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Biologically Active CompoundsVia 2-Aza-1,3-Dienes

Azadieni come intermedi di sostanze biologicamente attive

P.D. Thesis

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Introduction

Heterocyclic compounds represent almost two-thirds of all the known organic compounds: they are widely distributed in nature and play a key role in a huge number of biologically important molecules including some of the most significant for human beings. The use of natural and synthetic heterocyclic compounds in many commercially important spheres is enormous. It is not surprising, therefore, that this class of compounds has received special attention by chemists of different origin to provide selective synthetic access to the huge variety of structural features typical of this class. Furthermore, in the 21st century an imperative factor in the organic synthesis is the control of the absolute stereochemistry of all the relevant chiral centers. Experimental and theoretical investigations on the reaction mechanisms become thus important not only from an academic point of view, but also in optimizing reactions' pathways: knowledge of detailed reaction mechanism in fact is usually the basis for development of new transformation and improvements of existing procedures, improvements that often mean enhancement of diastereomeric and enantiomeric excesses.

Synthetic methodology employing azadienes represents a straightforward and efficient approach to the synthesis of nitrogen-containing heterocycles, which have a range of potential biological activities and are building blocks for many therapeutically useful materials[1,2]. The use of 3-trialkylsilyloxy-2-aza-1,3-dienes has been demonstrated particularly attractive in this context. In fact, these compounds are easily accessible by synthesis and show a wide range of chemical-physical properties and a varying reactivity depending on their substitution patterns.

Chapter 1

Azadienes in organic synthesis

The azadienes, or iminodienes, are among the most used heterodienes in organic chemistry. These are interesting intermediates in the synthesis of heterocyclic compounds and specifically nitrogen compounds, because their typical reactivity foresees their participation in the electrocyclization reactions, particularly, Diels Alder reactions.[1-3] The advance of the azadiene imino Diels-Alder reaction to the status of general synthetic method owes much to the development of methods to activate the azadiene system. In fact, a limitation to the application of azadienes relative to the more commonly used oxodienes is that azadienes generally require some form of activation to achieve general synthetic utility. Anyway, with appropriate substitution pattern, 1-aza-1,3-butadienes and 2-aza-1,3-butadienes are reactive as either electron rich or electron deficient Diels-Alder dienes. Reviews featuring the general synthetic utility of azadienes and their utility in the Diels-Alder reaction specifically have appeared in recent years. [1,4-10]

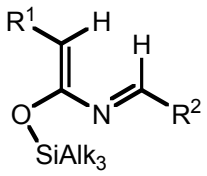
1.1 1- and 2-Azabuta-1,3-dienes

1-Azadienes, or enimine dienes, react with ketenes through [2+2] cycloadditions giving rise to the formation of 4-vinyl-β-lactams.[11] They give also rise to five-membered rings through carbenes addition or 1,3 dipolar cycloaddition.[12] 1-Azadiene complexes of the early-transition metals have been reported and are precursors of metallacyclic alkylidene complexes.[13] Anyway their main application is in the field of six-membered rings formation *via* Diels-Alder reaction (Chapter 3). Owing to their electron deficient character simple 1-azadienes are less reactive toward standard electron deficient dienophiles. They therefore tend to undergo inverse electron demand Diels-Alder reactions when they do react. These reactions usually do not reach high yields because of the unfavourable *s*-

trans/s-cis equilibrium and the electrophilicity of nitrogen atom: self-condensations, dimerizations, imine additions, tautomerization of the imine to enamine become competitive reactions.[3,14] The introduction of electron-donor groups in the diene makes them electron-rich and allows their participation to normal electron demand Diels Alder reactions, by raising their HOMO energy.

2-Azadienes are key intermediates in the preparation both of heterocyclic and open-chain polyfunctionalised compounds. While generally more reactive, their electronic properties mirror the 1-azadienes' ones: depending on the electronic features of their substituents, they can be electron deficient (electron-withdrawing substituents), electron rich (electron donating substituents) or electronically neutral. Their chemistry consists, most of all, of [4+2] cycloaddition reactions with alkenes, alkynes and heterodienophiles such as enamines, carbonylic compounds, nitrogen and nitroso compounds. The main difference between 1- and 2-aza-1,3-dienes is the efficacy of Lewis acid catalysis in the 2-azadienes cycloadditions. The success of Lewis acid mediated catalysis depends on the identification of a Lewis acid which, by complexing an appropriate functional group, activates the dienophiles and does not irreversibly complex the azadiene nitrogen.

Among the electron-rich azadienes, this study takes into account the preparation and reactivity of 3-trialkylsilyloxy-2-aza-1,3-dienes **A** (Fig. 1.1).



A

Fig 1.1: 3-Trialkylsilyloxy-2-aza-1,3-dienes

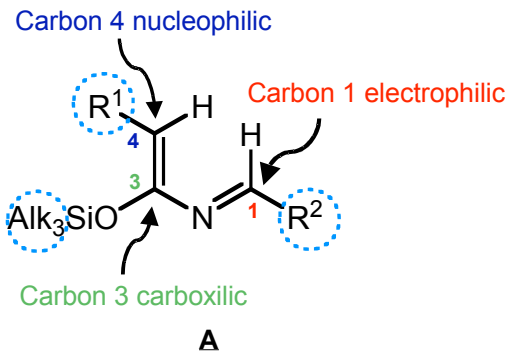
1.2 3-Trialkylsilyloxy-2-aza-1,3-dienes

2-Aza-1,3-dienes bearing in position 3 a trialkylsilyloxy- group (**A**, Fig. 1.1) firstly appeared in literature in the 1980's,[15] authored by Prof. Léon Ghosez research group. Since then, their chemistry has been mainly developed by Prof. Ghosez and Prof. Bongini-Prof. Panunzio's research groups.

3-Trialkylsilyloxy-2-aza-1,3-dienes' structure was designed in order to obtain azadienes reactive toward the hetero Diels-Alder reaction with electron-deficient dienophiles. The unsubstituted azadienes' reactivity depends on conformational factors: the reactive conformation is the *s-cis* one, whereas often the most stable is the *s-trans*. The introduction of a substituent in the position 3 of an azadiene enhances the reactivity of the π system by increasing the population of the *s-cis* conformer. In the mean time, the electron donating nature of the trialkylsilyloxy- substituent raises up the HOMO energy and, in the HOMO, the C-4 coefficient, thus favouring the electron-deficient dienophile's attack in this position.[16] The hetero Diels-Alder reaction will be discussed in detail in the Chap. 3.

- ***Structure analysis and properties***

A careful analysis of the structure of these azadienes (Fig. 1.2) shows that they are highly functionalised and thus potentially highly reactive: first, their dienic nature allows them to take part to a series of reactions (electrocyclic reactions) which occur, in principle, without any charge development. The C-1 atom is an iminic ones and therefore electrophilic; the C-3 atom is carboxylic, being so the precursor of an amidic or an acidic function. The C3-C4 framework is a silylenolether, thus conferring nucleophilic character to the C-4 atom. The C-1 and C-4 atoms can be variously functionalised both with satured or unsatured carbo- or hetero-groups, and with aromatic or non aromatic carbo- or hetero-cycles. By changing the silicon substituents (Alk) it is possible to obtain azadienes with varying stability. The most utilised groups are the trimethylsilyloxy- and the *tert*-butyldimethylsilyloxy groups, the latter conferring higher stability.

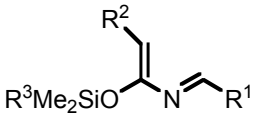


A

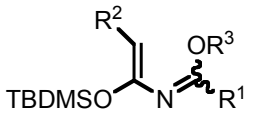
Fig 1.2: 3-Trialkylsilyloxy-2-aza-1,3-dienes' structure analysis

NOMENCLATURE: Obviously, by varying the substituents on the diene, the carbon atoms' priority will change and thus the carbon atoms' enumeration. However, for the sake of the semplicity, along this thesis, the carbon skeleton enumeration reported in Fig. 1.2 will be adopted, regardless the substituents' nature.

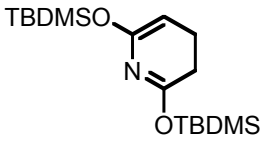
In Fig. 1.3 the azadienes more frequently utilized by the Prof. Ghosez's group are reported. These azadienes are colourless oils. They are purified by distillation and they are sufficiently stable to be stored for several months at –20°C. With respect to their substitution pattern, the substituents at C-1 and C-4 can be alkylic bearing or not one or two oxygenated substituent at C-1. This characteristic increases their reactivity as enophiles.

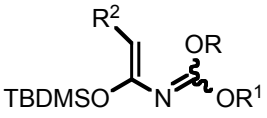


R^1= Ph, -C(Me_3)=CHPh, CH=CH_2, CH_2Ph(OMe)*m,p*
R^2= H, Me,Ph
R^3= Me, *t*-Bu



R^1= H, Me
R^2= H, Me, Cl, F, Ph, CH_2Ph, Bu
R^3= *t*-BuMe_3Si, *i*-Pr, Et





R= *i*-Pr, Et
R^1, R^2= H, Me

Fig. 1.3: Ghosez's azadienes

In previous works, the azadienes reported in Fig. 1.4 have been synthesised by Prof. Panunzio's group: they belong to different series which mainly differ in the C-4 substituent: hydrogen (no substituent), amidic groups, chlorine, bromine, iodine, thioaryl and benzyloxy groups have been placed in this position, whereas at carbon C-1 several aliphatic and aromatic substituents, more or less substituted, are present.

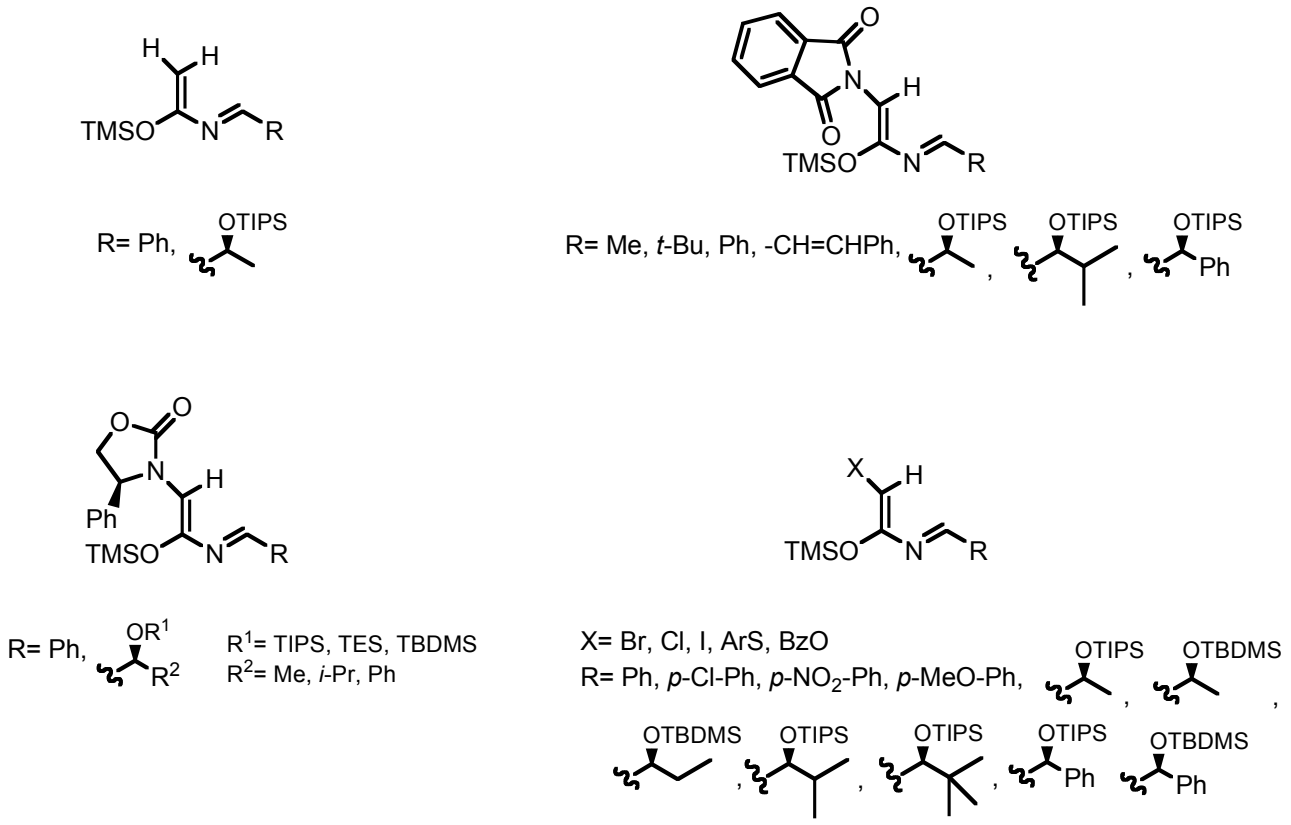
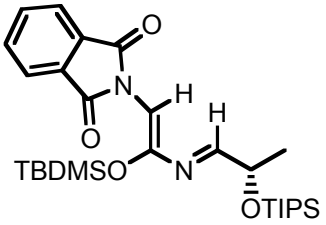


Fig. 1.4: Panunzio's azadienes

Their synthesis and their reactivity will be discussed in the next chapters. They contain several functional groups and are sufficiently stable to be analysed and sometimes stored at –20°C for some days. They are colourless or pale yellow oils and are used after their synthesis as such without any further purification. The only exception is the azadiene **B** reported in Fig. 1.5, which is sufficiently stable to be purified by flash chromatography in silica gel (cyclohexan/ethyl acetate 80/20), thanks to the *tert*-butyldimethylsilyl- group.[17]



B

Yield= 85%; $[\alpha]_D^{20}$= -26 (c=1.0, $CHCl_3$); IR ($CHCl_3$): 1735 cm-1;

^{1}H NMR (200 MHz, $CDCl_3$): 7.96 (d, 1H, J=6.4Hz), 7.82 (m, 2H), 7.68 (m, 2H), 5.47 (s, 1H), 4.48 (m, 1H), 1.32 (d, 3H, J=6.5 Hz), 1.02 (m, 21H), 0.75 (s, 9H), 0.02 (s, 6H) ppm;

^{13}C NMR (50 MHz, $CDCl_3$): 168.1, 166.6, 155.7, 133.9, 132.3, 123.2, 90.5, 70.4, 25.5, 21.7, 17.9, 17.6, 12.2, -4.1, -4.2 ppm.

Fig.1.5:(5*S*)-2-(*tert*-Butyldimethylsilyloxy)-1-phtalimido-5-(triisopropilsilyloxy)-3-aza-esa-1,3-diene and its spectral properties.

- *Stereochemistry*

The comprension of the stereochemistry of this compounds is essential in order to elucidate the mechanisms of their formation reaction and their further reactivity. The two double bonds configurations are responsible for the dienes themselves configuration, whereas the dihedral angle between the two double bonds' planes determine the azadienes' conformation. Configuration and conformation have been deduced from ^{1}H, ^{13}C, ^{15}N NMR spectra (Fig. 1.6, 1.7), from theoretical study of stability for a representative diene (Fig. 1.8) and, *a posteriori*, from the careful analysis of the products arising from azadienes themselves.

The double bond C=N's configuration has been assigned[18] from the geminal coupling constant $^{2}J_{NH}$ value in the ^{15}N NMR spectrum: it is small and positive, thus demonstrating that the lone pair on the nitrogen is *trans* with respect to the iminic hydrogen and so that the C=N double bond is *E*.

The vicinal coupling constant $^{3}J(N\text{-}H)$ through the enaminic π bond has been used as a parameter to determine the double bond C=C's configuration: its value is small and positive, thus showing the *cis* relation between the nitrogen and the enaminic hydrogen and so the (*Z)* configuration of the double bond C=C. Concerning the conformation, the existence of long range coupling constants $^{4}J(C\text{-}H^{4})$ e $^{5}J(C\text{-}H^{5})$ in the ^{13}C NMR spectrum demonstrates the presence of the *s-trans* conformation (Fig. 1.6).

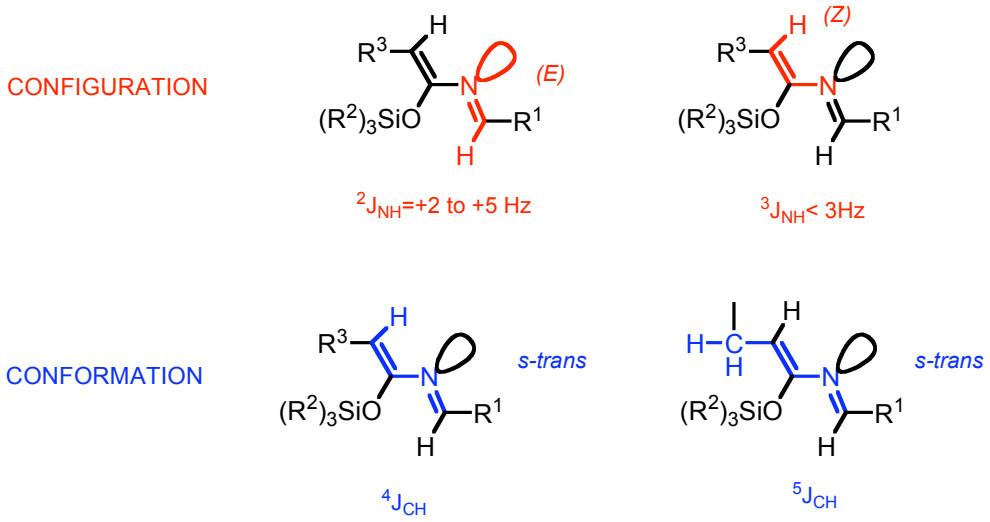
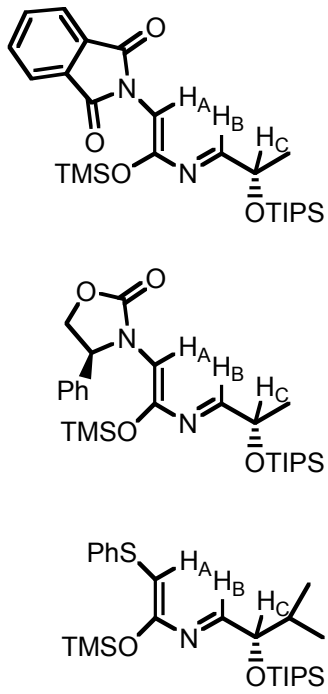


Figure1.6: ^{13}C, ^{15}N-NMR results upon 3-trialkylsilyloxy-2-aza-1,3-dienes

Despite this, as it was already noted, the presence of a substituent in the position 3 of the azadiene increases the population of the *s-cis* conformer. In fact, ^1H NMR NOE experiments have been reported, which demonstrate the proximity of C1-H and C4-H (H_B and H_A respectively) (Fig. 1.7).[17,19]



irradiations	NOE effects
$H_A \rightarrow H_B$	7.0%
$H_B \rightarrow H_A$	1.4%
$H_B \rightarrow H_C$	2.1%
Me $\rightarrow H_B$	1.6 %
Me $\rightarrow H_C$	4.0%

irradiations	NOE effects
$H_A \rightarrow H_B$	3.1%
$H_B \rightarrow H_A$	3%
$H_B \rightarrow H_C$	2.0%

irradiations	NOE effects
$H_A \rightarrow H_B$	1.13%
$H_B \rightarrow H_A$	1.78%
$H_B \rightarrow H_C$	2.32%
$H_C \rightarrow H_B$	2.50 %

Figure 1.7: NOE Experiment representative example

Furthermore, *ab initio* quantomechanical calculations upon the simple azadiene reported in Figure 1.8 show the existence of a long range interaction of the silicon with the nitrogen atom (0.084 e^-) responsible for the stabilization of a twisted (46°) *s-cis* conformation. This form is the absolute minimum of all possible conformers[7], thus explaining the reactivity of these dienes in Diels-Alder reactions.

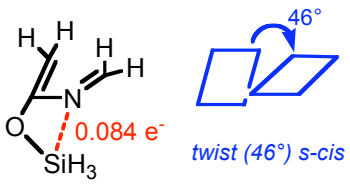


Figure 1.8: MP2/6-31G* calculations' results

In conclusion, the configuration of 3-trimethylsililoxy-2-aza-1,3-dienes is, without doubt, *EZ*. The most stable conformations are the *s-cis* and the *s-trans* ones. By the use of different approaches both of them have been identified in the NMR spectra. Anyway the conformation reactive toward electrocyclizations is the *s-cis* one.

1.3 3-Trialkylsilyloxy-2-aza-1,3-dienes synthesis

All the several synthetic methods to 3-trialkylsilyloxy-2-aza-1,3-dienes can be represented as in the retrosynthetic sketch of Fig. 1.9: convergent synthesis which combines a carboxylic acid synthon and an iminic synthon.

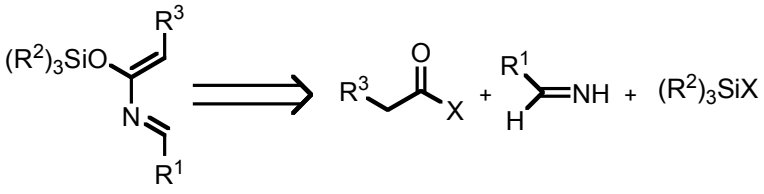


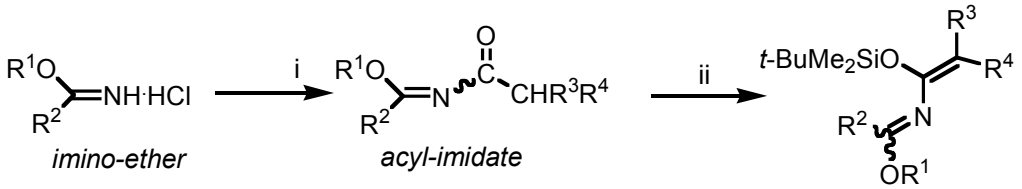
Figure 1.9: Retrosynthetic approach to 3-trialkylsilyloxy-2-aza-1,3-dienes

Four different synthetic strategies have been used[18] which differ in the iminic synthon: synthesis from iminoethers, from imides, from imines and from aldehydes. Except for the second one, the acidic synthon is always represented by an acyl chloride.

A brief overview about the literature-reported syntheses of 3-trialkylsilyloxy-1,3-azadienes is presented.

- ***Synthesis from iminoethers***

1,3-Diactivated 2-aza-1,3-dienes **C** can be prepared via the acylation of an iminoether hydrochloride, followed by silylation of the resulting acyl-imidate (Scheme 1.1). The imino-ethers can be obtained by the Pinner procedure[20] or by reaction of an amide with an alcohol in the presence of benzylic chloride.[21]This synthesis presents some limitation about the substituents R^1 and R^2, because of the tendency of the iminoethers toward trimerization.

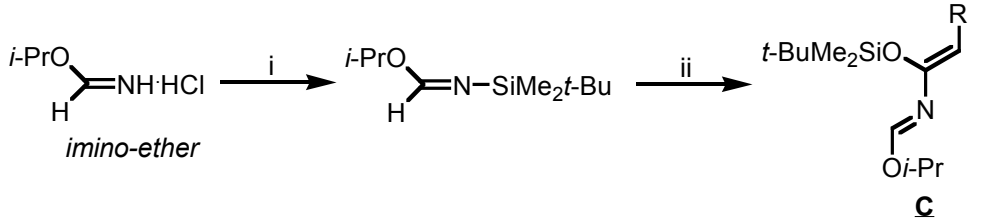


i): $R^3R^4CHCOCl$ **3**; ii): t-$BuMe_2SiOTf$, TEA, Et_2O.

R^1= *i*-C_3H_7, C_2H_5, CH_3;
R^2= H, CH_3, Ph;
R^3= H, CH_3, *n*-C_4H_9, Ph, $C_6H_4CH_2$, $C(CH_3)_3$, $CH=CH_2$, F, Cl, CO_2Me
R^4= H, CH_3

Scheme 1.1: Synthesis from iminoethers

Sometimes it can be helpful to invert the reaction sequence, by silylating the iminoether before and then acylating the resulting *N*-silyl-imino-ether (Scheme 1.2).[18]



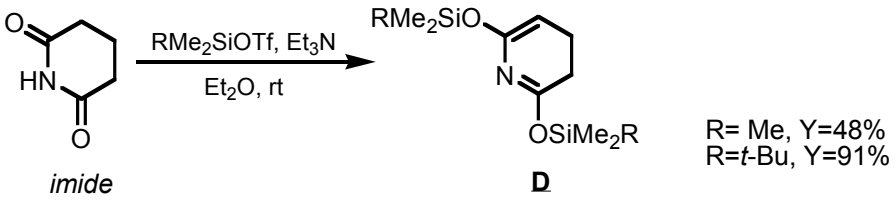
i): *t*-$BuMe_2SiOTf$, TEA (22eq), CH_2Cl_2, -40°C; ii): RCH_2COCl, TEA, Et_2O, r.t

R= H, Me, *n*-Bu, Ph, $PhCH_2$, *t*-Bu, $CH=CH_2$, F, Cl, CO_2Me.

Scheme 1.2: Synthesis from iminoethers

- ***Synthesis from imides***

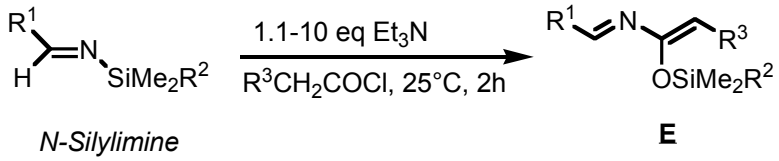
The cyclic dienes **D** represented in the Scheme 1.3 has been obtained by silylation of both the glutaryl imide's oxygens with trialkylsilyl-triflates in the presence of triethylamine (Scheme 1.3).[22]



Scheme 1.3: Synthesis from imides

- ***Synthesis from N-silyl-imines***

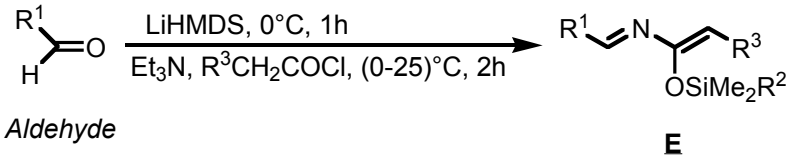
N-Silylimines, prepared and, if possible, purified following the literature procedure, have been acylated with acyl chloride in the presence of an excess of triethylamine, obtaining azadienes. This method is quite general, but can not be applied to the synthesis of azadienes bearing a strong electron withdrawing group at C-1 (Scheme 1.4).[18]



Scheme 1.4: Synthesis from *N*-silyl-imines

- ***Synthesis from aldehydes***

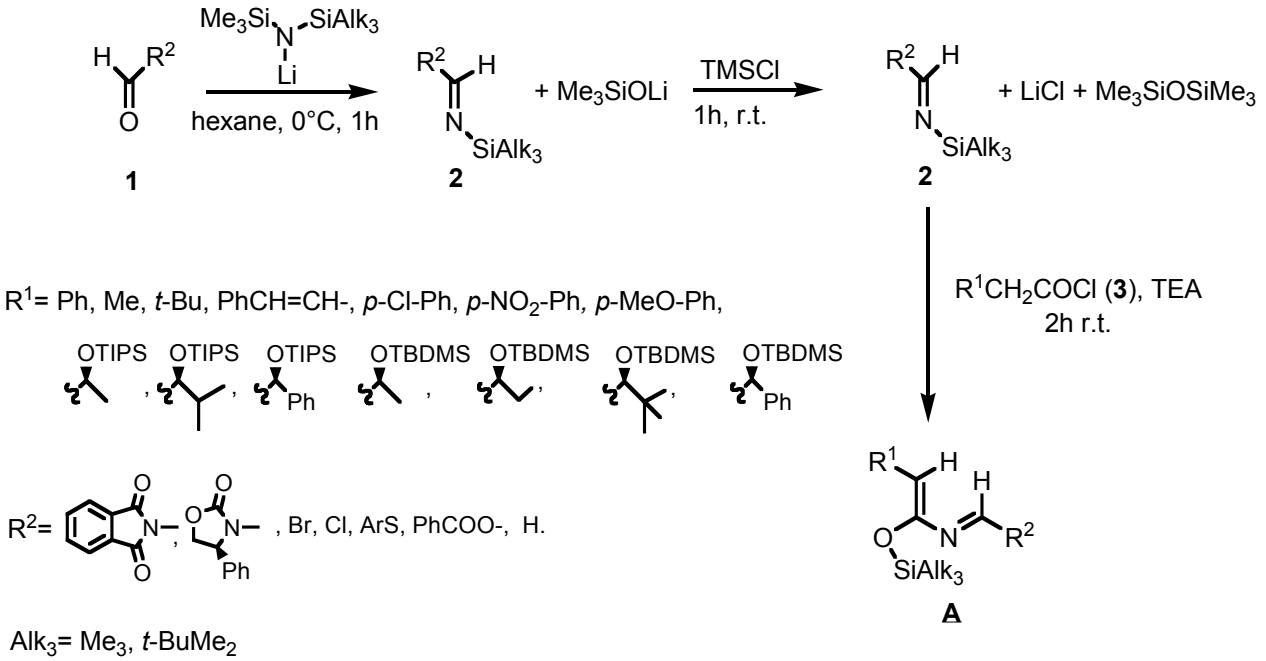
The same authors have tempted to carry out the azadienes' synthesis avoiding the silylimines' isolation and thus to obtain azadienes from aldehydes in just one step. *N*-Trimethylsilylimines have been obtained by treating the aldehydes with LiHMDS and acylated with acyl chloride in the presence of triethylamine. This method gives the same results than the previous and is more practical when applied to non-enolisable aldehydes.



Scheme 1.5: Synthesis from aldehydes

1.4 3-Trialkylsilyloxy-2-aza-1,3-dienes synthesis: our protocol

In our research group 3-trialkylsilyloxy-2-aza-1,3-dienes **A** have been synthesized starting from aldehydes **1** through the corresponding *N*-trialkylsilylimines **2** and acylchloride **3**, as represented in the Scheme 1.6.



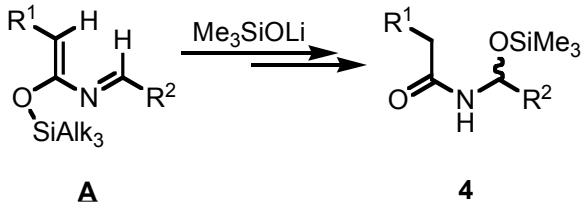
Scheme 1.6: Synthesis of azadienes **A**

The reaction has been carried out on a wide variety of reagents, the conditions depending on the substituents, on the aldehydes **1** and on the acylchlorides **3**. The general reaction procedure for the preparation of the most used azadiens is herein reported:

Aldehyde **1** (1 mmol) was added to a solution of LiHMDS 1M in THF (1.1 mmol) and hexane (5 mL) at 0°C under inert atmosphere. The reaction mixture was stirred at 0°C for 1 h. Trimethylchlorosilane (1 mmol) was added in one portion and after stirring 10 min at 0°C the mixture was allowed to stir for 1 h at room temperature. A white precipitate formed. The mixture was cooled at 0°C, triethylamine (2 mmol) was added in one portion and after 5 min a solution of acylchloride **3** (1 mmol) in 5 mL of hexane was added. Stirring was mantained for 2 h and a conspicuous precipitate formed. The mixture was filtered through Celite® under inert atmosphere and the solvent was removed in vacuo to afford the azadiene **A** as an oil, which could be analyzed by ^{1}H NMR spectroscopy.

Some general consideration can be taken into account:

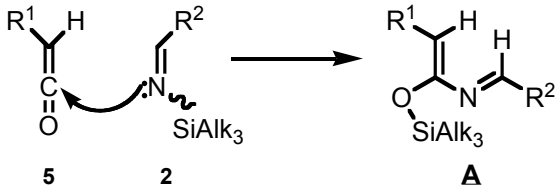
1) The starting aldehydes **1** are aliphatic, aromatic and heteroaromatic. Enolizable and non-enolizable type may be used as well. The corresponding *N*-trialkylsilylimines **2** are obtained adding a lithium *N*-bis-trialkylsilylamide solution to the aldehydes **1**, upon inert atmosphere, at 0°C.[23] As solvent hexane, heptane or tetrahydrofuran have been used. In the reaction with lithium hexamethyldisilyl amide, *N*-trimethylsilylimines are obtained. The use of lithium trimethyl-triisopropyl-disilylamide[24] or *tert*-butylpentamethyl-disilylamide gave rise to the formation of *N*-(triisopropylsilyl) imines and *N*-(*tert*-butyldimethylsilyl) imines, with elimination, regardless to the other trialkylsilylgroups linked to the nitrogen atom, of lithium trimethylsilanoate.[25,26] The reaction is quantitative and can be controlled by IR spectroscopy: the stretching of the C=NSiR$_3$ bond relies between 1650 and 1680 cm^{-1}. Moreover the formed trialkylsilylimines have (*E)*-geometry, as deducted from ^{1}H NMR through NOE measurements.
2) The lithium trimethylsilanoate, by-product of the reaction, is eliminated by adding trimethylsilylchloride to the reaction mixture, with precipitation of lithium chloride and formation of hexamethyl-disiloxane. The two by-products are subsequently eliminated by filtration and distillation respectively. The elimination of the lithium trimethylsilanoate from the reaction mixture has been demonstrated necessary to avoid its addition to the azadiene **A**, with the formation of the amidic product **4** (Scheme 1.7).



A **4**

Scheme 1.7: Trimethylsilanoate addition to azadiene **1**

3) Despite the fact that this reaction can be described as a base-mediated acylation of the *N*-silylimine,[27] it is thought that the ketene **5** (Scheme 1.8) is formed *in situ* in the reaction pot, adding triethylamine and acylchoride **3**. In fact, its formation in the reaction mixture has been demonstrated by a low temperature FTIR study of the reaction of acylchloride with imines in presence of a base.[28] The acylchloride **3** may be substituted in the α position by hydrogen,[29] alkyl, halogen,[30] amidic[7,17,31] or ethereal[32] groups. Thus, the reaction proceeds through a nucleophilic attack of the imine's nitrogen lone pair to the ketene (Scheme 1.8) with concomitant migration of the trialkylsilyl group from nitrogen to oxygen. This process is known as "silyltropism"; its significance in determining the reaction pathway will be discussed in the next paragraphs (Chapter 5).



5 **2** **A**

Scheme 1.8: Imine's nucleophilic attack upon ketene

4) The 3-trialkylsilyloxy-2-aza-1,3-dienes **A** with various substitution patterns are obtained in variable yields. Their stability largely depends on their substitution pattern. The substituents R^2 present in the aldehydes **1** (Scheme 1.6) seem not to have effects, whereas the ketenic substituents R^1 have a greater influence: it is possible to isolate and characterize by spectroscopy the azadienes deriving from ketenes carrying in the α-position two hydrogens, an amido groups, a halogen (chlorine or bromine) or a thioaryl group. The stability is mostly conferred by the nature of the silylimines **2** utilised. The most stable 3-trialkylsilyoxy-2-aza-1,3-dienes are the triisopropyl- and the *tert*-butyl-dimethyl-silyloxy ones because the triisopropyl- and *tert*-butyl-dimethylsilyl groups are not easily hydrolizable. It has

been even possible to purify by flash chromatography on a short silica gel-column the azadienes **B** carrying an amidic substituent in position 4 and a *tert*-butyl-dimethylsilyl group on the oxygen (Fig. 1.5).[7,33,34] The configuration of the isolated and purified azadienes has been determined by a serie of NOE experiments. In the Figure 1.7, the results obtained for some azadienes have been reported as example. Observing the increment values obtained, it can be deducted that the configuration of these azadienes is *s-cis-EZ.*[7,17]

Chapter **2**

Azadienes in elettrociclic [4+2] reaction

The Diels-Alder (DA) reaction is a powerful tool for organic synthesis, since ring structures are a common feature in many target molecules and dienes are required motifs within precursor molecules. The DA reaction can simplify certain synthetic problems and help shortcut synthetic pathways, allowing sometimes complicated ring structures to be built in a single step.

