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Organometallics in Regio- and Enantio-Selective Synthesis: Structures and Reactivity

Gabriella Barozzino Consiglio

members of jury

Prof. Giovanni POLI (Rapporteur)	Université Pierre et Marie Curie (Paris VI)
Prof. Paolo VENTURELLO (Rapporteur)	Università di Torino
Prof. Annie-Claude GAUMONT (Examiner)	Université de Caen
Prof. Vito CAPRIATI (Examiner)	Università di Bari
Prof. Hassan OULYADI (Directeur de Thèse à Rouen)	Université de Rouen
Dr. Alessandro MORDINI (Direttore di Tesi a Firenze)	Università di Firenze

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ABBREVIATIONS AND ACRONYMS

a.a.	amino acid
3-AP	3-aminopyrrolidine
3-APLi	lithium 3-aminopyrrolidide
AcOEt	ethyl acetate
aq	aqueous
Bn	benzyl
Boc	*tert*-butoxycarbonyl
$(Boc)_2O$	di-*tert*-butyl dicarbonate
Cp	cyclopropyl
Cy	cyclohexyl
Bu	*n*-butyl
^{t}Bu	*tert*-butyl
BuLi	*n*-butyllithium
Bus	*tert*-butylsulfonyl
D	diffusion coefficient
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DEE	diethyl ether
DEPC	diethylcyano-phosphonate
DEPT	diethylcyanophosphonate
(+)-L-DET	(+)-diethyl L-tartrate
(−)-D-DET	(−)-diethyl D-tartrate
DIBAL-H	di-*iso*-butylaluminium hydride
DIPEA	di-*iso*-propylethylamine
DIPA	di-*iso*-propylamine
(+)-L-DIPT	(+)-di-*iso*-propyl L-tartrate
(−)-D-DIPT	(−)-di-*iso*-propyl D-tartrate
DMAP	*N*,*N*-4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
dppp	1,3-bis(diphenylphosphino)propane
DMPU	*N*,*N′*-dimethylpropyldeneurea
e.e.	enantiomeric excess
eq	equation
equiv	equivalent
FW	formula weight
h	hour(s)
HMPA	hexamethylphosphoramide
HSAB	Hard and Soft Acids and Bases
KO^{t}Bu	potassium *tert*-butoxide

LDA	lithium di-*iso*-propylamide
LICKOR	*n*-butyllithium / potassium *tert*-butoxide
LIKNAOR	*n*-butyllithium / sodium *tert*-butoxide
LIDAKOR	lithium di-*iso*-propylamide / potassium *tert*-butoxide
MeLi	methyllithium
m-CPBA	*meta*-chloroperbenzoic acid
MOM	methoxymethyl
Ms	methanesulfonyl
m/z	mass/charge
MW	microwave
NaHMDS	sodium bis(trimethylsilyl)amide
NMM	*N*-methyl morpholine
NMDO	Modified Neglect Diatomic Overlap
(*S*)-(+)-MTPCl	(*S*)-(+)-α-methoxy-α-trifluoromethylphenylacetyl chloride
$Pd_2(dba)_3$	tris(dibenzylideneacetone)dipalladium
PMDTA	*N*,*N*,*N′*,*N′*,*N″*-pentamethyldiethylenetriamine
PPTS	pyridinium *para*-toluene sulfonate
Py	pyridine
REDAL-H	sodium bis(2-methoxyethoxy(aluminum hydride))
S	solvent
SAE	Sharpless asymmetric epoxidation
SKR	Sharpless kinetic resolution
solv.	solvation
r.t.	room temperature
TBAF	*N*,*N*,*N*,*N*-tetra-*n*-butylammonium fluorine
TBDMSCl	*tert*-butylchlorodimethylsilane
TBDMSOTf	*tert*-butyldimethylsilyl trifluoromethane sulfonate
TBDPSCl	*tert*-butylchlorodiphenylsilane
TBHP	*tert*-butyl hydroperoxide
TEA	*N*,*N*,*N*-triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMEDA	*N*,*N*,*N′*,*N′*-tetramethylethylenediamine
Ts	*para*-toluensulfonyl
v	volume
w	weight

NMR abbreviations

COSY	COrrelation SpectroscopY
DOSY	Diffusion Ordered SpectroscopY
EXSY	Exchange SpectroscopY
HMBC	Heteronuclear Multiple Bond Correlation
HMQC	Heteronuclear Multiple Quantum Correlation
HOESY	Heteronuclear Overhauser Enhancement SpectroscopY
NMR	Nuclear Magnetic Resonance
NOE	nuclear Overhauser effect
NOESY	Nuclear Overhauser Enhancement SpectroscopY
PGSE	Pulse Gradient Spin-Echo

ABSTRACTS

Résumé

Ce travail présente deux études en chimie organométallique (organolithiens).

Dans le premier chapitre, des réactions d'isomérisation réalisées en présence de superbases bimétalliques sont impliquées, et la transformation d'aziridines fonctionnalisées est examinée. Deux voies sont possibles: la β-élimination ou la cyclisation 4-*exo* intracyclique. Le processus réactionnel étant accompagné de la formation de centre(s) stéréogène(s), une approche asymétrique est explorée avec 3-APLi's.

Le deuxième chapitre s'intéresse à l'étude structurale de phosphines (boranes) lithiées dans le but d'aborder la synthése énantiosélective d'alkylphosphines P-stéréogéniques. Ce travail de thèse a permis d'examiner la structure en solution d'une phosphine borane lithiée modèle ($Ph_2P(BH_3)Li$) en solution par spectroscopie RMN multinoyaux (^{1}H,^{6}Li, ^{13}C, ^{11}B, ^{31}P). L'affinité du phosphure avec le BuLi puis la LDA a ensuite été examinée.

Riassunto

Questo lavoro di tesi è stato focalizzato su due tematiche correlate alla chimica degli organometalli (ed in particolare degli organolitio derivati).

Nella prima parte sono state studiate le reazioni di isomerizzazione in presenza di superbasi bimetalliche ed è stata esaminata la reattività di aziridine funzionalizzate. Due meccanismi sono possibili: la β-eliminazione e la ciclizzazione 4-*exo* intramolecolare. Dato che la reazione è accompagnata dalla formazione di uno o più centri stereogenici, è stata anche studiata una versione asimmetrica.

La seconda parte descrive uno studio di fosfine-borani litiati. Questo lavoro è parte di un programma consistente nella sintesi di alchilfosfine P-stereogeniche enantioarricchite. Il nostro contributo consiste nella determinazione della struttura di una litio fosfide-borano ($Ph_2P(BH_3)Li$) grazie alla tecnica di analisi NMR multinucleare (^{1}H,^{6}Li, ^{13}C, ^{11}B, ^{31}P). E' stata anche analizzata l'affinità della lithio fosfide per il BuLi e poi per l'LDA.

Abstract

This work focuses on two studies related to organometallic chemistry (organolithiums).

In the first chapter, isomerisation reactions are conducted in the presence of bimetallic superbases and the evolution of functionalized aziridines is examined. Two issues are possible for this transformation: the β-elimination or the 4-*exo* intracyclic cyclisation. Because the reaction leads to the formation of stereogenic center(s), an asymmetric version is also studied with 3-APLi's.

Abstract

The second chapter describes a structural study of lithiated phosphine-boranes. This work is part of a program consisting in the enantioselective synthesis of P-stereogenic alkylphosphines. Our contribution consists in the determination of the structure of a model lithiated phosphine-borane ($Ph_2P(BH_3)Li$) thanks to the multinuclear (^{1}H,^{6}Li, ^{13}C, ^{11}B, ^{31}P) NMR technique. The affinity for the phosphide to BuLi then LDA has also been examined.

1. GENERAL INTRODUCTION

1.1. Introduction

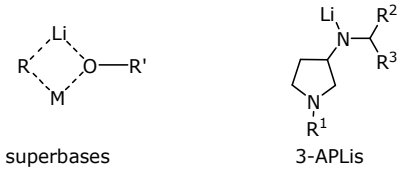
The development of new methodologies for the construction of novel compounds plays a crucial role in the field of synthetic chemistry. In this perspective the chemistry of organometallic compounds represents an important part. In fact their transformations, being highly chemio-, regio- and stereo-selective, are particularly useful for the synthesis of strategic and complex molecular structures and for this reason a great interest have been devoted towards their possible applications in many crucial scientific fields. In this framework the chemistry of organolithium compounds is assuming an important role, due to their high reactivity combined with a good selectivity. A great number of reactions is now possible with organolithium compounds, and the progress on the development of new methods for their regioselective synthesis has replaced their image of indiscriminate high reactivity with that of a controllable and subtle selectivity. So nowadays organolithium chemistry plays a central role in the selective construction of C-C bonds in both simple and complex molecules.[1] Indeed, their employment goes from directed metalation,[1, 2] reductive lithiation[1] and organolithium cyclization reactions[1, 3] to asymmetric inductions with the aid of ligands such as (−)-sparteine.[1, 4] But they are an important tool for the formation of C-N and C-P bonds too.[3] In these last years, indeed, the importance and prevalence of nitrogen-containing compounds in natural products and in medicinal drugs and that of phosphorous-containing compounds in catalysis has led to develop a new chemistry for their formation which engaged organolithium compounds.[5]

Theoretical studies have also played an important role in the development of these processes. Several reviews have appeared on the contribution of theoretical methods in organolithium chemistry.[6, 7] In addition Nuclear Magnetic Resonance Spectroscopy (NMR) and other spectroscopic techniques have been widely used in particular, a variety of high-resolution NMR techniques has been used in structural research in the field of organolithium compounds. Isotope shifts as well as homo- and heteronuclear shift correlations and nuclear Overhauser spectroscopy (NOE) provide detailed information about the aggregation behaviour of lithiated compounds.[8] In particular, techniques which utilize the nuclides ^{6}Li and ^{7}Li yield valuable insights into the course of lithiation reactions, aggregate formation and dynamics.

This thesis deals in general with some aspects of structural analysis and synthetical applications of organolithium compounds, lithium amides and lithium phosphides.

1.2. Aim of the project

This PhD's project was born in collaboration between the University of Florence, under the Dr. Alessandro Mordini's supervision, and the University of Rouen, under the direction of Prof. Hassan Oulyadi and Dr. Jacques Maddaluno. In this thesis the goal is finalized to the exploration of new reactivity of organolithium compounds, such as mixed organometallic bases, called superbases[11-14] or "Schlosser's bases" too, and chiral lithium amides derived from 3-aminopyrrolidines (3-APs)[15-20] (Figure 1), as well as to the study of lithium phosphides in solution.



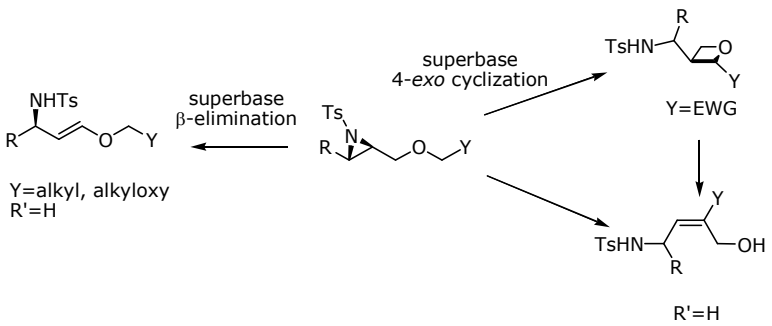
superbases 3-APLis

Figure 1

The superbases have been the subject of study since many years in the Florence's research group, while the 3-APLi's have been employed as chiral ligands for organolithium compounds since at least fifteen years in Rouen.

The study of lithium phosphide structures, on the contrary, is more recent and originated from the idea to continue the trend already started with lithium amides (3-APLi) in the group located in Rouen (Dr. J. Maddaluno) to extend the knowledge on these reactives which are not well explored yet.

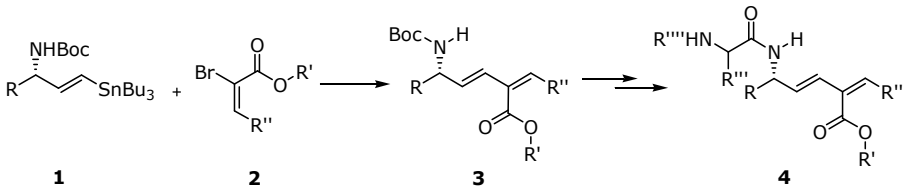
The first part of this manuscript is focused on the description of the application of superbases to strained heterocycles isomerizations. At the beginning a brief summary on the previous results obtained into the Florence's research group about both epoxides and aziridines will be reported,[21-23] followed by a new detailed study regarding the superbases-mediated *β*-eliminations or 4-*exo* cyclizations of aziridinyl ethers (Scheme 1).



Scheme 1

Then, a completely new approach is described, devoted to investigate the possibility of selectively promoting the isomerizations of epoxides or aziridines by means of irradiation by microwaves (MWs). The aim of such study is to find a new way, alternative to superbase, to activate organolithium reagents in metalation induced processes.

The use of microwaves irradiation for activating chemical processes is a focus of interest in the group in Florence, where this work was carried out, and in this thesis has been also applied to other reactions, such as the Stille Coupling.[24-29] In particular this process has been used in the synthesis of peptidomimetics through Pd(0) catalysed coupling reactions between vinyl stannanes **1**, derived from amino acids, and bromoacrylates **2**.[30] The products **3**, then, can be further elaborated to give dipeptides **4**, useful from a biological point of view (Scheme 2).



1 **2** **3** **4**

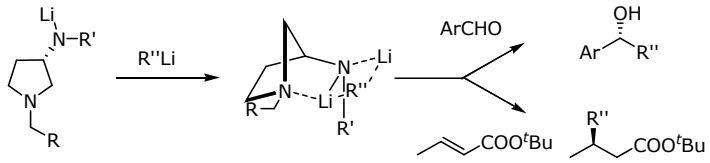
Scheme 2

With the collaboration of Dr. Gianna Reginato a series of Stille Coupling reactions with a wide range of vinyl stannanes have been studied, making use of MWs irradiation.

The common feature of this part of work is MW activation and amino acids elaboration.

Finally the enantiomeric version of the epoxides and aziridines rearrangements by using chiral lithium amide 3-APs as bases or chiral superbases is presented. Such project, due to the collaboration between the Florence and the Rouen groups, was planned in order to verify if lithium amides derived from 3-APs, already largely used as ligands of organolithium compounds,[15-20] could also be exploited as chiral bases.

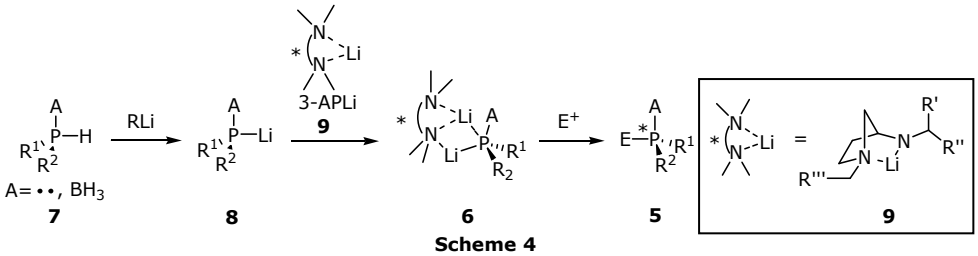
The Rouen's research group has developed a large set of chiral 3-aminopyrrolidines[31] and their corresponding lithium amides in combination with alkyllithium species (*n*-butyllithium and methyllithium mainly), have been tested in the enantioselective 1,2- and 1,4-nucleophilic additions to aromatic aldehydes and *α*,*β*-unsaturated esters respectively (Scheme 3).[16-18, 31]



Scheme 3

Besides, NMR characterizations and computational interpretations have been simultaneously and complementarily conducted to understand the stereo-selection observed.[20, 31]

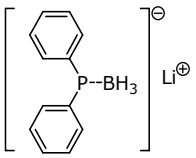
The second part of this PhD thesis is devoted to a NMR study of lithium phosphides in THF-d_8 solution. The project was realized thank to an interregional collaboration, called CRUNCH, between the University of Rouen and the University of Caen. The main objective was the synthesis of new chiral alkyl phosphines **5** bearing a stereogenic phosphorous atom which are obtained through an alkylation reaction of a chiral lithiated phospha-anion **6** (obtained by deprotonation of secondary phosphines **7** with alkyllithium compounds associated to chiral lithium amides **9**, derived from 3-aminopyrrolidines, as chiral ligands) and an achiral electrophile (Scheme 4).



Scheme 4

This project was simultaneously followed by a complementary structural investigation of lithium phosphide borane adducts **8** (A=BH_3). In fact, despite their wide use as reagents, lithium phosphide structures **8** in solution are not well known yet. The results presented in this thesis represent only a first step towards the above objective and mainly correspond to a theoretical and NMR structural study.

In this part of the thesis, an introductive excursus on the already known enantioselective P-C coupling reactions is first reported, followed by our results in the field. The larger part is dedicated to the study of lithium diphenylphosphide borane structure **10**-Li (Figure 2) in THF solution by a series of one- and two-dimensional multinuclear NMR experiments.



10-Li

Figure 2

This investigation has required six-labeled BuLi and six-labeled LDA, as bases, and THF-d_8 as solvent. At the end of this second section, some synthetic applications of these NMR studies are showed; in particular reductions of carbonyl compounds into alcohols with lithium phosphides have been extensively studied and the obtained results are presented here.

1.3. Organolithium chemistry

The term "organolithium" refers formally to a compound characterized by the presence of a Li-C bond, but nowadays, this terminology has been extended to all organic skeletons containing a bond between a lithium atom and a more electronegative element as, for example, Li-N in lithium amides (RR'NLi), Li-O in lithium enolates (RC(=CR'R'')OLi) or in lithium alcoholates (ROLi), Li-P in lithium phosphides (R_3PLi), and so on. Typical opinion considers that the nature of Li-C bound in organolithium species is mainly covalent, even if a large ionic character is present.[6] According to the Pauling electronegative scale the C-Li bond presents a 43% value of ionic character.[32] This justifies features of organolithium compounds, such as the high solubility of some organolithium compounds in non-polar solvents. However the lithium atom can be also assimilated to a Li^+ ion with only two electrons in a 1s orbital.[33-35] This ionic aspect could explain in part the tendency of these reagents to form oligomeric structure in non-polar aprotic solvents. Hence the nature of lithium-carbon (or heteroatom) bond has been the subject of considerable studies in recent years.[6, 32]

1.3.1. Organolithium structures

According to the HSAB theory,[36] lithium has been defined like a "hard Lewis acid", because of its small size and low electronegativity (0.98, according to the "Pauling scale"[37]). For this reason this ion interacts strongly with "hard bases" such as OH^-, F^-, Cl^- ions or with "Lewis' bases", called ligands (L). In the case of neutral donors ligands (alcohols, amines or thiols, for example) the stability of the lithium complexes decreases according to the order OH> N> S.

The Li^+ coordination number in a complex is determined by the number of sites of the potential ligands around the lithium. These ligands are mainly anions (ion-ion interactions are present) or negative poles of a neutral compound or a solvent (in this case ion-dipole interactions exist). According to the literature[32] coordination number goes from 2 to 8 (or even more). The Li^+ properties permit a wide polyvalence of the coordination number and, therefore, a large variety of structures. Usually lithium adopts 4 coordination number, which confers a tetrahedral geometry[35, 38-41] to these structures, but numerous exceptions exist.[38]

The introduction of an element of chirality onto one ligand allows these complexes to be used in enantioselective reactions.

There are essentially two efficient ways to use organolithium compounds in enantioselective synthesis:

- through the coordination of a chiral complexing agent Y* (or a chiral aprotic solvent) on Li^+ (Figure 3);

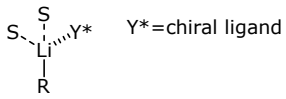


Figure 3

- through the interaction between an organolithium compound (RLi) and a second chiral organolithium species (Y*Li) by dipole-dipole interaction, which leads to homo-bimetallic complexes, called mixed-aggregates (Figure 4).

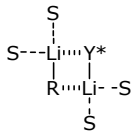


Figure 4

1.3.2. Organolithium aggregates

Lithium compounds are known to associate in solvents, in crystals and in gas phase. It is doubtful that the monomeric species can exist except under very unusual conditions. Experiments consisting of colligative measurements,[42-45] NMR investigations,[39-41, 46] X-ray crystal structure determinations,[47-49] mass spectroscopy determinations and other methods have shown that aggregation is typical of these compounds.

The simplest lithium compound that forms aggregates is LiH, but a wide number of organolithium compounds generate aggregates of the type $(RLi)_n$, in any state in which they are.

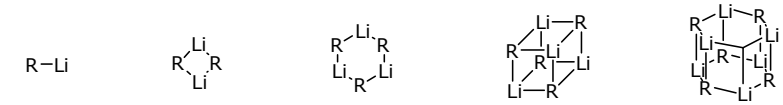


Figure 5

Classical observed arrangements are hexamers, tetramers, trimers or dimers (Figure 5). It is not obvious to predict in advance the aggregation state of a species in a specific experimental condition. However, some parameters can lead to understand the probable structure of an organolithium compound, such as the temperature, the concentration, the nature of the "R" substituent and the polarity of the solvent. For example, the increase of the size of the "R" group tends to decrease the aggregation state.[50] At the same time, the presence of coordinative "R" groups lead to encourage the formation of small aggregates.[51-53] The influence of the temperature on the aggregation state depends on the nature of the solvent. In fact, the reduction of the temperature leads to an increase of the aggregation in apolar solvents, while in polar ones, the lower aggregation is preferred. On the other side in similar conditions, the increase of the concentration moves the equilibriums towards the formation of more voluminous aggregates.[54]

Generally we can say that the aggregation state of an organolithium influences the reactivity of that specific compound.[51, 55, 56] However, it is very difficult to evaluate the real influence of the aggregation state on the regio-, chemio- and stereo-selectivity and on the reaction rate. Usually small aggregates tend to be more reactive,[57, 58] but this rule is not always applicable.[59]

Another parameter which has a great influence on the aggregation state and, hence, on the reactivity of organolithium compounds, is the solvation. In hydrocarbon solvents (pentane, hexane, toluene, ect) organolithium compounds form mainly large size aggregates (tetramers, hexamers, oligomers), while in coordinative solvents (DME or THF, for instance (Figure 6, the last two examples) the formation of solvated tetramers or dimers is more preferred.[60, 61] Moreover, the presence of complexing agents (for example, hexamethylphosphoramide (HMPA), *N*,*N*,*N′*,*N′*,*N″*-pentamethyldiethylenetriamine (PMDTA), (–)-sparteine, *N*,*N′*-dimethylpropyldeneurea (DMPU), *N*,*N*,*N′*,*N′*-tetra-methylethylenediamine (TMEDA), etc. (Figure 6, the first five examples)), leads to a further reduction of the aggregation state of organolithium compounds.

The monomeric species are only observed in presence of very strong coordinating ligands, that increase the anionic character of the organolithium and improve their basic and nucleophilic properties,[61-64] or in the case of very bulky anions.[65]

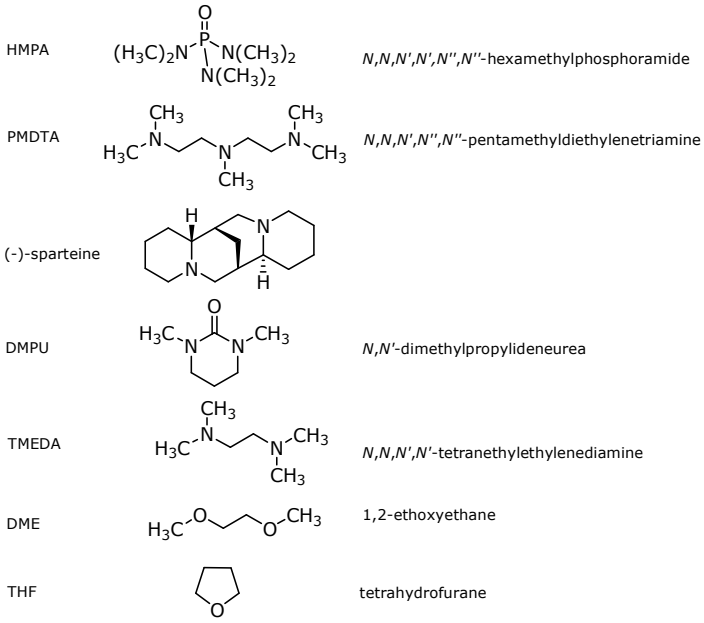


Figure 6

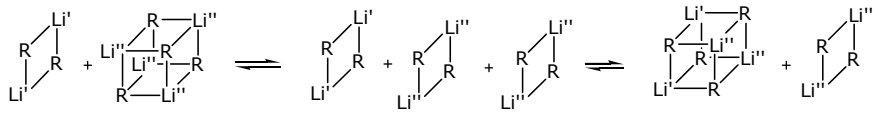
So an intimate relation among reactivity, solvation and aggregation of organolithium compounds exists.[59] However, this triptych is impossible to summarize in some simple rules; every system is different and other factors (such as temperature and concentration) can influence each others.

1.3.3. Dynamic of organolithium compounds

The organolithium compounds are very dynamic species; intra- and inter-molecular exchanges of lithium cores are present in solution. For this reason many works have been dedicated to the study of the dynamics of organolithiums, and in particular of the alkyllithium compounds.[39, 61, 66] The first who evidenced these exchanges between different aggregates was Brown in 1970.[67] From then on many publications have treated this topic.

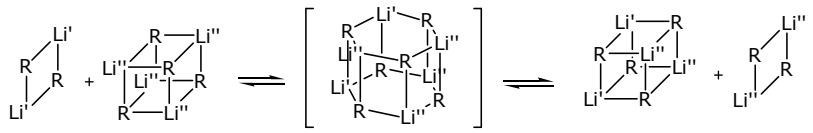
Several mechanisms of exchange have been discovered.

The first is a dissociative mechanism which involves a disintegration of tetramers into dimers and the following re-association of these dimeric aggregates to tetramers (Scheme 5).[67, 68]



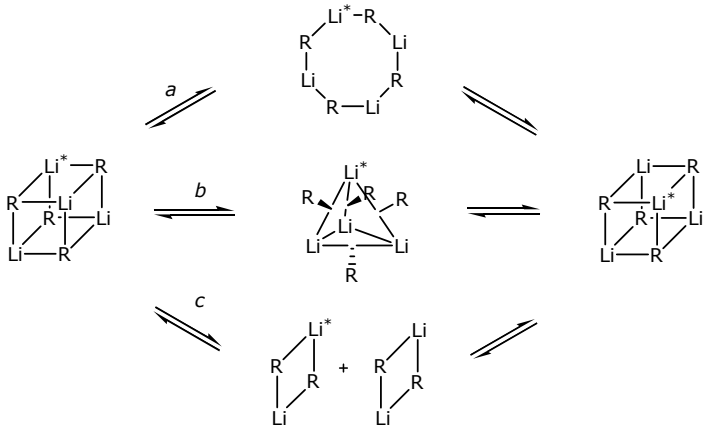
Scheme 5

The second one regards an associative mechanism according to which a dimer enters in collision with the face of a tetramer forming a new couple dimer-tetramer with an exameric structure, which evolves giving again a tetramer and a dimer (Scheme 6).[69, 70]



Scheme 6

Studies about intramolecular exchanges are based mainly on the influence of the temperature on ^{1}J(C-Li) coupling constant measurements in the alkyllithium compounds.[39, 41, 65, 69-79] Indeed aggregates undergo rapid intramolecular exchanges. At low temperatures they are minimized, however, when the temperature rises these exchanges increase too, averaging to zero the lithium-carbon coupling constant.[41, 80]



Scheme 7

Publications about intramolecular exchanges by the Brown's,[81] Schleyer's,[82] and Thomas's[80] research groups consider three mechanisms (scheme 6):
the first one is a rearrangement of the tetramer *via* an eight-member intermediated cycle (Scheme 7, *a* pathway); the second one is an exchange by concerted rotation of the alkylic groups (Scheme 7, *b* pathway); the third one is a mechanism which foresees the dissociation of the tetramer into two separated dimers and a rotation of these dimers before the recombination to tetramer (Scheme 7, *c* pathway), These three mechanisms are summarized in Scheme 7.

1.3.4. Analysis of organolithium compounds

The major part of the structures of organolithium compounds in the solid state has been determined by X-ray diffraction of mono-crystals.[35, 38, 83-85] However these structures are not always representative of the real species present in solution and, besides, it is very difficult to get pure mono-crystals because of the high reactivity of these species.

For all these reasons nowadays the Nuclear Magnetic Resonance (NMR) spectroscopy is the most used technique to study organolithium compounds. The great advantage of this method is represented by the possibility to analyze directly the species in solution, and hence to understand their reactivity in those conditions.

Although NMR spectroscopy of a lot of nuclides finds widespread applications due to the biological importance of certain metals, as alkaline and alkaline earth ones (sodium, magnesium and calcium are the most significant examples),[86-93] it suffers for the large quadrupole moments which lead to severe line broadening. Notable exceptions are beryllium, ^{9}Be, caesium, ^{133}Cs, and in particular the lithium isotopes, ^{6}Li and ^{7}Li, which can be successfully employed in various one- and two-dimensional NMR experiments. Especially ^{6}Li, which has got the smaller quadrupole moment of all stable nuclides with quantum number I>1/2, and which has been classified ludicrously as an *"honorary spin-1/2 nucleus"*,[94] is an important tool for the elucidation of structures and dynamics in lithiated carbon, nitrogen and phosphorous compounds.

In addition, the NMR technique permits to vary easily some parameters as the temperature, the concentration, or the nature of the solvent.

The first structural studies of organolithium compounds by ^{6}Li- and ^{7}Li- (in natural isotopic abundance) NMR spectroscopy go back to the pioneer works of the Brown's[81, 95-97] and Wehrli's[98, 99] groups. But the development of the ^{6}Li-NMR spectroscopy was realized by Fraenkel[73] and Seebach[74], which were the leaders in the grow up of organolithiums knowledge.[40, 100-103]

FIRST PART

2. BASE-PROMOTED REARRANGEMENT OF STRAINED HETEROCYCLES

The present part of the thesis reports work carried out in the field of base-induced rearrangements of strained heterocycles, like epoxides and aziridines.

The selective replacement of a hydrogen by a metal (metalation) in organic substrates has always been a challenge for chemists since the very beginning of organometallic chemistry. In particular, regio- and stereo-chemical issues are often difficult to address in metalation reactions. In this respect, superbases can be a very useful tool to be used not only to deprotonate substrates possessing low acidity, but also to overcome many regioselective problems. For example, they have been successfully employed in the isomerizations of epoxides[23, 104] and oxyranyl ethers[21, 22, 105] and, more recently, in the aziridines / allyl amines[106, 107] rearrangements.

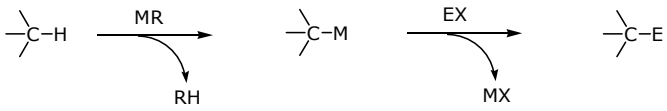
Due to these previous important findings, we have decided to investigate a possible use of superbases for the regioselective rearrangement of aziridinyl ether in analogy with what is well-known for oxyranyl ethers.

Moreover, we have also studied the effect of microwave activation as a tool alternative to the use of superbases in the regioselective base-induced rearrangements of epoxides and aziridines.

At the end of this section the results obtained in the enantioselective version of the superbase-promoted rearrangement of epoxides and aziridines are reported.

2.1. Superbases

Since the first decades of the last century the need to find new efficient methods to deprotonate and subsequently functionalize organic substrates with low acidity has pushed to search new strongly basic organometallic reagents that could allow such transformation efficiently, selectively and under simple reactions conditions (Scheme 8).



Scheme 8

The discovery by Schlosser[11] in 1967 of the strong activation that potassium *tert*-butoxide confers to organolithium compounds in metalation reactions constituted an important turning-point in organometallic chemistry. Since then many kind of mixed organolithium compounds-sodium or potassium alcoholates

reagents were extensively studied and several reviews appeared on this subject by Schlosser[14, 108-110] and Mordini.[12, 13, 111, 112]
The discovery of such reagents, later called superbases, has solved many of the problems indicated above allowing the deprotonation of substrates possessing low acidity and, at the same time, with a good control of the regio- and stereoselectivity associated with the reactions.

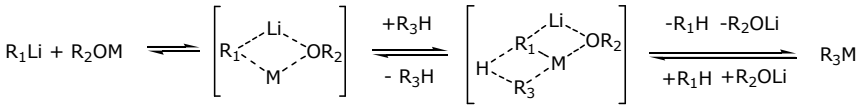
Most of these reagents are constituted by an equimolar amount of an organolithium compound or lithium amide and sodium or potassium alcoholate (RLi/MOR' or R_2NLi/MOR'), such as LICKOR (butyllithium and potassium *tert*-butoxide), LICNAOR (butyllithium and sodium *tert*-butoxide) and LIDAKOR (lithium diisopropylamide and potassium *tert*-butoxide). The wide use of RLi/MOR' or R_2NLi/MOR' mixtures in recent years is due, in addition to the efficiency and selectivity revealed in metalation reactions, to the ease of their preparation and safe handling compared to the corresponding organosodium or potassium analogues.

The most recent definition of the term "superbase" (or "Schlosser's base") is due to Caubère[113] that has underlined as such term should be referred only to an organometallic base resulting from a mixture of two (or more) bases leading to new basic features. Thus, the term superbase does not necessarily mean that the reagent is thermodynamically or kinetically stronger than a normal monometallic base, but it is referred to a newly created organometallic entity of new formation having modified properties, in terms of its reactivity and regio-, stereo- and typo-selectivity.

2.1.1. Structures and reactivity

Despite a long and still open debate concerning their nature in solution, the real constitution of superbases still remains obscure.

Little is known for sure. However, it has been postulated that superbasic reagents are characterized by a "mixed aggregate" type interaction which strongly polarizes the organometallic bonds leading to an increase in reactivity compared with the neat organolithium reagent, as originally conceived by Schlosser too (scheme 9).[11]

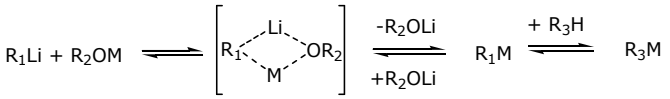


Scheme 9

The real constitution of these aggregates is still unknown; probably they may exist also as equilibria of several kinds of mixed aggregates having different

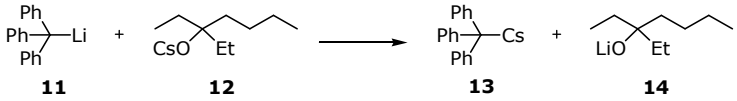
stoichiometry and undergoing a morphological evolution in the course of the reaction.

Other hypothesis is that in a superbasic mixture a metathetical exchange occurs, producing a new reactive organometallic species (Scheme 10).



Scheme 10

The existence of discrete species rather than mixed aggregates has been supported by NMR investigations coupled with MNDO (modified neglect diatomic overlap) calculations of triphenylmethyllithium **11** / caesium 3-ethylheptoxide **12** mixture. The authors found that this particular mixture in THF does not form any mixed aggregates, but rather individual species (**13** and **14**) in which a metal exchange has taken place (Scheme 11).[114]



11 **12** **13** **14**

Scheme 11

On the other hand, the existence of butyllithium / metal alkoxides aggregates is established beyond any doubt. For example, butyllithium was found to form tetrameric aggregates with lithium *tert*-butoxide in THF solution.[115] A variety of additional evidence supports[113] the idea that the formation of mixed aggregates is a general phenomenon occurring whenever metal species are mixed. The simple methatetic exchange between lithium and a second alkali metal has also been ruled out by comparative experiments.[116-120] For instance, the butyllithium / potassium *tert*-butoxide mixture and butylpotassium reagent exhibit striking differences in their reactivity and also solubility toward ethereal solvents.

For these reasons the more probable nature of superbasic reagents is that of a mixed aggregate.

In summary, at present the following features about superbases are known:

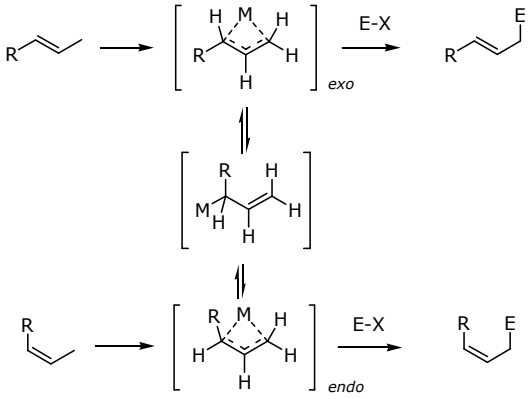
- they are very strong bases and weak nucleophiles;
- they show high selectivity (typo-, regio- and stereo-selectivity) in metalation reactions:
- they present different reactivity if compared with each single partner;
- they can be used in a wide range of temperatures (from –100°C to + 50°C);
- ethereal and paraffinic solvents are allowed;

- they are suitable for deprotonations of allylic, benzylic, aromatic and olefinic sities;
- the metallation product, after reaction with superbases, contains mainly, although not exclusively, the heavier alkali metal.

2.1.2. Applications

These features have allowed superbases to be widely and successfully employed in organic synthesis.

The main areas in which superbases have found interesting applications are the stereoselective metalation of alkenes,[14] the metalation of arenes and heteroarenes[121] and the selective rearrangements of oxiranes and aziridines.[104, 106] While the latter will be discussed in more details in the following paragraphs and chapters, some examples of lithiation of alkenes and arenes are illustrated below. Milestones in this field are the stereoselective metalation of 2-alkenes,[14, 122-130] which allows the preparation of stereochemically pure substituted alkenes, and the metalation of aromatic and hetero-aromatic compounds. The stereochemical control in alkene metalation is due to the fact that once the allylic derivative of potassium is formed, after metalation with a superbase, it generally shows a high preference for adopting mainly one of the two possible conformations if the reaction mixture is submitted to torsional isomerization under thermal[122, 131, 132] or catalytic conditions (Scheme 12).[133]



Scheme 12

Even if simple organolithium reagents can be often basic enough to deprotonate hetero-substituted arenes, the use of a superbasic reagent may result in a different regiochemical behaviour through a directed *ortho*-metalation.[134] The *ortho*-directing effect has been attributed either to the electronegativity of the

hetero-substituent[135] or to the coordinating property of the electron-donor ligand particularly towards lithium atoms.[136]

These two effects (inductive and coordinative) often operate simultaneously[109] and the higher contribution of one with respect to the other depends not only on the hetero-substituent but also on the deprotonation reagent used. As a rule of thumb, weakly solvated organolithium compounds optimally exploit the coordinative capacities of a substituent, whereas the superbasic mixture butyllithium / potassium *tert*-butoxide preferentially deprotonates such positions where charge excess is most efficiently stabilized.[137] This mechanism-based matching of neighboring groups and reagents has allowed the metalation of a large number of arenes carrying two different heterosubstituents, with the so-called "*optional site selectivity*".[108, 121, 137, 138]

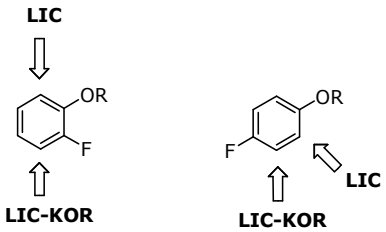


Figure 7

The concept of optional site selectivity is better illustrated by a simple example (Figure 7). Both 2- and 4-fluoroanisole undergo clean deprotonation of an oxygen-adjacent position[139] by butyllithium alone which takes advantage of the coordination by the methoxy group. Contrarily when LICKOR is used, the metalation occurs at the fluorine adjacent position.[139] The reagent being optimally coordinated this time from the beginning, the relative basicities of the organometallic intermediate becomes now the crucial factor.

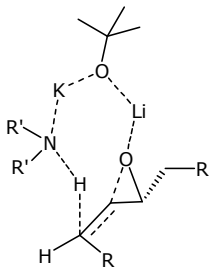


Figure 8

Concerning the base-induced isomerization of strained heterocycles, it is known that superbases, as LIDAKOR, promote a selective syn-periplanar *β*-deprotonation with the formation of a cyclic transition state (Figure 8). The

hypothesis is that the lithium cation coordinates the oxygen of the ring and, simultaneously, potassium cation increases the amidic basicity leading to facilitate the direct replacement of a hydrogen by a metal atom.

Thus, the discovery and large use of superbases in organic synthesis has allowed to develop new efficient selective strategies for the construction of complex molecules through an easy and direct approach. In this thesis superbases have been often employed for this purpose.

2.2. Epoxides and aziridines

Epoxides and aziridines are saturated three-membered heterocyclic compounds having an oxygen or a nitrogen atom respectively. They are notably versatile reagents thanks to their structural characteristics[140-142] such as the polarization of the carbon-heteroatom bond and the high ring strain (27.2 Kcal/mol and 27.1 kcal/mol respectively), only slightly lower than that of cyclopropanes[143] (27.5-28.0 kcal/mol).

These features have led them to be largely used in organic synthesis in a wide series of reactions (nucleophilic ring-openings, rearrangements, deprotonations) and many methods are known for their preparation, particularly concerning the oxygenated rings.[140]

On the other hand allylic alcohols **15** and allyl amines **16** are versatile intermediates for organic synthesis, but multistep sequences are often required for their preparation (Figure 9).[144-150]

15 **16**

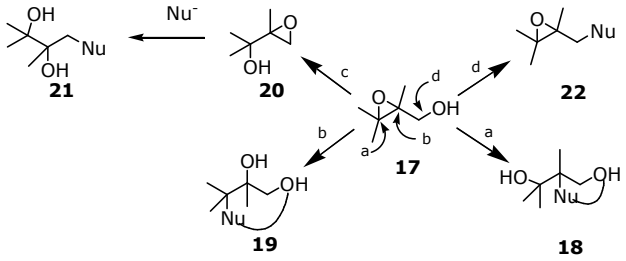
Figure 9

Therefore the lithium amide-mediated rearrangement of epoxides into allylic alcohols and aziridines into allylic amines are attractive approaches, which have been thoroughly investigated due to their synthetic potential and interesting mechanistic features.[151, 152]

2.2.1. Epoxides

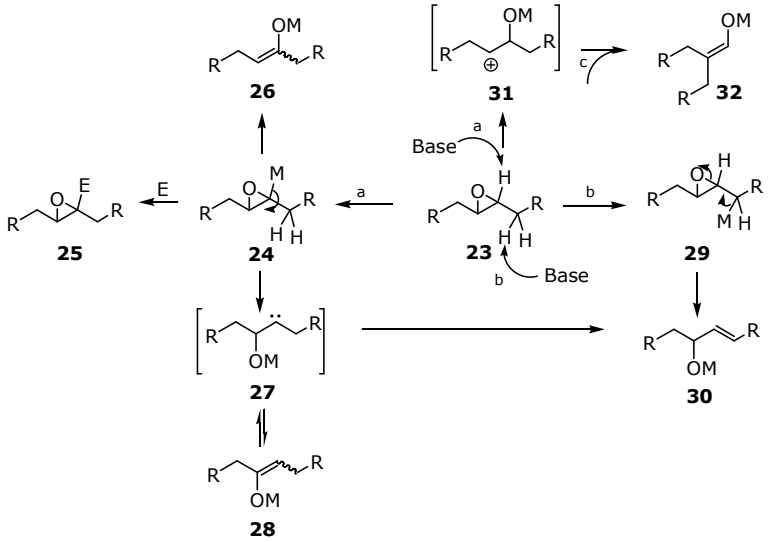
Due to their versatility and easy availability, epoxides have found a widespread use in organic synthesis.[140] A large array of reactions with electrophiles, nucleophiles, acids, bases and reduction agents has been reported.

In addition to this, the discovery and development of new methods for their synthesis in enantiomerically enriched form has further improved their scope in organic synthesis. In particular the Sharpless asymmetric epoxidation (SAE) and the Sharpless kinetic resolution (SKR) of allylic alcohols[153-155] and the oxidation of alkenes in the presence of transition metal complexes discovered by Jacobsen[155] provide a plethora of very useful starting compounds for further transformations (scheme 13 and 14).



Scheme 13

Epoxides and epoxyalcohols **17** can be conveniently opened in a number of ways by nucleophiles: attack on both positions (a, b) of the ring may afford diols or cyclic alcohols **18** and **19** if the attack is intramolecular; a Payne rearrangement (**20**) followed by nucleophilic ring opening (c) leads to the isomeric diols **21**; a suitable activation of the hydroxyl group may lead to nucleophilic displacement (d) thus providing an additional series of oxiranes **22** (Scheme 13).[155]



Scheme 14

In terms of the general reactivity of epoxides with organometallic bases, the deprotonations in *α*- or *β*-position are the most common reactions (Scheme 14).

In the first case (a), when the epoxide ring **24** is suitably activated, the functionalization of the anular carbon atoms (**25**) can be obtained after addition of electrophiles; *α*-deprotonations can also lead to the formation of the vinyl alcoholate **26** or the carbene **27** followed by rearrangement to vinyl alcoholate **28** or allyl alcoholate **30**. In the second case (b), a *β*-deprotonation (**29**) followed by elimination (**30**) occurs.[104, 151] It has been reported also that a ring opening promoted by the metal (**31**) may take place leading eventually to the vinyl alcoholate **32** (Scheme 14).

2.2.2. Aziridines

A similar wide use and knowledge is not found in the literature for aziridines, even if in the last years an increasing interest toward their employment has occurred.[141] Such difference is probably due to the lack of general and direct methods for their preparation, particularly in enantiopure form.

Due to the considerable ring tension, the nucleophilic opening of aziridines is the most studied class of reactions. In this context aziridines can schematically be divided in two groups[156] that differ for the nature of the substituent on the nitrogen atom. "Non-activate" aziridines (R=H, alkyl, aryl), Figure 10, left) are characterized by a basic nitrogen and require therefore protonation, quaternarization[157, 158] or formation of Lewis acids in order to be attacked by nucleophilic reagents.

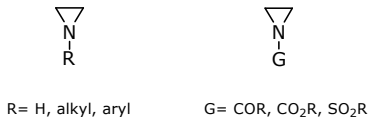


Figure 10

"Activated" aziridines (G=COR, CO_2R, SO_2R, Figure 10, right), that are those which have a group able to stabilize a negative charge through conjugation, instead, can undergo nucleophilic attacks with extreme ease. This is the most studied class of aziridines and a large amount of information are available on their reactivity.[159]

The nucleophilic attack generally occurs according to a S_N2 mechanism[160] with inversion of configuration and it usually takes place on the less hindered carbon atom in analogy to the well-known mechanism for oxiranes.

The presence of further functional groups on the aziridine ring makes these substrates even more useful from a synthetic point of view, allowing the access to

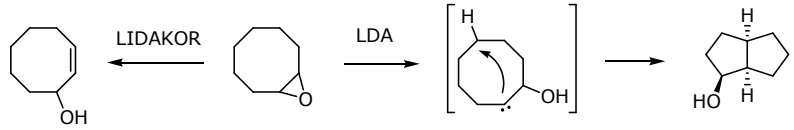
highly functionalized molecules even if the rationalization of the regiochemical outcome of nucleophilic ring opening is more difficult. A large number of studies have been made on aziridinyl alcohols[161] and carboxilates,[162] as precursors of amino acids through nucleophilic ring opening. It has been found that, according to the number and the nature of the *N*-substituents, the regiochemical result can be completely different.[142, 161-163]

Not many information about the reactivity of aziridines with organometallic bases are available in the literature. It is well-known that the ring carbon can be deprotonated and therefore functionalized with strong bases, if the aziridine nitrogen atom is sufficiently activated. Such deprotonation always competes with the ring opening and therefore organometallic reagents endowed with a low nucleophilicity and high basicity are required in order to drive the reaction towards a selective metalation.[164, 165]

2.3. Previous results about the base-induced isomerizations of epoxides

Lithium amides deprotonation of epoxides is a convenient method for the preparation of allylic alcohols. Since the first report by Cope in 1958[166] the area has received much attention.

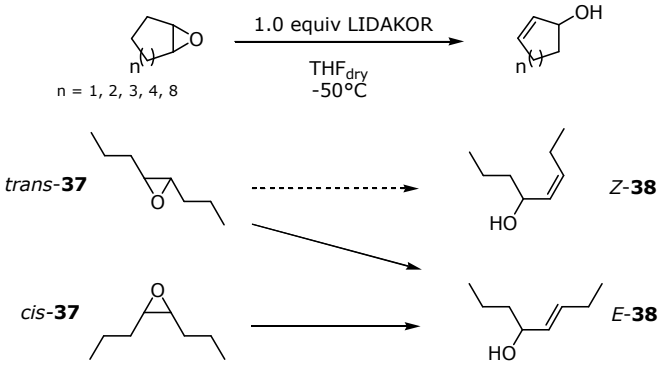
The isomerization is known to occur via *α*- or *syn*-*β*-lithiation pathways,[167] the latter being more desirable because it leads exclusively to allylic alkoxides. In contrast, *α*-metalation may produce saturated alkoxides, enolates, or allylic alkoxides as described above (Scheme 14). Although the regioselectivity of the lithiation depends on the choice of base, solvent, and substrate, many synthetically useful methods have been developed. It has been shown that the use of the superbasic mixture lithium diisopropylamide / potassium *tert*-butoxide (LIDAKOR) has a strong influence on this process with oxiranes[104] always leading to the expected *β*-elimination product exclusively. The superbase-promoted isomerization shows good selectivity on simple alkyl-substituted oxiranes as well as epoxycycloalkanes, the latter being usually more difficult substrates to be rearranged to allylic alcohols (Scheme 14). As an example, epoxycyclooctane **33** is transformed into 2-cyclooctenol **34** by LIDAKOR[104] while treatment with LDA leads to the bicyclic alcohol **35** as the main product which derives by *α*-lithiation followed by formation of a carbene species **36** and a transanular C–H insertion reaction (Scheme 15).



34 **33** **36** **35**

Scheme 15

The use of superbases has also allowed to clearly establish that the oxirane isomerisation proceeds through a *β*-elimination *syn*-periplanar mechanism with usually good stereocontrol (Scheme 16).[104]



Scheme 16

By supposing, in fact, that the reaction occurs through a mechanism of this type, the conformations of the *cis*-**37** and *trans*-**37** epoxides, from which the elimination is possible (Figure 11), present different steric hindrances. While, for instance, the "a" conformation, which constitutes the precursor of the alcohol *Z*-**38**, results much less favourable for reasons of steric repulsion than the "b" conformation, the "c" and "d" conformations, don't experience the same level of steric discrimination.

As this molecular model suggests, therefore, the expected selectivity is bigger in the case of the *cis*-epoxide because of steric effects.

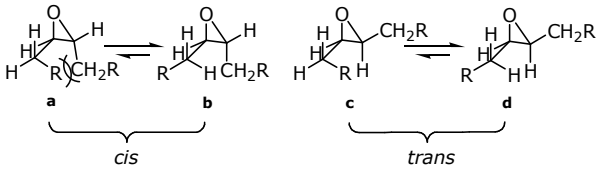
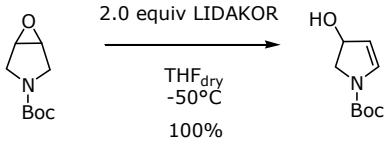


Figure 11

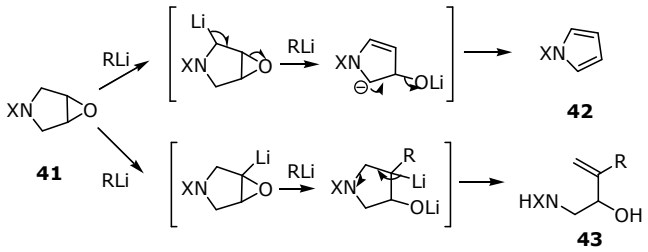
There are examples which clearly show the superbase effect in these reactions. Amino oxiranes also undergo a clean rearrangement to hydroxy enamines as illustrated by the example of the *N*-Boc-3,4-epoxypirrolydine **39** which clearly isomerizes to *N*-Boc-4-hydroxy-2,3-dihydropyrrolidine **40** in quantitative yield (Scheme 17).



39 **40**

Scheme 17

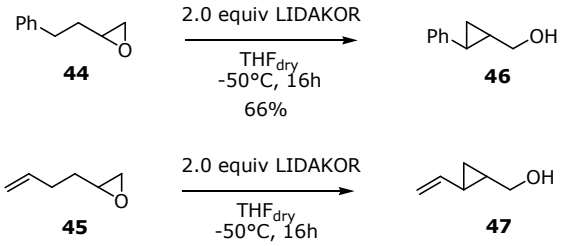
Interestingly when the same rearrangement is attempted by using usual organolithium reagents, completely different pathway are followed[168, 169] leading either to *N*-Boc-pyrrole **42** or to ring-opened product **43** (Scheme 18). This shows again the outstanding effect of superbases on rearrangement reactions.



41 **42** **43**

Scheme 18

It is known that oxiranes carrying strong electron withdrawing substituents such as nitriles,[170-172] esters,[173, 174] amides,[175] ketones,[176] sulfones[177-179] or sulfides,[180] easily undergo 3-*exo* ring closure to the corresponding cyclopropanes with usual bases. It has been found in Florence that superbasic mixtures can be conveniently used for the 3-*exo* cyclization of suitably substituted oxiranes lacking strong activators. Both phenyl- **44** and allyl-substituted oxiranes **45** undergo a clean and selective conversion to the corresponding cyclopropanes **46** and **47** with high yields and selectivity (Scheme 19).[23]

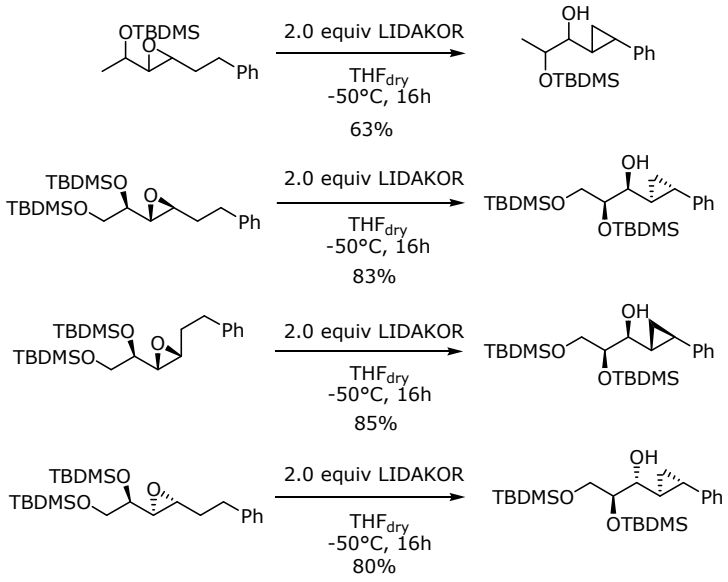


44 **46**

45 **47**

Scheme 19

The reaction is quite general. It can be done with di- and tri-substituted oxiranes and, more importantly, with highly functionalized substrates as those reported in the Scheme 20.

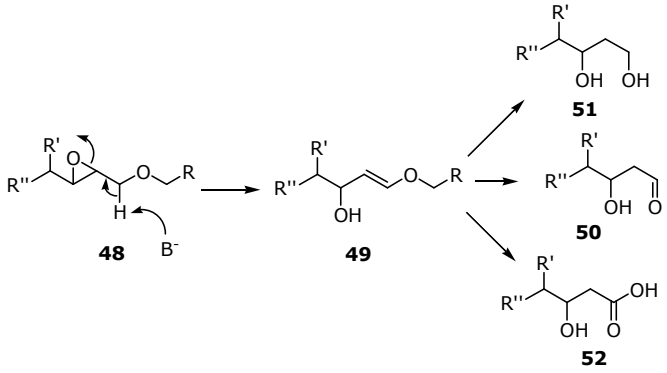


Scheme 20

2.4. Previous results about the base-induced isomerizations of epoxy ethers

The research group, where I developed part of my PhD thesis, has been interested for several years to the synthetic applications of oxyranyl ethers. It has been clearly demonstrated that the superbase-promoted isomerization of small ring heterocycles offers its best potentialities when applied to hetero-substituted substrates in sight of further synthetic application of the rearranged products. Most of the efforts have been devoted[181-183] to alkoxy-substituted compounds which can be obtained from allylic alcohols through the SAE reaction[153-155] followed by alkylation.

Alkoxy-substituted oxiranes of type **48** when treated with the superbasic mixture LIDAKOR are selectively transformed into the corresponding hydroxy-vinylethers **49** (Scheme 21). Such reaction is quite general and occurs with high selectivity and yields. Due to a *syn*-periplanar *β*-elimination pathway, the vinylic ether is usually obtained with a high *E*-selectivity (as reported into Figure 11). The rearranged products **49** can be conveniently transformed into 3-hydroxyaldehyde **50** by simple deprotection, and these intermediates can then undergo a number of synthetically useful transformations leading for example to *β*-hydroxy-alcohols **51** or *β*-hydroxy-acids **52** (Scheme 21).[182]

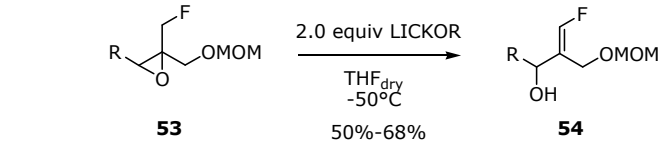


Scheme 21

Very interesting is the reaction conducted on alkoxyl oxiranes derived from amino acids (R'=NHBoc). Thanks to the use of superbases, the isomerization leads to enantiopure amino-diols or amino-hydroxyl aldehydes, useful as peptido-mimetics precursors.[183]

Interestingly oxiranyl ethers can also contain additional functional groups then allowing the rearrangement to highly functionalized compounds without losing the high selectivity mentioned above.

As an example fluoro oxyranyl ethers **53**, obtained in a multistep synthetic sequence starting with a Baylis–Hilmann condensation of aldehydes and ethyl acrylate, are rearranged to dihydroxy vinyl fluorides **54** with a surprisingly high regio- and stereoselectivity, the *E*-vinyl fluoride being the only detected product in most cases (Scheme 22).

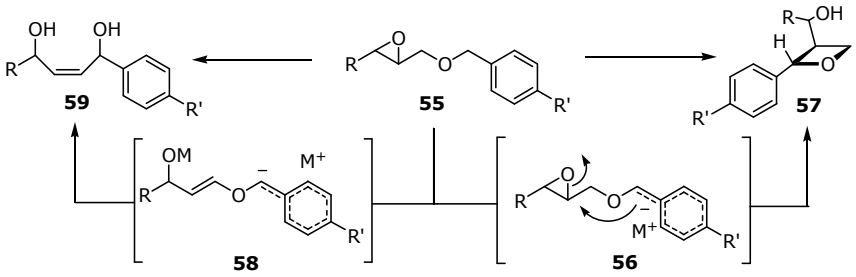


53 50%-68% **54**

R=H, C_5H_{11}, $CH(OBn)CH_3$, $CH(NHBoc)CH_3$

Scheme 22

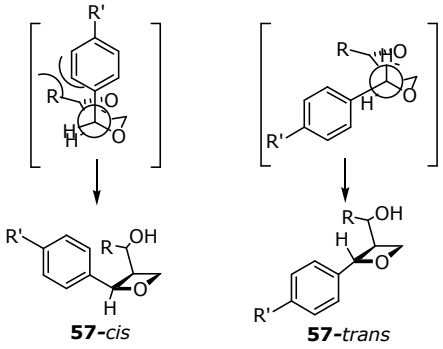
Both the substitution pattern of the oxirane and the nature of the R group have been shown to play an important role in driving the isomerization process with bases. When R is an alkyl, alkoxy, carboalkoxy or thioaryl group, the reaction follows the pathway described above but if R is an aryl substituent (**55**) then an alternative process takes place. Deprotonation of the benzylic position leads indeed to a benzylmetallic species **56** which is capable of opening the oxirane ring through an intramolecular nucleophilic attack to afford a di-substituted oxetane **57** (Scheme 23).[184]



Scheme 23

The 4-*exo* ring closure occurs with high diastereoselectivity leading to the *trans*-disubstituted oxetane as unique product (Scheme 24).

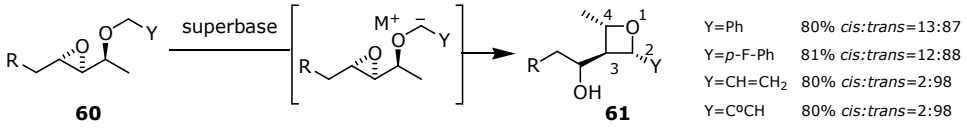
As a drawback this reaction occurs only with R' being an unsubstituted phenyl ring. *para*-Substituted aromatic groups both with electron withdrawing (R'= CF_3, F) and electrodonating moieties (R'=$C(CH_3)_3$, OCH_3) lead invariably to mixture of oxetanes and hydroxy vinyl ethers. Most notably in the case of *para*-methoxy benzyl oxiranyl ethers (R'=OCH_3), an excess of base eventually leads to *Z*-1,4-diol **59** *via* a 1,2-Wittig rearrangement of the intermediate benzylmetallic species **58**.[184]



Scheme 24

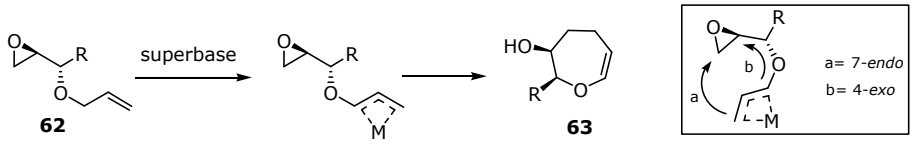
Oxiranyl ethers derived from secondary allylic alcohols **60**, due to the presence of an alkyl group on the methylene adjacent to the oxirane ring, behave in a more selective way. Deprotonation occurs exclusively on the activated methylene far from the three-member ring and then a 4-*exo* ring closure takes place leading to (2,3-*trans*)-tri-substituted oxetanes **61** (Scheme 25). The relative stereochemistry of substituents at position 3 and 4 is related to the configuration of the starting oxirane derived from the SKR.[185] This is an interesting reaction which occurs with high yields and selectivities only when performed with superbasic mixtures such as LICKOR[11] or LIDAKOR.[12] Many activating groups such as aryl, vinyl, alkynyl, thioaryl can be used leading to a large variety of oxetanes.

The 4-*exo* preference during the ring closure process is general, no traces of 5-*endo* derived heterocycles having ever been detected.



Scheme 25

A different behaviour is found when mono-substituted allyl oxiranyl ethers **62** are submitted to treatment with superbases (Scheme 26).

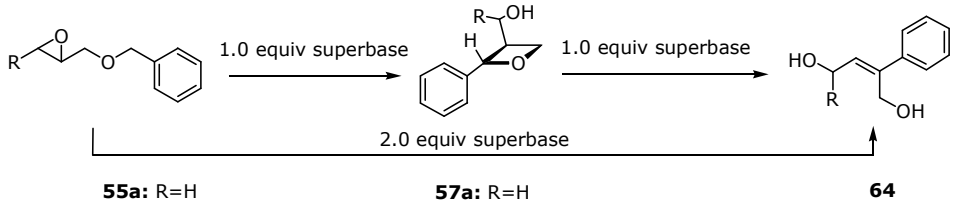


Scheme 26

In this case only the 7-*endo* cyclization takes place leading to *trans*-disubstituted tetrahydrooxepines **63** as unique products.[22]

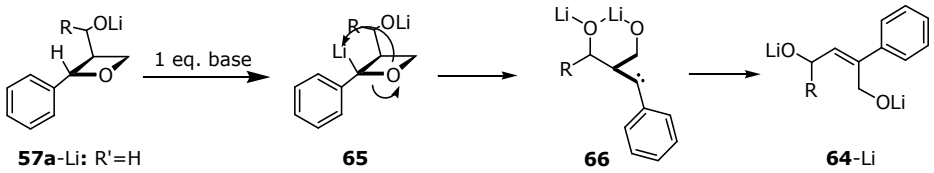
It is worthwhile noting the importance of the use of superbases; simple organolithium or lithium amide reagents afford mixtures of 4-*exo* and 7-*endo* products in a very low yield.[186] The high selectivity encountered with superbases is probably due to the high preference of allyl potassium species to react with the γ-position.

Oxetanes **57a** may even undergo a subsequent rearrangement when treated with an organometallic base affording (*Z*)-2-alkene-1,4-diols **63**.[21, 105] The same products are also easily obtained using an excess of a superbase directly on the oxiranyl ethers **55a** (Scheme 27).



Scheme 27

The mechanism foresees an *α*-ring opening of the lithiated oxetane **65**, followed by a carbene type intermediate **66** from which an alkyl-1,2-shift to the dialcoholate **64**-Li occurs (Scheme 28)

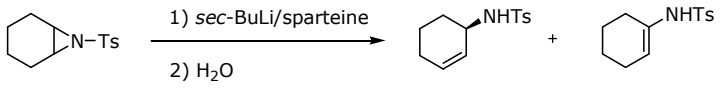


57a-Li**:** R'=H **65** **66** **64**-Li

Scheme 28

2.5. Previous results about the base-induced isomerizations of aziridines

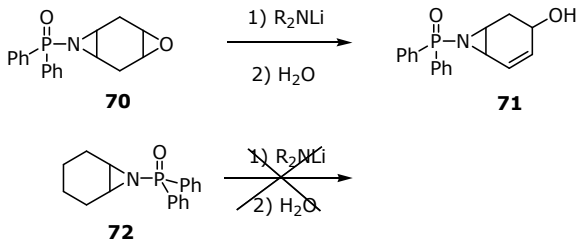
Despite this large array of information on oxiranes, the base-promoted isomerization of aziridines has been almost ignored until ten years ago. Probably the first example of aziridine–allylamine conversion was reported by Scheffold in 1993[187] by using cob(I)alamin as a catalyst, although the reaction was very slow and took place actually through an addition–elimination pathway. The first true base-promoted isomerization was published in 2001 by Müller[188] who described the desymmetrization of the *meso*-sulfonyl aziridine **67** with *sec*-butyllithium / (–)-sparteine. Unfortunately, under these conditions, the aziridine isomerization was not regioselective yielding both *α*- and *β*-deprotonation (to the enamine **69** and allylamine **68**-(*R*) respectively, (Scheme 29) and the enantioselectivity in the formation of the allylamine **68** was quite low.



67 **68-(*R*)** **69**

Scheme 29

In addition, O'Brien showed that the *meso*-aziridino cyclohexene oxide **70** underwent rearrangement on the oxirane ring only (to the aziridino allylic alcohol **71**, Scheme 30, top) and that in the absence of the epoxide ring (**72**) no reaction occurred when employing inactivated bases such as lithium diisopropylamide (Scheme 30, bottom).[189] The reactivity of aziridines with bases seems then much lower in comparison with the analogous oxygenated heterocycles.

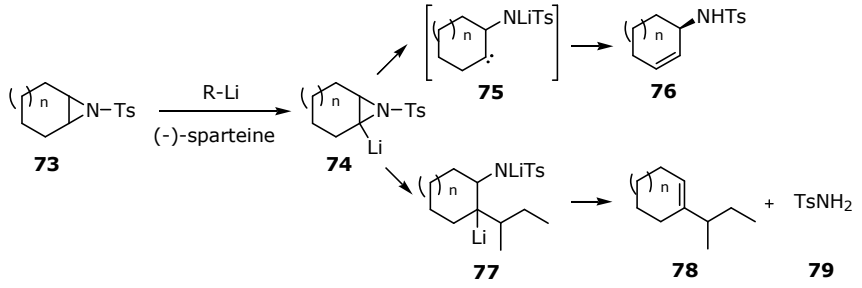


70 **71**

72

Scheme 30

O'Brien[152] revisited Müller's work on the isomerisation of aziridines with *sec*-butyllithium / (−)-sparteine with the purpose to rationalize previous results.



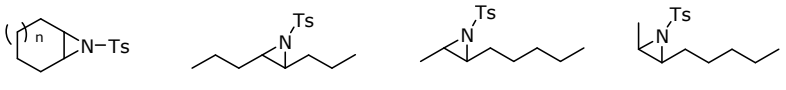
Scheme 31

He carried out a study on the reaction of alkyllithiums with a series of cycloalkene *N*-tosyl aziridines in the presence of (−)-sparteine finding that the expected allylic amine **76** was formed together with *p*-toluenesulfonamine **79** as a by-product (Scheme 31). This has been explained by assuming that an irreversible *α*-lithiation of the *N*-tosyl aziridines **73** leads first to the lithiated intermediate **74**. A subsequent insertion into the adjacent C–H bond either directly or via the carbenes **75** (generated by *α*-elimination of lithiated aziridines **74**) produces the allylic sulfonamides (*R*)-**76** after aqueous work-up. However, by analogy with epoxides, lithiated aziridines **74** are also likely to possess significant electrophilic character and this opens up another possible reaction pathway. Attack of lithiated aziridines **74** by a second equivalent of *sec*-butyllithium may lead to dilithiated adducts **77** from which elimination of $TsNLi_2$ would generate alkenes **78** and $TsNH_2$ **79** after aqueous workup.

2.5.1. Isomerizations of aziridines

Despite a number of reports in the literature dealing with the reactivity of *N*-tosyl aziridines with organolithium compounds and (−)-sparteine, many aspects on this topic have to be still clarified in depth. For this reason in the last few years the group of Florence has extended the studies of superbase reactivity to both non-functionalized and alkoxy substituted aziridines.

A careful investigation was first carried out on a series of different *N*-substituted activated aziridines[106] finding that the tosyl group is certainly the best one among several others for the purpose of promoting a base-induced rearrangement. Then several bi- and mono-cyclic *N*-tosyl aziridines were submitted to treatment with superbasic reagents (Figure 12).

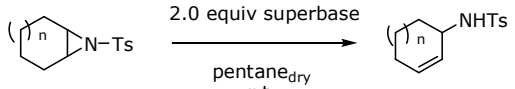


73a n=0 **73b** n=1 **73c** n=3 | **80** | **81a** | **81b**

Figure 12

All aziridines showed a reactivity which is similar to the corresponding oxiranes but required more drastic reaction conditions; while oxiranes react with superbases even in THF at low temperature,[104] aziridines give usually the best results when treated in pentane at room temperature.

6-Tosyl-6-azabicyclo[3.1.0]hexane **73a** was converted into the corresponding allyl tosylamide **76a** in low yields (42%, Scheme 32). Higher yields were obtained with 7-tosyl-7-azabicyclo[4.1.0]heptane **73b** (46% in pentane (Scheme 32), which increased to 64% in THF).

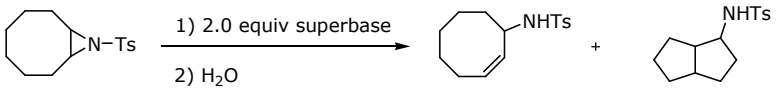


73a **73b**

76a: n=0 42%
76b: n=1 46%

Scheme 32

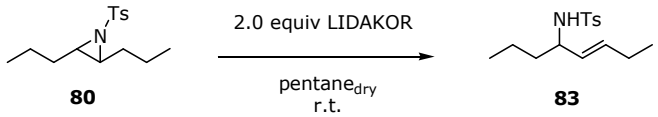
9-Tosyl-9-azabicyclo[6.1.0]nonane **73c** (n=3), instead, showed an interesting reactivity with superbases. When treated with LIDAKOR in pentane at room temperature a completely regioselective conversion to the 1-*N*-tosylamino[3.3.0]octane **82** in a 64% yield was observed. If the reaction was conducted at lower temperature in THF with LICKOR, then a mixture of **82** and the *N*-tosyl allyl amine **76c** (n=3) was obtained (Scheme 33). At -20° C still the bicyclic amine was preferred over the allylic one with a 80:20 ratio while at -50° C, an almost equal amount (45:55) of the two amines was formed in a 60% overall yield.



73c | **76c** | **82**

Scheme 33

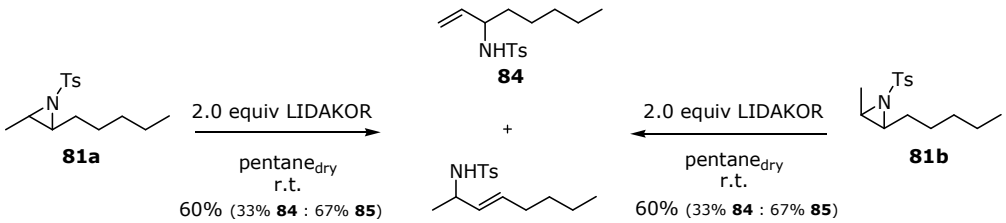
The monocyclic symmetrical aziridine **80** was also regio- and stereo-selectively converted into the corresponding allylic amine **83** by treatment with LIDAKOR in pentane at room temperature (Scheme 34).



80 **83**

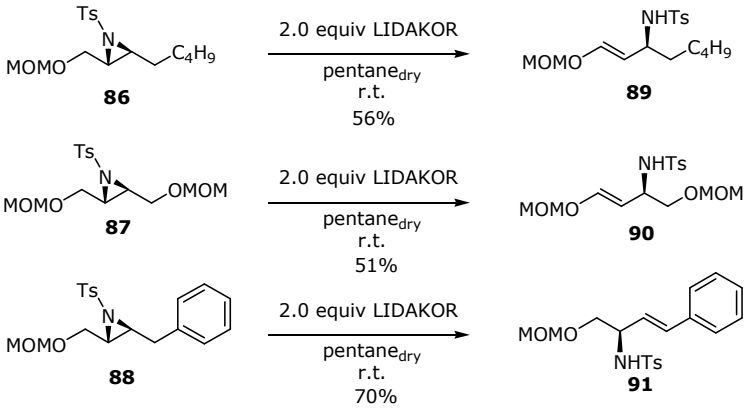
Scheme 34

It is worth noting that compound **83** was obtained as a pure *E*-isomer, while the LIDAKOR promoted isomerization of the corresponding oxirane affords a 1:2, *Z*/*E* mixture of allylic alcohols.[104] The higher selectivity showed by tosyl aziridines may be due to an increased steric crowding caused by the presence of the large tosyl group on nitrogen in the *syn*-periplanar arrangement required for the elimination.[190] Both *Z*- and *E*-aziridines **81** behave exactly in the same way affording a mixture of the two tosyl allyl amines **84** and **85** in the same ratio (33:67) with a 60% overall yield (Scheme 35).



Scheme 35

The presence of additional functional groups on the aziridine substrates was also investigated. Alkyl **86**, alkoxy **87** and aryl **88** substituted MOM-protected hydroxy-aziridines were prepared and tested with superbases (Scheme 36).[107]

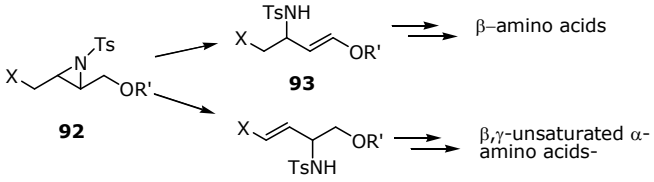


Scheme 36

2.5.2. Elaboration of allyl amines

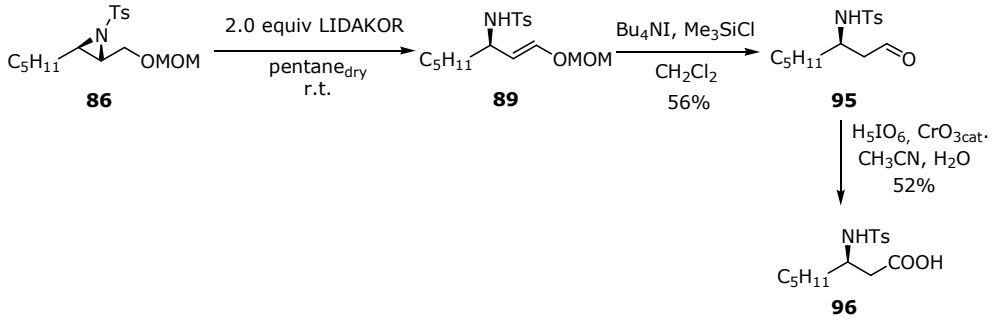
Functionalized aziridines may give access to a wide variety of amino derivatives of synthetic interest.

For example, it has been clearly established that alkoxy allyl amines **93** or **94** are a very useful building block for further transformations into amino acids (Scheme 37).[107]



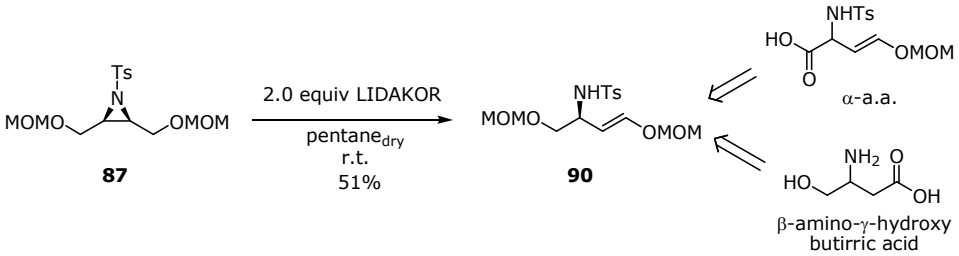
Scheme 37

This approach has been demonstrated by the conversion of the aziridinyl ether (2*R*,3*S*)-2-[(methoxymethoxy)methyl]-3-pentyl-1-tosyl-aziridine **86** into the allylamines **89**, followed by an easy deprotection to the amino aldehydes **95** and, finally, oxidation to the *β*-amino acid **96** (Scheme 38).



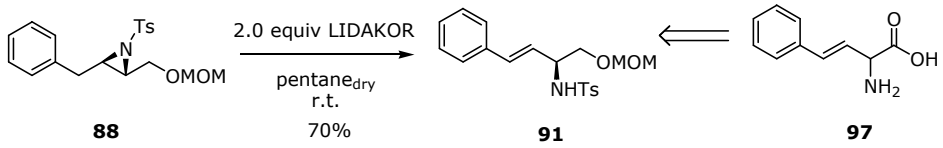
Scheme 38

Both processes occur under mild reaction conditions and without epimerization thus leading to amino aldehydes and amino acids having the same optical purity as the starting aziridines. In order to validate the process this reaction sequence has been extended to some other differently substituted and / or functionalized aziridines. For instance the symmetrical aziridine **87**, has been converted into the amino vinyl ether **90** with good yield and high selectivity (Scheme 39). Compound **90** is a very useful building block due to the large number of functional groups which can be conveniently transformed. It can give access to *α*- or *β*-amino acids, such as *β*-amino-*γ*-hydroxybutirric acid.



Scheme 39

When the same reaction conditions have been applied to aziridine **88**, having an additional acidic position (the benzylic methylene group), a different reaction pathway was found, leading this time to the cinnamyl amino ether **91** in a very selective manner (Scheme 40).



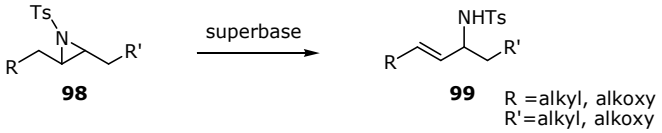
Scheme 40

This compound **91** is a precursor of the *β*,*γ*-unsaturated *α*-amino acid, cinnamylglucine **97**, and the extension of this methodology to other similar substrates could find an interesting application into the synthesis of a large variety of unsaturated *α*-amino acids. Therefore, depending on the nature of the substituents on the aziridine ring, the base-promoted rearrangement may disclose new pathways to unnatural *α*- and *β*-amino acid precursors. In particular for *β*-amino acids, less abundant than *α*-analogues, this represents an interesting synthetic strategy.

3. REARRANGEMENTS OF AZIRIDINYL ETHERS MEDIATED BY SUPERBASES

3.1. Introduction

As shown in the previous chapter (paragraph 2.5) aziridines **98** (R=alkyl, R'=alkyl) and aziridinyl ethers **98** (R=alkyl or alkoxy, R'=alkyl or alkoxy) are selectively and easily converted to allyl amines **99** (R=alkyl, R'=alkyl) and amino vinyl ethers **99** (R=alkoxy, R'=alkyl) or alkoxy allylamines **99** (R=alkyl, R'=alkoxy) by treatment with mixed metal bases (Scheme 41).[107]



98 **99** R =alkyl, alkoxy
R'=alkyl, alkoxy

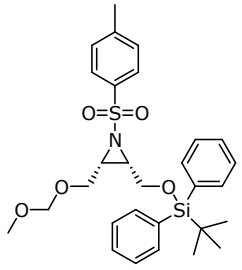
Scheme 41

Moreover, the base-promoted isomerization of oxiranyl ethers **55** or epoxides **23** has shown that these substrates can be stereoselectively converted into a number of synthetically useful products by treatment with superbases (paragraphs 2.3 and 2.4).[11, 12, 112]

For all these reasons, in order to further extend the synthetic application of superbases in the field of base-induced rearrangements of strained heterocycles, we decided to undertake a more deep investigation of the reactivity of the nitrogen analogues, in comparison with what already well established for oxiranes. First of all we have examined the reactivity of a series of new differently functionalized aziridines in order to generalize the aziridines / allylamine isomerization, then we have begun a study on the possibility to induce 4-*exo* type cyclizations to amino oxetanes.

3.2. Synthesis of aziridinyl ethers

A more detailed investigation of the reactivity of a variety of aziridines with superbases has been carried out in this thesis. In particular we have chosen (2*S*,3*R*)-2-[(*tert*-butyldiphenylsilyl)oxy]methyl-3-(methoxymethoxy)methyl-*N*-(*para*-toluensulfonyl) aziridine **100** as our starting building block, from which other differently functionalized aziridinyl ethers have been subsequently derived (Figure 13).



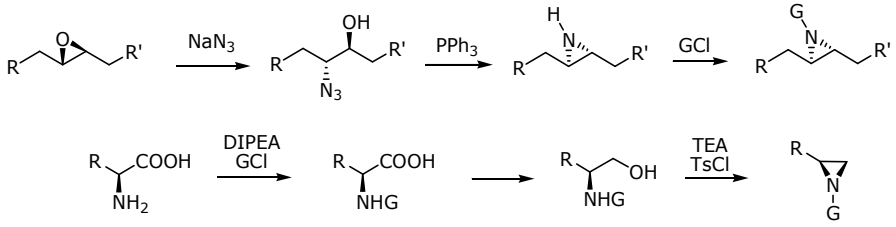
100

Figure 13

Aziridinyl ether **100** was selected for two main reasons:

- it is a valuable building block for interesting molecules, such as amino acids and *β*-lactames;[191]
- the presence of two orthogonal protective groups, the silyloxyl and MOM moieties, allows easy conversions into other functional groups, thus leading to a wide variety of differently substituted aziridines.

Enantiomerically enriched aziridinyl ethers can be prepared in a number of ways,[192, 193] among which elaborations of the corresponding oxiranyl ethers by opening and further closing to aziridine (Scheme 42, top), or transformations of *chiral pool* molecules (Scheme 42, bottom) seem to be the more general and efficient. For our investigation we have initially selected the sequences starting from epoxy ethers.

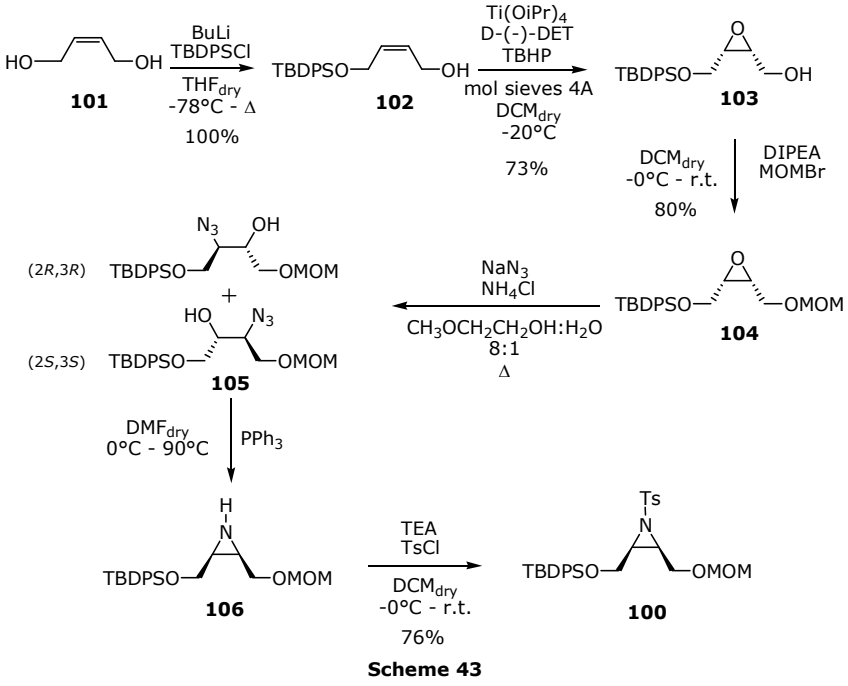


Scheme 42

3.2.1. Synthesis of (2*S*,3*R*)-2-[(*tert*-butyldiphenylsilyl)oxy]methyl-3-(methoxy-methoxy)methyl-*N*-(*para*-toluensulfonyl)-aziridine **100**

The synthesis of compound **100** (Figure 13) requires six steps beginning from the commercially available (*Z*)-but-2-ene-1,4-diol **101** which was mono-silylated by means of TBDPSCl and BuLi in anhydrous THF (Scheme 43). The use of other less hindered silyl chlorides (for instance TBDMSCl) led to mono- and di-protected diol mixtures.

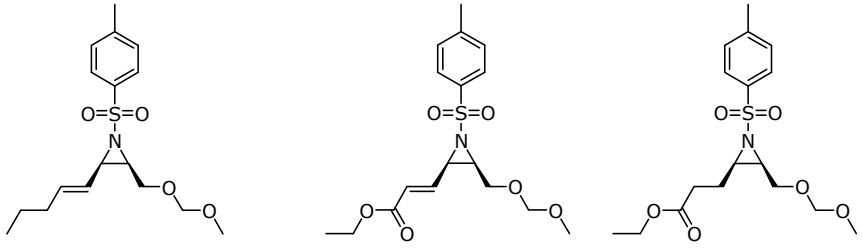
The resulting (*Z*)-4-[(*tert*-butyldiphenylsilyl)oxy]-but-2-en-1-ol **102** was then oxidized into the chiral epoxide **103** by SAE reaction[153] ($[\alpha]_D^{24}$=+9.26, $CHCl_3$) followed by OH protection with a methoxymethyl group. Enantiomerically pure 2,3-epoxy ether **104** was then easily and stereoselectively transformed into the corresponding aziridine **106** by a straightforward series of operations:[194-196] ring-opening of epoxides with sodium azide and NH_4Cl generated the aziridino alcohol **105** as a regioisomeric mixture, which was then cyclised to the aziridine **106** by using triphenylphosphine according to the Staudinger protocol.[191, 197-199] Finally the aziridine **106** was protected with a tosyl group by means of TsCl and TEA in CH_2Cl_2 (Scheme 43).



Scheme 43

3.2.2. Synthesis of derivatives of the aziridine **100**

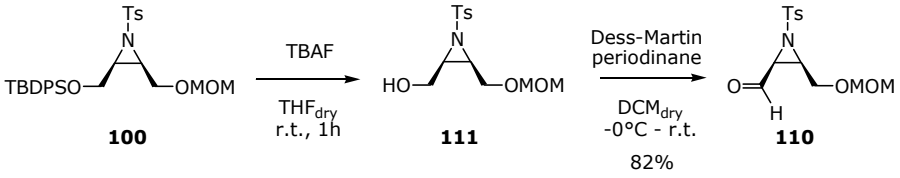
Further transformations of the aziridinyl ether **100** led to the derivatives (2*R*,3*R*)-2-((methoxymethoxy)-methyl)-3-((*E*)-pent-1-enyl)-*N*-(*para*-toluensulfonyl)-aziridine **107**, (*E*)- ethyl-3-((2*R*,3*R*)-3-((methoxymethoxy)-methyl)-*N*-(*para*-toluensulfonyl)-aziridin-2-yl)-acrylate **108** and ethyl-3-((2*R*,3*R*)-3-((methoxymethoxy)-methyl)-*N*-(*para*-toluen-sulfonyl)-aziridin-2-yl)propanoate **109** (Figure 14).



107 **108** **109**

Figure 14

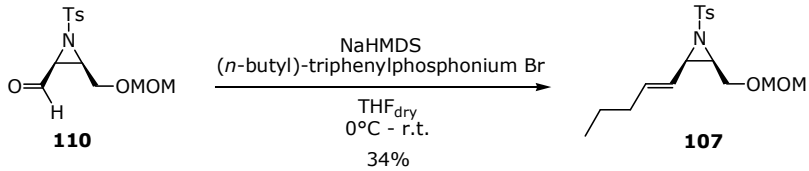
The key-step in all these transformations was the synthesis of (2*S*,3*R*)-3-((methoxymethoxy)-methyl)-*N*-(*para*-toluensulfonyl)-aziridine-2-carbaldehyde **110**, obtained from the desilylation of aziridinyl ether **111** and further oxidation of the deprotected OH moiety with Dess-Martin periodinane (Scheme 44).



100 **111** **110**

Scheme 44

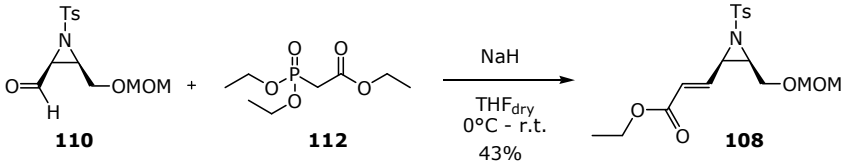
The aldehydic moiety (**110**) was then transformed in a C=C double bond by Wittig reaction with sodium bis(trimethylsilyl)amide and (*n*-butyl)-triphenylphosphonium bromide in anhydrous THF (Scheme 45);



110 **107**

Scheme 45

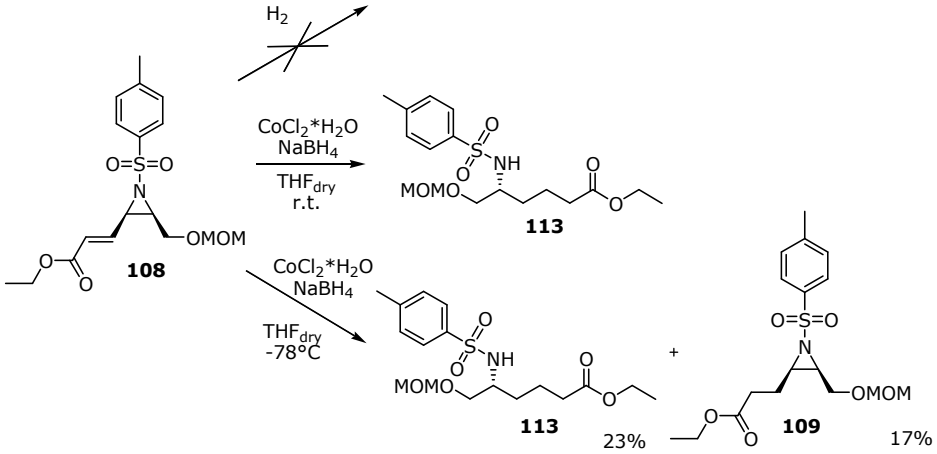
or in an *α*,*β*-unsaturated ester through a Horner-Emmons reaction by using NaH and diisopropyl-(ethoxycarbonylmethyl)-phosphonate **112** in dried THF (Scheme 46).



110 **112** **108**

Scheme 46

The C=C double bond of the *α*,*β*-unsaturated ester **108** was then reduced in order to obtain ester **109** (Scheme 47).

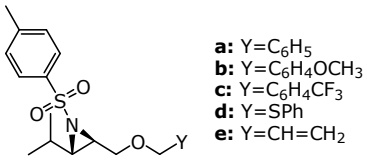


Scheme 47

The first attempt was carried out in H_2 atmosphere, since it is reported in the literature[200] that molecular hydrogen can reduce the double bond without interferences with the ester moiety. Unfortunately in our case only decomposition products were obtained (Scheme 47, top).

Therefore $NaBH_4$ in the presence of $CoCl_2*H_2O$ was used. Under these conditions the reaction is instantaneous but leads again to the formation of ring-opening by-products. When the reaction occurred at temperatures over 0° C the aziridinyl ring **108** underwent opening to afford (*R*)-ethyl-6-(methoxymethoxy)-*N*-(*para*-toluensulfonyl)-amino)-hexanoate **113**, whereas if the reaction was carried out at -78°C we obtained a mixture of the aziridinyl ester **109** and amino-ester **113**, from which the desired aziridine was separated albeit in low yield.

3.2.3. (2*R*,3*S*)-2-Methylether-3-*iso*-propyl-*N*-(*para*-toluensulfonyl)-aziridines **114**



a: Y=C_6H_5
b: Y=$C_6H_4OCH_3$
c: Y=$C_6H_4CF_3$
d: Y=SPh
e: Y=$CH=CH_2$

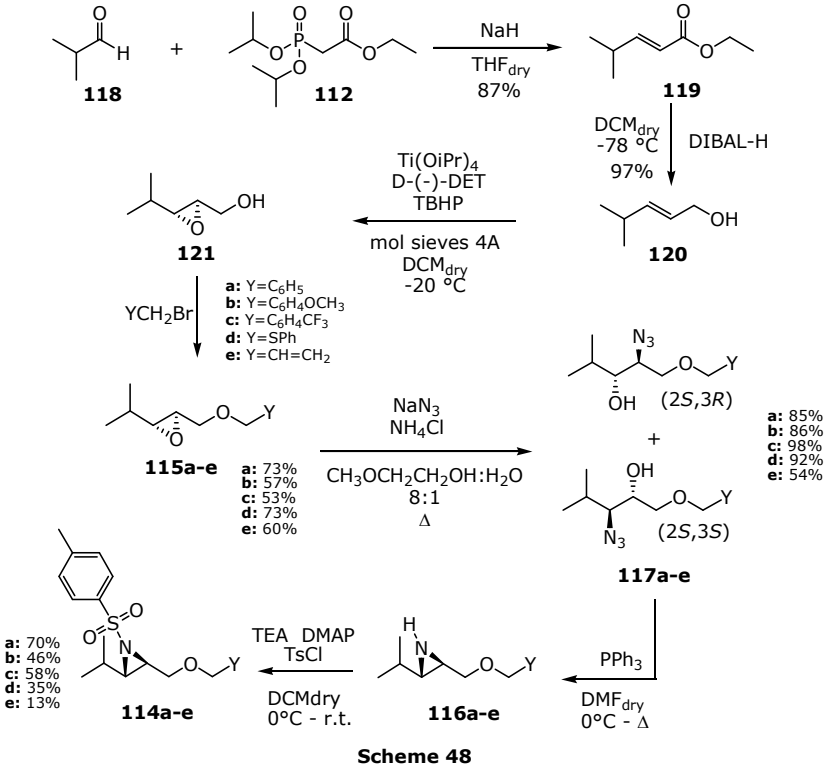
114

Figure 15

The synthesis of (2*R*,3*S*)-2-(benzyloxy)methyl-3-*iso*-propyl-*N*-(*para*-toluensulfonyl)aziridine **114a** and its *para*-benzyloxy substituted **114b-c** and SPh

114d or allyloxy **114e** analogues (Figure 15) was performed following in all cases a similar strategy based on the transformation of the enantiomerically pure epoxy ethers **115** into aziridine **116** by ring-opening with NaN_3 (**117**) and following closure with PPh_3 (Scheme 48).

We started from the commercially available butyraldehyde **118**, which was first converted into *α*,*β*-unsaturated ester **119** through a Horner-Emmons reaction by using NaH and diisopropyl-(ethoxycarbonylmethyl)-phosphonate **112** in freshly distilled THF. The resulting ester **119** was, then, quantitatively reduced to allylic alcohol **120** with DIBAL-H in CH_2Cl_2 and the latter was oxidized to epoxy alcohol **121** by SAE methodology[153] with e.e. comparable to literature data.[201] The following step imply the protection of the hydroxyl moiety with the required substituent Y (-phenyl; -*para*-methoxyphenyl; -*para*-trifluomethan-phenyl;-phenylthio;-vinyl) and was performed using the standard procedure with NaH in THF and YCH_2Br (Y=C_6H_5, $C_6H_4OCH_3$, $C_6H_4CF_3$, SPh and CH=CH_2). Finally the epoxide ring **115** was opened with NaN_3 and NH_4Cl and the resulting (2*S*,3*R*) and (2*S*,3*S*) azido alcohols **117** were treated with triphenylphosphine to form the aziridines **116**. The nitrogen atom of **116** was protected with a tosyl group by using TsCl and TEA in anhydrous CH_2Cl_2.



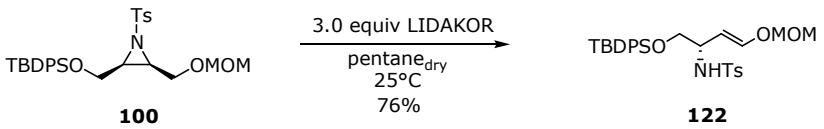
Scheme 48

3.3. Isomerizations of aziridinyl ethers

All the substrates obtained as shown were then submitted to isomerization with superbases.

3.3.1. β-Eliminations

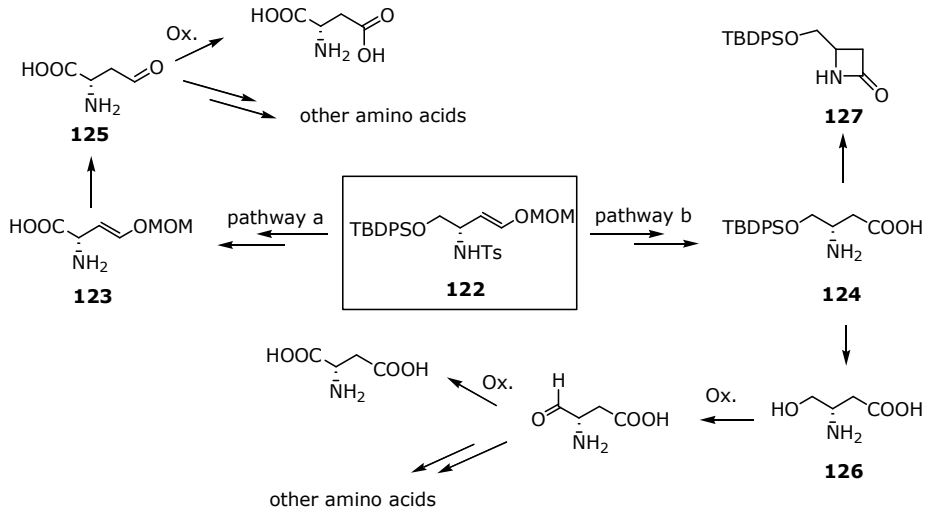
(2*S*,3*R*) -2-[(*tert*-Butyldiphenylsilyl)oxy]methyl-3-(methoxymethoxy)methyl-*N*-(*para*-toluensulfonyl)-aziridine **100** was reacted with LIDAKOR in pentane at room temperature giving the corresponding amino vinyl ether **122** with total regio- and (*E*)-stereo-selectivity and in high yield (Scheme 49).



100 **122**

Scheme 49

This represents an interesting result, since the compound **122** is a very useful building block due to the presence of functional groups which can be conveniently elaborated (Scheme 50).



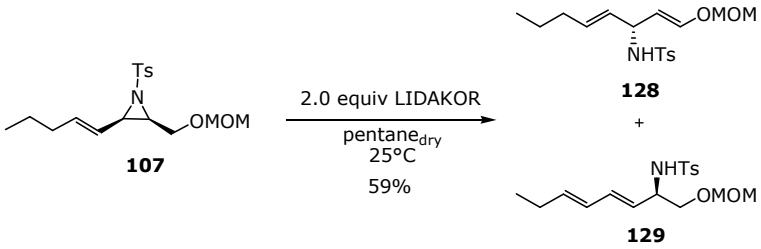
Scheme 50

It can give access, indeed, to *α*- or *β*-amino acids **123** and **124**, depending on the reaction conditions chosen to remove either the *tert*-butyldiphenylsilyl (pathway a) or the methoxymethyl (pathway b) protective group, and following oxidations of the free hydroxy group (Scheme 50).

Moreover the additional function can generate further transformations. For instance the *α*-amino acid **123** can be submitted to MOM deprotection giving (*S*)-2-amino-3-formylpropanoic acid **125**. The aldehydic moiety could be, then, conveniently transformed, or oxidized into carboxylic acid.

On the other hand, the *β*-amino acid **124** could be desilylated without difficulty with TBAF affording the corresponding (*S*)-3-amino-4-hydroxybutanoic acid **126** and the deprotected OH, then, could be conveniently transformed to give other useful non-natural amino acids. Moreover *β*-amino acids, as **124**, can be easily converted into *β*-lactams **127**, which are an interesting class of compounds due to their bactericide properties (Scheme 50).

(2*R*,3*R*)-2-((Methoxymethoxy)-methyl)-3-((*E*)-pent-1-enyl)-*N*-(*para*-toluen-sulfonyl)-aziridine **107** was also rearranged with two equivalents of LIDAKOR in pentane at 25° C to (1*E*,4*E*)-1-(methoxymethoxy)-*N*-(*R*)-((*para*-toluensulfonyl)-octa-1,4-dien-3-amine **128** and (3*E*,5*E*)-1-(methoxymethoxy)-*N*-(*R*)-((*para*-toluensulfonyl)octa-3,5-dien-2-amine **129**, the latter being the major product (Scheme 51).

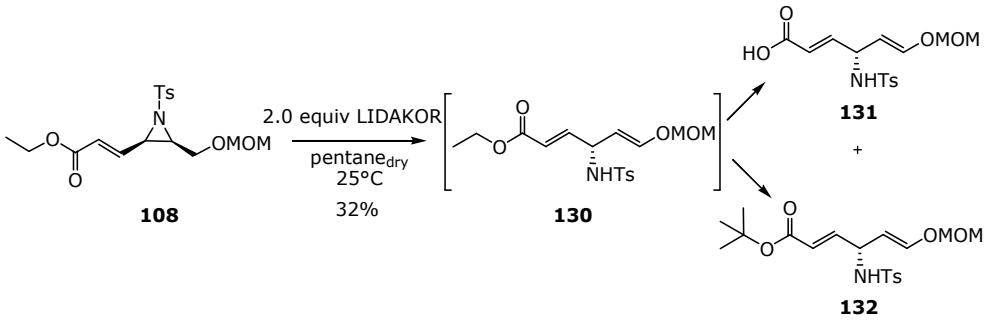


107 **128** **129**

Scheme 51

The lack of regioselectivity in this case derives by a competition between the two *β*-elimination sites, on the methylene next to the aziridine ring and on the allylic position.

Compound **108**, when treated with LIDAKOR in pentane at room temperature, rearranged to **130** by *β*-elimination on CH_2OMOM position but the ester moiety underwent a partial hydrolysis and transesterification, giving the carboxylic acid **131** and *tert*-butylester **132** (Scheme 52).

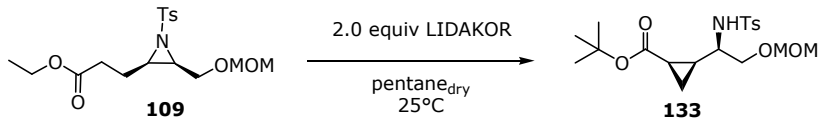


108 **130** **131** **132**

Scheme 52

A different reaction mechanism has been found when the saturated analogue, ethyl-3-((2*R*,3*R*)-3-((methoxymethoxy)-methyl)-*N*-(*para*-toluen-sulfonyl)-aziridin-2-yl)-propanoate **109**, has been submitted to treatment with the superbase LIDAKOR in pentane at room temperature.

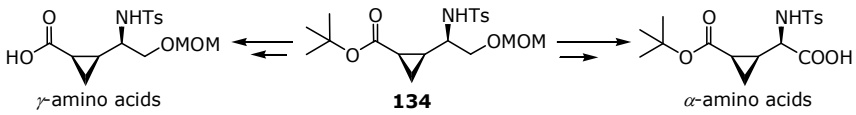
In fact in this case the initial removal of the hydrogen next to the ester group was followed by a 3-*exo* cyclization and transesterification due to the presence of K^{t}BuO (Scheme 53).



109 **133**

Scheme 53

Although the yields are not good probably due to the partial loss of the hydrolyzed product in the aqueous phases during work up, this result is interesting nevertheless because it allows non-natural cyclopropanic *α*- or *γ*-amino acids to be formed in a straightforward manner (scheme 54).



134

Scheme 54

3.3.2. 4-*exo* Intramolecular cyclizations

3.3.2.1 *Amino-oxetanes*

Although oxetanes have been known since 1858, when for the first time a molecule with an oxygenated four-membered ring was isolated,[202] they received

particular attentions only many years later, at the beginning of the 50s. Since then, they have been investigated with increasing interest owing to their reactivity (ring strain is of 25.4 kcal/mol, only 2 kcal/mol lower than the oxiranes value) and, above all, to the fact that the oxetane ring is present in several molecules having considerable biological and pharmacological properties.

Some examples of natural amino-oxetanes are reported below (Figure 16).

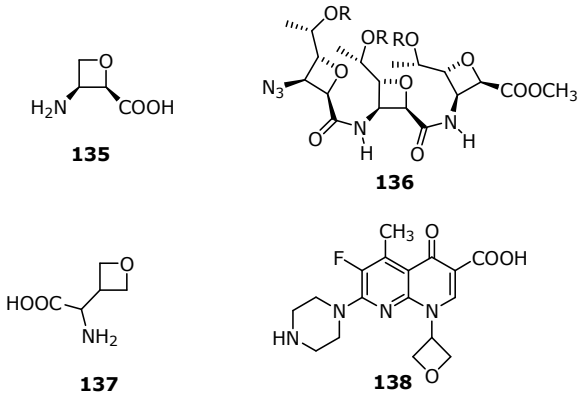
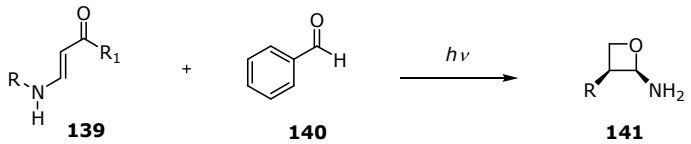


Figure 16

Oxetin **135** is the only natural *β*-amino acid having an oxetane ring.[203] It presents notable antibiotic properties and it is mainly employed as starting material for the synthesis of *β*-peptides, such as **136**. 3-Oxetanglycine **137** has been studied for its ability to displace [^{3}H]-glycine from the glycine site of the NMDA receptor complex.[204] The compound **138** and its analogues are powerful bactericides against *Staphylococcus Aureus* 209P.

Amino-oxetanyl rings are generally synthesized by formation of two new bonds by means of [2+2] photochemical cycloaddition reactions (Paternò-Büchi reaction)[205] between electron-poor enamines and aldehydes (Scheme 55). The regioselectivity is driven by the relative stability of the intermediate diradical species during the formation of the C-O bond.



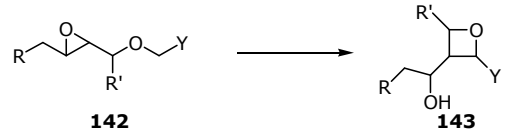
Scheme 55

If we are in the presence of *N*-acyl or *N*-alcoxycarbonyl enamines **139** and aldehydes **140,** the reaction occurs affording *cis*-substituted 3-amino-oxetanes

141 with good regio- and diastereoselectivity, while the use of aliphatic aldehydes leads to products with lower diastereoselectivity and lower yields, too.

The lack of efficient and general methodologies for the synthesis of enantiopure amino-oxetanes prompted us to look for a new and easy strategy based on a 4-*exo* intramolecular cyclization of enantiomerically enriched aziridinyl ethers.

As already discussed in chapter 2, the superbasic reagents efficiently promote the rearrangements of benzyl, propargyl or phenylthiomethyl oxiranyl ethers **142** to the corresponding di- or tri-substituted oxetanes **143** (Scheme 56).[21, 22, 105].[21, 22, 104, 105, 107]



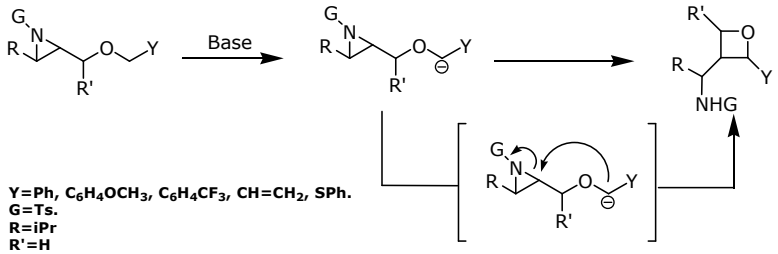
142 **143**

R=H, alkyl
R'=H, alkyl
Y=Ph, $C_6H_4OCH_3$, C_6H_4F, C≡C, SPh

Scheme 56

Key of the process is the presence in the Y position of an electron withdrawing group, which renders the *a*-CH_2 protons the more acidic in the substrate.

In analogy to the oxyranyl ethers **142** we have decided to investigate the possibility to promote 4-*exo* cyclization also on aziridinyl substrates and for this purpose we needed to study aziridines having an electron withdrawing substituent in the Y position, in analogy to the well-known process of oxiranyl ethers (scheme 57).[21, 22] Deprotonation of the methylene would lead to a lithium species which then should undergo an intramolecular cyclization by attack on the aziridine carbon atom.



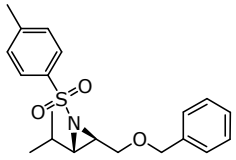
Y=Ph, $C_6H_4OCH_3$, $C_6H_4CF_3$, $CH=CH_2$, SPh.
G=Ts.
R=iPr
R'=H

Scheme 57

The substrates **114** whose synthesis has been described in the previous paragraphs were chosen at first.

*3.3.2.2 Isomerizations of aziridinyl ethers **114***

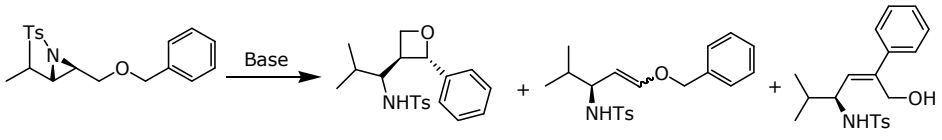
(2*R*,3*S*)-2-(Benzyloxy)methyl-3-*iso*-propyl-*N*-(*para*-toluensulfonyl)-aziridine **114a** (Figure 17) was our first test substrate in view of its similarity with the best performing oxiranyl ether.[21]



114a

Figure 17

Compound **114a** was reacted with a series of bases, such as LIDAKOR, LICKOR and BuLi/PMDTA, under different experimental conditions in order to have a general view on its reactivity. The expected products are reported in Scheme 58.



114a **144a-*trans*** **145a-*Z*:*E*** **146a-*Z***

Scheme 58

The results obtained are collected in Table 1.

entry	base	experimental conditions	products		total conversion(%)[a]	yield (%)[b]
1	3 equiv LIDAKOR	THF, -50°C, 36h	**144a-*trans***	1	30%	6%
			145a-*E*	1		9%
2	3 equiv LIDAKOR	DEE, -30°C, 36h	**144a-*trans***	1	45%	11%
			145a-*E*	1		9%
3	3 equiv LIDAKOR	pentane, r.t., 24h	**144a-*trans***	1	100%	39%
			145a-(*E*:*Z*=5:1)	3		22%
4	3 equiv LICKOR	THF, -50°C, 36h	-		0%	0%
5	3 equiv LICKOR	DEE, -30°C, 36h	-		0%	0%
6	3 equiv LICKOR	pentane, r.t., 24h	**145a-(*E*:*Z*=4:1)**		100%	45%
7	3 equiv BuLi/PMDTA	THF, -50°C, 24h	**144a-*trans***		30%	8%
8	3 equiv BuLi/PMDTA	pentane, r.t., 16h	**144a-*trans***	3	100%	52%
			146a-*Z*	1		

Table 1: [a] determined by ^{1}H-NMR
[b] determined after purification *via* chromatography

The same experimental conditions (2 equivalents of BuLi / diisopropylamine and potassium *tert*-butoxide in THF at -50° C - entry 1) which were used with oxiranes, were applied first, showing that in this case the reaction was slower and had a scarce selectivity. The addition of a third equivalent of base and more than 36 hours were required to reach a 30% conversion with a low selectivity: both the 4-*exo* cyclization **144a-*trans*** and *β*-elimination **145a-*E*** products, with an overall yield of 15%, were formed.

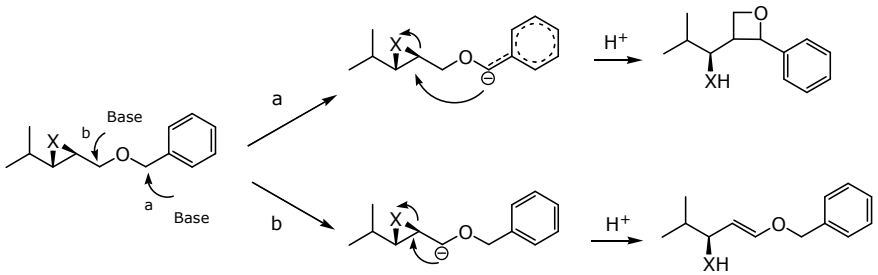
The use of anhydrous ether (entry 2), didn't lead to any improvement neither in terms of yield nor in selectivity. In an attempt to push the reaction toward the formation of the cyclization product **144a**, the isomerization was carried out in pentane at 25° C with three equivalents of LIDAKOR (entry 3). In this case a better conversion was indeed achieved but the selectivity was even lower: a 5:1 mixture of *E* and *Z* vinyl ether **145a** were obtained together with amino-oxetane **144a**.

The use of a different superbase like LICKOR in the same conditions used for LIDAKOR (entries 4, 5 and 6) didn't give any better result.

The use of ethereal solvents at low temperature gave no isomerisation product while when the reaction was performed in pentane at room temperature the aziridine **114a** was exclusively transformed into the *β*-elimination product **145a**, as a 80:20 mix of *E* and *Z* stereoisomers.

From these first results, it clearly appeared that aziridines are more reluctant to react in 4-*exo* fashion than the corresponding epoxy ethers.

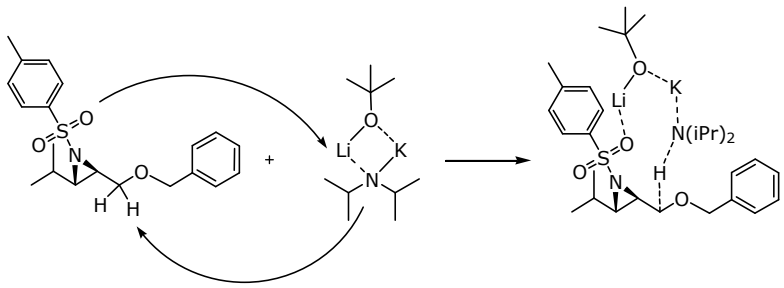
The reasons which drive the process towards a 4-*exo* ring closure or a β-elimination are rather complex but for sake of clarity we can simply suppose that while a deprotonation *α* to the phenyl ring leads to the 4-*exo* pathway (Scheme 59, a), the removal of the hydrogen close to the ring leads to the *β*-elimination reaction (Scheme 59, b).[206]



Scheme 59

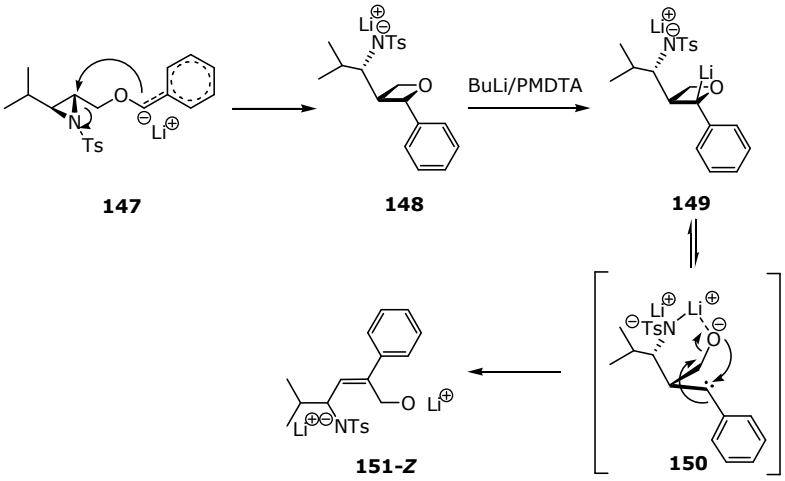
Benzyloxy oxiranes (X=O) show a clear preference for the 4-*exo* pathway[206] while the corresponding aziridines (X=NTs) give mainly *β*-elimination under the same reaction conditions. We can assume perhaps that an interaction between the tosyl group on nitrogen and the base can be responsible for this event: the base

becomes proximal to the hydrogen close to the ring and the β-elimination become the predominant if not the exclusive process (Scheme 60).



Scheme 60

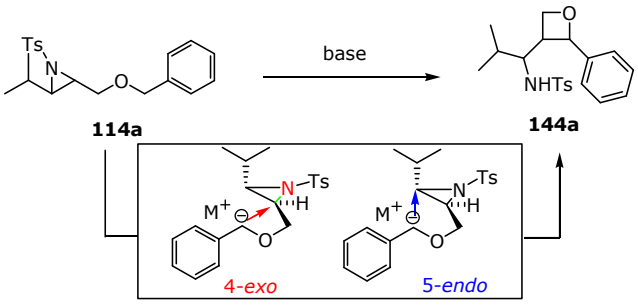
It is known that sometimes the use of different bases can completely change the regioselective course of a reaction. The optional site selectivity discussed in chapter 2 is an example. The use of strong bases such as LICKOR or of organolithium complexed with polyamines like PMDTA or TMEDA can give regioisomeric products when the presence of functional groups on a substrate to be deprotonated can influence the course of the reaction. For this reason we decided to test on our substrate the BuLi-pentamethyldiethylenetriamine (PMDTA) equimolar mixture, thus hoping to change the site of the attack of the base by avoiding the supposed complexation due to the tosyl group. Indeed when we used three equivalents of this mixture in THF at -50° C (entry 7), *N*-tosyl-aziridine **114a** was selectively converted to oxetane **144a-*trans*** even if the yield was very low (8%). In order to increase the conversion, the reaction conditions were modified and when three equivalents of BuLi/PMDTA were used at 25° C in pentane (entry 8) the conversion became satisfactory (no trace of the starting material were detected). The excess of base in this case led however to the formation of an additional rearranged product, the (*Z*)-5-methyl-2-phenyl-4-(*N*-*para*-toluensulfonylamino)hex-2-en-1-ol **146a,** whose formation can be explained in analogy with what has been established in the case of oxiranes.[21, 207, 208] We think that the aziridinyl ether **147** rearranges first to oxetane **148** and the 2-phenyl substituted oxetane **148** can be then deprotonated with excess of base in the benzylic position to give the intermediate **149** which is probably stable at low temperature. As soon as the temperature is raised, an *a*-ring opening of the lithiated oxetane **149** occurs, leading to a carbene type intermediate **150** followed by an alkyl-1,2-shift to the aminoalcoholate **151**. The phenyl group probably on one side assists the development of the carbene and on the other reduces (along with steric effects) the possibility of alkyllithium addition to the carbene itself (Scheme 61).



