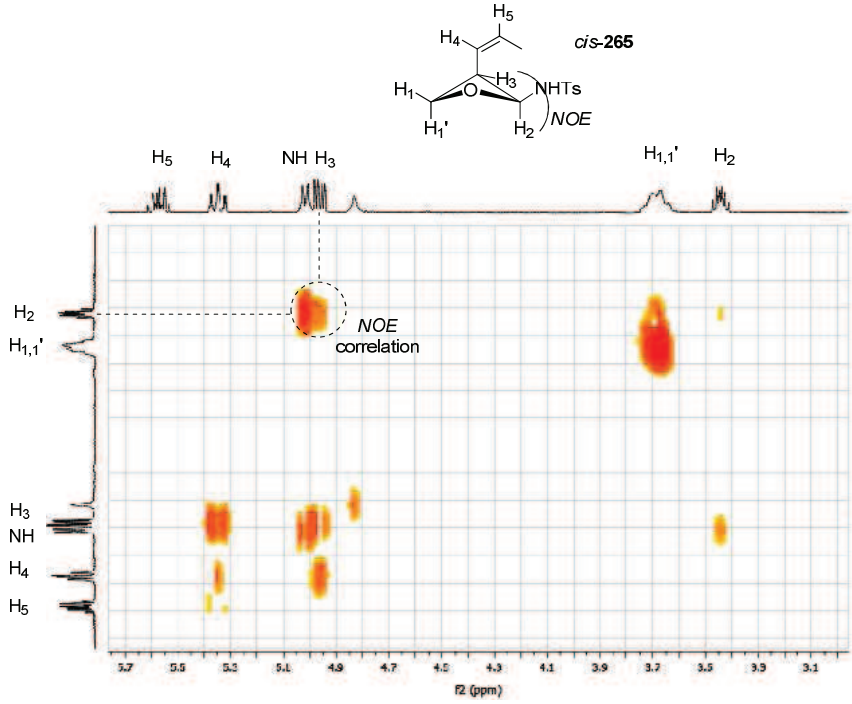
Aryl aziridinols **230** and **231** (Table 3.5, entries 7 and 8) were also successfully converted to vinyl oxetanes **269** and **270**, respectively in good yields over one reaction step because these substrates were previously purified by column chromatography. Vinyl aziridinols generated from the *cis*-hexadienols, led to the *cis*-disubstituted vinyl oxetanes rings (Table 3.5, entries 2 and 3), while vinyl aziridinols generated from the *trans*-hexadienols, led to the *trans*-disubstituted vinyl oxetanes rings vinyl oxetanes rings (Table 3.5, entries 1, 4, 6-8).



Scheme 3.40. NOESY experiment of *trans*-**234**.

The relative stereochemistry of each substrate was verified by NOE experiments of the *cis*- and *trans*-substituted oxetanes compounds **234** and **265**, respectively (Table 3.5). Thus, in the *trans* isomer a relevant *NOE* correlation between H_2 and H_4 is observed, which indicates that H_2 and the

vinyl group are from the same side of the molecule. Moreover, no *NOE* between H_2 and H_3 is observed (Scheme 3.40). On the contrary, in the *cis* isomer no *NOE* correlation between H_2 and H_4 is detected while a *NOE* is observed between H_2 and H_3 (Scheme 3.41). This facts, allow us to confirm the relative configuration of the substituents of the oxetane ring for the different substrates.



Scheme 3.41. NOESY experiment of *cis*-**265**.

Considering all the possible competing ring-opening reactions of vinyl aziridinols by a chloride source (Scheme 3.36), we can conclude that an efficient regioselective and stereoselective one-pot formation of vinyl aziridinols to vinyl oxetanes has been developed, since only the corresponding vinyl oxetanes in good yields (over two reaction steps) as single diastereoisomer were isolated. The reaction evolves through a set of

consecutive reactions: a) nucleophilic selective aziridine ring cleavage promoted by a simple chloride source, b) proton transfer with concomitant formation of the alkoxide and c) intramolecular ring closing to form the vinyl oxetane.

3.4. CONCLUSIONS

From the study described in this chapter, the following conclusions can be extracted:

i) The treatment of vinyl aziridinol **218** with I^{t}Bu (1 equiv.) in THF at room temperature provides the product **236** in 10% isolated yield. This compound **236** incorporates a new carbon (C7) and a new *N*-tosyl moiety.

ii) In the formation of **236** the *N*-heterocyclic carbene (I^{t}Bu) only acted as a base.

iii) The new C7 presents in **236**, was originated from trace amounts of dichloromethane present in the reaction mixture after the aziridination process.

iv) The new *NTs* moiety presents in **236**, stemmed from the excess of tosyl amide remaining in the reaction mixture after the aziridination mixture.

v) An alternative methodology for the synthesis of vinyl oxetanes was developed. This new procedure was found to proceed through a *one-pot* conversion of vinyl aziridinols to vinyl oxetanes through a consecutive ring-opening/ring-closing reaction promoted by a simple *chloride anion*.

From the newly developed procedure based on a one-pot conversion of vinyl aziridinols to vinyl oxetanes promoted by a chloride source the following conclusions can be extracted:

i) The reaction evolves through a set of consecutive reactions in a one-pot procedure: a) nucleophilic selective aziridine ring cleavage promoted by a simple chloride source, b) proton transfer with concomitant formation of the alkoxide and c) intramolecular ring closing to form the vinyl oxetane.
ii) Good yields for *cis*- and *trans*-aziridinols, trisubstituted vinyl aziridinols and aryl aziridinols were obtained.
iii) The reaction is completely regioselective since only the formation of vinyl oxetane over all the possible competing ring-opening/ring closing reactions was observed.
iv) The reaction is stereospecific, since *cis*-vinyl oxetanes led to the *cis*-disubstituted vinyl oxetane rings, and vinyl *trans*-aziridinols led to the *trans*-disubstituted vinyl oxetanes rings.

3.5. EXPERIMENTAL PART

GENERAL EXPERIMENTAL CONDITIONS

All chemicals used were reagent grade and used as supplied unless otherwise specified. HPLC grade dichloromethane (CH_2Cl_2), tetrahydrofuran (THF) and dimethylformamide (DMF) were dried using a solvent purification system (Pure S**OLV** system-4®). Toluene was purified using standard procedure.[56]

^{1}H and ^{13}C NMR spectra were recorded on a Varian® Mercury VX 400 (400 MHz and 100.6 MHz respectively) or Varian 400-MR

spectrometer in $CDCl_3$ as solvent, with chemical shifts (δ) referenced to internal standards $CDCl_3$ (7.26 ppm ^1H, 77.23 ppm ^{13}C) or Me_4Si as an internal reference (0.00 ppm). 2D correlation spectra (gCOSY, NOESY, gHSQC, gHMBC) were visualized using VNMR program (Varian®). ESI MS were run on an Agilent® 1100 Series LC/MSD instrument.

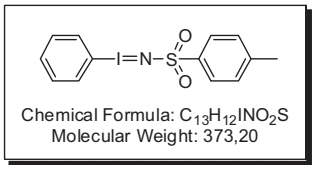
Reactions were monitored by TLC carried out on 0.25 mm E. Merck® silica gel 60 F_{254} glass or aluminium plates. Developed TLC plates were visualized under a short-wave UV lamp (250 nm) and by heating plates that were dipped in ethanol/H_2SO_4 (15:1) and basic solution of potassium permanganate. Flash column chromatography was carried out using forced flow of the indicated solvent on Fluka® or Merck® silica gel 60 (230-400 mesh). Radial chromatography was performed on 1 or 2 mm plates of Kieselgel 60 PF_{254} silica gel, depending on the amount of product. Flash column chromatography (FCC) was performed using flash silica gel (32–63 μm) and using a solvent polarity correlated with TLC mobility.

General procedure for the one-pot synthesis of vinyl oxetanes from 2,4-dien-1-ols:

A 10 ml Schlenk containing a magnetic stirring bar was charged with catalyst (0.001 mmol, 1%) and the alcohol (0.1 mmol), the flask was flushed three times with argon and then, anhydrous dichloromethane (5 ml) was added. A freshly prepared PhINTs (0.11 mmol) was added in 4 portions over 2h and the mixture was stirred for an additional hour after the last addition. Finally the solvent was removed under vacuum and the resulting crude was characterized without purification because vinyl aziridines are unstable by silica gel or neutral alumina. Then, a 10 ml Schlenk containing the crude vinyl aziridine (0.1 mmol, 1 equiv.) was flushed three times with argon. Anhydrous tetrahydrofurane (4ml) was added. Next,

tetraalkylammonium chloride salt (0.1 mmol, 1 equiv.) was added at room temperature. The reaction was monitored by ^{1}H-NMR until full conversion. Water was then added to quench the reaction mixture, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried and evaporated under vacuum. The product was isolated by silica gel chromatography.

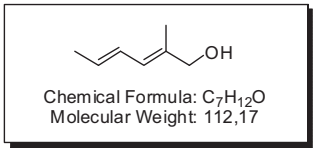
Procedure for the preparation of PhINTs:



Chemical Formula: $C_{13}H_{12}INO_2S$
Molecular Weight: 373,20

KOH (2.8 g, 50 mmol) was dissolved in methanol (100 ml) at room temperature for 30 minutes before *p*-toluenesulfonamide (3.42 g, 30 mmol) was added. Then, the solution was cooled in a saturated NaCl water-ice bath and diacetoxyiodobenzene (6.40 g, 19.9 mmol) was added at that temperature. After stirring the mixture for 2h the crude was warmed at room temperature and it was stirred 2 h more. The crude was concentrated under vacuum for 20 minutes and then it was kept on the fridge overnight. The precipitated solid was filtered via cannula and dried under vacuum.

(2*E*, 4*E*)-2-Methylhexa-2,4-dien-1-ol (196):

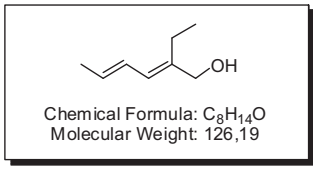


Chemical Formula: $C_7H_{12}O$
Molecular Weight: 112,17

In a 250 ml round bottom flask equipped with a stir bar a suspension of $LiAlH_4$ in Et_2O was stirred at 0ºC. A solution of ethanol in Et_2O was added slowly and H_2 evolution was noted. In a second round bottom flask equipped with a stir bar (2E, 4E)-2-methyl-2,4-hexadionate as a solution in Et_2O was stirred at 0ºC. To the unsaturated ester was slowly added lithium aluminium monoethoxyhydride solution and the flask was stirred at 0ºC for 1h. This process was repeated an additional three times until a total of the reagent had been added. The solution was then quenched

using a 30% aqueous solution of Rochelle's salt (potassium sodium tartrate). The resulting suspension was filtered and washed with H_2O and Et_2O before the layers were separated. The aqueous phase was extracted three times with 25 ml of Et_2O. The organic layers were combined, dried and concentrated. The residue was purified by flash column chromatography on silica gel using hexane/AcOEt (8:2) as the eluent to give **196** (367.9 mg, 41%) as a colourless oil: **^{1}H NMR** (400 MHz, $CDCl_3$): δ in ppm 6.25 (ddd, *J* = 14.9, 10.9, 1.5 Hz, 1H), 5.98 (d, *J* = 10.9 Hz, 1H), 5.74 – 5.62 (m, 1H), 4.01 (s, 2H), 1.77 (d, *J* = 6.8 Hz, 2H), 1.74 (s, 3H). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ in ppm 134.6, 129.6, 127.4, 125.3, 68.7, 18.5, 14.2. NMR data are in agreement with reported data.

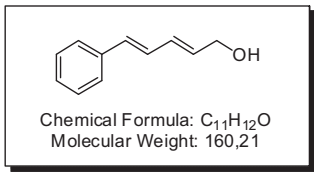
(2*E*, 4*E*)-2-Ethylhexa-2,4-dien-1-ol (197):



Chemical Formula: $C_8H_{14}O$
Molecular Weight: 126,19

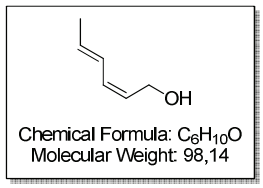
Ester **211** (2 g, 11.9 mmol) was dissolved in anhydrous CH_2Cl_2 (60 ml) and the solution was cooled at -40ºC before DIBAL (30 ml, 29.7 mmol, 1M) was added drop wise. After stirring for one hour to stir at that temperature the solution was warmed at 0ºC and it was stirred 2h before the mixture was carefully pure into an ice-water saturated solution of Rochelle salt and the suspension was vigorously stirred for 2h. The phases were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were washed with brine and then dried over anhydrous $MgSO_4$. The residue was purified by flash column chromatography on silica gel using hexane/AcOEt (8:2) as the eluent to give **197** (1.2 g, 81%) as a colourless oil: **^{1}H NMR** (400 MHz, $CDCl_3$): δ in ppm 7.10 (d, *J* = 11.6, 1H), 6.42 – 6.29 (m, 1H), 6.08 (dqd, *J* = 14.5, 6.8, 0.7 Hz, 1H), 4.20 (q, *J* = 3.2, 2H), 2.38 (q, *J* = 7.5 Hz, 2H), 1.86 (dt, *J* = 6.8, 2.6 Hz, 2H), 1.28 (t, *J* = 6.8, 3H), 1.01 (t, *J* = 7.6, 3H). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ in ppm 193.20, 168.49, 138.23, 138.03, 127.25, 60.51, 20.40, 19.11, 14.52, 14.48.

(2*E*, 4*E*)-5-Phenylpenta-2,4-dien-1-ol (198):



Ester **205** (2.64g, 13 mmol) was dissolved in anhydrous CH_2Cl_2 (60 ml) and the solution was cooled at -40ºC before DIBAL (33 ml, 33 mmol, 1M) was added drop wise. After stirring for one hour to stir at that temperature the solution was warmed at 0ºC and it was stirred 2h before the mixture was carefully pure into an ice-water saturated solution of Rochelle salt and the suspension was vigorously stirred for 2h. The phases were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were washed with brine and then dried over anhydrous $MgSO_4$. The residue was purified by flash column chromatography on silica gel using hexane/AcOEt (8:2) as the eluent to give **198** (1.2 g, 60%) as a white solid: **^{1}H NMR** (400 MHz, $CDCl_3$): δ in ppm 7.39 (d, *J* = 7.4 Hz, 1H), 7.31 (t, *J* = 7.5 Hz, 1H), 7.22 (t, *J* = 7.3 Hz, 1H), 6.79 (dd, *J* = 15.6, 10.5 Hz, 1H), 6.55 (d, *J* = 15.7 Hz, 1H), 6.42 (dd, *J* = 15.2, 10.5 Hz, 1H), 5.96 (dt, *J* = 15.2, 5.9 Hz, 1H), 4.25 (d, *J* = 5.0 Hz, 1H), 1.36 (s, 1H). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ in ppm 137.3, 133.0, 132.7, 131.9, 128.8, 128.3, 127.8, 126.6, 63.7. NMR data are in agreement with reported data.

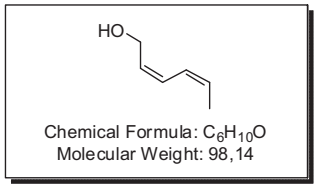
(2*Z*, 4*E*)-Hexa-2,4-dien-1-ol (199):[43]



Compound **216** (700 mg, 1.9 mmol) was dissolved in anhydrous THF, the solution was cooled at 0ºC before TBAF (0.05 mL, 4.9, 1M) was added and the solution was heated to 40ºC for 2h. The solvent was removed under vacuum and the residue was directly purified by flash column chromatography on silica gel using hexane/AcOEt (7:3) as the eluent to give **198** (124.9 mg, 67% over two reaction steps) as a colorless oil: **^{1}H NMR** (400MHz, $CDCl_3$): δ in ppm 6.39 (tq, 1H, *J* = 11.6, 1.2 Hz), 6.29-6.21 (m, 1H), 5.66-5.59 (m, 2H), 4.31 (d, 2H, *J* = 7.0 Hz), 1.72 (dd,

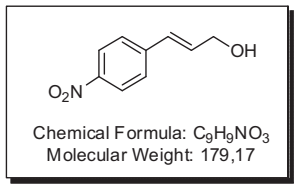
3H, *J* = 5.6, 1.6), 1.72 (1H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ = 129.3, 128.7, 125.6, 123.9, 58.8, 13.3. **HR ESI-TOF MS** for $[M+Na]^+$ $C_6H_{10}NaO^+$ (*m/z*): calc. 121.0629; found: 121.0600.

(2*Z*,4*Z*)-2,4-Hexadien-1-ol (200):[43]



Compound **216** (600 mg, 1.6 mmol) was dissolved in anhydrous THF (25 ml), the solution was cooled at 0ºC before TBAF (3.8 mL, 1.9, 1M) was added and the solution was heated to 40ºC for 3h. The solvent was removed under vacuum and the residue was directly purified by flash column chromatography on silica gel using hexane/AcOEt (7:3) as the eluent to give **199** (133 mg, 85%) as a yellowish oil: **^{1}H NMR** (400MHz, $CDCl_3$): δ in ppm 6.39 (tq, 1H, *J* = 11.6, 1.2 Hz), 6.29-6.21 (m, 1H), 5.66-5.59 (m, 2H), 4.31 (d, 2H, *J* = 7.0 Hz), 1.72 (dd, 3H, *J* = 5.6, 1.6), 1.72 (1H). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ in ppm 129.3, 128.7, 125.6, 123.9, 58.8, 13.3. **HR ESI-TOF MS** for $[M+Na]^+$ $C_6H_{10}NaO^+$ (*m/z*): calc. 121.0629; found: 121.0600.

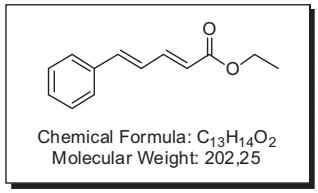
(2*E*)-3-(4-Nitrophenyl)prop-2-en-1-ol (202):[44]



$[Cp^*IrCl_2]_2$] (1.6 mg, 0.002mmol) and Ts(en) (1.2 mg, 0.0048mmol) were suspended in degassed distilled water (15 ml). After the reaction mixture had been stirred at 80ºC for 1h, HCOONa (6.8 g, 0.1mol) and benzaldehyde (20 mmol) were added to the resulting solution. The reaction mixture was rapidly degassed three times through vacuum-argon cycles and then heated at 80ºC until the complete conversion of benzaldehyde monitoring the reaction by TLC chromatography. After cooling to room temperature, the organic compounds were extracted with Et_2O. The combined organic layers were

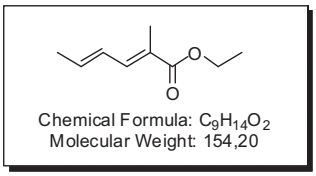
dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel using hexane/AcOEt (9:1) as the eluent to give **202** (311.7 mg, 87%): **^{1}H NMR** (400MHz, $CDCl_3$): δ in ppm 8.20 (d, J=8.6 Hz, 2H), 7.60 (d, J=8.6 Hz, 2 H), 7.75 (d, J= 16.1 Hz, 1H), 6.57 (m, 1H), 4.30 (d, J= 6.0 Hz, 2H), 3.10 (br. s, 1H). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ in ppm 147.3, 144.5, 128.6, 127.4, 124.5, 123.0, 63.5. **HR ESI-TOF MS** for $[M+H]^+$ $C_9H_{10}NO_3^+$ (*m/z*): calc. 180.0582; found: 180. 0836.

(2*E*, 4*E*)-Ethyl 5-phenylpenta-2,4-dienoate (205):[38]


Chemical Formula: $C_{13}H_{14}O_2$
Molecular Weight: 202,25

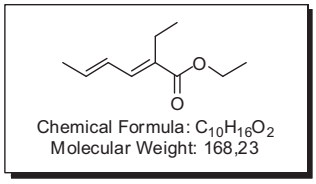
To a dry 100 ml round bottom flask equipped with a stir bar was added (carbethoxymethylene) triphenylphosphorane (5g, 14.35 mmol). The flask was seeded under Ar and CH_2Cl_2 (6 ml) was added to the flask while stirring at room temperature. Cinnamaldehyde (2.7 ml, 17.22 mmol) was added drop rise over 10 minutes and the flask was fitted under reflux condenser and placed in an oil bath at 60ºC and refluxed for 3 h. The flask was then removed from the oil bath and concentrated to half its original volume. Then petroleum ether (7ml) was added and the solution was then filtered to remove the triphenylphosphine oxide. The solid was washed with additional petroleum ether, and the solution was once again concentrated. The residue was purified by flash column chromatography on silica gel using hexane/AcOEt (9:1) as the eluent to give **205** (3.2 g, 91%) as a colourless oil: **^{1}H NMR** (400MHz, $CDCl_3$): δ in ppm 7.50 – 7.41 (m, 1H), 7.39 – 7.27 (m, 1H), 6.89 (s, 1H), 6.89 – 6.87 (m, 1H), 5.99 (d, *J* = 15.3 Hz, 1H), 4.23 (q, *J* = 7.1 Hz, 1H), 1.32 (t, *J* = 7.1 Hz, 1H). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ in ppm 167.1, 144.71, 140.5, 136.0, 129.2, 127.6, 126.3, 121.6, 60.6, 14.6. NMR data are in agreement with reported data.

(2*E*, 4*E*)-Ethyl 2-methylhexa-2,4-dienoate (208):



To a dry 100 ml round bottom flask equipped with a stir bar was added (carbethoxyethylene) triphenyl phosphorane (3.624g, 10 mmol). The flask was seeded under Ar and CH_2Cl_2 (6 ml) was added to the flask while stirring at room temperature. Crotonaldehyde (711.6 µl, 12 mmol) was added drop rise over 10 miniutes and the flask was fitted with a reflux condenser and placed in an oil bath at 60ºC and refluxed for 3 h. The flask was then removed from the oil bath and concentrated to half its original volume. Then, petroleum ether (7ml) was added and the solution was then filtered to remove the triphenylphosphine oxide. The solid was washed with additional petroleum ether, and the solution was once again concentrated. The residue was purified by flash column chromatography on silica gel using hexane/AcOEt (9:1) as the eluent to give **208** (1.3 g, 72%) as a colourless oil: **^{1}H NMR** (400 MHz, $CDCl_3$): δ in ppm 7.17 – 7.04 (m, 1H), 6.41 – 6.20 (m, 1H), 6.13 – 5.95 (m, 1H), 4.27 – 4.09 (m, 2H), 1.93 – 1.84 (m, 3H), 1.79 (dd, *J* = 15.4, 6.8 Hz, 3H), 1.31 – 1.19 (m, 4H). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ in ppm 168.7, 138.5, 137.6, 127.5, 124.9, 60.5, 18.9, 14.4, 12.6. NMR data are in agreement with reported data.

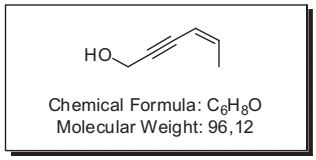
(2*E*, 4*E*)-Ethyl 2-ethylhexa-2,4-dienoate (211):[39]



MeMgBr (7ml, 21 mmol, 3M in Et2O) was added dropwise to a stirred solution of the required phosphonate (5 ml, 21 mmol) in THF (25 ml) at room temperatura and stirred for 15 minutes. Crotonaldehyde (2 ml, 23.1 mmol) dissolved in THF (15 ml) was added via cannula and the reaction mixture heated to reflux for 18h. The reaction was quenched with saturated aqueous NH_4Cl (20 ml) and extracted

with Et_2O. The combined organic layers were then washed with brine, dried and concentrated. The residue was purified by flash column chromatography on silica gel using hexane/AcOEt (9:1) as the eluent to give **211** (2.2 g, 58%) as a yellowish oil: **^{1}H NMR** (400 MHz, $CDCl_3$): δ in ppm 7.10 (d, *J* = 11.6, 1H), 6.42 – 6.29 (m, 1H), 6.08 (dqd, *J* = 14.5, 6.8, 0.7 Hz, 1H), 4.20 (q, *J* = 3.2, 2H), 2.38 (q, *J* = 7.5 Hz, 2H), 1.86 (dt, *J* = 6.8, 2.6 Hz, 2H), 1.28 (t, *J* = 6.8, 3H), 1.01 (t, *J* = 7.6, 3H). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ in ppm 193.20, 168.49, 138.23, 138.03, 127.25, 60.51, 20.40, 19.11, 14.52, 14.48.

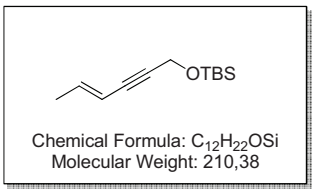
(4*Z*)-2-Hexyn-4-en-1-ol (214):[40]



$PdCl_2(PPh_3)_2$ (300 mg, 0.42 mmol) was dissolved in freshly distilled piperidine (40 mL) and THF (40 ml) and *Z*-bromopropene (2 mL, 23.5 mmol) was added. The solution was stirred at room temperature for 30 minutes and before propargyl alcohol (1.23 mL, 21.4 mmol) and CuI (164.7 mg, 0.86 mmol) were added. The yellow solution was stirred at room temperature for 10 h. The crude was diluted with diethyl ether (50 ml) and water (20 ml). Then a solution of HCl (50 ml, 1M) was slowly added to neutralize the piperidine. The layers were separated and the aqueous phase was extracted with diethyl ether (2x20 ml). The combined organic layers were washed with 10% HCl aqueous solution (20 mL), saturated $NaHCO_3$ solution (20 ml) and brine. Then, it was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel using hexane/AcOEt (9:1 to 8:2) as the eluent to give **214** (1.4 g, 68%) as a beige oil: **^{1}H NMR** (400MHz, $CDCl_3$): δ in ppm 5.97 (dq, 1H, *J* = 10.6, 6.8 hz), 5.49 (dq, 1H, *J* = 10.6, 1.6 Hz), 4.47 (s, 2H), 1.86 (d, 3H, *J* = 6.8 Hz). 0.91 (s, 12H), 0.14 (s, 3H), 0.13

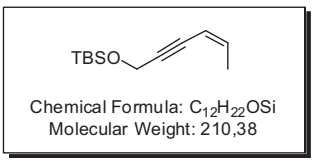
(s, 3H). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ in ppm 139.4, 109.5, 91.9, 82.5, 51.8, 16.2. NMR data are in agreement with reported data.

(4E)-*tert*-Butyldimethylsilyloxy-hex-2-yn-4-ene ((*E*)-215):[41]



Enyne **214** (10 mmol) was dissolved in dichloromethane (50 mL) and *tert*-butyldimethylsilyl chloride (1.6 g, 11 mmol), triethylamide (3 mL, 22 mmol) and DMAP (10%) were successively added. The mixture was stirred at room temperature for 6h. The crude was quenched with saturated NH_4Cl aqueous solution and the aqueous phase was extracted with dichloromethane. The combined organic layers were dried over anhydrous $MgSO_4$. The solvent was removed under vacuum and the residue was directly purified by flash column chromatography on silica gel using hexane as the eluent to give **215** (2.1 g, 97%) as a yellowish oil: **^{1}H NMR** (400MHz, $CDCl_3$): δ in ppm 5.97 (dq, 1H, *J* = 12.4, 6.8 Hz), 5.49 (dq, 1H, *J* = 12.3, 1.6 Hz), 4.47 (s, 2H), 1.86 (d, 3H, *J* = 6.8 Hz), 0.91 (s, 12H), 0.14 (s, 3H), 0.13 (s, 3H). **^{13}C NMR** ($CDCl_3$, 100.6 MHz): δ in ppm 138.8, 109.9, 52.5, 26.1, 25.9, 18.6, 16.1, -4.9. **HR ESI-TOF MS** for $[M+H]^+$ $C_{12}H_{23}OSi^+$ (*m/z*): calc. 211.1440; found: 211.1444.

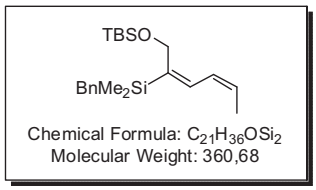
***(4Z)*-1-*O*-*tert*-Butyldimethylsilyl-2-hexyn-4-en-1-ol ((*Z*)-215):**[41]



Enyne **214** (10 mmol) was dissolved in dichloromethane (50 mL) and *tert*-butyldimethylsilyl chloride (1.6 g, 11 mmol), triethylamide (3 mL, 22 mmol) and DMAP (10%) were successively added. The mixture was stirred at room temperature overnight. The crude was quenched with saturated NH_4Cl aqueous solution and the aqueous phase was extracted with

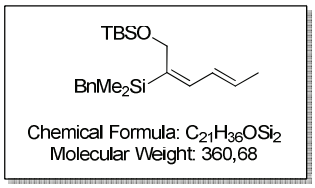
dichloromethane. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel using hexane as the eluent to give **215** (2.4 g, 97%): **^{1}H NMR** (400MHz, $CDCl_3$): δ in ppm 5.97 (dq, 1H, *J* = 10.6, 6.8 hz), 5.49 (dq, 1H, *J* = 10.6, 1.6 Hz), 4.47 (s, 2H), 1.86 (d, 3H, *J* = 6.8 Hz). 0.91 (s, 12H), 0.14 (s, 3H), 0.13 (s, 3H). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ in ppm 138.8, 109.9, 52.5, 26.1, 25.9, 18.6, 16.1, -4.9. NMR data are in agreement with reported data.

(2Z,4E)-2-Benzyldimethylsilyl-O-*tert*-butyldimetylsilyl-hexa-2,4-dien-1-ol ((*Z*,*E*)-216):[42]



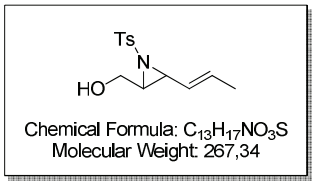
To a solution of alkyne **215** (1.4 g, 6.4 mmol) and benzyldimethylsilane (1.2 ml, 7.7 mmol) was added $PtCl_2$ (0.16 g, 0.6 mmol) and the solution was stirred overnight at 25ºC. The solvent was removed under vacuum. The residue was purified by flash column chromatography on silica gel using hexane as the eluent to give **216** (1.7 g, 75%) as a clear oil: **^{1}H NMR** (400MHz, $CDCl_3$): δ in ppm 7.21 (t, 2H, *J* = 7.6 Hz), 7.07 (t, 1H, *J* = 7.6 Hz), 7.01 (d, 2H, *J* = 7.6 Hz), 5.87 (m, 2H), 5.55 (dq, 1H, *J* = 11.2, 6.8 Hz), 4.14 (d, 2H, *J* = 5.6 Hz), 2.17 (s, 2H), 1.47 (dd, 3H, *J* = 6.4, 1.2 Hz), 0.92 (s, 9H), 0.06 (s, 6H), 0.05 (s, 6H). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ in ppm 140.5, 140.1, 138.1, 128.7, 128.5, 128.3, 125.5, 124.2, 62.4, 26.2, 25.1, 18.6, 14.5, -3.8, -4.8. **HR ESI-TOF MS** for $[M+Na]^+$ $C_{21}H_{36}NaOSi_2^+$ (*m/z*): calc. 383.2212; found: 383.2154.

(2Z,4E)-2-Benzyldimethylsilyl-O-Dimethyl-tert-butylsilyl-hexa-2,4-dien-1-ol ((*Z*,*E*)-216):[42]



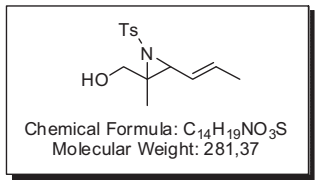
A mixture of **215** (1.2 ml, 10 mmol) and platinum complex (37 mg, 2.5 %) was heated at 60ºC for 3h (incubation process) and the mixture was cooled at room temperature and a solution of enyne (500 mg, 2.3 mmol) in THF (5 mL) was slowly added, then by stream argon the solvent was removed and the neat solution was heated at 60ºC for 13h. The crude was evaporated under vacuum. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ in ppm 7.19 (dd, 2H, *J* = 8.0, 7.0 Hz), 7.06 (t, 1H, *J* = 7.0 Hz), 6.99 (d, 2H, *J* = 8.0 Hz),5.86 (t, 1H, *J* = 5.6 Hz), 5.85 (dq, 1H, *J* = 10.0, 1.8 Hz), 5.54 (dq, 1H, *J* = 10.0, 7.0 Hz), 4.11 (d, 2H, *J* = 5.6 Hz), 2.14 (s, 2H), 1.45 (dd, 3H, *J* = 7.0, 1.8 Hz), 0.90 (s, 9H), -0.16 (s, 6H). **HR ESI-TOF MS** for $[M+Na]^+$ $C_{21}H_{36}NaOSi_2^+$ (*m/z*): calc. 382.2202; found: 383.2154.