Although for many years the reaction has been limited to the all-carbon DA reaction, in the last twenty years, hetero DA (HDA) reactions involving heterodienes and/or heterodienophiles have become pivotal steps in the preparative synthesis of a huge range of products.

2.1 Diels-Alder reactions

Under suitable conditions, conjugated dienes undergo a cycloaddition reaction with multiple bonds to form unsaturated six-membered rings (Fig. 2.1). In conventional terminology, this is a 1,4-addition of a diene and a dienophile. It occurs thermally and it is called [4+2]-cycloaddition reaction because four π electrons from the diene and two π electrons from the dienophiles are directly involved in bonding change. This reaction has a great synthetic importance and Otto Diels and Kurt Alder received the 1950 Nobel Prize in Chemistry "for their discovery and development of the diene synthesis".

The simplest DA reaction is the reaction of a 1,3-butadiene and ethylene to yield cyclohexene.

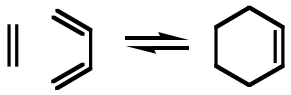


Figure 2.1: The Diels-Alder reaction of ethylene and butadiene

There is not a single mechanism for all DA reactions.[35] At first approximation, we can divide them into two classes:

1) Synchronous and symmetrical (concerted) mechanisms when the two new bonds formed simultaneously. In the transition state, the two forming bonds have the same lengths. The combination of ethylene and butadiene is one example.
2) Multistage (non-concerted) and asynchronous mechanisms. The transition state is a di-radical, one bond being formed, the other not.

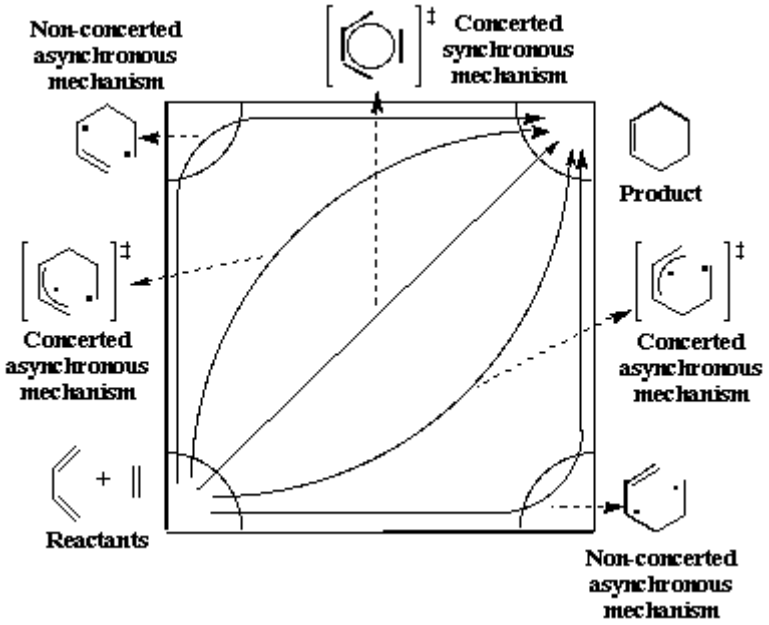


Figure 2.2: Possible mechanisms for DA reactions.

Concerted mechanism leads to a stereospecific and completely *syn* (*suprafacial*) addition with respect to both the alkene and the diene. Non-concerted asynchronous processes pass through open chain intermediate in which there can be a rotation at the unbound termini, leading to loss of stereospecificity. Real mechanisms are a mixture of these two extremes, one bond being more properly formed and thus shorter than the other.

When both the diene and the dienophile are suitably substituted, a stereochemical feature arises because the reactants may approach each other in two distinct orientations

(Figure 2.3). The substituent on the dienophile may be directed toward the diene (*endo* approach) or away from the diene (*exo* approach).

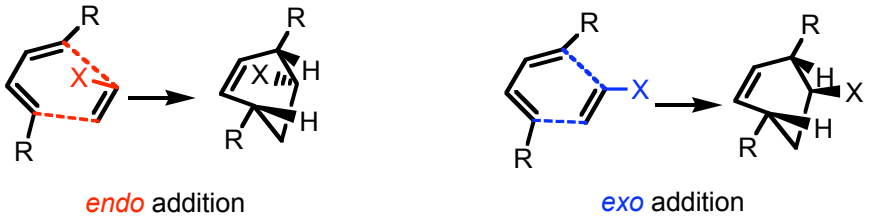


Figure 2.3: *Endo/exo* approaches of the dienophile to the diene

In most DA reactions, when the product distribution is under kinetic control, the *endo* adduct is preferentially, sometimes exclusively, formed. Several hypotheses have been made to explain this selectivity.[36-38]

According to the FMO (Frontier Molecular Orbital) theory[39] the DA reaction is controlled by the energy gap between HOMO (Highest Occupied Molecular Orbital) and LUMO (Lower Unoccupied Molecular Orbital). For the most common case, which involves dienophiles with electron-withdrawing substituents, the frontier orbital are Ψ_2 of the diene (which is the HOMO) and π^* of the dienophiles (which is the LUMO). These reactions are called *normal electron demand* DA reactions: they are particularly efficient and rapid when the dienophiles contains one or more electron-attracting groups and still more if the diene also contains electron-releasing groups. There are also examples where the substituents are reversed so that the dienophile is electron-rich and the diene is electron-deficient, these are called inverse electron demand DA reactions and involve HOMO(dienophile) and LUMO(diene) (Figure 2.4).

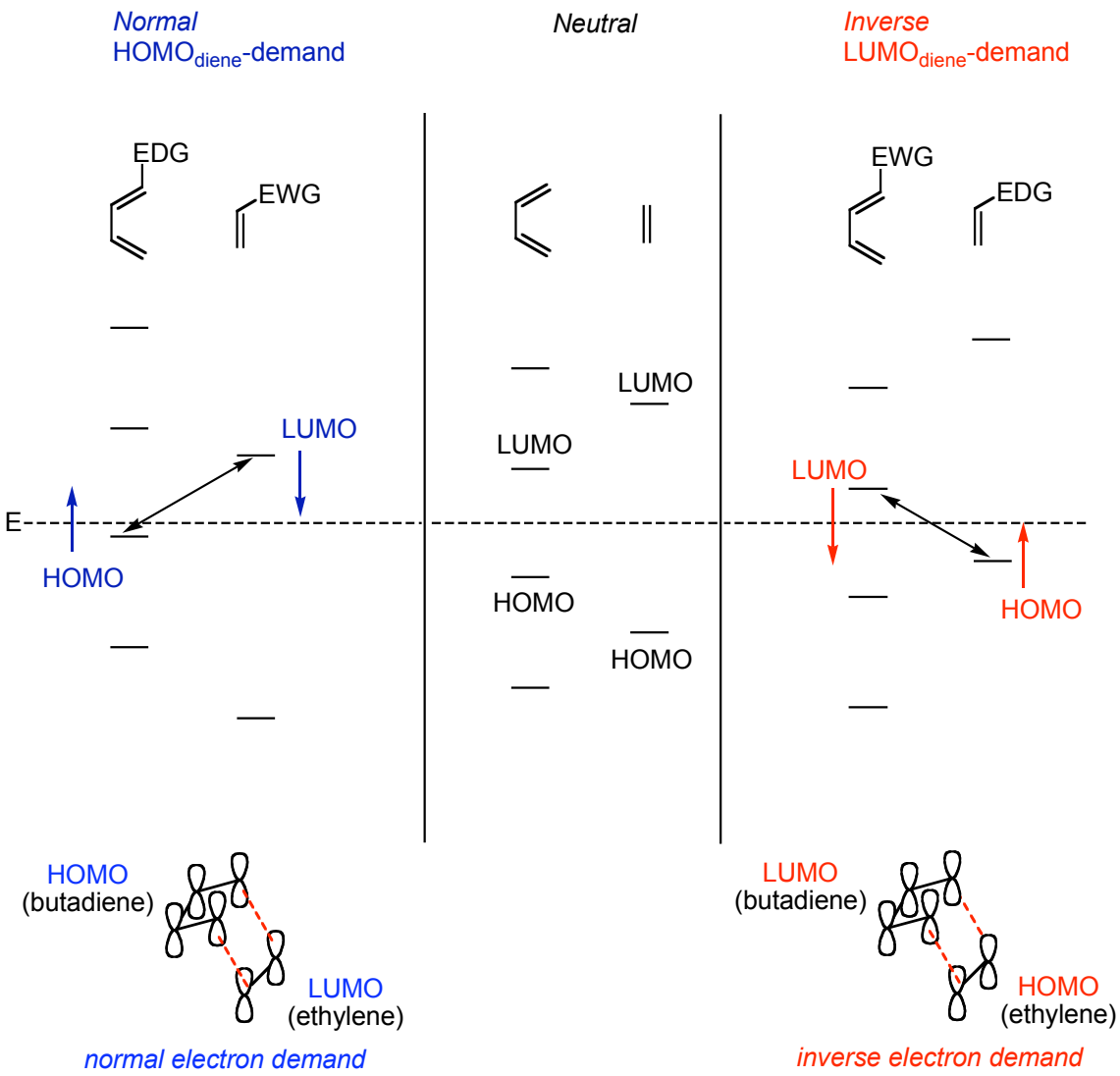


Fig 2.4: Normal/Inverse electron demand DA reactions

The regiochemistry of the reaction is sentive to the nature of the substituents and can be predicted on the basis of the generalization that the strongest interactions will be between the centres on the frontier orbitals having the largest orbital coefficients.

By swapping carbon atoms on the diene and/or the dienophile component with heteroatoms, the so-called **hetero-Diels-Alder (HDA)** takes place. It is a very useful method for constructing heterocyclic rings and is widely used as a key step in the synthesis of natural products.[3,40-47] Compared to the numerous theoretical calculations on the normal DA reactions, only very few theoretical studies of HDA reactions have been performed.[48,49] It has been pointed out that the reaction can change from a concerted non-syncronous mechanism to a stepwise mechanism depending on the substituents on the reacting species and on the reaction conditions.

2.2 3-Trimethylsilyloxy-2-aza-1,3-dienes in HDA

Conjugated systems containing nitrogen, typified by the 1- and 2-azabutadienes systems, show diminished reactivity toward representative electron-deficient dienophiles, meaning that the introduction of a nitrogen atom into conjugated systems will confer electrophilic character to the system.[1,2] Actually this recognition led to the investigation, demonstration, and, subsequent development of the inverse electron demand ($LUMO_{diene}$ controlled) DA reactions. Obviously the introduction of complementary electron-withdrawing groups accentuates the electron-deficient nature of the azadiene, thus permitting the use of electron-rich, strained, or even simple olefins as dienophiles. Alternatively, the complemetary addition of strong electron-donating substituents to the azadienic system increases nucleophilic character of the azadiene system and permits the use of conventional electron-deficient dienophiles in DA reactions. In such instances, the introduction of the electron-donor group raises the $HOMO_{azadiene}$ energy, thus diminishing the magnitude of the $HOMO_{azadiene}$ -$LUMO_{dienophile}$ energy separation: these energetic variations result in the participation of the diene in normal ($HOMO_{diene}$ controlled) DA reactions (Fig. 2.5).

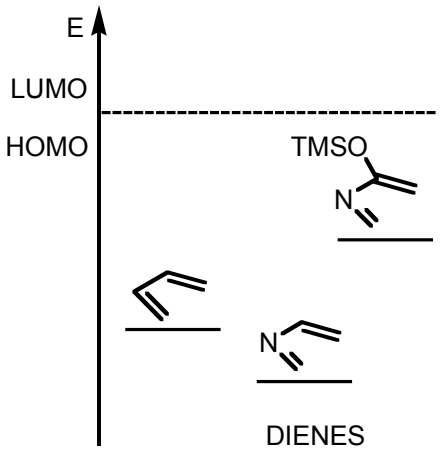


Fig. 2.5: Energetic effect of the substituents on the diene

3-trialkylsilyloxy-1,3-azadienes **A**, subject of this thesis, are electron-rich dienes, due to the strong electron-donating properties of trialkysilyloxy-subtituent. Therefore, they partecipate to normal electron demand HDA reactions with electron-deficient dienophiles.

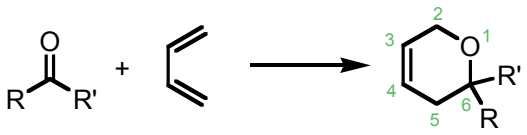
The presence of the trialkylsilyloxy group at C-3 also decreases the energy barrier between the *cisoid* and *transoid* conformation of the diene, thus favouring the cycloaddition over reactions on the nitrogen atom.[50,51]

3-Trialkylsilyloxy-2-aza-1,3-dienes **A** have been used in HDA reactions with a variety of dienophiles furnishing pyridones, isoquinolones, tetrahydropyridones, piperidones, pyrimidones, tetrahydrooxazinones with various substitution patterns.[23] This chemistry has been mainly developed by Prof. Ghosez' and Prof. Bongini- Prof. Panunzio's groups.

2.3 Dienophiles in HDA

- *Carbonyl compounds*

Cycloaddition reactions of a 1,3-diene with a carbonyl compound provides a 5,6-dihydro-2H-pyran derivative (Scheme 2.1).



Scheme 2.1: Carbonylic compounds as dienophiles in HDA

The transition state of the HDA reaction is generally found to be unsymmetrical. For the reaction of formaldehyde with 1,3-butadiene, Houk et al. have calculated the C-C and the C-O bond lenghts to be different in the transition state represented in Fig. 2.6.[48] Unsymmetrical *exo* or *endo* transition states have been calculated also investigating the reaction of BH_3-coordinated formaldehyde with 1,3-butadiene. This coordination confers polar character to the transition state and lowers the activation energy of the reaction considerably. In fact, generally reactions of this type involving aliphatic or aromatic aldehydes or ketones proceed poorly unless highly reactive diene and/or catalysts are used: simple aldehydes

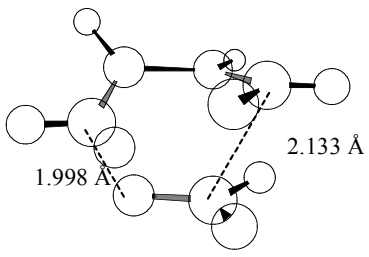


Figure 2.6: The transition state (ab initio calculations) of the HDA reaction of formaldehyde with 1,3-butadiene.

react readily with many electron-rich oxygenated dienes under Lewis acid catalysis (Fig. 2.7).

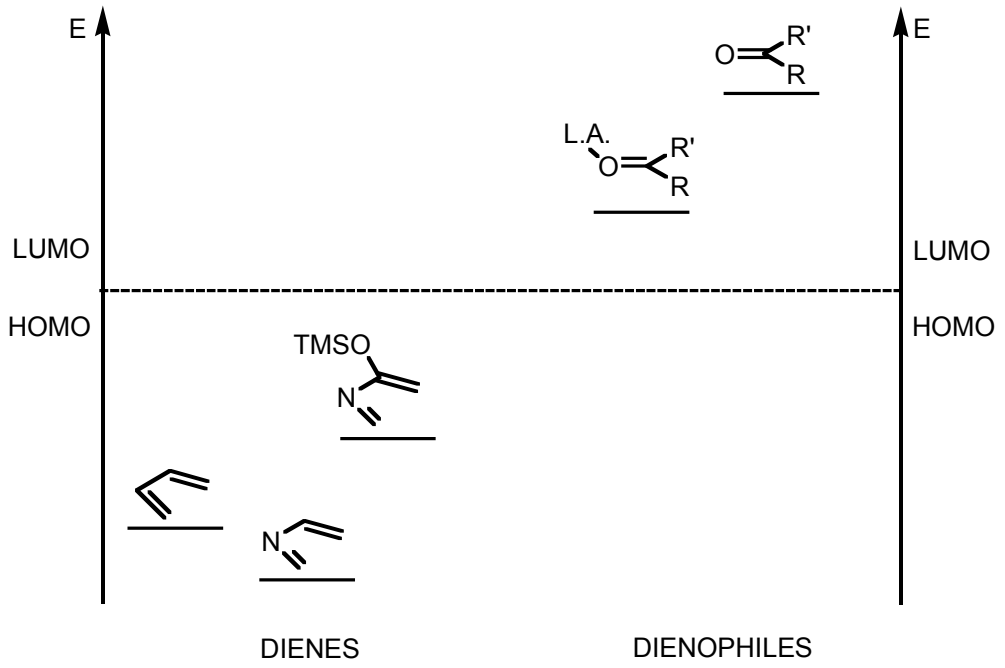
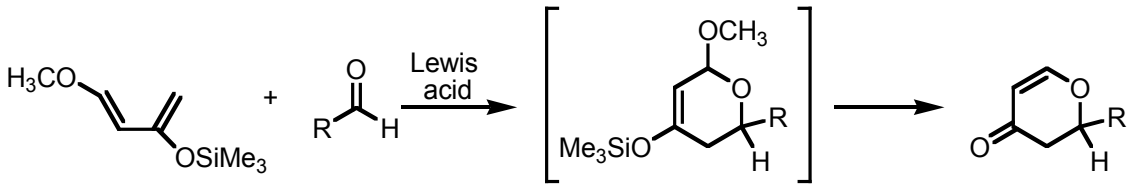


Fig. 2.7: Energetic effect of the substituents on the diene and dienophile

A pioneering work in this field has been done by Prof. Danishefsky group: the 1-methoxy-3-trimethylsilyloxy-1,3-butadiene, which is known as Danishefsky diene, reacts with a wide range of unactivated aldehydes under Lewis acid (zinc chloride, boron trifluoride etherate, $Eu(fod)_3$) catalysis to directly afford 2,3-dihydro-δ-pyrone (Scheme 2.2).



Danishefsky diene

Scheme 2.2: HDA reaction between Danishefsky diene and carbonylic compounds

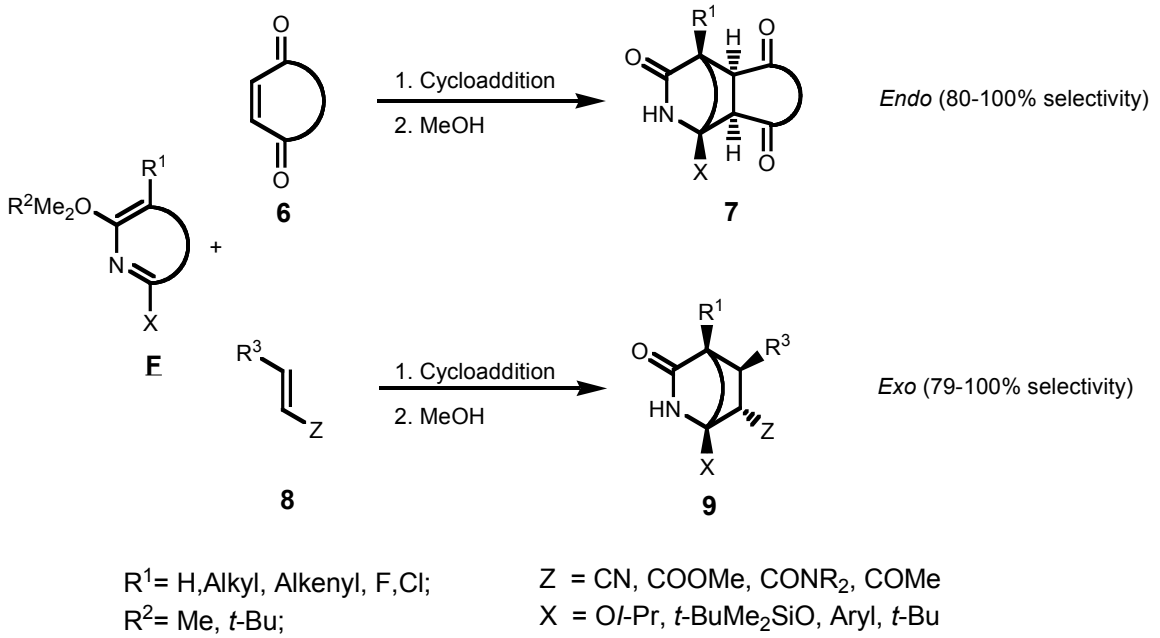
The mechanism, the stereochemistry and the applicability of the reaction have been full described. Two mechanicistic pathways have generally been taken into account for these LA mediated HDA reactions: 1) the traditional DA pathway or 2) the formation of the HDA adduct by Mukaiyama-aldol reaction pathway. Depending on the catalyst and/or the solvent used and on the reaction substrates, pericyclic and/or Mukaiyama aldol-like

pathways may be invoked.[52] Similar remarks will be drawn for reaction of 3-trimethylsilyloxy-2-aza-1,3-dienes **A** and carbonilic compounds (Fig. 3.1, Fig. 3.2).

- ***Electron deficient olefins***

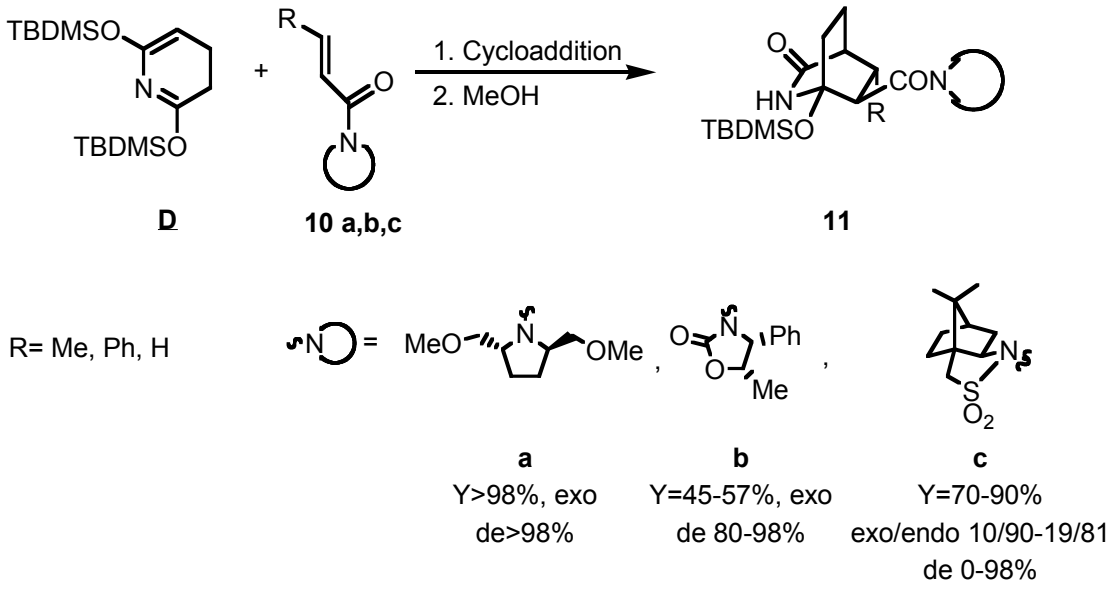
Several examples of Diels Alder reactions between electron-rich 2-azadienes and olefinic dienophiles have been reported in literature.

Cycloaddition of 3-trialkylsilyloxy-2-azadienes **F** with cyclic electron-deficient olefins **6** took place with *endo*-selectivity (product **7**), whereas acyclic dienophiles **8** gave an unexpected high kinetic *exo*-selectivity (product **9)**, (Scheme 2.3). This stereochemical dichotomy has been assigned to different reacting conformations by authors.[51]



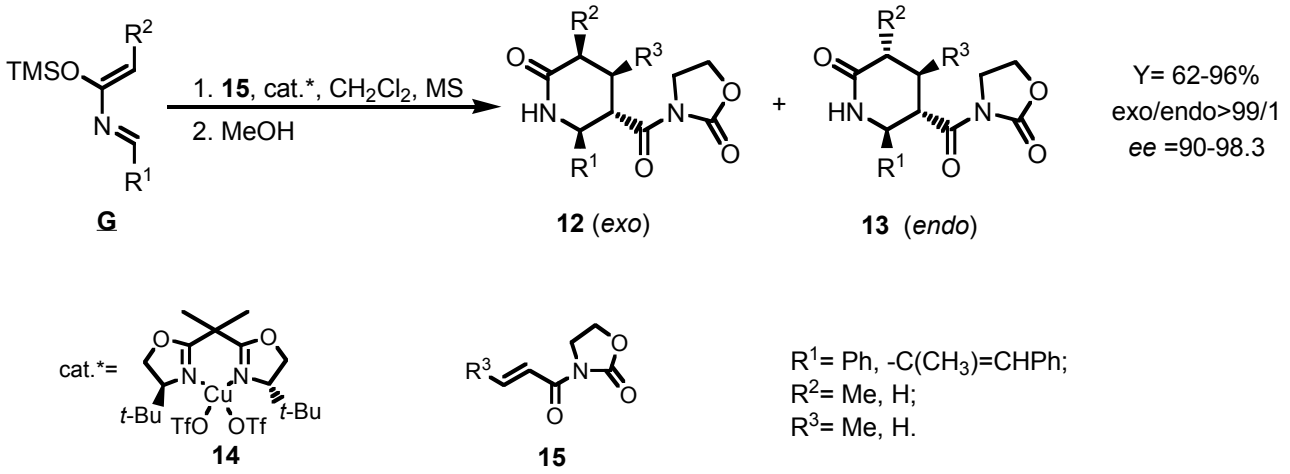
Scheme 2.3: Electron deficient olefins as dienophiles

Highly selective asymmetric cycloadditions to the azadiene **D** have been observed with unsatured amides derived from C_2 symmetric pyrrolidines **10a**, whereas less satisfactory results have been achieved by using Evans', and Oppolzer's dienophiles, **10b** and **10c** respectively (Scheme 2.4).[51]



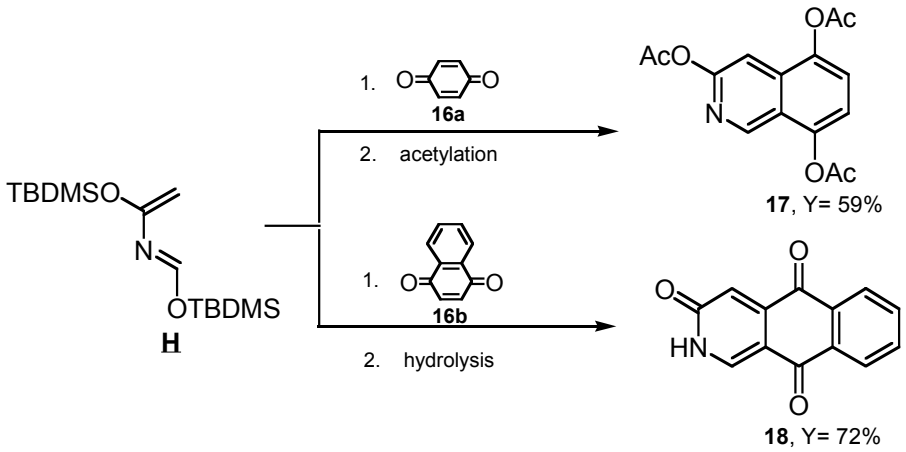
Scheme 2.4: Unsaturated amides as dienophiles

Otherwise an asymmetric version of the HDA reaction upon 3-trialkylsilyloxy-2-azadienes **G** has been obtained by using as chiral catalyst the Evans' mild Lewis acid **14** derived from copper (II) triflate and a C_2-symmetric bis (oxazoline) ligand. This catalyst is tolerated by the azadiene **G** by binding selectively the bidentate imide group of the dienophile **15** (Scheme 2.5)[50] and works well between –45°C and room temperature.



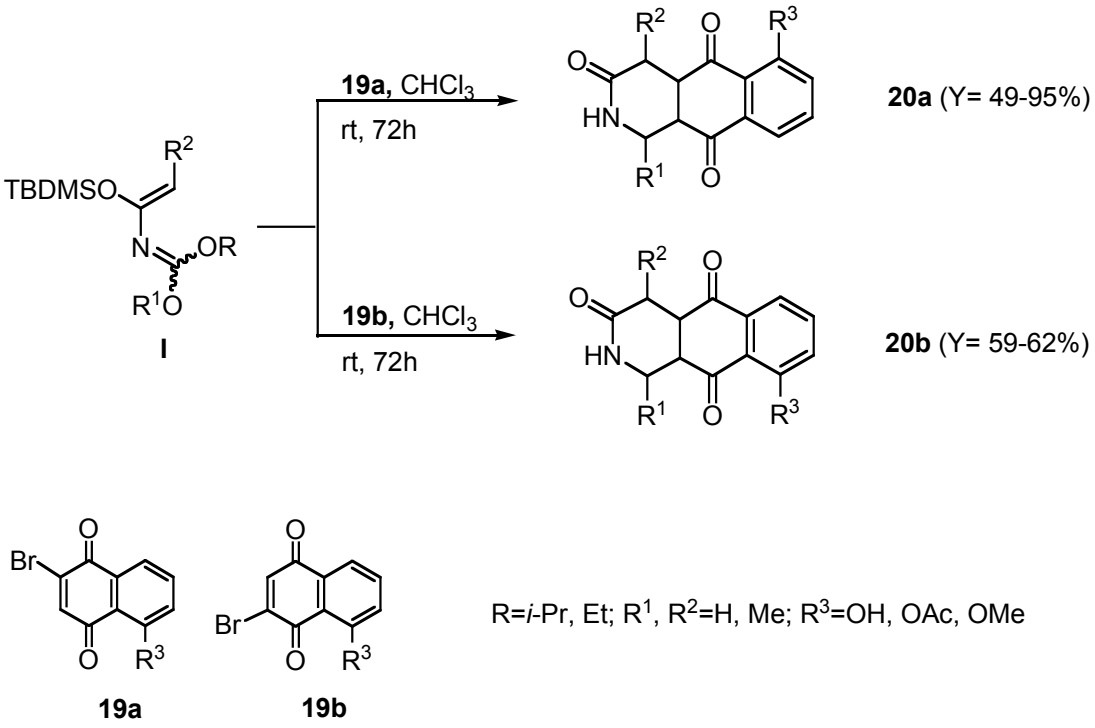
Scheme 2.5: Enantioselective HDA reaction

The enhanced *exo*-selectivity has been imputed to the large size of the copper complex bound to the imide dienophile.



Scheme 2.6: Quinones as dienophiles

2-Azadienes **H** cycloadd also to quinones **16a,b** giving the corresponding aromatised cycloadducts **17**, **18** (Scheme 2.6).[50] It is possible to carry out the reaction with a one-pot multicomponent procedure, which combines the *N*-*t*-butyldimethylsilyl iminoether, an acetyl chloride derivatives (precursors of the 2-azadiene **H**) and a dienophile in the presence of triethylamine without isolation of any intermediate. In general the one-pot procedure gave higher yields than the two-step process involving the synthesis and isolation of 2-azadienes.

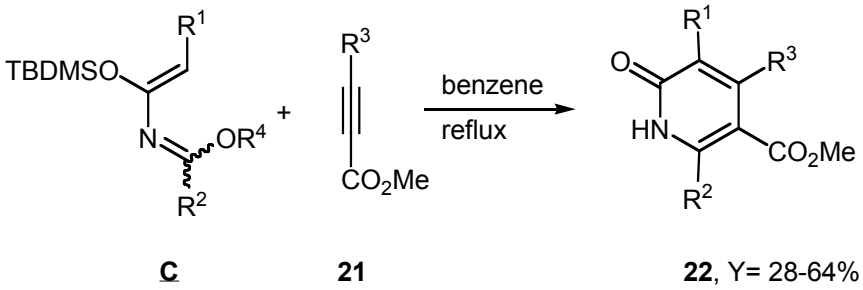


Scheme 2.7: Bromo-quinones as dienophiles

Polisubstituted 2-azaantraquinon-3-ones **20 a, b** of biological interest have been regiospe-cifically and in high yields obtained by cycloaddition of the 2-azadiene **I** to bromonaphtoquinones **19 a, b** (Scheme 2.7).[53,54] The presence of the bromine improves regiocontrol and yields of the reaction respect to unbrominated quinones. The acidic hydrolysis of the 3-silyloxy group is not necessary, because of the *in situ* formation of HBr.

- ***Acetylenes as dienophiles***

Azadienes cycloadd also to electron-deficient acetylenic dienophiles **21** yielding pyridones **22** (Scheme 2.8). Also in this case it is possible to carry out the reaction in a one-pot multicomponent way, obtaining higher yields than the two-step process.



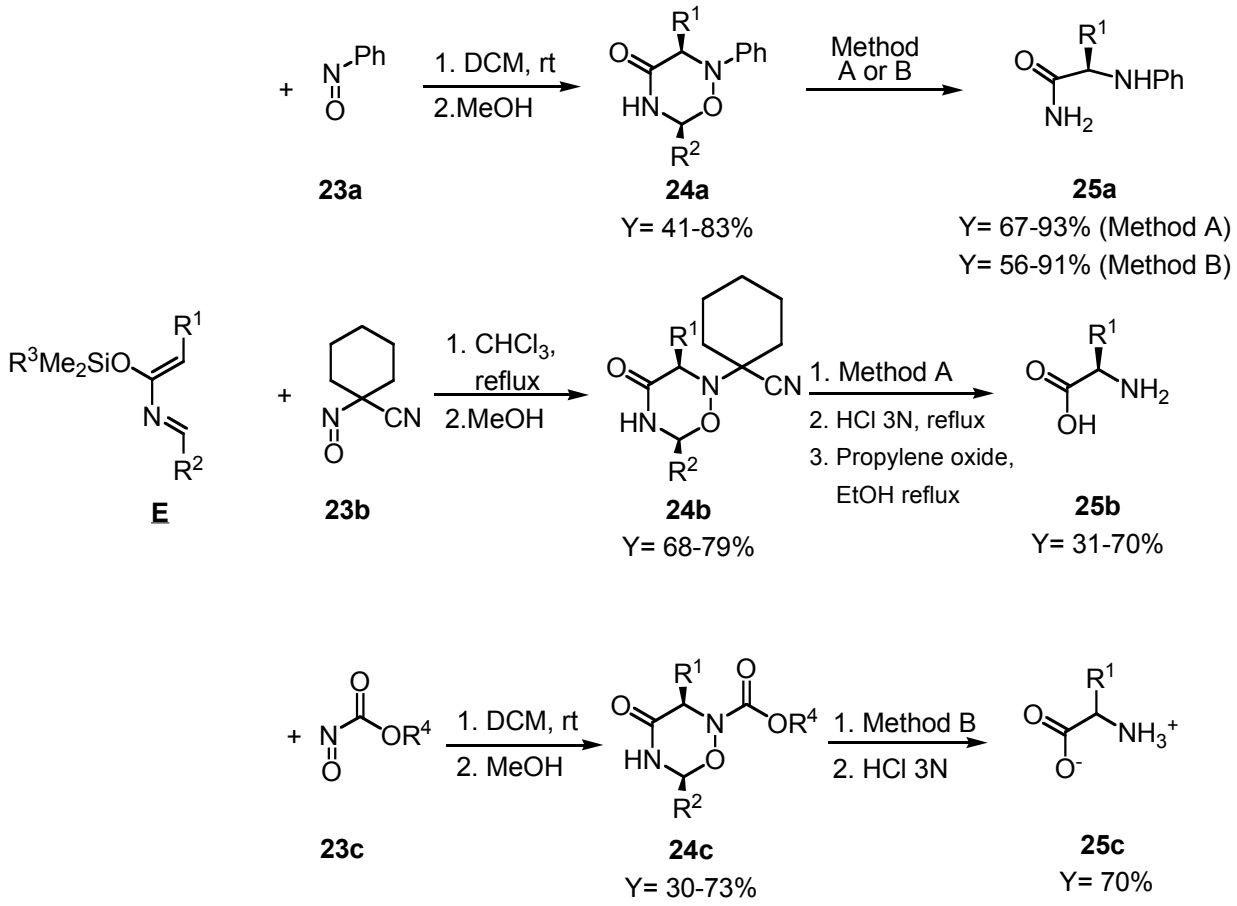
C **21** **22**, Y= 28-64%

R^1= H, Me, Cl, F, Ph, Bu; R^3= H, Me, CO_2Me;
R^2= H, Me; R^4= *t*-$BuMe_3Si$, *i*-Pr, Et

Scheme 2.8: Acetylenic compounds as dienophiles

- ***Nitroso compounds as dienophiles. Aminoacids synthesis***

The addition of nitroso compounds, **23a-c**, to 2-azadienes **E** is the route for obtaining α-aminoacids, **25a-c**.[55] In detail arylnitroso compounds **23a** react with azadiene **E** to give the adducts [1,2,5]oxadiazinan-4-one **24a** that are potential precursors of α-*N*-arylamino acids **25a**; α-cyanonitroso and acylnitroso compounds, **23b** and **23c**, lead to [1,2,5]oxadiazinan-4-ones **24b** and **24c** that are converted into α-amino acid derivatives **25b** and **25c** (Scheme 2.9).