147 **148** **149** **150** **151-*Z***

Scheme 61

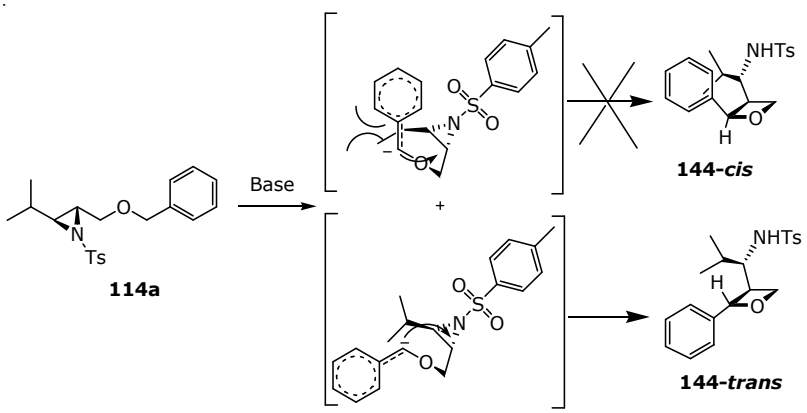
The formation of the oxetane ring as the unique cyclised product can be explained, in analogy with what has been found for the oxiranes analogues, by stereoelectronic considerations. The benzylmetallic species meets the stereoelectronic requirements for an intramolecular nucleophilic attack on the carbon which gives a 4-ring product while the attack on the other carbon, which would furnish a 5-ring compound, is disfavoured (Scheme 62).[209]



114a **144a**

Scheme 62

As shown below the only amino-oxetane formed is the one with a *trans* stereochemistry. The stereospecificity of these reactions can be explained with a steric interactions between the phenyl ring and the alkyl chain in the transition state for the *cis*-selective closure, which is completely absent in the transition state for the *trans* one (Scheme 63).



Scheme 63

The *trans* relationship in compound **144a** has been verified by NOE experiments. Irradiation of the hydrogen atom at carbon 2 of the ring caused a nuclear Overhauser effect on the methine bonded to the amino group (Figure 18, *a*) while irradiation on hydrogen at carbon 3 caused an effect on the phenyl hydrogen atoms in the *ortho* position (Figure 18, *b*).

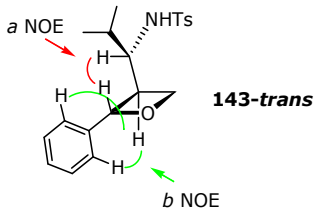
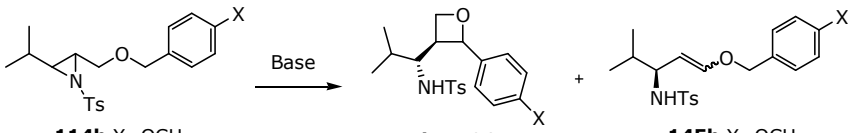


Figure 18

These first results prompted us to extend the base-promoted methodology on other differently Y protected substrates **114**, in order to understand if and how the structure of the substrate can influence the outcome of the reaction. At first we chose the two *para*-substituted benzyloxy aziridines **114b** and **114c** which were reacted in different reaction conditions and with different bases. (Scheme 64 and Table 2).



Scheme 64

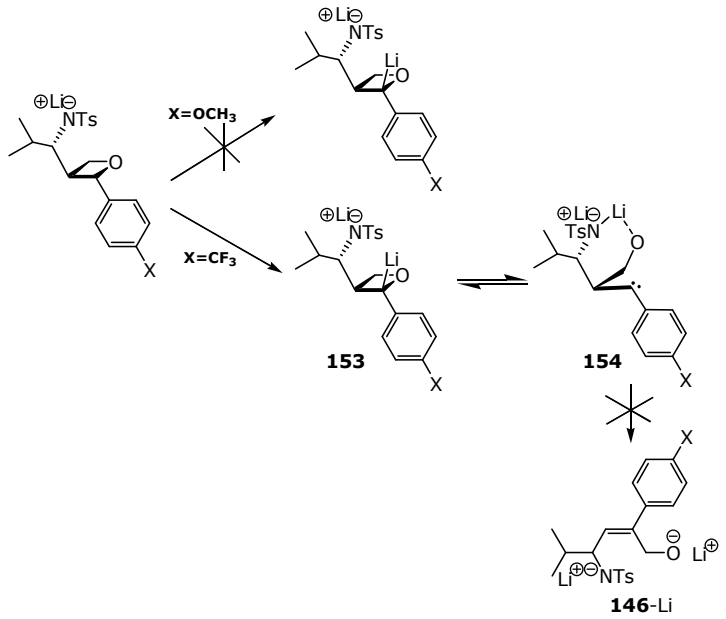
entry	X	base	experimental conditions	products	total conversion(%)[a]	yield (%)[b]
1	OCH_3	3 equiv LIDAKOR	THF, –50°C, 36h	-	0%	0%
2	OCH_3	3 equiv LIDAKOR	pentane, r.t., 24h	**145b** (***E***:***Z***=80:20)	55%	40%
3	OCH_3	3 equiv BuLi/PMDTA	THF, –50°C, 24h	**144b-*trans*** **116b**	100%	8% 50%
4	OCH_3	3 equiv BuLi/PMDTA	pentane, r.t., 16h	**144b-*trans*** **152**	100%	50% 18%
5	CF_3	3 equiv LIDAKOR	THF, –50°C, 36h	-	0%	0%
6	CF_3	3 equiv LIDAKOR	pentane, r.t., 24h	**145c** (***E***:***Z***=85:15)	56%	23%
7	CF_3	3 equiv BuLi/PMDTA	THF, –50°C, 36h	-	0%	0%
8	CF_3	3 equiv BuLi/PMDTA	pentane, r.t., 36h	**144c-*trans***	45%	30%

Table 2: [(a)] determined by ^{1}H-NMR
[(b)] determined after purification by chromatography

As expected, when they were treated with LIDAKOR in THF at low temperature no isomerization product was obtained (entries 1 and 5). The use of more drastic conditions (pentane at room temperature) led to the conversion to vinyl ether **145b** or **145c**, (entries 2 and 6) mainly in the *E* form. BuLi-PMDTA gave again the 4-*exo* cyclization product as exclusive product with both aziridine **114b** and **114c**. The former was converted into the corresponding oxetane both working at low temperature in THF and in pentane at 25 °C. In both cases however, part of the starting material followed a different route either by detosylation (entry 3) leading to aziridine **116** in THF or to the *N*-methyl aziridine **152** (entry 4) when the reaction was made in pentane in the presence of HMPA which is known to act as methylating agent. On the other hand the aziridine **114c** could be converted into the desired oxetane with good chemo-, regio-, and stereo-selectivity only when working at room temperature in pentane (entries 7 and 8).

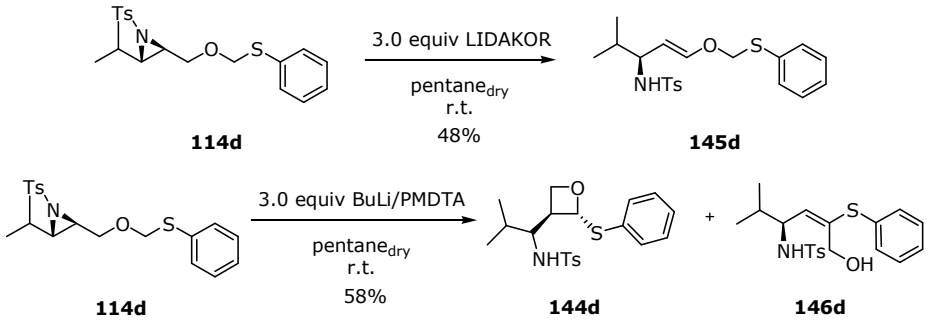
The different reactivity compared with the *N*-tosylaziridine **114a** could just be due to the presence of the substituent in *para* position. Actually the further rearrangement to 1,4-aminoalcohol was never observed in the case of the OCH_3 substituted aziridine owing to an insufficient acidity of the hydrogen in the carbon 2 of the oxetane **144b**. On the other hand, in the case of the CF_3 substituent, the hydrogen on the carbon 2 of the oxetane ring of **144c** is sufficiently acidic to be deprotonated (**153**), but probably the carbene intermediate **154** is too stable to

induce the 1,2 migration which leads to the 1,4-aminoalcohol **146**-Li (Scheme 65).



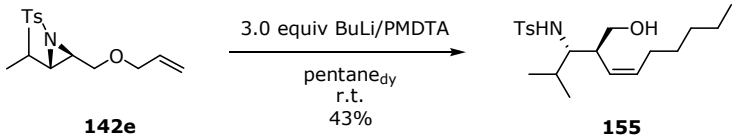
Scheme 65

Aziridine **114d** showed a behaviour similar to that of **114a**: treatment with LIDAKOR in pentane at room temperature gave the vinyl ether **145d** as a pure *E*-stereoisomer (Scheme 66, top), while in presence of three equivalents of BuLi and PMDTA a mixture of oxetane **144d** and 1,4-aminoalcohol **146d** was obtained in a 4:1 ratio (Scheme 66, bottom).



Scheme 66

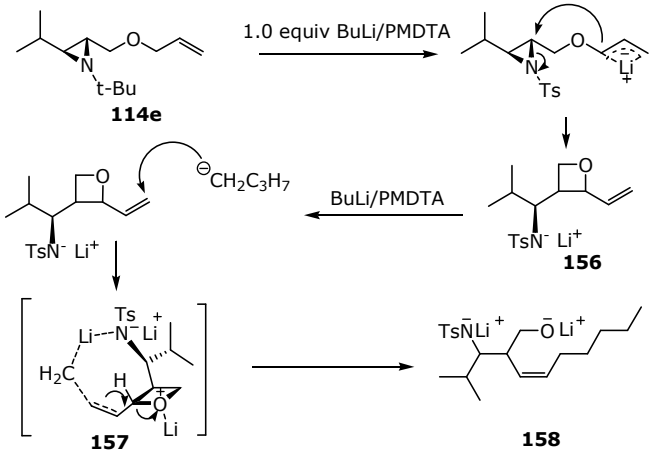
A different pathway has been observed when aziridine **114e** was treated with three equivalents of BuLi/PMDTA. In fact (*Z*)-2-(*S*)-((S)-2-methyl-1-(*N*-*para*-toluensulfonylamino)propyl)non-3-en-1-ol **155** was formed as the only reaction product with perfect stereocontrol (Scheme 67).



142e **155**

Scheme 67

This result can be explained by the presence of an excess of BuLi (Scheme 68): the first equivalent of base metalated the allylic position thus producing the corresponding oxetane **156**, then a second equivalent attacked the terminal carbon of the vinylic moiety of **155** leading to ring-opening (**157**) and further rearrangement to the unsaturated amino al6coholate **158**.



114e **156** **157** **158**

Scheme 68

The mechanism is totally regioselective; only the *Z* stereoisomer was formed and this may be the consequence of a cyclic transition state due to lithium cation chelation between the butyl carbanion and the nitrogen of the tosyl group (**157**).

In summary, superbases and complex organometallic bases have offered the chance to open new routes for the transformation of aziridinyl ethers in addition to what is already well established for oxiranes (see schemes 23 and 56). In particular *β*-elimination rearrangements of new functionalized aziridinyl substrates and 4-*exo* cyclizations have been studied. Despite a clear difference in the reactivity profile between aziridines and oxiranes, it has been possible to set up conditions suitable for both kind of reactions which allow us to have access to allyl amines and amino-oxetanes with good yields and selectivities. Future studies will be focused on the analysis of the 7-*endo* intra molecular cyclizations and on the achievement of experimental procedures in order to improve yields and selectivity of these processes.

4. BASE-INDUCED REARRANGEMENTS OF EPOXIDES AND AZIRIDINES MEDIATED BY MICROWAVES

4.1. Introduction

The research in the field of the development of new methodologies in organic synthesis is still of a paramount importance and a lot of efforts have been devoted in the last years to find new routes to known and new molecules which are required to answer the present needs in terms of health, materials, energy etc. etc. These new methodologies have to be characterized by high efficiency and selectivity and have to be in line with the requirements of a sustainable developments. For this reasons research in the area of new catalytic processes, new reaction media and new alternative energy sources like microwaves are absolutely important and up-to-date. In this chapter we will describe our results on the use of microwave activation as a useful tool for performing selective isomerizations of epoxides and aziridines without the use of superbases.

4.1.1. Aim of the study

As we have described in details in the previous chapters, superbases are useful tools to selectively replace a hydrogen atom with a metal in non-acidic positions, but often they need a special care in their preparation and handling. To find alternative, easier methods and / or more available reagents for performing the same kind of reactions, is then very attractive and important.

It is known, and we have widely described it in the previous chapters, that the reactivity of organolithium reagents is strictly related to their tendency to form aggregates in solution. Such oligomeric structures usually decrease the basic power of the organometallic reagents and, in order to perform metalations of not activated substrates, ligands or high polar solvents which are capable to break the oligomers are employed (Figure 6).

Keeping in mind these results, we have reasoned that perhaps microwave irradiations, either through a thermal or electromagnetic effect, could have a remarkable effect in breaking up these aggregates, thus increasing the metalating activity of simple organolithium reagents and promoting isomerizations of substrates which are not easy to rearrange under standard conditions.[210] The base-promoted isomerisation of oxiranes and aziridines, which we have deeply studied and discussed, seemed to us a good benchmark in order to verify our hypothesis. It is worth to remind that both oxiranes and aziridines require the use of superbases in order to rearrange to the corresponding allyl alcohols or amines

with good yields or selectivities. We can argue that MWs could replace superbases in these processes.

4.1.2. Microwave Theory

Microwave irradiation is an electromagnetic irradiation in the frequency range of 0.3 to 300 GHz. All microwave reactors for chemical synthesis operate at a frequency of 2.45 GHz to avoid interference with telecommunication and cellular phone frequencies. The energy of the microwave photon in this frequency region is 0.0016 eV, therefore, it cannot induce chemical reactions too low to break chemical bonds and also lower than the energy of Brownian motion.[211-214] Microwave enhanced chemistry is based on the efficient heating of materials by "microwave dielectric heating" effects. This phenomenon, depending on the ability of a specific material (solvent or reagent) to absorb microwave energy and convert it into heat, is caused by two main mechanisms: dipolar polarization and ionic conduction. Irradiation of the sample at microwave frequencies results in the dipoles or ions aligning along the applied electric field.

As the applied field oscillates, the dipole or ion field attempts to realign itself with the alternating electric field and, in the process, energy is lost in the form of heat through molecular friction and dielectric loss. The amount of heat generated by this process is directly related to the ability of the matrix to align itself with the frequency of the applied field. If the dipole does not have enough time to realign, or reorients too quickly with the applied field, no heating occurs. The ability of a specific substance to convert electromagnetic energy into heat at a given frequency and temperature is determined by the so-called "loss factor tand". This loss factor is expressed as the quotient tand=e''/e', where e'' is the dielectric loss, which is indicative of the efficiency with which electromagnetic radiation is converted into heat, and e' is the dielectric constant describing the ability of molecules to be polarized by the electric field. A reaction medium with a high tand value is required for efficient absorption and, consequently, for rapid heating. In general, the tand>0.5 means high capacity to adsorb microwave irradiations, tand between 0.1–0.5 medium capacity and tand<0.1 scarce ability to adsorb microwave irradiations. In any case low tand values don't preclude the use of microwave-heating. Since either the substrates or some of the reagents / catalysts are likely to be polar, the overall dielectric properties of the reaction medium will in most cases allow sufficient heating by microwaves.

Traditionally, organic synthesis is carried out by conductive heating with an external heat source (for example, an oil bath). This is a comparatively slow and inefficient method for transferring energy into the system, since it depends on the thermal conductivity of the various materials that must be penetrated, and results in the temperature of the reaction vessel being higher than that of the reaction mixture. In contrast, microwave irradiation produces efficient internal heating (in-

core volumetric heating) by direct coupling of microwave energy with the molecules (solvents, reagents, catalysts) that are present in the reaction mixture.

The acceleration of reactions and sometimes altered product distributions compared to oil-bath experiments by microwave exposure results from material-wave interactions leading to thermal effects (which may easily estimated by temperature measurements) and specific (non-purely thermal and athermal) effects. Clearly, a combination of these two contributions can be responsible for the observed effects.[215-221] In the majority of cases the reason for the observed rate enhancements is a purely thermal / kinetic effect, that is, a consequence of the high reaction temperatures that can rapidly be attained when irradiating polar materials in a microwave field. This effect can be rationalized by consideration under the Arrhenius law[222, 223]

$$k=A\ \exp(-\Delta G^{\neq}/RT) \qquad \textbf{\textit{eq 1}}$$

where k is the rate constant, A the pre-exponential factor or simply the prefactor, $\Delta G^{\neq}$ the activation energy, T the temperature in Kelvin and R is the gas constant. The increase of the pre-exponential factor A is representative of the possibility of molecular impacts. Decrease in activation energy is certainly connected to dipolar polarization.

In addition to the above mentioned thermal / kinetic effects, microwave effects that are caused by the uniqueness of the microwave dielectric heating mechanisms must also be considered. These effects should be termed "specific microwave effects" and shall be defined as accelerations that cannot be achieved or duplicated by conventional heating, but essentially are still thermal effects. In this category fall, for example:

- the superheating effect of solvents at atmospheric pressure;[224-226]
- the selective heating of, for example, strongly microwave absorbing heterogeneous catalysts or reagents in a less polar reaction medium;[227-232]
- the formation of "molecular radiators" by direct coupling of microwave energy to specific reagents in homogeneous solution (microscopic hotspots);[229]
- the elimination of wall effects caused by inverted temperature gradients. It should be emphasized that rate enhancements falling under this category are essentially still a result of a thermal effect (that is, a change in temperature compared to heating by standard convection methods), although it may be difficult to experimentally determine the exact reaction temperature.

We have to add also the possibility of "nonthermal microwave effects" (also referred to as athermal effects). These should be classified as accelerations that cannot be rationalized by either purely thermal / kinetic or specific microwave effects. Non-thermal effects essentially result from a direct interaction of the electric field with specific molecules in the reaction medium. It has been argued that the presence of an electric field leads to orientation effects of dipolar

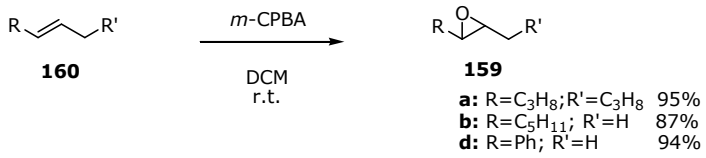
molecules and hence changes the pre-exponential factor *A* or the activation energy (entropy term) in the Arrhenius equation.[215-217] A similar effect should be observed for polar reaction mechanisms, where the polarity is increased going from the ground state to the transition state, thus resulting in an enhancement of reactivity by lowering the activation energy.[217] Our investigation on polar organometallic reactivity rely both on purely thermal effect and in non-thermal effect due to the presence of an external electric field.

4.2. Synthesis of the substrates

For our initial investigation, to verify the real efficiency of the MWs on rearrangement reactions we decided to avoid structural complexity and focused on small heterocycles without any functional group.

4.2.1. Synthesis of epoxides

All non commercially available epoxides **159** were obtained in *meso*-form through an epoxidation reaction with *meta*-chloroperbenzoic acid from the corresponding alkenes **160**. The reaction occurred under mild conditions affording pure products in high yields without the need of further purification steps (Scheme 69).



160 **159**

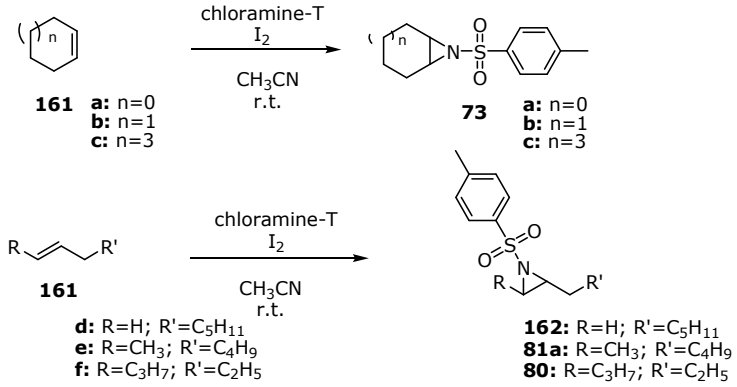
a: R=C_3H_8;R'=C_3H_8 95%
b: R=C_5H_{11}; R'=H 87%
d: R=Ph; R'=H 94%

Scheme 69

4-Octene oxide **159a**, 2-octene oxide **159b** and *β*-methylstirene **159c** were synthesized following this procedure.

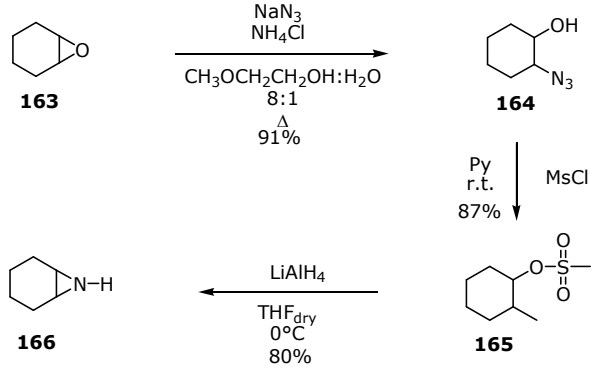
4.2.2. Synthesis of aziridines

Most aziridines were synthesized by a straightforward direct aziridination of alkenes with chloramine-T and substoichiometric amount of iodine. Different racemic *para*-toluensulfonyl aziridines **73**, **162**, **80** and **81a** were thus formed from the corresponding alkenes **161** (Scheme 70) in reasonable yields, after purification.[233, 234] Despite the yields are not excellent we must point out that it is a single step process starting from very cheap materials.



Scheme 70

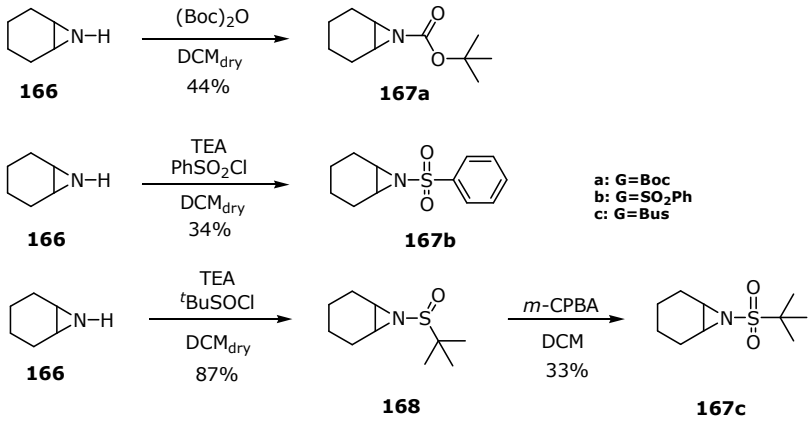
An alternative, longer but usually high yielding method, is the three-step procedure which leads for example to N-H aziridine **166** from cyclohexene oxide **163** through opening with sodium azide (**164**), OH mesylation (**165**) and reductive ring closure with lithium aluminum hydride (**166**)[159, 198, 235] (Scheme 71).



Scheme 71

From the aziridine **166**, then, a set of differently *N*-protected aziridines (G=Boc, SO_2Ph and Bus) were synthesized following usual procedures (Scheme 72).

In particular, *tert*-butyl 7-azabicyclo[4.1.0]heptane-7-carboxylate **167a** was formed by treatment with di-*tert*-butyl dicarbonate and DMAP; *N*-benzene-sulfonyl-7-azabicyclo[4.1.0]heptane **167b** was prepared with benzenesulfonyl choride and TEA; 7-(*tert*-butyl-sulfonyl)-7-azabicyclo [4.1.0]heptane **167c** was synthesized in two step by treatment with *tert*-butylsulfinyl chloride, to give **168** which was further oxidized with *m*-CPBA.



Scheme 72

4.3. MWs mediated base-promoted isomerizations of strained heterocycles

The set of epoxycycloalkanes or epoxyalkanes and cycloalkyl and alkyl aziridines obtained as described above, has been treated with LDA under microwave irradiations (Figure 19).

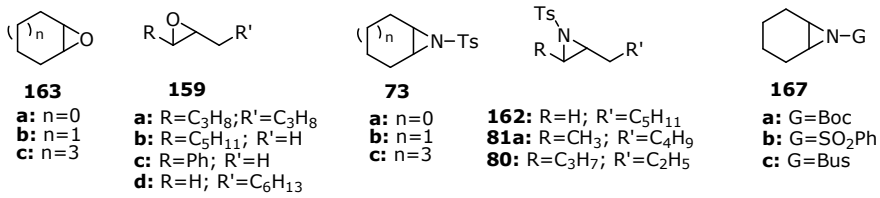


Figure 19

LDA has been chosen as the base because of its strong, non-nucleophilic character and because of its tendency to self-aggregation (dimer in THF, for instance).[236-242]

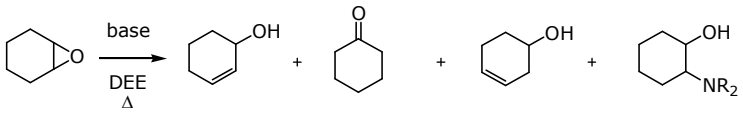
4.3.1. Isomerization of epoxides

4.3.1.1. Cyclohexene oxide

Cyclohexene oxide **163b** was chosen as model molecule to set up the optimal reaction conditions.

The deprotonation of cyclohexene oxide **163b** with a lithium amide to obtain the allylic alcohol **169b**, indeed, is a well-known methodology. Since the first

report by Krandall in 1967,[243] where a 67% conversion was reported, the area has received much attention. In 1972 a more systematic investigation was carried out by Rickborn.[244] A set of lithium amides were tested with cyclohexene oxide in ether under reflux (Scheme 73)



163b **169b** **170b** **171** **172**

Scheme 73

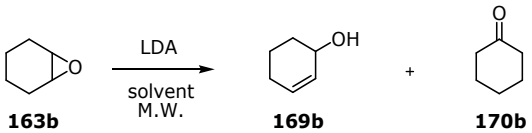
entry	base $LiNR_2$	Yd(%) 169b	Yd(%) 170b	Yd(%) 171	Yd(%) 172
1	R=C_2H_5	86	3	0	10
2	R=*n*-C_3H_7	99	0	0	0
3	R=*n*-C_4H_9	97	0	0	3
4	R=*iso*-C_3H_7	38	33	0	0
5	R=*iso*-C_4H_9	68	10	5	18
6	R=*sec*-C_4H_9	40	46	0	13
7	R=*c*-C_6H_{11}	54	39	0	3

Table 3: Results of the isomerization of cyclohexene oxide **163b** in DEE at reflux with different lithium amides

It was found that depending on the base used a series of isomerization products were formed together with the expected allylic alcohol (Table 3).[151]

As anticipated in the previous chapters, the lack of selectivity of these reactions was successively almost solved with the employment of superbases, in particular LIDAKOR (see chapter 2).[104]

In this work a set of reactions by changing solvent, amount of base, temperature, time and irradiation power were carried out (Scheme 74).



163b **169b** **170b**

Scheme 74

The results are collected in Table 4.

entry	solvent	power (W)	time	temperatures (°C)	Yd (%)[(a)]169a	Yd (%)[(a)]151
1	pentane	300	15′	60	40	23
2	pentane	300	10′	60	48	16
3	pentane	300	10′	50	42	8
4	pentane	300	10′	40	40	8
5	pentane	300	5′	60	54	27
6	pentane	200	20′	60	30	29
7	pentane	200	10′	60	49	13
8	pentane[(b)]	100	10′	60	48	27
9	pentane	50	10′	60	47	17
10	THF	300	5′	60	44	8
11	DEE	300	5′	50	42	8
12	DME	300	5′	60	5	0
13	diossane	300	5′	60	27	0

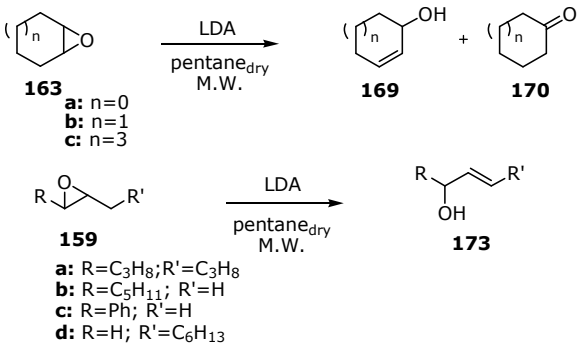
Table 4: Results of the isomerization of cyclohexene oxide **163b** under microwaves irradiation
[(a)] measured by GC/MS
[(b)] partial conversion (Conv=90%)

All these reactions have shown a non-total selectivity towards the formation of the allylic alcohol **169b**. A mixture of cyclohexen-2-ol **169b** and cyclohexanone **170b** was always obtained. The first attempts were focused on the treatment of cyclohexene oxide **163b** with LDA in pentane. Increasing the irradiation time caused a decrease in the yield and ratio between allylic alcohol **169b** and ketone **170b** (entries 1, 2 and 5) while a change of the irradiation power did not affect product compositions and yields (entries 2, 7, 8 and 9). The temperature seems to play a less determinant role on the reaction outcome (entries 2 to 4). The choice of the solvent, on the other hand, is more significant:[188] changing from pentane to THF or DEE causes a decrease of the overall yield (entries 5, 10 and 11), but an increase of the ratio between **169b** and **170b**; DME and 1,4-dioxane gave the product **169b** only with low yield.

After this first series of experiment, we can then conclude that the use of two equivalents of LDA in pentane with a MW irradiation time of 5′ at 300 W resulted the best conditions even if yields and selectivity were not better than using conventional methods.

4.3.1.2. *Other epoxides*

In an attempt to generalize the microwave-mediated isomerisation, other epoxides, such as the bi- **163** (n=0, 3) or mono-cyclic **159** compounds mentioned above, were submitted to MW irradiation in the presence of LDA under the same reaction condition found for cyclohexene oxide **163b** (Scheme 75). The result are reported in Table 5, where we have also collected, for sake of comparison, the yields obtained by traditional heating with oil bath and by superbases.



Scheme 75

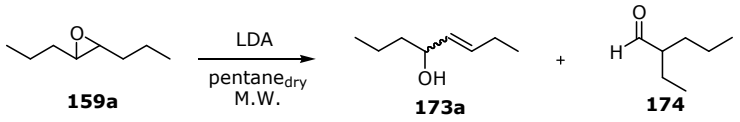
entry	LIDAKOR[104]	traditional heating[(a)]	MWs (Yd)[(b)]
1	**169a:** 58%	**169a:** 53% **170a:** 9%	**169a:** 71% **170a:** 7%
2	**169b:** 60%	**169b:** 65% **170b:** 30%	**169b:** 54% **170b:** 27%
3	**169c:** 70%	**169c:** 8% **35:** 92%	**35:** 100%
4	**173a:** 65%	**173a:**[(c)] 39% **174:** 8%	**173a:**[(c)] 23% **174:** 8%
5	**173b:** 90%	**173b:** 60%	**173b:** 71%
6	**173c:** 32% **176:** 32	**173c:** 22% **175:** 11% **176:** 32% **177:** 35%	**173c:** 38% **175:** 0% **176:** 21% **177:** 36%
7	**178:** 97%	**178:** 38% **179:** 46%	**178:** 25% **179:** 55%

Table 5: Results of the isomerization of epoxides **163** and **159** under microwaves irradiation.
[(a)] 2.0 equiv LDA in pentane 6-12h;
[(b)] 2.0 equiv LDA in pentane, MW irradiation (300W) for 5' at 60°C. Yield measured by GC/MS;
[(c)] partial conversion (Conv=85% for traditional heating, Conv=92% for MW heating).

An analysis of the results obtained by using the different methodologies shows that the use of MW irradiations increases the yields of the isomerised

product in most cases, but does not lead to a total selectivity in favour of the allylic alcohols as observed with superbases. In fact from all three bicyclic oxiranes **163** both allylic alcohol **169a** and **169b** and ketones **170a** and **170b** or bicyclic alcohol **35** are formed. In particular yields were improved by using MW irradiation in the case of cyclopentene oxide **163a** and cyclooctene oxide **163c** (entries 1 and 3). The latter showed a total selective conversion to the bicyclic alcohol **35** through an *α*-lithiation followed by a transanular insertion (see Scheme 15, paragraph 2.3). The isomerization of cyclohexene oxide **163b**, instead, exhibited lower yields (entry 2).

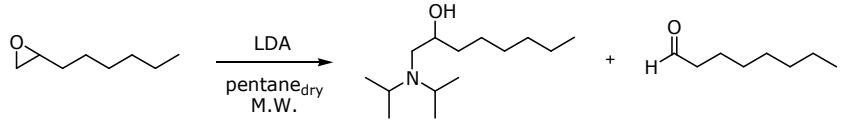
The epoxide **159b** gave instead a completely selective isomerization to the corresponding allylic alcohol (entry 5). The higher tendency of the base to deprotonate the methyl on C-1, rather than of the methylene in C-4 (less acidic for steric and electronic reasons), has lead to the exclusive formation of the alcohol **173b**. In oxirane **159a** such steric discrimination is not present and the same reaction conditions leads to a mixture of products (entry 4, Scheme 76).



159a **173a** **174**

Scheme 76

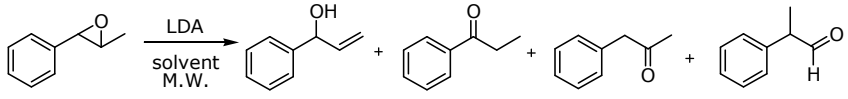
Probably due to a lower steric hindrance on the ring carbon, the epoxide **159d** is the only example in which the nucleophilic addition (**178**) of the base has been found in competition to the isomerisation (**179**) (Scheme 77).



159d **178** **179**

Scheme 77

Even more complicate is the case of the *β*-methylstirene oxide **159c** which is known to give four isomerization products when treated with LDA under conventional conditions. The use of MWs doesn't lead to any significative improvement: three out of the four possible products are observed anyway (Scheme 78).



159c **173c** **175** **176** **177**

Scheme 78

However, in all cases a drastic diminution of the reaction times was observed.

4.3.2. Isomerization of aziridines

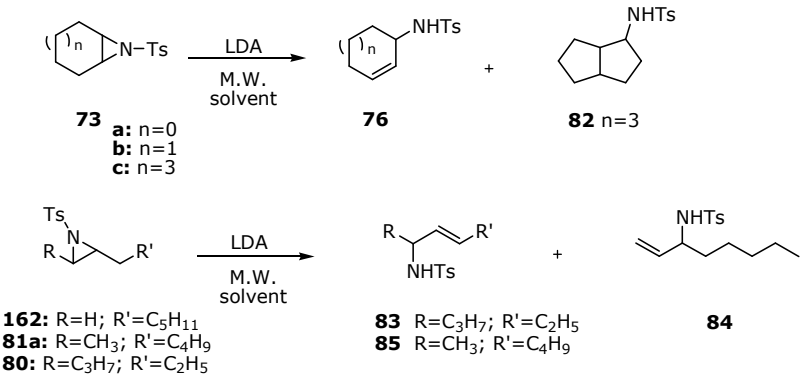
A similar investigation was carried out on aziridines. It is worth noting, as already underlined previously, that no literature information is available on their isomerization by LDA only. According to O'Brien finding in fact, no aziridine isomerization takes place when employing unactivated bases such as LDA[189] but organolithiums in the presence of (–)-sparteine[152, 245] or superbases[106] have to be used.

The aim of this part of the project, therefore, was focused on the attempt to extend the MWs mediated isomerization methodology to aziridines which is a more intriguing case than the oxirane rearrangement.

We first decided to verify if LDA is really not able to promote any rearrangement and for doing this we performed a series of experiments under different reaction conditions. We found, with our surprise that LDA in pentane at reflux or even at room temperature was able promote the conversion to allyl amine; in particular the better condition was recorded by working at room temperature. These data, therefore, goes in contrast with the known literature references.

We decided anyway to investigate the effect of the MW irradiation as promoter of the rearrangement of aziridines (Scheme 79). The results are collected in Table 6, where a comparison with the rearrangement by LDA and superbase is also reported.

As a general result we can observe that microwave irradiation gives access to isomerization products in similar or, even, higher yields (entries 1, 4, 7, 11 and 12). For instance the irradiation of the bicyclic aziridines **73a** and **73b** led to improved yields of the corresponding allylic alcohols **76a** and **76b** with respect both to the use of superbases and LDA (entries 1 and 2) and the bicyclic alcohol **82** was formed in good yield and selectivity upon treatment of the aziridine **73c** (entry 3).



73 **a:** n=0 **b:** n=1 **c:** n=3 **76** **82** n=3

162: R=H; R'=C_5H_{11}
81a: R=CH_3; R'=C_4H_9
80: R=C_3H_7; R'=C_2H_5

83 R=C_3H_7; R'=C_2H_5
85 R=CH_3; R'=C_4H_9

84

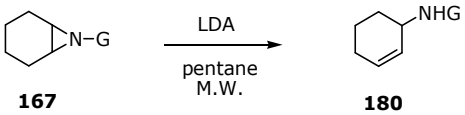
Scheme 79

entry	aziridine	solvent	superbase[(a)] [106]	LDA at r.t.[(b)]	MWs condition[(c)]
1	**73a**	pentane	42%	49%	51%
2	**73a**	THF	-	-	0%
3	**73a**	DEE	-	-	44%
4	**73b**	pentane	46%	41%	61%
5	**73b**	THF	-	-	0%
6	**73b**	DEE	-	-	38%
7	**73c**	pentane	**160:** 64%	**160:** 27%	**160:** 63%
8	**73c**	THF	-	-	0%
9	**73c**	DEE	-	-	0%
10	**162**	pentane	0%	-0%	0%
11	**81a**	pentane	**85: 84 =** 67 : 33 (Yd_{tot}=60%)	**85:** 13% **84:** 4%	**85:** 21% **84:** 4%
12	**80**	pentane	**83:** 48%	**83:** 19%	**83:** 32%

Table 6: Results of the isomerization of aziridines **145** under microwaves irradiation
[(a)] 2.0 equiv LIDAKOR in pentane 12-24h at r.t..
[(b)] 2.0 equiv LDA in pentane 4-6h at r.t.. Yield determined after flash chromatography
[(c)] 2.0 equiv LDA in pentane, MW irradiation (300W) for 2' at 60°C. Yield determined after flash chromatography

The treatment of acyclic aziridines with LDA in pentane resulted more complex. The mono-substituted aziridine **162** did not give any isomerization but only degradation products were recovered instead (entry 10). The two disubstituted aziridines **80** and **81a** furnished the isomerized products in yields higher than those obtained with LDA (entries 11 and 12). The influence of the solvent was also analyzed. On the contrary of what observed with epoxides, the reaction outcome is dramatically dependent on the choice of the solvent. Only the reaction in pentane gave access to the isomerization in good yields. The same reactions, carried out in DEE (entries 3, 6 and 9), led to a lower conversions and in THF (2, 5 and 8) to extensive decomposition.

Finally the influence of the *N*-protective group was analyzed. Three different groups were chosen: benzensulfonyl (G=SO_2Ph), *tert*-butylsulfonyl (G=Bus) and *tert*-butylcarboxylate (G=Boc). A series of experiments were carried out in pentane under microwave irradiation (Scheme 80) and these results were compared with traditional methodologies (LDA in pentane at room temperature and LIDAKOR in pentane at room temperature).



167
a: G=Boc
b: G=SO_2Ph
c: G=Bus

180

Scheme 80

All results are collected in Table 7.

entry	aziridine	superbase[a] [106]	LDA at r.t.[b]	MW condition[c]
1	**167a**	**166:** (not known)	0%	0%
2	**167b**	42%	50%	67%
3	**167c**	12%	50%	60%

Table 7: Results of the isomerization of aziridines **167** under microwaves irradiation
[a] 2.0 equiv LIDAKOR in pentane 12-24h at r.t..
[b] 2.0 equiv LDA in pentane 4-6h at r.t.. Yield determined after flash chromatography
[c] 2.0 equiv LDA in pentane, MW irradiation (300W) for 2' at 60°C. Yield determined after flash chromatography

As shown in the Table 7, while treatment of *N*-Boc-protected aziridine **167a** gave no isomerized product (entry 1), with *N*-benzene-sulfonyl-7-azabicyclo[4.1.0]heptane **167b** the use of microwaves gave the best results (entry 2) which are confirmed also in the case of the Bus-protected substrate although with a slightly worse yield.

From this set of experiment we can thus conclude that the use of microwave irradiation on promoting isomerizations of epoxides and aziridines has led to a reduction of reaction times and to an increase of the yields in many cases, although the performance of superbases are often still the best concerning the selectivity. However MW irradiation has allowed to perform reactions on substrates for which traditional heating is not effective at all. These technique, which had never applied before in this field, can be thus very promising.

5. SYNTHESIS OF A NEW FAMILY OF 2-ETHYLIDENE-γ-UNSATURATED δ-AMINO ESTER VIA MICROWAVE ACTIVATED STILLE COUPLING

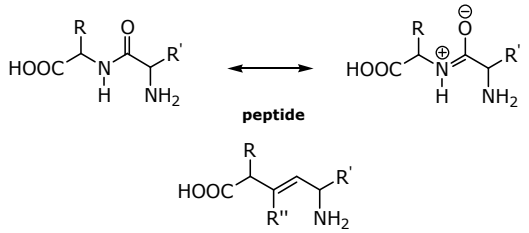
5.1. Introduction

Microwaves activation as a non-conventional energy source has become a very popular and useful technology in organic chemistry. The number of annual publications on microwave assisted organic chemistry is growing rapidly with almost one thousand publications in print since the pioneering work of Gedye in 1986.[246] Most of these publications describe important accelerations for a wide range of organic reactions, accomplished often by an improvement of selectivity.

In this thesis work our studies on microwave activation have been extended, in collaboration with Dr. Gianna Reginato, to another class of reactions: Stille Coupling reactions. Over the past few years, the efficiency of microwave flash heating in accelerating cross-coupling reactions has been successfully demonstrated and very fast Stille reactions have been achieved in solution as well as on solid phase.[28, 29] Microwave activation of this process, using a particular class of highly sensitive electrophiles, has been studied and applied to the synthesis of a new family of enantiomerically enriched *δ*-amino ester.

5.1.1. Peptidomimetics and Isosters

Peptidomimetics are valuable tools for conformational investigations of bioactive peptides and proteins, and for the development of peptide leads for pharmaceuticals. This class of compounds has been a field of interest in the group where this work has been carried out, with the aim of developing new procedures for biologically active molecular scaffolds (see chapter 2).

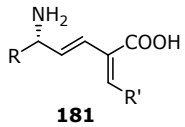


Scheme 81

In particular, the replacement of the peptide amidic moiety with a chemically more resistant and *in vivo* stable functionality is an important research area in

medicinal chemistry. In recent years, many non-hydrolysable mimetics have been developed and among the others the relatively rigid tri-substituted (*E*)-alkene ψ[(*E*)–C(R)=CH)] isosters have been used in a number of enzyme inhibitors or antibiotics (Scheme 81).[247-250]

Basically, in many cases, the isosteric replacement of a dipeptide unit requires the preparation of a *δ*-amino acid. Very recently, this class of compounds has stimulated a great interest since, as in the homologous *β*- and *γ*-peptides, conformational analysis of *δ*-peptides revealed a considerable potential of secondary structure formation.[251-254] In particular, it has been shown that the elongation of the backbone of the amino acid constituents might enrich the field of folded structures and for this reason *δ*-peptides and *δ*-amino acids are considered a useful tool also in peptides and foldamers design and in material sciences.[255, 256] For these reasons, we envisaged unsaturated *δ*-amino acids as those reported in structure **181** (Figure 20) bearing an ethylidenic conjugated double bond, as an interesting class of new molecules that could be exploited, for instance, as rigid spacers[257-259] and as Michael acceptor-binding sites for the design of new enzyme inhibitors.[260, 261]



181

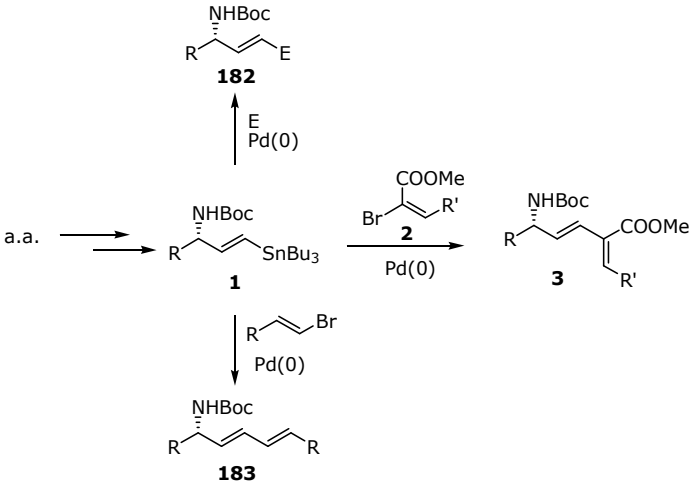
Figure 20

To the best of our knowledge, this class of compounds was not reported previously.

5.1.2. Aim of the project

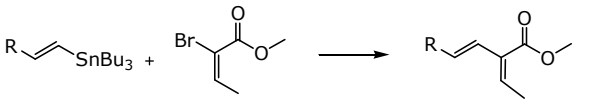
Naturally occurring amino acids have useful application as building blocks for organic synthesis.[262] This fact has found a great number of applications and has been a focus of interest in the research group were this work has been carried out.[263-267] Stemming from this experience, and in consideration of the above mentioned properties of peptidomimetics, we have been particularly attracted by the possibility of designing a new and flexible method to prepare orthogonally protected polyunsaturated-*δ*-amino esters such as **3** (Scheme 82). Key intermediates in the approach we suggest were chiral *tert*-Boc-protected stannylallylamines **1**, which are easily accessible from amino acids using standard procedures developed in the laboratory were this thesis work was carried out.[30] This compounds are versatile synthons, and can be coupled with several electrophiles under Pd(0) catalysis (Stille conditions) to afford a wide range of *γ*-

substituted allylamines **182**,[30] or dienylamines **183**[264, 265] (Scheme 82). This protocol is mild, stereospecific, highly chemoselective and suitable for chiral substrates.[268, 269] Accordingly, we envisaged that *δ*-amino esters **3** could be simply obtained using 2-bromo-alkanoates **2** as coupling partners.



Scheme 82

Although 1-alkenyl halides are probably the most widely used organic electrophiles in Stille coupling,[24] to our knowledge 2-bromoalkenoates have never been employed before. Moreover acrylate fragments are known to be valuable building blocks in organic chemistry and have been employed in many asymmetric transformations. However, few good routes exist to prepare even simple 1-substituted species.[270, 271] Thus, during these studies, we have investigate the MW activation of Stille Coupling reactions in comparison with traditional heating methodologies, using (*E*)-methyl-2-bromobutenoate **2a** (R'=CH_3) as electrophile.



184: R=Ph
185: R=thiophene
186: R=alkyne

187: R=Ph
188: R=thiophene
189: R=alkyne

Scheme 83

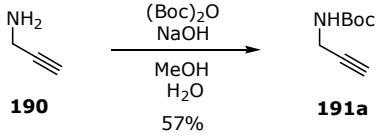
The process has been studied aiming to obtain *δ*-amino esters **3** (Scheme 82) and then extended to a set of commercially available or easy to synthesize stannanes **184-186** in order to give access to a simple and general method to achieve 1-substituted butenoates **187-189** (Scheme 83).

5.2. Results and discussion

5.2.1. Synthesis of substrates

*5.2.1.1. Synthesis of propargylamines **191a-d** and **196***

The prop-2-ynyl-carbamic acid *tert*-butyl ester **191a** was obtained by protecting the commercially available propargylamine **190** as *tert*-butoxycarbonate with carbonic acid di-*tert*-butyl ester (Scheme 84).

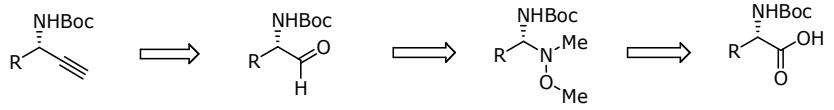


190 **191a**

Scheme 84

This kind of protecting group was chosen because it could withstand a wide range of chemical manipulations, among the others it was stable in basic conditions, and could be easily removed by treatment with TFA under mild conditions to regenerate the primary amine moiety.

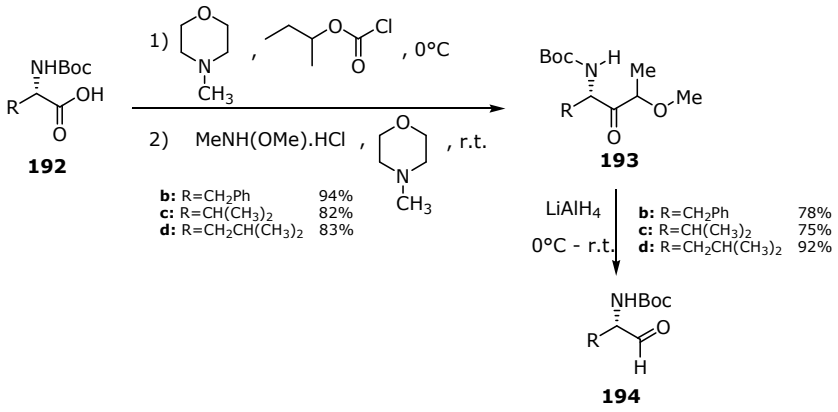
The enantioselective synthesis of propargylamines **191b-d** is based on a synthetic elaboration of naturally occurring amino acids, as reported in the retrosynthetic scheme 85. In particular we started from phenylalanine **192b**, valine **192c** and leucine **192d**.



191b: R=CH_2Ph **194b:** R=CH_2Ph **193b:** R=CH_2Ph **192b:** R=CH_2Ph
191c: R=$CH(CH_3)_2$ **194c:** R=$CH(CH_3)_2$ **193c:** R=$CH(CH_3)_2$ **192c:** R=$CH(CH_3)_2$
191d: R=$CH_2CH(CH_3)_2$ **194d:** R=$CH_2CH(CH_3)_2$ **193d:** R=$CH_2CH(CH_3)_2$ **192d:** R=$CH_2CH(CH_3)_2$

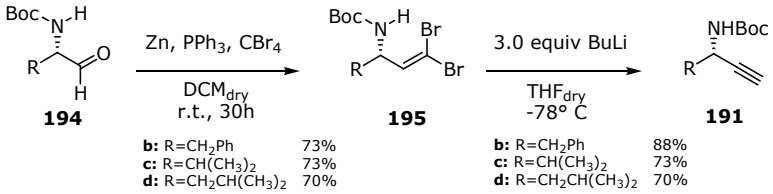
Scheme 85

The amino acids were transformed into the corresponding *N*-methoxy-*N*-methylamides **193**, and then the amido group reduced to aldehyde **194**, using $LiAlH_4$ (Scheme 86).



Scheme 86

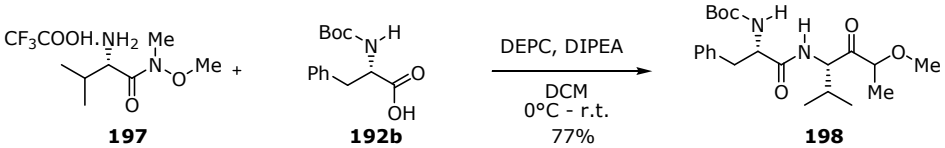
Many synthetic methods are described for aldehyde-to-alkyne homologation. In this case a two steps sequence *via* dibromovinyl intermediates **195** was chosen in order to obtain propargylamines **191**. Following the well known procedure originally developed by McKelvie[272] and later extended by Corey and Fuchs,[273] aldehydes **194** were transformed into the corresponding 3,3-dibromoalkenes **195**, from which it is possible to obtain the target compounds **191** simply by treatment with BuLi at low temperature (Scheme 87).



Scheme 87

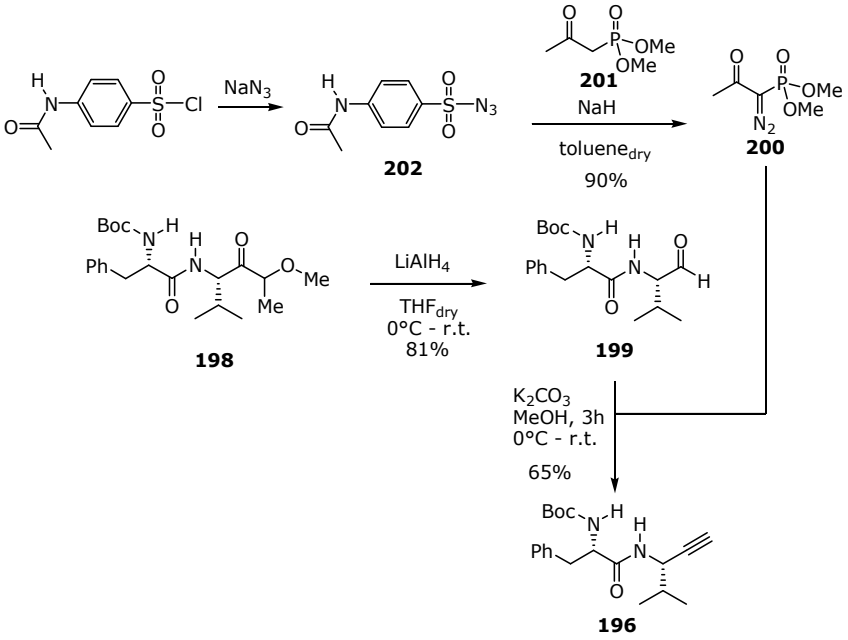
Dibromo-ethylene triphenylphosphorane was prepared by mixing Zn, PPh_3 and CBr_4 in CH_2Cl_2, and reacted with aldehyde **194** at room temperature. The dibromoalkene **195** obtained in this way, was then converted in high yields into the correspondent propargylic amines in the presence of three equivalents of BuLi.

Dipeptido Boc-(*S*)-Phe-(*S*)-Val-propargylamine **196** was prepared in an alternative way. [264, 265] The reaction sequence started from the Weinreb amide of valine **197** which was coupled with *N*-(*tert*-Boc)-(*S*)-phenylalanine **192b** in presence of di-*iso*-propylethylamine and DEPC (Scheme 88).



Scheme 88

Aldehyde **199** was then generated by reduction with $LiAlH_4$ (Scheme 89). The aldehyde-to-alkyne transformation was carried out using a diazo strategy.[274-279] The dimethyl-1-diazo-2-oxopropyl phosphonate **200** was synthesized according to the literature by reaction of commercially available dimethyl 2-oxopropylphosphonate **201** and 4-acetylamino-benzensulfonyl azide **202** using NaH in toluene (Scheme 89). After chromatographic purification, this was recovered in good yields (90%) and reacted with aldehyde **199** using MeOH as solvent in the presence of K_2CO_3 as base, to obtain the corresponding alkyne **196** in 65% yield after purification by flash chromatography.

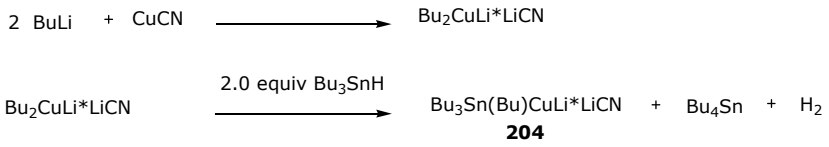


Scheme 89

Epimerization at the stereogenic center next to the carbonyl was not observed, as confirmed by ^{1}H-NMR and ^{13}C-NMR spectra of the crude mixture of **196** in which only one diastereoisomer was present.

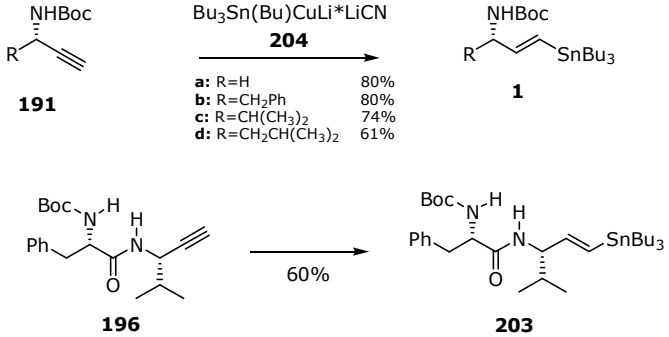
5.2.1.2. *Synthesis of γ-stannylalamines **1a-d** and **203***

Propargylamines **191a-d** and **196** were transformed into the corresponding stannylallylamines **1a-d** (R'=CH_3) and **203** following a well known procedure based on the addition of stannylcuprate **204** across the triple bond.[30] This reagent can be easily generated from lithium butylcuprate and tributyltinhydride as reported in Scheme 90.



Scheme 90

Addition on the triple bond proceeded with high regio and stereochemical control and without racemisation, affording enantiomerically enriched γ-(*E*)-stannylallylamines **1a-d** and **203** as the only reaction products (Scheme 91), which were isolated in high yields after purification.

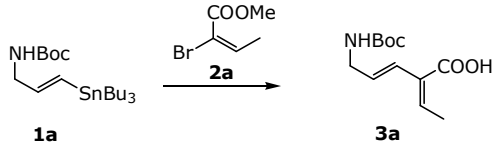


Scheme 91

5.2.2. Stille Coupling with (*E*)-methyl-2-bromobutenoate **2a**: synthesis of *δ*-aminoesters **3**

*5.2.2.1. [(E)-3-tributylstannanyl-allyl]-carbamic acid tert-butyl ester **3a***

The reaction conditions were optimized starting from commercially available (*E*)-methyl-2-bromobutenoate **2a**, as electrophile, and [(*E*)-3-tributylstannanyl-allyl]-carbamic acid *tert*-butyl ester **1a**, as model substrate (Scheme 92 and Table 8).



Scheme 92

We used at first very general conditions, thus $Pd[P(Ph)_3]_4$ was selected as catalyst and DMF as solvent (entry 1). The result was a 55% yield after 24 h at

80° C. The use of a different catalyst such as $Pd(AsPh_3)_4$[264, 265] (entry 3) or a higher reaction temperature (entry 2) did not improve the final yield.

The reaction was, then, performed in anhydrous toluene with the best catalyst, $Pd[P(Ph)_3]_4$, and the amino ester **3a** was actually recovered in 60% yield after 16 h at 80° C (entry 4).

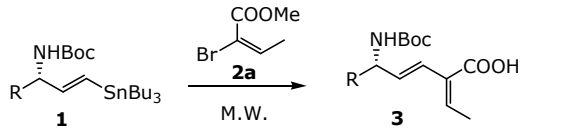
entry	solvent	catalyst	experimental conditions	yield (%)[(a)]
1	DMF	$Pd[P(Ph)_3]_4$	24h, 80°C	55%
2	DMF	$Pd[P(Ph)_3]_4$	24h, 100°C	53%
3	DMF	$Pd(AsPh_3)_4$	24h, 80°C	35%
4	toluene	$Pd[P(Ph)_3]_4$	16h, 80°C	60%
5	toluene	$Pd[P(Ph)_3]_4$	30', MW, 200W	76%

Table 8: Stille Coupling reaction between [(*E*)-3-tributylstannanyl-allyl]-carbamic acid *tert*-butyl ester **3a** and (*E*)-methyl-2-bromobutenoate **2a** in different reaction conditions.
[(a)] determined after chromatography

To improve the yields an investigation on the effect of microwave irradiation on our coupling process was carried out. We were pleased to find that under optimized conditions (80° C with a 200 W microwave source for 30 min in toluene) the reaction led to quantitative conversion of stannane **1a**. ^{1}H-NMR analysis of the crude mixtures showed that no isomerization of the double bonds occurred as exclusively the anticipated isomer **3a** having *E*, *Z* geometry was recovered and, after workup and chromatography, isolated in 76% yield.

*5.2.2.2. Enantiopure stannylallylamines **1b-d***

The same reaction conditions were used with our non racemic substrates **1b-d**, derived, respectively, from phenylalanine, valine and leucine (Scheme 93).



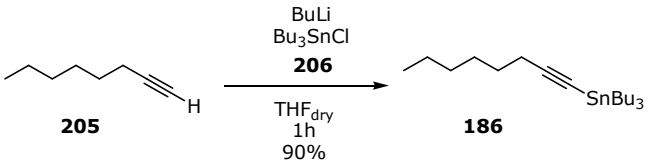
b: R=CH_2Ph 66%
c: R=$CH(CH_3)_2$ 81%
d: R=$CH_2CH(CH_3)_2$ 70%

Scheme 93

The corresponding *γ*-amino esters **3b–d** were recovered in good yields after purification.

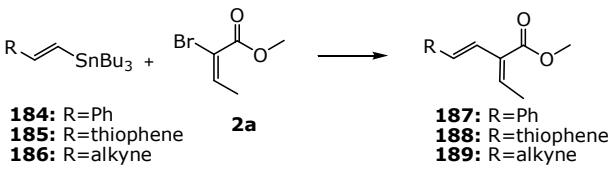
5.2.3. Stille Coupling with (*E*)-methyl-2-bromobutenoate **2a**: synthesis of 1-substituted butenoates **187-189**

As we have already mentioned, substituted acrylate fragments are valuable building blocks in organic chemistry owing to their reactivity. To exploit the generality of our procedure, three different stannanes were used: tributyl(phenyl) stannanes **184**, tributyl(thiophen-2-yl)stannanes **185**, tributyl(oct-1-ynyl) stannanes **186**. The latter, being not commercially available, was prepared in good yield from 1-octine **205** and tributyl-tin-chloride **206** using BuLi in THF (Scheme 94).



Scheme 94

The results obtained clearly show that the formation of 1-substituted butenoates (**187-189**) always occurs smoothly (Scheme 95, Table 9).



Scheme 95

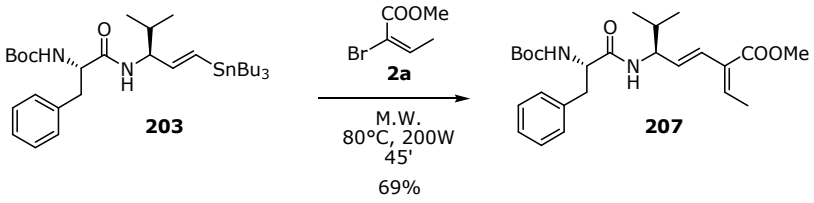
entry	stannanes	MW heating[(a)]
1	**184**	**187:** 75%
2	**185**	**188:** 68%
2	**186**	**189:** 72%

Table 9: Stille Coupling reaction between stannanes **184-186** and (*E*)-methyl-2-bromobutenoate **2a** in toluene under MW irradiations.
[a]Yield determined after chromatography.

5.2.4. Stille Coupling with (*E*)-methyl-2-bromobutenoate **2a**: synthesis of 2-ethylidene-γ-unsaturated δ-amido ester **207**

Finally the procedure was applied on the dipeptidostannane **203**. Since it is known that the synthetic elaboration of dipeptides can often be challenging

because of their sensitivity,[280] we considered it would be relevant to verify if our reaction condition were mild enough to be used also with such substrates. Thus the dipeptido stannane **203** was reacted in the same experimental condition and once again the expected coupling compound **207** was recovered in good yield, after purification. (Scheme 96).

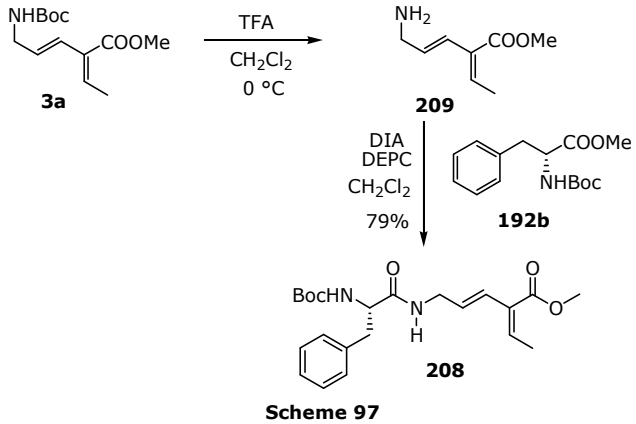


Scheme 96

It is remarkable that compound **207** was obtained as a single diastereoisomer as both ^{1}H- and ^{13}C-NMR spectra showed no peaks due to epimerization at the *δ*-carbon of the amino ester moiety, thus confirming that no racemization of the starting material or isomerization of the double bond occurred.

5.2.5. Synthesis of the dipeptide **208**

Finally, to demonstrate that *δ*-aminoesters **3** are capable of undergoing typical reactions associated with peptide synthesis, *tert*-Boc-aminoester **3a** was deprotected with TFA and the free amine **209** was coupled with *tert*-Boc-phenylalanine **192b** using DEPC/DIPEA procedure. After purification, the expected dipeptide **208** was indeed obtained in 79% yield (Scheme 97).



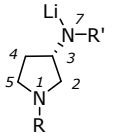
Scheme 97

In conclusion, in this part of the work, we have shown that organostannanes can be coupled under Pd catalysis with the commercially available (*E*)-methyl-2-bromobutenoate in mild conditions using MW activation. The procedure discloses an easy access to (*Z*)-1-substituted butenoates and has been applied to chiral stannylated allylamines derived from naturally occurring amino acids or dipeptides to obtain a novel family of polyunsaturated *δ*-amino esters which were previously unreported and might be useful intermediate in the synthesis of peptidomimetics.

6. ENANTIOSELECTIVE BASE-PROMOTED ISOMERIZATION OF EPOXIDES INTO ALLYLIC ALCOHOLS

6.1. Introduction

The preparation of enantiomerically enriched allylic alcohols *via* desymmetrisation of *meso*-epoxides with chiral lithium amide reagents is a widely studied asymmetric rearrangement and a useful reaction in asymmetric synthesis.[147, 281-294] The interest of the Florence's research group in epoxide rearrangement reactions, spanning in the last twenty years, has focused on the development of superbase-induced rearrangements of oxiranyl ethers[21-23, 104, 105, 183] and on extending these procedures to aziridinyl analogues.[107] But chiral reagents have not been used yet. For this reason during my PhD study a collaboration with the Rouen's research group has begun in order to test chiral lithium amides derived from 3-APs as bases **210**-Li (Figure 21), chiral ligands for organolithium compounds and components of superbasic mixtures to promote enantioselective epoxide / allylic alcohol transformations.



210-Li

Figure 21

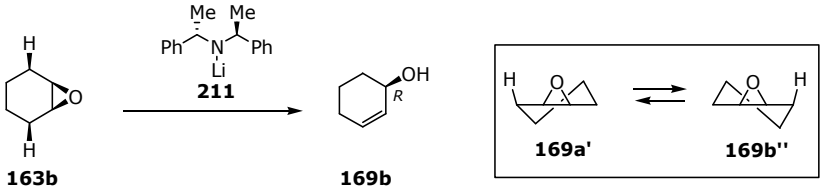
Synthesis and applications of 3-APs **210**-H and **210**-Li have been the subject of study for many years in the group located in Rouen.[16-18, 20]

6.1.1. Previous studies about enantioselective isomerizations of epoxides

Desymmetrisation of an achiral or *meso* molecule to yield enantiomerically enriched products is a well established synthetic tool. In general, to achieve an enantioselective symmetry breaking synthetic operation, two enantiotopic functional groups must be differentiated; this can be achieved by the use of a chiral reagent or catalyst. So far the greatest number of enantioselective desymmetrisations involve the use of chiral lithium amides.[281, 284, 295-297] These chiral bases have been exploited in a variety of efficient enantioselective reactions such as deprotonation of prochiral cyclic ketones,[298] kinetic resolution of racemic ketones,[299] enantioselective dehydrohalogenation,[300] alkylation of achiral ketones,[301] deracemization of chiral ketones by protonation,[302] etc.

Rearrangement of *meso*-epoxides into optically active allylic alcohols using chiral lithium amides is the larger scope of chiral lithium amides and has received much attention as a useful method for the preparation of chiral products.[147, 281-294]

The first example of an enantioselective desymmetrization of oxiranes was reported by Whitesell and Felman in 1980.[303] Cyclohexene oxide **163b** was treated with various chiral, non-racemic lithium amides; the lithium amide **211** was found to discriminate between the two *syn* *β*-protons leading to the allylic alcohol **169b** in a moderate (36%) enantiomeric excess. Although this result was not spectacular, the principle that a chiral lithium amide could distinguish between enantiotopic conformation **169b'** and **169''** was first demonstrated (Scheme 98).



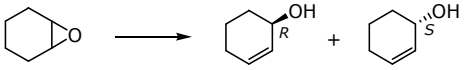
163b **169b** **169a'** **169b''**

Scheme 98

Since 1980, the enantioselective rearrangement of oxiranes has been extensively investigated and reviewed. In Table 10 the most used lithium amides are reported together with the results in terms of chemical yield and enantiomeric excess which have been obtained in the isomerization of cyclohexene oxide, the typical test molecule (Scheme 99).

As shown in Table 1 the proline derived lithium amide **211**, first introduced by Asami in 1984,[304] is still among the best reagents for this isomerization. Some structural modification (**212** and **213**) and a careful study of the reaction conditions allow to reach high level of enantioselectivity (over 90%)[285] even in a catalytic version[286] with 0.2 equiv of the amine in the presence of an excess LDA (1.5 eq.).

The limitation of (*S*)-proline derived amine is that they allow access only to (*S*)-cyclohexanol. More recently Andersson has found that the lithium amide of (1*S*,3*R*,4*R*)-3-(*N*-pyrrolidinyl)methyl-2-azabicyclo[2.2.1]-heptane **216** is very efficient in promoting the conversion of cyclohexene oxide in (*R*)-cyclohexenol with 97% e.e. in a stoichiometric version and 96% e.e. in a catalytic modification, the highest level of enantioselectivity for cyclohexene oxide isomerization.[294] A further advantage of the lithium amide **216** is that it gives very good results with a series of oxiranes, thus representing the most general in scope among the known lithium amides. The limitation derives, instead, by the fact that the Andersson system typically comprises an excess of DBU (5 equiv), since it is essential for the high enantioselectivity.



Scheme 99

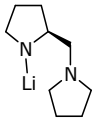
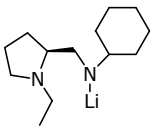
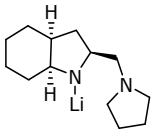
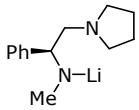
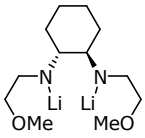
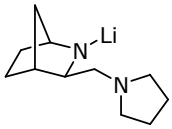
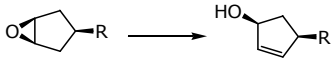
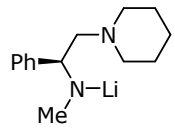
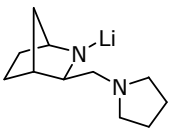
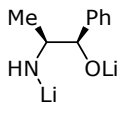
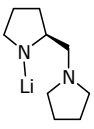
	**211**	Asami:[304] 77%, 79% e.e. (*S*) Asami:[285] 80%, 81% e.e. (*S*)[a] Asami:[286] 71%, 75% e.e. (*S*)[b]		**212**	Asami:[285] 80%, 78% e.e. (*R*)
	**213**	Asami:[285] 86%, 89% e.e. (*S*) Asami:[285] 89%, 94% e.e. (*S*)[c]		**214**	Singh:[147] 60%, 77% e.e. (*S*)
	**215**	Alexakis:[287] 68%, 76% e.e. (*R*) Alexakis:[287] 47%, 67% e.e. (*R*)[c]		**216**	Andersson:[294] 87%, 97% e.e. (*R*) Andersson:[294] 91%, 96% e.e. (*R*)[c]

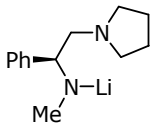
Table 10: [(a)] In the presence of 1.65 eq DBU;
[(b)] Catalytic amount of base + 6 eq DBU;
[(c)] Catalytic amount of base

Epoxides other than cyclohexene oxide have been investigated with the aim of developing new synthetic routes towards useful natural and unnatural products. In the tables 11 and 12 the chemical yields, enantiomeric excesses and literature references for some representative examples of 3-mono- and di-substituted cyclopentene oxide (Schemes 100 and 101) are compared.



Scheme 100

	**217**	Singh:[147] R=*cis*-OTBDMS, 66%, 97% e.e. Singh:[292] R=*cis*-CH_2OTBDMS, 20%, 80% e.e.		**216**	Andersson:[294] R=*cis*-OTBDMS, 85%, 95% e.e. Andersson:[294] R=*cis*-OTBDMS, 60%, 67% e.e[a] Andersson:[294] R=*trans*-CH_2OTBDMS, 42%, 95% e.e.
	**218**	Milne: R=*cis*-OCH_2Ph, 98%, 80% e.e. Hodgson: R=*cis*-CH_2OH, 66%, 95% e.e.		**211**	Asami: R=*cis*-OTBDMS, 92%, 90%, e.e. Asami: R=*cis*-$NHCOOCH_2Ph$, 59%, 83% e.e.

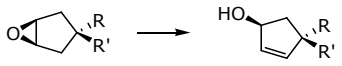


219

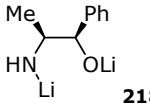
O'Brien: R=*cis*-NHCOPh, 51%, 92% e.e.

O'Brien: R=*cis*-NHCOCF$_3$, 73%, 88% e.e.

Table 11: [(a)]In the presence of 1.65 eq DBU;
[(b)]Catalytic amount of base + 6 eq DBU;
[(c)]Catalytic amount of base



Scheme 101

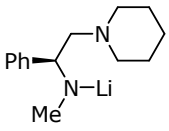


218

Hodgson:[283] R=Me, R'=CH_2OH, 63%, 99% e.e.

Hodgson:[283] R=Bu, R'=CH_2OH, 67%, 96% e.e.

Hodgson:[283] R=CH_2OBn, R'=CH_2OH, 76%, 89% e.e.

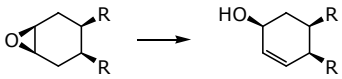


217

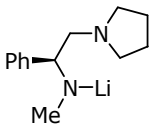
Singh:[147] R=$C_{16}H_{33}$, R'=OTMS, 70%, 94% e.e.

Table 12

In Table 13 some results of differently 3,4-disubstituted cyclohexene oxides (Scheme 102) have been collected.



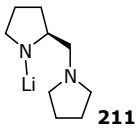
Scheme 102



219

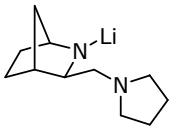
O'Brien:[289] R=*cis*-OTBDMS, 38%, 92%, e.e.

O'Brien:[289] R=*trans*-OTBDMS, 94%, 94% e.e.



211

Kasai: R=*trans*-Me, 34%, 98% e.e.



216

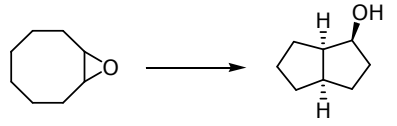
Andersson:[294] R=*trans*-Me, 93%, 94% e.e. [a]

Table 13: [(a)]Catalytic amount of base

From the numerous examples shown in the table 11, 12 and 13 it is clear that the reaction has a quite wide scope. It is difficult to make a critical comparison of all the procedures reported in the literature but we can draw some general comments. The Andersson's base **216** seems at present the one with the best

performances and the wider applicability; Asami's proline derived lithium amide is still the best compromise between efficiency and ease of use, being commercially available; the catalytic version of the oxirane isomerization is nowadays possible mainly using the procedures developed by Andersson and Asami; for some particular substrates (e.g. mono- and disubstituted cyclopentene oxide) some other bases may represent an efficient and easy alternative (the ephedrine derived lithium amide **218**).

Some medium-size cyclic and bicyclic epoxides are also isomerized through *a*-elimination and carbenoid intermediate formation to afford ketones and cross-ring insertion products in non polar media. Particularly interesting and widely investigated is the cyclooctene oxide **163c**. It was reported already by Cope[166] in 1958 that the latter, by treatment with lithium diethylamide in boiling ether, afforded (–)-*endo*-*cis*-bicyclo[3.3.0]octan-2-ol **35** through *a*-deprotonation followed by a transanular C-H insertion of the resulting carbenoid species (see Scheme 15, chapter 2). The enantioselective version of this metalation reaction has been later reported by Hodgson who used *iso*-propyllithium in combination with (–)-sparteine obtaining **35** in 86% yield and 84% enantiomeric excess.[305] A catalytic version of the same reaction with (–)-*a*-*iso*-sparteine was also reported affording almost the same results. A considerable yield enhancement (98%) in the formation of the bicyclic alcohol **35** has been recently achieved by Alexakis by the use of $BF_3{\cdot}OEt_2$ in conjunction with (–)-sparteine during the deprotonation of cyclooctene oxide by *sec*-butyllithium.[287]



163c **35**

^{i}PrLi/(–)-sparteine	Hodgson:[305] 86%, 84% e.e.
s-BuLi/(–)-sparteine/$BF_3{\cdot}Et_2O$	Alexakis:[287] 98%, 61%, e.e.

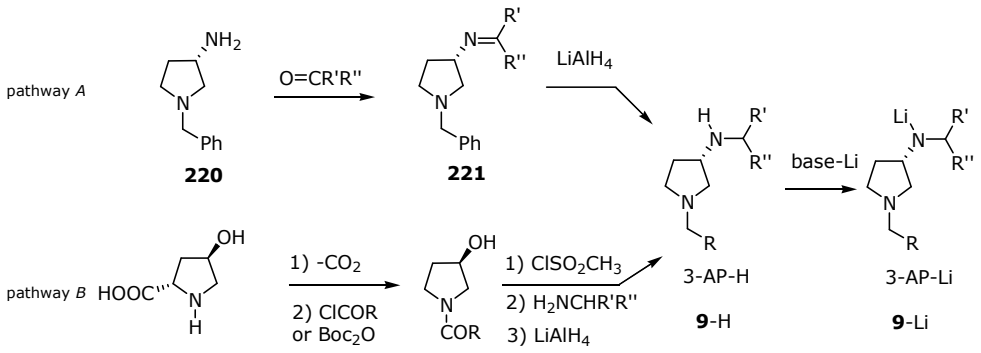
Table 14: Enantioselective isomerization of cyclooctene oxide **163c** to (1*S*)-octahydropentalen-1-ol **35**

6.1.2. Previous studies about enantioselective applications of 3-APLi's as chiral ligands

J. Maddaluno's research group is interested, since almost two decades, in the synthesis, and their applications as chiral ligands for enantioselective transformations, of chiral 3-aminopyrrolidine lithium amides **210**-Li.

6.1.2.1. *Synthetic application of 3-APLis*

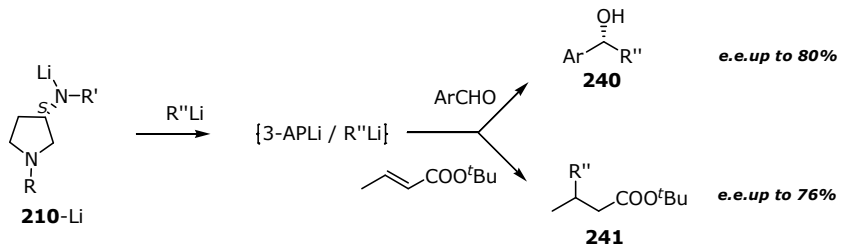
Two main routes have been optimized to synthesize a set of 35 3AP-H **210** precursors.[19, 31] One of the chemical scheme starts from the commercial (3*S*) 1-benzyl-3-aminopyrrolidine **220** (pathway *A*, Scheme 103). After condensation with variously substituted ketones or aldehydes, the imine-intermediate **221** is reduced in the presence of lithium aluminium hydride. The other route, which presents the advantage of varying the substitution of the pyrrolidinic nitrogen, begins with a decarboxylation, immediately followed by a *N*-carbamate protection, of the commercially available *trans*-4-hydroxy-(L)-proline **222** (pathway *B*, Scheme 103). The lateral amino chain on the C^3 carbon is thus introduced thanks to a stereoselective nucleophilic substitution. A final reduction of the carbamate **223** affords the expected amines **210**. All these amines were obtained with e.e.>95%.[31]



Scheme 103

Table 15 collects the whole range of 3-APLi's that have been synthesized so far with their overall yields and enantiomeric purities.

The corresponding lithium amides have then been tested as chiral ligands in the enantioselective nucleophilic 1,2- and 1,4-additions of organolithium compounds to non-enolizable aldehydes and *α*,*β*-unsaturated esters, respectively (Scheme 104). E.e's up to 80% have been reached.



Scheme 104

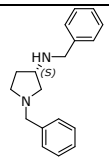
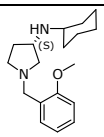
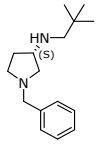
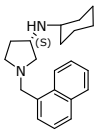
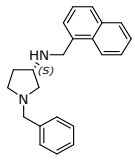
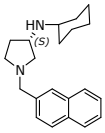
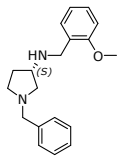
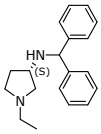
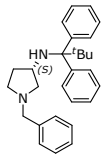
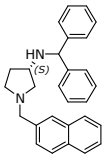
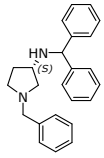
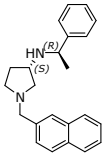
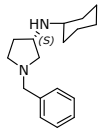
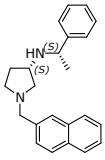
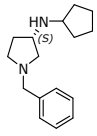
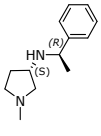
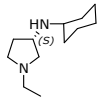
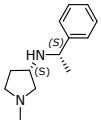
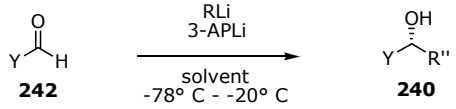
entry	3-AP	pathway	Yd (%)	entry	3-AP	pathway	Yd (%)
1	 **224**	*A*	91	10	 **233**	*B*	38
2	 **225**	*A*	94	11	 **234**	*B*	40
3	 **226**	*A*	91	12	 **235**	*B*	50
4	 **227**	*A*	84	13	 **236**	*B*	30
5	 **228**	*A*	56[a]	14	 **237**	*B*	24
6	 **229**	*A*	69	15	 **238a**	*B*	15-20
7	 **230**	*A*	75	16	 **238b**	*B*	15-20
8	 **231**	*A*	53	17	 **239a**	*B*	35
9	 **232**	*B*	32	18	 **239b**	*B*	33

Table 15: [a] prepared from 3-amino-*N*-benzylpyrrolidine and $Ph_2{}^tBuSiCl$

Concerning the 1,2 nucleophilic additions, 3-AP lithium amides used in conjugation with methyl, *n*-butyl and phenyllithium give access to the expected alcohols **240** in good yields and satisfactory e.e. in THF at -78° C (Scheme 105).



242 **240**

Y=Ph, *o*-Toyl, *o*-MeO-C_6H_4, 1-naphthyl, ^{t}Bu

Scheme 105

An accurate investigation has been done in order to achieve the best reaction conditions.

entry	RLi	YCHO	yield[(a)] (%)	e.e.[(b)] (%)
1	*n*-BuLi	PhCHO	80	42 (*R*)
2	*n*-BuLi	α-naphthyl-CHO	65	55 (*R*)
3	*n*-BuLi	β-naphthyl-CHO	69	33 (*R*)
4	*n*-BuLi	*o*-MeC_6H_4-CHO	72	67 (*R*)
5	MeLi	PhCHO	76	57 (*R*)

Table 16: Asymmetric addition of alkyllithium compounds to aldehydes **242** using (*S*)-1-benzyl-3-aminopyrrolidine lithium amide **230**
[(a)] calculated by integration of ^{1}H-NMR spectra
[(b)] determined by HPLC

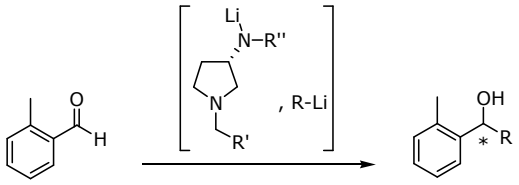
In the initial studies, six different aldehydes **242** (benzaldehyde, *o*-tolualdehyde, *o*-anisaldehyde, 1-naphthaldehyde, 2-naphthaldehyde, and pivalaldehyde) were reacted with *n*-butyllithium or methyllithium in different solvents (THF, Et_2O, DME or toluene) varying the reaction temperature (–78 to –20° C, Scheme 105).[16] From these preliminary investigations turned out that *o*-tolualdehyde was the best substrate to reach significant inductions (Table 16, entry 4). A clear dependence between the enantioselectivity and the bulkiness of the aromatic aldehyde's *ortho* substituent was observed.

Moreover, these data confirm that THF is, by far, the best solvent in terms of enantioselectivity. In diethyl ether a significant decrease was observed, while in DME-DEE (1:1) mixture and in toluene the induction was poor (entries 1, 4 5 and 6, Table 17).

The diamines **224** to **237** (one single *S* stereogenic center on C^3) were initially compared to optimize the reaction conditions (entries 1 to 14, Table 15) with *ortho*-tolualdehyde **242** (Y=*o*-Toyl) as model substrate (Scheme 106).

The results obtained with the first 14 diamines considered suggested that the influence of the substituent on the intracyclic nitrogen was relatively meaningless. Only 3-APLi's bearing a hindered lateral amino-chain led to acceptable chemical yields and e.e.'s.

Thus, amines **229** to **237** provided the butylated alcohol in e.e.'s higher than 50%, at –78° C (Table 17).



242 Y=*o*-Toyl

Scheme 106

entry	3-APLi	solvent	RLi	Conv[(a)] (%)	e.e.[(b)] (%)
1	**229**Li	THF	*n*-BuLi	77	73 (*R*)
2	**229**Li	THF	MeLi	80	68 (*R*)
3	**229**Li	THF	PhLi	75	58 (*S*)
4	**229**Li i	DEE	*n*-BuLi	96	50 (*R*)
5	**229**Li	DME-DEE (1:1)	*n*-BuLi	92	3 (*R*)
6	**229**Li	toluene	*n*-BuLi	99	21 (*R*)
7	**230**Li	THF	*n*-BuLi	72	67 (*R*)
8	**231**Li	THF	*n*-BuLi	63	63 (*R*)
9	**232**Li	THF	*n*-BuLi	72	63 (*R*)
10	**233**Li	THF	*n*-BuLi	71	60 (*R*)
11	**234**Li	THF	*n*-BuLi	65	50 (*R*)
12	**235**Li	THF	*n*-BuLi	67	74 (*R*)
13	**236**Li	THF	*n*-BuLi	66	64 (*R*)
14	**237**Li	THF	*n*-BuLi	98	64 (*R*)
15	**238a**Li	THF	*n*-BuLi	95	77 (*R*)
16	**238b**Li	THF	*n*-BuLi	91	51 (*S*)
17	**239a**Li	THF	*n*-BuLi	97	80 (*R*)
18	**239b**Li	THF	*n*-BuLi	98	74 (*S*)

Table 17: Enantioselective hydroxyalkylation of *o*-tolualdehyde **242** by R-Li in the presence of 3-APLi's

[(a)] calculated by integration of ^{1}H-NMR spectra

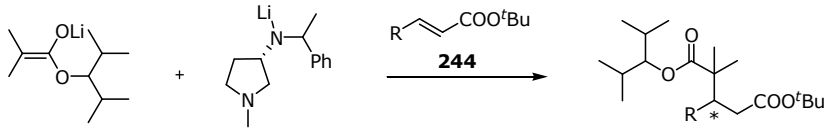
[(b)] determined by HPLC

The temperature has a dramatic effect on the outcome of this reaction. It has been established, on both chemical and, recently, spectroscopic grounds, that the aggregation between the lithium amide and the nucleophile has to be performed at –20 °C for at least 30 min. The resulting reaction mixtures have then to be cooled at –78 °C before addition of the aldehyde.

The influence of a second stereogenic center (C^8) introduced on the lateral amino chain was studied at this point. Thus, 3-AP **238** and **239** were employed in the nucleophilic addition of *n*-BuLi on *o*-tolualdehyde, in THF, at –78 °C. The results are reported in Table 17 (entries 15 to 18).

Diamines **238a,b** and **239a,b** led to e.e.'s up to 80%. Interestingly, the sense of the induction appeared to depend on the configuration of the second stereogenic center.

Indeed, while the (3*S*,8*R*)-3-APs **238a** and **239a** were in favour of alcohol *R*, the *S* enantiomer were mainly formed in the presence of the (3*S*,8*S*)-3-APs **238b** and **239b**. This observation suggested that, in this case, the sense of induction was driven by the second stereogenic center, dimming that of the original C^3. The racemic analogues at C^3 of **239a** (i.e., 3*S*,8*R* / 3*R*,8*R*) and **239b** (i.e., 3*S*,8*S* / 3*R*,8*S*) were then synthesized to further clarify this phenomenon. Accordingly, the hydroxyalkylations of *o*-tolualdehyde with *n*-BuLi led to similar e.e.'s and inductions with **239a**,**b** or their racemic analogues.



243 **239a**-Li (3*S*,8*R*) **239b**-Li (3*S*,8*S*) **245** (R=Me) **246** (R=Ph) **247** (R=*iso*-Pr)

Scheme 107

entry	3-APLi	ratio[a]	solvent	yield (%)	e.e.[b] (%)
1	**239a**-Li	1.3 : 1.3 : 1.0	THF	**245** (68)	72 (+)
2	**239a**-Li	1.7 : 1.3 : 1.0	THF	**245** (83)	74 (+)
3	**239a**-Li	2.6 : 1.3 : 1.0	THF	**245** (81)	71 (+)
4	**239a**-Li	2.4 : 2.0 : 1.0	THF	**245** (82)	76 (+)
5	**239a**-Li	1.7 : 1.3 : 1.0	toluene	**245** (52)	62 (–)
6	**239b**-Li	1.7 : 1.3 : 1.0	THF	**245** (95)	55 (–)
7	**239b**-Li	2.4 : 2.0 : 1.0	THF	**245** (91)	54 (–)
8	**239b**-Li	2.4 : 2.0 : 1.0	toluene	**245** (45)	45 (+)
9	**239a**-Li	2.4 : 2.0 : 1.0	THF	**246** (52)	12 (+)
10	**239b**-Li	2.4 : 2.0 : 1.0	THF	**246** (52)	50 (–)
11	**239a**-Li	2.4 : 2.0 : 1.0	THF	**247** (75)	11 (+)
12	**239b**-Li	2.4 : 2.0 : 1.0	THF	**247** (79)	15 (+)

Table 18: Conjugate addition of lithium enolate **243** on *α*,*β*-unsaturated esters **244** in presence of chiral 3-APLi's
[(a)] ratio between amide:enolate:ester
[(b)] measured by HPLC

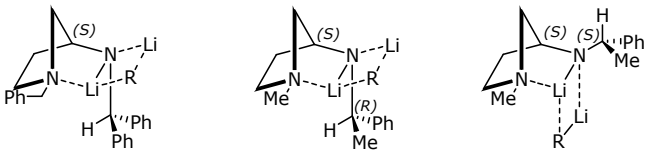
Concerning the 1,4-addition, mixed aggregates of chiral lithium amides **239a-b** and lithium ester enolates **243** have been employed in the enantioselective conjugate addition on *a*,β-unsaturated esters **244** (Scheme 107).

Michael adducts were obtained in e.e.'s up to 76% combining a lithium enolate and a chiral 3-aminopyrrolidine lithium amide (Scheme 107).[18, 20]

The sense of the induction was found to be determined by both the relative configuration of the stereogenic centers brought by the amide and the solvent in which the reaction was conducted (Table 18).

6.1.2.2. *Structural NMR studies of 3-APLis*

Theoretical[17, 306, 307] and multinuclear (^{1}H, ^{6}Li, ^{13}C and ^{15}N) NMR studies[15, 17] have thus been undertaken to better understand the induction phenomenon. The formation of non-covalent robust 1:1 complexes between *n*-butyl- or methyllithium and the lithium amides in THF-d_8 solution (Figure 22) was put into evidence. In all cases, the amide partner adopts an aza-norbornyl-like conformation due to the chelation of the lithium cation with the intracyclic nitrogen of the pyrrolidine, and it is organized around a quadrilateral C-Li-N-Li core.



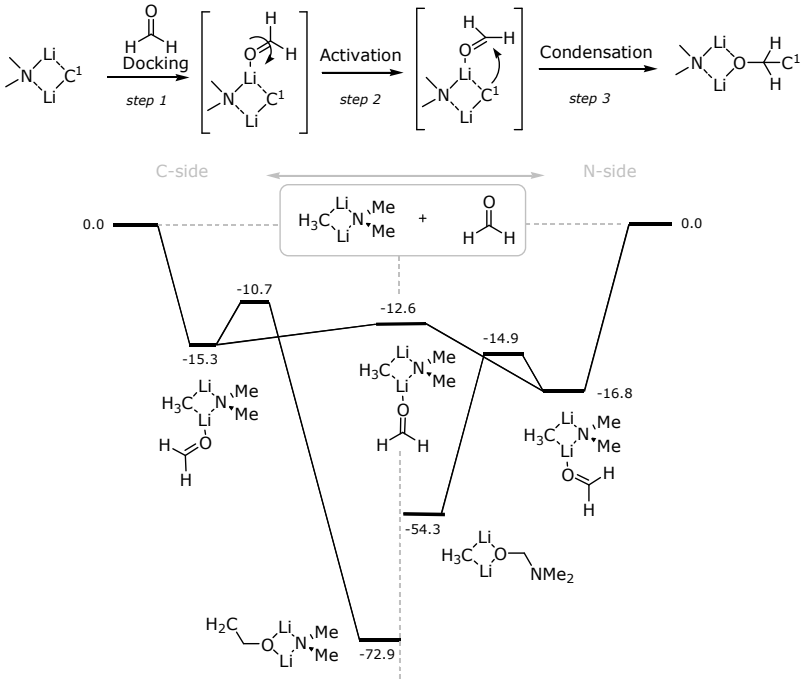
229 *exo* **239a *exo*** **239b *endo***

Figure 22

The precise arrangement of the aggregate depends not only on the structure of the *N*-substituent in the lateral amino-chain, but also on the relative configuration of the lateral chain, when a second stereogenic center in C^{8} is present: while the (3*S*,8*R*) diastereoisomer **239a** lead to an *exo* complex, its (3*S*,8*R*) epimers **239b** adopts an *endo* conformation.[17] This result implies that the topology of the complexes formed between alkyllithiums and 3-AP lithium amides is completely determined by the relative configuration of the lateral asymmetric center with respect to that on the pyrrolidine ring.

The last step of the reaction that remains to be elucidated is the docking of the aldehyde on the above mixed aggregates. In the case of the condensation of *n*-butyllithium or methyllithium with aromatic aldehydes, the reaction runs too fast to be followed by NMR. A Density Functional Theory (DFT) computation approach thus revealed to be more suitable to tackle this problem. The work was focused on

the docking of formaldehyde on simple models (in vacuum at 0 K) of mixed dimer involving MeLi and lithium dimethylamide. The two lithium atoms of the quadrilateral were successively coordinated by a molecule of aldehyde (Scheme 108, step one). Three directions led to energetical minima (Scheme 109, aldehyde central, C-side and N-side) and in all those cases, early transition states were reached upon a simple rotation of the aldehyde around its C=O bond (Scheme 108, second step), and are activated, therefore, to very low activation barriers (<5 kcal mol^{-1}). The C-C bond formation (Scheme 109, third step) is always largely exothermic and yields a mixed aggregate of the lithium alcoholate and the remaining lithium amide (57 Kcal mol^{-1} for the C-C creation vs. 37-42 Kcal mol^{-1} for the C-N creation).



Scheme 108

6.1.3. Aim of the study

Despite it is well known, as described above, that lithium 3-aminopyrrolidides **210**-Li are optimal chiral ligands for organolithium compounds in the enantioselective nucleophilic additions to aldehydes and *α*,*β*-unsaturated esters (Scheme 104), nothing is known about their ability as base for enantioselective deprotonations. For this reason, we have decided to develop this new possible application of the chiral lithium amides derived from 3-APs.

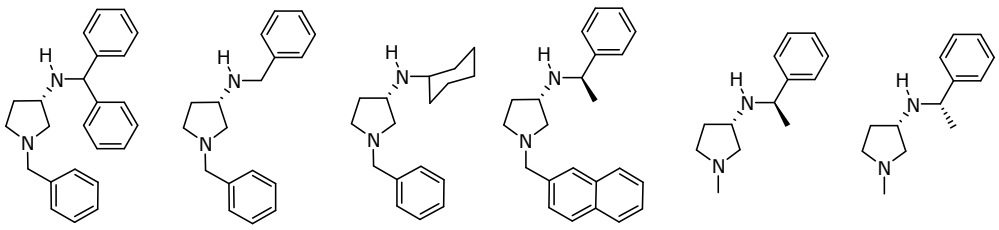
The main model reaction used to test new chiral lithium amides, as chiral bases, is the rearrangement process of epoxides. So the work has been divided in two parts:

- first we have carried out the evaluation of different 3-APLi bases as promoters in the rearrangement of the selected model cyclohexene oxide **163b** (and then also of other cyclic epoxides **163a** and **c**) to allylic alcohol **169b**;
- then we have studied the possibility of using the 3-APLis in chiral superbasic mixtures (1 : 1 3-APLi / K^{t}BuO) or as chiral ligands of organolithium compounds.

6.2. Results and discussion

6.2.1. Synthesis of 3-aminopyrrolidines

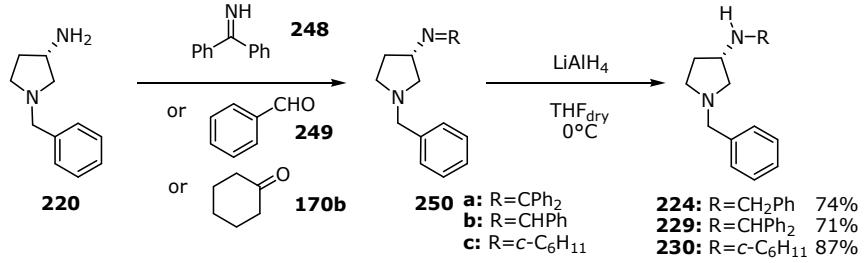
A set of six differently substituted 3-amminopyrrolidines was synthesized (Figure 23) following two methodologies: by varying the substitution of the lateral *N*-chain of 3-aminopyrrolidine **220**[16] or by transforming *trans*-4-hydroxy-L-proline **222**.[16, 17] (*S*)-1-Benzyl-3-((diphenylmethyl)amino)pyrrolidine **229**, (*S*)-1-benzyl-3-(benzyl-amino)-pyrrolidine **224** and (*S*)-1-benzyl-3-(cyclohexylamino-)pyrrolidine **230** were obtained following the first pathway in two steps.



229 **224** **230** **238a** **239a** **239b**

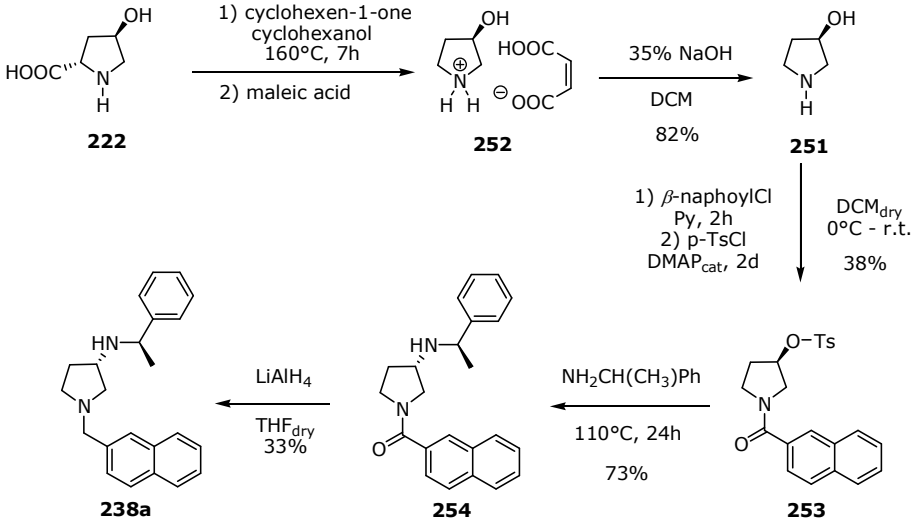
Figure 23

Reaction of (*S*)-(+)-1-benzyl-3-aminopyrrolidine **220** (commercially available product) with diphenylmethan-imine **248**, benzaldehyde **249** or cyclohexanone **170b** gave indeed the corresponding imines **250**. These latter, then, were reduced with lithium aluminum hydride to give the amines **224**, **229** and **230** (Scheme 109).



Scheme 109

(*S*)-1-(2-Naphthylmethyl)-3-[(1-(*R*)-phenylethyl)amino]-pyrrolidine **238a** was synthesized by the decarboxylation of 4-hydroxy-(L)-proline **222** as described in the literature[308] (Scheme 110). The (*R*)-3-pyrrolidinol **251** thus obtained was stored as the very stable maleate **252** and recovered quantitatively by the action of 12 M sodium hydroxide.

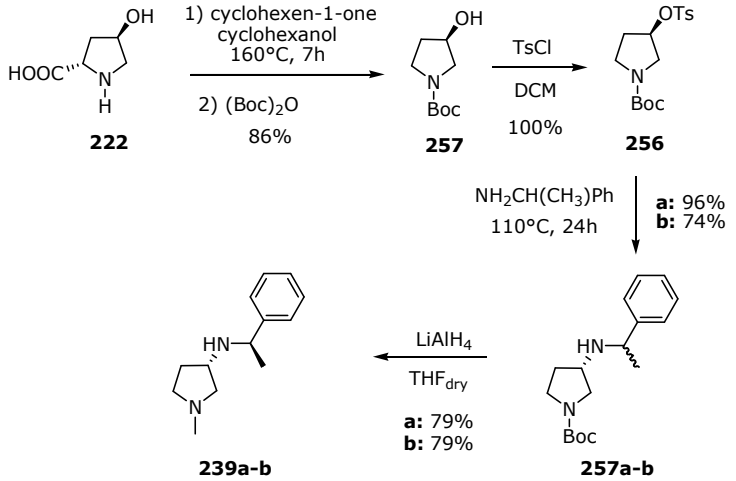


Scheme 110

In the following step the (*R*)-3-pyrrolidinol **251** was condensed with 1.0 equiv of *β*-naphthoyl chloride. After 2 h at 0° C *p*-tosyl chloride was added to afford amide **253**, isolated after flash chromatography in 38% yield. The tosyl group in **253** was then substituted by the *R* enantiomer of 1-phenylethylamine leading to amide **254** which was finally reduced to the diamine **238a** (Scheme 110).

The synthesis of the two epimers *N*-methyl-3-(*S*)-(1′-(*R*)-phenylethyl)amino-pyrrolidine **239a** and *N*-methyl-3-(*S*)-(1′-(*R*)-phenylethyl)aminopyrrolidine **239b** was achieved again through the decarboxylation of 4-(*R*)-hydroxy-L-proline **222**. The intermediate 3-(*R*)-hydroxypyrrolidine **251** thus obtained was not isolated but

reacted directly with di-*tert*-butyldicarbonate (Boc_2O), leading to **255**, which was then converted into tosyl derivative **256**. The second stereogenic center derived from the (*R*)- or (*S*)-methylbenzylamine was then introduced through a nucleophilic substitution on the tosylate, generating Boc-amines **257a** and **257b**. The reduction of the *N*-Boc protected diamines **257** with lithium aluminum hydride in THF at room temperature provided both (*S*,*R*) and (*S*,*S*) diastereomers of *N*-methyl-3-(*S*)-aminopyrrolidines **239a** and **239b**, respectively (Scheme 111).



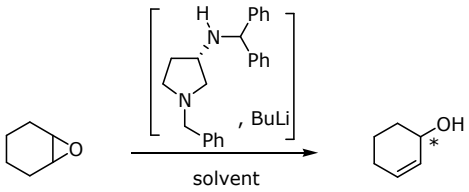
Scheme 111

6.2.2. Enantioselective isomerizations of *meso*-epoxides to allylic alcohols with 3-APLis as bases

Because of the lack of knowledge about the reactivity of chiral lithium amides derived by 3APs as bases, we wanted to use an empirical approach to investigate their metalating ability in relation also with their enantioselective efficiency. So we started from a diamine precursor model, the (*S*)-1-benzyl-3-((diphenylmethyl)-amino)pyrrolidine **229,** and we carried out a series of tests by changing the experimental conditions in order to achieve the best conditions to enantioselectively promote the isomerization of cyclohexene oxide **163b** into cyclohexen-2-ol **169b**. It is known from previous works that a direct correlation between enantiodifferentiation and epoxidic substrate / lithium amide steric repulsion exists.[282] Accordingly, our aim was also to identify the influence of structural changes on 3-APs. A set of diamines was chosen to represent variations of electronic character (aromatic **224**, **229**, **238a**, **239a** and **239b** or aliphatic **230** substituents on lateral chain), steric hindrance (**229** and **230** for lateral chain, **238** for *N*-pyrrolidinic substituent) and stereocentres (**238a**, **239a** and **239b**).

6.2.2.1. *Isomerizations of cyclohexene oxide with model 3-APLi* ***229****-Li*

As said above we first tested the amide derived from diamine **229** since it gave good results in term of yields and enantioselectivity in the nucleophilic additions of *n*-BuLi to *o*-tolualdehyde (Scheme 112).[31]



163b **169b**

Scheme 112

The results, collected in Table 19, show a clear dependence by the experimental procedures adopted.

entry	equiv base	solvent	temperatures	e.e. (%)[a]	conversions(%)[a]
1	1.0	pentane	r.t.	4% (*S*)	40%
2	2.0	pentane	-50°C	-	0%
3	2.0	pentane	r.t.	10% (*S*)	49%
4	3.0	pentane	r.t.	-	0%
5	1.0	THF	r.t.	10% (*S*)	39%
6	2.0	THF	-50°C	-	0%
7	2.0	THF	r.t.	55% (*S*)	99%
8	3.0	THF	r.t.	-	0%
9	2.0	DEE	r.t.	22% (*S*)	27%
10	2.0	pentane/DBU	r.t.	-	0%
11	2.0	THF/DBU	r.t.	-	0%
12	2.0	DEE/DBU	r.t.	-	0%
13	2.0	pentane (MW)	60°C	5% (*S*)	38%
14	2.0	THF (MW)	60°C	27% (*S*)	60%

Table 19: Enantioselective isomerizations of cyclohexene oxide **163b** into cyclohexen-2-ol **169b** with lithium (*S*)-1-benzyl-((diphenylmethyl)amino)pyrrolidine **229**-Li at different experimental procedures.
[(a)] measured by chiral CG

When the reaction was carried out at low temperatures no isomerization product was ever detected (entries 2 and 6). Only working at 25° C, or higher temperatures, partial conversions were recorded (entries 1, 3, 5, 7, 9, 13 and 14).

In particular with one equivalent of base only limited conversions, never over 40%, and low enantiomeric excesses were achieved (entries 1 and 5).

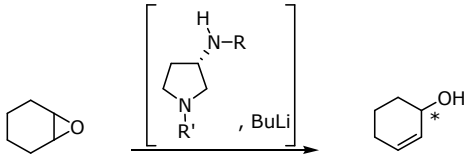
Surprisingly the treatment with three equivalents of base didn't lead to any isomerization process (entries 4 and 8). The best conditions, instead, were found using two equivalents of base in THF at room temperature , although conversions and e.e. were not excellent (entry 6). The same reaction performed in pentane and diethyl ether didn't show the same efficiency (entries 3 and 9).

In an attempt to improve the reaction performances, DBU and microwaves were also employed. In practice, concerning the use of DBU, the Andersson protocol was applied in the stoichiometric form.[294] It has been demonstrated, indeed, that enantioselectivity in base-mediated reactions is often influenced by the aggregation state of the lithium amides.[147, 285-294, 309] Lewis basic additives, such as DBU, are believed to act in favour of a highly enantioselective, monomeric catalyst species, by inhibiting the formation of unselective aggregates. In analogy microwaves could break out these aggregates and accelerate the reaction. Unexpectedly, however no isomerization took place when two equivalents of the base *rac*-**229**-Li were reacted with cyclohexene oxide **163b** in THF, DEE or pentane in the presence of DBU (entries 10 to 12). Probably DBU establishes a coordination with the amide **229**-Li preventing the base to react with the epoxide. MW irradiations didn't lead to any improvement in conversions and e.e. (entries 13 and 14). After one hour the reaction in pentane showed only a 38% conversion with 5% e.e.. Slightly better result were achieved in THF where nevertheless the conversion didn't overcome 60% with a very low e.e..

To check the generality of this phenomena and to try to correlate chemical results and structural data, we extended our investigations to the efficiency of new 3-aminopyrrolidines and, subsequently, of other *meso*-epoxides.

6.2.2.2. *Isomerizations of cyclohexene oxide with different 3-APLis*

Two equivalents of (*S*)-1-benzyl-3-(benzyl-amino)pyrrolidine **224**, (*S*)-1-benzyl-3-(cyclohexylamino)pyrrolidine **230**, (*S*)-1-(2-naphthylmethyl)-3-[(1-(*R*)-phenylethyl)-amino]-pyrrolidine **238a**, *N*-methyl-3-(*S*)-(1'-(*R*)-phenylethyl)-aminopyrrolidine **239a** and *N*-methyl-3-(*S*)-(1'-(*R*)-phenylethyl)aminopyrrolidine **239b** were reacted with BuLi and cyclohexene oxide **163b** (Scheme 113).



Scheme 113

entry	R	R'	Solvent	e.e. (%)[a]	conversions(%)[a]
1	$CHPh_2$	CH_2Ph	THF	55% (*S*)	99%
2	$CHPh_2$	CH_2Ph	pentane	10% (*S*)	49%
3	CH_2Ph	CH_2Ph	THF	70% (*S*)	89%
4	CH_2Ph	CH_2Ph	pentane	55% (*S*)	75%
5	*c*-C_6H_{11}	CH_2Ph	THF	70% (*S*)	100%
6	$CH(CH_3)Ph$ (*R*)	CH_3	THF	58% (*R*)	100%
7	$CH(CH_3)Ph$ (*S*)	CH_3	THF	62% (*S*)	100%
8	$CH(CH_3)Ph$ (*R*)	CH_2-*β*-napht	THF	81% (*R*)	82%

Table 20: Enantioselective isomerizations of cyclohexene oxide **163b** into cyclohexen-2-ol **169b** with different chiral lithium amide 3-APLi's.
[(a)] measured by chiral CG

As reported in Table 20, where also some previous results obtained with lithium (*S*)-1-benzyl-3-((diphenyl-methyl)amino)pyrrolidide **229**-Li are included (entries 1 and 2), almost all the experiments in THF gave a complete conversion, except the cases of the diamines **224** and **238a** (entries 3 and 8). THF, hence, was the best solvent for these reactions (entries 1, 3, 5 to 8) while the analogue reactions carried out in pentane afforded low conversions and e.e.'s (entries 2 and 4). The best result, in terms of enantiomeric excess, was found on treating cyclohexene oxide **163b** with the base **238a**-Li (81%, entry 8). From such a large array of results however, we can argue that apparently there is no direct correlation between the stereodifferentiation and the steric hindrance on the *N*-substituent on the pyrrolidinyl ring. By comparison between the amides **229**-Li and **230**-Li or **224**-Li, indeed, we can see that the better enantiomeric excesses were obtained with the latters. As a matter of fact, while the good result of entry 8 seems to be in agreement with a steric effect of the substituent on the pyrrolidine ring, most of the other results are less easy to rationalize in terms of a correlation between e.e. values and size of R. In fact while the benzylamide **224**-Li gave a 70% e.e. (entry 3), diphenylmethylene amide **229**-Li produced only a 55% e.e. (entry 1), despite the same *N*-substituent on pyrrolidinyl ring, and this value is lower also than that obtained with the amides **239a**-Li and **239b**-Li, which have, in addition, a small steric hindrance on pyrrolidinyl nitrogen (entries 6 and 7).

These data could be better explained by a more accurate conformation analysis of these reagents in THF solution (Figure 24).

The conformation of the lithium amides in solution, indeed, depends on the bulkiness of the lateral amine substituent.[15] Thus, whereas 3-benzylaminopyrrolidine **224** in THF at low temperature yields an undetermined oligomeric mixture, lithium amides **229**-Li, **230**-Li, **238a**-Li, **239a**-Li and **239b**-Li undergo, in the same conditions, a chelation of the lithium atom by the pyrrolidine

nitrogen, leading to an aza-norbornyl structure, as established by both spectroscopic[15] and theoretical[306] grounds. Therefore the diverse conformation of the amide **224**-Li could explain the different results in terms of conversions (lower than amide **229**-Li, although less bulky) and e.e.'s[31] (higher than amides **229**-Li, **239a**-Li and **239b**-Li, even if lateral amino chain is less hindered).

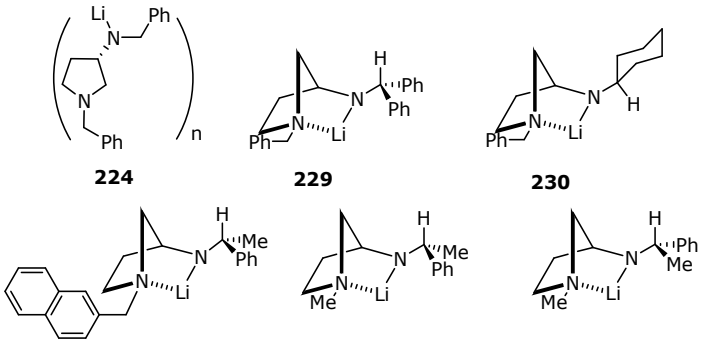


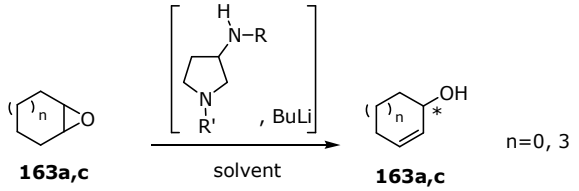
Figure 24

In the cases of the diamines **238a**, **239a** and **239b** the sense of the induction appeared to depend on the configuration of the second stereogenic center (entries 6 to 8).

The norbornyl conformation may explain the influence of the second stereogenic centre of amides **238a**-Li, **239a**-Li and **239b**-Li on determining the configuration of the isomerization product; NMR spectroscopic data and theoretical calculations have to be done in order to fully understand these reaction mechanisms.

6.2.2.3. *Isomerizations of cyclopentene oxide and cyclooctene oxide with 3-APLis*

Aiming at the development of a more general methodology making use of chiral lithium amides derived from 3-AP **210**-Li as bases, the base-promoted isomerization was extended to other *meso*-epoxides, such as cyclopentene oxide **163a** and cyclooctene oxide **163c** (Scheme 114).



163a,c **163a,c**

Scheme 114

All the reactions were carried out in the same condition which led to the best performances with cyclohexene oxide: two equivalents of base in THF at room temperature. The results obtained were very different depending on the substrate and the reagents used.

entry	n	R	R'	e.e. (%)[a]	conversions(%)[a]
1	1	$CHPh_2$	CH_2Ph	20% (*S*)	30%
2	1	CH_2Ph	CH_2Ph	28% (*R*)	92%
3	1	*c*-C_6H_{11}	CH_2Ph	58% (*R*)	100%
4	4	$CHPh_2$	CH_2Ph	36% (*S*)	20%
5	4	CH_2Ph	CH_2Ph	22% (*R*)	8%
6	4	*c*-C_6H_{11}	CH_2Ph	62% (*R*)	100%

Table 21: Enantioselective isomerizations of cyclopentene oxide **163a** and cyclooctene oxide **163c** with different chiral lithium amides.
[(a)] measured by chiral CG

As reported in Table 21, the treatment with cyclohexyl amide **230**-Li gave access to the best results in terms of conversion and e.e. (entries 3 and 6). In the other cases lower conversions and e.e.'s were obtained. In particular, when the *meso*-cyclopentene oxide **163a** was reacted with two equivalents of 3-APLi **229**-Li, a 30% yield was observed, and the e.e. was limited to 20% (*S* enantiomer, entry 1). With two equivalents of 3-APLi **224**-Li the yield increased to 92%, but the e.e. remained around 28% in favour of the *R* enantiomer (entry 2). In the case of *meso*-cyclooctene oxide **163c** low conversions (from 8% to 20%) and e.e.'s were obtained with both the amines **227** and **229** (entries 4 and 5): 36% e.e.'s of (*R*)-allylic alcohol with 3-APLi **229** and 22% of (*S*)-allylic alcohol with 3-APLi **224** were formed. These results seems to be related to the size of the heterocycle; in fact when a small ring, like cyclopentene oxide, is employed, the chiral lithium amide could not be able to discriminate between the spatial positions of the two hydrogen atoms to be removed; on the other hands larger rings, like the eight-membered heterocyclic epoxide, could be less easy to be coordinated by the amides **229**-Li and **224-**Li because of the high hindrance and so lower conversion are obtained. This framework can be completed by considering also the different conformational structures of the benzyl amide **224**-Li and diphenylmethylene amide **229**-Li and **230**-Li in solution (Figure 23).

In conclusion of this first part of the study we can say that the isomerization of epoxides **163** to allylic alcohols **169** promoted by 3-APLi **210**-Li bases is possible and that it strongly depends on the solvent, as well as the amount of base. Besides, the inversion of stereochemistry of such isomerization products, which has been recorded in some cases, can be explained by the different conformations of the amides in solution which have an influence on the transition

states of the enantioselective isomerisation. Finally it is worth noting that in all cases the isomerization of cyclic epoxides occurs with a perfect regiocontrol: only the allylic alcohols have been obtained and this can been explained by assuming a total *β*-elimination reaction mechanism.

Although better results in this field can be found in the literature,[294] our findings represent the first example of use of 3-APLi bases and constitute a good starting point for our further experiments.

6.2.3. Enantioselective isomerizations of *meso*-cyclohexene oxide to cyclohexen-2-ol with 3-APLis as chiral ligands of organolithium compounds

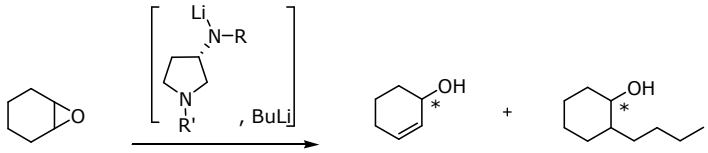
In view of the good results obtained in the chiral base-induced isomerization of epoxides with 3-APLi's, we decided to investigate the use of these reagents as chiral ligands for organolithium compounds and as components of superbasic mixtures.

A deep investigation of 3-APLis as chiral ligands in the condensation of *n*-butyllithium on aldehydes and *α*,*β*-unsaturated esters has led to excellent results in terms of yields and e.e.'s.[16-18, 20, 31] However, examples of their use as chiral ligands of organolithium compounds on promoting rearrangements of epoxides to allylic alcohols have not been verified yet. There are examples on the use of chiral ligands associated to organolithium compounds for the isomerization of epoxides in the literature. Studies by Hodgson[310-316] and O'Brien's[4] deal mainly with the use of (−)-sparteine as chiral ligand and the results in terms of yields and e.e.'s are closely related to the epoxide structure.

In principle, the noncovalent association between organolithium compounds and 3-APLis can lead to aggregates sufficiently stable in solution to be used in the asymmetric isomerizations. It has been clearly described, indeed, by Dr. Maddaluno that in the presence of an excess of butyllithium, 1:1 aggregates BuLi / 3-APLi are formed with a norbornyl-like arrangement of the diamino moiety no matter which lateral substituent is present (paragraph 6.1.2).[16-18, 31]. Such an arrangement is fundamental to explain the strong asymmetric induction they show (Figure 21).[16, 17, 20, 31] At this stage, butyllithium becomes "chiral" and could promote an enantioselective isomerization through diastereomeric transition states. Butyllithium is an excellent base, but a good nucleophilic agent, too, therefore a competitive alkylation reaction could take place. It is then also interesting to verify if both pathways occur simultaneously affording mixtures of isomerization and addition products. In any case the result of the reaction is interesting. In fact, only a few examples of alkylative desymmetrisation of epoxides with organolithium compounds are known in the literature mainly

concerning cyclooctene oxide, while cyclopentene oxide and cyclohexene oxide usually follow other reaction mechanism.[310]

Four different 3-aminopyrrolidines have been evaluated as chiral ligand precursors: (*S*)-1-benzyl-3-(benzyl-amino)pyrrolidine **224**, (*S*)-1-benzyl-3-(cyclohexylamino)pyrro-lidine **230**, *N*-methyl-3-(*S*)-(1'-(*R*)-phenylethyl)-aminopyrrolidine **239a** and *N*-methyl-3-(*S*)-(1'-(*R*)-phenylethyl) aminopyrrolidine **239b** while cyclohexene oxide **163b** has been chosen as model substrate. All the reactions were carried out with two equivalents of 3-APs and four of butyllithium in THF at -20° C, temperature below which the complex is not formed. A higher temperature, on the other hand can induce butyllithium degradation (Scheme 115).