***trans*-2-Hydroxymethyl-3-((*E*)-1-propen-1-yl)-1-tosylaziridine (218):**



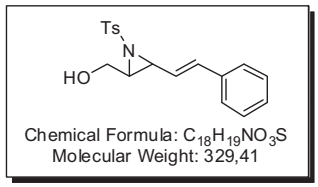
Characterization data extracted from the reaction mixture. **^{1}H NMR** (400 MHz, $CDCl_3$): δ in ppm 7.76 (d, 2H, *J* = 8.2 Hz), 7.26 (d, 2H, *J* = 8.2 Hz), 5.84 (dt, 1H, *J* = 15.2, 6.4 Hz), 5.51 (dd, 1H, *J* = 15.2, 8.8 Hz), 3.99 (dd, 1H, *J* = 12.8, 3.2 Hz), 3.77 (dd, 1H, *J* = 12.8, 6.6 Hz), 3.33 (dd, 1H, *J* = 8.8, 4.4 Hz), 3.19 (ddd, 1H, *J* = 6.6, 4.4, 3.2 Hz), 2.42 (s, 4H), 2.09-2.95 (m, 2H), 0.98 (t, 3H, *J* = 7.0 Hz). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ in ppm 144.6, 140.9, 129.9, 127.7, 127.5, 122.5, 61.0, 49.6, 48.5, 26.0, 22.0, 12.8. **HR ESI-TOF MS** for $[M+H]^+$ $C_{13}H_{18}NO_3S^+$ (*m/z*): calc. 268.0929; found: 268.1121.

trans-2-Hydroxymethyl-2-methyl-3-((*E*)-1-propen-1-yl)-1-tosylaziridine (220):



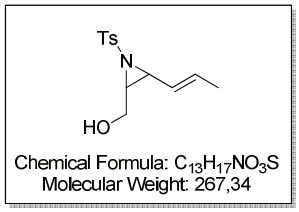
Characterization data extracted from the reaction mixture. **^{1}H NMR** (400 MHz, $CDCl_3$): δ in ppm 7.77 (d, 2H, *J* = 8.0 Hz), 7.38 (d, 2H, *J* = 8.0 Hz), 5.82 (dq, 1H, *J* = 15.0, 6.8 Hz), 5.22 (ddq, 1H, *J* = 15.0, 7.4, 1.6 Hz), 4.03 (d, 2H, *J* = 3.2 Hz), 3.56 (d, 1H, *J* = 7.4 Hz), 2.44 (s, 3H), 1.76 (brs, 1H), 1.69 (dd, 3H, *J* = 6.8, 1.6 Hz), 1.43 (s, 3H). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ in ppm 144.1, 137.5, 130.1, 129.3, 127.6. 127.0, 61.3, 56.2, 52.4, 21.7. **HR ESI-TOF MS** for $[M+Na]^+$ $C_{14}H_{19}NNaO_3S^+$ (*m/z*): calc. 304.0983; found: 304.1201.

trans-2-Hydroxymethyl-3-((*E*)-styryl)-1-tosylaziridine (224):



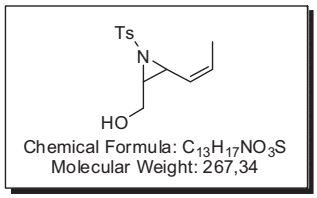
Characterization data extracted from the reaction mixture. **^{1}H NMR** (400 MHz, $CDCl_3$): δ in ppm 7.83 (d, 2H, *J* = 8.2 Hz), 7.37-7.26 (m, 6H), 7.19 (t, 1H, *J* = 7.6 Hz), 6.65 (d, 1H, *J* = 16.0 Hz), 6.25 (dd, 1H, *J* = 16.0, 8.8 Hz), 4.05 (dd, 1H, *J* = 12.8, 2.8 Hz), 3.84 (dd, 1H, *J* = 12.8, 6.8 Hz), 3.56 (dd, 1H, *J* = 8.8, 4.4 Hz), 3.33-3.30 (m, 1H), 2.42 (brs, 1H), 2.41 (s, 3H). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ in ppm 144.7, 137.7, 137.0, 130.4, 129.9, 128.9, 128.6, 127.7, 127.6, 126.8, 122.5, 60.9, 50.2, 48.4, 21.8. **HR ESI-TOF MS** for $[M+H]^+$ $C_{18}H_{20}NO_3S^+$ (*m/z*): calc. 330.1086; found: 330.1121.

cis-2-Hydroxymethyl-3-((_E_)-1-propen-1-yl)-1-tosylaziridine (226):



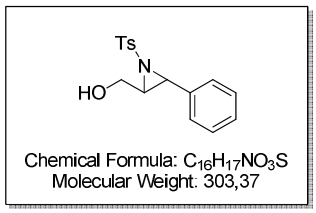
Characterization data extracted from the reaction mixture. **^{1}H NMR** (400 MHz, $CDCl_3$): δ in ppm 7.82 (d, 2H, *J* = 8 Hz), 7.33 (d, 2H, *J* = 8.4 Hz), 5.84 (dt, 1H, *J* = 15.2, 6.4 Hz), 5.51 (dd, 1H, *J* = 15.2, 8.8 Hz), 3.73 (dd, 1H, *J* = 12, 4.8 Hz), 3.62 (m, 1H), 3.58 (dd, 1H, *J* = 12, 7.2 Hz), 3.17 (ddd, 1H, *J* = 7.2, 7.2, 4.8 Hz), 2.43 (s, 3H), 1.72 (dd, 3H, *J* = 6.8, 1.6 Hz). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ in ppm 143.7, 131.9, 130.2, 127.6, 127.7, 126.6, 121.1, 59.4, 46.5, 42.1, 20.8, 13.1. **HR ESI-TOF MS** for $[M+Na]^+$ $C_{13}H_{17}NNaO_3S^+$ (*m/z*): calc. 290.0929; found: 290.1232.

cis-2-Hydroxymethyl-3-((_Z_)-1-propen-1-yl)-1-tosylaziridine (228):



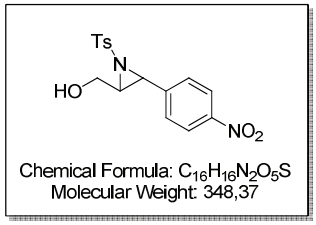
Characterization data extracted from the reaction mixture. **^{1}H NMR** (400 MHz, $CDCl_3$): δ in ppm 7.82 (d, 2H, *J* = 8 Hz), 7.33 (d, 2H, *J* = 8.4 Hz), 5.79 (dqd, 1H, *J* = 10.8, 7.2, 1.2 Hz), 5.17 (ddq, 1H, *J* = 10.8, 8.4, 2 Hz), 3.73 (dd, 1H, *J* = 12, 4.8 Hz), 3.62 (m, 1H), 3.58 (dd, 1H, *J* = 12, 7.2 Hz), 3.17 (ddd, 1H, *J* = 7.2, 7.2, 4.8 Hz), 2.43 (s, 3H), 1.72 (dd, 3H, *J* = 6.8, 1.6 Hz). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ in ppm 144.9, 133.0, 129.9, 129.8, 128.1, 126.6, 121.5, 60.0, 45.6, 41.2, 21.9, 13.7. **HR ESI-TOF MS** for $[M+Na]^+$ $C_{13}H_{17}NNaO_3S^+$ (*m/z*): calc. 290.0929; found: 290.0112.

***trans*-2-Hydroxymethyl-3-phenyl-1-tosylaziridine (230):**



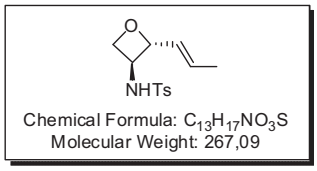
Characterization data extracted from the reaction mixture. **^{1}H NMR** (400 MHz, $CDCl_3$): δ in ppm 7.81 (d, 2H, *J* = 8 Hz), 7.28-7.24 (m, 5H), 7.15-7.13 (m, 2H), 4.32 (ddd, 1H, *J* = 12.8, 9.2, 2.4 Hz), 4.17 (ddd, 1H, *J* = 13.2, 8.4, 4 Hz), 4.02 (d, 1H, J = 4.4 Hz), 3.20-3.15 (m, 1H), 2.39 (s, 3H). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ in ppm 144.6, 137.2, 134.7, 129.8, 128.8, 128.7, 128.6, 128.5, 128.5, 127.3, 126.5, 60.8, 54.8, 46.5, 21.7. **HR ESI-TOF MS** for $[M+H]^+$ $C_{16}H_{18}NO_3S^+$ (*m/z*): calc. 304.0929; found: 304.0722.

***trans*-2-Hydroxymethyl-3-(4-nitrophenyl)-1-tosylaziridine (231):**



Characterization data extracted from the reaction mixture. **^{1}H NMR** (400 MHz, $CDCl_3$): δ in ppm 7.8-7.78 (m, 4H), 7.29-7.25 (m, 4H), 4.39-4.32 (m, 1H), 4.19 (dd, 1H, J = 13.6, 8 Hz), 4.09 (d, 1H, J = 4.4 Hz), 3.18-3.15 (m, 1H), 2.41 (s, 3H). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ in ppm 146.0, 145.2, 137.1, 136.2, 129.1, 129.1, 128.5, 124.3, 124.3, 124.0, 120.2, 60.1, 55.3, 45.2, 26.3. **HR ESI-TOF MS** for $[M+H]^+$ $C_{16}H_{17}N_2O_5S^+$ (*m/z*): calc. 349.0780; found: 349.7961.

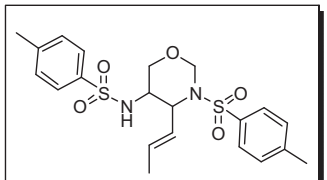
***trans*-2-((*E*)-Propen-1-yl)-3-tosylamido-oxetane (234):**



The title compound was prepared following the general procedure described above, starting from (2*E*, 4*E*)-2-Hexa-2,4-dien-1-ol (**196**) (9.8 mg, 0.1 mmol). After standard workup the crude was purified by column chromatography (9:1 to 6:4 Hexane/EtOAc) to afford **234** (17.9 mg, 61%) as a colorless syrup. **^{1}H NMR** (400 MHz, $CDCl_3$): δ in ppm 7.75 (d, 2H, J = 8.1 Hz), 7.32 (d, 2H, J = 8.1 Hz), 5.59

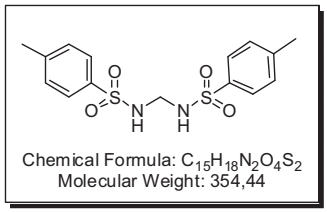
(dqd, 1H, J = 16.8, 3.6, 1.6 Hz), 5.44 (dd, 1H, J = 21.2, 8.8 Hz), 4.94 (d, 1H, J = 7.6 Hz), 4.35 (m, 1H), 3.84 (m, 1H), 3.59-3.48 (m, 2H), 2.38 (s, 3H), 1.39 (dd, 3H, J = 6.8, 1.6 Hz) **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ in ppm 143.9, 135.7, 130.0, 127.7, 127.6, 127.4, 76.9, 65.0, 56.6, 56.4, 24.9, 21.7. **HR ESI-TOF MS** for $[M+H]^+$ $C_{13}H_{18}NO_3S^+$ (*m/z*): calc. 268.0929; found: 268.1312.

4-(*E*)-Propen-1-yl)- 5-tosylamido-3-tosyl-tetrahydro-1,3-oxazine (236):


Chemical Formula: $C_{21}H_{26}N_2O_5S_2$
Molecular Weight: 450,57

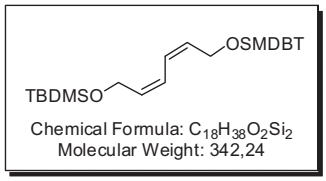
A 10 ml Schlenk containing a magnetic stirring bar was charged with the free carbene **233** (18mg, 0.1 mmol), the flask was flushed three times with argon then, anhydrous tetrahydrofurane (5 ml) was added. Then, tosylamide **237** (17.1 mg, 0.1 mmol) was added and the mixture was stirred for 15 minutes until a white solution was observed. Finally the solvent was removed under vacuum and a solution of the vinyl aziridine **218** (0.1 mmol) in anhydrous dichloromethane (5 ml) was added. The resulting mixture was stirred for three hours. Finally the solvent was removed under vacuum and the resulting crude was directly purified with column chromatography: hexanes/AcOEt: 9:1 to 6:4, 4.5 mg of **236** was obtained in 10% yield as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ in ppm 7.80 (d, *J* = 8.3 Hz, 1H), 7.72 – 7.61 (m, 3H), 7.34 – 7.26 (m, 4H), 5.55 (dqd, *J* = 14.9, 6.5, 1.8 Hz, 1H), 5.32 – 5.19 (m, 2H), 4.88 (d, *J* = 9.7 Hz, 1H), 4.76 (s, 1H), 4.53 (d, *J* = 11.1 Hz, 1H), 4.23 (dd, *J* = 3.2, 1.6 Hz, 1H), 3.65 (dd, *J* = 12.1, 1.9 Hz, 1H), 3.53 (d, *J* = 12.0 Hz, 1H), 3.25–3.15 (m, 1H). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ in ppm 144.5, 143.9, 137.9, 137.2, 131.0, 130.2, 130.0, 129.9, 127.4, 127.1, 126.6, 124.7, 77.5, 77.2, 76.9, 73.9, 67.8, 58.5, 50.8, 21.8, 21.8, 18.1. **HR ESI-TOF MS** for $[M+Na]^+$ $C_{21}H_{26}N_2NaO_5S_2^+$ (*m/z*): calc. 473.1181; found: 473.1173.

(N,N)-di-Tosyl-methylenediamide (240):



A 10 ml Schlenk containing a magnetic stirring bar was charged with the free carbene **233** (18mg, 0.1 mmol), the flask was flushed three times with argon then, anhydrous tetrahydrofurane (5 ml) was added. Then, tosylamide **237** (17.1 mg, 0.1 mmol) was added and the mixture was stirred for 15 minutes until a white solution was observed. Finally the solvent was removed under vacuum and the resulting crude was re-dissolved in anhydrous dichloromethane (5 ml). The resulting mixture was stirred for an additional hour. Finally the solvent was removed under vacuum and the resulting crude was directly purified with column chromatography: hexanes/AcOEt: 9:1 to 8:2, 34.1 mg of **240** was obtained as a white solid in quantitative yield. **^{1}H NMR** (400 MHz, $CDCl_3$): δ in ppm 7.76 (d, 2H, J = 8.2 Hz), 7.26 (d, 2H, J = 8.2 Hz), 4.91 (s, 1H), 2.34 (s, 3H). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ in ppm 141.4, 137.6, 129.1, 128.3, 47.1, 21.5. **HRMS** (*m/z*) calcd for $C_{15}H_{19}N_2O_4S_2$ $[M]^{+H}$: 355.0708, found: 355.0264.

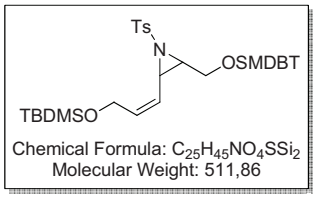
(2Z,4Z)-1,6-Bis-*tert*-butyldimethylsilyloxy-hexa-2,4-diene (254):



Dienol **253** (10 mmol) was dissolved in dichloromethane (50 mL) and *tert*-butyldimethylsilyl chloride (1.6 g, 11 mmol), triethylamide (3 mL, 22 mmol) and DMAP (10%) were successively added. The mixture was stirred at room temperature overnight. The crude was quenched with saturated NH_4Cl aqueous solution and the aqueous phase was extracted with dichloromethane. The combined organic layers were dried over anhydrous $MgSO_4$ and then the solvent was removed under vacuum. The residue was purified by flash column chromatography on silica gel using hexane as the eluent to give **254** (3.3 g, 97 %) as a colourless oil: **^{1}H NMR** (400 MHz,

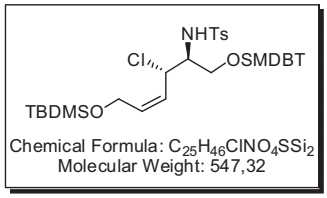
$CDCl_3$): δ in ppm 6.20 (dd, 1H, *J* = 7.6, 2.0 Hz), 5.58 (m, 1H), 4.35 (d, 2H, *J* = 6.4 Hz), 0.89 (s, 9H), 0.06 (s, 6H). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ in ppm 132.4, 123.4, 59.5, 26.1, 18.5, -4.9. **HR ESI-TOF MS** for $[M+H]^+$ $C_{18}H_{39}O_2Si_2^+$: calc. 343.2410; found: 343.3993.

***cis*-2-*tert*-Butyldimethylsilyloxy-3-((Z)-*3-tert*-butyldimethylsilyloxy-propen-1-yl)-1-tosylaziridine (255):**



A 10 ml Schlenk containing a magnetic stirring bar was charged with [$Tp^{Br,*}$Ag] catalyst (0.0025 mmol, 2.5%) and diene **254** (0.1 mmol), the flask was flushed three times with argon then, anhydrous dichloromethane (5 ml) was added. A freshly prepared PhINTs (0.11 mmol) was added in 4 portions over 2h and the mixture was stirred for an additional hour after the last addition. Finally the solvent was removed under vacuum and the resulting crude was characterized without purification because vinyl aziridines are unstable by silica gel or neutral alumina. Characterization data extracted from the reaction mixture. **^{1}H NMR** (400 MHz, $CDCl_3$): δ in ppm 7.81 (d, 2H, *J* = 8 Hz), 7.30 (d, 2H, *J* = 8 Hz), 5.79 (dtd, 1H, *J* = 11.2, 5.6, 1.2 Hz), 5.12 (ddt, 1H, *J* = 11.6, 8, 2 Hz), 4.31 (dd, 2H, *J* = 6.0, 2.0 Hz), 3.60 (dd, 2H, *J* = 5.6, 3.2 Hz), 3.05 (dd, 1H, *J* = 13.6, 6.4 Hz), 0.89 (s, 9H), 0.79 (s, 9H), 0.07 (d, 6H, *J* = 2.0 Hz), -0.05 (d, 6H, *J* = 8.4 Hz). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ in ppm 144.6, 137.4, 135.2, 129.8, 128.2, 121.4, 60.7, 60.1, 46.2, 40.3, 26.1, 25.9, 21.8, 18.5, 18.4, -5.0, -5.3. **HR ESI-TOF MS** for $[M+H]^+$ $C_{25}H_{46}NO_4SSi_2^+$ (*m/z*): calc. 512.2608; found: 512.29121.

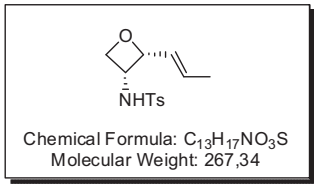
(4*Z*)-1,6-Bis-*tert*-butyldimethylsilyloxy-3-chloro-2-tosylamido-4-hexene (256):



Chemical Formula: $C_{25}H_{46}ClNO_4SSi_2$
Molecular Weight: 547,32

A 10 ml Schlenk containing the crude vinyl aziridine **255** (0.1 mmol) was flushed three times with argon, anhydrous tetrahydrofurane (4 ml) was added. Next, the tetraalkylammonium chloride salt (0.1 mmol, 1 equiv.) was added at room temperature. The reaction was monitored by ^{1}H-NMR until full conversion. Water was then added to quench the reaction mixture, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried and evaporated under vacuum. The residue was purified by flash column chromatography on silica gel using hexane/AcOEt (9:1 to 6:4) as the eluent to give **256** (31.2 mg, 57% over two reaction steps) as a white solid: **^{1}H NMR** (400 MHz, $CDCl_3$): δ in ppm 7.74 (d, 2H, *J* = 8 Hz), 7.30 (d, 2H, *J* = 8.8 Hz), 5.65 (dtd, 1H, *J* = 13.6, 6.1, 0.4 Hz), 5.48 (ddt, 1H, *J* = 11.2, 11.2, 3.2 Hz), 5.09 (dd, 1H, *J* = 9.6, 4 Hz), 4.90 (d, 1H, *J* = 9.2 Hz), 4.22 (m, 2H), 3.61 (dd, 1H, *J* = 10, 4 Hz), 3.51 (dd, 1H, *J* = 9.6, 6.4 Hz), 3.45 (m, 1H), 2.42 (s, 3H), 0.83 (s, 9H), 0.01 (d, 6H, *J* = 4 Hz). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ in ppm 144.0, 132.9, 129.9, 128.2, 127.3, 61.7, 58.7, 58.6, 56.1, 25.9, 21.7, 18.3, -5.3, -5.4. **HR ESI-TOF MS** for $[M+H]^+$ $C_{25}H_{47}ClNO_4SSi_2^+$ (*m/z*): calc. 329.1086; found: 329.1121.

***cis*-2-((*E*)-Propen-1-yl)-3-tosylamido-oxetane (264):**

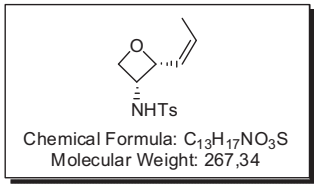


Chemical Formula: $C_{13}H_{17}NO_3S$
Molecular Weight: 267,34

The title compound was prepared following the general procedure described above, starting from (2*Z*,4*E*)-2,4-Hexadiene-1-ol (**200**) (9.8 mg, 0.1 mmol). After standard workup the crude was purified by column chromatography (9:1 to 7:3 Hexane/EtOAc) to afford **264** (15.5 mg, 59%) as a colorless syrup. **^{1}H NMR** (400 MHz, $CDCl_3$): δ in ppm 7.67 (d, 2H, J = 8.4 Hz), 7.34 (d, 2H, J = 8.4 Hz), 5.77

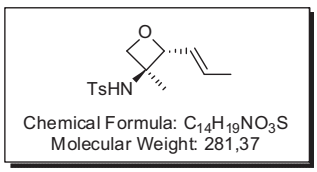
(dq, 1H, J = 14.2, 7.2 Hz), 5.55 (ddq, 1H, J = 14.4, 10.4. 2 Hz), 5.00 (d, 1H, J = 8.4 Hz), 4.89 (dd, 1H, J = 10, 4.4 Hz), 3.51 (m, 2H), 3.31 (m, 1H), 2.43 (s, 3H), 1.76 (dd, 3H, J = 6.8, 2 Hz). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ in ppm 143.1, 139.1, 131.4, 128.9, 128.9, 127.7, 126.9, 126.8, 62.5, 59.4, 56.6, 22.8, 14.1. **HR ESI-TOF MS** for $[M+H]^+$ $C_{13}H_{18}NO_3S^+$ (*m/z*): calc. 268.0929; found: 268.0999.

***cis*-2-((*Z*)-Propen-1-yl)-3-tosylamido-oxetane (265):**



The title compound was prepared following the general procedure described above, starting from (2*Z*,4*Z*)-2,4-Hexadiene-1-ol (**199**) (9.8 mg, 0.1 mmol). After standard workup the crude was purified by column chromatography (9:1 to 7:3 Hexane/EtOAc) to afford **265** (16.2 mg, 60%) as a colorless syrup. **^{1}H NMR** (400 MHz, $CDCl_3$): δ in ppm 7.77 (d, 2H, J = 8.4 Hz), 7.31 (d, 2H, J = 8.4 Hz), 5.57 (dq, 1H, J = 11.2, 7.2 Hz), 5.35 (ddq, 1H, J = 10.4, 10.4. 2 Hz), 5.01 (d, 1H, J = 8.4 Hz), 4.96 (dd, 1H, J = 10, 4.4 Hz), 3.7 (m, 2H), 3.44 (m, 1H), 2.43 (s, 3H), 1.66 (dd, 3H, J = 6.8, 2 Hz). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ in ppm 144.1, 137.2, 130.3, 129.9, 129.9, 127.4, 126.7, 126.6, 62.3, 59.3, 56.7, 21.7, 13.4. **HR ESI-TOF MS** for $[M+H]^+$ $C_{13}H_{18}NO_3S^+$ (*m/z*): calc. 268.0929; found: 268.1113.

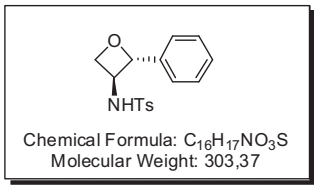
***trans*-2-((*E*)-Propen-1-yl)-3-methyl-3-tosylamido-oxetane (268):**



The title compound was prepared following the general procedure described above, starting from (2*E*,4*E*)-2-Methylhexa-2,4-dien-1-ol (**196**) (11.2 mg, 0.1 mmol). After standard workup the crude was purified by column chromatography (9:1 to 7:3 Hexane/EtOAc) to afford **268** (19.2 mg, 69%) as a colorless syrup. **^{1}H NMR** (400 MHz, $CDCl_3$): δ in ppm 7.76 (d, 2H, J = 8.4 Hz), 7.29 (d, 2H, J

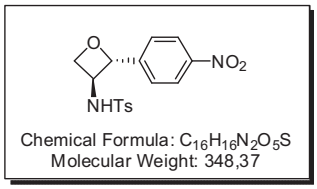
= 8.4 Hz), 5.77 (dq, 1H, J = 14.8, 6.4 Hz), 5.48 (ddq, 1H, J = 13.2, 13.2, 1.6 Hz), 4.90 (s, 1H), 4.53 (d, 1H, J = 10 Hz), 3.8 (dd, 1H, J = 11.6, 5.2 Hz), 3.61 (dd, 1H, J = 11.6, 6.4 Hz), 2.43 (s, 3H), 1.67 (dd, 3H, J = 7.0, 2.1 Hz), 1.07 (s, 3H). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ in ppm 141.5, 137.6, 131.3, 128.4, 128.4, 128.0, 62.4, 59.6, 54.9, 21.2, 17.9. **HR ESI-TOF MS** for $[M+H]^+$ $C_{14}H_{20}NO_3S^+$ (*m/z*): calc. 282.1086; found: 282.1312.

***trans*-2-Phenyl-3-tosylamido-oxetane (269):**



The title compound was prepared following the general procedure described above, starting from 3-Phenyl-2-propen-1-ol (**201**) (13.4 mg, 0.1 mmol). After standard workup the crude was purified by column chromatography (9:1 to 7:3 Hexane/EtOAc) to afford **269** (23.8 mg, 79%) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ in ppm 7.56 (d, 2H, J = 8 Hz), 7.22 (m, 7H), 5.26 (d, 1H, J = 8.8 Hz), 4.96 (d, 1H, J = 6.8 Hz), 3.96 (dt, 1H, J = 9.2, 4.4 Hz), 3.76-3.65 (m, 2H), 2.41 (s, 3H). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ in ppm 143.8, 137.4, 137.1, 129.9, 128.8, 128.7, 127.6, 127.2, 62.2, 61.3, 60.6, 21.7. **HR ESI-TOF MS** for $[M+H]^+$ $C_{16}H_{18}NO_3S^+$ (*m/z*): calc. 304.0929; found: 304.0996.

***trans*-2-(4-Nitro-phenyl)-3-tosylamido-oxetane (270):**



The title compound was prepared following the general procedure described above, starting from (2*E*)-3-(4-nitrophenyl)prop-2-en-1-ol (**202**) (13.4 mg, 0.1 mmol). After standard workup the crude was purified by column chromatography (9:1 to 7:3 Hexane/EtOAc) to afford **270** (26.4 mg, 76%) as a yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ in ppm 7.66 (d, 2H, J = 8 Hz), 7.10 (m, 6H), 5.26 (d, 1H, J = 8.3 Hz), 5.12 (d, 1H, J = 6.4 Hz), 4.01 (dt, 1H, J = 9.2, 4.4 Hz), 3.89-3.77 (m, 2H), 2.43 (s, 3H). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ in ppm

144.1, 137.9, 137.2, 130.2, 129.2, 129.0, 127.6, 127.0, 63.1, 61.2, 60.9, 21.3. **HR ESI-TOF MS** for $[M+H]^+$ $C_{16}H_{17}N_2O_5S^+$ (*m/z*): calc. 349.0780; found: 349.2136.

3.6. REFERENCES

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CHAPTER 4

ENANTIOSELECTIVE BRØNSTED ACID CATALYZED DESYMMETRIZATION OF *MESO*-AZIRIDINES AND KINETIC RESOLUTION OF RACEMIC TERMINAL AZIRIDINES

The concepts and design of the work presented in this chapter were conceived by Professor Benjamin List and Mr. Mattia Ricardo Monaco in the Max-Plank Institute für Kohlenforschung and the experimental work was performed in List's laboratories.

4.1. INTRODUCTION

4.1.1. IMPORTANCE OF β-AMINO ALCOHOLS

The β-amino alcohol and α-hydroxy-β-amino acid moieties are found in a large variety of biologically important compounds, *e.g.* natural products and peptides, as well as in a growing number of ligands and chiral auxiliaries for asymmetric catalysis.[1]

Hydroxy amino acids are the most common class of naturally occurring compounds containing the β-amino alcohol subunit. For example, the vancomycin[2] class of antibiotics contains an arylserine moiety (Figure 4.1).

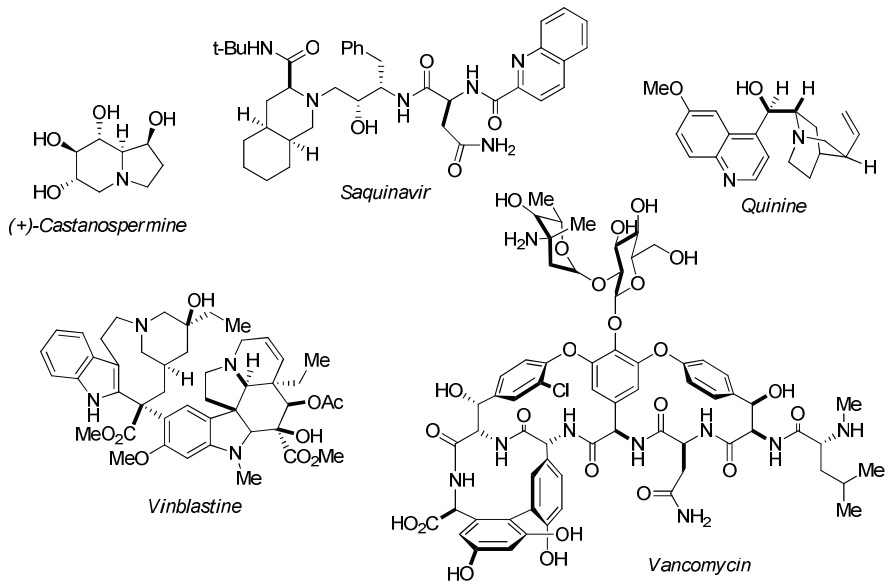
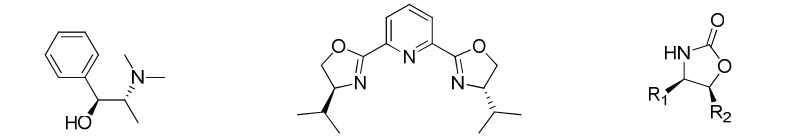


Figure 4.1. Biologically active β-Amino alcohols.

Another large group of biologically active natural products, which includes numerous alkaloids, is constituted by the cyclic amino alcohols. Pertinent examples are vinblastine,[3] used in cancer therapy, and quinine that

is used in malaria treatment. The polyhydroxylated alkaloids, known as *aza*-sugars, also belong to the group of cyclic amino alcohols. For instance, the (+)-castanospermine[4] is a potent inhibitor of α- and β-glucosidases. The peptidomimetics constitute the most important group of synthetically produced pharmacologically active amino alcohols. One of these compounds, Saquinavir, is used as HIV-1 protease inhibitor (Figure 4.1).[5]

β-Amino alcohols also play an important role as chiral ligands and chiral auxiliaries in asymmetric catalysis, and are usually derived from natural sources. The amino alcohols are generally derivatized to improve their chelating ability or to increase their steric effect.[6] Figure 4.2 depicts β-amino alcohol derivatives used in asymmetric synthesis.[7]



(+)-N-methyl ephedrine *(S,S)-i-Pr-PyBOX* *Evan's Oxazolidinonne*

Figure 4.2. Examples of β-amino alcohol-containing chiral ligands and auxiliaries.