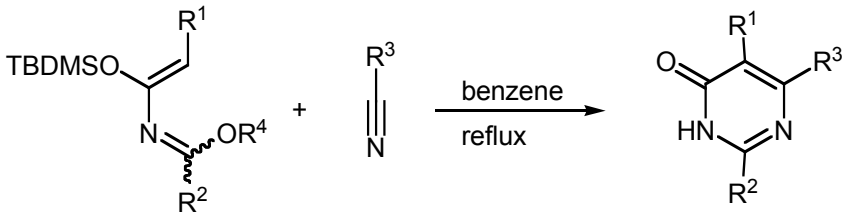
R^1=H, Me, Ph,CH_2Ph, $CH=CH_2$, $CH_2Ph(OMe)$m,p;
R^2=Ph, *i*-PrO;
R^3=Me, *t*-Bu;
R^4=Ph, CH_2Ph.

Method A: Na/Hg/MeOH;
Method B: $Mo(CO)_6/CH_3CN/H_2O$

Scheme 2.9: Nitroso compounds as dienophiles

- ***Activated nitriles as dienophiles***

2-Azadienes **C** cycloadd also to activated nitriles **26** yielding polisubstituted pyrimidones **27** (Scheme 2.10).[50] In this case too, the one-pot multicomponent reaction gives better results respect to the two-step procedure.



C **26** **27**

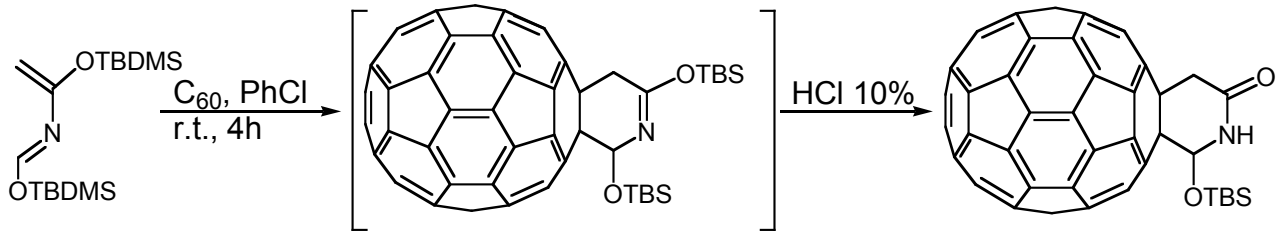
Y= 49-94%

R^1=H, Me, Cl, F, Bu;
R^2=H, Me;
R^3=*p*-Tos, Cl_3C, CO_2Et;
R^4=*i*-Pr, Et

Scheme 2.10: Nitriles as dienophiles

- ***Particular dienophiles***

The HDA reaction of the electron rich 1,3-bis(silyloxy)-2-aza-1,3-diene **L** with low LUMO-lying C_{60} **28** proceeds smoothly at room temperature to give 2-piperidone-fused C_{60} **29** after hydrolysis (Scheme 2.11).[56]

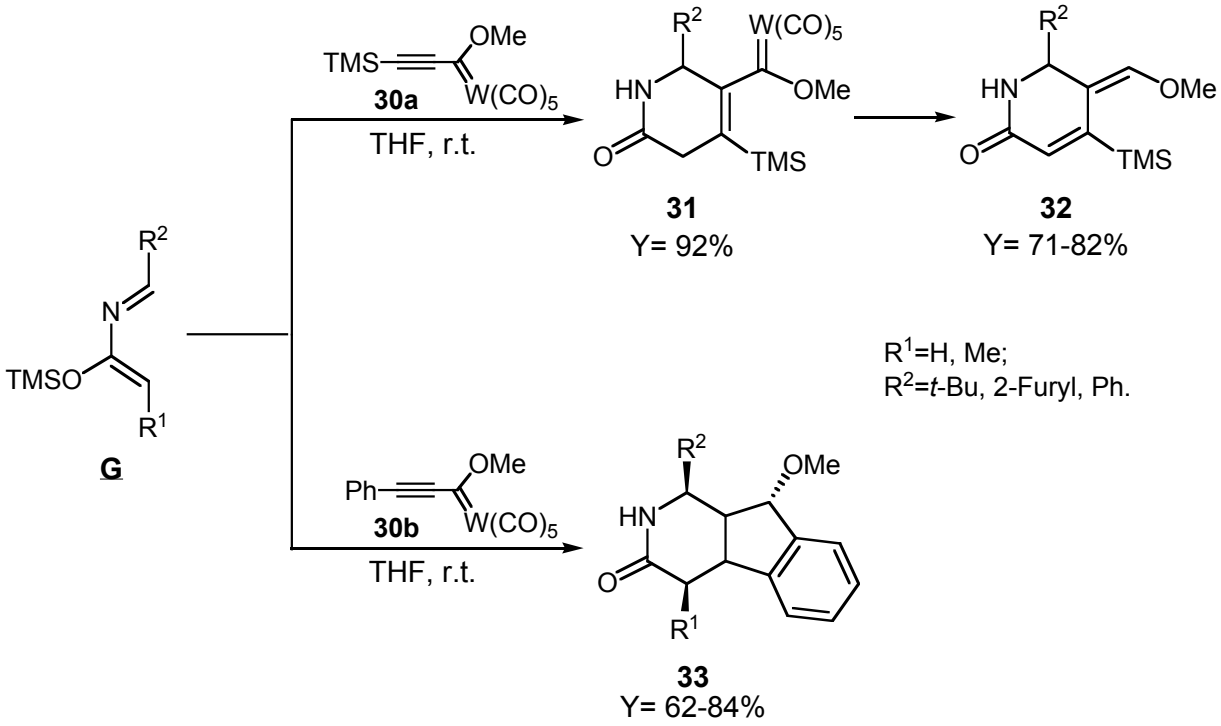


L **28** **29**

Y= 77%

Scheme 2.11: C_{60} as dienophile

Barluenga in a recent paper regarding the cycloaddition reactions of Fisher carbene complexes to 2-aza-1,3-butadienes has reported some HDA reaction examples.[57] The [(trimethylsilyl) ethylnyl] carbene **30a** gives rise to metal-containing and metal-free [4+2] cycloadducts, **31** and **32** respectively, whereas the (phenylethynyl) carbene **30b** furnishes azafluorenones **33** by a tandem [4+2] cycloaddition/pentaannulation process (Scheme 2.12).



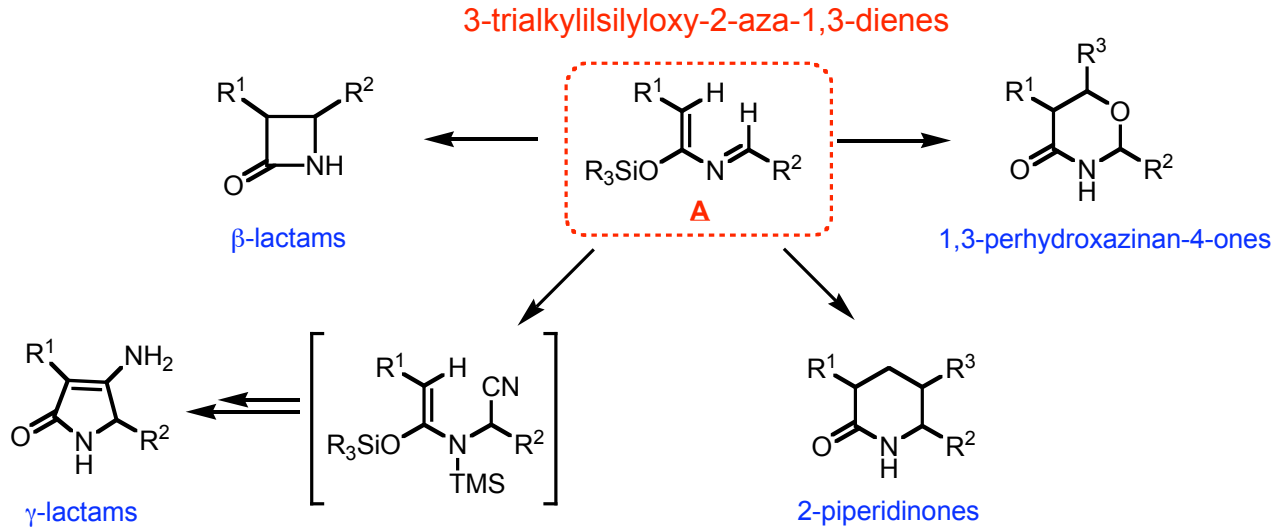
Scheme 2.12: Fisher carbene complexex as dienophiles

Chapter **3**

3-Trimethylsilyloxy-2-Azadienes in elettrociclic [4+2] reaction. Part two. Our experience.

Earlier studies[7,8,17,29-31] from this laboratory have shown that a wide variety of 3-trimethylsilyloxy-2–aza-1,3-butadienes could be prepared in an easy way starting from silylimines and ketene. The different reactivity of these compounds is due to the functionalities present on the skeleton of the azadiene.

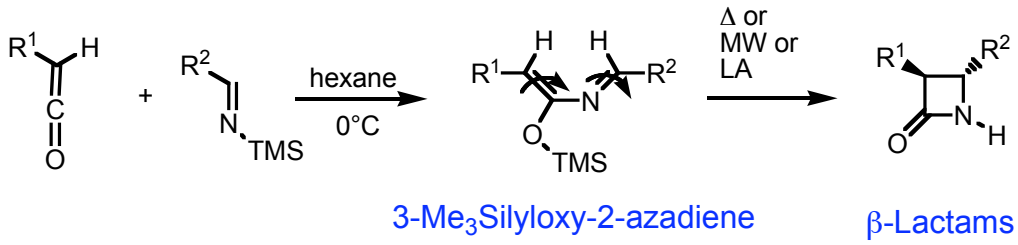
For these reasons, 3-trialkylsilyloxy-2–aza-1,3-butadienes **A** may be considered precursors of a wide range of nitrogen containing biologically activity compounds. Herein is reported a summarizing scheme of the compounds whose synthesis have been elaborated from our research group.



Scheme **3.1**: Reactivity of 3-trialkylsilyloxy-2-azadienes in our reaserch group

- ***β-Lactams: elettrociclic [2+2] reaction***

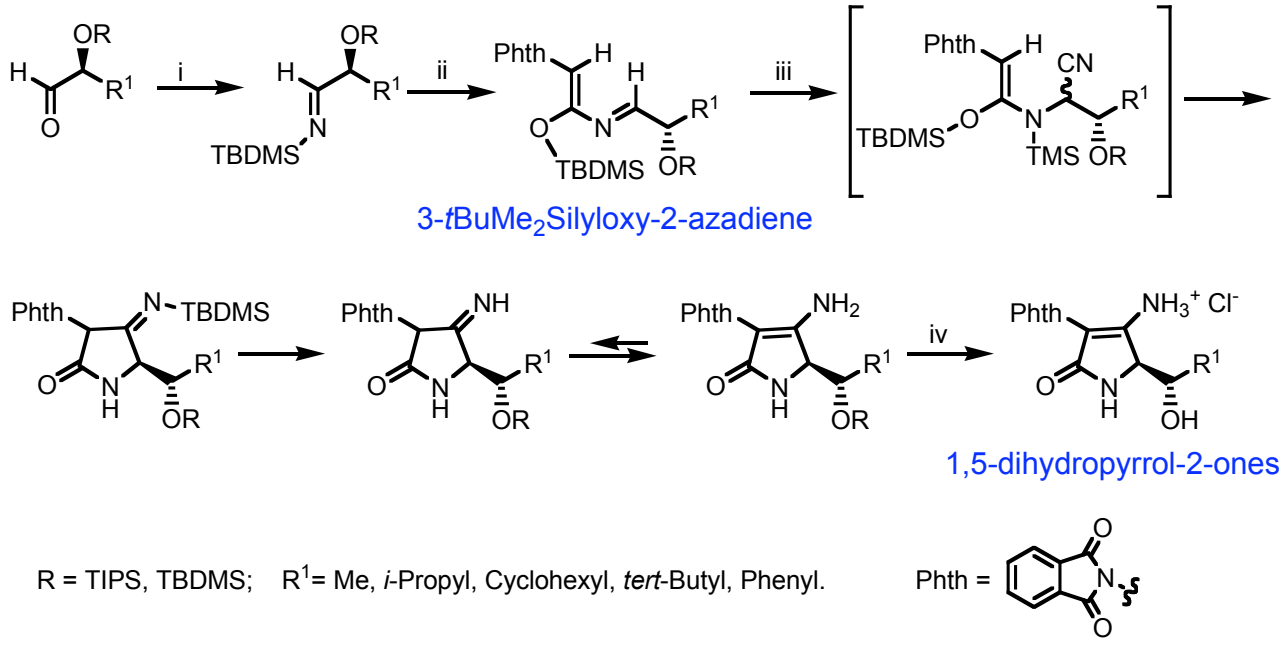
Our reaserch reported the synthesis of several β-lactams obtained starting from 2-azadiene through a formal two-step Staudinger reaction. The 3-trimethylsilyloxy-2–aza-1,3-butadienes may be considered a neutral equivalent to the classical zwitterionic intermediate invoked in the Staudinger reaction ([2+2] cycloaddition of an imine and a ketene). Both neutral and zwitterionic intermediates undergo conrotatory electrocyclization. Recently, in a series of papers, we have proved that the ring closure could be activated in several ways: traditional heating (reflux in toluene for several hours), microwave irradiation or catalyzing with Lewis acid (BF3).



Scheme **3.2**: The Staudinger reaction

- ***γ-Lactams: C-iminic addition***

Stereoselective Lewis acid catalyzed addition of a cyano group to the azadiene, followed by intramolecular ring closure, in a four-step one-pot synthesis, results in the formation of γ-lactams in satisfactory yields.[58] The 1,5-dihydropyrrol-2-ones so obtained are key compounds for the preparation of tetramic acid analogues.



Reagent and conditions: (i) TMS-N(Li)-STBDM, heptane, 0°C then TMSCl;
(ii) phthaloylglycine cloride,TEA;
(iii)TMSCN, $TiCl_4$, 12h; (iv) HCl 6N, 12h (80%).

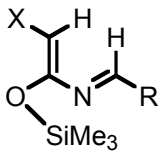
Scheme **3.3**: Synthesis of tetramic acids analogues

- ***δ-Lactams: elettrociclic [4+2] reaction***

The dienic nature of azadienes makes those intermediates interesting starting materials for elettrocyclic [4+2] reactions. The application of hetero Diels-Alder (HDA) strategy to heterocycles and natural products synthesis has been well known for long time.[3] An important part of this strategy takes into account the use of imino Diels-Alder reaction which provide a rapid stream to the construction of functionalized six-membered nitrogen-containing heterocyclic structures[2], with regio-, diastereo- and enantioselectivity control.[59]

The HDA adducts thus obtained, in turn, have been used as such for the synthesis of more complex cyclic structure, or have been easily converted into new heterocycles or into open-chain compounds.

Recent years have witnessed the usefulness of azadiene of type **A** in the preparation of important intermediates in organic synthesis.[1,7,9,60]



A

X = NR^1R^2, ARO, Halogen, ArS, H

R = Alkyl, Aryl.

Our reaserch group have been reported the application of our methodology in the synthesis of perhydrooxazin-2-ones, using 3-trimethylsilyloxy-2–aza-1,3-butadienes **A** and a wide range of aliphatic, aromatic and heteroaromatic carbonyl compounds as dienophiles, with particular emphasis on the diastereoselectivity of the reaction.

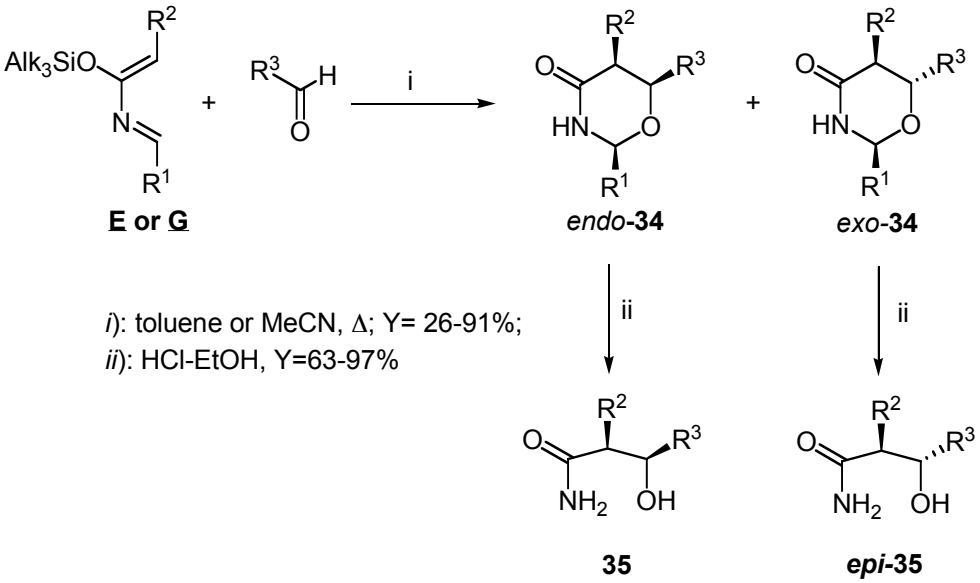
Recently we reported the extension of our protocol to different type of dienophile to obtain piperidin-2-ones to convert in new class of biologically active compounds.

The formation of six-membered nitrogen-containing heterocyclic structures is the mainly argument of this PhD thesis and will be well discussed in the next paragraphs.

3.1 Synthesis of Perhydroxazinan-4-ones

- ***Uncatalyzed reactions***

The highly activated azadiene **E** and **G**, prepared by Ghosez and described in Par. 1.3, are sufficiently reactive to cycloadd to various aldehydes without Lewis acid catalysis (Scheme 3.4).[61,62] The cycloaddition works well both with aromatic and aliphatic aldehydes; a wide variety of substituents at C-4 of the diene are allowed; *endo*-selectivity is observed in most cases. Ethanolysis of 1,3-oxazinones **34** stereoselectively yields the corresponding β-hydroxyamides **35**.



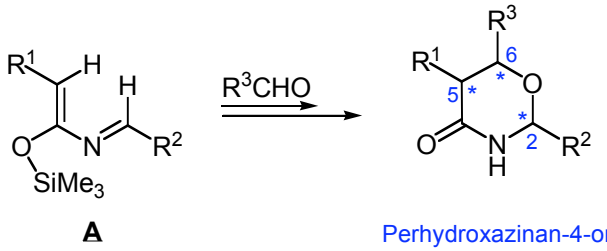
i): toluene or MeCN, Δ; Y= 26-91%;
ii): HCl-EtOH, Y=63-97%

R^1= *i*-PrO, Ph, *t*-Bu;
R^2= Me, Ph, Cl, F, PhthN, AcO;
R^3= Ph, 2-Furyl, *p*-MeO-Ph, *p*-Cl-Ph, *p*-NO2-Ph, *n*-Pr, *i*-Bu, CO_2Et.
Alk_3Si= TBDMS when R^1=*i*-PrO or Me,
TMS when R1=Ph or *t*-Bu.

Scheme 3.4: Carbonylic compounds as dienophiles, uncatalysed reactions

- ***Lewis acid mediated reactions***

In our research group, the Lewis acid mediated reactions between 4-substituted-3-trialkylsilyloxy-2-aza-1,3-dienes **A** and aldehydes leading to perhydro-1,3-oxazin-4-ones have been reported (Scheme 3.5).[19,63,64]



A Perhydroxazinan-4-ones

Scheme 3.5: Carbonylic compounds as dienophiles, LA mediated reactions

As already anticipated in Chapter 2, the formation of the six-membered rings *via* LA catalized HAD reaction takes place through and asynchronous concerted mechanism or an aldolic two-step one-pot.[3b,c] The competitive existence of both reaction pathways has been demonstrated by the stereochemical analysis of the three new stereogenic centers

(C-2, C-5, C-6) formed in the products. The degree of diastereoselection in both mechanism appears to be dependent upon the steric and electronic nature of the dienophile and the diene used.

Diastereoselection in pericyclic reactions has been explained in terms of *exo*-/*endo*-transition states depending on the Lewis acid and the steric demand of the substituents on the dienophile. When the Lewis acid coordinate the aldehyde oxygen *syn* to the hydrogen force the R group into an endo-position in the transition state **TS-1** leading to the C5-H/C6-H-*cis*-product **P-1** characterized by a basket conformation of C2-H, C5-H and C6-H (Fig. 3.1). Aldehydes having R group larger than the coordinating LA can react via a pericyclic *exo*-mode **TS-2** affording the C5-H/C6-H-*trans*-product **P-2** (Fig. 3.1).

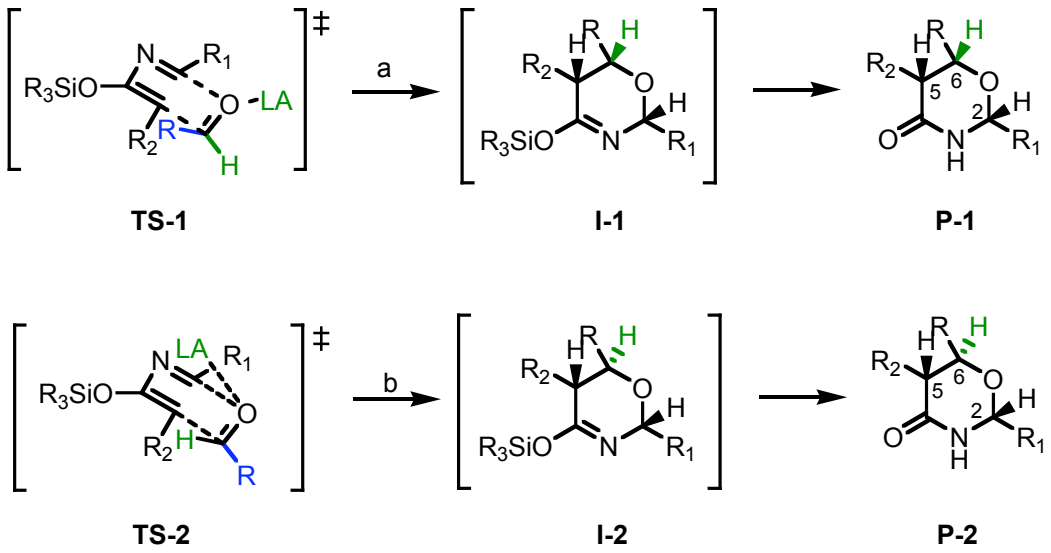


Fig. 3.1:concerted HDA mechanism.

The HAD reaction was expected to produce *endo*- or *exo*-products in which a *cis*-relationship is established between C2-H and C5-H. However, analysis of the reaction mixture, in some cases, shows the presence of diastereoisomers with a *trans*-relationship between C2-H and C5-H. There are two possible explanation for the formation of C2-H/C5-H *trans*-products: the first involves epimerization of the C2-H and/or C5-H stereogenic centers during the reaction; alternatively, a stepwise Mukaiyama mechanism may be occurring. Formulation in terms of the Mukaiyama silylenol-ether aldol process leads to the intermediates **I-3** and **I-4** which, upon ring closure, give rise to the product **P-1** and/or **P-3** (Fig. 3.2) and **P-2** and/or **P-3** (Fig. 3.1). Once again, the substituents play a decisive role for the mechanism and therefore for the stereochemistry of the final products.

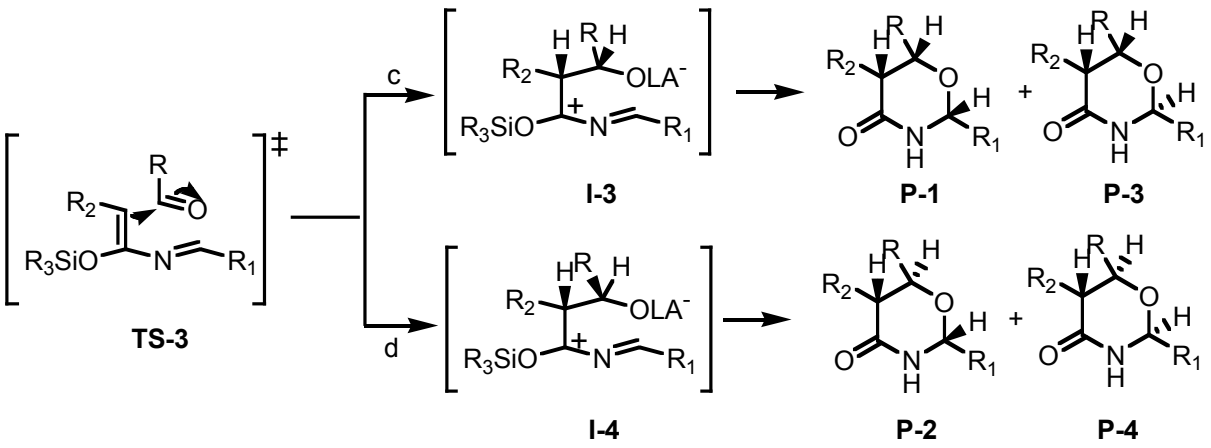
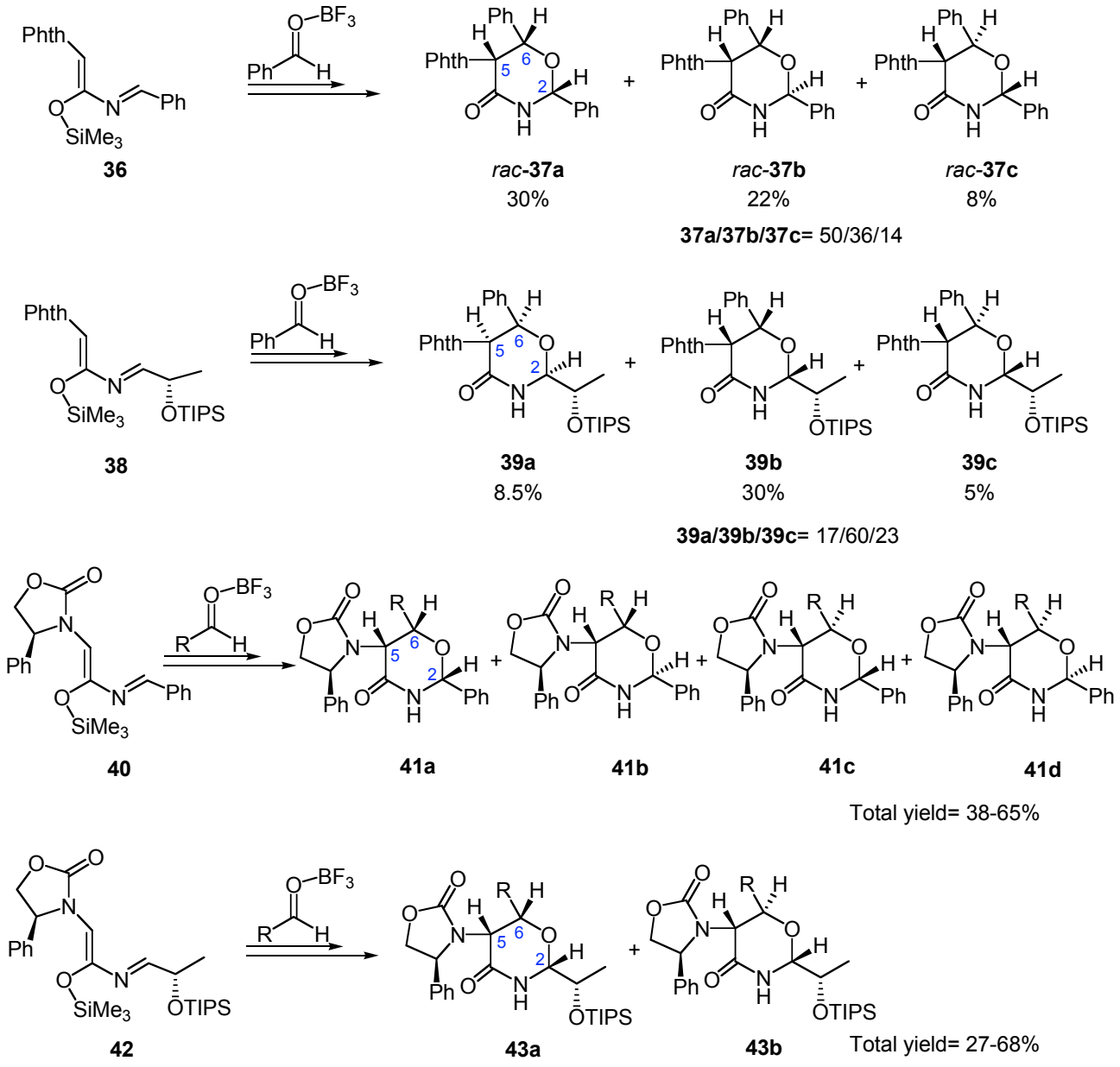


Fig. 3.2: Aldolic Mukaiyama type mechanism.

- ***Stereoselection***

The HAD reaction between a 2-azadiene and aldehyde as dienophile, provides the formation of three new stereogenic centers (C-2, C-5, C-6) in the perhydroxazinonic ring. Its diastereoselectivity has been deeply investigated by the use of various combination of achiral and chiral azadienes and aliphatic, aromatic or heteroaromatic aldehydes (Scheme 3.6).[8] Herein we report the first synthesis optimized by our research group using azadienes with an amido group in position 4. The results are illustrated in Scheme 3.6. A complete study regarding the configuration of the products obtained is reported and it's also important for the determination of the configurations of the perhydroxazinones with different substituents.

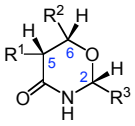
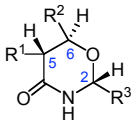
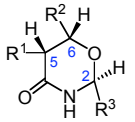
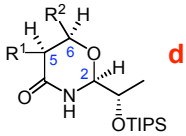
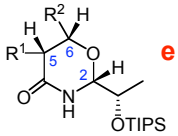
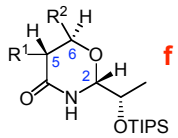
Treatment of the azadiene **36 - 42** with an aldehyde in the presence of a stoichiometric amount of boron trifluoride etherate (CH_2Cl_2, -78°C to 20°C for 8 h), followed by aqueous work-up, gives rise to the formation of the perhydrooxazinones **37 - 43** (Scheme 3.6).



R= *n*-Pr, *i*-Pr, *n*-Heptyl, Ph, *p*-MeO-Ph, 3-(*N*-Boc)-Indolenyl, Cyclohexyl, Et, 3-Pyridyl, 2-Thienyl, 2-Furyl

Scheme 3.6: Carbonyl compounds as dienophiles. Background

Relative configuration of the products has been attributed by NOE measurements and on the basis of the coupling constant $J(H_5\text{-}H_6)$ and $J(H_2\text{-}H_{2'})$ at ^1H NMR spectra. In Table 3.1 the typical coupling constants values and the observable NOE effects for the generic compounds **a-f** are reported. It is well known that in cyclic systems a small coupling constant is observed between two vicinal protons when their relative configuration is *cis*, a large one is obtained when they are in a *trans* relationship.

Products	$J_{5\text{-}6}$ (Hz)	$J_{2\text{-}2'}$ (Hz)	NOE
 **a** - *rac*	3.7 – 5.9	---	2 ⟶ 6; 5 ⟶ 6
 **b** - *rac*	9.6 – 10.5	---	---
 **c** - *rac*	3.7 – 5.9	---	5 ⟶ 6
 **d**	3.7 – 5.9	7.7	2 ⟶ 6; 5 ⟶ 6
 **e**	3.7 – 5.9	3.2 – 4.7	2 ⟶ 6; 5 ⟶ 6
 **f**	9.6 – 10.5	3.2 – 4.7	

Tab. 3.1: Coupling constants and NOE results for perhydroxazinones

These observations have been confirmed by the existence of NOE effects between H5 and H6 for **a**, **c**, **d**, **e** type products (Table 3.1). Further, the existence of NOE effects between H2 and H6 shows that these protons are in a *cis* orientation in **a**, **d**, **e** type products.

Moreover, it has been demonstrated by calculations that it is possible to assign the relative configuration between H2 and H2' on the basis of their coupling constants: a small value indicating a *syn* relatioship, a large value an *anti* one (Table 3.1, products **d-f**). In fact, a full AM1 conformational analysis (Hypercube, Inc. Hyperchem; Rel. 5.11 ed.: Waterloo, Ontario, Canada) of the model diastereoisomers **(*RS*)** and **(*SS*)** (Fig. 3.3) shows that in both isomers the system is best described by the two conformations **(*RS*)**[3] and **(*SS*)**[1] in which a bonding interaction between the silyloxy oxygen and the amino group is operating. The coupling constant of the conformer **(*SS*)**[1], with the two hydrogens *anti* to

each other, was expected to be greater than that of the **(*RS*)**^{3}-conformer, in which the two hydrogens have a *gauche*-relationship. The experimentally observed coupling constants of about 7 and 4 Hz, respectively (Table 3.1), allow the absolute configuration of the C-(2) stereocentres to be established.

By combining all these informations, the absolute configuration of **a-f** type compounds has been assigned.

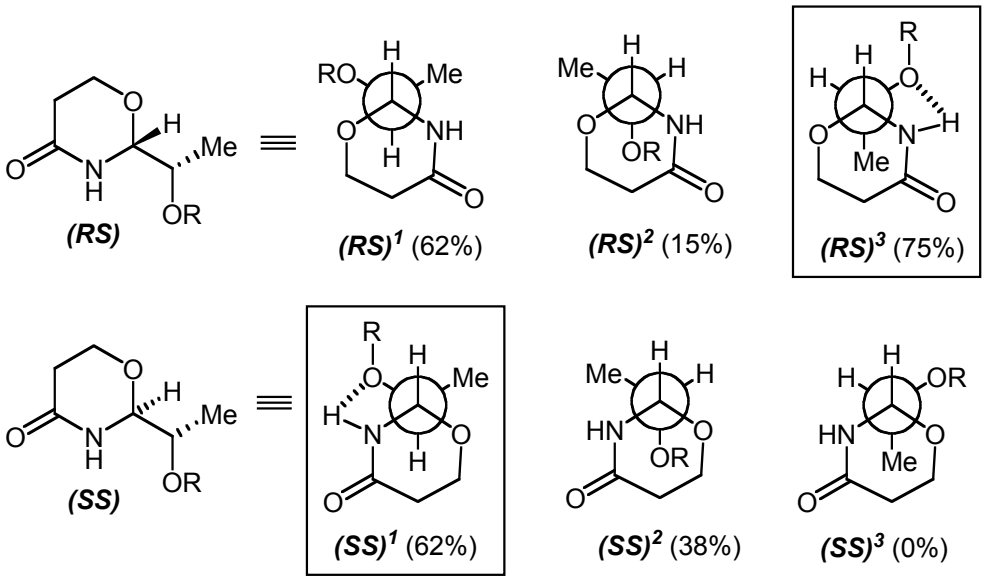
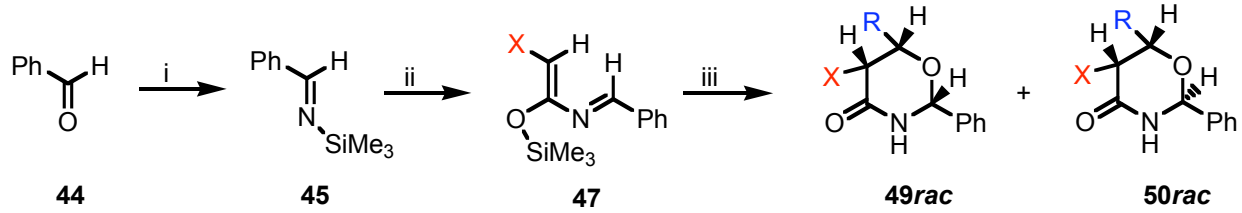


Figure 3.3: AM1 calculated percentage population of the (R,S)- and (S,S)-conformers

3.2 Novel Synthesis of Perhydroxazinan-4-ones

In continuation of our studies on the use of hetero Diels-Alder strategy in the synthesis of heterocyclic compounds with different substitution pattern and their use for the preparation of acyclic derivatives we would like to present here our recent results on the synthesis of new perhydrooxazinan-4-ones. The aim of our researches is the synthesis of 5-substituted oxazinan-4-ones with the position five of the heterocyclic adduct substituted by an easy removable group (alogen, tiophenyl) for further elaborations. We have been also investigating to find new synthetic protocols which allow the preparation of perhydrooxazinan-4-ones with milder conditions: the use of microwaves as non conventional heating source and the use of Lewis acid in catalytic amount.