163b **169b** **258**

Scheme 115

All the results are collected in Table 22.

entry	R	R'	169b : 258	e.e. (%)[a] 169b	e.e. (%)[a] 258	Conv (%)[a]
1	CH_2Ph	CH_2Ph	22:78	11% (*S*)	32%	100%
2	*c*-C_6H_{11}	CH_2Ph	100:0	84% (*S*)	-	100%
3	$CH(CH_3)Ph$ (*R*)	CH_3	45:55	23% (*R*)	33%	100%
4	$CH(CH_3)Ph$ (*S*)	CH_3	43:57	21% (*S*)	30%	100%

Table 22: Enantioselective isomerizations of cyclohexene oxide **163b** with chiral lithium amides 3-APLi as chiral ligands.
[(a)] measured by chiral CG

A total conversion of the starting substrate **163b** with exclusive formation of the allylic alcohol **169b** was observed only by using the cyclohexyl amide **230**-Li / BuLi mixture (entry 2). By comparison with the analogue reaction carried out with 3-APLi **230**-Li as base we can notice an increase of e.e.'s from 70% to 84% (Tables 20 and 22). In all other cases a mixture of cyclohexen-2-ol **169b** and 2-butylcyclohexanol **258** was always obtained with different ratios depending on the 3-AP used and the level of e.e. observed was low (entries 1, 3 and 4). In particular in the case of 3-APLi **224** a 22:78 ratio between the product **169b** and **258** was found, while concerning the 3-APLis **239a** and **239b** this value decreased to 45:55 and 43:57 respectively, probably due to the lower steric hindrance on *N*-pyrrolidinic substituent (entries 3 and 4). Moreover also in this

case the presence of a second stereogenic center in the lateral amino chain of 3-APLi determines the sense of asymmetric induction of the isomerization product (entries 3 and 4).

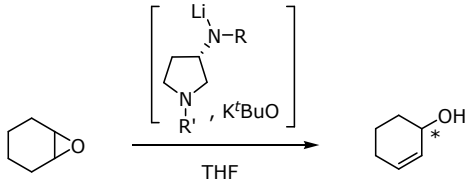
In conclusion, this series of experiments has demonstrated the possibility to rearrange oxiranes with 3-APLis as chiral ligand of organolithium compounds and that this process is strongly dependent by the typology of the 3-AP. Only the use of lithium (*S*)-1-benzyl-3-(cyclohexylamino) pyrrolidide **230**-Li gave the isomerization product **163b** with high conversion, regioselectivity and enantiomeric excess. This result represents a good starting point in order to develop a valuable tool for promoting the enantioselective isomerization of epoxides, as an alternative to the well-known chiral lithium amide rearrangements. Further investigations will be focused on the scope of the process by varying the oxirane structure and extending it to the analogous aziridines.

6.2.4. Enantioselective isomerizations of *meso*-cyclohexene oxide to cyclohexen-2-ol with 3-APLis as superbasic mixture with potassium *tert*-butoxide

As part of our program devoted to the development of new applications of 3-APLi, we decided to test also the possibility to use chiral superbases to promote enantioselective isomerizations. The approach to chiral superbase can be faced from two different perspectives, either making use of a chiral alcoholate or a chiral lithium amide. Concerning the alcoholate approach, previous investigations were carried out with potassium (1*R*, 2*S*, 5*R*)-(–)-menthoxide,[317, 318] but the results in terms of enantioselective induction were not good, probably due to the high distance between the stereogenic center and the reaction site. The approach which makes use of chiral lithium amides looks therefore more attractive and nothing is known in the literature concerning the use of chiral superbase of this kind in the rearrangement of epoxides to allylic alcohols.

For this set of reactions with cyclohexene oxide **163b** we chose to test lithium (*S*)-1-benzyl-3-(cyclohexylamino)pyrrolidide **230**-Li, lithium (*S*)-1-(2-naphthylmethyl)-3-[(1-(*R*)-phenylethyl)amino]-pyrrolidide **238a**-Li, lithium *N*-methyl-3-(*S*)-(1'-(*R*)-phenylethyl) -aminopyrrolidine **239a**-Li and lithium *N*-methyl-3-(*S*)-(1'-(*R*)-phenylethyl)amino-pyrrolidine **239b**-Li as components of chiral superbases.

All reactions were carried out in anhydrous THF at different temperatures (Scheme 116 and Table 23).



163b **169b**

Scheme 116

As it happened for the reactions carried out with 3-APLis as bases, also in this case the isomerization occurred only at room temperature (entries 3, 6, 8 and 10) while the use of a classical superbase, as LIDAKOR, allows a complete rearrangement also at low temperature (entry 1). Compared with the reactions with chiral 3-APLi as bases, the reactivity in this case was notably increased as the reaction times passed from 24-36 hours to 12-16 hours (entries 2 and 3) but, unfortunately, the e.e. values were always low (Tables 20 and 23). It is interesting to note the change of configuration of the stereogenic centre of the isomerized product **169b** compared with the situation of the 3-APLi base-promoted rearrangement (Tables 20 and 23).

entry	base	alcoholate	times (h)	temperatures	e.e. (%)[a]	Conv (%)[a]
1	LDA	K^{t}BuO	16	-50°C	-	100%
2	**230**-Li	-	24	r.t.	70% (*S*)	100%
3	**230**-Li	K^{t}BuO	16	r.t.	52% (*R*)	100%
4	**238a**-Li	K^{t}BuO	36	-50°C	-	0%
5	**238a**-Li	K^{t}BuO	24	0°C	-	0%
6	**238a**-Li	K^{t}BuO	16	r.t.	46% (*S*)	100%
7	**239a**-Li	K^{t}BuO	24	-50°C	-	0%
8	**239a**-Li	K^{t}BuO	16	r.t.	10% (*S*)	100%
9	**239b**-Li	K^{t}BuO	24	-50°C	-	0%
10	**239b**-Li	K^{t}BuO		r.t.	10% (*R*)	100%

Table 23: Enantioselective isomerizations of cyclohexene oxide **163b** with chiral lithium amides 3-APLi as superbasic mixture with K^{t}BuO.
[(a)] measured by chiral CG

Such change is probably due to a different mechanism operating in this case but no mechanistic studies in order to rationalize such results have been done yet.

In conclusion, although a comparison with the 3-APLi base-promoted reactions show that these results are worse at the present stage, the possibility to enantioselectively rearrange oxiranes with chiral superbases may be useful particularly in view of their use in those cases (aziridines for examples) where a

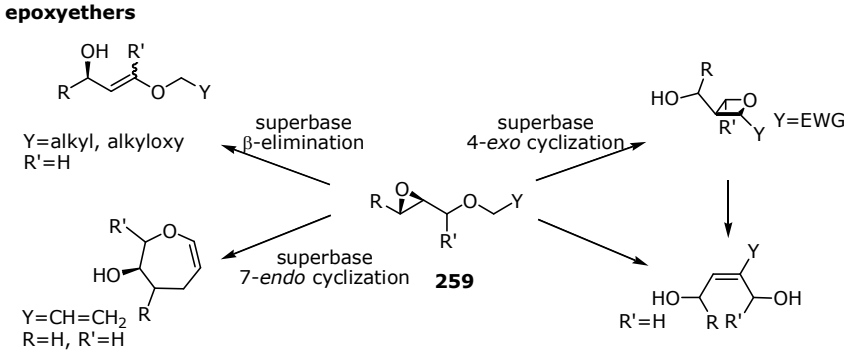
simple chiral lithium amides is not effective. Further studies in this direction are in progress.

7. CONCLUSIONS OF THE FIRST PART

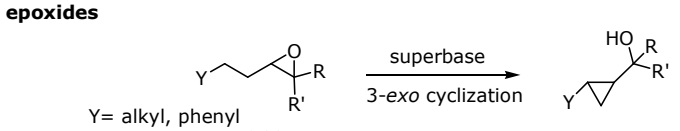
7.1. Results

In the last twenty years, the Mordini's group in Florence has focused his research on the development of superbase-induced rearrangements of epoxides and aziridines finding interesting results in terms of the selectivities of the processes and of their synthetic utility. Part of this thesis has been therefore devoted to these topics aiming at extending the scope of these reactions to:
(a) new substrates;
(b) new synthetical methodologies;
(c) new possible asymmetric applications.

(a) new substrates
Due to the encouraging results obtained with oxiranes **259** oxiranyl ethers and **260** (Scheme 117 and 118), new possible isomerizations of aziridinyl systems, such as the base-induced *β*-eliminations or the intramolecular 4-*exo* cyclizations, have been investigated with the aim to give access to new allylic amine or amino-oxetane structures, both very useful from a practical point of view.

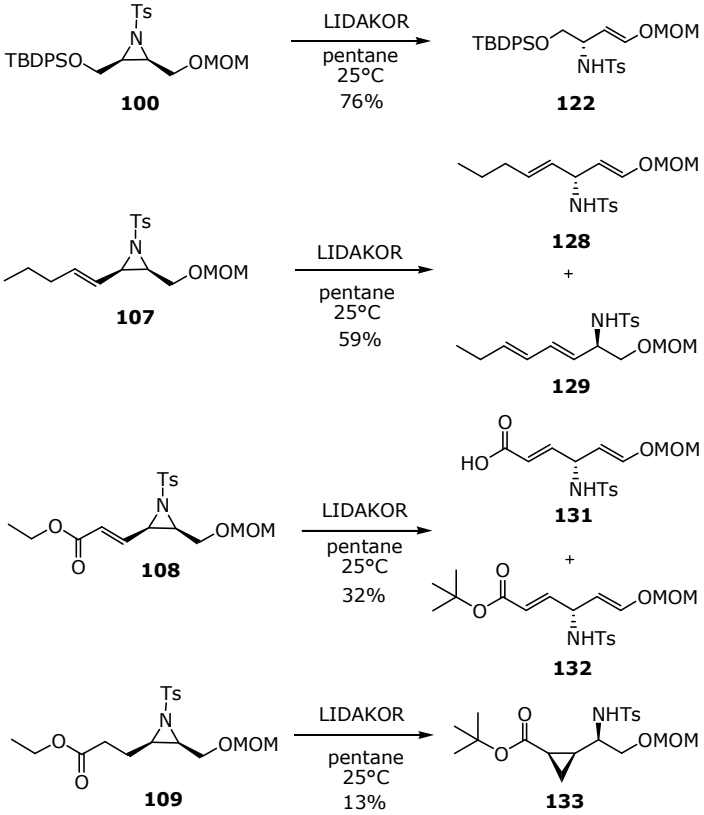


Scheme 117



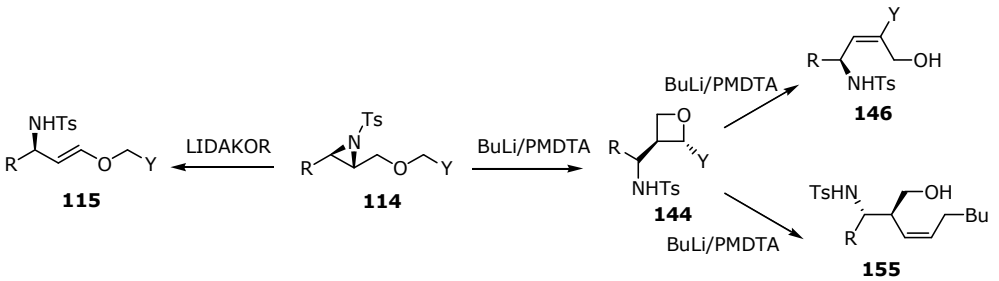
Scheme 118

To summarize the results achieved, a new highly functionalized aziridine [(2*S*,3*R*)-2-[(*tert*-butyldiphenylsilyl)oxy]methyl-3-(methoxymethoxy)methyl-*N*-(*para*-toluen-sulfonyl)-aziridine **100** and its derivatives **107**, **108** and **109** have been studied showing the feasibility of the base-promoted rearrangement which leads, with reasonable to good selectivity, to allyl amines (or cyclopropylamine **133**), direct precursors of *α*- or *β*-amino acids (Scheme 119).



Scheme 119

In addition, activated aziridinyl ethers carrying benzyl, *para*-substituted benzyl, phenylthiomethoxy and allyloxy substituents **114** have been converted by a similar process, to the corresponding 4-*exo* cyclized products. Despite these reactions leading to amino-oxetanes, are more difficult and less selective than the corresponding carried out on oxiranes **260**, they have allowed to give access to a new class of oxetanes **144** which seems promising for future applications. In some case additional rearrangement reactions on the newly formed oxetanes have also been observed, leading to highly functionalized amino alcohols **146** or **155** (Scheme 120).

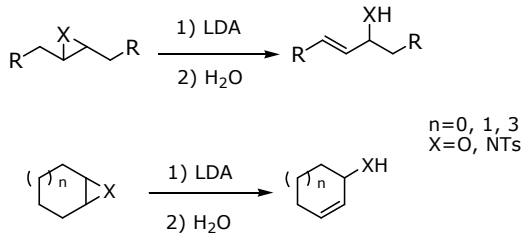


Scheme 120

(b) new synthetical methodologies

The present thesis has intended to cover also the field of new selective and efficient methodologies to promote isomerization processes, such as the use of new alternative energy sources like microwaves, thus avoiding superbases which often require particular experimental care. The possibility to take advantage of MW irradiation in conjunction with simple organolithium reagents would be rather appealing and this is the reason which has pushed our studies in the field.

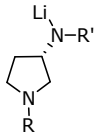
The results obtained with non-functionalized epoxides and aziridines and lithium diisopropylamide, as base, have shown in all cases reduction of reaction times, milder conditions, good yields in terms of isomerization products, and, often, good selectivities thus opening a new route which seems very promising and needs to be explored more in details (Scheme 121).



Scheme 121

(c) new possible asymmetric applications

Finally, the collaboration between the Maddaluno's and Mordini's groups has opened a completely new field of research which has concerned the use of 3-APLis (Figure 25) as promoter of enantioselective isomerizations.

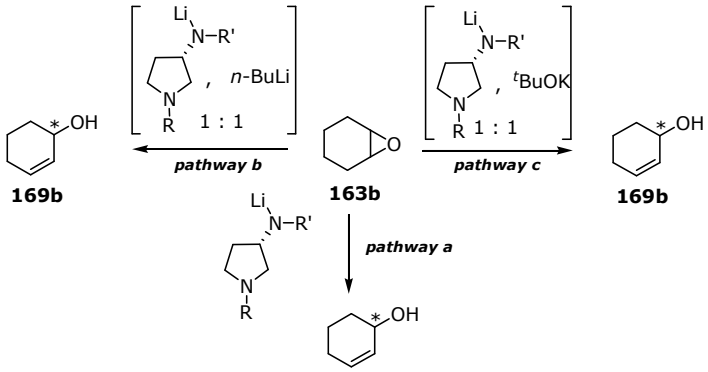


224-Li **:** R=CH_2Ph; R'=CH_2Ph
229-Li **:** R=CH_2Ph; R'=$CHPH_2$
230-Li **:** R=CH_2Ph; R'=Cy
238a-Li**:** R=CH_2Napht; R'=(*R*)$CH(CH_3)Ph$
239a-Li**:** R=CH_3; R'=(*R*)$CH(CH_3)Ph$
239b-Li**:** R=CH_3; R'=(*S*)$CH(CH_3)Ph$

Figure 25

The early experiences of the Rouen group on 3-APLis and the knowledge of the Florence group on strained heterocycles rearrangement, has constituted the backbone of this collaboration. We have investigated in details 3-APLis as chiral base (pathway a, Scheme 122), then, as chiral ligands of organolithium compounds (pathway b, Scheme 122) and, finally, as component of superbasic mixtures (pathway c, Scheme 122). In all cases, the isomerization process from epoxides into allylic alcohols has shown to be possible and, under accurately

chosen reaction conditions, the results are quite good if compared with what is known in the literature.

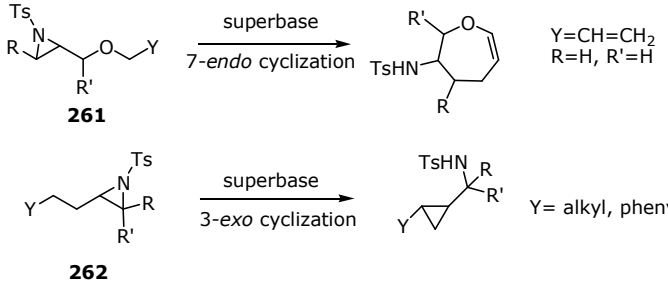


Scheme 122

Ours is the first application of 3-APLis as bases or ligands in deprotonation reactions and the results are quite promising even if a more careful mechanistic study is certainly required to better understand the process and the nature of the species involved.

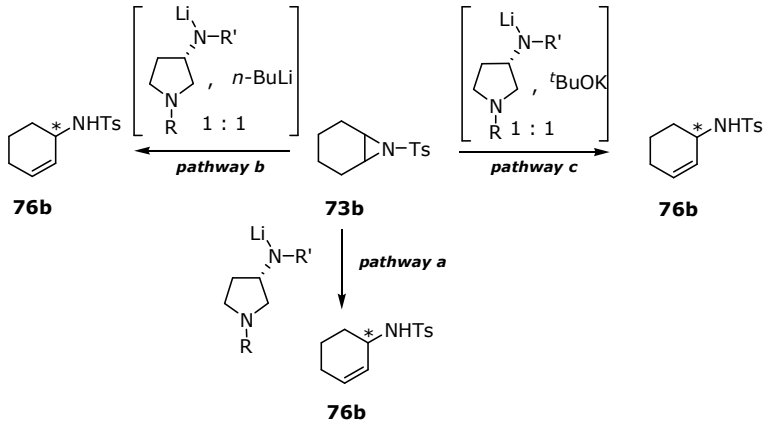
7.2. Perspectives

Future developments of this project will be focused on evaluating the possibility to obtain also 7-*endo* and 3-*exo* cyclization processes from aziridinyl ethers **261** and aziridines **262** as the well-known examples of the oxiranyl ethers **259** and aryloxetanes **260** (Scheme 123).



Scheme 123

About the 3-APLi's, their employment in isomerisation reactions of aziridines is also an interesting target (Scheme 124). In fact, in literature only few examples are reported of enantioselective aziridine / allyl amine transformation, all making use of (–)-sparteine as chiral auxiliary.[152, 245]



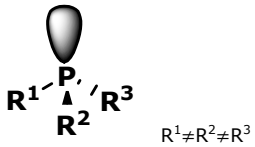
Scheme 124

Also in this case, 3-APLi's will be tested as chiral bases (pathway a, Scheme 124), chiral ligands (pathway b, Scheme 124) and superbases (pathway c, Scheme 124).

Second Part

8. INTRODUCTION

This section of the thesis deals with a NMR structural study of lithium phosphides in solution. It is part of a project, that aims at synthesizing, and testing as chiral ligands, enantioenriched P-stereogenic phosphines (Figure 26).



$R^1 \neq R^2 \neq R^3$

Figure 26

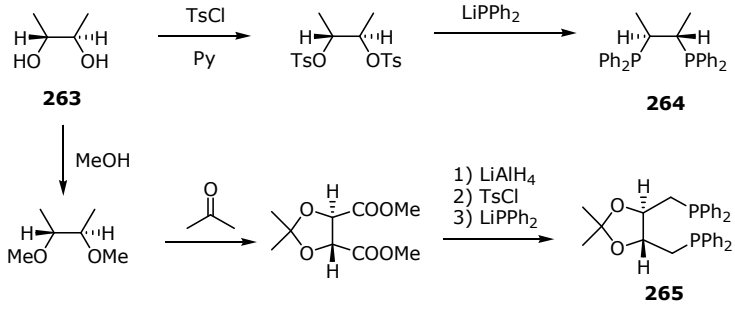
The synthetic developments are mainly conducted in the group of Prof. Annie-Claude Gaumont at the University of Caen (Lower Normandy),[319-322] while the spectroscopic studies are carried out at the University of Rouen (Upper Normandy), under the supervision of Prof. Hassan Oulyadi and Dr. Jacques Maddaluno.[15-20, 31, 323]

8.1. Chiral phosphines and chiral phosphine boranes

Chiral trivalent phosphorus compounds represent one of the most important classes of ligands for the transition-metal asymmetric catalysis[324, 325] (hydrogenation,[326-329] hydrosilylation,[330, 331] hydrocarbonylation,[332] C–C coupling reactions,[333, 334] isomerization[335, 336]). If a large number of synthetic methods is reported in the literature to attain phosphine derivatives,[337, 338] less is known to prepare chiral ones,[339] and among the strategies elaborated to create P–C bonds, substitution reactions play a pivotal role. The chirality on a trivalent phosphine can either be located (and it is actually often the case) on a substituent connected to the phosphorus atom,[340] or, this later is the stereogenic center itself, being substituted by three different appendages.[341]

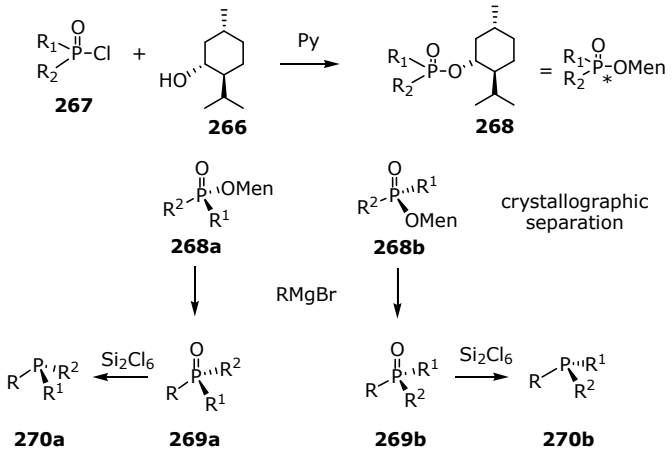
In general, up to now only three main approaches to obtain enantiomerically pure trivalent phosphorus compounds with chiral carbon skeleton or stereogenic phosphorus are known:[342]

- by the exploitation of chiral starting materials from natural substances or easily accessible (chiral pool synthesis, for instance from binaphtol, tartaric acid (Scheme 125),[343] amino-acids, carbohydrates…). Thus, tartaric acid **263**, for example, can be derived into (*S*,*S*)-CHIRAPHOS **264** or (–)-DIOP **265**, two of the most employed ligands in enantiomeric catalyses;[344]



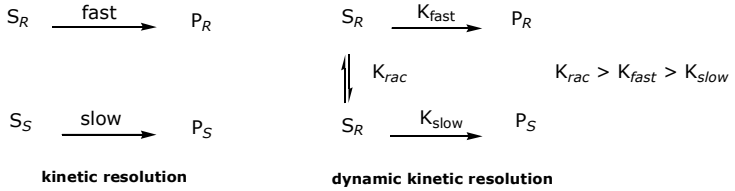
Scheme 125

- by utilization of chiral auxiliaries,[345] including the use of enzymes,[346] non-metal-based catalysts[347] and metal catalyst.[324, 340, 344, 348-350] One of first examples deals with the addition of (−)-menthol **266** to phosphinic chloride **267** to prepare compounds **268**, which is easily separated in **268a** and **268b** and, subsequently, transformed in **269a** and **269b** and reduced with inversion of configuration to useful C,P-chiral phosphine ligands **270** (Scheme 126);[351, 352]



Scheme 126

- *via* kinetic resolution or dynamic kinetic resolution by the use of resolving agents such as (−)-sparteine[353] or transition metal complexes[341] (Scheme 127).[354-356]



Scheme 127

Among the inconveniences presented by these methods, one can note the length of the procedures, their high cost, and the fact that they often require the introduction of a stoichiometric amount of chiral auxiliary, that must be fixed to the precursor and then eliminated at the end of the synthesis (diastereoselective synthesis, which adds two "unproductive" steps to the sequence).

Note also that trivalent phosphines are particularly sensitive to air, and easily oxidized. As a consequence, their handling and storage require special equipment and a know-how not always available in all laboratories. On the other hand, and complementarily, these compounds are prone to racemization and therefore require additional stabilization. Such drawbacks can be overcome by the temporary protection of the phosphorus atom setting up a dative bond with a borane group (BH_3). Indeed, investigations by Schmidbaur and others show that P–borane complexes (or P–borane adducts) display unique properties:[357, 358] i) they can be conveniently prepared and smoothly cleaved; ii) due to the reduction in polarity of the B–H and P–B bonds, P–boranes are remarkably inert and can resist towards a range of different reaction conditions.[359] Once involved in the B–P bond, BH_3 is supposed to lose its hydroboration activity and the electronic properties of the phosphorus atom are changed. Phosphine borane adducts, indeed, give clean reactions *via* electrophilic or nucleophilic substitution on the phosphorus center or in *α*-position of one of the phosphorus substituents.[360]

In 1985, Imamoto took advantage of the potential of P–boranes entities to synthetize chiral phosphines ligands.[361, 362] Since then, an increasing number of new ligands has been prepared *via* this intermediate.[360, 363-378] Some examples are reported below, in particular, starting from (+)-ephedrine (Figure 27).[378]

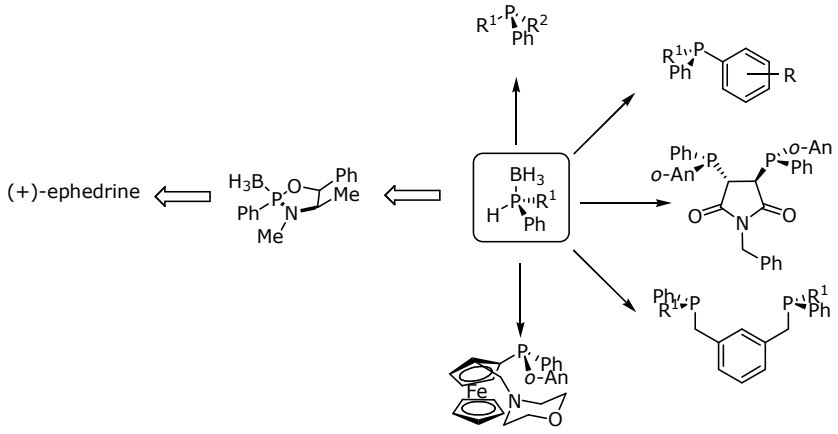
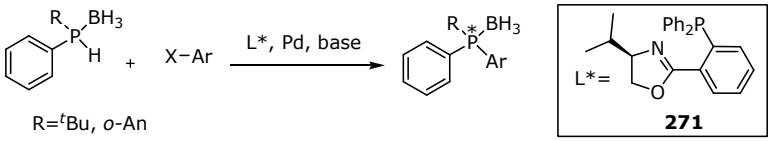


Figure 27

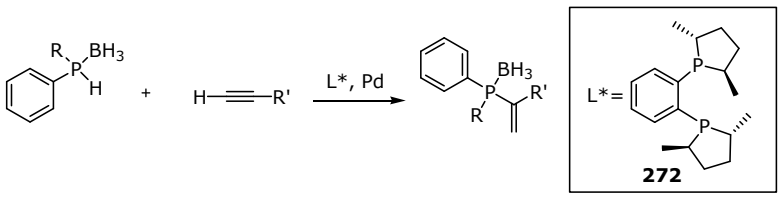
8.2. Aim of the project

In the last ten years, Prof. Gaumont's group in Caen has been interested in the asymmetric synthesis of chiral P-stereogenic phosphines.[319-321, 379, 380] Two metal-catalyzed reactions have been developed: a carbon-phosphorous coupling reaction, which leads to arylphosphines,[321] and the hydrophosphination of alkynes, affording vinylphosphines.[380] In the first case, an enantioselective version of a C–P cross-coupling reaction mediated by palladium between racemic secondary phosphine-boranes and aryl iodide derivatives is carried out (Scheme 128). This study involved a screening of a series of parameters such as chiral ligand, base, solvent, as well as temperatures. The best results (45% e.e.) were obtained with (*R*)-(+)-2-[2-(diphenylphosphino)phenyl]-4-(1-methylethyl)-4,5-dihydrooxazole **271**,[381] $Pd(OAc)_2$, CH_3CN, and K_2CO_3 at room temperature.



Scheme 128

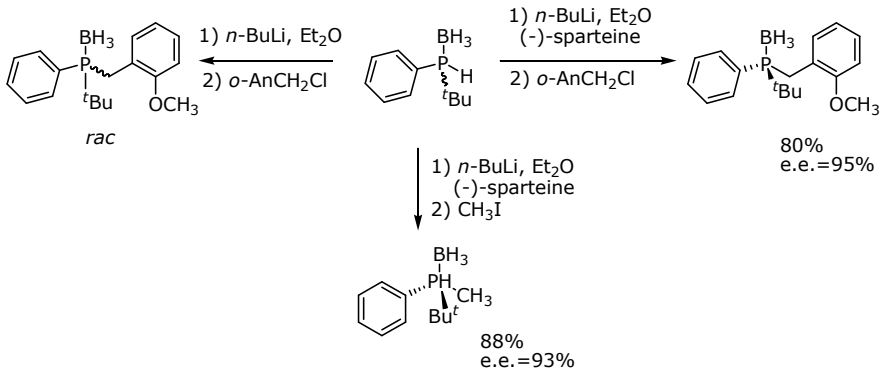
The hydrophosphination approach involves unactivated alkynes (Scheme 129) and two procedures have been developed: the addition of a racemic secondary phosphine–borane to an alkyne leads to the anti-Markovnikov adducts (thermal conditions); in contrast, using a metallo-catalyzed activation (catalytic system composed by a 5 mol% of a $[Pd_2(dba)_3]$ and dppp mixture) affords the Markovnikov derivatives.[320] The asymmetric version of the latter reaction has given access to P-stereogenic vinylphosphines by assuming a transfer of chirality from the catalyst to the product. So a series of ligands was tested and their induction monitored varying other experimental parameters (solvent, metal / ligand ratio, temperature and amount of alkyne). High conversion (70%) and enantiomeric excess up to 42% e.e. were obtained in presence of $Pd(OAc)_2$ and (*R*,*R*)-MeDuphos **272** as catalyst in toluene at 50° C after 17h.



Scheme 129

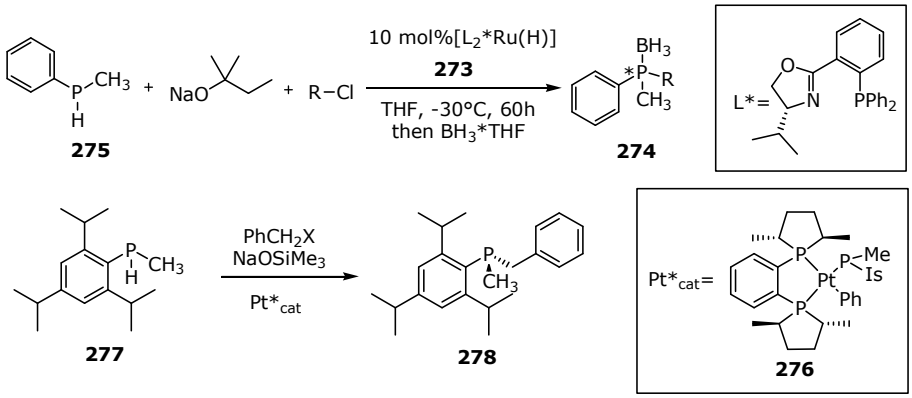
An enantioselective strategy to **reach enantioenriched alkylphosphines** would consist in achieving the alkylation of an enantioenriched phospha-anion by

reaction with an achiral electrophile. Such an approach has already been initiated by Livinghouse in 1998. The use of the butyllithium-sparteine couple is mentioned[353] and the enantioselectivity assigned to a dynamic resolution / alkylation of the lithiated phospha-anion coordinated to the sparteine (Scheme 130).[360, 382-384]



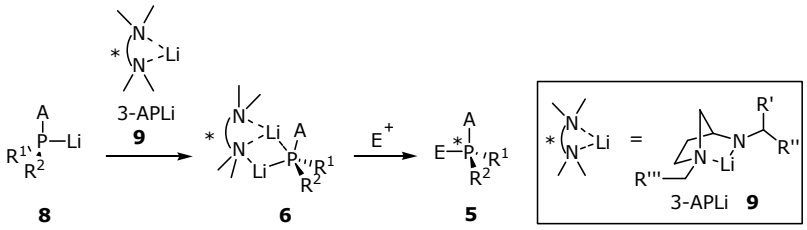
Scheme 130

Examples of metallo-catalyzed (platinum and ruthenium) alkylation of unprotected secondary phosphines have been published more recently (Scheme 131).[385-388] The enantiomeric excesses vary from 20% to 95% in depending on the substrate, the electrophile and the chiral catalyst. The employment of di-*iso*-propyl-phosphine-oxazoline ruthenium-hydride catalytic complex **273**, [L*$_2$Ru(H)], gave access, for instance, to phosphine boranes **274** in 79%-94% starting from methylphenylphosphine **275** (Scheme 131, top); while the phosphido Pt(Me-Dupos)(Ph)(PMeIs) **276** catalyzed the alkylation of PHMeIs **277** (Is=2,4,6-(iPr)$_3$C$_6$H$_2$) with benzyl choride or, more quickly, benzyl bromide, in the presence of the base NaOSiMe$_3$ to give PMeIs(CH$_2$Ph) **278** (Scheme 131, bottom).



Scheme 131

To our knowledge, studies combining a phosphide and a chiral lithium amide to form an inductive complex able to react stereoselectively with an achiral electrophile has no precedent in the literature. Such initiative is at the origin of the collaboration between the groups located in Caen (A.-C. Gaumont) and Rouen (J. Maddaluno).[389]



Scheme 132

The idea consists in getting enantioenriched P-stereogenic trialkylphosphines boranes (**5**, Scheme 132) reacting an alkyl cation (E^+) through a mixed aggregate (**6**) involving a racemic lithiated phospha-anion (**8**) and an enantiopure 3-aminopyrrolidine lithium amide **9** (3-APLi). Complex **6** is expected to set up a kinetic or kinetic-dynamic resolution when reacting with the electrophile.

In a complementary contribution, a multinuclear (^{1}H, ^{6}Li, ^{13}C, ^{31}P and ^{11}B) NMR study and theoretical calculations have been planned to evaluate the configurational and conformational stability of **6**, and thus give a rational description of the stereochemical outcome.

The results presented in this section represent a first step toward the above objective and mainly corresponds to an NMR structural study. It is divided in two parts (Figure 28):

- the characterization, in THF, of the structure of lithium diphenylphosphide borane ($Ph_2P(BH_3)Li$), a model lithium phosphide borane.
- the evaluation of the ability for the selected model phosphide to aggregate with either *n*-butyllithium (*n*-BuLi), or diisopropyllithium amide (LDA).

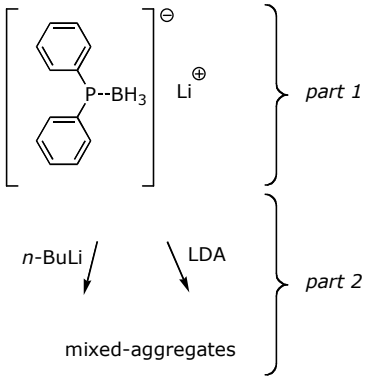


Figure 28

8.3. General considerations about the NMR techniques applied to organolithium derivatives

NMR spectroscopy is probably now the most frequently employed technique for structural studies of organolithium compounds.[390] Even though the degree of homo- and hetero-aggregation has been determined for a long time by colligative measurements,[44, 391] scalar *J*-coupling NMR measurements, as well as the observation of homo- and hetero bi-dimensional NMR correlations afford more reliable data.

For our investigation, we have decided to carry out a series of one- and two-dimensional multinuclear (^{1}H, ^{6}Li, ^{11}B, ^{13}C and ^{31}P nuclei) NMR analyses.

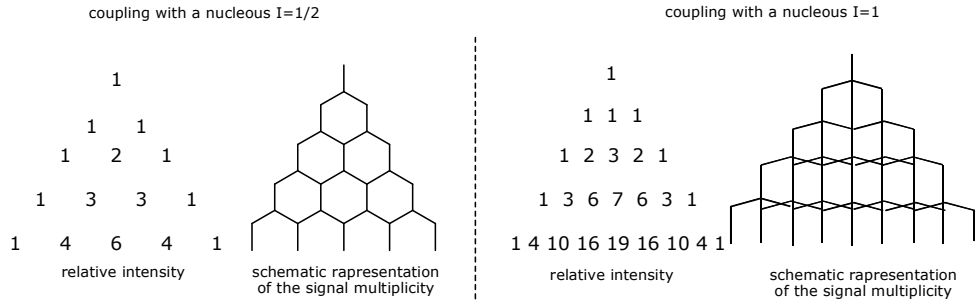
Six-labelled lithium isotope is preferred to the naturally and more abundant seven Li one (see Table 1 for main properties of lithium isotopes). Indeed, both ^{6}Li and ^{7}Li have a spin number different from the required ½, and therefore exhibit a quadrupolar moment Q, that decreases the relaxation times T_1 and T_2. This results in broader signals since $\Delta_{1/2} = 1/\pi T_2$. However, the very low ^{6}Li-Q value makes this parameter almost negligible in the relaxation process, explaining why this less sensitive isotope gives thinner, and thus better signals.

properties	**^{6}Li**	**^{7}Li**
spin	1	3/2
natural abundance	7.59%	92.41%
chemical shift range	28 ppm, from -16 to +11	28 ppm, from -16 to +11
frequency ratio (Ξ)	14.716086%	38.863797%
quadrupolar moment Q	$-8.0*10^{-32}$ m^2	$-4.5*10^{-30}$ m^2
reference compound	^{6}LiCl	^{7}LiCl
linewidth of reference	0.03 Hz	0.07 Hz
receptivity rel. to ^{1}H at natural abundance	6.45×10^{-4}	0.271
receptivity rel. to ^{1}H when enriched	8.50×10^{-3}	0.29
receptivity rel. to ^{13}C at natural abundance	3.79	1590
receptivity rel. to ^{13}C when enriched	49.9	1721

Table 24: Lithium-6 and Lithium-7 nuclear features

The spin number of ^{6}Li being I=1, the multiplicity of the X-nuclei directly bonded to this atom presents a different trend than that usually observed for NMR-active nuclei having I=1/2 (Scheme 133). The general rule for the signal multiplicity (N) remaining N = 2*n*I+1 (*n* corresponding to the number of equivalent lithium atoms), the signal will present 3, 5 or 7 peaks on the 1D

spectra of neighbour X, depending if X is coupled to 1, 2 or 3 lithium cations, respectively. Such multiplicity is particularly observable on the ^{13}C-carbon spectra.



Scheme 133

Speaking about ^{13}C-carbon NMR spectra, the very low natural abundance of the ^{13}C isotope (1.1%, Table 25) is not an obstacle to measure the $^{1}J(^{13}C,^{6}Li)$ couplings constant. According to the Bauer, Winchester and Schleyer empirical rule,[65] $^{1}J(^{13}C,^{6}Li) = (17 \pm 2)/n$ Hz, measuring this constant gives access to the number of lithium nuclei surrounding the observed carbon (n).

Otherwise, ^{13}C-NMR experiments is expected to supply fruitful information when conducting the lithium phosphides analyses. Although 1D ^{13}C-NMR spectra are usually recorded while decoupling the proton, this does not prevent the observation of couplings with other atoms, such as the carbon-phosphorus (^{31}P) ones. The value of the ^{13}C-^{31}P couplings constant is directly correlated to the scalar distance between the two nuclei: $^{1}J(^{13}C,^{31}P)$ is about 40-60 Hz, $^{2}J(^{13}C,^{31}P)$ 8-10 Hz and $^{3}J(^{13}C,^{31}P)$ around 10 Hz.

properties	**^{13}C**
spin	1/2
natural abundance	1.108%
chemical shift range	220 ppm, from -10 to +210
frequency ratio (Ξ)	25.145020%
quadrupolar moment	0 m^2
reference compound	TMS
linewidth of reference	0.19 Hz
receptivity rel. to ^{1}H at natural abundance	1.70×10^{-4}
receptivity rel. to ^{1}H when enriched	0.0159
receptivity rel. to ^{13}C at natural abundance	1.00
receptivity rel. to ^{13}C when enriched	93.5

Table 25: Carbon-13 nuclear features

1D Phosphorus ^{31}P NMR experiments are much less sensitive than proton ^{1}H, but better than carbon ^{13}C (Table 26).

properties	**^{31}P**
spin	1/2
natural abundance	100%
chemical shift range	430 ppm, −180 ≠ 250
frequency ratio (Ξ)	40.480742%
quadrupolar moment	0 m^2
reference compound	85% H_3PO_4 in H_2O = 0 ppm
linewidth of reference	1 Hz
receptivity rel. to ^{1}H at natural abundance	6.63 $\times 10^{-3}$
receptivity rel. to ^{1}H when enriched	6.63 $\times 10^{-3}$
receptivity rel. to ^{13}C at natural abundance	37.7
receptivity rel. to ^{13}C when enriched	37.7

Table 26: Phosphorus-31 nuclear features

This nucleus usually shows sharp lines and presents a wide chemical shift range. One-bond ^{31}P-^{1}H couplings have generally a 200-400 Hz order of magnitude, in particular 220.0 Hz for secondary phosphines. This value increases to 385.0 Hz with phosphine-borane adducts.

The large range of the chemical shift scale (−180 ppm to +250 ppm) allows a good distinction of the different phosphorus species. For instance, the range of phosphides goes from −20 to −150 ppm (Figure 29). Triorganophosphines, instead, present values between +40 and −50 in dependence on the "R" substituent. The replacement of organo-substituents with a withdrawing hetero-substituent (O or X) results in a downfield shift.

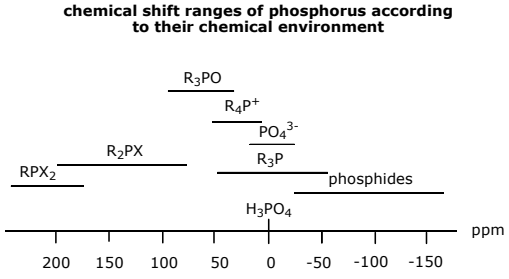


Figure 29

The last element of particular interest to our study is boron, which presents two isotopes: ^{10}B and ^{11}B. Both nuclei have spins higher than 1/2 and so, a

nonzero quadrupolar moment responsible for large peaks (Table 27). Boron-11 is preferred to boron-10, having the lower quadrupolar moment and being more sensitive. Therefore, the acquisition is regularly conducted on the ^{11}B isotope frequency.

properties	**^{10}B**	**^{11}B**
spin	3	3/2
natural abundance	19.9%	80.1%
chemical shift range	210 ppm, from -120 to +90	210 ppm, from -120 to +90
frequency ratio (Ξ)	10.743658%	32.083974%
quadrupolar moment	$8.5*10^{-30}$ m^2	$4.5*10^{-30}$ m^2
reference compound	$BF_3.OEt_2$	$BF_3.OEt_2$
linewidth of reference	9 Hz	5 Hz
receptivity rel. to ^1H at natural abund.	3.96×10^{-3}	0.206
receptivity rel. to ^1H when enriched	0.0199	0.165
receptivity rel. to ^{13}C at natural abund.	23.2	777
receptivity rel. to ^{13}C when enriched	117	970

Table 27: Boron-10 and Boron-11 nuclear features

Here again, a nuclear spin quantum I ≠ 1/2 leads to a different multiplicity scheme of the signals (Figure 30).

1

1 1 1 1

1 2 3 4 3 2 1

1 3 6 10 12 12 10 6 3 1

1 4 20 31 40 44 31 20 10 4 1

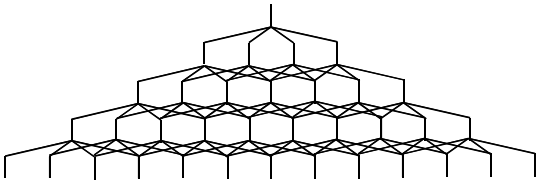


Figure 30

In general for triorganophosphine boranes adducts the ^{11}B range of chemical shifts is placed between –20.0 ppm and –50.0 ppm. But there is a variety of types of borane compounds whose chemical shift values range in a wider part of ppm. Below a collection of ^{11}B NMR chemical shifts of a selected compilation of representative organoborane and boron compounds is gathered (Figure 31). The trialkylboranes, for instance, are found in a narrow low field region, 83-93 ppm. The presence of an OR' or OH group bonded to the boron results in ^{11}B resonance at higher fields as compared to the corresponding alkylboranes. The boronhydride resonances are shifted to higher field, –26 to –45 ppm, more than most all other boron species. Replacement of a hydrogen with an alkyl group shifts the resonances to downfield.

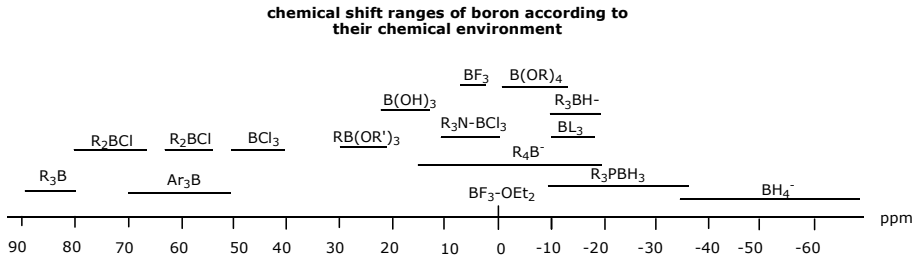


Figure 31

In general the addition of a ligand or base to the empty *p*-orbital on boron results in an upfield shift as compared to the tricoordinate borane. This effect is also seen with coordinating solvents such as THF or DEE. The chemical shift is dependent on the strength of the coordination complex, with the stronger complexes shifted to higher field.

8.4. Presentation and order of the NMR sequences carried out for our study

All studies have been initiated recording a first series of mono-dimensional NMR experiments (^{1}H, ^{6}Li, ^{11}B, ^{13}C and ^{31}P). Different temperatures have been applied (from 170K to 330K) to determine the best compromise in terms of resolution.

Two-dimensional NMR experiments were then run when necessary to a good description of the solution-structures examined. Among those,

- homo- and hetero-nuclear sequences based on scalar couplings: ^{1}H/^{1}H-COSY[392] (Correlation SpectroscopY) and ^{1}H/^{13}C-HMQC[392] (Heteronuclear Multiple Quantum Correlation) or HMBC (Heteronuclear Multiple Bond Correlation) made possible the assignment of the proton and carbon signals belonging the different species;
- homo- and hetero- nuclear sequences based on nuclear Overhauser effects (NOE: comes from spatial interactions between nuclei): ^{1}H/^{1}H-NOESY,[392] ^{6}Li/^{6}Li-EXSY[100, 393] and ^{6}Li/^{1}H-HOESY[8, 15, 17, 40, 114, 393-397] are essential to support conformational hypotheses.

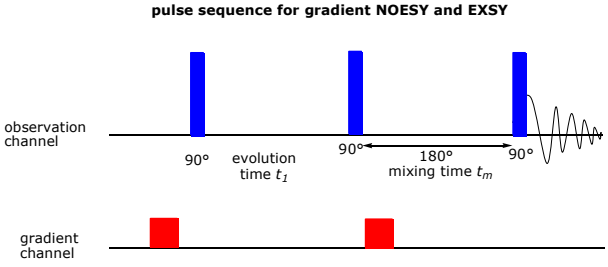


Figure 32

We have used a gradient enhanced NOESY pulse sequence (Figure 32). In this case, the mixing time (t_m) was imposed in the second half of T_1 to improve the sensitivity.[398, 399] When running quantitative NOESY, short mixing times and long relaxation delays were applied. Comparison of the cross-peak integrals in a quantitative NOESY is used as a measure of the distance between the protons.

The 2D ^{6}Li/^{1}H HOESY (Heteronuclear Overhauser Effect SpectroscopY) sequence (Figure 33) has been introduced by Bauer.[397] The delay τ_m between the second 90° pulse on the ^{1}H channel and the acquiring pulse on ^{6}Li channel allows NOE transfer information between the two nuclei. The optimal value of this mixing time can be estimated from the equation $\tau_m = 2T_1(^1\text{H})$[400] where T_1 is the longitudinal or spin-lattice relaxation.

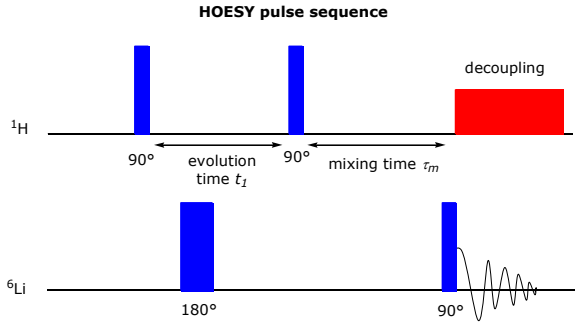


Figure 33

Another technique used to discriminate between the species in solution consists in comparing their "size" (hydrodynamic radius) *via* the measurement of their "diffusion coefficient D". This parameter, which is representative of the translational movements of the molecules in a liquid (also called Brownian molecular movements), is a function of the size and volume of the molecular arrangement, as well as the temperature and the viscosity of the solution (Figure 34, right), and can be measured by the NMR.[401]

The first sequence measuring diffusion coefficients by NMR (PGSE = Pulsed Gradient Spin Echo) is monodimensional and has been introduced by Stejskal and Tanner in 1965.[402, 403, 404] In 1992, Johnson established the two-dimensional PGSE sequence, in which one dimension affords the chemical shift information while the other represents the separation of the species according to their size.[103] This 2D experiment is called Diffusion-Ordered NMR spectroscopy or DOSY and has found applications in many different fields such as medical and biological sciences[405-410] or material sciences.[411-417] Its use to tackle problems in structural organometallic chemistry questions emerged at the end of the nineties when Williard's showed that *n*-butyllithium in THF generates a mixture of dimeric/tetrameric oligomers.[418]

Later on, the same group then studied more complex systems involving (chiral) lithium amides, lithium alkoxides and enolates.[419-424]

$$D = \frac{kT}{6\pi\eta r_s}$$

k = Boltzmann constant
T = temperature
η = viscosity
r_s = hydrodynamic radii.

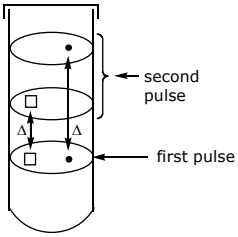


Figure 34

The D measurement principle (schematized Figure 34, right) starts by the application of a first magnetic field gradient that encodes the initial position of each structure through their Larmor frequency. A consecutive delay (D) is then observed letting translate each compound (smaller molecules moving faster than bigger ones). A second gradient pulse is then applied reflecting the new positions of the species. The measurement signal is the integral over the whole sample volume and the NMR signal intensity is attenuated depending on the diffusion time D and the gradient parameters.

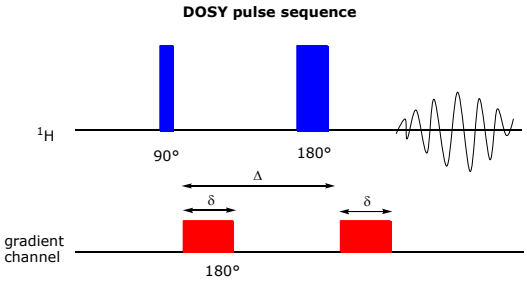


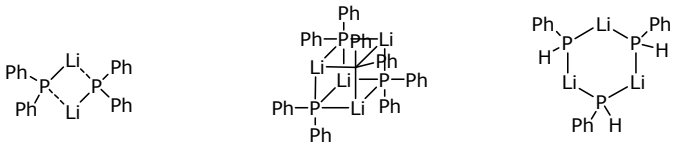
Figure 35

This intensity is given by the following relation: $I = I_0 \exp(-D\gamma^2 g^2 \delta^2 (\Delta - \delta/3))$ with I corresponding to the observed intensity, I_0 the reference intensity (unattenuated signal intensity), D the diffusion coefficient, g the gyromagnetic ratio of the observed nucleus, g the gradient strength, d the length of the gradient and D the diffusion time (Figure 35).

8.5. Structural NMR studies of lithiated phosphides

Little is known about the structure, in solution as in solid phase, of alkali-metal diorganophosphides. The few publications related to this subject show that the first results were obtained by Colquhoun *et al.* in the early eighties.[425] In a

^{31}P-NMR / ^{7}Li-NMR study conducted at 200 K in diethyl ether, the authors show that the signal of the lithium cation of Ph_2P-Li exhibits a coupling with two phosphorus atoms, and vice versa (Figure 36, left). A cyclic dimer **279**, is thus suggested.[425] The same year, and still using the NMR techniques, Issleib *et al.* suggest a tetrameric arrangement **280** (Figure 36, middle) for the same phosphide at 175 K in THF.[426] These workers also examined the structure of PhPH-Li and, this time, a cyclic trimer **281** was evidenced (Figure 36, right).[425]



279 **280** **281**

Figure 36

A full study examining the behavior of the negative charge initially located on the phosphorus atom of variously substituted phosphides (dialkyl-, diaryl-, alkyl/aryl- phosphides, Figure 37) was complementarily carried out, still by Issleib using multinuclear (^{1}H, ^{7}Li, ^{13}C, ^{31}P) NMR spectroscopy.[427] The main information these authors obtained were i) the proof of a partial delocalization of the charge throughout the entire structure and, ii) the existence of an equilibrium between solvated monomeric ion pairs and solvated dimers. This later is solvent dependent.

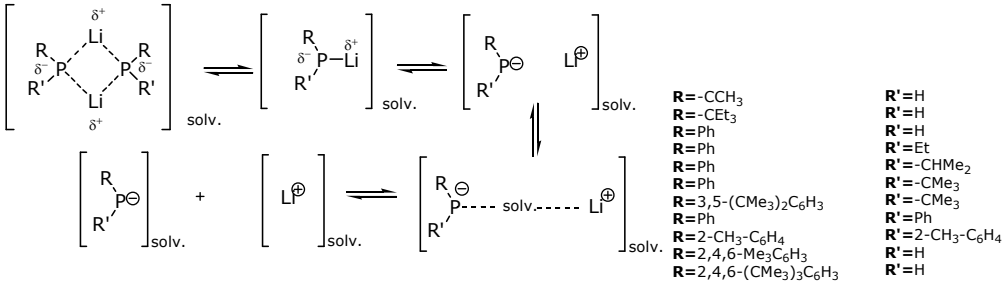


Figure 37

It is in 1994 that Reich *et al* brought an indubitable proof of the degree of aggregation of Ph_2PLi in ethereal solvents (Et_2O, THF).[428] At –120° C, the dimeric arrangement is confirmed in diethyl ether, while Ph_2PLi is announced as a monomer in tetrahydrofuran. Progressive addition of HMPA leads to first a mono HMPA-contact ion pair, that evolve in a separated ion pair in the presence of an excess of the phosphorazide.

Considering now the X-ray structures that have been obtained from non protected lithium phosphides the following complexes have been described (Figure 38): polymeric $[Ph_2PLi.Et_2O]_\infty$ **282**, $[Ph_2PLi.(THF)_2]_\infty$ **283**, and $[(C_6H_{11})_2PLi.THF]_\infty$ **284**,[429] dimeric $[Ph_2PLi.TMEDA]_2$ **285**,[430] lutetium-lithium mixed dimer of Ph_2P anion in the presence of TMEDA **286**,[431] monomeric $Ph_2PLi.PMDTA$ **287**,[430] a 12-crown-4-complexed separated ion pair **288**[432] and tetrameric $\{[(tBu)_2PLi]_2.THF\}_2$ **289**.[433]

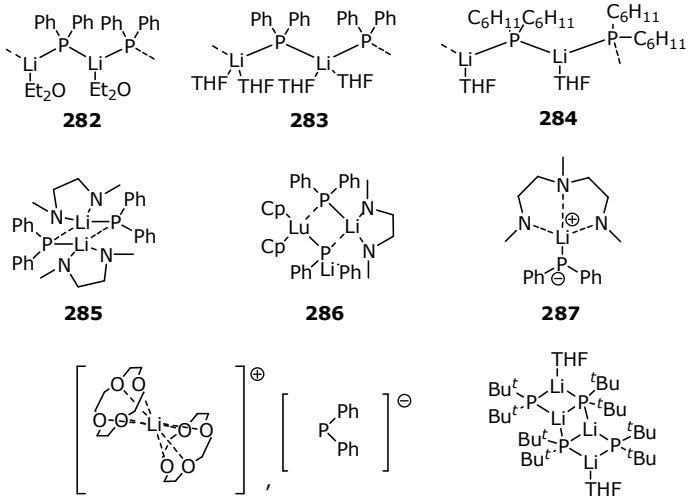


Figure 38

Considering phosphide-borane derivatives, no structures in solution were found to our knowledge. Only an X-ray description of a $Me_2P(BH_3)Li.TMEDA$ complex by Muller was found (Figure 39).[434] The structure shows a lithium cation pentacoordinated with the phosphorus element, two hydrogens of the borane group and the two nitrogens of the TMEDA.

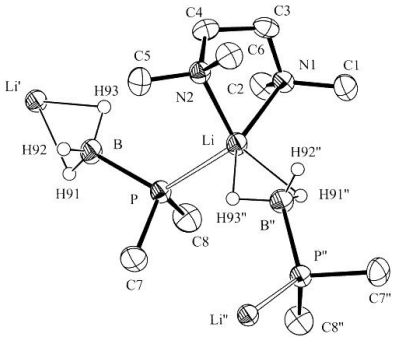


Figure 39

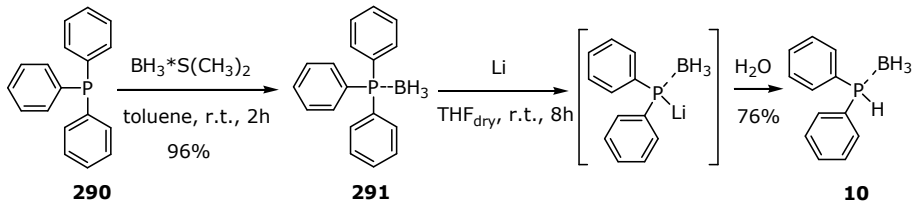
9. RESULTS OBTAINED

9.1. Structure in THF solution of model $Ph_2P(BH_3)Li$

9.1.1. Synthesis of the starting materials and their NMR descriptions

9.1.1.1. The diphenylphosphine borane

As already mentioned before, diphenylphosphine borane has been chosen as a molecular model for our NMR experiments. This compounds is prepared from commercial triphenylphosphine **290** (Scheme 134) following Le Corre's protocol.[435] In a first step, **290** is converted into its borane derivative **291** in a 96% yield by the addition of borane disulfide in toluene at room temperature. A metallation using lithium metal in THF is conducted at room temperature in a next step, that realizes the reductive cleavage of a P-C phenyl bond. The addition of water on the lithium phosphide borane intermediate provides the expected diphenylphosphine borane **10** in the 76% yield.



Scheme 134

NMR spectra of **10** in THF-d_8 were then conduced both at room temperature (298K) and at −78°C (195 K).

^{1}H-NMR spectrum at 298 K (Figure 40, top) shows i) two sets of signals at 7.40-7.60 and 7.70-7.85 representative of the ten aromatic protons; ii) a doublet of quartets centred at 6.30 ppm, representative of the P-H hydrogen: this multiplicity is the consequence of a ^1J coupling of this hydrogen with the phosphorus atom ($^1J_{H\text{-}P}$=381.0 Hz) and a ^3J coupling of the same proton with the hydrogens of the borane group ($^3J_{H\text{-}H}$=7.2 Hz); iii) a 1:1:1:1 wide quartet at 1.04 ppm attributed to the three B-H hydrogens and with a ^1J coupling of those with boron-11 ($^1J_{H\text{-}B}$=97.0 Hz). Registration of the spectrum at 195 K results in a lower resolution (Figure 40, bottom), particularly for the borane hydrogens giving a broad band at δ=1.00 ppm.

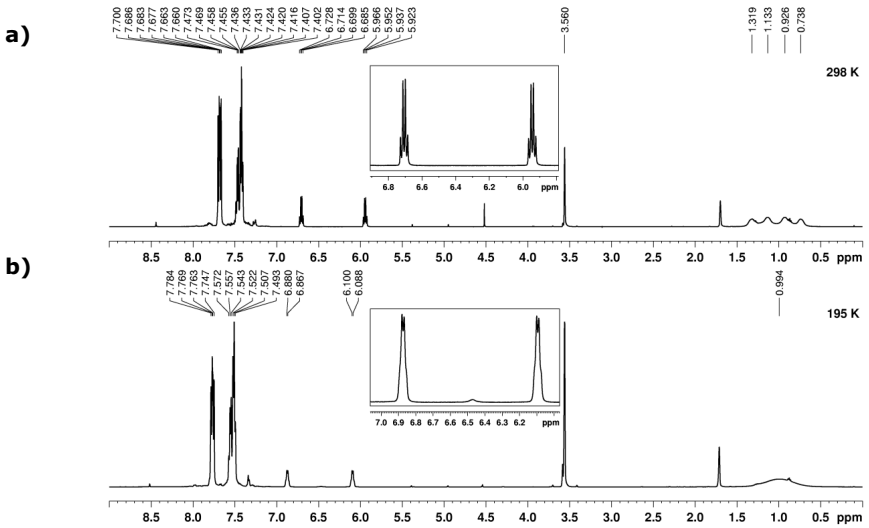


Figure 40: ^{1}H-NMR spectra of diphenylphosphine borane **10** in THF-d_8 a) at 298 K and b) 195 K

Mono-dimensional ^{11}B (Figure 41) and ^{31}P NMR (Figure 42) experiments were also carried out. The ^{11}B-NMR signal at room temperature shows a well-resolved quartet of doublets at –41.40 ppm. The coupling values are 100.0 Hz for a $^{1}J_{B\text{-}H}$ and 41.0 Hz for a $^{1}J_{B\text{-}P}$. In the same way as the ^{1}H-NMR spectrum, only a large broad singlet at –40.65 ppm is detectable.

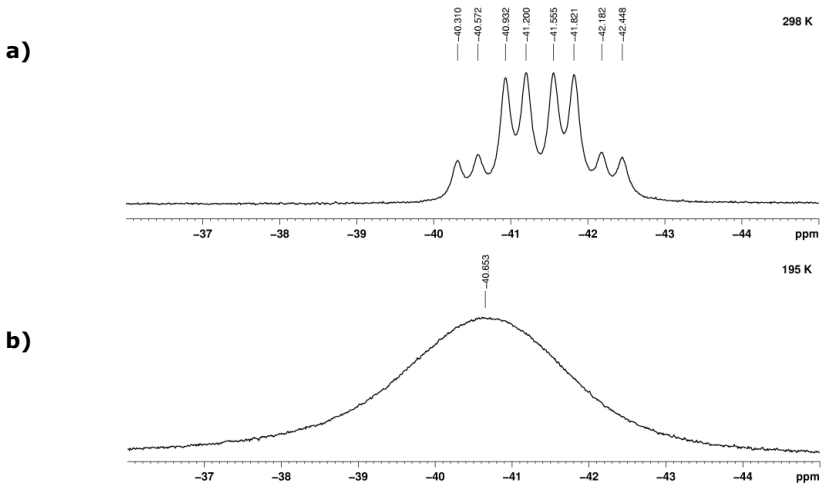


Figure 41: ^{11}B-NMR spectra of diphenylphosphine borane **10** in THF-d_8 a) at 298 K and b) 195 K

The ^{31}P-NMR spectrum obtained at 298 K (Figure 42, top) evidences a doublet of multiplets at –17.00 ppm while at 195 K (Figure 42, bottom), only the doublet is observed at a slightly higher field (–21.10 ppm). The coupling measured

for the doublets is a $^{1}J_{P\text{-}H}$, with 385 Hz of amplitude. The P-B coupling disappears because quadrupolar relaxation is more efficient at lower temperature.

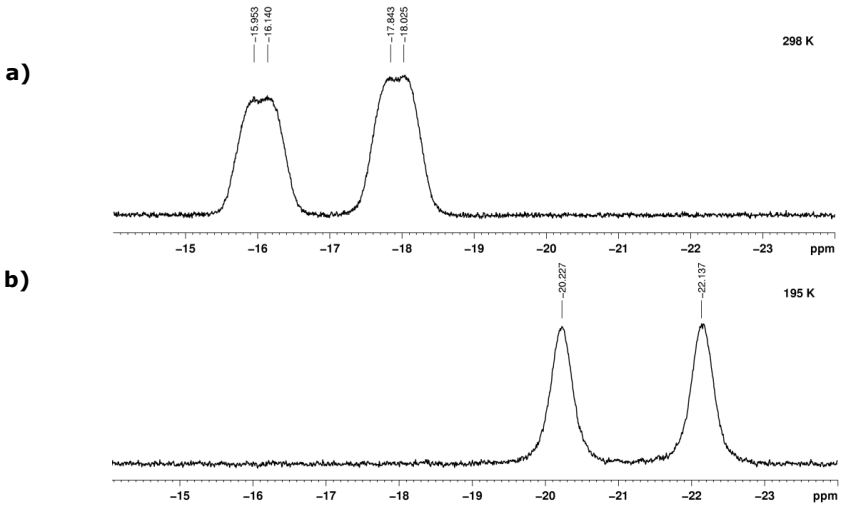


Figure 42: ^{31}P-NMR Spectra of diphenylphosphine borane **10** in THF-d_8 a) at 298 K and b) 195 K

About the ^{13}C-NMR spectra, no significant change is observed between 298 K and 195 K (Figure 43).

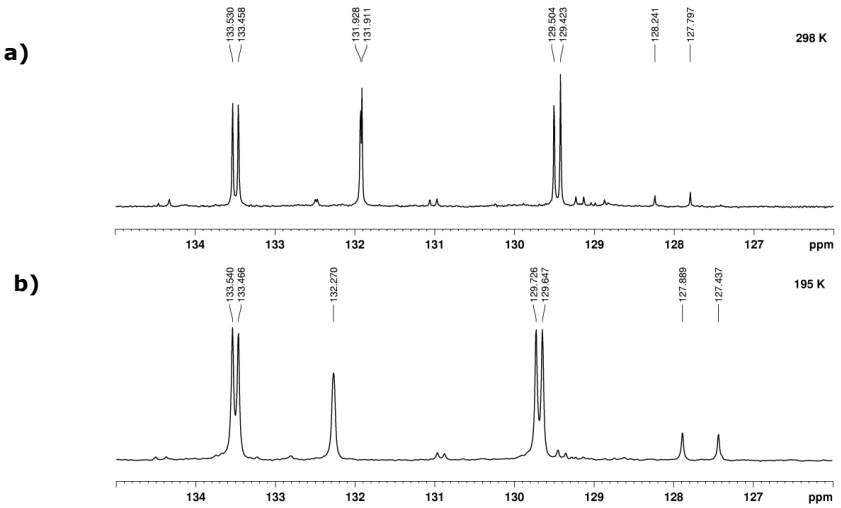


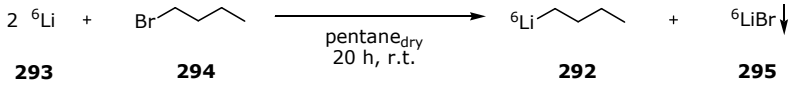
Figure 43: ^{13}C-NMR Spectra of diphenylphosphine borane **10** in THF-d_8 a) at 298 K b) and 195 K

Four distinguishable sets of aromatic carbons are observed in ^{13}C-NMR spectrum at 298 K: the quaternary carbons giving a doublet ($^{1}J_{C\text{-}P}$=57.0 Hz) at 128.0 ppm, the C^{meta} represented by a doublet ($^{3}J_{C\text{-}P}$=10.0 Hz) at 129.5 ppm, the

C^{para} showing a singlet at 131.9 ppm and, the C^{ortho} identified by a doublet ($^2J_{C\text{-}P}$= 9.4 Hz) at 133.5 ppm.[360]

9.1.1.2. The ^{6}Li labelled n-butyllithium

^{6}Li Labelled *n*-butyllithium **292** being not commercially available, this reagent was synthesized, salt-free, in pentane (c ≈ 1.5 M).[39] The procedure foresees a halogen-metal exchange between *n*-bromobutane **294** and pure ^{6}Li metallic lithium **293** (Scheme 135).



293 **294** **292** **295**

Scheme 135

After 20 hours of stirring at room temperature in anhydrous pentane, the precipitated lithium bromide **295** was centrifuged and the hydrocarbon solution of *n*-Bu^{6}Li was extracted from the reaction flask *via* a syringe to be stored under argon in a clean and dry glassware. Titration of the solution was carried out following Duhamel and Plaquevent's method[436] and indicated a concentration c = 1.55 M (78%).

THF-d_8 solution of ^{6}Li labelled *n*-butyllithium was prepared concentrating an aliquot (2 mL) of the above pentane solution of **292**. Freshly distilled THF (2 mL) was slowly added at low temperature to the "dry" reactant (white solid) and a second evaporation was realized to eliminate last traces of pentane. Final solution of **292** in THF-d_8 was obtained adding a new volume of the deuterated solvent (2 mL). Titration gave c = 1.0 M.

The NMR analyses of *n*-Bu^{6}Li in THF-d_8 have mainly been conducted at 195 K.

The ^{1}H-NMR spectrum shows two major multiplets (signal 1 at –1.00 and signal 2 at –1.12 ppm), that correspond to protons neighbouring a lithium such as RC**H$_2$**-Li (Figure 44). When registering the spectrum at higher temperature, a coalescence of the two signals takes place.

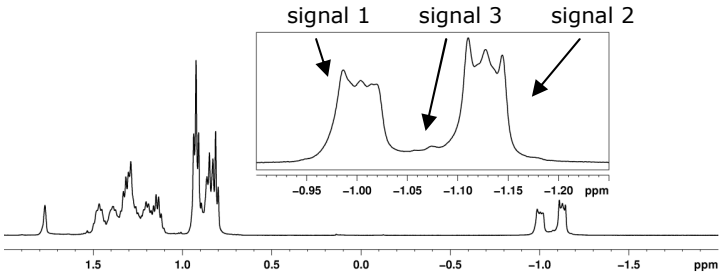


Figure 44: ^{1}H-NMR Spectrum of *n*-Bu^{6}Li **292** in THF-d_8 at 195 K

As already described in the literature,[41, 70, 115, 397,418] the two signals correspond to two oligomeric shapes that are a dimer (–1.00 ppm) and a cubic tetramer (–1.12 ppm) (Figure 45).

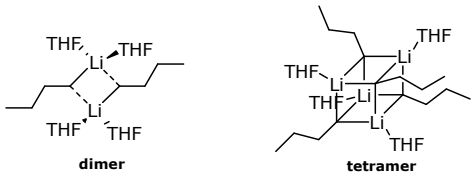


Figure 45

Note the presence of a minor signal at –1.07 ppm (signal 3, Figure 44). This later has been attributed to the oxygen-derived impurities BuO^{6}Li and BuOO^{6}Li (Figure 46). In spite of the high level of precaution taken to avoid any trace of air, oxygen cannot be totally excluded, which has the effect of oxidizing little amount of the alkyllithium. Both oxygenated species are known to organize in a cubic tetramers arrangement in THF solution.[115]

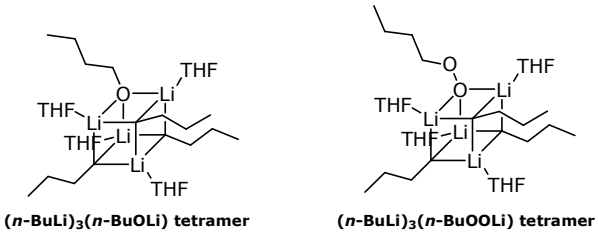


Figure 46

The quantity of this impurity is variable and, interestingly, its presence has been clearly shown running an ^{1}H / ^{13}C HMQC experiment (Figure 47), on which strong correlations were nearby.

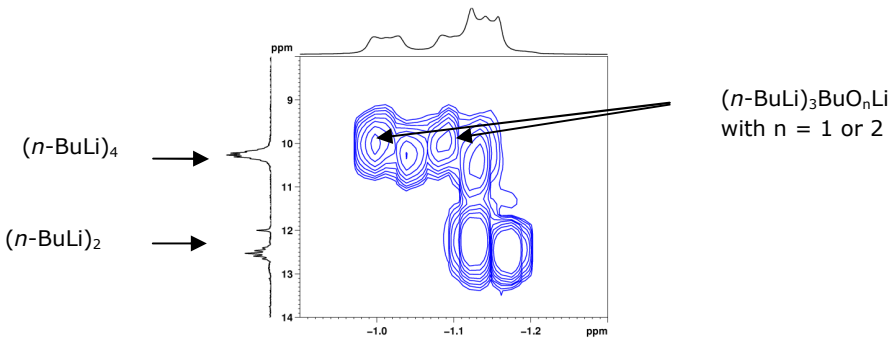


Figure 47: ^{1}H/^{13}C HMQC spectrum of *α*-CH$_2$ part of *n*-Bu^{6}Li **292** in THF-d_8 at 170 K

The two oligomers of **292** are also observable on the ^{13}C NMR spectrum which holds two signals at 10.3 and 12.5 ppm, with a heptet and a quintet multiplicity, respectively (Figure 48). According to Bauer, Winchester and Schleyer rule,[65] the number of lithium surrounding the carbon at higher field is 3, letting prove that this signal corresponds to the cubic tetramer. Similarly, the number of lithium surrounding the carbon at higher field is 2, which is corresponding to the dimeric arrangement.

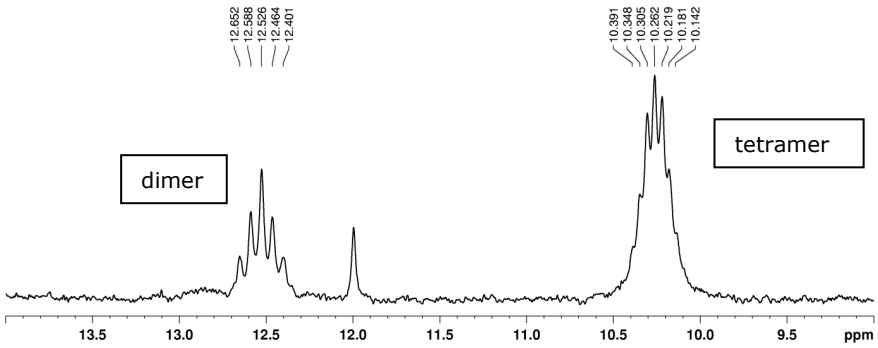


Figure 48: ^{13}C-NMR spectrum of *α*-CH_2 part of *n*-Bu^{6}Li **292** in THF-d_8 at 170 K

The ^6Li-NMR analysis expectedly shows two singlets at 1.08 and 1.49 ppm (Figure 46). ^6Li-^1H HOESY sequence as well as data from the litterature,[418] attribute the higher field peak to the tetramer and the lower one to the dimer.

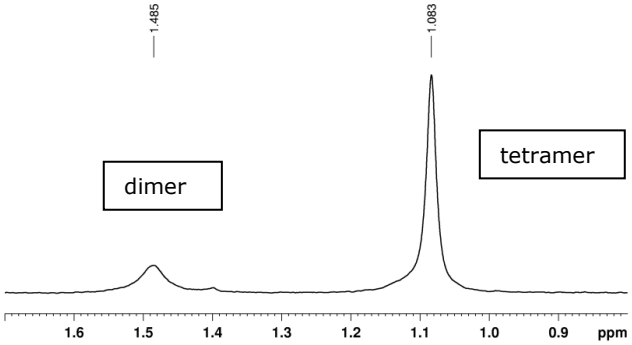
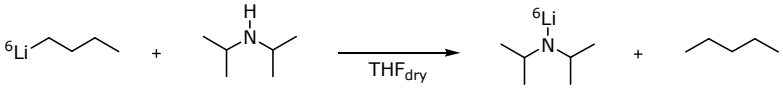


Figure 49: ^6Li-NMR spectrum of *n*-Bu^{6}Li **292** in THF-d_8 at 195 K

9.1.1.3. *The ^6Li labelled lithium diisopropylamide*

Six-labelled LDA **2966** was prepared in THF-d_8 reacting freshly prepared *n*-Bu^{6}Li **292** with an equimolar amount of di-*iso*-propylamine **297** (Scheme 136). The reaction run in 30' at −78° C. The following titration indicated a concentration c = 1.0 M (100%).



292 **297** **296** **298**

Scheme 136

The corresponding ^{1}H-NMR spectrum was recorded in THF-d_8 at 195 K and shows a heptet at 2.94 ppm ($(CH_3)_2C\mathbf{H}$) and a doublet at 0.99 ppm ($(C\mathbf{H_3})_2CH$) (Figure 50). The two additional signals at 1.29 and 0.92 ppm belong to butane **298**, which is formed in the reaction.

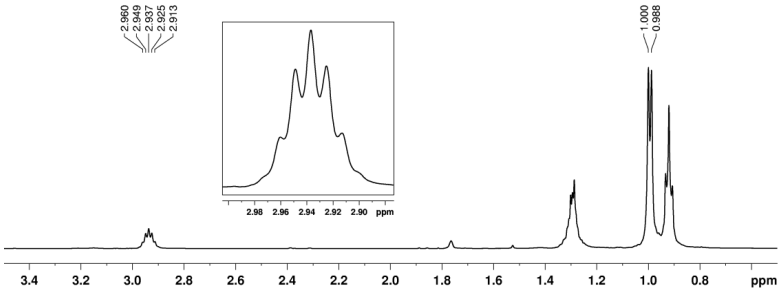


Figure 50: ^{1}H-NMR spectrum of ^{6}LDA **296** in THF-d_8 at 195 K

The ^{6}Li-NMR spectrum shows a singlet at 1.55 ppm (Figure 51).

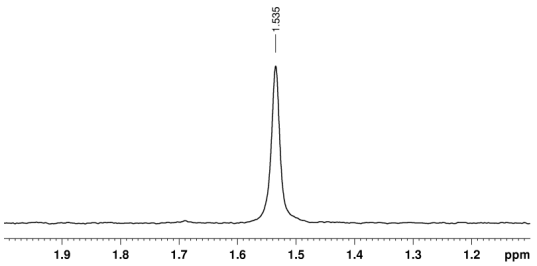


Figure 51: ^{6}Li-NMR Spectrum of ^{6}LDA **296** in THF-d_8 at 195 K

The homo-aggregation of LDA in THF solution has been fully described in the literature and corresponds to a disolvatated cyclic dimer (Figure 52).[236-242]

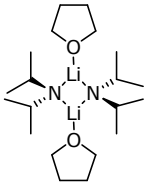


Figure 52

9.1.2. Synthesis of lithium diphenylphosphide borane and NMR analyses

9.1.2.1. Preparation of the NMR samples

NMR samples of lithium diphenylphosphine borane $Ph_2P(BH_3)Li$ **10**-Li have been directly prepared in NMR tubes fitted with a septum and flushed under dried argon (obtained by bubbling argon in a commercial solution of BuLi). A known amount of phosphines **10** (~0.1 mmol, 20.00 mg) was introduced in THF-d_8 solution (0.50 mL, c = 0.2 M) in the tube. Progressive amounts of *n*-Bu^{6}Li **292** or ^{6}LDA **296** solution were then added under argon atmosphere at −78° C. A manual stirring was then realized taking care of maintaining the temperature at −78°C.

9.1.2.2. NMR analyses in THF-d_8 of $Ph_2P(BH_3)Li$ obtained from a 1 : 1 of $Ph_2P(BH_3)H$ / n-Bu^{6}Li

Comparison of the ^{1}H-NMR spectra obtained before ($Ph_2P(BH_3)H$) and after ($Ph_2P(BH_3)Li$) addition of Bu^{6}Li (Figure 53) highlights the total disappearance of the doublet of quartets at 6.30 ppm that are assigned to the P-H hydrogen of the starting material. Such observation proves the efficiency of the deprotonation, that, in this case, is quantitative.

Among the other change observed on the $Ph_2P(BH_3)Li$ **10**-Li ^{1}H-NMR spectrum i) a slight move of the BH_3 signal at lower field (0.64 ppm instead 1.04 ppm), ii) the separation of the signal representative of the aromatic *ortho*-hydrogens now independently observed from the para one at the lower 6.90-7.00 ppm chemical shift.

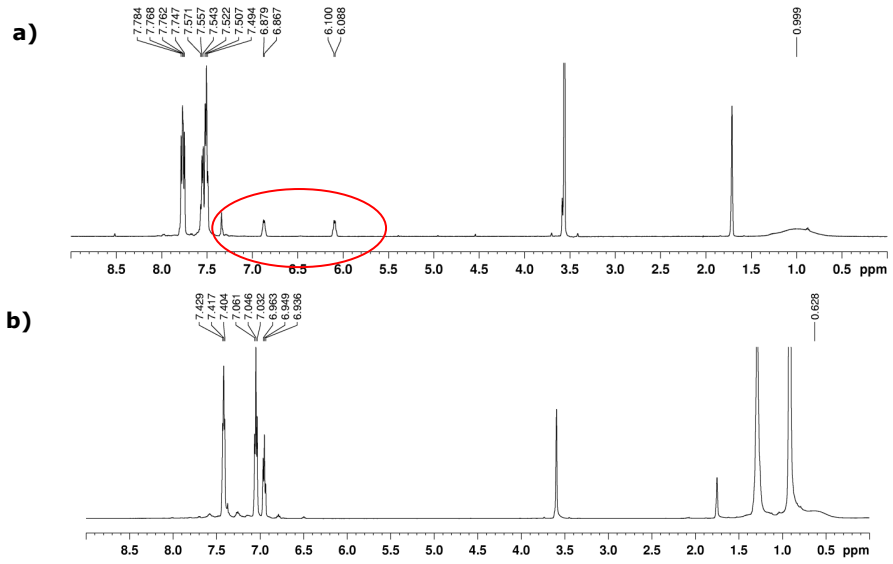


Figure 53: ^{1}H-NMR spectra of a) diphenylphosphine borane **10**-H and b) lithium diphenylphosphide borane **10**-Li in THF-d_8 at 195 K

One dimensional ^{6}Li-, ^{11}B-, and ^{31}P- experiments were then executed, still at 195K. The ^{6}Li-NMR spectrum consists in a singlet at –0.86 ppm (Figure 54, left). On the ^{11}B one (Figure 54, middle), a broad signal at –31.5 ppm is shown (the δ was –40.6 ppm for the phosphine precursor). ^{31}P Phosphorus signal now results in a singlet at –49.82 ppm (Figure 54, right) instead of the P-H doublet at –21.18 ppm, confirming by this way the success of the deprotonation.

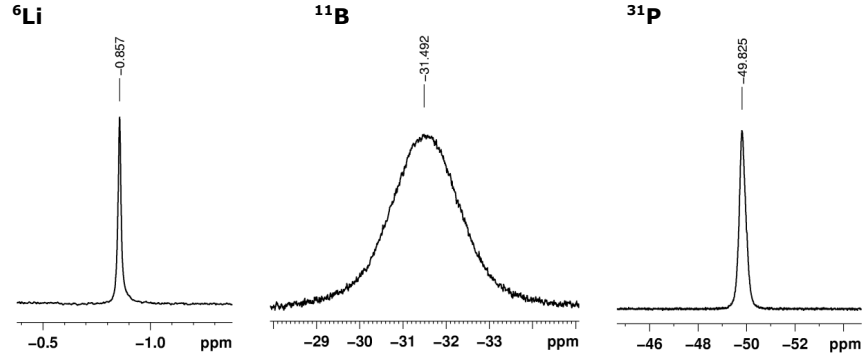


Figure 54: ^{6}Li- (left), ^{11}B- (middle), ^{31}P- (right) NMR spectra of lithium diphenylphosphide borane **10**-Li in THF-d_8 at 195 K

Let us say that the series of spectra above first raised astonishments by their too great simplicity. Indeed, none of them show any couplings like $J^{1}_{P\text{-}Li}$ or $J^{1}_{P\text{-}B}$.

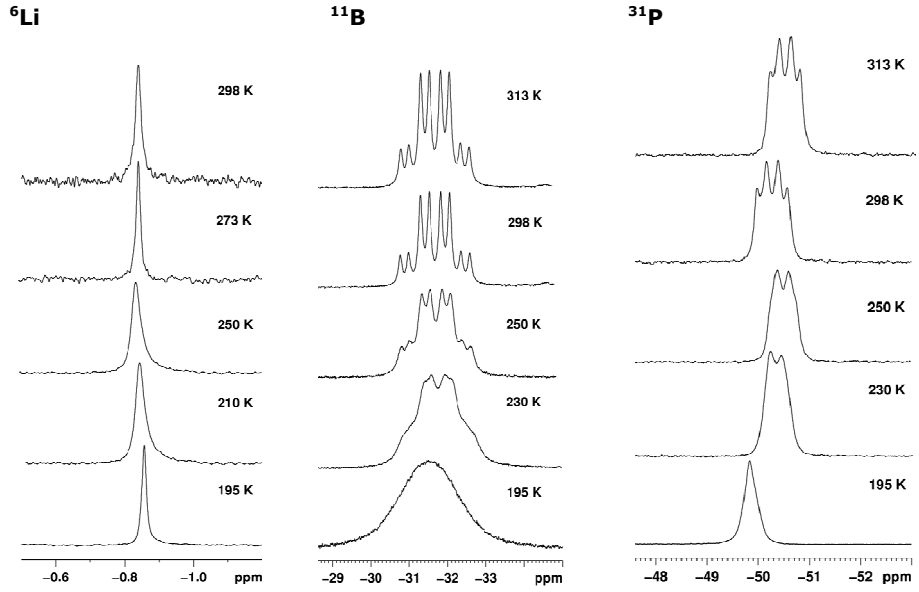


Figure 55: ^{6}Li- (left), ^{11}B- (middle), ^{31}P- (right) NMR spectra of lithium diphenylphosphide borane **10**-Li in THF-d_8 between 195 K and 313 K.

In an attempt to observe some couplings, successive registrations of the three nuclei NMR spectra have been managed varying the temperature from 195 K to 313 K (Figure 55). No effect is noticed on the ^{6}Li dimension except a slight shift at lower field and a temporary enlargement of the singlet. In contrast, emergence of multiplicities takes place for both ^{11}B and ^{31}P spectra increasing the temperature. A well-resolved quartet of doublets is seen at 313 K on the ^{11}B spectrum. The two coupling are representative of a $^{1}J_{B\text{-}H}$ (88.0 Hz) and a $^{1}J_{B\text{-}P}$ (38.0 Hz). About the ^{31}P spectrum, note the almost 1:1:1:1 quartet planned for this atom when coupled to one 11-boron. However, the resolution remains insufficient to announce an enough precise value of the $^{1}J_{P\text{-}B}$ coupling expected to be 38.0 Hz.

The lack of P-Li coupling, either on the ^{6}Li spectrum or the ^{31}P one, and whatever the temperature of the NMR analyses, lets think that this bond is inexistent and the lithium cation places in another environment. The lithium cation can indeed coordinate with the phenyl groups thanks to π-cation interactions or the hydrogens, behaving like hydrides, of the borane appendage. It also cannot-interfere with the anionic entity, both forming a separated ionic pair. Computational calculations conducted by Prof. Hélène Gérard tend to reinforce the hypothesis of a lithium coordination with the borane group (see paragraph 9.1.3.). This proposition is also consistent with results of the literature describing an X-ray structure ($Me_2P(BH_3)$Li-TMEDA) bonding the lithium atom with two hydrogens of the BH_3 moiety (see Figure 38, chapter 8).[434]

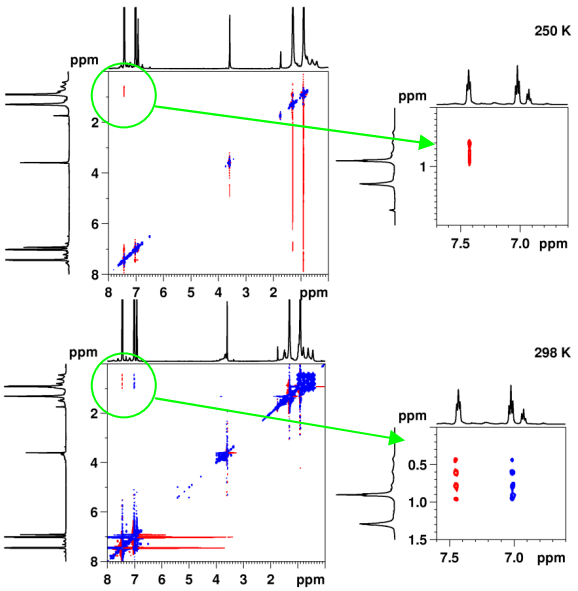


Figure 56: ^{1}H,^{1}H-NOESY spectra of lithium diphenylphosphide borane **10**-Li in THF-d_8 a) at 250 K and b) at 298 K

In order to provide evidence of the hypothesis just retained, bi-dimensional NMR experiments, and above all $^{1}H,^{1}H$-NOESY and $^{6}Li,^{1}H$-HOESY, were carried out. The NOESY spectra (Figure 56), recorded at several temperatures between 195 K and 298 K, did not afford any crucial indication (just "obvious" correlations between aromatic protons and the borane hydrogens).

Contrariwise, the HOESY provided the irrefutable data: the presence of a correlation between the Li cation and the three hydrogens of BH_3 (Figure 57).

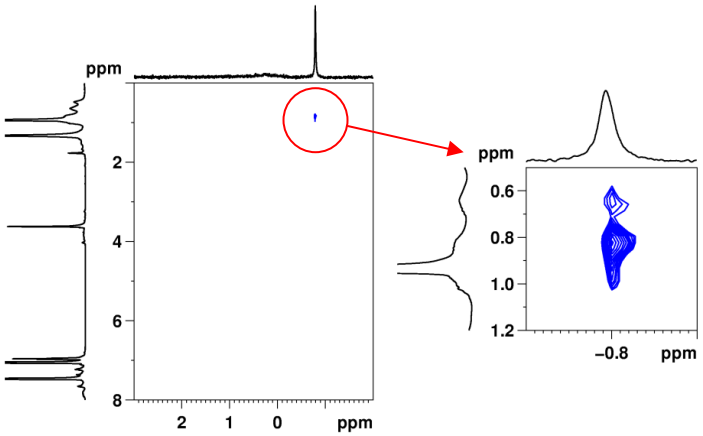


Figure 57: $^{6}Li,^{1}H$-HOESY spectrum of lithium diphenylphosphide borane **10**-Li in THF-d_8 at 250 K

From this series of two-dimensional experiments, one can propose the general structure depicted Figure 58, with n representing the degree of oligomerization of the phosphide and m accounting for the number of THF solvating the entire structure.

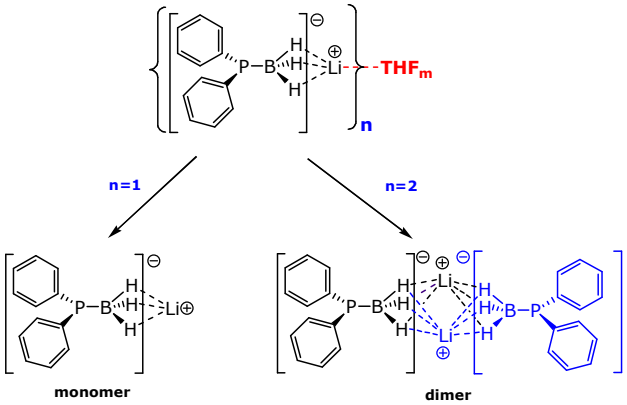


Figure 58

To determine n and m, we resorted to the DOSY sequence. In practice we applied the "Williard's methodology".[423]

The Williard's research group has been interesting since 2000 to the applications of DOSY methodology to calculate formula weight (FW) of reactive intermediates and organometallic complexes in order to characterize their composition, aggregation number, and solvatation state.[423] In fact, a direct correlation between FW and diffusion coefficient exists and this derives by the Stokes-Einstein equation (eq 2),[437] which correlates the diffusion coefficients and hydrodynamic radii:[402]

$$D = \frac{kT}{6\pi\eta r_s} \qquad \textit{eq 2}$$

where *k* is the Boltzmann constant, T is the temperature, η is the viscosity, r_s hydrodynamic radii.

Comparison of numerous solid state X-ray crystal structures carried out in Williard's laboratories and structures in the Cambridge Crystal Database has revealed that the densities of most organolithium aggregates are very similar, i.e., ~1.0 g/cm^3. Also it has been noted that all the aggregates have been determined by crystal structures are relatively spherical. Hence, it's possible make the assumption that the volumes of these organolithium aggregates are proportional to their FW. Thus there should be a linear correlation between the diffusion coefficient determined by DOSY and FW as originally noted by Johnson *via* eq 3:[438]

$$D = A(FM)^{\alpha} \qquad \textit{eq 3}$$

where D is the diffusion coefficient, A and α are experimental constant correlated to the molecular typology.

This equation is easily linearized by taking the logarithm of both sides (eq 4).

$$\mathrm{Log}D = \alpha\ \mathrm{Log}(FM) + A \qquad \textit{eq 4}$$

According to eq 4, there will be a linear correlation between the logarithm of measured diffusion coefficients and the logarithm of FWs of molecules in solution. Extending this relationship to a set of cautiously chosen molecules, it is possible to use the FW of known molecules to establish a calibration curve. Thus, empirical FW of unknown aggregates can be interpolated and/or extrapolated from the curve thereby providing us with a rapid and convenient determination of these values.

The choice for suitable internal references had first been regarded.[423] Note that the requirements to properly select those are:

- they must be inert to the studied component (no reaction and coordination possible);
- their chemical shifts cannot overlap with other components;
- they must be fully soluble in the NMR solvents of the study;
- they must have a homogeneous molecular weight distribution.

In a first attempt, phosphide **10**-Li and phosphine precursor **10** have been separately subjected to DOSY analyses at the two temperatures of 195 K and 250 K, respectively. A superposition of the four spectra is presented in the Figure 59.

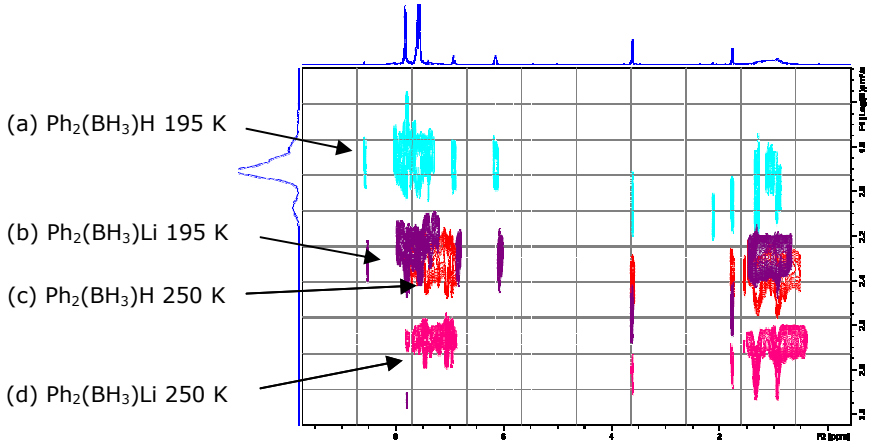


Figure 59: Superposition of the ^{1}H-DOSY experiments in THF-d_8 of a) diphenylphosphine borane **10** at 195 K, b) lithium diphenylphosphide borane **10**-Li at 195 K, c) diphenylphosphine borane **10** at 250 K and d) lithium diphenylphosphide borane **10**-Li at 250 K

The reasoning starts considering that diphenylphosphine borane **10** is a monomer in THF-d_8.[424] The expectation for its lithiated derivative **10**-Li is either an also monomeric structure, or a bigger oligomer (if n = 2: dimer), which consequence would be the obtention of an identical diffusion parameter value (**10**-Li monomer) or a lower one (**10**-Li dimer or bigger oligomer). For both temperatures applied, D obtained for **10** remains always lower than the for **10**-Li. This result is incoherent since it cannot exist a lower aggregate than a monomer, and for this reason, the consistency of the D measurements has been questioned. Indeed, the two solutions (phosphine and phosphide) do not present at all a same viscosity, avoiding by this way any comparisons.

In a next strategy, a single sample mixing the lithium phosphide **10**-Li and the internal references has been engaged in the analyses, thereby eliminating the problem of viscosity evoked earlier. A THF-d_8 1:1 **10** / **10**-Li mixture has thus been obtained adding 0.5 equivalent of *n*-butyllithium **145** to a solution of **10** and the DOSY experiment run (Figure 60). In this case, the coefficients of diffusion $D_{\mathbf{10}}$ and $D_{\mathbf{10}\text{-Li}}$ are similar ($D_{\mathbf{10}}$=1.21µm^{2}s^{-1} and $D_{\mathbf{10}\text{-Li}}$ = 1.19µm^{2}s^{-1}).

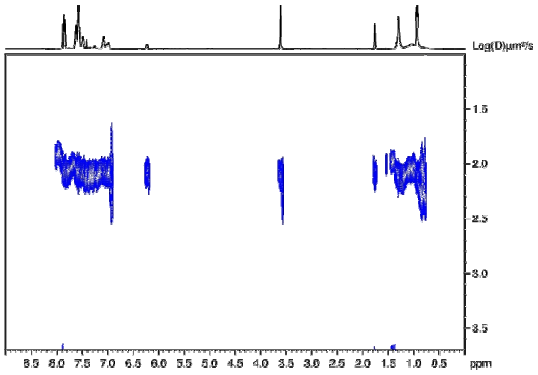
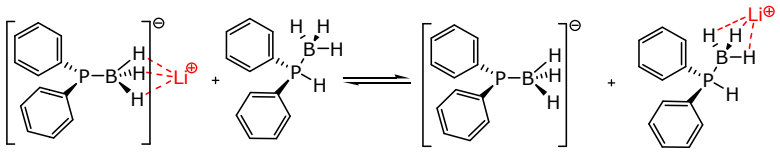


Figure 60: ^{1}H-DOSY obtained at 170 K after adding in THF-d_8 0.5 equiv of *n*-Bu^{6}Li **292** to 1.0 equiv of diphenylphosphine borane **10**.

Such results let think that the lithium phosphide **10**-Li probably behaves as a monomer in the THF solvent. Now, we are reserved by this possibility since the signals of the two entities, and in particular the aromatic one, are not fully distinct, which prevent good calculation of the D value. Otherwise, it was observed that the lithium cation tends to exchange between the two borane groups present on each species (Scheme 137).



Scheme 137

This is particularly evident at higher temperature (250 k, Figure 61, right), where the aromatic signals of the two compounds are totally overlapped. But perhaps a slower lithium exchange may occur also at 170 K by leading to average D values of the two phophinyl species.

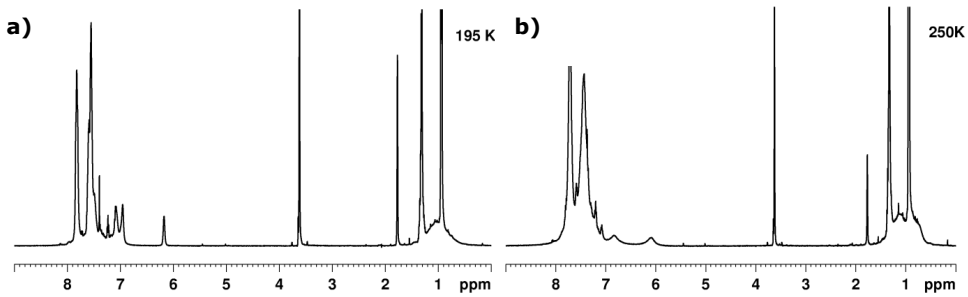
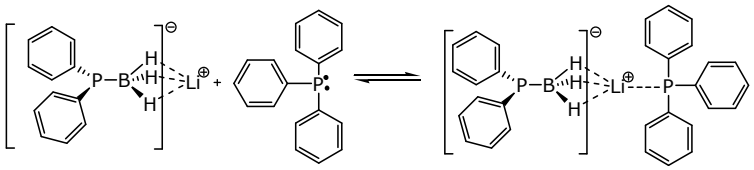


Figure 61: ^{1}H-NMR spectra of diphenylphosphine borane **10** and 0.5 equiv *n*-Bu^{6}Li **292** a) at 195 K and b) at 250 K

So a change of the internal reference had to be realized and we decided to another phosphine for structure similitude, this time, free of the borane appendage. Thus, triphenylphosphine **290** has been chosen. Unfortunately, this alternative proved to be unsuccessful as well for still undesired coordinative interactions (**299**) that this time take place between the lithium cation and the electron-pair-donating of the PPh_3 phosphorus atom (Scheme 138). The coordination is actually more obvious at higher temperatures.



10-Li **290** **299**

Scheme 138

In a last attempt to chose the appropriate internal references, we decided to take advantage of some of the derivatives used by Williard.[418, 422, 423] Among those, tetramethylsilane ($C_4H_{12}Si$, 88 g/mol), cyclooctene (C_8H_{14}, 110 g/mol) and 1,3,5-tri-*tert*-butyllbenzene ($C_{18}H_{30}$, 246 g/mol) have been retained (Figure 62).

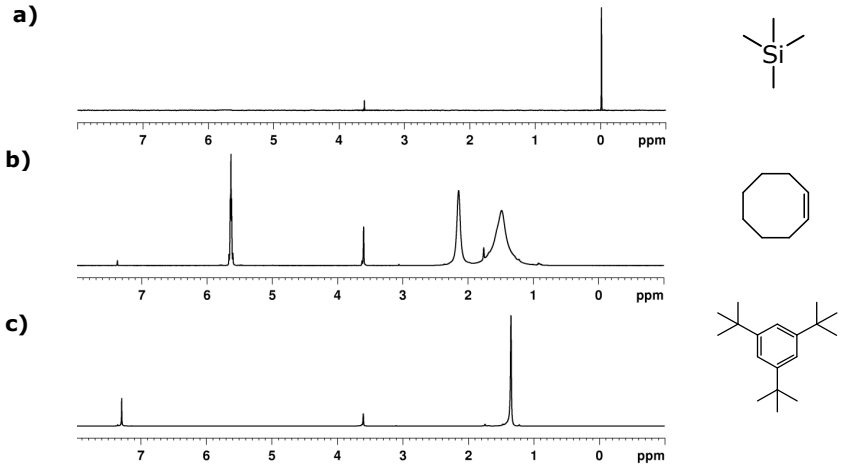


Figure 62: ^{1}H-NMR spectra of the three internal references in THF-d_8 at 195K: a) tetramethylsilane; b) cyclooctene; c) 1,3,5-tri-*tert*-butylbenzene.

Promising results were thus obtained. After having optimized the DOSY pulse program, the resulting spectrum obtained at 195 K in THF-d_8 afforded consistent diffusion-coefficient values with lighter species diffusing more rapidly than heavier compounds (Figure 63).

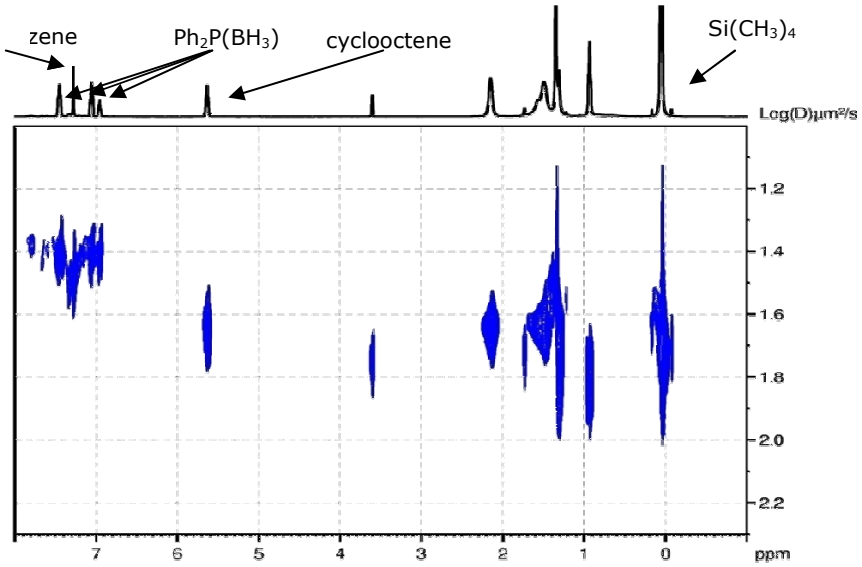
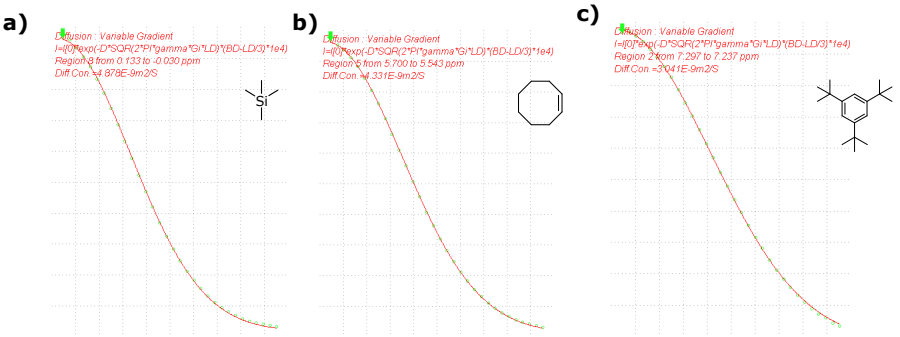


Figure 63: ^{1}H-DOSY spectrum of lithium diphenylphosphide borane **10**-Li and the three internal references in THF-d_8 at 195 K

The DOSY spectrum also shows a clear separation of all components in the diffusion dimension, even if some signals result covered by the presence of by-products (such as butane at 1.20÷1.00 ppm, which overlaps the aliphatic signal resonances of cyclooctene and 1,3,5-tri-*tert*-butylbenzene, allowing to utilize only the corresponding olefinic and aromatic moiety signals of these two products).

The diffusion coefficients were generated by using curve fitting of signal attenuation data.[438-443] The signal attenuation curves of peak area provides some insight into the performance of the diffusion and in this case the signal attenuation was attained after 32 steps of increasing gradient strength from 2% to 95% linearly (Figure 64). A good agreement between the predicted (red curve) and experimental (blue points) values is found.



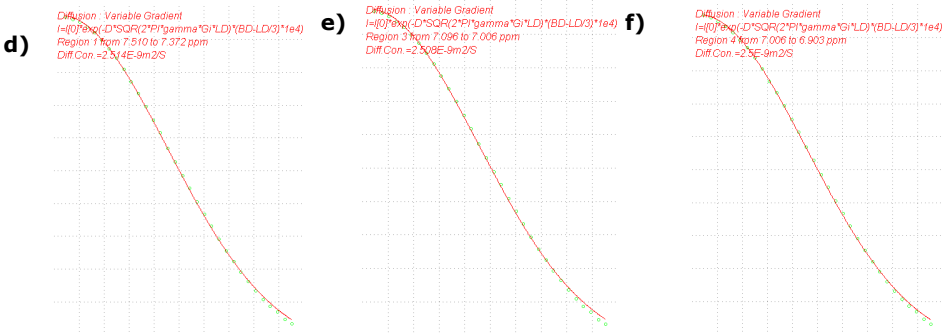


Figure 64: Signal attenuation curves for ^{1}H-DOSY data for the internal references (a, b, c) and for lithium diphenylphosphide borane **10**-Li (d, e, f).

The internal references diffusion coefficients were generated from the signals at 7.27 ppm for 1,3,5-tri-*tert*-butylbenzene, at 5.63 ppm for cyclooctene, and at 0.00 ppm for tetramethylsilane. Concerning to lithium diphenylphosphide we have three signals derived by the *ortho*, *meta* and *para* aromatic protons at δ=7.44, 7.06 and 6.97 ppm respectively, from which three diffusion coefficient values were calculated. But only the average value was used to extrapolate its molecular weight.

At the beginning, we deduced a calibration curve by the diffusion coefficient values of the three references, then, the unknown measurement of lithium diphenylphosphide borane molecular weight could be extrapolated (Figure 65 and Table 28).

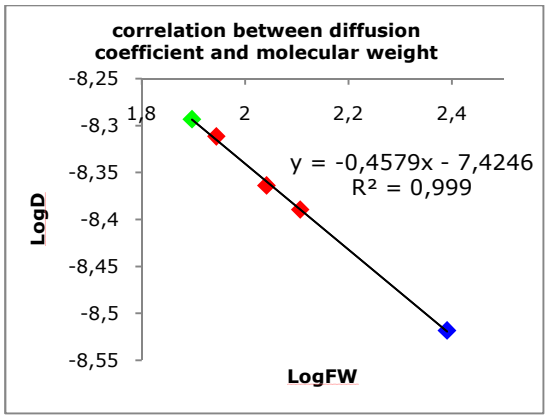


Figure 65: D-FW analysis of ^{1}H-DOSY of lithium diphenylphosphide borane **10**-Li and the three internal references at 195 K

entry	product	FW (g/mol)	LogFW	D (m^2/s)	LogD
1	THF-d_7	79	1,897627091	5,54E-09	-8,256804
2	tetramethylsilane	88	1,944482672	4,88E-09	-8,31158
3	cyclooctene	110	2,041392685	4,33E-09	-8,363713
4	1,3,5-tri-*tert*-butylbenzene	246	2,390935107	3,03E-09	-8,518414
5	lithium diphenylphosphide borane (peack 1; δ=7.44 ppm)	368,4859651	2,566420951	2,51E-09	-8,599808
6	lithium diphenylphosphide borane (peack 2; δ=7.06 ppm)	370,4150762	2,568688655	2,51E-09	-8,600846
7	lithium diphenylphosphide borane (peack 3; δ=6.97 ppm)	373,0102072	2,571720716	2,50E-09	-8,602234
8	lithium diphenylphosphide borane (average value)	370,6303302	2,568940957	2,51E-09	-8,600961

Table 28

A good correlation of the values of the internal references (in red) with a very high r^2 value of 0.999 was found. Note that a good FW (79 g/mol, 3.60 ppm) value was found for THF-d_8 (in green), even if it has not been considered as a supplementary internal reference because of its capacity to coordinate **10**-Li. To reinforce this hypothesis, the little signal next to that of THF-d_8 at 3.60 ppm which can be attributed to complexed THF (Figure 66). No more information such as the number of THF solvating **10**-Li could be extracted from this observation, the main reason being the overlapping of the signals.

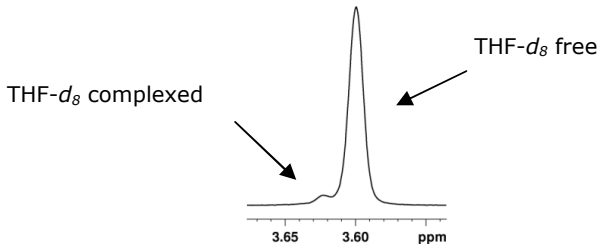


Figure 66

Going back to the main data provided by the DOSY above, the linear equation that has been deduced for the three internal references is:

$$\mathbf{y = -0.4579x - 7,4246}$$

corresponding to

$$\mathbf{logD = -0.4579logFW - 7,4246}$$

The second equation has been used to get the molecular weight of $[Ph_2P(BH_3)Li)_n].[THF]_m$. The result obtained is 370 g/mol (entry 8, Table 28). After imagining all combinations from n = 1 to 2 and m = 1 to 4 (Table 29), the closer molecular weight is 363, corresponding to a disolvated monomer (n = 1, m = 2, Figure 67).

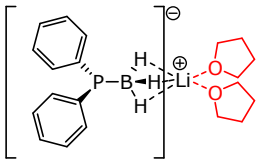


Figure 67

Lithium Phosphide Borane	**molecular weight**	**LogFW**
lithium diphenylphosphide borane monomer	205	2,311754
lithium diphenylphosphide borane monomer + 1 THF-d_7	284	2,453318
lithium diphenylphosphide borane monomer + 2 THF-d_7	363	2,559907
lithium diphenylphosphide borane dimer	410	2,612784
lithium diphenylphosphide borane monomer + 3 THF-d_7	442	2,645422
lithium diphenylphosphide borane dimer + 1 THF-d_7	489	2,689309
lithium diphenylphosphide borane monomer + 4 THF-d_7	521	2,716838
lithium diphenylphosphide borane dimer + 2 THF-d_7	568	2,754348
lithium diphenylphosphide borane dimer + 3 THF-d_7	647	2,810904

Table 29

Similar results and conclusions are obtained at room temperature: r^2 = 0.99 and FW = 373 (Figure 68 and Table 30).

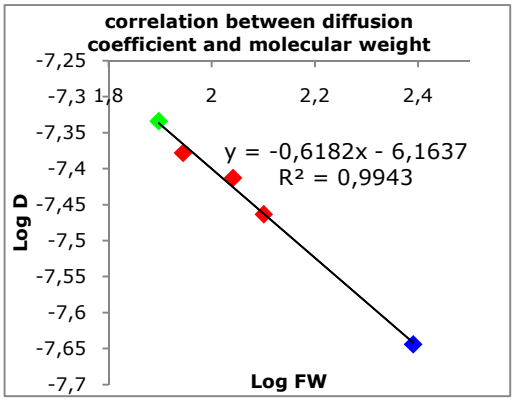
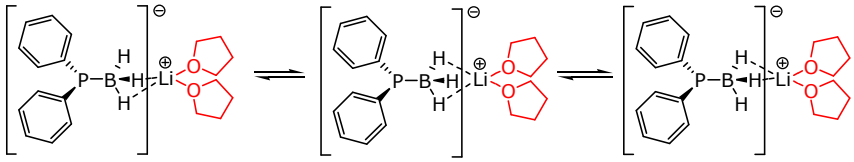


Figure 68: D-FW analysis of ^{1}H-DOSY of lithium diphenylphosphide borane **6**-Li and the three internal references at 298 K

entry	product	FW (g/mol)	LogFW	D (m^2/s)	LogD
1	THF-d_7	79	1,897627091	4,63E-08	-7,334231
2	tetramethylsilane	88	1,944482672	4,19E-08	-7,378097
3	cyclooctene	110	2,041392685	3,87E-08	-7,412851
4	1,3,5-tri-*tert*-butylbenzene	246	2,390935107	2,27E-08	-7,643974
5	lithium diphenylphosphide borane (peack 1)	370,762411	2,569095698	1,78E-08	-7,750313
6	lithium diphenylphosphide borane (peack 2)	377,6708113	2,577113421	1,76E-08	-7,755228
7	lithium diphenylphosphide borane (peack 3)	370,762411	2,569095698	1,78E-08	-7,751313
8	lithium diphenylphosphide borane (average value)	373,0652	2,57176827	1,77E-08	-7,75228

Table 30

In conclusion to this part, the structure of lithium diphenylphosphide borane in THF-d_8 has been characterized from −78°C to room temperature. It corresponds to a di-solvated monomer in which the lithium cation coordinates the borane-hydrogens and is solvated by two THF. It is still not founded if the three hydrogens of BH_3 are simultaneously connected to the metal or if, like for the crystal structure described in the literature,[434] two H only make the coordination. A rapid exchange between the three protons would take place affording an average value of the chemical shifts (Scheme 139). This hypothesis is also comforted by the fact that the lithium atom generally prefers to be at the centre of a tetrahedral system, being thus tetra-coordinated, instead of penta-coordinated.



Scheme 139

9.1.2.3. *NMR analyses in THF-d_8 of $Ph_2P(BH_3)Li$ obtained from a 1 : 1 of $Ph_2P(BH_3)H$ / ^{6}LDA*

Diphenylphosphide lithium **10**-Li was next prepared adding one equivalent of 6-labelled lithium diisopropylamide **296** to a solution of phosphine **10** in THF-d_8. It was indeed interesting to verify if i) the deprotonation takes place in the same

way as *n*-butyllithium; ii) the structure of the phosphide remains the same as that observed with *n*-BuLi, but this time in the presence of an amine (the diisopropylamine **297** formed by the deprotonation) in the solution. At last, LDA was introduced at this level of the study to anticipate and mime the chiral lithium amides we wish to use ultimately to run an enantiomeric synthesis of P-stereogenic phosphines.

Once the NMR sample ready (see 9.1.2.1.), a new series of multinuclear mono- and bi-dimensional NMR experiments has been conducted, starting at 195 K.

Comparison of the ^{1}H-NMR spectra of **10** (Figure 69, top) and **10**-Li prepared in this way (Figure 69, bottom) evidences a quantitative deprotonation of the starting material since the signals representative of the P-H hydrogen (doublet of quartets at 6.50 ppm) fully disappeared.

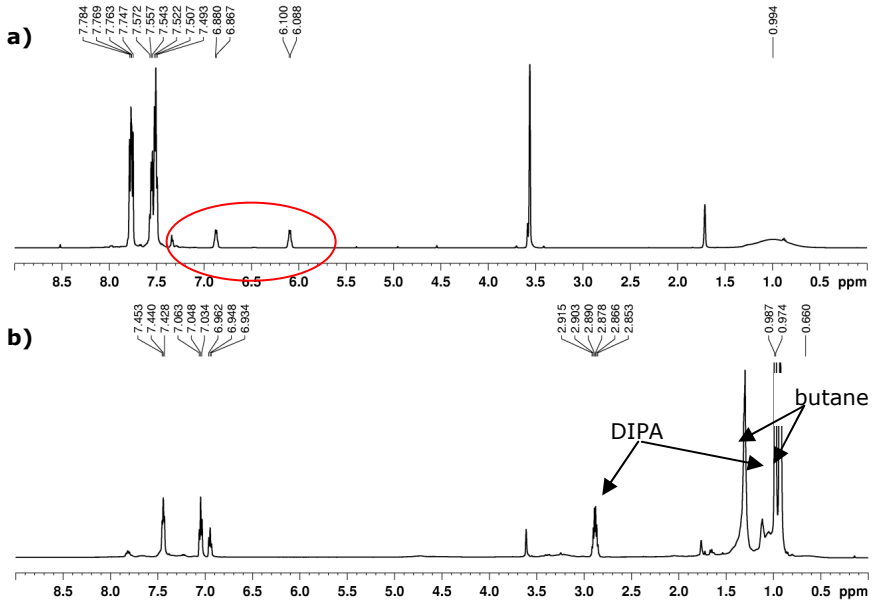


Figure 69: ^{1}H-NMR spectra of a) diphenylphosphine borane **10** and b) lithium diphenylphosphide borane **10**-Li in THF-d_8 at 195 K

The multiplets at 2.85 ppm and 0.92 ppm belong to diisopropylamine formed during the lithiation, instead those at 1.30 ppm and 0.90 ppm to butane present into *n*-Bu^{6}Li solution used for the preparation of LDA.

The ^{11}B- and ^{31}P-NMR spectra (Figure 70, middle and right) are also identical to those obtained when using *n*-BuLi **292**, each representing a broad singlet at –31.5 ppm and a sharp singlet at –49.8 ppm, respectively. On the ^{6}Li dimension

(Figure 70, left), a singlet is still observed, but at a higher frequency than for the study with *n*-BuLi (–0.71 ppm instead of –0.86 ppm).