4.1.2. SYNTHESIS OF β-AMINO ALCOHOLS

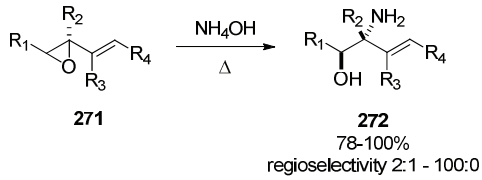
Synthetic routes toward enantiomerically pure β-amino alcohols have traditionally relied on the derivatization of amino acids, with their inherent limitation.[8] To gain access to compounds with other functionalities, considerable efforts have been made to develop asymmetric routes to β-amino alcohols, which to date can be divided into two strategically different approaches:

1) Introduction of the β-amino alcohol moiety on a pre-existing carbon skeleton.
2) Concomitant formation of a new carbon-carbon bond and one or two of the vicinal stereogenic centers in a single step.

Amino Alcohols from a Pre-Existing Carbon Skeleton

The most common approach to stereoselective synthesis of β-amino alcohols starts from a pre-existing carbon skeleton. Functionalization of alkenes is the most common approach to obtain aminoalcohols. A major drawback of these reactions is often the low regioselectivity, which can generally be circumvented if the substrate contains a regio-directing group.

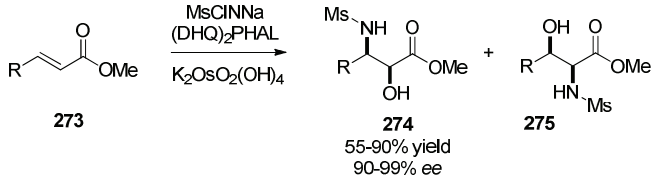
Thus, one of the most investigated routes towards enantiomerically pure β-amino alcohols is the opening of epoxides **271** with nitrogen nucleophiles. Since both *cis*- and *trans*-epoxides are available with high enantiomeric purity, this approach can be employed in the synthesis of both *syn*- and *anti*-β-amino alcohols. The regioselectivity of epoxide openings is often poor but can be controlled by introduction of regio-directing groups, most commonly phenyl or vinyl since the attack of hard nucleophiles usually proceeds at the activated benzylic or allylic carbon (Scheme 1).[9]



Scheme 4.1. Aminolysis of vinylepoxides.

β-Amino alcohols can also be obtained in an analogous fashion through the ring opening of other cyclic substrates such as aziridines,[10]

sulfates[11] and carbonates.[12] The most direct approach towards the enantioselective synthesis of β-amino alcohols is the *Sharpless* asymmetric aminohydroxylation of alkenes in which the same chiral catalyst than in the asymmetric dihydroxylation reaction is utilized. α,β-Unsaturated **273** esters and phosphonates have proven to be the most suitable substrates for this reaction (Scheme 4.2).[13] Although this transformation is attractive for the direct enantioselective synthesis of amino alcohols, the yields are often moderate due to regioselectivity issues.



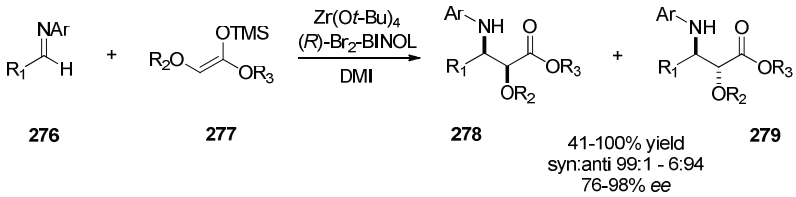
Scheme 4.2. *Sharpless* asymmetric aminohydroxylation.

Amino Alcohols from C-C Bond Forming Reactions

The amino alcohol moiety can also be constructed by the coupling of two fragments: one containing the oxygen functionality and one containing the nitrogen functionality, with a concomitant formation of a new carbon-carbon bond and two vicinal stereogenic centers. For this approach to be efficient, both enantio- and diastereocontrol are required. However, this approach is limited to certain types of substrates. There are mainly two strategies employed for the enantioselective synthesis of amino alcohols based on C-C bond forming reactions: the Mannich-type reactions[14] and the addition of glycine derived enolates to aldehydes.[15]

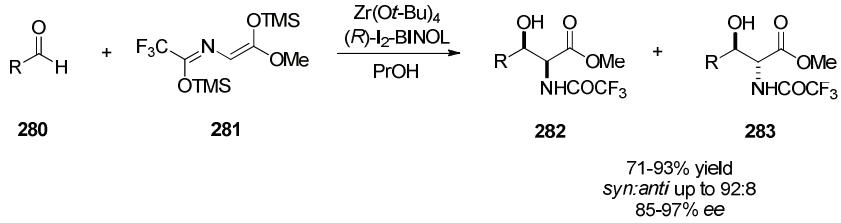
One elegant example of a highly stereoselective Mannich-type reaction is based on the nucleophilic addition of α-alkoxy enolates **277** to imines **276**, affording amino alcohols with high to excellent

enantioselectivity (Scheme 4.3).[16] Depending on the choice of the enolate, both *syn* (R_2 = TBS) and *anti* (R_2 = Bn) amino alcohols can be formed with high diastereoselectivity.



Scheme 4.3. Enantioselective Mannich-type approach.

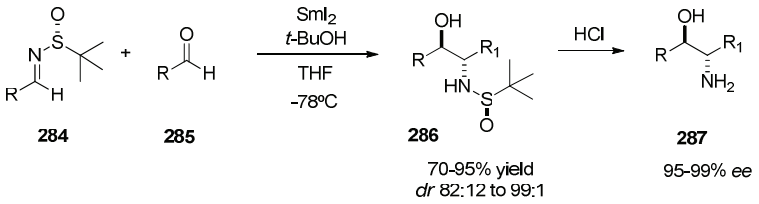
Amino alcohols can also be synthesized by Lewis acid-catalyzed aldol reactions. Zirconium/BINOL-catalyzed reactions of glycine derived silyl ketene acetals **281** to aldehydes furnish *anti*-α-amino-β-hydroxy acids in excellent yields and enantioselectivities (Scheme 4.4).[17]



Scheme 4.4. Enantioselective aldol approach.

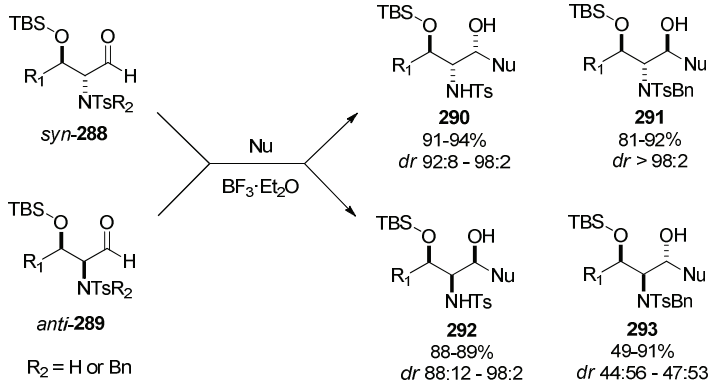
One of the most direct approaches for the synthesis of β-amino alcohols would be to couple carbonyl functionalities with imine functionalities in a pinacol-type cross coupling. However, achieving both chemoselectivity and stereoselectivity is a significant synthetic challenge. Recently, this situation has been addressed by the development of a highly diastereoselective pinacol-type cross-coupling between enantiomerically pure *N-tert*-butylsulfinyl imines **284** and aliphatic aldehydes **285** leading to

enantiomerically pure *anti*-β-amino alcohols **287** in excellent yields (Scheme 4.5).[18]



Scheme 4.5. Diastereoselective SmI_2-mediated Pinacol-type Cross coupling.

Another approach consists in taken advantage of the stereodirecting effect of a preexisting stereogenic center in order to control the enantioselectivity. This could be performed by nucleophilic additions to α-amino aldehydes, which usually proceed with good diastereoselectivity. A recent example of a divergent protocol for substrate-controlled diastereoselective synthesis of aminodiols based on nucleophilic *Mukaiyama* aldol additions to α-amino-β-silyloxy aldehydes *syn,anti*-**288** is depicted in Scheme 4.6.[19]



Scheme 4.6. Aminodiols from diastereoselective *Mukaiyama* Aldol additions.

The above-mentioned methods for the stereoselective synthesis of β-amino alcohol constitute a brief survey of the recent development in the area and highlight the importance of this class of compounds in organic synthesis.

4.1.3. CHIRAL BRØNSTED PHOSPHORIC ACIDS AS CATALYSTS

The electrophilic activation of a substrate by means of a Brønsted acid is certainly the most straightforward and common approach used to promote catalytic organic transformations. However, the synthetic utility of Brønsted acids as catalysts for stereoselective reactions has been limited until recent years as it was generally accepted that the Brønsted acid must exhibit a "proton-like" character to effectively activate a substrate and that the conjugate base (A^-) only influences the catalytic activity and has no effect on the stereo- and regioselectivity of the reaction.

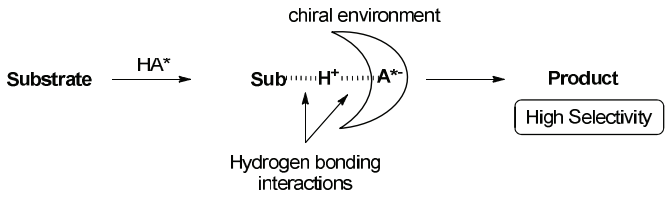
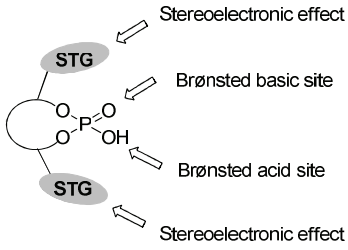


Figure 4.3. Catalysis by chiral Brønsted acids.

However, in the past decade, the development of chiral Brønsted acid catalysis has emerged as a powerful tool to obtain enantioenriched products. The key to obtain enantioselective catalysis using a chiral Brønsted acid is the hydrogen bonding interactions between a protonated

substrate (Sub-H^+) and the chiral conjugate base (A^{*-}) (Figure 4.3). Therefore, the organic transformations proceed in a chiral environment created by the chiral conjugated base (A^{*-}), which is in the proximity of the substrate through hydrogen bonding interactions. In this context, phosphoric acids attracted much attention because they were expected to capture electrophilic components through hydrogen bonding interactions without the formation of ion-pairs due to their relatively strong but appropriate acidity (for example pK_a of $(EtO)_2P(O)OH$ is 1.39).[20]

As the phosphoryl oxygen acts as a Brønsted basic site, an acid/base bifunctional catalysis can be anticipated. Furthermore, the introduction of a ring structure bearing substituents (STG) can prevent the free rotation at the α-position of the phosphorus centre and provide a chiral environment during the transformation (Figure 4.4). This characteristic cannot be found in other Brønsted acids such as carboxylic and sulfinic acids. Therefore an efficient substrate recognition site can be constructed at the vicinity of the activating function of the phosphoric acid catalyst, namely the acidic proton.



Xa = H
Xb = Ph
Xc = 4-NO_2-phenyl
Xd = 4-β-naph-phenyl
Xe = 4-Cl-phenyl
Xf = 3,5-$(CF_3)_2$-phenyl
Xg = 3,5-dimesitiy-phenyl

Xh = 1-naphtyl
Xi = 2,4,6-$(iPr)_3$-phenyl
Xj = 9-anthryl
Xk = 9-phenanthryl
Xl = biphenyl
Xm = 2-naphtyl
Xn = $SiPh_3$

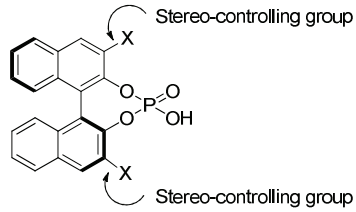


Figure 4.4. Structural features and representative examples of (*R*)-BINOL-derived phosphoric acids.

Binaphthol (BINOL) is a well known molecule having C_2 symmetry, whose derivatives have been extensively used as chiral ligand for metal catalysis. Thus, the BINOL derivatives were selected as chiral sources to assemble the catalyst with the advantage that both enantiomers are commercially available and that numerous protocols for introducing substituents at the 3,3'-positions of the binaphthyl backbone are reported.[21] A few examples of (*R*)-BINOL-derived phosphoric acids used as catalysts in a number of reactions are displayed in Figure 4.4.[22]

In this context, it became evident that chiral phosphoric acids exhibit a tremendous potential as catalysts for novel asymmetric transformations. Although the application of these catalysts has been limited for a long time to nitrogen-based electrophiles such as imines, the incorporation of the *N*-trifluoromethanesulfonyl (NTf) group into the phosphoric acid structure (Figure 4.5) made the activation of carbonyl compounds possible and this stronger chiral phosphoric acid was applied in the asymmetric Diels-Alder reaction.[23] It was reported that substitution of the oxygen atom in the P-O bond in an *N*-triflyl phosphoramide with sulfur or selenium further decrease the pK_a of the catalyst and as such allow the broadening of the scope of Brønsted acid organocatalysis.[24]

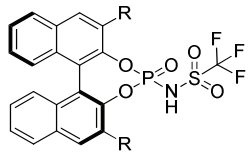


Figure 4.5. BINOL-derived *N*-triflylphosphoramide compounds.

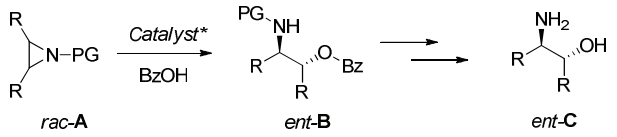
Although the Brønsted acid catalysts developed to date greatly differ in structure and that various mechanisms for electrophilic activation and catalysis using these compounds were reported, there is however a

common design feature consisting in a single or dual hydrogen bond donor site flanked by functionalities for secondary interactions with substrates containing aromatic, basic or acidic groups. In the following section, the application of such phosphoric acids to the desymmetrization of *meso*-aziridines as well as in the kinetic resolution of terminal aziridines will be described in detail.

4.2. OUTLOOK & CONCEPT

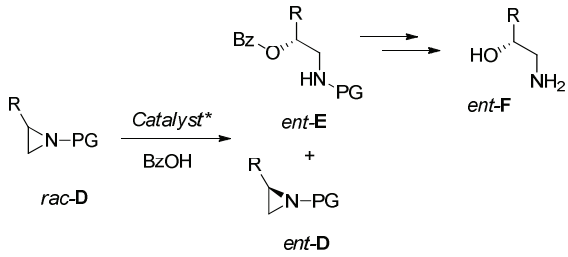
Several successful studies were reported using enantiopure starting materials or chiral auxiliaries for the stereoselective synthesis of β-amino alcohols with regard to the development of an enantioselective procedure. However, no attention has been done in the asymmetric ring-opening of aziridines using oxygen-nucleophiles in spite of its potential in the synthesis of optically active β-amino alcohols with one or two stereogenic centers in a single step.

In this context, the goal of this work was to develop an organocatalytic approach for the asymmetric desymmetrization of *meso*-aziridines and the kinetic resolution of terminal aziridines using oxygen-nucleophiles. The desymmetrization of *meso*-aziridines **A** was expected to generate the enantiomerically enriched β-amidoesthers **B**, important precursors for the synthesis of β-amino alcohols **C** (Scheme 21).



Scheme 4.7. Desymmetrization of *meso*-aziridines using oxygen-nucleophiles.

In addition, the kinetic resolution of the terminal aziridines **D** catalyzed by the appropriate chiral phosphoric acids would generate enantiomerically enriched β-amido esthers **E**, important precursors for the synthesis of β-amino alcohols **F** together with the enantiomerically enriched terminal aziridine *ent*-**D** (Scheme 4.8).



Scheme 4.8. Kinetic resolution of terminal aziridines using oxygen-nucleophiles.

Although there are a wide range of successful studies in the organocatalytic desymmetrization of *meso*-aziridines using several nucleophiles (*Chapter 1, Section 3.1.2*), there are currently no report on the utilization of oxygen-nucleophiles.

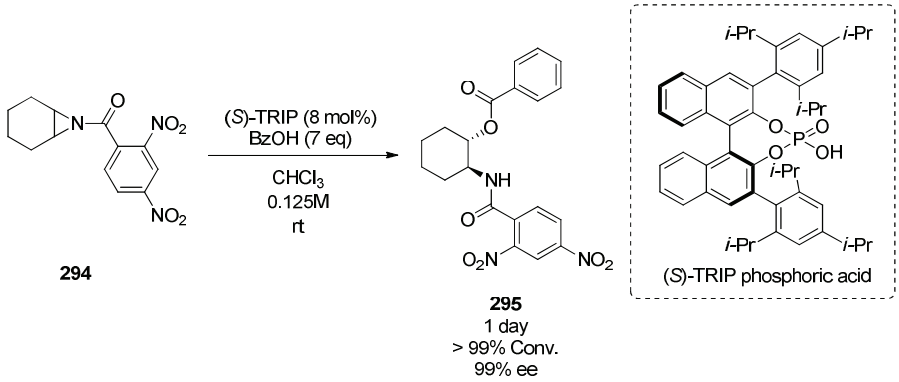
4.3. RESULTS AND DISCUSSION

4.3.1. DESYMMETRIZATION OF *MESO*-AZIRIDINES

4.3.1.1. PREVIOUS RESULTS OBTAINED IN LIST'S LABORATORIES

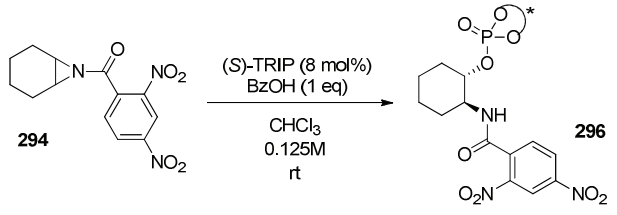
The initial screening of catalysts and reaction conditions was conducted by *M. Ricardo* and *B. Poladura* using the cyclohexane-derived aziridine **294** as substrate and benzoic acid (BzOH) as the nucleophile (Scheme 4.9). Chloroform was found to be the optimal solvent. (*S*)-TRIP-

phosphoric acid was used as the catalyst for the optimization of reaction conditions due to its superior behaviour in terms of enantioselectivity over all other catalysts studied. The highest enantioselectivity (99% *ee*) together with excellent conversion (up to 98%) was obtained using 7 equivalents of benzoic acid and 8 mol% of catalyst loading at high substrate concentration (0.125 M) after 24h.



Scheme 4.9. Optimized reaction conditions for the desymmetrization of cyclohexane derived *meso*-aziridine **294**.

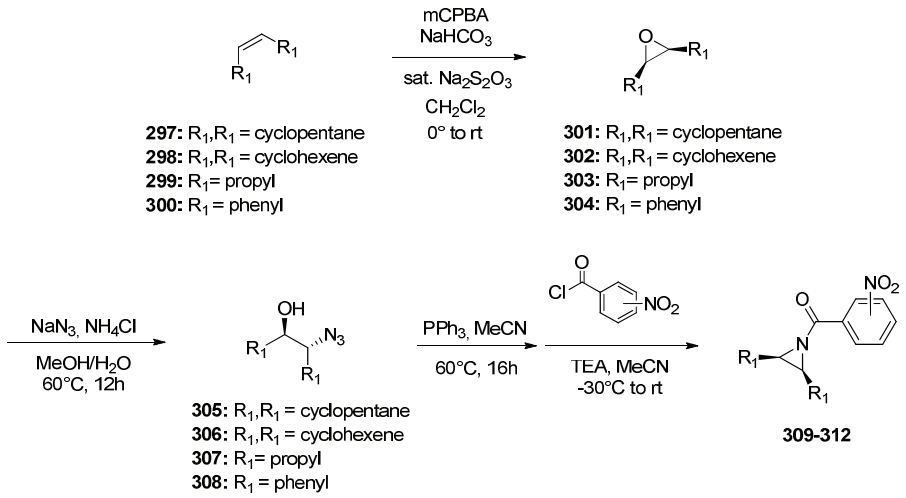
Interestingly, full conversions were not obtained when lower amounts of benzoic acid were employed due to the competitive nucleophilic addition of the catalyst to the substrate **294** forming the inactive form of the catalyt **295** (Scheme 4.10).[25]



Scheme 4.10. Formation of the inactive specie of the catalyst **296**.

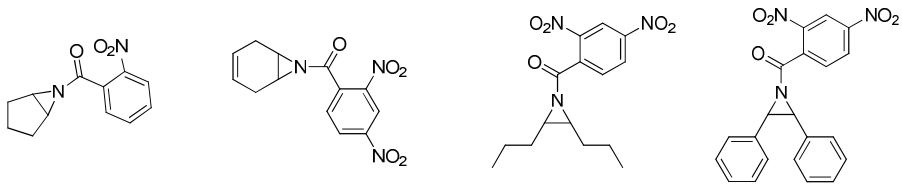
4.3.1.2. SYNTHESIS OF MESO-AZIRIDINES

A series of *meso*-aziridines containing 2-nitro and 2,4-dinitrobenzoyl *N*-protecting groups was prepared using a one pot protocol. The main procedure for the synthesis of these *meso*-aziridines is described in Scheme 4.11.[26]



Scheme 4.11. Procedure used for the synthesis of *meso*-aziridines **309-312**.

The epoxidation of alkene **297-300** with peracid gave the corresponding oxirane **301-304** in quantitative yields.[27] The azidolysis reaction of these epoxides with sodium azide gave the corresponding azido alcohols **305-308**. The azido alcohols were then treated with triphenylphosphine under *Staudinger* reaction conditions to reduce the azide under mild conditions providing the free aziridine. Protection of the desired aziridine was accomplished by the addition of triethylamine followed by the addition of the corresponding nitrobenzoyl chlorides, which were previously synthesized from the related benzoic acids in the presence of an excess of phosphorus oxychloride.



309 42 % yield | **310** 24 % yield | **311** 33% yield | **312** 30 % yield

Figure 4.6. Stuctures of the m*eso*-aziridines synthesised in this work.

Following this procedure, the terminal aziridines **309-312** were prepared providing 24-42% yields over four reaction steps (Figure 4.6).[28] In the following section, the optimization of the reaction conditions for each of these new substrates will be described.

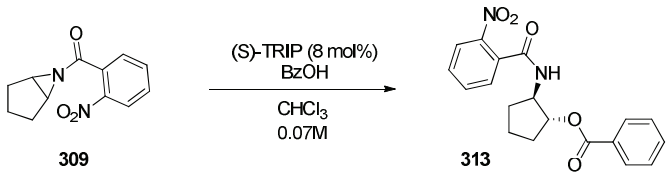
4.3.1.3. DESYMMETRIZATION OF MESO-AZIRIDINES PROMOTED BY (*S*)-TRIP PHOSPHORIC ACID USING OXYGEN NUCLEOPHILES

Due to the distinct properties of the aziridines used in this work (some containing cycloalkanes, acyclic aliphatic and aryl substituents), an optimization of the reaction conditions was performed for each substrate, as described below. For several aziridines, the main parameter affecting the conversion was the ratio of benzoic acid to aziridine and to afford full conversions, high loaddings of benzoic acid were necessary.

Several solvents were screened for the desymmetrization of the cyclopentane derived *meso*-aziridine **309**, and it was determined that chloroform was also the solvent of choice to obtain the highest enantioselectivity. The optimization of the ring-opened product of cyclopentane-derived aziridine **309** is shown in Table 4.1. Several ratios of benzoic acid to aziridine were tested for the formation of product **313**. The highest enantioselectivity was obtained using 7 equivalents of benzoic acid

(Table 4.1, entry 1). The highest enantioselectivity was obtained when the reaction was carried out at -10ºC using 7 equivalents of benzoic acid (Table 4.1, entry 4).

Table 4.1. (*S*)-TRIP-catalyzed desymmetrization of **309** with BzOH.[a]



309 313

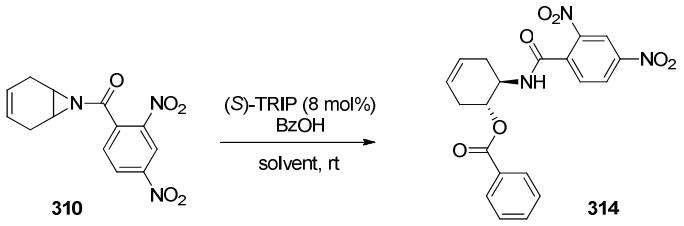
Entry	Ratio BzOH:309	T (ºC)	Time (h)	Conv (%)[b]	e.r.[c]
1	7:1	RT	22	> 98	93:7
2	6:1	RT	22	> 98	91:9
3	5:1	RT	22	> 98	92:8
4	7:1	-10ºC	28	> 98	97:3

[a]General reaction conditions: **309** (0.05 mmol), (*S*)-TRIP (0.004 mmol), in chloroform. [b]Conversion was determined by ^{1}H-NMR. [c]The enantiomeric excess was determined by chiral HPLC.

Several solvents were tested in the desymmetrization of the cyclopentane derived *meso*-aziridine **309**, and it was determined that chloroform was also the solvent of choice to obtain the highest enantioselectivity. The optimization of the ring-opened product of cyclopentane-derived aziridine **309** is shown in Table 4.1. Several ratios of benzoic acid to aziridine were tested for the formation of product **313**. The highest enantioselectivity was obtained using 7 equivalents of benzoic acid (Table 4.1, entry 1). The enantioselectivity was improved to 97:3 e.r when the reaction was carried out at -10ºC using 7 equivalents of benzoic acid (Table 4.1, entry 4).

Table 4.2 summarised the optimisation of the reaction conditions for the cyclohexene derived *meso*-aziridine **310**. After testing several benzoic acid to aziridine ratios, it was observed that using 7 and 5 equivalents of benzoic acid result in the same enantioselectivity (Table 4.2, entries 1 and 2).

Table 4.2. (*S*)-TRIP-catalyzed desymmetrization of **310** with BzOH.[a]



310 **314**

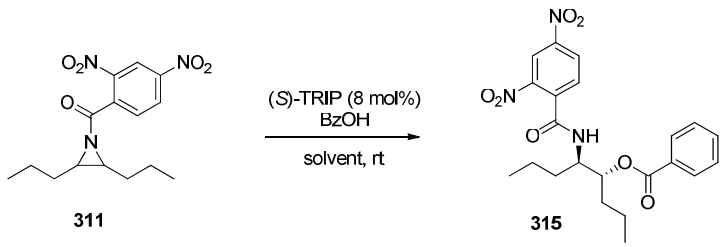
Entry	Ratio BzOH:310	Solvent	[S][b]	Time (h)	Conv (%)[c]	e.r.[d]
1	5:1	$CHCl_3$	0.035	12	> 98	98:2
2	7:1	$CHCl_3$	0.035	12	> 98	98:2
3	5:1	CH_2Cl_2	0.035	12	> 98	96:4
4	5:1	$CHCl_3$	0.125	12	> 98	99:1

[a]General reaction conditions: **310** (0.05 mmol), (*S*)-TRIP (0.004 mmol) at rt. [b][S] = Substrate concentration. [c]Conversion was determined by ^{1}H-NMR. [d]The enantiomeric excess was determined by chiral HPLC.

When dichloromethane was used as solvent, a slight decrease in enantioselectivity to 96:4 er was observed (Table 4.2, entry 3). Interestingly, in this case, when the concentration of the substrate was increased, an increase in the enantioselectivity was observed (Table 4.2, entry 4). The highest enantiodiscrimination was obtained in 0.125M of substrate concentration, carrying out the reaction at room temperature and affording 98% conversion and 99:1 enantiomeric ratio (Table 4.2, entry 4).

Table 4.3 summarises the optimisation of the reaction conditions for the asymmetric desymmetrization of **311**. The results were similar to those of the cyclopentane derived aziridine **309**.

Table 4.3. (*S*)-TRIP-catalyzed desymmetrization of **311** with BzOH.[a]



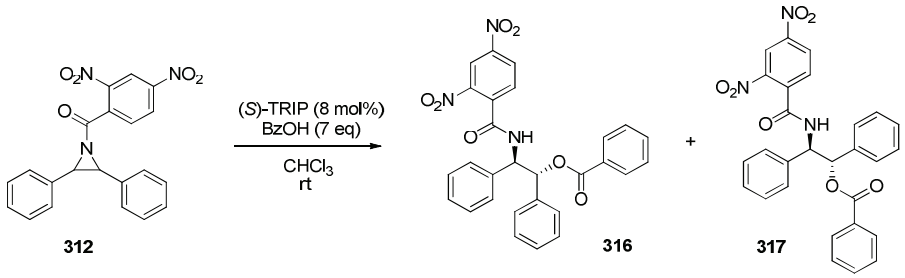
Entry	Ratio BzOH:311	Solvent	[S][b]	Time (h)	Conv (%)[c]	er[d]
1	5:1	$CHCl_3$	0.035	24	> 98	94:6
2	6:1	$CHCl_3$	0.035	24	> 98	94:6
3	7:1	$CHCl_3$	0.035	24	> 98	94:6
4	5:1	CH_2Cl_2	0.035	24	> 98	93:7
5	5:1	$CHCl_3$	0.025	24	> 98	95:5
6	5:1	$CHCl_3$	0.05	24	> 98	94:6
7	5:1	$CHCl_3$	0.125	12	> 98	91:9
8	5:1	$CHCl_3$	0.1	12	> 98	92:8

[a]General reaction conditions: **311** (0.05 mmol), (*S*)-TRIP (0.004 mmol) at rt. [b][S] = Substrate concentration. [c]Conversion was determined by ^{1}H-NMR. [d]The enantiomeric excess was determined by chiral HPLC.

When several ratios of benzoic acid to aziridine were tested, no effect on the enantiodiscrimination was observed (Table 4.3, entries 1 to 3). The use of dichloromethane as solvent resulted in a slight decrease in the enantioselectivity of the ring-opened product **315** (Table 4.3, entry 4). The substrate concentration was also varied (Table 4.3, entries 4 to 8) and the best enantiodifferentiation conditions were achieved using 0.025M of substrate, resulting in 98% conversion and 95:5 er (Table 4.3, entry 5).

Finally, the use of (*S*)-TRIP-phosphoric acid for the ring-opening of the aziridine containing aryl substituents **312** resulted in the formation of a diastereoisomeric mixture using 7 equivalents of benzoic acid and chloroform as solvent at room temperature (Table 4.4).

Table 4.4. (*S*)-TRIP-catalyzed desymmetrization of **312** with BzOH.[a]



Entry	[S][b]	Time (h)	Conv (%)[c]	d.r (313: 314)[d]	e.r.[e] 316	e.r.[e] 317
1	0.025	26	96	3:1	96:4	84:16
2	0.02	72	72	4:1	97:3	84:16
3	0.016	51	51	4:1	95:5	82:18

[a]General reaction conditions: **312** (0.05 mmol), (*S*)-TRIP (0.004 mmol) in chloroform at rt. [b][S] = Substrate concentration. [c]Conversion was determined by ^{1}H-NMR. [d]The enantiomeric excess was determined by chiral HPLC. [e]The diastereoisomeric ratio was determined by ^{1}H-NMR and chiral HPLC.

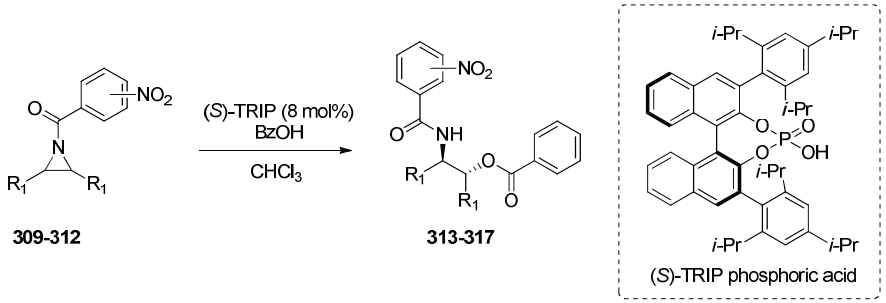
When several substrate concentrations were tested, 0.025 M provided the highest conversion with a 3:1 (**316:317**) diastereoisomeric ratio. Each diastereoisomer was obtained in 96:4 and 84:16 e.r, respectively (Table 4.4, entry 1). Running the reaction using 0.02 M of substrate concentration, full conversion was not afforded due to the degradation of the catalyst after 72h. Only 72% conversion was obtained under these conditions with a diastereoisomeric ratio of 4:1 (**316:317**) obtaining each diastereoisomer in 97:3 and 84:16 e.r, respectively (Table 4.4, entry 2). Decreasing the substrate concentration to 0.016 M, the degradation of the

catalyst was observed after 51h and only 51% conversion was obtained with a diastereoisomeric ratio of 4:1 (**316:317**) with 95:5 and 82:18 e.r, respectively (Table 4.4, entry 3). As both diastereoisomers were enantioenriched, we hypothesized that the activation of the *meso*-aziridine by coordination of the Brønsted acid functionality let to the aziridine ring-opening with the concomitant carbocation formation resulting in the isomerization of the aziridine carbon center.