- ***From 4-halo-3-Me$_3$SiO-2-azadienes to 5-halo-1,3-oxazinan-4-ones***



44 **45** **47** **49*rac*** **50*rac***

X= Cl, Br, I
R= Me, *n*-Propyl, *i*-Propyl, *t*-Butyl, *n*-Heptyl, Ph, *p*-NO_2Ph

Reagent and conditions. i) LiHMDS, TMSCl; ii) XCH_2COX^1**46**, (X^1=Cl, Br), TEA; iii) BF_3, RCHO **48**

Scheme 3.7: Synthesis of 5-halo-2-phenyl-1,3-oxazinan-4-ones

The azadiene **47** was prepared from he corrisponding acid halides **46** and N-trimethylsilyl imines **45** following the procedure describe (Paragraph 1.4). Table 3.2 summarize the results of the cicloaddition reactions of **47** with aldehyde **48**, activated with boron trifluride etherate, to give the six-membered ring adducts **49** e **50**.

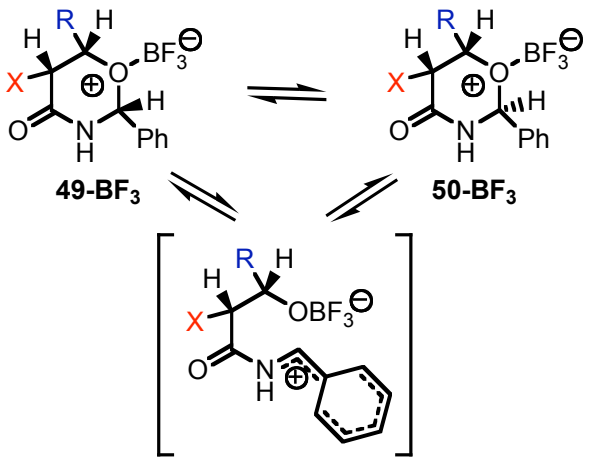
Entry	X	R^1	Products	Ratio	Yield(%)
1	Cl	Me	**49a/50a**	>98	40
2	Br	Me	**49b/50b**	>98	45
3	I	Me	**49c/50c**	92/8	48
4	Br	Propyl	**49d/50d**	94/6	56
5	Br	*n*-Heptyl	**49e/50e**	>98	50
6	Br	*n*-Heptyl	–	–	0
7	Br	*i*-Propyl	**49g/50g**	9/91	52
8	Br	*i*-Propyl	**49g/50g**	9/91	45
9	Br	*t*-Butyl	**49h/50h**	30/70	40
10	Br	Ph	**49i/50ib**	61/39	40
11	Br	*p*-NO_2-Ph	**49j/50j**	80/20	41

Tab. 3.2: Cycloaddition of azadienes **47** with aldehydes **48**

The relative configurations of C2-H, C5-H and C6-H in the product **49** and **50** were established on the basis of ^{1}H NMR chemical shifts, coupling costants and NOE values according to the results of Tab. 3.1. The basket configuration of the protons (H_2-H_5-H_6), in the series of compounds **49**, has been demonstrated by the values of coupling constant (H_5-H_6) and by a positive NOE effect between the H_2 and H_6. The absence of this effect for the compounds **50** allow the configurations to be assigned (Tab. 3.1).

Examination of Table 3.2 leads to the following remarks:

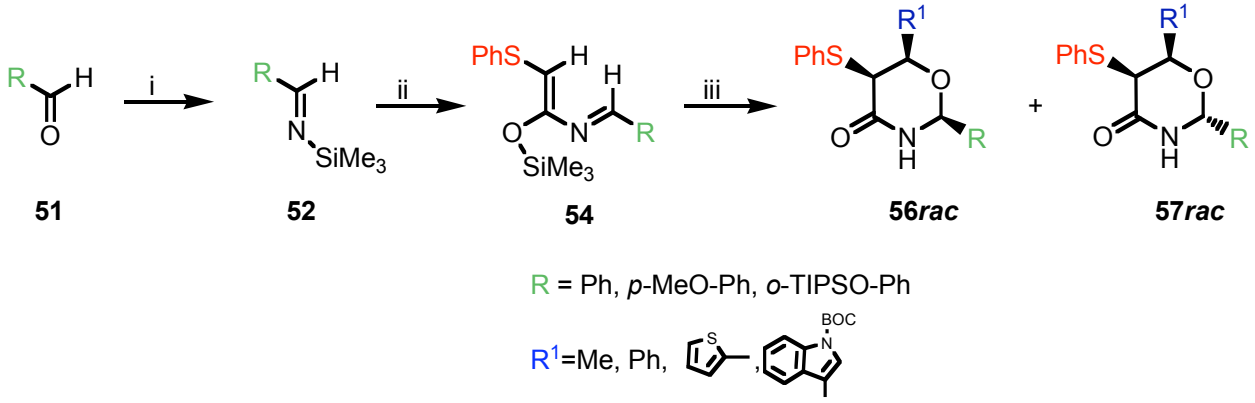
1) Diastereomeric ratio was evalueted by ^{1}H NMR analysis of the crude reaction mixture. No changes were observed after silica gel column purification.
2) Yields were calculated on the basis of mmol of benzaldehyde **44** used for the preparation of azadiene **47** and refer to chromatographically isolated products.
3) Irrespective of the nature of R in the dienophilic aldehyde **48**, the cycloaddition takes place with a complete (H_5-H_6)-*cis* diastereoselectivity.
4) The HDA cycloaddition works well with linear aliphatic aldehyde with an almost complete (H_2-H_5-H_6) relative diastereoselectivity (*entries 1-5*). Accordingly, the final cycloaddition adducts **49** resulted from an *endo* approach of the reactants.
5) The reaction takes place al low/ambient temperature under BF_3 mediated cycloaddition, whereas no cycloadduct products were obtained under Ghosez conditions (acetonitrile/reflux/no LA added, *entry 6*).
6) Using aliphatic aldehydes with branched side chains (*entries 7-9*) or aromatic aldehydes (*entries 10-11*) mixtures of cycloadducts **49** and **50** in variable ratio are obtained. The products of series **50** show a complete cis-diastereoselectivity between C5-H and C6-H but a trans relationship between C2-H and C5-H.
7) The formation of isomer **50** could be assigned to the epimerization of the stereocenter 2 in the product **49**. As already known, an equilibrium between the cyclic perhydrooxazinan-4-ones and the open-chain derivatives may exist (Schema 3.8). An extra experiment (*entry 8*), quenching the reaction mixture at low temperature (-78°C) after 90 min makes this hypothesis likely.



Schema 3.8: equilibrium between the cycloadducts and the open-chain derivatives

The 5-halo-oxazinan-2-ones obtained with the reported procedure have been converted, mainly, in *cis* epoxides via *N*-Boc protection as illustrated in Chapet 4.

- ***From 4-PhS-3-Me$_3$SiO-2-azadienes to 5-PhS-1,3-oxazinan-4-ones***

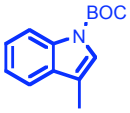


Reagent and conditions. i) LiHMDS, TMSCl; ii) PhSCH$_2$COCl **53**, TEA; iii) BF_3, R^{1}CHO **55**

Scheme 3.9: Synthesis of 5-phenylthio-1,3-oxazinan-4-ones

5-Phenylthio-1,3-oxazinan-4-ones **56** and **57** with various sobstituent patterns at the C2 and the C6 atoms, have been obtained from the easily available 1,3-azadienes **54**, prepared from silylimines **52** and acylchloride **53,** in presence of triethylamine, and using aldehydes **55** as dienophiles (Scheme 3.9, Table 3.3). In the present study, the starting azadiene **54** is a neutral 3-trimethylsilyloxy-4-thioaryl-2-aza-1,3-diene, already used in a

previous study for the preparation of a β-lactam ring by a 4π-conrotatory electrocyclization.[60]

Entry	R	R^1	Products	Ratio	Yield(%)
1	Ph	Ph	**56a/57a**	90/10	35
2	Ph	Ph	**56a/57a**	74/24	35
3	Ph		**56b/57b**	40/60	38
4	*p*-MeO-Ph	Ph	**56c/57c**	80/20	55
5	*o*-TIPSO-Ph	Ph	**56d/57d**	85/15	48
6	Ph	Me	**56e/57e**	50/50	51
7	Ph		**56f/57f**	40/60	41

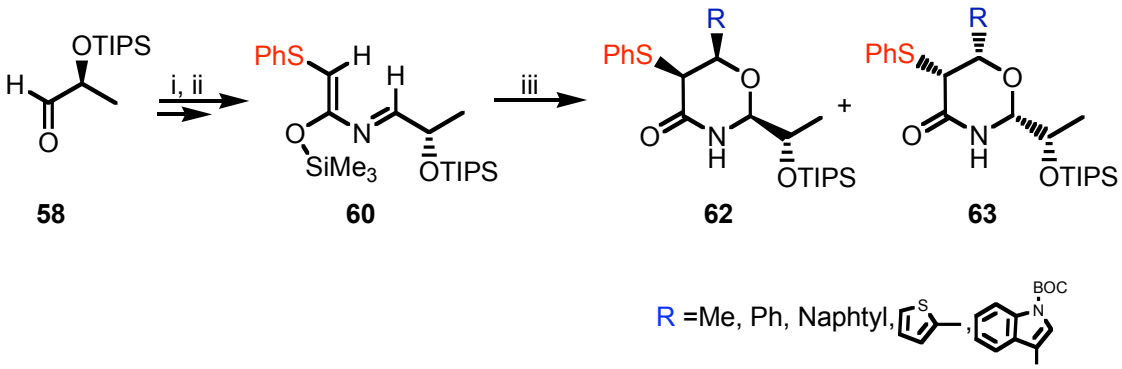
Tab. 3.3: Cycloaddition of azadienes **54** with aldehydes **55**

The results shown in Table 3.3 warrant some comments:

1) Diastereomeric ratio was evalueted by ^{1}H NMR analysis of the crude reaction mixture. No changes were observed after silica gel column purification.
2) Yields were calculated on the dienophilic aldehyde **51** and refer to chromatographically isolated products.
3) No traces of azetidinones, arising from a 4π-conrotatory electrocyclization, have been detected in the crude reaction mixture.
4) All the reactions are completely regioselective.
5) Irrespective of the nature of R^1 in the dienophilic aldehyde **55**, the cycloaddition takes place with a complete (H_5-H_6)-*cis* diastereoselectivity.
6) Two groups of cycloadducts are present: one (compounds **56**) presenting the three ring protons in a basket conformation and an other group (compounds **57**) presenting the same *cis* –configuration between C5-H and C6-H but a *trans*-relationship between C2-H and C5-H as pointed out by the combined analysis of coupling constants and NOEs.
7) In order to ascertain if this stereo-difference is originate from a different cyclization mechanism (HDA vs Mukaiyama) or from the presence of the equilibrium reported in Scheme 3.8, we added an excess of BF_3 etherate to pure **56a** in methylene chloride for 4 h at room temperature. A mixture of **56a** and **57a** in 90/10

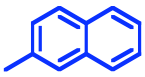
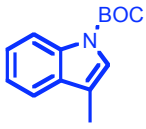
diastereomeric ratio was obtained. This is a clear evidence that some degree of isomerization could take place after the formation of the Diels-Alder adducts.

In order to develop a chiral version of the HDA reaction, a stereocenter was introduced in the structure of the starting azadiene **59** using enantiopure lactic aldehyde **58** in its synthesis.



Reagent and conditions. i) LiHMDS, TMSCl; ii) $PhSCH_2COCl$ **59**, TEA; iii) BF_3, RCHO **61**

Scheme 3.10: Synthesis of enantio-pure 5-phenylthio-1,3-oxazinan-4-ones

Entry	R	Products	Ratio	Yield(%)
1	Ph	**62a/63a**	50/50	81
2		**62b/63b**	60/40	90
3	Me	**62c/63c**	50/50	32
4		**62d/63d**	50/50	41
7		**62e/63e**	63/37	55

Tab. 3.4: Cycloaddition of azadienes **60** with aldehydes **61**

Also for the results of Tab 3.4 is possible to do some comments:

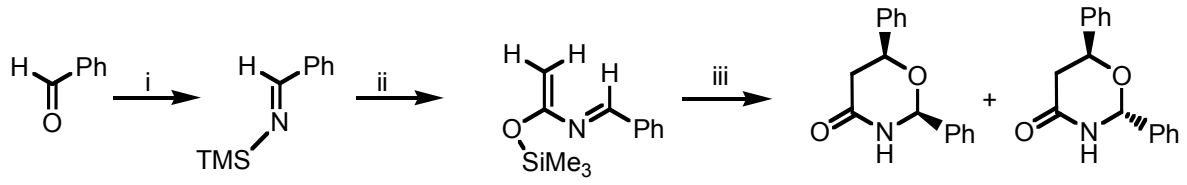
1) Diastereomeric ratio was evalueted by ^1H NMR analysis of the crude reaction mixture. No changes were observed after silica gel column purification.

2) Yields were calculated on the dienophilic aldehyde **61** and refer to chromatographically isolated products.
3) The two diastereoisomer **62** and **63** present the same basket configuration for the protons on the heterocyclic ring but an opposite absolute configuration on the C2, C5 and C6 stereocenters.
4) The stereochemistry of the obtained products **62** and **63** is a further confirmation of the presence of the equilibrium between the cyclic perhydrooxazinan-4-one and the open-chain derivates (Scheme 3.8). The hydroxy-alkyl group on the C2 stereocenter doesn't favor the formation of a positive charge; in fact, we obtained only the HDA adducts arising from a concerted mechanism.

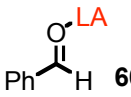
The cycloadducts thus prepared have been shown to be useful intermediates for the synthesis of 1,3 aminoalcohols, valuable intermediates in the preparation of biologically significant molecules (Chapter 4).

- ***Lanthanides Lewis acids in the synthesis of 1,3-oxazinan-4-ones***

A target of our researches is the formation of the six-member heterocycles in the presence of a catalyst. This has been possible using lanthanides Lewis acid and the highly efficient MAOS (Microwave Assisted Organic Synthesis) technique.. This has been possible using lanthanides Lewis acid and the highly efficient MAOS (microwave assisted organic synthesis). The starting 4-unsubstitued-azadienes **65** used in this study have been prepared according reported procedure starting from the silylimine **45** and acetyl chloride **64** in the presence of triethylamine.



44 **45** **65** **67*rac*** cis **68*rac*** trans

Reagent and conditions. i) LiHMDS, TMSCl; ii) CH_3COCl **64**, TEA; iii)  **66**

LA= EuFOD, $EuCl_3$, $Eu(Tf)_3x10H_2O$, YbFOD, $Sc(Tf)_3$

Scheme 3.11: Lanthanides Lewis acids in HDA reactions

Several different lanthanides Lewis acids have been tested using the azadienes **65** (2 mmol) and benzaldehydes **66** (1 mmol) in the presence of a catalyst [catalyst LA (0.1 mmol, 5%)] in chlorobenzene (5mL). The mixture were placed in a flask and submitted to MW-irradiation in a Prolabo oven for the time reported in Table 3.5. Afterwards, the solvent was evaporated under vacuum and the reaction mixture was filtered on silica gel eluting with a mixture of hexane and ethyl acetate (3:2) to give the cyclic adducts in the yields and diastereomeric ratio reported in Table 3.5.

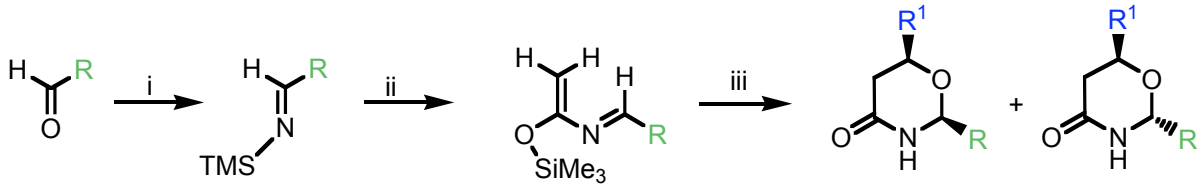
Entry	LA	Temp °C	Time	Yield%	Cis/Trans	Method
1	EuFOD (5%)	r.t.	7 gg	5	n.d.	CH
2	EuFOD (5%)	reflux	60 min	59	78/22	CH
3	$EuCl_3$ (5%)		30 min	Traces	n.d.	DH
4	$Eu(Tf)_3x\ 10H_2O$ (5%)		40 min	Traces	n.d.	DH
5	EuFOD (5%)		5 min	84	78/22	DH
6	EuFOD (5%)		30 min	5	n.d.	DH
7	YbFOD (5%)		40 min	47	86/14	DH
8	$Sc(Tf)_3$ (5%)		30 min	20	69/31	DH

Table 3.5: Lanthanides LA catalyst in HDA

The results shown in Table 3.5 warrants some comments:

1) Diastereomeric ratio was evalueted by ^{1}H NMR analysis of the crude reaction mixture. No changes were observed after silica gel column purification.
2) Yields were calculated on the dienophilic aldehyde **66** and refer to chromatographically isolated products.
3) The best results in term of yields and reaction time have been achieved using EuFod as catalyst, MAOS technique and a ratio diene:dienophile:catalyst 2:1:0.05.
4) Comparison between dielectric heating (DH Table 3.5) and conventional heating (CH, Table 3.5) not surprisingly demonstrates the advantages of MAOS, in term of higher yields of the cycloadduct and shorter reaction time, on the conventional heating.
5) No difference has been noted in the diastereomeric ratio between the two procedure.

The versatility of the methodology was tested using different substituents on the diene and on the dienophile (Scheme 3.12). Exploiting EuFOD (5%) as catalyst satisfactory, from the total yields point of view, results are obtained (Table 3.6).



51 **52** **69** **71*rac*** cis **72*rac*** trans

Reagent and conditions. i) LiHMDS, TMSCl; ii) CH_3COCl **64**, TEA; iii) R^1CHO **70**, EuFOD (5%)

Scheme 3.12: EuFOD in HDA reactions

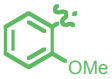
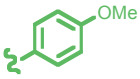
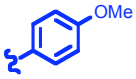
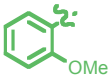
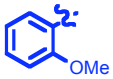
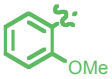
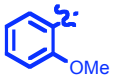
Entry	R	R^1	LA	Time	Yield%	Cis/Trans	Method
a		Ph	EuFOD (5%)	8 min	49	54/46	DH
b		Ph	EuFOD (5%)	30 min	49	80/20	DH
c		Ph	EuFOD (5%)	40 min	45	100	DH
d	Ph		EuFOD (5%)	40 min	35	50/50	DH
e			EuFOD (5%)	30 min	50	75/25	DH
f			YbFOD (5%)	30 min	43	79/21	DH
g		Ph	EuFOD (5%)	40 min	10	26/74	DH

Table 3.6: EuFOD in HDA reactions

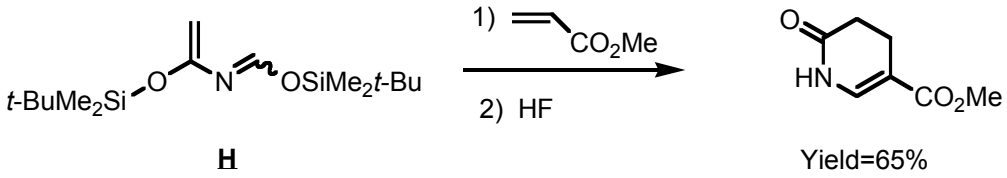
The above reported procedure must be considered efficient and valuable in view of the possibility to build up a small library of oxazinan-2-ones, which may in turn, be elaborated to a 1,3-aminols according to protocols illustrate in Chaper 4.

3.3 Synthesis of Piperidones *via* HDA

The Diels-Alder reaction is one of the most versatile routes for the construction of carbocycles.[1-3] Appropriate selection of diene and dienophiles allows for a wide range of structural and functional variations in the adducts. The syntheses till now reported, show the reaction of an azadiene with carbonylic compounds as dienophiles. In order to expand the versatility of the HDA reaction we started to investigate the use of olefinic dienophiles for the preparation of piperidinones.

3-Trimethylsilyloxy-2-aza-1,3-dienes **A** are electron-rich dienes able to undergo [4+2] cycloadditions with electron-poor dienophiles. Ghosez[65] had reported the reaction

between the 3-t-butyl dimethylsilyloxy-2-aza-1,3-diene **H** and methyl acrylate for direct synthesis of functionalized piperidines.



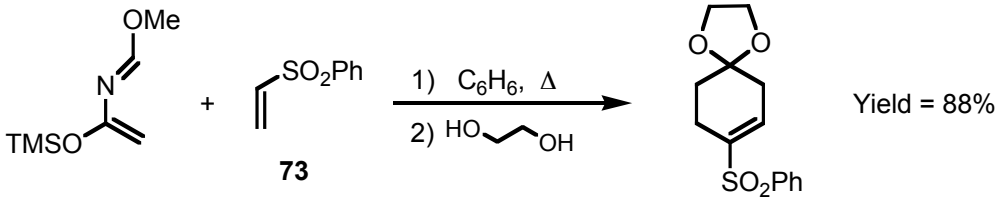
H Yield=65%

Scheme 3.13: Ghosez piperidines' synthesis

More recently the same group obtained enantiomerically pure piperidinones **12** and **13** starting from highly nucleophilic azadienes **G** and 3-alkenoyl-1,3-oxazolidin-2-ones **15** activated by Evans mild Lewis acid **14** derived from copper(II)triflate and a C2-symmetric bis(oxazoline) ligand (Scheme 2.5).[50]

The main theme of our research has always been the formation of cycloadducts cointaining several functional groups in order to generate more complex cyclic structure, new heterocycles or new class of biologically active compounds. For these reasons we have selected phenyl vinylsulfone **73**, one of the most useful functionalities in organic synthesis[66], as oleifinic dienophile on the HDA reaction with 2-aza-1,3-dienes.

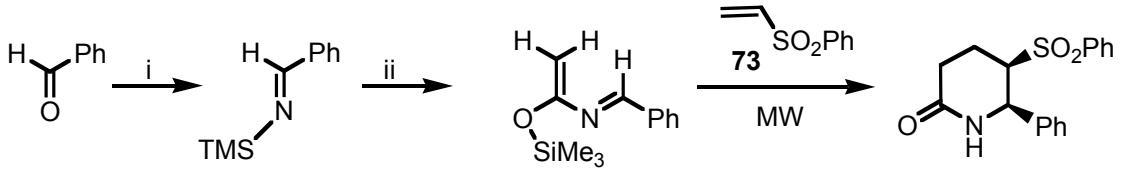
Several examples of cycloaddition with phenyl vinylsulphone have been reported in literature.[66,67] Herein we reported the addition of phenyl vinylsulphone to Danishefsky diene to obtain a sulfonyl functionalized adduct in high yield after a direct ketalization (Scheme 3.14).[68]



73

Schema 3.14: Cycloaddition of phenyl vinylsulphone to the Danishefsky diene.

Now we report our result obtained from cycloaddition of azadienes and phenyl vinylsulphone. In a preliminary study, a simple 3-trimethylsilyloxy-2-azadiene **65**, without substituent in position 4, has been used in order to evaluate the best reaction conditions.



44 **45** **65** ***74 rac*** cis

Reagent and conditions. i) LiHMDS, TMSCl; ii) CH_3COCl **64**, TEA.

Scheme 3.15: Synthesis of piperidinones

Several different reaction conditions have been tested and the results are reported in Table 3.7.

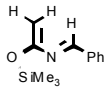
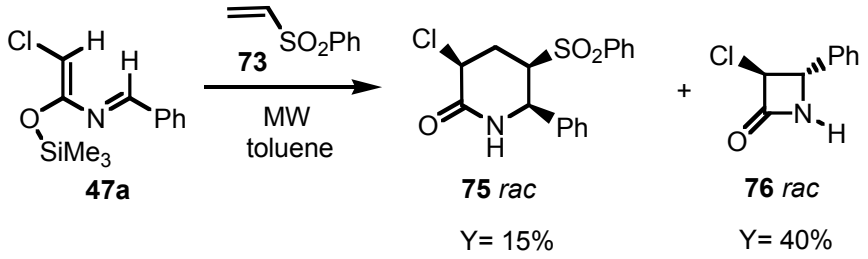
Entry			**Solvent**	**MW**	**Temp °C**	**Time**	**Yields %**
1	1 eq	1 eq	ClBn	√	132	5'	38
2	1 eq	1.5 eq	ClBn	√	132	10'	32
3	1 eq	1 eq	Toluene		110	20 h	40

Table 3.7: HAD ractions with phenyl vinylsulphone

The results shown in Table 3.7 warrant some comments:

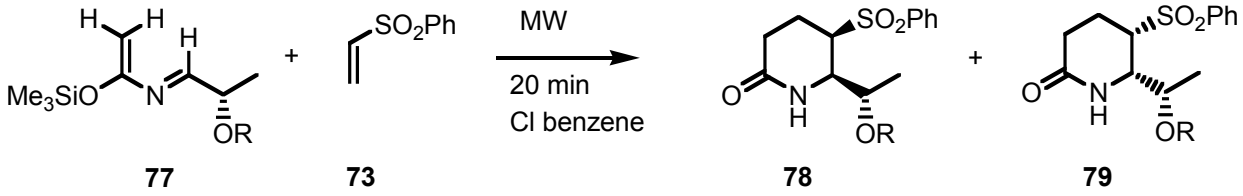
1) Yields were calculated on the aldehyde **44** used for the formation of the silylimine and refer to chromatographically isolated or crystallize products.
2) The reaction is completely regioselective and diasteroselective: we have obtained only one racemic product with *cis* relationship between C5-H and C6-H.
3) Also in this case the methodology MAOS has been furnished the best reaction conditions: the same yield obtained with conventional heating (CH, Table 3.7) but a very short time (5 min instead 20h).

The same reaction applied to 5-halo-oxazinan-4-one **47a** gives rise to a competitive reaction between a [4+2] cyclization, with the formation of the six-membered cycloadduct **75**, and an intramolecular reaction to give *trans* 4-halo-azetidinone **76** (Scheme 3.16). Every effort to change the reaction condition resulted in unsatisfactory results.



Scheme 3.16: Synthesis of *rac*-5-halo-piperidinones

However, the major interest of our research is the synthesis of enantiomerically pure piperidinones. Thus adducts have been obtain introducing a stereocenter in the structure of the azadiene (Scheme 3.17). Also in this case several different reaction condition have been tried and the results are reported in Table 3.8.



R= *t*-$BuMe_2Si$, $(i\text{-}Pr)_3Si$

Scheme 3.17: Synthesis of enantiopure piperidinones

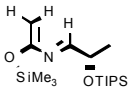
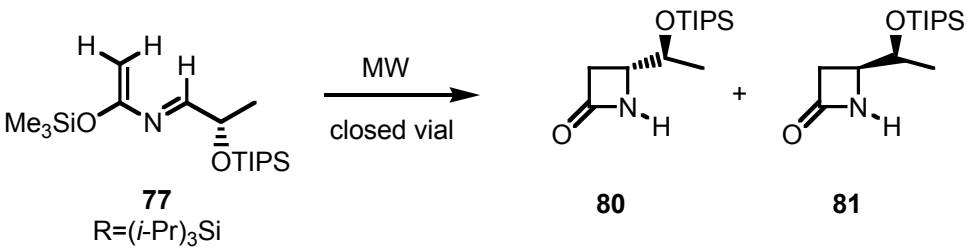
Entry			Solvent	MW	Watt	Temp °C	Time	Yields %	Ratio 78/79
1	1	1	ClBn	√	300	132	30’	46	60/40
2	1	1	ClBn	√	300		20'	37	64/40
3	1	1	diglyme	√	300	162	30’	25	70/30
4	2	1	toluene			110	20 h	35	65/35

Table 3.8: enantiopure HAD with phenyl vinylsulphone.

The results shown in Table 3.8 warrants some comments:

1) Yields were calculated on the aldehyde **58** used for the formation of the silylimine and refer to chromatographically isolated or crystallize products.
2) Strictly reaction conditions furnished a mixture of HDA-adduct **78** and **79** and a diastereomeric mixture of azetidinones **80** and **81** in some 1/1 ratio and 80/20 diastereomeric mixture in β-lactams (Scheme 3.18).



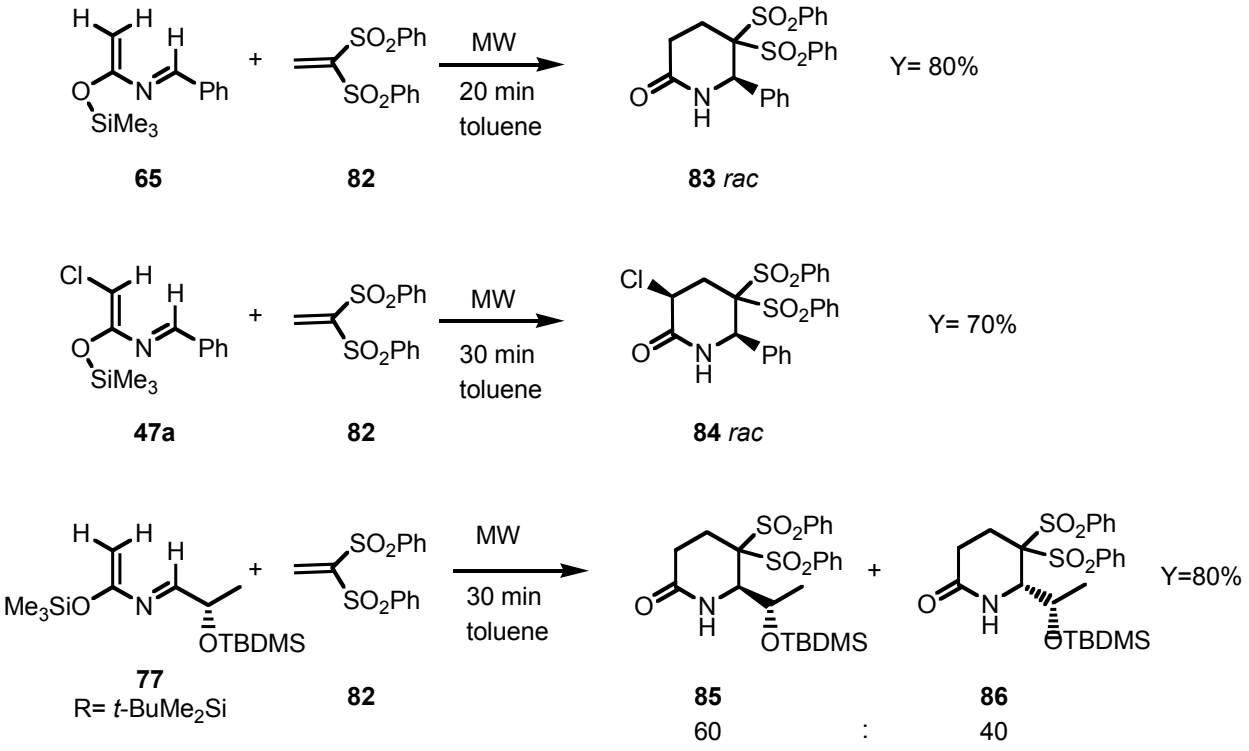
77
R=(*i*-Pr)$_3$Si

80 **81**

Scheme 3.18: Azetidinones formation

3) Use of diglyme as solvent (bp 162°C), entry 3, Table 3.8, furnished the same results, apart from a lowering (5%). of yield.
4) Once again, the methodology MAOS has been furnished the best reaction conditions. Entry 4, Table 3.8, reports the azadiene derived from (*S*)-lactic aldehyde OTBDMS protected. With conventional heating, the reaction time is much longer than using dielectric heating.

Activation with Lewis acids doesn't produce satisfactory results for the poor nucleophilicity of the oxygen atom of the sulfonyl group. Better results obtained by the use of a bis-sulfonyl ethylene **82** due to the increasing of the electron-withdrawing ability of the dienophile. As a matter of fact, this class of compounds are characterized by a high dienophiles reactivity and by the fact that the activating groups can be readily removed. The use of 1,1-bis(phenylsulfonyl)ethylene as dienophile in HDA reaction with 3-trimethylsilyloxy-2-aza-1,3-dienes has been given excellent results with all the substrates utilized (Scheme 3.19) .



Scheme 3.19: Synthesis of piperidinones with bis-sulfonyl olefin *via* HDA

Scheme 3.19 reports the high yields obtained in a very short time using mild reaction conditions. Also in the example with 4-halo-azadiene **47a**, with great satisfaction, only the six-membered cycloadduct was obtained.

All these compounds are particulary interesting for further elaboration to biologically active compounds.

Chapter **4**

3-Trimethylsilyloxy-2-Azadienes for the synthesis of biologically active compounds.

Hetero Diels-Alder cycloaddition is a versatile strategy for the synthesis of natural compounds containing six-membered heterocyclic rings.[2,3,6,41] Moreover, this strategy has found important applications through the elaboration of the cyclic adducts thus obtained to acyclic compounds with a well-defined stereo- and regio-control of the present functionalities.

Our reaserch group have already reported on the possibility of synthesizing biologically active compounds starting from perhydroxazinan-4-ones **I**, a useful intermediate obtained with an HDA reaction of 3-trialkysilyloxy-2-aza-1,3-dienes and aldehyde or ketone as dienophile (Chapter 3). The synthesis of a large amount of biologically active compounds is due to the high degree of functionalization of these cycloadducts as illustrated in Fig 4.1.