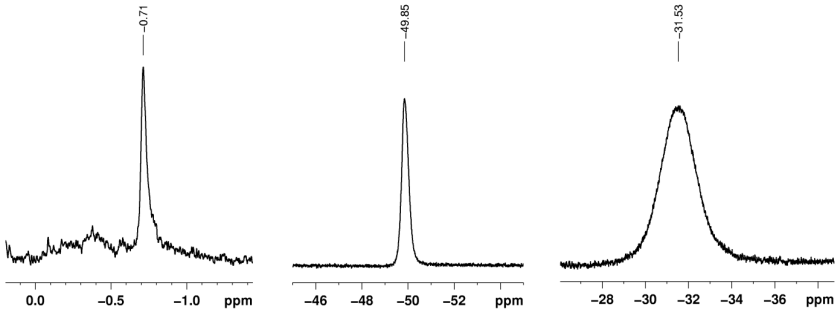


Figure 70: ^{6}Li-NMR spectrum of lithium diphenylphosphide borane **10**-Li in THF-d_8 at 195 K

Running the ^{6}Li,^{1}H-HOESY sequence demonstrates that no correlation exists between the lithium signal and the borane-hydrogens this time (Figure 71).

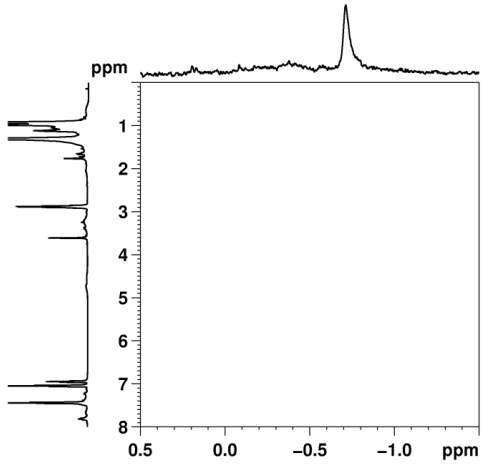


Figure 71: ^{1}H/^{6}Li HOESY spectrum of lithium diphenylphosphide borane **10**-Li in THF-d_8 at 195 K

This result let us think that the structural topology of the phosphide is not fully identical to the one determined previously. If, the option of having a P-Li connection is still to be avoided in view of the absence of coupling between these two nuclei, the possibility of being now in the presence of a separated ionic pair (Figure 72) is reasonable. One can suggest that the amine generated in the reaction mixture takes away the lithium cation from the borane group.

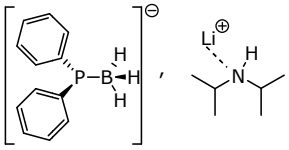


Figure 72

9.1.3. Theoretical view of the lithium diphenylphosphine borane structure

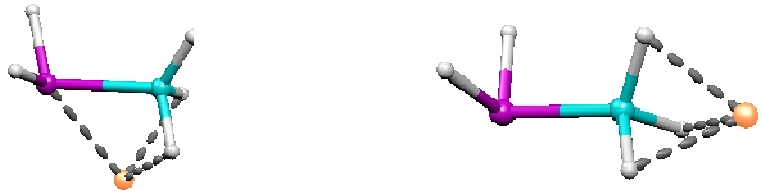
Some computational calculations have been carried out by Prof. Hélène Gérard from the University of Paris VI in order to confirm and understand the structural data extracted from the NMR study. In particular, the effect of solvation and temperature on the structure of the lithium diphenylphosphide **10**-Li was examined.

9.1.3.1. Computational details

In order to minimize the calculation time, the simple model $H_2P(BH_3)Li$ **300** has been studied. Solvation effects were included using explicit representation of the solvent molecules. In that connection, Me_2O has been chosen as a mimic of THF.

9.1.3.2. Results in absence of solvation (structures $\mathbf{300(S)_0}$*)*

In absence of Me_2O molecules coordinated to the lithium cations, two monomeric structures can be optimized. In a first arrangement, the coordination of the lithium cation is fixed on the three borane-hydrogens (Figure 73, right, $\mathbf{300_{H3}(S)_0}$).



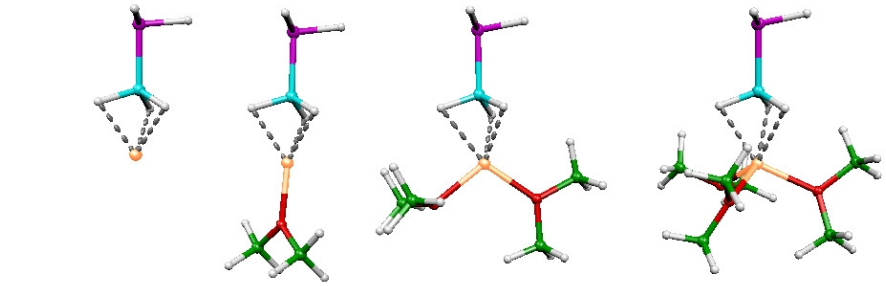
$\mathbf{300_{P\text{-}H2}(S)_0}$**:** 0.0 $\mathbf{300_{H3}(S)_0}$**:** 4.9

Figure 73: $H_2P(BH_3)Li$ **300** with lithium cation coordinated to the three H of BH_3 (right) or to P and two H of BH_3 (left). The relative energies of the two structures are given below (in kcal.mol^{-1}).The H atoms are represented in white, the P atoms in pink, the B atoms in blue and the Li atoms in yellow.

In a second one, coordination of the lithium to the P lone pair was sought (Figure 73, left), but after optimization it was found to be systematically complemented by two additional interaction with two borane hydrogens (**$300_{P\text{-}H2}(S)_0$**). This second structure is found to be the most stable in these conditions by nearly 5 kcal.mol^{-1}.

9.1.3.3. *Impact of solvation on the optimized structures*

This impact was examined by coordinating up to three Me_2O molecules to the lithium atoms and reoptimizing geometries for both coordination modes.



$300_{H3}(S)_0$ **$300_{H3}(S)_1$** **$300_{H3}(S)_2$** **$300_{H3}(S)_3$**

Figure 74: $H_2P(BH_3)Li$ **300** with lithium cation coordinated to the three H of BH_3 as a function of the number of OMe_2 molecules coordinated to the lithium cation. The H atoms are represented in white, the P atoms in pink, the B atoms in blue, the Li atoms in yellow, the O atoms in red and the C atoms in green.

Examining the Li-BH_3 structure, solvation has no dramatic effect compared with the solvent-free structures (Figure 74, Table 31).

$300_{H3}(S)_0$		**$300_{H3}(S)_1$**		**$300_{H3}(S)_2$**		**$300_{H3}(S)_3$**	
bond	**distance**	**bond**	**distance**	**bond**	**distance**	**bond**	**distance**
Li…H	1.861 Å	Li…H	1.885 Å	Li…H	1.924 Å	Li…H	2.053 Å
Li…H	1.867 Å	Li…H	1.906 Å	Li…H	1.931 Å	Li…H	2.055 Å
Li…H	1.877 Å	Li…H	1.913 Å	Li…H	2.103 Å	Li…H	2.110 Å
P…B	1.968 Å	P…B	1.971 Å	P…B	1.977 Å	P…B	1.982 Å

Table 31: Bond distances in the $H_2P(BH_3)Li$ **300** structure with lithium cation coordinated to the three H of BH_3 as a function of the number of OMe_2.

The lithium cation remains bonded to the three BH_3 hydrogens and only bond-lengths are changed: the Li-H distance increases from about 1.87 Å in the absence of solvent up to 2.05 Å in the presence of three molecules of Me_2O around the metal.

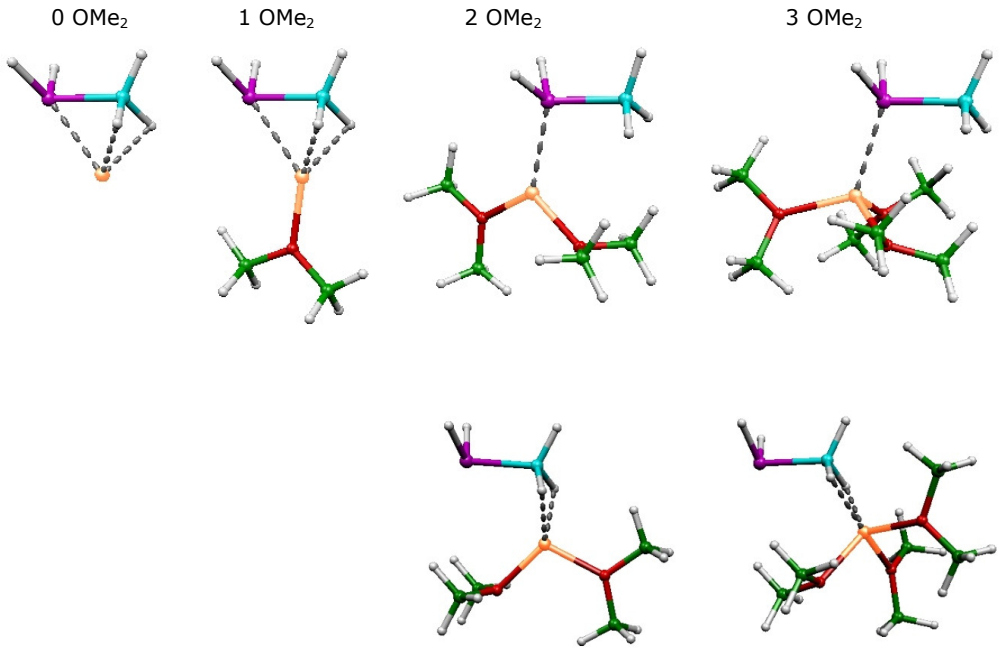


Figure 75: $H_2P(BH_3)Li$ **300** with lithium cation coordinated to P and/or two H of BH_3 as a function of the number of OMe_2 molecules coordinated to the lithium cation. The H atoms are represented in white, the P atoms in pink, the B atoms in blue, the Li atoms in yellow, the O atoms in red and the C atoms in green.

On the opposite, strong structural changes are observed in the Li-P system when increasing the number of Me_2O (Figure 75, Table 32).

bond or angle	**300** $_{P\text{-}H2}(S)_0$	**300** $_{P\text{-}H2}(S)_1$	**300** $_{P}(S)_2$	**300** $_{H2}(S)_2$	**300** $_{P}(S)_3$	**300** $_{H2}(S)_3$
Li…H (Å)	1.875	1.886	3.529	1.840	3.585	1.882
Li…H (Å)	1.877	1.886	3.524	1.838	3.689	1.933
Li…P (Å)	2.370	2.438	2.428	3.174	2.504	3.723
P…B (Å)	2.019	2.020	2.006	2.006	2.010	2.001
Li…P…B (°)	55.3	54.9	104.3	43.1	105.7	33.5

Table 32: Bond distances and angles in the $H_2P(BH_3)Li$ **300** structure with lithium cation coordinated to P and/or two H of BH_3 as a function of the number of OMe_2.

Indeed, for the solvent-free system, the lithium cation coordinates the P atom and two H atoms of the BH_3 adduct and this trend persists in the mono-solvatated structure (**300**$_{P\text{-}H2}(S)_1$). Upon addition of a second and then a third molecule of solvent, the lithium cation diminishes its number of interaction to the system and only coordination to either P (**300**$_{P}(S)_2$ and **300**$_{P}(S)_3$) or BH_2

(**$300_{H2}(S)_2$** and **$300_{H2}(S)_3$**) is kept. This is clearly evidenced in Table 32 either by the lengthening of the Li…P distance in the **$300_{H2}(S)_n$** structures or by the lengthening of the Li…H distances in the **$300_P(S)_n$** ones.

It is now necessary to examine how the strong structural changes are observed in the Li-P system when increasing the number of solvent molecules impacts the energy difference between the various species (Table 33).

solvation number (n)	$300_{H3}(S)_n$	$300_{P\text{-}H2}(S)_n$	$300_P(S)_n$	$300_{H2}(S)_n$
0	4.9	0.0	N.O.	N.O.
1	3.8	0.0	N.O.	N.O.
2	1.6	N.O.	6.6	0.0
3	0.0	N.O.	2.2	0.2

Table 33: Relative energies (in kcal.mol^{-1}, with respect to the most stable structure for each n) of the various structural arrangement for compound **300** as a function of the solvation number n.

When coordination to both P and two H is possible, that is for one or two solvent molecules, the **$300_{P\text{-}H2}(S)_n$** is the most stable species. When adding the second solvent molecule on the lithium, the loss of the P…Li bonds does not greatly destabilizes structure **$300_{H2}(S)_2$** which remains the most stable, whereas loss of the interactions to the two hydrogens of BH_3 is very destabilizing for structure **$300_P(S)_2$** which become the less stable. Finally, when adding a third OMe_2 molecule, all three structures become very close in energy, the least stable being still **$300_P(S)_3$** whereas **$300_{H2}(S)_3$** and **$300_{H3}(S)_3$** are quasi-isoenergetic.

9.1.3.4. *Most stable species in solution*

Determining the most stable (and thus experimentally observed) species in solution requires taking into account altogether solvation and temperature effects as entropic effects are supposed to strongly affect the solvent coordination at lithium. As a consequence, it is necessary to determine the relative free enthalpies of the species described above at the temperature of the experiment that is 195 K. In these conditions, four structures fall between 0 and 2 kcal.mol^{-1}: the two di-solvated structures with the lithium cation interacting with two or three H of the BH_3 and their two tri-solvated analogues. As a consequence, it is not possible to conclude definitely which is the structure observed in solution from an energetic of enthalpic point of view, as it can be very sensitive to temperature effects (as the free enthalpy difference between di- and tri-solvated structure can be strongly affected by temperature changes) and the energy difference between these values

is within the margin of error of the DFT used, as well as could be influenced from solvent and compound modelling (no inclusion of steric effects).

But this is in line with the DOSY experimental data, for which coordination number two was obtained. In addition, even though not definitive, the existence of structures with only two hydrogens of the BH_3 group interacting with lithium could explain the 2D NMR data and especially the absence of correlation between the lithium and one of the BH_3 hydrogen.

temperature	solvation number (n)	$300_{H3}(S)_n$	$300_{P\text{-}H2}(S)_n$	$300_{P}(S)_n$	$300_{H2}(S)_n$
195 K	0	21.0	16.6	N.O.	N.O.
	1	5.6	2.8	N.O.	N.O.
	2	0.5	N.O.	5.6	**0.0**
	3	1.2	N.O.	3.8	1.3

Table 34: Relative free energies at 195 K (in kcal.mol^{-1}, with respect to the most stable structure, all n included) of the various structural arrangement for compound **300** as a function of the solvation number n.

9.2. NMR analyses of 1 : 1 $Ph_2P(BH_3)Li$ / RLi mixtures (R = *n*-Bu, DA)

The following step of our study consisted in examining the ability for lithium diphenylphosphide borane **10**-Li to aggregate with another lithiated species such as an alkyllithium (*n*-BuLi **292**) or a lithium amide (LDA **296**). In all cases, **10-**Li has been prepared in THF-d_8 adding one equivalent of *n*-BuLi to phosphine **10**, suggesting that the structure of the phosphide corresponds to the topology in which the lithium cation is coordinated to the BH_3 group. The conclusions drawn from this part of the work should be helpful to interpret the kinetic or dynamic resolution phenomenon expected in the enantioselective process that has been imagined to get enantiopure P-stereogenic phosphines.

9.2.1. RLi = *n*-BuLi

One equivalent of *n*-butyllithium **292** in solution in THF-d_8 has been introduced at 195 K in an NMR tube containing a freshly prepared solution of **10**-Li in the same solvent. The ^{1}H-NMR spectrum registered at 195 K for the resulting mixture has been compared with the one of **10**-Li (Figure 76). It appears that signals attributed to the phosphide partner are exactly identical (same shape, same chemical shift) with those observed for free **10**-Li.

Changing the temperature from 195 K to 250 K did not modify this observation (Figure 77).

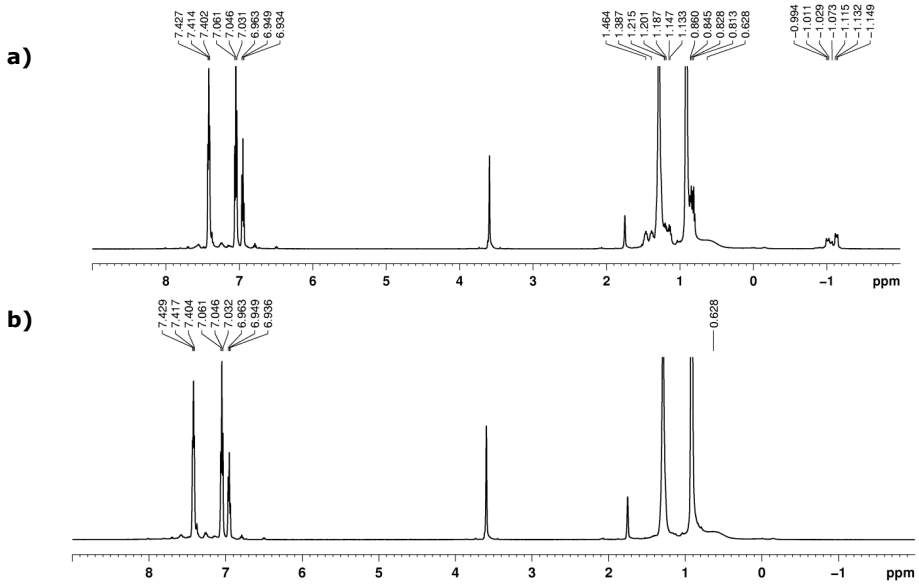


Figure 76: ^{1}H-NMR spectrum of a) lithium diphenylphosphide borane **10**-Li and b) lithium diphenylphosphide borane **10**-Li with 1.0 equiv of *n*-BuLi **292** in THF-d_8 at 195 K.

The main modifications are i) a better resolution of the BH_3 signal and ii) a coalescence of the two signals representative of the Li-C**H$_2$** protons of dimeric and tetrameric *n*-Bu^{6}Li.

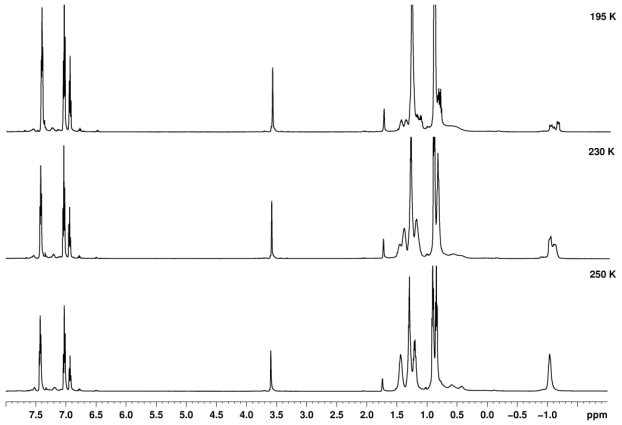


Figure 77: ^{1}H-NMR spectrum of lithium diphenylphosphide borane **10**-Li with 1.0 equiv of *n*-BuLi **292** in THF-d_8 a) at 195 K, b) 230 K and c) 250 K

^{6}Li-, ^{11}B- and ^{31}P-NMR spectra did not show either particular evolution from **10**-Li to **10**-Li+*n*-BuLi, whatever is the temperature between 170 K and 250 K (Figure 78). Only the already mentioned effects of temperature on the resolution

of the different spectra (lower for lithium and better for boron and phosphorus) are noticed. One can note at least from the ^{6}Li spectra that the *n*-BuLi dimer / tetramer ratio evolves with the change of temperature. Thus, at 170 K, the proportions are 2 : 1 in favour of the dimer, and becomes 0.9 : 1 (more tetramer) at 195 K.

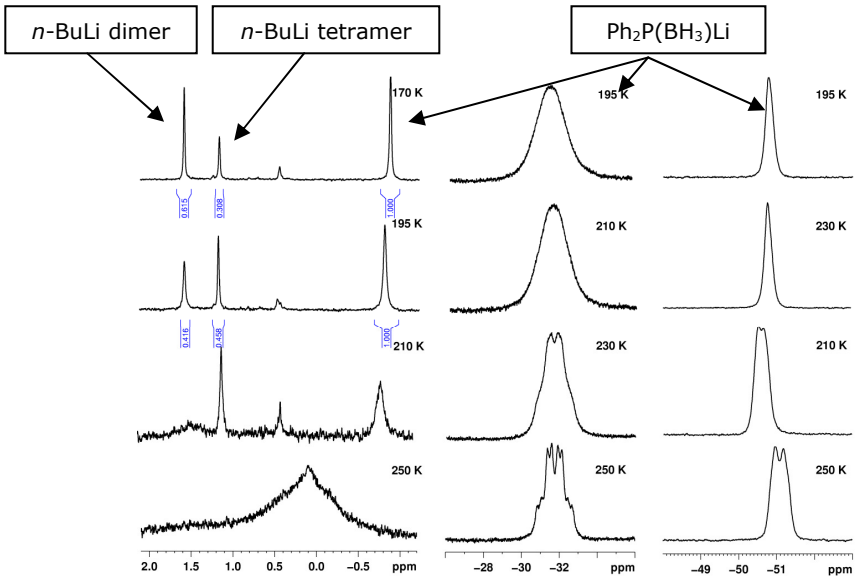


Figure 78: ^{6}Li- (left), ^{11}B- (middle), ^{31}P- (right) NMR spectra of lithium diphenylphosphide borane **10**-Li with 1.0 equiv of *n*-BuLi **292** in THF-d_8 between 170 K and 250 K.

In order to complete the general framework also the ^{13}C-NMR spectrum has been reported (Figure 79). This does not show particular differences compared to the spectrum of *n*-BuLi free in THF-d_8 solution (see Figure 48)

The mono-dimensional experiments let think that no interaction takes place between the lithium phosphide and *n*-Bu^{6}Li. Bi-dimensional analyses have thus been undertaken to expand our range of evidence.

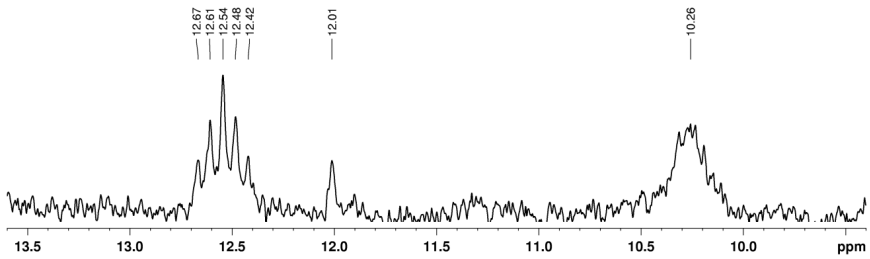


Figure 79: ^{13}C-NMR spectrum of lithium diphenylphosphide borane **10**-Li with 1.0 equiv of *n*-BuLi **292** in THF-d_8 at 195 K.

NOESY spectra recorded at 170 K, then at 195 K, present few differences (Figure 80). At 170 K, intra- and inter-molecular correlations are shown (Figure 80, top), and interesting is the one observed between aromatic protons of **6**-Li and the *a*-CH_2 signals of *n*-BuLi. Warming at 195 K proved to be unbeneficial for this correlation.

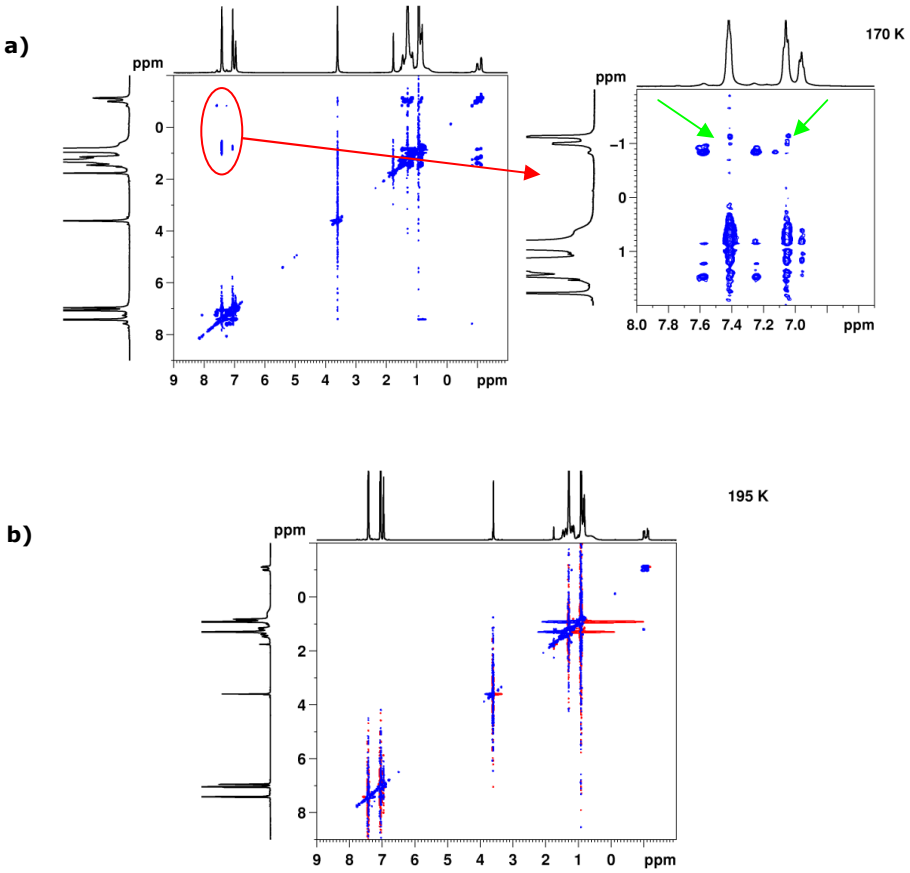


Figure 80: $^{1}H/^{1}H$ NOESY spectra of lithium diphenylphosphide borane **10**-Li with 1.0 equiv of *n*-BuLi **292** in THF-d_8 a) at 170 K and b) at 195 K.

By contrast to the NOESY, the HOESY spectrum registered at 195 K appeared more informative than the one obtained at 170K (Figure 81). At this later temperature, only intramolecular correlations are observed. At 195 K, the lithium atom of the phosphide shows correlations with the *a*-CH_2 signals of the two aggregates of *n*-butyllithium.

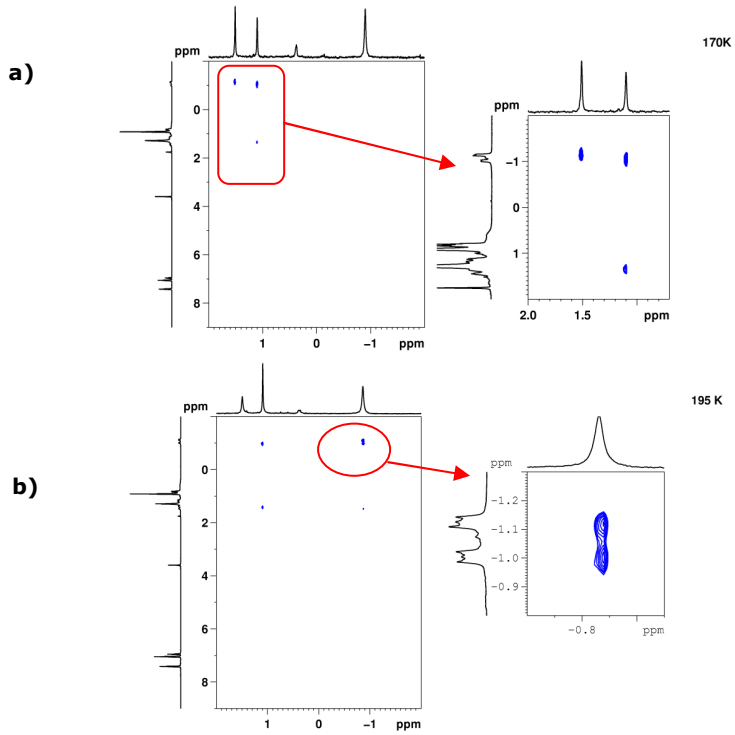


Figure 81: $^{1}H/^{6}Li$ HOESY spectra of lithium diphenylphosphide borane **10**-Li with 1.0 equiv of *n*-BuLi **292** in THF-d_8 a) at 170 K and b) at 195 K.

The complementary EXSY spectrum recorded at 170 K evidences a weak "exchange" between the dimeric aggregate of *n*-BuLi and **10**-Li. When working at 195 K, all species exchange between each other (Figure 82).

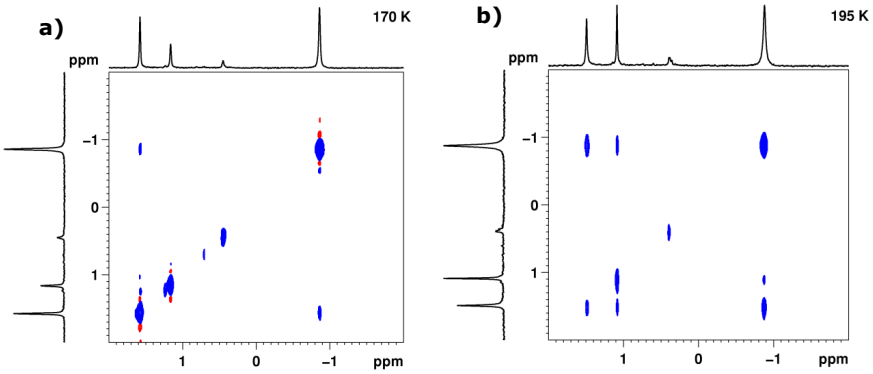


Figure 82: $^{6}Li/^{6}Li$ EXSY spectra of lithium diphenylphosphide borane **10**-Li with 1.0 equiv of *n*-BuLi in THF-d_8 a) at 170 K and b) at 195 K.

At this level of the study, we assumed that i) the presence of correlations in the HOESY spectrum at 195 K is the consequence of a cation exchanges; ii) the

correlation observed at 170 K between the aromatic protons of **10**-Li and the *α*-CH_2 of butyllithium in the NOESY spectrum would not be significant, being part of the background noise. Both information reinforce the hypothesis that the two dipolar species would not interact.

The ultimate proof showing that **10**-Li and *n*-BuLi evolve independently when mixed together in a THF solution has been brought by a DOSY experiment. The temperature chosen to realize this sequence has been fixed at 170 K in order to avoid any exchange. A preliminary measurement has been done on a **10**-Li+*n*-BuLi sample without internal reference (Figure 83).

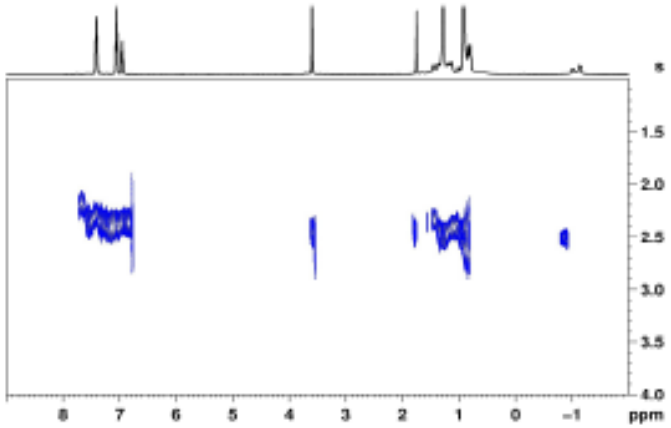
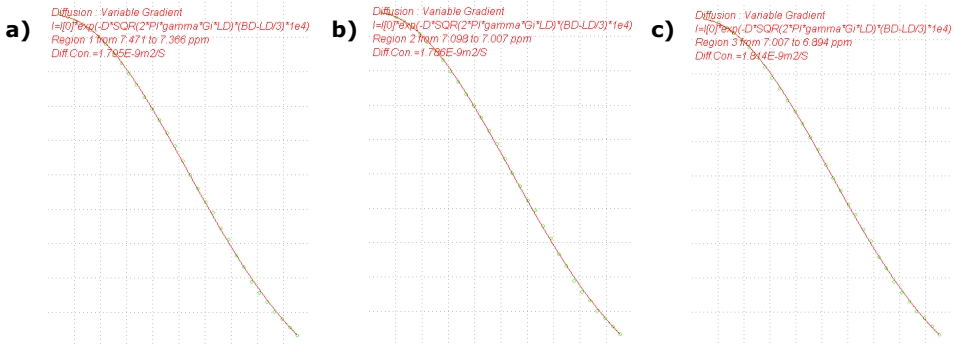


Figure 83: ^{1}H-DOSY spectrum of lithium diphenylphosphide borane **10**-Li with 1.0 equiv of *n*-BuLi **292** in THF-d_8 at 195 K

Related diffusion coefficients have been generated by using curve fitting of signal attenuation data.[438-443] The signal attenuation curves were attained after 32 steps of increasing gradient strength from 2% to 95% linearly (Figure 84).



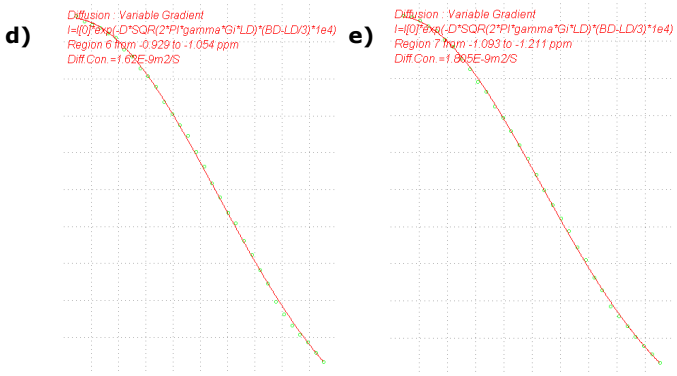


Figure 84: Signal attenuation curves for ^{1}H-DOSY data for lithium diphenylphosphide borane **10**-Li (a, b, c), *n*-BuLi **292** dimer (d) and *n*-BuLi tetramer(e).

The diffusion coefficients could then be deduced from the signals at –1.00 ppm for tetrameric *n*-BuLi, –1.10 ppm for dimeric *n*-BuLi, and an average made from D values obtained on three aromatic signals of **10**-Li (*ortho*, *meta* and *para* aromatic protons at δ=7.45, 7.05 and 6.95 ppm, respectively) (Table 35).

entry	**product**	**FW** (g/mol)	**LogFW**	**D** (m^2/s)	**LogD**
1	THF-d_7 (peak one)	79	1,897627091	3,33E-09	-8,477425
2	THF-d_7 (peak two)	79	1,897627091	3,29E-09	-8,483332
3	THF-d_7 (average value)	79	1,897627091	3,31E-09	-8,480369
4	lithium diphenylphosphide borane (peak 1)	-	2,646787777	1,80E-09	-8,744969
5	lithium diphenylphosphide borane (peak 2)	-	2,657068561	1,78E-09	-8,748605
6	lithium diphenylphosphide borane (peak 3)	-	2,644741909	1,80E-09	-8,744245
7	lithium diphenylphosphide borane (average value)	-	2,649520913	1,80E-09	-8,745936
8	*n*-BuLi dimer	442	2,645422269	1,81E-09	-8,741363
9	*n*-BuLi tetramer	568	2,754348336	1,64E-09	-8,785686

Table 35

From this preliminary set of results, note that the D values of the dimeric and the tetrameric aggregates of *n*-BuLi are well distinct, with a higher value logically obtained for the bigger oligomer. Otherwise, the dimeric oligomer of *n*-BuLi and phosphide **10**-Li present the same diffusion coefficient, which is probably the consequence of the lithium exchange mentioned earlier between the two species.

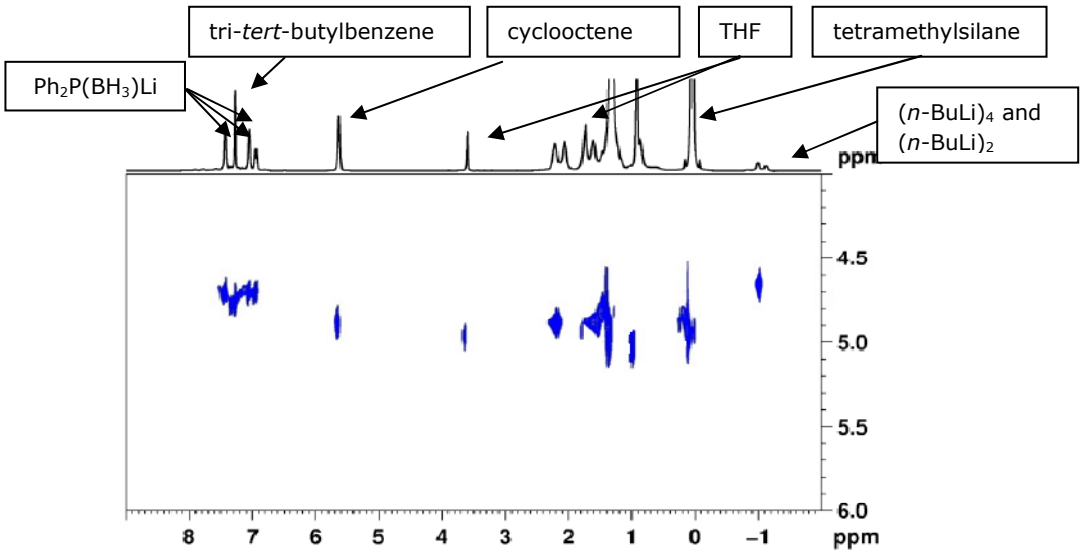


Figure 85: ^{1}H-DOSY spectrum of lithium diphenylphosphide borane **10**-Li with 1.0 equiv *n*-BuLi **292** and the three internal references in THF-d_8 at 195 K

A second DOSY experiment has then been conducted, this time with internal references. Thus tetramethylsilane, cyclooctene and 1,3,5-tri-*tert*-butylbenzene were added to the **10**-Li + *n*BuLi mixture and the resulting spectra shows a good separation of the signals on each species (Figure 85).

After required treatment of the data, a linear correlation between D and FW could be settled with r^2 = 0.989 (Table 36, Figure 86).

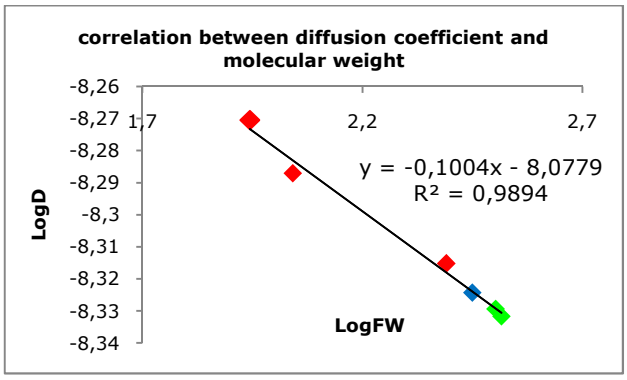


Figure 86: D-FW analysis of ^{1}H-DOSY of lithium diphenylphosphide borane **10**-Li (blue) with 1.0 equiv BuLi **292** (green) and the three internal references (red) at 170 K.

entry	product	FW (g/mol)	LogFW	D (m^2/s)	LogD
1	tetramethylsilane	88	1,944482672	5,37E-09	-8,27043
2	cyclooctene	110	2,041392685	5,16E-09	-8,287014
3	1,3,5-tri-*tert*-butylbenzene	246	2,390935107	4,84E-09	-8,315244
4	THF-d_7	79	1,897627091	5,56E-09	-8,255081
5	BuLi tetramer + 4 THF	568	2,515788765	4,66E-09	-8,331707
6	BuLi dimer + THF	442	2,449355717	4,74E-09	-8,324313
7	lithium diphenylphosphide borane (average value)			4,68E-09	-8,329383

Table 36

The molecular weight found for the two oligomers of *n*-butyllithium are characteristic of the "free" tetra-solvated tetrameric and dimeric aggregates of this partner, and calculated FW of **10**-Li corresponds to 316 g/mol. This value is between that of a mono-solvated **10**-Li (285 g/mol) and that of a di-solvated **10**-Li (363 g/mol). One can suggest an equilibrium between this two possibilities of solvation (Figure 87).

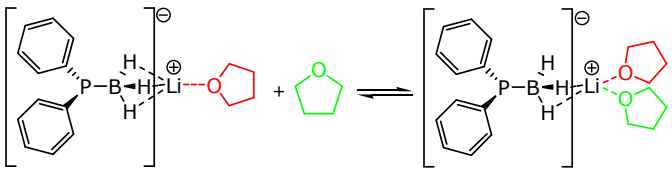


Figure 87

In conclusion, this part of the work evidences that *n*-butyllithium and lithium diphenylphosphide borane **6**-Li do not form any complex when mixed together in THF.

9.2.2. RLi = LDA

The ultimate goal underlying our work being to association of a lithium phosphide anion to a lithium amide, we examined the possibility to aggregate **10**-Li with the model lithium amide, diisopropylamide **296**. The sample has been prepared adding, at 195 K, an equimolar amount of freshly prepared ^{6}LDA **296** in

THF-d_8 to a solution of **10**-Li, also in THF-d_8. Two samples ("a" and "b") have been prepared.

9.2.2.1. Sample "a"

Following the usual analytical protocol, the ^{1}H-NMR spectrum has first been recorded at 195 K. We can distinguish three sets of signals that are those corresponding to the "free" phosphide **10**-Li (*ortho*, *meta* and *para* aromatic protons at δ=7.44, 7.06 and 6.97 ppm, respectively), those related to "free" LDA (δ=2.96 ppm and δ=1.05 ppm corresponding to the C**H**$(CH_3)_2$ and CH(C**H$_3$**$)_2$ protons), and peaks at 3.22 ppm and -1.10 ppm attributed to ^{6}LDA-Bu^{6}Li complex (Figure 88).

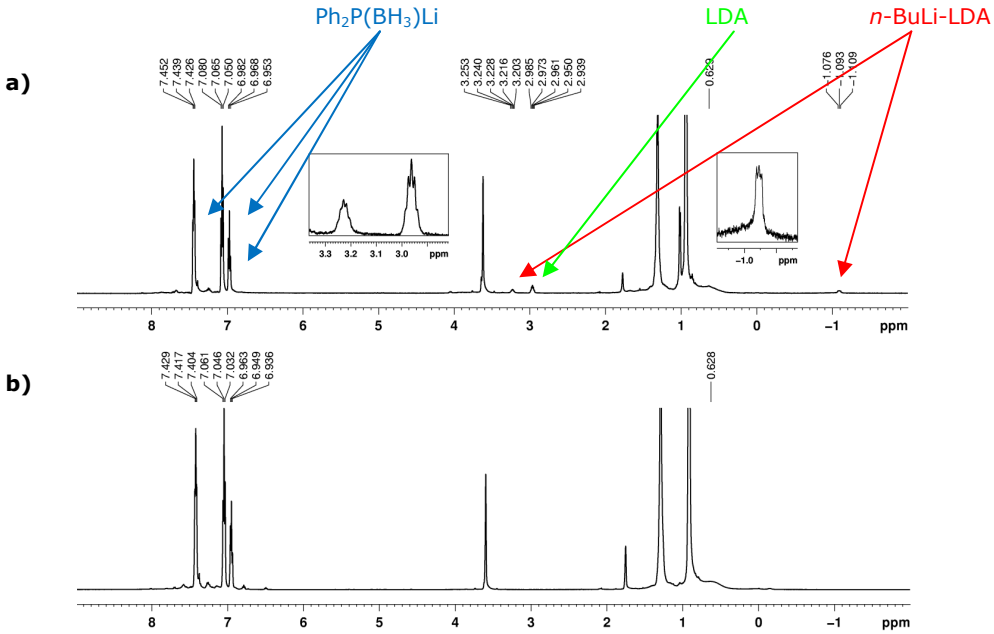


Figure 88: ^{1}H-NMR spectrum of a) lithium diphenylphosphide borane **10**-Li and b) lithium diphenylphosphide borane **10**-Li with 1.0 equiv of LDA **296** in THF-d_8 at 195 K.

The presence of extra *n*-BuLi in the first sample probably comes from an slight excess of this reactant introduced when preparing the LDA.

The heteronuclear analysis at 195 K revealed an additional signal into the ^{6}Li- (at δ=-0.83 ppm) and ^{31}P-NMR (at δ=-49.9 ppm) spectra besides those of $Ph_2P(BH_3)Li$ **10**-Li (at δ=-0.81 ppm and at δ=-49.5 ppm in the corresponding spectra, Figure 89). Lithium spectrum shows also the signals related to "free" LDA (δ=1.56 ppm) and the "free" BuLi-LDA complex (δ=1.72 ppm).

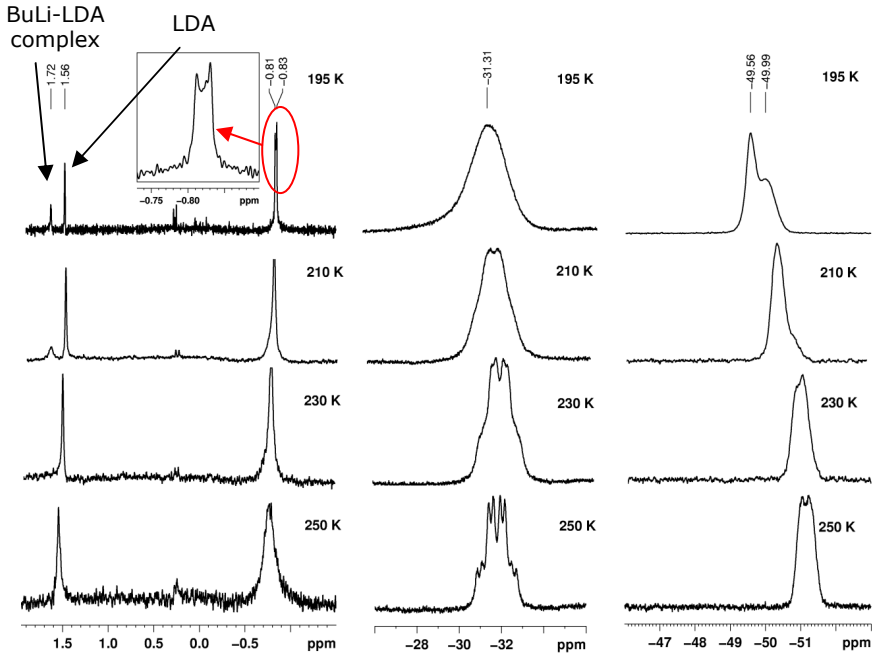


Figure 89: ^{6}Li- (left), ^{11}B- (middle) and ^{31}P-NMR (right) spectra of lithium diphenylphosphide borane **10**-Li with 1.0 equiv of LDA **296** in THF-d_8 at 195 K.

This signal, which could be correlated to the presence of a second phosphinyl species, tends to disappear when the temperature increases.

However, this additional phosphinyl compound does not show in the ^{11}B-NMR (Figure 89, middle) and HOESY spectra (Figure 90). The latter, moreover, shows only one correlation related to Li of LDA with its CH(C**H$_3$**)$_2$ protons.

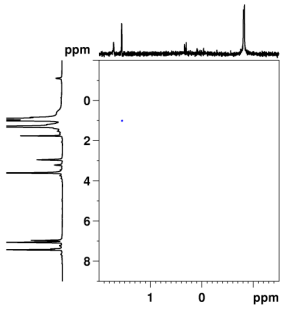


Figure 90: ^{6}Li/^{1}H HOESY of lithium diphenylphosphide borane **10**-Li with 1.0 equiv of ^{6}LDA **296** in THF-d_8 at 195 K.

9.2.2.2. Sample "b"

In order to understand the cause of the presence of additional signals in ^{6}Li- and ^{31}P-NMR spectra, a second sample, this time free of extra *n*-BuLi, was

prepared and analyzed. Actually, a slight excess of DIPA is now observed (Figure 91).

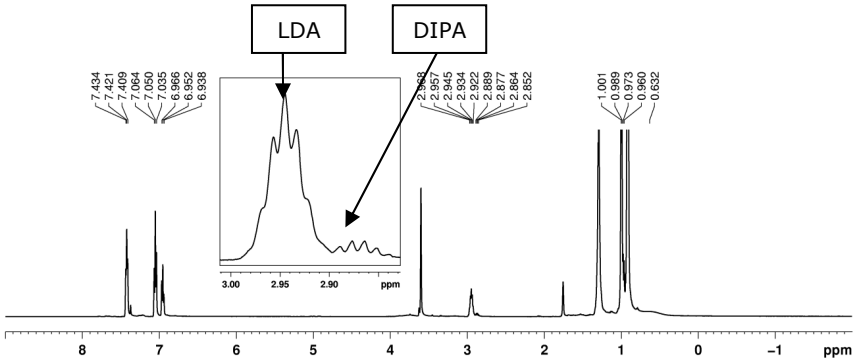


Figure 91: ^{1}H-NMR spectrum of lithium diphenylphosphide borane **10**-Li with 1.0 equiv of LDA **296** in THF-d_8 at 195 K.

The ^{1}H-NMR spectrum (Figure 91) shows signals that are characteristic of those known for "free" **10**-Li and LDA.

The heteronuclear investigation, this time, does not present any additional signal to those of isolated species, **10**-Li and LDA (Figure 92).

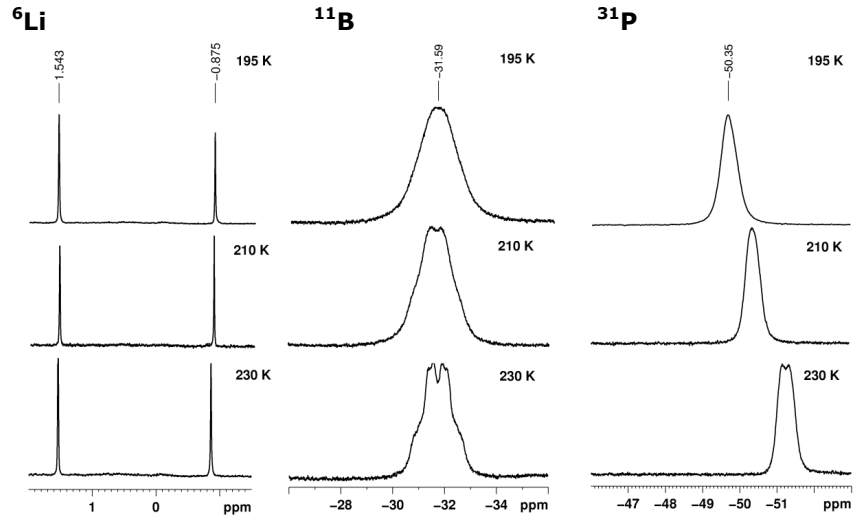


Figure 92: ^{6}Li- (left), 11B (middle) and 31P-NMR (right) spectra of lithium diphenylphosphide borane **10**-Li with 1.0 equiv of LDA **296** in THF-d_8 at 195 K.

No change is noticed upon variation of the temperature.

This trend was then confirmed by 2D spectra (Figure 93). NOESY does not present particular correlations; while the HOESY spectrum exhibits only the expected intramolecular Li/CH and Li/CH_3 of LiDA and Li/BH_3 of $Ph_2P(BH_3)$Li **10**-Li

correlations, suggesting once again that no interaction occurs between the two entities.

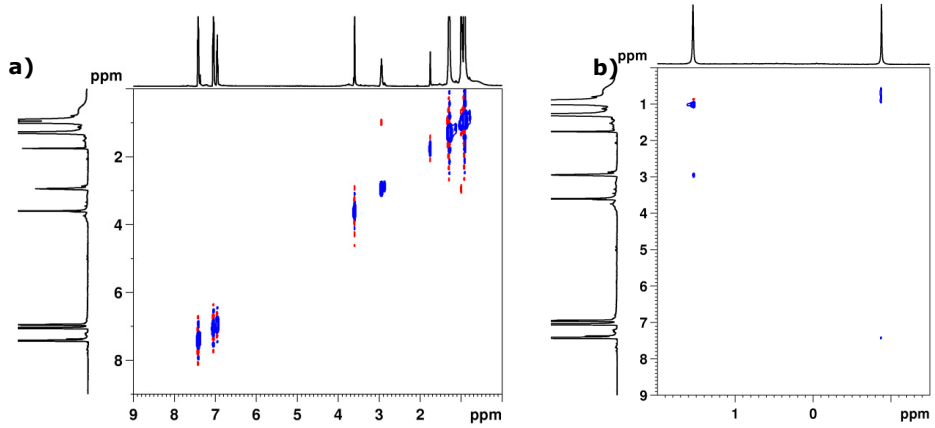


Figure 93: a) $^{1}H/^{1}H$ NOESY and b) $^{6}Li/^{1}H$ HOESY spectrum of lithium diphenylphosphide borane **10**-Li with 1.0 equiv of LDA **296** in THF-d_8 at 195 K.

This conclusion leads us to assume that the presence of additional signals into ^{6}Li- and ^{31}P-NMR spectra in the first sample could be due to the BuLi-LDA complex. In order to further support this hypothesis, 1.0 equivalent of *n*-Bu^{6}Li was added into the second sample solution.

However, no additional signal appeared at 195 K. Actually, ^{1}H-, ^{6}Li-, ^{11}B- and ^{31}P-NMR spectra exhibit only the signals of lithium diphenylphosphide borane **10**-Li, LDA and the BuLi-LDA complex at the same frequencies that assigned to the "free" species (Figure 94).

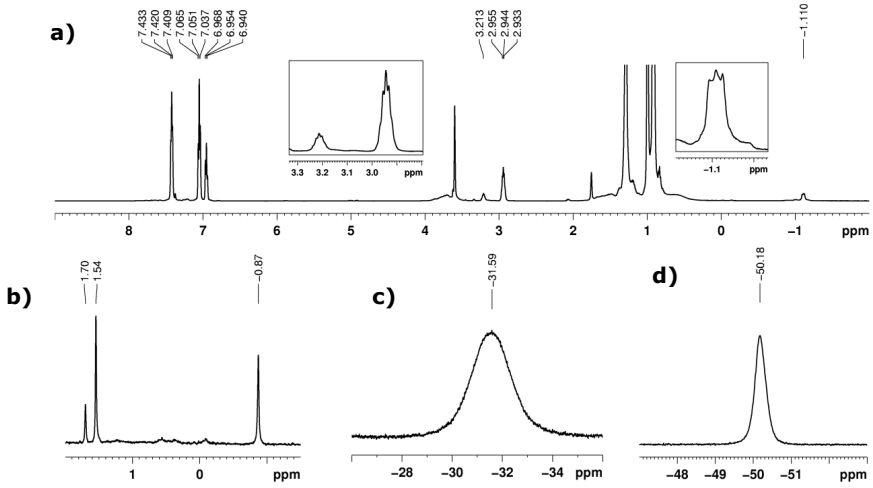


Figure 94: a) ^{1}H-, b) ^{6}Li-, c) ^{11}B-, and d) ^{31}P NMR spectra of lithium diphenylphosphide borane **10**-Li with 1.0 equiv of *n*-Bu^{6}Li and ^{6}LDA **296** in THF-d_8 at 195 K.

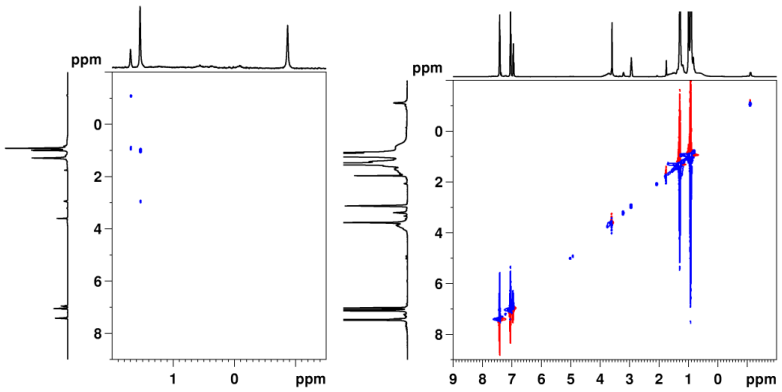
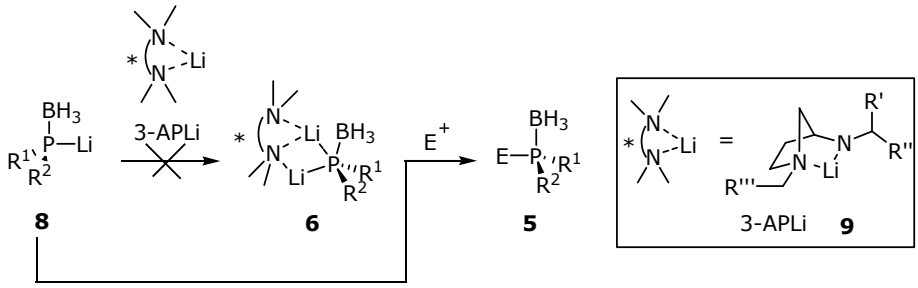


Figure 95: $^{6}Li/^{1}H$ HOESY (left), b) $^{1}H/^{1}H$ NOESY (right) spectra of lithium diphenylphosphide borane **10**-Li with 1.0 equiv of *n*-Bu^{6}Li and ^{6}LDA **296** in THF-d_8 at 195 K.

The same trends were observed for the 2D NOESY and HOESY at 195 K (Figure 95).

In conclusion neither *n*-BuLi nor LDA form mixed aggregates with lithium diphenylphosphide borane **10**-Li. The experiments carried out without extra *n*-Bu^{6}Li (sample two) and the addition of *n*-Bu^{6}Li **292** to this solution have confirmed this point. Therefore, the additional peaks in the lithium-6 and phosphorus-31 NMR spectra of the first sample could be due to an unknown impurity.

At this stage, let us remind the reader that the latter NMR results aimed at evaluating the affinity of alkyllithiums and lithium amides for lithium phosphides. Our analyses suggest that lithium amides, such as chiral lithium 3-aminopyrrolidines **9**-Li, cannot form non-covalent mixed aggregates with lithium phosphide **8**. Obviously, these data jeopardize the project of the enantioselective alkylation of lithium phospha-anion **6** by achiral electrophiles (Scheme 140).

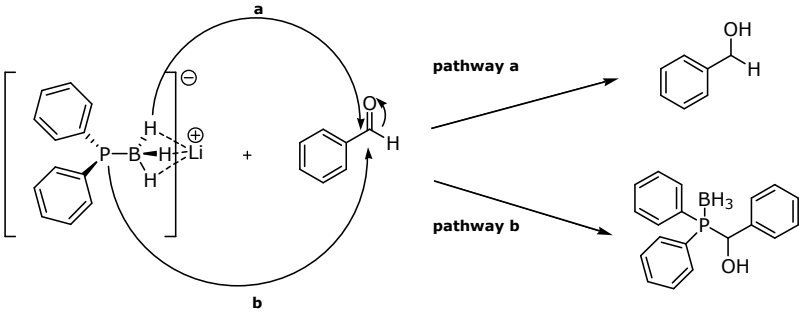


Scheme 140

Investigations on the enantioselective alkylation of racemic secondary phosphine boranes in presence of 3-APLi are currently in progress.

10. REDUCTIONS OF CARBONYL SPECIES WITH LITHIUM PHOSPHIDES

Our previous structural NMR studies have shown that, in THF, lithium diphenylphosphide borane **10**-Li presents a topology that places the lithium cation next to the hydrogens of the borane group. Otherwise, lets mention the general analogies that can have **10**-Li with classical reactants such as lithium or sodium borohydrides ($LiBH_4$, $NaBH_3CN$),[444] as well as lithium aminoborohydrides.[445-447] These compounds are known to be efficient reductive reagents of carbonyls, imines, cyanides and azides. One can wonder if lithium phosphoborohydrides analogues, and **10**-Li is one of them, have the same reductive property. Thus, we thought it would be interesting to check if **10**-Li prefers to react as a P-nucleophile (pathway a on Scheme 141) or an H-nucleophile (hydride, pathway b on Scheme 141).



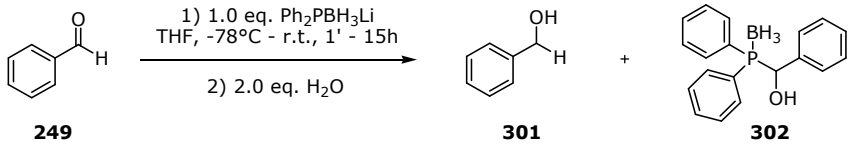
Scheme 141

The competitive reactivity mentioned above has been experimentally checked reacting **10**-Li with benzaldehyde in THF solution. A complementary work aiming to interpret the mechanisms evolved has also been undertaken and consists in examining and characterize by NMR the intermediates of the reaction in solution.

This study has been realized in collaboration with Pierre Queval, 2nd year PhD student in the group of Prof. Annie-Claude Gaumont, University of Caen.

10.1. Results in synthesis

As already announced in the introduction, the reactivity of lithium diphenylphosphide borane **10**-Li has been examined reacting it with benzaldehyde **249** in THF (Scheme 142). Several temperatures have been applied, as well as the time of the reactions that have been changed.



249 **301** **302**

Scheme 142

Lithium diphenylphosphide borane was first prepared in THF by addition, at –78° C, exactly 1.0 equivalent of a solution of *n*-BuLi in hexane into a solution of diphenylphosphine borane **10** in freshly distilled THF. After 30' of stirring at this temperature, an equimolar amount of benzaldehyde **296** was introduced dropwise. The resulting mixture was stirred from 1' to 15h at either room temperature or –78°C.

When the reaction is carried out at room temperature for 15 h, benzyl alcohol **301** was exclusively obtained in a 84% yield after hydrolysis and purification by flash chromatography.

Running the reaction at –78° C leads to the major formation of *a*-hydroxyphosphine borane **302**.

This first series of results seems to indicate that at low temperatures, **10**-Li reacts as a P-nucleophile, while higher temperature would exalts the hydride addition. Two possibilities must be considered at this level (Figure 96):

- the products **301** and **302** are formed from two distinct pathways, **301** being thermodynamically more stable than **302** (Figure 16, left);
- **301**, thermodynamic product, derives from kinetic product **302** (Figure 16, right).

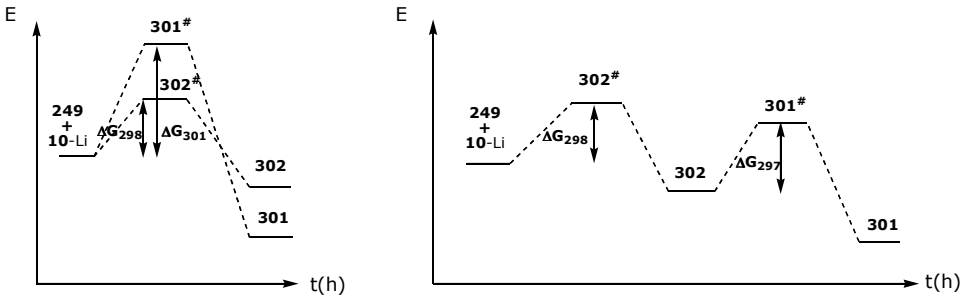


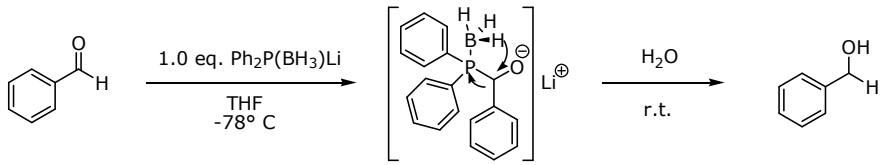
Figure 96

Successive experiments have thus been repeated at room temperature and varying the time of the reaction in order to better understand the origin of each product (Table 37).

entry	times	ratio 249 : 301 : 302[a]
1	1′	65 : 7 : 28
2	10′	45 : 33 : 18
3	30′	28 : 54 : 18
4	1h	24 : 61 : 15
5	2h	8 : 89 : 3
6	3h	0 : >99 : <1
7	4h	0 : 100 : 0
8	5h	0 : 100 : 0
9	15h	0 : 100 : 0

Table 37: Series of experiments at r.t. carried out at different reaction times
[(a)] determinate by ^{1}H-NMR

One can notice that in the early minutes of the reaction (entry 1), *α*-hydroxy-benzyldiphenylphosphine borane **302** is the major product formed (28%) and **301** the minor one. Increase of the reaction time reverse the **302** / **301** ratio in favour of the product of reduction (entries 2-6). Such profile let us retain the second energetic diagram suggesting that **301** comes from **302**. The mechanism proposed to justify the **302** to **301** transformation corresponds to a rearrangement that would take place before hydrolysis (at the **302**-Li level). It would consist in an intramolecular addition of a hydride of the BH_3 group on the "hemiphosphinal" carbon of **302**-Li. This attack would provoke the departure of the phosphine borane appendage (Scheme 143).



249 **302**-Li **301**

Scheme 143

10.2. Structural NMR investigation: results obtained

To rationalize the mechanistic assumptions made during the synthetic work, a multinuclear NMR study of the reaction has been carried out at different temperatures. The NMR samples were prepared adding 1.0 equivalent of benzaldehyde to a solution of lithium diphenylphosphide borane **10**-Li in THF-d_8.

A first set of spectra has been registered at low temperature and corresponded to the ^{1}H, ^{6}Li, ^{11}B, ^{13}C and ^{31}P one dimensions (Figure 97).

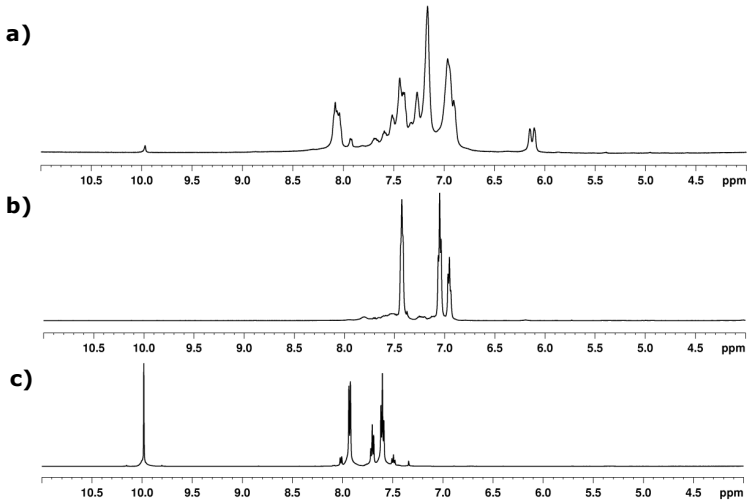


Figure 97: ^{1}H-NMR spectra of a) lithium diphenylphosphide borane **10**-Li with 1.0 equiv of benzaldehyde **249**, b) lithium diphenylphosphide borane **10**-Li; c) benzaldehyde **249** in THF-d_8 at 195 K.

On the ^{1}H-NMR spectrum (Figure 97), one can notice only traces of residual starting material, indicating by this way that the reaction runs pretty fast at –78° C.

About the product formed, it was not observed signals characteristic of the alcoholate **301**-Li. In fact, as represented into the spectrum of the reaction mixture after 15h at room temperature and before quenching (Figure 98), the C**H$_2$**OLi of benzyl alcoholate **301**-Li is placed at δ=4.59 ppm. We thus assumed that such spectrum in figure 97 is representative of the lithium-hemiphosphine **302**-Li.

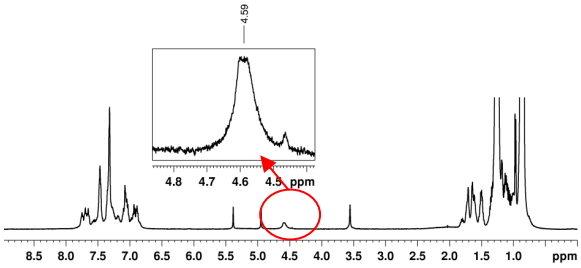


Figure 98

Some precise assignments have been possible thanks to bi-dimensional ^{1}H/^{13}C HMQC and HMBC (Figure 99).

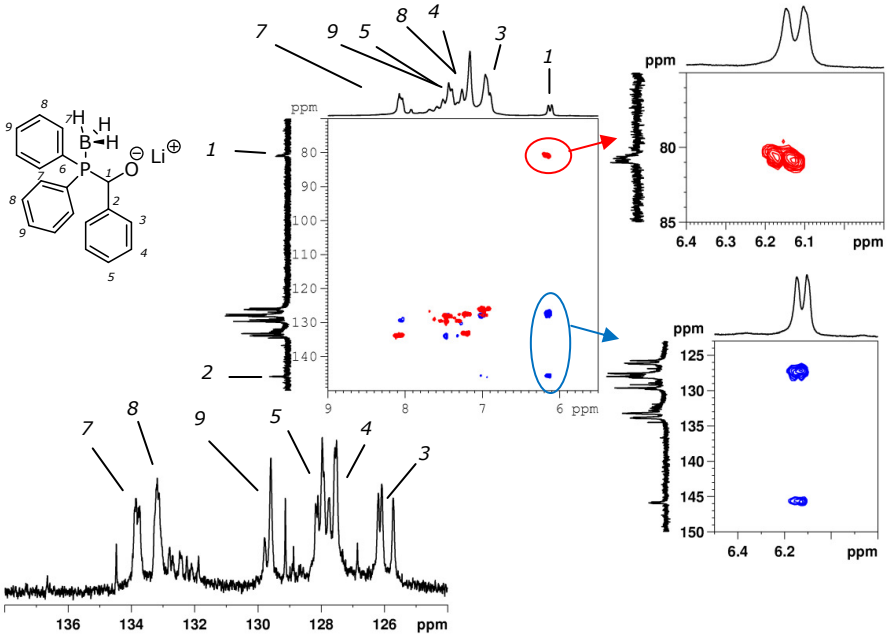


Figure 99: $^{1}H/^{13}C$ HMQC (red) and HMBC (blue) of lithium diphenylphosphide borane **10**-Li with 1.0 equiv benzaldehyde **249** in THF-d_8 at 195 K.

Thus, it became clear that the multiplet at 6.10 ppm belongs to the C^1 in *α*-position to the oxygen. In fact a direct C-H correlation between carbon signal at δ=80.8 ppm and proton signal at δ=6.15 ppm and multibonding correlation among C^2 and C^3 with the same proton signal occur. Our attention was, then, focused on this signal.

Such signal could correspond to a doublet or two singlets. The only possibility of coupling being with the phosphorus atom, the ^{1}H $\{^{31}P\}$ spectrum was registered (Figure 100).

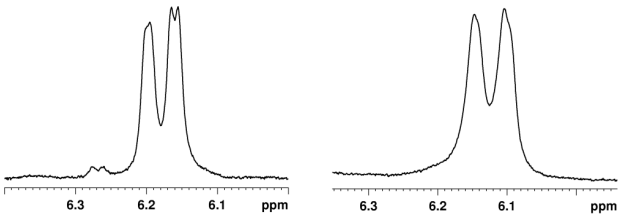


Figure 100: a) ^{1}H-NMR and b) ^{1}H-NMR{31P} spectra of lithium diphenylphosphide borane **10**-Li with 1.0 equiv of benzaldehyde **249** in THF-d_8 at 195 K.

No changes were actually observed between the coupled and the uncoupled ^{1}H-NMR spectra, evidencing by this way that we are in the presence of two singlets, probably belonging to two different species of similar structures.

Other characteristic of this signal is represented by the change of shape in dependence of the temperature: increasing the temperature led to a coalescence of the two peaks of this signal (Figure 101).

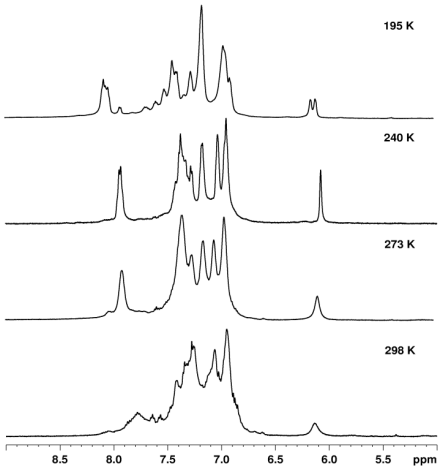


Figure 101: a) ^{1}H-NMR spectrum of lithium diphenylphosphide borane **10**-Li with 1.0 equiv of benzaldehyde **249** in THF-d_8 at different temperatures.

Similar observations have been done on the lithium-6 and phosphorus-31 experiments. In both cases, there are two signals at low temperature, which evolve in a broad singlet above 210 K (Figure 102). These observations point out that we are in the presence of two species in exchange.

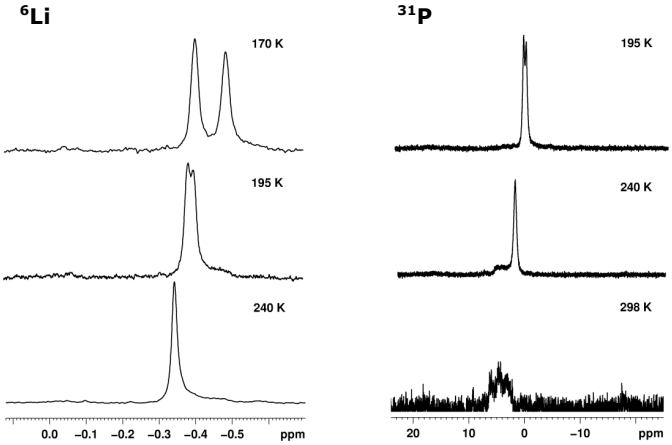


Figure102: ^{6}Li- (left) and ^{31}P- (right) NMR spectra of lithium diphenylphosphide borane **10**-Li with 1.0 equiv of benzaldehyde **249** in THF-d_8 at different temperatures.

Note the shift of the ^{6}Li peaks from –0.81 ppm for **10**-Li to –0.44 ppm ppm for **302**-Li. Such move to higher frequency can suggest a change of the position of

the lithium cation that probably prefers to by next to the oxygen atom, instead of the borane-hydrogens (Figure 103).

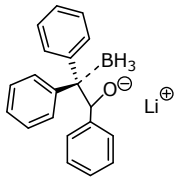


Figure 103

HOESY spectrum at 195 K (Figure 104) evidences a correlation between lithium cation and *ortho* aromatic hydrogen atoms of the phenyl group coming from the benzaldehyde. This observation suggests nearness of lithium and oxygen atom.

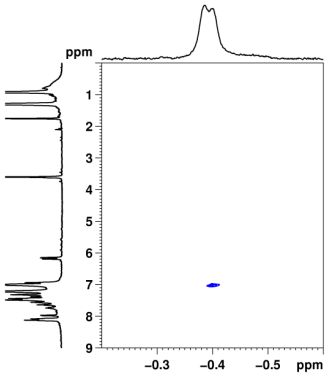


Figure 104: $^{6}Li/^{1}H$ HOESY spectrum of lithium diphenylphosphide borane **10**-Li with 1.0 equiv of benzaldehyde **249** in THF-d_8 at different temperatures.

Otherwise, the ^{11}B-NMR spectrum (Figure 105) obtained at 195 K shows a broad signal at -42.87 ppm. Such chemical shift is actually closer to the one of diphenylphosphine borane **10** than that the one of lithium diphenylphosphide borane **10**-Li. All these observations are consistent with a migration of the lithium cation.

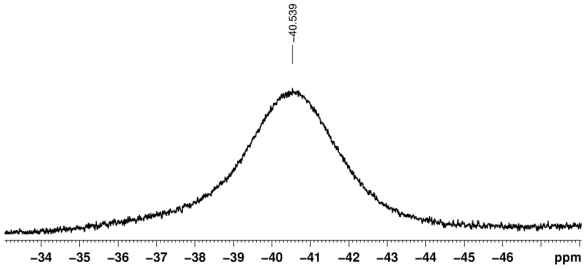


Figure 105: ^{11}B-NMR spectrum of lithium diphenylphosphide borane **10**-Li with 1.0 equiv of benzaldehyde **249** in THF-d_8 at different temperatures.

Trying to bring an interpretation to the two singlets at 6.10 ppm led us notice that **302**-Li has a stereogenic carbon (the hemiphosphinal carbon). Suggesting that this dipolar species homoaggregate as a dimer, the presence of a stereogenic centre should afford four combinations (*RR*, *SS*, *SR* and *RS*), that are distributed in two diastereomeric couples of enantiomers (couple *like* and couple *unlike*, Figure 106). Each singlet would be attributed to one couple.

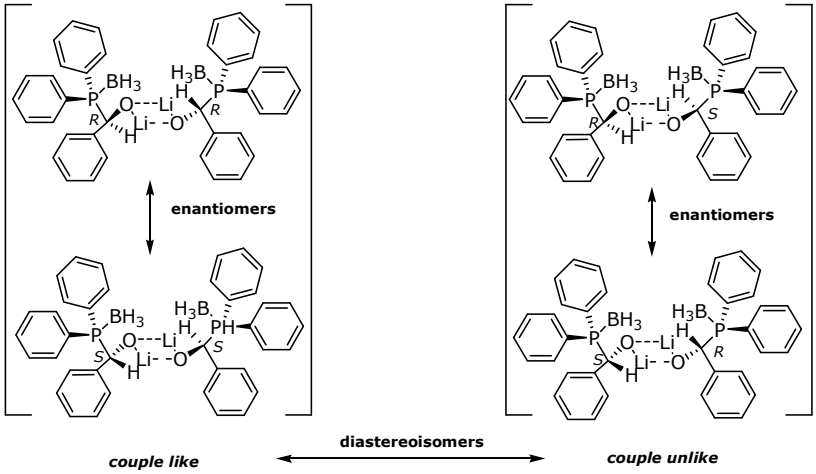
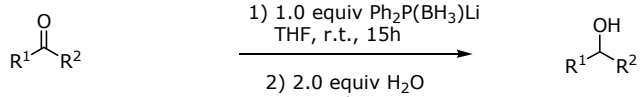


Figure 106

Measurements of diffusion in solution must be done at 195 K to validate or not the proposition above.

10.3. Extension of the reaction to other substrates: ketones

In order to determinate the limits of this reaction, we tried to extend the reaction to other compounds, such as ketones (Scheme 144).



303 **304**

a R^1=Ph, R^2=CH_3
b R^1=CH_3, R^2=*n*-C_2H_5
c R^1=CH_3, R^2=*n*-C_3H_7
d R^1=CH_3, R^2=*n*-C_5H_{11}
e R^1=*n*-C_2H_5, R^2=*n*-C_4H_9

Scheme 144

It is known that ketones are more difficult to reduce than aldehydes. Now, it is also true that lithium aminoborohydrides can reduce these species. Therefore,

we thought that lithium phosphoborohydrides (**10**-Li for example) could behave identically. Thus, various ketones **303** have been subjected to the reaction conditions depicted Scheme 144. Results obtained are gathered Table 38.

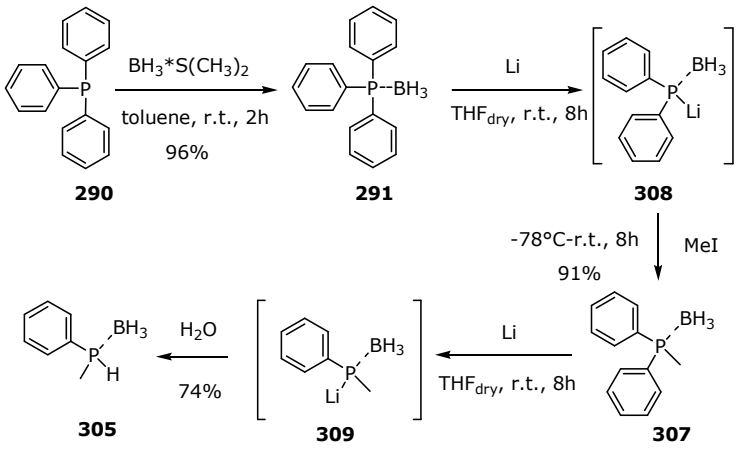
entry	R^1	R^2	time (h)	conversion (%)[a]
1	Ph	H	15	100
2	Ph	Me	15	49
3	Me	*n*-C_2H_5	15	100
4	Me	*n*-C_3H_7	15	97
5	Me	*n*-C_5H_{11}	15	95
6	Me	*n*-C_5H_{11}	22	100
7	Et	*n*-C_4H_9	15	77

Table 38: [(a)] Calculated by ^{1}H-NMR

Unlike benzaldehyde **249**, the reaction is not ended after 15 hours with aromatic (benzophenone **303a**: entry 2) and hindered ketones (3-heptanone **303e**: entry 7). The latters require more long times; 2-heptanone **303d**, for instance, is totally converted to **304d** in 22h. However it is evident that aliphatic substrates are easier to reduce than their aromatic analogues.

10.4. Reduction with other secondary phosphine boranes

Another extension of this project has been to evaluate the reductive properties of other secondary phosphine boranes. Racemic methylphenylphosphine borane **305** and *tert*-butylphenylphosphine borane **306** have been chosen for this study.

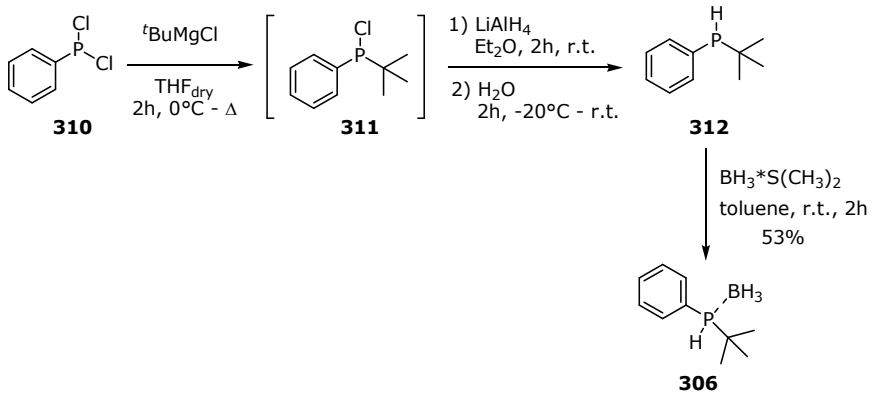


Scheme 145

In the first case the synthesis of the compound (±)-**305** followed an analogue procedure used to prepare diphenylphosphine borane **10**: Le Corre's protocol.

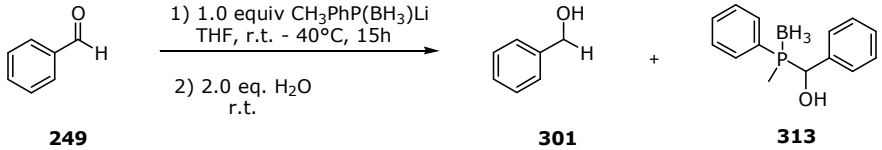
In fact triphenylphosphine **290** was first converted into the borane derivative **291** in a 96% yield by the addition of borane disulfide in toluene at room temperature. Then, the so-obtained diphenylphosphine borane **291** was twice metalated with lithium metal in THF to obtain first methyldiphenylphosphine borane **307**, by addition of MeI to **308**, and, successively, racemic methylphosphine borane **305**, after hydrolysis of **309** (Scheme 145).

(±)-*tert*-Butylphenylphosphine borane **306**, instead, was prepared in 53% overall yield by treatment of $PhPCl_2$ **310** in THF with *tert*-BuMgCl (1.0 equiv, 0 °C-reflux) followed by direct reduction (**311**) of the intermediate chlorophosphine **312** ($LiAlH_4$, freshly distilled Et_2O) and complexation with BH_3SMe_2 (Scheme 146).



Scheme 146

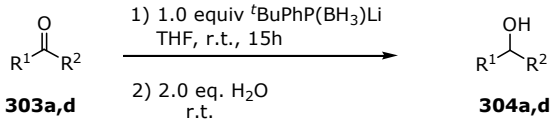
The results, obtained by using the phosphide **305**-Li to reduce benzaldehyde **249** (Scheme 147), evidence a lower reductive power of **305**-Li compared with **10**-Li. After 15 h at room temperature, a 14 : 86 mixture of benzyl alcohol **301** and *α*-hydroxy benzylmethylphosphine borane **313** is obtained, with a 96% overall conversion.



Scheme 147

Working with a bulkier structure, for example *tert*-butylphenylphosphide borane **306**-Li, better results were recorded. In fact this phosphide has been

reacted with unsymmetrical ketones **303** (Scheme 148, Table 39), leading to quantitative conversions when the reaction was conducted to 40° C.



303a,d **304a,d**

Scheme 148

entry	R^1	R^2	temperatures	conversion (%)
1	CH_3	*n*-C_5H_{11}	r.t.	67
2	CH_3	*n*-C_5H_{11}	40° C	100
3	Ph	CH_3	r.t.	34
4	Ph	CH_3	40° C	100

Table 39

In an attempt to increase the final conversion, indeed, two trials were experimented. The first one, at room temperature, occurred partial conversions of reduced product (entries 1 and 3); in second one (at 40° C), instead, quantitative conversions were observed (entries 2 and 4).

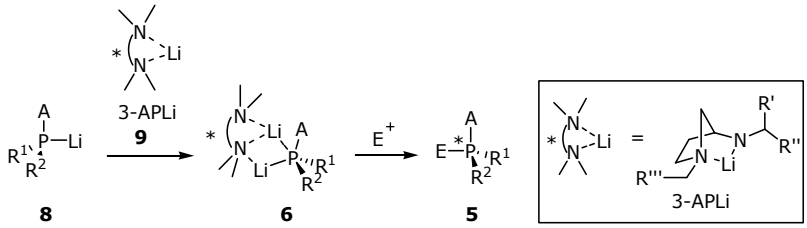
These final results represent an important starting point to exploit the reaction in enantioselective version. In fact the next step will foresee the passage to chiral lithium phosphides, such as the product **306**-Li, in order to verify the possibility to get enantioenriched reduction products.

These experiments are still in progress.

11. CONCLUSIONS OF THE SECOND PART

11.1. Results

This section of the thesis has been devoted to a NMR structural study of lithiated borylphosphines. The idea was born from the collaboration between the University of Caen (Prof. Annie-Claude Gaumont) and the University of Rouen (Dr. Jacques Maddaluno and Prof. Hassan Oulyadi) to develop a new synthetic methodology toward enantioenriched P-stereogenic alkylphosphines (Scheme 149).



Scheme 149

The project consisted in getting enantioenriched P-stereogenic trialkylphosphines borane adducts through the enantioselective alkylation of a mixed aggregated **6**, involving a racemic lithiated phospha-anion **8** and an enantiopure 3-APLi **9**, and an electrophilic alkyl moiety (E^+). A complementary approach by NMR structural studies and theoretical calculations has been planed to analyze the structures of lithium phosphides, such as **8**, and evaluate the configurational and conformational stability of their mixed aggregates with organolithium compounds or lithium amides, in particular of the type **6**.

This work encompasses the first part of this project and corresponds merely to a NMR structural study. It has been divided into three parts:

(a) characterization of the structure of the lithium diphenylphosphide borane **10**-Li in THF;
(b) evaluation of the ability of this lithium phosphide **10**-Li to aggregate with *n*-butyllithium or lithium diisopropylamide;
(c) use of lithium phosphide borane complexes as reducing agents toward carbonyl compounds.

Lithium diphenylphosphide borane **10**-Li has been chosen as model lithium phosphide borane for our NMR study. It has been obtained from diphenylphosphine borane **10** through a metallation with six-labelled-Li *n*-BuLi **292** or six-labelled-Li LDA **296**.

The following multinuclear one- and two-dimensional NMR investigations, carried out at different temperatures, have clearly established that when the base is *n*-BuLi **292**, the structure of **10**-Li is a disolvated monomer with the lithium cation coordinated to the borane (Figure 107).

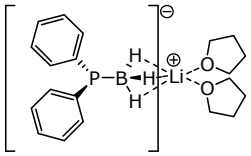


Figure 107

In particular HOESY analysis has pointed out the Li/BH_3 correlation (see Figure 57, chapter 9). The diffusion measurements, carried out through "Williard's methodology",[423] have allowed to determinate the degree of oligomerization (monomer) and the solvating state (disolvation).

Finally, theoretical calculations carried out by Prof. Hélène Gérard (University of Paris VI) have confirmed that the lithium cation can coordinate simultaneously to only two of the three hydrogens of BH_3. A rapid exchange between these three hydrides would take place, affording an average value of their NMR chemical shifts (Figure 108). This hypothesis is in line with the fact that lithium cation tends to form tetra-coordination rather than penta-coordination.[8, 35, 38, 39, 41]

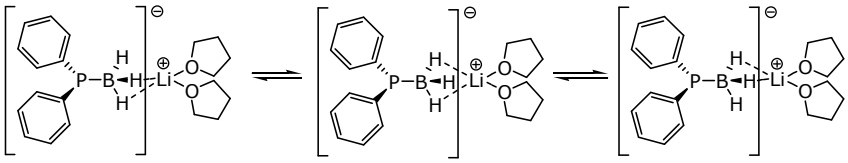


Figure 108

The use of LDA **296** as a base has leads, instead, to the formation of a separated ions pair (Figure 109). This difference could be due to the presence of DIPA, in the reaction mixture, which coordinates the lithium cation and keeps it away from the borane group.

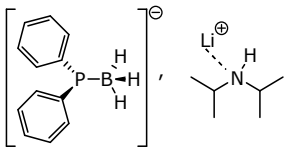


Figure 109

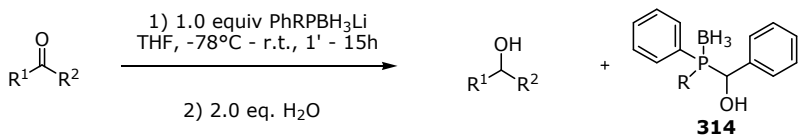
The second step of this work has been centred on the evaluation of the ability of lithium phosphide **10**-Li to aggregate with *n*-butyllithium or lithium diisopropylamide.

Different from the well-known case of lithium amides, the addition of one equivalent of Bu^6Li, or ^6LDA, on lithium phosphide **8** did not lead to the expected $Ph_2P(BH_3)Li$ / *n*-BuLi or $Ph_2P(BH_3)L$ / LDA mixed aggregates. All multinuclear NMR analyses displayed only the signals of non-interacting "free" species. The absence of aggregation could be confirmed by bi-dimensional HOESY and DOSY experiments.

Similarly, lithium di-*iso*-propylamide, retained as a model for the 3-APLi's, does not aggregate with lithium phosphide **8**, jeopardizing the project of enantioselective alkylation of lithium phospha-anion **6** with achiral electrophiles

Finally, the structural analogy between **10**-Li and classical ate-complexes such as $LiBH_4$ or lithium aminoborohydrides led us to determine whether lithium phosphide boranes could behave as reducing agents of carbonyl compounds.

The results are very promising. A set of different lithium borohydrides has been tested on different aldehydes and ketones in diverse reaction conditions (Scheme 150).

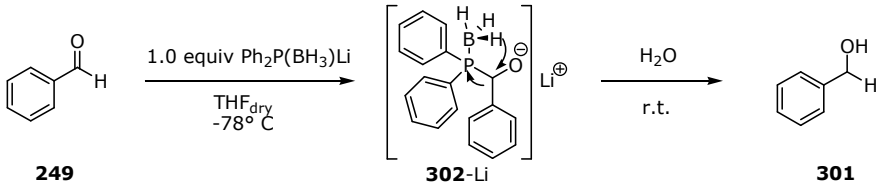


Scheme 150

It has been shown that the reaction occurs well at room temperature in presence of one equivalent of lithium borylphosphide. When the same reaction is carried out at low temperature, the intermediate product of addition of lithium phosphide borane on the carbonyl moiety (**314**) has been identified.

Lithium diphenylphosphide borane **10**-Li has exhibited the best reducing activity, giving access to a series of alcohols in high yields. Lithium methylphosphide borane **305**-Li and lithium *tert*-butylphenylphosphide borane **306**-Li have shown lower reactivity, lithium phosphide **306**-Li behaving better than **305**-Li. In particular, the total reduction of unsymmetrical ketones has been achieved at 40° C in presence of **306**-Li. Both benzaldehyde and different kinds of ketones has been tested to explore the scope of the reactivity of these lithium borohydrides. Benzaldehyde has shown to be the best substrate, while aromatic ketones required longer reaction times to be converted into the corresponding alcohols.

Simultaneously a multinuclear NMR investigation has been carried out in order to understand the mechanism of this reduction. Benzaldehyde **249** and lithium diphenylphosphide borane **10**-Li have been chosen as model system in THF.



Scheme 151

The NMR and the previous experiments have established that i) the reduction process passes through a hemiphosphine intermediate **302**-Li from which the hydride addition follows (Scheme 151); ii) the hemiphosphine **302**-Li is stable at low temperature. However, at room (or higher) temperature a rearrangement takes place that triggers the transfer of an hydride; iii) **302**-Li seems to form a dimer in THF at low temperature (Figure 110).

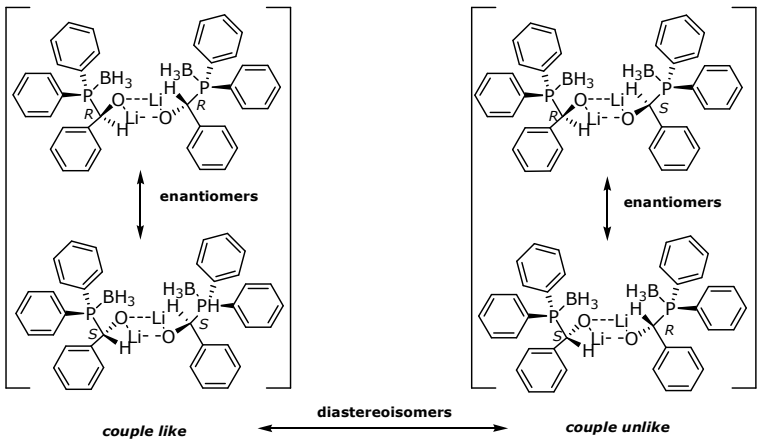


Figure 110

The latter observation derives from a series of mono- and bi-dimensional NMR experiments in particular focused on two singlets at 6.10 ppm on the proton spectrum at 195 K (Figure 111).

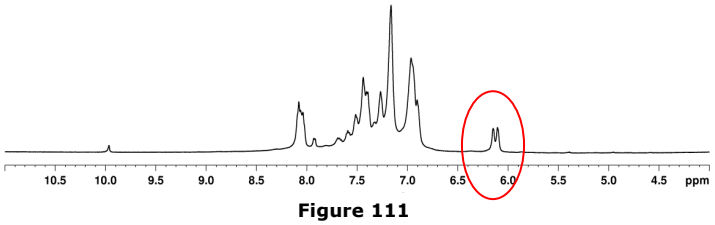


Figure 111

This signal can be analyzed either as a doublet (and thus necessarily assigned to a H-P coupling) or as two singlets. The first hypothesis being ruled out by a $^{1}H\{^{31}P\}$ NMR spectrum, we assume that the two singlets correspond to the presence of two diastereoisomers in a 50:50 ratio. The hemiphosphine **302**-Li bearing only one stereogenic center, only the uncontrolled formation of a homogeneous dimer can justify the observation of two diastereoisomers.

Measurements of diffusion are in progress to (un)validate this hypothesis.

11.2. Perspectives

Future developments of this study will be focused on the spectroscopic and synthetic aspects.

The NMR investigations will be pursued toward the analysis of new lithium phosphides (Figure 112).

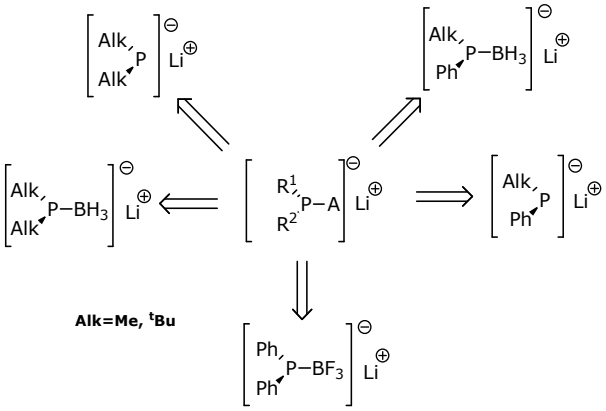
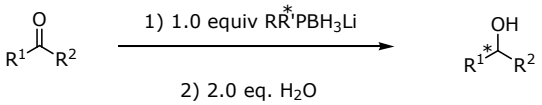


Figure 112

We think worth of efforts to evaluate in particular the particular influence of:

- i) the BH_3 adduct (by analyzing other lithium phosphides free of the borane group or bearing other boranes such as BF_3);
- ii) the "R" substituents (use of alkyl groups);
- iii) the solvent (changing THF with toluene and ether).

The synthetic part could focus on the development of the reduction reaction using lithium phosphide boranes. In particular, an exciting enantioselective version seems at reach of chiral lithium phosphide boranes (Scheme 152).



Scheme 152

Third Part

12. EXPERIMENTAL PART

12.1. Experimental details

12.1.1. Solvent Purification

Tetrahydronfuran was dried by distillation over metallic sodium with benzophenone, as indicator, until the appearance of a persistent deep violet coloration due to the generation of the sodium diphenyl ketyl species *in situ*.[448]
Diethyl ether was anhydrified by means of a distillation over metallic sodium and two additional over $LiAlH_4$ and used freshly-distilled after cooling under nitrogen.

THF-d_8 was anhydrified by distillation over metallic sodium and benzophenone in a mini-distillation apparatus.

Benzene, toluene, xylene, 1,4-dioxane and DME were anhydrified by distillation over metallic sodium and benzophenone, as indicator.

Pentane was dried by distillation over $LiAlH_4$ and used freshly-distilled after cooling under nitrogen.

Pyridine was distilled over CaH_2.

Dichloromethane was distilled over CaH_2 and stored over activated molecular sieves (4 Å).

The molecular sieves 4 Å were activated for 12-24 hours under vacuum at 250° C.

12.1.2. Reagents

All solvents and reagents used in the laboratory were purchased from Sigma-Aldrich, Carlo Erba, Alfa Aesar, CTI, and Janssen. If not otherwise specified, they were used as such, without any treatment.

Potassium *ter*-butoxide was furnished by Janssen or Sigma-Aldrich, stored under nitrogen atmosphere and used after sublimation.

All amines (DIPA, DIPEA, TEA, DBU, TMEDA, PMDTA and HMPA) were purified by distillation over CaH_2 and kept under a nitrogen atmosphere over KOH.

n-Bromobutane was distilled over CaH_2 and used freshly-distilled after cooling under argon.

1,2-Dibromoethane was washed with conc. HCl, then with water, aqueous $NaHCO_3$ solution, dried over $CaCl_2$ and finally distilled over activated molecular sieves 4 Å.

sec-Butanol was anhydrified by distillation over a small amount of metallic sodium.
Benzaldehyde was purified by distillation at reduced pressure after washing with NaOH, Na_2SO_3 sat. solution and H_2O, followed by drying over $MgSO_4$.

Cyclohexanone was purified by distillation over activated molecular sieves 4 Å.
The commercial epoxides were distilled over CaH_2 immediately before use.

Water is distilled water.

12.1.3. Manipulation of Air-Sensitive Compound

All non-aqueous reactions were carried out under nitrogen or argon using oven-dried glassware (120° C for at least 12h). The elimination of air from reaction environment was effected using "Schlenk techniques",[449] which consist of a series of repeated cycles of aspiration under vacuum with a pump and filling ultrapure nitrogen or argon.

Some reactions required an extremely dried atmosphere of inert gas. In these cases nitrogen, or argon, was further dried and deoxygenated by bubbling through a commercial solution of *n*-butyllithium in hexanes (1.6 M).

12.1.4. Titration of Organometallic Products of Lithium

Butyllithium and the other lithiated compounds were periodically titrated with the method of the "double titration of Gilman"[450] or by "titration with a solution of 2-butanol in xylene in presence of 4-phenylbenzylidene, as colorimetric indicator".[436]

12.1.5. Temperatures

The room temperature is indicated as 25° C. The temperature of –78° C was obtained by saturating a bath of ethanol or acetone with dry ice; –23° C by saturating a bath of carbon tetrachloride, while 0° C was reached with ice / water bath.

Intermediate temperatures were achieved through the aid of a cryostat (Neslab ULT-80 model or Bioblock Circulator/Heater, model POLYSTATAT 33, apparatus).

12.1.6. Chromatographic Techniques

Chromatographic analyses were performed on thin layer plates with support in glass or aluminum, stratified with Merck 60 F254s (from 0.25 nm) silica gel. Detection was made by using a UV light at 254 nm or chemical products ($KMnO_4$ basic solution, phosphomolybdic acid reagent 20% *w/v* solution in ethyl alcohol, solutions of ninhydrin, vanilline or *para*-anisaldehyde and iodine crystals). Chromatographic separations were carried out according to the technique of *flash column chromatography*[451] using silica gel 60 Å (400-300 mesh, Merck Kiesegel 60) or Florisil® (100-200 meshes, Janssen Chemistry), where specified, as stationary phase. Eluents are indicated case by case; with the term *petroleum ether* the fraction 40° C - 60° C is meant, if it's not otherwise specified.

12.1.7. Gas-Chromatography

Gas-chromatographic analyses were obtained by using a 5890 Series II Hewlett Packard apparatus, equipped with Agilent HP-5ms capillary GC column (30.0 m length, 0.25 μm thickness, 0.32 mm inside diameter), Ar (10 psi) as carrier gas, FID detector and HP 3395/3396 integrator. The starting temperature was set to 50° C, the final one to 250° C and the ramp was posed to 10°C/min. Unless otherwise indicated, the determination of enantiomeric mixtures was accomplished by Chrompack® Chirasil Dex-CB (30.0 m length, 0.25 μm thickness, 0.25 mm inside diameter) column under isothermic conditions, with Ar (10 psi) as carrier gas, FID detector and HP 3395/3396 integrator.

12.1.8. Mass Spectrometry

Mass spectra were recorded on a SHIMADZU QP5050A apparatus, under electronic impact conditions (EIMS) at 70 eV ionizing potential. This instrument was connected to a SHIMADZU 17° gas chromatograph, equipped with a column Factor FOUR FV-5m (30.0 m length, 0.25 μm thickness, 0.25 mm inside diameter). In some cases mass spectra were recorded after direct injection.

Only the values of the most significant peaks are reported. Every signal is expressed in mass / charge (*m/z*). The abundance peaks in relationship to the basic peak are showed between parenthesis and, in the case of particularly diagnostic signals, a possible interpretation is furnished too.

12.1.9. Spectroscopy of Nuclear Magnetic Resonance

^{1}H-, ^{13}C-, ^{19}F-NMR and ^{31}P-NMR spectra were recorded on a Bruker DPX300 spectrometer operating at 300 MHz, 75 MHz, 282.2 MHz and 121.4 MHz, respectively. Some proton, carbon and fluorine spectra were recorded on a Varian Gemini 200 spectrometer operating at 200 MHz, 50.3 MHz and 188.1 MHz, respectively, or on a Varian Mercury 400 spectrometer operating at 400 MHz (^{1}H) and 100.6 MHz (^{13}C).

The values of chemical shift are expressed in parts-per-million (ppm), according to the *δ*-scale. The values of coupling constants (*J*) are reported in Hz. The abbreviations used (and their meanings) are the followings: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sext (sextet), sep (septet), oct (octet), m (multiplet), br (broadened signal), ps (pseudo signal), app (apparent signal). Multiplets are indicated with intervals of chemical shifts, instead, more complex signals with the average value of frequencies.

The proton or any other heteronucleus, to which a signal has been attributed, are indicated in bold alphabetic character.

When it's not specified, the temperature at which a spectrum was recorded is room temperature.

In all cases chemical shifts were determined relatively to the residual solvent peak of $CHCl_3$ (δ=7.26 ppm for ^{1}H-NMR; δ=77.0 ppm for ^{13}C-NMR), except for the spectra of Mosher's esters[452, 453] in which benzene-d_6 was used as internal reference (δ=7.24 ppm for ^{1}H and δ=128.0 ppm for ^{13}C).

All structural experiments of P-Li's complexes were performed on a Bruker Avance DMX 500 spectrometer, equipped with a z-gradient unit and 5 mm {^{1}H-X} BBI Bruker probe or 5 mm {^{1}H, ^{6}Li, ^{13}C and ^{15}N} quadruple-resonance probe. Measuring frequencies were 500 MHz (^{1}H), 256 MHz (^{11}B), 202 MHz (^{31}P), 125 MHz (^{13}C) and 73 MHz (^{6}Li). ^{1}H and ^{13}C chemical shifts were referenced to the solvent THF-d_8 signals at δ=1.73 ppm and δ=25.37 ppm respectively. Boron-11 spectra and phosphorus-31 NMR spectra were referenced (δ=0.0 ppm) to calculated boron and phosphorus frequencies in BF_3Et_2O and 85% H_3PO_3 references compounds[454] and lithium-6 spectra were referenced to the external 0.30 M ^{6}LiCl solution in THF-d_8 (δ=0.0 ppm).

All one-dimensional data were recorded with standard parameters. To remove ^{13}C-^{1}H and ^{31}P-^{1}H couplings, the one-dimensional ^{13}C- and ^{31}P-NMR spectra were recorded with broad band proton decoupling.

The bi-dimensional measurements are the following:

- *^{1}H/^{1}H-COSY:* 512 experiments with 2048 data points and 16 scans each time;
- *^{1}H/^{13}C-HMQC:* 512 experiments with data points and 16 scans each time;
- *^{1}H/^{1}H-NOESY:* 256 experiments with 2048 data points and 16 scans each time
- *^{6}Li/^{1}H-HOESY:* 256 experiments with 2048 data points and 16 scans each time;
- *^{6}Li/^{6}Li-EXSY:* 256 experiments with 2048 data points and 8 scans each time;
- *^{1}H-DOSY:* The standard Bruker pulse program, ledbpgp2d, employing a double stimulated echo sequence and linear gradient pulses for diffusion, was utilized. Linear gradients were used with total durations 0.5-3.0 ms. Gradient recovery delays was 0.5 ms. Diffusion times were between 100 and 2000 ms. Individual rows of the quasi-2D diffusion databases were phased and baseline corrected.

Processing of NMR data was performed on PC computer, using the manufacturer's program Topspin (Bruker) and the diffusion coefficient was measured by T1/T2 relaxation module.

12.1.10. Optical Rotations

Optical rotations has been performed on a JAS.CO Dip-370 polarimeter, using quartz cells (d=1 dm) with $CHCl_3$ solution and the sodium D line (λ=589 nm); the temperatures and the concentrations are specified case by case. Values are given in units of 10^{-1} deg cm^2 g^{-1} and reported by using the following formula: $[\alpha]_D^T=(\alpha_{obs}/C)*100$.

12.1.11. Elemental Analysis

Elemental analyses were measured on a Perkin Elmer Analyzer 2400 series II CHNS/O instrument.

12.1.12. Microwave Reactions

All microwave irradiation experiments were carried out using a CEM Focused Microwave™ Synthesis System, Model Discover microwave oven equipped with an infrared temperature control system. All microwave reactions were performed in sealed 10 mL microwave vials.

12.1.13. Computational Details

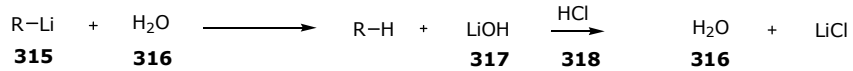
The theoretical study is based in structure optimizations carried out using the Gaussian 09 set of programs. The calculations were carried out within the framework of the density functional theory (DFT) at the B3LYP level, using a 6-31++G** basis set (necessary to properly reproduce the hydride character of the BH_3 hydrogens).

Vibrational frequencies were computed within the harmonic approximation without scaling factors and the thermal contributions to internal energy, enthalpy and free enthalpy were evaluated using the standard procedure implemented in Gaussian. In the following, ΔE refers to B3LYP energy variation (0 K internal energy without zero-point energy corrections) whereas ΔG(T) refers to the thermally corrected free enthalpy.

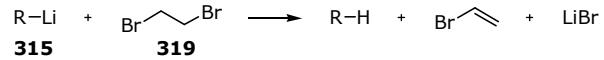
First Part

12.2. Titration of organolithium compounds

12.2.1. Double titration of Gilman[450]



315 **316** **317** **318** **316**

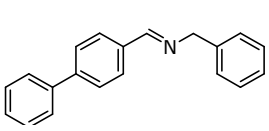


315 **319**

To determine the total content of base, an aliquot (usually from 0.50 to 1.50 ml, depending on the expected concentration) of the solution of the organolithium to be analyzed **315** was quenched with 20.00 ml of water **316**. The resulting solution of LiOH **317** was titrated with a solution of standard hydrochloric acid **318**, using phenolphthalein as indicator, until complete disappearance of the pink colour. To determine the residual content of base of the organolithium, an aliquot (preferably the same amount as before) of the organolithium **315** was reacted with 1,2-dibromoethane **319** as follows (second reaction): 0.20 ml (2.3 mmol, 1.0 equiv) of anhydrous 1,2-dibromoethane **319** were dissolved in 3.00 ml of dry DEE in an inert atmosphere. The organolithium **315** was added dropwise with vigorous stirring. After 5 minutes of stirring, the solution was diluted with 20.00 ml of water and, later on the addition of the indicator, titrated as described above. This procedure destroys the organolithium **315** without producing LiOH **317**, so that the difference of the two titrations gives the exact concentration of the organolithium **315**.

12.2.2. Titration of Duhamel and Plaquevent[436]

12.2.2.1. **4-phenylbenzylidene (320)**



1.00 g Of activated 4 Å molecular sieves and, then, a solution of 4-phenylbenzaldehyde (1.86 g, 10.2 mmol, 1.0 equiv) in 30.00 mL of freshly distilled DCM were introduced in a two-necked round flask, maintained under argon atmosphere. To this mixture 1.20 mL (11.0 mmol, 1.1 equiv) of benzylamine were added dropwise at room temperature. The reaction mixture was kept under stirring for 48 hours. Filtration and elimination of the solvent under vacuum gave 2.47 g of crude product **320**. The following recrystallization (5.00 mL of Et_2O with 15.00 mL of hot pentane, then 16 hours at room temperature) gave a pale yellow solid (1.27 g, 4.7 mmol, 47%, m.p.=62 °C). A second amount of the pure product **320** (0.36 g, 13%, m.p.=55 °C) was derived by removal of the solvent from mother liquors and recrystallization of the residue in 5.00 mL of hexane. The two crops are polymeric forms of the compound **320**, and both

materials were used as colorimetric indicators for titrations of organolithium compounds.

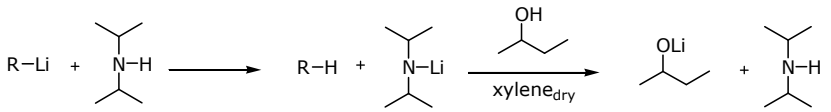
320

$C_{20}H_{17}N$ **M**=217.17

^{1}H-NMR δ ($CDCl_3$, 300 MHz)**:** 8.45 (1H, s, C**H**=$NHCH_2$); 7.88-7.86 (2H, m [AA' part of a AA'BB' spin system], C**H** *ortho* aromatics to CH=$NHCH_2$); 7.68-7.62 (2H, m [BB' part of a AA'BB' spin system and AA' parts of a AA'BB'C spin system], C**H** *meta* aromatics to CH=$NHCH_2$ e *ortho* aromatics to C_6H_4CH=$NHCH_2$); 7.68-7.62 (2H, m [BB' part of a AA'BB'C spin system], C**H** *meta* aromatics to C_6H_4CH=$NHCH_2$); 7.38-7.36 (5H, m, C**H** aromatics to CH_2Ph); 7.30-7.28 (1H, m [C part of a AA'BB'C spin system], C**H** *para* aromatic to C_6H_4CH=$NHCH_2$); 4.86 (2H, s, C**H_2**Ph).

^{13}C-NMR{^{1}H} δ ($CDCl_3$, 75 MHz)**:** 161.6 (**C**H=$NHCH_2$Ph); 143.5 (**C_{ipso}** aromatic to CH_2); 140.4 (**C_{ipso}** aromatic to CH=$NHCH_2$); 139.3 (**C_q** *para* aromatic to CH=$NHCH_2$); 135.1 (**C_{ipso}** aromatic to C_6H_4CH=$NHCH_2$); 128.8 (2C, **C**H *ortho* aromatics to CH=$NHCH_2$); 128.7 (2C, **C**H *meta* aromatics to C_6H_4CH=$NHCH_2$); 128.5 (2C, **C**H *ortho* aromatics to CH_2Ph); 128.0 (2C, **C**H *ortho* aromatics to CH_2Ph); 127.7 (**C**H *para* aromatic to C_6H_4CH=$NHCH_2$); 127.3 (2C, **C**H *meta* aromatics to CH=$NHCH_2$); 127.1 (2C, **C**H *ortho* to aromatics C_6H_4CH=$NHCH_2$); 127 (**C**H *para* aromatic to CH_2Ph); 65.1 (**C**H_2Ph).

12.2.2.2. <u>Titration</u>



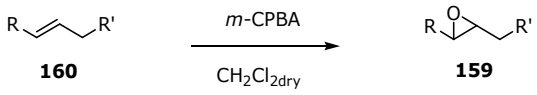
315 **297** **297**

In a round flask, purged and flamed under vacuum and, then, maintained under argon atmosphere, a 0.25 mL aliquot of the solution to be analyzed **315** was added at room temperature to a solution of anhydrous diisopropylamine **297** (0.14 g, an excess) and of *ca.* 8.00-10.00 mg of imine **320** in 1.00 mL of dried THF. The deep blue coloration of the azaallyllithium anion appeared immediately after the addition. The solution was then titrated with a 1.0 M solution of 2-butanol in xylene. The colour turned from blue to red a few drops before the end point, which was reached when the colour changed to pale yellow. In a second determination, a new 0.25 mL aliquot of the solution to be analyzed **315** was added to the previous mixture, and the resulting blue solution was again titrated with a 1.0 M solution of 2-butanol in xylene. The same thing was made for the following titrations. The first titration is not good for the determination of the titration. So at least other two following titrations were done and the average value was taken as titre of the solution.

12.3. Synthesis of Epoxides

12.3.1. Synthesis of *meso*-epoxides with *m*-CPBA

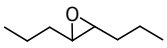
12.3.1.1. *General procedure for the preparation of the alkylepoxides*



160 **159**

m-CPBA (70%, 1.5 equiv) was added portion wise to a solution of the alkene **160** (1.0 equiv) in dichloromethane (0.2 M) cooled to 0° C, in a round flask. The resulting reaction mixture was kept under stirring overnight at room temperature. After NMR check, the reaction was cooled at –20° C in order to facilitate the precipitation of *m*-chlorobenzoic acid, which is formed during the epoxidation. This white solid was filtered on a celite pad and washed with DCM. The filtrate was quenched with a saturated aqueous $Na_2S_2O_3$ solution, in order to eliminate the excess of *m*-CPBA remained, washed with a saturated aq. $NaHCO_3$ solution, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product **159** was used for the next reactions without further purifications.

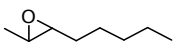
12.3.1.1.1. 2,3-Dipropyloxirane (159a)[455, 456]



Following the general procedure 1.21 g (9.45 mmol, 95%) of the epoxide **159a** were obtained starting from (*E*)-oct-4-ene **160a** (1.60 mL, 10.20 mmol, 1.0 equiv), 70% *m*-CPBA (3.76 g, 15.3 mmol, 1.5 equiv) and 50.00 mL of DCM.

159a
$C_8H_{16}O$ M=128.16
^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 2.70-2.60 (2H, C**H** epoxidic); 1.54-1.38 (8H, C**H_2**C**H_2**CH_3); 0.99-0.91 (6H, CH_2CH_2C**H_3**).
^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 58.4 (2C, **C**H epoxidic); 34.0 (2C, CH**C**$H_2CH_2CH_3$); 19.2 (2C, $CHCH_2$**C**H_2CH_3); 13.7 (2C, $CHCH_2CH_2$**C**H_3).
MS (EI) *m/z*(%)**:** 128 (0.02, M^+); 113 (1, $M^+ - CH_3$); 99 (9, $M^+ - CH_2CH_3$); 85 (6, M^+ – Pr); 81 (7); 72 (55, $CH_2CH(O)CH^+$); 57 (100, $CH_3CH(O)CH^+$); 55 (76, $CCH(O)CH^+$).

12.3.1.1.2. 2-Methyl-3-pentyloxirane (159b)[457]



According to the general procedure (*E*)-oct-2-ene **160b** (1.60 mL, 10.2 mmol, 1.0 equiv), *m*-CPBA (3.69 g, 15.0 mmol. 1.5 equiv) and 50.00 mL of DCM were mixed to give 1.12 g (8.7 mmol, 87%) of the crude product **159b**

159b

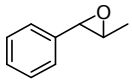
$C_8H_{16}O$ M=128.16

^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 2.74 (1H, qd, *J*=5.2, 2.2, $CH_3C\mathbf{H}$ epoxidic); 2.70-2.59 (1H, m, $C\mathbf{H}CH_2$ epoxidic); 1.58-1.40 (4H, m, $C\mathbf{H_2}C\mathbf{H_2}CH_2CH_2CH_3$); 1.40-1.30 (4H, m, $CH_2CH_2C\mathbf{H_2}C\mathbf{H_2}CH_3$); 1.30 (3H, d, *J*=5.2, $C\mathbf{H_3}CH$); 0.92-0.86 (3H, m, $CH_2CH_2CH_2CH_2C\mathbf{H_3}$).

^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 59.4 ($\mathbf{C}HCH_2$ epoxidic); 54.1 ($CH_3\mathbf{C}H$); 31.7 ($CH_2CH_2\mathbf{C}H_2CH_2CH_3$); 31.4 ($\mathbf{C}H_2CH_2CH_2CH_2CH_3$); 25.4 ($CH_2\mathbf{C}H_2CH_2CH_2CH_3$); 22.3 ($CH_2CH_2CH_2\mathbf{C}H_2CH_3$); 17.4 ($\mathbf{C}H_3CH$); 13.7 ($CH_2CH_2CH_2CH_2\mathbf{C}H_3$).

MS (EI) *m/z*(%)**:** 113 (2, $M^+ - CH_3$); 99 (3, $M^+ - CH_2CH_3$); 85 (21, M^+ – Pr); 83 (13); 82 (13); 71 (21, $CH_3CH(O)CHCH_2^+$); 57 (50, $CH_3CH(O)CH^+$); 56 (100, $CH_3CH(O)C^+$); 55 (61).

12.3.1.1.3. 2-Methyl-3-phenyloxirane (159c)[458, 459]



According to the general procedure 2-methyl-3-phenyloxirane **159c** (1.27 g, 9.4 mmol, 94%) was obtained at beginning from 1-((*E*)-prop-1-enyl)benzene **160c** (1.30 mL, 10.0 mmol, 1.0 equiv) and *m*-CPBA (3.77 g, 15.3 mmol, 1.5 equiv) in 50.00 mL of DCM.

159c

$C_9H_{10}O$ M=134.10

^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 7-40-7.30 (5H m, C**H** aromatics); 3.58 (1H, d, *J*=1.8, C**H** epoxidic); 3.04 (1H, qd, *J*=5.2, 2.2, $C\mathbf{H}CH_3$ epoxidic); 1.46 (3H, d, *J*=5.0, $CHC\mathbf{H_3}$).

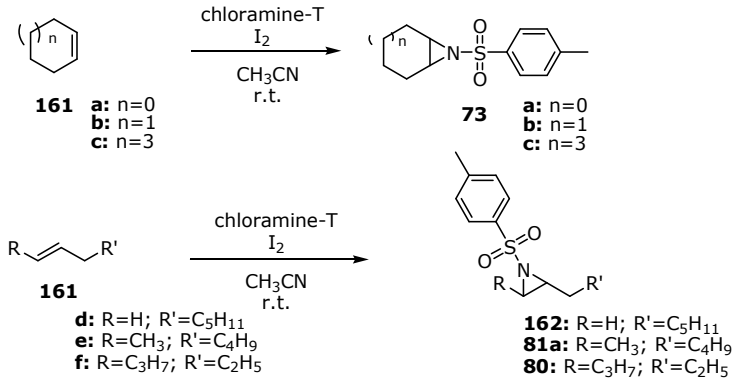
^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 137.5 ($\mathbf{C_{\textit{ipso}}}$ aromatic); 128.2 (2C, **C**H *meta* aromatics); 127.8 (**C**H *para* aromatic); 125.3 (2C, **C**H *ortho* aromatics); 59.3 (**C**H epoxidic); 58.8 (**C**H epoxidic); 17.7 ($\mathbf{C}H_3$).