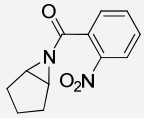
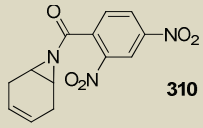
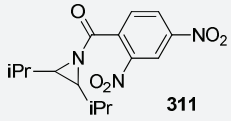
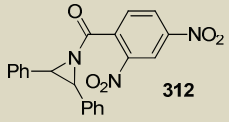
Our studies showed that (*S*)-TRIP-phosphoric acid-catalyzed desymmetrization of various *meso*-aziridines derived from cycloalkanes, containing acyclic aliphatic and aryl substituents proceeds efficiently using benzoic acid as oxygen-nucleophile. (*S*)-TRIP-phosphoric acid derived from BINOL proved to be an excellent catalyst in terms of enantioselectivity, for the desymmetrization of all the *meso*-aziridines (Table 4.5). The five membered-ring derived aziridine **312** was transformed in good yield and enantioselectivity (Table 4.5, entry 1). The cyclohexane ring derivative was obtained with higher enantioselectivity (Table 4.5, entry 2), possibly due to the greater rigidity of the cyclohexane ring. The use of aziridines bearing acyclic aliphatic substituents resulted in a lower enantioselectivity (Table 4.5, entry 3).

This result could also be a consequence of the lower rigidity of the acyclic compound. However, the use of (*S*)-TRIP-phosphoric acid for the ring-opening of the aziridine containing aryl substituents **312** resulted in a very good er for the product **316**, although the epimer **317** was obtained in a lower er and only 72% conversion was afforded (Table 4.5, entry 4).

Table 4.5. Summary of the Brønsted acid-catalyzed desymmetrization of *meso*-aziridines **309-312** under optimized conditions.

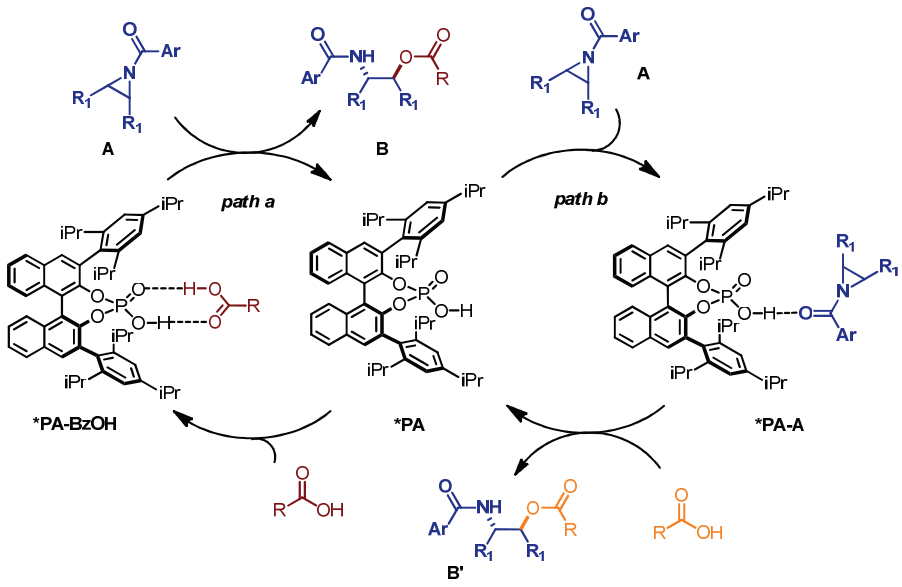


309-312 313-317

Entry	Substrate	Time (h)	Yield (%)[e]	e.r.[g]
1[a]	 **309**	28	87	(**313**) 97:3
2[b]	 **310**	12	83	(**314**) 99:1
3[c]	 **311**	24	94	(**315**) 95:5
4[d]	 **312**	72	68(72)[f]	(**316:317**) 4:1 d.r[h] 97:3/84:6 e.r

[a]Reaction conditions: **309** (0.2 mmol), BzOH (1.4 mmol), (*S*)-TRIP (0.016 mmol); T = -10ºC (0.07 M). [b]Reaction conditions: **310** (0.2 mmol), BzOH (1 mmol), (*S*)-TRIP (0.016 mmol); T = rt (0.125 M). [c]Reaction conditions: **311** (0.2 mmol), BzOH (1 mmol), (*S*)-TRIP (0.016 mmol); T = rt (0.025 M). [d]Reaction conditions: **312** (0.2 mmol), BzOH (1.4 mmol), (*S*)-TRIP (0.016 mmol); T = rt (0.02 M). [e]Isolated Yield. [f]NMR Conversion. [g]The enantiomeric excess was determined by chiral HPLC. [h]The diastereoisomeric ratio was determined by ^{1}H-NMR and chiral HPLC.

To explain the potential isomerization of the aziridine carbon centre, we speculated that the (*S*)-TRIP-phosphoric acid-catalyzed desymmetrization of *meso*-aziridines could take place *via* two mechanistic pathways (Scheme 4.12, *paths a and b*).



Scheme 4.12. Proposed mechanisms for the asymmetric desymmetrization of *meso*-aziridines promoted by (*S*)-TRIP phosphoric acid using oxygen-nucleophile.

If the reaction mechanism proceeds through *path a*, the first step of the reaction would involve the activation of the **BzOH** by coordination to the Brønsted acid and base functionalities of the catalyst, resulting in the formation of the chiral adduct (***PA-BzOH**). Next, the **BzOH** coordinated to the ***PA** undergoes nucleophilic attack to the *meso*-aziridine, resulting in the product **B** and the regeneration of the catalyst (***PA**). In contrast, if the reaction mechanism proceeds through *path b,* the first step of the reaction would involve the activation of the *meso*-aziridine **A** by coordination of the Brønsted acid functionality of the catalyst, resulting in the formation of the

chiral adduct (***PA-A**). Next, the *meso*-aziridine unit of the chiral adduct (***PA-A**) undergoes nucleophilic attack from **BzOH**, resulting in the formation of product **B'** and the regeneration of the catalyst (***PA**). This mechanism is actually under investigation in *List*'s group.

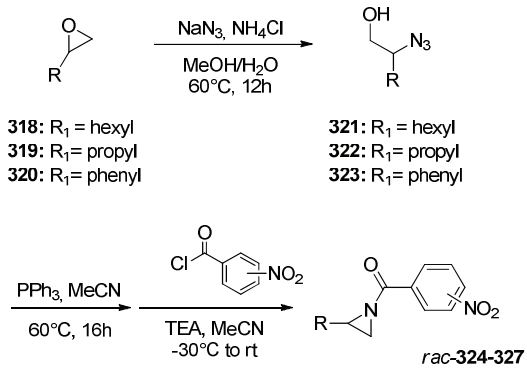
To summarize this section, from the study of the enantioselective Bronsted acid-catalyzed desymmetrization of *meso*-aziridines with oxygen-nucleophiles, the following conclusions can be extracted: i) (*S*)-TRIP-phosphoric acid was found to be an excellent catalyst for this enantioselective process. ii) The aziridine to benzoic acid ratio was found to affect the conversion of the process due to a competitive reaction between the desymmetrization process and the catalyst degradation. iii) Various *meso*-aziridines protected with N-benzoyl groups and bearing different substituents were applied in their asymmetric desymmetrization. The cyclic aziridines **309** and **310** resulted in the formation of the ring-opened product in good yield (87 and 83%, respectively) and excellent enantioselectivity (97:3 and 99:1 e.r, respectively). The aziridine **311** containing acyclic aliphatic substituents resulted in the formation of the product in excellent yield and good enantioselectivity (94% yield and 95:5 e.r). Finally, the aziridines containing aryl substituents **312** provided a diastereoisomeric mixture in moderate yield and good enantioselectivities for both diastereoisomers (Table 4.5, entry 4).

4.3.2. KINETIC RESOLUTION OF TERMINAL AZIRIDINES

Encouraged by the excellent results obtained in the asymmetric desymmetrization of *meso*-aziridines, we decided to study the kinetic resolution of terminal aziridines promoted by (*S*)-TRIP phosphoric acid.

4.3.2.1. SYNTHESIS OF TERMINAL AZIRIDINES

First, the syntheses of the terminal aziridines **321-323** containing 2-nitro and 2,4-dinitrobenzoyl *N*-protecting groups, were carried out from the corresponding epoxides **318-320** in a one-pot procedure over three reaction steps (Scheme 4.13).



Scheme 4.13. Synthesis of racemic terminal aziridines.

The azidolysis reaction of the epoxides **318-320** with sodium azide gave the corresponding azido alcohols **321-323**. The azido alcohol was treated with triphenylphosphine under *Staudinger* reaction conditions to reduce the azide under mild conditions providing the free aziridine.

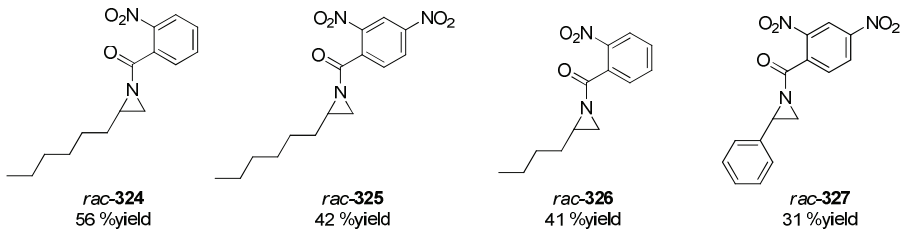


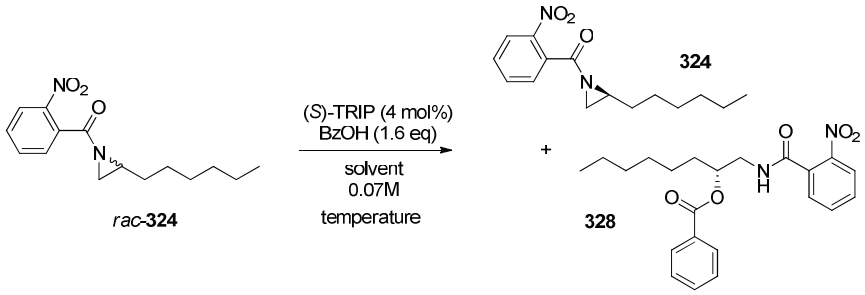
Figure 4.7. Set of racemic terminal aziridines.

Protection of the desired aziridine was accomplished by the addition of triethylamine followed by the addition of nitrobenzoyl chloride, which had been previously synthesized from the related benzoic acid in the presence of an excess of phosphorus oxychloride. Using this procedure, the racemic terminal aziridines *rac*-**324-327** were prepared in 31-56% yields over three reaction steps (Figure 4.7).

4.3.2.2. KINETIC RESOLUTION OF TERMINAL AZIRIDINES PROMOTED BY (*S*)-TRIP PHOSPHORIC ACID USING OXYGEN NUCLEOPHILES

Initially, the catalytic kinetic resolution of the terminal aziridine *rac*-**324** promoted by (*S*)-TRIP-phosphoric acid was optimized varying the solvent and the reaction temperature using 1.6 equivalents of benzoic acid as the oxygen-nucleophile and 4 mol% of catalyst. The results are summarized in Table 4.6. All catalytic screenings showed that ring-cleavage of the terminal aziridine was totally regioselective to the corresponding C2-substituted product. When the reaction was performed in dichloromethane, 62% conversion was obtained after 40 minutes and almost no changes were observed after 2h and 18h. Under these conditions, the product **328** was afforded with 82:18 e.r. while 95:5 e.r. was measured for the enantioenriched aziridine **324** (Table 4.6, entries 2 and 3). Interestingly, the conversion and enantioselectivity of the process remains almost unchanged after 40 minutes, probably due to the degradation of the catalyst. When the reaction was performed in dichloroethane, lower conversion was obtained after 45 minutes (35%) and increased to 46% after 2h although no further changes were observed after 18h. Under these conditions, the product **328** was afforded with 86:14 e.r. while 72:28 er was measured for the enantioenriched aziridine **324** (Table 4.6, entries 5 and 6).

Table 4.6. (*S*)-TRIP-catalyzed kinetic resolution of *rac*-**324** with BzOH.[a]



Entry	Solvent	T (ºC)	Time (h)	Conv (%)[b]	e.r.[c]	
					324	328
1	CH_2Cl_2	rt	0.66	62	93:7	81:19
2			2	63	94:6	82:18
3			18	63		
4	$ClCH_2CH_2Cl$	rt	0.75	35	74:26	85:15
5			2	46	72:28	86:14
6			18	46		
7	CCl_4	rt	0.75	52	34:66	79:21
8			2	54	76:24	76:24
9			18	54		
10	$CHCl_3$	rt	0.75	44	72:28	81:19
11			2	44		
12			18	44		
13	$CHCl_3$	0ºC	1	41	72:28	81:19
14			2	45	75:25	81:19
15			18	45		
16	CH_2Cl_2	0ºC	0.5	57	98:2	86:14
17			1.15	63	95:5	86:14
18			2.15	63		

[a]General reaction conditions: **324** (0.05 mmol), BzOH (0.08 mmol), (*S*)-TRIP (0.002 mmol). [b]Conversion was determined by ^{1}H-NMR. [c]The enantiomeric excess was determined by chiral HPLC.

When the reaction was carried out in tetrachloromethane, 52% conversion was obtained after 45 minutes and 54% of conversion was observed after 2h and 18h. Under these conditions, the product **328** and the enantioenriched aziridine were both afforded with 76:24 e.r. (Table 4.6, entries 8 and 9). Running the reaction in chloroform, 44% conversion was obtained after 45 minutes and no increase was observed after 2h and 18 h, probably due to the formation of an inactive catalyst species. Under these conditions, a lower enantiodiscrimination was obtained in this process, as the product **328** was afforded with 81:19 e.r. while 72:28 e.r. was measured for the enantioenriched aziridine **324** (Table 4.6, entries 10, 11 and 12). Decreasing the temperature to 0ºC, the degradation of the catalyst occurs after 2h achieving 45% conversion in chloroform and no further improvement in yield and enantiodiscrimination was afforded (Table 4.6, entries 13, 14 and 15). Finally, the best enantiodifferentiating reaction conditions identified dichloromethane as the optimal solvent running the reaction at 0ºC. Under these conditions, 57% conversion to compound **328** was afforded after 30 minutes with 86:14 er. The remaining aziridine **324** was recovered with 95:5 er (Table 4.6, entry 16).

In order to study the degradation of the catalyst, an NMR tube was charged with equimolecular mixtures of the aziridine *rac*-**324** and (*S*)-TRIP phsophoric acid in deuterated dichloromethane. After 1h, full conversion of the substrate was observed. After complete NMR characterization, we concluded that the set of signals detected corresponds to the product **329** resulting from the catalyst nucleophilic addition to the terminal aziridine (Figure 4.8a).

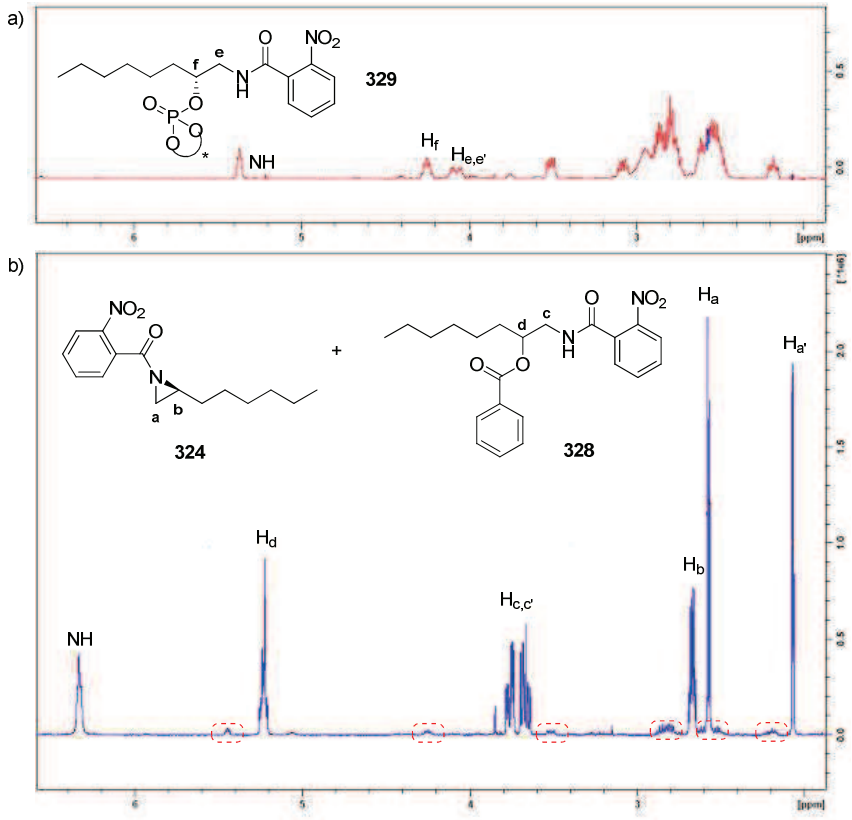


Figure 4.8. a) ^{1}H-NMR spectra of the reaction mixture of the nucleophilic catalyst resulting from the addition to the terminal aziridine *rac*-**324**. b) ^{1}H-NMR spectra of the reaction mixture of the kinetic resolution of terminal aziridine *rac*-**324** after 1h.

Next, the (*S*)-TRIP kinetic resolution of *rac*-**324** was studied at room temperature in an NMR tube in the presence of 1.6 equivalents of benzoic acid using 4 mol% of (*S*)-TRIP-phosphoric acid in CD_2Cl_2 as solvent. After 1h, 38% conversion of the substrate was observed. The resonances corresponding to the desired ring opened product **328** were readily detected in the ^{1}H-NMR spectrum together with a second set of signals (Figure 4.8b) corresponding to the by-product. These latter signals are highlighted with red cycles and correspond to the catalyst degradation product and not to a regioisomer of the reaction product. The ^{1}H-NMR

conversion was again checked after 18h and no increase in conversion was observed, which confirmed that the catalyst was degraded.

Once dichloromethane was established as the optimal solvent, the loading of benzoic acid, the temperature and the substrate concentration were optimized using 4mol% of (*S*)-TRIP-catalyst. The results are summarized in Table 4.7. When the reaction was performed at -30ºC, 10% conversion was obtained after 10 minutes and increased to 38% after 45 minutes, to 43% after 1h20, to 50% after 2h and 62% after 18h (Table 4.7, entries 1 to 5). These results suggest that under this reaction conditions the degradation of the catalyst did not occur. Good selectivity was obtained under these reaction conditions, the product **328** was afforded with 95:5 e.r. and 87:13 e.r. was measured for the enantioenriched aziridine **324** (Table 4.7, entry 4). Interestingly, using the same reaction conditions but decreasing the temperature to -40ºC, 32% conversion after 2 h was achieved, and even after 10h, the reaction did not reach 50% conversion. This result suggests that the reaction rate decreases significantly at -40ºC. The product **328** was afforded with 96:4 e.r. while 69:21 e.r. was measured for the enantioenriched aziridine **324** at 32% conversion (Table 4.7, entries 9 and 10).

The concentration of the substrate was also varied. Thus, running the reaction at 0.05M at -30ºC, 44% conversion was obtained after 30 minutes and increased to 56% after 55 minutes, to 63% after 1h and 30 minutes, to 70% after 2h, reaching 99% after 3h 50 minutes (Table 4.7, entries 11 to 15). At 56% conversion, moderate selectivity was obtained, the product **328** was afforded with 95:5 e.r. while 78:22 e.r. was measured for the enantioenriched aziridine **324** (Table 4.7, entry 12).

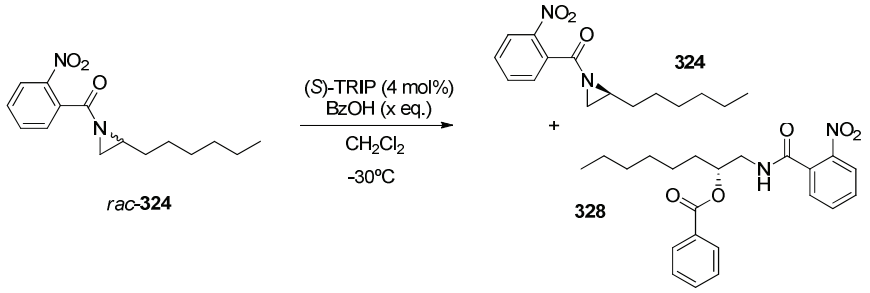
Table 4.7. (*S*)-TRIP-catalyzed kinetic resolution of *rac*-**324** with BzOH.[a]

Entry	Reaction Conditions	Time (h)	Conv (%)[b]	e.r.[c]	
				324	328
1	1.6 eq. BzOH -30°C 0.7M	0.15	10	64:36	99:1
2		0.75	38	74:26	96:4
3		1.3	43	80:20	95:5
4		2	50	87:13	95:5
5		18	62	99:1	84:16
6	1.6 eq. BzOH -40°C 0.7M	0.5	18	59:41	97:3
7		1	26	64:36	97:3
8		1.5	28	68:32	96:4
9		2	32	69:21	96:4
10		10	32	69:21	96:4
11	1.6 eq. BzOH -30°C 0.05M	0.5	44	72:28	95:5
12		1	56	78:22	95:5
13		1.5	63	81:19	94:6
14		2	70	85:15	94:6
15		3.5	99	99:1	84:16
16	3 eq. BzOH -30°C 0.05M	0.5	19	63:37	97:3
18		1.55	33	79:21	96:4
19		2.15	36	80:20	96:4
20		4	52	91:9	91:9
21		13	61	99:1	86:14
22	3 eq. BzOH -30°C 0.025M	1.15	27	69:31	97:3
23		1.6	36	77:23	96:4
24		2.8	43	82:18	95:5
25		3.9	45	87:13	95:5
26		16.5	56	98:2	96:4
27		24.3	59	99:1	89:11

[a]General reaction conditions: **324** (0.05 mmol), (*S*)-TRIP (0.002 mmol), in dichloromethane. [b]Conversion was determined by ^{1}H-NMR. [c]The enantiomeric excess was determined by chiral HPLC.

Interestingly, increasing the loading of benzoic acid (3 equivalents), an increase in the enantiodiscrimination of the process was observed since the product **328** and the enantioenriched aziridine **324** were both afforded in 91:9 e.r. at 52% conversion after 4h (Table 4.7, entry 20). The selectivity of the process was further improved running the reaction decreasing the substrate concentration to 0.025M. Thus, after 16h and 25 minutes conversion achieved 56% and the product **328** was afforded with 96:4 e.r. while 98: 2 e.r. was measured for the enantioenriched aziridine **324** (Table 4.7, entry 20).

Table 4.8. (*S*)-TRIP-catalyzed kinetic resolution of *rac*-**324** with BzOH.[a]



Entry	BzOH (eq.)	[S][b]	Time (h)	Conv (%)[c]	e.r.[d]		S[e]
					324	328	
1	5	0.025	14	54	98:2	90:10	39
2	7	0.025	14	55	99:1	90:10	49
3	7	0.016	7	40	82:18	98:2	117
4	7	0.0125	16	50	94:6	95:5	42
5	7	0.01	16	50	94:6	94:6	50
6	7	0.02	15	35	74:26	96:4	41
7	7	0.014	15	43	85:15	96:4	51

[a]General reaction conditions: **324** (0.05 mmol), (*S*)-TRIP (0.002 mmol), in dichloromethane; T = -30ºC. [b][S] = Substrate concentration. [c]Conversion was determined by ^{1}H-NMR. [d]The enantiomeric excess was determined by chiral HPLC. [e]See Chapter 1, Section 1.3.2.1.

Since the BzOH:aziridine ratio affects the enantiodiscrimination of the process, a screening of the loading of benzoic acid as well as the substrate concentration was performed. The results are summarized in Table 4.8. Increasing the loading of benzoic acid to 5 equivalents, (S)-TRIP (4 mol%) catalyzed the kinetic resolution of terminal aziridine *rac*-**324** in dichloromethane (0.025M) and afforded the opened product **328** with 90:10 er and the enantioenriched aziridine **324** with 98:2 er at 54% conversion after 14h with S = 39 (Table 4.8, entry 1). An increase of the selectivity of the process was observed increasing the loading of benzoic acid to 7 equivalents, the product **328** was afforded with 90:10 e.r. while 99:1 e.r. was measured for the enantioenriched aziridine **324** at 55% conversion after 14h with S = 39 (Table 4.8, entry 2).

Further optimization revealed that 0.016M of substrate concentration was optimal (Figure 4.9), resulting in an increased S factor (S = 116). At 40% conversion, both **321** and **325** were obtained in high er's 82:18 and 98:2 er, respectively after 7h (Table 4.8, entry 3). Higher concentration afforded a decrease in the S factor (Table 4.8, entries 7 to 8).

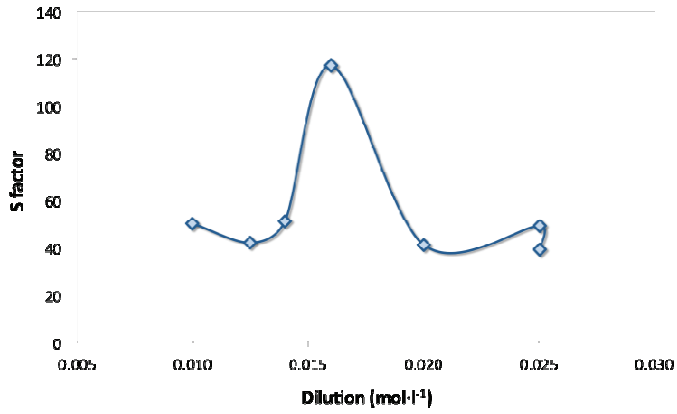
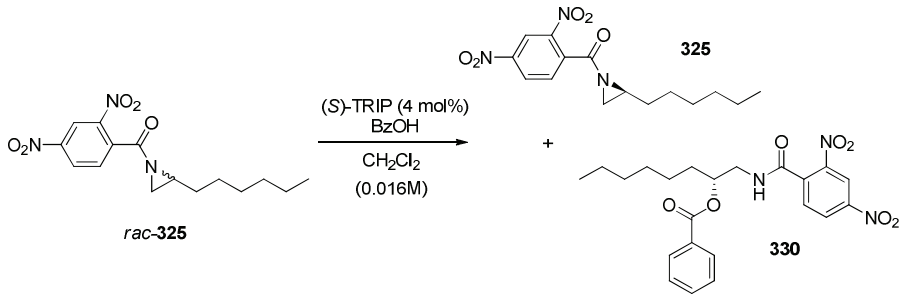


Figure 4.9. Substrate concentration reaction *vs* S factor.

Due to the excellent results in the kinetic resolution of terminal aziridine **324** catalyzed by (S)-TRIP phosphoric acid, we decided to vary the protecting group at the nitrogen atom of the aziridine.

Table 4.9. (*S*)-TRIP-catalyzed kinetic resolution of *rac*-**325** with BzOH.[a]



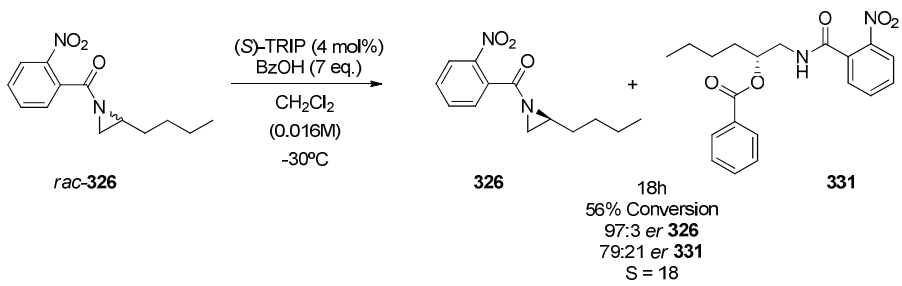
Entry	BzOH (eq.)	T (ºC)	Time (h)	Conv (%)[b]	e.r.[c] 325	e.r.[c] 330	*S*
1	7	-30	16	52	98:2	91:9	40
2	6	-40	24	44	85:15	95:5	39
3	7	-40	24	43	83:17	94:6	35
4	8	-40	24	51	92:8	89:11	23

[a]General reaction conditions: **325** (0.05 mmol), (*S*)-TRIP (0.002 mmol), 3ml of solvent. [b]Conversion was determined by ^{1}H-NMR. [c]The enantiomeric excess was determined by chiral HPLC.

We then tested the desymmetrization of the *N*-2,4-dinitrobenzoyl derived terminal aziridine **325** under the optimized reaction conditions for the terminal aziridine **324**. The results are summarized in Table 4.9. In this case, when the reaction was performed under the optimized reaction conditions, lower selectivity was obtained. The product **330** was afforded with 91:9 e.r. while 98:2 e.r. was measured for the enantioenriched aziridine **325** at 52% conversion after 16h with S = 40 (Table 4.9, entry 1). Decreasing the temperature to -40ºC, lower S factor was obtained (S = 35), affording the opened product **330** with 95:5 e.r. and the enantioenriched

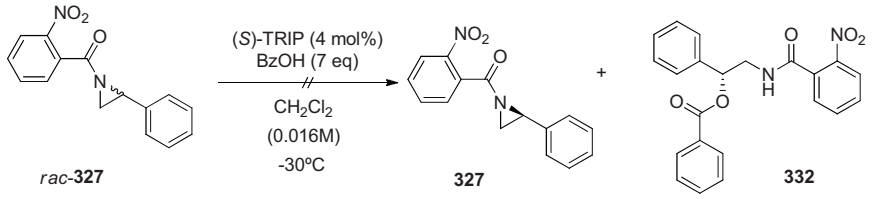
aziridine **325** with 85:15 at 43% conversion after 24h (Table 4.9, entry 2). Various amounts of benzoic acid were tested, but lower er's were obtained (Table 4.9, entries 3 and 4). Therefore, the optimized reaction conditions for the terminal *N*-2,5-dinitrobenzoyl derived aziridine *rac*-**321** revealed to be similar to those for the terminal *N*-2-nitrobenzoyl derived aziridine *rac*-**322**.

At this point, we tested the desymmetrization of the *N*-2-nitrobenzoyl derived terminal aziridine **326** under the optimized reaction conditions for the terminal aziridine **324** (Scheme 4.14). Lower selectivity was obtained in the (*S*)-TRIP-catalyzed kinetic resolution of *rac*-**325** with BzOH, the opened product **331** was afforded with 79:21 er and the enantioenriched aziridine **326** with 97:3 er at 56% conversion after 18h with an S factor of 18. Surprisingly, a small change in the length of the alkyl chain caused a strong decrease in the e.r of the opened product. However, the e.r in the unreacted aziridine is high in both cases.



Scheme 4.14. Kinetic resolution of terminal aziridine *rac*-**326** catalyzed by (S)-TRIP phosphoric acid under identical optimized conditions.

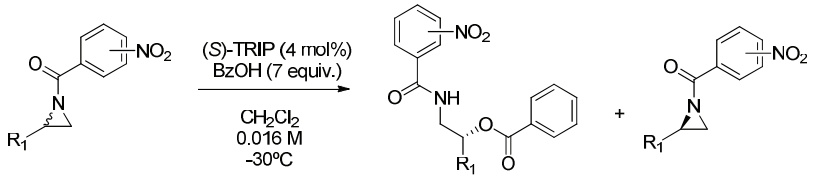
Finally, the desymmetrization of the *N*-2-nitrobenzoyl derived terminal aziridine **327** was tested under the optimized reaction conditions for the terminal aziridine **324** (Scheme 4.15). Unfortunately, no evolution of the reaction was observed even after 7 days (Scheme 4.15).