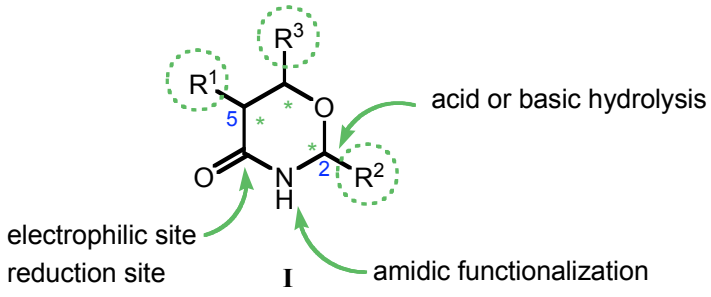


Fig. 4.1: Perhydroxazinones' functionality

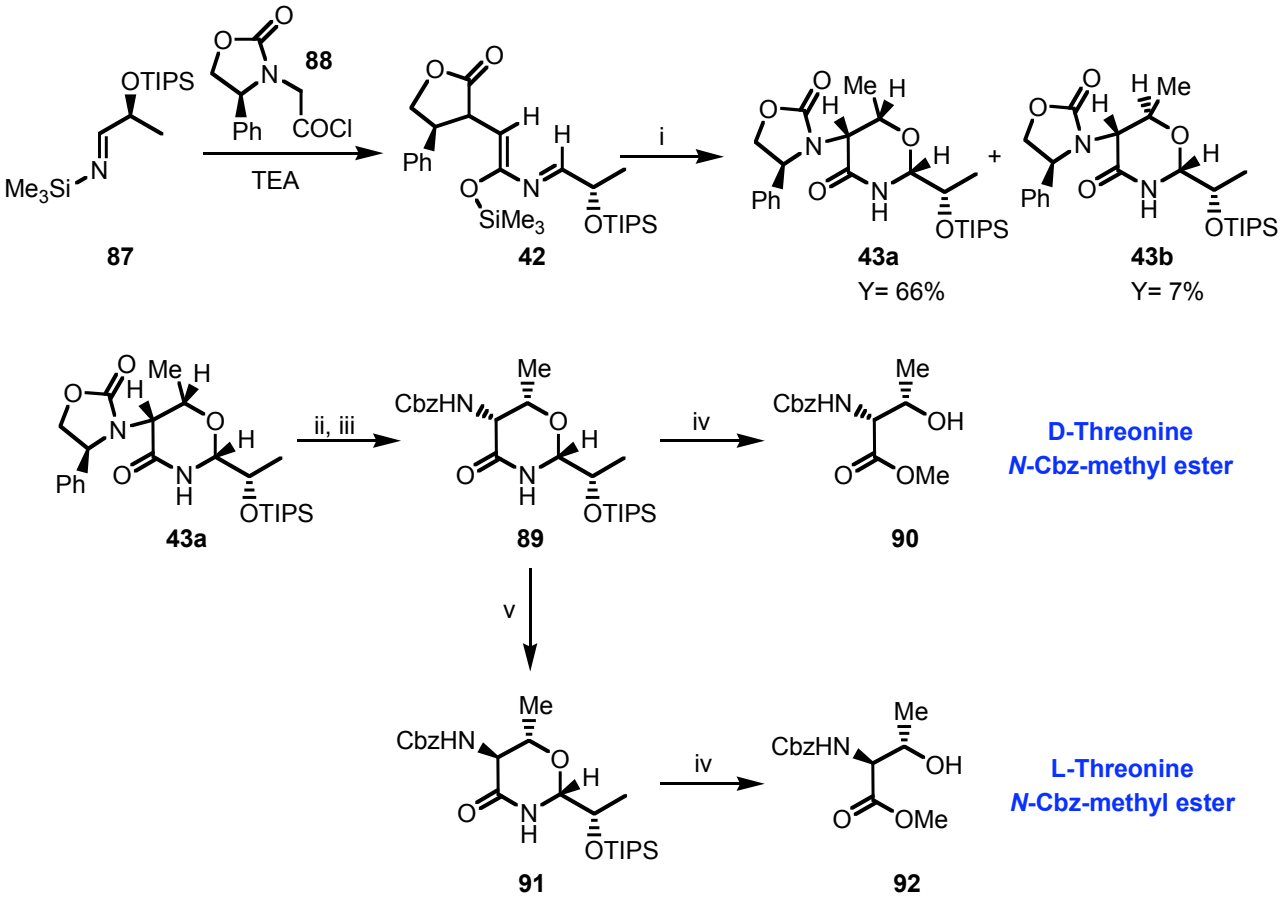
Analyzing the structure of the perhydroxazinones **I** it's possible to deduct some informations about its reactivity:

- three new stereocenters can be introduced during the course of [4+2] cycloaddition and their configurations controlled to a large extent.
- An aminalic carbon is present in position 2. The ring can be opened by a simple hydrolysis in acid or basic conditions
- The carboxyl of the amidic function can be reduced or can be attack by nucleophiles
- R^1, R^2, R^3 can be variously functionalized with satured or unsatured carbo- or hetero-groups, and with aromatic or non aromatic carbo- or hetero-cycles
- The position 5 can be substituted by an easily removable group.

4.1 Perhydroxazinones precursors of biologically active compounds. Part one.

- ***Threonine synthesis***

In the past few years we have reported on the possibility of synthesizing 5-amido-perhydroxazinan-4-ones as useful precursors of β-hydroxy-α-amino acids: D-threonine **90** and D-*allo*-threonine **92** have been obtained starting from (2*R*,5*R*,6*R*)-2-[(*S*)-1-[triisopropyl)oxy]ethyl]-5-[(benzyloxycarbonyl)amino]-6-methylperhydro-1,3-oxazinan-4-one **43a** (Schema 4.1).[19]



Reagents and conditions: i) MeCHO, $BF_3{\cdot}Et_2O$, -78°C, CH_2Cl_2; ii) Li/NH_3, -78°C, THF;
iii) CbzCl, acetone/ H_2O, NH_4Cl; iv) HCl/ MeOH; v) DBU/DMF, 80°C.

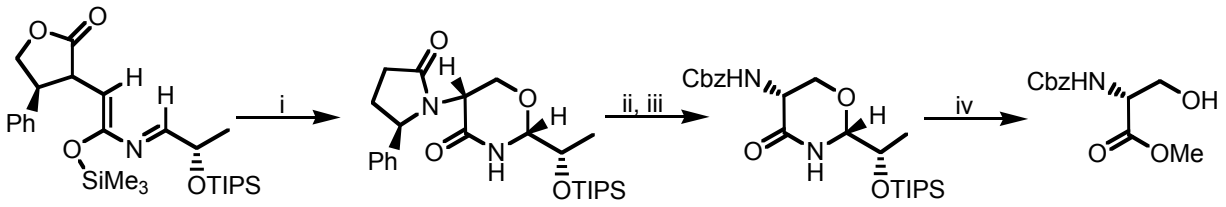
Scheme 4.1: Threonine synthesis

The reaction between *N*-trimethylsilylimine **87** of (*S*)-lactic aldehyde **58** and acid chloride **88**, in presence of triethylamine, gave the azadiene **42**. Compounds **43** were obtained via a hetero Diels-Alder reaction between the azadiene **42**, and acetaldehyde in the presence of BF_3 etherate in dichloromethane at –78°C. After chromatographic purification, one-pot-two-step removal of the Evans' oxazolidinone in **43a** and in situ formation of the corresponding N-Cbz derivative, the oxazin-4-one **89** was obtained. Ring opening of this product by methanolic HCl furnished the (D)-*N*-Cbz-threonine methyl ester **90** in 39% overall yield calculated on starting (*S*)-lactaldehyde. Epimerization of the C-5H stereocenter of **89** with DBU in DMF and treatment with methanolic HCl furnished the (L)-*N*-Cbz-threonine methyl ester **92**.

- ***Serine synthesis***

Interest in the field of stereoselective synthesis of β-hydroxy-α-amino acids is in continuous growth because of their presence in nature as metabolites or components of biologically active compounds. Moreover, due their high degree of functionalization, they find wide use as chiral starting materials in asymmetric synthesis.

In order to demonstrate the utility of our approach in the synthesis of non-proteinogenic amino acids, we have also reported the enantioselective synthesis of (+)-D-serine **95** protected as N-Cbz- methyl ester obtained with 24% overall yield calculated on starting (*S*)-lactaldehyde.[69]



42 **93** **94** **95**

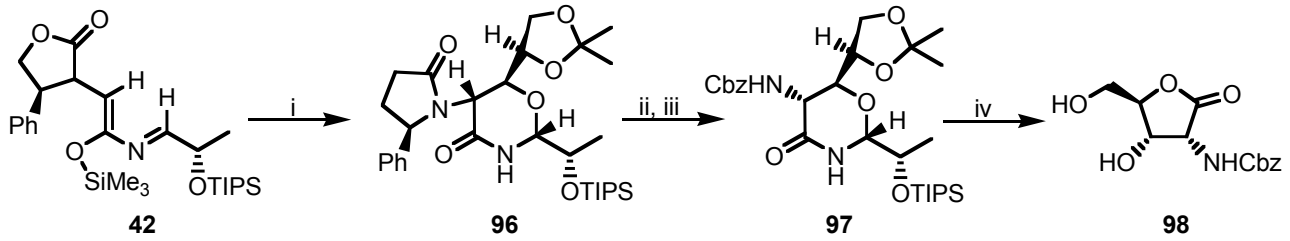
D-Serine
***N*-Cbz-methyl ester**

Reagents and conditions: i) HCHO, $BF_3{\cdot}Et_2O$, -78°C, CH_2Cl_2; ii) Li/NH_3, -78°C, THF; iii) CbzCl, acetone/ H_2O, NH_4Cl; iv) HCl/ MeOH.

Scheme 4.2: Serine synthesis

- ***Polyoxamic acid synthesis***

The same reaction sequence upon the cycloadduct **96**, obtained by the use of (D)-gliceraldehyde acetonide as dienophile, gives rise, after acidic work-up, to the cyclic form of scalemic 2,4-di-epi-polyoxamic acid **98** in 54% overall yield calculated on starting (*S*)-lactaldehyde.[63]

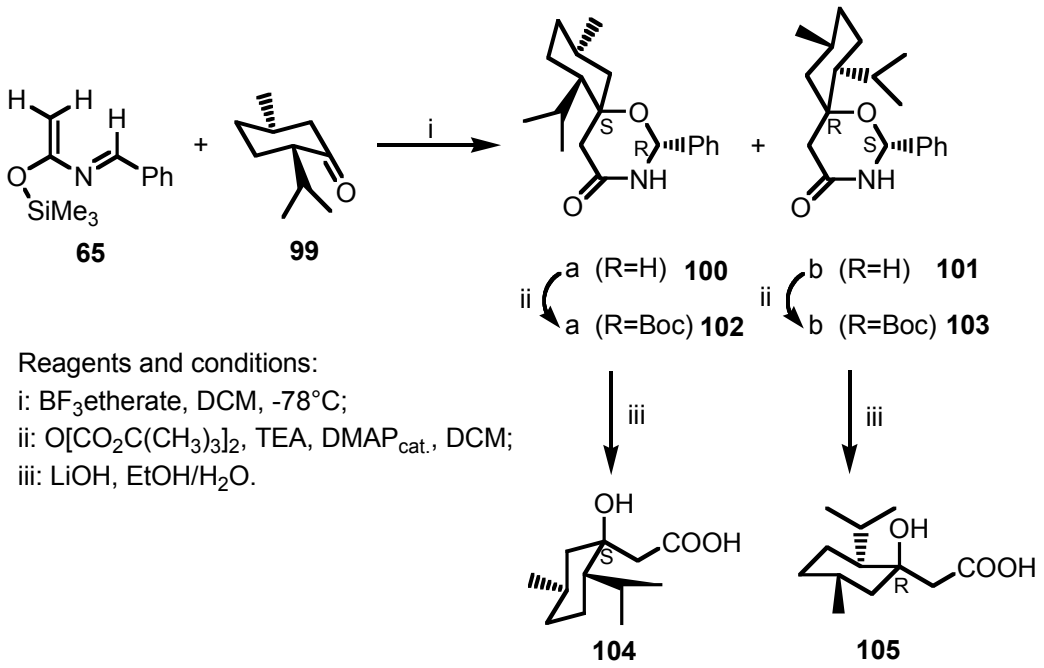


Reagents and conditions: i) D-Gliceraldehyde acetonide, $BF_3 \cdot Et_2O$, -78°C, CH_2Cl_2; ii) Li/NH_3, -78°C, THF; iii) CbzCl, acetone/ H_2O, NH_4Cl; iv) HCl/ MeOH.

Schema 4.3: Polyoxamic acid synthesis

- ***β-hydroxy acids synthesis***

On the other hand, the use of ketones as dienophiles has permitted the synthesis of 6,6-disubstituted perhydroxazinones as useful precursors of 3,3-disubstituted-β-hydroxy acids.[29] The possibility of preparing optically pure β-hydroxy perhydroxazinones and, therefore, β-hydroxy acids has been tested using optically pure starting material as diene or dienophiles. The use of the azadiene **65** and the optically pure (-)menthone **99** as dienophile achieved the synthesis of oxazinones **100** and **101** with a very high selectivity. (ratio 91/9 respectively). Trasformation of **100** and **101** into Boc derivatives **102** and **103** and treatment of such compounds with LiOH in $EtOH/H_2O$ solution, afforded the β-hydroxy acids **104** and **105** in almost quantitative yields.



Scheme 4.4: β-Hydroxyacids synthesis

4.2 Perhydroxazinones precursors of biologically active compounds. Part two. New synthesis.

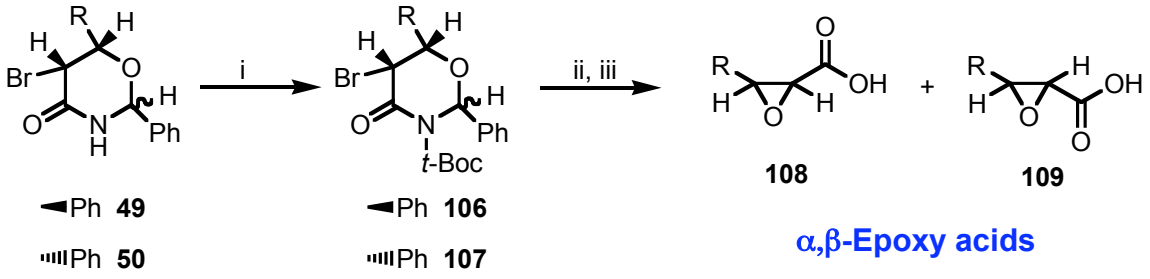
Recent studies on the synthesis of perhydroxazinones with an easy removable group (halogen, thioaryl) in position five of the heterocyclic adducts allow us to achieve new classes of biologically active compounds.

- ***α,β-Epoxy acids synthesis***

The preparation of the 5-halo-1,3-oxazinan-4-ones **49** and **50** have been illustrated in chapter 3.2. We now describe the results of our study on the synthesis of α,β-epoxy-carboxylic acids by the above reported HDA strategy. Carboxylic acids bearing in α,β–position an oxirane ring functionality are, in fact, useful intermediates in the synthesis of biologically active compounds. They have recently found application in the synthesis of Taxol and Taxotere derivatives and the carboxy-acid functionality presents several

advantages over the corrisponding carboxy-ester in the coupling reaction of Bacchatin 10 and side chains,[70] adding extra value to their synthesis.

The HAD adducts, obtained from 4-halo-3-trimethylsilyloxy-2-aza-1-phenyl-1,3-butadiene **47** and aldehydes **48** activated with BF_3 etherate (Tab 3.2), were processed to the final oxirane **108** and **109**by the sequential reactions shown in Scheme 4.5. In order to facilitate the lactamic ring opening the corrisponding *t*-Boc-derivatives **106** and **107** were prepared.[71]



49b:R=Me; **49d**:R=Propyl; **49e**:R=*n*-Heptyl;
49g, **50g**:R=*i*-Propyl; **49h**, **50h**:R=*t*-Butyl;
49i, **50i**:R=Ph; **49j**, **50j**:R=*p*-NO_2-Ph.

Reagent and Conditions: i) TEA, di-*tert*-butyl-dicarbonate, DMAP, DCM, 20°C;
ii) Method A: LiOH, THF, rt; Method B: LiOH, H_2O_2, EtOH/H_2O, rt;
iii) HCl 1N, 0°C.

Scheme 4.5: α,β-Epoxy acids synthesis

It is well know that a facile opening of lactamic ring takes place when a *t*-Boc group is directly linked to the lactamic nitrogen.[72] Final ring closure to the expected oxirane was studied in detail. Among the methods tested, in order to achieve one-spot two-step perhydroxazionone ring opening and nucleophilic substitution of alogen atom with the formation of the final oxirane ring, the best conditions have been proved to be those reported in the Scheme 4.5 as Method A and Method B. The two methods differ each other in the presence of hydrogen peroxide (Method B). The basis for the use of method B is to allow the use of oxygen nucleophiles that have positive deviation from the Bronsted-type nucleophilicity plot. These molecolues are said to exhibit an α-effect, a term describing a nucleophile alpha to an atom having a lone pair of electrons.[73,74] The most extensive class of α-nucleophiles are peroxy anions, which include peroxide salts. Our objective was to take advantage of this increased nucleophilicity for a faster ring opening of the perhydroxazinones, in the hope of lowering the rate of isomerization and side

product formation. Unfortunately (entry 1 and 2, Table 4.1) a better yield corresponds with a decreasing diastereomeric ratio (diasteromeric ratio was evalueted by ^{1}H NMR of the crude reaction mixture). In fact, partial isomerization at the C5-H stereocenter, presumibly due to the basic condition used, is observed with both methods. This side reaction takes place at the perhydroxazinone stage because of the high lability of the C5-H proton under the basic condition used. A direct isomerization of the epoxy acid lithium salts is unreasonable. Indeed, such isomerization are known to require drastic condition on the corrisponding epoxy esters.[75] Most important are the results reported in entries 5, 6 and 7 (Table 4.1). Using as starting perhydroxazinones the compounds of series **106** and **107**, the expected oxiranes were obtained in almost the same diastereomeric ratio compared to that obtained starting from single pure isomer. For this reason a mixture of the diastereomeric perhydroxazinones has been used as starting material for the final step of our strategic plane.

Entry	Compound	R	Yield (%)	Method	Products	Ratio	Hrs
1	**106b**	Me	55	A	**108b/109b**	90/10	8
2	**106b**	Me	90	B	**108b/109b**	70/30	3
3	**106d**	Propyl	60	A	**108d/109d**	75/25	3
4	**106e**	*n*-Heptyl	80	A	**108e/109e**	80/20	3
5	**106g**	*i*-Propyl	60	A	**108g/109g**	95/5	3
6	**106g**	*i*-Propyl	80	A	**108g/109g**	80/20	3
7	**106g+107g** (10/90)	*i*-Propyl	78	A	**108g/109g**	88/12	3
8	**106h+107h** (30/70)	*t*-Butyl	70	B	**108h/109h**	48/52	48
9	**106i+107i** (61/39)	Ph	85	A	**108i/109i**	>98/2	8
10	**106j+107j** (47/53)	*p*-NO_2-Ph	75	B	**108j/109j**	45/55	3

Table 4.1: Epoxy acids from *t*-BOC perhydroxazinones derivatives

The synthetic protocol for the synthesis of *cis* a,b-epoxy oxiranes, here described, may be considered a convergent synthesis of *cis*-epoxydes in good to high stereochemical fashion, due to the strict control of the stereoselectivity during the formation of the C5-C6 stereocenters. The lack of high stereocontrol in the formation of the C2 stereocenter is not

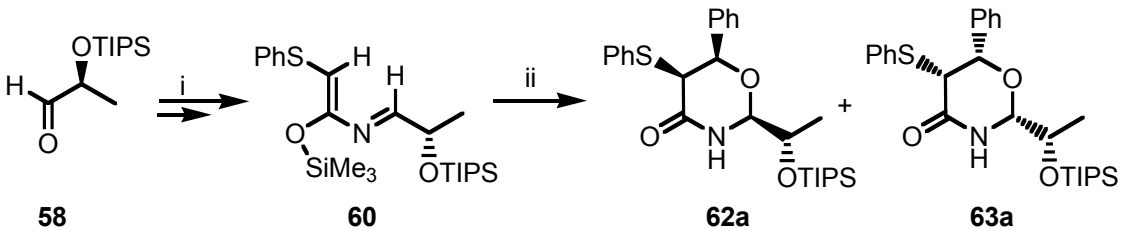
crucial for our strategy, since this stereocenter is destroyed during the final step of the oxirane formation.

- ***Optically active 1,3-aminols:(R)- and (S)-Fluoxetine synthesis***

In continuation of our studies on the use of HDA strategy in the synthesis of heterocyclic compounds with different substitution pattern and their use for the preparation of acyclic derivatives, we report the synthesis and use of the 5-phenylthio-substituted oxazinan-4-ones. Its importance is due to an easily removable group, as the thiophenyl one, in the position five of the heterocyclic adduct.

Reported in this section are our recent results on the synthesis of Fluoxetine (Prozac®)[76,77] and Duloxetine (Cymbalta®),[78-80] two potent and highly selective inhiborts of neutral serotonin-reuptake and among the most important drugs for the treatment of psychiatric disorders and metabolic problems.

Using our experience on the synthesis of optically active perhydroxazinones via HDA, we have been formed the cycloadduct **62** and **63** starting from the azadiene **60**, in turn derived from the trimethylsilylimine of the (*S*)-lactic aldehyde **58** and the 2-phenylthioacetylchloride **59** as source of the ketene, and benzaldehyde activated with BF_3 etherate in DCM at –78°C.(Scheme 3.10, Table 3.4). Perhydroxazinones **62a** and **63a** (Scheme 4.6) were obtained in 50/50 diastereomeric ratio and 81% overall yield (and the two diastereoisomers were separated by flash chromatography eluiting with cyclohexane/ethylacetate 7/3.

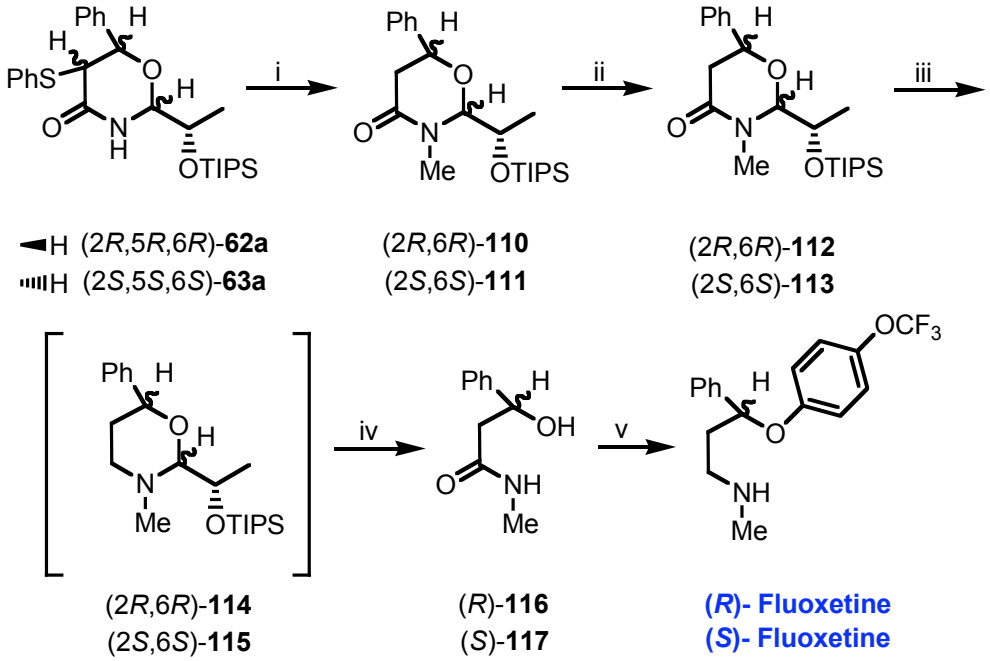


58 **60** **62a** **63a**

Reagent and conditions. i) LiHMDS, TMSCl; $PhSCH_2COCl$ **59**, TEA; ii) BF_3, PhCHO

Scheme 4.6: Synthesis of cycloadducts precursors of Fluoxetine

Compounds **62a** and **63a** were easily desulfurated by the use of Nickel-Raney in a *novel microwave-mediated*[81-85] *desulfurization reaction*.[86-90] Thus treatment of such compounds with Nickel-Raney under MAOS conditions have been allowed to obtain, in a very short time (2 min) and high yields (90% and 98% respectively) the corresponding desulfurated derivatives **110** and **111**. These compounds were treated with LiHMDSA and methyl iodide in order to get the corresponding *N*-metyl derivatives **112** and **113** in quantitative yields. Reduction of carboxy functionality occurred with diphenyl silane in the presence of catalytic amount of tris(triphenylphosphine)rhodium(I) carbonyl hydride to give the perhydroxazinones **114** and **115** in yields up to 98%. Due to their relative instability, the crude reaction mixture of **114** and **115** was used as such in the subsequent step of our process. Accordingly, final mild ring opening of these compounds by means of diluted HCl furnished the enantiomerically pure (1*R*)- and (1*S*)-aminoalcohols **116** and **117b** in 60% and 67% respectively overall yields based on the desulfurated products **110** and **111**. Final conversion of intermediates **116** and **117** to the title compounds was achieved according to literature procedures.[81]

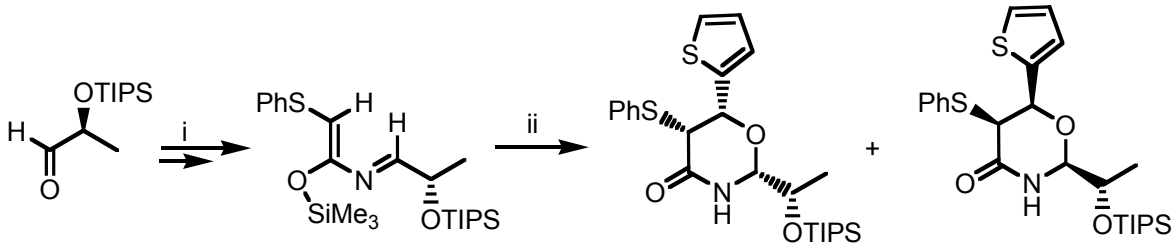


Reagent and conditions: i) MW, Nickel-Raney/EtOH; ii) LiHMDS, MeI, THF; iii) $Ph_2Si_2H_2$, $RhH(CO)(PPh_3)_3$, THF; iv) HCl_{aq}; v) Ref 81

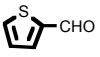
Scheme 4.7: (*R*)- and (*S*)-Fluoxetine synthesis

- ***Optically active 1,3-aminols: (R)- and (S)-Duloxetine synthesis***

Using the same optically active azadiene **60** above reported but 2-thiophene-carboxaldehyde as dienophile we obtained the proper perhydrossazinones required for the synthesis of enantiomerically pure (*R*)- and (*S)*-Duloxetine (Scheme 3.10, Table 3.4).
The 3-silyloxy-2-aza-1,3-diene **60**, prepared from the trimethylsilylimine of the (*S*)-lactic aldehyde **58** and the 2-phenylthioacetylchloride **59** as source of the ketene, and 2-thiophenecarboxaldehyde activated with BF_3 etherate reacted in DCM at –78°C to give perhydroxazinones **62b** and **63b** in 60/40 diastereomeric ratio and 90% overall yield after purification by flash chromatography eluiting with cyclohexane/ethylacetate 8/2 (Scheme 4.8).

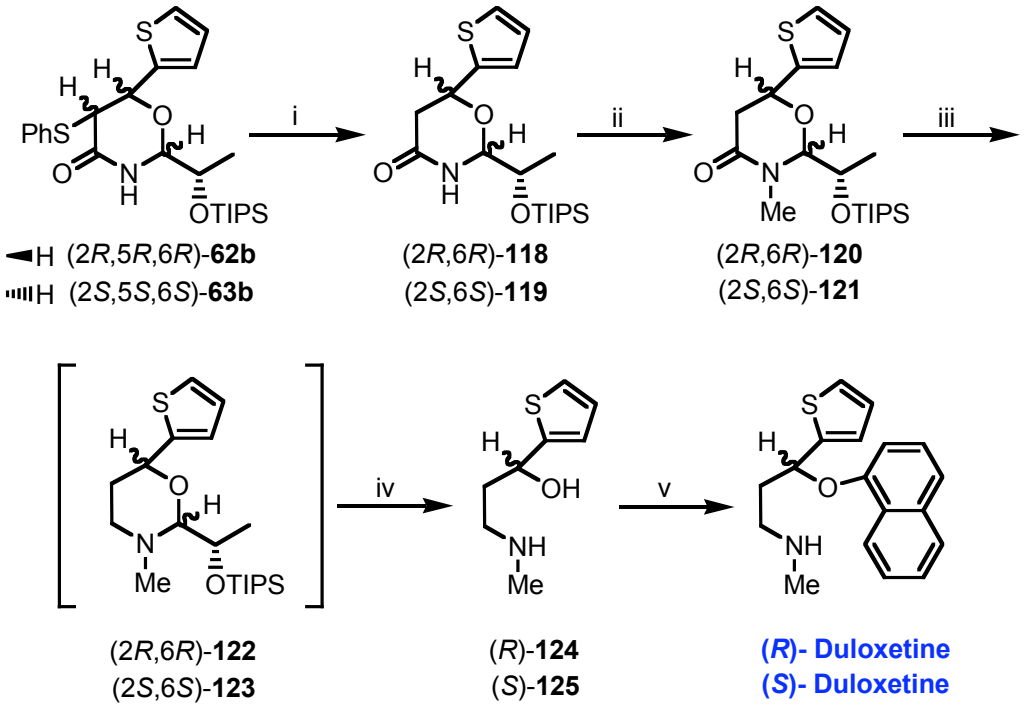


58 **60** **62b** **63b**

Reagent and conditions. i) LiHMDS, TMSCl; $PhSCH_2COCl$ **59**, TEA; ii) BF_3, 

Scheme 4.8: Synthesis of cycloadducts precursors of Duloxetine

Desulfuration of oxazinan-4-ones **62b** and **63b** by the above reported microwave-mediated Nickel-Raney methodology partially failed when applied to this compounds giving rise to low yields of the desired 5-unsubstituted derivatives **118** and **119**, probably due to side reactions on the thienyl ring. We have found that desulfuration with aluminum amalgam[91] was the method of choice. The crude reaction mixture was used for the next step without any purification. Methylation by LiHMDS and methyl iodide gave rise to the *N*-methyl intermediates **120** and **121** in quantitative yields. Reduction of the amide functionality by means of Ph_2SiH_2 in the presence of 1 mol % $RhH(CO)(PPh_3)_3$[92] in THF, resulted in the production of the partially unstable intermediates **122** and **123**. Ring opening by aqueous hydrochloridric acid furnished the corrisponding aminol **124** and **125**. (*R*)-and (*S*)-Duloxetine were obtained by means of arylation of **12** and **125** according to a literature procedure.[93]



Reagent and conditions: i) aluminium amalgam, *i*-PrOH; ii) LiHMDS, MeI, THF; iii) $Ph_2Si_2H_2$, $RhH(CO)(PPh_3)_3$, THF; iv) HCl_{aq}; v) Ref 93.

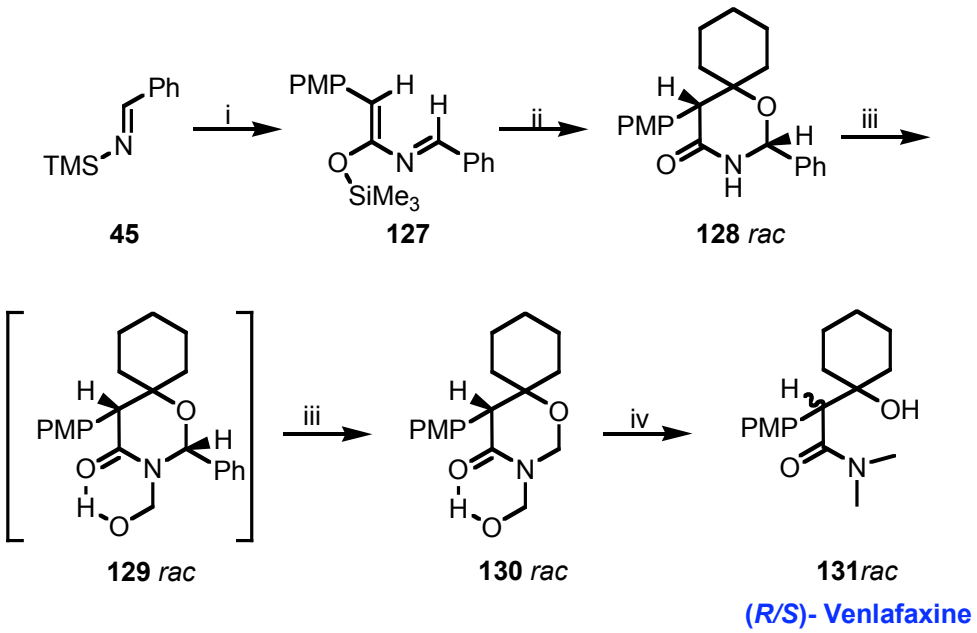
Scheme 4.9: (*R*)- and (*S*)-Duloxetine synthesis

- *Optically active 1,3-aminols: (R/S)-Venlafaxine synthesis*

In continuation of our studies on the use of hetero Diels-Alder strategy in the synthesis of heterocyclic adducts and their use for the preparation of acyclic optically active compounds, 5-(4-methoxy-phenyl)-2-phenyl-1-oxa-3-aza-spiro[5,5]undecan-4-one **128**, precursor of the Venlafaxine,[94] an important drug for the treatment of psychiatric disorders, has been prepared.

The reaction of *N*-trimethylsilylimine of benzaldehyde **45** and the *p*-methoxyacetylchloride **126** in presence of triethylamine gave rise the azadiene **127**. The subsequence cyclization with ciclohexanone activated by BF_3 etherate in DCM at –78°C produced the racemic perhydroxazinones **128** in 66% overall yield after purification by flash chromatography eluiting with cyclohexane/ethylacetate 8/2 (Scheme 4.10). A *novel microwave*[81-85]*-mediated transketalization reaction* has been developed in our laboratories. Compound **128** in presence of formic acid and formic aldehyde, in MW oven for 3 min

gave rise to compound **130** through the intermediate **129**. A simple reduction with lithium aluminum hydride furnished the desidered aminol **131**.



Reagent and conditions: i) $PMPCH_2COCl$ **126**, TEA;
ii) BF_3, ciclohexanone, DCM, -78°C, 8h;
iii) HCOOH, HCHO, MW; iv) $LiAlH_4$.

Scheme 4.10: (*R/S*)-Venlafaxine synthesis

Chapter **5**

Theoretical calculations

This part has been added for the sake of a complete overview on the reactivity of the azadiene from a theoretical point of view. Further studies are currently under developments and a full paper is in preparation and will be published in due course.[95]

The HAD reaction of carbonyl compounds with dienes is a convenient synthetic procedure for the preparation of six-membered heterocyclic compounds. In recent years an intensitive effort has been performed to achieve asymmetric HDA reactions. According to previous calculations performed on a similar substrate the cyclization reaction is considered to happen by a concerted HDA mechanism through the formation of an oxazinic ring, but, in analogy with what is known for similar reaction, a stepwise mechanism with the formation of an aldol-type intermediate cannot be ruled out (Fig. 3.1, Fig. 3.2).

The stereochemical outcome of the reaction depends on the structure of the imine, on the ketene precursor, on the substituents of reagents and on the LA utilized.

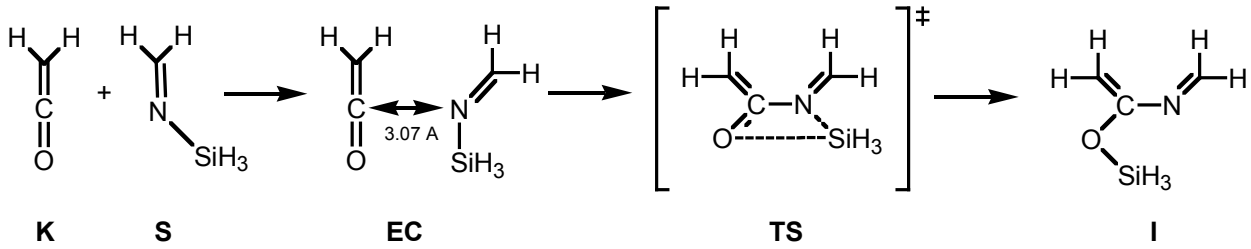
With the aim of gaining a deeper insight into this subject we performed a DFT computational study on both the uncatalyzed and Lewis acid catalyzed reaction.

5.1 Azadiene geometry

The formation of the azadiene consist in the coupling reaction of the *N*-trimethylsilylimine **2** with the ketene n obtained in situ from the parent acyl chloride **3** and TEA (Scheme 1.6).