MS (EI) *m/z*(%)**:** 134 (43, M^+); 133 (49, $M^+ - H$); 119 (8, $M^+ - CH_3$); 105 (46, $M^+ - CH_2CH_3$); 90 (100, $M^+ - OCHCH_3$); 77 (27, $C_7H_7^+$); 63 (27); 51 (38).

12.4. Synthesis of Aziridines

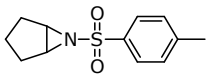
12.4.1. Synthesis of *meso*-aziridines by nitrene transfer on a double C=C bond[233, 460-462]

12.4.1.1. *General procedure for the synthesis of N-para-toluensulfonyl-aziridines from alkenes*



To a stirred solution of chloramine-T (0.5 equiv) and iodine (0.2 equiv) in acetonitrile (0.5 M) in a round flask, the alkene **161**, was added and the resulting mixture was kept for 24h at room temperature. The reaction was monitored by TLC, and when the reaction was finished the solution was diluted in water. The aqueous portion was separated and extracted twice with CH_2Cl_2. The combined organic components were washed twice with H_2O and a saturated aq. NaCl solution, dried over Na_2SO_4, filtered and concentrated. Then the residue was purified through a chromatographic column to give the pure aziridines **73**, **162**, **80** and **81a**.

12.4.1.1.1. 6-(*N*-(*para*-toluensulfonyl))-6-aza-bicyclo[3.1.0]hexane (73a)[106]

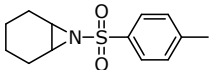


According to the general procedure 2.65 mL (30.0 mmol, 1.0 equiv) of cyclopentene **161a**, 4.64 g (16.5 mmol, 0.5 equiv) of chloramine-T, 1.64 g (6.5 mmol, 0.2 equiv) of I_2 and 60.00 mL of CH_3CN gave, after purification by flash chromatography (silica, eluent: 6:1 petroleum ether/ethyl acetate), 1.71 g (7.2 mmol, 24%) of the pure aziridine **73a**.

73a
$C_{12}H_{15}NO_2S$ **M=**237.15

^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 7.83-7.79 (2H, m [AA' part of a AA'BB' spin system], C**H** *ortho* aromatics SO_2); 7.34-7.30 (2H, m [BB' part of a AA'BB' spin system], C**H** *meta* aromatics to SO_2); 7.34-7.30 (2H, m, [AA' part of a AA'BB' spin system], C**H** *ortho* aromatics to SO_2); 3.33 (2H, br-s_{app}, C**H** aziridinic); 2.44 (3H, s, C$\mathbf{H_3}$ tosyl group); 2.00-1.80 (4H, m, C$\mathbf{H_2}$CH); 1.70-1.50 (2H, m, C$\mathbf{H_2}CH_2$CH).
^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 143.9 (**C_q** *para* aromatic to SO_2); 135.9 (**C_{ipso}** aromatic to SO_2); 129.5 (2C, **C**H *meta* aromatics to SO_2); 127.5 (2C, **C**H *ortho* aromatics to SO_2); 46.7 (2C, **C**H aziridinic); 26.9 (2C, **C**H_2CH); 21.6 (**C**H_3 tosyl group); 19.5 (**C**H_2CH_2CH).
MS (EI) *m/z*(%)**:** 173 (3); 155 (0.3, Ts^+); 144 (0.4); 139 (0.3); 118 (1); 105 (0.3); 91 (12, $C_7H_7^+$); 82 (59, M^+ – Ts); 65 (14); 55 (100).

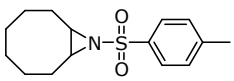
12.4.1.1.2. 7-(*N*-(*para*-toluensulfonyl))-7-aza-bicyclo[4.1.0]heptane (73b)[106]



7-Tosyl-7-aza-bicyclo[4.1.0]heptane **73b** (1.00 g, 4.0 mmol, 20%) was synthesized from 2.05 mL (20.2 mmol, 1.0 equiv) of cyclohexene **161b**, 2.87 g (10.2 mmol, 0.5 equiv) of chloramine-T, 1.07 g (4.2 mmol, 0.2 equiv) of iodine and 40.00 mL of CH_3CN and purified through a flash column chromatography on silica gel (eluent: 10:1 petroleum ether/ethyl acetate).

73b
$C_{13}H_{17}NO_2S$ **M=**251.17
^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 7.83-7.79 (2H, m [AA' part of a AA'BB' spin system], C**H** *ortho* aromatics to SO_2); 7.34-7.30 (2H, m [BB' part of a AA'BB' spin system], C**H** *meta* aromatics to SO_2); 2.97-2.95 (2H, m, $(CH_2CH_2C\mathbf{H})_2$NTs aziridinic); 2.43 (3H, s, C$\mathbf{H_3}$ tosyl group); 1.81-1.75 (4H, m, $(CH_2C\mathbf{H_2}CH)_2$NTs); 1.50-1.20 (4H, m, $(C\mathbf{H_2}CH_2CH)_2$NTs).
^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 143.9 (**C_q** *para* aromatic to SO_2); 135.8 (**C_{ipso}** aromatic to SO_2); 129.5 (2C, **C**H *meta* aromatics to SO_2); 127.5 (2C, **C**H *ortho* aromatics to SO_2); 39.8 (2C, **C**H aziridinic); 22.8 (2C, $(CH_2\mathbf{C}H_2CH)_2$NTs); 21.6 (**C**H_3 tosyl group); 19.4 (2C, $(\mathbf{C}H_2CH_2CH)_2$NTs).
MS (EI) *m/z*(%)**:** 55 (2, Ts^+); 133 (0.4); 106 (1); 96 (100, M^+ – Ts); 91 (24, $C_7H_7^+$); 69 (65); 65 (23); 55 (14).

12.4.1.1.3. 9-(*N*-(*para*-toluensulfonyl))-9-aza-bicyclo[6.1.0]nonane (73c)[106]



As reported in the general procedure, 9-tosyl-9-aza-bicyclo[6.1.0]nonane **73c** (0.89 g, 3.2 mmol, 8%) was obtained from cyclooctene **161c** (5.25 mL, 40.3 mmol, 1.0 equiv), chloramine-T (5.70 g, 20.2 mmol, 0.5 equiv),

iodine (2.11 g, 8.3 mmol, 0.2 equiv) and 80.00 mL of acetonitrile, after purification by flash chromatography (silica, eluent: 5:1 petroleum ether/diethyl ether).

73c

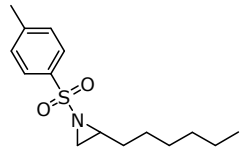
$C_{15}H_{23}NO_2S$ **M=**281.23

^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 7.83-7.79 (2H, m [AA' part of a AA'BB' spin system], C**H** *ortho* aromatics to SO_2); 7.34-7.30 (2H, m [BB' part of a AA'BB' spin system], C**H** *meta* to aromatics SO_2); 2.80-2.75 (2H, m, C**H** aziridinic); 2.44 (3H, s, C**H_3** tosyl group); 2.04-1.97 (2H, m, (CH_2CH_2CH**H'**$CH)_2NTs$); 1.60-1.20 (10H equiv, m, (C**H_2**C**H_2**C**H**H'$CH)_2NTs$).

^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 143.8 (**C** *para* aromatic to SO_2); 135.6 (**C_{ipso}** aromatic to SO_2); 129.4 (2C, **C**H *meta* aromatics to SO_2); 127.3 (2C, **C**H *ortho* aromatics to SO_2); 43.9 (2C, **C**H aziridinic); 26.4 (2C, (CH_2CH_2**C**$H_2CH)_2NTs$); 26.2 (2C, (**C**$H_2CH_2CH_2CH)_2NTs$); 25.2 (2C, (CH_2**C**$H_2CH_2CH)_2NTs$); 21.6 (**C**H_3 tosyl group).

MS (EI) *m/z*(%)**:** 210 (3); 184 (1); 155 (4, Ts^+); 139 (1); 124 (75, M^+ – Ts); 97 (15); 91 (19, $C_7H_7^+$); 65 (12); 55 (100).

12.4.1.1.4. 2-Hexyl-*N*-(*para*-toluensulfonyl)-aziridine (162)[463, 464]



2-Hexyl-*N*-tosylaziridine **162** (2.02 g, 7.2 mmol, 24%) was synthesized, as indicated in the general procedure, from 1-octene **161d** (R=H, R'=C_5H_{11}, 4.70 mL, 30.0 mmol, 1.0 equiv), chloramine-T (4.31 g, 15.3 mmol, 0.5 equiv), I_2 (1.66 g, 6.5 mmol, 0.2 equiv) and 60.00 mL of CH_3CN, and purified by chromatography on silica gel with a 14:1 petroleum ether/ethyl acetate mix as eluent.

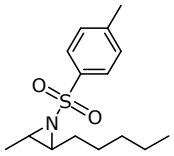
162

^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 7.84-7.80 (2H, m [AA' of a AA'BB' spin system], C**H** *ortho* aromatics to SO_2); 7.35-7.31 (2H, m [BB' of a AA'BB' spin system], C**H** *meta* aromatics to SO_2); 2.75-2.60 (2H, m, C**H_2** aziridinic); 2.44 (3H, s, C**H_3** tosyl group); 2.05 (1H, d, *J*=5.2, C**H** aziridinic); 1.30-1.00 (10H, m, C**H_2** a); 0.87-0.81 (3H, m, C**H_3**).

^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 144.1 (**C** aromatic *para* to SO_2); 134.8 (**C_{ipso}** aromatic to SO_2); 129.3 (2C, **C**H aromatics *meta* to SO_2); 127.7 (2C, **C**H aromatics *ortho* to SO_2); 40.2 (**C**H_2 aziridinic); 33.4 (CH**C**$H_2(CH_2)_4CH_3$); 31.4 ($(CH_2)_3$**C**H_2CH_3); 31.1 ($(CH_2)_2$**C**$H_2(CH_2)_2CH_3$); 28.4 (**C**H aziridinic); 26.5 (CH_2**C**$H_2(CH_2)_3CH_3$); 22.2 ($(CH_2)_4CH_2CH_3$); 21.3 (**C**H_3 tosyl group); 19.1 ($(CH_2)_5$**C**H_3).

MS (EI) *m/z*(%)**:** 282 (0.3, M^+ + 1); 252 (2); 212 (9); 184 (16); 172 (11); 155 (38, Ts^+); 147 (6); 126 (64, M^+ – Ts); 110 (19); 91 (92, $C_7H_7^+$); 65 (41); 56 (54); 55 (100, $CH_2(N)CHCH_2^+$).

12.4.1.1.5. *trans-N*-(*para*-Toluensulfonyl)-2-methyl-3-pentylaziridine (81a)[106, 463]



According to the general procedure, 2-octene **161e** (4.70 mL, 30.1 mmol, 1.0 equiv), chloramine-T (4.31 g, 15.3 mmol, 0.5 equiv), iodine (1,67 g, 6.6 mmol, 0.2 equiv) and acetonitrile (60.00 mL) were mixed to afford, after purification *via* chromatography (silica, eluent: 7:1 petroleum ether/ethyl acetate), 2.53 g (9.0 mmol, 30%) of the pure aziridine **81a**.

81a

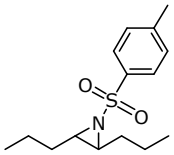
$C_{15}H_{23}NO_2S$ **M=**281.23

^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 7.85-7.81 (2H, m [AA' of a AA'BB' spin system], C**H** *ortho* to aromatics SO_2); 7.32-7.28 (2H, m [BB' of a AA'BB' spin system], C**H** *meta* aromatics to SO_2); 2.74-2.63 (2H, m, C**H** aziridinics); 2.42 (3H, s, C**H$_3$** tosyl group); 1.54 (3H, d, *J*=5.6, C**H$_3$**CH); 1.40-1.00 (8H, m, (C**H$_2$**)$_4$$CH_3$); 0.78-0.84 (3H, m, ($CH_2$)$_4$C**H$_3$**).

^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 143.5 (**C$_q$** *para* aromatic to SO_2); 137.8 (**C$_{ipso}$** to aromatic SO_2); 129.1 (2C, **C**H *meta* aromatics to SO_2); 127.1 (2C, **C**H *ortho* aromatics to SO_2); 49.5 (CH_3**C**H aziridinics); 45.7 (**C**HCH_2 aziridinics); 31.0 (CH**C**H$_2$$CH_2$$CH_2$$CH_2$$CH_3$); 30.2 (CH($CH_2$)$_2$**C**H$_2$$CH_2$$CH_3$); 26.7 ($CHCH_2$**C**H$_2$($CH_2$)$_2$$CH_3$); 22.2 (CH($CH_2$)$_3$**C**H$_2$$CH_3$); 21.3 (**C**H$_3$ tosyl group); 14.6 (**C**H$_3$CH); 13.7 (CH(CH_2)$_4$**C**H$_3$).

MS (EI) *m/z*(%)**:** 282 (0.1, M^+ + 1); 266 (0.3); 252 (0.4); 210 (6); 198 (1); 184 (0.3); 155 (5, Ts^+); 126 (100, M^+ – Ts); 110 (2); 91 (27, $C_7H_7^+$); 83 (15); 56 (54); 55 (65).

12.4.1.1.6. *trans-N*-(*para*-Toluensulfonyl)-2,3-dipropylaziridine (80)[106]



A 4.75 mL aliquot (30.0 mmol, 1.0 equiv) of 4-octene **161f** 4.40 g (15.6 mmol, 0.5 equiv) of chloramine-T, 1.85 g (1.3 mmol, 0.2 equiv) of iodine and 60.00 mL of CH_3CN was reacted, according to the general procedure, to afford, after purification (chromatography on silica gel, eluent: 12:1 petroleum ether/ethyl acetate), 2.45 g (8.7 mmol, 29%) of the pure aziridine **80**.

80

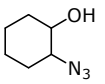
$C_{15}H_{23}NO_2S$ **M=**281.23

^{1}H-NMR δ($CDCl_3$, 200 MHz)**:** 7.84-7.80 (2H, m [AA' of a AA'BB' spin system], C**H** *ortho* aromatics to SO_2); 7.32-7.28 (2H, m [BB' of a AA'BB' spin system], C**H** *meta* aromatics to SO_2); 2.64 (2H, t, *J*=5.2, C**H** aziridinics); 2.42 (3H, s, C**H$_3$** tosyl

group); 1.54 (3H, d, *J*=5.6, C**H**$_3$CH); 1.78-1.50 (4H, m, (C**H**$_2$CH$_2$CH$_3$); 1.50-1.21 (4H, m, C**H**$_2$CH$_2$CH$_3$); 0.94-0.86 (3H, m, (CH$_2$)$_2$C**H**$_3$).
^{13}C-NMR{^{1}H} δ(CDCl$_3$, 50 MHz)**:** 143.5 (**C** aromatic *para* to SO$_2$); 137.7 (**C**$_{ipso}$ aromatic to SO$_2$); 129.1 (2C, **C**H *meta* aromatics to SO$_2$); 127.1 (2C, **C**H *ortho* aromatics to SO$_2$); 49.4 (2C, **C**H aziridinics); 31.7 (2C, CH**C**H$_2$CH$_2$CH$_3$); 21.6 (**C**H$_3$ tosyl group); 20.6 (2C, CHCH$_2$**C**H$_2$CH$_3$); 13.5 (2C, CHCH$_2$CH$_2$**C**H$_3$).
MS (EI) *m/z*(%)**:** 252 (0.1); 238 (1); 155 (3, Ts$^+$); 140 (0.2); 126 (100, M$^+$ - Ts); 98 (1); 91 (20, C$_7$H$_7^+$); 84 (17); 72 (10); 65 (12); 57 (18); 55 (34).

12.4.2. Synthesis of *meso*-*N*-protect-aziridines from cyclohexene oxide

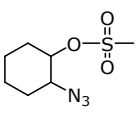
12.4.2.1. 2-Azido-cyclohexanol (164)[106]



A mixture of cyclohexene oxide **163b** (4.05 mL, 40.0 mmol, 1.0 equiv), NaN$_3$ (16.02 g, 246.4 mmol, 6.2 equiv), NH$_4$Cl (4.62 g, 83.3 mmol, 2.1 equiv) in 180.00 mL of 2-methoxyethanol and 25.00 mL of H$_2$O was heated at 80° C for 1h in a two-necked round bottomed flask, equipped with a condenser. After cooling to room temperature, the solution was quenched with water (200.00 mL).The two phases were separated: the aqueous portion was extracted with ether (3 x 50.00 mL) and the combined organic components were washed with H$_2$O (4 x 50.00 mL) and brine (2 x 50.00 mL), dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure to give 5.12 g (36.3 mmol, 91%) of the desired product **164**.

164
C$_6$H$_{11}$N$_3$O **M=**141.11
^{1}H-NMR δ (CDCl$_3$, 200 MHz)**:** 3.50-3.42 (1H, m, C**H**OH); 3.24-3.12 (1H, m, C**H**N$_3$); 2.22 (1H, br-d, *J*=3.0, O**H**); 2.14-1.95 (2H, m, C**H**$_2$CHOH); 1.82-1.70 (2H, m, C**H**$_2$CHN$_3$); 1.45-1.20 (4H, m, C**H**$_2$ γ and δ to OH).
^{13}C-NMR{^{1}H} δ (CDCl$_3$, 50 MHz)**:** 73.1 (**C**HOH); 66.6 (**C**HN$_3$); 33.0 (**C**H$_2$CHOH); 29.7 (**C**H$_2$CHN$_3$); 23.9 (**C**H$_2$CH$_2$CHN$_3$); 23.6 (**C**H$_2$CH$_2$CHOH).
MS (EI) *m/z*(%)**:** 141 (2, M$^+$); 112 (1, M$^+$ – H – N$_2$); 98 (1, M$^+$ – H – N$_3$); 84 (8, M$^+$ + 2 – N$_3$ – OH); 70 (12); 57 (100); 56 (67); 55 (20).

12.4.2.2. 2-Azidocyclohexyl methanesulfonate (165)



3.37 mL (43.6 mmol, 1.2 equiv) of methanesulfonyl chloride was added to a solution of azidoalcohol **164** (5.12 g, 36.3 mmol, 1.0 equiv) in 73.00 mL of anhydrous pyridine in a Schlenk tube, after having completed a series of vacuum / nitrogen cycles, at 0° C and maintained under nitrogen. The resulting reaction mixture was left to stir for 16h at room temperature. Then, after a NMR monitoring, the mixture was diluted

in 80.00 mL of ether, washed with a 20% aq. $CuSO_4$ solution (5 x 50.00 mL), dried over Na_2SO_4, filtered and concentrated under vacuum to afford 6.92 g (31.6 mmol, 87%) of the pure product **165**.

165

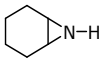
$C_7H_{13}N_3O_3S$ **M=**219.13

^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 4.41-4.29 (1H, m, C**H**OSO_2CH_3); 3.50-3.40 (1H, m, C**H**N_3); 3.11 (3H, s, OSO_2C**H_3**); 2.35-2.40 (1H, m, C**H**H'$CHOSO_2CH_3$); 2.40-2.10 (1H, m, CH**H'**$CHOSO_2CH_3$); 1.90-1.65 (2H, m, C**H_2**CHN_3); 1.65-1.45 (2H, m, C**H_2**$CH_2CHOSO_2CH_3$); 1.20-1.45 (2H, m, C**H_2**CH_2CHN_3).

^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 83.1 (**C**$HOSO_2CH_3$); 62.8 (**C**HN_3); 38.1 (OSO_2**C**H_3); 31.8 (**C**$H_2CHOSO_2CH_3$); 30.1 (**C**H_2CHN_3); 23.1 (**C**$H_2CH_2CHN_3$); 23.0 (**C**$H_2CH_2CHOSO_2CH_3$).

MS (EI) *m/z*(%)**:** 162 (0.1, $M^+ - N_3 + CH_3$); 135 (4); 122 (4); 112 (4); 106 (7); 84 (35, $M^+ - N_3 - OSO_2CH_3 + 2$); 79 (77, $SO_2CH_3^+$); 67 (88), 57 (72, $CH_2CH_2CH_2CH_3^+$); 56 (31,$CH_2CH_2CH_2CH_2^+$); 55 (100, $CH_2CH_2CH_2CH^+$); 54 (77, $CH_2CH_2CH_2C^+$).

12.4.2.3. 7-Azabicyclo[4.1.0]heptane (166)[106, 465, 466]



In a Schlenk tube, 3.60 g (94.8 mmol, 3.0 equiv) of $LiAlH_4$ were added portionwise to a solution of 6.92 g (31.6 mmol, 1.0 equiv) of the mesylate **165** in 65.00 mL of freshly distilled THF at –20° C under nitrogen. After 3h stirring at room temperature, the reaction was over (monitoring *via* TLC: 5:1 petroleum ether/ethyl acetate). The reaction was quenched with careful addition of water and a saturated aqueous NH_4Cl solution at 0° C for a 30' period. After other 30' under stirring the mixture was filtered on a celite pad. The aqueous layer was separated and extracted with DEE (2 x 50.00 mL), while the combined organic portions were washed with brine (1 x 50.00 mL), dried over sodium sulfate, filtered and concentrated to afford 2.45 g (25.3 mmol, 80%) of the product **166**, as a pale yellow oil.

166

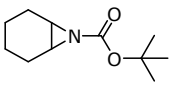
$C_6H_{11}N$ **M=**97.11

^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 2.20-2.10 (2H, C**H**NH); 1.90-1.70 (5H, $(CH_2C$**H_2**$CH)_2NH$ and N**H**); 1.43-1.17 (4H, $(C$**H_2**$CH_2CH)_2NH$).

^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 29.0 (**C**HNH); 24.3 (2C, $(CH_2$**C**$H_2CH)_2NH$); 19.8 (2C, $($**C**$H_2CH_2CH)_2NH$).

MS (EI) *m/z*(%)**:** 97 (2, M^+); 96 (11, $M^+ - H$); 82 (42, $M^+ - NH$); 69 (46, $M^+ -$ CHNH); 68 (100, $M^+ -$ HCHNH); 56 (9); 55 (5); 54 (11).

12.4.2.4. *tert*-Butyl 7-azabicyclo[4.1.0]heptane-7-carboxylate (167a)[106, 467]



In a Schlenk tube, under nitrogen, di-*tert*-butyl dicarbonate (4.77 g, 21.8 mmol, 2.6 equiv) was added to a solution of DMAP (21.8 mmol, 2.6 equiv) and the aziridine **166** (0.82 g, 8.4 mmol, 1.0 equiv) in 17.00 mL of anhydrous DCM at 0° C and under nitrogen flow. After the reaction was completed (50', TLC monitoring: 4:1 petroleum ether/ethyl acetate), the reaction mixture was partitioned between 20.00 mL of DEE and 20.00 mL of a saturated aq. NH_4Cl solution. The two layers were separated and the aqueous portion was extracted with ether (2 x 20.00 mL). The combined organic components were washed once with a saturated aq. $KHSO_4$ solution, a saturated aq. Na_2CO_3 solution and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was, then, purified by flash column chromatography (silica, eluent: 12:1 petroleum ether/ethyl acetate) to afford 0.73 g (3.7 mmol, 44%) of the pure aziridine **167a**.

167a

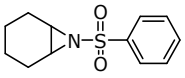
$C_{11}H_{19}NO_2$ **M=**197.19

^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 2.60-2.50 (2H, m, C**H**NCOOC$(CH_3)_3$); 2.00-170 (4H, m, $(CH_2C\mathbf{H_2}CH)_2NCOOC(CH_3)_3$); 1.44 (9H, s, NCOOC(C$\mathbf{H_3}$)$_3$); 1.60-1.20 (2H, m, $(C\mathbf{H_2}CH_2CH)_2NCOOC(CH_3)_3$).

^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 162.9 (**C**OOC$(CH_3)_3$); 80.1 (COO**C**$(CH_3)_3$); 36.6 (2C, **C**HNCOOC$(CH_3)_3$); 27.7 (COOC(**C**$H_3)_3$); 23.5 (2C, $(CH_2\mathbf{C}H_2CH)_2NCOOC(CH_3)_3$); 19.6 (2C, (**C**$H_2CH_2CH)_2NCOOC(CH_3)_3$).

MS (EI) *m/z*(%)**:** 141 (4, M^+ – H – ^{t}Bu); 124 (1, M^+ – O^{t}Bu); 97 (12, M^+ + H – COO^{t}Bu); 96 (13, M^+ – COO^{t}Bu); 82 (21, M^+ – NCOO^{t}Bu); 69 (19); 57 (100, ^{t}Bu$^+$); 55 (7).

12.4.2.5. *N*-Benzenesulfonyl-7-azabicyclo[4.1.0]heptane (167b)[106, 467]



In a Schlenk tube, under nitrogen, TEA (1.76 mL, 12.6 mmol, 1.5 equiv), DMAP (catalytic amount) and benzenesulfonyl choride (1.19 g, 9.3 mmol, 1.1 equiv) were added sequentially to a solution of the aziridine **166** (0.82 g, 8.4 mmol, 1.0 equiv) in 17.00 mL of anhydrous DCM at 0° C and under nitrogen. After one night under stirring at room temperature, the reaction mixture was quenched (TLC monitoring: 3:1 petroleum ether/ethyl acetate) with 17.00 mL of a 1N aq. HCl solution and extracted with DCM (3 x 20.00 mL). The organic portions were combined, washed with a saturated aq. $NaHCO_3$ solution (3 x 20.00 mL) and brine (2 x 20.00 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (eluent: 8:1 petroleum ether/ethyl acetate) to afford 0.68 g (2.9 mmol, 34%) of the pure benzenesulfonylaziridine **167b**.

167b

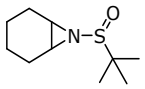
$C_{12}H_{15}NO_2S$ **M=**237.15

^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 7.97-7.92 (2H, m [AA' part of a AA'BB'C spin system], C**H** *ortho* aromatics to SO_2Ph); 7.66-7.49 (3H, m [BB' and C part of a AA'BB'C spin system], C**H** *meta* and *para* aromatics to SO_2Ph); 3.10-3.00 (2H, m, C**H**NSO_2Ph); 1.90-1.70 (4H, m, $(CH_2C\mathbf{H_2}CH)_2NSO_2Ph$); 1.50-1.10 (4H, m, $(C\mathbf{H_2}CH_2CH)_2NSO_2Ph$).

^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 138.5 (**C_{ipso}** aromatic to SO_2Ph); 133.0 (**C**H *para* aromatic to SO_2Ph); 128.7 (2C, **C**H *meta* aromatics to SO_2Ph); 127.2 (2C, **C**H *ortho* aromatics to SO_2Ph); 39.8 (2C, **C**HNSO_2Ph); 22.6 (2C, $(CH_2\mathbf{C}H_2CH)_2NSO_2Ph$); 19.2 (2C, $(\mathbf{C}H_2CH_2CH)_2NSO_2Ph$).

MS (EI) *m/z*(%)**:** 141 (2, SO_2Ph^+); 119 (1); 96 (100, $M^+ - SO_2Ph$); 77 (32, $C_7H_7^+$); 69 (59); 55 (16); 51 (28).

12.4.2.6. 7-(*N*-2-Methylpropan-2-sulfinyl)-7-aza-bicyclo[4.1.0]heptane (168)



In a Schlenk tube, under nitrogen, 12.87 mL (12.8 mmol, 1.5 equiv) of dried TEA, a catalytic amount of DMAP and, after 10', 1.78 mL (9.3 mmol, 1.1 equiv) of *tert*-butylsulfinyl chloride were sequentially added to a precooled (0° C) solution of the aziridine **166** (0.83 g, 8.5 mmol, 1.0 equiv) in 17.00 mL of anhydrous CH_2Cl_2, and the resulting reaction mixture was stirred at room temperature. After the reaction was completed (6h, TLC check: 6:1 petroleum ether/ethyl acetate), 17.00 mL of a 1N aq. HCl solution were added. The acidic phase was separated and extracted with DCM (3 x 30.00 mL); the combined organic components were washed with a saturated aqueous $NaHCO_3$ solution (3 x 30.00 mL) and brine (1 x 50.00 mL), dried over sodium sulfate, filtered and concentrated to afford 1.49 g (7.4 mmol, 87%) of the pure aziridine **168**.

168

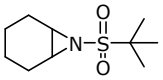
$C_{10}H_{19}NOS$ **M=**201.19

^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 2.88-2.82 (1H, m, C**H**$NSOC(CH_3)_3$); 2.38-2.31 (1H, m, C**H'**$NSOC(CH_3)_3$); 1.75-1.90 (2H, m, $(CH_2C\mathbf{H}H'CH)_2SOC(CH_3)_3$); 1.60-1.20 (6H, m, $(C\mathbf{H_2}CH_2CH)_2NSOC(CH_3)_3$ and $(CH_2CH\mathbf{H'}CH)_2SOC(CH_3)_3$); 1.22 (9H, s, $SOC(C\mathbf{H_3})_3$).

^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 56.2 ($SO\mathbf{C}(CH_3)_3$); 33.1 (1C, **C**H$NSOC(CH_3)_3$); 29.9 (1C', **C**H$NSOC(CH_3)_3$); 23.4 (1C, $(CH_2\mathbf{C}H_2CH)_2NSOC(CH_3)_3$); 23.1 (1C', $(CH_2\mathbf{C}H_2CH)_2NSOC(CH_3)_3$); 22.7 ($SO\mathbf{C}(CH_3)_3$); 20.0 (2C, $(\mathbf{C}H_2CH_2CH)_2NSOC(CH_3)_3$); 19.9 (2C', $(\mathbf{C}H_2CH_2CH)_2NSOC(CH_3)_3$).

MS (EI) *m/z*(%)**:** 202 (0.14, $M^+ + H$); 185 (0.1, M^+ - O); 145 (52, $M^+ + H - {}^t$Bu); 128 (6, $M^+ - O - {}^t$Bu); 97 (22, $M^+ + H - SO{}^t$Bu); 96 (21, $M^+ - SO{}^t$Bu); 82 (66, $M^+ - NSO{}^t$Bu); 81 (92, $M^+ - H - SO{}^t$Bu); 67 (59); 57 (100, ^{t}Bu$^+$); 54 (25).

12.4.2.7. 7-(*tert*-Butyl-sulfonyl)-7-azabicyclo[4.1.0]heptane (167c)[468-470]



In a Schlenk tube, under nitrogen, 2.01 g (8.1 mmol, 1.1 equiv) of 70% *m*-CPBA were added to a solution of the aziridine **168** (1.49 g, 7.4 mmol, 1.0 equiv) in dried DCM (40.50 mL). The resulting reaction mixture was kept under stirring for 24h at room temperature before it was treated with 40.00 mL of a saturated aqueous $Na_2S_2O_3$ solution. Then the quenched mixture was cooled to –20° C and the resulting white precipitate was filtered on celite pad and washed with DCM. The filtrate was worked separating the two phases: the aqueous one was extracted with DCM (2 x 20.00 mL), the combined organic portions were washed with a saturated aq. $NaHCO_3$ solution (2 x 30.00 mL) and with a saturated aqueous NaCl solution, filtered and concentrated. The crude product (1.33 g) was, then, purified by flash column chromatography on silica gel with a 10:1 petroleum ether/ethyl acetate mix as eluent to give 0.53 g (2.4 mmol, 33%) of the pure product **167c**.

167c

$C_{10}H_{19}NO_2S$ **M=**217.19

^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 2.90-2.95 (2H, m, C**H**$NSO_2C(CH_3)_3$); 1.82-1.90 (4H, m, $(CH_2C\mathbf{H_2}CH)_2NSO_2C(CH_3)_3$); 1.60-1.16 (4H, m, $(C\mathbf{H_2}CH_2CH)_2NSO_2C(CH_3)_3$); 1.47 (9H, s, $SO_2C(C\mathbf{H_3})_3$).

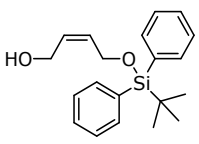
^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 58.2 ($SO_2\mathbf{C}CH_3$); 38.7 (2C, $\mathbf{C}HNSO_2C(CH_3)_3$); 23.7 ($SO_2C\mathbf{C}H_3$); 22.6 (2C, $(CH_2\mathbf{C}H_2CH)_2NSO_2C(CH_3)_3$); 19.2 (2C, $(\mathbf{C}H_2CH_2CH)_2NSO_2C(CH_3)_3$).

MS (EI) *m/z*(%)**:** 218 (0.1, M^+ + H); 161 (0.3, M^+ – ^{t}Bu + H); 138 (3); 96 (100, M^+ – $SO_2{}^t$Bu); 82 (47, M^+ – $NSO_2{}^t$Bu); 69 (88); 57 (97, ^{t}Bu$^+$); 55 (22).

12.5. Synthesis of Aziridinyl Ethers

12.5.1. Synthesis of (2*S*,3*R*)-2-[(*tert*-butyldiphenylsilyl)oxy]methyl-3-(methoxymethoxy)methyl-*N*-(*para*-toluensulfonyl)-aziridine **100** and its derivatives

12.5.1.1. (*Z*)-4-[(*tert*-Butyldiphenylsilyl)oxy]-but-2-en-1-ol (102)[105, 471, 472]



In a three-necked round bottomed flask, equipped with a bubble condenser and maintained under nitrogen, 30.00 mL (1.6 M solution in hexanes, 45.0 mmol, 1.0 equiv) of BuLi were carefully added dropwise to a solution of (*Z*)-2-buten-1,4-diol **101** (3.70 mL, 45.0 mmol, 1.0 equiv) in 90.00 mL of freshly distilled THF at –78° C. After 20', 11.70 mL (45.0 mmol, 1.0 equiv) of TBDPSCl were introduced and the resulting colourless reaction mixture was stirred

at room temperature for 1h and at reflux for the next 16h. After cooling to room temperature the mixture was diluted in 50.00 mL of ether and quenched with water. The aqueous phase was separated and extracted with DEE (3 x 30.00 mL). The combined organic components were washed with H_2O (2 x 30.00 mL) and brine (2 x 30.00 mL), dried over Na_2SO_4, filtered and concentrated under reduce pressure to afford 14.70 g (45.0 mmol, 100%) of the monosilylated allylic alcohol **102**, which was used for the next reaction without further purifications.

102

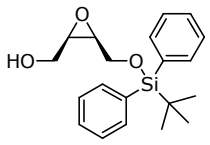
$C_{20}H_{26}O_2Si$ **M=**326.26

^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 7.72-7.68 (4H, m [AA' part of a AA'BB'C spin system], C**H** *ortho* aromatics to Si); 7.45-7.37 (6H, m, [BB' and C parts of a AA'BB'C spin system], C**H** *meta* and *para* aromatics to Si); 5.78-5.58 (2H, m, C**H** olefinic); 4.27 (2H, br-d, *J*=5.2, C**H_2**OSi$Ph_2{}^t$Bu); 4.01 (2H, bd, *J*=5.4, C**H_2**OH); 1.06 (9H, s, C(C**H_3**)$_3$).

^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 135.3 (4C, **C**H *ortho* aromatics to Si); 133.1 (**C_{ipso}** aromatic to Si); 130.3 (**C**HCH_2OH olefinic); 129.8 (**C**HCH_2OSi olefinic); 129.5 (2C, **C**H *para* aromatics to Si); 127.5 (4C, **C**H *meta* aromatics to Si); 60.0 (CH**C**H_2OH); 58.1 (CH**C**H_2OSi); 26.6 (3C, $SiPh_2C(\mathbf{C}H_3)_3$); 18.9 ($SiPh_2\mathbf{C}(CH_3)_3$).

MS (EI) *m/z*(%)**:** 269 (6, M^+ - ^{t}Bu); 251 (1); 223 (2); 199 (100, $SiPh_2OH^+$); 191 (4); 181 (8); 167 (5); 139 (22); 121 (6, $OSiPh^+$); 105 (5, $SiPh^+$); 91 (4, $C_7H_7^+$); 77 (14, $C_6H_5^+$); 57 (4, ^{t}Bu$^+$); 55 (1).

12.5.1.2. [(2*R*,3*S*)-3-[(*tert*-Butyldiphenylsilyl]oxy)methyl–oxyranyl]-methanol (103)[473, 474]



2.56 mL (8.8 mmol, 0.25 equiv) Of $Ti(OiPr)_4$, 1.80 mL (10.5 mmol, 0.30 equiv) of (–)-D-DET and 13.00 mL (71.5 mmol, 2.0 equiv, 5.5 M solution in decane) of TBHP were added to a suspension of 1.00 g of powdered activated 4 Å molecular sieves in 120.00 mL of anhydrous DCM precooled to –20° C and placed in a Schlenk tube under nitrogen. After 30' a solution of allylic alcohol **102** (14.70 g, 45.0 mmol, 1.0 equiv) in 30.00 mL of dried DCM was added and the resulting reaction mixture was stirred for 12h at –20° C. After TLC monitoring (5:1 petroleum ether/ethyl acetate) the mixture was poured into a precooled (0° C) solution of $FeSO_4{\cdot}7H_2O$ (15.0 g, 54.0 mmol, 1.2 equiv) and tartaric acid (4.00 g, 27.0 mmol, 0.6 equiv) in 45.00 mL of water. The two phases were separated and the aqueous one was extracted with ether (2 x 30.00 mL). The combined organic components were kept under stirring with a 30% (*w*/*v*) aq. NaOH solution for 1h at 0° C, then diluted with water (40.00 mL). The two layers were separated and extracted with DEE (2 x 30.00 mL). The combined organic portions were washed with brine (2 x 30.00 mL), dried over $NaSO_4$, filtered and concentrated under reduced pressure to afford 20.00 g of the crude product **103**. An analytical

sample was purified through flash chromatography (340.00 mg, silica, eluent: 5:1 petroleum ether/ethyl acetate) giving 190.10 mg (0.56 mmol, 73%) of the pure epoxyalcohol **103**.

103

$C_{20}H_{26}O_3Si$ **M=**342.26

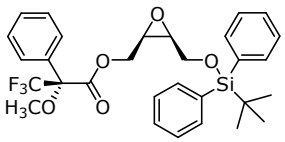
^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 7.70-7.65 (4H, m [AA' part of a AA'BB'C spin system], C**H** *ortho* aromatics to Si); 7.46-7.38 (6H, m, [BB' and C parts of a AA'BB'C spin system], C**H** *meta* and *para* aromatics to Si); 3.95-3.87 (1H, m, C**H**H'OH); 3.78-3.64 (3H, m, C**H$_2$**OSi and CH**H'**OH); 3.28-3.17 (2H, m, C**H** epoxidics); 1.88 (1H, t, *J*=6.6, CH_2O**H**); 1.06 (9H, s, C(C**H$_3$**)$_3$).

^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 135.4 (4C, **C**H *ortho* aromatics to Si); 132.7 (**C$_{ipso}$** aromatic to Si); 129.9 (2C, **C**H *para* aromatics to Si); 127.7 (4C, **C**H *meta* aromatics to Si); 62.2 (CH**C**H_2OSi); 60.7 (CH**C**H_2OH); 56.4 (**C**H epoxidic); 56.2 (**C**H epoxidic); 26.7 (3C, $SiPh_2C$(**C**H_3)$_3$); 19.2 ($SiPh_2$**C**$(CH_3)_3$).

MS (EI) *m/z*(%)**:** 281 (0.4); 267 (1, M^+ – ^{t}Bu – H_2O); 255 (1, $OSiPh_2{}^t$Bu); 241 (36); 223 (30); 207 (27); 199 (81, $SiPh_2OH^+$); 183 (24); 181 (35); 163 (100); 139 (17); 121 (10, $OSiPh^+$); 105 (26, $SiPh^+$); 91 (13, $C_7H_7^+$); 77 (26, $C_6H_5^+$); 57 (9, ^{t}Bu$^+$).

[α]$_D^{24}$=+9.26 (c=1.22, $CHCl_3$).

12.5.1.3. 3,3,3-Trifluoro-2-methoxy-2-phenyl-propionic acid (2*R*,3*S*)-3-[(*tert*-butyldiphenylsilyl)oxy]-oxiranylmethyl ester (317)



In a Schlenk tube, under nitrogen, (*S*)-(+)-MTPCl (25.00 µL, 0.13 mmol,1.3 equiv) was added to a solution of [(2*R*,3*S*)-3-([(*tert*-butyldiphenylsilyl]oxy)-methyl–oxyranyl]-methanol **103** (43.20 mg, 0.09 mmol, 1.0 equiv) in 0.20 mL of CCl_4 and 0.20 mL of pyridine. The resulting reaction mixture was stirred for 12 at room temperature under nitrogen. Then it was diluted with H_2O and ether. The aqueous layer was extracted with Et_2O and the organic combined portions were washed once with a 5% aqueous HCl solution, a saturated aq. $NaHCO_3$ solution and brine and dried over sodium sulfate. After evaporation of the solvent, a pale yellow oil, corresponding to the Mosher's ester **317** (46.20 mg, 0.08 mmol, 87%), was obtained.

317

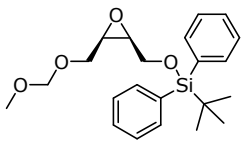
$C_{30}H_{33}O_5F_3Si$ **M=**558.33

^{1}H-NMR δ (C_6D_6, 200 MHz)**:** 7.72-7.36 (15H, m, C**H** aromatics Ph); 4.50-4.20 (2H, m, C**H$_2$**OCO); 3.96-3.62 (2H, m, C**H$_2$**OSi); 3.55 (3H, br-s, OC**H$_3$**); 3.32-3.18 (2H, m, C**H** epoxidics); 1.07 (9H, s, C(C**H$_3$**)$_3$).

^{19}F-NMR δ (C_6D_6, 188 MHz)**:** –71.7 (3F, s, CF_3 minor); –71.8 (3F, s, CF_3 major).

d.r.: 87%

12.5.1.4. (((2*S*,3*R*)-3-((Methoxymethoxy)-methyl)-oxiran-2-yl)-methoxy)-(*tert*-butyl)-diphenylsilane (104)



At 0° C 15.00 mL (86.1 mmol, 1.9 equiv) of di-*iso*-propylethylamine were added to a solution of the epoxyalcohol **103** (45.0 mmol, 1.0 equiv) in 90.00 mL of anhydrous DCM at 0° C, placed in a Schlenk tube, under magnetic stirring. After 30', 5.60 mL (68.6 mmol, 1.5 equiv) of methoxymethyl bromide were injected with a Hamilton syringe and the resulting reaction mixture was allowed to warm to room temperature. After completion (TLC check: 5:1 petroleum ether / ethyl acetate), it was poured in 90.00 mL of a 1N aq. HCl solution. The two phases were separated: the acidic portion was extracted with dichloromethane (3 x 30.00 mL) and the combined organic components were washed with a saturated aqueous $NaHCO_3$ solution (2 x 30.00 mL) and brine (2 x 300.00 mL), dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was, then, purified by flash chromatography (silica, eluent: 7:1 petroleum ether/ethyl acetate), from which 13.96 g (36.1 mmol, 80%, calculated on two reactions: epoxidation and further alkylation of alcoholic moiety) were obtained as a pale yellow oil.

104

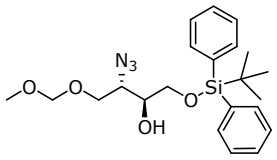
$C_{22}H_{30}O_4Si$ **M=**386.30

^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 7.70-7.66 (4H, m [AA' part of a AA'BB'C spin system], C**H** *ortho* aromatics to Si); 7.46-7.38 (6H, m, [BB' and C parts of a AA'BB'C spin system], C**H** *meta* and *para* aromatics to Si); 4.60 (2H, s, $CH_3OC\mathbf{H_2}O$); 3.80-3.77 (2H, m, $C\mathbf{H_2}OMOM$); 3.65-3.58 (1H, m, C**H**H'OH); 3.50-3.41 (1H, m, CH**H'**OH); 3.31 (1H, s, $C\mathbf{H_3}OCH_2O$); 3.26-3.17 (2H, m, C**H** epoxidics); 1.06 (9H, s, $C(C\mathbf{H_3})_3$).

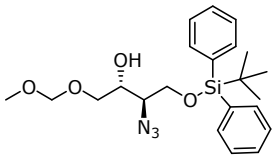
^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 135.4 (4C, **C**H *ortho* aromatics to Si); 133.0 (1C, $\mathbf{C_{ipso}}$ aromatic to Si); 132.7 (1C', $\mathbf{C_{ipso}}$ aromatic to Si); 129.7 (2C, **C**H *para* aromatics to Si); 127.6 (4C, **C**H *meta* aromatics to Si); 96.3 ($CH_3OC\mathbf{H_2}O$); 65.6 ($CH\mathbf{C}H_2OMOM$); 62.1 ($CH\mathbf{C}H_2OSi$); 56.0 (**C**H epoxidic); 55.2 ($C\mathbf{H_3}OCH_2O$); 54.7 (**C**H epoxidic); 26.7 (3C, $SiPh_2C(\mathbf{C}H_3)_3$); 19.1 ($SiPh_2\mathbf{C}(CH_3)_3$).

MS (EI) *m/z*(%)**:** 297 (3); 267 (10); 255 (2, $OSiPh_2{}^tBu$); 241 (7); 225 (6); 223 (9); 213 (34); 207 (9); 199 (11, $SiPh_2OH^+$); 183 (18); 181 (12); 163 (36); 153 (6); 135 (14); 121 (5, $OSiPh^+$); 115 (9); 105 (15, $SiPh^+$); 91 (100, $C_7H_7^+$); 77 (11, $C_6H_5^+$); 59 (10); 57 (10, $^tBu^+$).

12.5.1.5. (2*S*,3*S*)-3-Azido-4-(*tert*-butyl-diphenyl-silanyloxy)-1-methoxy methyl-butan-2-ol (105) (2*R*,3*R*)-2-Azido-4-(*tert*-butyl-diphenyl-silanyloxy)-1-methoxy methyl-butan-3-ol (105)



(2*S*,3*S*)



(2*R*,3*R*)

A mixture of 13.96 g (36.1 mmol, 1.0 equiv) of the epoxyether **104**, 13.94 g (214.4 mmol, 5.9 eq) of NaN_3 and 4.08 g (76.3 mmol, 2.0 equiv) of NH_4Cl in 160.00 mL of a 8:1 2-methoxyethanol / water mix was heated at reflux for 16h in a 500 mL two-necked round bottomed flask, equipped with a bubble condenser. After cooling to room temperature, the reaction mixture was diluted in 100.00 mL of ether and 100.00 mL of H_2O. The aqueous layer was separated and extracted several times with ether. The organic layers were combined, washed with water (5 x 30.00 mL) and a saturated aq. NaCl solution (2 x 30.00 mL), dried over sodium sulfate, filtered and concentrated *in vacuo* to afford 15.05 g (35.1 mmol, 97%) of pure **105**, as a 53:47 mixture of two regioisomers **105 (2*S*,3*S*)** and **105 (2*R*,3*R*)**. An analytical amount of this crude product **105** (131.00 mg) was purified *via* flash column chromatography on silica gel with a 5:1 petroleum ether/ethyl acetate mix, as eluent, giving 87.20 mg (0.20 mmol) of the regioisomer **105 (2*S*,3*S*)** and 26.30 mg (0.06 mmol) of the regioisomers **105 (2*R*,3*R*)**.

105 (2*S*,3*S*)

$C_{22}H_{31}N_3O_4Si$ **M=**429.31

^{1}H-NMR δ ($CDCl_3$, 400 MHz)**:** 7.69-7.65 (4H, m [AA' part of a AA'BB'C spin system], C**H** *ortho* aromatics to Si); 7.46-7.38 (6H, m, [BB' and C parts of a AA'BB'C spin system], C**H** *meta* and *para* aromatics to Si); 4.66-4-64 (2H, m [AB spin system], $CH_3OC\mathbf{H_2}O$); 3.88-3.70 (6H, m, C$\mathbf{H_2}$OMOM, C**H**OH, C**H**N_3 and C$\mathbf{H_2}$OSi); 2.42 (1H, br-s, CHO**H**); 1.08 (9H, s, C(C$\mathbf{H_3}$)$_3$).

^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 135.4 (4C, **C**H *ortho* aromatics to Si); 132.7 (**C_{ipso}** aromatic to Si); 129.8 (2C, **C**H *para* aromatics to Si); 127.7 (4C, **C**H *meta* aromatics to Si); 96.6 ($CH_3OC\mathbf{H_2}O$); 71.6 (**C**HOH); 68.0 (**C**H_2CHOH); 64.5 (**C**H_2CHN_3); 61.9 (**C**HN_3); 26.8 (3C, $SiPh_2C(\mathbf{C}H_3)_3$); 19.2 ($SiPh_2\mathbf{C}(CH_3)_3$).

MS (EI) *m/z*(%)**:** 207 (6); 240 (45); 200 (23); 199 (100, $SiPh_2OH^+$); 181 (6); 163 (2); 77 (16, $C_6H_5^+$); 51 (2).

$[\alpha]_D^{21}$=+11.91 (c=1.88, $CHCl_3$).

105 (2*R*,3*R*)

$C_{22}H_{31}N_3O_4Si$ **M=**429.31

^{1}H-NMR δ ($CDCl_3$, 400 MHz)**:** 7.70-7.67 (4H, m [AA' part of a AA'BB'C spin system], C**H** *ortho* aromatics to Si); 7.47-7.39 (6H, m, [BB' and C parts of a

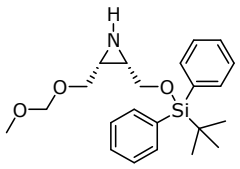
AA'BB'C spin system], C**H** *meta* and *para* aromatics to Si); 4.62 (2H, s, $CH_3OC\mathbf{H_2}O$); 3.94-3.78 (3H, m, $C\mathbf{H_2}$OMOM and C**H**OH); 3.64 (1H, dd, *J*=10.4, 4.4, C**H**H'OSi); 3.59-3.55 (3H, m, CH**H'**OSi and C**H**N_3); 3.34 (1H, s, $C\mathbf{H_3}OCH_2O$); 2.62 (1H, br-s, CHO**H**); 1.08 (9H, s, $C(C\mathbf{H_3})_3$).

^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 135.5 (4C, **C**H *ortho* aromatics to Si); 132.6 (**C_{ipso}** aromatic to Si); 129.7 (2C, **C**H *para* aromatics to Si); 127.8 (4C, **C**H *meta* aromatics to Si); 97.0 ($CH_3OC\mathbf{H_2}O$); 70.1 (**C**HOH); 69.7 (**C**H_2CHOH); 64.6 (**C**H_2CHN_3); 64.3 (**C**HN_3); 26.7 (3C, $SiPh_2C(\mathbf{C}H_3)_3$); 19.1 ($SiPh_2\mathbf{C}(CH_3)_3$).

MS (EI) *m/z*(%)**:** 282 (100); 240 (45); 199 (67, $SiPh_2OH^+$); 177 (26); 162 (73); 135 (46); 121 (13, $OSiPh^+$); 105 (14, $SiPh^+$); 91 (14, $C_7H_7^+$); 77 (37, $C_6H_5^+$); 57 (28, $^tBu^+$).

$[\alpha]_D^{22}$=-12.51 (c= 1.02, $CHCl_3$).

12.5.1.6. (2*S*,3*R*)-2-[(*tert*-Butyldiphenylsiyl)oxy]methyl-3-(methoxy-methoxy)methyl-aziridine (106)



In a two-necked round bottomed flask, equipped with a bubble condenser and under nitrogen, 9.04 g (34.5 mmol, 1.1 equiv) of triphenylphosphine were added portionwise to a solution of the **(2*S*,3*S*)** and **(2*R*,3*R*)** azido-alcohols mix **105** (14.62 g, 34.1 mmol, 1.0 equiv) in 140.00 mL of dried DMF at 0° C. The resulting reaction mixture was stirred for 1h at 0° C; then for other 2h at room temperature and for the next 6h at reflux. After TLC monitoring (3:1 petroleum ether/ethyl acetate), which showed the total disappearance of the starting material, the reaction mixture was cooled at 0° C and, then, diluted in ether and quenched with 140.00 mL of water. The aqueous phase was separated and extracted with ether (5 x 30.00 mL), and the organic portions were combined, washed with water (5 x 30.00 mL) and brine (2 x 30.00 mL), dried over sodium sulfate, filtered and concentrated *in vacuo* to afford 17.97 g of a white solid corresponding on a mixture of the aziridine **106** together with triphenylphosphine and triphenylphosphinoxide, which was used for the next reaction without further purifications.

106

$C_{22}H_{31}NO_3Si$ **M=**385.31

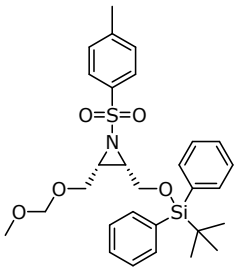
^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 7.70-7.38 (10H, m, C**H** aromatics); 4.61 (2H, s, $CH_3OC\mathbf{H_2}O$); 3.83-3.36 (4H, m, $C\mathbf{H_2}$OMOM and $C\mathbf{H_2}$OSi); 3.32 (1H, s, $C\mathbf{H_3}OCH_2O$); 2.40-2.30 (2H, m, C**H** aziridinics); 1.06 (9H, s, $C(C\mathbf{H_3})_3$).

^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 135.3-127.2 (12C, **C_q** and **C**H aromatics); 96.2 ($CH_3O\mathbf{C}H_2O$); 66.9 ($CH\mathbf{C}H_2OMOM$); 63.4 ($CH\mathbf{C}H_2OSi$); 55.0 ($\mathbf{C}H_3OCH_2O$); 34.9 (**C**H aziridinic); 33.1 (**C**H aziridinic); 26.7 (3C, $SiPh_2C(\mathbf{C}H_3)_3$); 19.0 ($SiPh_2\mathbf{C}(CH_3)_3$).

MS (EI) *m/z*(%)**:** 328 (11); 310 (3); 296 (43); 284 (5); 266 (28); 254 (16, $OSiPh_2{}^tBu$); 250 (67); 240 (31); 225 (24); 213 (64); 206 (25); 199 (100,

$SiPh_2OH^+$); 183 (62); 181 (40); 162 (83); 153 (42); 139 (38); 135 (37); 121 (18, $OSiPh^+$); 105 (31, $SiPh^+$); 91 (55, $C_7H_7^+$); 77 (36, $C_6H_5^+$); 72 (57); 69 (53); 68 (53); 57 (19, $^tBu^+$).

12.5.1.7. (2*S*,3*R*)-2-[(*tert*-Butyldiphenylsilyl)oxy]methyl-3-(methoxy-methoxy) methyl-*N*-(*para*-toluensulfonyl)-aziridine (100)



In a Schlenk tube, under nitrogen, 7.20 mL (51.7 mmol, 1.5 equiv) of TEA, a catalytic amount of DMAP and 6.53 g (34.2 mmol, 1.0 equiv) of TsCl were added sequentially to a solution of the aziridine **106** (17.97 g, 34.1 mmol, 1.0 equiv) in 69.00 mL of dried dichloromethane at 0° C under nitrogen. The resulting reaction mixture was kept under stirring at room temperature for 16h; after which it was quenched with a 1N aq. HCl solution and extracted with CH_2Cl_2. The organic phases were combined, washed with a saturated aq. $NaHCO_3$ solution (3 x 30.00 mL) and brine (2 x 30.00 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was, then, purified through a flash column chromatography (silica, eluent: 2:1 petroleum ether/ethyl acetate) giving 13.98 g (25.9 mmol, 76%) of pure aziridine **100**.

100

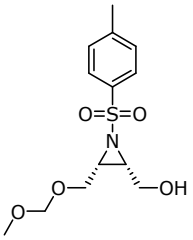
$C_{29}H_{37}NO_5SiS$ M=539.37

^{1}H-NMR δ ($CDCl_3$, 400 MHz)**:** 7.84-7.82 (2H, m [AA' part of a AA'BB' spin system], C**H** *ortho* aromatics to SO_2); 7.59-7.55 (4H, m [AA' part of a AA'BB'C spin system], C**H** *ortho* aromatics to Si); 7.43-7.43 (6H, m [BB' and C parts of a AA'BB'C spin system], C**H** *meta* and *para* aromatics to Si); 7.27-7.25 (2H, m [BB' part of a AA'BB' spin system], C**H** *meta* aromatics to SO_2); 4.50-4.45 (2H, m [AB spin system], $CH_3OC\mathbf{H_2}O$); 3.70-3.68 (2H, m, $C\mathbf{H_2}OSi$); 3.52-3.50 (2H, m, $C\mathbf{H_2}OMOM$); 3.20 (3H, s, $C\mathbf{H_3}OCH_2O$); 3.18-3.14 (2H, m, C**H** aziridinics); 2.38 (3H, $C\mathbf{H_3}$ tosyl group); 0.97 (9H, s, $C(C\mathbf{H_3})_3$).

^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 144.3 ($\mathbf{C_q}$ *para* aromatic to SO_2); 135.4 (4C, **C**H *ortho* aromatics to Si); 134.8 ($\mathbf{C_{\textit{ipso}}}$ aromatic to SO_2); 132.7 (2C, $\mathbf{C_{\textit{ipso}}}$ aromatic to Si); 129.8 (2C, **C**H *para* aromatics to Si); 129.5 (2C, **C**H *meta* aromatics to SO_2); 128.0 (2C, **C**H *ortho* aromatics to SO_2); 127.7 (4C, **C**H *meta* aromatics to Si); 96.0 ($CH_3O\mathbf{C}H_2O$); 64.0 ($CH\mathbf{C}H_2OMOM$); 60.9 ($CH\mathbf{C}H_2OSi$); 55.2 ($\mathbf{C}H_3OCH_2O$); 44.2 (**C**H aziridinic); 41.7 (**C**H aziridinic); 26.6 (3C, $SiPh_2C(\mathbf{C}H_3)_3$); 21.6 ($\mathbf{C}H_3$ tosyl group); 19.0 ($SiPh_2\mathbf{C}(CH_3)_3$).

$[\alpha]_D^{23}$=-9.69 (c=1.59, $CHCl_3$).

12.5.1.8. ((2*S*,3*R*)-3-((Methoxymethoxy)-methyl)-*N*-(*para*-toluen-sulfonyl)-aziridin-2-yl)methanol (111)



51.80 mL (51.8 mmol, 2.0 equiv) Of 1 M TBAF solution in THF were added to a stirred solution of the aziridine **100** (13.98 g, 25.9 mmol, 1.0 equiv) in 260.00 mL of anhydrous THF. After 30' the reaction mixture was quenched with water and the two phases were separated. The aqueous portion was extracted with ether (3 x 100.00 mL), the combined organic components were washed twice with water (30.0. mL) and brine (30.00 mL), dried over Na_2SO_4, filtered and concentrated under vacuum to afford 10.21 g (25.9 mmol, 100%) of a mixture, composed of the desilylated aziridine **111** and *tert*-butyldiphenylsilyl fluoride, which was used without further purification. An analytical sample (201.10 mg) was purified through a flash chromatography on silica (eluent: 2:1 petroleum ether/ethyl acetate) giving 48.26 mg (0.16 mmol) of the pure product **111**.

111

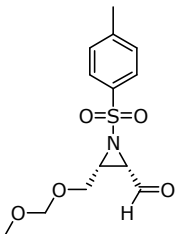
$C_{13}H_{19}NO_5S$ **M=**301.19

^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 7.84-7.80 (2H, m [AA' part of a AA'BB' spin system], C**H** *ortho* aromatics to SO_2); 7.37-7.33 (2H, m [BB' part of a AA'BB' spin system], C**H** *meta* aromatics to SO_2); 4.58 (2H, s, $CH_3OC\mathbf{H_2}O$); 3.84-3.48 (4H, m, $C\mathbf{H_2}OSi$ and $C\mathbf{H_2}OMOM$); 2.45 (3H, s, $C\mathbf{H_3}OCH_2O$); 3.14-3.09 (2H, m, C**H** aziridinics); 2.45 (3H, $C\mathbf{H_3}$ tosyl group); 2.23 (1H, dd, *J*=7.2, 5.8, $CH_2O\mathbf{H}$).

^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 144.6 ($\mathbf{C_q}$ *para* aromatic to SO_2); 134.2 ($\mathbf{C_{\textit{ipso}}}$ aromatic to SO_2); 129.5 (2C, **C**H *meta* aromatics to SO_2); 127.8 (2C, **C**H *ortho* aromatics to SO_2); 96.2 ($CH_3O\mathbf{C}H_2OCH_2$); 63.8 ($CH_3OCH_2O\mathbf{C}H_2$); 58.9 ($\mathbf{C}H_2OH$); 55.2 ($\mathbf{C}H_3OCH_2OCH_2$); 43.5 (**C**H aziridinic); 42.3 (**C**H aziridinic); 21.5 ($\mathbf{C}H_3$ tosyl group).

MS (EI) *m/z*(%)**:** 226 (62, M^+ – CH_2OMOM); 210 (9); 155 (74, Ts^+); 139 (8); 91 (100, $C_7H_7^+$); 70 (8); 65 (33); 56 (13).

12.5.1.9. (2*S*,3*R*)-3-((Methoxymethoxy)-methyl)-*N*-(*para*-toluen-sulfonyl)-aziridine-2-carbaldehyde (110)



In a Schlenk tube, under nitrogen, 15.91 g (37.50 mmol, 1.5 equiv) of Dess-Martin periodinane were added to a stirred solution of the aziridine **111** (10.00 g, 25.00 mmol, 1.0 equiv) in 250.00 mL of dried CH_2Cl_2. After the total oxidation of the alcohol into aldehyde (TLC check: 4:1 petroleum ether/ethyl acetate), the reaction mixture was diluted with 100.00 mL of ether and quenched with 250.00 mL of a saturated aq. $Na_2S_2O_3$ solution. The two phases were separated and the aqueous portion was extracted with Et_2O, while the organic

combined components were washed once with a saturated aq. $NaHCO_3$ solution and brine, dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was finally purified by flash chromatography (silica, eluent: from 10:1 to 2:1 petroleum ether/ethyl acetate) to give 6.13 g (20.5 mmol, 82%) of the pure product **110**.

110

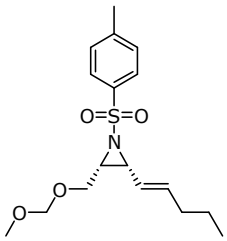
$C_{13}H_{17}NO_5S$ **M=**299.17

^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 9.28 (1H, d, *J*=5.0, C**H**O); 7.86-7.82 (2H, m [AA' part of a AA'BB' spin system], C**H** *ortho* aromatics to SO_2); 7.39-7.35 (2H, m [BB' part of a AA'BB' spin system], C**H** *meta* aromatics to SO_2); 4.51 (2H, s, $CH_3OC\mathbf{H_2}O$); 3.85-3.68 (2H, m, $C\mathbf{H_2}$OMOM); 3.35-3.28 (2H, m, C**H** aziridinics); 3.26 (3H, s, $C\mathbf{H_3}OCH_2O$); 2.46 (3H, $C\mathbf{H_3}$ tosyl group).

^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 194.2 (**C**HO); 145.4 ($\mathbf{C_q}$ *para* aromatic to SO_2); 130.0 (2C, **C**H *ortho* aromatics to SO_2); 129.6 ($\mathbf{C_{\textit{ipso}}}$ aromatic to SO_2); 128.1 (2C, **C**H *meta* aromatics to SO_2); 96.2 ($CH_3O\mathbf{C}H_2OCH_2$); 62.8 ($CH_3OCH_2O\mathbf{C}H_2$); 55.5 ($\mathbf{C}H_3OCH_2OCH_2$); 45.8 (**C**H aziridinic); 44.5 (**C**H aziridinic); 21.7 ($\mathbf{C}H_3$ tosyl group).

MS (EI) *m/z*(%)**:** 281 (0.02); 270 (1); 258 (0.3); 226 (81, $M^+ - CH_2OMOM$); 210 (3); 171 (3); 155 (78, Ts^+); 139 (7); 91 (100, $C_7H_7^+$); 70 (7); 65 (26); 56 (10).

12.5.1.10. (2*R*,3*R*)-2-((Methoxymethoxy)-methyl)-3-((*E*)-pent-1-enyl)-*N*-(*para*-toluensulfonyl)-aziridine (107)



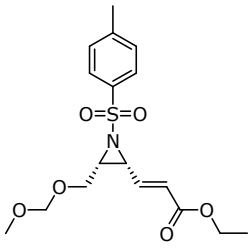
Three equivalent of ylide were prepared in a Schlenk tube, under nitrogen, for addition of NaHMDS (6.00 mL, 6.0 mmol, 3.0 equiv) to (*n*-butyl)-triphenylphosphonium bromide (2.40 g, 6.0 mmol, 3.0 equiv) in 15.00 mL of freshly distilled THF at 0° C and under nitrogen. The Schlenk vessel was allowed to warm to room temperature and, after 1h stirring, the reaction mixture was again cooled to 0° C and a solution of the aldehyde **110** (2.0 mmol, 1.0 equiv) in 5.00 mL of freshly distilled THF was added. Then the temperature was increased to 25° C and the reaction mixture was left to stir for 16, after which it was quenched with a saturated aq. NH_4Cl solution and extracted with ether (3 x 5.00 mL). The combined organic layers were washed twice with a saturated aq. $NaHCO_3$ solution and brine and dried over sodium sulfate. After filtration, evaporation and purification by chromatography (silica, eluent: 5:1 petroleum ether/ethyl acetate) 0.23 g (0.68 mmol, 34%) of the pure product **107** were obtained.

107

$C_{16}H_{25}NO_4S$ **M=**339.25

^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 7.85-7.81 (2H, m [AA' part of a AA'BB' spin system], C**H** *ortho* aromatics to SO_2); 7.34-7.30 (2H, m [BB' part of a AA'BB' spin system], C**H** *meta* aromatics to SO_2); 5.72 (1H, dt, *J*=11.2, 7.6, CH=C**H**CH_2); 4.55-4.48 (2H, m, [AB spin system], $CH_3OC\mathbf{H_2}O$); 3.64-3.54 (3H, m, C$\mathbf{H_2}$OMOM and C**H**CH aziridinic); 3.27 (3H, s, $C\mathbf{H_3}OCH_2O$); 3.23-3.16 (1H, m, C**H**CH_2 aziridinic); 2.44 (3H, C$\mathbf{H_3}$ tosyl group); 2.18-2.04 (2H, m, C$\mathbf{H_2}CH_2CH_3$); 2.43-1.14 (2H, m, $CH_2C\mathbf{H_2}CH_3$); 0.89 (3H, t, *J*=7.2, $CH_2CH_2C\mathbf{H_3}$).
^{13}C-NMR{^{1}H} δ($CDCl_3$, 50 MHz)**:** 144.3 ($\mathbf{C_q}$ *para* aromatic to SO_2); 138.2 (**C**H=$CHCH_2CH_2CH_3$); 134.9 ($\mathbf{C_{\textit{ipso}}}$ aromatic to SO_2); 129.4 (2C, **C**H *meta* aromatics to SO_2); 127.7 (2C, **C**H *ortho* aromatics to SO_2); 120.5 (CH=**C**H$CH_2CH_2CH_3$); 96.0 ($CH_3O\mathbf{C}H_2OCH_2$); 64.1 ($CH_3OCH_2O\mathbf{C}H_2$); 55.1 ($\mathbf{C}H_3OCH_2OCH_2$); 43.5 (**C**H aziridinic); 40.2 (**C**H aziridinic); 29.7 (CH=CH**C**$H_2CH_2CH_3$); 22.3 ($CH=CHCH_2\mathbf{C}H_2CH_3$); 21.5 (**C**$H_3$ tosyl group); 13.5 ($CH=CHCH_2CH_2\mathbf{C}H_3$).
MS (EI) *m/z*(%)**:** 281 (1); 258 (5); 229 (10); 216 (58); 215 (100); 201 (36); 183 (8, M^+ – Ts); 155 (10, Ts^+); 125 (14); 107 (2); 91 (1, $C_7H_7^+$); 77 (32, $C_6H_5^+$); 57 (3); 51 (27).

12.5.1.11. (*E*)-Ethyl-3-((2*R*,3*R*)-3-((methoxymethoxy)-methyl)-*N*-(*para*-toluensulfonyl)-aziridin-2-yl)acrylate (108)

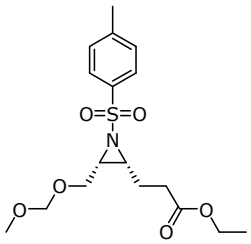


A suspension of NaH in freshly distilled THF (50.00 mL) was prepared in a Schlenk tube, under nitrogen, from 861.00 mg (21.3 mmol, 1.15 equiv) of a 60% NaH dispersion in mineral oils, after washings with pentane to remove the paraffins. Then, a solution of diisopropyl-(ethoxycarbonylmethyl)-phosphonate (4.84 mL, 20.4 mmol, 1.1 equiv) in 12.00 mL of dried THF was added to 0° C and the resulting reaction mixture was stirred for 30' at room temperature before introducing the aldehyde **110** (5.53 g, 18.5 mmol, 1.0 equiv) at 0° C. After 12h the reaction mixture was quenched with a saturated aq. NH_4Cl solution and extracted with ether. The combined organic phases were washed with water and brine, dried over Na_2SO_4, filtered and concentrated under vacuum to afford 5.01 g of the crude product **108**. After purification by flash chromatography on silica (eluent: 3:1 petroleum ether/ethyl acetate), 2.94 g (7.8 mmol, 43%) of the pure aziridine **108** were obtained.

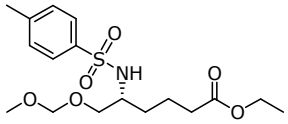
108
$C_{17}H_{23}NO_6S$ **M=**369.23
^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 7.84-7.80 (2H, m [AA' part of a AA'BB' spin system], C**H** *ortho* aromatics to SO_2); 7.36-7.32 (2H, m, [BB' part of a AA'BB' spin system], C**H** *meta* aromatics to SO_2); 6.66 (1H, dd, *J*=15.6, 6.8, C**H**=CHCOOEt); 6.08 (1H, d, *J*=15.6, CH=C**H**COOEt); 4.54-4.46 (2H, m [AB spin system],

$CH_3OC\mathbf{H_2}O$); 4.16 (2H, q, *J*=7.0, $OC\mathbf{H_2}CH_3$); 3.57-3.47 (3H, m, $OC\mathbf{H_2}CH$ and $OCH_2C\mathbf{H}$ aziridinic); 3.31-3.21 (1H, m, C**H**CH=CH aziridinic); 3.25 (3H, s, $C\mathbf{H_3}OCH_2O$); 2.44 (3H, s, $C\mathbf{H_3}$ tosyl group); 1.26 (3H, t, *J*=7.0, $OCH_2C\mathbf{H_3}$).
^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 164.7 (**C**OOEt); 144.6 ($\mathbf{C_q}$ *para* aromatic to SO_2); 138.1 (**C**H=CHCOOEt); 134.2 ($\mathbf{C_{\textit{ipso}}}$ aromatic to SO_2); 129.5 (2C, **C**H *meta* aromatics to SO_2); 127.7 (2C, **C**H *ortho* aromatics to SO_2); 126.3 (CH=**C**HCOOEt); 96.0 ($CH_3O\mathbf{C}H_2OCH_2$); 63.4 ($CH_3OCH_2O\mathbf{C}H_2$); 60.4 ($COO\mathbf{C}H_2CH_3$); 55.0 ($\mathbf{C}H_3OCH_2OCH_2$); 43.9 (**C**H aziridinic); 41.9 (**C**H aziridinic); 21.4 ($\mathbf{C}H_3$ tosyl group); 13.9 ($COOCH_2\mathbf{C}H_3$).
MS (EI) *m/z*(%)**:** 237 (1); 168 (31); 152 (7); 138 (2); 124 (26); 123 (16); 122 (48); 106 (23); 92 (52); 91 (100, $C_7H_7^+$); 80 (20); 65 (20); 64 (34); 51 (18).

12.5.1.12. Ethyl-3-((2*R*,3*R*)-3-((methoxymethoxy)-methyl)-*N*-(*para*-toluen-sulfonyl)-aziridin-2-yl)propanoate (109) (*R*)-Ethyl-6-(methoxymethoxy)-*N*-(*para*-toluensulfonyl)-amino)-hexanoate (113)



109



113

285.80 mg (1.2 mmol, 0.2 equiv) Of $CoCl_2{\cdot}H_2O$ was added to a solution of the aziridine **108** (2.22 g, 6.0 mmol, 1.0 equiv) in 24.00 mL of methanol at 0° C. After 30' stirring at room temperature, 227.0 mg of $NaBH_4$ (6.0 mmol, 1.0 equiv) were added to the resulting pink solution precooled at −78° C, and immediately the reaction was quenched by adding 24.00 mL of water. After 5', the two phases were separated and the aqueous portion was extracted with dichloromethane (3 x 10.00 mL). The washing of the combined organic components with water (3 x 20.00 mL) and brine and the evaporation of the solvent afforded the crude product, composed by a mixture of ethyl 3-((2*R*,3*R*)-3-((methoxymethoxy)-methyl)-*N*-(*para*-toluensulfonyl)-aziridin-2-yl)-propanoate **109** and (*R*)-ethyl 6-(methoxymethoxy)-*N*-(*para*-toluensulfonyl)-amino)-hexanoate **113**. The two products were separated by chromatography (silica, eluent: 2:1 pentane/ethyl acetate) giving 512.30 mg (1.38 mmol, 23%) of **109** and 380.70 mg (1.02 mmol, 17%) of **113**.

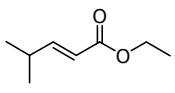
109
$C_{17}H_{25}NO_6S$ **M=**371.25
^{1}H-NMR δ ($CDCl_3$, 400 MHz)**:** 7.76-7.74 (2H, m [AA' part of a AA'BB' spin system], C**H** *ortho* aromatics to SO_2); 7.30-7.28 (2H, m, [BB' part of a AA'BB' spin system], C**H** *meta* aromatics to SO_2); 4.55-4.50 (2H, m [AB spin system], $CH_3OC\mathbf{H_2}O$); 4.12 (2H, q, *J*=7.2, $OC\mathbf{H_2}CH_3$); 3.28 (3H, s, $C\mathbf{H_3}OCH_2O$); 3.10-3.05

(1H, m, C**H**CH_2O aziridinic); 2.94-2.89 (1H, m, C**H**CH_2); 2.45 (3H, C$\mathbf{H_3}$ tosyl group); 2.36-2.28 (2H, m, $CH_2C\mathbf{H_2}COOEt$); 1.98-1.88 (2H, m, C**H**H'CH_2COOEt); 1.67-1.60 (2H, m, CH**H'**CH_2COOEt); 1.25 (3H, t, *J*=7.2, $COOCH_2C\mathbf{H_3}$).
^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 172.1 (**C**OOEt); 144.4 ($\mathbf{C_q}$ *para* aromatic to SO_2); 129.5 (2C, **C**H *meta* aromatics to SO_2); 127.9 (2C, **C**H *ortho* aromatics to SO_2); 126.9 ($\mathbf{C_{ipso}}$ aromatic to SO_2); 96.7 ($CH_3O\mathbf{C}H_2OCH_2$); 63.9 ($CH_3OCH_2O\mathbf{C}H_2$); 60.6 ($O\mathbf{C}H_2CH_3$); 55.3 ($\mathbf{C}H_3OCH_2OCH_2$); 43.2 (**C**H aziridinic); 42.8 (**C**H aziridinic); 31.8 ($\mathbf{C}H_2CH_2COOEt$); 22.4 ($CH_2\mathbf{C}H_2COOEt$); 21.3 ($\mathbf{C}H_3$ tosyl group); 14.3 ($COOCH2\mathbf{C}H_3$).
MS (EI) *m/z*(%)**:** 238 (1); 210 (38); 184 (83); 156 (49); 155 (42, Ts^+); 138 (19); 126 (24); 110 (28); 98 (51); 91 (100, $C_7H_7^+$); 82 (30); 65 (38); 55 (27).

113
$C_{17}H_{27}NO_6S$ **M=**373.27
^{1}H-NMR δ ($CDCl_3$, 400 MHz)**:** 7.76-7.74 (2H, m [AA' part of a AA'BB' spin system], C**H** *ortho* aromatics to SO_2); 7.30-7.28 (2H, m, [BB' part of a AA'BB' spin system], C**H** *meta* aromatics to SO_2); 4.92 (1H, br-d, *J*=8.4, N**H**Ts); 4.48-4.42 (2H, m [AB spin system], $CH_3OC\mathbf{H_2}O$); 4.10 (2H, q, *J*=7.2, $OC\mathbf{H_2}CH_3$); 3.42 (1H, dd, *J*=9.6, C**H**H'CHNHTs); 3.37-3.31 (1H, m, C**H**NHTs); 3.27 (3H, s, $C\mathbf{H_3}OCH_2O$); 3.26 (1H, dd, *J*=10.0, 4.0, CH**H'**CCHNHTs); 2.42 (3H, C$\mathbf{H_3}$ tosyl group); 2.24-2.21 (2H, m, $CH_2CH_2C\mathbf{H_2}COOEt$); 1.58-1.51 (4H, m, (2H, m, $C\mathbf{H_2}C\mathbf{H_2}CH_2COOEt$); 1.24 (3H, t, *J*=7.2, $COOCH_2C\mathbf{H_3}$).
^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 173.2 (**C**OOEt); 143.3 ($\mathbf{C_q}$ *para* aromatic to SO_2); 138.1 ($\mathbf{C_{ipso}}$ aromatic to SO_2); 129.6 (2C, **C**H *meta* aromatics to SO_2); 127.0 (2C, **C**H *ortho* aromatics to SO_2); 96.8 ($CH_3O\mathbf{C}H_2OCH_2$); 69.4 ($CH_3OCH_2O\mathbf{C}H_2$); 60.3 ($O\mathbf{C}H_2CH_3$); 55.4 ($\mathbf{C}H_3OCH_2OCH_2$); 53.2 (**C**HNHTs); 33.7 ($CH_2CH_2\mathbf{C}H_2COOEt$); 31.8 ($\mathbf{C}H_2CH_2CH_2COOEt$); 21.5 ($\mathbf{C}H_3$ tosyl group); 21.0 ($CH_2\mathbf{C}H_2CH_2COOEt$); 14.2 ($OCH_2\mathbf{C}H_3$).
MS (EI) *m/z*(%)**:** 342 (0.1); 309 (1); 298 (30); 252 (42); 250 (3); 226 (2); 210 (3); 186 (4); 155 (85, Ts^+); 139 (5); 98 (4); 91 (100, $C_7H_7^+$); 65 (20); 55 (16).

12.5.2. Synthesis of 2-methylether-3-isopropyl-*N*-(*para*-toluensulfonyl)-aziridines

12.5.2.1. ***(E)*-Ethyl 4-methyl-pent-2-enoate (119)[475]**



In a Schlenk tube, under nitrogen, a suspension of NaH (34.5 mmol, 1.15 equiv) in 50.00 mL of freshly distilled THF was prepared from 1.36 g of a 60% dispersion NaH in mineral oils, after washings with pentane to remove the paraffins and drying *in vacuo*. Then a solution of di-*iso*-propyl-(ethoxycarbonylmethyl)-phosphonate **112** (7.85 mL, 33.0 mmol, 1.1 equiv) in 20.00 mL of anhydrous THF

was added dropwise to the suspension precooled to 0° C and under stirring. After addition, the cooling bath was removed and the stirring was continued at room temperature for 30'. The reaction vessel was then cooled again with a ice-bath and 2.74 mL (30.0 mmol, 1.0 equiv) of *iso*-butyrraldehyde **118** were added. The resulting reaction mixture was stirred for 1h at room temperature. Then, the TLC monitoring (10:1 petroleum ether/ethyl acetate) showed the total disappearance of the starting material and the contemporary formation of a new species. So, the reaction was quenched with 100.00 mL of a saturated aqueous NH_4Cl solution and extracted with diethyl ether (2 x 30.00 mL). The combined organic components were washed with a saturated aq. $NaHCO_3$ solution (3 x 30.00 mL) and a saturated aq. NaCl solution (1 x 30.00 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford 3.71 g (26.1 mmol, 87%) of the ester **119**, which was employed for the next reaction without further purifications.

119

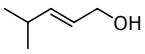
$C_8H_{14}O_2$ **M=**142.14

^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 6.94 (1H, dd, *J*=15.8, 6.6, iPrC**H**=CH); 5.76 (1H, dd, *J*=15.8, 1.2, iPrCH=C**H**); 4.18 (2H, q, *J*=6.8, OC**H_2**CH_3); 2.46 (1H, ps-oct, *J*=6.6, 1.4, C**H**$(CH_3)_2$); 1.29 (3H, t, *J*=6.8, OCH_2C**H_3**); 1.06 (6H, d, *J*=6.6, $CH(C$**H_3**$)_2$).

^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 166.2 (**C**$OOCH_2CH_3$); 154.6 (iPr**C**H=CH); 118.3 (iPrCH=**C**H); 59.5 (O**C**H_2CH_3); 30.5 (**C**H$(CH_3)_2$); 20.8 (CH(**C**$H_3)_2$); 13.9 (OCH_2**C**H_3).

MS (EI) *m/z*(%)**:** 142 (32, M^+); 114 (51, $M^+ - CH_2CH_3$); 99 (24); 97 (87, $M^+ - OCH_2CH_3$); 81 (20); 69 (100, $M^+ - COOCH_2CH_3$); 59 (55); 56 (33, $iPrC^+$); 55 (32); 53 (37).

12.5.2.2. (*E*)-4-Methyl-pent-2-en-1-ol (120)[476, 477]



In a 500 mL two-necked round bottomed flask, purged and flamed under vacuum and equipped with a dropping funnel, 65.25 mL (65.25 mmol, 2.5 equiv) of a 1.0 M DIBAL-H solution in DCM were added dropwise at –78° C to a solution of the ester **119** (3.71 g, 26.1 mmol, 1.0 equiv) in 52.20 mL of anhydrous DCM under vigorous stirring. After 30 minutes (TLC monitoring: 10:1 petroleum ether/ethyl acetate) the reaction was over and 26.10 mL of MeOH were slowly added at 0° C, in order to destroy the excess of the hydride. Then 65.00 mL of a saturated aq. sodium and potassium tartrate solution were added under vigorously stirring to break the white emulsion of aluminium salts and the two phases were separated. The aqueous portion was extracted with DCM (2 x 30.00 mL) and the combined organic layers were washed with brine (2 x 30.00 mL) and dried over sodium sulfate. After evaporation of the solvent, 2.56 g (25.5 mmol, 97%) of the pure allylic alcohol **120** were obtained.

120

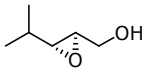
$C_6H_{12}O$ M=100.12

^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 6.73-5.53 (2H, m, C**H** olefinic); 4.09 (2H, d, *J*=4.8, C**H_2**OH); 2.30 (1H, ps-oct, *J*=6.8, C**H**$(CH_3)_2$); 0.99 (6H, d, *J*=6.8, CH(C**H_3**$)_2$).

^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 139.5 (iPr**C**H=CHCH$_2$OH); 125.8 (iPrCH=**C**HCH$_2$OH); 63.3 (CH=CH**C**H$_2$OH); 30.5 (**C**H$(CH_3)_2$); 22.1 (2C, CH(**C**H$_3$$)_2$).

MS (EI) *m/z*(%)**:** 100 (0.02, M^+); 69 (56, M^+ - CH_2OH); 67 (34); 59 (47); 57 (100, iPrCH^+); 56 (41).

12.5.2.3. ((2*R*,3*R*)-3-*iso*-Propyl-oxiranyl)methanol (121)[153, 476, 478-480]



In a Schlenk tube, under nitrogen, 261.30 µL (1.27 mmol, 5%) of (–)-D-DET, 380.80 µL (1.53 mmol, 6%) of $Ti(OiPr)_4$ and 9.25 mL (50.9 mmol, 2.0 equiv) of 5.5 M TBHP solution in DCM (previous dried over activated pellet 4 Å molecular sieves) were sequentially added into a suspension of 0.80 g of powdered activated 4 Å molecular sieves in 70.00 mL of anhydrous dichloromethane at –20° C and under nitrogen. After 30', a solution of the allylic alcohol **120** (2.56 g, 25.5 mmol, 1.0 equiv) in 15.00 mL of dried DCM was added and the resulting reaction mixture was kept under stirring for 30h at –20° C. Then it was poured into a precooled solution (0° C) consisting on $FeSO_4 \cdot 7H_2O$ (2.49 g, 30.5 mmol) and tartaric acid (2.29 g, 15.2 mmol) in 25.50 mL of water under vigorously stirring. After 10', the two phases were separated and the aqueous portion was extracted with DEE (2 x 5.00 mL). The combined organic components were left to stir with a 30% (*w*/*v*) NaOH aq. solution at 0° C during 1h. Then the mixture was diluted with 20.00 mL of H_2O and the two layers were separated. The aqueous part was extracted with ether (3 x 30.00 mL) and the organic components were combined, washed with brine (2 x 30.00 mL), dried over sodium sulfate, filtered and concentrated to afford 4.15 g of crude product **125**. A little amount of this residue (0.52 g) was purified by chromatography (silica, eluent: 2:1 petroleum ether/ethyl acetate) to give the pure epoxyalcohol **121** (146.60 mg, 1.3 mmol).

121

$C_6H_{12}O_2$ M=116.12

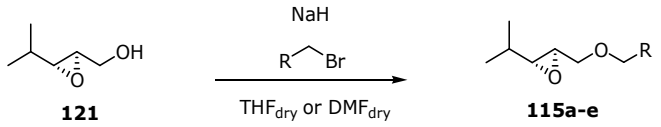
^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 3.92 (1H, dd, *J*=12.4, 2.2, C**H**H'OH); 3.61 (1H, dd, *J*=12.4, 4.0, CH**H'**OH); 2.99-2.94 (1H, m, C**H**CH_2 epoxidic); 2.75 (1H, dd, *J*=6.80, 2.4, iPrC**H** epoxidic); 1.83 (1H, br-s, O**H**); 1.58 (1H, ps-oct, *J*=6.8, C**H**$(CH_3)_2$); 1.02 (3H, d, *J*=6.6, CH(C**H_3**$)_2$); 0.97 (3H, d, *J*=6.6, CH(C**H_3**$)_2$).

^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 61.9 (**C**H_2OH); 61.2 (**C**H epoxidic); 57.6 (**C**H epoxidic); 30.0 (**C**H$(CH_3)_2$); 18.9 (1C, CH(**C**$H_3$$)_2$); 18.3 (1C', CH(**C**$H_3$$)_2$).

MS (EI) *m/z*(%)**:** 98 (0.1, $M^+ - H_2O$); 85 (0.1, $M^+ - CH_2OH$); 73 (M^+ – iPr); 56 (100, M^+ – iPr – OH); 55 (77, M^+ – iPr – H_2O, iPr-C^+).

$[\alpha]_D^{23}$=+24.89 (c=1.075, $CHCl_3$).

12.5.2.4. *General procedure for the synthesis of oxyranyl ethers*[481]



121 **115a-e**

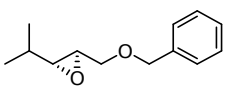
Protocol A

In a Schlenk tube, purged and flamed under vacuum, a solution of the epoxyalcohol **121** (1.0 equiv) in anhydrous THF was added to a suspension of NaH (60% dispersion in mineral oils, previously washed with pentane to remove the tracks of paraffin, 1.5 equiv) in freshly distilled THF (0.5 M) at 0° C and under nitrogen. The resulting grey mixture was stirred for 30' at room temperature; then, the reaction vessel was again cooled to 0° C with an ice-bath before introducing the desired alkyl halide (1.1 equiv). The resulting reaction mixture was left to stir at room temperature and monitored *via* TLC. After the total conversion of the starting epoxide into epoxyether **115**, the mixture was poured in precooled water (0° C); then, the aqueous phase was separated and extracted twice in ether. The combined organic layers were washed with water and brine, dried over sodium sulfate, filtered and concentrated. The crude product **115** was then purified by chromatography.

Protocol B

A suspension of NaH (2.0 equiv) in anhydrous DMF (0.5 equiv) was prepared in the usual way in a Schlenk tube, under nitrogen. After cooling to 0° C, the epoxyalcohol **121** (1.0 equiv) was added and then the temperature was allowed to 25 °C. After 30', NaI (1.0 equiv) and the desired alkyl halide (1.0 equiv) were added at 0° C and the resulting reaction mixture was stirred at 25° C for 12-16h. After the reaction was over (TLC check), the mixture was poured in water and extracted with ether. The combined organic phases were washed with a saturated aq. NaCl solution, dried over Na_2SO_4, filtered and concentrated under reduce pressure. The residue **115** was, then, purified through a flash column chromatography.

12.5.2.4.1. (2*R*,3*R*)-2-(Benzyloxy)methyl-3-*iso*-propyloxirane (115a)

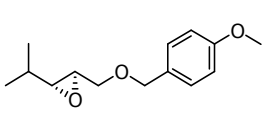


According to the protocol A, (2*R*,3*R*)-2-(benzyloxy)methyl-3-isopropyloxirane **115a** (1.59 g, 7.7 mmol, 73%) was synthesized starting from the epoxyalcohol **121** (1.22 g, 10.5 mmol, 1.0 equiv), NaH (631.20 mg, 15.78 mmol, 1.5 equiv), benzyl bromide (1.98 g, 11.57 mmol, 1.1 equiv) and 22.00 mL of freshly distilled THF and purified by flash chromatography (silica, eluent: 3:1 petroleum ether/ethyl acetate).

115a

$C_{13}H_{18}O_2$ **M=**206.18
^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 7.40-7.30 (5H, m, C**H** aromatics); 4.58 (2H, m [AB spin system], C**H_2**Ph); 3.73 (1H, dd, *J*=11.0, 3.1, C**H**H'OBn); 3.45 (dd, 1H, *J*=11.0, 5.8, CH**H'**OBn); 3.03-2.97 (1H, m, C**H**CH_2 epoxidic); 2.63 (1H, dd, *J*=6.6, 2.2, iPrC**H** epoxidic); 1.65-1.48 (1H, m, C**H**$(CH_3)_2$); 1.02 (3H, d, *J*=6.6, CH(C**H_3**)$_2$); 0.97 (3H, d, *J*=6.6, CH(C**H_3**)$_2$).
^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 137.7 (**C_{ipso}** aromatic to CH_2); 128.5 (**C**H *para* aromatic); 127.7 (2C, **C**H *ortho* aromatics); 127.0 (2C, **C**H *meta* aromatics); 72.4 (CH_2O**C**H_2Ph); 70.0 (**C**H_2OCH_2Ph); 60.3 (**C**H epoxidic); 55.2 (**C**H epoxidic); 29.6 (**C**H$(CH_3)_2$); 18.4 (CH(**C**H_3)$_2$); 17.9(CH(**C**H_3)$_2$).
MS (EI) *m/z*(%)**:** 205 (1, M^+ – H); 107 (84, OCH_2Ph^+); 91 (100, $C_7H_7^+$); 79 (37); 57 (47, iPr-CH_2^+); 56 (35, iPr-CH^+); 55 (43, iPr-C^+).

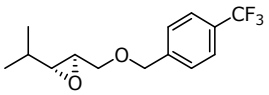
12.5.2.4.2. (2*R*,3*R*)-2-(4-Methoxy-benzyloxy)methyl-3-*iso*-propyloxirane (115b)



Following the protocol A, 1.39 g (12.00 mmol, 1.0 equiv) of the epoxide **121**, 720.00 mg (18.0 mmol, 1.5 equiv) of NaH and 1.90 mL (13.2 mmol, 1.1 equiv) of *para*-methoxybenzyl bromide in 24.00 mL of freshly distilled THF were reacted to afford, after purification by flash chromatography on silica gel (eluent: 12:1 petroleum ether/ethyl acetate), 1.61 g (6.8 mmol, 57%) of the pure product **115b**.

115b
$C_{14}H_{20}O_3$ **M=**236.20
^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 7.29-7.24 (2H, m [BB' of a AA'BB' spin system], C**H** *meta* aromatics to OMe); 6.92-6.84 (2H, m [AA' part of a AA'BB' spin system], C**H** *ortho* aromatics to OMe); 4.50 (2H, m [AB spin system], C**H_2**C_6H_4OMe); 3.81 (3H, s, OC**H_3**); 3.70 (1H, dd, *J*=11.4, 3.2, C**H**H'$OCH_2C_6H_4$OMe); 3.41 (1H, dd, *J*=11.4, 6.0, CH**H'**$OCH_2C_6H_4$OMe); 3.01-2.96 (1H, m, C**H**CH_2 epoxidic); 2.61 (1H, dd, *J*=6.8, 2.4, iPrC**H** epoxidic); 1.67-1.52 (1H, m, C**H**$(CH_3)_2$); 1.01 (3H, d, *J*=6.8, CH(C**H_3**)$_2$); 0.96 (3H, d, *J*=6.8, CH(C**H_3**)$_2$).
^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 158.8 (**C_{ipso}** aromatic to OCH_3); 130.0 (**C_q** *para* aromatic to OCH_3); 128.9 (2C, **C**H *meta* aromatics to OCH_3); 113.4 (2C, **C**H *ortho* aromatics to OCH_3); 72.4 (**C**$H_2C_6H_4$OMe); 69.9 (**C**$H_2OCH_2C_6H_4$OMe); 60.8 (**C**H epoxidic); 55.6 (O**C**H_3); 54.8 (**C**H epoxidic); 29.8 (**C**H$(CH_3)_2$); 18.6 (1C, CH(**C**H_3)$_2$); 18.1 (1C', CH(**C**H_3)$_2$).
MS (EI) *m/z*(%)**:** 236 (3, M^+); 137 (100, $OCH_2C_6H_4OCH_3^+$); 121 (94, $CH_2C_6H_4OCH_3^+$); 109 (17); 91 (8, $C_7H_7^+$); 77 (21, $C_6H_5^+$); 57 (14, iPr-CH_2^+); 56 (9, iPr-CH^+); 55 (25, iPr-C^+).

12.5.2.4.3. (2*R*,3*R*) 2-(4-Trifluoromethyl-benzyloxy)methyl-3-*iso*-propyl oxirane (115c)



According to the protocol A, (2*R*,3*R*)-2-(4-trifluoromethyl-benzyloxy)-methyl -3- isopropyloxirane **115c** (1.74 g, 6.34 mmol, 53%) was obtained from 1.39 g (12.00 mmol, 1.0 equiv) of the epoxide **121**, 0.72 g (18.0 mmol, 1.5 equiv) of NaH and 3.16 g (13.2 mmol, 1.1 equiv) of *para*-(trifluoromethyl)benzyl bromide in 24.00 mL of freshly distilled THF and purified by flash chromatography (silica, eluent: 12:1 petroleum ether/ethyl acetate).

115c

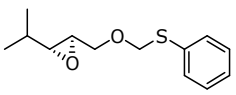
$C_{14}H_{17}O_2F_3$ **M=**274.17

^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 7.62-7.58 (2H, m [AA' part of a AA'BB' spin system], C**H** *ortho* aromatics to CF_3); 7.47-7.43 (2H, m [BB' part of a AA'BB' spin system], C**H** *meta* aromatics to CF_3); 4.63 (2H, m [AB spin system], OC**H$_2$**$C_6H_5CF_3$); 3.80 (1H, dd, *J*=11.4, 3.2, C**H**H'$OCH_2C_6H_4OCF_3$); 3.44 (1H, dd, *J*=11.4, 6.0, CH**H'**$OCH_2C_6H_4CF_3$); 3.04-2.99 (1H, m, C**H**CH_2 epoxidic); 2.63 (1H, dd, *J*=6.7, 2.1, iPrC**H** epoxidic); 1.63-1.50 (m, 1H, C**H**$(CH_3)_2$); 1.02 (3H, d, *J*=6.6, CH(C**H$_3$**$)_2$); 0.96 (d, 3H, *J*=6.6, CH(C**H$_3$**$)_2$).

^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 142.0 (**C_q** *para* aromatic to CF_3); 128.9 (**C_{ipso}** aromatic to CF_3); 127.0 (4C, **C**H *ortho* and *meta* aromatics to CF_3); 124.8 (**C**F_3); 71.7 (**C**$H_2C_6H_4CF_3$); 70.6 (**C**$H_2OCH_2C_6H_4CF_3$); 59.8 (**C**H epoxidic); 55.4 (**C**H epoxidic); 29.8 (**C**H$(CH_3)_2$); 18.4 (1C, CH(**C**$H_3)_2$); 13.7(1C, CH(**C**$H_3)_2$).

MS (EI) *m/z*(%)**:** 255 (0.25, M^+ – F); 213 (2); 175 (28, $OCH_2C_6H_4CF_3^+$); 159 (100, $CH_2C_6H_4CF_3^+$); 145 (3, $C_6H_4CF_3^+$); 109 (19); 85 (18, iPrCH(O)CH^+); 57 (84, iPr-CH_2^+); 56 (71, iPr-CH^+); 55 (45, iPr-C^+).

12.5.2.4.4. (2*R*,3*R*)-2-(Phenylthio-methoxy)methyl-3-*iso*-propyloxirane (115d)



According to the protocol B, the epoxyether **115d** (1.05 g, 4.4 mmol, 73%) was synthesized starting from the epoxialcohol **121** (1.57 g, 6.0 mmol, 1.0 equiv), NaH (480.00 mg, 12.0 mmol, 2.0 equiv), NaI (899.00 mg, 6.0 mmol, 1.0 equiv) and chloromethyl-phenyl sulfide (0.80 mL, 6.0 mmol, 1.0 equiv) in 12.00 mL of anhydrous DMF and purified through a flash column chromatography on silica gel with 12:1 petroleum ether/ethyl acetate mix as eluent.

115d

$C_{13}H_{18}O_2S$ **M=**238.18

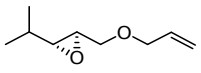
^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 7.50-7.46 (2H, m, C**H** *ortho* aromatics); 7.34-7.22 (3H, m, C**H** *meta* and *para* aromatics); 5.04 (2H, m [AB spin system], OC**H$_2$**SPh);

3.87 (1H, dd, *J*=11.3, 3.3, C**H**H'OCH_2SPh); 3.60 (1H, dd, *J*=11.3, 5.9, CH**H'**OCH_2SPh); 3.01-2.95 (1H, m, C**H**CH_2 epoxidic); 2.62 (1H, dd, *J*=6.8, 2.2, iPrC**H** epoxidic); 1.62-1.51 (1H, m, C**H**$(CH_3)_2$); 1.02 (3H, d, *J*=6.8, CH(C$\mathbf{H_3}$)$_2$); 0.95 (3H, d, *J*=6.8, CH(C$\mathbf{H_3}$)$_2$).

^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 135.2 (**C_{ipso}** aromatic to S); 129.5 (2C, **C**H *meta* aromatics to S); 128.3 (2C, **C**H *ortho* aromatics to S); 126.1 (**C**H *para* aromatic to S); 75.5 (O**C**H_2SPh); 68.0 (**C**H_2OCH_2SPh); 60.7 (**C**H epoxidic); 54.9 (**C**H epoxidic); 29.7 (**C**H$(CH_3)_2$); 18.5 (1C, CH(**C**$H_3)_2$); 17.9 (1C', CH(**C**$H_3)_2$).

MS (EI) *m/z*(%)**:** 238 (5, M^+); 165 (15, M^+ – iPrHCO); 123 (19, $PhSCH_2^+$); 110 (32, PhS^+); 73 (100, $iPrHCO^+$); 69 (26); 57 (14, iPr-CH_2^+); 56 (7, iPr-CH^+); 55 (71, iPr-C^+).

12.5.2.4.5. (2*R*,3*R*)-2-(Allyloxy)-methyl-3-*iso*-propyloxirane (115e)



(2*R*,3*R*)-2-(allyloxy)methyl-3-isopropyloxirane **115e** (0.94 g, 6.0 mmol, 60%) was obtained from the epoxide **121** (1.16 g, 12.00 mmol, 1.0 equiv), NaH (0.60 g, 15.0 mmol, 1.5 equiv), allyl bromide (0.93 mL, 11.0 mmol, 1.1 equiv) and 20.00 mL of freshly distilled THF, after purification *via* flash chromatography (SiO_2, eluent: 12:1 petroleum ether/ethyl acetate), as indicated on the protocol A of the general procedure.

115e

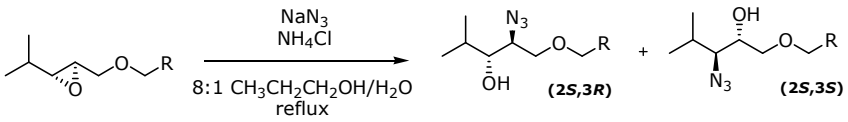
$C_9H_{16}O_2$ **M=**156.12

^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 5.90 (1H, ddt, *J*=17.8, 10.1, 6.6, C**H**=CH_2); 5.28 (1H, dd, *J*=17.8, 1.4, CH=CH$\mathbf{H_{trans}}$); 5.20 (1H, dd, *J*=10.1, 1.4, CH=CH$\mathbf{H_{cis}}$); 4.03 (2H, m, OC$\mathbf{H_2}$ allyl group); 3.70 (1H, dd, *J*=11.4, 3.0, C**H**H'$OCH_2CH=CH_2$); 3.42 (1H, dd, *J*=11.4, 5.4, CH**H'**$OCH_2CH=CH_2$); 3.00-2.95 (1H, m, C**H**CH_2 epoxidic); 2.62 (dd, 1H, *J*=7.0, 2.2, iPrC**H** epoxidic); 1.63-1.50 (1H, m, C**H**$(CH_3)_2$); 1.01 (3H, d, *J*=6.6, CH(C$\mathbf{H_3}$)$_2$); 0.96 (3H, d, *J*=6.3, CH(C$\mathbf{H_3}$)$_2$).

^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 134.1 (OCH_2**C**H=CH_2); 116.2 (OCH_2CH=**C**H_2); 71.4 (O**C**$H_2CH=CH_2$); 70.0 (**C**$H_2OCH_2OCH=CH_2$); 60.5 (**C**H epoxidic); 55.3 (**C**H epoxidic); 29.8 (**C**H$(CH_3)_2$); 18.4 (CH(**C**$H_3)_2$); 17.6 (CH(**C**$H_3)_2$).

MS (EI) *m/z*(%)**:** 141 (1, M^+ – CH_2); 113 (2); 99 (1, M^+ – $OCH_2CH=CH_2$); 85 (10, $iPrCH(O)CH^+$); 71 (37, $CH_2OCH_2CH=CH_2^+$); 57 (96, iPr-CH_2^+); 56 (57, iPr-CH^+); 55 (100, iPr-C^+).

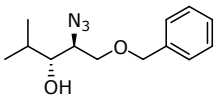
12.5.2.5. *General procedure for the synthesis of azido alcohols from oxyranyl ethers*

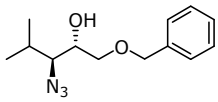


115a-e **117a-e**

In a two-necked round bottomed flask, equipped with bubble condenser, a mixture of the oxyranyl ether **115** (1.0 equiv), NaN_3 (6.0 equiv), NH_4Cl (2.0 equiv) and a 8:1 2-methoxyethanol / water mix (0.2 M) was heated to 80° C - 125° C. After completion (TLC check), the reaction mixture was cooled to room temperature, diluted in ether and quenched with H_2O. The two layers were separated and the aqueous portion was extracted with ether (four times), while the combined organic components were washed with water (four times) and brine (twice), dried over sodium sulfate, filtered and concentrated. The so-obtained crude product **117** contains two regioisomers **(2*S*,3*R*)** and **(2*S*,3*S*)**, which were employed for the next reaction without separation.

12.5.2.5.1. **<u>(2*S*,3*R*)-2-Azido-1-(benzyloxy)-4-methylpentan-3-ol</u> (117a)**
<u>(2*S*,3*S*)-3-Azido-1-(benzyloxy)-4-methylpentan-2-ol</u> (117a)


(2*S*,3*R*)


(2*S*,3*S*)

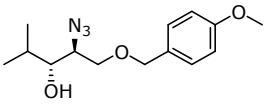
According to the general procedure, the epoxyether **115a** (1.59 g, 17.7 mmol, 1.0 equiv), NaN_3 (3.01 g, 46.3 mmol, 6.0 equiv), NH_4Cl (823.43 mg, 15.4 mmol, 2.0 equiv) and a 8:1 $CH_3CH_2CH_2OH$ / H_2O mix (38.50 mL) were heated to 125° C for 12h to give 1.64 g (6.6 mmol, 85%) of a 60:40 **117a (2*S*,3*R*)** and **117a (2*S*,3*S*)** mix.

Major regioisomer 117a
$C_{13}H_{19}O_2N_3$ **M=**249.19
^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 7.37-7.34 (5H, m, C**H** aromatics); 4.58 (2H, s, OC**H_2**Ph); 3.82-3.31 (4H, m, C**H**OH, C**H**N_3 e C**H_2**OBn); 2.15-1.96 (1H, m, C**H**$(CH_3)_2$); 1.03 (3H, d, *J*=6.6, CH$(CH_3)_2$); 0.93 (3H, d, *J*=6.6, CH(C**H_3**$)_2$).
MS (EI) *m/z*(%)**:** 220 (0.3, $M^+ + 1 - N_2$); 190 (0.3); 174 (0.1); 148 (20, M^+ – iPrCHOH – N_2); 108 (10); 91 (100, $C_7H_7^+$); 73 (20, iPrCHOH$^+$); 65 (21); 55 (27, iPr-C$^+$); 43 (57, iPr$^+$); 41 (21).

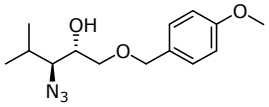
Minor regioisomer 117a
$C_{13}H_{19}O_2N_3$ **M=**249.19

^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 7.37-7.34 (5H, m, C**H** aromatics); 4.58 (2H, s, OC**H_2**Ph); 3.82-3.31 (4H, m, C**H**OH, C**H**N_3 e C**H_2**OBn); 1.89-1.78 (1H, m, C**H**$(CH_3)_2$); 0.96 (3H, d, *J*=2.0, CH(C**H_3**$)_2$); 0.93 (3H, d, *J*=2.0, CH(C**H_3**$)_2$).
MS (EI) *m/z*(%)**:** 220 (0.1, $M^+ + 1 - N_2$); 178 (1); 107 (8, $M^+ - OH - CH_2Ph$); 91 (100, $C_7H_7^+$); 72 (37, $iPrCHN^+ + 2$); 65 (16); 43 (39, iPr^+); 41 (18).

12.5.2.5.2. (2*S*,3*R*)-2-Azido-1-(4-methoxybenzyloxy)-4-methyl-pentan-3-ol (117b) (2*S*,3*S*)-3-Azido-1-(4-methoxybenzyloxy)-4-methyl-pentan-2-ol (117b)



(2*S*,3*R*)



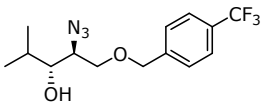
(2*S*,3*S*)

Following the general procedure, a 61:39 **117b (2*S*,3*R*)** and **66b (2*S*,3*S*)** mix (1.59 g, 5.7 mmol, 86%) was synthesized from the oxyranyl ether **115b** (1.61 g, 6.8 mmol, 1.0 equiv), NaN_3 (2.66 g, 40.9 mmol, 6.0 equiv), NH_4Cl (782.38 mg, 13.6 mmol, 2.0 equiv) and a 8:1 $CH_3CH_2CH_2OH$ / H_2O mix (34.10 mL).

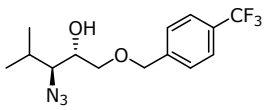
Major regioisomer 117b
$C_{13}H_{21}O_3N_3$ **M=**279.21
^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 7.30-7.26 (2H, m [BB' part of a AA'BB' spin system], C**H** *meta* aromatics to OCH_3); 6.92-6.88 (2H, m [AA' part of a AA'BB' spin system], C**H** *ortho* aromatics to OCH_3); 4.51 (2H, br-s, C**H_2**$OC_6H_4OCH_3$); 3.81 (3H, s, OC**H_3**); 3.77-3.30 (4H, m, C**H**OH, C**H**N_3 and C**H_2**$OCH_2C_6H_4OCH_3$); 2.45 (1H, br-d, *J*=5.6, O**H**); 2.07-1.96 (1H, m, C**H**$(CH_3)_2$); 1.02 (3H, d, *J*=6.8, CH(C**H_3**$)_2$); 0.93 (3H, d, *J*=6.8, CH(C**H_3**$)_2$).
MS (EI) *m/z*(%)**:** 250 (1, $M^+ + 1 - N_2$); 220 (1, $M^+ - N_2 - OCH_3$); 178 (26, M^+ – iPrCHOH – N_2); 138 (6); 121 (100, $CH_2C_6H_4OCH_3^+$); 109 (3); 91 (5, CH_2Ph^+); 73 (12, $iPrCHOH^+$); 65 (6); 55 (12, iPr-C^+); 43 (42, iPr^+); 41 (14).

Minor regioisomer 117b
$C_{13}H_{21}O_3N_3$ **M=**279.21
^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 7.30-7.26 (2H, m [BB' part of a AA'BB' spin system], C**H** *meta* aromatics to OCH_3); 6.92-6.88 (2H, m [AA' part of a AA'BB' spin system], C**H** *ortho* aromatics to OCH_3); 4.46 (2H, br-s, C**H_2**$OC_6H_4OCH_3$); 3.81 (3H, s, OC**H_3**); 3.77-3.30 (4H, m, C**H**OH, C**H**N_3 and C**H_2**$OCH_2C_6H_4OCH_3$); 2.20 (1H, br-d, *J*=4.8, O**H**); 1.88-1.74 (1H, m, C**H**$(CH_3)_2$); 0.96 (3H, d, *J*=2.7, CH(C**H_3**$)_2$); 0.93 (3H, d, *J*=2.7, CH(C**H_3**$)_2$).
MS (EI) *m/z*(%)**:** 208 (2); 180 (0.1); 162 (2); 136 (14); 121 (100, $CH_2C_6H_4OCH_3^+$); 109 (4); 91 (7, $C_7H_7^+$); 72 (50, $iPrCHN^+ + 2$); 56 (6, iPr-CH^+); 43 (30, iPr^+); 41 (16).

12.5.2.5.3. (2*S*,3*R*)-2-Azido-1-(4-trifluoromethyl-benzyloxy)-4-methyl-pentan-3-ol (117c) (2*S*,3*S*)-3-Azido-1-(4-trifluoromethyl-benzyloxy)-4-methyl-pentan-2-ol (117c)



(2*S*,3*R*)



(2*S*,3*S*)

1.74 g (6.3 mmol, 1.0 Equiv) of the epoxy ether **115c**, 2.47 g (38.0 mmol, 6.0 equiv) of NaN_3, 0.68 g (12.7 mmol, 2.0 equiv) of NH_4Cl and 31.70 mL of a 8:1 $CH_3CH_2CH_2OH$ / H_2O mix were heated, as reported in the general procedure above, to afford a 70:30 **117c (2*S*,3*R*)** and **117c (2*S*,3*S*)** mix (1.98 g, 6.2 mmol, 98%).

Major regioisomer 117c

$C_{14}H_{18}O_2N_3F_3$ **M=**317.18

^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 7.65-7.61 (2H, m [AA' part of a AA'BB' spin system], C**H** *ortho* aromatics to CF_3); 7.48-7.44 (2H, m [BB' of a AA'BB' spin system], C**H** *meta* aromatics to CF_3); 4.64 (2H, s, OC**H$_2$**$C_6H_4CF_3$); 3.91-3.32 (4H, m, C**H**OH, C**H**N_3 and C**H$_2$**$OC_6H_4CF_3$); 2.41 (1H, br-d, *J*=4.8, O**H**); 2.13-1.97 (1H, m, C**H**$(CH_3)_2$); 1.04 (3H, d, *J*=6.7, CH(C**H$_3$**$)_2$); 0.94 (3H, d, *J*=6.7, CH(C**H$_3$**$)_2$).

MS (EI) *m/z*(%)**:** 270 (0.1); 258 (0.6); 216 (12, M^+ - iPrCHOH - N_2); 188 (2); 159 (82, $CH_2C_6H_4CF_3^+$); 140 (4); 127 (5); 119 (4); 109 (15); 89 (3); 73 (46, $iPrCHOH^+$); 69 (15); 55 (48, iPr-C^+); 43 (100, iPr^+); 41 (11).

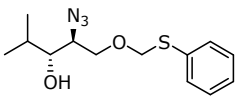
Minor regioisomer 117c

$C_{14}H_{18}O_2N_3F_3$ **M=**317.18

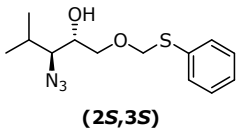
^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 7.65-7.61 (2H, m [AA' part of a AA'BB' spin system], C**H** *ortho* aromatics to CF_3); 7.48-7.44 (2H, m [BB' part of a AA'BB' spin system], C**H** *meta* aromatics to CF_3); 4.77 (2H, s, OC**H$_2$**$C_6H_4CF_3$); 3.91-3.32 (4H, m, C**H**OH, C**H**N_3 and C**H$_2$**$OC_6H_4CF_3$); 1.92-1.74 (1H, m, C**H**$(CH_3)_2$); 0.96 (6H, d, *J*=7.0, CH(C**H$_3$**$)_2$).

MS (EI) *m/z*(%)**:** 246 (0.1); 228 (1); 219 (2); 175 (3, M^+ - 1 - iPr); 159 (100, $CH_2C_6H_4CF_3^+$); 140 (3); 127 (3); 119 (3); 109 (11); 72 (14, $iPrCHN^+$ + 2); 56 (9, iPr-CH^+); 43 (68, iPr^+); 41 (21).

12.5.2.5.4. (2*S*,3*R*)-2-Azido-4-methyl-1-(phenethyloxy)pentan-3-ol (117d) (2*S*,3*S*)-3-Azido-4-methyl-1-(phenethyloxy)pentan-2-ol (117d)



(2*S*,3*R*)



(2*S*,3*S*)

According to the general procedure, (2*S*,3*R*)-2-azido-4-methyl -1- (phenethyloxy)-pentan-3-ol and (2*S*,3*S*)-2-

azido-4-methyl-1-(phenethyloxy)pentan-3-ol **117d** (1.13 g, 4.0 mmol, 92%) were obtained as 65:35 mix starting from the epoxy ether **115d** (1.05 g, 4.4 mmol, 1.0 equiv), NaN_3 (1.71 g, 26.3 mmol, 6.0 equiv), NH_4Cl (0.47 g (8.8 mmol, 2.0 equiv) and 22.00 mL of a 8:1 $CH_3CH_2CH_2OH$ / H_2O mix.

Major regioisomer 117d

$C_{13}H_{19}O_2N_3S$ **M=**281.19

^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 7.50-7.43 (2H, m, C**H** *ortho* aromatics to S); 7.36-7.22 (3H, m, C**H** *meta* and *para* aromatics to S); 5.06 (2H, m [AB spin system], OC**H_2**SPh); 3.94-3.26 (4H, m, C**H**OH, C**H**N_3 and C**H_2**OCH_2SPh); 2.26 (1H, br-d, *J*=5.2, O**H**); 2.15-1.98 (1H, m, C**H**$(CH_3)_2$); 0.94 (6H, d, *J*=6.6, CH(C**H_3**$)_2$).

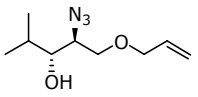
MS (EI) *m/z*(%)**:** 218 (100, M^+ – iPr – N_2); 185 (30); 154 (32); 109 (80, SPh^+); 77 (28, $C_6H_5^+$); 65 (47); 51 (28); 39 (46).

Minor regioisomer 117d

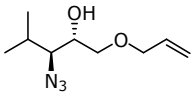
$C_{13}H_{19}O_2N_3S$ **M=**281.19

^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 7.50-7.43 (2H, m, C**H** *ortho* aromatics to S); 7.36-7.22 (3H, m, *meta* and *para* C**H** aromatics to S); 5.08 (2H, m [AB spin system], OC**H_2**SPh); 3.94-3.26 (4H, m, C**H**OH, C**H**N_3 e C**H_2**OCH_2SPh); 2.44 (1H, br-d, *J*=4.4, O**H**); 1.99-1.75 (1H, m, C**H**$(CH_3)_2$); 1.02 (6H, d, *J*=7.0, CH(C**H_3**$)_2$).

12.5.2.5.5. <u>(2*S*,3*R*)-1-Allyloxy-2-azido-4-methylpentan-3-ol (117e)</u> <u>(2*S*,3*S*)-1-Allyloxy-3-azido-4-methylpentan-2-ol (117e)</u>



(2*S*,3*R*)



(2*S*,3*S*)

Following the general procedure 0.94 g (6.0 mmol, 1.0 equiv) of the epoxy ether **115e**, 2.35 g (36.1 mmol, 6.0 equiv) of NaN_3, 0.64 g (12.0 mmol, 2.0 equiv) of NH_4Cl and 30.10 mL of a 8:1 $CH_3CH_2CH_2OH$ / H_2O mix were mixed at 125° C to give a 70:30 **117e (2*S*,3*R*)** and **117e (2*S*,3*S*)** mix (0.60 g, 3.2 mmol, 54%).

Major regioisomer 117e

$C_9H_{17}O_2N_3$ **M=**185.15

^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 6.02-5.82 (1H, m, C**H**=CH_2); 5.34-4.97 (2H, m, CH=C**H_2**); 4.05 (2H, dd, *J*=5.6, 1.2, C**H_2** allylic group); 3.88-3.05 (4H, m, C**H**OH, C**H**N_3 and C**H_2**OCH_2CH=CH_2); 2.12-1.96 (1H, m, C**H**$(CH_3)_2$); 1.05 (3H, d, *J*=6.6, CH(C**H_3**$)_2$); 0.94 (3H, d, *J*=6.6, CH(C**H_3**$)_2$).

MS (EI) *m/z*(%)**:** 171 (1, M^+ – N_2); 141 (4, M^+ – CH_2); 128 (6); 112 (2); 98 (22, iPrCHCH(N)CH^+); 84 (8); 82 (5); 56 (100, iPrCH^+); 43 (38, iPr^+); 41 (23).

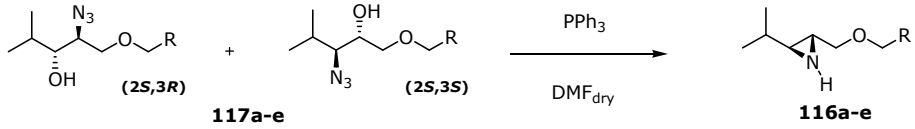
Minor regioisomer 117e

$C_9H_{17}O_2N_3$ **M=**185.15

^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 6.02-5.82 (1H, m, C**H**=CH_2); 5.34-4.97 (2H, m, CH=C**H_2**); 3.98 (2H, m, C**H_2** allylic group); 3.88-3.05 (4H, m, C**H**OH, C**H**N_3 and

C**H**$_2$OCH$_2$CH=CH$_2$); 1.90-1.70 (1H, m, C**H**(CH$_3$)$_2$); 0.98 (3H, d, *J*=2.8, CH(C**H$_3$**)$_2$); 0.88 (3H, d, *J*=2.8, CH(C**H$_3$**)$_2$).