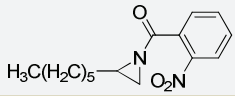
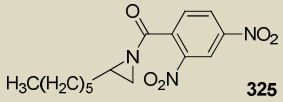
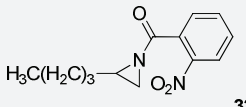
Scheme 4.15. Kinetic resolution of terminal aziridine *rac*-**327** catalyzed by (S)-TRIP phosphoric acid under identical optimized conditions.

Our studies showed that (*S*)-TRIP-phosphoric acid successfully catalyzes the kinetic resolution of various acyclic aliphatic substituted terminal aziridines using benzoic acid as oxygen-nucleophile. (*S*)-TRIP-phosphoric acid derived from BINOL proved to be an excellent catalyst in terms of regioselectivity and enantioselectivity, for the kinetic resolution of terminal aziridines (Table 4.10). The *N*-2,4-(dinitro)-benzoyl hexyl derived aziridine *rac*-**324** exhibited excellent levels of selectivity (Table 4.10, entry 1). When the *N*-2-(nitro)-benzoyl hexyl derived aziridine *rac*-**325** was used**,** 51% conversion was obtained and the starting aziridine and the opened product **330** were recovered with excellent enantioselectivities (98:2 and 91:9 e.r, respectively) (Table 4.10, entry 2). Thus, the highest selectivity for the kinetic resolution process is obtained using less activated aziridines. Finally, the *N*-2-(nitro)-benzoyl propyl derived aziridine *rac*-**326,** resulted in the lowest selectivity (Table 4.10, entry 3), at 56% conversion the starting terminal aziridine **326** and the opened product **331** were recovered with good enantioselectivities (97:3 and 79:21 e.r, respectively). This result suggested that the steric hindrance at the C-2 of the terminal aziridine affects the selectivity of the kinetic resolution process.

Table 4.10. Scope of various racemic terminal aziridines. [a]



rac-**324-326** **328-331** **324-326**

Entry	Substrate	Time (h)	%Yield.[b]	e.r[c]		S
				TA[d]	OP[e]	
1	 **324**	7	40	82:18	98:2	117
2	 **325**	16	52	98:2	91:9	40
3	 **326**	18	56	97:3	79:21	18

[a]Reaction conditions: **324-326** (0.2 mmol), BzOH (1.4 mmol), (*S*)-TRIP (0.008 mmol); T = -30ºC (0.016 M). [b]Isolated Yield. [c]The enantiomeric excess was determined by chiral HPLC. [d]TA = terminal aziridine. [e]OP = opened product.

To summarize this section, the successful use of (*S*)-TRIP phosphoric acid-catalyzed in this asymmetric oxygen-nucelophile ring-opening protocol was further demonstrated in the kinetic resolution of racemic terminal aziridines. From this study, the following conclusions can be extracted: i) (*S*)-TRIP-phosphoric acid is an excellent catalyst for this reaction, especially in terms of regioselectivity and enantioselectivity, ii) the ring-cleavage of the terminal aziridine takes place with high regioselectivity to the 2-substituted product, iii) the-benzoic acid aziridine ratio was found to affect the conversion of the reaction (catalyst degradation) iii) the terminal aziridines **324**, **325**, **326** and **327** protected with *N*-benzoyl groups

were applied as substrates in this kinetic resolution and good to excelent selectivities were obtained, recovering the terminal aziridine and the corresponding opened products (β-amidoesthers) with good enantioselectivities and iv) the nature of the *N*-benzoyl protecting group and the steric hindrance of the C-2 substituents of the terminal aziridine affect the selectivity (*S*) of the kinetic resolution process.

4.4. CONCLUSIONS

From the study of the enantioselective Brønsted-acid catalyzed desymmetrization of *meso*-aziridines promoted by oxygen-nucleophiles, the following conclusions can be extracted:

i) (*S*)-TRIP-phosphoric acid is an excellent catalyst in this reaction and affords high enantioselectivity.
ii) The benzoic acid to aziridine ratio affects the conversion of the reaction (catalyst degradation).
iii) A range of *meso*-aziridines **306**, **307**, **308** and **309** protected with *N*-benzoyl groups were applied in their asymmetric desymmetrization and excellent conversions (up to 98%) and enantioselectivities (87 to 99% *ee*) were obtained.

From the study of the Bronsted-acid catalyzed kinetic resolution of racemic terminal aziridines promoted by oxygen nucleophiles, the following conclusions can be extracted:

i) (*S*)-TRIP-phosphoric acid is an excellent catalyst for this reaction and yielded high enantioselectivities.

ii) The ring-cleavage of the terminal aziridine was totally regioselective to the corresponding 2-substituted product.

iv) The benzoic acid to aziridine ratio affects the conversion of the reaction (catalyst degradation).

v) The terminal aziridines **324**, **325**, **326** and **327** protected with *N*-benzoyl groups were applied as substrates in this kinetic resolution and good to excelent selectivities were obtained, recovering the terminal aziridine and the corresponding opened products (β-amidoesthers) with good enantioselectivities.

vi) The nature of the *N*-benzoyl protecting group as well as the steric hindrance of the C-2 substituents of the terminal aziridine affect the selectivity (*S*) of the kinetic resolution process.

4.5. EXPERIMENTAL PART

4.5.1. GENERAL EXPERIMENTAL CONDITIONS

Solvents and reagents

All solvents were purified by distillation before use following standard procedures.[29] Absolute diethyl ether, tetrahydrofuran and toluene were obtained by distilling over sodium, using benzophenone as indicator. Absolute acetonitrile, chloroform and dichloromethane were obtained by distillation over calcium hydride. Commercial reagents were obtained from various commercial sources and used as received.

Inert gas atmosphere

Air and moisture-sensitive reactions were conducted under an argon atmosphere. Argon obtained from the company *Linde* with a purity of

99.998 % was dried with silica gel and phosphorous pentoxide (both with color indicator for humidity), and deoxygenated with the BTS-catalyst from *BASF* before use.

Thin layer chromatography (TLC)

Materials: *Macherey-Nagel* MN POLYGRAM Sil G/UV254 plates (0.25 mm thick). The spots were visualized in UV-light (λ = 254 nm) and/or by staining with iodine, ninhydrin, vanilline or phosphomolybdic acid.

Column chromatography

Materials: *Macherey-Nagel* MN Silicagel 60, 230-400 mesh (0.04-0.063 mm).

Analytical high performance liquid chromatography (HPLC)

Apparatus: *Merck-Hitachi* L-6200A Intelligent Pump and L-4500 Diode-Array Detector. Materials: *Daicel* Chiralpak AD column (0.46 cm × 25 cm) *Daicel* Chiralcel OJ column (0.46 cm × 25 cm) Experimental Part 107.

Nuclear magnetic resonance spectroscopy (NMR)

Apparatus: *Bruker* AC 250 (^{1}H: 250 MHz, ^{13}C: 62.5 MHz), *Bruker* AC 300 (^{1}H: 300 MHz, ^{13}C: 75 MHz), *Bruker* DPX 300 (^{1}H: 300 MHz, ^{13}C: 75 MHz), *Bruker* DRX 500 (^{1}H: 500 MHz, ^{13}C: 125 MHz). Spectra were recorded at room temperature (298 K) unless otherwise stated. Chemical shifts for protons and carbons were reported in parts per million (ppm) downfield from tetramethylsilane (TMS) and were referenced to residual proton in the NMR solvents (e.g. $CHCl_3$: δ 7.24) and carbon resonances of the solvents (e.g. $CDCl_3$: δ 77.0) respectively. The coupling constants (*J*) were reported in Hertz (Hz). For the fine-structure interpretation the abbre*via*tions of the signals are the following: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet.

Mass spectrometry (MS)

Apparatus: *Finnigan* MAT 900S (EB-Trap-Geometry) Syringes pump Model 22.

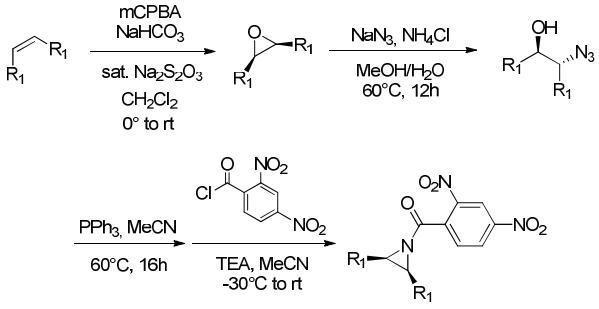
Specific rotation ([α])

Apparatus: *Perkin Elmer* 343plus Optical rotations were measured using a 1 mL cell with a 1 dm path length. Measurements were carried out in different wavelengths using sample solution in chloroform at 20 °C. The sample concentrations are given in g/100 mL unit.

4.5.2. ENANTIOSELECTIVE DESYMMETRIZATION OF *MESO*-AZIRIDINES

4.5.2.1. PREPARATION OF THE STARTING MATERIALS

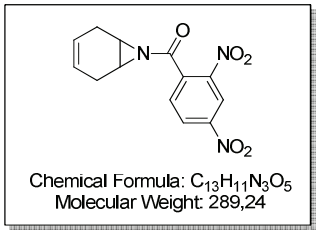
Aziridines **309, 310, 311** and **312** were prepared following a reported procedure.[30]



A round bottom flask was charged with a stir bar, the corresponding epoxide and mixture of MeOH:H_2O (3:1) was added. Sodium azide (2eq) and ammonium chloride (1.5 eq) were added to this solution. The reaction was stirred for 12 hours at 60°C. Methanol was removed in a rotary

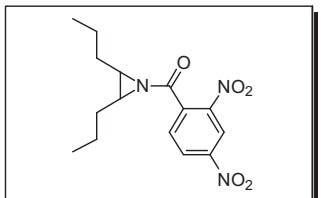
evaporator and the remaining solution was extracted with dichloromethane. The organic layers were combined, washed with brine solution, and dried over anhydrous $MgSO_4$. The mixture was filtered, and volatiles were then removed by rotary evaporator. The total crude azido alcohol was dissolved in 30 ml of acetonitrile under argon. Triphenylphosphine (1eq) was added, and the solution was heated for 12 hours at 60°C. The reaction mixture was cooled to -30°C with stirring, and triethylamine (1.2 eq) was added via syringe. In a flame dried flask, 2-nitrobenzoyl chloride (1 eq) was dissolved in a minimal amount of acetonitrile and then transferred to the reaction flask dropwise via syringe. The reaction mixture was allowed to stir at -30°C for 50 minutes, 0°C for 30 minutes, and room temperature for 30 minutes. De-ionized water was added and the solution was extracted with ethyl acetate. The organic layers were combined, washed with brine solution, and dried over anhydrous $NaSO_4$. The mixture was filtered, and volatiles were then removed by rotary evaporator. The crude product was purified immediately via flash column silica gel chromatography eluting with hexanes/AcOEt: 85/15.

7-(2,4-Dinitrobenzoyl)-7-azabicyclo[4.1.0]hept-3-ene (310):



Prepared from 5 mmol of 1,4-cyclohexadiene to afford 311 mg (1 mmol, 24% yield) of **310** as a yellow solid. **^{1}H NMR** (500 MHz, $CDCl_3$): δ in ppm 8.80 (d, J = 2.1 Hz, 1H), 8.52 (dd, J = 8.3, J = 2.1 Hz, 1H), 7.93 (d, J = 8.3 Hz, 1H), 5.52 (s, 2H), 3.12 (s, 2H), 2.44 (t, J = 20.5 Hz, 4H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ in ppm 175.5, 148.4, 147.5, 138.1, 130.8, 127.9, 121.9, 119.8, 37.0, 23.9. **HR ESI-TOF MS** for $[M+Na]^+$ $C_{13}H_{11}N_3NaO_5^+$ (*m/z*): calc. 312.0596; found: 312.0591.

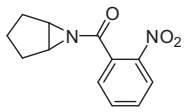
cis-1-(2,4-Dinitrobenzoyl)-2,3-di-_n_-propylaziridine (311):



Chemical Formula: $C_{15}H_{19}N_3O_5$
Molecular Weight: 321,32

Prepared from 5 mmol of cis-4-octene to afford 465mg (1.44 mmol, 33% yield) of **311** as a yellow solid. **^{1}H NMR** (500 MHz, $CDCl_3$): δ in ppm 8.86 (d, J = 1.9 Hz, 1H), 8.54 (dd, J = 8.3, J = 2.1 Hz, 1H), 7.91 (d, J = 8.3 Hz, 1H), 2.82 (dt, J = 10.8, J = 6.2 Hz, 2H), 1.59-1.32 (m, 8H), 0.91 (t, J = 7.3 Hz, 6H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ in ppm 171.4, 148.4, 147.1, 138.6, 130.9, 128.1, 120.1, 43.3, 29.7, 20.9, 13.9. **HR ESI-TOF MS** for $[M+Na]^+$ $C_{15}H_{19}N_3NaO_5^+$ (*m/z*): calc. 344.1218; found: 344.1217.

6-(2-Nitrobenzoyl)-6-azabicyclo[3.1.0]hexane (313):



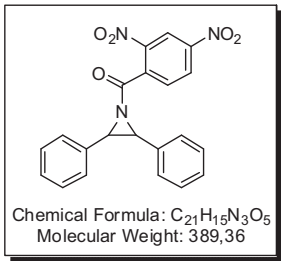
Chemical Formula: $C_{12}H_{12}N_2O_3$
Molecular Weight: 232,23

Prepared from 5 mmol of cyclopentane oxirane to afford 487.6mg (2.01 mmol, 42% yield) of **313** as a yellow solid. **^{1}H NMR** (500 MHz, $CDCl_3$): δ in ppm 7.84 (d, J = 10 Hz, 1H), 7.62-7.58 (m, 2H), 7.52-7.49 (m, 1H), 3.2 (s, 2H), 1.97-1.90 (m, 2H), 1.66-1.50 (m, 3H), 1.43-1.35 (m, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ in ppm 176.7, 147.7, 133.4, 132.8, 130.9, 129.4, 124.2, 44.4, 27.1, 19.6. **HR ESI-TOF MS** for $[M+Na]^+$ $C_{12}H_{12}N_2NaO_3^+$ (*m/z*): calc. 255.0742; found: 255.0740.

NOTE! It`s important to keep the temperature at -30°C until complete product formation, in the last acylation step of the synthesis.

***cis*-1-(2,4-Dinitrobenzoyl)-2,3-diphenylaziridine (312)**:

NOTE! This aziridine was prepared following a modified procedure.[31]

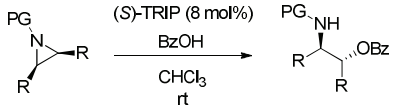


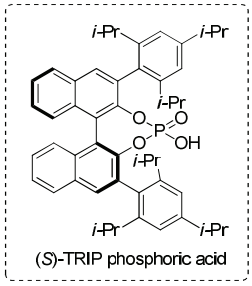
Prepared from 5.6 mmol of *Z*-stilbene to afford 580mg (1.49 mmol, 30% yield) of **312** as a white solid. **^{1}H NMR** (500 MHz, $CDCl_3$): δ in ppm 8.86 (d, *J* = 2 Hz, 1H), 8.51 (dd, *J* = 8.3 Hz, *J* = 2 Hz, 1H), 8.06 (d, *J* = 8.3 Hz, 1H), 7.16-7.13 (m, 10H), 4.33 (s, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ in ppm 176.2, 148.7, 147.5, 137.7, 132.7, 130.6, 128.5, 128.5, 128.4, 128.3, 128.3, 127.7, 127.6, 120.3, 47.2. **HR ESI-TOF MS** for $[M+Na]^+$ $C_{21}H_{15}N_3NaO_5^+$ (*m/z*): calc. 412.0909; found: 412.1000.

4.5.2.2. GENERAL PROCEDURE FOR THE PREPARATION OF RACEMIC PRODUCTS

A solution of benzoic acid (0.35 mmol) and an equimolar mixture of (*R*) and (*S*)-TRIP phosphoric acid (8 mol%) in dry chloroform (0.4 ml) was added to the corresponding aziridine (0.05 mmol). The reaction was stirred at room temperature until complete product formation. The reaction was monitored by TLC and ^{1}H-NMR. The reaction was diluted in dichloromethane, concentrated on silica gel, and purified by flash column chromatography.

4.5.2.3. GENERAL PROCEDURE FOR (S)-TRIP DESYMMETRIZATION OF *MESO*-AZIRIDINES

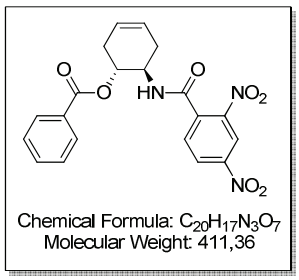




A solution of benzoic acid (1.4 mmol, 7 eq) and (*S*)-TRIP phosphoric acid (8 mol%) in dry chloroform (1.6 ml) was added to the corresponding aziridine (0.2 mmol). The reaction was stirred at room temperature until complete product formation. The reaction was monitored by TLC and ^{1}H-NMR. The reaction was diluted in dichloromethane, concentrated on silica gel, and purified by flash column chromatography using hexanes/ethyl acetate as the eluent, and analyzed by HPLC on a chiral stationary phase.

4.5.2.4. SYNTHESIS OF β-AMIDOESTERS

trans-_O_-Benzoyl-_N_-(2,4-Dinitrobenzoyl)-2-amino-cyclohex-4-en-1-ol (314):

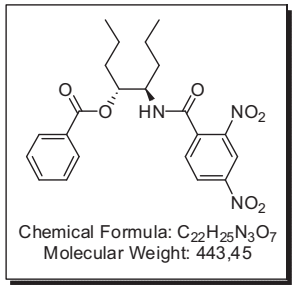


Purification: hexanes/AcOEt 8:1 to 8:2. White solid 73.1 mg (83% yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ in ppm 8.78 (s, 1H), 8.3 (d, *J* = 10 Hz, 1H), 7.98 (d, *J* = 10 Hz, 2H), 7.59 (m, 1H), 7.44 (m, 2H), 7.36 (d, *J* = 10 Hz, 1H), 6.59 (d, *J* = 10 Hz, 1H), 5.69 (m, 2H), 5.3 (m, 1H), 4.55 (m, 1H), 2.86-2.82 (m, 1H), 2.65-2.61 (m, 1H), 2.55-2.50 (m, 1H), 2.25-2.19 (m, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ in ppm 167.6, 164.5, 148.3,

146.6, 137.9, 133,8, 130.2, 129.9, 129.6, 128.7, 128.2, 124.6, 124.2, 120.2, 71.7, 50.2, 31.6,31.0. **HR ESI-TOF MS** for $[M+Na]^+$ $C_{20}H_{17}N_3NaO_7^+$ (*m/z*): calc. 434.0960; found: 434.0958. **$[\alpha]_D^{25}$:** -23.729° (*c* 0.295, $CHCl_3$).

The enantiomeric ratio was determined by **HPLC** analysis using Daicel Chiralcel AD-3 column: *n*Hept:*i*PrOH = 80:20, flow rate 1 mL/min, λ = 206 nm: τ_1 = 10.43 min, τ_2 = 13.04 min.

_O_-Benzoyl-_N_-(2,4-dinitrobenzoyl)-5-amino-octan-4-ol (315):

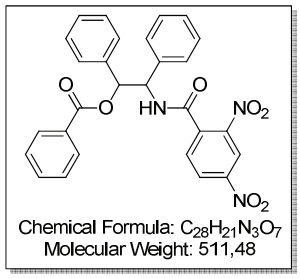


Chemical Formula: $C_{22}H_{25}N_3O_7$
Molecular Weight: 443,45

Purification: hexanes/AcOEt 8:1. White solid 83.4 mg (94% yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ in ppm 8.86 (s, 1H), 8.42 (d, *J* = 5 Hz, 1H), 8.00 (d, *J* = 10 Hz, 2H), 7.6-7.52 (m, 2H), 7.45 (m, 2H), 6.02 (d, *J* = 5 Hz, 1H), 5.29 (m, 1H), 4.47 (m, 1H), 1.89-1.43 (m, 9H), 0.99-0.96 (m, 6H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ in ppm 166.8, 164.4, 148.4, 147.1, 138.2, 133.7, 130.3, 129.9, 129.8, 128.8, 128.2, 120.4, 75.9, 52.8, 34.7, 34.1, 19.1, 18.9, 14.2, 14.1. **HR ESI-TOF MS** for $[M+Na]^+$ $C_{22}H_{25}N_3NaO_7^+$ (*m/z*): calc. 466.1588; found: 466.1585. **$[\alpha]_D^{25}$:** -89.855° (*c* 0.345, $CHCl_3$).

The enantiomeric ratio was determined by **HPLC** analysis using Daicel Chiralcel AD-3 column: *n*Hept:*i*PrOH = 90:10, flow rate 1 mL/min, λ = 306 nm: τ_1 = 15.00 min, τ_2 = 18.28 min.

_O_-Benzoyl-_N_-(2,4-Dinitrobenzoyl)-2-amino-1,2-diphenyl-ethan-1-ol diaestereoisomeric mixture (316+317):



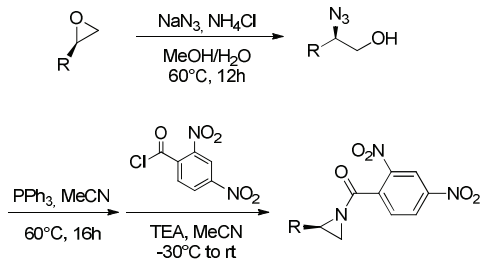
Purification: hexanes/AcOEt 8:1. White solid 87.4 mg (94% yield). Diastereoisomeric mixture (**12:13**/3:1). **^{1}H NMR** (500 MHz, $CDCl_3$): δ in ppm 8.77 (d, *J* = 2 Hz, 1H), 8.72 (d, *J* = 2 Hz, 0.3H), 8.55 (dd, *J* = 10 Hz, *J* = 2 Hz, 0.3H), 8.31 (m, 1.3H), 8.06 (m, 3H), 7.59 (m, 1.3H), 7.45 (m, 3H), 7.27 (m, 13H), 7.05 (m, 3H), 6.9 (m, 1.3H), 6.40 (d, *J* = 11 Hz, 1H), 6.08 (d, *J* = 13 Hz, 0.3H), 5.78 (d, *J* = 13 Hz, 0.3H), 5.75 (t, *J* = 11 Hz, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ in ppm 167.2, 164.1, 148.5, 146.8, 137.8, 137.1, 136.5, 133.9, 130.3, 130.2, 130.1, 128.9, 128.8, 128.7, 128.5, 128.2, 128.1, 127.9, 127.7, 127.5, 126.6, 120.3, 78.4, 59.6. **HR ESI-TOF MS** for $[M+Na]^+$ $C_{28}H_{21}N_3NaO_7^+$ (*m/z*): calc. 510.1307; found: 510.1306.

The enantiomeric ratio was determined by **HPLC** analysis using Daicel Chiralcel IC-3 column: *n*Hept:EtOH = 85:15, flow rate 1 mL/min, λ = 220 nm: $\tau_{1(major)}$ = 8.11 min, $\tau_{2(major)}$ = 8.92 min, $\tau_{1(minor)}$ = 11.03 min, $\tau_{1(minor)}$ = 12.33 min.

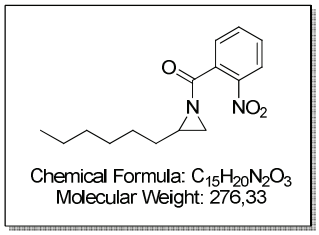
4.5.3. KINETIC RESOLUTION OF TERMINAL AZIRIDINES

4.5.3.1. PREPARATION OF THE STARTING MATERIALS

Terminal aziridines were prepared using the same general procedure as for the synthesis of *meso*-aziridines (see section 4.5.2.1)



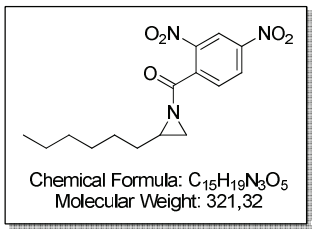
2-Hexyl-1-(2-nitrobenzoyl)-aziridine (324):



Prepared from 10mmol of 1,2-epoxyoctane to afford 1.55g (5.6mmol, 56% yield) of **324** as a colorless liquid. **^{1}H NMR** ($CDCl_3$, 500 MHz): δ in ppm 7.96 (dd, J = 10 Hz, J = 0.5 Hz, 1H), 7.7-7.65 (m, 2H), 7.59-7.55 (m, 1H), 2.7-2.7 (m, 1H), 2.62 (d, J = 5 Hz, 1H), 2.12 (d, J = 3.5 Hz, 1H), 1.54-1.48 (m, 2H), 1.32-1.14 (m, 8H), 0.83 (t, J = 6.8 Hz, 3H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ in ppm 177.7, 146.9, 133.4, 132.4, 132.9, 130.6, 129.2, 124.1, 38.7, 32.0, 31.6, 28,8, 26,7, 22,5, 14,0. **HR ESI-TOF MS** for $[M+Na]^+$ $C_{15}H_{19}N_3NaO_5^+$ (*m/z*): calc. 299.1369; found: 299.1366.

The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralcel AD-3 column: *n*Hept:*i*PrOH = 98:2, flow rate 1 mL/min, λ = 254 nm: τ_1 = 8.01 min, τ_2 = 12.40 min.

1-(2,4-Dinitrobenzoyl)-2-hexyl-aziridine (325):

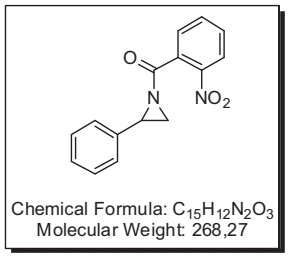


Prepared from 10 mmol of 1,2-epoxyoctane to afford 1.33g (4.1mmol, 42% yield) of **325** as a colorless liquid. **^{1}H NMR** ($CDCl_3$, 500 MHz): δ in ppm 8.84 (s, 1H), 8.55 (d, J = 8.35 Hz, 1H), 7.94 (d, J = 10 Hz, 1H), 2.81 (dt, J = 10

Hz, *J* = 5 Hz 1H), 2.68 (d, *J* = 10 Hz, 1H), 2.19 (d, *J* = 5 Hz, 1H), 1.59-1.53 (m, 2H), 1.37-1.20 (m, 9H), 0.86 (t, *J* = 5 Hz, 3H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ in ppm 175.5, 148.5, 147.3, 138.3, 130.9, 128.2, 120.0, 39.5, 32.4, 32.1, 31.8, 28.9, 26.9, 22.7, 14.2. **HR ESI-TOF MS** for $[M+Na]^+$ $C_{15}H_{19}N_3NaO_5^+$ (*m/z*): calc. 344.1214; found: 344.1217.

The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralcel AD-3 column: *n*Hept:*i*PrOH = 95:5, flow rate 1 mL/min, λ = 254 nm: τ_1 = 8.88 min, τ_2 = 10.12 min.

1-(2-Nitrobenzoyl)-2-phenyl-aziridine (327):



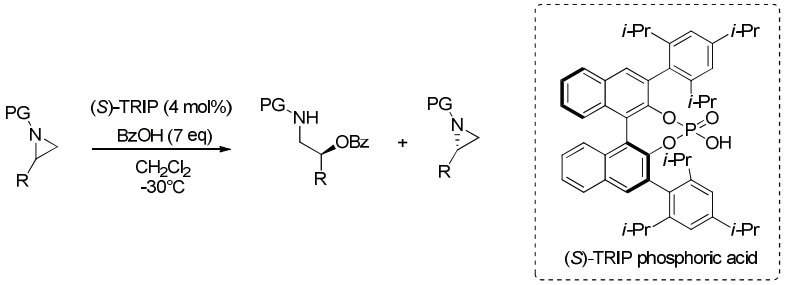
Prepared from 5 mmol of styrene oxide to afford 42 mg (0.16 mmol, 31% yield) of **327** as a colorless liquid. **^{1}H NMR** (500 MHz, $CDCl_3$): δ in ppm 7.95 (m, 1H), 7.75-7.61 (m, 3H), 7.4 (m, 4H), 4.89 (dd, J = 9 Hz, J = 4 Hz, 1 H), 4.55 (dd, J = 11.5 Hz, J = 4 Hz, 1 H), 4.43 (dd, J = 11 Hz, J = 9 Hz, 1 H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ in ppm 165.1, 135.3, 133.1, 132.9, 132.0, 131.8, 129.9, 129.8, 129.1, 127.2, 127.1, 124.1, 123.9, 68.5, 63.9. **HR ESI-TOF MS** for $[M+Na]^+$ $C_{15}H_{12}N_2NaO_3^+$ (*m/z*): calc. 291.0740; found: 291.0740.

4.5.3.2. General Procedure for the Preparation of Racemic Products

A solution of benzoic acid (0.35 mmol, 7 eq) and a mixture of (*R*) and (*S*)-TRIP phosphoric acid (4 mol%) in dry dichloromethane (3 ml) was added to the corresponding terminal aziridine (0.05 mmol) at -30°C. The reaction was stirred at -30°C until complete product formation. The reaction was

easily monitored by TLC and ^{1}H-NMR. The reaction was diluted in dichloromethane, concentrated on silica gel, and purified by flash column chromatography.

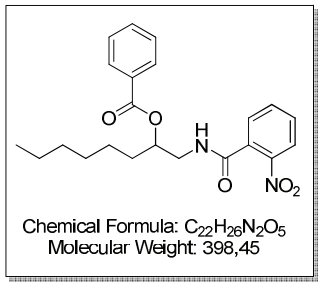
4.5.3.3. GENERAL PROCEDURE FOR (*S*)-TRIP KINETIC RESOLUTION OF TERMINAL AZIRIDINES



A solution of benzoic acid (0.35 mmol, 7 eq) and (*S*)-TRIP phosphoric acid (4 mol%) in dry dichloromethane (3 ml) was added to the corresponding terminal aziridine (0.05 mmol) at -30°C. Samples (ca. 600 μL) were removed from the reaction mixture and quenched by diluting the sample with THF. Subsequently, the product and remaining starting material were isolated by silica gel chromatography using hexane/ethyl acetate as the eluent, and analyzed by HPLC on a chiral stationary phase. Conversions were calculated by ^{1}H-NMR directly from the reaction mixture.

4.5.3.4. SYNTHESIS OF β-AMIDOESTHERS

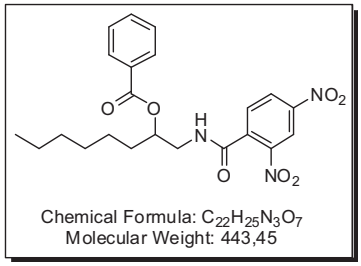
_O_-Benzoyl-_N_-(2-nitrobenzoyl)-1-amino-octan-2-ol (328):



Purification: hexanes/AcOEt 9.5:0.5 to 8:2. White solid, 46% yield. **^{1}H NMR** (500 MHz, $CDCl_3$): δ in ppm 8.03 (m, 3H), 7.63-7.52 (m, 3H), 7.48-7.43 (m, 3H), 6.3 (m, 1H), 5.29 (m, 1H), 3.82 (m, 1H), 3.71 (m, 1H), 1.84-1.74 (m, 2H), 1.49-1.25 (m, 9H), 0.83 (t, J = 7 Hz, 3H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ in ppm 171.0, 133.4, 132.4, 132.2, 131.1, 130.8, 129.8, 129.1, 128.2, 123.6, 73.5, 66.5, 35.2, 31.4, 28.9, 25.4, 22.3, 13.7. **HR ESI-TOF MS** for $[M+Na]^+$ $C_{22}H_{26}N_2NaO_5^+$ (*m/z*): calc. 421.1739; found: 431.1121. **$[\alpha]_D^{25}$:** +13.279° (*c* 0.300, $CHCl_3$).

The enantiomeric ratio was determined by **HPLC** analysis using Daicel Chiralcel AD-3 column: *n*Hept:*i*PrOH = 90:10, flow rate 1 mL/min, λ = 254 nm: τ_1 = 11.73 min, τ_2 = 21.37 min.