According to the proposed mechanism,[96-98] ketene formation takes place at the first step, followed by nucleophilic attack of the imine nitrogen atom on the ketene sp carbon

atom. To test if the presence of the *N*-silyl group is compatible with this mechanism, an ab initio study (MP2/6-31G* level using the Gaussian 94 series of program) was performed, using as model compounds ketene **K** and *N*-silylformaldimine **S**; the results are shown in Scheme 5.1.



Scheme 5.1: nucleophilic attack of the imine nitrogen atom on the ketene

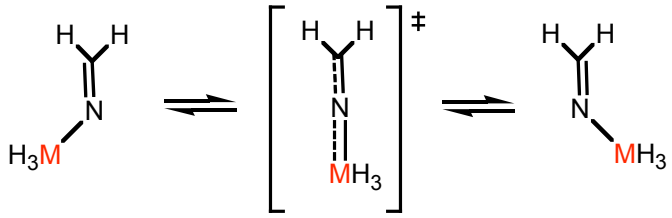
The calculations show the preliminary formation of a stabilizing electrostatic complex **EC** followed by the generation of a polar-type transition state **TS**. The length and the bond order of the C-N bond being formed (1.792 Å, 0.44 bond order) and the angle between the planes of the two subunits (44°) are in agreement with the transition state already calculated for a (non-silyl)imine.[98] The presence of the silyl atom, however, stabilized **TS** in a *syn* form due to a weak bonding interaction between the oxygen atom and the silicon itself. Next, the simultaneous formation of the C-N and Si-O bonds takes place, resulting in the formation of the neutral silyloxyazadiene **I**, in which the long range interaction of the silicon with the nitrogen atom (0.084e$^-$) is responsible for the stabilization of a twisted (46°) ***s-cis* conformation**.

In addition, when substituents are present on C1 and C4 of the azadiene, we have been able to assign sperimentally the ***E,Z* configuration** of the azadienes. In our case, due to the high stability of the neutral silyloxyazadiene, the stereoselectivity is already established at the moment of the azadiene formation. In fact we have been able to isolate azadiene as a unique compound which has been determined by NOE experiments (Fig. 1.7).[17,19]

A more difficult aspect to explain is how such an azadiene geometry arises, because silylimines are reported to adopt the *anti* configuration[99] and the attack of an *anti* imine to the less hindered side of a ketene should lead to a (*Z,Z*)-azadiene.

If we examine the geometry of **TS** we note that the chelating effect of the silicon atom on the ketene oxygen atom constrains the structure in a *syn* forming which the two methylene groups on the ketene and the imine are close together. This fact enhances the

steric repulsive effect of the substituents, especially when they are bulky as in our cases, and forces the attack to give the less-crowded *E,Z* form. To obtain this result the imine must easily change its configuration. The change of configuration in imine takes place by pyramidal inversion at the nitrogen atom. Alkylimines have a high inversion barrier (27 kcal mol^{-1})[100] but it is known that such a barrier is significantly lowered by higher row atoms belonging to group IVa (germanium) directly linked to the inversion center. In this context we determined the inversion barrier of *N*-silylformaldimine by ab initio calculations. The barrier is taken as the energy difference between the bent form and a linear transition state. The calculated value is 9.3 kcal mol^{-1}. For the sake of comparison these calculations were also performed on *N*-methyl- and *N*-germylformaldimine; the results are reported in Table 5.1. The value of the *N*-silylimine is predictably lower than that for *N*-alkylimines and allows for the facile inversion at the nitrogen atom as requested from the steric requirements.



M	calc
C	32.5
Si	9.3
Ge	14.9

Table 5.1: MP2/6-31G* inversion barrier energies (kcal mol^{-1})

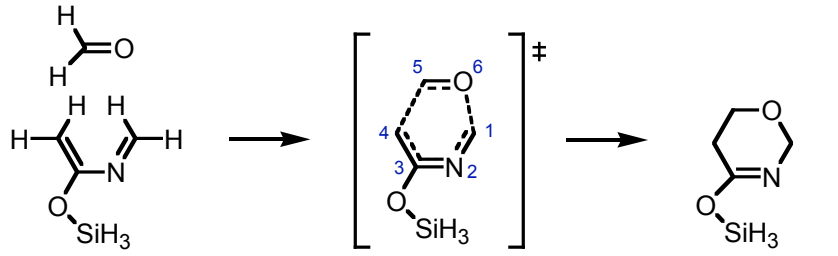
NOE studies and ab initio calculations show that the azadiene intermediate prefers two *s-cis* conformations (Scheme 5.2): a twisted conformation with a C=N-C=C dihedral angle of about 45° (rotamer P) and the corresponding counter clockwise conformation (rotamer M).

Scheme 5.2: Azadiene conformation

5.2 Uncatalyzed cyclization

In order to determine the preferred pathways for the cyclization reaction, the calculations were performed using the unsubstitued 3-silyloxy-2-azadiene and formaldehyde as model starting compounds.[101]

The calculations show the preliminary formation of a stabilizing electrostatic complex **EC1** with a mean distance of a 3 Å between the two molecules (Scheme 5.3). The subsequent transition state **TS-1** has an energy 12.6 kcal mol-1 higher than that of the electrostatic complex and has the same sign of the two dihedral angles C1-N2-C3-C4 and N2-C3-C4-C5 of 10° and 53° respectively. The strong planarization of the azadiene skeleton in the transition state (10° against 41° in the EC1), the neat pyramidalization of C1, C4 and C5 (150-160°), the equality of the lengths of the two forming bonds C4-C5 and C1-O6 (2.14 and 2.15 Å) and the values of their bond orders (0.32 and 0.17 e^-) make these geometry features very similar to those found for the transition structure of concerted pathways in related reactions[102] and are good evidence for a synchronous pericyclic reaction. An HAD-type cyclized compound, characterized by the presence of a localized C3=N2 double bond in the ring, originates from the transition state. The strong exothermicity of the cyclization reaction provides the driving force for this process. No transition state suggestive of a stepwise reaction was found. All attempts to form a zwitterionic aldol-type structure starting from the *s-cis* or *s-trans* azadiene form resulted either in the formation of TS1 or in separation to the reactants.

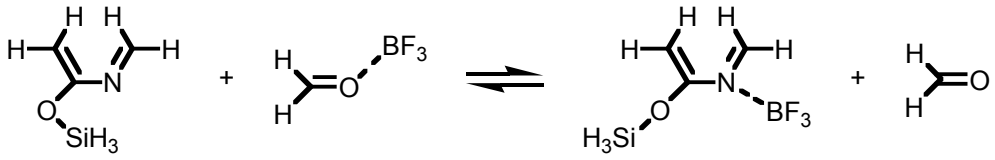


Scheme 5.3: Uncatalyzed cyclization

5.3 Lewis acid catalyzed cyclization

The addition of a Lewis acid such as BF_3 can lead to different reactions pathways depending on where the LA coordinates. In such reactions BF_3 is generally regarded as coordinating the aldehyde oxygen,[3] although it is known that azadiene can coordinate to BF_3 through the imine nitrogen.[60]

Calculations show that BF_3 can coordinate to both sites with a length and bond order of 1.92 Å, 0.23 e^- and 1.70 Å, 0.43 e^- respectively. In the isodesmic reaction shown in Scheme 5.4 the right-hand part is 5.8 kcal mol-1 more stable, thus showing that the azadiene nitrogen must be considered to be preferred coordination site.



Scheme 5.4: Coordination site of BF_3

As a consequence, cyclization would occur between the complexed azadiene and the free aldehyde. On the other hand, and according to frontier molecular orbital (FMO) theory, the cycloaddition of carbonyl dienophiles with 2-aza-1,3-dienes has been shown to be a $LUMO_{dienophile}$- $HOMO_{diene}$ controlled process.[19,49] In order to analyze the effect of the coordination of BF_3 on such orbitals, we reported in Table 5.2 the calculated energies for uncomplexed and complexed formaldehyde and azadiene.

	HOMO	LUMO
Formaldehyde	-	-1,15
Formaldehyde BF_3	-	-2,67
Azadiene	-6,19	-
Azadiene BF3	-7,35	-

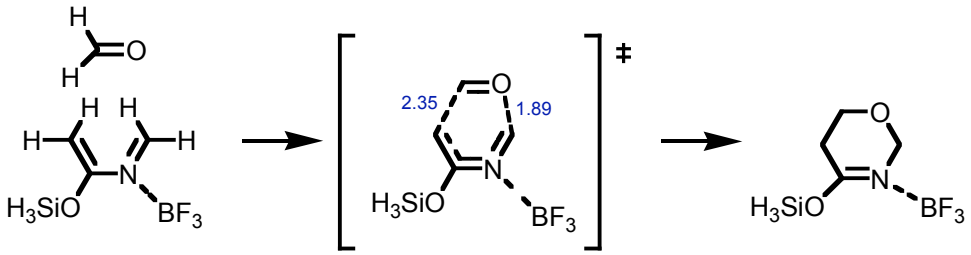
Table 5.2: B3LYP/6-31G* energies [eV] of FMO orbitals

An analysis of the values shows thar the strong electron-withdrawing effect exerted on the substrate by BF_3 causes alowering in energy of the orbitals of both substrates.

Upon comparing the energies of the involved interacting orbitals it becomes clear that the cyclization via formaldehyde complexation should be strongly favored with respect to that via azadiene complexation (ΔE=3.52 and 6.20 eV, respectively), whilst the uncatalyzed cyclization (ΔE=5.04 eV) would be just in the middle. As the acid-base equilibrium in Scheme 5.4 would favor the *O*-complexed cyclization path, calculations were performed for both cases.

- ***N-Complexation***

The complexation of the azadiene with BF_3 does not change the geometry of the azadiene skeleton[60] subsequentially and consequently, the behavior of the system is very similar to that of the uncatalyzed cyclization. The calculations show the preliminary formation of a stabilizing electrostatic complex **EC2** (Scheme 5.5) with a mean distance of 3 Å between the two molecules. A transition state **TS2** was located with an energy 16.4 kcal mol^{-1} higher than that of the electrostatic complex.



EC2 -18.5 kcal/mol | **TS2** -2.1 kcal/mol | **CY2** -53.3 kcal/mol

Scheme 5.5: Energies transition state values for *N*-complexation

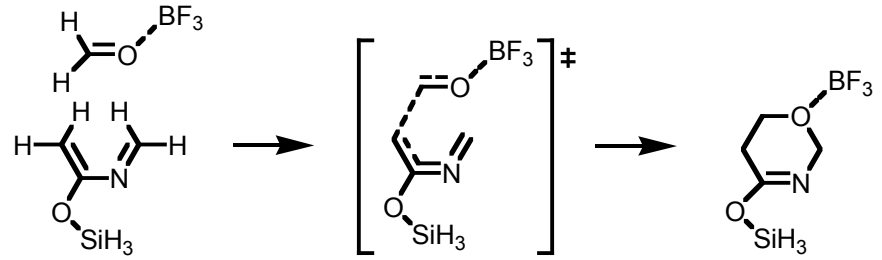
The transition state **TS2**, which has the same configuration as **TS1**, is characterized by a minor twisting of the azadiene skeleton (19°) with respect to that in **EC2** (47°), a neat pyramidalization of C1, C4 and C5 (150-160°) and by the presence of two incipient bonds (C4-C5 and C1-O6).

The coordination with BF_3 increases the electrophilic character of C1 and favors the bonding to the aldehyde oxygen, as shown by the lenghts and bond orders of the two forming bonds (2.35 Å, 0.28 e^- and 1.89 Å, 0.41 e^- respectively). However, these lenghts and the overall geometry of the transition state allow us to consider this reaction as an HAD concerted reaction with a certain degree of asynchronicity. No transition state

accountable for a step-wise reaction was found. All the attemps to form a zwitterionic aldol-type structure starting from the *s-cis* or *s-trans* azadiene form resulted either in the formation of **TS2** or in a separation to the reactants.

- ***O-Complexation***

BF_3-complexed formaldehyde can approach the *s-cis* azadiene skeleton in an *endo* or *exo* fashion. In the *endo* approach no formation of a zwitterionic or HDA-type transition state is observed due to the steric hindrance between the BF_3 and the azdiene imine bond. In the *exo* approach a preliminary formation of a tight, stabilizing electrostatic complex **EC3**, very close in distance (2.5 Å).

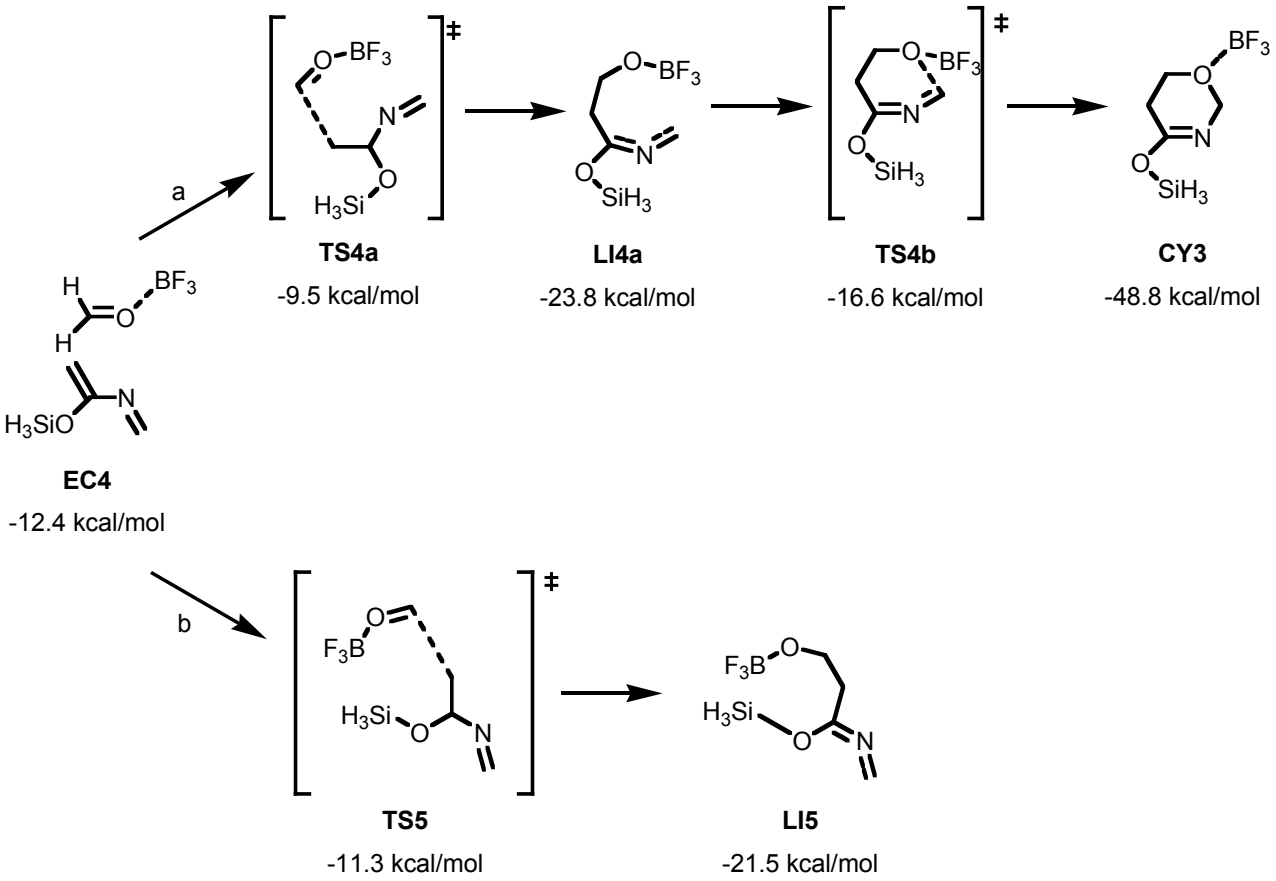


Scheme 5.6: Energies transition state values for *O*-complexation, azadiene *s-cis, exo* approach

A transition state originate from this electrostatic complex **TS3** has an energy of 0.4 kcalmol^{-1} higher than that of the corrisponding electrostatic complex. The azadiene skeleton is more twisted than in the previously observed transition states (18°) and, due to the coordination to the BF_3, which increases the electrophilic character of the aldehyde carbon, the transition state is characterized by the presence of only one incipient bond between C4 and C5, as shown by the values of the bonds lenghts and bond orders (2.25 Å, 0.29 e$^-$), by the neat pyramidalization of C4 and C5 (150-160°) and by the long distance between C1 and O6 (3.2 Å). **TS3**, which has the geometry apt to directly form a ring, close to **CY3** even though the incipient bond between C1 and O6 is failing in the transition states. All the attempts to find an acyclic intermediate failed, and a separation of the reactants or a cyclization to CY3 occurred. Therefore, even if only one incipient bond is formed in the transition state and the presence of a single transition state, the reaction

describe in Scheme 5.6 can be considered as one-step HDA-type reaction characterized by a high level of asynchronicity.

In contrast to what is observed in the previous cases, the attack of the complexed formaldehyde on the *s-trans* form of the azadiene is now possible. In this case a preliminary formation of a stabilizing electrostatic complex (**EC4**) with a mean distance of 3 Å between the two molecules also takes place, followed by bond formation between C4 and C5. As many orientations of the two molecules are possible in the formation of the new bond, all the relevant geometries in discrete staggered conformations were examined, with BF_3 *endo* or *exo* to the azadiene skeleton (dihedral angles B-O6-C5-C4 of +90° or –90°, respectively). The results are shown in Scheme 5.7.



Scheme 5.7: Energies transition state values for *O*-complexation, azadiene *s-trans, exo* and *endo* approach

Only two transition states were found (**TS4a** and **TS5**) with an energy 2.9 and 1.1 kcalmol^{-1} higher than that of the electrostatic complex and showing only one net incipient bond between C4 and C5 (2.22 Å, 0.34 e$^-$ for **TS4a** and 2.21 Å, 0.32 e$^-$ for **TS5**). They are characterized by a different geometry around the incipient bond, with **TS4a** having the C-O

bond eclipsed to the C3-C4 bond (0.1°) and BF_3 *exo* to the azdiene skeleton and **TS5** having the C-O bond in a *gauche* conformation with the C3-C4 bond (-69.5°) and BF_3 *endo* to the azadiene skeleton. In both cases an acyclic aldol-like structure is formed (**LI4** and **LI5** in Scheme 5.7) due to the stabilization effect of the LA catalyst, which neutralizes the negative charge on the oxygen through the formation of a neat O-B single bond (2.21 Å, 0.65 e^-). The two structures present a different geometry that strongly affects their reactivity. In **LI5** the BF_3 and the SiH_3 groups are on the same side of the molecule, with a stabilizing interaction between the silicon atom and one of the fluorine atoms (Si•••F 2.20 Å). This geometry forces the C=N bond onto the other side of the C-O bond, with the consequence that the long distance between C1 and O6 (4.50 Å) prevent a further cyclization to **CY3**. In **LI4**, however, the BF_3 and the SiH_3 groups are on opposite side of the molecule and C1 and O6 are enough close (3.41 Å) and have the right geometry to allow cyclization to **CY3**. This happen to the transition state **TS4b** which is characterized by an incipient bond between C1 and O6 (2.50 Å, 0.11 e^-). The presence of two transition states and an acyclic intermediate in path a of Scheme 5.7 allows us to consider this path as that of an aldolic two-step cyclization, which is competitive with the reaction paths describe in Scheme 5.6. the latter, however, is favored by the very low activation energy of its unique transition state.

A plot of the relative energy reation coordinates for the LA-catalyzed reaction paths (Fig. 5.1) shows that the *N*-complexation path is characterized by the highest activation energy. As a consequence, even if *N*-complexation is favored over *O*-complexation path 3 and 4 (Fig. 5.1) are neatly favored.

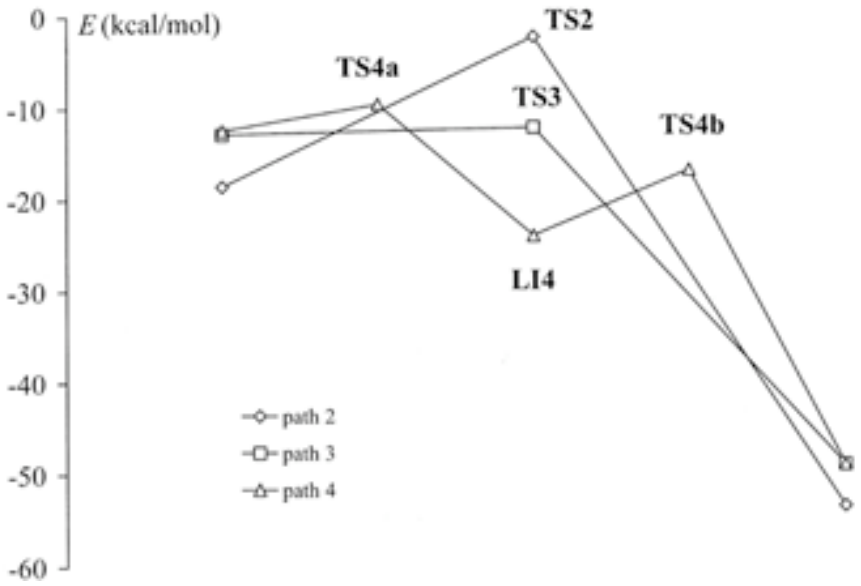


Fig. 5.1: Path profile for LA_catalyzed reactions.

At this point we should draw attention to the activation energy values that we found for the BF_3 *O*-complexed, uncatalyzed, and BF_3 *N*-complexed HDA reactions (0.4-0.8, 12.6 and 16.4 kcal mol-19, which have the same trend of the $LUMO_{dienophile}$-$HOMO_{diene}$ energy difference (ΔE= 3.52, 5.04 and 6.20 eV, Table 5.2), thus confirming the effectiveness of FMO theory in predicting the reactivity of such systems. The different observed need for the presence of a Lewis acid catalyst to perform a cyclization[8,19,61,62] can therefore be ascribe to the effect exerted on the frontier orbitals by the substituents. Accordingly, electron-donor substituents present on the azadiene substrate,[61,62] which increase the azadiene HOMO energy,[39] have the effect of decreasing the $LUMO_{dienophile}$-$HOMO_{diene}$ energy difference and the reaction proceeds without acid catalyst. The same effect may be observed when strong electrophilic aldehydes are used.[62] In this case the decrease of the aldehyde LUMO energy[39] allows the reaction to take place without a catalyst. Finally, with electron-withdrawing or neutral substituents present on the azadiene substrate[8,19] the gap energy is higher and an LA catalyst is necessary in order for a reaction between the azadiene and the aldehyde moieties to take place. Under such conditions, in the absence of an acid catalyst, an electrocyclic conrotatory closure of the azadiene moiety is preferred, leading to a four-membered cyclic azetidinone.[7,103]

Summarizing the results obtained we can conclude that the uncatalyzed cyclization is a classic hetero Diels-Alder reaction that occurs through a synchronous mechanism, as shown by the structure of the transition state. In the LA-catalyzed reaction BF_3 can

coordinate to either the azadiene or the aldehyde moiety. In the first case, the reduced nucleophilicity of the azadiene strongly increases the energy activation of the HAD-type cyclization and makes this reaction path the less probable one, whereas in the second case the enhanced electrophilicity of the aldehyde leads to an easier cyclization, which can take place through an HAD asynchronous concerted mechanism or an aldolic two-step one. The presence of substituents with a different stereoelectronic character can shift the reaction toward one or the other of these possible ways.

Chapter 6

Experimental

6.1 General

Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on Varian VXR-200 or on Varian-Mercury 400 MHz spectrometers. Chemical shifts are reported in □ scale and coupling constants (J) are reported in Hertz. Infrared spectra were recorded on a Perkin–Elmer Spectrum BX spectrophotometer in $CHCl_3$. Mass spectra were recorded on Finnigan MAT GCQ instrument. Optical rotation measurements were carried out on a Perkin-Elmer 343 Polarimeter and specific rotation $[\square]_D^{20}$ was reported in deg per dm at the specified temperature and with the concentration [*c*] given in g per 100 mL in $CHCl_3$. Microwave mediated synthesis have been performed in a Prolabo Sinthewave 400 Microwave System and on

Solvents were distilled according to standard procedures before use and were stored on molecular sieves (4 Angstrom) and they have been checked at Karl-Fisher apparatus showing the presence of less then 20 ppm of water.

6.2 5-Halol-1,3-oxazinan-4-ones preparations

General procedure for the preparation of azadiene (47). GP1

1 mL of benzaldehyde **44** (1 mmol) was added to a solution of LiHMDS (1.1 mL of 1 M sol in THF) and heptane (5 mL) at 0°C under inert atmosphere. The reaction mixture was stirred at 0°C for 1 h. IR analysis confirmed the formation of silylimine **45** ($\square_{CN}$=1655 cm^{-1}). TMSCl (0.14 mL, 1 mmol) was added in one portion and after stirring for 10 min at 0°C the mixture was allowed to stir for 1 h at rt. A white precipitate formed. The mixture was cooled at 0°C, triethylamine (0.3 mL, 2 mmol) was added in one portion and after 5 min a solution of halo-acid halide **46** (1 mmol) in 5 mL of heptane was added. Stirring was maintained for

2 h and precipitate appeared. The mixture was filtered through Celite under argon and the solvent was removed in vacuo to afford **47** as an oil, which was analyzed by ^{1}H NMR and ^{13}C NMR spectroscopy.

1-Chloro-2-trimethylsilyloxy-3-aza-4-phenylbutan-1,3-diene 47a. Prepared according GP1 starting from benzaldehyde and chloro acetylchloride. ^{1}H NMR (400 MHz, $CDCl_3$): 8.39 (s, 1H), 7.81 (m, 2H), 7.45 (m, 3H), 6.00 (s, 1H), 0.35 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): 155.1, 153.5, 135.7, 131.3, 128.7, 101.3, 0.6.

1-Bromo-2-trimethylsilyloxy-3-aza-4-phenylbutan-1,3-diene 47b. Prepared according GP1 starting from benzaldehyde and bromo acetylbromide. ^{1}H NMR (400 MHz, $CDCl_3$): 8.40 (s, 1H), 7.80 (m, 2H), 7.44 (m, 3H), 5.93 (s, 1H), 0.37 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): 160.4, 155.6, 135.5, 131.3, 128.8,128.6, 88.0, 0.9.

1-Iodo-2-trimethylsilyloxy-3-aza-4-phenyl-butan-1,3-diene 47c. Prepared according GP1 starting from benzaldehyde and iodo acetyl chloride. ^{1}H NMR (400 MHz, $CDCl_3$): 8.37 (s, 1H), 7.78 (m, 2H), 7.44 (m, 3H), 5.56 (s, 1H), 0.37 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): 159.2, 156.8, 135.1, 131.6, 128.9,128.7, 92.6, 1.1.

General procedure for the preparation of perhydrooxazin-4-ones 49 and 50. GP2

Azadiene **47** (1 mmol), prepared as reported above, was dissolved in anhydrous CH_2Cl_2 (20 mL) and cooled at -78°C. Aldehyde **48** (1 mmol) dissolved in CH_2Cl_2 (2 mL) was added followed by a very slow addition of BF_3 etherate (0.12 mL, 1 mmol) in hexane (10 mL). The solution was stirred overnight while the temperature was allowed to reach rt. The mixture was poured into saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layers were dried and the solvent was removed in vacuo. The reaction mixture was purified by flash chromatography on silica gel, eluting with cyclohexane/ethyl acetate 70/30. Yields and diastereomeric ratio are reported in Tab. 3.2.

(2R*,5R*,6S*)-5-Chloro-6-methyl-2-phenyl-[1,3]-oxazinan-4-one (49a). Prepared according GP2 starting from azadiene **47a** and acetaldehyde. ^{1}H NMR (400 MHz, $CDCl_3$): 7.48 (m, 2H), 7.41 (m, 3H), 6.67 (bs, 1H), 5.77 (s, 1H), 5.27 (dq,1H, J=6.0, 2.4 Hz), 4.16 (d, 1H, J=2.4 Hz), 1.45 (d, 3H,J=6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 165.7, 137.0,130.1, 128.8,

126.9, 85.9, 72.9, 57.1, 17.8; IR ($cm^{-}1$): 3395,1686; MS m/z: 226, 224, 148, 146, 105, 83. Anal. calcd for $C_{11}H_{12}ClNO_2$: C 58.54; H 5.36. Found: C 58.44; H 5.37.

(2R*,5R*,6S*)-5-Bromo-6-methyl-2-phenyl-[1,3]-oxazinan-4-one (49b). Prepared according GP2 starting from azadiene **47b** and acetaldehyde. Mp=156–157 °C; ^{1}H NMR(400 MHz, $CDCl_3$): 7.50 (m, 2H), 7.43 (m, 3H), 6.29 (bs,1H), 5.84 (s, 1H), 4.29 (d, 1H, J=2.0 Hz), 4.04 (dq, 1H, J=2.0, 6.0 Hz), 1.43 (d, 3H, J=6.0 Hz); ^{13}C NMR (100 MHz,$CDCl_3$): 166.4, 137.2, 130.3, 129.0, 127.1, 86.0, 72.4, 48.8,19.6; IR (cm^{-1}) 3395, 1685; MS m/z: 270, 268, 149, 122, 105, 77. Anal. calcd for $C_{11}H_{12}BrNO_2$: C 48.91; H 4.48.Found: C 48.98; H 4.50.

(2R*,5R*,6S*)-5-Iodo-6-methyl-2-phenyl-[1,3]oxazinan-4-one (49c). Prepared according GP2 starting from azadiene **47c** and acetaldehyde. ^{1}H NMR (400 MHz, $CDCl_3$): 7.51 (m,2H), 7.40 (m, 3H), 6.54 (bs, 1H), 5.93 (s, 1H), 4.49 (d, 1H,J=2.4 Hz), 3.12 (dq, 1H, J=6.0, 2.4 Hz), 1.35 (d, 3H, J=6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 168.1, 137.3, 129.9,128.7, 126.9, 85.9, 71.9, 30.1, 23.5; IR (cm^{-1}): 3395, 1677; MS m/z: 316, 189, 174, 168, 147, 105, 77. Anal. calcd for$C_{11}H_{12}INO_2$: C 41.66; H 3.81. Found: C 41.75; H 3.84.

(2S*,5R*,6S*)-5-Iodo-6-methyl-2-phenyl-[1,3]oxazinan-4-one (50c). Prepared according GP2 starting from azadiene **47c** and acetaldehyde. ^{1}H NMR (400 MHz, $CDCl_3$): 7.43 (m, 6H), 6.10 (s, 1H), 4.51 (d, 1H, J=2.4 Hz), 3.09 (dq, 1H, J=6.0, 2.4 Hz), 1.23 (d, 3H, J=6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 168.5, 138.5, 129.2, 128.7, 126.4, 82.2, 65.7, 30.1,22.9; IR ($cm^{-}1$): 3395, 1677; MS m/z: 316, 189, 174, 168,147, 105, 77. Anal. calcd for $C_{11}H_{12}INO_2$: C 41.66; H 3.81.Found: C 41.80; H 3.84.

(2R*,5R*,6S*)-5-Bromo-6-propyl-2-phenyl-[1,3]-oxazinan-4-one (49d). Prepared according GP2 starting from azadiene **47b** and butyraldehyde. ^{1}H NMR (400 MHz, $CDCl_3$): 7.70 (bs, 1H), 7.48 (m, 2H), 7.38 (m, 3H), 5.77 (s, 1H), 4.19 (d,1H, J=2.0 Hz), 3.74 (m, 1H), 1.42 (m, 1H), 1.29 (m, 1H),1.20 (m, 2H), 0.95 (t, 3H, J=7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 167.0, 137.4, 129.8, 128.7, 126.9, 85.7, 75.8, 47.4,35.2, 17.9, 13.7; IR ($cm^{-}1$) 3395, 1682; MS m/z: 298, 296, 254, 252, 218, 175, 146, 122, 105, 77. Anal. calcd for $C_{13}H_{16}BrNO_2$: C 52.36; H 5.41. Found: C 52.48; H 5.44.

(2S*,5R*,6S*)-5-Bromo-6-propyl-2-phenyl-[1,3]-oxazinan-4-one (50d). Prepared according GP2 starting from azadiene **47b** and butyraldehyde.^{1}H NMR (400 MHz, $CDCl_3$): 8.15

(bs, 1H), 7.42 (m, 5H), 6.12 (s, 1H), 4.23 (d, 1H, J=2.4 Hz), 3.65 (m, 1H), 1.75 (m, 1H), 1.46 (m, 1H), 1.32 (m, 1H), 1.19 (m, 1H), 0.78 (t, 3H, J=7.2 Hz); ^{13}C NMR (100 MHz ,$CDCl_3$): 167.2, 138.0, 129.1, 128.6, 126.4, 82.2, 69.1, 50.0, 35.1, 18.0, 13.7; IR ($cm^{-}1$) 3399, 1682; MS m/z: 298, 296,254, 252, 146, 105, 77. Anal. calcd for $C_{13}H_{16}BrNO_2$: C52.36; H 5.41. Found: C 52.56; H 5.44.

(2R*,5R*,6S*)-5-Bromo-6-heptyl-2-phenyl-[1,3]-oxazinan-4-one (49e). Prepared according GP2 starting from azadiene **47b** and octaldehyde.^{1}H NMR (400 MHz, $CDCl_3$): 7.50 (m, 2H), 7.40 (m, 3H), 7.11 (bs, 1H), 5.79 (s, 1H), 4.22 (d, 1H, J=1.6 Hz), 3.74 (m, 1H), 1.83 (m, 1H), 1.63 (m, 1H),1.28 (m, 10H), 0.87 (t, 3H, J=7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 166.8, 137.4, 129.9, 128.8, 127.0, 85.9, 76.2, 47.5, 33.2, 31.6, 29.2, 29.0, 24.6, 22.5, 14.0; IR($cm^{-}1$); 3396, 1682; MS m/z: 355, 353, 293, 291, 273. Anal.calcd for $C_{17}H_{24}BrNO_2$: C 57.63; H 6.83. Found: C 57.73; H 6.88.

(2R*,5R*,6S*)-5-Bromo-6-isopropyl-2-phenyl-[1,3]oxazinan-4-one (49g). Prepared according GP2 starting from azadiene **47b** and isopropylaldehyde.^{1}H NMR (400 MHz, $CDCl_3$):7.50 (m, 2H), 7.43 (m, 3H), 6.58 (bs, 1H), 5.79 (s, 1H), 4.37(d, 1H, J=2.0 Hz), 3.27 (dd, 1H, J=2.0, 9.2 Hz), 2.06 (m,1H), 1.07 (d, 3H, J=6.8 Hz), 0.92 (d, 3H, J=6.4 Hz); ^{13}CNMR (100 MHz, $CDCl_3$): 166.6, 137.4, 130.1, 128.9, 127.0, 86.2, 82.2, 46.0, 30.9, 18.9, 17.1; IR (cm^{-1}): 3401, 1681; MS m/z: 299, 298, 297, 296, 256, 254, 228, 226, 216, 146,132, 107. Anal. calcd for $C_{13}H_{16}BrNO_2$: C 52.36; H 5.41.Found: C 52.18; H 5.43.

(2S*,5R*,6S*)-5-Bromo-6-isopropyl-2-phenyl-[1,3]oxazinan-4-one (50g). Prepared according GP2 starting from azadiene **47b** and isopropylaldehyde. ^{1}H NMR (400 MHz, $CDCl_3$):7.40 (m, 6H), 6.14 (s, 1H), 4.28 (d, 1H, J=2.0 Hz), 3.05 (dd, 1H, J=2.0, 9.2 Hz), 1.99 (m, 1H), 0.85 (d, 3H, J=6.4 Hz), 0.76 (d, 3H, J=6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 167.4, 137.9, 129.0, 128.4, 126.6, 82.3, 74.6, 46.7,31.0, 19.0, 17.1; IR (cm^{-1}): 3401, 1681; MS m/z: 299, 298, 297, 296, 256, 254, 228, 226, 216, 146, 132, 107. Anal.calcd for $C_{13}H_{16}BrNO_2$: C 52.36; H 5.41. Found: C 52.46; H5.45.