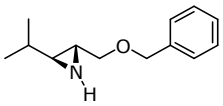
12.5.2.6. *General procedure for the synthesis of azidoalcohols from oxyranyl ethers*[159, 235]



117a-e **116a-e**

Triphenylphosphine (1.0 equiv) was added portionwise to a stirred solution of azidoalcohol **117** (1.0 equiv) in anhydrous DMF (0.25 M) precooled at 0° C in a three-necked round bottomed flask, equipped with a bubble condenser, under nitrogen. The resulting reaction mixture was stirred for 1h at 0° C, then, for another hour at 25° C and, finally, it was heated to 90° C during the next 3h. After this period the temperature was allowed to return to 25 °C and the mixture was kept under stirring overnight. After completion of the reaction (TLC monitoring), the mixture was partitioned between water and ether. The two phases were separated and the aqueous portion was extracted several time with DEE, while the organic layers were combined, washed with H_2O (five times) and brine (twice) and dried over Na_2SO_4. After filtration and concentration *in vacuo* the desired aziridine **116** was obtained as mixture with triphenylphosphine and the corresponding triphenylphosphinoxide. This mixture was used for the next reactions without purifications.

12.5.2.6.1. (2*R*,3*S*)-2-(Benzyloxy)methyl-3-*iso*-propylaziridine (116a)



According to the general procedure 1.72 g (6.6 mmol, 1.0 equiv) of PPh_3, 1.64 g (6.6 mmol, 1.0 equiv) of the azidoalcohol **117a** and 26.30 mL of dried DMF were mixed to afford 3.24 g of the crude product **116a**.

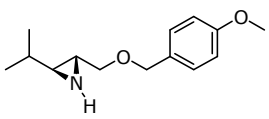
116

C$_{16}$H$_{23}$O$_3$NS **M=**205.19

^{1}H-NMR δ (CDCl$_3$, 200 MHz)**:** 7.30-7.40 (5H, m, C**H** aromatics); 4.55 (2H, s, C**H$_2$**Ph); 3.62 (1H, dd, *J*=10.6, 4.2, C**H**H'OBn); 3.41 (1H, dd, *J*=10.6, 5.7, CH**H'**OBn); 1.98 (1H, m, C**H**CH$_2$ aziridinic); 1.62 (1H, dd, *J*= 7.5, 3.1, iPrC**H** aziridinic); 1.30-1.15 (1H, m, C**H**(CH$_3$)$_2$); 0.98 (6H, ps-t, *J*=6.4, CH(C**H$_3$**)$_2$).

MS (EI) *m/z*(%)**:** 204 (0.1, M$^+$ – H); 190 (0.6); 162 (1, M$^+$ – iPr); 146 (2); 132 (2);114 (2); 98 (24, M$^+$ – OBn); 97 (60, iPrCH(NH)CHCH$^+$); 91 (100, C$_7$H$_7^+$); 82 (84, iPrCH(N)C$^+$); 68 (26); 65 (26); 56 (78, iPrCH$^+$); 54 (83).

12.5.2.6.2. (2*R*,3*S*)-2-(4-Methoxybenzyloxy)methyl-3-*iso*-propyl-aziridine (116b)



According to the general procedure reported above, 1.49 g (5.6 mmol, 1.0 equiv) of PPh_3, 1.59 g (5.7 mmol, 1.0 equiv) of the azidoalcohol **117b** and 22.70 mL of dried DMF were mixed to afford 4.24 g of the crude product **116b**.

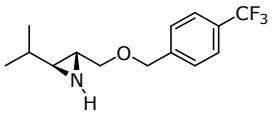
116

$C_{14}H_{21}O_2N$ **M=**235.21

^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 7.29-7.24 (2H, m [BB' part of a AA'BB' spin system], C**H** *meta* aromatics to OMe); 6.90-6.86 (2H, m [AA' part of a AA'BB' spin system], C**H** *ortho* aromatic to OMe); 4.48 (2H, s, C**H$_2$**C_6H_4OMe); 3.80 (3H, s, OC**H$_3$**); 3.70-3.50 (1H, m, C**H**H'$OCH_2C_6H_4$OMe); 3.36 (1H, dd, *J*=10.6, 5.8, CH**H**'$OCH_2C_6H_4$OMe); 1.80-2.05 (1H, m, C**H**CH_2 aziridinic); 1.59 (1H, dd, *J*=7.2, 2.4, iPrC**H** aziridinic); 1.28-1.16 (1H, m, C**H**$(CH_3)_2$); 0.99 (6H, ps-t, *J*=6.6, CH(C**H$_3$**)$_2$).

MS (EI) *m/z*(%)**:** 220 (0.2, $M^+ - CH_3$); 192 (1, M^+ – iPr); 175 (5); 162 (2); 136 (14, $M^+ - CH_2OCH_2C_6H_4OCH_3$); 121 (69, $CH_2C_6H_4OCH_3^+$); 109 (4); 91 (5, $C_7H_7^+$); 77 (10, $C_6H_5^+$); 56 (100, iPrCH^+) 55 (14, iPrC^+); 54 (14).

12.5.2.6.3. (2*R*,3*S*)-2-(4-(Trifluoromethylbenzyloxy)methyl-3-*iso*-propylaziridine (116c)



The aziridine **116c** (3.28 g) was synthesized from 1.64 g (6.3 mmol, 1.0 equiv) of PPh_3, 1.98 g (6.3 mmol, 1.0 equiv) of the azidoalcohol **117c** and 25.00 mL of anhydrous DMF, as reported on the general experimental procedure.

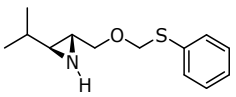
116c

$C_{14}H_{18}ON_3F_3$ **M=**273.18

^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 7.62-7.55 (2H, m [AA' part of a AA'BB' spin system], C**H** *ortho* aromatics to CF_3); 7.49-7.42 (2H, m [BB' part of a AA'BB' spin system], C**H** *meta* aromatics to CF_3); 4.60 (2H, s, C**H$_2$**$C_6H_4CF_3$); 3.64 (1H, dd, *J*=10.6, 4.4, C**H**H'$OCH_2C_6H_4CF_3$); 3.40 (1H, dd, *J*=10.5, 6.1, CH**H'**$OCH_2C_6H_4CF_3$); 2.04-1.97 (1H, m, C**H**CH_2 aziridinic); 1.62 (1H, dd, *J*=7.6, 2.8, iPrC**H** aziridinic); 1.25-1.16 (1H, m, C**H**$(CH_3)_2$); 1.00 (6H, ps-t, *J*=6.2, CH(C**H$_3$**)$_2$).

MS (EI) *m/z*(%)**:** 258 (1); 230 (1); 194 (3); 173 (2); 159 (49, $CH_2C_6H_4CF_3^+$); 145 (3, $C_6H_4CF_3^+$); 127 (5); 119 (5); 97 (45); 82 (88, iPrCH(N)CH^+); 56 (82); 54 (100); 43 (43, iPr$^+$); 41 (56).

12.5.2.6.4. (2*R*,3*S*)-2-(Phenylthio)methoxy-methyl-3-*iso*-propylaziridine (116d)



Following the general procedure, the aziridine **116d** (1.95 g) was synthesized from 1.05 g (4.0 mmol, 1.0 equiv) of PPh_3, 1.13 g (4.0 mmol, 1.0 equiv) of the azidoalcohol **117d** and 16.00 mL of dried DMF.

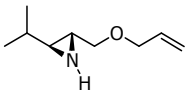
116d

$C_{13}H_{19}ONS$ **M=**237.19

^{1}H-NMR δ($CDCl_3$, 200 MHz)**:** 7.50-7.32 (2H, m, C**H** *ortho* aromatics to S); 7.27-7.15 (3H, m, C**H** *meta* and *para* aromatics to S); 4.96 (2H, m [AB spin system], OC**H_2**SPh); 3.78 (1H, dd, *J*=10.4, 4.4, C**H**H'OCH_2SPh); 3.52 (1H, dd, *J*=10.4, 6.0, CH**H'**OCH_2SPh); 1.91 (1H, m, C**H**CH_2 aziridinic); 1.55 (1H, dd, *J*=6.8, 2.2, iPrC**H** aziridinic); 1.47 (1H, m, C**H**$(CH_3)_2$); 0.98 (6H, ps-t, *J*=7.0, CH(C**H_3**$)_2$).

MS (EI) *m/z*(%)**:** 262 (100); 183 (88); 170 (3); 157 (5); 152 (12); 108 (46, SPh^+); 91 (1, $C_7H_7^+$); 77 (4, $C_6H_5^+$); 57 (5); 51 (15); 39 (8).

12.5.2.6.5. (2*R*,3*S*)-2-(Allyloxy)methyl-3-*iso*-propylaziridine (116e)



According to the general procedure, the aziridine **116e** (2.52 g) was obtained from 0.85 g (3.3 mmol, 1.0 equiv) of PPh_3, 0.60 g (3.3 mmol, 1.0 equiv) of the azidoalcohol **117e** and 13.00 mL of dried DMF.

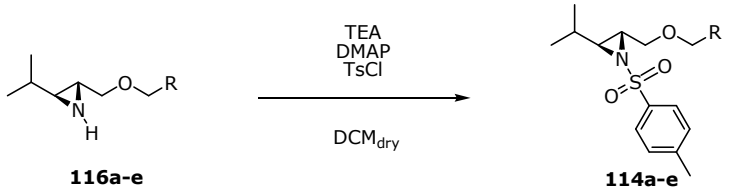
116e

$C_9H_{17}ON$ **M=**155.17

^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 6.01-5.82 (1H, m, C**H**=CH_2); 5.33-5.06 (2H, m, CH=C**H_2**); 4.02 (2H, br-d, *J*=5.8, C**H** allylic group); 3.59 (1H, dd, *J*=10.6, 4.4, C**H**H'OCH_2CH=CH_2); 3.37 (dd, *J*=10.6, 5.6, CH**H'**OCH_2CH=CH_2); 2.00-1.93 (1H, m, C**H**CH_2 aziridinic); 1.62 (dd, 1H, *J*=7.7, 3.0, iPrC**H** aziridinic); 1.35-1.13 (1H, m, C**H**$(CH_3)_2$); 1.01 (6H, ps-t, *J*=6.6, CH(C**H_3**$)_2$).

MS (EI) *m/z*(%)**:** 112 (22, M^+ – iPr); 98 (12, M^+ – OCH_2CH=CH_2); 97 (5, iPrCH(NH)$CHCH^+$); 82 (57, iPrCH(N)C^+); 70 (21); 68 (15); 57 (8, OCH_2CH=CH_2^+); 56 (42, iPrCH^+); 55 (40, iPrC^+); 54 (83); 43 (29, iPr$^+$); 41 (100, CH_2CH=CH_2).

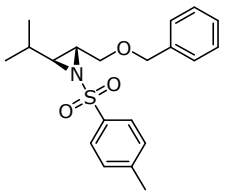
12.5.2.7. *General procedure for the protection of the aziridinic nitrogen*



116a-e **114a-e**

In a Schlenk tube, under nitrogen, triethylamine (1.5 equiv), DMAP (catalytic amount) and TsCl (1.1 equiv) were sequentially added to a solution of the aziridine **116** (1.0 equiv) in dried dichloromethane (0.5 M) at 0° C and under N_2. Then the resulting reaction mixture was stirred at room temperature. After completion the reaction (TLC monitoring), the mixture was quenched with a 1N aqueous HCl solution and extracted in DCM. The combined organic layers were washed with a saturated aq. $NaHCO_3$ solution and brine, filtered and concentrated. The residue was, then, purified to afford the pure aziridine **114**.

12.5.2.7.1. (2*R*,3*S*)-2-(Benzyloxy)methyl-3-*iso*-propyl-*N*-(*para*-toluensulfonyl)aziridine (114a)



Following the general procedure, the aziridine **116a** (3.24 g, 6.6 mmol, 1.0 equiv), TEA (1.38 mL, 7.9 mmol, 1.5 equiv), DMAP and TsCl (1.38 g, 7.2 mmol, 1.1 equiv) were mixed to afford, after flash chromatography (silica, eluent: 8:1 petroleum ether/ethyl acetate), 1.65 g (4.6 mmol, 70%) of the pure aziridine **114a**.

114a

$C_{20}H_{25}O_3NS$ **M=**359.25

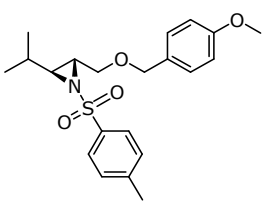
^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 7.87-7.83 (2H, m [AA' part of a AA'BB' spin system], C**H** *ortho* aromatics to SO_2); 7.33-7.24 (7H, m, C**H** *meta* aromatics to SO_2 [BB' part of a AA'BB' spin system] and C**H** aromatics Ph); 4.52 (2H, s, C**H$_2$**Ph); 3.94 (1H, dd, *J*=10.4, 5.8, C**H**H'OBn); 3.82 (1H, dd, *J*=10.4, 6.2, CH**H'**OBn); 2.85-2.95 (1H, m, C**H**CH_2 aziridinic); 2.63 (1H, dd, *J*=8.2, 4.6, iPrC**H** aziridinic); 2.41 (3H, s, C**H$_3$** tosyl group); 1.78-1.55 (1H, m, C**H**$(CH_3)_2$); 0.94 (3H, d, *J*=6.8, CH(C**H$_3$**)$_2$); 0.88 (3H, d, *J*=6.8, CH(C**H$_3$**)$_2$).

^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 143.7 (**C$_q$** *para* aromatic to SO_2); 137.6 (**C$_{ipso}$** aromatic to CH_2); 137.1 (**C$_{ipso}$** aromatic to SO_2); 129.2 (2C, **C**H *meta* aromatics to SO_2); 128.1 (2C, **C**H *ortho* aromatics to CH_2); 127.5 (3C, **C**H *meta* and *para* aromatics to CH_2); 127.4 (2C, **C**H *ortho* aromatics to SO_2); 73.1 (**C**H_2Bn); 67.7 (**C**H_2OCH_2Bn); 53.0 (**C**H aziridinic); 47.2 (**C**H aziridinic); 29.6 (**C**H$(CH_3)_2$); 21.6 (**C**H_3 tosyl group); 20.2 (CH(**C**$H_3)_2$); 19.9 (CH(**C**$H_3)_2$).

MS (EI) *m/z*(%)**:** 360 (0.02, M^+ + H); 260 (4); 210 (29, M^+ – iPr – OBn); 204 (8, M^+ – Ts); 155 (16, Ts^+); 91 (100, Bn^+ and $C_7H_7^+$ of Ts); 65 (18).

12.5.2.7.2. (2*R*,3*S*)-2-(4-Methoxy-benzyloxy)-methyl-3-*iso*-propyl-*N*-(*para*-toluensulfonyl)aziridine (114b)

The tosyl aziridine **114b** (1.02 g, 2.6 mmol, 46%) was obtained, as reported in the general procedure described above, starting from the aziridine **116b** (4.24 g, 5.7 mmol, 1.0 equiv), TEA (1.19 mL, 8.5 mmol, 1.5 equiv), DMAP, TsCl (1.19 g,



8.5 mmol, 1.5 eq) and 12.00 ml of anhydrous DCM, after purification *via* flash column chromatography on silica gel with a 8:1 petroleum ether/ethyl acetate mix as eluent.

114b

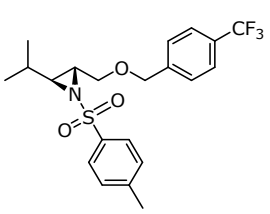
$C_{21}H_{27}O_4NS$ **M=**389.27

^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 7.87-7.83 (2H, m [AA' part of a AA'BB' spin system], C**H** *ortho* aromatics to SO_2); 7.29-7.26 (2H, m [BB' part of a AA'BB' spin system], C**H** *meta* aromatics to SO_2); 7.23-7.19 (2H, m [BB' part of a AA'BB' spin system], C**H** *meta* aromatics to OMe); 6.88-6.84 (2H, m [AA' part of a AA'BB' spin system], C**H** *ortho* aromatics to OMe); 4.45 (2H, s, C**H$_2$**C_6H_4OMe); 3.92 (1H, dd, *J*=10.8, 5.8, C**H**H'$OCH_2C_6H_4$OMe); 3.81 (3H, s, OC**H$_3$**); 3.78 (1H, dd, *J*=10.8, 5.8, CH**H'**$OCH_2C_6H_4$OMe); 2.91-2.83 (1H, m, C**H**CH_2 aziridinic); 2.61 (1H, dd, *J*=8.2, 4.4, iPrC**H** aziridinic); 2.42 (3H, s, C**H$_3$** tosyl group); 1.72-1.51 (1H, m, C**H**$(CH_3)_2$); 0.93 (3H, d, *J*=6.6, CH(C**H$_3$**)$_2$); 0.86 (3H, d, *J*=6.6, CH(C**H$_3$**)$_2$).

^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 158.7 (**C_{ipso}** aromatic to OMe); 143.4 (**C_q** *para* aromatic to SO_2); 136.8 (**C_{ipso}** aromatic to SO_2); 129.4 (**C_q** *para* aromatic to OMe); 128.9 (2C, **C**H *meta* aromatic to SO_2); 128.8 (2C, **C**H *meta* aromatic to OMe); 127.2 (2C, **C**H *ortho* aromatic to SO_2); 113.3 (2C, **C**H *ortho* aromatic to OMe); 72.4 (**C**$H_2C_6H_4$OMe); 67.1 (**C**$H_2OCH_2C_6H_4$OMe); 54.9 (O**C**H_3); 52.7 (**C**H aziridinic); 47.1 (**C**H aziridinic); 29.3 (**C**H$(CH_3)_2$); 21.3 (**C**H_3 tosyl group); 19.9 (1C, CH(**C**$H_3)_2$); 19.6 (1C', CH(**C**$H_3)_2$).

MS (EI) *m/z*(%)**:** 316 (0.02); 290 (6); 234 (35, M^+ – Ts); 210 (36, M^+ – $OCH_2C_6H_4$OMe – iPr); 155 (35, Ts^+); 137 (21, $OCH_2C_6H_4OMe^+$); 121 (100, $CH_2C_6H_4OMe^+$); 98 (22); 91 (43, $C_7H_7^+$); 77 (14, $C_6H_5^+$); 65 (14); 55 (12).

12.5.2.7.3. (2*R*,3*S*)-2-(4-Trifluoromethyl-benzyloxy)methyl-3-*iso*-propyl-*N*-(*para*-toluensulfonyl)aziridine (114c)



The aziridine **116c** (3.28 g, 6.2 mmol, 1.0 equiv) was converted into the tosyl aziridine **114c** (1.53 g, 3.6 mmol, 58%) by reaction with TEA (1.30 mL, 9.4 mmol, 1.5 equiv), DMAP (catalytic amount) and TsCl (1.31 g, 6.9 mmol,1.1 equiv) in dried DCM (12.50 mL) and a further purification (flash chromatography on silica gel, eluent: 6:1 petroleum ether/ethyl acetate).

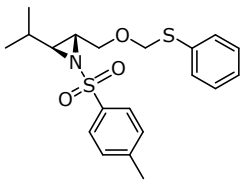
114c

$C_2H_{24}O_3NSF_3$ **M=**427.24

^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 7.87-7.82 (2H, m [AA' part of a AA'BB' spin system], C**H** *ortho* aromatics to SO_2); 7.60-7.56 (2H, m [AA' of a AA'BB' spin system], C**H** *ortho* aromatics to CF_3); 7.40-7.36 (2H, m [BB' part of a AA'BB' spin system], C**H** *meta* aromatics to SO_2); 7.28-7.24 (2H, m [BB' part of a AA'BB' spin

system], C**H** *meta* to CF_3); 4.48 (2H, s, C$\mathbf{H_2}C_6H_4CF_3$); 4.01-3.82 (2H, m, C$\mathbf{H_2}OCH_2C_6H_4CF_3$); 2.96-2.87 (1H, m, C**H**CH_2 aziridinic); 2.63 (1H, dd, *J*=8.4, 4.6, iPrC**H** aziridinic); 2.41 (3H, s, C$\mathbf{H_3}$ tosyl group); 1.67 (1H, ps-oct, *J*=7.0, C**H**$(CH_3)_2$); 0.94 (3H, d, *J*=6.8, CH(C$\mathbf{H_3}$)$_2$); 0.87 (3H, d, *J*=6.8, CH(C$\mathbf{H_3}$)$_2$).
^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 143.6 (**C$_q$** *para* aromatic to CF_3); 141.8 (**C** *para* aromatic to SO_2); 136.9 (**C$_{ipso}$** aromatic SO_2); 129.0 (4C, **C**H *ortho* and *meta* aromatics to SO_2); 127.3 (2C, **C**H *meta* aromatics to CF_3); 127.0 (2C, **C**H *ortho* aromatics to CF_3); 124.8 (**C$_{ipso}$** aromatic to CF_3); 124.7 (**C**F_3); 71.8 (**C**$H_2C_6H_4CF_3$); 67.9 (**C**$H_2OCH_2C_6H_4CF_3$); 52.5 (**C**H aziridinic); 47.0 (**C**H aziridinic); 29.3 (**C**H$(CH_3)_2$); 21.2 (**C**H_3 tosyl group); 19.9 (1C, CH(**C**$H_3)_2$); 19.6 (1C', CH(**C**$H_3)_2$).
MS (EI) *m/z*(%)**:** 354 (1); 328 (4); 272 (14, M^+ – Ts); 210 (15, M^+ – $OCH_2C_6H_4CF_3$ – iPr); 159 (100, $CH_2C_6H_4CF_3^+$); 109 (9); 91 (25, $C_7H_7^+$); 65 (9).

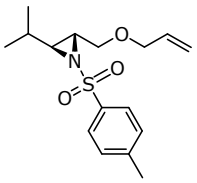
12.5.2.7.4. (2*R*,3*S*)-2-(Phenylthio-methoxy)methyl-3-*iso*-propyl-*N*-(*para*-toluensulfonyl)aziridine (114d)



Following the general procedure reported above, the aziridine **114d** (0.28 g, 0.7 mmol, 35%) was obtained from the aziridine **116d** (0.97 g, 2.0 mmol, 1.0 equiv) by reaction with TEA (0.42 mL, 3.0 mmol, 1.5 equiv), DMAP, TsCl (0.42 g, 2.2 mmol, 1.1 equiv) in DCM (4.00 mL) and was then purified by flash chromatography on silica gel (eluent: 5:1 petroleum ether/ethyl acetate).

114d
$C_{20}H_{25}O_3NS_2$ **M=**391.25
^{1}H-NMR δ($CDCl_3$, 200 MHz)**:** 7.86-7.82 (2H, m [AA' part of a AA'BB' spin system], C**H** *ortho* aromatics to SO_2); 7.47-7.43 (2H, m [BB' part of a AA'BB' spin system], C**H** *meta* aromatics to SO_2); 7.33-7.25 (5H, m, C**H** aromatics to SPh); 4.99 (2H, m [AB spin system], OC$\mathbf{H_2}$SPh); 4.02 (2H, d_{app}, *J*=6.0, C$\mathbf{H_2}OCH_2$SPh); 2.90-2.81 (1H, m, C**H**CH_2 aziridinic); 2.61 (1H, dd, *J*=8.3, 4.5, iPrC**H** aziridinic); 2.42 (3H, s, C$\mathbf{H_3}$ tosyl group); 1.69-1.50 (1H, m, C**H**$(CH_3)_2$); 0.92 (3H, d, *J*=10.2, CH(C$\mathbf{H_3}$)$_2$); 0.85 (3H, d, *J*=10.2 CH(C$\mathbf{H_3}$)$_2$).
^{13}C-NMR{^{1}H} δ($CDCl_3$, 50 MHz)**:** 143.8 (**C$_q$** *para* aromatic to SO_2); 136.9 (**C$_{ipso}$** aromatic to SO_2); 135.4 (**C$_{ipso}$** aromatic to S); 129.8 (2C, **C**H *meta* aromatics to SO_2); 129.2 (2C, **C**H *meta* aromatics to S); 128.7 (2C, **C**H *ortho* aromatics to SO_2); 127.4 (2C, **C**H *ortho* aromatics to S); 126.5 (**C**H *para* aromatics to S); 76.0 (**C**H_2SPh); 65.7 (**C**H_2OCH_2SPh); 53.0 (**C**H aziridinic); 46.7 (**C**H aziridinic); 29.5 (**C**H$(CH_3)_2$); 21.6 (**C**H_3 tosyl group); 20.1 (1C, CH(**C**$H_3)_2$); 19.7 (1C', CH(**C**$H_3)_2$).
MS (EI) *m/z*(%)**:** 391 (0.1, M^+); 348 (1, M^+ – iPr); 282 (10, M^+ – SPh); 252 (11, M^+ – CH_2OSPh); 226 (50); 184 (21); 155 (60, Ts^+); 139 (19, CH_2OSPh^+); 123 (24); 109 (7, SPh^+); 91 (100, $C_7H_7^+$); 82 (24); 65 (20); 45 (46); 41 (28).

12.5.2.7.5. (2*R*,3*S*)-2-(Allyloxy)methyl-3-*iso*-propyl-*N*-(*para*-toluensulfonyl)aziridine (114e)



According to the general procedure, the aziridine **114e** (0.19 g, 0.6 mmol, 13%) was synthesized from the aziridine **116e** (2.52 g, 3.3 mmol, 1.0 equiv) by reaction with TEA (0.68 mL, 4.9 mmol, 1.5 equiv), DMAP and TsCl (0.68 g, 3.6 mmol, 1.1 equiv) in DCM (6.50 mL) and then purified by flash chromatography (silica, eluent: 8:1 petroleum ether/ethyl acetate).

114e

$C_{20}H_{25}O_3NS$ **M=**309.23

^{1}H-NMR δ ($CDCl_3$, 400 MHz)**:** 7.85-7.81 (2H, m [AA' part of a AA'BB' spin system], C**H** *ortho* aromatics to SO_2); 7.30-7.21 (2H, m [BB' part of a AA'BB' spin system], C**H** *meta* aromatics to SO_2); 5.94-5.74 (1H, m, C**H**=CH_2); 5.26-5.13 (2H, m, CH=C**H$_2$**); 3.97 (2H, br-d, *J*=5.2, C**H$_2$** allylic group); 3.84 (1H, dd, *J*=11.0, 6.0, C**H**H'OCH_2CH=CH_2); 3.76 (dd, *J*=11.0, 6.3, CH**H**'OCH_2CH=CH_2); 2.88-2.80 (1H, m, C**H**CH_2 aziridinic); 2.63 (dd, 1H, *J*=8.3, 4.8, iPrC**H** aziridinic); 2.40 (3H, s, C**H$_3$** tosyl group); 1.58-1.69 (1H, m, C**H**$(CH_3)_2$); 0.92 (3H, d, *J*=6.8, CH(C**H$_3$**)$_2$); 0.84 (3H, d, *J*=6.8, CH(C**H$_3$**)$_2$).

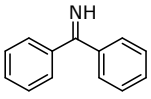
^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 136.3 (**C$_q$** *para* aromatic to SO_2); 130.0 (**C$_{ipso}$** aromatic to SO_2); 129.2 (2C, **C**H *meta* aromatics to SO_2); 127.5 (2C, **C**H *ortho* aromatics to SO_2); 127.4 (**C**H=CH_2); 117.1 (CH=**C**H_2); 72.0 (**C**H_2OCH_2CH=CH_2); 67.4 (**C**H_2CH=CH_2); 53.1 (**C**H aziridinic); 47.2 (**C**H aziridinic); 29.6 (**C**H$(CH_3)_2$); 21.7 (**C**H_3 tosyl group); 20.1 (CH(**C**H_3)$_2$); 19.8 (CH(**C**H_3)$_2$).

MS (EI) *m/z*(%)**:** 266 (1, M^+ – CH_2CH=CH_2); 252 (3); 238 (10, M^+ – CH_2OCH_2CH=CH); 210 (24, M^+ – iPr – OCH_2CH=CH_2); 198 (5); 155 (36, Ts^+); 126 (47); 91 (100, $C_7H_7^+$); 85 (15); 70 (57); 65 (39); 55 (46, $iPrC^+$).

12.6. Synthesis of Chiral Lithium Amides

12.6.1. Synthesis of chiral aminopyrrolidines from 1-benzyl-3-amino-pyrrolidine

12.6.1.1. *N*,*N*-Diphenylmethanimine (248)[16]



In a three-necked round bottomed flask, purged and flamed under vacuum, some drops of bromobenzene were added to a suspension of magnesium (4.00 g, 165.0 mmol, 1.4 eq) in 6.00 mL of freshly distilled DEE at room temperature and under argon. Then a solution of bromobenzene (15.80 mL, 150.0 mmol, 1.2 equiv) in 36.00 mL of dry Et_2O was added dropwise in 30 minutes at room temperature.

When the addition was concluded the reaction mixture was placed at reflux for 1.5 hours. The flask was then cooled to room temperature and a solution of 12.25 mL (120.0 mmol, 1.0 equiv) of benzonitrile in 28.00 mL of dry Et_2O was added dropwise in a period of 30 minutes. The resultant reaction mixture was kept stirring under argon atmosphere at room temperature for one night. After TLC monitoring (4:1 petroleum ether/ethyl acetate) the temperature was cooled to 0° C and 60.00 mL of dry methanol were added dropwise. The quenched mixture was kept under stirring for one hour, then it was filtered on a celite pad (the corresponding precipitate is magnesium bromomethylate) and washed with DEE to afford, after evaporation of the solvent, 24.07 g of the crude product **248**, as an orange oil. The purification through distillation at reduced pressure gave 15.58 g (86.0 mmol, 72%) of the pure product **248** in the form of a yellow oil.

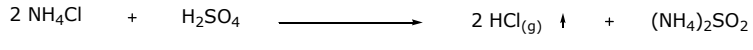
248

$C_{13}H_{11}N$ **M**=181.11

^{1}H-NMR δ ($CDCl_3$, 300 MHz)**:** 9.65 (1H, s, C=N**H**); 7.60-7.57 (4H, m, C**H** *ortho* aromatics to C=NH); 7.48-7.42 (6H, m, C**H** *meta* and *para* aromatics to C=NH).

^{13}C-NMR{^{1}H} δ ($CDCl_3$, 75 MHz)**:** 178.2 (Ph_2**C**=NH); 139.2 (2C, **C_{ipso}** aromatic to C=NH); 130.2 (2C, **C**H *para* aromatics to C=NH); 128.3 (8C, **C**H *ortho* and *meta* aromatics to C=NH).

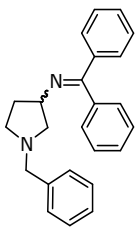
12.6.1.2. Preparation of an ethereal solution of hydrochloridric acid (323)



321 **322** **323**

In a two necked round bottomed flask, equipped with a dropping funnel and joined to a trap full of dry diethyl ether, under argon, 8.0 mL (149.7 mmol, 1.0 equiv) of 98% sulfuric acid **322** were added dropwise in 30 minutes to NH_4Cl in powder **321** (16.30 g, 305.0 mmol, 2.0 equiv) and the mixture was vigorously stirred until the gaseous HCl **323**, which was formed stopped bubbling into dry Et_2O. The resulting solution **323** was, then, titrated with a standard solution of 4N NaOH, using phenolphthalein as the indicator (c≈3.5 M).

12.6.1.3. 1-Benzyl-3-((*N*-diphenylmethylidene)amino)pyrrolidine (250a)[16]



In a two-necked round bottomed flask (250 mL), equipped with a bubble condenser fitted to a balloon of dried argon, a solution of HCl in dry Et_2O **323** (3.5 M, 10.40 mL, 36.4 mmol, 1.23 equiv) was added dropwise to a stirred solution of 1-benzyl-3-aminopyrrolidine (5.23 g, 29.7 mmol, 1.0 equiv) in 100.00 mL of freshly distilled diethyl ether in a 30' period. Then, the solvent

was evaporated and the residue was dissolved in 90.00 mL of freshly distilled DCM. Finally a solution of 6.47 g (35.7 mmol, 1.2 equiv) of the imine **248** in 15.00 mL dry DCM was added dropwise at room temperature and the resultant reaction mixture was kept under stirring overnight at room temperature. The day after the TLC monitoring (4:1 petroleum ether/ethyl acetate) showed the total disappearance of the starting material. Therefore the mixture was filtered through a celite pad and washed with ethyl acetate. After evaporation of the solvents, the residue was dissolved in diethyl ether and filtered again. Finally, after evaporation of the solvent under vacuum, 11.19 g (29.7 mmol, 100%) of the crude product **250a** were obtained, as an orange oil, which were used for the next reaction without further purifications.

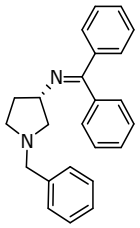
250a

$C_{24}H_{24}N_2$ **M**=340.24

^{1}H-NMR δ ($CDCl_3$, 300 MHz)**:** 7.70-7.00 (15H, m, C**H** aromatics); 3.92-3.88 (1H, m, C**H**NH=C$(Ph)_2$); 3.64-3.52 (2H, m [AB spin system], C**H_2**Ph); 2.77 (1H, dd, *J*=9.1, 7.0, NC**H**H'CHN=C$(Ph)_2$); 2.70-2.57 (2H, m, NC**H_2**CH_2CHN=C$(Ph)_2$); 2.52 (1H, dd, *J*=9.1, 6.1, NCH**H'**CHN=C$(Ph)_2$); 2.00-1.77 (2H, m, NCH_2C**H_2**CHN=C$(Ph)_2$).

^{13}C-NMR{^{1}H} δ ($CDCl_3$, 75 MHz)**:** 167.0 (N=**C**$(Ph)_2$); 139.9 (**C_{ipso}** aromatic to C=N); 139.1 (**C_{ipso}** aromatic to CH_2); 137.2 (**C'$_{ipso}$** aromatic to C=N); 129.8 (1C, **C**H *para* aromatic to C=N); 128.9 (2C, **C**H *ortho* aromatic to C=N); 128.4 (2C, **C**H *meta* aromatics to C=N); 128.3 (2C, **C**H *ortho* aromatics to CH_2); 128.2 (**C**H *para* aromatic to CH_2); 128.1 (2C, **C**H *meta* aromatics to CH_2); 128.0 (2C', **C**H *ortho* aromatics to C=N); 127.8 (2C', **C**H *meta* aromatics to C=N); 126.8 (1C', **C**H *para* aromatic to C=N); 61.6 (N**C**H_2CHN=C$(Ph)_2$); 60.8 (NCH_2**C**HN=C$(Ph)_2$); 60.3 (N**C**H_2CH_2CHN=C$(Ph)_2$); 53.7 (**C**H_2Ph); 33.4 (NCH_2**C**H_2CHN=C$(Ph)_2$).

12.6.1.4. (S)-(Benzyl-3-((*N*-diphenylmethylidene)amino)pyrrolidine (250a)[16]



Following the same procedure of the previous reaction, 6.00 mL (3.1 M, 18.6 mmol, 1.1 equiv) of a HCl solution in dry DEE was added dropwise to a stirred solution of (*S*)-1-benzyl-3-aminopyrrolidine (3.11 g, 17.6 mmol, 1.0 equiv) in 60.00 mL of freshly distilled diethyl ether in a 30' period at 0° C. After 30 minutes by stirring at room temperature, the solvent was evaporated and the resultant white solid was dissolved in 50.00 mL of freshly distilled DCM. At this point a solution of the imine **248** (3.83 g, 21.1 mmol, 1.2 equiv) in 20.00 mL of freshly distilled DCM was added dropwise. After one night the reaction was over (check by TLC: 4:1 petroleum ether/ethyl acetate) and was then worked up following the same procedure used for the previous reaction. 6.17 g (17.6 mmol, 100%) Of desired

product **250a**, as a deep yellow oil, were obtained. The crude compound was used for the next reaction without any purification.

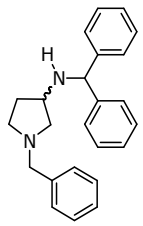
250a (3*S*)

$C_{24}H_{24}N_2$ **M**=340.24

^{1}H-NMR δ ($CDCl_3$, 300 MHz)**:** 7.54-7.00 (15H, m, C**H** aromatics); 3.95-3.86 (1H, m, C**H**NH=C(Ph)$_2$); 3.66-3.53 (2H, m [AB spin system], C**H$_2$**Ph); 2.78 (1H, dd, *J*=9.1, 7.0, NC**H**H'CHN=C(Ph)$_2$); 2.66 (2H, q_{app}, *J*=7.5, NC**H$_2$**CH$_2$CHN=C(Ph)$_2$); 2.54 (1H, dd, *J*=9.1, 6.1, CH**H'**CHN=C(Ph)$_2$); 2.00-1.77 (2H, m, NCH$_2$C**H$_2$**CHN=C(Ph)$_2$).

^{13}C-NMR{^{1}H} δ ($CDCl_3$, 75 MHz)**:** 167.0 (N=**C**(Ph)$_2$); 139.9 (**C$_{ipso}$** aromatic to C=N); 139.1 (**C$_{ipso}$** aromatic to CH$_2$); 137.2 (**C'$_{ipso}$** aromatic to C=N); 129.8 (1C, **C**H *para* aromatic to C=N); 128.9 (2C, **C**H *ortho* aromatic to C=N); 128.4 (2C, **C**H *meta* aromatics to C=N); 128.3 (2C, **C**H *ortho* aromatics to CH$_2$); 128.2 (**C**H *para* aromatic to CH$_2$); 128.1 (2C, **C**H *meta* aromatics to CH$_2$); 128.0 (2C', **C**H *ortho* aromatics to C=N); 127.8 (2C', **C**H *meta* aromatics to C=N); 126.8 (1C', **C**H *para* aromatic to C=N); 61.6 (N**C**H$_2$CHN=C(Ph)$_2$); 60.8 (NCH$_2$**C**HN=C(Ph)$_2$); 60.3 (N**C**H$_2$CH$_2$CHN=C(Ph)$_2$); 53.7 (**C**H$_2$Ph); 33.4 (NCH$_2$**C**H$_2$CHN=C(Ph)$_2$).

12.6.1.5. 1-Benzyl-3-((diphenylmethyl)amino)pyrrolidine (229)[16]



A solution of 1-benzyl-3-((*N*-diphenylmethylidene)amino)-pyrrolidine **250a** (11.19 g, 29.7 mmol, 1.0 equiv) in 50.00 mL of freshly distilled THF was added at 0 °C to a stirred suspension of $LiAlH_4$ (3.11 g, 82.0 mmol, 2.8 equiv) in 50.00 mL of freshly distilled THF in a two-necked round bottomed flask, equipped with a bubble condenser fitted to a balloon of dried argon. The resulting red coloured reaction mixture was stirred for 4 hours at room temperature and refluxed for another hour. A subsequent TLC monitoring (4:1 petroleum ether/ethyl acetate) showed the total disappearance of the starting material and the formation of a new product. For this reason the reaction was quenched at 0 °C adding 3.00 mL of H_2O dropwise, followed by 6.0 mL of a 4 M aq. NaOH solution and 3.00 mL of H_2O. The mixture was then filtered on celite pad and the residue washed with DCM (50.00 mL). The solvent was evaporated and the corresponding residue was dissolved in DEE (100.00 mL). Product **229** was extracted with a 1 N HCl solution (2 x 100.00 mL); the water layer was washed with ethyl acetate (2 x 100.00 mL), and a little amount of powdered $NaHCO_3$ and 20.00 mL of a 4 N aq. NaOH solution were added in order to alkalinize the solution. Then the product was extracted from water phase with DCM (2 x 100.00 mL) and finally the combined organic phases were dried over $MgSO_4$, filtered and concentrated under vacuum to afford 9.56 g of crude product, as an orange oil. The purification of the amine **229** was made by flash column chromatography

(silica, eluent: 10:1 and 1:1 cyclohexane/ethyl acetate) giving 7.71 g (22.5 mmol, 77%) of the pure product **229** in form of yellow oil.

229

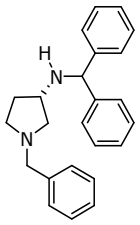
$C_{24}H_{26}N_2$ **M**=342.26

^{1}H-NMR δ ($CDCl_3$, 300 MHz)**:** 7.40-7.10 (15H, m, C**H** aromatics); 4.80 (1H, s, NHC**H**); 3.60-3.49 (2H, m [AB spin system], C**H_2**Ph); 3.23-3.18 (1H, m, C**H**NH); 2.65-2.58 (2H, m, NC**H_2**CHNH); 2.45-2.37 (2H, m, NC**H_2**CH_2CHNH); 2.14-2.02 (1H, m, NCH_2C**H**H'CHNH); 1.69-1.61 (1H, m, NCH_2CH**H'**CHNH).

^{13}C-NMR{^{1}H} δ ($CDCl_3$, 75 MHz)**:** 144.1 (1C, **C_{ipso}** aromatic to NHCH); 144.0 (1C, **C_{ipso}** aromatic to NHCH); 139.2 (**C_{ipso}** aromatic to CH_2); 128.8 (2C, **C**H *ortho* aromatics to CH_2); 128.4 (2C, **C**H *meta* aromatics to NHCH); 128.3 (2C', **C**H *meta* aromatics to NHCH); 128.2 (2C, **C**H *meta* aromatics to CH_2); 127.4 (2C, **C**H *ortho* aromatics to NHCH); 127.3 (2C', **C**H *ortho* aromatics to NHCH); 126.9 (2C, **C**H *para* aromatics to NHCH); 126.8 (**C**H *para* aromatic to CH_2); 65.4 (**C**HNH); 60.7 (N**C**H_2CHNH); 60.5 (**C**H_2Ph); 55.0 (NCH_2**C**HNH); 53.0 (N**C**H_2CH_2CHNH); 32.3 (NCH_2**C**H_2CHNH).

MS (EI) *m/z*(%)**:** 342 (0.4, M^+); 299 (0.2); 282 (0.4); 265 (0.2); 251 (0.5); 222 (1); 182 (30); 175 (28); 167 (52); 161 (44); 152 (15); 132 (42); 120 (51); 91 (86, $C_7H_7^+$); 77 (9, $C_6H_5^+$); 65 (18); 42 (100).

12.6.1.6. (*S*)-1-Benzyl-3-((diphenylmethyl)amino)pyrrolidine (229)[16]



Following the same procedure of the previous reaction, a solution of 1-benzyl-3-(*S*)-((*N*-diphenylmethylidene)amino)pyrrolidine **2510a** (6.17 g, 17.6 mmol, 1.0 equiv) in 30.00 mL of freshly distilled THF was added to a suspension of $LiAlH_4$ (1.82 g, 50.0 mmol, 2.8 equiv) in anhydrous THF. After 4 hours at room temperature and one hour at reflux, the reaction mixture was stopped (check by TLC: 4:1 petroleum ether/ethyl acetate) and worked up to afford 4.92 g of crude product **229**, as a deep yellow oil. The purification by flash column chromatography on silica gel (eluent: from 10:1 to 1:1 cyclohexane/ethyl acetate) gave 4.44 g (13.0 mmol, 74%) of the pure product **229**, as a yellow oil.

229 (3*S*)

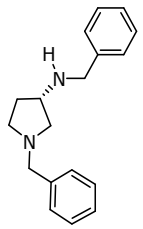
$C_{24}H_{26}N_2$ **M**=342.26

^{1}H-NMR δ ($CDCl_3$, 300 MHz)**:** 7.36-7.10 (15H, m, C**H** aromatics); 4.80 (1H, s, NHC**H**); 3.60-3.49 (2H, m [AB spin system], C**H_2**Ph); 3.23-3.18 (1H, m, C**H**NH); 2.65-2.58 (2H, m, NC**H_2**CHNH); 2.47-2.37 (2H, m, NC**H_2**CH_2CHNH); 2.11-2.03 (1H, m, NCH_2C**H**H'CHNH); 1.69-1.61 (1H, m, NCH_2CH**H'**CHNH).

^{13}C-NMR{^{1}H} δ ($CDCl_3$, 75 MHz)**:** 144.1 (1C, **C_{ipso}** aromatic to NHCH); 144.0 (1C', **C_{ipso}** aromatic to NHCH); 139.1 (**C_{ipso}** aromatic to CH_2); 128.8 (2C, **C**H *ortho* aromatics to CH_2); 128.4 (2C, **C**H *meta* aromatics to NHCH); 128.3 (2C', **C**H *meta*

aromatics to NHCH); 128.2 (2C, **C**H *meta* aromatics to CH_2); 127.4 (2C, **C**H *ortho* aromatics to NHCH); 127.3 (2C', **C**H *ortho* aromatics to NHCH); 126.9 (2C, **C**H *para* aromatics to NHCH); 126.8 (**C**H *para* aromatic to CH_2); 65.4 (**C**HNH); 60.7 (N**C**H_2CHNH); 60.5 (**C**H_2Ph); 54.9 (NCH_2**C**HNH); 53.0 (N**C**H_2CH_2CHNH); 32.3 (NCH_2**C**H_2CHNH).
MS (EI) *m/z*(%)**:** 342 (0.4, M^+); 299 (0.2); 282 (0.4); 265 (0.2); 251 (0.5); 222 (1); 182 (30); 175 (28); 167 (52); 161 (44); 152 (15); 132 (42); 120 (51); 91 (86, $C_7H_7^+$); 77 (9, $C_6H_5^+$); 65 (18); 42 (100).
$[\alpha]_D^{23}$=-6.06 (c=1.20, $CHCl_3$).

12.6.1.7. (*S*)-1-Benzyl-3-(benzylamino)pyrrolidine (224)[16]

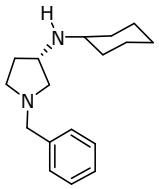


A solution of 2.67 g (15.7 mmol, 1.0 equiv) of (*S*)-1-benzyl-3-aminopyrrolidine **220** in freshly distilled toluene and 4.60 mL (45.1 mmol, 3.0 equiv) of dried benzaldehyde **249** were stirred overnight at room temperature and under argon atmosphere in a one-necked round bottomed flask, containing ~2.00 g of activated molecular sieves 4 Å. The day after the resulting solution of imine (*S*)-1-benzyl-3-((*N*-phenylmethylidene)amino) pyrrolidine and the excess of benzaldehyde **249** were filtered and added to a stirred suspension of $LiAlH_4$ (3.02 g, 79.6 mmol, 5.3 equiv) in 30.00 mL of freshly distilled THF at 0 °C and under argon. After 3h at room temperature (check by TLC: 4:1 petroleum ether/ethyl acetate) the reaction was quenched at 0° C by careful dropwise addition of H_2O (3.00 mL), a 4 M aq. NaOH solution (3.00 mL) and H_2O (3.00 mL). The resulting white solid was removed by filtration on celite pad and washed with DCM. The filtrate was, then, concentrated under vacuum. The residue was dissolved in diethyl ether (50.00 mL) and the diamine **224** was extracted by a 1 N aq. HCl solution (2 x 50.00 mL) and the acidic solution was washed with ethyl acetate (2 x 50.00 mL) before being treated with solid $NaHCO_3$ and then a 4 M aq. NaOH solution. Finally the aminopyrrolidine **224** was extracted with DCM (2 x 100.00 mL) and the combined organic layers were anhydrified over $MgSO_4$. The evaporation of the solvent gave 3.05 g of the crude product **224**, as an orange oil, which were purified by flash column chromatography on silica with 1:1 dichloromethane/methanol mix as eluent to afford 2.83 g (10,7 mmol, 71%) of a yellow oil.

224
$C_{18}H_{22}N_2$ **M**=266.22
^{1}H-NMR δ ($CDCl_3$, 300 MHz)**:** 7.33-7.21 (15H, m, C**H** aromatics); 3.73 (2H, s, NHC**H_2**Ph); 3.69-3.56 (2H, m [AB spin system], NC**H_2**Ph); 3.38-3.32 (1H, m C**H**NHCH_2Ph); 2.76 (1H, dd, *J*=9.3, 6.6, NC**H**H'CHNHCH_2Ph); 2.69-2.61 (1H, m, NC**H**H'CH_2CHNHCH_2Ph); 2.58-2.52 (1H, m, NCH**H'**CH_2CHNHCH_2Ph); 2.41 (1H, dd,

J=9.3, 5.1, NCH**H'**CHNHCH$_2$Ph); 2.17-2.11 (1H, m, NCH**H'**CHNHCH$_2$Ph); 1.68-1.57 (1H, m, NCH**H'**CHNHCH$_2$Ph).
^{13}C-NMR{^{1}H} δ ($CDCl_3$, 75 MHz)**:** 140.3 (1C, **C*$_{ipso}$*** aromatic to NHCH$_2$); 139.0 (1C', **C*$_{ipso}$*** aromatic to CHCH$_2$); 128.8-126.9 (8C, **C**H aromatics); 60.8 (N**C**H$_2$CHNHCH$_2$Ph); 60.6 (N**C**H$_2$Ph); 56.7 (N**C**HNHCH$_2$Ph); 53.2 (N**C**H$_2$CH$_2$CHNHCH$_2$Ph); 52.4 (NH**C**H$_2$Ph); 32.2 (NCH$_2$**C**H$_2$CHNHCH$_2$Ph).
MS (EI) *m/z*(%)**:** 266 (1, M+); 235 (0.4); 223 (1); 175 (4); 161 (12); 146 (5); 132 (32); 120 (15); 106 (5); 91 (88, $C_7H_7^+$); 77 (3); 65 (19); 42 (100).
[α]$_D^{23}$=+2.05 (c=1.25, $CHCl_3$).

12.6.1.8. (*S*)-1-Benzyl-3-(cyclohexylamino)pyrrolidine (230)[16]



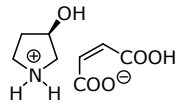
In an apparatus equipped with a Dean-Stark trap arranged for azeotropic removal of water, (*S*)-1-benzyl-3-aminopyrrolidine **220** (2.66 g, 15,1 mmol, 1.0 equiv) and dried cyclohexanone **170b** (4.95 mL, 45.3 mmol, 3.0 equiv) were dissolved in 30.00 mL of freshly distilled toluene and heated to reflux overnight under argon atmosphere. The resulting solution of (*S*)-1-benzyl-3-((*N*-cyclohexylimino)pyrrolidine and the excess of cyclohexanone **170b** were, then, added into a stirred suspension of $LiAlH_4$ (2.75 g, 72,5 mmol, 4.8 equiv) in 25.00 mL of freshly distilled THF at 0 °C and under argon. After one night at room temperature (reaction check by TLC: 1:1 dichloromethane / methanol) the reaction was quenched with 3.00 mL of H_2O, 3.00 mL of a 4 M aq. NaOH solution and 3.00 mL of H_2O. The resultant white precipitate was filtered on celite pad and washed with DCM. The filtrate was then concentrated under vacuum and the residue was diluted in 50.00 mL of Et_2O. The diamine was extracted in a 1 N aq. hydrochloric acid solution and the acidic solution was first washed with AcOEt (2 x 50.00 mL) and then treated with $NaHCO_3$ and a 4 N aq. NaOH solution. The diamine was then extracted in DCM (2 x 50.00 mL) and the resulting organic solution was dried over magnesium sulfate, filtered and concentrated under vacuum to afford 3.42 g of the crude product **230** in form of a yellow oil. After purification by flash column chromatography (silica, eluent: 96.5:2.5:0.5 dichloromethane / methanol / triethylamine), 3.38 g (13.1 mmol, 87%) of the pure diamine **230**, as a yellow oil, were obtained.

230
$C_{17}H_{26}N_2$ **M**=258.26
^{1}H-NMR δ ($CDCl_3$, 300 MHz)**:** 7.40-7.20 (5H, m, C**H** aromatics); 3.63-3.57 (2H, m [AB spin system], C**H$_2$**Ph); 3.50-3.40 (1H, m C**H**NHCy); 2.78 (1H, dd, *J*=9.3, 6.6, NC**H**H'CHNHCy); 2.59-2.53 (2H, m, NC**H$_2$**CH$_2$CHNHCy); 2.45-2.35 (1H, m, NHC**H** cyclohexyl group); 2.27 (1H, dd, *J*=9.3, 5.4, NCH**H'**CHNHCy); 2.20-2.09 (1H, m, NC**H**H'CHNHCy); 1.87-1.83 (2H, m, CHC**H$_2$** cyclohexyl group); 1.73-1.68 (2H, m,

CHC**H'$_2$** cyclohexyl group); 1.25-1.00 (6H, m, CHCH$_2$C**H$_2$**, CHCH$_2$C**H'$_2$** and CHCH$_2$CH$_2$C**H$_2$** cyclohexyl group).
^{13}C-NMR{^{1}H} δ ($CDCl_3$, 75 MHz)**:** (**C$_{ipso}$** aromatic to CH_2); 128.8 (2C, **C**H *ortho* aromatics to CH_2); 128.1 (2C, **C**H *meta* aromatics to CH_2); 61.4 (N**C**H$_2$CHNHCy); 60.6 (N**C**H$_2$Ph); 55.0 (**C**HNHCy); 53.9 (NH**C**H cyclohexyl group); 53.0 (N**C**H$_2$CH$_2$CHNHCy); 34.0 (CH**C**H$_2$ cyclohexyl group); 33.8 (CH**C**H$_2'$ cyclohexyl group); 32.7 (NCH$_2$**C**H$_2$CHNHCy); 26.1 (CHCH$_2$CH$_2$**C**H$_2$ cyclohexyl group); 25.1 (CHCH$_2$**C**H$_2$ cyclohexyl group); 25.0 (CHCH$_2$**C**H$_2'$ cyclohexyl group).
MS (EI) *m/z*(%)**:** 258 (2, M^+); 201 (1); 159 (7, M^+ – CyNH); 132 (45); 120 (7); 91 (47, $C_7H_7^+$); 56 (16); 42 (100).
[α]$_D^{22}$=–0.71 (c=1.08, $CHCl_3$).

12.6.2. Synthesis of chiral aminopyrrolidines from *trans*-4-hydroxy-(L)-proline

12.6.2.1. *(R)*-3-Hydroxypyrrolidinium hydrogen fumarate (252)[16]

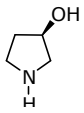


9.80 g (74.6 Mmol, 1.0 equiv) of *trans*-4-hydroxy-(L)-proline **222**, 1.50 mL (15.5 mmol, 0.2 equiv) of cyclohexen-1-one and 75.00 mL (1.0 M) of cyclohexanol were introduced in a 500 mL round bottomed flask, and the resulting suspension was heated at 160 °C for 7h. Then the deep brown solution was cooled to room temperature and 8.87 g (76.4 mmol, 1.0 equiv) of maleic acid were added. After 30' under vigorous stirring, 200.00 mL of ethyl acetate were added and the reaction mixture was stirred overnight at room temperature. A deep yellow precipitate was formed and, after filtration, it was washed with a 7:3 AcOEt/cyclohexane mix and with AcOEt (2 x 60.00 mL) and then dried at 40° C. Product **252** was obtained as a white solid (15.25 g) and was used without further purification for the next step.

252
$C_4H_{10}NO$, $C_4H_3O_4$ **M**=203.13
^{1}H-NMR δ (CD_3OD, 300 MHz)**:** 6.79 (2H, s, C**H** olefinic of fumaric acid); 5.07 (2H, br-s, N**H**); 4.60-4,65 (1H, m, C**H**OH); 3,53-3.48 (2H, m, C**H$_2$**CHOH); 4.45-4.35 (2H, m, C**H$_2$**CH$_2$CHOH); 3.35-3.30 (1H, m, CHO**H**); 2.20-2.10 (2H, m, CH$_2$C**H$_2$**CHOH).
^{13}C-NMR{^{1}H} δ (CD_3OD, 75 MHz)**:** 171.5 (2C, **C**OOH); 136.3 (2C, **C**H olefinic); 70.7 (**C**HOH); 54.2 (N**C**H$_2$CHOH); 44.8 (N**C**H$_2$CH$_2$CHOH); 34.2 (NCH$_2$**C**H$_2$CHOH).

12.6.2.2. *(R)*-3-Hydroxypyrrolidine (251)[16]

A 35% aq. NaOH solution (26.00 mL, 300.00 mmol, 4.0 equiv) was added at room temperature to a suspension of 15.23 g (75.0 mmol, 1.0 equiv) of (*R*)-3-



hydroxypyrrolidinium hydrogen fumarate **252** in 375.00 mL of CH_2Cl_2 contained in a 1 L round bottomed flask. The mixture was stirred for 90' in presence of K_2CO_3 (75.00 g, 542.7 mmol, 7.0 equiv) and charcoal and then filtered on celite pad. The solid phase was extracted with DCM (2 x 100.00 mL). Evaporation of the solvent gave a deep yellow oil **251** (3.37 g, 61.6 mmol, 82%), which was utilized without further purification.

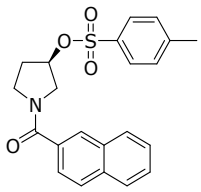
251

$C_4H_{10}NO$ **M**=87.09

^{1}H-NMR δ ($CDCl_3$, 300 MHz)**:** 4.40-4.31 (1H, m, C**H**OH); 3.16-3.07 (1H, m, NC**H**H'CH_2CHOH); 2.92-2.80 (5H, m, NCH**H'**CH_2CHOH, NC**H_2**CHOH, N**H** and CHO**H**); 2.00-1.88 (1H, m, NCH_2C**H**H'CHOH; 1.75-1.60 (1H, m, NCH_2CH**H'**CHOH).

^{13}C-NMR{^{1}H} δ ($CDCl_3$, 75 MHz)**:** 72.1 (**C**HOH); 55.9 (N**C**H_2CHOH); 45.2 (N**C**H_2CH_2CHOH); 35.6 (NCH_2**C**H_2CHOH).

12.6.2.3. (*R*)-1-(2-Naphthoyl)-3-(tosyloxy)pyrrolidine (253)[16]



38.00 mL (469.8 Mmol, 7.6 equiv) of pyridine were added to a solution of (*R*)-3-hydroxypyrrolidine **252** (3.37 g, 61.6 mmol, 1.0 equiv) in 300.00 mL of freshly distilled DCM at 0° C contained in a Schlenk tube, under argon. After 15' 11.50 g (60.3 mmol, 1.0 equiv) of 2-naphthoyl chloride were introduced and the resulting reaction mixture was stirred for 2h before adding 46.47 g (243.8 mmol, 4.0 equiv) of *p*-toluensulfonyl chloride and a catalytic amount of DMAP. After two days at room temperature, the solvent and pyridine were evaporated; the residue was taken up in 100.00 mL of Et_2O, and the addition to this solution of 100.00 mL of petroleum ether resulted in the precipitation of a brown oil. After separation from the supernatant, which contained essentially the excess of *p*-toluensolfonyl chloride, this oil was washed once with 1:1 Et_2O / petroleum ether and then chromatographed on silica gel (SiO_2, eluent: 1:1 petroleum ether / ethyl acetate) to afford 9.40 g (23.8 mmol, 38%) of a translucent solid **253**.

253

$C_{22}H_{21}NO_4S$ **M**=395.21

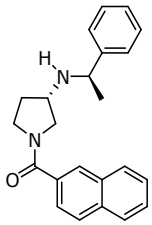
The presence of two rotamers "*a*" and "*b*" in a 58/42 ratio in $CDCl_3$ resulted in the splitting of several signals in ^{1}H and ^{13}C NMR.

^{1}H-NMR δ ($CDCl_3$, 300 MHz)**:** 8.10-7.32 (11H, m, C**H** aromatics); 5.15 (1H, m, C**H**OTs *a* rotamer); 5.03 (1H, m, C**H**OTs *b* rotamer); 3.91-3.50 (4H, m, NC**H_2**CHOTs and NC**H_2**CH_2CHOTs); 2,47 (3H, s, C**H_3** tosyl group *a* rotamer); 2.29 (3H, s, C**H_3** tosyl group *b* rotamer); 2.40-2.00 (2H, NCH_2C**H_2**CHOTs).

^{13}C-NMR{^{1}H} δ ($CDCl_3$, 75 MHz)**:** 169.7 (**C**=O); 145.2-124.2 (16C, **C** aromatics); 80.1 (**C**HOTs, *b* rotamer); 79.5 (**C**HOTs, *a* rotamer); 54.6 (NC**H_2**CHOTs, *b* rotamer); 52.2 (N**C**H_2CHOTs, *a* rotamer); 47.0 (N**C**H_2CH_2CHOTs, *b* rotamer); 43.9

(N**C**H_2CH_2CHOTs, *a* rotamer); 33.1 (NCH_2**C**H_2CHOTs, *b* rotamer); 30.7 (NCH_2**C**H_2CHOTs, *a* rotamer); 21.6 (**C**H_3 tosyl group, *b* rotamer); 21.4 (**C**H_3 tosyl group, *a* rotamer).

12.6.2.4. (*S*)-1-(2-Naphthoyl)-3-[(1-(*R*)-phenylethyl)amino]-pyrrolidine (254)[16]



A mixture of (*R*)-1-(2-naphthoyl)-3-tosyloxy)-pyrrolidine **253** (9.40 g, 23.8 mmol, 1.0 equiv) and (*R*)-1-phenylethylamine (35.00 g, 274.4 mmol, 11.5 equiv) was heated for 20 h at 110 °C. After cooling, the reaction mixture, diluted by AcOEt (150.00 mL), was vigorously stirred with a 4 M aq. NaOH solution (100.00 mL). After decantation, the aqueous basic layer was extracted with ethyl acetate (2 x 100.00 mL); both organic phases were dried over $MgSO_4$, filtered and, then, concentrated leading to a brown oil. After being washed with pentane to remove the excess of the primary amine, the residue (10.23 g of a deep yellow oil) was purified by flash column chromatography on silica gel with 99:1 dichloromethane/methanol mix as eluent to afford 5.90 g (17.2 mmol, 73%) of the pure product **254**, as a yellow oil.

254

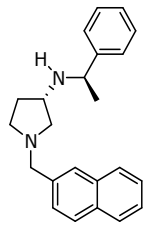
$C_{23}H_{24}N_2O$ **M**=344.24

^{1}H-NMR δ ($CDCl_3$, 300 MHz) (two rotamers observed *a*:*b*=81:19)**:** 7.80-7.60 (2H, m, C**H** naphthoyl aromatics); 7.60-7.50 (2H, m, C**H** naphthoyl aromatics); 7.40-7.00 (8H, m, C**H** naphthoyl aromatics and C**H** phenyl aromatics); 4.14 (1H, q, *J*=6.6, NHC**H**(CH_3)Ph); 3.92-3.14 (5H, m, NC**H_2**CHNH, NC**H_2**CH_2CHNH and N**H**); 2.30-1.72 (2H, m, NCH_2C**H_2**CHNH); 1.42 (3H, d, *J*=6.6, NHCH(C**H_3**)Ph *a* rotamer); 1.31 (3H, d, *J*=6.6, NHCH(C**H_3**)Ph *b* rotamer).

^{13}C-NMR{^{1}H} δ ($CDCl_3$, 75 MHz) (two rotamers observed)**:** 169.6 (**C**=O); 145.2-124.4 (16C, **C** aromatics); 56.6 (NH**C**H(CH_3)Ph *a* rotamer); 56.2 (NH**C**H(CH_3)Ph *b* rotamer); 56.0 (**C**HNHCH(CH_3)Ph *a* rotamer); 52.6 (**C**HNHCH(CH_3)Ph *b* rotamer); 48.0 (N**C**H_2CHNH *b* rotamer); 44.7 (N**C**H_2CHNH *a* rotamer); 32.2 (N**C**H_2CH_2CHNH *b* rotamer); 30.7 (N**C**H_2CH_2CHNH *a* rotamer); 24.7 (NHCH(**C**H_3)Ph *b* rotamer); 24.3 (NHCH(**C**H_3)Ph *a* rotamer).

12.6.2.5. (*S*)-1-(2-Naphthylmethyl)-3-[(1-(*R*)-phenylethyl)amino]-pyrrolidine (238a)[16]

In a Schlenk tube, under argon, a solution of (*S*)-1-(2-naphthoyl)-3-[(1-(*R*)-phenylethyl)amino]-pyrrolidine **254** (5.90 g, 17.2 mmol, 1.0 equiv) in 50.00 mL of freshly distilled THF was added dropwise to a suspension of $LiAlH_4$ (3.22 g, 84.8 mmol, 4.9 equiv) in 40.00 mL of freshly distilled THF at 0 °C. After one night at room temperature (reaction check *via* TLC: 20:1 dichloromethane / methanol) the reaction was stopped adding carefully 3.00 mL of H_2O, 3.00 mL of a 4 N aq. NaOH



solution and other 3.00 mL of H_2O at 0° C. After stirring for one hour, the resulting white solid was filtered on celite pad and washed with DCM (100.00 mL). Then the filtrate was concentrated and the residue was solubilized in 50.00 mL of DEE. The diamine **238a** was then extracted with a 1 N aq. HCl solution (2 x 50.00 mL); then the acidic layer was washed with AcOEt (2 x 50.00 mL) and treated with powdered $NaHCO_3$ and a 4 M aqueous NaOH solution. The diamine **238a** was extracted from the resultant basic solution with DCM (2 x 50.00 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford 2.54 g of crude product. The further purification by flash chromatography gave 1.85 g (5.6 mmol, 33%) of **238a** as a pale yellow oil.

238a

$C_{23}H_{26}N_2$ **M=**330.26

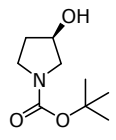
^{1}H-NMR δ ($CDCl_3$, 300 MHz)**:** 7.82-7.75 (3H, m, C**H** naphthylmethyl aromatics); 7.45-7.33 (3H, m, C**H** naphthylmethyl aromatics); 7.30-7.20 (5H, m, C**H** aromatics of Ph); 7.15-7.10 (1H, m, C**H** naphthylmethyl aromatic); 3.76 (1H, q, *J*=6.6, NHC**H**(CH_3)Ph); 3.72 (2H, m, [AB spin system], C**H_2**naphthyl); 3.19-3.12 (1H, m, C**H**NHCH(CH_3)Ph); 2.69-2.57 (2H, m, NC**H**H'CHNH and NC**H**H'CH_2CHNH); 2.55-2.40 (1H, m, NCH**H'**CH_2CHNH); 2.27 (1H, dd, *J*=9.3, 5.4, NCH**H'**CHNH); 2.15-2.00 (1H, m, NCH_2C**H**H'CHNH); 1.66-1.57 (1H, m, NCH_2CH**H'**CHNH); 1.32 (3H, d, *J*=6.6, NHCH(C**H_3**)Ph).

^{13}C-NMR{^{1}H} δ ($CDCl_3$, 75 MHz)**:** 145.5 (**C_{ipso}** aromatic to NHCH(CH_3)); 136.5 (**C_{ipso}** naphthyl aromatic); 133.3 (1C, **C_q** aromatic at bridge of naphthyl); 132.6 (1C', **C_q** aromatic at bridge of naphthyl); 138.3-125.5 (12C, **C**H aromatics); 61.2 (**C**H_2CHNH); 60.7 (**C**H_2 naphthyl); 56.2 (NH**C**H(CH_3)Ph); 54.7 (**C**HNHCH(CH_3)Ph; 53.2 (**C**H_2CH_2CHNH); 31.7 (CH_2**C**H_2CHNH); 24.3 (NHCH(**C**H_3)Ph).

MS (EI) *m/z*(%)**:** 330 (5, M^+); 211 (82); 183 (93); 182 (78); 141 (92); 115 (74); 105 (100); 56 (69).

[α]$_D^{22}$=+26.00 (c=1.46, $CHCl_3$).

12.6.2.6. *N*-(*tert*-Butoxycarbonyl)-3-(*R*)-hydroxypyrrolidine (255)[17]



In a 500 mL two-necked round bottomed flask, equipped with a bubble condenser fitted with a balloon of dried argon, a solution of *trans*-4-(*R*)-hydroxyl-(L)-proline **222** (18.80 g, 143.4 mmol, 1.0 equiv) and 2-cyclohexen-1-one (3.00 mL, 31.0 mmol, 0.2 equiv) in 150.00 mL of cyclohexanol was heated at 160° C for 7h, until all solid was dissolved and a deep brown colouration appeared. The resulting solution was cooled to room temperature and 150.00 mL of a 20% aqueous acetic acid solution and 220.00 mL of toluene were added. After separation of the two layers, the aqueous portion was washed with toluene (3 x 80.00 mL) and then K_2CO_3 was

introduced until pH=9 (~30.00 g) was reached. Then the basic resultant solution was transferred in a 500 mL round flask and 150.00 mL of dioxane, followed by 35.70 g of di-*tert*-butyl dicarbonate (163.6 mmol, 1.09 equiv), were added at 0° C under vigorously stirring. The reaction mixture was left to react for 20h, whereupon the organic materials were extracted twice with ether and the combined organic components were concentrated under reduced pressure. Finally 150.00 mL of ethanol were added to the residue and this resulting solution was heated under reflux for 20h. Then the solvent was evaporated affording 26.26 g of the crude product **255**, as a black solid, which were purified by column chromatography (silica, eluent: 1:9 hexane/ethyl acetate) giving a 23.13 g (123.6 mmol, 86%) of **255** as a pale yellow oil.

255

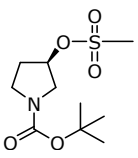
$C_9H_{17}NO_3$ **M=**187.17

The presence of two rotamers "*a*" and "*b*" in a 58/42 ratio in $CDCl_3$ resulted in the splitting of several signals in ^{13}C NMR.

^{1}H-NMR δ ($CDCl_3$, 300 MHz)**:** 4.41 (1H, s_{app}, C**H**OH); 3.50-3.25 (4H, m, NC**H_2**CHOH and NC**H_2**CH_2CHOH); 2.74 (1H, br-d, *J*=17.4, CHO**H**); 1.96-1.80 (2H, m, NCH_2C**H_2**CHOH); 1.43 (9H, s, COOC(C**H_3**)$_3$).

^{13}C-NMR{^{1}H} δ ($CDCl_3$, 75 MHz)**:** 158.0 (**C**OOC(CH_3)$_3$); 79.3 (COO**C**(CH_3)$_3$); 70.9 (**C**HOH, *a* rotamer); 70.1 (**C**HOH, *b* rotamer); 54.3 (N**C**H_2CHOH, *a* rotamer); 54.1 (N**C**H_2CHOH, *b* rotamer); 43.9 (N**C**H_2CH_2CHOH, *a* rotamer); 43.4 (N**C**H_2CH_2CHOH, *b* rotamer); 33.9 (NCH_2**C**H_2CHOH, *a* rotamer); 33.5 (NCH_2**C**H_2CHOH, *a* rotamer); 28.5 (COOC(**C**H_3)$_3$).

12.6.2.7. *N*-(*tert*-Butoxycarbonyl)-3-(*R*)-methylsulfonyloxypyrrolidine (256)[17]



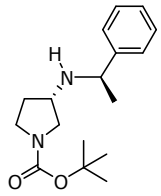
In a 1 L round bottomed flask, pyridine (21.00 mL, 260.7 mmol, 2.1 equiv), mesylchloride (20.00 mL, 258.4 mmol, 2.1 equiv) and DMAP (30.00 mg) were added to a solution of *N*-(*tert*-butoxycarbonyl)-3-(*R*)-hydroxypyrrolidine **255** (23.13 g, 123.6 mmol, 1.0 equiv) in 450.00 mL of freshly distilled DCM at 0° C under argon atmosphere. The resulting reaction mixture was stirred for 72h, after which a TLC check (7:3 cyclohexane/ethyl acetate), showed the presence of a new species and the contemporaneous absence of the starting material. So the reaction mixture was concentrated under vacuum and 100.00 mL of AcOEt were added in order to allow the salts to precipitate. After filtration 49.32 g of the crude product **256** (as a dense dark oil) were obtained. The purification by filtration on silica gel afforded 32.77 g (23.1 mmol, 100%) of the pure product **256**.

256

$C_{10}H_{19}NO_5$ **M=**265.19

The presence of two rotamers "*a*" and "*b*" in a 58/42 ratio in $CDCl_3$ resulted in the splitting of several signals in ^{13}C NMR.
^{1}H-NMR δ ($CDCl_3$, 300 MHz): 5.25-5.22 (1H, m, C**H**OMs); 3.67-3,43 (4H, m, NC**H$_2$**CHOMs and NC**H$_2$**CH_2CHOMs); 2.99 (3H, s, C**H$_3$** mesyl group); 2.30-2.00 (2H, m, NCH_2C**H$_2$**CHOMs); 1.44 (9H, s, C(C**H$_3$**)$_3$).
^{13}C-NMR{^{1}H} δ ($CDCl_3$, 75 MHz): 154.4 (**C**=O); 79.9 (**C**HOMs, *a* rotamer); 79.8 (**C**$(CH_3)_3$); 79.5 (**C**HOMs, *b* rotamer); 52.1 (NC**H$_2$**CHOTs, *a* rotamer); 51.7 (N**C**H_2CHOTs, *b* rotamer); 43.5 (N**C**H_2CH_2CHOTs, *b* rotamer); 43.2 (N**C**H_2CH_2CHOTs, *a* rotamer); 38.7 (**C**H_3 mesyl group) 32.6 (NCH_2**C**H_2CHOTs, *b* rotamer); 31.6 (NCH_2**C**H_2CHOTs, *a* rotamer); 28.4 (C(**C**$H_3)_3$).

12.6.2.8. *N*-(*tert*-Butoxycarbonyl)-3-(*S*)-(1-(*R*)-phenylethyl)amino pyrrolidine (257a)[17]

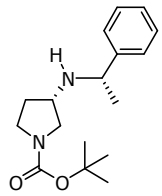


In a 250 mL round bottomed flask, equipped with a bubble condenser, a mixture of *N*-(*tert*-butoxycarbonyl)-3-(*R*)-methylsulfonyloxypyrrolidine **256** (16.32 g, 61.8 mmol, 1.0 equiv) and (*R*)-methylbenzylamine (61.00 mL, 475.8 mmol, 7.7 equiv) was heated at 110° C for 24h. After cooling to room temperature 50.00 mL of AcOEt and 100.00 mL of a 4 M aq. NaOH solution were added and the resultant reaction mixture was stirred vigorously before separating the two layers. The aqueous portion was extracted with ethyl acetate (2 x 100.00 mL) and the organic components were combined, washed with brine (150.00 mL), dried over magnesium sulfate, filtered and concentrated under reduced pressure to afford 70.74 g of a brown oil. This crude product **257a** was purified by distillation at reduced pressure, in order to eliminate the excess of primary amine and then purified by flash chromatography (silica, eluent: 4:1 dichloromethane /methanol) giving 17.21 g (59.3 mmol, 96%) of the pure diamine **257a**, as a pale brown oil.

257a
$C_{17}H_{26}N_2O_2$ **M=**290.26
The presence of two rotamers "*a*" and "*b*" in a 58/42 ratio in $CDCl_3$ resulted in the splitting of several signals in ^{13}C NMR.
^{1}H-NMR δ ($CDCl_3$, 300 MHz)**:** 7.33-7.20 (5H, C**H** aromatics Ph); 3.84 (1H, q, *J*=6.6, NHC**H**(CH_3)Ph); 3.52-2.87 (5H, m, C**H**NHCH(CH_3)Ph, NC**H$_2$**CHNHCH(CH_3)Ph and NC**H$_2$**CH_2CHNHCH(CH_3)Ph); 2.05-1.98 (1H, m, NCH_2C**H**H'CHNHCH(CH_3)Ph); 1.80-1.70 (1H, m, NCH**H'**CH_2CHNHCH(CH_3)Ph); 1.38 (9H, s, C(C**H$_3$**)$_3$); 1.27 (3H, d, *J*=6.6, NHCH(C**H$_3$**)Ph).
^{13}C-NMR{^{1}H} δ ($CDCl_3$, 75 MHz): 154.5 (**C**=O); 145.13 (**C_{ipso}** aromatics to NHCH(CH_3)); 128.6-126 (5C, **C**H aromatics); 79.0 (O**C**$(CH_3)_3$); 56.6 (**C**HNHCH(CH_3)Ph, *a* rotamer); 55.3 (NH**C**H(CH_3)Ph, *a* rotamer); 54.5 (NH**C**H(CH_3)Ph, *b* rotamer); 52.1 (**C**HNHCH(CH_3)Ph, *b* rotamer); 52.1

(N**C**H_2CHNH, *a* rotamer); 51.7 (N**C**H_2CHNH, *b* rotamer); 44.3 (N**C**H_2CH_2CHNH, *b* rotamer); 43.9 (N**C**H_2CH_2CHNH, *a* rotamer); 31.7 (NCH_2**C**H_2CHNH, *b* rotamer); 31.0 (NCH_2**C**H_2CHNH, *a* rotamer); 28.4 (OC(**C**$H_3)_3$); 24.6 (NHCH(**C**H_3)Ph, *a* rotamer); 24.4 (NHCH(**C**H_3)Ph, *b* rotamer).

12.6.2.9. *N*-(*tert*-Butoxycarbonyl)-3-(*S*)-(1-(*S*)-phenylethyl)amino-pyrrolidine (257b)[17]



N-(*tert*-butoxycarbonyl)-3-(*S*)-(1-(*S*)-phenylethyl)amino-pyrrolidine **257b** was prepared from *N*-(*tert*-butoxycarbonyl)-3-(*R*)-methylsulfonyl-oxypyrrolidine **256** (16.39 g, 61.8 mmol, 1.0 equiv) and (*S*)-methylbenzylamine (64.00 mL, 501.7 mmol, 8.1 equiv) in the same way used for the product **257a,** giving a pale brown oil (13.27 g, 45.71 mmol, 74%).

257b

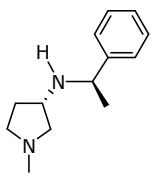
$C_{17}H_{26}N_2O_2$ **M=**290.26

The presence of two rotamers "*a*" and "*b*" in a 58/42 ratio in $CDCl_3$ resulted in the splitting of several signals in ^{13}C-NMR.

^{1}H-NMR δ ($CDCl_3$, 300 MHz): 7.35-7.24 (5H, C**H** aromatics Ph); 3.84 (1H, q, *J*=6.6, NHC**H**(CH_3)Ph); 3.59-3.01 (5H, m, C**H**NHCH(CH_3)Ph, NC**H$_2$**CHNHCH(CH_3)Ph and NC**H$_2$**CH_2CHNHCH(CH_3)Ph); 1.91-1.87 (1H, m, NCH_2C**H**H'CHNHCH(CH_3)Ph); 1.70-1.55 (1H, m, NCH**H'**CH_2CHNHCH(CH_3)Ph); 1.44 (9H, s, C(C**H$_3$**)$_3$); 1.33 (3H, d, *J*=6.6, NHCH(C**H$_3$**)Ph).

^{13}C-NMR{^{1}H} δ ($CDCl_3$, 75 MHz): 154.6 (**C**=O); 145.3 (**C$_{ipso}$** aromatics to NHCH(CH_3)); 128.6-126 (5C, **C**H aromatics); 79.0 (O**C**(CH_3)$_3$); 56.6 (**C**HNHCH(CH_3)Ph, *b* rotamer); 55.3 (NH**C**H(CH_3)Ph, *b* rotamer); 54.5 (NH**C**H(CH_3)Ph, *a* rotamer); 53.7 (**C**HNHCH(CH_3)Ph, *a* rotamer); 51.8 (N**C**H_2CHNH, *b* rotamer); 51.3 (N**C**H_2CHNH, *a* rotamer); 44.3 (N**C**H_2CH_2CHNH, *a* rotamer); 44.0 (N**C**H_2CH_2CHNH, *b* rotamer); 32.6 (NCH_2**C**H_2CHNH, *a* rotamer); 31.9 (NCH_2**C**H_2CHNH, *b* rotamer); 28.4 (OC(**C**$H_3)_3$); 24.8 (NHCH(**C**H_3)Ph, *a* rotamer); 24.7 (NHCH(**C**H_3)Ph, *b* rotamer).

12.6.2.10. *N*-Methyl-3-(*S*)-(1'-(*R*)-phenylethyl)aminopyrrolidine (239a)[17]



In a Schlenk tube, under argon, a solution of *N*-(*tert*-butoxycarbonyl)-3-(*S*)-(1-(*R*)-phenylethyl)aminopyrrolidine **257a** (17.21 g, 59.3 mmol, 1.0 equiv) in anhydrous THF (50.00 mL) was added to a suspension of lithium aluminum hydride (3.22g, 84.85 mmol, 4.94 equiv) in 40.00 mL of freshly distilled THF, placed under argon and cooled to 0 °C. The mixture was stirred for 6h at room temperature and, after cooling at 0 °C, the

excess of $LiAlH_4$ was hydrolyzed by successive additions of cold water (3.00 mL), a 4 M aqueous sodium hydroxide solution (3.00 mL) and cold water (3.00 mL). The white solid was filtered on celite pad and washed with DCM. The filtrate was concentrated and the residue dissolved in ether (50.00 mL). A 1 N aqueous hydrochloric acid solution (50.00 mL) was added and the solution was stirred at room temperature for 15'. The acidic aqueous layer was washed with ethyl acetate; sodium powdered hydrogen carbonate was slowly introduced until pH=9, followed by a few drops of a 4 N aqueous sodium hydroxide solution. The medium was then extracted with DCM (3 x 50.00 mL). The organic layers were collected, dried ($MgSO_4$), filtered and concentrated to give the pure product **239a** as a pale brown oil (9.93 g, 48.6 mmol, 79%).

239a

$C_{13}H_{20}N_2$ **M=**204.20

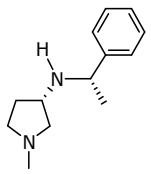
^{1}H-NMR δ ($CDCl_3$, 300 MHz)**:** 7.28-7.15 (5H, C**H** aromatics Ph); 3.75 (1H, q, *J*=6.6, NHC**H**(CH_3)Ph); 3.15-3.05 (1H, m, C**H**NHCH(CH_3)Ph); 2.59-2.53 (1H, m, NC**H**H'CH_2CHNHCH(CH_3)Ph); 2.49-2.44 (1H, m, NC**H**H'CHNHCH(CH_3)Ph); 2.39-2.31 (1H, m, NCH**H'**CH_2CHNHCH(CH_3)Ph); 2.21 (3H, s, NC**H_3**); 2.28-2.18 (1H, m, NCH**H'**CHNHCH(CH_3)Ph); 2.10-1.90 (1H, m, NCH_2C**H**H'CHNHCH(CH_3)Ph); 1.70-1.55 (1H, m, NCH_2CH**H'**CHNHCH(CH_3)Ph); 1.30 (3H, d, *J*=6.6, NHCH(C**H_3**)Ph).

^{13}C-NMR{^{1}H} δ ($CDCl_3$, 75 MHz)**:** 145.1 (**C_{ipso}** aromatics to NHCH(CH_3)); 128.3 (2C, **C**H *meta* aromatics to NHCH(CH_3)); 126.9 (**C**H *para* aromatic to NHCH(CH_3)); 126.8 (2C, **C**H *ortho* aromatics to NHCH(CH_3)); 63.4 (N**C**H_2CHNH); 56.2 (NH**C**H(CH_3)Ph); 55.3 (N**C**H_2CH_2CHNH); 55.2 (**C**HNHCH(CH_3)Ph); 42.2 (N**C**H_3); 32.6 (NCH_2**C**H_2CHNH); 24.3 (NHCH(**C**H_3)Ph).

MS (EI) *m/z*(%)**:** 204 (20, M^+); 99 (70); 85 (100).

[α]$_D^{22}$=+66.00 (c=1.01, $CHCl_3$).

12.6.2.11. *N*-Methyl-3-(*S*)-(1'-(*S*)-phenylethyl)aminopyrrolidine (239b)[17]



Following the same procedure used for the synthesis of the product **239a**, *N*-methyl-3-(*S*)-(1'-(*S*)-phenylethyl)-aminopyrrolidine **239b** was prepared from *N*-(*tert*-butoxycarbonyl)-3-(*S*)-(1-(*S*)-phenylethyl) aminopyrrolidine **257b** (13.27 g, 45.71 mmol, 1.0 equiv) and $LiAlH_4$ (10.50 g, 271.4 mmol, 5.94 equiv) giving 7.33 g of **239b** (35.9 mmol, 79%), as a pale brown oil.

239b

$C_{13}H_{20}N_2$ **M=**204.20

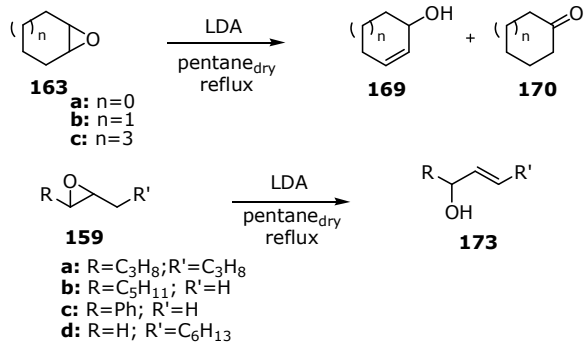
^{1}H-NMR δ ($CDCl_3$, 300 MHz)**:** 7.28-7.15 (5H, C**H** aromatics Ph); 3.73 (1H, q, *J*=6.6, NHC**H**(CH_3)Ph); 3.13-3.05 (1H, m, C**H**NHCH(CH_3)Ph); 2.62-2.57 (1H, m, NC**H**H'CH_2CHNHCH(CH_3)Ph); 2.49-2.40 (1H, d_{app}, *J*=5.4, NC**H_2**CHNHCH(CH_3)Ph); 2.30-2.22 (1H, m, NCH**H'**CH_2CHNHCH(CH_3)Ph); 2.25 (3H, s, NC**H_3**); 2.06-1.94

(1H, m, $NCH_2CHH'CHNHCH(CH_3)Ph$); 1.55-1.40 (1H, m, $NCH_2CHH'CHNHCH(CH_3)Ph$); 1.29 (3H, d, *J*=6.6, $NHCH(CH_3)Ph$).
^{13}C-NMR{^{1}H} δ ($CDCl_3$, 75 MHz)**:** 145.5 (**C_{ipso}** aromatics to $NHCH(CH_3)$); 128.4 (2C, **C**H *meta* aromatics to $NHCH(CH_3)$); 126.7 (**C**H *para* aromatic to $NHCH(CH_3)$); 126.7 (2C, **C**H *ortho* aromatics to $NHCH(CH_3)$); 62.5 (NCH_2CHNH); 56.5 ($NHCH(CH_3)Ph$); 55.2 (NCH_2CH_2CHNH); 55.1 (**C**$HNHCH(CH_3)Ph$); 42.3 (NCH_3); 33.3 (NCH_2CH_2CHNH); 24.5 ($NHCH(CH_3)Ph$).
MS (EI) *m/z*(%)**:** 204 (20, M^+); 99 (70); 85 (100).
$[\alpha]_D^{22}$=–80.00 (c=1.01, $CHCl_3$).

12.7. Base-promoted isomerization of epoxides

12.7.1. Isomerizations with LDA

12.7.1.1. *General procedure for the isomerization of meso-epoxides using LDA in pentane at reflux*



In a three-necked round bottomed flask, purged and flamed under vacuum and equipped with a bubble condenser, a solution of *n*-BuLi in hexanes (1.6 M, n mmol, n equiv) was mixed with anhydrous pentane (0.5 M) and DIPA (2.0 mmol, 2.0 equiv) under nitrogen. The mixture was stirred at 0° C for 15', after which the epoxide **159** or **163** (1.0 mmol, 1.0 equiv) was added and allowed to react for 8-16h at reflux. After cooling, the reaction was quenched with water and extracted with ether (3 times). The combined organic layers were washed twice with H_2O and brine, dried over sodium sulfate, filtered and concentrated to give the isomerization product **169**, **170** or **173**.

12.7.1.1.1. Isomerization of **cyclopentene oxide (163a)**

Cyclopentene oxide **163a** (0.87 mL, 10.0 mmol, 1.0 equiv) was reacted at reflux with 2.0 equiv of LDA for 5h giving 445.84 mg of cyclopenten-2-ol **169a** (5.3 mmol, 53%) and 58.88 mg (0.7 mmol, 9%) of cyclopentanone **170a**.

169a: Cyclopenten-2-ol[104, 243]

C_5H_8O **M=**84.12

^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 5.95-5.91 (1H, m, C**H**=CHCHOH); 5.81-5.76 (1H, m, CH=C**H**CHOH); 4.84-4.80 (1H, m, CH=CHC**H**OH); 2.50-2.40 (2H, m, C**H_2**CHOH); 2.30-1.95 (3H, m, C**H_2**CH_2CHOH and O**H**).

MS (EI) *m/z*(%)**:** 84 (32, M^+); 83 (100, M^+ – 1); 69 (7); 67 (9); 66 (14); 65 (15); 56 (26, M^+ – CHO); 55 (100, M^+ – CH_2O).

170a: Cyclopentanone[243]

C_5H_8O **M=**84.12

^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 2.19-2.12 (4H, m, C**H_2**C=O); 1.98-1.09 (4H, m, C**H_2**CH_2C=O).

^{13}C-NMR δ ($CDCl_3$, 200 MHz)**:** 221.1 (**C**=O); 37.2 (2C, **C**H_2C=O); 23.1 (2C, **C**H_2CH_2C=O).

MS (EI) *m/z*(%)**:** 84 (67, M^+); 81 (0.1); 56 (63, M^+ – CHO); 55 (100, M^+ – CH_2O).

12.7.1.1.2. Isomerization of **cyclohexene oxide (163b)**

Cyclohexene oxide **163b** (0.51 mL, 5.0 mmol, 1.0 equiv) was reacted at reflux with 2.0 equiv of LDA for 3h affording a 74:26 mix of cyclohexen-2-ol **169b** (3.3 mmol, 65%) and cyclohexanone **170b** (1.5 mmol, 30%).

169b: Cyclohexen-2-ol[104, 243, 482]

$C_6H_{10}O$ **M=**98.15

^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 5.88-5.70 (2H, m, C**H** olefinics); 4.55-4.25 (1H, m, C**H**OH); 2.06- 1.94 (2H, C**H_2**CH=CHCHOH); 1.80-1.50 (5H, m, O**H**, C**H_2**CHOH and C**H_2**CH_2CHOH).

^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 129.9 (CH=**C**HCHOH); 129.6 (**C**H=CHCHOH); 65.1 (CH=CH**C**HOH); 31.8 (**C**H_2CHOH); 24.9 (**C**$H_2CH_2CH_2$CHOH); 19.0 (CH_2**C**H_2CH_2CHOH).

MS (EI) *m/z*(%)**:** 98 (27, M^+); 97 (33, M^+ – H); 83 (44); 79 (20); 70 (100, M^+ – H_3O); 69 (31); 55 (47).

170b: Cyclohexanone[243, 482]

$C_6H_{10}O$ **M=**98.15

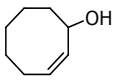
^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 2.36-2.26 (4H, m, C**H_2**C=O); 1.91-1.67 (6H, m, C**H_2**CH_2C=O and C**H_2**CH_2CH_2C=O).

^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 41.7 (CH_2CH_2**C**H_2CO); 26.9 (CH_2**C**H_2CH_2CO); 24.1 (**C**$H_2CH_2CH_2$CO).

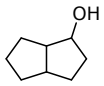
MS (EI) *m/z*(%)**:** 98 (24, M^+); 83 (6); 80 (4); 70 (15); 69 (23); 55 (100).

12.7.1.1.3. Isomerization of **cyclooctene oxide (163c)**

Mixing 648.00 mg (5.0 mmol, 1.0 equiv) of cyclooctene oxide **163c** and 2.0 equiv of LDA, after 5h at reflux a 92:8 mix of octahydropentalen-1-ol **35** (0.9 mmol, 92%) and (*Z*)-cyclooct-2-enol **169c** (0.08 mmol, 8%) was obtained.



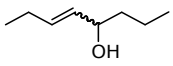
169c: (*Z*)-Cyclooct-2-enol[104, 152, 483]
$C_8H_{14}O$ **M=**126.14
^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 5.67-5.46 (2H, m, C**H** olefinics); 4.70-4.57 (1H, m, C**H**OH); 2.20-2.00 (1H. m O**H**); 1.90-1.00 (10H, m, (C**H_2**)$_5$CH=CHCHOH).
MS (EI) *m/z*(%)**:** 126 (15, M^+); 111 (10); 109 (1, M^+ – OH); 98 (11); 93 (20); 83 (100, M^+ – CHCHOH); 82 (34); 79 (29); 70 (63); 67 (62); 58 (8); 55 (83).



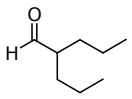
35: Octahydropentalen-1-ol[152, 483]
$C_8H_{14}O$ **M=**126.14
^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 4.30-4.10 (1H, m, C**H**OH); 2.50-2.30 (C**H** at bridge of bicycle); 2.00-1.20 (10H, m, C**H_2** of bicycle).
MS (EI) *m/z*(%)**:** 126 (0.6, M^+); 124 (0.5, M^+ – 2); 108 (16, M^+ – H_2O); 95 (4, M^+ – H_2O – CH_2); 93 (14); 82 (35, M^+ – CH_2CHOH); 80 (30); 67 (100); 58 (25); 57 (29).

12.7.1.1.4. Isomerization of **4-octene oxide (159a)**

Mixing 128.20 mg (1.0 mmol, 1.0 equiv) of 4-octene oxide **159a** with 2.0 equiv of LDA the isomerization products **173a** (4:1 *E*/*Z*, 50.00 mg, 0.4 mmol, 39%) and **174** (10.25 mg, 0.08 mmol, 8%) were obtained after 3h at reflux as a 85% overall conversion.



173a: oct-5-en-4-ol[104, 484, 485]
$C_8H_{16}O$ **M=**128.16
^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 7.77-7.71 (1H, m, C**H**=CHOH); 5.48-5.32 (1H, m, CH=C**H**OH); 4.04 (1H, m, C**H**CHO); 2.09-2.00 (2H, m, C**H_2**CH=CH); 1.80-1.00 (2H, C**H_2**C**H_2**CH_3); 0.70-1.00 (6H, m, CH_2CH_2C**H_3** and C**H_3**CH_2CH=CH).
MS (EI) *m/z*(%)**:** 128 (2, M^+); 113 (1); 99 (39, M^+ – Et); 85 (95 , M^+ – *n*Pr); 67 (51, M+ – H_2O – *n*Pr); 57 (100, Bu^+); 55 (70).

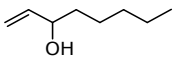


174: 2-propylpentanal[485]
$C_8H_{16}O$ **M=**128.16
^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 9.56 (1H, d, *J*=3.2, C**H**O); 2.25 (1H, m, C**H**CHO); 1.90-1.15 (8H, m, C**H_2** aliphatics); 1.10-0.70 (6H, m, C**H_3** aliphatics).

MS (EI) *m/z*(%)**:** 129 (1, M^+ + H); 128 (12, M^+); 99 (2); 85 (43, M^+ – *n*Pr); 71 (71, M+ – *n*Bu); 58 (59); 57 (100, Bu^+); 55 (11).

12.7.1.1.5. Isomerization of **2-octene oxide (159b)**

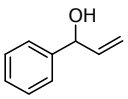
2-Octene oxide **159b** (128.20 mg, 1.0 mmol, 1.0 equiv) was mixed with 2.0 equiv of LDA at reflux for 5h giving the isomerized alcohol **173b** (76.90 mg, 0.6 mmol, 60%).



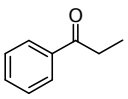
173a: oct-1-en-3-ol[104, 484, 486]
$C_8H_{16}O$ **M=**128.16
^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 5.86 (1H, ddd, *J*=17.0, 10.6, 6.2, CH_2=C**H**CHOH); 5.14 (2H, dd, *J*=17.0, 10.6, C**H_2**=CHCHOH); 4.13-4.04 (1H, m, CH_2=CHC**H**OH); 1.75 (1H, br-s, CHO**H**); 1.53-1.46 (2H, m, CH(OH)C**H_2**$CH_2CH_2CH_2CH_3$); 1.36-1.15 (6H, m, CH_2(C**H_2**$)_3CH_3$); 0.91-0.84 (3H, m, $CH_2(CH_2)_3$C**H_3**).
MS (EI) *m/z*(%)**:** 127 (0.1, M^+ – H); 112 (0.03); 99 (4, M^+ – CH_2CH_3); 85 (7, M^+ – $CH_2CH_2CH_3$); 72 (15); 57 (100, CH_2=$CHCHOH^+$); 55 (15).

12.7.1.1.6. Isomerization of **β-methylstirene oxide (159c)**

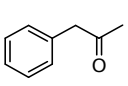
130.20 mg (1.0 mmol, 1.0 equiv) of 2-methyl-3-phenyloxirane **159c** were heated at reflux with 2.0 equiv of LDA for 5h to afford a 22:11:32:35 non-separable mix of 1-phenylprop-2-en-1-ol **173c**, 1-phenylpropan-2-one **176**, propiophenone **175** and 2-phenylpropanal **177**.



173c: 1-phenylprop-2-en-1-ol[487-490]
$C_9H_{10}O$ **M=**134.10
^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 7.39-7.23 (5H, m, C**H** aromatics); 6.15-5.98 (1H, m, CH_2=C**H**CHOH); 5.40-5.18 (3H, m, C**H_2**=CHCHOH and CH_2=CHC**H**OH); 1.28 (1H, d, *J*=6.2, CHO**H**).
MS (EI) *m/z*(%)**:** 134 (49, M^+); 133 (100, M^+); 115 (33); 105 (75, M^+ – CH=CH); 92 (66); 91 (37, $C_7H_7^+$); 79 (89); 77 (99, $C_6H_5^+$); 56 (18); 55 (69); 51 (68).

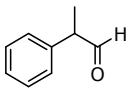


175: propiophenone[491]
$C_9H_{10}O$ **M=**134.10
^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 7.98-7.96 (2H, C**H** *ortho* aromatics C=O); 7.59-7.22 (3H, C**H** *meta* and *para* aromatics C=O); 2.99 (2H, q, *J*=7.2, C**H_2**CH_3); 1.22 (3H, t, *J*=7.2, CH_2C**H_3**).
MS (EI) *m/z*(%)**:** 135 2, M^+ + H); 134 (18, M^+); 105 (100, M^+ – CH_2CH_3); 91 (1, $C_7H_7^+$); 77 (63, $C_6H_5^+$); 63 (2); 51 (35).



176: 1-phenylpropan-2-one[491-493]
$C_9H_{10}O$ **M=**134.10

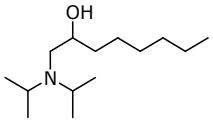
^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 7.35-7.19 (5H, m, C**H** aromatics); 3.70 (2H, s, C**H_2**C=O); 2.16 (C**H_3**C=O).
MS (EI) *m/z*(%)**:** 134 (37, M^+); 92 (40); 91 (100, $C_7H_7^+$); 77 (3, $C_6H_5^+$); 65 (40); 51 (16).



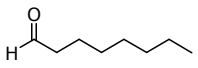
177: <u>2-phenylpropanal</u>[494-497]
$C_9H_{10}O$ **M=**134.10
^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 9.69 (1H, d, *J*=1.0, C**H**O); 7.50-7.10 (5H, m, C**H** aromatics); 3.70-3.60 (1H, m, C**H**CH_3); 1.45 (3H, d, *J*=7.0, CHC**H_3**).
MS (EI) *m/z*(%)**:** 134 (13, M^+); 105 (100, M^+ – CHO); 91 (9, $C_7H_7^+$); 79 (25); 77 (24, $C_6H_5^+$); 63 (5); 51 (19).

12.7.1.1.7. <u>Isomerization of **1-octene oxide (159d)**</u>

0.77 mL (5.0 Mmol, 1.0 equiv) of 1-octene oxide **159d** were mixed with 2.0 equiv of LDA at reflux for 5h giving a 44:56 mix of octanal **179** (1.9 mmol, 38%) and 1-(di-*iso*-propylamino)octan-2-ol **178** (2.3 mmol, 46%).

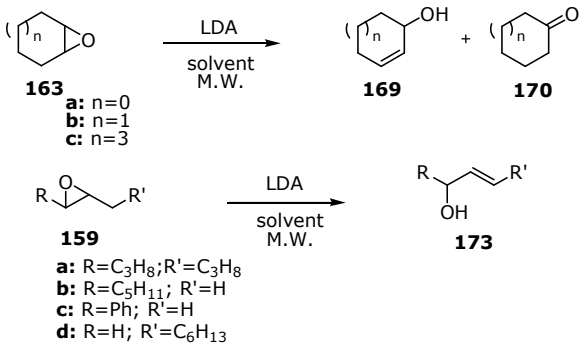


178: <u>1-(di-*iso*-propylamino)octan-2-ol</u>[498]
$C_{14}H_{31}NO$ **M=**229.31
^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 3.55-3.40 (1H, m, C**H**OH); 3.03 (2H, sep, *J*=7.0, N(C**H**$(CH_3)_2)_2$); 2.58 (1H, dd, *J*=13.6, 3.8, C**H**H'CHOH); 2.13 (1H, dd, *J*=13.6, 10.8, CH**H'**CHOH); 1.70-1.40 (10H, m, CH(C**H_2**$)_5CH_3$); 1.04 (6H, d, *J*=6.6, N(CH(C**H_3**$)_2)_2$); 0.98 (6H, d, *J*=6.6, N(CH(C**H_3**$)_2)_2$); 0.95-0.80 (3H, m, $CH(CH_2)_5$C**H_3**).
^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 66.3 (**C**HOH); 50.5 (**C**H_2CHOH); 47.8 (**C**H$(CH_3)_2$); 35.3 (CH(OH)**C**H_2); 31.8 ($CH_2CH_2CH_2$**C**$H_2CH_2CH_3$); 29.5 (CH_2CH_2**C**$H_2CH_2CH_2CH_3$); 25.9 (CH_2**C**$H_2CH_2CH_2CH_2CH_3$); 22.6 (CH(**C**$H_3)_2$); 19.1 ($CH_2CH_2CH_2CH_2$**C**H_2CH_3); 14.0 ($CH_2CH_2CH_2CH_2CH_2CH_3$).
MS (EI) *m/z*(%)**:** 214 (2, M^+ – CH_3); 186 (1); 144 (9); 114 (100, $(iPr)_2NCH_2^+$); 102 (2); 72 (35); 55 (6).



179: <u>octanal</u>[499]
$C_8H_{16}O$ **M=**128.16
^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 9.76 (1H, t, *J*=2.0, C**H**O); 2.42 (2H, td, *J*=7.4, 2.0, CHOC**H_2**$(CH_2)_5CH_3$); 1.55-1.20 (10H, m, $CHOCH_2$(C**H_2**$)_5CH_3$); 0.95-0.80 (3H, m, $CHOCH_2(CH_2)_5$C**H_3**).
^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 237.4 (**C**HO); 43.8 (CHO**C**H_2); 29.1 ($CHOCH_2CH_2$**C**$H_2(CH_2)_3CH_3$); 29.0 ($CHO(CH_2)_3$**C**$H_2(CH_2)_2CH_3$); 25.0 ($CHO(CH_2)_4$**C**H_2CH_3); 22.0 ($CHOCH_2$**C**$H_2(CH_2)_4CH_3$); 14.0 ($CHO(CH_2)_6$**C**H_3).
MS (EI) *m/z*(%)**:** 128 (0.1, M^+); 110 (5, M^+ – H_2O); 100 (9, M^+ – CO); 95 (8); 84 (48, M^+ – $COHCH_2$); 81 (24); 69 (37); 68 (29); 67 (25); 56 (100); 55 (81).

12.7.1.2. *General procedure for the isomerization of meso-epoxides mediate by microwaves using LDA*



In a vessel for microwaves reactions, equipped with a septum and maintained under nitrogen, a solution of LDA (2.0 mmol, 2.0 equiv) in organic solvent (THF, DEE or pentane, 0.5 M) was prepared at low temperatures from BuLi (1.6 M solution in hexanes, n mmol, n equiv) and di-*iso*-propylamine (n mmol, n equiv). After 30', the epoxide **159** or **163** (1.0 equiv) was introduced and the resulting reaction mixture was heated (40°-80° C) by microwave irradiations at 100 – 300 W (value previously settled on the Microwave oven) for 1 - 10 minutes depending on the substrate. The solution was then diluted in ether and quenched with a saturated aq. NH_4Cl solution. The two phases were separated and the aqueous portion was extracted with ether. The combined organic layers were washed with H_2O and brine, anhydrified over Na_2SO_4, filtered and concentrated *in vacuo* to afford the isomerization product **169**, **170** or **173** and other possible by-products. Conversions and yields were calculated by GC and/or ^{1}H-NMR.

12.7.1.2.1. Isomerization of **cyclopentene oxide (163a)** with 2.0 equiv of LDA in pentane

Cyclopentene oxide **163a** (0.09 mL, 1.0 mmol, 1.0 equiv) and LDA (2.0 equiv) in anhydrous pentane were heated by M.W. irradiations at 60° C (300 W) for 5' and then worked-up to afford a 98:2 mix of cyclopenten-2-ol **169a** (0.7 mmol, 71%) and cyclopentanone **170a** (0.07 mmol, 7%).

12.7.1.2.2. Isomerization of **cyclopentene oxide (163a)** with 2.0 equiv of LDA in THF

Cyclopentene oxide **163a** (0.10 mL, 1.0 mmol, 1.0 equiv) and LDA (2.0 equiv) in dried THF were heated by M.W. irradiations at 60° C (300 W) for 5'. After work-up a 91:9 mix of cyclohexen-2-ol **169a** (0.57 mmol, 57%) and cyclopentanone **170a** (0.06 mmol, 6%) was obtained

12.7.1.2.3. Isomerization of **cyclopentene oxide (163a)** with 2.0 equiv of LDA in DEE

Heating cyclopentene oxide **163a** (0.10 mL, 1.0 mmol, 1.0 equiv) and LDA (2.0 equiv) in dried DEE by M.W. irradiations at 50° C (300 W) for 5', produced a 98:2 mix of cyclohexen-2-ol **169a** (0.5 mmol, 52%) and cyclopentanone **170a** (0.01 mmol, 1%).

12.7.1.2.4. Isomerization of **cyclohexene oxide (163b)** with 2.0 equiv of LDA in pentane

Cyclohexene oxide **163b** (0.10 mL, 1.0 mmol, 1.0 equiv) and LDA (2.0 equiv) in pentane were heated by M.W. irradiations at 60° C (300 W) for 5' and then worked-up to afford a 2:1 mix of cyclohexen-2-ol **169b** (0.5 mmol, 50%) and cyclohexanone **170b** (0.29 mmol, 29%).

12.7.1.2.5. Isomerization of **cyclohexene oxide (163b)** with 2.0 equiv of LDA in THF

A cyclohexene oxide **163b** (0.10 mL, 1.0 mmol, 1.0 equiv) and LDA (2.0 equiv) solution in THF was irradiated by M.W. irradiations at 60° C (300 W) for 5', as reported into the general procedure. The resulting reaction mixture was then worked-up to afford a 6:1 mix of cyclohexen-2-ol **169b** (0.4 mmol, 44%) and cyclohexanone **170b** (0.08 mmol, 8%).

12.7.1.2.6. Isomerization of **cyclohexene oxide (163b)** with 2.0 equiv of LDA in DEE

Cyclohexene oxide **163b** (0.10 mL, 1.0 mmol, 1.0 equiv) and LDA (2.0 equiv) in diethyl ether were heated by M.W. irradiations at 50° C (300 W) for 5' and then worked-up to afford a 5:1 mix of cyclohexen-2-ol **169b** (0.4 mmol, 42%) and cyclohexanone **170b** (0.08 mmol, 8%).

12.7.1.2.7. Isomerization of **cyclooctene oxide (163c)** with 2.0 equiv of LDA in pentane

Cyclooctene oxide **163c** (127.90 mg, 1.0 mmol, 1.0 equiv) and LDA (2.0 equiv) in pentane were heated by M.W. irradiations at 60° C (300 W) for 10' and then worked-up to afford pure octahydropentalen-1-ol **35** (1.0 mmol, 100%).

12.7.1.2.8. Isomerization of **cyclooctene oxide (163c)** with 2.0 equiv of LDA in THF

Cyclohexene oxide **163c** (129.40 mg, 1.0 mmol, 1.0 equiv) and LDA (2.0 equiv) in THF were irradiated by M.W. at 60° C (300 W) for 5'. After work-up a 4:1 mix

of octahydropentalen-1-ol **35** (0.7 mmol, 70%) and (*Z*)-cyclooct-2-enol **169c** (0.2 mmol, 23%) was obtained.

12.7.1.2.9. Isomerization of **cyclooctene oxide (163c)** with 2.0 equiv of LDA in DEE

A cyclooctene oxide **163c** (131.10 mg, 1.0 mmol, 1.0 equiv) and LDA (2.0 equiv) mixture in diethyl ether was heated by M.W. irradiations at 50° C (300 W) for 5' and then worked-up to afford pure octahydropentalen-1-ol **35** (0.9 mmol, 90%).

12.7.1.2.10. Isomerization of **4-octene oxide (159a)** with 2.0 equiv of LDA in pentane

4-Octene oxide **159a** (71.40 mg, 0.56 mmol, 1.0 equiv) and LDA (2.0 equiv) were heated in pentane by M.W. irradiations at 60° C (300 W) for 10' and then worked-up to afford a 78:22 mix of the allylic alcohol **173a** (0.13 mmol, 23%) and the aldehyde **174** (0.04 mmol, 8%) with a 92% conversion.

12.7.1.2.11. Isomerization of **4-octene oxide (159a)** with 2.0 equiv of LDA in THF

4-Octene oxide **159a** (66.10 mg, 0.52 mmol, 1.0 equiv) and LDA (2.0 equiv) were heated in THF by M.W. irradiations at 60° C (300 W) for 10' and then worked-up to give 25.32 mg of oct-3-en-5-ol **173a** (0.2 mmol, 38%).

12.7.1.2.12. Isomerization of **4-octene oxide (159a)** with 2.0 equiv of LDA in DEE

4-Octene oxide **159a** (53.30 mg, 0.42 mmol, 1.0 equiv) and LDA (2.0 equiv) in diethyl ether were heated by M.W. irradiations at 50° C (300 W) for 5' and then worked-up to afford a 83:17 mix of the allylic alcohol **173a** (4:1 *E*/*Z*, 16.66 mg, 0.13 mmol, 31%) and the aldehyde **174** (10.87 mg, 0.04 mmol, 8%) with a 85% conversion.

12.7.1.2.13. Isomerization of **2-octene oxide (159b)** with 2.0 equiv of LDA in pentane

2-Octene oxide **159b** (0.15 mL, 0.48 mmol, 1.0 equiv) and LDA (2.0 equiv) in pentane were heated by M.W. irradiations at 60° C (300 W) for 10' and then worked-up to afford the allylic alcohol **173b** (34.08 mg, 0.34 mmol, 71%).

12.7.1.2.14. Isomerization of **2-octene oxide (159b)** with 2.0 equiv of LDA in THF

2-Octene oxide **159b** (70.10 mg, 0.54 mmol, 1.0 equiv) and LDA (2 eq.) were reacted in THF at 60° C under M.W. irradiation (300 W) for 5' and then worked-up to give 58.80 mg of oct-1-en-3-ol **173b** (0.4 mmol, 84%).

12.7.1.2.15. Isomerization of **2-octene oxide (159b)** with 2.0 equiv of LDA in DEE

2-Octene oxide **159b** (68.50 mg, 0.53 mmol, 1.0 equiv) and LDA (2.0 equiv) were reacted in DEE under M.W. irradiation (300 W) for 5' and then worked-up to give 9.03 mg (0.07 mmol, 13%) of the allylic alcohol **173b**.

12.7.1.2.16. Isomerization of **β-methylstirene oxide (159c)** with 2.0 equiv of LDA in pentane

β-Methylstirene oxide **159c** (67.00 mg, 0.50 mmol, 1.0 equiv) and LDA (2.0 equiv) were heated in pentane by M.W. irradiations at 60° C (300 W) for 10' and then worked-up to afford a 40:38:22 mix of the aldehyde **177** (26.82 mg, 0.2 mmol, 38%), the allylic alcohol **173c** (24.21 mg, 0.18 mmol, 36%) and the ketone **176** (14.01 mg, 0.1 mmol, 21%).

12.7.1.2.17. Isomerization of **β-methylstirene oxide (159c)** with 2.0 equiv of LDA in THF

β-Methylstirene oxide **159c** (56.50 mg, 0.42 mmol, 1.0 equiv) and LDA (2.0 equiv) in THF solution were irradiated under M.W. irradiations at 60° C (300 W) for 10' and then worked-up to afford a 61:20:19 mix of the ketone **175** (26.80 mg, 0.2 mmol, 48%), the aldehyde **177** (8.79 mg, 0.07 mmol, 17%) and the ketone **176** (8.35 mg, 0.06 mmol, 14%).

12.7.1.2.18. Isomerization of **β-methylstirene oxide (159c)** with 2.0 equiv of LDA in DEE

β-Methylstirene oxide **159c** (65.10 mg, 0.49 mmol, 1.0 equiv) and LDA (2.0 equiv) in diethyl ether were heated by M.W. irradiations at 50° C (300 W) for 5' and then worked-up to afford a 39:30:18:13 mix of the allylic alcohol **173c** (21.78 mg, 0.16 mmol, 33%), the aldehyde **177** (16.76 mg, 0.13 mmol, 27%), the ketone **176** (10.05 mg, 0.07 mmol, 14%) and the ketone **175** (7.26 mg, 0.05 mmol, 10%).

12.7.1.2.19. Isomerization of **1-octene oxide (159d)** with 2.0 equiv of LDA in pentane

1-Octene oxide **159d** (0.15 mL, 1.0 mmol, 1.0 equiv) and LDA (2.0 equiv) in pentane were heated by M.W. irradiations at 60° C (300 W) for 5' and then worked-up to afford a 68:32 mix of the aminoalcohol **178** (0.6 mmol, 55%) and the aldehyde **179** (0.3 mmol, 25%).

12.7.1.2.20. Isomerization of **1-octene oxide (159d)** with 2.0 equiv of LDA in THF

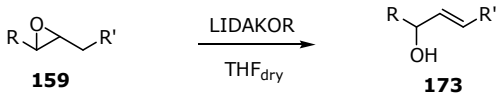
1-Octene oxide **159d** (1.0 mmol, 1.0 equiv) and LDA (2.0 equiv) were heated in THF by M.W. irradiations at 60° C (300 W) for 5' and then worked-up to afford a 77:23 mix of octanal **179** (0.8 mmol, 85%) and 1-(di-*iso*-propylamino)octan-2-ol **178** (0.08 mmol, 8%).

12.7.1.2.21. Isomerization of **1-octene oxide (159d)** with 2.0 equiv of LDA in DEE

1-Octene oxide **159d** (0.15 mL, 1.0 mmol, 1.0 equiv) and LDA (2.0 equiv) in diethyl ether were heated by M.W. irradiations at 50° C (300 W) for 5' and then worked-up. A 48.31 mg mixture (0.4 mmol, 38%) of octanal **179** and 17.79 mg (0.08 mmol, 8%) of 1-(diisopropylamino)octan-2-ol **178** was obtained

12.7.2. Isomerizations with superbases

12.7.2.1. *General procedure for the isomerization of meso-epoxides using LIDAKOR in THF at low temperatures*



159 **173**

a: R=C_3H_8;R'=C_3H_8
b: R=C_5H_{11}; R'=H
c: R=Ph; R'=H
d: R=H; R'=C_6H_{13}

A solution of LIDAKOR was prepared in a Schlenk tube, under nitrogen, from BuLi (2.0 mmol, 2.0 equiv, 1.6 M solution in hexanes, the hexanes were evaporated before the addition of the solvent), DIPA (2.0 mmol, 2.0 equiv) and K^{t}BuO (2.0 mmol, 2.0 equiv) in anhydrous THF (0.5 M) at –78° C. After 30' a solution of the epoxides **159** (1.0 equiv) in dried THF was added dropwise and the resulting reaction mixture was stirred at –50° C for 12 - 36h. Then the mixture was quenched with water and the two layers were separated. The aqueous portion was extracted with ether (3 times) and the combined organic components were washed twice with H_2O and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the allyl alcohol **173**.

12.7.2.1.1. Isomerization of **4-octene oxide (159a)**

4-Octene oxide **159a** (66.10 mg, 0.52 mmol, 1.0 equiv) was reacted with 2.0 equiv of LIDAKOR at –50° C in anhydrous THF for 12h giving 43.30 mg (0.34 mmol, 65%) of the product **173a**, as 10:1 *E*:*Z* mix.

12.7.2.1.2. Isomerization of **2-octene oxide (159b)**

2-Octene oxide **159b** (67.00 mg, 0.50 mmol, 1.0 equiv) was reacted with 2.0 equiv of LIDAKOR at –50° C in anhydrous THF for 12h giving 57.70 mg (0.45 mmol, 90%) of the isomerization product **173b**.

12.7.2.1.3. Isomerization of **β-methylstirene oxide (159c)**

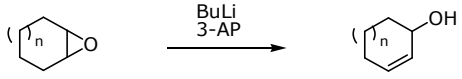
β-Methylstirene oxide **159c** (79.70 mg, 0.59 mmol, 1.0 equiv) was reacted with 2.0 equiv of LIDAKOR at –50° C in anhydrous THF for 12h giving 35.70 mg (0.27 mmol, 45%) of the ketone **176** and 25.50 mg (0.2 mmol, 32%) of the allylic alcohol **173c**.

12.7.2.1.4. Isomerization of **1-octene oxide (159d)**

1-Octene oxide **159d** (66.10 mg, 0.52 mmol, 1.0 equiv) was reacted with 2.0 equiv of LIDAKOR at –50° C in anhydrous THF for 12h giving 223.30 mg of **178** (0.5 mmol, 97%).

12.7.3. Isomerizations with 3-APLi's

12.7.3.1. *General procedure for the enantioselective isomerization of meso-epoxides using chiral lithium amide derived by 3-aminopyrrolidines*



163 **a:** n=0 **b:** n=1 **c:** n=3 **169**

In a Schlenk tube, under nitrogen, *n*-BuLi (n mmol, n equiv, 1.6 M solution in hexanes) was added dropwise over 5' to a solution of 3-aminopyrrolidine (**224**, **229**, **230**, **238a**, **239a**, **239b**) (n mmol, n equiv) in anhydrous organic solvent (THF, Et_2O or pentane) at low temperatures. The resulting solution was stirred for 30' and the racemic epoxide **163** (1.0 equiv) in dried organic solvent, containing *n*-decane (*ca*. 20.0 mg, as internal reference for GC analysis) was added dropwise during a 10' period. The reaction mixture was stirred for 4h at low temperature and, then, allowed to slowly warm to room temperature. After completion (NMR check) the reaction mixture was partitioned between a saturated aq. NH_4Cl solution and ether. The two phases were separated and the aqueous portion was extracted with DEE (three times), while the combined organic components were washed with water and brine, dried over sodium sulfate, filtered and concentrated to afford the crude product **169**. Conversion and enantiomeric excess were determined by chiral GC.

12.7.3.1.1. Isomerization of **cyclopentene oxide (163a)** with 2.0 equiv of lithium (*S*)-1-(benzyl-3-((*N*-diphenylmethylidene)amino)pyrrolidide in THF

Cyclopentene oxide **163a** (0.09 mL, 1.00 mmol, 1.0 equiv) was stirred with 2.0 equiv of the 3-APLi derived from the 3-AP **229** in anhydrous THF at room temperature for 48h to afford the allylic alcohol **169a** with a 30% conversion and a 20% (*S*) e.e..

12.7.3.1.2. Isomerization of **cyclopentene oxide (163a)** with 2.0 equiv of lithium (*S*)-1-benzyl-3-(benzylamino)pyrrolidide in THF

Cyclopentene oxide **163a** (0.09 mL, 1.00 mmol, 1.0 equiv) was reacted with 3-APLi (derived from the 3-AP **224**, 2.0 equiv) in anhydrous THF at room temperature for 48h to afford the allylic alcohol **169a** with a 92% conversion and 28% (*R*) e.e..

12.7.3.1.3. Isomerization of **cyclopentene oxide (163a)** with 2.0 equiv of lithium (*S*)-1-benzyl-3-(cyclohexylamino)pyrrolidide in THF

Cyclopentene oxide **163a** (0.09 mL, 1.00 mmol, 1.0 equiv) was reacted with 3-APLi (derived from the 3-AP **230**, 2.0 equiv) in anhydrous THF at room temperature for 16h to afford the allylic alcohol **169a** with a 100% conversion and 58% (*R*) e.e..