_O_-Benzoyl-_N_-(2,4-dinitrobenzoyl)-1-amino-octan-2-ol (330):

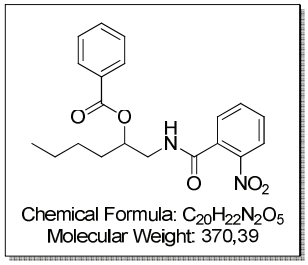


Purification: hexanes/AcOEt 9.5:0.5 to 8:2. White solid, 62% yield. **^{1}H NMR** (500 MHz, $CDCl_3$): δ in ppm 8.77 (d, J = 5 Hz, 1H), 8.41 (dd, J = 10 Hz, J = 5 Hz, 1H), 7.9 (m, 2H), 7.62 (d, J = 10 Hz, 1H), 7.58 (m, 1H), 7.44 (m, 2H), 6.75 (m, 1H), 5.27 (m, 1H), 3.81 (m, 1H), 3.68 (m, 1H), 1.86-7.72 (m, 2H), 1.49-1.21 (m, 9H), 0.87 (t, J = 5Hz, 3H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ in ppm 167.4, 164.7, 148.3, 146.8, 137.9, 133.6, 130.4, 129.8, 128.7, 128.2, 120.2, 74.2, 44.5, 32.3, 31.7, 29.2, 25.4, 22.7, 14.2. **HR ESI-TOF MS** for $[M+Na]^+$

$C_{22}H_{25}N_3NaO_7^+$ (*m/z*): calc. 466.1587; found: 466.1585. **$[\alpha]_D^{25}$:** +13.878° (*c* 0.245, $CHCl_3$).

The enantiomeric ratio was determined by **HPLC** analysis using Daicel Chiralcel AS-3 column: *n*Hept:*i*PrOH = 70:30, flow rate 1 mL/min, λ = 229 nm: τ_1 = 13.79 min, τ_2 = 20.64 min.

***O*-Benzoyl-*N*-(2-nitrobenzoyl)-1-amino-hexan-2-ol (331):**



Purification: hexanes/AcOEt 9.5:0.5 to 8:2. Colorless oil, 56% yield. **^{1}H NMR** (500 MHz, $CDCl_3$): δ in ppm 8.06-7.98 (m, 3H), 7.61-7.5 (m, 3H), 7.46-7.41 (m, 3H), 6.48 (s, H), 5.28 (m, 1H), 3.78 (m, 1H), 3.69 (m, 1H), 1.85-1.74 (m, 2H), 1.45-1.36 (m, 4H), 0.91 (t, *J* = 5 Hz, 3H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ in ppm 167.1, 166.7, 146.6, 133.8, 133.6, 133.4, 132.8, 130.6, 130.2, 129.9, 129.8, 128.8, 128.5, 124.6, 74.3, 44.1, 31.9, 27.6, 22.6, 14.1. **ESI-TOF MS** for $[M+Na]^+$ $C_{20}H_{22}N_2NaO_5^+$ (*m/z*): calc. 393.1422; found: 393.1421. **$[\alpha]_D^{25}$:** +31.131° (*c* 0.260, $CHCl_3$).

The enantiomeric ratio was determined by **HPLC** analysis using Daicel Chiralcel AD-3 column: *n*Hept:*i*PrOH = 90:100, flow rate 1 mL/min, λ = 254 nm: τ_1 = 13.79 min, τ_2 = 21.89 min.

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CHAPTER 5

KINETIC RESOLUTION OF RACEMIC VINYL AZIRIDINES PROMOTED BY CHIRAL BRØNSTED PHOSPHORIC ACIDS

5.1. OUTLOOK & CONCEPT

It is noteworthy that currently there are no catalytic methods for the synthesis of highly enantioenriched hydroxymethyl vinyl aziridines (neither via metal catalysis nor organocatalysis), while they would be of interest for the synthesis of a variety of compounds used as intermediates in the synthesis of relevant natural products such as sphingosine. A strategy based on kinetic resolution could be particularly interesting for the preparation of enantioenriched aziridines. To date there are only a few reports on their production by kinetic resolution (*Chapter 1, Section 3.2*). Therefore, such a strategy could be applied to the preparation of optically active hydroxymethyl vinyl aziridines. The establishment of a regio- and stereoselective aziridination of non-symmetric dienes together with the successful development of the *Antilla's* phosphoric acid-catalyzed desymmetrization of *meso*-aziridines,[1] encouraged us to explore the activation of vinyl aziridines with chiral Brønsted phosphoric acids and their asymmetric ring-opening by kinetic resolution using thiols. In general terms, the desired ring-opening transformation was envisioned to proceed *via* Brønsted acid activation of vinyl aziridines by chiral BINOL-derived Brønsted-phosphoric-acids.

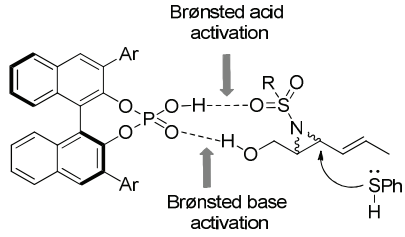
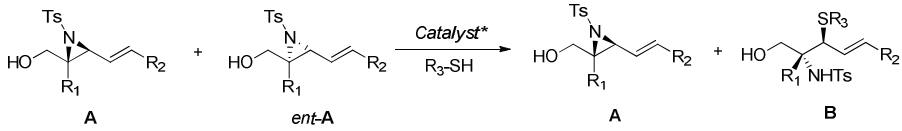


Figure 5.1. Proposed chiral Brønsted phosphoric acid activation of methoxy vinyl aziridines.

The oxygen center of the *N*-sulfonyl protecting group of our vinyl aziridine could be activated by coordinating to the Brønsted acid functionality of the catalyst and the hydroxylic group of the vinyl aziridine could coordinate to its Brønsted base function (Figure 5.1). It was expected that pre-organization of these two functionalities (Brønsted acid and Brønsted base) within a single molecule with an appropriate chiral environment would be an efficient activator of the substrate.

In general terms, the ring-opening of racemic vinyl aziridines in the presence of an appropriate chiral catalyst would lead to kinetic resolution: one enantiomer of the vinyl aziridine (e.g. *ent*-**A**) would be converted to the corresponding *N*-tosyl-*β*-amidothioether **B** whereas the other (e.g. **A**) would remain unchanged (Scheme 5.1).



Scheme 5.1. General concept for the kinetic resolution of vinyl aziridines.

In the present chapter, the results corresponding to the third objective of this thesis will be presented.

5.2. RESULTS AND DISCUSSION

The excellent results in terms of activity and selectivity obtained with BINOL phosphates as powerful Brønsted acid catalysts[2] encouraged us to study the asymmetric ring opening of vinyl aziridines promoted by chiral Brønsted phosphoric acids *via* kinetic resolution. In the following section the synthesis of the selected chiral BINOL-derived Brønsted phosphoric acids are detailed.

5.2.1. SYNTHESIS OF CHIRAL BRØNSTED PHOSPHORIC ACIDS

A wide range of chiral BINOL-derived Brønsted phosphoric acids with various substituents at the 3,3'-position of the binaphthyl backbone ((*S*)- **333** to **338**) were synthesized (Figure 5.2). BINOL- and VAPOL-derived phosphoric acids ((*S*)-**333** and (*S*)-**334**) were purchased from commercial sources.

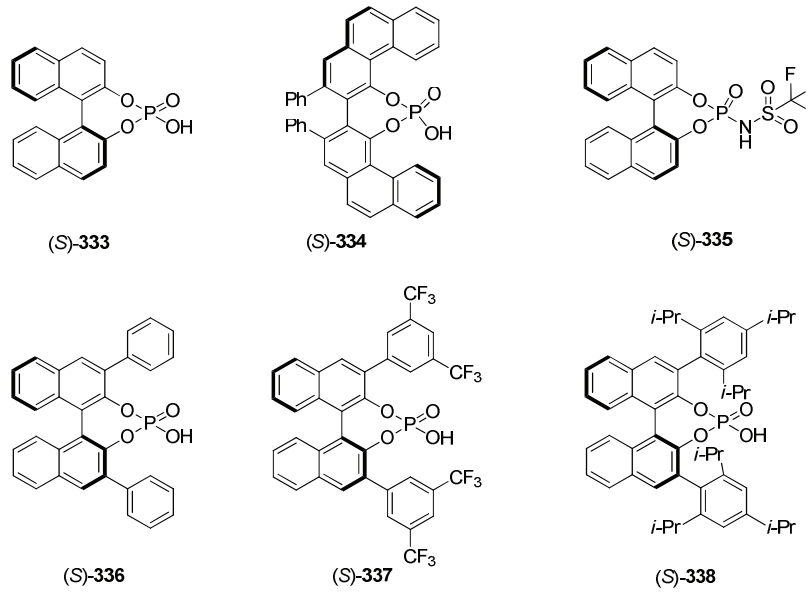
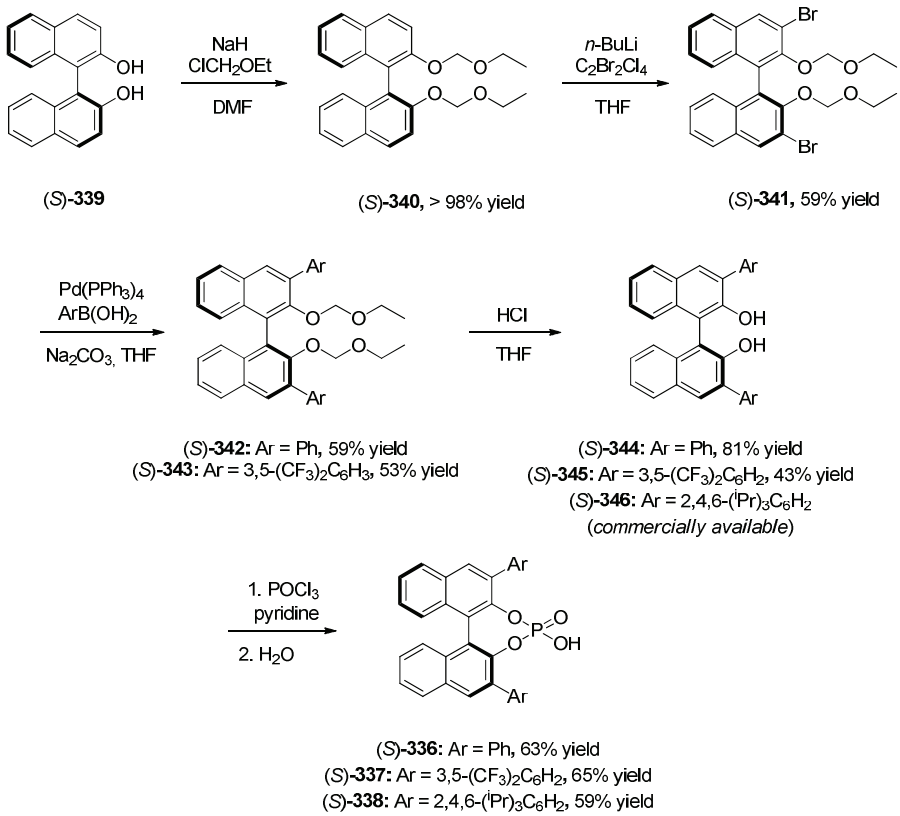


Figure 5.2. Chiral Brønsted catalysts used in this study.

BINOL-derived phosphoric acid catalysts ((*S*)-**336**, **337** and **338**) were synthesized in five steps as described in Scheme 5.2. Initially, the (*S*)-BINOL (**339**) was deprotonated using NaH and protected using chloromethyl ethyl ether.[3] The product (*S*)-**340** was isolated in quantitative yield after purification by column chromatography.



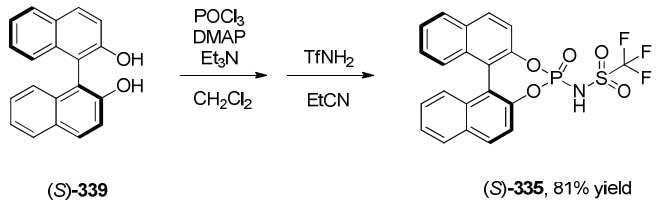
Scheme 5.2. Synthesis of BINOL-derived phosphoric acid catalysts.

Metalation with *n*BuLi and subsequent iodination reaction gave the 3,3'-dihalogenated BINOL derivative in low yield (23%) due to the formation of a considerable amount of the monohalogenated byproduct during the reaction. Alternatively, bromination led to the corresponding 3,3'-dibrominated species in moderate yield (59%). Thus, ortho-metalation using *n*BuLi and dibromotetrachloroethane afforded pure product (*S*)-**341** after column chromatography and recrystallisation.[4] It was reported by Terada that 3,3'-substitution with aromatic moieties induced higher enantioselectivity in the Mannich reaction.[5] Therefore, standard Suzuki cross-coupling conditions[6] were employed to extend the aromatic backbone

and provide the 3,3'-substituted compounds ((*S*)-**342** and **343**). These reactions proceeded in good yields using THF as solvent. Removal of the methoxyethyl protecting groups was achieved by reflux with hydrochloric acid in THF (Scheme 5.2).[7] Column chromatography followed by recrystallisation in acetonitrile afforded the pure diols products ((*S*)-**344** and **345**). The final step was the reaction of the diols (*S*)-**344** and **345** with phosphorus oxychloride in dry pyridine followed by water addition.[8] Pyridine was removed by acidic work-up to afford the resulting phosphoric acids ((*S*)-**336**, **337** and **338**) after purification by column chromatography.

The mild p*K*a values (p*K*a of diethylphosphate is 1.3) of BINOL-based phosphates restrict these catalysts to the activation of basic aldimine and ketimine substrates. Therefore, to lower their p*K*a values and thus broaden the scope of substrate activation, the introduction of strongly electron-withdrawing groups at the phosphate scaffold is required. In this context, it is well known that introduction of a triflate functionality into potentially acidic groups leads to a substantial increase of their acidity.[9] The application of this concept to BINOL phosphates should lead to the corresponding BINOL-derived *N*-triflylphosphoramides with an estimated p*K*a value of around –3 to –4, a range in which carbonyl activation is feasible. Therefore, we synthesized the non-substituted BINOL-derived N-triflylphosphoramide (*S*)-**335** in order to study and compare its catalytic activity with the BINOL-based phosphates analogues in the ring-opening reaction of vinyl aziridines.

The phosphoramidation step was performed following a similar procedure to that described by *Yamamoto* and co-workers.[10] Treatment of (*S*)-**339** with phosphoroxychloride generated the appropriate BINOL-phosphoroxychloride, which was quenched *in situ* with Tf-NH_2 to give the desired N-triflylphosphoramide (*S*)-**335** in good yield (81%, Scheme 5.3).

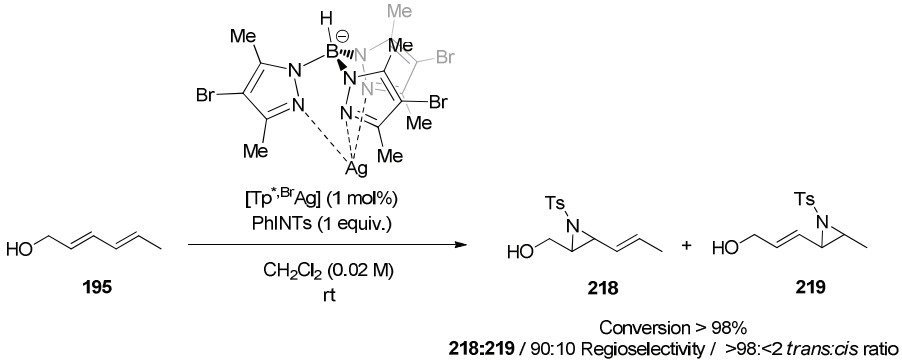


Scheme 5.3. Synthesis of the BINOL-derived phosphoroamide catalyst (*S*)-**335**.

With these chiral BINOL-derived Brønsted phosphoric acid catalysts in hands, an evaluation of their catalytic ability out in the asymmetric ring opening reaction of vinyl aziridines was carried.

5.2.2. PRELIMINARY RESULTS

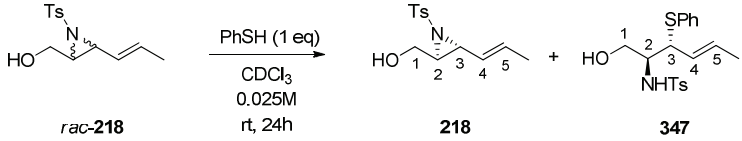
Vinyl aziridine **218** was prepared following the literature procedure reported by our group (Scheme 5.4). This methodology was previously described in the third chapter (*section 3.3.1*) of this thesis. Vinyl aziridine **218** decomposed during column chromatography and their reactivity was therefore directly explored using the reaction mixture.



Scheme 5.4. Synthesis of vinyl aziridine **218**.

Initially the reaction of vinyl aziridine **218** with thiophenol at room temperature was studied in an NMR tube in the absence of catalyst as a blank test. After 1h, 70% conversion to the desired ring-opened product **347** was obtained in deuterated dichloromethane as the solvent. Interestingly, the ring opening reaction was totally regioselective under these conditions and only the product resulting from the attack of thiophenol at the allylic position was obtained, as result of an S_N2 process. The formation of **347** was confirmed by ^1H and ^{13}C NMR. The ^1H and ^{13}C NMR data for the vinyl aziridine **218** and the new ring-opened product **347** are given in Table 5.1.

Table 5.1. Characterization of **218** and **347** by ^1H and ^{13}C-NMR spectroscopy.

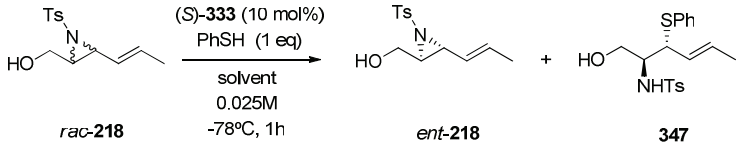


rac-**218** **218** **347**

Compound	NMR Characterization		1	1'	2	3	4	5
218	^1H-NMR	δ	3.99	3.77	3.19	3.3	5.51	5.84
		M	dd	dd	ddd	dd	dd	dt
		J (Hz)	12.8 3.2	12.8 6.6	6.6 4.4 3.2	8.8 4.4	15.2 8.8	15.2 6.4
	^{13}C-NMR	δ	61.0		49.6	48.5	129.9	127.7
347	^1H-NMR	δ	3.82	3.70	3.38	3.56	5.35	5.07
		M	dd	dd	ddd	dd	dd	ddq
		J (Hz)	11.6 5.6	11.6 4.4	6.4 4.4 5.6	8.8 6.4	15.2 6.4	15.2 9.2 1.6
	^{13}C-NMR	δ	62.1		56.2	45.1	127.1	130.4

At this point, the ring-opening reaction of racemic vinyl aziridine **218** with thiophenol in the presence of 10 mol% of the non-substituted phosphoric acid (*S*)-**333** was studied as model reaction, and the effect of solvent was investigated. For this purpose, once the vinyl aziridine **218** was generated in situ, the dichloromethane present in the reaction mixture was evaporated and the resulting mixture was redissolved in 4 ml of the corresponding solvent. The mixture was then treated with 1 equivalent of thiophenol as a nucleophile and 10 mol% of (*S*)-**333** as catalyst. The reaction was carried out at –78 ºC in order to decrease the reaction rate of the uncatalysed, achiral process. The evolution of the reaction was monitored by ^{1}H-NMR spectroscopy by taking a 600 µl aliquot of the reaction mixture and performing a basic aqueous work-up. The effect of solvent on the catalytic asymmetric vinyl aziridine ring-opening reaction promoted by (*S*)-**333** is summarized in Table 5.2.

Table 5.2. Solvent screening.[a]



rac-**218** *ent*-**218** **347**

Entry[b]	Solvent	Conversion (%)[c]	e.r. 347[c]
1	$(CH_3CH_2)_2O$	>98	75:25
2	CH_2Cl_2	>98	67:33
3	$(C_6H_5)CH_3$	>98	60:40
4	*tert*-BuOMe	>98	90:10
5	$(CH_3)_2CO$	>98	50:61

[a] Vinyl aziridine **218** was formed in situ from the corresponding allylic alcohol (0.1 mmol) and PhINTs as a nitrene source (0.11 mmol) in the presence of [Tp*,^{Br}Ag] as catalyst (0.001 mmol) in 5 ml of CH_2Cl_2. [b] General reaction conditions: **218** (0.1 mmol), thiophenol (0.11 mmol), 0.20 equiv of (*S*)-**333** (0.01 mmol), 4ml of solvent; t = 1h. [c] Determined by ^{1}H-NMR. [d] Isolated yield. [e] Determined by chiral HPLC (Chiralpack IA, 87 hexane/ iso-propanol = 87:13, 0.7 ml/min).

As seen from Table 5.2, all the solvents gave full conversions after 1h, with excellent regio- and stereoselectivities and moderate to good enantioselectivities (Table 5.2, entries 1 to 5). This level of enantioselectivity at assumed conversions of up to 98% was not expected. Indeed, since the substrate used in this study is a racemic mixture, a kinetic resolution process would only produce such enantiodiscrimination at *ca.* 50-60% of conversion. In the case that both enantiomers of the substrate could react within the reaction time used and thus provide total conversion, a racemic mixture of ring-opened products should be obtained. A *dynamic* kinetic resolution is not expected, because there is no additional catalyst present that could epimerize the starting material.

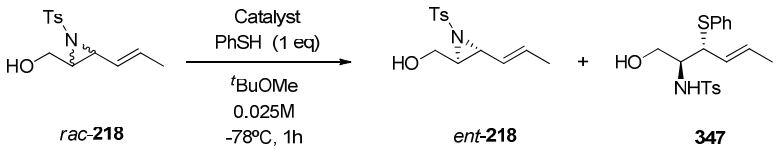
In other solvents also full conversions and non-racemic mixtures were obtained (Table 5.2, entries 2-5). Results were particularly relevant when *tert*-butyl methyl ether was used as solvent, since the ring-opened product **347** was afforded in high enantiomeric ratio (Table 5.2, entry 4).

To explain these results, we first hypothesized that the unreacted vinylaziridine could disappear through a side reaction. To obtain more information on the selectivity of the reaction and looking for a slower reaction, an initial catalyst screening using the chiral Brønsted phosphoric acids (*S*)**-333**-**338**, *tert*-butyl methyl ether as the solvent and the vinyl aziridine **218** as the model substrate was performed. Full conversions but yields around 40–60% were obtained in all cases, and the ring-opened product **347** was isolated in each test. The results are summarized in Table 5.3. Initially, experiment of Table 1, entry 4 was reproduced obtaining 58% yield and identical enantioselectivity (90:10 e.r) (Table 5.3, entry 1). A slight decrease in the enantiodiscrimination of the process was obtained when 10 mol% of (*S*)**-334** catalyst were used (Table 5.3, entry 2). Interestingly, when the catalyst loading was decreased to 5 mol%, the enantioselectivity decreased dramatically (Table 5.3, entry 3) suggesting a competitive reaction between the uncatalysed process and the catalysed

reaction. Using 10 mol% of the BINOL-derived *N*-triflylphosphoramide catalyst (*S*)**-335**, the ring-opened product was obtained with full conversion in 55% yield and with a decrease in the enantioselectivity (Table 5.3, entry 4) in comparison with catalyst (*S*)**-333**, which suggests that the catalyst acidity plays an important role in the enantiodiscrimination of the process. Interestingly, when 10 mol% of the 3,3'-disubstituted catalyst (*S*)**-336** was employed, the ring-opened product was obtained with full conversion in 49% yield and a decrease in the enantioselectivity (71:29 e.r.) was observed (Table 5.3, entry 5) compared to the results obtained with catalyst (*S*)**-333**. Additionally, when the reaction was performed using 10 mol% of catalyst (*S*)**-337**, which contains a 3,5-(bis-trifluoromethyl)phenyl group at the 3,3'-position of the binaphthyl backbone, the ring-opened product was obtained with full conversion in 47% yield, and again, a decrease in the enantioselectivity (74:26 e.r.) was observed (Table 5.3, entry 6) compared to the results obtained with catalyst (*S*)**-333**.

Finally, when various loadings of catalyst (*S*)**-338** which contains a 2,4,6-(triisopropyl)phenyl group at the 3,3'-position of the binaphthyl backbone were employed, the ring-opened product was obtained with full conversion in good to moderate yield and the enantiodiscrimination of the process was even lower (Table 5.3, entries 6 to 8). Therefore, lower enantioselectivities were obtained when substituted catalysts were employed in comparison with the non-substituted catalyst (*S*)**-333**. These results were surprising since the introduction of substituents at the 3,3'-positions of the binaphthyl backbone was expected to provide a better substrate recognition site. This suggests that the incorporation of hindered groups at the binaphthyl backbone retards the chiral, catalyzed reaction, thus promoting a competitive uncatalysed reaction.

Table 5.3. Catalytic asymmetric ring opening of vinyl aziridine **218** promoted by catalysts (*S*)-**333** to **338**.[a]



rac-**218** *ent*-**218** **347**

Entry[b]	Catalyst	Catalyst Loading (mmol %)	Conv. (%)[c]	Yield. (%)[d]	e.r 347[e]
1	(*S*)-**333**	10	>98	58	90:10
2	(*S*)- **334**	10	>98	53	85:15
3		5	>98	41	63:37
4	(*S*)- **335**	10	>98	55	56:44
5	(*S*)- **336**	10	>98	49	71:29
6	(*S*)- **337**	10	>98	47	74:26
7	(*S*)- **338**	10	>98	53	79:21
8		4	>98	47	76:24
9		2	>98	34	70:30

[a] Vinyl aziridine **218** was formed in situ from the corresponding allylic alcohol (0.1 mmol) and PhINTs as a nitrene source (0.11 mmol) in the presence of [Tp*,^{Br}Ag] as catalyst (0.001 mmol) in 5 ml of CH_2Cl_2. [b] General reaction conditions: **218** (0.1 mmol), thiophenol (0.11 mmol), 4ml of solvent; t = 1h. [c] Determined by ^{1}H-NMR. [d] Isolated yield. [e] Determined by chiral HPLC (Chiralpack IA, 87 hexane/ iso-propanol = 87:13, 0.7 ml/min).

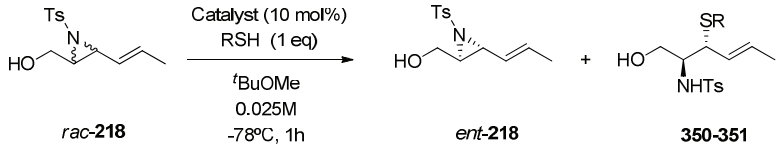
To summarize, conversions up to 98% and yields from 34 to 58% were obtained in all cases and variations of the level of enantiodiscrimination were observed, with the less sterically hindered catalyst being the most selective. The low yields obtained for the ring-opened product **347** are in agreement with a kinetic resolution process while the remaining untransformed substrate most likely disappears at some point during the process or during the work-up of the reaction. However, since the isolated yields over two reaction steps (aziridination process and asymmetric ring-opening reaction) are relatively high, the possibility of a

double isomerization *via* an unknown dynamic kinetic resolution process, although highly improbable, should not be discarded too lightly.

5.2.3. CATALYST AND NUCLEOPHILE SCREENING

To obtain more information on the ring-opening of aziridines with thiols, we decided to test substituted thiols as nucleophiles **348** and **353** in the kinetic resolution of vinyl aziridine **218** using a set of chiral phosphoric acids (*S*)-**333-337**.

Table 5.4. Catalyst and nucleophile screening.[a]



rac-**218** *ent*-**218** **350-351**

Entry[b]	R	Catalyst	Product	Conv. (%)[c]	Yield. (%)[d]	e.r.[e]
1	2-$CH_3(C_6H_4)$ (**348**)	(*S*)-**333**	**350**	>98	62	57:43
2		(*S*)-**334**		>98	61	78:22
3		(*S*)-**335**		>98	54	52:48
4		(*S*)-**336**		>98	63	56:44
5		(*S*)-**337**		>98	49	63:37
6	2,6-$(CH_3)_2C_6H_3$ (**349**)	(*S*)-**333**	**351**	>98	61	83:17
7		(*S*)-**334**		>98	64	71:29
8		(*S*)-**335**		>98	58	50:50
9		(*S*)-**336**		>98	60	64:36
10		(*S*)-**337**		>98	60	50:50

[a] Vinyl aziridine **218** was formed in situ from the corresponding allylic alcohol (0.1 mmol) and PhINTs as a nitrene source (0.11 mmol) in the presence of [$Tp^{*,Br}Ag$] as catalyst (0.001 mmol) in 5 ml of CH_2Cl_2; [b] General reaction conditions: **218** (0.1 mmol), thiophenol derived (0.11 mmol), 0.10 equiv of (*S*)-catalyst (0.01 mmol), 4ml of solvent; t = 1h; [c] Determined by ^{1}H-NMR; [d] Isolated yield; [e] Determined by chiral HPLC.

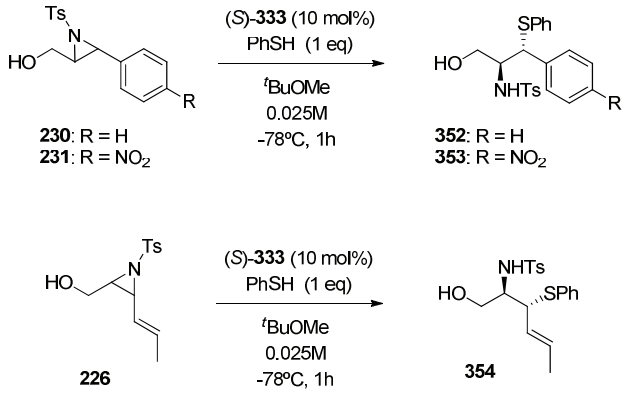
The results are summarized in Table 5.4. The same behavior was observed in all cases and conversions up to 98% and yields in the range of 49 to 64% were obtained. Variations of the level of enantiodiscrimination were observed, with the less sterically hindered catalyst (*S*)-**333** and the more hindered nucleophile **349** being the most selective system (Table 5.4, entry 6). Unfortunately, the enantioselectivity of the reaction was lower than that with thiophenol as the nucleophile, suggesting that the less hindered nucleophiles provided better chiral induction. The yields obtained for the ring-opened products **350** and **351** (from 49 to 64%) are in agreement with a kinetic resolution process.

5.2.4. SUBSTRATE SCREENING

To assess the contribution of the vinyl aziridine structure in the selectivity of the process, we screened other vinyl and benzyl aziridines with (*S*)-**333** as catalyst, thiophenols as nucleophile and *tert*-buthyl methyl ether as solvent at –78ºC. Thus, we decided to explore aziridines **230–226** (*the synthesis was already described in the third chapter of this thesis, Section 3.3.1.*). These substrates could provide insight into the effect of the substitution (aziridines **225**, **230** and **231**), on activity and stereocontrol in the asymmetric ring-opening process. Substrates **226**, **230** and **231** were tested in their asymmetric ring-opening reactions and the results are summarized in Table 5.5. The asymmetric ring-opening reaction of **226**, **230** and **231** was studied in the presence of 10 mol% of (*S*)-**333** catalyst, with equimolar mixtures of aziridine and thiophenol. The ring-opening reaction of **230** with thiophenol using (*S*)-**333** catalyst under the optimized reaction conditions afforded a yield of 57% and an enantiomeric ratio of 81:19 er. Similarly, when this system was used in the ring-opening reaction

of the substrates **231** and **226**, similar yields were obtained with almost identical enantiomeric ratio (*ca.* 80:20 er).

Table 5.5. Substrate screening.[a]



Entry[b]	Aziridine	Product	Conv. (%)[c]	Yield (%)[d]	e.r.[e]
1	**230**	**352**	> 98	57[f]	81:19
2	**231**	**353**	> 98	61[f]	78:22
3	**226**	**354**	> 98	56	80:20

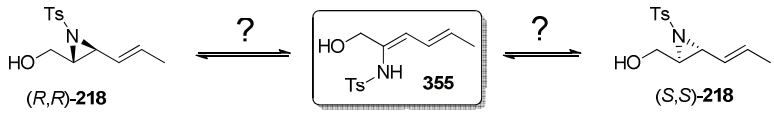
[a] Aziridines **230**, **231** and **226** were formed in situ from the corresponding allylic alcohol (0.1 mmol) and PhINTs as a nitrene source (0.11 mmol) in the presence of [Tp*,^{Br}Ag] as catalyst (0.001 mmol) in 5 ml of CH_2Cl_2. [b] General reaction conditions: the corresponding aziridine (0.1 mmol), thiophenol (0.11 mmol), (*S*)-**333** (0.01 mmol), 4ml of solvent; t = 1h. [c] Determined by ^{1}H-NMR. [d] Isolated yield over two reaction steps. [e] Determined by chiral HPLC. [f] Isolated yield over one reaction step (benzylic aziridin-1-ol **230** and **231** were previously isolated).