(2R*,5R*,6S*)-5-Bromo-6-*tert*-butyl-2-phenyl-[1,3]oxazinan-4-one (49h). Prepared according GP2 starting from azadiene **47b** and pivalaldehyde. ^{1}H NMR (400 MHz, $CDCl_3$):7.53 (m, 2H), 7.42 (m, 3H), 6.69 (bs, 1H), 5.77 (s, 1H), 4.37 (d, 1H, J=0.8 Hz), 3.53 (d, 1H, J=0.8 Hz), 1.09 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): 167.1, 137.7, 129.9, 128.8,

126.9, 86.3, 82.5, 43.9, 34.9, 26.4; IR (cm^{-1}): 3401, 1686; MS m/z: 313, 311, 257, 255, 177. Anal. calcd for $C_{14}H_{18}BrNO_2$: C 53.86; H 5.81. Found: C 53.98; H 5.85.

(2S*,5R*,6S*)-5-Bromo-6-*tert*-butyl-2-phenyl-[1,3]oxazinan-4-one (50h). Prepared according GP2 starting from azadiene **47b** and pivalaldehyde. ^1H NMR (400 MHz, $CDCl_3$): 7.42 (m, 5H), 7.16 (bs, 1H), 6.23 (s, 1H), 4.34 (d, 1H, J=1.6 Hz), 3.45 (d, 1H, J=1.6 Hz), 0.90 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): 167.7, 137.6, 129.4, 128.6, 126.9, 82.4, 75.4, 44.3, 34.6, 26.3; IR (cm^{-1}): 3401, 1686; MS m/z: 313,311, 257, 255, 177. Anal. calcd for $C_{14}H_{18}BrNO_2$: C 53.86;H 5.81. Found: C 53.98; H 5.87.

(2R*,5R*,6S*)-5-Bromo-2,6-diphenyl-[1,3]oxazinan-4-one (49i). Prepared according GP2 starting from azadiene **47b** and benzaldehyde. Mp: 173–175 °C; ^1H NMR (400 MHz,$CDCl_3$): 7.62–7.34 (m, 10H), 6.65 (bs, 1H), 6.02 (s, 1H), 5.17 (d, 1H, J=2.0 Hz), 4.54 (d, 1H, J=2.0 Hz); ^{13}C NMR(100 MHz, $CDCl_3$): 166.4, 137.2, 136.5, 130.3, 128.9, 128.3, 127.2, 125.5, 86.1, 77.1, 47.9; IR (cm^{-1}): 3396, 1682; MS m/z: 332, 330, 252, 227, 225, 211, 109, 184, 182,146, 118, 77. Anal. calcd for $C_{16}H_{14}BrNO_2$: C 57.85; H4.25. Found: C 57.71; H 4.23.

(2S*,5R*,6S*)-5-Bromo-2,6-diphenyl-[1,3]oxazinan-4-one (50i).
Prepared according GP2 starting from azadiene **47b** and benzaldehyde. Mp: 127–129 °C; ^1H NMR (400 MHz,$CDCl_3$): 8.20 (bs, 1H), 7.52–7.33 (m, 10H), 6.33 (s, 1H), 5.07 (d, 1H, J=2.0 Hz), 4.56 (d, 1H, J=2.0 Hz); ^{13}C NMR(100 MHz, $CDCl_3$): 167.1, 137.7, 136.5, 129.5, 128.9, 128.3, 128.2, 126.6, 125.7, 82.4, 71.3, 47.7; IR (cm^{-1}): 3396, 1682; MS m/z: 332, 330, 252, 227, 225, 211, 209, 146,131, 118, 77. Anal. calcd for $C_{16}H_{14}BrNO_2$: C 57.85; H4.25. Found: C 57.98; H 4.27.

(2R*,5R*,6S*)-5-Bromo-6-p-nitrophenyl-2-phenyl-[1,3]oxazinan-4-one (49j). Prepared according GP2 starting from azadiene **47b** and *p*-NO_2-benzaldehyde. ^1H NMR (400 MHz, $CDCl_3$): 8.23 (d, 2H, J=6.7 Hz), 7.59 (m, 2H), 7.52 (d, 2H, J=6.7 Hz), 7.48 (m, 3H), 6.83 (bs, 1H), 6.04 (s, 1H), 5.28 (d,1H, J=2.0 Hz), 4.57 (d, 1H, J=2.0 Hz); ^{13}C NMR(100 MHz, $CDCl_3$): 165.7, 147.8, 143.5, 136.7, 130.5,129.0, 127.2, 126.6, 123.6, 86.2, 76.5, 46.6; IR (cm^{-1}): 3395, 1682; MS m/z: 377, 375, 297, 256, 254, 176, 146, 105,78. Anal. calcd for $C_{16}H_{13}BrN_2O_4$: C 50.95; H 3.47. Found:C 51.15; H 3.50.

(2S*,5R*,6S*)-5-Bromo-6-p-nitrophenyl-2-phenyl-[1,3]oxazinan-4-one (50j). Prepared according GP2 starting from azadiene **47b** and *p*-NO_2-benzaldehyde. ^{1}H NMR (400 MHz, $CDCl_3$):8.24 (d, 2H, J=6.6 Hz), 7.50 (d, 2H, J=6.6 Hz), 7.43 (m,5H), 7.22 (bs, 1H), 6.37 (s, 1H), 5.17 (d, 1H, J=2.4 Hz),4.54 (d, 1H, J=2.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$):165.9, 147.8, 143.7, 137.2, 129.8, 129.1, 126.7, 126.5, 123.6, 82.6, 70.9, 46.5; IR (cm^{-1}): 3395, 1682; MS m/z: 377, 375, 297, 256, 254, 176, 146, 105, 78. Anal. calcd for$C_{16}H_{13}BrN_2O_4$: C 50.95; H 3.47. Found: C 51.08; H 3.49.

6.3 α,β Epoxy acids preparations

General procedure for the preparation of *N-t-Boc*-oxazinan-4-ones 106 and 107. GP3

Perhydroxazinones **49** and **50** prepared as reported above (1 mmol), were dissolved in CH_2Cl_2 (10 mL); Et_3N (1.2 mmol), DMAP (cat) and di-*tert*-butyldicarbonate (2 mmol) were added. The mixture was stirred at rt until the starting material disappeared (3 h) then it was poured into saturated aqueous NH_4Cl and extracted with CH_2Cl_2.The organic layers were dried and the solvent was removed in vacuo. The residue was purified by flash chromatography on silica gel, eluting with cyclohexane/ethyl acetate 90/10.

(2R*,5R*,6S*)-5-Bromo-6-methyl-4-oxo-2-phenyl-[1,3]oxazinane-3-carboxylic acid *tert*-butyl ester (106b). Prepared according GP3 starting from oxazinan-2-one **49b**. Y= 80%; Mp=174–176 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 7.50 (m,2H), 7.40 (m, 3H), 6.13 (s, 1H), 4.37 (d, 1H, J=2.0 Hz), 4.03 (dq, 1H, J=6.0, 2.0 Hz), 1.40 (d, 3H, J=6.0 Hz), 1.14(s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): 164.4, 149.9, 137.6,129.8, 128.6, 127.5, 90.2, 84.4, 71.3, 49.7, 27.2, 19.1; IR(cm^{-1}): 1776, 1735; MS m/z: 370, 368, 316, 314, 298, 296, 270, 268, 190, 122, 105, 77. Anal. calcd for $C_{16}H_{20}BrNO_4$:C 51.90; H 5.44. Found: C 52.07; H 5.46.

(2R*,5R*,6S*)-5-Bromo-6-propyl-4-oxo-2-phenyl-[1,3]oxazinane-3-carboxylic acid tert-butyl ester (106d). Prepared according GP3 starting from oxazinan-2-one **49d**. Y= 90%; ^{1}H NMR (400 MHz, $CDCl_3$): 7.48 (m, 2H), 7.37 (m, 3H),6.09 (s, 1H), 4.38 (d, 1H, J=1.2 Hz), 3.80 (m, 1H), 1.83–1.32 (m, 4H), 1.11 (s, 9H), 0.92 (t, 3H, J=7.2 Hz); ^{13}CNMR (100 MHz, $CDCl_3$): 164.4, 149.8, 137.6, 129.7, 128.5, 127.4, 90.3, 85.1, 75.0, 48.3, 34.8, 27.4, 17.8, 13.7; IR(cm^{-1}): 1776, 1734; MS m/z: 344, 342, 326, 324, 298, 296, 218, 122, 105, 77. Anal. calcd for $C_{18}H_{24}BrNO_4$: C 54.28; H6.07. Found: C 54.48; H 6.10.

(2R*,5R*,6S*)-5-Bromo-6-hepthyl-4-oxo-2-phenyl-[1,3]oxazinane-3-carboxylic acid *tert*-butyl ester (106e). Prepared according GP3 starting from oxazinan-2-one **49e**. Y= 98%; ^{1}HNMR (400 MHz, $CDCl_3$): 7.49 (m, 2H), 7.39 (m, 3H), 6.11(s, 1H), 4.40 (d, 1H, J=1.6 Hz), 3.79 (m, 1H), 1.81 (m, 1H), 1.61 (m, 1H), 1.26 (m, 10H), 1.13 (s, 9H), 0.86 (t, 3H, J=6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 164.5, 149.7, 137.7, 129.5, 128.6, 127.4, 90.3, 84.3, 75.3, 48.3, 32.7, 31.6, 29.1, 28.9, 27.1, 24.5, 22.5, 14.0; IR (cm^{-1}): 1777, 1738; MSm/z: 400, 398, 382, 380, 354, 352, 274, 105. Anal. calcd for$C_{22}H_{32}BrNO_4$: C 58.15; H 7.10. Found: C 58.10; H 7.08.

(2R*,5R*,6S*)-5-Bromo-6-isopropyl-4-oxo-2-phenyl-[1,3]oxazinane-3-carboxylic acid *tert*-butyl ester(106g). Prepared according GP3 starting from oxazinan-2-one **49g**. Y= 98%; ^{1}H NMR (400 MHz, $CDCl_3$): 7.50 (m, 2H), 7.40 (m,3H), 6.09 (s, 1H), 4.49 (d, 1H, J=1.6 Hz), 3.29 (dd, 1H, J=1.6, 9.2 Hz), 2.03 (m, 1H), 1.14 (s, 9H), 1.05 (d, 3H, J=6.8 Hz), 0.90 (d, 3H, J=6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 164.6, 149.7, 137.8, 129.8, 128.6, 127.4, 90.5, 84.3, 81.1, 46.9, 30.6, 27.2, 18.7, 17.1; IR (cm^{-1}): 1776, 1726; MS m/z: 326, 324, 298, 296, 218, 176, 132, 122, 105. Anal.calcd for $C_{18}H_{24}BrNO_4$: C 54.28; H 6.07. Found: C 54.48; H 6.09.

(2S*,5R*,6S*)-5-Bromo-6-isopropyl-4-oxo-2-phenyl-[1,3]oxazinane-3-carboxylic acid *tert*-butyl ester(107g). Prepared according GP3 starting from oxazinan-2-one **50g**. Y= 97%; Mp: 155–156 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 7.38 (m, 3H), 7.30 (m, 2H), 6.68 (s, 1H), 4.31 (d, 1H, J=2.0 Hz), 3.02 (dd, 1H, J=2.0, 9.2 Hz), 1.97 (m, 1H), 1.40 (s, 9H), 0.82 (d, 3H, J=6.4 Hz), 0.74 (d, 3H, J=6.4 Hz); ^{13}C NMR(100 MHz, $CDCl_3$): 165.5, 150.1, 137.6, 129.1, 128.6, 126.5, 86.1, 84.2, 74.9, 48.6, 30.9, 27.7, 18.6, 16.7; IR(cm^{-1}): 1776, 1726; MS m/z: 398, 344, 342, 326, 324, 298, 296, 218, 176, 132, 122, 105. Anal. calcd for $C_{18}H_{24}BrNO_4$:C 54.28; H 6.07. Found: C 54.39; H 6.09.

(2R*,5R*,6S*)-5-Bromo-6-*tert*-butyl-4-oxo-2-phenyl-[1,3]oxazinane-3-carboxylic acid *tert*-butyl ester(106h). Prepared according GP3 starting from oxazinan-2-one **49h**. Y= 80%; ^{1}H NMR (400 MHz, $CDCl_3$): 7.53 (m, 2H), 7.40 (m,3H), 6.06 (s, 1H), 4.50 (d, 1H, J=2.0 Hz), 3.52 (d, 1H, J=2.0 Hz), 1.14 (s, 9H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): 164.8, 149.9, 137.8, 129.6, 128.4, 127.7, 90.8, 84.2, 81.4, 44.8, 34.9, 27.2, 26.5; IR (cm^{-1}):

1774, 1726; MSm/z: 413, 411, 358, 356, 340, 338, 314, 312, 311, 310, 256, 254, 232, 146, 132, 106. Anal. calcd for $C_{19}H_{26}BrNO_4$: C55.35; H 6.36. Found: C 55.55; H 6.38.

(2S*,5R*,6S*)-5-Bromo-6-*tert*-butyl-4-oxo-2-phenyl-[1,3]oxazinane-3-carboxylic acid *tert*-butyl ester(107h). Prepared according GP3 starting from oxazinan-2-one **50h**. Y= 85%; Mp: 162–165 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 7.36(m, 3H), 7.32 (m, 2H), 6.69 (s, 1H), 4.36 (d, 1H, J=2.0 Hz), 3.32 (d, 1H, J=2.0 Hz), 1.37 (s, 9H), 0.86 (s, 9H); ^{13}CNMR (100 MHz, $CDCl_3$): 165.7, 150.0, 137.3, 129.1, 128.5, 126.6, 86.2, 83.1, 74.8, 46.6, 34.6, 27.7, 26.3; IR (cm^{-1}):1774, 1726; MS m/z: 413, 411, 358, 356, 340, 338, 314, 312, 311, 310, 256, 254, 232, 146, 132, 106. Anal. calcd for $C_{19}H_{26}BrNO_4$: C 55.35; H 6.36. Found: C 55.45; H 6.39.

(2R*,5R*,6S*)-5-Bromo-4-oxo-2,6-diphenyl-[1,3]-oxazinane-3-carboxylic acid *tert*-butyl ester (106i). Prepared according GP3 starting from oxazinan-2-one **49i**. Y= 67%; Mp:167–170 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 7.58 (m, 2H), 7.44 (m, 3H), 7.32 (m, 5H), 6.30 (s, 1H), 5.15 (d, 1H, J=2.0 Hz), 4.62 (d, 1H, J=2.0 Hz), 1.18 (s, 9H); ^{13}C NMR(100 MHz, $CDCl_3$): 164.4, 149.9, 137.5, 135.8, 129.9, 128.5, 128.4, 128.3, 127.7, 125.5, 90.3, 84.5, 76.0, 48.9, 27.2; IR (cm^{-1}): 1777, 1735; MS m/z: 332, 330, 252, 146, 31, 105, 77. Anal. calcd for $C_{21}H_{22}BrNO_4$: C 58.34; H5.13. Found: C 58.44; H 5.15.

(2S*,5R*,6S*)-5-Bromo-4-oxo-2,6-diphenyl-[1,3]oxazinane-3-carboxylic acid *tert*-butyl ester (107i). Prepared according GP3 starting from oxazinan-2-one **50i**. Y= 69%; Mp: 180–182 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 7.38–7.25(m, 10H), 6.89 (s, 1H), 4.92 (d, 1H, J=2.0 Hz), 4.53 (d, 1H,J=2.0 Hz), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$):165.3, 150.1, 137.2, 136.3, 129.3, 128.9, 128.3, 128.2, 126.5, 125.4, 86.1, 84.5, 70.7, 49.9, 27.7; IR (cm^{-1}): 1777, 1735; MS m/z: 332, 330, 252, 227, 225, 146, 131, 105, 77.Anal. calcd for $C_{21}H_{22}BrNO_4$: C 58.34; H 5.13. Found: C58.45; H 5.15.

(2R*,5R*,6S*)-5-Bromo-6-(4-nitro-phenyl)-4-oxo-2-phenyl-[1,3]oxazinane-3-carboxylic acid *tert*-butylester (106j). Prepared according GP3 starting from oxazinan-2-one **49j**. Y= 35%; ^{1}H NMR (400 MHz, $CDCl_3$): 8.22 (d, 2H, J=6.7 Hz), 7.69 (m, 3H), 7.47 (m, 4H), 6.33 (s, 1H), 5.29 (d,1H, J=2.0 Hz), 4.65 (d, 1H, J=2.0 Hz), 1.18 (s, 9H); ^{13}CNMR (100 MHz, $CDCl_3$): 163.6, 149.6, 147.9, 142.7, 137.0, 130.2, 128.7, 127.7, 126.5, 123.6, 90.3, 84.9,

75.4, 47.7, 27.2; IR (cm^{-1}): 1778, 1735; MS m/z: 477, 475, 377, 375,297, 256, 254. Anal. calcd for $C_{21}H_{21}BrN_2O_6$: C 52.84; H4.43. Found: C 52.80; H 4.41.

(2S*,5R*,6S*)-5-Bromo-6-(4-nitro-phenyl)-4-oxo-2-phenyl-[1,3]oxazinane-3-carboxylic acid *tert*-butylester (107j). Prepared according GP3 starting from oxazinan-2-one **50j**. Y= 40%; ^{1}H NMR (400 MHz, $CDCl_3$): 8.23 (d, 2H, J=6.6 Hz), 7.71 (d, 2H, J=6.6 Hz), 7.53–7.40 (m, 5H), 6.91 (s,1H), 5.12 (d, 1H, J=2.0 Hz), 4.58 (d, 1H, J=2.0 Hz), 1.43 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): 163.7, 149.9, 147.6, 142.8, 136.5, 130.0, 128.7, 127.6, 126.4, 123.5, 86.4, 84.78, 69.9, 48.6, 27.7; IR (cm^{-1}): 1778, 1735; MS m/z: 477, 475, 377, 375, 297, 256, 254. Anal. calcd for $C_{21}H_{21}BrN_2O_6$: C52.84; H 4.43. Found: C 52.94; H 4.44.

General procedure for the preparation of epoxide 108 and 109. GP4

Method A. *N-t*-Boc-perhydroxazinone **106** and/or **107** (1 mmol) were dissolved in THF (10 mL) and LiOH 1 M (3 mmol) was added. The mixture was stirred at rt until TLC showed the disappearance of the starting material. The crude mixture was concentrated to half of the starting volume, water (5 mL) was added and the mixture was extracted with ether. The aqueous layers were made acidic by HCl 1 N at 0°C. Extraction with ethyl acetate and removal of the solvent, purification of the crude mixture by short flash chromatography (eluted with toluene/CH_3COOH 4/1) yielded the epoxy acids **96** and **97**. The yields are reported in Table 4.1.

Method B. *N-t*-Boc-perhydroxazinone **106** or **107** (1 mmol) were dissolved in a solution of ethanol/water 5/1 (10 mL). LiOH(5 mmol) and H_2O_2 30% (5 mmol) were added. The mixture was stirred at rt until TLC showed the disappearance of the starting material. The crude mixture was concentrated to half of the starting volume, water (5 mL) was added and the mixture was extracted with ether. The aqueous layers were made acidic by HCl 1 N at 0°C. Extraction with ethylacetate and removal of the solvent, followed by purificationof the crude mixture by short flash chromatography (eluted with toluene/CH_3COOH 4/1) yielded the epoxyacids **108** and **109**. The yields are reported in Table 4.1. Analytical data for known compounds are in ageement with those reported in literature.

(2S*,3S*)-3-Methyl-oxirane-2-carboxylic acid (108b). Prepared according GP4 starting from *N-t*-Boc-oxazinan-2-one **106b**, Method A and B. ^{1}H NMR (400 MHz, $CDCl_3$): 7.38 (bs,

1H), 3.56 (d, 1H, J=4.8 Hz), 3.36 (dq, 1H, J=4.8, 5.2 Hz), 1.43 (d, 3H, J=5.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 173.30, 54.02, 52.67, 12.89; IR (cm^{-1}): 3580, 1736.

(2S*,3R*)-3-Methyl-oxirane-2-carboxylic acid (109b). Prepared according GP4 starting from *N*-*t*-Boc-oxazinan-2-one **107b**, Method A and B. ^{1}H NMR (400 MHz, $CDCl_3$): 7.40 (bs, 1H), 3.28 (dq, 1H, J=2.0, 5.2 Hz), 3.22 (d, 1H, J=2.0 Hz), 1.42 (d,3H, J=5.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 174.34, 55.08, 53.43, 17.12; IR (cm^{-1}): 3580, 1736.

(2S*,3S*)-3-Propyl-oxirane-2-carboxylic acid (108d). Prepared according GP4 starting from *N*-*t*-Boc-oxazinan-2-one **106d**, Method A. ^{1}H NMR (400 MHz, $CDCl_3$): 3.57 (d, 1H, J=4.4 Hz), 3.24(m, 1H,), 1.74–1.42 (m, 4H), 0.97 (t, 3H, J=7.2 Hz); ^{13}CNMR (100 MHz, $CDCl_3$): 172.78, 58.06, 52.88, 29.28, 19.46, 13.74.

(2S*,3R*)-3-Propyl-oxirane-2-carboxylic acid (109d). Prepared according GP4 starting from *N*-*t*-Boc-oxazinan-2-one **107d**, Method A. ^{1}H NMR (400 MHz, $CDCl_3$): 6.65 (bs, 1H), 3.26(d, 1H, J=1.6 Hz), 3.18 (m, 1H), 1.65–1.20 (m, 4H), 0.98 (t,3H, J=7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 174.06, 58.80, 52.95, 29.69, 18.99, 13.73.

(2S*,3S*)-3-Heptyl-oxirane-2-carboxylic acid (108e). Prepared according GP4 starting from *N*-*t*-Boc-oxazinan-2-one **106e**, Method A. ^{1}H NMR (400 MHz, $CDCl_3$): 8.05 (bs, 1H), 3.57 (d, 1H, J=4.8 Hz), 3.23 (m, 1H), 1.62 (m, 2H), 1.26 (m, 10H), 0.87 (t, 3H, J=7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 173.57, 58.25, 52.66, 31.41, 29.16, 28.19, 27.28, 26.11, 22.57, 14.05.

(2S*,3R*)-3-Heptyl-oxirane-2-carboxylic acid (109e). Prepared according GP4 starting from *N*-*t*-Boc-oxazinan-2-one **107e**, Method A. ^{1}H NMR (400 MHz, $CDCl_3$): 8.10 (bs, 1H), 3.25(d, 1H, J=2.0 Hz), 3.19 (m, 1H), 1.65 (m, 2H), 1.31 (m,10H), 0.87 (t, 3H, J=7.2 Hz); ^{13}C NMR (100 MHz,$CDCl_3$): 174.62, 59.05, 52.66, 31.66, 29.07, 28.16, 27.26, 25.62, 22.58, 14.05.

(2S*,3S*)-3-Isopropyl-oxirane-2-carboxylic acid (108g). Prepared according GP4 starting from *N*-*t*-Boc-oxazinan-2-one **106g** or **107g** or **106g+107g**, Method A. ^{1}H NMR (400 MHz, $CDCl_3$): 3.57 (d, 1H, J=4.4 Hz), 2.90 (dd, 1H, J=4.4, 9.2 Hz), 1.64 (m, 1H), 1.13

(d, 3H, J=6.8 Hz), 0.95 (d, 3H, J=6.8 Hz); ^{13}C NMR(100 MHz, $CDCl_3$): 172.58, 63.39, 53.14, 27.10, 20.09, 18.30.

(2S*,3R*)-3-Isopropyl-oxirane-2-carboxylic acid (109g). Prepared according GP4 starting from *N*-*t*-Boc-oxazinan-2-one **106g** or **107g** or **106g+107g**, Method A.^{1}H NMR (400 MHz, $CDCl_3$): 3.28 (d, 1H, J=2.0 Hz), 2.30 (dd, 1H, J=2.0, 6.8 Hz), 1.45 (m, 1H), 1.03 (d, 3H, J=6.8 Hz), 0.99 (d, 3H, J=6.8 Hz); ^{13}C NMR(100 MHz, $CDCl_3$): 173.90, 63.75, 51.79, 30.06, 18.67, 18.01.

(2S*,3S*)-3-*tert*-Butyl-oxirane-2-carboxylic acid (108h). Prepared according GP4 starting from *N*-*t*-Boc-oxazinan-2-one **106h+107h**, Method B. ^{1}H NMR (400 MHz, $CDCl_3$): 3.51 (d, 1H, J=4.8 Hz), 3.00 (d, 1H, J=4.8 Hz), 1.02 (s, 9H); ^{13}C NMR(100 MHz, $CDCl_3$): 172.10, 66.55, 53.69, 31.86, 25.72.

(2S*,3R*)-3-*tert*-Butyl-oxirane-2-carboxylic acid (109h). Prepared according GP4 starting from *N*-*t*-Boc-oxazinan-2-one **106h+107h**, Method B. ^{1}H NMR (400 MHz, $CDCl_3$): 3.35 (d, 1H, J=2.0 Hz), 3.02 (d, 1H, J=2.0 Hz), 0.96 (s, 9H); ^{13}C NMR(100 MHz, $CDCl_3$): 174.56, 66.53, 49.98, 31.04, 25.52.

(2S*,3S*)-3-Phenyl-oxirane-2-carboxylic acid (108i). Prepared according GP4 starting from *N*-*t*-Boc-oxazinan-2-one **106i+107i**, Method A. ^{1}H NMR (400 MHz, $CDCl_3$): 7.36 (m, 5H), 4.32 (d, 1H, J=4.8 Hz), 3.87 (d, 1H, J=4.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 171.51, 132.02, 128.47, 128.12, 126.64, 57.87, 55.38.

(2S*,3S*)-3-*p*-nitrophenyl-oxirane-2 carboxylic acid (108j). Prepared according GP4 starting from *N*-*t*-Boc-oxazinan-2-one **106j+107j**, Method B. ^{1}H NMR (400 MHz, $CDCl_3$): 8.30 (d, 2H, J=6.7 Hz), 7.62 (d, 2H, J=6.7 Hz), 4.50 (bs, 1H), 4.39 (d, 1H,J=4.8 Hz), 3.94 (d, 1H, J=4.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 171.3, 141.6, 131.1, 128.4, 123.5, 56.9, 55.4. **-methyl ester** ^{1}H NMR (400 MHz, $CDCl_3$):8.22 (d, 2H, J=6.7 Hz), 7.60 (d, 2H, J=6.7 Hz), 4.34 (d,1H, J=4.8 Hz), 3.91 (d, 1H, J=4.8 Hz), 3.57 (s, 3H); ^{13}CNMR (100 MHz, $CDCl_3$): 167.5, 141.9, 130.6, 127.6, 123.8, 56.7, 55.7, 52.4; MS m/z: 223, 207, 192, 166.4.

(2S*,3R*)-3-p-Nitrophenyl-oxirane-2-carboxylicacid (109j). Prepared according GP4 starting from *N*-*t*-Boc-oxazinan-2-one **106j+107j**, Method B. ^{1}H NMR (400 MHz, $CDCl_3$):

8.20 (d, 2H, J=6.6 Hz), 7.48 (d, 2H, J=6.6 Hz), 4.60 (bs, 1H), 4.24 (d, 1H, J=1.6 Hz), 3.52 (d, 1H, J=1.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 169.7, 139.4, 127.7, 123.9, 123.2, 57.0, 56.5. **-methyl ester** ^{1}H NMR (400 MHz, $CDCl_3$):8.19 (d, 2H, J=6.6 Hz), 7.47 (d, 2H, J=6.6 Hz), 4.21 (d, 1H, J=2.0 Hz), 3.85 (s, 3H), 3.50 (d, 1H, J=2.0 Hz); ^{13}CNMR (100 MHz, $CDCl_3$): 166.0, 139.7, 126.5, 123.4, 123.2, 56.9, 56.8, 52.9; MS m/z: 223, 207, 192, 166.

6.4 5-Thiophenyl-1,3-oxazinan-4-ones preparations

General procedure for the preparation of azadiene (54). GP5

1 mL of aldehyde **51** (1 mmol) was added to a solution of LiHMDS (1.1 mL of 1 M sol in THF) and hexane (5 mL) at 0°C under inert atmosphere. The reaction mixture was stirred at 0°C for 1 h. IR analysis confirmed the formation of silylimine **52** (ν_{CN}=1655 cm^{-1}). TMSCl (0.14 mL, 1 mmol) was added in one portion and after stirring for 10 min at 0°C the mixture was allowed to stir for 1 h at rt. A white precipitate formed. The mixture was cooled at 0°C, triethylamine (0.3 mL, 2 mmol) was added in one portion and after 5 min a solution of thiophenyl acetylchloride **53** (1 mmol) in 5 mL of hexane was added. Stirring was maintained for 2 h and precipitate appeared. The mixture was filtered through Celite under argon and the solvent was removed in vacuo to afford **54** as an oil, which was used for the next step.

General procedure for the preparation of perhydrooxazin-4-ones 56 and 57. GP6

Azadiene **54** (2 mmol), prepared as reported above, was dissolved in anhydrous CH_2Cl_2 (20 mL) and cooled at -78°C. Aldehyde **55** (1 mmol) dissolved in CH_2Cl_2 (2 mL) was added followed by a very slow addition of BF_3 etherate (0.12 mL, 1 mmol) in CH_2Cl_2(10 mL). The solution was stirred overnight while the temperature was allowed to reach rt. The mixture was poured into saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layers were dried and the solvent was removed in vacuo. The reaction mixture was purified by flash chromatography on silica gel, eluting with cyclohexane/ethyl acetate 70/30. Yields and diastereomeric ratio are reported in Tab. 3.3.

(2S*,5S*,6R*)-2,6-Diphenyl-5-phenylthio-[1,3]oxazinan-4-one 56a. Prepared according GP6 starting from azadiene **54** (R= Ph) and benzaldehyde. Mp 173–174 °C; IR: 1674 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$): 7.60–7.10 (m, 15H), 6.30 (br s, 1H), 5.92 (s, 1H), 5.41 (d, J=2.4 Hz, 1H), 3.82 (d, J=2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$):169.1, 137.5, 136.9, 134.6, 133.2, 130.0, 128.8, 128.7, 128.1, 127.9, 127.8, 127.1, 125.9, 86.1, 78.6, 55.4; MS m/z: 361, 255, 106, 91, 77; E.A. Calcd for $C_{22}H_{19}NO_2S$: C 73.10; H 5.30. Found: C 73.29; H 5.33.

(2R*,5S*,6R*)-2,6-diphenyl-5-phenylthio-[1,3]oxazinan-4-one 57a. Prepared according GP6 starting from azadiene **54** (R= Ph) and benzaldehyde. IR: 1667 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): 7.78–7.00 (m, 15H), 6.53 (br s, 1H), 6.03 (s, 1H), 5.37 (d, J=3.6 Hz,1H), 4.03 (d, J=3.6 Hz, 1H). ^{13}C NMR (100 MHz,$CDCl_3$): 169.4, 138.0, 136.1, 134.3, 132.9, 129.4, 128.8, 128.7, 128.3, 128.2, 127.7, 126.7, 126.6, 82.0, 73.6, 53.9. MS m/z: 361, 255, 106, 91, 77. E.A. Calcd for $C_{22}H_{19}NO_2S$: C 73.10; H 5.30. Found: C 73.32; H 5.31.

(2S*,5S*,6S*)-2-Phenyl-6-(thiophen-2-yl)-5-phenylthio-[1,3]oxazinan-4-one 56b. Prepared according GP6 starting from azadiene **54** (R= Ph) and 2-thiophenecarboxaldehyde. IR:1676 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$):7.43 (m, 7H),7.33 (dd, J_1=1.0 Hz, J_2=5.0 Hz, 1H), 7.24 (m, 3H), 7.06(m, 1H), 7.01 (dd, J_1=3.4 Hz, J_2=5.0 Hz, 1H), 6.54 (br s,1H), 5.93 (s, 1H), 5.60 (dd, J_1=0.6 Hz, J_2=2.4 Hz, 1H),3.82 (d, J=2.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$):168.8, 139.3, 137.1, 134.6, 132.9, 130.0, 128.9, 128.8, 127.8, 127.1, 126.37, 125.9, 125.5, 86.0, 76.3, 55.3. MS m/z: 368 (M+1), 323, 255, 212, 184, 152, 121, 106, 91, 77. E.A. Calcd for $C_{21}H_{19}NOS_2$: C 69.01; H 5.24. Found: C 70.39; H 5.34.

(2R*,5S*,6S*)-2-phenyl-6-(thiophen-2-yl)-5-phenylthio-[1,3]oxazinan-4-one 57b. Prepared according GP6 starting from azadiene **54** (R= Ph) and 2-thiophenecarboxaldehyde. IR (CHCl3):1675 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$):7.50–7.38(m, 8H), 7.33 (br s, 1H), 7.26 (m, 4H), 7.14 (m, 1H), 7.05 (dd, J_1=3.2 Hz, J_2=5.2 Hz, 1H), 5.83 (s, 1H), 5.57 (d, J=4.8 Hz, 1H), 4.23 (dd, J_1=3.6 Hz, J_2=4.8 Hz, 1H). ^{13}CNMR (100 MHz, $CDCl_3$):168.6, 137.6, 137.5, 134.4, 133.5, 129.7, 129.0, 128.8, 127.2, 126.8, 126.7, 81.6, 72.1, 53.4. MS m/z: 366 (M^{+-1}), 322, 255, 212, 186, 152, 121, 106, 77. E.A. Calcd for $C_{21}H_{19}NOS_2$: C, 69.01; H,5.24; N, 3.83. Found: C, 70.39; H, 5.34.

(2S*,5S*,6R*)-2-(4-Methoxy-phenyl)-6-phenyl-5-phenylthio-[1,3]oxazinan-4-one 56c; Prepared according GP6 starting from azadiene **54** (R=*p*-MeO-Ph) and benzaldehyde. Mp 181–183 °C. IR ($CHCl_3$): 1672 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$):7.46–7.16 (m, 12H), 6.93

(d, J=8.8 Hz, 2H), 6.45 (br s,1H), 5.86 (s, 1H), 5.38 (d, J=2.0 Hz, 1H), 3.83 (s, 3H),3.80 (d, J=2.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$):169.5, 160.8, 140.3, 136.9, 134.6, 133.2, 129.2, 128.8,128.6, 128.1, 126.4, 125.9, 114.1, 85.8, 78.4, 55.4. MS m/z: 392 (M++1), 334, 316, 299, 285, 187, 162, 136, 105,91, 77. E.A. Calcd for C24H23NO2S: C, 74.00; H, 5.95.Found: C, 75.48; H, 6.07.

(2R*,5S*,6R*)-2-(4-methoxy-phenyl)-6-phenyl-5-phenylthio-[1,3]oxazinan-4-one 57c. Prepared according GP6 starting from azadiene **54** (R=*p*-MeO-Ph) and benzaldehyde. IR ($CHCl_3$):1673 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$):7.40–7.20 (m, 12H), 6.90 (d, J=8.6 Hz, 2H), 6.27 (br s, 1H), 5.96 (s,1H), 5.38 (d, J=3.8 Hz, 1H), 4.08 (d, J=3.8 Hz, 1H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, CDCl3):169.7, 160.7,1 36.4, 134.6, 133.1, 130.3, 129.1, 128.5, 128.4, 128.0, 127.9, 127.1, 114.4, 82.1, 73.9, 55.6, 54.1. MS m/z: 392(M++1), 316, 299, 285, 281, 210, 136, 105, 91, 77. E.A.Calcd for $C_{24}H_{23}NO_2S$: C, 74.00; H, 5.95. Found: C,75.48; H, 6.07.