12.7.3.1.4. Isomerization of **cyclohexene oxide (163b)** with 1.0 equiv of lithium (*S*)-1-(benzyl-3-((*N*-diphenylmethylidene)amino)pyrrolidide in pentane

Cyclohexene oxide **163b** (0.10 mL, 1.00 mmol, 1.0 equiv) was reacted with 1.1 equiv of 3-APLi (obtained from the 3-AP **229**) in pentane at room temperature for 48h to afford the allylic alcohol **169b** with a 40% conversion and 4% (*S*) e.e..

12.7.3.1.5. Isomerization of **cyclohexene oxide (163b)** with 2.0 equiv of lithium (*S*)-1-(benzyl-3-((*N*-diphenylmethylidene)amino)pyrrolidide in pentane

Cyclohexene oxide **163b** (0.10 mL, 1.00 mmol, 1.0 equiv) was reacted with 2.0 equiv of 3-APLi (derived from the 3-AP **229)** in pentane at room temperature for 48h to afford the allylic alcohol **169b** with a 20% conversion and 10% (*S*) e.e..

12.7.3.1.6. Isomerization of **cyclohexene oxide (163b)** with 2.0 equiv of lithium (*S*)-1-(benzyl-3-((*N*-diphenylmethylidene)amino)pyrrolidide mediated by M.W. in pentane

Cyclohexene oxide **163b** (0.10 mL, 1.00 mmol, 1.0 equiv) and 3-APLi (derived from the 3-AP **229**, 2.0 equiv) were heated by M.W. irradiations in pentane at 60° C (300 W) for 60' and then worked-up to give the allylic alcohol **169b** with a 38% conversion and 5% (*S*) e.e..

12.7.3.1.7. Isomerization of **cyclohexene oxide (163b)** with 1.0 equiv of lithium (*S*)-1-(benzyl-3-((*N*-diphenylmethylidene)amino)pyrrolidide in THF

Cyclohexene oxide **163b** (0.10 mL, 1.00 mmol, 1.0 equiv) was reacted with 1.1 equiv of the 3-APLi derived from the 3-AP **229** in THF at room temperature for 48h to afford the allylic alcohol **169b** with a 39% conversion and 10% (*S*) e.e..

12.7.3.1.8. Isomerization of **cyclohexene oxide (163b)** with 2.0 equiv of lithium (*S*)-1-(benzyl-3-((*N*-diphenylmethylidene)amino)pyrrolidide in THF

Cyclohexene oxide **163b** (0.10 mL, 1.00 mmol, 1.0 equiv) was reacted with 2.0 equiv of 3-APLi (derived from the 3-AP **229**) in THF at room temperature for 48h to give the allylic alcohol **169b** with a 99% conversion and 55% (*S*) e.e..

12.7.3.1.9. Isomerization of **cyclohexene oxide (163b)** with 2.0 equiv of lithium (*S*)-1-(benzyl-3-((*N*-diphenylmethylidene)amino)pyrrolidide mediated by M.W. in THF

Cyclohexene oxide**163b** (0.10 mL, 1.00 mmol, 1.0 equiv) and 3-APLi (derived from the 3-AP **229**, 2.0 equiv) were heated by M.W. irradiations in THF at 60° C (300 W). After 60' the allylic alcohol **169b** was obtained with a 60% conversion and 27% (*S*) e.e..

12.7.3.1.10. Isomerization of **cyclohexene oxide (163b)** with 2.0 equiv of lithium (*S*)-1-(benzyl-3-((*N*-diphenylmethylidene)amino) pyrrolidide in DEE

Cyclohexene oxide **163b** (0.10 mL, 1.00 mmol, 1.0 equiv) was reacted with 3-APLi (derived from the 3-AP **229**, 2.0 equiv) in diethyl ether at room temperature for 48h to give the allylic alcohol **169b** with a 27% conversion and 22% (*S*) e.e..

12.7.3.1.11. Isomerization of **cyclohexene oxide (163b)** with 2.0 equiv of lithium (*S*)-1-benzyl-3-(benzylamino)pyrrolidide in pentane

Cyclohexene oxide **163b** (0.10 mL, 1.00 mmol, 1.0 equiv) was reacted with 3-APLi (derived from the 3-AP **224**, 2.0 equiv) in pentane at room temperature for 48h to afford the allylic alcohol **169b** with a 75% conversion and 55% (*S*) e.e..

12.7.3.1.12. Isomerization of **cyclohexene oxide (163b)** with 2.0 equiv of lithium (*S*)-1-benzyl-3-(benzylamino)pyrrolidide mediated by M.W. in pentane

Cyclohexene oxide **163b** (0.10 mL, 1.00 mmol, 1.0 equiv) and 3-APLi (derived from the 3-AP **224**, 2.0 equiv) were heated by M.W. irradiations in pentane at 60° C (300 W) for 60' and then worked-up to afford the allylic alcohol **169b** with a 60% conversion and 38% (*S*) e.e..

12.7.3.1.13. Isomerization of **cyclohexene oxide (163b)** with 2.0 equiv of lithium (*S*)-1-benzyl-3-(benzylamino)pyrrolidide in THF

Cyclohexene oxide **163b** (0.10 mL, 1.00 mmol, 1.0 equiv) was reacted with 3-APLi (derived from the 3-AP **224**, 2 equiv) in THF at room temperature for 48h to give cyclohexen-2-ol **169b** with a 89% conversion and 69% (*S*) e.e..

12.7.3.1.14. Isomerization of **cyclohexene oxide (163b)** with 2.0 equiv of lithium (*S*)-1-benzyl-3-(benzylamino)pyrrolidide mediated by M.W. in THF

Cyclohexene oxide **163b** (0.10 mL, 1.00 mmol, 1.0 equiv) and 3-APLi (derived from the *rac*-3-AP **224**, 2.0 equiv) were heated by M.W. irradiations in THF at 60° C (300 W) for 60' and then worked-up to afford the allylic alcohol **169b** with a 80% conversion and 58% (*S*) e.e..

12.7.3.1.15. Isomerization of **cyclohexene oxide (163b)** with 2.0 equiv of lithium (*S*)-1-benzyl-3-(benzylamino)pyrrolidide in DEE

Cyclohexene oxide **163b** (0.10 mL, 1.00 mmol, 1.0 equiv) was reacted with 3-APLi (derived from the 3-AP **224**, 2 equiv) in DEE at room temperature for 48h to give the allylic alcohol **169b** with a 83% conversion and 32% (*S*) e.e..

12.7.3.1.16. Isomerization of **cyclohexene oxide (163b)** with 2.0 equiv of lithium (*S*)-1-benzyl-3-(cyclohexylamino)pyrrolidide in THF

Cyclohexene oxide **163b** (0.10 mL, 1.00 mmol, 1.0 equiv) was reacted with 3-APLi (derived from the 3-AP **230**, 2 equiv) in THF at room temperature for 48h to give the allylic alcohol **169b** with a 100% conversion and 70% (*S*) e.e..

12.7.3.1.17. Isomerization of **cyclohexene oxide (163b)** with 2.0 equiv of lithium *N*-methyl-3-(*S*)-(1'-(*R*)-phenylethyl)aminopyrrolidide in THF

Cyclohexene oxide **163b** (0.10 mL, 1.00 mmol, 1.0 equiv) was reacted with 3-APLi (derived from the 3-AP **239a**, 2 equiv) in THF at room temperature for 48h to give the allylic alcohol **169b** with a 99% conversion and 58% (*R*) e.e..

12.7.3.1.18. Isomerization of **cyclohexene oxide (163b)** with 2.0 equiv of lithium *N*-methyl-3-(*S*)-(1'-(*S*)-phenylethyl)aminopyrrolidide in THF

Cyclohexene oxide **163b** (0.10 mL, 1.00 mmol, 1.0 equiv) was reacted with 3-APLi (derived from the 3-AP **239b,** 2.0 equiv) in THF at room temperature for 48h giving the allylic alcohol **169b** with a 99% conversion and 62% (*S*) e.e..

12.7.3.1.19. Isomerization of **cyclohexene oxide (163b)** with 2.0 equiv of lithium *N*-methyl-3-(*S*)-(1'-(*S*)-phenylethyl)aminopyrrolidide in THF

Cyclohexene oxide **163b** (0.10 mL, 1.00 mmol, 1.0 equiv) was reacted with 3-APLi (derived from the 3-AP **239b**, 2.0 equiv) in THF at room temperature for 48h giving the allylic alcohol **169b** with a 99% conversion and 62% (*S*) e.e..

12.7.3.1.20. Isomerization of **cyclohexene oxide (163b)** with 2.0 equiv of lithium (*S*)-1-(2-naphthylmethyl)-3-[(1-(*R*)-phenylethyl)amino]-pyrrolidide in THF

Cyclohexene oxide **163b** (0.10 mL, 1.00 mmol, 1.0 equiv) was reacted with 3-APLi (derived from the 3-AP **238a**, 2.0 equiv) in THF at room temperature for 48h giving the allylic alcohol **169b** with a 100% conversion and 81% (*S*) e.e..

12.7.3.1.21. Isomerization of **cyclooctene oxide (163c)** with 2.0 equiv of lithium (*S*)-1-(benzyl-3-((*N*-diphenylmethylidene)amino)-pyrrolidide in THF

Cyclohexene oxide **163c** (126.40, 1.00 mmol, 1.0 equiv) was reacted with 3-APLi (derived from the 3-AP **229**, 2.0 equiv) in THF at room temperature for 48h giving the allylic alcohol **169c** with a 20% conversion and 36% (*S*) e.e..

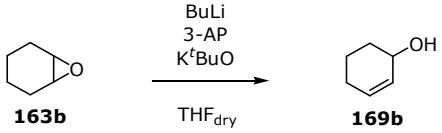
12.7.3.1.22. Isomerization of **cyclooctene oxide (163c)** with 2.0 equiv of lithium (*S*)-1-benzyl-3-(benzylamino)pyrrolidide in THF

Cyclooctene oxide **163c** (126.40 mg, 1.00 mmol, 1.0 equiv) was reacted with 3-APLi (derived from the 3-AP **224**, 2.0 equiv) in THF at room temperature for 48h to afford the allylic alcohol **169c** with a 8% conversion and 22% (*R*) e.e..

12.7.3.1.23. Isomerization of **cyclooctene oxide (163c)** with 2.0 equiv of lithium (*S*)-1-benzyl-3-(cyclohexylamino)pyrrolidide in THF

Cyclooctene oxide **163c** (126.30 mg, 1.00 mmol, 1.0 equiv) was reacted with 3-APLi (derived from the 3-AP **230**, 2.0 equiv) in THF at room temperature for 16h to afford the allylic alcohol **169c** with a 100% conversion and 62% (*R*) e.e..

12.7.3.2. *General procedure for the enantioselective isomerization of meso-epoxides using chiral superbases derived by lithium 3-aminopyrrolidides and K^{t}Bu*



163b **169b**

In a Schlenk tube, under nitrogen, *n*-BuLi (2.0 mmol, 2.0 equiv, 1.6 M solution in hexanes) was added dropwise over 5' to a solution of 3-aminopyrrolidines (**230**, **238a**, **239a**, **239b**) (2.0 mmol, 2,0 equiv) in freshly distilled THF at –78° C under N_2. Then, K^{t}BuO (2.0 mmol, 2.0 equiv) was added and the resulting superbase was stirred for 30' at low temperatures, after which the racemic epoxide **163** (1.0 equiv) in anhydrous THF, containing *n*-decane (*ca*. 20.0 mg, as internal reference for GC analysis) was added dropwise during a 10' period. The reaction mixture was stirred for 4h at low temperature and, then, allowed to warm slowly to room temperature. After completion (NMR check), the reaction mixture was partitioned between a saturated aq. NH_4Cl solution and ether. The phases were separated and the aqueous portion was extracted with DEE (three times), while the combined organic components were washed with water and brine, dried over sodium sulfate, filtered and concentrate to afford the crude product **169**. Conversion and enantiomeric excess were determinate by chiral GC.

12.7.3.2.1. Isomerization of **cyclohexene oxide (163b)** with 2.0 equiv of lithium (*S*)-1-benzyl-3-(cyclohexylamino)pyrrolidide in THF

Cyclohexene oxide **163b** (0.10 mL, 1.00 mmol, 1.0 equiv) was reacted with 2.0 equiv of the chiral superbase, obtained from the 3-AP **230**, BuLi and K^{t}BuO, in THF at room temperature for 12h giving the allylic alcohol **169b** with a 100% conversion and 52% (*R*) e.e..

12.7.3.2.2. Isomerization of **cyclohexene oxide (163b)** with 2.0 equiv of chiral superbase lithium *N*-methyl-3-(*S*)-(1'-(*R*)-phenylethyl)-aminopyrrolidide

Cyclohexene oxide **163b** (0.10 mL, 1.00 mmol, 1.0 equiv) was reacted with 2.0 equiv of chiral superbase, obtained from the 3-AP **239a**, BuLi and K^{t}BuO in THF at room temperature for 12h giving the allylic alcohol **169b** with a 99% conversion and 44% (*S*) e.e..

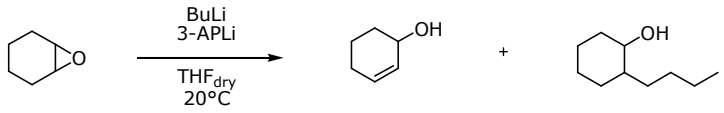
12.7.3.2.3. Isomerization of **cyclohexene oxide (163b)** with 2.0 equiv of lithium *N*-methyl-3-(*S*)-(1'-(*S*)-phenylethyl)aminopyrrolidide

Cyclohexene oxide **163b** (0.10 mL, 1.00 mmol, 1.0 equiv) was reacted with 2.0 equiv of chiral superbase, obtained from the 3-AP **239b**, BuLi and K^{t}BuO in THF at room temperature for 12h giving the allylic alcohol **169b** with a 100% conversion and 10% (*R*) e.e..

12.7.3.2.4. Isomerization of **cyclohexene oxide (163b)** with 2.0 equiv of lithium 1-(2-naphthylmethyl)-3-[(1-(*R*)-phenylethyl)amino]-pyrrolidide

Cyclohexene oxide **163b** (0.10 mL, 1.00 mmol, 1.0 equiv) was reacted with 2.0 equiv of the chiral superbase, obtained from the 3-AP **238a**, BuLi and K^{t}BuO, in THF at room temperature for 12h giving the allylic alcohol **169b** with a 100% conversion and a 10% (*S*) e.e..

12.7.3.3. *General procedure for the enantioselective isomerization of meso-epoxides using lithium 3-aminopyrrolidides as chiral ligand of n-BuLi*



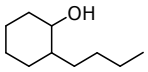
163b **169b** **258**

In a Schlenk tube, under nitrogen, *n*-BuLi (2.0 mmol, 2.0 equiv, 1.6 M solution in hexanes) was added dropwise over 5' to a solution of 3-aminopyrrolidines (**224**, **230 239a** and **239b**) (2.0 mmol, 2,0 equiv) in freshly distilled THF at –20° C under N_2. After 30', other 2.0 equiv of BuLi (2.0 mmol) were added and the resulting complex was stirred for further 30', after which the racemic epoxide **163b** (1.0 equiv) in anhydrous THF, containing *n*-decane (*ca*. 20.0 mg, as internal reference for GC analysis) was introduced dropwise during a 10' period. After completion (NMR check) the reaction mixture was partitioned between a saturated aq. NH_4Cl solution and ether. The phases were separated and the aqueous portion

was extracted with DEE (three times), while the combined organic components were washed with water and brine, dried over sodium sulfate, filtered and concentrate to afford a crude product consisting of a mixture of the product **169b** and **258**. Conversion and enantiomeric excess were determined by chiral GC.

12.7.3.3.1. Isomerization of **cyclohexene oxide (163b)** with 2.0 equiv of lithium *N*-methyl-3-(*S*)-(1'-(*R*)-phenylethyl)aminopyrrolidide

Cyclohexene oxide **163b** (0.10 mL, 1.00 mmol, 1.0 equiv) was reacted with 2.0 equiv of the complex, obtained from the 3-AP **239a** and BuLi, at –20° C for 12h giving a 45:55 mix of the allylic alcohol **169b** and the addition product **258** with a 100% overall conversion and a 23% (*R*) and 33% e.e., respectively.



258: 2-Butylcyclohexanol
$C_{10}H_{20}O$ **M=**156.20
^{1}H-NMR δ($CDCl_3$, 200 MHz)**:** 3.32-3.05 (1H, m, C**H**OH); 2.00-1.00 (15H, m, C**H_2**); 0.89 (3H, m, C**H_3**).
MS (EI) *m/z*(%)**:** 155 (0.3, M^+ – H); 138 (15); 109 (1); 96 (29); 95 (29); 82 (82); 81 (46); 67 (74); 57 (100, $C_4H_9^+$); 55 (56).

12.7.3.3.2. Isomerization of **cyclohexene oxide (163b)** with 2.0 equiv of lithium *N*-methyl-3-(*S*)-(1'-(*S*)-phenylethyl)aminopyrrolidide

Cyclohexene oxide **163b** (0.10 mL, 1.00 mmol, 1.0 equiv) was reacted with 2.0 equiv of the complex, obtained from the 3-AP **239b** and BuLi, at –20° C for 12h giving a 43:57 mix of the allylic alcohol **169b** and the addition product **258** with a 100% overall conversion and a 21% (*R*) and 30% e.e. respectively.

12.7.3.3.3. Isomerization of **cyclohexene oxide (163b)** with 2.0 equiv of lithium (*S*)-1-benzyl-3-(benzylamino)pyrrolidide

Cyclohexene oxide **163b** (0.10 mL, 1.00 mmol, 1.0 equiv) was reacted with the complex formed by 2.0 equiv of the 3-AP **224** and BuLi (4 equiv) at –20° C for 12h affording a 22:78 mix of the allylic alcohol **169b** and the addition product **259** with a 100% overall conversion and a 11% (*S*) e.e. and a 32% e.e. respectively.

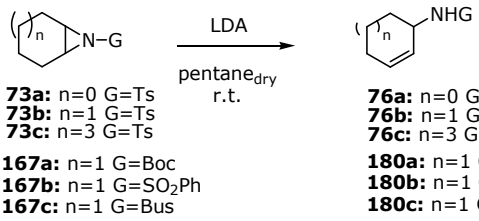
12.7.3.3.4. Isomerization of **cyclohexene oxide (163b)** with 2.0 equiv of lithium (*S*)-1-benzyl-3-(cyclohexylamino)pyrrolidide in THF

Cyclohexene oxide **163b** (0.10 mL, 1.00 mmol, 1.0 equiv) was reacted with the complex formed by 2.0 equiv of the 3-AP **230** and BuLi (4 equiv) at –20° C for 12h giving the allylic alcohol **169b** with a 100% conversion and a 84% (*S*) e.e..

12.8. Base-promoted isomerization of aziridines and aziridinyl ethers

12.8.1. Isomerizations with LDA

12.8.1.1. *General procedure for the isomerization of meso-aziridines using LDA at room temperature*

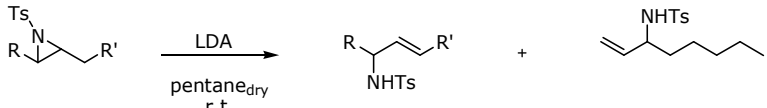


73a: n=0 G=Ts
73b: n=1 G=Ts
73c: n=3 G=Ts

167a: n=1 G=Boc
167b: n=1 G=SO_2Ph
167c: n=1 G=Bus

76a: n=0 G=Ts
76b: n=1 G=Ts
76c: n=3 G=Ts

180a: n=1 G=Boc
180b: n=1 G=SO_2Ph
180c: n=1 G=Bus



162: R=H; R'=C_5H_{11}
81a: R=CH_3; R'=C_4H_9
80: R=C_3H_7; R'=C_2H_5

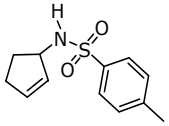
83 R=C_3H_7; R'=C_2H_5
85 R=CH_3; R'=C_4H_9

84

A solution of LDA was prepared in a Schlenk tube, under nitrogen, from BuLi (2.0 mmol, 2.0 equiv) and DIPA (2.0 mmol, 2.0 equiv) in anhydrous pentane (0.5 M) at 0°. After 30' a solution of the aziridine **73** (or **80**, **81a** **162** and **167**) (1.0 equiv) in dried pentane was added dropwise and the resulting reaction mixture was stirred at room temperature for 2 - 4h. Then the mixture was quenched with water and worked by separating the two layers. The aqueous portion was extracted with ether (3 times) and the combined organic components were washed twice with H_2O and brine, anhydrified (Na_2SO_4), filtered and concentrated under reduced pressure to afford the allyl amine **76**, **83-85** and **180**. The residue was finally purified by flash column chromatography.

12.8.1.1.1. Isomerization of **6-(*N*-(*para*-toluensulfonyl))-6-aza-bicyclo-[3.1.0]hexane (73a)**

6-(*N*-(*para*-Toluensulfonyl))-6-aza-bicyclo[3.1.0]hexane **73a** (118.60 mg, 0.50 mmol, 1.0 equiv) was reacted with 2.0 equiv of LDA for 2h giving, after purification (silica, eluent: 5:1 petroleum ether/ethyl acetate), the pure allyl amine **76a** (G=Ts) (58.10 mg, 0.25 mmol, 49%), as a pale yellow solid.

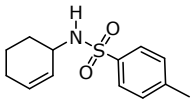


76a: 3-*N*-*para*-Toluensulfonylamino-cyclopentene
$C_{12}H_{15}NO_2S$ **M=**237.15
^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 7.79-7.75 (2H, m [AA' part of a AA'BB' spin system], C**H** *ortho* aromatics to SO_2); 7.32-7.28

(2H, m [BB' part of a AA'BB' spin system], C**H** *meta* aromatics to SO_2); 5.88-5.22 (1H, m, CHCH=C**H**); 5.47-5.40 (1H, m CHC**H**=CH); 4.55 (1H, br-d, *J*=9.0, N**H**Ts); 3.46-3.32 (1H, m, C**H**CH=CH); 2.43 (3H, s, CH_3 tosyl group); 2.40-2.00 (2H, m, C$\mathbf{H_2}$ cyclopentene); 1.80-1.20 (2H, m, C$\mathbf{H_2}$ cyclopentene).
^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 143.2 (**C_q** *para* aromatic to SO_2); 138.0 (**C_{ipso}** aromatic to SO_2); 134.9 (CH**C**H=CH); 130.3 (CHCH=**C**H); 129.6 (2C, **C**H *meta* aromatics to SO_2); 127.0 (2C, **C**H *ortho* aromatics to SO_2); 59.8 (**C**HCH=CH); 31.5 (**C**H_2CHNHTs); 30.8 (**C**H_2CH_2CHNHTs); 21.5 (**C**H_3 tosyl group).
MS (EI) *m/z*(%)**:** 237 (2, M^+); 173 (12); 172 (14); 155 (8, Ts^+); 139 (5); 105 (8); 91 (82, $C_7H_7^+$); 82 (100, M^+ – Ts); 67 (50); 65 (66); 55 (44).

12.8.1.1.2. Isomerization of 7-(*N*-(*para*-toluensulfonyl))-7-aza-bicyclo-[4.1.0] heptane (73b)

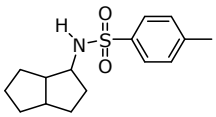
7-(*N*-(*para*-Toluensulfonyl))-7-aza-bicyclo[4.1.0]hexane **73b** (131.30 mg, 0.52 mmol, 1.0 equiv) was reacted with 2.0 equiv of LDA for 2h giving, after purification (silica, eluent: 6:1 petroleum ether/ethyl acetate), 54.00 mg (0.21 mmol, 41%) of the allyl amine **100b** (G=Ts) as a pale yellow solid.



76b: 3-*N*-*para*-Toluensulfonylamino-cyclohexene
$C_{13}H_{17}NO_2S$ **M=**251.17
^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 7.79-7.75 (2H, m [AA' part of a AA'BB' spin system], C**H** *ortho* aromatics to SO_2); 7.32-7.28 (2H, m [BB' part of a AA'BB' spin system], C**H** *meta* aromatics to SO_2); 5.80-5.72 (1H, m, CHCH=C**H**); 5.37-5.29 (1H, m CHC**H**=CH); 4.59 (1H, br-d, *J*=8.4, N**H**Ts); 3.87-3.70 (1H, m, C**H**CH=CH); 2.42 (3H, s, C$\mathbf{H_3}$ tosyl group); 2.00-1.10 (6H, m, C$\mathbf{H_2}$ cyclohexene).
^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 143.0 (**C_q** *para* aromatic to SO_2); 138.2 (**C_{ipso}** aromatic to SO_2); 131.4 (CH**C**H=CH); 129.5 (2C, **C**H *meta* aromatics to SO_2); 126.9 (3C, **C**H *ortho* aromatics to SO_2 and CHCH=**C**H); 49.0 (**C**HCH=CH); 30.4 (CH_2CH_2**C**H_2CHNHTs); 24.6 (**C**$H_2CH_2CH_2$CHNHTs); 21.6 (**C**H_3 tosyl group); 19.4 (CH_2**C**H_2CH_2CHNHTs).
MS (EI) *m/z*(%)**:** 251 (0.3, M^+); 250 (0.3, M^+ – H); 223 (9); 187 (17); 172 (4); 155 (23, Ts^+); 144 (6); 139 (5); 105 (9); 96 (54, M^+ – Ts); 91 (100, $C_7H_7^+$); 79 (25,); 67 (20); 65 (61); 55 (16).

12.8.1.1.3. Isomerization of 9-(*N*-(*para*-toluensulfonyl))-9-aza-bicyclo-[6.1.0]nonane (73c)

9-(*N*-(*para*-Toluensulfonyl))-9-aza-bicyclo[6.1.0]hexane **73c** (130.10 mg, 0.47 mmol, 1.0 equiv) was reacted with 2.0 equiv of LDA for 2h giving, after purification (silica, eluent: 10:1 petroleum ether/ethyl acetate), 35.40 mg (0.13 mmol, 27%) of the bicyclic amine **82** as a yellow solid.



82: 1-*N*-*para*-Toluensulfonylaminobicyclo[3.3.0]-octane

$C_{15}H_{23}NO_2S$ **M=**281.23

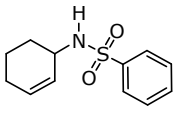
^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 7.79-7.75 (2H, m [AA' part of a AA'BB' spin system], C**H** *ortho* aromatics to SO_2); 7.30-7.26 (2H, m [BB' part of a AA'BB' spin system], C**H** *meta* aromatics to SO_2); 4.77 (1H, d, *J*=7.8, N**H**Ts); 3.60-3.45 (1H, m, C**H**NHTs); 2.42 (3H, s, C**H_3** tosyl group); 2.40-2.20 (2H, m, C**H** bicyclic group); 2.00-1.00 (10H, m, C**H_2** bicyclic group).

^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 143.0 (**C_q** *para* aromatic to SO_2); 137.8 (**C_{ipso}** aromatic to SO_2); 129.4 (2C, **C**H aromatics *meta* to SO_2); 127.0 (2C, **C**H *ortho* aromatics to SO_2); 57.1 (**C**HNHTs); 45.6 (**C**HCHNHTs); 41.3 (**C**HCH_2CH_2CHNHTs); 35.6 (**C**$H_2CH_2CH_2$CHCHNHTs); 30.6 (**C**H_2CHNHTs); 29.5 (**C**H_2CHCHNHTs); 28.2 (**C**H_2CH_2CHNHTs); 27.4 (**C**H_2CH_2CHCHNHTs); 21.6 (**C**H_3 tosyl group).

MS (EI) *m/z*(%)**:** 280 (1, M^+ + H); 279 (7, M^+); 250 (9); 210 (58); 184 (12); 155 (49, Ts^+); 124 (65, M^+ – Ts); 107 (20); 91 (100, $C_7H_7^+$); 79 (31); 65 (38); 55 (21).

12.8.1.1.4. Isomerization of 7-(*N*-benzenesulfonyl)-7-azabicyclo[4.1.0]-heptane (167b)

N-Benzenesulfonyl-7-azabicyclo[4.1.0]heptane **167b** (G=SO_2Ph, 123.30 mg, 0.52 mmol, 1.0 equiv) was reacted with 2.0 equiv of LDA for 4h to afford, after purification (silica, eluent: 6:1 petroleum ether/ethyl acetate), the allyl amine **180b** (G=SO_2Ph) (54.30 mg, 0.23 mmol, 44%), as a pale yellow solid.



180b: 3-*N*-Benzenesulfonylamino-cyclohexene

$C_{12}H_{15}NO_2S$ **M=**237.15

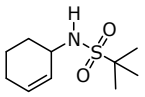
^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 7.92-7.87 (2H, m [AA' part of a AA'BB'C spin system], C**H** *ortho* aromatics to SO_2); 7.55-7.48 (3H, (2H, m [BB' and C parts of a AA'BB'C spin system], C**H** *meta* and *para* aromatics to SO_2); 5.78-5.68 (1H, m, C**H**=CHCHNH); 5.36-5.27 (1H, m, CH=C**H**CHNH); 5.00 (1H, br-s, CHN**H**); 3.90-3.70 (1H, m, C**H**NH); 1.95-1.85 (2H, m, C**H_2**CH=CHCHNH); 1.85-1.65 (1H, m, C**H**H'CHNH); 1.65-1.40 (3H, C**H_2**CH_2CHNH e CH**H'**CHNH).

^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 141.1 (**C_{ipso}** aromatic to SO_2); 132.3 (**C**H *para* aromatic to SO_2Ph); 131.4 (CH=**C**HCHNH); 128.9 (2C, **C**H *meta* aromatics to SO_2Ph); 127.2 (3C, **C**H *ortho* aromatics to SO_2Ph and **C**H=CHCHNH); 49.0 (**C**HNH); 30.1 (**C**H_2CHNH); 24.4 (**C**H_2CH=CH); 19.2 (**C**H_2CH_2CH=CH).

MS (EI) *m/z*(%)**:** 209 (17); 172 (18); 141 (14); 126 (6); 96 (60); 77 (100, $C_6H_5^+$); 68 (60); 51 (44).

12.8.1.1.5. Isomerization of 7-(*tert*-butyl-sulfonyl)7-azabicyclo[4.1.0]-heptane (167c)

7-(*tert*-Butyl-sulfonyl)7-azabicyclo[4.1.0]heptane **167c** (G=Bus, 108.60 mg, 0.50 mmol, 1.0 equiv) was reacted with 2.0 equiv of LDA for 4h giving, after purification (silica, eluent: 6:1 petroleum ether/ethyl acetate), 54.30 mg (0.25 mmol, 50%) of the allyl amine **180c** (G=Bus), as a pale yellow solid.



180c: 3-*N*-*tert*-Butyl-sulfonylamino-cyclohexene

$C_{10}H_{19}NO_2S$ **M=**217.19

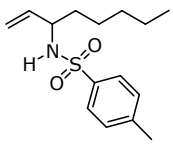
^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 5.86-5.78 (1H, m, C**H**=CHNH); 5.70-5.64 (1H, m, CH=C**H**NH); 4.40-3.80 (1H, m, C**H**NH); 2.04-1.88 (4H, m, C**H_2**CH=CHCHNH and C**H_2**CHNH); 1.75-1.55 (2H, m, C**H_2**CH_2CHNH); 1.37 (9H, s, C(C**H_3**)$_3$).

^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 130.9 (CH=**C**HCHNHSO$_2$C(CH$_3$)$_3$); 128.1 (**C**H=CHCHNHSO$_2$C(CH$_3$)$_3$); 59.5 (SO$_2$**C**(CH$_3$)$_3$); 50.3 (**C**HNHSO$_2$C(CH$_3$)$_3$); 31.5 (**C**H$_2$CH=CH); 24.5 (**C**H$_2$CHNHSO$_2$C(CH$_3$)$_3$); 24.2 (SO$_2$C(**C**H$_3$)$_3$); 19.5 (**C**H$_2$CH$_2$CHNHSO$_2$C(CH$_3$)$_3$).

MS (EI) *m/z*(%)**:** 189 (1); 160 (1, M$^+$ – ^{t}Bu); 138 (1); 97 (22, M$^+$ – SO$_2$^{t}Bu); 96 (42, M$^+$ – H – SO$_2$^{t}Bu); 82 (12, M$^+$ – NHSO$_2$^{t}Bu); 69 (62); 57 (100, ^{t}Bu).

12.8.1.1.6. Isomerization of *trans*-*N*-(*para*-toluensulfonyl)-2-methyl-3-pentyl aziridine (181a)

trans-*N*-(*para*-Toluensulfonyl)-2-methyl-3-pentylaziridine **181a** (290.30 mg, 1.0 mmol, 1.0 equiv) was reacted with 2.0 equiv of LDA for 2h giving, 47.80 mg of a 80:20 mix of two regioisomers **84** and **85**, which were separated by flash chromatography on silica (eluent: 10:1:1 petroleum ether / ethyl acetate / triethylamine). 38.25 mg (0.17 mmol, 13%) Of 2-*N*-(*para*-toluensulfonylamino-3-octene **85** and 11.25 mg (0.04 mmol, 4%) of 3-*N*-(*para*-toluensulfonylamino-1-octene **84** were obtained.

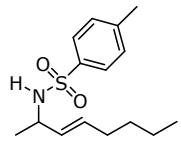


84: 3-*N*-(*para*-Toluensulfonylamino)-1-octene

$C_{15}H_{23}NO_2$ **M=**281.23

^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 7.78-7.74 (2H, m [AA' part of a AA'BB' spin system], C**H** *ortho* aromatics to SO_2); 7.33-7.29 (2H, m [BB' part of a AA'BB' spin system], C**H** *meta* aromatics to SO_2); 5.54 (1H, ddd, *J*=16.8, 10.0, 6.4, CH_2=C**H**); 4.98 (1H, d, *J*=16.8, CHC**H_{trans}**=CH); 4.95 (1H, d, *J*=10.0, CHC**H_{cis}**=CH); 4.57 (1H, m, NHTs); 3.85 (1H, ps-q, *J*=6.4, C**H**NHTs); 2.43 (3H, s, C**H_3** tosyl group); 1.40-0.80 (11H, m, C**H_2** and C**H_3** aliphatics).

MS (EI) *m/z*(%)**:** 210 (53); 155 (44, Ts$^+$);126 (4); 110 (4); 91 (100, $C_7H_7^+$); 81 (4); 65 (43); 55 (17).



85: (*E*)-2-*N*-(*para*-Toluensulfonylamino)-3-octene

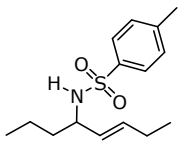
$C_{15}H_{23}NO_2S$ **M=**281.23

^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 7.75-7.71 (2H, m [AA' part of a AA'BB' spin system], C**H** *ortho* aromatics to SO_2); 7.29-7.25 (2H, m [BB' part of a AA'BB' spin system], C**H** *meta* aromatics to SO_2); 5.39 (1H, dt, *J*=15.5, 6.4, CHCH=C**H**); 5.14 (1H, dd, *J*=15.5, 6.6, CHC**H**=CH); 4.55 (1H, m, N**H**Ts); 3.73 (1H, ps-quint, *J*=6.6, C**H**(NHTs)CH=CH); 2.43 (3H, s, C**H_3** tosyl group); 1.85-1.40 (2H, m, C**H_2**$CH_2CH_2CH_3$); 1.40-0.80 (10H, m, C**H_3**CHNH and CH_2C**H_2**C**H_2**C**H_3**).

MS (EI) *m/z*(%)**:** 266 (12); 224 (6); 223 (9); 198 (8); 155 (37, Ts^+);126 (26); 110 (29); 91 (100, $C_7H_7^+$); 70 (20); 67 (15); 65 (20); 55 (31).

12.8.1.1.7. Isomerization of ***trans*-*N*-(*para*-toluensulfonyl)-2,3-dipropylaziridine (80)**

trans-*N*-(*para*-Toluensulfonyl)-2,3-dipropylaziridine **80** (295.00 mg, 1.05 mmol, 1.0 equiv) was reacted with 2.0 equiv of LDA for 2h at room temperature to afford 152.50 mg of the crude product **83**, which was purified by flash chromatography on silica (eluent: 10:1 petroleum ether/ethyl acetate). 56.10 mg (0.2 mmol, 19%) Of the pure allyl amine **83** were obtained.



83: (*E*)-5-*N*-(*para*-toluensulfonylamino)-3-octene

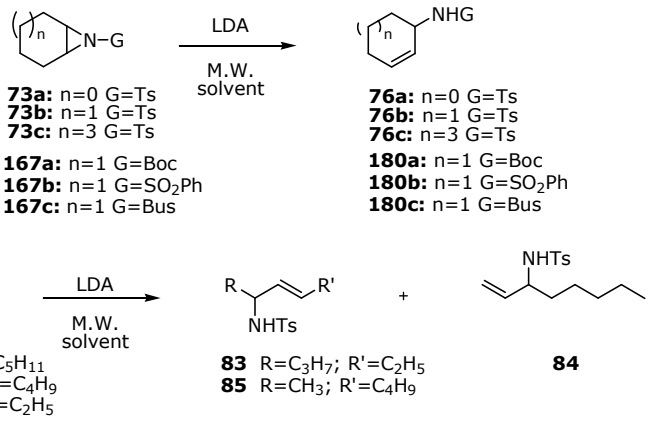
$C_{15}H_{23}NO_2S$ **M=**281.23

^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 7.73-7.69 (2H, m [AA' part of a AA'BB' spin system], C**H** *ortho* aromatics to SO_2); 7.27-7.23 (2H, m [BB' part of a AA'BB' spin system], C**H** *meta* aromatics to SO_2); 5.36 (1H, dt, *J*=15.4, 6.2, CHCH=C**H**); 5.01 (1H, dd, *J*=15.4, 7.2, CHC**H**=CH); 4.66 (1H, d, *J*=7.6, N**H**Ts); 3.69 (1H, d, *J*=7.2 C**H**(NHTs)CH=CH); 2.39 (3H, s, C**H_3** tosyl group); 1.80 (2H, quint, *J*=6.2, CH=CHC**H_2**CH_3); 1.50-1.10 (4H, m, CHC**H_2**C**H_2**CH_3); 0.82 (3H, t, *J*=7.2, C**H_3**);0.76 (3H, t, *J*=7.6, C**H_3**).

^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 142.7 (**C_q** *para* aromatic to SO_2); 138.3 (**C_{ipso}** aromatic to SO_2); 134.0 (CH=**C**HCHNHTs); 129.2 (2C, **C**H *meta* aromatics to SO_2); 128.2 (CH=**C**HCHNHTs); 127.1 (2C, **C**H *ortho* aromatics to SO_2); 56.0 (**C**HNHTs); 38.3 (CH=CH**C**$H_2CH_2CH_3$); 25.1 (CH=CH**C**H_2CH_3); (21.6 (**C**H_3 tosyl group); 18.7 (CH=CHCH$_2$**C**H_2CH_3); 13.8 (CH=CHCH$_2$**C**H_3); 13.2 (CH=CHCH_2CH_2**C**H_3).

MS (EI) *m/z*(%)**:** 252 (1); 238 (68); 223 (9); 155 (46, Ts^+);126 (4); 98 (3); 91 (100, $C_7H_7^+$); 82 (17); 65 (25); 55 (12).

12.8.1.2. *General procedure for the isomerization of meso-aziridines mediated by microwaves using LDA*



A solution of LDA (n mmol, n equiv) in organic solvent (THF, DEE or pentane, 0.5 M) was prepared at low temperatures from BuLi (1.6 M solution in hexanes, n mmol, n equiv)) and DIPA (n mmol, n equiv) in a vessel for microwaves reactions. After 30', the aziridine **73** (or **80**, **81a 162** and **167**) (1.0 equiv) was introduced and the resulting reaction mixture was heated (40° C - 80° C) by microwave irradiations at 100 - 300 W (value previously settled on the Microwave oven) for 1 - 5 minutes depending on the substrate. The solution was then diluted in ether and quenched with water. The two phases were divided and the aqueous portion was extracted with ether. The combined organic layers were washed with H_2O and brine, anhydrified over Na_2SO_4, filtered and concentrated *in vacuo* to afford the isomerization products **76, 83-85** and **180**, which were purified by flash column chromatography.

12.8.1.2.1. Isomerization of **6-(*N*-(*para*-toluensulfonyl))-6-aza-bicyclo-[3.1.0]hexane (73a)** in pentane

6-(*N*-(*para*-Toluensulfonyl))-6-aza-bicyclo[3.1.0]hexane **73a** (123.70 mg, 0.52 mmol, 1.0 equiv) and LDA (2.0 equiv) were heated by M.W. irradiations in anhydrous pentane at 40° C (100 W) for 2' and then worked-up to afford the allyl amine **76a** (62.89 mg, 0.27 mmol, 51%).

12.8.1.2.2. Isomerization of **6-(*N*-(*para*-toluensulfonyl))-6-aza-bicyclo-[3.1.0]heptane (73a)** in diethyl ether

6-(*N*-(*para*-Toluensulfonyl))-6-aza-bicyclo[3.1.0]hexane **73a** (123.00 mg, 0.52 mmol, 1.0 equiv) and LDA (2.0 equiv) were heated by M.W. irradiations in anhydrous DEE at 40° C (300 W) for 5' and then worked-up to afford the allyl amine **76a** (55.20 mg, 0.23 mmol, 44%).

12.8.1.2.3. Isomerization of **7-(*N*-(*para*-toluensulfonyl))-7-aza-bicyclo-[4.1.0]hexane (73b)** in pentane

7-(*N*-(*para*-toluensulfonyl))-7-aza-bicyclo[4.1.0]hexane **73b** (127.90 mg, 0.51 mmol, 1.0 equiv) and LDA (2.0 equiv) were heated by M.W. irradiations in anhydrous pentane at 60° C (100 W) for 5', to afford after work-up and purification by chromatography (silica, eluent: 6:1 petroleum ether/ethyl acetate) 3-*N*-*para*-toluensulfonylamino-cyclohexene **76b** (77.90 mg, 0.31 mmol, 61%).

12.8.1.2.4. Isomerization of **7-(*N*-(*para*-toluensulfonyl))-7-aza-bicyclo-[4.1.0]heptane (73b)** in diethyl ether

7-(*N*-(*para*-Toluensulfonyl))-7-aza-bicyclo[4.1.0]hexane **73b** (123.40 mg, 0.49 mmol, 1.0 equiv) and LDA (2.0 equiv) were heated by M.W. irradiations in anhydrous DEE at 40° C (100 W) for 10' to afford, after work-up and purification by chromatography (silica, eluent: 6:1 petroleum ether/ethyl acetate) 3-*N*-*para*-toluensulfonylamino-cyclohexene **76b** (58.50 mg, 0.19 mmol, 38%).

12.8.1.2.5. Isomerization of **9-(*N*-(*para*-toluensulfonyl))-9-aza-bicyclo-[6.1.0]nonane (73c)** in pentane

9-(*N*-(*para*-Toluensulfonyl))-9-aza-bicyclo[6.1.0]hexane **73c** (34.60 mg, 0.13 mmol, 1.0 equiv) and LDA (2.0 equiv) were heated by M.W. irradiations in anhydrous pentane at 60° C (300 W) for 10' to afford, after work-up and purification by chromatography (silica, eluent: 10:1 petroleum ether/ethyl acetate) 1-*N*-*para*-toluensulfonylaminobicyclo-[3.3.0]octane **82** (22.90 mg, 0.08 mmol, 63%).

12.8.1.2.6. Isomerization of **7-*N*-(*tert*-butyl-sulfonyl)-7-azabicyclo[4.1.0] heptane (167c)** in pentane

7-*N*-(*tert*-Butyl-sulfonyl)-7-azabicyclo[4.1.0]heptane **167c** (133.30 mg, 0.52 mmol, 1.0 equiv) and LDA (2.0 equiv) were heated by M.W. irradiations in anhydrous pentane at 60° C (100 W) for 10' to afford, after work-up and purification by chromatography (silica, eluent: 6:1 petroleum ether/ethyl acetate) 67.73 mg (0.31 mmol, 60%) of the allyl amine **180c** as a pale yellow solid.

12.8.1.2.7. Isomerization of **7-(*N*-benzenesulfonyl)-7-azabicyclo[4.1.0]-heptane (167b)** in pentane

N-Benzenesulfonyl-7-azabicyclo[4.1.0]heptane **167b** (121.90 mg, 0.51 mmol, 1.0 equiv) and LDA (2.0 equiv) were heated by M.W. irradiations in anhydrous pentane at 60° C (300 W) for 5' to afford, after work-up the pure allyl amine **180b** (81.00 mg, 0.34 mmol, 67%), without need of further purifications.

12.8.1.2.8. Isomerization of **7-(*N*-benzenesulfonyl)-7-azabicyclo[4.1.0]-heptane (167b)** in DEE

N-Benzenesulfonyl-7-azabicyclo[4.1.0]heptane **167b** (97.00 mg, 0.41 mmol, 1.0 equiv) and LDA (2.0 equiv) were heated by M.W. irradiations in anhydrous DEE at 50° C (300 W) for 5' to afford, after work-up and purification by chromatography (silica, eluent: 6:1 pentane/ethyl acetate) the allyl amine **180b** (34.00 mg, 0.14 mmol, 35%), as a pale yellow solid.

12.8.1.2.9. Isomerization of ***trans*-*N*-(*para*-toluensulfonyl)-2-methyl-3-pentylaziridine (81a)**

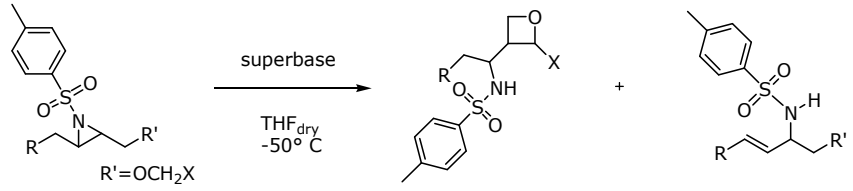
trans-*N*-(*para*-Toluensulfonyl)-2-methyl-3-pentyl aziridine **37e** (139.90 mg, 0.5 mmol, 1.0 equiv) and 2.0 equiv of LDA in pentane were heated by M.W. irradiation at 60° C (300 W) for 10' giving, after work-up and purification by chromatography (silica, eluent: 10:1 petroleum ether/ethyl acetate), 29.53 mg (0.11 mmol, 21%) of 2-*N*-(*para*-toluensulfonylamino-3-octene **85** and 5.62 mg (0.02 mmol, 4%) of 3-*N*-(*para*-toluensulfonylamino-1-octene **84**.

12.8.1.2.10. Isomerization of ***trans*-*N*-(*para*-toluensulfonyl)-2,3-dipropyl aziridine (80)**

trans-*N*-(*para*-Toluensulfonyl)-2,3-dipropylaziridine **80** (152.10 mg, 0.54 mmol, 1.0 equiv) and 2.0 equiv of LDA in were heated by M.W. irradiation at 40° C (300 W) for 2' giving, after work-up and purification by chromatography (silica, eluent: 10:1 petroleum ether/ethyl acetate), 48.60 mg (0.17 mmol, 32%) of pure (*E*)-5-*N*-(*para*-toluensulfonylamino-3-octene **83**.

12.8.2. Isomerizations with superbases

12.8.2.1. *General procedure for the isomerization of meso-aziridine and hetero-substituted aziridines using LICKOR or LIDAKOR in THF at low temperature*



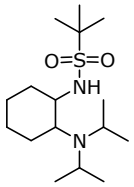
114a-e **144a-e** **145a-e**

In a Schlenk tube, under nitrogen, hexane was stripped off from a BuLi (n mmol, n equiv) solution and precooled anhydrous THF (0.5 M) was added at –78° C under nitrogen, followed by K^{t}BuO (n mmol, n equiv) (and DIPA (n mmol, n equiv) too, in the case of the preparation of LIDAKOR). After 30' a solution of the

aziridine **114** (1.0 equiv) in freshly distilled THF was added dropwise and the resulting reaction mixture was stirred at –50° C for 16-48h. Then the mixture was quenched with water and the two layers were separated. The aqueous portion was extracted with ether (3 times) and the combined organic components were washed twice with H_2O and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the isomerization product **144**, **145** or both, which were purified by flash column chromatography.

12.8.2.1.1. Isomerization of **7-(*tert*-butyl-sulfonyl)-7-azabicyclo[4.1.0]-heptane (167c)** with 2.0 equiv of LIDAKOR

7-(*tert*-Butyl-sulfonyl)-7-azabicyclo[4.1.0] heptane **167c** (146.50 mg, 0.7 mmol, 1.0 equiv) was reacted with 2.0 equiv of LIDAKOR at –30° C for 24h giving a mix of the allyl amine **180c** (17.46 mg, 0.08 mmol, 12%) and 2-methyl-propan-2-sulfonyl-(2–di-*iso*-propylaminocyclohexyl)amide **319** (2.07 mg, 0.01 mmol, 1%), which were separated by chromatography (silica, eluent: from 20:1 to 5:1 pentane/ethyl acetate).



319: 2-Methyl-propan-2-sulfonyl-(2–diisopropylamino-cyclohexyl)amide

$C_{16}H_{24}N_2O_2S$ M=308.24

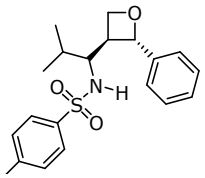
^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 3.65 (2H, sept, *J*=6.4, C**H**$(CH_3)_2$); 3.24-3.11 (2H, m, C**H**NHBus e C**H**N(iPr)$_2$); 2.12-1.70 (8H, m, (C**H$_2$**)$_4$); 1.36 (9H, s, C(C**H$_3$**)$_3$); 1.09 (12H, d, *J*=6.4, NH(CH(C**H$_3$**)$_2$)$_2$).

^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 58.6 (**C**$(CH_3)_3$); 50.0 (**C**HN(iPr)$_2$); 62.3 (**C**H$(CH_3)_2$); 47.4 (**C**HNHBus); 37.9 (**C**H$_2$CHNHBus); 31.7 (**C**H$_2$CHN(iPr)$_2$); 26.3 (**C**H$_2$CH$_2$CHN(iPr)$_2$); 26.1 (**C**H$_2$CH$_2$CHNHBus); 24.3 (C(**C**H$_3$)$_3$); 23.4 (CH(**C**H$_3$)$_2$); 23.2 (CH(**C**H$_3$)$_2$).

MS (EI) *m/z*(%)**:** 259 (2); 243 (1); 217 (1); 195 (96); 180 (17); 152 (21); 126 (100); 84 (89); 57 (65, ^{t}Bu).

12.8.2.1.2. Isomerization of **(2*R*,3*S*)-2-(benzyloxy)methyl-3-isopropyl-*N*-(*para*-toluensulfonyl)aziridine (114a)** with 3.0 equiv of LIDAKOR

(2*R*,3*S*)-2-(Benzyloxy)methyl-3-isopropyl-*N*-(*para*-toluensulfonyl)aziridine **114a** (220.08 mg, 0.6 mmol, 1.0 equiv) was reacted with 3.0 equiv of LIDAKOR in anhydrous THF at –30° C for 36h to afford, after purification (silica, eluent: 5:1 pentane/ethyl acetate), a 1:1 mix of the amino-oxetane **144a** (12.93 mg, 0.04 mmol, 6%) and the *E*-vinyl ether **145a** (19.40 mg, 0.05 mmol, 9%), with a 30% conversion.



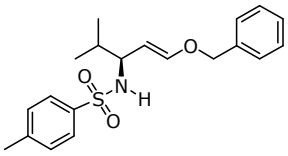
144a: (*R*)-*N*-(2-Methyl-1-((2*S*,3*S*)-2-phenyl-oxetan-3-yl) propyl)-*para*-toluensulfonylamine

$C_{20}H_{25}O_3NS$ **M=**359.25

^{1}H-NMR δ($CDCl_3$, 400 MHz)**:** 7.82-7.80 (2H, m [AA' part of a AA'BB' spin system], C**H** *ortho* aromatics to SO_2); 7.36-7.27 (5H, m, C**H** aromatics Ph); 7.33-7.31 (2H, m, [BB' part of a AA'BB' spin system], C**H** *meta* aromatics to SO_2); 5.41 (1H, d, *J*=7.2, C**H**Ph oxetane); 4.76 (1H, br-d, *J*=8.8, N**H**); 4.46-4.39 (2H, m, C$\mathbf{H_2}$ oxetane); 3.55-3.50 (1H, m, C**H**NHTs); 3.04 (1H, ps-quint, *J*=7.6, C**H**CHNHTs oxetane); 2.43 (3H, s, C$\mathbf{H_3}$ tosyl group); 1.70-1.60 (1H, m, C**H**$(CH_3)_2$); 0.68 (3H, d, *J*=7.2, CH(C$\mathbf{H_3}$)$_2$); 0.54 (3H, d, *J*=7.2, CH(C$\mathbf{H_3}$)$_2$).

^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 143.5 (**C_q** *para* aromatic to SO_2); 141.5 (**C_{ipso}** aromatic to oxetane); 138.3 (**C_{ipso}** aromatic to SO_2); 129.7-125.9 (9C, **C**H aromatics); 85.2 (**C**HPh oxetane); 70.1 (**C**H_2 oxetane); 59.8 (**C**H-NHTs); 47.2 (**C**HCHNHTs oxetane); 30.5 (**C**H$(CH_3)_2$); 19.1 (**C**H_3 tosyl group); 17.0 (CH(**C**$H_3)_2$); 14.2 (CH(**C**$H_3)_2$).

MS (EI) *m/z*(%)**:** 286 (72, M^+ – Ph); 207 (6, M^+ – Ts); 174 (3); 155 (36, Ts^+); 143 (8); 130 (45, M^+ – TsNHCHiPr); 115 (32); 103 (7); 91 (100, $C_7H_7^+$); 77 (13, $C_6H_5^+$); 65 (27); 51 (10).



145a: (*E*)-*N*-(3-Benzyloxy-1-*iso*-propyl-allyl)-*para*-toluensulfonylamine

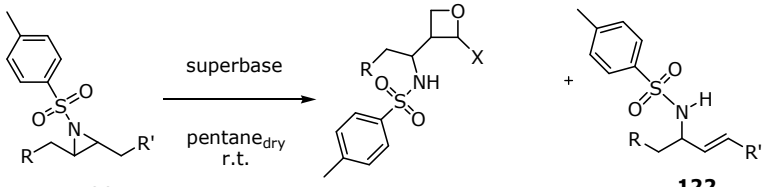
$C_{20}H_{25}O_3NS$ **M=**359.25

^{1}H-NMR δ($CDCl_3$, 400 MHz)**:** 7.71-7.69 (2H, m [AA' part of a AA'BB' spin system], C**H** *ortho* aromatics to SO_2); 7.40-7.27 (5H, m, C**H** aromatics to CH_2); 7.25-7.23 (2H, m [BB' part of a AA'BB' spin system], C**H** *meta* aromatics to SO_2); 6.12 (1H, d, *J*=12.4, CH=C**H**OBn); 4.65 (2H, s, OC$\mathbf{H_2}$Ph); 4.44 (1H, dd, *J*=12.4, 9.2, C**H**=CHOBn); 4.33 (1H, br-d, *J*=7.6, N**H**); 3.52-3.46 (1H, m, C**H**-NH); 2.38 (3H, s, C$\mathbf{H_3}$ tosyl group); 1.80-1.60 (1H, m, C**H**$(CH_2)_3$); 0.86 (3H, d, *J*=6.6, CH(C$\mathbf{H_2}$)$_3$); 0.84 (3H, d, *J*=6.6, CH(C$\mathbf{H_2}$)$_3$).

^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 148.6 (CH=**C**HOBn); 142.8 (**C_{ipso}** aromatic to CH_2); 138.5 (**C_q** *para* aromatic to SO_2); 136.4 (**C_{ipso}** aromatic to SO_2); 129.3 (2C, **C**H *meta* aromatics to SO_2); 128.4 (2C, **C**H *meta* aromatics to CH_2); 127.9 (**C**H *para* aromatic to CH_2); 127.3 (4C, **C**H *ortho* aromatics to SO_2 and CH_2); 101.9 (**C**H=CHOBn); 70.9 (**C**H_2Ph); 59.1 (**C**HNHTs); 33.5 (**C**H$(CH_3)_2$); 21.4 (**C**H_3 tosyl group); 18.8 ((CH(**C**$H_3)_2$); 17.9 ((CH(**C**$H_3)_2$).

MS (EI) *m/z*(%)**:** 316 (11, M^+ – iPr); 224 (1, M + 1 – iPr – Bn); 200 (1); 172 (1); 155 (4, Ts^+); 145 (6); 117 (6); 91 (100, $C_7H_7^+$); 77 (2, $C_6H_5^+$); 65 (10).

12.8.2.2. *General procedure for the isomerization of meso-aziridine and hetero-substituted aziridines using LICKOR or LIDAKOR in pentane at room temperature*



100
107
108
109
114a-e

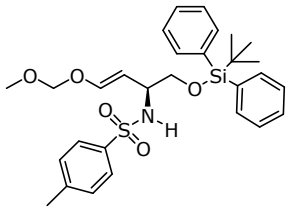
144a-e

122
128
129
131
132
145a-e

A solution of LICKOR (or LIDAKOR) was prepared in a Schlenk tube, under nitrogen, from BuLi (n mmol, n equiv, 1.6 M solution in hexanes) and K^{t}BuO (n mmol, n equiv) (and DIPA (n mmol, n equiv) in the case of LIDAKOR) in anhydrous pentane (0.5 M) at 0° C. After 30' a solution of the aziridine **100-114** (1.0 equiv) in dried pentane (or pentane/HMPA mix, if the aziridine isn't soluble in pentane only) was added dropwise and the resulting reaction mixture was stirred at room temperature for 16-48h. Then the mixture was quenched with water and the two layers were separated. The aqueous portion was extracted with ether (3 times) and the combined organic components were washed twice with H_2O and brine, anhydrified over Na_2SO_4, filtered and concentrated under reduced pressure to afford the oxetane **144** and the allyl amines **122**-**145**, or both, which were purified by flash column chromatography.

12.8.2.2.1. Isomerization of **(2*S*,3*R*)-2-[(*tert*-butyldiphenylsiyl)oxy]-methyl-3-(methoxymethoxy)methyl-*N*-(*para*-toluensulfonyl)-aziridine (100)** with 3.0 equiv of LIDAKOR

A (2*S*,3*R*)-2-[(*tert*-Butyldiphenylsilyl)oxy]methyl-3-(methoxymethoxy)methyl-*N*-(*para*-toluensulfonyl)aziridine **100** (269.00 mg, 0.5 mmol, 1.0 equiv) and LIDAKOR (3.0 equiv) mixture in anhydrous 2:1 THF/HMPA (0.5 M) was reacted at room temperature for 24h to afford, after purification (silica, eluent: 4:1 pentane/ethyl acetate), 205.00 mg (0.38 mmol, 76%) of the allyl amine **122**, as a yellow oil.



122: (*E*)-1-(Methoxymethoxy)-4-[(*tert*-butyl-diphenylsilyl)oxy]-*N*-(*R*)-((*para*-toluensulfonyl) but-1-en-3-amine

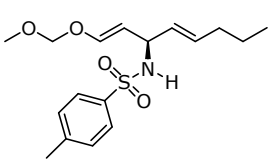
$C_{29}H_{37}NO_5SiS$ **M=**539.37

^{1}H-NMR δ ($CDCl_3$, 400 MHz)**:** 7.72-7.70 (2H, m [AA' part of a AA'BB' spin system], C**H** *ortho* aromatics to

SO_2); 7.63-7.53 (4H, m [AA' part of a AA'BB'C spin system], C**H** *ortho* aromatics to Si); 7.48-7.36 (6H, m [BB' and C parts of a AA'BB'C spin system], C**H** *meta* and *para* aromatics to Si); 7.27-7.25 (2H, m [BB' part of a AA'BB' spin system], C**H** *meta* aromatics to SO_2); 6.21 (1H, d, *J*=12.4, OC**H**=CH); 4.96 (1H, br-d, *J*=5.6, N**H**Ts); 4.80 (1H, dd, *J*=12.4. 8.4, OCH=C**H**); 4.66 (2H, s, $CH_3OC\mathbf{H_2}O$); 4.50-4.38 (2H, m, $C\mathbf{H_2}OSi$); 3.75-3.65 (1N, C**H**NHTs); 3.32 (3H, s, $C\mathbf{H_3}OCH_2O$); 2.41 (3H, s, $C\mathbf{H_3}$ tosyl group); 1.03 (9H, s, $C(C\mathbf{H_3})_3$).
MS (EI) *m/z*(%)**:** 352 (11); 270 (10); 238 (27); 213 (3); 199 (8); 189 (6); 181 (5); 155 (9, Ts^+); 135 (13); 91 (15, $C_7H_7^+$); 77 (4, $C_6H_5^+$); 45 (100).

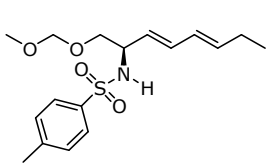
12.8.2.2.2. Isomerization of **(2*R*,3*R*)-2-((methoxymethoxy)methyl)-3-((*E*)-pent-1-enyl)-*N*-(*para*-toluensulfonyl)aziridine (107)** with 2.0 equiv of LIDAKOR

(2*R*,3*R*) -2- ((Methoxymethoxy)methyl)-3-((*E*)-pent-1-enyl)-*N*-(*para*-toluen sulfonyl)aziridine **107** (206.30 mg, 0.52 mmol, 1.0 equiv) and 2.0 equiv of LIDAKOR in 2:1 pentane/HMPA were stirred for 24h at room temperature to afford a 45:65 mix of the two regioisomers **128** and **129**, which were separated by chromatography on silica gel (eluent: 8:1 pentane/ethyl acetate) giving 48.60 mg (0.27 mmol, 51%) of (*E*)-5-*N*-(*para*-toluensulfonylamino-3-octene **129** and 19.40 mg (0.06 mmol, 11%) of (1*E*,4*E*)-1-(methoxymethoxy)-*N*-(*R*)-((*para*-toluensulfonyl)octa-1,4-dien-3-amine **128**.



128: (1*E*,4*E*)-1-(Methoxymethoxy)-*N*-(*R*)-((*para*-toluensulfonyl)octa-1,4-dien-3-amine
$C_{16}H_{25}NO_4S$ **M=**339.25
^{1}H-NMR δ ($CDCl_3$, 400 MHz)**:** 7.73-7.71 (2H, m [AA' part of a AA'BB' spin system], C**H** *ortho* aromatics to SO_2); 7.28-7.26 (2H, m, [BB' part of a AA'BB' spin system], C**H** *meta* aromatics to SO_2); 6.28 (1H, dd, *J*=12.8, 1.2, OC**H**=CH); 5.36 (1H, dt, *J*=10.4, 7.2, $CH=C\mathbf{H}CH_2CH_2CH_3$); 5.14 (1H, dd, *J*=10.4, 9.2, $C\mathbf{H}=CHCH_2CH_2CH_3$); 4.88 (1H, dd, *J*=12.4, 6.8, OCH=C**H**); 4.71 (2H, s, $CH_3OC\mathbf{H_2}O$); 4.64-4.54 (1H, m, C**H**NHTs); 4.32 (1H, br-d, *J*=5.6, N**H**Ts); 3.34 (3H, s, $C\mathbf{H_3}OCH_2O$); 2.42 (3H, $C\mathbf{H_3}$ tosyl group); 1.90 (2H, q, *J*=7.2, $CH=CHC\mathbf{H_2}CH_2CH_3$); 1.35-1.20 (2H, m, $CH=CHCH_2C\mathbf{H_2}CH_3$); 0.85 (3H, t, *J*=7.2, $CH=CHCH_2CH_2C\mathbf{H_3}$).
^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 146.6 (O**C**H=CH); 142.2 ($\mathbf{C_q}$ *para* aromatic to SO_2); 135.8 ($\mathbf{C_{\textit{ipso}}}$ aromatic to SO_2); 132.6 (**C**H=$CHCH_2CH_2CH_3$); 128.0 (2C, **C**H *meta* aromatics to SO_2); 127.1 (CH=**C**$HCH_2CH_2CH_3$); 126.9 (2C, **C**H *ortho* aromatics to SO_2); 101.9 (OCH=**C**H); 96.9 ($CH_3O\mathbf{C}H_2OCH_2$); 67.3 (**C**HNHTs); 56.7 ($\mathbf{C}H_3OCH_2OCH_2$); 34.9 ($CH=CH\mathbf{C}H_2CH_2CH_3$); 22.6 ($CH=CHCH_2\mathbf{C}H_2CH_3$); 22.3 ($\mathbf{C}H_3$ tosyl group); 13.8 ($CH=CHCH_2CH_2\mathbf{C}H_3$).

MS (EI) *m/z*(%)**:** 258 (24); 226 (35); 198 (4); 155 (46, Ts^+); 141 (4); 113 (37); 91 (69, $C_7H_7^+$); 81 (9); 79 (8); 71 (100, $C_5H_{11}^+$); 65 (36); 55 (17).



129: (3*E*,5*E*)-1-(Methoxymethoxy)-*N*-(*R*)-((*para*-toluensulfonyl)octa-3,5-dien-2-amine

$C_{16}H_{25}NO_4S$ M=339.25

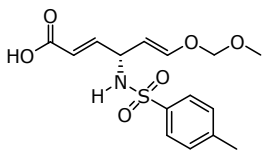
^{1}H-NMR δ ($CDCl_3$, 400 MHz)**:** 7.73-7.71 (2H, m [AA' part of a AA'BB' spin system], C**H** *ortho* aromatics to SO_2); 7.28-7.26 (2H, m, [BB' part of a AA'BB' spin system], C**H** *meta* aromatics to SO_2); 6.01 (1H, dd, *J*=15.2, 10.8, CH=C**H**-CH=CH); 5.82 (1H, dd, *J*=14.8, 10.8, CH=CH-C**H**=CH); 5.64 (1H, dt, *J*=14.8, 6.4, CH=CH-CH=C**H**); 5.28 (1H, dd, *J*=15.2, 10.0, CH=CH-CH=C**H**); 4.99 (1H, d, *J*=6.8, NHTs); 4.52 (2H, s, $CH_3OC\mathbf{H_2}O$); 3.95 (1H, ps-quint, *J*=5.6, C**H**NHTs); 3.48 (2H, d, *J*=4.8, $CH_3OCH_2OC\mathbf{H_2}$); 3.30 (3H, s, $C\mathbf{H_3}OCH_2O$); 2.41 (3H, $C\mathbf{H_3}$ tosyl group); 1.90 (2H, q, *J*=7.2, CH=CHC$\mathbf{H_2}CH_2CH_3$); 2.06(2H, ps-quint, *J*=7.2, CH=CHC$\mathbf{H_2}CH_3$); 0.98 (3H, t, *J*=7.2, CH=CHC$H_2C\mathbf{H_3}$).

^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 143.2 ($\mathbf{C_q}$ *para* aromatic to SO_2); 137.9 ($\mathbf{C_{ipso}}$ aromatic to SO_2); 137.7 (**C**H=CH-CH=CH); 133.4 (CH=CH-CH=**C**H); 129.5 (2C, **C**H *meta* aromatics to SO_2); 128.0 (CH=**C**H-CH=CH); 127.4 (2C, **C**H *ortho* aromatics to SO_2); 126.6 (CH=CH-**C**H=CH); 96.7 ($CH_3O\mathbf{C}H_2OCH_2$); 70.4 ($CH_3OCH_2O\mathbf{C}H_2$); (**C**HNHTs); 55.3 ($\mathbf{C}H_3OCH_2OCH_2$); 29.7 (CH=CH**C**HCH$_3$); 25.6 (CH=CHC$H_2\mathbf{C}H_3$); 21.5 ($\mathbf{C}H_3$ tosyl group).

MS (EI) *m/z*(%)**:** 264 (78); 207 (12); 184 (8); 155 (39, Ts^+); 149 (7); 139 (8); 122 (7); 108 (100); 94 (12); 93 (38); 91 (93, $C_7H_7^+$); 80 (33); 79 (8); 65 (26); 55 (8).

12.8.2.2.3. Isomerization of (*E*)-ethyl-3-((2*R*,3*R*)-3-((methoxymethoxy)-methyl) -*N*-(*para*-toluensulfonyl)-aziridin-2-yl)acrylate (108) with 2.0 equiv of LIDAKOR

(*E*)- Ethyl-3-((2*R*,3*R*)-3-((methoxymethoxy)-methyl)-*N*-(*para*-toluensulfonyl)-aziridin-2-yl)acrylate **108** (166.20 mg, 0.45 mmol, 1.0 equiv) was reacted with 2.0 equiv of LIDAKOR in 3:1 pentane/HMPA mix at room temperature for 24h. A mixture of the amino carboxylic acid **130** (15.40 mg, 0.05 mmol, 10%) and the ester **131** (39.30 mg, 0.1 mmol, 22%) was obtained after purification by flash column chromatography (silica gel, eluent: 4:1 pentane/ethyl acetate).

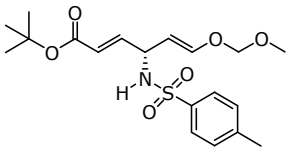


130: (2*E*,5*E*)-(*R*)-6-Methoxymethoxy-4-(*N*-*para*-toluen-sulfonylamino)hexa-2,5-dienoic acid

$C_{15}H_{19}NO_6S$ M=341.19

^{1}H-NMR δ ($CDCl_3$, 400 MHz)**:** 10.20 (1H, bs, COO**H**); 7.76-7.74 (2H, m [AA' part of a AA'BB' spin system], C**H** *ortho* aromatics to SO_2); 7.31-7.29 (2H, m, [BB'

part of a AA'BB' spin system], C**H** *meta* aromatics to SO_2); 7.24 (1H, dd, *J*=15.2, 7.0, COOHCH=C**H**-CH-CH=CH); 6.37 (1H, d, *J*=14.8, COOHCH=CH-CH-CH=C**H**); 6.01 (1H, d, *J*=15.2, COOHC**H**=CH-CH-CH=CH); 5.28 (1H, dd, *J*=14.8, 7.0, COOHCH=CH-CH-C**H**=CH); 5.01 (1H, d, *J*=8.0, N**H**Ts); 4.55-4.49 (2H, m [AB spin system], $CH_3OC\mathbf{H_2}O$); 3.31 (3H, s, $C\mathbf{H_3}OCH_2O$); 3.92-3.85 (1H, m, C**H**NHTs); 2.43 (3H, C$\mathbf{H_3}$ tosyl group).



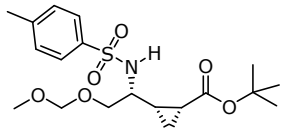
131: <u>(2*E*,5*E*)-(*R*)-6-Methoxymethoxy-4-(*N*-*para*-toluensulfonylamino)hexa-2,5-dienoic acid *tert*-butyl ester</u>

$C_{15}H_{19}NO_6S$ M=341.19

^{1}H-NMR δ ($CDCl_3$, 400 MHz)**:** 7.76-7.74 (2H, m [AA' part of a AA'BB' spin system], C**H** *ortho* aromatics to SO_2); 7.31-7.29 (2H, m, [BB' part of a AA'BB' spin system], C**H** *meta* aromatics to SO_2); 7.01 (1H, dd, *J*=15.2, 7.0, COOHCH=C**H**-CH-CH=CH); 6.35 (1H, d, *J*=14.8, COOHCH=CH-CH-CH=C**H**); 5.95 (1H, d, *J*=15.2, COOHC**H**=CH-CH-CH=CH); 5.00 (1H, dd, *J*=14.8, 7.0, COOHCH=CH-CH-C**H**=CH); 4.65 (1H, d, *J*=8.0, N**H**Ts); 4.40-4.35 (2H, m [AB spin system], $CH_3OC\mathbf{H_2}O$); 3.31 (3H, s, $C\mathbf{H_3}OCH_2O$); 3.92-3.85 (1H, m, C**H**NHTs); 2.43 (3H, C$\mathbf{H_3}$ tosyl group); 1.41 (9H, s, $C(C\mathbf{H_3})_3$).

12.8.2.2.4. <u>Isomerization of **ethyl-3-((2*R*,3*R*)-3-((methoxymethoxy)-methyl)-*N*-(*para*-toluensulfonyl)aziridin-2-yl)propanoate (109)** with 2.0 equiv of LIDAKOR</u>

Ethyl-3-((2*R*,3*R*)-3-((methoxymethoxy)-methyl)-*N*-(*para*-toluensulfonyl)-aziridin-2-yl)propanoate **109** (109.10 mg, 0.29 mmol, 1.0 equiv) was reacted with 2.0 equiv of LIDAKOR in 2:1 pentane/HMPA mix at room temperature for 24h to afford after purification by flash chromatography (silica, eluent: 8:1 pentane/ethyl acetate) (1*S*,2*R*)-*tert*-butyl 2-((*R*)-2-(methoxy methoxy)-1-(*N*-*para*-toluensulfonylamino)ethyl) **133** (13.8 mg, 0.03 mmol, 12%).



133: <u>(1*R*,2*S*)-*tert*-Butyl-2-((*R*)-2-(methoxymethoxy)-1-(*N*-*para*-toluensulfonylamino)ethyl) cyclopropane-carboxylate</u>

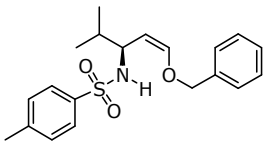
$C_{19}H_{29}NO_6S$ M=399.29

^{1}H-NMR δ ($CDCl_3$, 400 MHz)**:** 7.76-7.74 (2H, m [AA' part of a AA'BB' spin system], C**H** *ortho* aromatics to SO_2); 7.31-7.29 (2H, m, [BB' part of a AA'BB' spin system], C**H** *meta* aromatics to SO_2); 5.02 (1H, d, *J*=8.0, N**H**Ts); 4.53-4.47 (2H, m [AB spin system], $CH_3OC\mathbf{H_2}O$); 3.52 (1H, dd, *J*=10.0, 4.0, $CH_3OCH_2OC\mathbf{H}H'$); 3.36 (1H, dd, *J*=10.0, 4.0, $CH_3OCH_2OCH\mathbf{H'}$); 3.31 (3H, s, $C\mathbf{H_3}OCH_2O$); 2.92-2.87 (1H, m, C**H**NHTs); 2.43 (3H, C$\mathbf{H_3}$ tosyl group); 1.60-1.55 (2H, m, $CHC\mathbf{H_2}CH$); 1.42 (9H, s, $C(C\mathbf{H_3})_3$); 1.39-1.35 (2H, m, C$\mathbf{H_2}$ cyclopropane);

1.06-1.01 (1H, m, $CH_2C\mathbf{H}$ cyclopropane); 0.77-0.72 (1H, m, $C\mathbf{H}COOC(CH_3)_3$ cyclopropane).
^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 172.5 ($\mathbf{C}OOC(CH_3)_3$); 143.3 ($\mathbf{C_q}$ *para* aromatic to SO_2); 137.8 ($\mathbf{C_{ipso}}$ aromatic to SO_2); 129.6 (2C, **C**H *meta* aromatics to SO_2); 127.0 (2C, **C**H *ortho* aromatics to SO_2); 96.6 ($CH_3O\mathbf{C}H_2OCH_2$); 80.4 ($O\mathbf{C}(CH_3)_3$); 69.6 ($CH_3OCH_2O\mathbf{C}H_2$); 55.8 (**C**HNHTs); 55.5 ($\mathbf{C}H_3OCH_2OCH_2$); 28.1 (3C, $OC(\mathbf{C}H_3)_3$); 23.7 (**C**HCHCOOC$(CH_3)_3$ cyclopropane); 21.6 ($\mathbf{C}H_3$ tosyl group); 19.8 (CH**C**HCOOC$(CH_3)_3$ cyclopropane); 12.9 ($\mathbf{C}H_2$ cyclopropane).
MS (EI) *m/z*(%)**:** 324 (19); 294 (5); 268 (66); 250 (17); 222 (2); 184 (6); 155 (51, Ts^+); 139 (5); 122 (7); 111 (2); 91 (100, $C_7H_7^+$); 68 (50); 65 (22); 55 (8).

12.8.2.2.5. Isomerization of **(2*R*,3*S*)-2-(benzyloxy)methyl-3-*iso*-propyl-*N*-(*para*-toluensulfonyl)aziridine (114a)** with 2.0 equiv of LICKOR

(2*R*,3*S*)-2-(Benzyloxy)methyl-3-isopropyl-*N*-(*para*-toluensulfonyl)-aziridine **114a** (179.60 mg, 0.5 mmol, 1.0 equiv) was reacted with 3.0 equiv of LICKOR in anhydrous pentane at room temperature for 24h to afford a 4:1 *E*/*Z* mix of the allyl amine **145a** (80.83 mg, 0.23 mmol, 45%), which was analyzed without purification by chromatography.



145a: (*Z*)-*N*-(3-Benzyloxy-1-*iso*-propyl-allyl)-*para*-toluensulfonylamine
$C_{20}H_{25}O_3NS$ **M=**359.25
^{1}H-NMR δ($CDCl_3$, 400 MHz)**:** 7.68-7.66 (2H, m AA' part of a AA'BB' spin system], C**H** *ortho* aromatics to SO_2); 7.40-7.27 (5H, m, C**H** aromatics to CH_2); 7.19-7.17 (2H, m [BB' part of a AA'BB' spin system], C**H** *meta* aromatics to SO_2); 5.87 (1H, d, *J*=6.4, CH=C**H**OBn); 4.87 (1H, br-d, *J*=8.0, N**H**); 4.13 (1H, dd, *J*=8.4, 6.4, C**H**=CHOBn); 3.95-3.90 (1H, m, C**H**NHTs); 2.41 (3H, s, $\mathbf{CH_3}$ tosyl group); 1.90-1.70 (1H, m, C**H**$(CH_2)_3$); 0.87 (3H, d, *J*=6.6, $CH(C\mathbf{H_2})_3$); 0.82 (3H, d, *J*=6.6, $CH(C\mathbf{H_2})_3$).
^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 145.8 (CH=**C**HOBn); 142.5 ($\mathbf{C_{ipso}}$ aromatic to CH_2); 138.0 ($\mathbf{C_q}$ *para* aromatic to SO_2); 136.7 ($\mathbf{C_{ipso}}$ aromatic to SO_2); 129.0-127.5 (9C, **C**H aromatics); 104.6 (**C**H=CHOBn); 67.7 ($\mathbf{C}H_2$Bn); 60.3 (**C**HNHTs); 33.5 ($\mathbf{C}H(CH_3)_2$); 21.0 ($\mathbf{C}H_3$ tosyl group); 18.6 (($CH(\mathbf{C}H_3)_2$); 17.8 (($CH(\mathbf{C}H_3)_2$).
MS (EI) *m/z*(%)**:** 316 (11, M^+ – iPr); 224 (1, M + 1 – iPr – Bn); 172 (1); 155 (3, Ts^+); 145 (5); 139 (1); 117 (7); 91 (100, $C_7H_7^+$); 77 (1, $C_6H_5^+$); 70 (3); 65 (11).

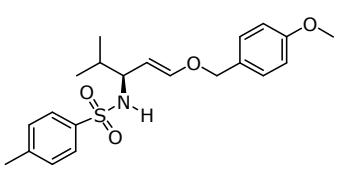
12.8.2.2.6. Isomerization of **(2*R*,3*S*)-2-(benzyloxy)methyl-3-*iso*-propyl-*N*-(*para*-toluensulfonyl)aziridine (114a)** with 3.0 equiv of LIDAKOR

2*R*,3*S*)-2-(Benzyloxy)methyl-3-isopropyl-*N*-(*para*-toluensulfonyl)aziridine **114a** (179.60 mg, 0.5 mmol, 1.0 equiv) was reacted with 3.0 equiv of LIDAKOR in

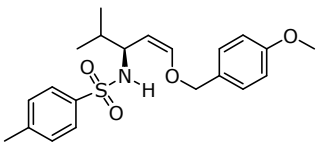
anhydrous pentane at room temperature for 24h to afford a 3:1 mix of allyl amine **145a** and the oxetane **144a**, which were separated by chromatography (silica, eluent: 5:1 pentane/ethyl acetate). 39.50 mg (0.11 Mmol, 22%) of the oxetane **144a**, as a pale yellow oil, and 70.00 mg (0.2 mmol, 39%) of the vinyl ether **145a**, in 75:25 *E*/*Z* diastereomeric mix, were obtained.

12.8.2.2.7. Isomerization of **(2*R*,3*S*)-2-(4-methoxy-benzyloxy)-methyl-3-*iso*-propyl-*N*-(*para*-toluensulfonyl)aziridine (114b)** with 3.0 equiv of LIDAKOR

(2*R*,3*S*) -2- (4-Methoxy-benzyloxy)methyl-3-*iso*-propyl-*N*-(*para*-toluensulfonyl)-aziridine **114b** (251.10 mg, 0.6 mmol, 1.0 equiv) was reacted with 3.0 equiv of LIDAKOR in anhydrous pentane at room temperature for 24h to afford, after purification by flash chromatography (silica, eluent: 3:1 pentane/ethyl acetate), the allyl amine (80:20 *E*/*Z*) **145b** (93.40 mg, 0.24 mmol, 40%), as a pale yellow oil.



145b: (*E*)-*N*-(1*S*)-(3-(4-Methoxy-benzyl-oxy)-1-*iso*-propyl-allyl)-*para*-toluensulfonylamine
$C_{20}H_{25}O_3NS$ M=389.27
^{1}H-NMR δ($CDCl_3$, 400 MHz)**:** 7.76-7.72 (2H, m [AA' part of a AA'BB' spin system], C**H** *ortho* aromatics to SO_2); 7.31-7.28 (2H, m [BB' part of a AA'BB' spin system], C**H** *meta* aromatics to SO_2); 7.25-7.21 (2H, m [BB' part of a AA'BB' spin system], C**H** *meta* aromatics to OCH_3); 6.95-6.91 (2H, m [AA' part of a AA'BB' spin system], C**H** *ortho* aromatics to OCH_3); 6.11 (1H, d, *J*=14.4, CH=C**H**O); 4.66 (1H, br-d, *J*=7.8, N**H**); 4.58-4.38 (3H, m, C**H$_2$**$C_6H_4OCH_3$ and C**H**=CHO); 3.81 (3H, s, OC**H$_3$**); 3.54-3.42 (1H, m, C**H**NHTs); 2.35 (3H, s, C**H$_3$** tosyl group); 1.71 (1H, ps-oct, *J*=6.6, C**H**$(CH_3)_2$); 0.82 (6H, ps-t, *J*=6.8, CH(C**H$_3$**)$_2$).
^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 158.7 (**C$_{ipso}$** aromatic to OMe); 148.4 (CH=**C**HO); 143.6 (**C$_q$** *para* aromatic to SO_2); 136.8 (**C$_{ipso}$** aromatic to SO_2); 129.6 (4C, **C**H *ortho* and *meta* aromatics to SO_2); 129.4 (**C$_q$** *para* aromatic to OMe); 127.2 (2C, **C**H *ortho* aromatic to SO_2); 113.3 (2C, **C**H *ortho* aromatic to OMe); 102.6 (**C**H=CHO); 69.9 (**C**$H_2C_6H_4OCH_3$); 59.0 (**C**HNHTs); 54.9 (O**C**H_3); 33.3 (**C**H$(CH_3)_2$); 21.5 (**C**H_3 tosyl group); 18.8 (CH(**C**$H_3)_2$); 17.9 (CH(**C**$H_3)_2$).
MS (EI) *m/z*(%)**:** 316 (36, M^+ – iPr); 290 (2); 168 (2, M^+ – Ts); 155 (37, Ts^+); 139 (10); 121 (100, $CH_2C_6H_4OMe^+$); 109 (13); 91 (48, $C_7H_7^+$); 70 (8); 65 (14); 43 (12, iPr^+).

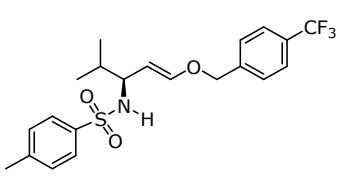


145b: (*Z*)-*N*-(1*S*)-(3-(4-Methoxy-benzyloxy)-1-*iso*-propyl-allyl)-*para*-toluensulfonylamine
$C_{20}H_{25}O_3NS$ M=389.27

^{1}H-NMR δ($CDCl_3$, 400 MHz)**:** 7.72-7.68 (2H, m [AA' part of a AA'BB' spin system], C**H** *ortho* aromatics to SO_2); 7.29-7.27 (2H, m [BB' part of a AA'BB' spin system], C**H** *meta* aromatics to SO_2); 7.19-7.15 (2H, m [BB' part of a AA'BB' spin system], C**H** *meta* aromatics to OCH_3); 6.90-6.86 (2H, m [AA' part of a AA'BB' spin system], C**H** *ortho* aromatics to OCH_3); 6.08 (1H, d, *J*=8.4, CH=C**H**O); 4.60 (1H, br-d, *J*=6.8, N**H**); 4.58-4.38 (3H, m, C**H$_2$**$C_6H_4OCH_3$ and C**H**=CHO); 3.77 (3H, s, OC**H$_3$**); 3.54-3.42 (1H, m, C**H**NHTs); 2.32 (3H, s, C**H$_3$** tosyl group); 1.70 (1H, ps-oct, *J*=6.6, C**H**$(CH_3)_2$); 0.80 (6H, ps-t, *J*=6.8, CH(C**H$_3$**)$_2$).
^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 158.2 (**C$_{ipso}$** aromatic to OMe); 148.0 (CH=**C**HO); 143.3 (**C$_q$** *para* aromatic to SO_2); 136.5 (**C$_{ipso}$** aromatic to SO_2); 129.2 (4C, **C**H *ortho* and *meta* aromatics to SO_2); 129.0 (**C$_q$** *para* aromatic to OMe); 127.0 (2C, **C**H *ortho* aromatic to SO_2); 112.9 (2C, **C**H *ortho* aromatic to OMe); 102.4 (**C**H=CHO); 69.7 (**C**$H_2C_6H_4OCH_3$); 58.4 (**C**HNHTs); 54.6 (O**C**H_3); 33.0 (**C**H$(CH_3)_2$); 21.1 (**C**H_3 tosyl group); 18.6 (CH(**C**$H_3)_2$); 17.5 (CH(**C**$H_3)_2$).
MS (EI) *m/z*(%)**:** 316 (35, M^+ – iPr); 290 (4); 168 (1, M^+ – Ts); 155 (38, Ts^+); 139 (9); 121 (100, $CH_2C_6H_4OMe^+$); 109 (14); 91 (50, $C_7H_7^+$); 70 (8); 65 (12); 43 (17, iPr^+).

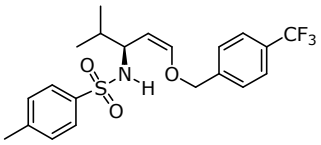
12.8.2.2.8. Isomerization of (2*R*,3*S*)-2-(4-trifluoromethyl-benzyloxy)-methyl-3-*iso*-propyl-*N*-(*para*-toluensulfonyl)aziridine (114c) with 3.0 equiv of LIDAKOR

(2*R*,3*S*)-2-(4-Trifluoromethyl-benzyloxy)methyl-3-*iso*-propyl-*N*-(*para*-toluen-sulfonyl)aziridine **114c** (427.10 mg, 0.5 mmol, 1.0 equiv) was reacted with 3.0 equiv of LIDAKOR in a 2:1 pentane/HMPA mix at room temperature for 24h giving 191.1 mg of crude product corresponding to a 86:14 mix of two *E*/*Z* diastereoisomers **145c**, with a 56% conversion. After purification by flash chromatography (silica, eluent: 5:1 pentane/ethyl acetate), the allyl amine (85:15 *E*/*Z*) **145c** (49.13 mg, 0.12 mmol, 23%) was obtained.



145c: (*E*)-(1*S*)-*N*-(3-(4-Trifluoromethyl-benzyloxy)-1-isopropyl-allyl)-*para*-toluen-sulfonylamine
$C_{21}H_{24}F_3O_3NS$ M=427.24
^{1}H-NMR δ($CDCl_3$, 400 MHz)**:** 7.74-7.70 (2H, m [AA' part of a AA'BB' spin system], C**H** *ortho* aromatics to SO_2); 7.62-7.58 (2H, m [AA' part of a AA'BB' spin system], C**H** *ortho* aromatics to CF_3); 7.36-7.32 (2H, m [BB' part of a AA'BB' spin system], C**H** *meta* aromatics to SO_2); 7.26-7.22 (2H, m [BB' part of a AA'BB' spin system], C**H** *meta* aromatics to CF_3); 6.14 (1H, d, *J*=14.4, CH=C**H**O); 4.76 (1H, br-d, *J*=7.8, N**H**); 4.58-4.38 (3H, m, C**H$_2$**$C_6H_4CF_3$ and C**H**=CHO); 3.54-3.42 (1H, m, C**H**NHTs); 2.35 (3H, s, C**H$_3$** tosyl group); 1.71 (1H, ps-oct, *J*=6.6, C**H**$(CH_3)_2$); 0.82 (6H, ps-t, *J*=6.8, CH(C**H$_3$**)$_2$).

^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 148.4 (CH=**C**HO); 142.9 (**C_q** *para* aromatic to CF_3); 140.6 (**C_q** *para* aromatic to SO_2); 138.4 (**C_{ipso}** aromatic to SO_2); 129.3 (4C, **C**H *ortho* and *meta* aromatics to SO_2); 129.1 (**C_{ipso}** aromatic to CF_3); 127.3 (2C, **C**H *meta* aromatic to CF_3); 127.1 (2C, **C**H *ortho* aromatics to CF_3); 125.5 (**C**F_3); 102.6 (**C**H=CHO); 69.9 (**C**$H_2C_6H_4CF_3$); 59.0 (**C**HNHTs); 33.3 (**C**H$(CH_3)_2$); 21.5 (**C**H_3 tosyl group); 18.8 (CH(**C**$H_3)_2$); 17.9 (CH(**C**$H_3)_2$).
MS (EI) *m/z*(%)**:** 384 (36, M^+ – iPr); 356 (1); 336 (1, M^+ – C_7H_7); 310 (2); 272 (0.4, M^+ – Ts); 228 (3); 216 (2); 201 (2); 185 (2); 172 (4); 159 (100, $CH_2C_6H_4CF_3^+$); 155 (39, Ts^+); 139 (10); 109 (13); 91 (49, $C_7H_7^+$); 70 (8); 65 (14); 43 (12, iPr^+); 41 (17).



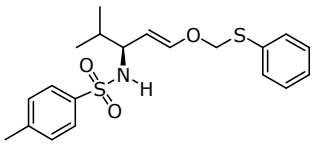
145c: <u>(*Z*)-(1*S*)-*N*-(3-(4-Trifluoromethyl-benzyloxy)-1-isopropyl-allyl)-*para*-toluensulfonylamine</u>

$C_{21}H_{24}F_3O_3NS$ M=427.24

^{1}H-NMR δ($CDCl_3$, 400 MHz)**:** 7.72-7.68 (2H, m [AA' part of a AA'BB' spin system], C**H** *ortho* aromatics to SO_2); 7.63-7.59 (2H, m [AA' part of a AA'BB' spin system], C**H** *ortho* aromatics to CF_3); 7.38-7.34 (2H, m [BB' part of a AA'BB' spin system], C**H** *meta* aromatics to SO_2); 7.19-7.15 (2H, m [BB' part of a AA'BB' spin system], C**H** *meta* aromatics to CF_3); 5.86 (1H, d, *J*=6.6, CH=C**H**O); 4.98 (1H, br-d, *J*=8.4, N**H**); 4.25-4.03 (3H, m, C**H_2**$C_6H_4CF_3$ and C**H**=CHO); 3.54-3.40 (1H, m, C**H**-NHTs); 2.37 (3H, s, C**H_3** tosyl group); 1.30-1.22 (1H, m, C**H**$(CH_3)_2$); 0.88-0.79 (6H, m, CH(C**H_3**$)_2$).
^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 145.5 (CH=**C**HO); 142.7 (**C_q** *para* aromatic to CF_3); 140.8 (**C_q** *para* aromatic to SO_2); 137.4 (**C_{ipso}** aromatic to SO_2); 129.7 (**C_{ipso}** aromatic to CF_3); 127.2 (2C, **C**H *meta* aromatic to CF_3); 127.1 (4C, **C**H *ortho* and *meta* aromatics to SO_2); 126.7 (**C**F_3); 125.4 (2C, **C**H *meta* aromatics to CF_3); 125.3(2C, **C**H *ortho* aromatics to CF_3); 105.5 (**C**H=CHO); 73.0 (**C**$H_2C_6H_4CF_3$); 55.0 (**C**HNHTs); 29.7 (**C**H$(CH_3)_2$); 21.5 (**C**H_3 tosyl group); 18.6 (CH(**C**$H_3)_2$); 17.8 (CH(**C**$H_3)_2$).
MS (EI) *m/z*(%)**:** 384 (36, M^+ – iPr); 238 (6); 228 (4); 216 (1); 201 (2); 185 (1); 172 (5); 159 (100, $CH_2C_6H_4CF_3^+$); 155 (41, Ts^+); 139 (11); 119 (4); 109 (15); 91 (54, $C_7H_7^+$); 70 (13); 65 (16); 43 (12, iPr^+); 41 (19).

12.8.2.2.9. <u>Isomerization of **(2*R*,3*S*)-2-(phenylthio-methoxy)methyl-3-*iso*-propyl-*N*-(*para*-toluensulfonyl)aziridine (114d)** with 3.0 equiv of LIDAKOR</u>

(2*R*,3*S*)-2-(Phenylthio-methoxy)-methyl-3-*iso*-propyl-*N*-(*para*-toluensulfonyl)-aziridine **114d** (71.92 mg, 0.2 mmol, 1.0 equiv) was reacted with 3.0 equiv of LIDAKOR in anhydrous pentane at room temperature for 24h giving the *E*-allyl amine **145d** with a 85% conversion (37.60 mg, 0.1 mmol, 48%, after purification by flash chromatography on silica gel, eluent: 5:1 cyclohexane/ethyl acetate).



145d: (*E*)-(1*S*)-*N*-(3-(Phenylthio-methoxy)-1-iso-propyl-allyl)-*para*-toluensulfonylamine

$C_{20}H_{33}O_3NS_2$ **M=**391.25

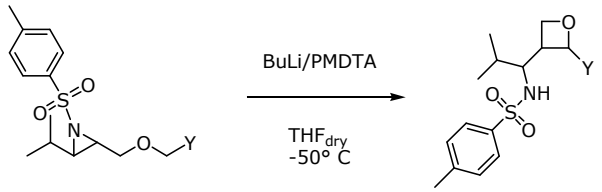
^{1}H-NMR δ($CDCl_3$, 400 MHz)**:** 7.73-7.69 (2H, m [AA' part of a AA'BB' spin system], C**H** *ortho* aromatics to SO_2); 7.41-7.19 (7H, m, C**H** *meta* aromatics to SO_2 and aromatics Ph); 5.97 (1H, d, *J*=12.4, C**H**=CHO); 4.88 (2H, m [AB spin system], OC**H_2**SPh); 4.58 (1H, dd, *J*=12.4, 9.0, C**H**=CHO); 4.39 (1H, br-d, *J*=7.2, N**H**); 3.50 (1H, td_{app}, C**H**NHTs); 2.33 (3H, s, C**H_3** tosyl group); 1.81-1.58 (1H, m, C**H**$(CH_3)_2$); 0.86 (3H, d, *J*=6.8, CH(C**H_3**$)_2$); 0.84 (3H, d, *J*=6.8, CH(C**H_3**$)_2$).

^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 146.5 (CH=**C**$HOCH_2$SPh); 143.0 (**C_{ipso}** aromatic to SO_2); 138.3 (**C_q** *para* aromatic to SO_2); 134.7 (**C_{ipso}** aromatic to S); 130.6 (2C, **C**H *meta* aromatic to S); 129.4 (2C, **C**H *meta* aromatic to SO_2); 129.0 (2C, **C**H *ortho* aromatic to S); 127.3 (**C**H *para* aromatic to S); 127.2 (2C, **C**H *ortho* aromatic to SO_2); 105.4 (**C**H=CHOCH_2SPh); 74.6 (**C**H_2SPh); 58.7 (**C**HNHTs); 33.4 (**C**H$(CH_3)_2$); 21.5 (**C**H_3 tosyl group); 18.7 (CH(**C**$H_3$$)_2$); 18.0 (CH(**C**$H_3$$)_2$).

MS (EI) *m/z*(%)**:** 348 (3, M^+ – iPr); 238 (1, M^+ – Ts + 2); 226 (1); 184 (2); 177 (8, M^+ – iPr – NHTs); 155 (3, Ts^+); 149 (4); 139 (1, OCH_2SPh^+); 123 (100, CH_2SPh^+); 91 (19, $C_7H_7^+$); 77 (5, $C_6H_5^+$); 65 (6); 45 (44); 41 (7).

12.8.3. Isomerizations with BuLi / PMDTA

12.8.3.1. *General procedure for the isomerization of meso-aziridine and hetero-substituted aziridines using a BuLi / PMEDTA mixture in THF at low temperature*



114a Y=Ph
114b Y=$C_6H_4CF_3$
114c Y=$C_6H_4OCH_3$
114d Y=SPh
114e Y=CH=CH_2

144a Y=Ph
144b Y=$C_6H_4CF_3$
144c Y=$C_6H_4OCH_3$
144d Y=SPh
144e Y=CH=CH_2

In a Schlenk tube, after three vacuum / nitrogen cycles, hexane was stripped off from a solution of BuLi (n mmol, n equiv) and precooled anhydrous THF (0.5 M) was added at –78° C under nitrogen, followed by anhydrous PMDTA (n mmol, n equiv). After 30' a solution of the aziridine **114** (1.0 equiv) in freshly distilled THF was added dropwise and the resulting reaction mixture was stirred at –50° C for 16 - 48h. Then the mixture was quenched with water and worked by separating the two layers. The aqueous portion was extracted with ether (3 times) and the

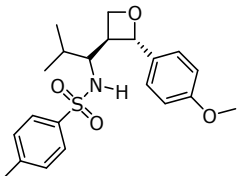
combined organic components were washed twice with H_2O and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the isomerization product **144**, which was purified by flash column chromatography.

12.8.3.1.1. Isomerization of **(2*R*,3*S*)-2-(benzyloxy)methyl-3-*iso*-propyl-*N*-(*para*-toluensulfonyl)aziridine (114a)** with 2.0 equiv of BuLi / PMDTA

A 180.00 mg (0.5 mmol, 1.0 equiv) aliquot of (2*R*,3*S*)-2-(benzyloxy)methyl-3-isopropyl-*N*-(*para*-toluensulfonyl)aziridine **114a** was reacted with 2.0 equiv of BuLi / PMDTA in anhydrous THF at –50° C for 24h affording, after purification *via* flash chromatography (silica, eluent: 4:1 pentane/ethyl acetate), the oxetane **2,3-*trans*-144a** (15.65 mg, 0.04 mmol, 8%) with a 30% conversion.

12.8.3.1.2. Isomerization of **(2*R*,3*S*)-2-(4-methoxy-benzyloxy)-methyl-3-*iso*-propyl-*N*-(*para*-toluensulfonyl)aziridine (114b)** with 3.0 equiv of BuLi / PMDTA

(2*R*,3*S*)-2-(4-Methoxy-benzyloxy)methyl-3-*iso*-propyl-*N*-(*para*-toluensulfonyl)-aziridine **114b** (250.00 mg, 0.6 mmol, 1.0 equiv) and 3.0 equiv of BuLi / PMDTA were left to stir in THF at –50° C for 24h to afford a 17:83 mix of the oxetane **2,3-*trans*-144b**, and the de-tosylated benzyloxy-aziridine **116**, which were separated by chromatography (eluent: 3:1 pentane/ethyl acetate). A 18.68 mg (0.05 mmol, 8%) aliquot of (*R*)-*N*-(2-methyl-1-((2*S*,3*S*)-2-phenyl-oxetan-3-yl)-propyl)-*para*-toluensulfonylamine **144b** and 16.80 mg (0.3 mmol, 50%) of (2*R*,3*S*)-2-(4-methoxybenzyloxy)methyl-3-*iso*-propylaziridine **116** were obtained.



144b: (*R*)-*N*-(2-Methyl-1-((2*S*,3*S*)-2-(4-methoxy phenyl)-oxetan-3-yl)propyl)-*para*-toluensulfonyl-amine

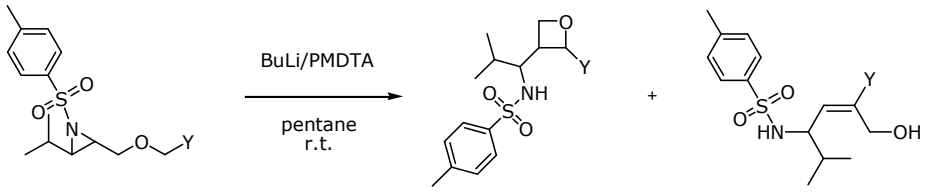
$C_{21}H_{27}O_4NS$ **M=**389.27

^{1}H-NMR δ($CDCl_3$, 400 MHz)**:** 7.80-7.78 (2H, m [AA' part of a AA'BB' spin system], C**H** *ortho* aromatics to SO_2); 7.32-7.30 (2H, m [BB' part of a AA'BB' spin system], C**H** *meta* aromatics to SO_2); 7.29-7.27 (2H, m [BB' part of a AA'BB' spin system], C**H** *meta* aromatics to OMe); 6.88-6.86 (2H, m [AA' part of a AA'BB' spin system], C**H** *ortho* aromatics to OMe); 5.32 (1H, d, *J*=7.2, C**H**Ph oxetane); 4.59 (1H, br-d, *J*=9.2, N**H**); 4.40-4.32 (2H; m, C$\mathbf{H_2}$ oxetane); 3.80 (3H, s, OC$\mathbf{H_3}$); 3.53-3.50 (1H, m, C**H**NHTs); 3.04 (1H, ps-quint, *J*=7.6, C**H**CHNHTs oxetane); 2.43 (3H, s, C$\mathbf{H_3}$ tosyl group); 1.68-1.58 (1H, m, C**H**$(CH_3)_2$); 0.68 (3H, d, *J*=6.8, CH(C$\mathbf{H_3}$)$_2$); 0.53 (3H, d, *J*=6.8, CH(C$\mathbf{H_3}$)$_2$).

^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 159.7 (**C_{ipso}** aromatic to OMe); 143.5 (**C** aromatic *para* to SO_2); 138.4 (**C_{ipso}** aromatic to SO_2); 133.6 (**C_q** *para* aromatic to OMe); 129.7 (2C, **C**H *meta* aromatics to SO_2); 127.7 (2C, **C**H *ortho* aromatics to SO_2); 127.1 (2C, **C**H *meta* aromatics to OMe); 113.9 (2C, **C**H *ortho* aromatics to

OMe); 85.1 (**C**HPh oxetane); 70.0 (**C**H_2 oxetane); 59.9 (**C**H-NH); 55.3 (O**C**H_3); 47.3 (**C**HCHNHTs oxetane); 30.4 (**C**H$(CH_3)_2$); 21.5 (**C**H_3 tosyl group); 19.0 (CH(**C**$H_3)_2$); 16.9 (CH(**C**$H_3)_2$).
MS (EI) *m/z*(%)**:**316 (100, M^+ – iPr – OMe); 281 (1, M^+ – $C_6H_4OCH_3$); 237 (1, M^+ + 1 – $C_6H_4OCH_3$ – iPr); 207 (8); 188 (30, M^+ – iPr – Ts); 173 (34); 160 (55); 155 (29, Ts^+); 145 (79, M^+ – CH(NHTs)iPr); 91 (92, $C_7H_7^+$); 77 (13, $C_6H_5^+$); 65 (31).

12.8.3.2. *General procedure for the isomerization of meso-aziridine and hetero-substituted aziridines using a BuLi / PMDTA mixture in pentane at room temperature*



114a Y=Ph
114b Y=$C_6H_4CF_3$
114c Y=$C_6H_4OCH_3$
114d Y=SPh
114e Y=CH=CH_2

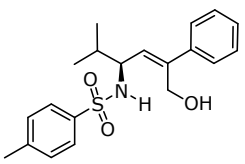
144a Y=Ph
144b Y=$C_6H_4CF_3$
144c Y=$C_6H_4OCH_3$
144d Y=SPh
144e Y=CH=CH_2

146a Y=Ph
146b Y=$C_6H_4CF_3$
146c Y=$C_6H_4OCH_3$
146d Y=SPh
146e Y=CH=CH_2

In a Schlenk tube, after three vacuum/nitrogen cycles, BuLi (2.0 mmol, 2.0 equiv) was mixed with dried PMDTA (n mmol, n equiv) in anhydrous pentane (0.5 M) at 0° C and under nitrogen flux. After 30' a solution of the aziridine **114** (1.0 equiv) in dried pentane was added dropwise and the resulting reaction mixture was stirred at room temperature for 16-48h depending on the substrate. Then the mixture was quenched with water and worked by separating the two layers. The aqueous portion was extracted with ether (3 times) and the combined organic components were washed twice with H_2O and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the isomerization product **144**, **146** or both, which were purified by flash column chromatography.

12.8.3.2.1. Isomerization of **(2*R*,3*S*)-2-(benzyloxy)methyl-3-*iso*-propyl-*N*-(*para*-toluensulfonyl)aziridine (114a)** with 2.0 equiv of BuLi / PMDTA

Mixing 179.50 mg (0.5 mmol, 1.0 equiv) of (2*R*,3*S*)-2-(benzyloxy)methyl-3-isopropyl-*N*-(*para*-toluensulfonyl)-aziridine **114a** with 3.0 equiv of BuLi / PMDTA in anhydrous pentane at room temperature for 16h. The crude product was purified *via* flash chromatography (silica, eluent: 4:1 pentane/ethyl acetate) giving the oxetane **2,3-*trans*-144a** and the aminoalcohol **146a** (92.90 mg, 0.26 mmol, 52%), which were resulted difficult to separated.



146a: (*Z*)-5-Methyl-2-phenyl-4-(*N*-*para*-toluensulfonylamino)hex-2-en-1-ol

$C_{20}H_{25}O_3NS$ M=359.25

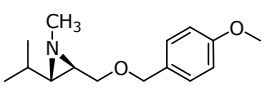
^{1}H-NMR δ($CDCl_3$, 400 MHz)**:** 7.75-7.73 (2H, m [AA' part of a AA'BB' spin system], C**H** *ortho* aromatics to SO_2); 7.36-7.20 (5H, m, C**H** aromatics Ph); 7.27-7.25 (2H, m [BB' part of a AA'BB' spin system], C**H** *meta* aromatics to SO_2); 5.40 (1H, d, *J*=10.4, C**H**=C(Ph)CH_2OH); 4.74 (1H, bd, *J*=6.2, N**H**); 4.56 (1H, d_{app} , *J*=12.8, C**H'**HOH); 4.31 (1H, dd, *J*=12.8, 5.4, CH'**H**CHOH); 4.08 (1H, ps-dt, *J*=10.4, 6.8, C**H**NH); 2.36 (3H, s, C**H$_3$** tosyl group); 1.74 (1H, ps-oct, *J*=6.8, C**H**$(CH_3)_2$); 0.89 (6H, p-t, *J*=6.8, CH(C**H$_3$**)$_2$).

^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 143.0 (**C$_q$** *para* aromatic to SO_2); 141.1 (**C$_{ipso}$** aromatic Ph); 140.2 (CH=**C**H(Ph)CH_2OH); 137.9 (**C$_{ipso}$** aromatic to SO_2); 129.5-126.3 (9C, **C**H aromatics); 97.0 (**C**H=CH(Ph)CH_2OH); 57.4 (**C**H_2OH); 51.8 (**C**HNHTs); 33.2 (**C**H$(CH_3)_2$); 21.6 (**C**H_3 tosyl group); 18.8 (CH(**C**$H_3)_2$); 18.5 (CH(**C**$H_3)_2$).

MS (EI) *m/z*(%)**:** 316 (0.1, M M^+ – Ph); 210 (13); 207 (8, M^+ – Ts); 174 (2); 155 (41, Ts^+); 143 (7); 130 (28, M^+ – TsNHCHiPr); 115 (22); 103 (6); 91 (100, $C_7H_7^+$); 77 (13, $C_6H_5^+$); 65 (12).

12.8.3.2.2. Isomerization of **(2*R*,3*S*)-2-(4-methoxy-benzyloxy)-methyl-3-*iso*-propyl-*N*-(*para*-toluensulfonyl)aziridine (114b)** with 3.0 equiv of BuLi / PMDTA

(2*R*,3*S*) -2- (4-Methoxy-benzyloxy)methyl-3-*iso*-propyl-*N*-(*para*-toluensulfonyl)-aziridine **114b** (194.64 mg, 0.5 mmol, 1.0 equiv) and 3.0 equiv of BuLi/PMDTA were reacted in a 4:1 pentane/HMPA mix at room temperature for 16h to afford, after purification by chromatography (SiO_2, eluent: 3:1 pentane/ethyl acetate), (*R*)-*N*-(2-methyl-1-((2*S*,3*S*)-2-phenyl-oxetan-3-yl)propyl)-*para*-toluensulfonyl-amine **144b** (97.30 mg, 0.25 mmol, 50%) and (2*R*,3*S*)-2-(4-methoxy-benzyloxy)-methyl-3-*iso*-propyl *N*-(methyl)-aziridine **152** (22.40 mg, 0.1 mmol, 18%).



152: (2*R*,3*S*)-2-(4-Methoxy-benzyloxy)-methyl-3-*iso*-propyl *N*-(methyl)aziridine

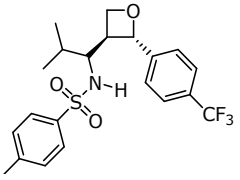
$C_{15}H_{23}NO_2$ M=249.23

^{1}H-NMR δ($CDCl_3$, 400 MHz)**:** 7.22-7.20 (2H, m [BB' part of a AA'BB' spin system], C**H** *meta* aromatics to OMe); 6.88-6.86 (2H, m [AA' part of a AA'BB' spin system], C**H** aromatics to OMe); 4.39 (2H, m [AB spin system], C**H$_2$**OC_6H_4OMe); 3.80 (3H, s, OC**H**$_3$); 3.72 (1H, dd, *J*=10.8, 3.2, C**H**H'O$CH_2C_6H_4$OMe); 3.62 (1H, dd, *J*=10.8, 4.4, CH**H'**O$CH_2C_6H_4$OMe); 2.57 (1H, dt, *J*=4.0, 3.2, C**H**CH_2 aziridinic); 2.32 (1H, dd, *J*=7.4, 3.2, iPrC**H** aziridinic); 2.10

(3H, s, N-C**H$_3$**); 1.53 (1H, p-oct, *J*=6.8, C**H**(CH$_3$)$_2$); 1.04 (3H, d, *J*=6.8, CH(C**H$_3$**)$_2$); 0.96 (3H, d, *J*=6.8, CH(C**H$_3$**)$_2$).
^{13}C-NMR{^{1}H} δ (CDCl$_3$, 50 MHz)**:** 159.2 (**C$_{ipso}$** aromatic to OCH$_3$); 128.3 (2C, **C**H *meta* aromatics to OCH$_3$); 126.7 (**C$_q$** *para* aromatic to OCH$_3$); 113.7 (2C, **C**H *ortho* aromatics to OCH$_3$); 72.6 (O**C**H$_2$C$_6$H$_4$OCH$_3$); 66.9 (**C**H$_2$OCH$_2$C$_6$H$_4$OCH$_3$); 55.3 (O**C**H$_3$); 51.5 (iPr**C**H epoxidic); 45.1 (N**C**H$_3$); 41.7 (CH$_2$**C**H epoxidic); 30.3 (**C**H(CH$_3$)$_2$); 20.1 (CH(**C**H$_3$)$_2$); 19.4 (CH(**C**H$_3$)$_2$).
MS (EI) *m/z*(%)**:** 249 (0.02, M$^+$); 207 (0.4); 156 (2); 141 (5, M$^+$ – C$_6$H$_5$OCH$_3$); 126 (25); 121 (100, CH$_2$C$_6$H$_4$OCH$_3^+$); 98 (2, CH$_2$OCH$_2$C$_6$H$_4$OCH$_3^+$); 84 (38, M$^+$ + 1 – iPr – CH$_2$C$_6$H$_4$OCH$_3^+$); 82 (9); 77 (8, C$_6$H$_5^+$); 60 (5); 55 (6).

12.8.3.2.3. Isomerization of **(2*R*,3*S*)-2-(4-trifluoromethyl-benzyloxy)-methyl-3-*iso*-propyl-*N*-(*para*-toluensulfonyl)aziridine (114c)** with 3.0 equiv of BuLi / PMDTA

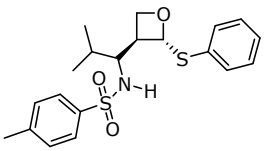
(2*R*,3*S*) -2- (4-Trifluoromethyl-benzyloxy)methyl-3-*iso*-propyl-*N*-(*para*-toluen-sulfonyl)aziridine **114c** (213.60 mg, 0.5 mmol, 1.0 equiv) was reacted with 3.0 equiv of BuLi / PMDTA in a 4:1 pentane / HMPA mix at room temperature for 16h and worked to give, after purification (silica, eluent: 5:1 pentane/ethyl acetate), 64.10 mg (0.15 mmol, 30%) of the oxetane **2,3-*trans*-144c**.



144c: (*R*)-*N*-(2-Methyl-1-((2*S*,3*S*)-2-(4-trifluoro methyl-phenyl)oxetane-3-yl)propyl)-*para*-toluen-sulfonylamine
C$_{21}$H$_{24}$F$_3$O$_3$NS M=427.24
^{1}H-NMR δ(CDCl$_3$, 400 MHz)**:** 7.81-7.79 (2H, m [AA' part of a AA'BB' spin system], C**H** *ortho* aromatics to SO$_2$); 7.63-7.61 (2H, m [AA' part of a AA'BB' spin system], C**H** *ortho* aromatics to CF$_3$); 7.50-7.48 (2H, m [BB' part of a AA'BB' spin system], C**H** *meta* aromatics to SO$_2$); 7.34-7.32 (2H, m [BB' part of a AA'BB' spin system], C**H** *ortho* aromatics to CF$_3$); 5.58 (1H, d, *J*=7.2, C**H**Ph oxetane); 4.55 (1H, d, *J*=9.6, N**H**); 4.50 (2H; dd, *J*=8.2, 1.8, C**H$_2$** oxetane); 3.53-3.47 (1H, m, C**H**NHTs); 3.01 (1H, ps-quint, *J*=7.6, C**H**CHNHTs oxetane); 2.43 (3H, s, C**H$_3$** tosyl group); 1.65-1.59 (1H, m, C**H**(CH$_3$)$_2$); 0.66 (3H, d, *J*=6.8, CH(C**H$_3$**)$_2$); 0.56 (3H, d, *J*=7.2, CH(C**H$_3$**)$_2$).
^{13}C-NMR{^{1}H} δ (CDCl$_3$, 50 MHz)**:** 145.7 (**C$_q$** *para* aromatic to CF$_3$); 143.6 (**C$_q$** *para* aromatic to SO$_2$); 138.1 (**C$_{ipso}$** aromatic to SO$_2$); 129.7 (2C, **C**H *meta* aromatics to SO$_2$); 127.0 (2C, **C**H *ortho* aromatics to SO$_2$); 125.9 (4C, **C**H *ortho* and *meta* aromatics to CF$_3$); 125.5 (**C$_{ipso}$** aromatic to CF$_3$); 125.4 (**C**F$_3$); 84.2 (**C**HPh oxetane); 69.9 (**C**H$_2$ oxetane); 59.3 (**C**H-NH); 47.2 (**C**HCHNHTs oxetane); 30.8 (**C**H(CH$_3$)$_2$); 21.6 (**C**H$_3$ tosyl group); 19.0 (CH(**C**H$_3$)$_2$); 17.4 (CH(**C**H$_3$)$_2$).
MS (EI) *m/z*(%)**:** 354 (56, M$^+$ – CF$_3$); 281 (8, M$^+$ – C$_6$H$_4$CF$_3$); 242 (1); 226 (3); 210 (59, M$^+$ – OCH$_2$C$_6$H$_4$CF$_3$ – iPr); 207 (35); 178 (7); 155 (80, Ts$^+$); 149 (7); 133 (5); 91 (100, C$_7$H$_7^+$); 77 (4, C$_6$H$_5$); 72 (25), 65 (22).

12.8.3.2.4. Isomerization of **(2*R*,3*S*)-2-(phenylthio-methoxy)methyl-3-*iso*-propyl-*N*-(*para*-toluensulfonyl)aziridine (114d)** with 3.0 equiv of BuLi / PMDTA

(2*R*,3*S*) -2- (Phenylthio-methoxy)methyl-3-*iso*-propyl-*N*-(*para*-toluensulfonyl)-aziridine **114d** (137.40 mg, 0.23 mmol, 1.0 equiv) was let to stir in presence of 3.0 equiv of BuLi / PMDTA in a 3:1 pentane / HMPA mix at 25° C for 16h. Work up and purification through a flash column chromatography (silica, eluent: 5:1 pentane/ethyl acetate) gave a non-separable 4:1 mix of the oxetane **144d** (34.20 mg, 0.09 mmol, 38%) and the aminoalcohol **146d** (17.10 mg, 0.04 mmol, 19%).



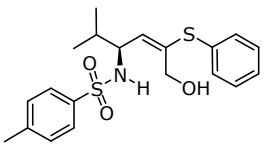
144d: (*R*)-*N*-(2-Methyl-1-((2*R*,3*S*)-2-fenyltio-oxetane-3-yl)propyl)-*para*-toluensulfonylamine

$C_{20}H_{25}O_3NS_2$ **M=**391.25

^{1}H-NMR δ($CDCl_3$, 400 MHz)**:** 7.72-7.70 (2H, m [AA' part of a AA'BB' spin system], C**H** *ortho* aromatics to SO_2); 7.35-7.28 (2H, m [BB' part of a AA'BB' spin system], C**H** *meta* aromatics to SO_2); 7.29-7.23 (5H, m, C**H** aromatics SPh); 5.92 (1H, d, *J*=7.4, C**H**SPh oxetane); 4.48 (1H, d, *J*=9.2, N**H**); 4.47 (2H, p-t, *J*=5.8, C**H**H' oxetane); 4.28 (1H, dd, *J*=7.2, 6.8, CH**H'** oxetane); 3.60-3.55 (1H, m, C**H**NHTs); 3.10 (1H, m, C**H**CHNHTs oxetane); 2.41 (3H, s, C**H$_3$** tosyl group); 2.21-2.11 (1H, m, C**H**$(CH_3)_2$); 0.80 (3H, d, *J*=6.8, CH(C**H$_3$**)$_2$); 0.70 (3H, d, *J*=6.8, CH(C**H$_3$**)$_2$).

^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 143.3 (**C$_q$** *para* aromatic to SO_2); 138.1 (**C$_{ipso}$** aromatic to SO_2); 134.1 (**C$_{ipso}$** aromatic to S); 132.3-126.8 (9C, **C**H aromatics); 93.2 (**C**HSPh oxetane); 62.3 (**C**H_2 oxetane); 59.7 (**C**HNHTs); 55.9 (**C**HCHNHTs oxetane); 29.6 (**C**H$(CH_3)_2$); 21.3 (**C**H_3 tosyl group); 21.6 (CH(**C**$H_3)_2$); 20.7 (CH(**C**$H_3)_2$).

MS (EI) *m/z*(%)**:** 361 (0.1); 281 (0.1, M^+ – PhH); 226 (44, TsNHCHiPr$^+$); 207 (6); 177 (3); 155 (40, Ts^+); 136 (62); 109 (SPh^+); 91 (87, $C_7H_7^+$); 77 (8, $C_6H_5^+$); 71 (16); 57 (32); 43 (62, iPr^+); 32 (100, S^+).