It was therefore concluded that the structure of the substrate does not significantly influence the enantioselectivity of the reaction, although slightly higher enantioselectivity was obtained using the model vinyl aziridine **218**. Several aziridines were tested and moderate selectivity was obtained, probably due to the fact that yields higher than 50% were obtained as a consequence of the difficulty of controlling the evolution of the reaction.

5.2.5. MECHANISTIC STUDY

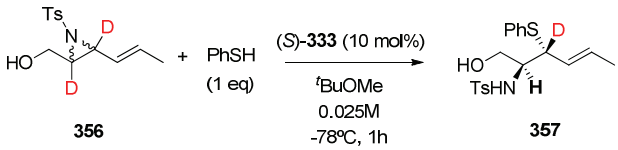
As it was mentioned above, since the isolated yields over two reaction steps are relatively high, the possibility of a double isomerization *via* an unknown dynamic kinetic resolution process, should not be discarded. To discard or confirm the dynamic kinetic resolution hypothesis, a mechanistic study was carried out using deuterium labeling experiments.

We postulated that racemization of the substrate could eventually take place via a double isomerization of C2 and C3 centers via an achiral intermediate such **355** (Scheme 5.5). The Brønsted (H-A*) acid would catalyze the ring-opening reaction of one of the enantiomers of vinyl aziridine **218** using thiophenol as nucleophile providing selectively the one isomer of the corresponding ring-opened product **347**. In a second reaction or sequence of reactions the other enantiomer **218** would react to give the achiral intermediate enamine **355**, thus equilibrating the two enantiomers.



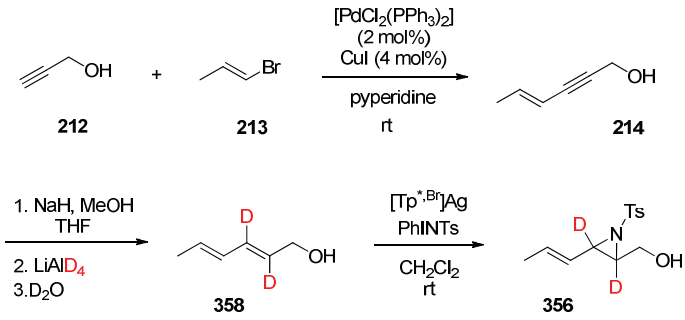
Scheme 5.5. Achiral intermediate proposed for double isomerization.

To probe such hypothesis, the synthesis of the dideuterated vinyl aziridine **356** was proposed, as in the elimination reaction deuterium exchange with the protons of the medium should be evidenced (Scheme 5.6), and certainly the product originated from the enantiomer less reactive in the catalytic reaction should contain at most one deuterium atom.



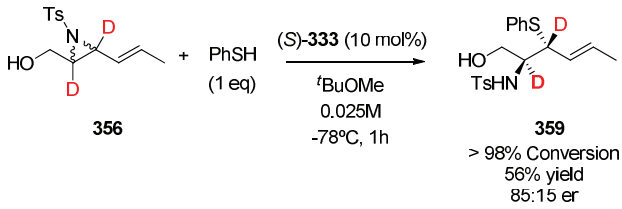
Scheme 5.6. Proposed experiment in order to elucidate the mechanism.

The synthesis of the dideuterated vinyl aziridine **356** was carried out from propargyl alcohol **212** and (*E*)-1-bromopropene **213** in three steps (Scheme 5.7). Sonogashira coupling[11] between vinyl bromide **213** and propargyl alcohol **212** gave the enyne **214**, which was reduced by lithium aluminium deuteride to afford dideuterated diene **358** in 82% yield (Scheme 5.7). The aziridination of **358** was performed in the presence of 1mol% [Tp^{*,Br}]Ag catalyst loading and an equimolar mixtures of the diene **358** and PhINTs, affording the aziridine **356** with excellent diastereoselectivity, obtaining a *trans:cis* ratio = >98:2.



Scheme 5.7. Synthesis of dideuterated aziridines **356**.

When the ring-opening reaction of the dideuterated aziridine **356** was performed under optimized conditions, no deuterium exchange at C-2 was observed and the corresponding dideuterated ring-opened product **359** was obtained in 56% yield and an enantiomeric ratio of 85:15 (Scheme 5.8).

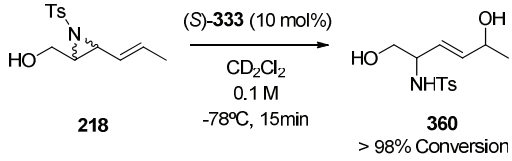


Scheme 5.8. Catalytic asymmetric ring-opening reaction of dideuterated vinyl aziridine **356** promoted by (*S*)-**333** catalyst.

These results show that the ring-opened product **359** is not formed via a double isomerization by a dynamic kinetic resolution process through enamine **355**. Therefore we are indeed dealing with a highly selective kinetic resolution and the loss of unreacted aziridine during the work-up process remains as the only possibility for explaining the absence of the remaining aziridine in the final product mixture.

In addition to the deuterated study we conducted another series of experiments to show that the incomplete mass balance is responsible for the high *ee*s obtained via a kinetic resolution.

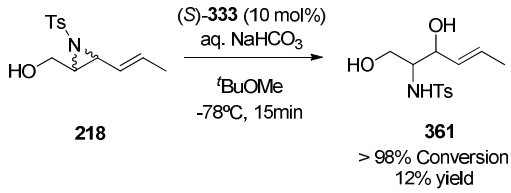
In a study aiming at checking the evolution of the reaction by NMR spectroscopy, a solution of 0.1 mmol of the vinyl aziridine **218** in 1ml of deuterated dichloromethane was charged in an NMR tube, which was cooled to –78ºC.



Scheme 5.9. Ring-opening reaction of vinyl aziridines **218** by water promoted by (*S*)-**333** catalyst.

Then, 10 mol% of the (*S*)**-333** catalyst was added into the NMR tube. After 15 minutes, and before adding the thiol, the ^{1}H-NMR spectra only revealed the presence of the ring-opened product **360** obtained *via* an S_N2' process, namely involving the water present in the deuterated solvent (Scheme 5.9). This result suggests that under the basic work-up treatment, necessary to check the conversion of the asymmetric ring-opening reaction of vinyl aziridine **218** by ^{1}H-NMR, the unreacted enantiomer of the vinyl aziridine that remained in the catalytic mixture undergoes ring-opening to **360**. This particular ring-opened product resulting from the basic treatment remains in the aqueous phase after the separation of the layers during the work-up and this can explains that only the ring-opened product resulting from the attack of thiophenol **347** was detected by ^{1}H NMR in the experiments described in the previous sections.

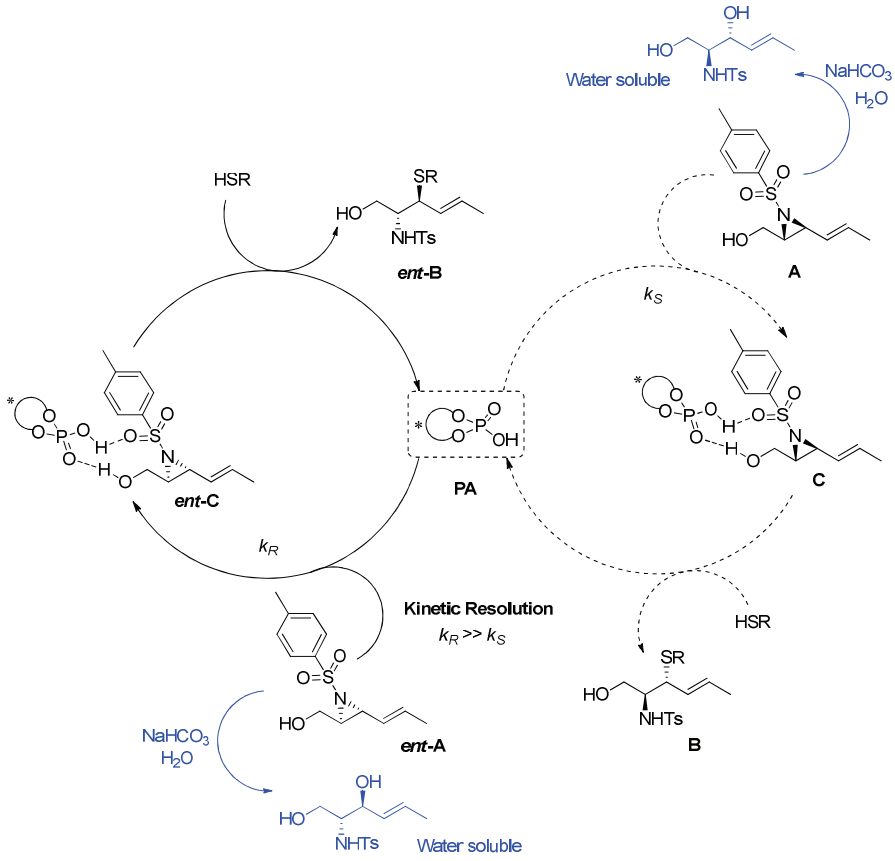
To prove definitively this hypothesis, vinyl aziridine **218** was treated under work-up conditions. Thus, when 0.1 mmol of the vinyl aziridine **218** was treated with 10 mol% of (*S*)**-333** catalyst and 1ml of a saturated aqueous solution of $NaHCO_3$ using *tert*-buthylmethylether as solvent at –78 ºC. After 15 minutes, full conversion to the ring-opened product **361**, which in this case corresponds to a S_N2 process which is favoured under basic conditions, namely the hydroxyl anion in the presence of $NaHCO_3$ (Scheme 5.10). The low yield obtained confirmed the loss of the product in the aqueous solution and during purification.



218 **361**
> 98% Conversion
12% yield

Scheme 5.10. Opening reaction of vinyl aziridines **218** by basic aqueous treatment.

Based on these results, we speculated that the Brønsted acid catalytic ring-opening reaction of vinyl aziridine *via* kinetic resolution could occur via the following pathway (Scheme 5.11).



Scheme 5.11. Proposed mechanism for the asymmetric ring-opening reaction of vinyl aziridines *via* kinetic resolution.

The first step of the reaction involves the activation of the aziridine by coordination to the Brønsted acid and base functionalities of the catalyst (**PA**), resulting in the formation of the chiral ion pair (**C** or ***ent*-C**). Species **C** or ***ent*-C** then undergoes nucleophilic attack by the thiophenol, resulting in the product **B** or ***ent*-B** and the regeneration of the catalyst (**PA**). The

difference in reaction rates (k_R, k_S) of the substrate enantiomers (**A**, ***ent*-A**) during the transformation to produce **B** and ***ent*-B** by a chiral catalyst *via* diastereomeric transition state (**C**, ***ent*-C**), could result in the recovery of the product ***ent*-B** and the unreacted substrate enantiomer ***ent*-A** (Scheme 5.11). Absolute configurations have not been determined and the reverse process ($k_S > k_R$) can take place.

To summarize, it was concluded that the mechanism of the asymmetric ring opening reaction of vinyl aziridine **218** occurs *via* a kinetic resolution process and that the real aziridine conversions were actually lower than described earlier in this chapter as is indicated by the isolated yield. Indeed, during the basic treatment employed to monitor the reaction, the unreacted enantiomer of the substrate was readily converted into product **361**, which remained in the aqueous phase of the work-up, and was thus not observed in the spectra, inducing an error in the calculations of the conversion. Further experiments are currently under investigation in our laboratory in order to optimize this kinetic resolution process.

5.3. CONCLUSIONS

From the study of the asymmetric ring-opening reaction of vinyl aziridines with chiral Brønsted BINOL-derived phosphoric acids, the following conclusions can be extracted:

i) The chiral Brønsted BINOL-derived phosphoric acids (*S*)-**333**-**338** were applied in the asymmetric ring-opening reaction of vinyl aziridine **218** using thiophenol as nucleophile. Yields are in agreement with a kinetic resolution. The best selectivity was obtained using the less sterically hindered non-substituted catalyst (*S*)-**333** (90:10 er).

ii) The nucleophiles **348** and **349** were also tested in the asymmetric ring-opening reaction of vinyl aziridine **218** using various chiral Brønsted phosphoric acids (*S*)-**334**-**337** as catalysts. Variations of the level of enantiodiscrimination were observed, with the less sterically hindered catalyst (*S*)-**333** and the more hindered nucleophile **349** being the most selective system. However no clear conclusions can be extracted since yields of 49 and 60% were obtained, and particularly in this second case this fact must have a strong influence on the enantioselectivity.

iii) Several aziridines **226**, **230** and **231** were also tested in the asymmetric ring-opening reaction using thiophenol as nucleophile in the presence of (*S*)-**333** as catalysts. The structure of the substrate was found not to influence the enantioselectivity of the process significantly.

iv) The mechanism of the asymmetric ring opening reaction of vinyl aziridine **218** occurs *via* a kinetic resolution process. The unreacted aziridine was not isolated due to an unexpected reaction with water during the basic work-up.

5.4. EXPERIMENTAL PART

5.4.1. GENERAL EXPERIMENTAL CONDITIONS

All chemicals used were reagent grade and used as supplied unless otherwise specified. HPLC grade dichloromethane (CH_2Cl_2), tetrahydrofuran (THF) and dimethylformamide (DMF) were dried using a

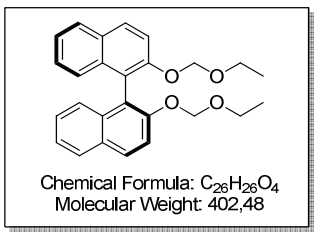
solvent purification system (Pure SOLV system-4®). Toluene was purified using standard procedure.[12]

^{1}H and ^{13}C NMR spectra were recorded on a Varian® Mercury VX 400 (400 MHz and 100.6 MHz respectively) or Varian 400-MR spectrometer in $CDCl_3$ as solvent, with chemical shifts (δ) referenced to internal standards $CDCl_3$ (7.26 ppm ^{1}H, 77.23 ppm ^{13}C) or Me_4Si as an internal reference (0.00 ppm). 2D correlation spectra (gCOSY, NOESY, gHSQC, gHMBC) were visualized using VNMR program (Varian®). ESI MS were run on an Agilent® 1100 Series LC/MSD instrument. Optical rotations were measured at room temperature in a Perkin-Elmer® 241 MC apparatus with 10 cm cells.

Reactions were monitored by TLC carried out on 0.25 mm E. Merck® silica gel 60 F_{254} glass or aluminium plates. Developed TLC plates were visualized under a short-wave UV lamp (250 nm) and by heating plates that were dipped in ethanol/H_2SO_4 (15:1) and basic solution of potassium permanganate. Flash column chromatography was carried out using forced flow of the indicated solvent on Fluka® or Merck® silica gel 60 (230-400 mesh). Radial chromatography was performed on 1 or 2 mm plates of Kieselgel 60 PF_{254} silica gel, depending on the amount of product. Flash column chromatography (FCC) was performed using flash silica gel (32–63 μm) and using a solvent polarity correlated with TLC mobility.

5.4.2. SYNTHESIS OF CHIRAL BRØNSTED PHOSPHORIC ACIDS

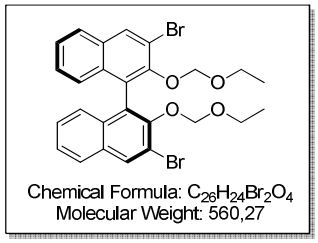
(*S*)-2,2'-*Bis*(ethoxymethoxy)-1,1'-binaphthalene ((*S*)-**340**):[3]



To a suspension of NaH (60% dispersion in mineral oil; 1.4g, 34.93 mmol) was added a solution of (*S*)-**339** (4g, 13.97 mmol) in DMF (30 ml) at 0 ºC. The mixture was stirred at the same temperature for 20 min, and $EtOCH_2Cl$ (2

ml, 13.97 mmol) was then added. The resulting mixture was gradually allowed to warm to room temperature for 1h, and water was added to quench the reaction. The organic layers were dried, and after evaporation, (*S*)-**340** was obtained in a quantitative yield (5.5g, 98% yield). **^{1}H NMR** (400MHz, $CDCl_3$): δ in ppm 7.96 (2H, d, J = 9.0 Hz, ArH), 7.88 (2H, d, J = 8.9 Hz, ArH), 7.61 (2H, d, J = 8.0 Hz, ArH), 7.28-7.39 (2H, m, ArH), 7.14-7.24 (2H, m, ArH), 7.15 (2H, d, J = 9.0 Hz, ArH), 5.14 (2H, d, J = 7.1 Hz, OCH2O), 5.02 (2H, d, J = 7.1 Hz, OCH_2O), 3.24-3.49 (4H, m, CH_2CH_3), 1.00 (6H, t, J = 7.1 Hz, CH_2CH_3). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ in ppm 153.2, 134.1, 130.6, 129.9, 128.1, 125.7, 124.2, 121.1, 117.9, 94.5, 64.2, 15.7.

(*S*)-3,3'-Dibromo-2,2'-bis(ethoxymethoxy)-1,1'-binaphthalene ((*S*)- **341**):[4]



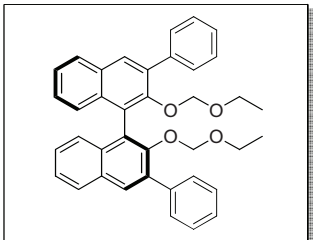
Compound (*S*)-**340** (5.74 g, 14.3 mmol, 1 equiv) was dissolved in dry Et_2O (200 mL) in a round bottom flask under an argon atmosphere. *n*BuLi (26.7 mL, 1.6 M in hexane, 3 equiv) was added at room temperature by syringe injection with stirring. After the reaction mixture was stirred for 3 h, THF (130 mL) was injected into the flask and the mixture was stirred for 1 h. The flask was cooled in an ice bath for 5 minutes and dibromotetrachloroethane (13.93 g, 42.7 mmol, 3 equiv) was quickly added in one portion giving a bright orange solution. The reaction mixture was stirred overnight and quenched with saturated aqueous ammonium chloride and water. The two phases were separated and the aqueous layer washed with Et_2O twice. All organic layers were combined, washed with brine, dried over sodium sulfate and concentrated. Crude product was purified by column chromatography (EtOAc/hexane = 1/10) to afford 4.7 g of the title

compound (*S*)-**341** in 59% yield. **^{1}H NMR** (400MHz, $CDCl_3$): δ in ppm 8.27 (2H, s, ArH), 7.82 (2H, d, J = 8.1 Hz, ArH), 7.39-7.45 (2H, m, ArH), 7.22 - 7.32 (2H, m, ArH), 7.09 (2H, d, J = 8.1 Hz, ArH) 4.90 (2H, d, J = 5.9 Hz, OCH2O), 4.83 (2H, d, J = 5.9 Hz, OCH2O), 2.96-3.08 (2H, m, OCH_2CH_3), 2.62-2.72 (2H, m, OCH_2CH_3), 0.60 (6H, t, J = 7.2 Hz, CH_2CH_3). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ in ppm 150.3, 133.1, 132.9, 131.5, 127.2, 126.9, 126.5, 125.9, 117.5, 97.8, 64.8, 14.3.

*General procedure for the synthesis of (S)-**342** and (S)-**343**:*[6]

Compound (*S*)-**341** (300mg, 0.479 mmol), (tetrakis(triphenylphosphine) palladium(0) (55.3 mg, 0.047 mmol) and sodium carbonate solution (1M, 5 ml) in 15 ml THF solution were added to 3-bromo-2,4-thienylboronic acid (350 mg, 2.874 mmol), and the solution was refluxed for 48 h. The saturated aqueous solution of sodium chloride was added and the resulting mixture was extracted with diethyl ether, the organic layers were dried over anhydrous sodium sulphate, and evaporated. The residue was purified using column chromatography.

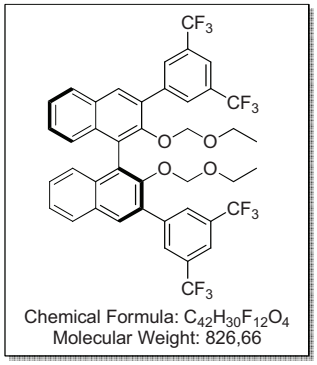
(S*)*-3,3'-Diphenyl-2,2'-*bis*(ethoxymethoxy)-1,1'-binaphthalene ((*S*)-342**):


Chemical Formula: $C_{38}H_{34}O_4$
Molecular Weight: 554,67

After column chromatography: hexanes/AcOEt: 10:1, 156.7 mg of (*S*)-**342** was obtained in 59% yield. **^{1}H NMR** (400MHz, $CDCl_3$): δ in ppm 7.95 (2H, ArH), 7.89 (2H, d, J = 8.1 Hz), 7.70–7.81 (4H, m, ArH), 7.22-7.55 (12H, m, ArH), 4.47 (2H, d, J = 5.8 Hz, OCH_2O), 4.44 (2H, d, J = 5.8 Hz, OCH_2O), 2.65-2.75 (2H, m, OCH_2CH_3), 2.38-2.49 (2H, m, OCH_2CH_3), 0.40 (6H, t, J = 7.1 Hz, OCH_2CH_3). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ in ppm 151.6,

139.1, 135.5, 133.6, 130.8, 130.5, 126.6, 128.3, 127.9, 127.2, 126.4, 126.3, 126.2, 125.0, 97.2, 64.2, 14.2.

(*S*)-3,3'-Bis(3,5-bis(trifluoromethyl)phenyl)-2,2'-bis(methoxyethoxy)-1,1'-binaphthalene ((*S*)-**343**):

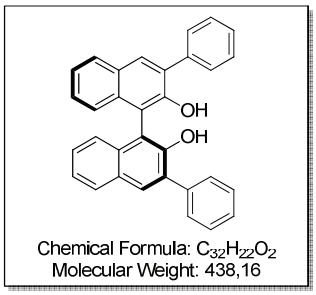


After column chromatography: hexanes/AcOEt: 10:1, 209.8 mg of (*S*)-**343** was obtained in 53% yield. **^{1}H NMR** (400MHz, $CDCl_3$): δ in ppm 8.23 (s, 4H), 8.01 (s, 2H), 7.95 (d, *J* = 8.1 Hz, 2H), 7.91 (s, 2H), 7.47 (td, *J* = 6.9, 1.2 Hz, 2H), 7.35 (td, *J* = 6.6, 1.2 Hz, 2H), 7.27 (d, *J* = 9.6 Hz, 2H), 4.38 (dd, *J* = 13.2, 6.0 Hz, 4H), 2.48 (s, 6H). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ in ppm 134.1, 132.7, 131.6 (q, $J^2_{C\text{-}F}$ = 32.5 Hz), 131.1, 130.7, 129.9, 128.2, 127.4, 126.3, 126.2, 125.9, 123.3 (q, $J^1_{C\text{-}F}$ = 275.0 Hz), 121.1, 99.1, 56.2.

*General procedure for the synthesis of (S)-**344** and (S)-**345**:*[7]

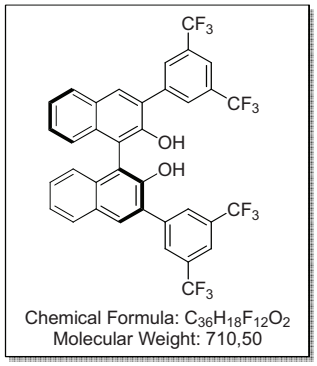
To a solution of (*S*)-**342** or (*S*)-**343** (0.387 mmol) in chloroform (15 ml) concentrated hydrochloric acid (5 ml) was added. The reaction mixture was refluxed for 5h and then 30 ml of water was added and the resulting solution was extracted with diethyl ether. The organic layer was dried over anhydrous sodium sulphate, and then the solvent was removed. The residue was purified using column chromatography.

(*S*)-3,3'-Diphenyl-1,1'-binaphthyl-2,2'-diol ((*S*)-**344**):



After column chromatography: hexanes/CH_2Cl_2: 1:10, 137.3 mg of (*S*)-**344** was obtained in 81% yield. **^{1}H NMR** (400MHz, $CDCl_3$): δ in ppm 8.03 (2H, s, ArH), 7.93 (2H, s, J = 8.1 Hz, ArH), 7.66-7.78 (4H, m, ArH), 7.45-7.55 (4H, m, ArH), 7.36-7.45 (4H, m, ArH), 7.28-7.35 (2H, m, ArH), 7.22-7.27 (2H, m, ArH), 5.38 (2H, s, OH). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ in ppm 150.2, 137.5, 132.9, 131.4, 130.7, 129.6, 129.4, 128.5, 128.4, 127.8, 127.3, 124.3, 124.3, 112.4.

(*S*)-3,3'-Bis(3,5-bis(trifluoromethyl)phenyl)-1,1'-binaphthyl-2,2'-diol ((*S*)-**345**):



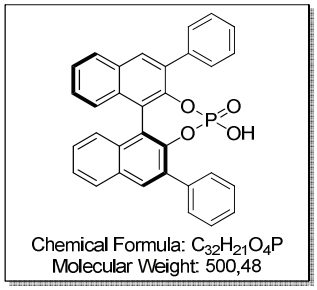
After column chromatography: hexanes/CH_2Cl_2: 1:10, 118.1 mg of (*S*)-**345** was obtained in 43% yield. **^{1}H NMR** (400MHz, $CDCl_3$): δ in ppm 8.27 (S, 4H), 8.12 (s, 2H), 8.00 (d, *J* = 8.0 Hz, 2H), 7.94 (s, 2H), 7.47 (td, *J* = 6.8, 1.2 Hz, 2H), 7.40 (td, *J* = 6.4, 1.2 Hz, 2H), 7.23 (d, *J* = 8.0 Hz, 2H), 6.05 (s, 2H). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ in ppm 133.5, 132.0, 131.5 (q, $J^2_{C\text{-}F}$ = 32.5 Hz), 129.8, 129.4, 129.7, 128.4, 127.9, 124.9, 124.1, 123.4 (q, $J^1_{C\text{-}F}$ = 275.0 Hz), 121.2, 112.3.

General procedure for the synthesis of (*S*)-**336**, (*S*)-**337** and (*S*)-**338**:[8]

To a solution of the corresponding BINOL-derived (0.367 mmol) in pyridine was added phosphoryl chloride (0.514 mmol) at room temperature for 3 minutes and the mixture was stirred for 2h at 90ºC. After the reaction mixture was cooled to room temperature, pyridine was removed in vacuo

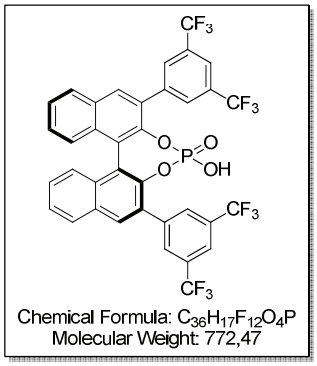
and 6N HCl was added and the resulting mixture was heated to reflux for 2h and cooled to 0ºC. The precipitate thus formed was collected by filtration and washed with water. The crude material was dissolved in ethanol and precipitated by addition of 6N HCl. The solids were collected by filtration and dissolved in CH_2Cl_2 and precipitated by addition of hexane. The resulting crystals were collected by filtration and washed with water to give the title compound. Purification was carried out by column chromatography.

(*S*)-{3,3'-Bis-(phenyl)-1,1'-binaphthalen-2,2'-diyl}phosphoric acid ((*S*)-**336**):



After column chromatography: *i*PrOH/CH_2Cl_2: 1:10, 116.1 mg of (*S*)-**336** was obtained in 63% yield. **^{1}H NMR** (400MHz, $CDCl_3$): δ in ppm 7.72-7.89 (4H, m, ArH), 7.30-7.50 (6H, m, ArH), 7.28 (2H, d, J = 8.5 Hz, ArH), 7.11-7.21 (2H, m, ArH), 7.09-6.77 (6H, m, ArH). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ in ppm 145.4 (d, J_{P-C} = 9.6 Hz), 140.9, 137.4, 134.4, 132.2, 131.4, 131.2, 129.9, 128.4, 128.2, 127.4, 127.1, 126.4, 125.9, 125.7, 122.8. **^{31}P NMR** (166 MHz, $CDCl_3$): δ = 2.62 (s).

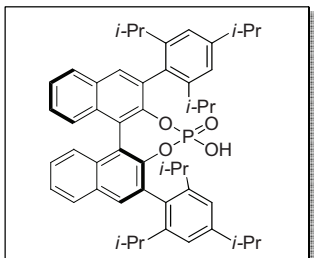
(*S*)-{3,3'-Bis-(3,5-(trifluoromethyl)phenyl)-1,1'-binaphthalen-2,2' yl}phosphoric acid ((*S*)- **337**):



After column chromatography: *i*PrOH/CH_2Cl_2: 1:10, 184.3 mg of (*S*)-**337** was obtained in 65% yield. **^{1}H NMR** (400MHz, $CDCl_3$): δ in ppm 8.01 (s, 8H), 7.61-7.58 (m, 4H), 7.42-7.39 (m, 4H). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ in ppm 143.5 (d, J_{P-C} = 9.3 Hz), 138.6, 132.3, 132.0, 131.4, 131.4 (q, J_{C-F} = 33.4 Hz), 131.1

(d, $J_{P\text{-}C}$ = 3.1 Hz), 129.9, 128.7, 127.6, 127.1, 126.8, 123.1 (q, $J_{C\text{-}F}$ = 272.9 Hz), 122.5 (d, $J_{P\text{-}C}$ = 1.9 Hz), 121.5. **^{31}P NMR** (166 MHz, $CDCl_3$): δ in ppm 4.61.

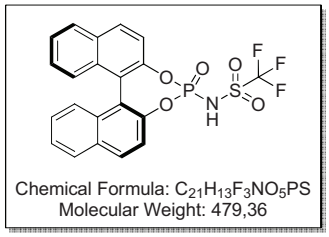
(*S*)-{3,3'-Bis-(2,4,6-triisopropylphenyl)-1,1'-binaphthalen-2,2'-diyl}phosphoric acid ((*S*)-**338**):



Chemical Formula: $C_{50}H_{57}O_4P$
Molecular Weight: 752,95

After column chromatography: *i*PrOH/CH_2Cl_2: 1:10, 163.0 mg of (*S*)-**338** was obtained in 59% yield. **^{1}H NMR** (400MHz, $CDCl_3$): δ in ppm 0.92 (d, *J* = 6.7 Hz, 12H), 0.99 (d, *J* = 6.6 Hz, 6H), 1.11 (d, *J* = 6.8 Hz, 6H), 1.20-1.25 (m, 12H), 2.54-2.60 (m, 4H), 2.81-2.86 (m, 2H), 6.94 (s, 2H), 6.97 (s, 2H), 7.26-7.32 (m, 4H), 7.47 (t, *J* = 7.8 Hz, 2H), 7.82 (s, 2H), 7.87 (d, J = 8.2 Hz, 2H). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ in ppm 149.5, 149.4, 147.9, 147.3, 146.6, 134.0, 133.5, 132.5, 131.1, 129.8, 128.5, 125.9, 125.9, 124.4, 122.5, 120.9, 119.7, 34.1, 30.9, 30.3, 26.6, 24.9, 24.5, 24.4, 23.7, 23.5. **^{31}P NMR** (166 MHz, $CDCl_3$): δ in ppm 3.68.