146d: (*E*)-5-Methyl-2-(phenylthio)-4-(*N*-*para*-toluensulfonylamino)hex-2-en-1-ol

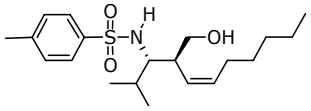
$C_{20}H_{25}O_3NS_2$ **M=**391.25

^{1}H-NMR δ($CDCl_3$, 400 MHz)**:** 7.74-7.72 (2H, m [AA' part of a AA'BB' spin system], C**H** *ortho* aromatics to SO_2); 7.32-7.30 (2H, m [BB' part of a AA'BB' spin system], C**H** *meta* aromatics to SO_2); 7.29-7.23 (5H, m, C**H** aromatics to S); 5.32 (1H, d, *J*=10.0, C**H** olefinic); 4.48 (1H, br-d, *J*=7.2, N**H**); 4.24 (1H, dd, *J*=13.2, 4.0, C**H**H'OH); 4.03-3.94 (2H, m, C**H**NHTs and CH**H'**OH); 2.45 (3H, s, C**H$_3$** tosyl group); 2.40 (1H, br-d, *J*=8.4, O**H**); 1.70-1.60 (1H, m, C**H**$(CH_3)_2$); 0.82 (3H, d, *J*=6.8, CH(C**H$_3$**)$_2$); 0.81 (3H, d, *J*=6.8CH(C**H$_3$**)$_2$).

^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 145.3 (CH=**C**HSPh); 143.5 (**C_q** *para* aromatic to SO_2); 138.2 (**C_{ipso}** aromatic to SO_2); 134.0 (**C_{ipso}** aromatic to SPh); 132.1 (2C, **C**H *meta* aromatics to SO_2); 129.6 (2C, **C**H *ortho* aromatics to S); 129.2 (2C, **C**H *ortho* aromatics to SO_2); 127.7 (**C**H=CHSPh); 126.9 (2C, **C**H *meta* aromatics to S); 126.8 (**C**H *para* aromatic to S); 60.2 (**C**H_2OH); 57.2 (**C**HNHTs); 33.2 (**C**H$(CH_3)_2$); 21.6 (**C**H_3 tosyl group); 18.7 (CH(**C**$H_3)_2$); 18.4 (CH(**C**$H_3)_2$).
MS (EI) *m/z*(%)**:** 350 (2); 348 (13, M^+ – iPr); 281 (0.35, M^+ + 1 – SPh); 220 (2); 177 (100); 155 (15, Ts^+); 149 (8); 135 (8); 116 (8); 109 (7, SPh^+); 91 (51, $C_7H_7^+$); 77 (8, $C_6H_5^+$); 65 (24); 55 (10, $iPrC^+$).

12.8.3.2.5. Isomerization of **(2*R*,3*S*)-2-(allyloxy)methyl-3-*iso*-propyl-*N*-(*para*-toluensulfonyl)aziridine (114e)** with 3.0 equiv of BuLi / PMDTA

Ethyl-3-((2*R*,3*R*)-3-((methoxymethoxy)-methyl)-*N*-(*para*-toluensulfonyl)aziridin-2-yl)propanoate **114e** (109.10 mg, 0.29 mmol, 1.0 equiv) was reacted with 2.0 equiv of BuLi / PMDTA in 2:1 pentane / HMPA mix at room temperature for 24h to afford after purification by flash chromatography (silica, eluent: 8:1 pentane/ethyl acetate) (1*S*,2*R*)-*tert*-butyl 2-((*R*)-2-(methoxy methoxy)-1-(*N*-*para*-toluensulfonylamino)ethyl) **155** (13.8 mg, 0.03 mmol, 12%).

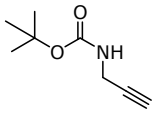


155: (*Z*)-2-(*S*)-((S)-2-Methyl-1-(*N*-*para*-toluen-sulfonylamino)propyl)non-3-en-1-ol
$C_{20}H_{33}O_3NS$ **M=**367.33
^{1}H-NMR δ($CDCl_3$, 400 MHz)**:** 7.77-7.75 (2H, m [AA' part of a AA'BB' spin system), C**H** *ortho* aromatics to SO_2); 7.30-7.28 (2H, m [BB' part of a AA'BB' spin system), C**H** *meta* aromatics to SO_2); 5.54-5.46 (1H, m, CH=C**H**(C_5H_{11})); 5.26 (1H, t_{app}, *J*=10.4, C**H**=CH(C_5H_{11})); 4.53 (1H, br-d, *J*=9.2, N**H**); 3.83 (1H, dd, *J*=11.2, 4.0, C**H**H'OH); 3.60-3.55 (1H, m, CH**H'**OH); 3.29 (1H, td, *J*=9.6, 2.8, C**H**NHTs); 2.52-2.45 (1H, m, C**H**CH_2OH); 2.42 (3H, s, C**H_3** tosyl group); 2.03-1.95 (2H, m, CHC**H_2**(C_4H_9)); 1.82 (1H, septd, *J*=11.2, 4.4, C**H**$(CH_3)_2$); 1.37-1.23 (4H, m, $CH_2(C_2$**H_4**$)C_2H_5$); 0.94-0.86 (5H, m, $(C_3H_6)C_2$**H_5**); 0.71 (3H, d, *J*=6.8, CH(C**$H_3)_2$**); 0.48 (3H, d, *J*=6.8, CH(C**$H_3)_2$**).
^{13}C-NMR{^{1}H} δ ($CDCl_3$, 100 MHz)**:** 143.3 (**C_q** *para* aromatic to SO_2); 138.3 (**C_{ipso}** aromatic to SO_2); 133.0 (**C**H=CH(C_5H_{11})); 129.5 (2C, **C**H *meta* aromatics to SO_2); 128.0 (CH=**C**H(C_5H_{11})); 127.0 (2C, **C**H aromatics to SO_2); 63.8 (**C**H_2OH); 59.7 (**C**HNHTs); 43.6 (**C**HCH_2OH); 31.6 (**C**H$(CH_3)_2$); 29.7-14.1 (8C, **C**H_3 tosyl group, CH(**C**$H_3)_2$, **C**$_5H_{11}$).
MS (EI) *m/z*(%)**:** 210 (14, M^+ – 2H – Ts); 208 (26); 155 (35, Ts^+); 133 (14); 126 (42); 96 (19); 91 (100, $C_7H_7^+$); 84 (34); 70 (40); 65 (17); 57 (84); 55 (16, $iPrC^+$).

12.9. Synthesis of a new family of 2-ethylidene-γ-unsaturated δ-amino esters *via* microwave activated Stille coupling

12.9.1. Synthesis of γ-stannylamines

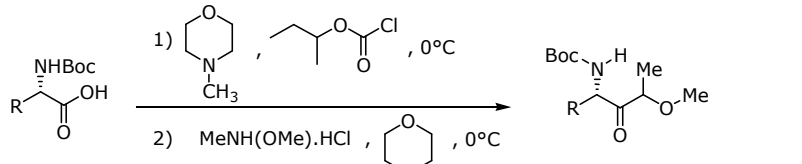
12.9.1.1. *N*-(*tert*-Butoxycarbonyl)-propargylamine (191a)[500]



In a 500 mL round bottomed flask, 2.56 mL (40.0 mmol, 1.0 equiv) of propargylamine **190** were dissolved into a solution of MeOH (80.00 mL), water (40.00 mL) and a 1 M aq. NaOH solution (100.00 mL, pH>11). $(Boc)_2O$ (9.59 g, 44.0 mmol, 1.1 equiv) was then added at 0° C and the resulting reaction mixture was left a room temperature for 12h. Methanol was evaporated under reduced pressure and the remaining aqueous solution layer was extracted with ethyl acetate (2 x 50.00 mL). The combined organic components were washed with water (3 x 30.00 mL) and dried (Na_2SO_4). After evaporation of the solvent, 3.51 g (23.00 mmol, 57%) of the crude product **191a** were obtained and used without further purification.

191a
$C_8H_{13}NO_2$ **M=**155.13
m.p.=40°-41° C
^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 4.85 (1H, br-s, N**H**Boc); 3.88 (2H, br-d, *J*=2.5, C**H_2**NHBoc); 2.19 (1H, t, *J*=2.5, C≡C**H**); 1.41 (9H, s, C(C**H_3**)$_3$).
MS (EI) *m/z*(%)**:** 140 (15, $M^+ - CH_3$); 100 (21); 99 (44); 59 (100); 57 (100, $C(CH_3)_3^+$); 56 (42); 43 (73); 41 (100).

12.9.1.2. *General procedure for the synthesis of N-(tert-butoxycarbonyl)-N-methylamides (**193**)*[501]



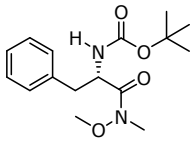
192b: R=CH_2Ph
192c: R=$CH(CH_3)_2$
192d: R=$CH_2CH(CH_3)_2$

193b: R=CH_2Ph
193c: R=$CH(CH_3)_2$
193d: R=$CH_2CH(CH_3)_2$

A solution of *N*-(*tert*-butoxycarbonyl)amino acid **192** (1.0 equiv) in ethyl acetate was cooled at 0° C and added with *N*-methylmorpholine (1.0 equiv) and *iso*-butylchloroformiate (1.0 equiv). After 15' at 0° C, *N*,*O*-dimethylhydroxylamine chloridrate (1.0 equiv) and *N*-methylmorpholine (1.0 equiv) were added. The reaction mixture was left for 15' at 0° C, then at room temperature for 12h. It was

diluted in ethyl acetate and washed with a 3 N aq. HCl solution, a saturated aq. Na_2CO_3 solution (three times) and brine (twice). After evaporation the solvent, the compound **193** was used in the next step without purification.

12.9.1.2.1. [(*S*)-1-(Methoxymethylcarbamoyl)-2-phenylethyl]-carbamic acid *tert*-butyl ester (193b)[501]



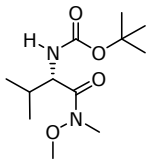
N-(*tert*-Butoxycarbonyl)-L-phenylalanine **192b** (3.61, 13.6 mmol, 1.0 equiv) was reacted according to the general procedure. The crude product **193b** was obtained in 94% conversion (3.94 g, 12.8 mmol), as a pale white oil.

193b

$C_{16}H_{24}N_2O_4$ **M=**308.24

^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 7.34-7.11 (5H, m, C**H** aromatics); 5.16 (1H, br-d, *J*=6.6, N**H**Boc); 4.93 (1H, m [X part of a ABX spin system], C**H**NHBoc); 3.64 (3H, s, OC**H$_3$**); 3.15 (1H, s, NC**H$_3$**); 3.05 (1H, m [AX part of a ABX spin system], J_{AX}=6.1, PhC**H**H'CHNH); 2.86 (1H, m [BX part of a ABX spin system], J_{BX}=6.1, PhCH**H'**CHNH); 1.37 (9H, s, C(C**H$_3$**)$_3$).

12.9.1.2.2. [(*S*)-1-(Methoxymethylcarbamoyl)-2-methyl-propyl]-carbamic acid *tert*-butyl ester (193c)[501]



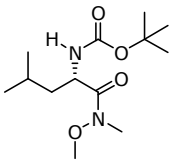
N-(*tert*-Butoxycarbonyl)-L-valine **192c** (8.60, 40.0 mmol, 1.0 equiv) was reacted following the general procedure from which the crude product **193c** in 82% yield (8.54 g, 32.8 mmol) was obtained as a pale yellow oil.

193c

$C_{12}H_{24}N_2O_4$ **M=**260.24

^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 5.15 (1H, br-m, N**H**Boc); 4.56 (1H, br-m, C**H**NHBoc); 3.76 (3H, s, OC**H$_3$**); 3.20 (3H, s, NC**H$_3$**); 1.96 (1H, m, C**H**(CH_3)$_2$); 1.42 (9H, s, C(C**H$_3$**)$_3$); 0.94 (3H, d, *J*=6.8, CH(C**H$_3$**)$_2$); 0.89 (3H, d, *J*=6.8, CH(C**H'$_3$**)$_2$).

12.9.1.2.3. [(*S*)-1-(Methoxymethylcarbamoyl)-3-methyl-butyl]-carbamic acid *tert*-butyl ester (193d)[501]



According to the general procedure *N*-(*tert*-Butoxycarbonyl)-L-leucine **192d** (3.75, 15.0 mmol, 1.0 equiv) was reacted affording

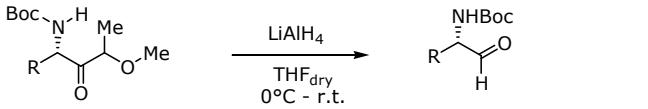
the crude product **193d** (8.54 g, 32.8 mmol, 83%), as a pale yellow oil.

193d

$C_{13}H_{24}N_2O_4$ **M=**272.24

^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 5.02 (1H, br-m, N**H**Boc); 4.70 (1H, br-m, C**H**NHBoc); 3.78 (3H, s, OC**H_3**); 3.19 (3H, s, NC**H_3**); 1.80-1.35 (3H, m, C**H_2**CH(CH_3)$_2$ and C**H**(CH_3)$_2$); 1.43 (9H, s, C(C**H_3**)$_3$); 0.96 (3H, d, *J*=7.0, CH(C**H_3**)$_2$); 0.92 (3H, d, *J*=7.0, CH(C**H'$_3$**)$_2$).

12.9.1.3. *General procedure for the synthesis of (S)-N-(tert-butoxycarbonyl)-amino aldehydes (**194**)*[501]

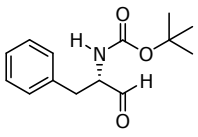


193b: R=CH_2Ph
193c: R=$CH(CH_3)_2$
193d: R=$CH_2CH(CH_3)_2$

194b: R=CH_2Ph
194c: R=$CH(CH_3)_2$
194d: R=$CH_2CH(CH_3)_2$

Weinreb amides **193** was dissolved in anhydrous THF under nitrogen. $LiAlH_4$ (1.25 equiv) was very carefully added at 0° C while development of H_2 was observed. The reaction was followed by TLC to avoid over-reduction, then quenched with a 0.5 M aq. $KHSO_4$ solution at 0° C and diluted with ether. The organic phase was separated from the lithium salts which were extracted again with DEE. The combined organic layers were washed with 3 N aqueous HCl solution, saturated $NaHCO_3$ solution and brine and dried over Na_2SO_4. After evaporation of the solvent, pure aldehyde **194** was obtained and used immediately in the sequent step to avoid racemization.

12.9.1.3.1. **[(*S*)-1-Benzyl-2-oxo-ethyl]carbamic acid *tert*-butyl ester (194b)**[501]



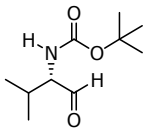
The Weinreb amide **193b** (3.93 g, 12.7 mmol, 1.0 equiv) was dissolved in 45.00 mL of freshly distilled THF and reduced with lithium aluminum hydride according to the general procedure. The aldehyde **194b** was obtained in 78% conversion (2.49 g, 10.0 mmol), as a white solid.

194b

$C_{14}H_{19}NO_3$ **M=**249.19

^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 9.65 (1H, s, C**H**O); 7.48-7.23 (5H, m, C**H** aromatics); 5.10 (1H, br-s, N**H**Boc); 4.45 (1H, m, C**H**NHBoc); 3.14 (2H, m [AB spin system], PhC**H_2**); 1.45 (9H, s, C(C**H_3**)$_3$).

12.9.1.3.2. [(*S*)-1-Formyl-2-methyl-propyl]-carbamic acid *tert*-butyl ester (194c)[501]



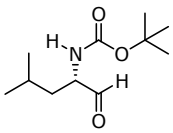
The amide **193c** (4.27 g, 16.4 mmol, 1.0 equiv) was reduced with lithium aluminum hydride (791.0 mg, 20.5 mmol, 1.25 equiv) according to the general procedure. The aldehyde **194c** was obtained in 75% conversion (2.47 g, 12.3 mmol), as a white solid.

194c

$C_9H_{19}NO_3$ **M=**189.19

^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 9.62 (1H, s, C**H**O); 5.12 (1H, br-s, N**H**Boc); 4.31-4.14 (1H, br-m, C**H**NHBoc); 2.26 (1H, m, C**H**$(CH_3)_2$); 1.43 (9H, s, C(C**H$_3$**$)_3$); 1.02 (3H, d, *J*=6.8, CH(C**H$_3$**$)_2$); 0.93 (3H, d, *J*=6.8, CH(C**H$_3$**$)_2$).

12.9.1.3.3. [(*S*)-1-Formyl-3-methyl-butyl]-carbamic acid *tert*-butyl ester (194d)[501]



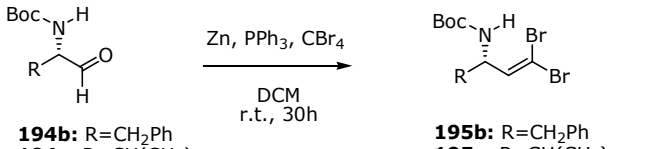
The amide **193d** (2.45 g, 9.0 mmol, 1.0 equiv) was reduced according to the general procedure affording the aldehyde **194d** (1.79 g, 8.3 mmol, 92%) as a white solid.

194d

$C_{11}H_{21}NO_3$ **M=**215.21

^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 9.55 (1H, s, C**H**O); 5.102 (1H, br-d, *J*=5.8, N**H**Boc); 4.19 (1H, br-m, C**H**NHBoc); 1.77-1.22 (3H, m, C**H$_2$**C**H**$(CH_3)_2$); 1.41 (9H, s, C(C**H$_3$**$)_3$); 0.93 (6H, d, *J*=6.8, CH(C**H$_3$**$)_2$).

12.9.1.4. *General procedure for the synthesis of (S)-N-(tert-butoxycarbonyl)-3,3-dibromo-2-propenamines (**195**)[30]*

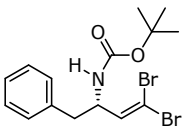


194b: R=CH_2Ph
194c: R=$CH(CH_3)_2$
194d: R=$CH_2CH(CH_3)_2$

195b: R=CH_2Ph
195c: R=$CH(CH_3)_2$
195d: R=$CH_2CH(CH_3)_2$

In a Schlenk tube, under nitrogen, powdered Zn (2.0 equiv), triphenylphosphine (2.0 equiv) and CBr_4 (2.0 equiv) were mixed together, then dissolved in dried DCM and left to react overnight under N_2. Freshly prepared aldehyde **194** (1.0 equiv) was dissolved in CH_2Cl_2 and added to the reagent. After 16h, the mixture was diluted with pentane. The resulting black residue was filtered and the solvent was evaporated. The crude product **195** was then purified by flash column chromatography.

12.9.1.4.1. [(*S*)-1-Benzyl-3,3-dibromo-allyl]carbamic acid *tert*-butyl ester (195b)[501]



The aldehyde **194b** (2.47 g, 9.9 mmol, 1.0 equiv) was reacted following the general procedure giving 6.13 g of a crude mixture. After purification by filtration on silica gel (eluent: CH_2Cl_2), the pure dibromo derivative **195b** (2.93 g, 7.2 mmol, 73%) was obtained as a white solid.

195b

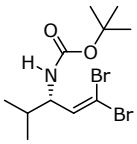
$C_{15}H_{19}NO_2Br_2$ **M=**404.99

m.p.=127-129° C

^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 7.35-7.25 (3H, m [BB' and C part of a AA'BB'C spin system], *meta* and *para* C**H** aromatics); 7.20-7.17 (2H, m [AA' part of a AA'BB'C spin system], *ortho* C**H** aromatics); 6.38 (1H, d, *J*=8.1, C**H**=CBr_2); 4.61-4.43 (2H, m, C**H**N**H**Boc); 2.89 (2H, m [AB spin system], PhC**H_2**); 1.41 (9H, s, C(C**H_3**)$_3$).

$[\alpha]_D^{21}$=+39.5 (c=1.00, $CHCl_3$).[30]

12.9.1.4.2. [(*S*)-3,3-Dibromo-1-isopropyl-allyl]carbamic acid *tert*-butyl ester (195c)[501]



The aldehyde **194c** (2.47 g, 9.9 mmol, 1.0 equiv) was reacted following the general procedure giving 6.13 g of a crude mixture. After purification by filtration on silica gel (eluent: CH_2Cl_2), the pure dibromo derivative **195c** (3.20 g, 8.9 mmol, 73%) was obtained as a white solid.

195c

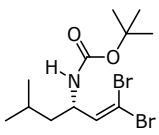
$C_{11}H_{19}NO_2Br_2$ **M=**356.99

m.p.=73-74° C

^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 6.29 (1H, d, *J*=9.2, C**H**=CBr_2); 4.60-4.45 (1H, m, CHN**H**Boc); 4.23-4.01 (1H, m, C**H**NHBoc); 1.95-1.70 (1H, m, C**H**$(CH_3)_2$); 1.44 (9H, s, C(C**H_3**)$_3$); 0.96 (3H, d, *J*=6.8, CH(C**H_3**)$_2$); 0.93 (3H, d, *J*=6.8, CH(C**H_3**)$_2$).

$[\alpha]_D^{24}$=+20.5 (c=0.99, $CHCl_3$).[30]

12.9.1.4.3. [(*S*)-(2,2-Dibromo-vinyl)-3-methyl-butyl]carbamic acid *tert*-butyl ester (195d)[501]



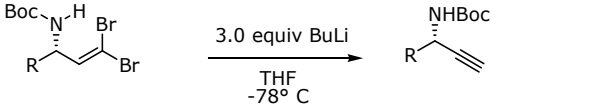
The aldehyde **194d** (1.79 g, 8.3 mmol, 1.0 equiv) was reacted following the general procedure giving 6.13 g of a crude mixture. After purification by filtration on silica gel (eluent: 5:1 petroleum ether/ethyl acetate), the pure dibromo derivative **195d** (2.28 g, 5.8 mmol, 70%) was obtained as a white low melting solid.

195d

$C_{12}H_{21}NO_2Br_2$ **M=**371.01

^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 6.29 (1H, d, *J*=8.4, C**H**=CBr_2); 4.60 (1H, br-s, CHN**H**Boc); 4.50-4.20 (1H, m, C**H**NHBoc); 1.95-1.70 (3H, m, C**H$_2$**C**H**(CH_3)$_2$); 1.44 (9H, s, C(C**H$_3$**)$_3$); 0.96 (3H, d, *J*=6.8, CH(C**H$_3$**)$_2$); 0.93 (3H, d, *J*=6.8, CH(C**H$_3$**)$_2$). **[α]$_D^{24}$**=+22.5 (c=0.98, $CHCl_3$).

12.9.1.5. *General procedure for the synthesis of (S)-N-(tert-butoxycarbonyl)-propargylamines (**191**)[30]*

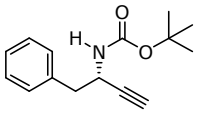


195b: R=CH_2Ph
195c: R=$CH(CH_3)_2$
195d: R=$CH_2CH(CH_3)_2$

191b: R=CH_2Ph
191c: R=$CH(CH_3)_2$
191d: R=$CH_2CH(CH_3)_2$

A Schlenk tube equipped with a magnetic stirring bar was dried under a flow of nitrogen. Then the dibromo-vinyl **195** was dissolved in freshly distilled THF (0.5 M) and cooled at –78° C. *n*-BuLi (3.0 equiv) was added and the reaction was stirred for 1h and then warmed to room temperature and checked by TLC. When the starting aldehyde had disappeared, it was cooled again at –78° C and hydrolyzed with a 0.01 M aq. NaOH solution, then it was extracted with ether. The organic phase was washed with brine twice and dried over Na_2SO_4. The solvent was evaporated and the obtained crude product **191** was purified by flash chromatography.

12.9.1.5.1. [(*S*)-1-Benzyl-prop-2-ynyl]-carbamic acid *tert*-butyl ester (191b)[501]

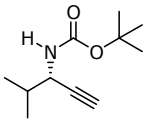


The product **195b** (2.64 g, 6.5 mmol, 1.0 equiv) was reacted following the general procedure. After work up 1.67 g of crude product were obtained, which were purified by flash chromatography on Florisil (eluent: 3:1 petroleum ether/ethyl acetate) giving the pure **191b** (1.40 g, 5.7 mmol, 88%) as a pale yellow solid.

191b
$C_{15}H_{19}NO_2$ **M=**245.19
m.p.=84°-87° C
^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 7.33-7.25 (5H, m, C**H** aromatics); 4.75-4.60 (2H, m, C**H**NHBoc and CHN**H**Boc); 2.96 (2H, m [AB spin system], C**H$_2$**Ph); 2.51 (1H, d, *J*=1.0, C≡C**H**); 1.42 (9H, s, C(C**H$_3$**)$_3$).
^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 154.5 (N**C**(O)OC(CH_3)$_3$); 136.3-126.9 (6C, **C$_q$** and **C**H aromatics); 82.8 (**C**≡CH); 80.4 (**C**(CH_3)$_3$); 72.1 (C≡**C**H); 42.8 (**C**HNH); 41.7 (**C**H_2Ph); 28.3 (C(**C**H_3)$_3$).

MS (EI) *m/z*(%)**:** 189 (8, M^+ – $C(CH_3)_3$); 154 (9); 129 (5); 128 (31); 91 (35, $C_7H_7^+$); 65 (11); 59 (23); 57 (100, $^tBu^+$).
[α]$_D^{20}$=-8.90 (c=1.21, $CHCl_3$).[30]

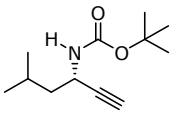
12.9.1.5.2. [(*S*)-1-Isopropyl-prop-2-ynyl]-carbamic acid *tert*-butyl ester (191c)[501]



The product **195c** (3.00 g, 8.4 mmol, 1.0 equiv) was reacted according to the general procedure, affording, after purification by flash chromatography (silica, eluent: 2:1 petroleum ether/ethyl acetate) 1.36 g (1.40 g, 6.9 mmol, 83%) of the pure propargylamine **191c** as a white solid.

191c
$C_{11}H_{19}NO_2$ **M=**197.19
m.p.=60°-61° C
^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 4.73 (1H, br-s, N**H**Boc); 4.38-4.22 (1H, m, C**H**NHBoc); 2.51 (1H, d, *J*=1.0, C≡C**H**); 2.25 (1H, d, *J*=2.6, C**H**$(CH_3)_2$); 1.45 (9H, s, C(C**H$_3$**)$_3$); 0.98 (6H, d, *J*=6.6, CH(C**H$_3$**)$_2$).
^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 154.8 (N**C**(O)OC$(CH_3)_3$); 81.9 (**C**≡CH); 79.6 (**C**$(CH_3)_3$); 71.6 (C≡**C**H); 48.4 (**C**HNHBoc); 32.8 (**C**H$(CH_3)_2$); 28.2 (3C, C(**C**$H_3)_3$); 18.5 (CH(**C**$H_3)_2$); 17.4 (CH(**C**$H_3)_2$).
MS (EI) *m/z*(%)**:** 154 (2, M^+ – $CH(CH_3)_2$); 141 (2); 130 (12); 116 (44, $NHBoc^+$); 97 (12); 72 (36); 71 (13); 69 (19); 57 (100, $^tBu^+$).
[α]$_D^{20}$=-48.70 (c=1.04, $CHCl_3$).[30]

12.9.1.5.3. [(*S*)-1-Ethynyl-3-methyl-butyl]-carbamic acid *tert*-butyl ester (191d)[501]

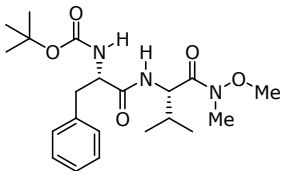


The product **195d** (1.65 g, 4.5 mmol, 1.0 equiv) was reacted according to the general procedure. After work up 3.20 g of crude product were obtained. The purification by flash chromatography (silica, eluent: 5:1 petroleum ether/ethyl acetate) gave 2.28 g (5.8 mmol, 70%) of the pure propargylamine **195d** as a white low melting solid.

195d
$C_{12}H_{21}NO_2$ **M=**211.19
^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 4.70 (1H, br-s, N**H**Boc); 4.40-4.20 (1H, m, C**H**NHBoc); 2.25 (1H, d, *J*=2.2, C≡C**H**); 1.85-1.25 (3H, m, C**H$_2$**$CH(CH_3)_2$ and CH_2C**H**$(CH_3)_2$); 1.45 (9H, s, C(C**H$_3$**)$_3$); 0.93 (6H, d, *J*=6.0, CH(C**H$_3$**)$_2$).
^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 154.7 (N**C**(O)OC$(CH_3)_3$); 83.8 (**C**≡CH); 77.6 (**C**$(CH_3)_3$); 70.7 (C≡**C**H); 45.1 (**C**HNHBoc); 41.2 (**C**H$(CH_3)_2$); 28.2 (3C, C(**C**$H_3)_3$); 24.8 (**C**$H_2CH(CH_3)_2$); 22.6 (CH(**C**$H_3)_2$); 21.3 (CH(**C**$H_3)_2$).

MS (EI) *m/z*(%)**:** 155 (2, $M^+ - CH_2CH(CH_3)_2$); 57 (100, $^tBu^+$).
$[\alpha]_D^{20}$=-43.20 (c=1.04, $CHCl_3$).[502]

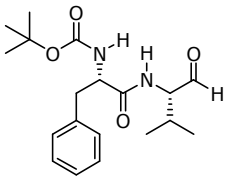
12.9.1.6. {(S)-1[(S)-(Methoxy-methyl-carbamoyl)-2-methyl-propyl-carbamoyl]-2-phenyl-ethyl}-carbamic acid *tert*-butyl ester (198)[30]



The Weinreb amide **197** (3.68 g, 14.1 mmol, 1.0 equiv) in DCM (40.00 mL) was treated with an excess of trifluoroacetic acid (17.50 mL) and triethylsilane (5.60 mL, 35.2 mmol, 2.5 equiv). The reaction was stirred until completion (1.5h). Then the solvent was evaporated and the residue **197** (5.90 g) was used in the next step without purification. In a round bottomed flask a solution of **197** (5.90, 15.0 mmol, 1.15 equiv) in 65.00 mL of DCM was cooled at 0° C and reacted with *N*-(*tert*-butoxycarbonyl)-(L)-phenylalanine **192b** (3.39 g, 13.0 mmol, 1.0 equiv), together with DIPA (6.50 mL, 37.5 mmol, 2.88 equiv) and DEPC (1.95 mL, 12.8 mmol, 1.0 equiv). The reaction mixture was stirred at room temperature overnight, then it was diluted with ethyl acetate (50.00 mL), washed with a saturated aq. NH_4Cl solution, brine and dried over Na_2SO_4. The solvent was evaporated to afford 5.30 g of crude product which were purified by flash chromatography on silica gel (eluent: 1:1 petroleum ether/ethyl acetate) to obtain the pure product **198** (4.01 g, 9.8 mmol, 77%).

198
$C_{21}H_{33}N_3O_5$ **M=**407.33
m.p.=39-42° C
^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 7.38-7.22 (5H, m, C**H** aromatics); 6.54 (1H, br-s, *J*=8.4, N**H**); 5.04 (1H, br-d, *J*=7.8, CHN**H**Boc); 4.94-4.85 (1H, m, C**H**NHBoc); 4.54-4.34 (1H, m, C**H**$CH(CH_3)_2$); 3.82 (3H, s, OC**H_3**); 3.23 (3H, s, NC**H_3**); 3.16-3.05 (2H, m [AB spin system], C**H_2**Ph); 2.02-1.91 (1H, m, C**H**$(CH_3)_2$); 1.42 (9H, s, C(C**H_3**)$_3$); 0.90 (3H, d, *J*=6.8, CH(C**H_3**)$_2$); 0.79 (3H, d, *J*=6.8, CH(C**H_3**)$_2$).
^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 171.9 (**C**ON); 171.2 (**C**ON); 155.0 (NH**C**OOC$(CH_3)_3$); 136.6 (**C_{ipso}** aromatic); 129.1 (2C, **C**H *meta* aromatics); 128.5 (2C, **C**H *ortho* aromatics); 126.7 (**C**H *para* aromatic); 79.8 (**C**$(CH_3)_3$); 61.4 (**C**H$CH(CH_3)_2$); 55.7 (**C**HNHBoc); 53.4 (O**C**H_3); 38.6 (**C**H_2Ph); 31.7 (N**C**H_3); 31.1 (**C**H$(CH_3)_2$); 28.1 (3C, C(**C**H_3)$_3$); 19.1 (CH(**C**H_3)$_2$); 17.5 (CH(**C**H_3)$_2$).
MS (EI) *m/z*(%)**:** 408 (2, MH^+); 347 (7); 291 (15, M^+ – NHBoc); 164 (15, $PhCH_2CHNHCOOH^+$); 127 (6); 120 (39, $PhCH_2CHNH_2^+$); 91 (9, $C_7H_7^+$); 72 (100); 57 (91, $^tBu^+$); 55 (11).
$[\alpha]_D^{19}$=–9.06 (c=1.06, $CHCl_3$).

12.9.1.7. [(*S*)-1-((*S*)-(1-Formyl-2-methyl-propylcarbamoyl]-2-phenyl-ethyl]-carbamic acid *tert*-butyl ester (199)[30]



In a Schlenk tube, under nitrogen, the product **198** (0.88 g, 2.2 mmol, 1.0 equiv) was dissolved in freshly distilled THF (6.00 mL) and at 0° C $LiAlH_4$ (115.00 mg, 3.0 mmol, 1.25 equiv) was added carefully portionwise. After 2h, the reaction was quenched by adding a 0.5 M aq. $KHSO_4$ solution at 0° C and DEE. The organic phase was separated from the lithium salts which were extracted again with DEE. The collected organic layers were washed with 3 N aq. HCl solution, saturated $NaHCO_3$ solution and brine. After anhydrification over sodium sulfate and evaporation of the solvent crude product **199** (0.63 g, 1.8 mmol, 81%) was recovered as a white solid that was immediately used in the next step.

199

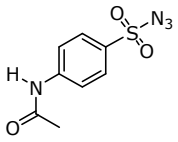
$C_{19}H_{28}N_2O_4$ **M=**348.28

^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 9.55 (1H, s, C**H**O); 7.36-7.16 (5H, m, C**H** aromatics); 6.56-6.38 (1H, br-m, N**H**); 5.08-4.92 (1H, br-m, CHN**H**Boc); 4.54-4.32 (2H, m, C**H**NHBoc and C**H**NH); 3.12-3.01 (2H, m [AB spin system], C**H_2**Ph); 2.32-2.10 (1H, m, C**H**$(CH_3)_2$); 1.41 (9H, s, C(C**H_3**$)_3$); 0.86 (3H, d, *J*=7.0, CH(C**H_3**$)_2$); 0.82 (3H, d, *J*=7.0, CH(C**H_3**$)_2$).

^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 199.4 (C**H**O); 171.7 (**C**ONH); 155.4 (NH**C**OOC$(CH_3)_3$); 136.5 (**C_{ipso}** aromatic); 129.2 (2C, **C**H *meta* aromatics); 128.7 (2C, **C**H *ortho* aromatics); 127.0 (**C**H *para* aromatic); 80.4 (**C**$(CH_3)_3$); 63.2 (**C**HCHO); 55.8 (**C**HNHBoc); 38.2 (**C**H_2Ph); 28.7 (**C**H$(CH_3)_2$); 28.1 (3C, C(**C**$H_3$$)_3$); 18.8 (CH(**C**$H_3$$)_2$); 17.4 (CH(**C**$H_3$$)_2$).

MS (EI) *m/z*(%)**:** 348 (4, M^+); 319 (4, M^+ – CHO); 292 (17); 275 (23, M^+ – OC$(CH_3)_3$); 264 (18); 248 (15); 203 (24); 202 (28); 164 (100 $PhCH_2CHNHCOOH^+$); 157 (19); 146 (16); 131 (24); 128 (23); 121 (68); 120 (92, $PhCH_2CHNH_2^+$); 103 (17); 91 (23, $C_7H_7^+$); 77 (9, $C_6H_5^+$); 72 (78); 65 (2); 57 (86, $^tBu^+$); 55 (11).

12.9.1.8. 4-Acetylamino-benzensulfonyl-azide (202)



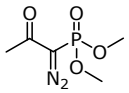
In a round bottomed flask NaN_3 (3.30 g, 51.2 mmol, 1.2 equiv) was added to a 0.5 M solution of 4-acetylamino benzenesulfonyl-chloride (10.00 g, 42.7 mmol, 1.0 equiv) in acetone and stirred at room temperature overnight. The mixture was, then, poured into 400.00 mL of water, where the azide **202** was precipitated. After 2h by stirring, the white solid was purified by recrystallization from toluene (80° C). Compound **202** was obtained as a white solid (6.06 g, 26.9 mmol, 59%).

202

$C_8H_7N_3O_3S$ **M=**225.07

^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 7.92-7.90 (2H, m [AA' part of a AA'BB spin system], C**H** *ortho* aromatics SO_2N_3); 7.88-7.86 (2H, m [BB' part of a AA'BB spin system], C**H** *meta* aromatics SO_2N_3); 2.02 (3H, s, COC**H_3**).

12.9.1.9. (1-Diazo-2-oxo-propyl)-phophonic acid dimethyl ester (200)[503]



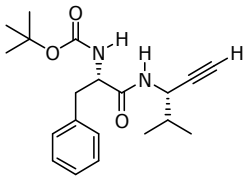
In a two-necked round bottomed flask a 60% NaH dispersion in mineral oils (478.00 mg, 11.9 mmol, 1.0 equiv) was washed by pentane and dried under nitrogen and then suspended in anhydrous toluene (26.00 mL) and THF (4.00 mL). A 1 M solution of 1.89 g (11.4 mmol, 1.0 equiv) of 2-oxopropyl phosphonate **201** in toluene was added dropwise at 0° C. After 1h 4-acetylamino-benzenesulfonyl azide **202** (3.00 g, 12.5 mmol, 1.1 equiv) was added and the resulting reaction mixture was stirred at room temperature for one night. After filtration through celite pad, the salts were washed thoroughly with toluene. The organic filtrate was concentrated under reduce pressure and the product **200** (2.22 g, 8.9 mmol) was obtained in good yield (90%) as a yellow oil.

200

$C_4H_9N_2P$ **M=**116.09

^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 3.83 (6H, d, $^3J_{H\text{-}P}$=12.2, P(OC**H_3**)$_2$); 2.56 (3H, s, CH_3).

12.9.1.10. [(*S*)-1-((*S*)-(1-isopropyl-prop-2-ynylcarbamoyl]-2-phenyl-ethyl]-carbamic acid *tert*-butyl ester (196)[30]



In a Schlenk tube, under nitrogen, dipeptide aldehyde **199** (0.61 g, 1.8 mmol, 1.0 equiv) was dissolved in MeOH (12.00 mL), cooled at 0° C and treated with **200** (0.54 mg, 2.8 mmol, 1.56 equiv) together with K_2CO_3 (0.49 g, 3.5 mmol, 1.9 equiv). After 1h, the reaction was left to warm to room temperature and stirred until completion. After usual work up and purification pure product **196** (396.00 mg, 1.0 mmol, 65%) was obtained as a white solid.

196

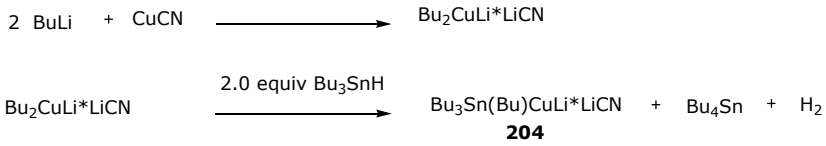
$C_{22}H_{28}N_2O_3$ **M=**368.28

m.p.=125-128

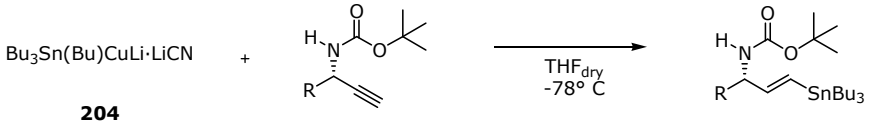
^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 7.34-7.19 (5H, m, C**H** aromatics); 6.08 (1H, br-d, *J*=8.4, N**H**); 5.05-4.85 (1H, br-m, CHN**H**Boc); 4.64-4.56 (1H, m, C**H**NHBoc); 4.36-4.26 (1H, m, C**H**NH); 3.10-3.04 (2H, m [AB spin system], C**H_2**Ph); 2.20 (1H,

d, *J*=2.2, C≡C**H**); 1.86-1.66 (1H, m, C**H**$(CH_3)_2$); 1.41 (9H, s, C(C**H$_3$**)$_3$); 0.89 (3H, d, *J*=6.5, CH(C**H$_3$**)$_2$); 0.80 (3H, d, *J*=6.5, CH(C**H$_3$**)$_2$).
^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 170.4 (**C**ONH); 155.3 (NH**C**OOC$(CH_3)_3$); 136.5 (**C*$_{ipso}$*** aromatic); 129.2 (2C, **C**H *meta* aromatics); 128.5 (2C, **C**H *ortho* aromatics); 126.8 (**C**H *para* aromatic); 81.1 (**C**≡CH); 80.9 (**C**$(CH_3)_3$); 71.9 (C≡**C**H); 55.7 (**C**HNHBoc); 46.9 (**C**HC≡CH); 38.3 (**C**H_2Ph); 32.3 (**C**H$(CH_3)_2$); 28.1 (3C, C(**C**$H_3)_3$); 18.5 (CH(**C**$H_3)_2$); 17.1 (CH(**C**$H_3)_2$).
[α]$_D^{18}$=+0.96 (c=1.08, $CHCl_3$).

12.9.1.11. *General procedure for the synthesis of γ-stannylamines*[30]



In a Schlenk tube, under nitrogen, CuCN (1.0 equiv) was suspended in anhydrous THF, cooled at –78° C and treated with *n*-BuLi (1.6 M solution in hexanes, 2.0 equiv). The resulting reaction mixture was stirred for 30', until copper cyanide was completely dissolved. Then, *n*-Bu_3SnH (2.0 equiv) was added dropwise and hydrogen evolution occurred. After other 20', the formation of bright-yellow-orange solution meant the reaction mixture with **204** was ready to react with the propargylaminic substrate **191** or **196**.

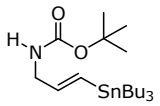


191b: R=CH_2Ph
191c: R=$CH(CH_3)_2$
191d: R=$CH_2CH(CH_3)_2$
196

1b: R=CH_2Ph
1c: R=$CH(CH_3)_2$
1d: R=$CH_2CH(CH_3)_2$
203

A solution of the alkyne **191** or **196** (1.0 equiv) in freshly distilled THF was added into stannylcuprate **204** at –78° C and allowed to react to completion. The reaction progress was monitored by TLC. After total conversion of the substrate, the reaction mixture was hydrolyzed with NH_4Cl / NH_4OH buffer solution at low temperature and extracted with DEE. The combined organic layers were washed with brine and dried over sodium sulfate. After evaporation of the solvent, the obtained crude product **1**, or **203**, was purified by flash column chromatography.

12.9.1.11.1. [(*E*)-3-Tributylstannyl-allyl]-carbamic acid *tert*-butyl ester (1a)[30]



The stannylcuprate **1a** was prepared according to the general procedure reported above from CuCN (865.00 mg, 9.7 mmol, 1.1 equiv), BuLi (12.00 mL, 19.3 mmol, 2.1 equiv), *n*-Bu_3SnH (2.43 mL, 18.0 mmol, 2.0 equiv), and 20.00 mL of anhydrous THF. Then the product **204** was converted into vinylstannane **1a** (3.21 g, 7.2 mmol, 80%) with 1.40 g (9.0 mmol, 1.0 equiv) of propargylamine **191a** and purified (silica, eluent: from 10:1 to 5:1 petroleum ether/ethyl acetate).

1a

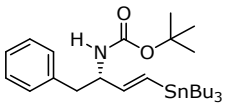
$C_{20}H_{41}NO_2Sn$ **M=**445.41

^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 6.04-6.15 (1H, m, C**H**=CHSnBu_3); 5.86-6.00 (1H, m, CH=C**H**SnBu_3); 4.59 (1H, br-s, N**H**Boc); 3.80-3.75 (2H, br-s, C**H_2**NHBoc); 1.55-1.20 (12H, m, Sn(CH_2C**H_2**C**H_2**CH_3)$_3$); 1.44 (9H, s, C(C**H_3**)$_3$); 0.97-0.82 (15H, m, Sn(C**H_2**CH_2CH_2C**H_3**)$_3$).

^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 155.5 (**C**OOC(CH_3)$_3$); 144.2 (CH_2**C**H=CH); 128.4 (CH_2CH=**C**H); 78.8 (COO**C**(CH_3)$_3$); 45.8 (NH(Boc)**C**H_2CH=CH); 28.9 (3C, Sn(CH_2**C**$H_2CH_2CH_3$)$_3$); 28.2 (3C, COOC(**C**H_3)$_3$); 27.1 (3C, Sn(CH_2CH_2**C**H_2CH_3)$_3$); 13.5 (3C, Sn($CH_2CH_2CH_2$**C**H_3)$_3$); 9.2 (3C, Sn(**C**$H_2CH_2CH_2CH_3$)$_3$).

MS (EI) *m/z*(%)**:** 404 (36); 348 (68); 330 (13); 292 (50); 177; (53); 162 (19); 135 (30); 119 (57); 114 (47); 70 (48); 69 (58); 59 (93); 57 (100, ^{t}Bu$^+$).

12.9.1.11.2. [(*E*)-(*S*)-Benzyl-3-tributylstannyl-allyl]-carbamic acid *tert*-butyl ester (1b)[30]



The general procedure was followed for the synthesis of the vinylstannane **1b**, using CuCN (332.60 mg, 3.7 mmol, 1.1 equiv), BuLi (4.25 mL, 6.8 mmol, 2.0 equiv), *n*-Bu_3SnH (1.83 mL, 6.8 mmol, 2.0 equiv), propargylamine **191b** (0.78 g, 3.4 mmol, 1.0 equiv) and 7.00 mL of anhydrous THF. After purification by flash chromatography (silica, eluent: from 10:1 to 5:1 petroleum ether/ethyl acetate), 1.45 g of the product **1b** were obtained (2.7 mmol, 80%), as a colourless oil.

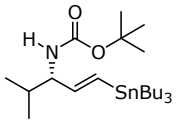
1b

$C_{27}H_{47}NO_2Sn$ **M=**535.47

^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 7.32-7.15 (5H, m, C**H** aromatics); 6.01 (1H, m [A part of a ABX spin system], J_{AB}=19.0, CH=C**H**SnBu_3); 5.89 (1H, m [B part of a ABX spin system], J_{BA}=19.0, J_{BX}=3.4, C**H**=CHSnBu_3); 4.58-4.32 (2H, m [X part of a ABX spin system], C**H**NHBoc, CHN**H**Boc); 2.84 (2H, m [AB spin system], C**H_2**Ph); 1.54-1.18 (12H, m, Sn(CH_2C**H_2**C**H_2**CH_3)$_3$); 1.41 (9H, s, C(C**H_3**)$_3$); 0.92-0.81 (15H, m, Sn(C**H_2**CH_2CH_2C**H_3**)$_3$).

$[\alpha]_D^{20}$=–5.60 (c=1.00, $CHCl_3$).[30]

12.9.1.11.3. [(*E*)-(*S*)-(1-Isopropyl-3-tributylstannyl-allyl]-carbamic acid *tert*-butyl ester (1c)[30]



The product **191c** (1.70 g, 8.6 mmol, 1.0 equiv) was reacted with **204** for 30' following the general procedure giving 4.60 g of crude product. Purification by flash chromatography (silica, eluent: from 10:1 to 5:1 petroleum ether/ethyl acetate) afforded 1.93 g (4.2 mmol, 74%) of **1c** as a colourless oil.

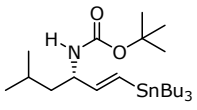
1c

$C_{23}H_{47}NO_2Sn$ **M=**487.47

^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 6.03 (1H, m [A part of a ABX spin system], J_{AB}=19.0, CH=C**H**$SnBu_3$); 5.83 (1H, m [B part of a ABX spin system], J_{BA}=19.0, J_{BX}=4.7, C**H**=CH$SnBu_3$); 4.48 (1H, br-s, N**H**Boc); 4.10-3.92 (1H, m C**H**NHBoc); 1.88-1.68 (1H, m, C**H**$(CH_3)_2$); 1.55-1.20 (12H, m, $Sn(CH_2C\mathbf{H_2}C\mathbf{H_2}CH_3)_3$); 1.44 (9H, s, $C(C\mathbf{H_3})_3$); 1.02-0.68 (21H, m, $Sn(C\mathbf{H_2}CH_2CH_2C\mathbf{H_3})_3$ and $CH(C\mathbf{H_3})_2$).

$[\alpha]_D^{22}$=–17.60 (c=1.11, $CHCl_3$).[30]

12.9.1.11.4. [(S)-3-Methyl-1-(*E*)-2-tributylstannyl-vinyl)-butyl]-carbamic acid *tert*-butyl ester (1d)[30]



The product **191d** (679.00 mg, 3.0 mmol, 1.0 equiv) was reacted with **204** for 30' following the general procedure. The pure product **1d** (192.00 mg, 1.8 mmol, 61%) was obtained after work up and purification by chromatography (silica, eluent: from 10:1 to 5:1 petroleum ether/ethyl acetate) as a colourless oil.

1d

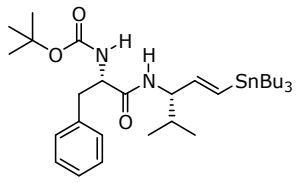
$C_{24}H_{47}NO_2Sn$ **M=**499.47

^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 6.04 (1H, m [A part of a ABX spin system], J_{AB}=19.1, CH=C**H**$SnBu_3$); 5.81 (1H, m [B part of a ABX spin system], J_{BA}=19.1, J_{BX}=4.7, C**H**=CH$SnBu_3$); 4.36 (1H, br-s, N**H**Boc); 4.20-4.05 (1H, m, C**H**NHBoc); 1.69-1.20 (15H, m, $C\mathbf{H_2}C\mathbf{H}(CH_3)_2$ and $Sn(CH_2C\mathbf{H_2}C\mathbf{H_2}CH_3)_3$); 1.43 (9H, s, $C(C\mathbf{H_3})_3$); 0.93-0.87 (21H, m, $Sn(C\mathbf{H_2}CH_2CH_2C\mathbf{H_3})_3$ and $CH(C\mathbf{H_3})_2$).

$[\alpha]_D^{20}$=–16.04 (c=1.105, $CHCl_3$).[30]

12.9.1.11.5. [(S)-1-[(*E*)-(S)-1-Isopropyl-3-tributylstannyl-allylcarbamoyl)-2-phenyl-ethyl]-carbamic acid *tert*-butyl ester (203)

Stannylcuprate **204** was prepared as reported and was reacted with 199.00 mg (0.6 mmol, 1.0 equiv) of **196**. Usual work-up afforded 850.00 mg of crude



product which, after purification (flash chromatography on silica, eluent: 6:1 petroleum ether/ethyl acetate), gave 228.00 mg (0.4 mmol, 60%) of **203** as a pale yellow oil.

203

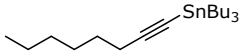
$C_{36}H_{56}N_2O_2Sn$ M=666.47

^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 7.30-7.17 (5H, C**H** aromatics); 5.93 (1H, d, *J*=19.2, CH=C**H**$SnBu_3$); 5.84-5.66 (2H, m, C**H**=CH$SnBu_3$); 5.10-4.90 (1H, br-m, CHN**H**); 4.41-4.22 (2H, br-s, N**H**Boc and C**H**NHBoc); 3.14-3.00 (2H, m, C**H_2**Ph); 1.74-1.20 (13H, m, C**H**$(CH_3)_2$ and $Sn(CH_2C\mathbf{H_2}C\mathbf{H_2}CH_3)_3$); 1.42 (9H, s, $C(C\mathbf{H_3})_3$); 1.00-0.62 (21H, m, $Sn(C\mathbf{H_2}CH_2CH_2C\mathbf{H_3})_3$ and $CH(C\mathbf{H_3})_2$).

^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 170.3 (**C**ONH); 155.3 (NH**C**$OOC(CH_3)_3$); 145.4 (**C**H=CHSn); 136.7 (**C_{ipso}** aromatic); 129.2 (2C, **C**H *meta* aromatics); 128.6 (2C, **C**H *ortho* aromatics); 128.4 (CH=**C**HSn); 126.8 (**C**H *para* aromatic); 80.0 (COO**C**$(CH_3)_3$); 58.6 (**C**HCH$(CH_3)_2$); 56.2 (**C**HNHBoc); 38.2 (**C**H_2Ph); 31.8 (**C**H$(CH_3)_2$); 28.9 (3C, $Sn(CH_2\mathbf{C}H_2CH_2CH_3)_3$); 28.1 (3C, $COOC(\mathbf{C}H_3)_3$); 27.1 (3C, $Sn(CH_2CH_2\mathbf{C}H_2CH_3)_3$); 18.3 ($CH(\mathbf{C}H_3)_2$); 17.5 ($CH(\mathbf{C}H_3)_2$); 13.5 (3C, $Sn(CH_2CH_2CH_2\mathbf{C}H_3)_3$); 9.3 (3C, $Sn(\mathbf{C}H_2CH_2CH_2CH_3)_3$).

MS (EI) *m/z*(%)**:** 580 (4,); 506 (28); 505 (100); 504 (66); 503 (88); 502 (39); 501 (51); 479 (34); 179 (18, $SnBu^+$); 177; (40); 17 (27); 174 (24); 164 (11, $PhCH_2CHNHCOOH^+$); 120 (88, $PhCH_2CHNH_2^+$); 92 (42); 91 (74, $C_7H_7^+$); 86 (28); 84 (26); 77 (9, $C_6H_5^+$); 65 (8); 59 (50); 58 (27); 57 (66, $^tBu^+$).

12.9.1.11.6. Tributyl(hexylethynyl)tin (186)



In a Schlenk tube, under nitrogen, 4.00 mL of BuLi (1.6 M solution in hexanes, 6.40 mL, 6.10 mmol, 1.0 equiv) were added dropwise to a precooled (–78° C) solution of 1-octine (0.90 mL, 6.10 mmol, 1.0 equiv) in 5.00 mL of anhydrous THF,. After 30' 1.50 mL (5.5 mmol, 1.1 equiv) of tributyl-tin-chloride were introduced and the resulting reaction mixture was stirred for 1h at room temperature, then partitioned between a 1 M aqueous NaOH solution and ether. The two phases were separated: the aqueous portion was extracted with ether (3 x 5.00 mL), while the combined organic layers were washed with water (2 x 5.00 mL) and brine (1 x 10.00 mL), dried (Na_2SO_4), filtered and concentrated. The residue was purified by flash column chromatography (silica, eluent: 50:1 petroleum ether/ethyl acetate) to give 2.14 g (5.5 mmol, 90%) of the pure stannane **186**.

186

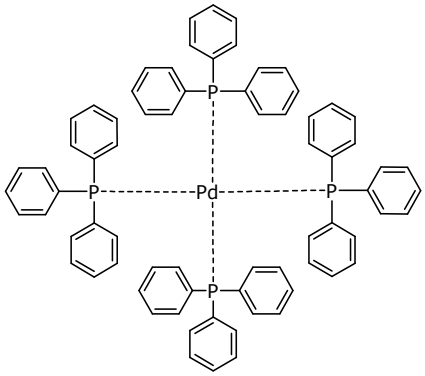
$C_{20}H_{40}Sn$ M=400.22

^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 2.24 (2H, t, *J*=6.8, C≡CC**H_2**$(CH_2)_4CH_3$); 1.75-1.20 (26H, m, $C{\equiv}CCH_2(C\mathbf{H_2})_4CH_3$ and $Sn(C\mathbf{H_2}C\mathbf{H_2}C\mathbf{H_2}CH_3)_3$); 1.00-0.75 (12, m, $C{\equiv}CCH_2(CH_2)_4C\mathbf{H_3}$ and $Sn(CH_2CH_2CH_2C\mathbf{H_3})_3$).

^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 111.9 (C≡**C**CH_2); 81,1 (**C**≡CCH_2); 31.4 ($C(CH_2)_3$**C**$H_2CH_2CH_3$); 29.1 (CCH_2**C**$H_2(CH_2)_3CH_3$); 29.0 (3C, $Sn(CH_2$**C**$H_2CH_2CH_3)_3$); 28.4 ($C(CH_2)_2$**C**$H_2(CH_2)_2CH_3$); 27.0 (3C, $Sn(CH_2CH_2$**C**$H_2CH_3)_3$); 22.6 (C**C**$H_2(CH_2)_4CH_3$); 20.2 ($C(CH_2)_4$**C**H_2CH_3); 14.0 ($C(CH_2)_5$**C**H_3); 13.7 (3C, $Sn(CH_2CH_2CH_2$**C**$H_3)_3$); 11.0 (3C, Sn(**C**$H_2CH_2CH_2CH_3)_3$).
MS (EI) *m/z*(%)**:** 343 (100, $M^+ - C_4H_9$); 287 (47, $M^+ - 2C_4H_9$); 229 (50, $M^+ - 3C_4H_9$); 175 (17); 121 (35); 107 (26); 67 (41); 57 (44, $C_4H_9^+$); 55 (31).

12.9.2. Still Coupling Reaction

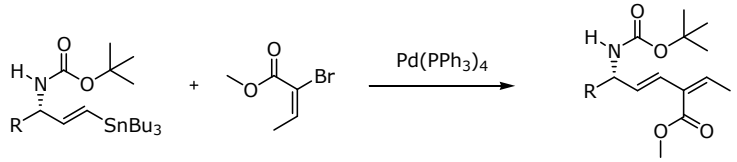
12.9.2.1. Tetrakis(triphenylphosphine)-palladium(0) (324)[504]



A mixture of 246.00 mg (1.4 mmol, 1.0 equiv) of palladium dichloride, 1.85 g (7.0 mmol, 5.0 equiv) of triphenylphosphine and 17.00 mL of dimethyl sulfoxyde were placed in a Schlenk tube equipped with a magnetic stirring bar and under nitrogen. The yellowish mixture was heated with an oil bath until solubilization (140° C). The bath was then removed and the solution vigorously stirred for approximately 15'. Hydrazine hydrate (0.28 mL, 4.0 equiv) was added and a vigorous reaction took place with evolution of nitrogen. The dark mixture was immediately cooled with an ice-bath; crystallization began to occur at 125° C. At this point the mixture was allowed to cool at room temperature and, then, it was filtered under nitrogen atmosphere. The solid was washed twice with ethanol (10.00 mL) and ether (10.00 mL). The product was kept under a slow steam of nitrogen overnight. The resulting yellow crystalline product **321** (1.49 g, 1.3 mmol, 93%) was stored into a Schlenk tube under nitrogen atmosphere.

324
$C_{72}H_{60}P_4Pd$ **M=**1155.02

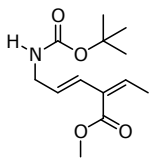
12.9.2.2. *General procedure for the Stille Coupling with vinylbromides*



1a-d **203** **2a** **3a-d** **207**

In a Schlenk tube, a catalytic amount of freshly prepared $Pd(Ph_3)_4$ **324** (0.01 equiv) was stirred for 15' under vacuum. Then it was dissolved in anhydrous DMF (or toluene) (0.5 M) under nitrogen atmosphere and the resulting solution was left to react for 1h with the electrophile **2a** (1.8 equiv). The nucleophile **1** (or **203**) (1.0 equiv) was then added and the reaction mixture was heated at 80° C for 16h. The solvent was evaporated and the residue was diluted in ether, and left under stirring with a 1 M aq. NaOH solution for 1h. After separating the two phases, the organic layer was washed with water and brine, the combined aqueous portions were extracted with EtOAc and the all organic components were combined, washed with brine, dried and concentrated. Purification of the crude product **3** (or **207**) was performed by flash column chromatography.

12.9.2.2.1. Synthesis of **(*E*)-5-*tert*-butoxycarbonylamino-2-eth-(*Z*)-ylidene-pent-3-enoic acid methyl ester (3a)** in DMF



Following the general procedure, the unsaturated δ-aminoester **3a** (30.00 mg, 0.12 mmol, 55%) was obtained from $Pd(PPh_3)_4$ **324** (13.00 mg, 0.01 mmol, 1.05 equiv), 2-bromo-but-2-enoic acid methyl ester **2a** (0.05 mL, 0.39 mmol, 1.8 equiv), the nucleophile **1a** (0.10 g, 0.22 mmol, 1.0 equiv) and 1.20 mL of anhydrous DMF, after purification by chromatography (silica, eluent: 5:1 petroleum ether/ethyl acetate).

3a

$C_{13}H_{21}NO_4$ **M=**255.21

^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 6.82 (1H, q, *J*=7.3, C=C**H**CH_3); 6.30-6.20 (1H, m [A part of a ABX_2 spin system], J_{AB}=16.4, CH_2CH=C**H**); 6.12-5.98 (1H, m [B part of a ABX_2 spin system], J_{BA}=16.4, J_{BX2}=5.9, CH_2C**H**=CH); 4.63 (1H, m, N**H**Boc); 3.88-3.80 (2H, m [X part of a ABX_2 spin system], BocNHC**H_2**CH=CH); 3.74 (3H, s, OC**H_3**); 1.85 (3H, d, *J*=7.3, CHC**H_3**); 1.42 (9H, s, C(C**H_3**)$_3$).

^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 166.7 (**C**$OOCH_3$); 155.7 (**C**$OOC(CH_3)_3$); 138.1 (CH_2**C**H=CH olefinic); 132.2 (CH_2CH=**C**H olefinic); 128.9 (CH_3CH=**C_q** olefinic); 122.5 (CH_3**C**H=C olefinic); 79.9 (**C**$(CH_3)_3$); 51.9 (O**C**H_3); 42.5 (**C**H_2NHBoc); 28.2 (C(**C**$H_3)_3$); 14.6 (**C**H_3CH=C).

MS (EI) *m/z*(%)**:** 199 (29, M^+ – ^{t}Bu); 167 (73, M^+ – ^{t}Bu – OMe); 155 (48, M^+ – NHBoc – OCH_3); 57 (100, $C(CH_3)_3^+$).

12.9.2.2.2. Synthesis of **(*E*)-5-*tert*-butoxycarbonylamino-2-eth-(*Z*)-ylidene-pent-3-enoic acid methyl ester (3a)** in toluene

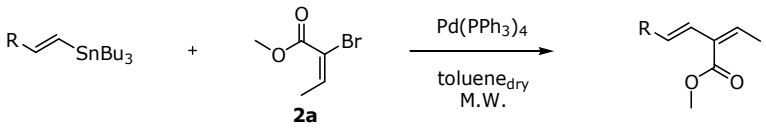
According to the general procedure reported above, the unsaturated δ-aminoester **1a** (33.18 mg, 0.13 mmol, 60%) was obtained from $Pd(PPh_3)_4$ **324** (13.00 mg, 0.01 mmol, 1.05 equiv), 2-bromo-but-2-enoic acid methyl ester **2a** (0.05 mL, 0.39 mmol, 1.8 equiv), the nucleophile **3a** (0.10 g, 0.22 mmol, 1.0 equiv) and

1.20 mL of anhydrous toluene, after purification by chromatography (silica, eluent: 5:1 petroleum ether/ethyl acetate).

12.9.2.2.3. Synthesis of **(*E*)-5-*tert*-butoxycarbonylamino-2-eth-(*Z*)-ylidene-pent-3-enoic acid methyl ester (3a)** in DMF catalyzed by $Pd(AsPh_3)_4$

In a Schlenk tube, 13.00 mg (0.01 mmol, 0.05 equiv) of triphenylarsine were stirred for 15' under vacuum, then, after a series of vacuum/nitrogen cycles, dissolved in 1.20 mL of anhydrous DMF under nitrogen atmosphere and at this point palladium(II) diacetate (0.88 mg, 0.004 mmol, 0.03 equiv) was introduced. The resulting solution was left to react for 1h with the electrophile **2a** (0.05 mL; 0.4 mmol, 1.8 equiv). The nucleophile **1a** (1.0 equiv) was added and the resulting reaction mixture was heated at 80° C for 16h. After cooling, the solvent was evaporated and the residue was worked as indicated on the general procedure for the Stille Coupling reaction to give, after purification (chromatography on silica, eluent: 5:1 petroleum ether/ethyl acetate), the unsaturated δ-aminoester **3a** (19.65 mg, 0.08 mmol, 35%).

1.8.2.2. *General procedure for the Stille Coupling with (E)-methyl-2-bromobutenoate **2a** mediated by microwaves*

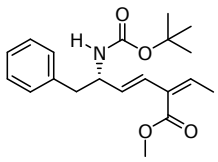


In a Schlenk tube, a catalytic amount of palladium tetrakis **324** (0.05 equiv) was transferred and vigorously stirred under vacuum for 15'. Then it was dissolved in anhydrous toluene (0.5 M) under nitrogen atmosphere and the resulting solution was left to react for 1h with the electrophile **2a** (1.8 equiv). The nucleophile (1.0 equiv) was then added and the mixture was transferred into a vessel for microwaves reactions, equipped with a septum and placed under argon atmosphere. The reaction mixture was heated by microwave irradiations. Then the solvent was evaporated and the residue was diluted in ether, and left under stirring with a 1 M aq. NaOH solution for 1h. After separating the two phases, the organic layer was washed with water and brine, the combined aqueous portions were extracted with EtOAc and the all organic components were combined, washed with brine, dried and concentrated. At the end the crude product was purified.

1.8.2.2.3. Synthesis of **(*E*)-5-*tert*-butoxycarbonylamino-2-eth-(*Z*)-ylidene-pent-3-enoic acid methyl ester (3a)** in toluene mediated by M.W.

After the addition of the nucleophile **1a** (0.30 g, 0.67 mmol, 1.0 equiv), the reaction mixture was heatedd by M.W. at 80° C (200 W) for 30' and then worked-up to afford, after purification (chromatography on silica, eluent: 5:1 petroleum ether/ethyl acetate), 116.00 mg (0.49 mmol, 76%) of the pure product **3a**.

1.8.2.2.4. Synthesis of (***E*)-(*S*)-5-*tert*-butoxycarbonylamino-2-eth-(*Z*)-ylidene -6-phenyl-hex-3-enoic acid methyl ester (3b)** in toluene mediated by M.W.



After the addition of the nucleophile **1b** (0.10 g, 0.19 mmol, 1.0 equiv), the reaction mixture was heated by M.W. irradiations at 80° C (200 W) for 45' and then worked-up to afford, after purification (chromatography on silica, eluent: 5:1 petroleum ether/ethyl acetate), 30.00 mg (0.08 mmol, 43%) of the pure product **3b**.

3b

$C_{20}H_{26}NO_4$ **M=**344.26

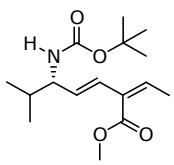
^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 7.40-7.10 (5H, m, C**H** aromatics); 6.78 (1H, q, *J*=7.4, C=C**H**CH_3); 6.22-6.10 (1H, m [A part of a ABX spin system], J_{AB}=16.0, BocNHCH($PhCH_2$)CH=C**H**); 6.10-5-92 (1H, m [B part of a ABX spin system], J_{BA}=16.0, J_{BX2}=5.4, BocNHCH($PhCH_2$)C**H**=CH); 4.60-4-40 (2H,m [X part of a ABX spin system], BocNHC**H**($PhCH_2$)CH=CH); 3.72 (3H, s, OC**H_3**); 3.00-2.70 (2H, m [AB spin system], C**H_2**Ph); 1.81 (3H, d, *J*=7.4, C=CHC**H_3**); 1.40 (9H, s, C(C**H_3**)$_3$).

^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 167.4 (**C**OOCH_3); 155.1 (**C**O$OC(CH_3)_3$); 138.4-121.2 (10C, **C**H aromatics and olefinics); 79.1 (**C**$(CH_3)_3$); 53.3 (BocNH**C**H($PhCH_2$)CH=CH); 51.6 (O**C**H_3); 41.7 (**C**H_2Ph); 28.3 (C(**C**H_3)$_3$); 14.6 (**C**H_3CH=C).

MS (EI) *m/z*(%)**:** 289 (1, M^+ – ^{t}Bu – $CH_2CH(CH_3)_2$); 254 (3, M^+ – CH_2Ph); 198 (33, M^+ – ^{t}Bu – CH_2Ph); 154 (48, M^+ – NHBoc – CH_2Ph); 122 (22, M^+ – NHBoc – CH_2Ph – OCH_3); 91 (27, $C_7H_7^+$); 57 (100, $C(CH_3)_3^+$).

$[\alpha]_D^{23}$=-5.06 (c=0.84, $CHCl_3$).

1.8.2.2.5. Synthesis of (***E*)-(*S*)-5-*tert*-butoxycarbonylamino-2-eth-(*Z*)-methyl-hept-3-enoic acid methyl ester (3c)** in toluene mediated by M.W.



After the addition of the nucleophile **1c** (0.18 g, 0.37 mmol, 1.0 equiv), the reaction mixture was heated by M.W. irradiations at 80° C (200 W) for 45' and then worked-up to afford, after purification (chromatography on silica, eluent:

5:1 petroleum ether/ethyl acetate), 89.20 mg (0.3 mmol, 81%) of the pure product **3c**

3c

$C_{16}H_{27}NO_4$ **M=**297.27

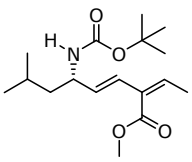
^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 6.80 (1H, q, *J*=7.4, C=C**H**CH_3); 6.30-6.16 (1H, m [A part of a ABX spin system], J_{AB}=16.0, BocNHCHCH=C**H**); 6.16-5-88 (1H, m [B part of a ABX spin system], J_{BA}=16.0, J_{BX2}=6.4, BocNHCHC**H**=CH); 4.65-4-40 (1H, m, CHN**H**); 4.20-3.90 (1H, m, C**H**NH); 3.73 (3H, s, OC**H_3**); 1.88 (3H, d, *J*=7.4, C=CHC**H_3**); 1.44 (9H, s, C(C**H_3**)$_3$); 0.92 (3H, d, *J*=7.4, CH(C**H_3**)$_2$); 0.91 0.92 (3H, d, *J*=7.4, CH(C**H_3**)$_2$).

^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 167.5 (**C**OOCH_3); 155.9 (**C**O$OC(CH_3)_3$); 138.1-122.4 (4C, **C**H olefinics); 79.2 (**C**$(CH_3)_3$); 58.2 (BocNH**C**H); 51.6 (O**C**H_3); 32.6 (**C**H$(CH_3)_2$); 28.4 (C(**C**H_3)$_3$); 18.7 (2C, CH(**C**H_3)$_2$); 14.6 (**C**H_3CH=C).

MS (EI) *m/z*(%)**:** 198 (38, M^+ – ^{t}Bu –CH$(CH_3)_2$); 181 (5, M^+ – NHBoc); 166 (25, M^+ – ^{t}Bu – CH$(CH_3)_2$OMe); 154 (93, M^+ – ^{t}Bu –CH$(CH_3)_2$ – CO_2); 122 (39, M+ – NHBoc – CH_2Ph – OCH_3 – CO); 57 (100, C$(CH_3)_3^+$).

[α]$_D^{23}$=–9.04 (c=1.25, $CHCl_3$).

1.8.2.2.6. Synthesis of (***E*)-(*S*)-5-*tert*-butoxycarbonylamino-2-eth-(*Z*)-methyl-hept-3-enoic acid methyl ester (3c)** in toluene mediated by M.W.



After the addition of the nucleophile **1d** (0.13 g, 0.7 mmol, 1.0 equiv), the reaction mixture was heated by M.W. irradiations at 80° C (200 W) for 45' and then worked-up to afford, after purification (chromatography on silica, eluent: 5:1 petroleum ether/ethyl acetate), 34.00 mg (0.3 mmol, 70%) of the pure product **3d**

3d

$C_{19}H_{29}NO_4$ **M=**335.29

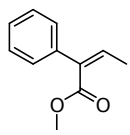
^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 6.80 (1H, q, *J*=7.4, C=C**H**CH_3); 6.30-6.16 (1H, m [A part of a ABX spin system], J_{AB}=16.0, BocNHCHCH=C**H**); 6.16-5-88 (1H, m [B part of a ABX spin system], J_{BA}=16.0, J_{BX2}=6.4, BocNHCHC**H**=CH); 4.65-4-40 (1H, m, CHN**H**); 4.20-3.90 (1H, m, C**H**NH); 3.73 (3H, s, OC**H_3**); 1.88 (3H, d, *J*=7.4, C=CHC**H_3**); 1.44 (9H, s, C(C**H_3**)$_3$); 0.92 (3H, d, *J*=7.4, CH(C**H_3**)$_2$); 0.91 0.92 (3H, d, *J*=7.4, CH(C**H_3**)$_2$).

^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 167.5 (**C**OOCH_3); 155.9 (**C**O$OC(CH_3)_3$); 138.1-122.4 (4C, **C**H olefinics); 79.2 (**C**$(CH_3)_3$); 58.2 (BocNH**C**H); 51.6 (O**C**H_3); 32.6 (**C**H$(CH_3)_2$); 28.4 (C(**C**H_3)$_3$); 18.7 (2C, CH(**C**H_3)$_2$); 14.6 (**C**H_3CH=C).

MS (EI) *m/z*(%)**:** 198 (38, M^+ – ^{t}Bu –CH$(CH_3)_2$); 181 (5, M^+ – NHBoc); 166 (25, M^+ – ^{t}Bu – CH$(CH_3)_2$OMe); 154 (93, M^+ – ^{t}Bu –CH$(CH_3)_2$ – CO_2); 122 (39, M+ – NHBoc – CH_2Ph – OCH_3 – CO); 57 (100, C$(CH_3)_3^+$).

$[\alpha]_D^{24}$=–20.8 (c=0.77, $CHCl_3$).

1.8.2.2.7. Synthesis of **(*E*)-2-phenyl-but-2-enoic acid methyl ester (187)** in toluene mediated by M.W.



After the addition of tributylphenylstannane **184** (0.15 g, 0.40 mmol, 1.0 equiv), the reaction mixture was heated by M.W. irradiations at 80° C (200 W) for 30' and then worked-up to afford, after purification (chromatography on silica, eluent: 5:1 petroleum ether/ethyl acetate), 52.24 mg (0.30 mmol, 75%) of the pure product **187**.

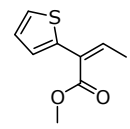
187

$C_{11}H_{12}O_2$ **M=**176.12

^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 7.60-7.30 (5H, m, C**H** aromatics); 6.25 (1H, q, *J*=,7.2, C=C**H**CH_3); 3.79 (3H, s, COOC**H_3**); 2.03 (3H, d, *J*=,7.2, C=CHC**H_3**).

^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 168.4 (**C**$OOCH_3$); 138.1 (**C**=$CHCH_3$); 135.4 (**C_{ipso}** aromatic); 135.3 (C=**C**HCH_3); 128.1 (2C, **C**H *meta* aromatics); 127.4 (**C**H *para* aromatics); 127.2 (2C, **C**H *ortho* aromatics); 51.5 (COO**C**H_3); 15.9 (C=CH**C**H_3).

1.8.2.2.8. Synthesis of **(*E*)-2-thiophen-2-yl-but-2-enoic acid methyl ester (188)** in toluene mediated by M.W.



After the addition of 2-tributylstannylthiophene **185** (0.10 g, 0.27 mmol, 1.0 equiv), the reaction mixture was heated by M.W. irradiations at 80° C (200 W) for 50' and then worked-up to afford, after purification (chromatography on silica, eluent: 5:1 petroleum ether/ethyl acetate), 33.07 mg (0.18 mmol, 68%) of the pure product **188**.

188

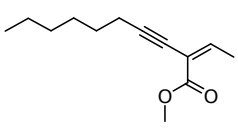
$C_9H_{10}O_2S$ **M=**182.10

^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 7.37 (1H, d, *J*=5.1, CH=C**H**S thiophene); 7.23 (1H, q, *J*=7.3, C=C**H**CH_3); 7.07-7.03 (H, m, **C**H=CHS thiophene); 6.97 (1H, d, *J*=3.7, C**H**=CS thiophene); 3.77 (3H, s, OC**H_3**); 1.91 (3H, d, *J*=7.3, CH=CHC**H_3**).

^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 167.1 (**C**$OOCH_3$); 142.0 (CH=**C**S thiophene); 135.2 (**C**=$CHCH_3$); 128.3 (C=**C**HCH_3); 127.8 (CH=**C**HS thiophene); 126.3 (**C**H=CS thiophene); 126.1 (**C**H=CHS thiophene); 52.2 (COO**C**H_3); 15.9 (C=CH**C**H_3).

MS (EI) *m/z*(%)**:** 182 (90); 123 (100, M^+ – $COOCH_3$).

1.8.2.2.9. Synthesis of **(*E*)-2-ethylidene-dec-3-ynoic acid methyl ester (189)** in toluene mediated by M.W.



After the addition of tributyl-(oct-1-ynyl)-stannane **186** (0.08 g, 0.20 mmol, 1.0 equiv), the reaction mixture was heated by M.W. irradiations at 80° C (200 W) for 15' and then worked-up to afford, after purification (chromatography on silica, eluent: 5:1 petroleum ether/ethyl acetate), 32.00 mg (0.14 mmol, 72%) of the pure product **189**.

189

$C_{13}H_{19}O_2$ **M=**207.19

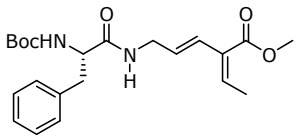
^{1}H-NMR δ ($CDCl_3$, 200 MHz)**:** 7.22 (1H, q, *J*=7.1, C=C**H**CH_3); 3.77 (3H, s, OC**H$_3$**); 2.42 (2H, t, *J*=6.7, C**H$_2$**C≡C); 2.00 (3H, d, *J*=7.1, C=CHC**H$_3$**); 1.34-1.17 (8H, m, C≡CCH_2C**H$_2$**C**H$_2$**C**H$_2$**C**H$_2$**CH_3); 0.92 (3H, t, *J*=6.2, C≡C$CH_2CH_2CH_2CH_2CH_2$C**H$_3$**).

^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 166.1 (**C**OOCH_3); 147.3 (C=**C**HCH_3); 130.9 (**C**=$CHCH_3$); 118.2 (CH_2**C**≡C); 98.0 (CH_2C≡**C**); 51.2 (COO**C**H_3); 31.3 (C≡C$CH_2CH_2CH_2$**C**$H_2CH_2CH_3$); 29.4 (C≡CCH_2**C**$H_2CH_2CH_2CH_2CH_3$); 28.7 (C≡CCH_2CH_2**C**$H_2CH_2CH_2CH_3$); 22.7 (C≡C$CH_2CH_2CH_2CH_2$**C**H_2CH_3); 19.7 (C≡C**C**$H_2CH_2CH_2CH_2CH_2CH_3$); 16.6 (C≡C$CH_2CH_2CH_2CH_2CH_2$**C**H_3); 14.1 (C=CHC**H$_3$**).

MS (EI) *m/z*(%)**:** 208 (1, M^+ + H); 193 (10); 177 (12); 161 (10); 147 (32, M^+ – $COOCH_3$); 133 (41); 119 (51); 105 (64); 95 (76); 91 (89, $C_7H_7^+$); 79 (100); 77 (92); 69 (22); 59 (84); 55 (55); 51 (57).

1.8.3. Synthesis of dipeptides

1.8.3.2. (*E*)-5-[(2*S*)-2-tert-butoxycarbonylamino-3-phenylpropionyl-amino)]-2-eth-(*Z*)-ylidene-pent-3-enoic acid methyl ester (208)



In a round bottomed flask the amino ester **3a** (50.00 mg, 0.2 mmol, 1.0 equiv) was dissolved into CH_2Cl_2 (2.00 mL) and, after cooling at –10° C, reacted with TFA (0.5 mL). After 15 min, the solvent was evaporated to give the deprotected amino acid **209** which was immediately reacted with Boc-Phe-OH (58.00 mg, 0.2 mmol, 1.0 equiv), di-*iso*-propylamine (67.00 mg, 0.7 mmol, 3.5 equiv) and diethylcyanophosphonate (54.00 mg, 0.3 mmol, 1.5 equiv). The reaction mixture was stirred overnight, then diluted with ethyl acetate (5.00 mL) and a NH_4Cl saturated solution (5.00 mL). After extraction, evaporation and purification (silica, eluent: 5:1 petroleum ether/AcOEt) 76.00 mg of **208** were obtained (yield 79%).

208

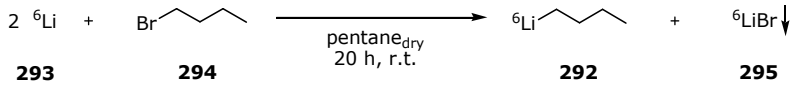
$C_{22}H_{30}N_2O_2$ **M=**402.30

^{1}H-NMR δ ($CDCl_3$, 400 MHz)**:** 7.30-7.28 (2H, m [AA' part of a AA'BB'C spin system], C**H** *ortho* aromatic $CH_2CHNHBoc$); 7.23-7.21 (3H, m [BB' and C parts of a AA'BB'C spin system], CH *meta* and *para* aromatic $CH_2CHNHBoc$); 6.19 (1H, d_{app}, *J*=16.0, C**H**$CCOOCH_3$ olefinic); 5.98-5.89 (2H, m, C**H**=$CHCCOOCH_3$ and C=C**H**CH_3 olefinics); 5.07 (1H, bs, N**H**Boc); 4.35-4.27 (1H, m, C**H**CH_2Ph); 3.92-3.88 (2H, m, C**H$_2$**CH=CH); 3.74 (3H, s, COOC**H$_3$**); 3.10-3.01 (2H, m [AB spin system], C**H$_2$**Ph); 1.86 (3H, d, *J*=7.0, C=CH(C**H$_3$**)); 1.39 (9H, s, C(C**H$_3$**)$_3$).
^{13}C-NMR{^{1}H} δ ($CDCl_3$, 50 MHz)**:** 170.8 (**C**$ONHCH_2$); 167.2 (**C**$OOC(CH_3)_3$); 155.3 (**C**$OOCH_3$); 138.9-123.9 (10C, **C**H aromatics and olefinics); 80.2 (**C**$(CH_3)_3$); 56.1 (COO**C**H_3); 51.8 (NH**C**HCO); 41.8 (**C**$H_2CH=CH$); 38.7 (**C**H_2Ph); 28.3 ($C($**C**$H_3)_3$).
MS (EI) *m/z*(%)**:** 402 (1, M^+); 346 (3); 57 (100, $C(CH_3)_3^+$).
Elemental Analysis: found: C=65.70; H=7.49; N=6.98. Calculated: C=65.65; H=7.51; N=6.96.
[α]$_D^{23}$=–0.32 (c = 1.05, $CHCl_3$).

Second Part

12.10. Synthesis of [^{6}Li] organolithium compounds

12.10.1. [^{6}Li] n-Butyllithium salt-free solution in pentane (292)[39]



293 **294** **292** **295**

Finely cut 6-lithium metal ribbon **293** (0.60 g, 100.0 mmol, 2.5 equiv) was introduced in a two-necked pear-shaped flask (100 mL) equipped with a balloon of dry argon. The metallic cuttings **293** were covered with 20.00 mL of freshly distilled pentane. After intensive stirring, the pentane was removed and the metal washed twice with 20.00 mL of this same solvent every time. A new amount of 20.00 mL of freshly distilled pentane was introduced and a solution of freshly distilled *n*-bromobutane **294** (4.30 mL, 40.0 mmol, 1.0 equiv) in 12.00 mL of dried pentane was added dropwise at room temperature over a 45' period under dried argon. In this space of time the formation of blue salts corresponding to ^{6}LiBr **295** was observed and the disappearance of the ^{6}Li metal **293** was noticed. The resulting reaction mixture was stirred for 20 hours at room temperature in argon atmosphere. Then the stirring was stopped allowing ^{6}LiBr **295** to settle. The hydrocarbon solution **292** was transferred into centrifugation tubes placed under dried argon. The residual traces of salt were centrifuged and the clear final solution (20.00 mL) **292** was collected in a dried flask flushed under dried argon. Finally this solution was titrated (1.55 M, 78%).

12.10.2. [^{6}Li] *n*-Butyllithium salt-free solution in tetrahydrofuran-d_8 (292)

A 2.50 mL aliquot of a solution of [^{6}Li] *n*-butyllithium **292** in pentane was syringed in a tube fitted with a septum and flushed under dried argon. The tube was placed, then, under vacuum (20 mmHg) for one hour to evaporate the pentane. The resultant dense pale yellow oil was dissolved in freshly distilled THF-d_8 and concentrated under vacuum for one hour in order to eliminate the last traces of hydrocarbon. Finally the resulting white solid was solubilised in 3.00-3.50 mL of freshly distilled THF-d_8 and the so-obtained solution was titrated (the concentration goes from 0.9 to 1.0 M).

292

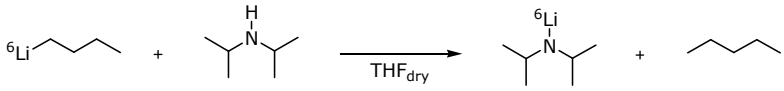
^{6}LiC$_4$H$_9$ **M**=63.11

^{1}H-NMR δ (THF-d_8, 500 MHz, 195K)**:** 0.90-0.88 (4H, ^{6}LiCH$_2$C**H$_2$**C**H$_2$**CH$_3$); 0.86-0.82 (3H, ^{6}LiCH$_2$CH$_2$CH$_2$C**H$_3$**); –1.03 - –1.06 (2H, ^{6}LiC**H$_2$**CH$_2$CH$_2$CH$_3$ tetramer); –1.15 - –1.18 (2H, ^{6}LiC**H$_2$**CH$_2$CH$_2$CH$_3$ dimer).

^{13}C-NMR{^{1}H} δ (THF-d_8, 126 MHz, 195 K)**:** 12.5 (quint, $^1J_{C\text{-}Li}$=7.8, ^{6}Li**C**H$_2$CH$_2$CH$_2$CH$_3$ tetramer); 10.3 (sep, $^1J_{C\text{-}Li}$=5.4, ^{6}Li**C**H$_2$CH$_2$CH$_2$CH$_3$ dimer).

^{6}Li-NMR δ (THF-d_8, 73 MHz, 195 K)**:** 1.49 (s, Bu**^{6}Li** dimer); 1.08 (s, Bu**^{6}Li** tetramer).

12.10.3. [^{6}Li] Lithium diisopropylamide salt-free solution in tetrahydrofuran-d_8 (296)



292 **297** **296** **298**

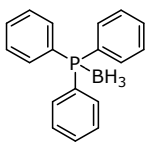
A 1.00 mL aliquot of a solution of [^{6}Li] *n*-butyllithium **292** in THF-d_8 was syringed in a tube fitted with a septum and flushed under dried argon. The solution was diluted with 0.50 mL of freshly distilled THF-d_8 and, afterwards, 0.13 mL of freshly distilled DIPA **297** (0.9 mmol, 1.0 equiv) were added. The resulting reaction mixture **296** was kept stirring at −78 °C for 30'. Successively it was titrated (*c*=0.6 M).

296
^{6}LiC$_6$H$_{14}$N **M**=106.14
^{1}H-NMR δ (THF-d_8, 500 MHz, 195 K)**:** 2.90 (2H, sep, *J*=6.0, ^{6}LiN(C**H**(CH$_3$)$_2$)); 0.96 (6H, d, *J*=6.0, ^{6}LiN(CH(C**H$_3$**)$_2$)).
^{6}Li-NMR δ (THF-d_8, 73 MHz, 195 K)**:** −1.53 (1Li, s, **^{6}Li**N(CH(CH$_3$)$_2$)).

12.11. Synthesis of phosphines

12.11.1. Synthesis of diphenylphosphine borane **10**

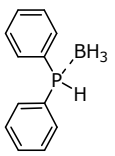
12.11.1.1. Triphenylphosphine Borane (291)



In a three-necked round bottomed flask, equipped with a nitrogen inlet, triphenylphosphine **290** (150.00 g, 572.0 mmol, 1.0 equiv) and freshly distilled toluene (270.00 mL) were introduced. Then, borane-dimethylsulfide complex (55.00 mL, 572.00 mol, 1.01 equiv) was added dropwise. After stirring at room temperature for 2 h, the solid was filtered and washed with toluene. The crude product **291** was dried under vacuum to afford 151.60 g (550 mmol, 96%) of a white solid, which was used for the next reaction without further purifications.

291
C$_{18}$H$_{18}$BP **M**=276.12
m.p.=189-190° C
^{1}H-NMR δ ($CDCl_3$, 300 MHz)**:** 7.62-7.42 (15H, m, C**H** aromatics); 1.29 (3H, qm, *J*=100.0, Ph$_3$PB**H$_3$**).
^{13}C-NMR{^{1}H} δ ($CDCl_3$, 75 MHz)**:** 133.1 (6C, d, $^2J_{C\text{-}P}$=9.8, **C**H *ortho* aromatics P); 131.2 (3C, d, $^4J_{C\text{-}P}$=2.0, **C**H *para* aromatics P); 129.1 (3C, $^1J_{C\text{-}P}$=57.8, **C$_{ipso}$** aromatics P). 128.7 (6C, $^3J_{C\text{-}P}$=10.0, **C**H *meta* aromatics P).

12.11.1.2. Diphenylphosphine Borane (10)[360, 435, 505]



In a three necked round flask, equipped with a nitrogen inlet, finely cut lithium wires (0.70 g, 100.0 mmol, 2.0 equiv) were added to a solution of triphenylphosphine borane **291** (13.80 g, 50.0 mmol, 1.0 eq.) in 70.00 mL of freshly distilled THF. The solution was stirred at room temperature for 8 hours. After cooling at 0 °C, the solution was slowly hydrolyzed with an excess of water (18.00 mL, 1.0 mol, 20.0 equiv). The aqueous portion was extracted with DCM (3 x 100.00 mL), and the organic layers were washed with brine (1 x 200.00 mL), dried on magnesium sulfate and concentrated under vacuum. A 13.00 g amount of the crude product **10** was obtained. This product was filtered on silica gel with toluene as eluent giving 7.40 g (36.4 mmol, 74%) of a white solid **10**.

10

$C_{12}H_{14}BP$ **M**=202.02

m.p.=44 - 45° C

^{1}H-NMR δ ($CDCl_3$, 300 MHz)**:** 7.70-7.64 (4H, m [AA' part of a AA'BB'C spin system], C**H** *ortho* aromatics); 7.52-7.42 (6H, m [BB' and C part of a AA'BB'C spin system], C**H** *meta* and *para* aromatics); 6.31 (1H, dq, $^1J_{H\text{-}P}$=379.5, $^3J_{H\text{-}BH3}$=6.9, $Ph_2P(BH_3)$**H**); 1.58-0.64 (3H, m, $Ph_2P(B\mathbf{H_3})H$).

^{13}C-NMR{^{1}H} δ ($CDCl_3$, 75 MHz)**:** 132.8 (4C, d, $^2J_{C\text{-}P}$=9.3, **C**H *ortho* aromatics); 131.5 (2C, d, $^4J_{C\text{-}P}$=2.4, **C**H *para* aromatics); 129.0 (4C, d, $^3J_{C\text{-}P}$=10.3, **C**H *meta* aromatics); 126.0 (2C, d, $^1J_{C\text{-}P}$=57.1, $\mathbf{C_{ipso}}$ aromatics).

^{31}P-NMR δ ($CDCl_3$, 101 MHz)**:** 0.3 (1P, dq, $^1J_{P\text{-}H}$=371.8, $^1J_{P\text{-}B}$=52.0, $Ph_2\mathbf{P}(BH_3)H$).

^{11}B-NMR δ ($CDCl_3$, 128 MHz)**:** –37.2 (1B, qd, $^1J_{B\text{-}H}$=94.3, $^1J_{B\text{-}P}$=52.0, $Ph_2P(\mathbf{B}H_3)H$).

^{1}H-NMR δ (THF-d_8, 500 MHz)**:** 7.73-7.69 (4H, m [AA' part of a AA'BB'C spin system], C**H** *ortho* aromatics); 7.52-7.47 (2H, m [C part of a AA'BB'C spin system], C**H** aromatics *para*); 7.48-7.43 (4H, m [BB' part of a AA'BB'C spin system], C**H** *meta* aromatics); 6.35 (1H, dq, $^1J_{H\text{-}P}$=381.0, $^3J_{H\text{-}BH3}$=7.0, $Ph_2P(BH_3)$**H**); 1.04 (3H, q (1:1:1:1), $^1J_{BH3\text{-}B}$=161.3, $Ph_2P(B\mathbf{H_3})H$).

^{13}C-NMR{^{1}H} δ (THF-d_8, 125 MHz)**:** 123.2 (4C, d, $^2J_{C\text{-}P}$=9.4, **C**H *ortho* aromatics); 123.6 (2C, d, $^4J_{C\text{-}P}$=2.5, **C**H *para* aromatics); 119.1 (4C, d, $^3J_{C\text{-}P}$=10.0, **C**H *meta* aromatics); 117.7 (2C, d, $^1J_{C\text{-}P}$=56.7, $\mathbf{C_{ipso}}$ aromatics).

^{31}P-NMR δ (THF-d_8, 202 MHz)**:** –17.84 (1P, dm, $^1J_{P\text{-}H}$=381.0, $Ph_2\mathbf{P}(BH_3)H$).

^{31}P-NMR{^{1}H} δ (THF-d_8, 202 MHz)**:** –17.84 (1P, q, $^3J_{P\text{-}BH3}$=46.5, $Ph_2\mathbf{P}(BH_3)H$).

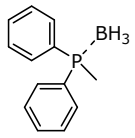
^{11}B-NMR δ (THF-d_8, 256 MHz)**:** –40.3 (1B, qd, $^1J_{B\text{-}H}$=161.3, $^1J_{B\text{-}P}$=69.1, $Ph_2P(\mathbf{B}H_3)H$).

^{1}H-NMR δ (THF-d_8, 500 MHz, 195 K)**:** 7.80-7.76 (4H, m [AA' part of a AA'BB'C spin system], C**H** *ortho* aromatics); 7.57-7.57 (2H, m [C part of a AA'BB'C spin system], C**H** *para* aromatics); 7.56-7.51 (4H, m [BB' part of a AA'BB'C spin system], C**H** *meta* aromatics); 6.50 (1H, dm, $^1J_{H\text{-}P}$=389.5, $Ph_2P(BH_3)$**H**); 1.00 (3H, br-s, $Ph_2P(B\mathbf{H_3})H$).

^{13}C-NMR{^{1}H} δ (THF-d_8, 125 MHz, 195 K)**:** 123.4 (4C, d, $^{2}J_{C\text{-}P}$=9.3, **C**H *ortho* aromatics); 122.1 (2C, s, **C**H *para* aromatics P); 119.4 (4C, d, $^{3}J_{C\text{-}P}$=10.1, **C**H *meta* aromatics); 117.5 (2C, d, $^{1}J_{C\text{-}P}$=56.7, **C_{ipso}** aromatics).
^{31}P-NMR δ (THF-d_8, 202 MHz, 195 K)**:** –21.19 (1P, d, $^{1}J_{P\text{-}H}$=385.8, Ph_2**P**(BH_3)H).
^{31}P-NMR{^{1}H} δ (THF-d_8, 202 MH, 195 K)**:** –21.14 (1P, s, Ph_2**P**(BH_3)H).
^{11}B-NMR δ (THF-d_8, 256 MHz, 195 K)**:** –40.92 (1B, br-s, Ph_2P(**B**H_3)H).

12.11.2. Synthesis of methylphenylphosphine borane **305**[360, 435, 505, 506]

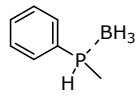
12.11.2.1. **Methyldiphenylphosphine Borane (307)**



In a three-necked round-bottomed flask, equipped with a nitrogen inlet, finely cut lithium wires were added to a solution of triphenylphosphine-borane **290** (8.30 g, 30.0 mmol) in anhydrous THF (45.00 mL). After 8 h at room temperature, the solution was cooled to 0° C and 2-chloro-2-methylpropane (3.91 mL, 36.00 mmol, 1.2 equiv) was added dropwise. The reaction mixture was stirred for 1 h at room temperature before being cooled to −78 °C. Then, iodomethane (2.05 mL, 33.00 mmol, 1.1 equiv) was added dropwise at this temperature. The solution was slowly warmed to room temperature and then stirred for 8 h. The reaction mixture was then hydrolyzed at 0° C with an excess of water (10.80 mL, 600.0 mmol, 20.0 equiv). The aqueous layer was extracted with toluene, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product **307** was then filtered on silica gel and washed with toluene to give 5.80 g (27.1 mmol, 91%) of a pale yellow oil.

307
$C_{13}H_{16}BP$ **M**=214.05
^{1}H-NMR δ ($CDCl_3$, 400 MHz)**:** 7.65-7.45 (6H, m [BB' and C parts of a AA'BB'C spin system], C**H** *meta* and *para* aromatics); 7.40-7.20 (4H, m [AA' part of a AA'BB'C spin system], C**H** *ortho* aromatics); 1.82 (3H, d, $^{2}J_{H\text{-}P}$=10.2, C**H_3**); 1.70-0.30 (3H, q, $^{1}J_{H\text{-}B}$=100.0, Ph_2CH_3PB**H_3**).
^{13}C-NMR{^{1}H} δ ($CDCl_3$, 75 MHz)**:** 131.5 (2C, $^{4}J_{C\text{-}P}$=2.5, **C**H *para* aromatics); 131.1 (4C, d, $^{2}J_{C\text{-}P}$=9.2, **C**H *ortho* aromatics); 128.5 (2C, $^{1}J_{C\text{-}P}$=55.2, **C_{ipso}** aromatics);127.4 (4C, $^{3}J_{C\text{-}P}$=10.2, **C**H *meta* aromatics); 129.1 (3C, $^{1}J_{C\text{-}P}$=57.8, **C_{ipso}** aromatics P); 128.7 (6C, $^{3}J_{C\text{-}P}$=10.0, **C**H *meta* aromatics); 7.4 (1C, d, $^{1}J_{C\text{-}P}$=36.2, **C**H_3).
^{31}P-NMR δ ($CDCl_3$, 162 MH)**:** 11.3 (1P, q, $^{1}J_{P\text{-}B}$=55.0, Ph_2CH_3**P**BH_3).

12.11.2.2. Methylphenylphosphine Borane (305)



In a three-necked round bottomed flask, equipped with a nitrogen inlet, finely cut lithium wires (0.29 g, 40.0 mmol, 2.0 equiv) were added to a solution of methyldiphenylphosphine-borane **307** (4.30 g, 20.0 mmol, 1.0 equiv) in anhydrous THF (30.00 mL). The solution was stirred overnight at room temperature. Then, after cooling to 0° C, the reaction mixture was hydrolyzed with an excess of water (7.20 mL, 400.0 mol, 20.0 equiv). The aqueous layer was extracted with dichloromethane, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product **305** was filtered on silica gel with toluene as eluent giving 2.15 g (15.6 mmol, 78%) of a translucent oil.

305

$C_7H_{12}BP$ **M**=137.96

^{1}H-NMR δ ($CDCl_3$, 400 MHz)**:** 7.80-7.63 (2H, m [AA' part of a AA'BB'C spin system], C**H** *ortho* aromatics), 7.51-7.43 (3H, m [BB' and C parts of a AA'BB'C spin system], C**H** *meta* and *para* aromatics), 5.55 (1H, dsept, $^1J_{H\text{-}P}$=372.0, $^3J_{H\text{-}H}$=6.0, P-**H**), 1.59 (3H, dd, $^2J_{H\text{-}P}$=11.0, $^3J_{H\text{-}H}$=6.0, C**H_3**), 1.50-0.10 (3H, qm, $^1J_{H\text{-}B}$=101.0, $PhCH_3P(B\mathbf{H_3})H$).

^{13}C-NMR{^{1}H} δ ($CDCl_3$, 75 MHz)**:** 132.2 (2C, d, $^2J_{C\text{-}P}$=9.0, **C**H *ortho* aromatics), 131.5 (d, $^4J_{C\text{-}P}$=2.5, **C**H *para* aromatic), 128.9 (2C, d, $^3J_{C\text{-}P}$=10.0, **C**H *meta* aromatics), 126.0 (d, $^1J_{C\text{-}P}$=57.0, **C_{ipso}** aromatic), 8.2 (d, $^1J_{C\text{-}P}$=39.0, **C**H_3).

^{31}P-NMR δ ($CDCl_3$, 162 MH)**:** –16.7 (1P, dq, $^1J_{P\text{-}B}$=372.0, $^1J_{P\text{-}B}$=48.0, $PhCH_3\mathbf{P}(BH_3)H$).

^{11}B-NMR δ ($CDCl_3$, 128 MHz)**:** –36.8 (1B, qd, $^1J_{B\text{-}H}$=101.0, $^1J_{B\text{-}P}$=48.0, $PhCH_3P(\mathbf{B}H_3)H$).

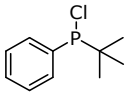
12.11.3. Synthesis of *tert*-butylpheylphosphine borane **306**[360]

12.11.3.1. *tert*-Butylmagnesiumchloride (325)

In a three-necked round bottomed flask, equipped with a nitrogen inlet, 12.30 g of magnesium (505.0 mmol) and 15.00 mL of freshly distilled THF were introduced. Then, 1.00 mL of pure *tert*-butylchloride was added to start the reaction. A solution of *tert*-butylchloride in THF (54.00 mL, 1.65 M) was then slowly added and the solution was refluxed in THF for 2h. The Grignard's reagent **325** (yield=77%) was back titrated by solutions of HCl (2.0 M) and NaOH (1.0 M).

12.11.3.2. *tert*-Butylchlorophenylphosphine (311)

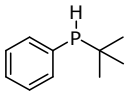
In a three-necked round bottomed flask, equipped with a nitrogen inlet, a solution of dichlorophosphine **310** in diethyl ether (128.00 mL, 257.0 mmol, 2.0 M) was



introduced. After cooling to 0° C, *tert*-butylmagnesiumchloride **325** in THF was slowly added dropwise. The solution was allowed to reach room temperature and then refluxed for 2 hours. Magnesium's salts were filtered on celite under inert atmosphere. Then the solvent was removed under vacuum affording the desired product **311** which was directly used in the next step without further purification.

311
$C_{10}H_{14}ClP$ **M**=200.64
^{31}P-NMR δ ($CDCl_3$, 162 MHz)**:** 107.8 (s).

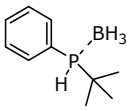
12.11.3.3. *tert*-Butylphenylphosphine (312)



In a three-necked round bottomed flask, equipped with a nitrogen inlet, $LiAlH_4$ (1.06 g, 28.0 mmol, 1.0 equiv) and diethyl ether (75.00 mL) were introduced. The mixture was cooled to –40° C and a solution of *tert*-butylchlorophenylphosphine **311** in diethyl ether (28.00 mmol, 2.8 M, 1.0 equiv) was slowly added dropwise *via* a cannula. Then, the reaction mixture was slowly warmed to room temperature and stirred for 2h. After hydrolysis with water (10.00 mL, 555.0 mmol, 20.0 equiv) at –20° C, the solution was stirred for 1h. Then, the mixture was filtered and dried over $MgSO_4$. Solvent was removed under vacuum affording the desired product **312** which was directly used in the next step without any further purification.

312
$C_{10}H_{15}P$ **M**=166.20
^{31}P-NMR δ ($CDCl_3$, 101 MHz)**:** –4.3 (s).

12.11.3.4. *tert*-Butylphenylphosphine Borane (306)



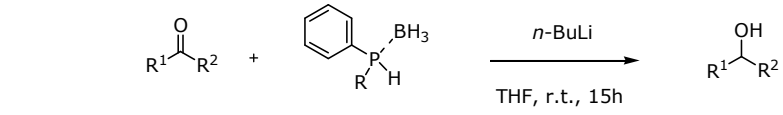
In a three-necked round bottomed flask, equipped with a nitrogen inlet, a solution of *t*-butylphenylphosphine **312** in diethyl ether was introduced. After cooling to 0° C, borane-dimethylsulfide complex was slowly added. The reaction mixture was stirred 2h at room temperature. Then, solvent was removed under vacuum affording the pure desired product **306** as a colourless oil (3.89 g, 36.0 mmol, global yield=53%).

306
$C_{10}H_{18}BP$ **M**=180.03
^{1}H-NMR δ ($CDCl_3$, 400 MHz)**:** 7.68-7.58 (2H, m [AA' part of a AA'BB'C spin system], C**H** *ortho* aromatics), 7.55-7.48 (3H, m [BB' and C parts of a AA'BB'C spin system], C**H** *meta* and *para* aromatics), 5.10 (1H, dq, $^{1}J_{H\text{-}P}$=363.9, $^{3}J_{H\text{-}H}$=6.7, P-**H**), 1.16 (9H, d, $^{3}J_{H\text{-}P}$=14.4, C(C**H$_3$**)$_3$), 1.30-0.30 (3H, m, Ph^{t}BuP(B**H$_3$**)H).

^{13}C-NMR δ ($CDCl_3$, 100 MHz)**:** 134.4 (2C, d, $^2J_{C\text{-}P}$=7.5, **C**H *ortho* aromatics), 132.1 (d, $^4J_{C\text{-}P}$=2.2, **C**H *para* aromatic), 129.1 (2C, d, $^3J_{C\text{-}P}$=9.4, **C**H *meta* aromatics), 125.2 (d, $^1J_{C\text{-}P}$=51.4, **C_{ipso}** aromatic), 28.9 (d, $^1J_{C\text{-}P}$=32.7, **C**$(CH_3)_3$), 26.9 (3C, d, $^2J_{C\text{-}P}$=2.3, C(**C**$H_3)_3$).
^{31}P-NMR δ ($CDCl_3$, 162 MHz)**:** 30.5 (1P, $^1J_{P\text{-}H}$=363.9, $^1J_{P\text{-}B}$=54.2, Ph^{t}Bu**P**(BH_3)H).

12.12. Reduction of carbonyl compounds to alcohols with lithium phosphides

12.12.1. *General procedure for the reduction reactions*



303
a R^1=Ph, R^2=CH_3
b R^1=CH_3, R^2=*n*-C_2H_5
c R^1=CH_3, R^2=*n*-C_3H_7
d R^1=CH_3, R^2=*n*-C_5H_{11}
e R^1=*n*-C_2H_5, R^2=*n*-C_4H_9

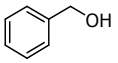
10 R=Ph
305 R=CH_3
305 R=^{t}Bu

304

A Schlenk tube equipped with a magnetic stirring bar was flame dried under a flow of nitrogen. Phosphine-borane **10**, **305** or **306** and degassed THF were added to the Schlenk tube. The solution was cooled to –78° C and *n*-butyllithium (1.0 equiv., 1.6 M in hexane) was added. The solution was allowed to warm to room temperature and the carbonyl compound **303** (1.0 equiv) was added. The reaction mixture was stirred until a white precipitate was formed. Then water (2.0 equiv) was added and the mixture was concentrated under reduced pressure to give the crude product **304**.

12.12.1.1. Reduction of **benzaldehyde (249)** with lithium diphenylphosphide borane **10**

Following the general procedure, benzyl alcohol **301** was prepared from diphenylphosphine-borane **10** (200.00 mg, 1.0 mmol, 1.0 equiv), *n*-butyllithium (0.625 mL, 1.0 mmol, 1.0 equiv, 1.6 M in hexane) and benzaldehyde **249** (0.102 mL, 1.0 mmol, 1.0 equiv). After stirring the reaction mixture for 15 h at room temperature, water (0,036 mL, 2.0 mmol, 2.0 equiv) was added. Benzylic alcohol **301** (91.00 mg, 0.8 mmol, 84 %) was obtained as a pure liquid after flash chromatography (eluent: 7:3 pentane/ethyl acetate).

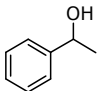


301: Benzyl alcohol[507]
C_7H_8O **M=**108.08
^{1}H-NMR δ ($CDCl_3$, 400 MHz)**:** 7.25-7.18 (5H, m, C**H** aromatics); 4.16 (2H, s, PhC**H_2**OH); 2.53 (1H, br-s, $PhCH_2$O**H**).

^{13}C-NMR δ ($CDCl_3$, 75 MHz)**:** 142.0 (**C_{ipso}** aromatic CH_2OH); 128.5 (2C, **C**H *ortho* aromatics); 127.9 (**C**H *para* aromatic); 127.7 (2C, **C**H *meta* aromatics); 64.1 (Ph**C**H_2OH).

12.12.1.2. Reduction of **acetophenone (303a)** with lithium diphenylphosphide borane **10**

According to the general procedure, acetophenone **303a** (0.12 mL, 1.0 mmol, 1.0 equiv), was added to a solution of diphenylphosphine-borane **10** (200.00 mg, 1.0 mmol, 1.0 equiv) and *n*-butyllithium (0.625 mL, 1.0 mmol, 1.0 equiv, 1.6 M in hexane) in THF affording, after 15h at room temperature, 1-phenylethanol **304a** with a 49% conversion.



304a: 1-Phenylethanol[508]
$C_8H_{10}O$ **M=**122.10
^{1}H-NMR δ ($CDCl_3$, 300 MHz)**:** 7.30-7.10 (5H, m, C**H** aromatics); 4.80 (1H, qd, *J*=7.0, 4.2, PhC**H**(CH_3)OH); 2.42 (1H, d, *J*=4.2, PhCH(CH_3)O**H**); 1.48 (3H, d, *J*=7.0, PhCH(C**H_3**)OH).
^{13}C-NMR δ ($CDCl_3$, 75 MHz)**:** 142.0 (**C_{ipso}** aromatic CH_2OH); 128.5 (2C, **C**H *ortho* aromatics); 127.9 (**C**H *para* aromatic); 127.7 (2C, **C**H *meta* aromatics).

12.12.1.3. Reduction of **2-butanone (303b)** with lithium diphenylphosphide borane **10**

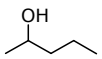
2-Butanone **303b** (0.09 mL, 1.0 mmol, 1.0 equiv) was reacted with a solution of diphenylphosphine-borane **10** (200.00 mg, 1.0 mmol, 1.0 equiv) and *n*-butyllithium (0.625 mL, 1.0 mmol, 1.0 equiv, 1.6 M in hexane) in THF for 15 h at room temperature, as reported into the general procedure, affording 2-butanol **304b** (Conv=100%).

304b: 2-Butanol[509, 510]
$C_4H_{10}O$ **M=**74.10
^{1}H-NMR δ ($CDCl_3$, 300 MHz)**:** 3.74 (1H, ps-set, *J*=7.0, C**H**OH); 2.11 (1H, d, *J*=7.0, CHO**H**); 1.45 (2H, m, CH_3CH_2C**H**(OH)CH_3); 1.15 (3H, d, *J*=7.0, C**H_3**CHOH); 0.89 (3H, t, *J*=7.0, CH_2C**H_3**).
^{13}C-NMR δ ($CDCl_3$, 75 MHz)**:** 68,1 (**C**HOH); 32.0 (**C**H_2CH_3); 24.3 (**C**H_3CHOH); 9.9 (CH_2**C**H_3).

12.12.1.4. Reduction of **2-pentanone (303c)** with lithium diphenylphosphide borane **10**

Following the general procedure, 2-pentanol **304c** (Conv=97%) was prepared from diphenylphosphine-borane **10** (200.00 mg, 1.0 mmol, 1.0 equiv), *n*-

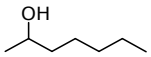
butyllithium (0.625 mL, 1.0 mmol, 1.0 equiv, 1.6 M in hexane) and 2-pentanone **303c** (0.11 mL, 1.0 mmol, 1.0 equiv).



304c: 2-pentanol[510]
$C_5H_{12}O$ **M=**88.12
^{1}H-NMR δ ($CDCl_3$, 300 MHz)**:** 3.80-3.75 (1H, m, C**H**OH); 2.00 (1H, br-d, *J*=5.6, CHO**H**); 1.55-1.13 (4H, m, $CH_3CH(OH)(C\mathbf{H_2})_2CH_3$); 1.10 (3H, d, *J*=7.0, $C\mathbf{H_3}CH(OH)(CH_2)_2CH_3$); 0.88 (3H, t, *J*=7.0, $CH_3CH(OH)(CH_2)_2C\mathbf{H_3}$).
^{13}C-NMR δ ($CDCl_3$, 75 MHz)**:** 67,3 (**C**HOH); 41.9 ($CH\mathbf{C}H_2CH_2CH_3$); 23.5 ($CH(CH_2)_2\mathbf{C}H_2CH_2CH_3$); 25.7 ($\mathbf{C}H_3CHOH$); 22.2 ($CHCH_2\mathbf{C}H_2(CH_2)_2CH_3$); 21.7 ($CHCH_2\mathbf{C}H_2CH_3$); 19.2 ($C\mathbf{H_3}CH(OH)CH_2CH_2CH_3$); 17.9 ($CH_3(OH)CHCH_2CH_2C\mathbf{H_3}$).

12.12.1.5. Reduction of **2-heptanone (303d)** with lithium diphenylphosphide borane **10**

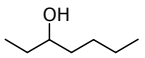
According to the general procedure, 2-heptanone **303d** (0.14 mL, 1.0 mmol, 1.0 equiv) was reacted with diphenylphosphine-borane **10** (200.00 mg, 1.0 mmol, 1.0 equiv) and *n*-butyllithium (0.625 mL, 1.0 mmol, 1.0 equiv, 1.6 M in hexane). After stirring for 15 h at room temperature, water (0,036 mL, 2.0 mmol, 2.0 equiv) was added and following work up gave 2-heptanol **304d** (Conv=95).



304d: 2-Heptanol[510]
$C_7H_{16}O$ **M=**116.16
^{1}H-NMR δ ($CDCl_3$, 300 MHz)**:** 3.80-3.74 (1H, m, C**H**OH); 1.77 (1H, d, *J*=6.0, CHO**H**); 1.55-1.10 (8H, m, $CH_3(C\mathbf{H_2})_4CH(OH)CH_3$); 1.10 (3H, d, *J*=7.0, $CH_3(CH_2)_4CH(OH)C\mathbf{H_3}$); 0.88 (3H, t, *J*=7.0, $C\mathbf{H_3}(CH_2)_4CH(OH)CH_3$).
^{13}C-NMR δ ($CDCl_3$, 75 MHz)**:** 66,9 (**C**HOH); 32.0 ($CH\mathbf{C}H_2(CH_2)_3CH_3$); 39.5 ($CH(CH_2)_2\mathbf{C}H_2CH_2CH_3$); 25.7 ($\mathbf{C}H_3CHOH$); 22.2 ($CHCH_2\mathbf{C}H_2(CH_2)_2CH_3$); 21.7 ($CH(CH_2)_3\mathbf{C}H_2CH_3$); 13.1 ($CH(CH_2)_4\mathbf{C}H_3$).

12.12.1.6. Reduction of **3-heptanone (303e)** with lithium diphenylphosphide borane **10**

Following the general procedure, 3-heptanone **303e** (0.14 mL, 1.0 mmol, 1.0 equiv) was reacted with diphenylphosphine-borane **10** (200.00 mg, 1.0 mmol, 1.0 equiv) and *n*-butyllithium (0.625 mL, 1.0 mmol, 1.0 equiv, 1.6 M in hexane) for 15 h at room temperature giving 3-heptanol **304e** (Conv=77).



304e: 3-Heptanol[510]
$C_7H_{16}O$ **M=**116.16
^{1}H-NMR δ ($CDCl_3$, 300 MHz)**:** 3.52-3.47 (1H, m, C**H**OH); 1.62 (1H, d, *J*=6.0, CHO**H**); 1.55-1.10 (8H, m, $CH_3C\mathbf{H_2}CH(OH)(C\mathbf{H_2})_3CH_3$); 1.00-0.85 (6H, m, $C\mathbf{H_3}CH_2CHOH$ and $(CH_2)_3C\mathbf{H_3}$).

^{13}C-NMR δ ($CDCl_3$, 75 MHz)**:** 72,1 (**C**HOH); 37.2 (CH**C**$H_2(CH_2)_2CH_3$); 31.2 (CH_3**C**H_2CHOH); 28.2 ($CHCH_2$**C**$H_2CH_2CH_3$); 21.9 ($CH(CH_2)_2$**C**H_2CH_3); 13.1 ($CH(CH_2)_3$**C**H_3); 9.3 (**C**H_3CH_2CHOH).

12.12.1.7. Reduction of **benzaldehyde (249)** with lithium methylphenyl-phosphide borane **305**

Following the general procedure, methylphenylphosphine-borane **305** (140.00 mg, 1.0 mmol, 1.0 equiv), *n*-butyllithium (0.625 mL, 1.0 mmol, 1.0 equiv, 1.6 M in hexane) and benzaldehyde **249** (0.10 mL, 1.0 mmol, 1.0 equiv) were reacted for 15 h at room temperature to afford a 86:14 mix of 1-hydroxybenzyl-methyl-phenylphosphine borane **302** and benzyl alcohol **301**.

12.12.1.8. Reduction of **2-heptanone (303d)** with lithium *tert*-butylphenyl-phosphide borane **306**

According to the general procedure 2-heptanone **303d** (0.14 mL, 1.0 mmol, 1.0 equiv), *tert*-butylphenylphosphine-borane **306** (200.00 mg, 1.0 mmol, 1.0 equiv), *n*-butyllithium (0.625 mL, 1.0 mmol, 1.0 equiv, 1.6 M in hexane), were reacted at room temperature to give 2-heptanol **304d** (Conv=67%).

12.12.1.9. Reduction of **2-heptanone (303d)** with lithium *tert*-butyl-phenylphosphide borane **306** at 40° C

According to the general procedure 2-heptanone **303d** (0.14 mL, 1.0 mmol, 1.0 equiv), *tert*-butylphenylphosphine-borane **306** (200.00 mg, 1.0 mmol, 1.0 equiv), *n*-butyllithium (0.625 mL, 1.0 mmol, 1.0 equiv, 1.6 M in hexane), were reacted at 40 °C to give 2-heptanol **304d** (Conv=100%).

12.12.1.10. Reduction of **acetophenone (303a)** with lithium *tert*-butylphenyl-phosphide borane **306**

According to the general procedure acetophenone **303a** (0.12 mL, 1.0 mmol, 1.0 equiv), *tert*-butylphenylphosphine-borane **306** (200.00 mg, 1.0 mmol, 1.0 equiv), *n*-butyllithium (0.625 mL, 1.0 mmol, 1.0 equiv, 1.6 M in hexane) were reacted at room temperature to give 1-phenylethanol **304a** (Conv=34%).

12.12.1.11. Reduction of **acetophenone (303a)** with lithium *tert*-butylphenylphosphide borane at 40° C

Reacting at 40° C acetophenone **303a** (0.12 mL, 1.0 mmol, 1.0 equiv), *tert*-butylphenyl-phosphine-borane **306** (200.00 mg, 1.0 mmol, 1.0 equiv) and *n*-butyllithium (0.625 mL, 1.0 mmol, 1.0 equiv, 1.6 M in hexane), 1-phenylethanol **304a** (Conv=100%) was obtained.

12.13. Procedures for NMR experiments

12.13.1. *General procedure for the preparation of NMR tubes*

All NMR samples were prepared directly into NMR tubes. Prior to each NMR experiment, NMR tubes were oven-dried, sealed with serum septa and parafilm, and filled with dried argon. Samples were prepared as 100.00 μmol of compound with NMR solvent added *via* syringe to bring the total volume up to 500.00 μL.

12.13.2. *General procedure for the preparation of NMR tubes for DOSY*

Following the same previous procedure, all samples were prepared by adding 100.00 μmol of compound, internal references in equimolar ratio and NMR solvent until a total volume of 600.00 μL.

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