*General procedure for the synthesis of (S)-***335**:[10]



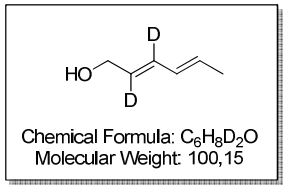
Chemical Formula: $C_{21}H_{13}F_3NO_5PS$
Molecular Weight: 479,36

To a solution of (*S*)-**339** (2 mmol) in dichloromethane were added Et_3N (14 mmol), $POCl_3$ (2.4 mmol) and DMAP (4 mmol) at 0ºC. After being stirred for 1h at room temperature, EtCN (12 ml) was poured to the reaction and $TfNH_2$ (4 mmol) was added at room temperature. Then the reaction was stirred at 100ºC for 12 hours. The reaction was quenched with H_2O and extracted with Et_2O twice. Combined organic layer was

washed with saturated aqueous $NaHCO_3$, then washed with aqueous 4N HCl twice. Resultant organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated. Purification of the crude product by column chromatography on silica gel provided phosphoroamide **335** which may be a salt. The product was extracted with aqueous 4N HCl again, dried over anhydrous Na_2SO_4 and filtered. The concentration of the solution provided 776.5 mg of the desired phosphoroamide (*S*)-**335** in 81% yield. **^{1}H NMR** (400MHz, $CDCl_3$): δ in ppm 8.00 (d, 2H, J = 8.8 Hz), 7.91 (d, 2H, J = 8.4 Hz), 7.49 (dd, 2H, J = 8.8, 5.6 Hz), 7.40-7.36 (m, 2H), 7.20-7.18 (m, 4H). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ in ppm 143.6, 143.5, 133.8, 133.8, 133.7, 133.5, 131.9, 131.6, 131.3, 131.0, 131.0, 130.1, 128.5, 128.4, 128.1, 127.8, 127.1, 126.9, 126.75, 126.70, 126.5, 126.2, 122.2, 122.1, 118.7 (q, J_{CF} = 319.2 Hz). **^{31}P NMR** (166 MHz, $CDCl_3$): δ in ppm – 2.97.

5.4.3. MECHANISTIC STUDY

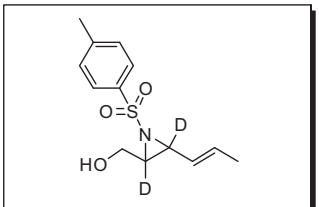
(2*E*,4*E*)-2,3-Dideutero-hexa-2,4-dien-1-ol (358):



To a solution of NaH (264 mg, 60% in oil, 11 mmol washed with n-hexane) in THF (10 ml) was added methanol (446 µl, 11 mmol) at 0 ºC. After evolution of hydrogen had ceased, a solution of (4*E*)-2-hexyn-4-en-1-ol **214**[13] (480.1 mg, 5 mmol) in THF (10 ml) was added and the mixture was stirred for 10 min. Then, $LiAlD_4$ (252 mg, 6 mmol) was added and the mixture was refluxed for 3.5 h. After the mixture was cooled to 0 ºC, deuterium oxide (5 ml) was added and the mixture was stirred for 5 min and the stirring continued for 5 min at rt. Following dilution with ether and water, the aqueous layer was extracted with ether twice. The combined organic extracts were washed with saturated aqueous NH_4Cl and brine, dried over anhydrous Na_2SO_4, filtered and carefully concentrated in vacuo under ice-cooled conditions to give crude volatile **358**

in 82% yield as a colourless liquid. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ in ppm 6.05 (dq, 1H, J = 15.2, 1.6 Hz), 5.69 (dq, 1H, J = 21.6, 6.8 Hz), 4.11 (s, 2H), 3.59 (br, s, 1H), 1.74 (dd, 3H, J = 6.4, 1.6 Hz). **^{13}C NMR** ($CDCl_3$, 100.6 MHz): δ in ppm **ESI-TOF MS** for $[M+H]^+$ $C_6H_9D_2O^+$ (*m/z*): calc. 101.0857; found: 101.1020.

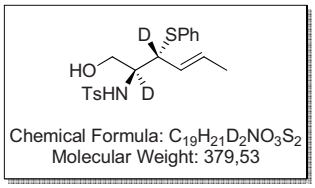
trans-1,2-Dideutero-2-hydroxymethyl-3-((*E*)-1-propen-1-yl)-1-tosyl-aziridine (356):



Chemical Formula: $C_{15}H_{21}D_2NO_3S$
Molecular Weight: 299,42

A 10 ml Schlenk containing a magnetic stirring bar was charged with catalyst (0.001 mmol, 1%) and the alcohol **358** (0.1 mmol), the flask was flushed three times with argon and then, anhydrous dichloromethane (5 ml) was added. A freshly prepared PhINTs (0.11 mmol) was added in 4 portions over 2h and the mixture was stirred for an additional hour after the last addition. Finally the solvent was removed under vacuum and the resulting crude was characterized without purification because vinyl aziridines are unstable by silica gel or neutral alumina. **^{1}H NMR** (400MHz, $CDCl_3$): δ in ppm 7.82 (d, 2H, *J* = 8 Hz), 7.33 (d, 2H, *J* = 8.4 Hz), 5.84 (dt, 1H, *J* = 15.2, 6.4 Hz), 5.51 (dd, 1H, *J* = 15.2, 8.8 Hz), 3.82 (d, 1H, J = 11.6 Hz), 3.75 (d, 1H, J = 12 Hz), 2.39 (s, 3H), 1.52 (d, 3H, J = 1.2 Hz). **^{13}C NMR** (100,6 MHz, $CDCl_3$): δ in ppm 143.7, 131.9, 130.2, 127.6, 127.7, 126.6, 121.1, 59.4, 46.7 (t, J = 21.4 Hz), 42.4 (t, J = 17.0 Hz), 20.8, 13.1. **ESI-TOF MS** for $[M+H]^+$ $C_{15}H_{22}D_2NO_3S_2^+$ (*m/z*): calc. 300.1245; found: 300.1306.

(*E*)-*N*-Tosyl-2-amino-2,3-dideutero-3-(phenylthio)-hex-4-en-1-ol (359):



A 10 ml Schlenk containing the crude d_2-vinyl aziridine **356** (0.1 mmol) was flushed three times with argon and then anhydrous *tert*-buthyl methyl ether (4ml) was added. Next, the chiral Brønsted phosphoric acid (0.01 mmol, 10 mol%) and thiophenol (0.1 mmol) were added at –78 ºC. The reaction was monitored by ^{1}H-NMR. Saturated aqueous $NaHCO_3$ was then added to quench the reaction mixture, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried and evaporated under vacuum. After column chromatography: Hexane/AcOEt: 9:1 to 7:3, 21.0 mg of **359** was obtained in 56% yield. **^{1}H NMR** (400MHz, $CDCl_3$): δ in ppm 7.81 (d, 2H, J = 8.4 Hz), 7.70 (d, 2H, J = 8.8 Hz), 7.28 (d, 2H, J = 8.4 Hz), 7.24–7.14 (m, 3H), 5.33 (dq, 1H, J = 15.2, 6.8 Hz), 5.12 (s, 1H), 5.05 (dq, 1H, J = 15.2, 1.6 Hz), 3.82 (d, 1H, J = 11.6 Hz), 3.75 (d, 1H, J = 12 Hz), 2.39 (s, 3H), 1.52 (d, 3H, J = 1.2 Hz). **^{13}C NMR** (100,6 MHz, $CDCl_3$): δ in ppm 143.8, 137.2, 132.7, 130.3, 129.8, 129.7, 128.9, 127.6, 127.4, 127.4, 127.3, 127.2, 127.0, 126.5, 62.8, 57.7 (t, J = 21.8 Hz), 53.4 (t, J = 17.1 Hz), 21.2, 17.8. **ESI-TOF MS** for $[M+H]^+$ $C_{19}H_{22}D_2NO_3S_2^+$ (*m/z*): calc. 380.1245; found: 380.1306. The enantiomeric ratio was determined by **HPLC** analysis using Daicel Chiralcel IA column: *i*PrOH: *n*Hexane = 17:83, flow rate 0.7 mL/min, λ = 254 nm. τ_1 = 19.70 min, τ_2 = 21.35 min.

5.4.4. Synthesis of Vinyl Aziridines

*The general procedure for aziridination of 2,4-dien-1-ols as well as the full characterization data of vinyl aziridines **226**, **230** and **231** was already described in the experimental part of the third chapter of this thesis.*

5.4.5. SYNTHESIS OF *N*-AMIDOTHIOETHERS

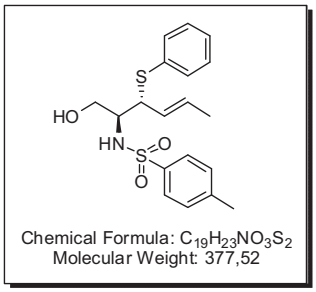
General procedure for the preparation of racemic products:

A 10 ml Schlenk containing the crude vinyl aziridine (0.1 mmol) was flushed three times with argon. Anhydrous *tert*-butylmethylether (4ml) was added. Next, diphenyl phosphoric acid (0.01 mmol, 10 mol%) and the corresponding nucleophile (0.1 mmol) were added at -78ºC. The reaction was monitored by ^{1}H-NMR. Saturated aqueous $NaHCO_3$ was then added to quench the reaction mixture, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried, and after evaporation, the enantiomeric excess of the product was determined directly, without prior purification.

General procedure for the asymmetric ring opening reaction of vinyl aziridines promoted by chiral Brønsted BINOL-derived phosphoric acids:

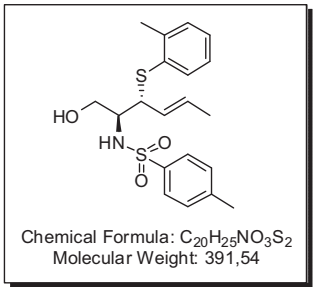
A 10 ml Schlenk containing the crude vinyl aziridine (0.1 mmol) was flushed three times with argon and then anhydrous *tert*-buthyl methyl ether (4ml) was added. Next, the chiral Brønsted phosphoric acid (0.01 mmol, 10 mol%) and the corresponding nucleophile (0.1 mmol) were added at –78 ºC. The reaction was monitored by ^{1}H-NMR. Saturated aqueous $NaHCO_3$ was then added to quench the reaction mixture, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried and evaporated under vacuum. The product was isolated by silica gel chromatography using hexanes/ethyl acetate as the eluent, and analyzed by HPLC on a chiral stationary phase.

(*E*)-*N*-Tosyl-2-amino-3-phenylthio-hexa-4-en-1-ol (347):



After column chromatography: hexanes/AcOEt: 9:1 to 7:3, 20.2 mg of **347** was obtained in 53% yield. **^{1}H NMR** (400MHz, $CDCl_3$): δ in ppm 7.89 (d, 2H, J = 8.4 Hz), 7.84 (d, 2H, J = 8 Hz), 7.38 (d, 2H, J = 8.4 Hz), 7.29 (m, 3H), 5.43 (dq, 1H, J = 15.2, 6.8 Hz), 5.26 (d, 1H, J = 7.2 Hz), 5.14 (ddq, 1H, J = 15.2, 9.6, 1.6 Hz), 5.07 (s, 1H), 3.89 (dd, 1H, J = 11.8, 5.2 Hz), 3.78 (dd, 1H, J = 11.6, 4 Hz), 3.64 (dd, 1H, J = 9, 6 Hz), 3.47 (m, 1H), 2.42 (s, 3H), 1.62 (dd, 3H, J = 6.6, 1.6 Hz). **^{13}C NMR** (100,6 MHz, $CDCl_3$): δ in ppm 143.9, 143.7, 137.1, 133.6, 132.8, 130.4, 130.1, 129.9, 129.0, 127.7, 127.4, 127.4, 126.6, 62.9, 58.1, 53.2, 53.8, 21.8, 21.7, 17.9. **ESI-TOF MS** for $[M+H]^+$ $C_{19}H_{24}NO_3S_2^+$ (*m/z*): calc. 378.119; found: 378.1263. The enantiomeric ratio was determined by **HPLC** analysis using Daicel Chiralcel IA column: *i*PrOH: *n*Hexane = 17:83, flow rate 0.7 mL/min, λ = 254 nm. τ_1 = 19.70 min, τ_2 = 21.35 min.

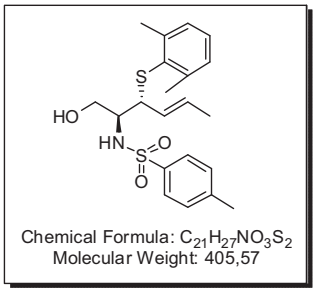
(*E*)-*N*-Tosyl-2-amino-3-(2-methylphenylthio)-2-hexa-4-en-1-ol (350):



After column chromatography: hexanes/AcOEt: 9:1 to 7:3, 23.8 mg of **350** was obtained in 62% yield. **^{1}H NMR** (400MHz, $CDCl_3$): δ in ppm 7.73 (d, 2H, J = 8.4 Hz), 7.25 (d, 2H, J = 10 Hz), 7.13 (d, 2H, J = 5.6 Hz), 7.03 (d, 2H, J = 5.6 Hz), 7.30 (ddd, 1H, J = 20.4, 12.8, 6.4 Hz), 7.07 (ddq, 1H, J = 14.8, 9.2, 1.6 Hz), 5.01 (d, 1H, J = 7.2 Hz), 3.85 (dd, 1H, J = 11.2, 11.2 Hz), 3.71 (dd, 1H, J = 11.6, 4.4 Hz), 3.54 (dd, 1H, J = 8.8, 6 Hz), 3.44-3.39 (m, 1H), 2.40 (s, 3H), 2.27 (s, 3H), 1.53 (dd, 3H, J = 6.4, 1.6 Hz). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ in ppm 143.9, 143.7, 139.4,

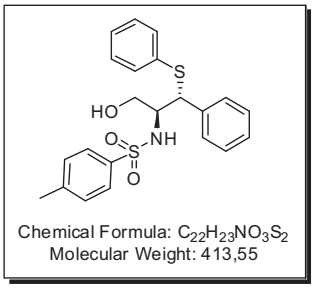
137.3, 133.8, 132.9, 130.4, 130.2, 129.9, 129.1, 127.7, 127.6, 127.5, 127.1, 126.7, 63.0, 58.3, 53.8, 21.8, 18.0. **ESI-TOF MS** for $[M+H]^+$ $C_{20}H_{26}NO_3S_2^+$ (*m/z*): calc. 392.1276; found: 392.1343. The enantiomeric ratio was determined by **HPLC** analysis using Daicel Chiralcel IA column: *i*PrOH: *n*Hexane = 17:83, flow rate 0.7 mL/min, λ = 254 nm. τ_1 = 15.64 min, τ_2 = 17.79 min.

(*E*)-*N*-Tosyl-2-amino-3-(2,6-dimethylphenylthio)-hexa-4-en-1-ol (351):



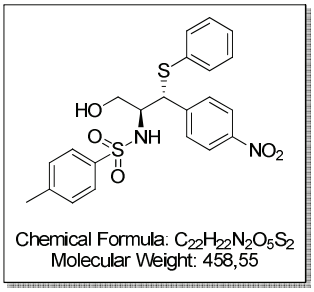
After column chromatography: hexanes/AcOEt: 9:1 to 7:3, 24.7 mg of **351** was obtained in 61% yield. **^{1}H NMR** (400MHz, $CDCl_3$): δ in ppm 7.75 (d, 2H, J = 6.4 Hz), 7.30 (d, 2H, J = 8.4 Hz), 7.09-7.01 (m, 3H), 7.05 (d, 2H, J = 6.8 Hz), 4.90 (ddq, 1H, J = 13.6, 9.6, 1.2 Hz), 4.81 (ddd, 1H, J = 19.2, 12.4, 6 Hz), 3.90 (dd, 1H, J = 11.6, 4.8 Hz), 3.75 (dd, 1H, J = 11.6, 3.6 Hz), 3.42-3.36 (m, 1H), 3.34 (dd, 1H, J = 9.2, 7.2 Hz), 2.42 (s, 3H), 2.35 (s, 6H), 1.35 (dd, 3H, J = 6, 1.6 Hz). **^{13}C NMR** (100,6 MHz, $CDCl_3$): δ in ppm 143.9, 143.8, 137.1, 131.4, 129.9, 129.2, 128.8, 128.3, 127.5, 127.3, 63.0, 58.5, 53.8, 22.3, 21.8, 17.7. **ESI-TOF MS** for $[M+NH_4]^+$ $C_{21}H_{31}N_2O_3S_2^+$ (*m/z*): calc. 423.1776; found: 423.1735. The enantiomeric ratio was determined by **HPLC** analysis using Daicel Chiralcel IA column: *i*PrOH: *n*Hexane = 17:83, flow rate 0.7 mL/min, λ = 254 nm. τ_1 = 15.83 min, τ_2 = 18.04 min.

(*E*)-*N*-Tosyl-2-amino-3-phenyl-3-(phenylthio)-propan-1-ol (352):



After column chromatography: hexanes/AcOEt: 9:1 to 7:3, 23.5 mg of **352** was obtained in 57% yield. **^{1}H NMR** (400MHz, $CDCl_3$): δ in ppm 7.91-7.80 (m, 5H), 7.39-7.29 (m, 4H), 5.27 (d, 1H, J = 9.1 Hz), 4.31 (d, 1H, J = 8.5 Hz), 4.16 (ddd, 1H, J = 18.8, 14, 8.5 Hz), 4.12 (dd, 1H, 9.2, 3.4 Hz), 2.43 (s, 3H). **^{13}C NMR** (100,6 MHz, $CDCl_3$): δ in ppm 144.1, 143.2, 139.7, 133.1, 130.6, 129.8, 129.2, 128.6, 128.5, 128.3, 127.2, 125.4, 122.1, 62.3, 59.1, 54.8, 27.8, 22.7. **ESI-TOF MS** for $[M+H]^+$ $C_{22}H_{24}NO_3S_2^+$ (*m/z*): calc. 414.1119; found: 414.0312. The enantiomeric ratio was determined by **HPLC** analysis using Daicel Chiralcel IA column: *i*PrOH: *n*Hexane = 20.11, flow rate 0.7 mL/min, λ = 254 nm. τ_1 = 18.98 min, τ_2 = 28.88 min.

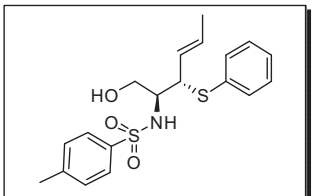
(*E*)-*N*-Tosyl-2-amino-3-(4-Nitrophenyl)-3-(phenylthio)–propan1-ol (353):



After column chromatography: hexanes/AcOEt: 9:1 to 7:3, 27.9 mg of **353** was obtained in 61% yield. **^{1}H NMR** (400 MHz, $CDCl_3$): δ in ppm 7.8-7.78 (m, 4H), 7.29-7.25 (m, 4H), 5.33 (d, 1H, J = 9.2 Hz), 4.35 (d, 1H, J = 8.4 Hz), 4.16 (ddd, 1H, J = 18.8, 14, 8.4 Hz), 4.09 (dd, 1H, 9.2, 3.6 Hz), 2.43 (s, 3H). **^{13}C NMR** (100,6 MHz, $CDCl_3$): δ in ppm 146.9, 143.8, 139.2, 132.8, 130.1, 129.9,129.7, 129.4, 129.5, 128.3, 127.1, 126.6, 123.6, 63.3, 59.0, 54.8, 29.9, 21.7. **ESI-TOF MS** for $[M+H]^+$ $C_{22}H_{23}N_2O_5S_2^+$ (*m/z*): calc. 459.0970; found: 459.1031. The enantiomeric ratio was determined by **HPLC** analysis using Daicel Chiralcel IA column:

*i*PrOH: *n*Hexane = 17:83, flow rate 0.7 mL/min, λ = 254 nm. τ_1 = 15.33 min, τ_2 = 28.88 min.

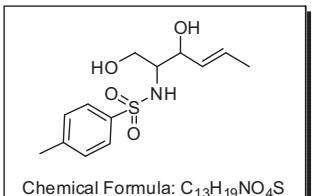
(*E*)-*N*-Tosyl-2-amino-3-(phenylthio)-hexa-4-en-1-ol (354):



Chemical Formula: $C_{19}H_{23}NO_3S_2$
Molecular Weight: 377,52

After column chromatography: hexanes/AcOEt: 9:1 to 7:3, 21.1 mg of **354** was obtained in 56% yield. **^{1}H NMR** (400 MHz, $CDCl_3$): δ in ppm 7.88 (d, 2H, J = 8.4 Hz), 7.79 (d, 2H, J = 8.4 Hz), 7.23 (d, 2H, J = 8.4 Hz), 7.10 (m, 3H), 5.28 (dq, 1H, J = 15.6, 6.8 Hz), 5.01 (m, 1H), 4.8 (s, 1H), 3.75 (dd, 1H, J = 12, 5.2 Hz), 3.63 (m, 1H), 3.50 (dd, 1H, J = 8.8, 6.4 Hz), 3.37 (m, 1H), 2.34 (s, 3H), 1.48 (dd, 3H, J = 6.4, 1.2 Hz). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ in ppm 143.9, 137.1, 132.8, 130.5, 129.0, 127.7, 126.6, 63.0, 58.2, 53.9, 21.7, 17.9. **ESI-TOF MS** for $[M+H]^+$ $C_{19}H_{24}NO_3S_2^+$ (*m/z*): calc. 378.1119; found: 378.1731. The enantiomeric ratio was determined by **HPLC** analysis using Daicel Chiralcel IA column: *i*PrOH: *n*Hexane = 17:83, flow rate 0.7 mL/min, λ = 254 nm. τ_1 = 14.13 min, τ_2 = 26.97 min.

(*E*)-*N*-Tosyl-2-amino-hex-4-en-1,3-diol (361):

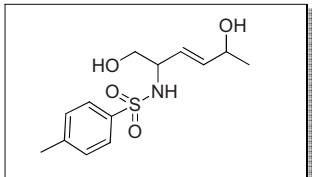


Chemical Formula: $C_{13}H_{19}NO_4S$
Molecular Weight: 285,35

A 10 ml Schlenk containing the crude vinyl aziridine **218** (0.1 mmol) was flushed three times with argon and then *tert*-buthyl methyl ether (1ml) was added. Next, saturated aqueous $NaHCO_3$ solution (4 ml) was added at –78 ºC. After 15 minutes the resulting mixture was dried over $MgSO_4$ and washed with EtOAc. The resulting solution was evaporated under vacuum and directly purified. After column chromatography: hexanes/AcOEt: 2:8 to 7:3, 3.4 mg of **361** was obtained in 12% yield. **^{1}H NMR** (400 MHz, $CDCl_3$): δ in

ppm 7.77 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.4 Hz, 2H), 5.72 (dt, *J* = 21.7, 6.5 Hz, 1H), 5.41 – 5.30 (m, 2H), 4.17 (s, 1H), 3.84 (dd, *J* = 11.5, 3.4 Hz, 1H), 3.50 (d, *J* = 8.2 Hz, 1H), 3.18 (td, *J* = 7.6, 3.7 Hz, 1H), 2.43 (s, 3H), 1.67 (d, *J* = 6.4 Hz, 3H). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ in ppm 144.06, 137.28, 130.02, 129.68, 129.66, 127.31, 77.55, 77.23, 76.91, 74.79, 62.22, 57.96, 21.84, 18.06. **ESI-TOF MS** for $[M+H]^+$ $C_{13}H_{20}NO_4S^+$ (*m/z*): calc. 286.1113; found: 286.1124.

(*E*)-*N*-Tosyl-2-amino-hex-3-en-1,5-diol (360):



The reaction was done in an NMR tube containing a solution of the crude vinyl aziridine **218** (0.1 mmol) and (*S*)-**333** (0.01 mmol) in deuterated dichloromethane (0.7 ml) at –78 ºC. The reaction was monitored by ^{1}H-NMR until full conversion. Characterization data was extracted from the reaction mixture. **^{1}H NMR** (400 MHz, $CDCl_3$): δ in ppm 7.78 – 7.68 (m, 2H), 7.27 (d, *J* = 6.5 Hz, 2H), 5.62 (d, *J* = 5.5 Hz, 1H), 5.57 – 5.33 (m, 2H), 4.12 (dt, *J* = 11.2, 5.7 Hz, 1H), 3.81 (d, *J* = 15.8 Hz, 1H), 3.64 – 3.46 (m, 2H), 2.40 (s, 1H), 1.06 (dd, *J* = 10.1, 6.4 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ in ppm 138.06, 129.74, 127.32, 126.28, 67.82, 65.36, 57.12, 29.71, 23.14, 21.77. **ESI-TOF MS** for $[M+H]^+$ $C_{13}H_{20}NO_4S^+$ (*m/z*): calc. 286.1113; found: 286.1123.

5.5. REFERENCES

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CHAPTER 6

GENERAL CONCLUSIONS

A general study of the reactivity of a series of hydroxymethyl vinyl aziridines has been carried out under different conditions (bases, NHC, halides, etc.). Particular conclusions of this study are the following:

- The treatment of vinyl aziridinol **218** with I^{t}Bu (1 equiv.) in THF at room temperature provides the oxazine **236** in 10% isolated yield. This compound **236** presents a new carbon center (C7) and a new tosylamino moiety. The reaction competes with the oxetane formation although the selectivity towards the oxazine formation can be improved.
- The new carbon C7 in **236** originates from dichloromethane, and the new *NTs* from tosyl amine.
- In the formation of **236**, the *N*-heterocyclic carbene (I^{t}Bu) only acted as a base activating tosylamine which then reacts with dichlorometane providing *N*-chloromethyl-tosyl amide **241** responsible for the formation of the oxazine.
- In parallel, NHC also reacts with dichloromethane affording an imidazolium chloride which is responsible for the oxetane formation.

Based in this last discovery, an alternative methodology for the synthesis of vinyl oxetanes was developed. This new procedure was found to proceed through a *one-pot* conversion of vinyl aziridinols to vinyl oxetanes through a consecutive ring-opening/ring-closing reaction promoted-catalyzed by a simple *chloride anion*. From this study the following particular conclusions can be extracted:

- The reaction evolves through a set of consecutive reactions in a one-pot procedure: a) nucleophilic selective aziridine ring cleavage promoted by a simple chloride source, b) proton transfer with

concomitant formation of the alkoxide and c) intramolecular ring closing to form the vinyl oxetane.

- Good yields were achieved for *cis*- and *trans*-aziridinols, trisubstituted vinyl aziridinols and aryl aziridinols.
- The reaction is totally regioselective since over all the possible competing ring-opening/ring closing reactions, only the formation of vinyl oxetanes was observed.
- The reaction is completely stereoselective, since *cis*-vinyl oxetanes led to the *cis*-disubstituted vinyl oxetane rings, and vinyl *trans*-aziridinols led to the *trans*-disubstituted vinyl oxetanes rings.

A study of the enantioselective Brønsted-acid catalyzed desymmetrization of *meso*-aziridines promoted by oxygen-nucleophiles to afford aminoalcohol derivatives has been carried out. From this study the following particular conclusions can be extracted:

- (*S*)-TRIP-phosphoric acid is an excellent catalyst in this reaction and affords high enantioselectivity.
- The benzoic acid to aziridine ratio affects the conversion of the reaction (catalyst degradation).
- A range of *meso*-aziridines protected with *N*-benzoyl groups were applied in their asymmetric desymmetrization and excellent conversions (up to 98%) and enantioselectivities (87 to 99% *ee*) were obtained.

A similar study using chiral Brønsted-acids was performed in the catalyzed kinetic resolution of racemic terminal aziridines promoted by oxygen nucleophiles. From this study the following conclusions can be extracted:

- (*S*)-TRIP-phosphoric acid is also the catalyst of choice for this reaction yielding high enantioselectivities.
- The ring-cleavage of the terminal aziridine was totally regioselective to the corresponding 2-substituted product.
- The benzoic acid to aziridine ratio affects the conversion of the reaction (catalyst degradation).
- Terminal aziridines protected with *N*-benzoyl groups were applied as substrates in this kinetic resolution and good to excelent selectivities were obtained, recovering the terminal aziridine and the corresponding opened products (β-amidoesthers) with good enantioselectivities.
- The nature of the *N*-benzoyl protecting group as well as the steric hindrance of the C-2 substituents of the terminal aziridine affect the selectivity (*S*) of the kinetic resolution process.

The study of the kinetic resolution of hydroxymethyl-vinyl aziridines by chiral Brønsted BINOL-derived phosphoric acids using thiols as nucleophiles was also carried out. The following conclusions can be extracted:

- The chiral Brønsted BINOL-derived phosphoric acids (*S*)-**333**-**338** were applied in the asymmetric ring-opening reaction of vinyl aziridine **218** using thiophenol as nucleophile. Yields are in agreement with a kinetic resolution. The best selectivity was obtained using the less sterically hindered non-substituted catalyst (*S*)**-333** (90:10 er).

- The nucleophiles **348** and **349** were also tested in the asymmetric ring-opening reaction of vinyl aziridine **218** using various chiral Brønsted phosphoric acids (*S*)-**334**-**337** as catalysts. Variations of the level of enantiodiscrimination were observed, with the less sterically hindered catalyst (*S*)-**333** and the more hindered nucleophile **349** constituting the most selective system.
- Several aziridines **230**, **231** and **226** were also tested in the asymmetric ring-opening reaction using thiophenol as nucleophile in the presence of (*S*)-**333** as catalysts. The structure of the substrate was found to not influence significantly the enantioselectivity of the process.

- The unreacted aziridine was not isolated due to an unexpected reaction with water during the basic work-up, affording the aminodiol derivative.

APPENDIX

PUBLICATIONS

M. R. Mónaco, M. Díaz de los Bernardos, B. List. **"Enantioselective Brønsted acid-catalyzed desymmetrization of *meso*-aziridines and kinetic resolution of terminal aziridines"** *Manuscript to be submitted.*

M. Díaz de los Bernardos, S. Castillón, P. W. M. N. van Leeuwen. **"Regio- and stereoselective synthesis of vinyl oxetanes from vinyl aziridines promoted by tetraalkylammonium halides"** *Manuscript to be submitted.*

CONGRESSES AND SCIENTIFIC MEETINGS

Díaz de los Bernardos, M.; Castillón, S.; van Leeuwen, W. N. M. P. **Formation of vinyl oxetanes catalyzed by chloride ammonium salts.** XXIV Reunión Bienal de Química Orgánica. Oral contribution. Donostia-San Sebastián, Spain, **2012**.

Díaz de los Bernardos, M.; Llaveria, J.; Beltrán, A.; Díaz-Requejo, M. M.; Matheu, M. I.; Castillón, S.; van Leeuwen, W. N. M. P.; Pérez, P. J. **Asymmetric aziridine ring-opening reaction promoted by chiral Bronsted phosphoric acids.** 17th European Symposium on Organic Chemistry. Poster contribution. Creete, Greece, **2011**.

Díaz de los Bernardos, M.; Llaveria, J.; Beltrán, A.; Díaz-Requejo, M. M.; Matheu, M. I.; Castillón, S.; van Leeuwen, W. N. M. P.; Pérez, P. J. **Asymmetric aziridine ring-opening reaction promoted by chiral**

Bronsted phosphoric acids. XXVIII Reunión Grupo Especializado en Química Organometálica. Poster contribution. Punta Umbría, Spain, **2010**.

Díaz de los Bernardos, M.; Castillón, S.; van Leeuwen, W. N. M. P. **New approaches for the synthesis of P-stereogenic phosphines.** VI Young research meeting. Societat Catalana de Química. Oral contribution. Valencia, Spain, **2010**.

2nd China Spain Bilateral Symposium on Catalysis. Institute of Chemical Research of Catalonia. Participation. Tarragona, Spain, **2010**.

ICIQ Summer School. Institute of Chemical Research of Catalonia. Participation. Tarragona, Spain, **2009**.

RESUMEN DE LA TESIS

Las aziridinas, compuestos heterocíclicos de tres miembros que presentan una funcionalidad amina, son intermedios sintéticos muy versátiles en química orgánica. Un buen número de moléculas biológicamente activas contienen en su estructura estos anillos heterocíclicos de tres miembros. En este contexto, la transformación selectiva de aziridinas en diversos aminoácidos, y otros heterociclos tales como β-lactamas, pirrolinas, piperidinas etc. ha generado un creciente interés en la comunidad científica. Actualmente, la organocatálisis es un área emergente en síntesis orgánica y puede definirse como una forma de catálisis en la que moléculas orgánicas actúan como catalizadores.

El presente trabajo tiene como objetivo desarrollar nuevas estrategias sintéticas en la transformación de aziridinas mediante catálisis selectiva basada en moléculas orgánicas, centrándose en desarrollar nuevas aplicaciones sintéticas para estos versátiles intermedios.