(2S*,5S*,6R*)-2-(2-Triisopropylsilyloxyphenyl)-6-phenyl-5-(phenylthio)-[1,3]oxazinan-4-one 56d; Prepared according GP6 starting from azadiene **54** (R=*o*-TIPSO-Ph) and benzaldehyde. IR ($CHCl_3$):1674 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$):7.62–6.85 (m, 14H), 6.36 (s, 1H), 6.22 (br s, 1H), 5.42 (d, J=2.4 Hz,1H), 3.84 (d, J=2.4 Hz, 1H), 1.10 (m, 21H). ^{13}C NMR(100 MHz, $CDCl_3$):168.8, 153.0, 137.1, 134.6, 133.2,130.3, 128.7, 128.1, 127.8, 127.6, 127.5, 127.2, 125.9, 121.5, 118.0, 80.5, 78.5, 55.5, 18.0, 12.9. MS m/z: 534,427, 385, 279, 234. E.A. Calcd for $C_{32}H_{41}NO_2SSi$: C,72.27; H, 7.77. Found: C, 74.44; H, 8.00.

(2R*,5S*,6R*)-2-(2-triisopropylsilyloxyphenyl)-6-phenyl-5-(phenylthio)-[1,3]oxazinan-4-one 57d. Prepared according GP6 starting from azadiene **54** (R=*o*-TIPSO-Ph) and benzaldehyde. IR ($CHCl_3$):1672 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$):7.45–7.05 (m, 14H), 6.33 (br s, 1H), 6.21 (s, 1H), 5.50 (d, J=4.0 Hz,1H), 4.10 (d, J=4.0 Hz, 1H), 1.05 (m, 21H). ^{13}C NMR(100 MHz, $CDCl_3$):168.4, 153.4, 135.6, 134.4, 132.9, 130.1, 128.8, 128.5, 128.3, 127.7, 127.4, 126.6, 121.1, 118.5, 77.6, 75.1, 53.4, 18.0, 13.0. MS m/z: 534, 427,385, 279, 234. E.A. Calcd for $C_{32}H_{41}NO_2SSi$: C, 72.27; H,7.77. Found: C, 74.44; H, 8.00.

(2S*,5S*,6R*)-6-Methyl-2-phenyl-5-phenylthio-[1,3]oxazinan-4-one 56e. Prepared according GP6 starting from azadiene **54** (R=Ph) and acetaldehyde. IR ($CHCl_3$):1672 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$):7.70 (m, 2H), 7.45–7.23 (m, 8H), 6.69 (br s, 1H), 5.74 (s, 1H),

4.34 (dq,J_1=6.4 Hz, J_2=2.8 Hz, 1H), 3.51 (d, J=2.8 Hz, 1H), 1.57 (d, J=6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$):d=169.7, 137.8, 135.1, 133.3, 130.2, 129.3, 129.0, 128.0, 127.3, 86.2, 74.2, 54.6, 18.6. MS m/z: 299, 255, 122, 106. E.A. Calcd for $C_{17}H_{17}NO_2S$: C, 68.20; H, 5.72; N,4.68. Found: C, 68.34; H, 5.73.

(2R*,5S*,6R*)-6-methyl-2-phenyl-5-phenylthio-[1,3]oxazinan-4-one 57e. Prepared according GP6 starting from azadiene **54** (R=Ph) and acetaldehyde. Mp 147–148 °C. IR($CHCl_3$): 1677 cm^{-1}. $_1$H NMR (400 MHz, $CDCl_3$): 7.61 (m, 2H), 7.50–7.15 (m, 8H), 6.67 (br s, 1H), 5.97(s, 1H), 4.34 (m, 1H), 3.82 (d, J=3.6 Hz, 1H), 1.48 (d, J=6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$):169.0, 138.7, 134.4, 132.8, 129.7, 129.3, 129.1, 128.0, 126.8, 82.0, 69.0, 54.1, 16.8. MS m/z: 299, 255, 122, 105, 91,77. E.A. Calcd for $C_{17}H_{17}NO_2S$: C, 68.20; H, 5.72; N,4.68. Found: C, 68.30; H, 5.71.

***tert*-Butyl-3-[(2S*,5S*,6R*)-4-oxo-2-phenyl-5-(phenylthio)-[1,3]oxazinan-6-yl]-1H-indole-1-carboxylate 56f**; Prepared according GP6 starting from azadiene **54** (R=Ph) and. *tert*-butyl-3-formyl-1H-indole-1-carboxylate. IR ($CHCl_3$): 1737, 1673 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): 7.75 (s, 1H), 7.60–7.05 (m, 14H), 6.21 (br s, 1H), 6.00 (s, 1H), 5.63 (dd,J_1=2.0 Hz, J_2=0.8 Hz, 1H), 4.04 (d, J=2.0 Hz, 1H), 1.66 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$):169.2, 149.8, 137.7, 134.5, 133.2, 130.3, 129.1, 128.9, 128.0, 127.9, 127.4, 124.8, 124.7, 123.0, 119.0, 118.1, 116.9, 115.7, 86.5, 84.2, 74.7, 54.1, 28.4. MS m/z: 399 (M+_t-Boc), 334, 255, 202, 106, 91, 77. E.A. Calcd for $C_{29}H_{28}N_2O_4S$: C, 69.58; H, 5.64; N, 5.60. Found: C, 69.75; H, 5.62

***tert*-butyl-3-[(2R*,5S*,6R*)-4-oxo-2-phenyl-5-(phenylthio)-[1,3]oxazinan-6-yl]-1H-indole-1-carboxylate 57f.** Prepared according GP6 starting from azadiene **54** (R=Ph) and. *tert*-butyl-3-formyl-1H-indole-1-carboxylate Mp 102–104 °C. IR ($CHCl_3$): 1738, 1673 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): 7.84 (s, 1H), 7.50–7.15 (m, 14H), 6.83 (br s, 1H), 5.78 (s, 1H), 5.67 (dd, J_1=4.8 Hz, J_2=0.8 Hz, 1H), 4.41 (d, J=4.8 Hz, 1H), 1.71 (s, 9H). ^{13}C NMR (100 MHz,CDCl3):168.7, 149.4, 137.7, 135.4, 134.2, 132.4, 129.6, 128.9, 128.8, 128.7, 127.6, 126.8, 125.2, 124.9, 122.9, 119.1, 115.4, 114.4, 84.3, 81.7, 70.0, 52.4, 28.1. MS(m/z): 456, 422, 399, 334, 255, 202, 186, 131, 107, 91, 77. E.A. Calcd for $C_{29}H_{28}N_2O_4S$: C, 69.58; H, 5.64; N, 5.60.Found: C, 69.77; H, 5.62.

Procedure for the preparation of azadiene (60).

1 mL of lactic aldehyde **58** (1 mmol) was added to a solution of LiHMDS (1.1 mL of 1 M sol in THF) and hexane (5 mL) at 0°C under inert atmosphere. The reaction mixture was stirred at 0°C for 1 h. IR analysis confirmed the formation of silylimine **52** (ν_{CN}=1655 cm^{-1}). TMSCl (0.14 mL, 1 mmol) was added in one portion and after stirring for 10 min at 0°C the mixture was allowed to stir for 1 h at rt. A white precipitate formed. The mixture was cooled at 0°C, triethylamine (0.3 mL, 2 mmol) was added in one portion and after 5 min a solution of thiophenyl acetylchloride **53** (1 mmol) in 5 mL of hexane was added. Stirring was maintained for 2 h and precipitate appeared. The mixture was filtered through Celite under argon and the solvent was removed in vacuo to afford **59** as an oil, which was used for the next step.

General procedure for the preparation of perhydrooxazin-4-ones 62 and 63. GP7

Azadiene **60** (2 mmol), prepared as reported above, was dissolved in anhydrous CH_2Cl_2 (20 mL) and cooled at -78°C. Aldehyde **61** (1 mmol) dissolved in CH_2Cl_2 (2 mL) was added followed by a very slow addition of BF_3 etherate (0.12 mL, 1 mmol) in CH_2Cl_2 (10 mL). The solution was stirred overnight while the temperature was allowed to reach rt. The mixture was poured into saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layers were dried and the solvent was removed in vacuo. The reaction mixture was purified by flash chromatography on silica gel, eluting with cyclohexane/ethyl acetate 70/30. Yields and diastereomeric ratio are reported in Tab. 3.4.

(2R,5R,6S)-2-[(S)-1-Triisopropylsilyloxyethyl]-6-phenyl-5-(phenylthio)-[1,3]oxazinan-4-one 62a; Prepared according GP7 starting from azadiene **60** and benzaldehyde. $[\alpha]_D^{20}$ 13.0 (c 0.7,$CHCl_3$); IR ($CHCl_3$): 1677 cm^{-1}; ^{1}H NMR (400 MHz,$CDCl_3$):7.45–7.05 (m, 10H), 6.22 (br s, 1H), 5.25 (d,J=2.0 Hz, 1H), 5.08 (d, J=2.8 Hz, 1H), 4.23 (m, 1H), 3.69 (d, J=2.8 Hz, 1H), 1.31 (d, J=7.2 Hz, 3H), 1.05 (s, 21H);^{13}C NMR (100 MHz, $CDCl_3$):169.1, 136.7, 135.0, 132.8, 128.7, 128.0, 127.9, 127.6, 126.0, 85.3, 77.8, 68.8, 56.3, 18.0, 17.9, 15.9, 12.1. MS m/z: 486, 442, 399, 379, 336, 239, 211, 188, 135, 77. E.A. Calcd for $C_{27}H_{39}NO_3SSi$:C 66.76, H 8.09; Found: C 66.86, H 8.11.

(2S,5S,6R)-2-[(S)-1-triisopropylsilyloxyethyl]-6-phenyl-5-(phenylthio)-[1,3]oxazinan-4-one 63a. Prepared according GP7 starting from azadiene **60** and benzaldehyde. $[\alpha]_D^{20}$ -41.5 (c 2.0,$CHCl_3$). IR ($CHCl_3$): 1676 cm^{-1}. ^{1}H NMR (400 MHz,$CDCl_3$):7.40–7.07 (m, 10H), 6.35 (br s, 1H), 5.22 (d,J=2 .4 Hz, 1H), 4.58 (d, J=8.0 Hz, 1H), 3.77 (m, 1H), 3.76 (d, J=2.4

Hz, 1H), 1.35 (d, J=5.6 Hz, 3H), 1.05 (s, 21H);^{13}C NMR (100 MHz, $CDCl_3$):168.2, 145.4, 137.0, 133.7, 128.9, 128.6, 128.2, 127.8, 125.7, 87.6, 78.0, 71.5,55.2, 19.5, 18.1, 18.0, 12.6. MS m/z: 486, 442, 379, 336, 284, 239, 211, 188, 135, 77. E.A. Calcd for $C_{27}H_{39}NO_3SSi$:C 66.76, H 8.09; Found: C 66.82, H8.10.

(2R,5R,6R)-2-[(S)-1-Triisopropylsilyloxyethyl]-6-(thiophen-2-yl)-5-(phenylthio)-[1,3]oxazinan-4-one 62b; Prepared according GP7 starting from azadiene **60** and 2-thiophenecarboxaldehyde $[\alpha]_D^{20}$ +33.5 (*c* 2.9,$CHCl_3$). IR ($CHCl_3$): 1672 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): 7.36 (m, 3H), 7.20 (m, 3H), 7.01 (m, 2H), 6.20(br s, 1H, NH), 5.46 (d, J=2.0 Hz, 1H), 5.09 (d, J=3.6 Hz,1H), 4.19 (dq, J_1=3.6 Hz, J_2=6.0 Hz, 1H), 3.71 (d, J=2.0 Hz, 1H), 1.26 (d, J=6.0 Hz, 3H), 1.07 (m, 21H).^{13}C NMR (100 MHz, $CDCl_3$):168.80, 139.61, 135.80, 132.32, 128.84, 127.60, 126.28, 126.03, 125.52, 85.51, 75.69, 68.72, 56.16, 18.02, 15.88, 12.14. MS m/z: 492,448, 379, 336, 187. Anal. Calcd for $C_{25}H_{37}NO_3S_2Si$: C,61.06; H, 7.58. Found: C, 61.20; H, 7.63

(2S,5S,6S)-2-[(S)-1-triisopropylsilyloxyethyl]-6-(thiophen-2-yl)-5-(phenylthio)-[1,3]oxazinan-4-one 63b. Prepared according GP7 starting from azadiene **60** and 2-thiophenecarboxaldehyde $[\alpha]_D^{20}$ -58.6 (c 2.5, $CHCl_3$). IR ($CHCl_3$): 1685 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): 7.42–7.20 (m, 6H), 7.02–6.98 (m, 2H), 6.33 (br s, 1H, NH), 5.41 (dd, J_1=1.2 Hz, J_2=2.4 Hz, 1H), 4.60 (d, J=8.0 Hz, 1H), 3.77 (d, J=2.4 Hz, 1H), 3.68 (m, 1H),1.31 (d, J=6.4 Hz, 3H), 1.08 (m, 21H). ^{13}C NMR(100 MHz, $CDCl_3$): 167.68, 139.66, 134.16, 133.56, 128.71, 127.96, 126.51, 125.54, 124.75, 87.66, 76.07, 71.35, 55.16, 19.43, 18.12, 12.58. MS m/z: 491, 446, 379, 336, 217, 186. Anal. Calcd for $C_{25}H_{37}NO_3S_2Si$: C,61.06; H, 7.58. Found: C, 61.18; H, 7.60

(2R,5R,6S)-2-[(S)-1-Triisopropylsilyloxyethyl]-6-methyl-5-(phenylthio)-[1,3]oxazinan-4-one 62c; Prepared according GP7 starting from azadiene **60** and acetaldehyde. $[\alpha]_D^{20}$ +40.0 (*c* 2.1, $CHCl_3$). IR ($CHCl_3$): 1670 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): 7.65 (m, 2H), 7.40–7.18 (m, 3H), 6.10 (br s,1H), 4.90 (d, J=3.2 Hz, 1H), 4.20 (dq, J_1=6.0 Hz, J_2=1.8 Hz, 1H), 4.06 (dq, J_1=6.4 Hz, J_2=3.2 Hz, 1H), 3.46 (d, J=1.8 Hz, 1H), 1.50 (d, J=6.0 Hz, 3H), 1.11 (d,J=6.4 Hz, 3H), 1.05 (s, 21H). ^{13}C NMR (100 MHz, $CDCl_3$):169.4, 135.6, 132.4, 129.0, 127.5, 85.4, 73.2, 68.8, 55.1, 18.0, 17.9, 15.7, 12.1. MS m/z: 423, 408, 380, 362, 336, 223, 187, 149, 77. E.A. Calcd for $C_{22}H_{37}NO_3SSi$: C, 62.37; H, 8.80; N, 3.31. Found: C, 62.40; H, 8.83.

(2S,5S,6R)-2-[(S)-1-triisopropylsilyloxyethyl]-6-methyl-5-(phenylthio)-[1,3]oxazinan-4-one 63c. Prepared according GP7 starting from azadiene **60** and acetaldehyde. $[\alpha]_D^{20}$ -40.7 (c 1.35, $CHCl_3$). IR ($CHCl_3$): 1667 cm^{-1}. ^1H NMR(400 MHz, $CDCl_3$):7.65 (m, 2H), 7.25 (m, 3H), 6.25 (bs, 1H), 4.39 (d, J=7.2 Hz, 1H), 4.14 (dq, J_1=6.4, J_2=2.4, 1H), 3.50 (m, 1H), 3.45 (d, J=2.4, 1H), 1.50 (d, J=6.4, 3H), 1.05 (s, 21H); ^{13}C NMR (400 MHz, $CDCl_3$): 138.3, 134.5, 133.4, 128.8, 127.7, 87.5, 73.4, 71.3, 54.5, 19.3, 18.1, 18.0, 12.6; MS m/z: 423, 408, 380, 362, 336, 222, 186, 149, 77. E.A. Calcd for $C_{22}H_{37}NO_3SSi$:C, 62.37; H, 8.80;. Found: C, 62.42; H, 8.84.

(2R,5R,6S)-2-[(S)-1-Triisopropylsilyloxyethyl]-6-(naphthalen-2-yl)-5-(phenylthio)-[1,3]oxazinan-4-one 62d; Prepared according GP7 starting from azadiene **60** and 2-naphthaldehyde. $[\alpha]_D^{20}$ -39.7(*c* 1.40, $CHCl_3$). IR ($CHCl_3$): 1678 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): 7.82 (m, 5H), 7.50 (m, 2H), 7.38 (m, 1H), 7.05 (m, 5H), 6.26 (br s, 1H), 5.41 (d, J=2.6 Hz, 1H), 5.15 (d, J=3.6 Hz, 1H), 4.29 (dq, J_1=6.4 Hz, J_2=3.6 Hz, 1H), 3.83 (d, J=2.6 Hz, 1H), 1.36 (d, J=6.4 Hz, 3H), 1.08 (s, 21H). ^{13}C NMR (100 MHz, $CDCl_3$):169.1, 134.8, 134.1, 132.9, 132.8, 132.7, 128.6, 128.1, 127.8, 127.7, 127.6, 126.2, 126.1, 125.2, 123.4, 85.5, 78.0, 68.8, 56.0, 18.1, 18.0, 16.0, 12.1. MS m/z: 535, 379, 336, 289, 261, 187. E.A. Calcd for $C_{31}H_{41}NO_3SSi$:C, 69.49; H, 7.71; N, 2.61. Found: C, 69.63; H, 7.73.

(2S,5S,6R)-2-[(S)-1-triisopropylsilyloxyethyl]-6-(naphthalen-2-yl)-5-(phenylthio)-[1,3]oxazinan-4-one 63d. Prepared according GP7 starting from azadiene **60** and 2-naphthaldehyde.$[\alpha]_D^{20}$ -14.2(*c* 1.70, $CHCl_3$). IR ($CHCl_3$): 1677 cm^{-1}. ^1H NMR(400 MHz, $CDCl_3$):7.85 (m, 5H), 7.55 (m, 2H), 7.38 (m, 1H), 7.22–7.05 (m, 5H), 6.42 (br s, 1H), 5.37 (d, J=2.2 Hz, 1H), 4.65 (d, J=7.6 Hz, 1H), 3.90 (d, J=2.2 Hz, 1H), 3.85 (m, 1H), 1.43 (d, J=6.4 Hz, 3H), 1.12 (s, 21H).^{13}C NMR (100 MHz, $CDCl_3$):168.1, 134.3, 134.1,133.7, 132.9, 132.8, 128.5, 128.1, 127.9, 127.8, 127.7,127.6, 126.2, 126.1, 124.9, 123.2, 87.6, 78.2, 71.5, 55.0, 19.6, 18.1, 18.0, 12.6. MS m/z: 535, 379, 336, 289, 261,187. E.A. Calcd for $C_{31}H_{41}NO_3SSi$: C, 69.49; H, 7.71; N,2.61. Found: C, 69.62; H, 7.71.

***tert*-Butyl-3-[(2R,5R,6S)-2-[(S)-1-triisopropylsilyloxyethyl]-4-oxo-5-(phenylthio)-[1,3]oxazin an-6-yl]-1Hindole-1-carboxylate 62e**; Prepared according GP7 starting from azadiene **60** and *tert*-butyl-3-formyl-1H-indole-1-carboxylate. $[\alpha]_D^{20}$ +24 (*c* 0.5, $CHCl_3$). IR ($CHCl_3$): 1738, 1674 cm^{-1}. ^1H NMR(400 MHz, $CDCl_3$):7.70 (s, 1H), 7.42–6.98 (m, 9H), 6.23

(br s, 1H), 5.46 (dd, J_1=2.2 Hz, J_2=1.2 Hz, 1H), 5.14 (d, J=3.2 Hz, 1H), 4.23 (dq, J_1=3.2 Hz, J_2=6.4 Hz, 1H), 3.92 (d, J=2.2 Hz, 1H), 1.68 (s, 9H), 1.30 (d, J=6.4 Hz, 3H), 1.08 (s, 21H). ^{13}C NMR (100 MHz, CDCl^3): 168.7, 149.5, 135.2, 134.4, 132.4, 128.5, 127.4, 124.6, 122.6, 118.6, 116.5, 115.4, 85.6, 83.9, 73.7, 68.8, 54.5,28.1, 18.0, 17.9, 15.9, 12.1. MS m/z: 567 (M+_t-Bu), 525, 473, 379, 336, 230, 188, 77. E.A. Calcd for$C_{34}H_{50}N_2O_5SSi$: C, 65.14; H, 8.04; N, 4.47. Found: C,65.41; H, 8.07

***tert*-butyl-3-[(2S,5S,6R)-2-[(S)-1-triisopropylsilyloxyethyl]-4-oxo-5-(phenylthio)-[1,3]oxazinan-6-yl]-1H-indole-1-carboxylate 63e.** Prepared according GP7 starting from azadiene **60** and *tert*-butyl-3-formyl-1H-indole-1-carboxylate. $[\alpha]_D^{20}$ -42.8(*c* 1.12, $CHCl_3$). IR ($CHCl_3$): 1737, 1671 cm^{-1}. ^{1}H NMR(400 MHz, $CDCl_3$): 7.65 (s, 1H), 7.40–7.00 (m, 9H), 6.38 (br s, 1H), 5.41 (dd, J_1=2.4 Hz, J_2=1.2 Hz, 1H), 4.66 (d, J=7.2 Hz, 1H), 3.97 (d, J=2.4 Hz, 1H), 3.76 (m, 1H),1.68 (s, 9H), 1.35 (d, J=6.4 Hz, 1H), 1.11 (s, 21H). ^{13}CNMR (100 MHz, $CDCl_3$):167.8, 149.6, 135.3, 133.8, 133.5, 132.5, 128.5, 127.8, 127.7, 124.6, 124.1, 122.7, 118.7, 116.8, 115.4, 87.8, 83.9, 74.1, 71.4, 53.6, 28.2, 19.5, 18.1, 18.0, 12.6. MS m/z: 567 (M+_t-Bu), 379, 336, 230, 188, 77. E.A. Calcd for $C_{34}H_{50}N_2O_5SSi$: C,65.14; H, 8.04; N, 4.47. Found: C, 65.41; H, 8.07

6.5 (*R*)- and (*S*)-Fluoxetine preparation

(2R,5R,6S)-2-[(S)-1-Triisopropylsilyloxyethyl]-6-phenyl-5-(phenylthio)-[1,3]oxazinan-4-one 61a; **(2S,5S,6R)-2-[(S)-1-triisopropylsilyloxyethyl]-6-phenyl-5-(phenylthio)-[1,3]oxazinan-4-one 62a.** The product have been prepared according GP7 as reported above.

(2R,6R)-2-((S)-1-Triisopropylsilyloxyethyl)-6-phenyl-1,3-oxazinan-4-one 110; (2S,6S)-2-((S)-1-Triisopropylsilyloxyethyl)-6-phenyl-1,3-oxazinan-4-one 111. MW-mediated de-sulfurization reaction: 5-Phenylsulfanyl-perhydrooxazinone **62a** (or **63a**) (0.24 mmol), Nickel-Raney (0.6 g), and EtOH (6 mL) were mixed in a 30 mL reaction tube. The tube was sealed and positioned in the reaction cavity. The sealed reaction was irradiated at 150 W for 2 min. The reaction mixture was filtered on Celite, and the solvent evaporated. The crude reaction mixture was purified by flash chromatography (3:7 EtOAc/cyclohexane) to give the desired product **110** in 98% yield (or **111** in 90% yield).

Compound **110**: IR (neat, cm^{-1}): 3201, 2942, 2866, 1675, 1463; ^1H NMR (400MHz, $CDCl_3$): 7.30 (m, 5H),6.37 (br s, 1H), 5.07 (d, 1H, J = 3.6 Hz), 4.86 (dd, 1H,J_1 = 4.4, J_2 = 10.8 Hz), 4.19 (dq, 1H, J_1 = 3.6, J_2 = 6.0Hz), 2.68 (dd, 1H, J_1 = 4.4, J_2 = 17.6 Hz), 2.61 (dd, 1H, J_1 = 10.8, J_2 = 17.6 Hz), 1.24 (d, 3H, J= 6.0Hz), 1.06 (m, 21H); ^{13}C NMR (100MHz, $CDCl_3$): 168.73, 139.61, 128.72, 128.39, 125.56,84.88, 76.09, 68.64, 39.75, 17.95, 15.74, 12.08; MS(m/z): 378, 334, 316, 202, 188, 131.

Compound **111**: oil. $[\alpha]_D$ = -37.3 (*c* = 0.82, CHCl3); IR (neat, cm^{-1}): 3201, 2942, 2866, 1675, 1463; ^1H NMR(400MHz, $CDCl^3$): 7.36 (m, 5H), 6.53 (br s, 1H), 4.83 (dd, 1H, J_1 = 3.6, J_2 = 12.0 Hz), 4.61 (d, 1H, J = 6.8 Hz), 3.90 (m, 1H), 2.71 (dd, 1H, J_1 = 3.6, J_2 = 17.2Hz), 2.59 (dd, 1H, J_1 = 12.0, J_2 =17.2 Hz),1.33 (d, 3H, J = 6.4 Hz), 1.09 (m, 21H). ^{13}C NMR(100MHz, $CDCl_3$): 168.10, 139.86, 128.63, 128.17,125.44, 87.51, 76.04, 71.45, 39.29, 19.72, 18.11, 12.65; MS (m/z): 334, 202, 187, 131. Anal. Calcd for$C_{21}H_{35}NO_3Si$: C 66.80; H 9.34. Found: C 66.92 H 9.38.

(2R,6R)-2-((S)-1-triisopropylsilyloxyethyl)-3-methyl-6-phenyl-1,3-oxazinan-4-one 112; (2S, 6S)-2-((S)-1-triisopropylsilyloxyethyl)-3-methyl-6-phenyl-1,3-oxazinan-4-one 113. To a solution of **110** (or **111**) (1 mmol) in THF (10 mL) at 0°C was added HMDSLi (1M in THF,1.0 eq, 1.0mL). The reaction was stirred for 20 min, MeI (8 eq, 0.498mL) added and the solution warmed to room temperature. Stirring was then maintained for 2h at the same temperature. A saturated solution of NH_4Cl was added, the organic solvent removed in vacuo and the obtained aqueous solution extracted with AcOEt. The organic phases were collected, dried over Na_2SO_4 and concentrated in vacuo. The crude reaction mixture was controlled by ^1H NMR analysis and used without purification for the next step. Yields >98%.

Compound **113**: oil. $[\alpha]_D$ = -62.5 (*c* = 0.92 $CHCl_3$); IR (neat, cm^{-1}): 3201, 2944, 2871, 1675, 1463; ^1H NMR(200 MHz, $CDCl_3$): 7.30 (m, 5H), 4.82 (d, 1H, J = 2.5 Hz), 4.78 (dd, 1H, J_1 = 2.2, J_2 = 11.4 Hz), 4.22 (m, 1H), 2.88 (s, 3H), 2.80–2.42 (m, 2H), 1.16 (d, 3H, J = 6.2 Hz), 1.00 (m, 21H); ^{13}C NMR (50 MHz, $CDCl_3$): 168.51, 139.87, 128.60, 127.85, 125.43, 90.75, 73.59, 68.84, 40.17, 29.57, 18.21, 16.54, 12.60; MS (m/z): 338(M^+-43), 216, 190, 131. Anal. Calcd for $C_{22}H_{37}NO_3Si$:C, 67.47; H, 9.52. Found: C, 67.35; H, 9.50.

(2R,6R)-2-((S)-1-Triisopropylsilyloxyethyl)-3-methyl-6-phenyl-1,3-oxazinane 114; (2S,6S)-2-((S)-1-Triisopropylsilyloxyethyl)-3-methyl-6-phenyl-1,3-oxazinane 115. Ph_2SiH_2 (2.5 equiv, 0.461 mL) and $RhH(CO)(PPh_3)_3$(1%) were added to a solution of **112** (or **113**) (1.0 mmol) in THF (10 mL) at room temperature and the stirring maintained for 15h. THF was removed in vacuo, HCl (1M) added and the reaction extracted with Et_2O.The aqueous phase was neutralized with NaOH 5M (pH = 10–12) and then extracted with Et_2O. The organic phases were dried over Na_2SO_4 and the solvent evaporated. The crude reaction mixture obtained was used without purification for the last step of the synthesis.

(R)-3-(Methylamino)-1-phenylpropan-1-ol 116; (S)-3-(Methylamino)-1-phenylpropan-1-ol 117. To a solution of **114** (or **115**) in MeOH (10mL) was added HCl 1M (5mL/mmol) and the mixture heated at 90°C for 1.5 h. The solution was cooled at room temperature, after which MeOH was removed in vacuo and the aqueous solution extracted with Et_2O. The aqueous solution was neutralized with NaOH 5M and extracted with CH_2Cl_2. The organic phases were collected, dried over Na_2SO_4 and the solvent removed in vacuo to give product **116** (or **117**) as a pure enantiomer.

Compound **116**: Yield: 60% calculated from **112**, $[\alpha]_D$ = +37.5 (*c* = 1.2, $CHCl_3$). IR (neat, cm^{-1}): 3303, 3061, 2938, 2854, 1492. ^1H NMR (300 MHz, $CDCl_3$): 7.30 (m, 5H), 4.95 (dd, 1H, J_1 = 3.3, J_2 = 8.7 Hz),4.20 (br s, 2H), 2.88 (m, 2H), 2.46 (s, 3H), 1.85 (m,2H). ^{13}C NMR (75 MHz, $CDCl_3$): 145.02, 128.14, 126.86, 125.54, 75.27, 50.21, 36.75, 35.82.
Compound **117**: Yield: 67% calculated from **113,** $[\alpha]_D$ = -36.0 (*c* = 1.0, $CHCl_3$); IR (neat, cm^{-1}): 3303, 3061, 2938, 2854, 1492; ^1H NMR(300MHz, $CDCl_3$): 7.30 (m, 5H), 4.95 (dd, 1H, J_1 = 3.3, J_2 = 8.7 Hz), 4.20 (br s, 2H), 2.88 (m, 2H), 2.46 (s, 3H), 1.85 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$):145.02, 128.14, 126.86, 125.54, 75.27, 50.21, 36.75, 35.82.

6.6 (*R*)- and (*S*)-Duloxetine preparation

(2R,5R,6R)-2-[(S)-1-Triisopropylsilyloxyethyl]-6-(thiophen-2-yl)-5-(phenylthio)-[1,3]oxazinan-4-one 62b; **(2S,5S,6S)-2-[(S)-1-Triisopropylsilyloxyethyl]-6-(thiophen-2-**

yl)-5-(phenylthio)-[1,3]oxazinan-4-one 63b. The product have been prepared according GP7 as reported above.

(2R,6R)-2-[(S)-1-Triisopropylsilyloxyethyl]-6-(thiophen-2-yl)-[1,3]oxazinan-4-one 118. (2S,6S)-2-[(S)-1-Triisopropylsilyloxyethyl]-6-(thiophen-2-yl)-[1,3]oxazinan-4-one 119. Aluminum (4.0 g) and 50 mL of a solution of $HgCl_2$ (1% in H_2O) were stirred for 1 min, the mixture was decanted and the residue was washed with water. The amalgam so prepared was added to a solution of compound **62b** (or **63b**) (0.9 mmol) in *i*-PrOH (50 ml) under inert atmosphere. The reaction was stirred overnight until the disappearance of starting materials (TLC test). The mixture was filtered through Celite and the solvent was removed in vacuo. Product **118** (or **119**)so obtained was used for the next step without any purification. An aliquot of the crude reaction mixture was utilized for identification of **118** (or **119**) after purification by a short flash chromatography on silica gel (8:2 cyclohexane/EtOAc).

Compound **118**: $[\alpha]_D^{20}$ +1.9 (*c* 1.3, $CHCl_3$).IR ($CHCl_3$): 1666 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): 7.33 (d, J=5.2 Hz, 1H), 7.05 (d, J=3.6 Hz, 1H), 7.00 (dd, J_1=3.6 Hz, J_2=5.2 Hz, 1H), 6.38 (br s, 1H, NH), 5.11 (dd, J_1=6.0 Hz, J_2=9.6 Hz, 1H), 5.07 (d, J =3.6 Hz, 1H),4.19 (dq, J_1=3.6 Hz, J_2=6.4 Hz, 1H), 2.77 (m, 2H), 1.19 (d, J=6.4 Hz, 3H), 1.07 (m, 21H). ^{13}C NMR (100 MHz, $CDCl_3$):168.18, 142.26, 126.77, 125.88, 124.88, 84.91, 72.13, 68.61, 39.66, 18.01, 15.69, 12.14. MS m/z: 384, 340, 322, 202, 187. Anal. Calcd for $C_{19}H_{33}NO_3SSi$: C,59.49; H, 8.67. Found: C, 60.68; H, 8.84.

Compound **119**: $[\alpha]_D^{20}$ -1.3 (*c* 2.1, $CHCl_3$). IR ($CHCl_3$): 1666 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): 7.32 (dd, J_1=1.6 Hz, J_2=4.8 Hz, 1H), 6.99 (m, 2H), 6.53 (br s, NH), 5.05 (dd, J_1=6.4 Hz, J_2=8.4 Hz, 1H), 4.62 (d, J=6.4 Hz, 1H), 3.87 (m, 1H), 2.78 (m, 2H), 1.32 (d, J=6.0 Hz, 3H), 1.07 (m, 21H). ^{13}C NMR (100 MHz,$CDCl_3$):167.52, 142.48, 126.70, 125.72, 124.36, 87.33, 72.32, 71.20, 38.95, 19.61, 18.06, 12.59. MS m/z: 384, 340, 322, 202, 187. Anal. Calcd for $C_{19}H_{33}NO_3SSi$: C,59.49; H, 8.67. Found: C, 60.68; H, 8.84.

(2R,6R)-*N*-Methyl-2-[(S)-1-triisopropylsilyloxyethyl]-6-(thiophen-2-yl)-[1,3]oxazinan-4-one 120. (2S,6S)-*N*-Methyl-2-[(S)-1-triisopropylsilyloxyethyl]-6-(thiophen-2-yl)-[1,3]oxazinan-4-one 121. To a solution of **118** (or **119**) (1 mmol) in THF (10mL) at 0°C was added HMDSLi (1M in THF,1.0 eq, 1.0mL). The reaction was stirred for 20 min, MeI

(8 eq, 0.498mL) added and the solution warmed to room temperature. Stirring was then maintained for 2h at the same temperature. A saturated solution of NH_4Cl was added, the organic solvent removed in vacuo and the obtained aqueous solution extracted with AcOEt. The organic phases were collected, dried over Na_2SO_4 and concentrated in vacuo. The reaction mixture was purified by flash chromatography on silica gel, eluting with cyclohexane/EtOAc 70/30.

Compound **120**: Y=65% calculated on product **62b**. $[\alpha]_D^{20}$ +36.3 (*c* 2.7, $CHCl_3$). R ($CHCl_3$): 1644 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$):d=7.31 (dd, J_1=1.6 Hz, J_2=4.8 Hz, 1H), 7.00 (m, 2H), 5.03 (dd, J_1=5.6 Hz, J_2=8.4 Hz, 1H), 4.96 (d, J=0.8 Hz,1H), 4.16 (dq, J_1=0.8 Hz, J_2=6.4 Hz, 1H), 3.06 (s, 3H), 2.76 (m, 2H), 1.17 (d, J=6.4 Hz, 3H), 1.06 (m, 21H). ^{13}CNMR (100 MHz, $CDCl_3$):167.45, 142.42, 126.66, 125.63, 124.53, 90.83, 71.14, 70.44, 40.26, 29.65, 18.03, 16.70, 12.19. MS m/z: 397, 354, 216, 137. Anal. Calcd for $C_{20}H_{35}NO_3SSi$: C, 60.41; H, 8.87. Found: C, 62.22; H,9.14.

Compound **121**: Y=54% calculated on product **63b**. $[\alpha]_D^{20}$ -67.4 (*c* 2.2, $CHCl_3$). IR ($CHCl_3$): 1646 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): 7.29 (dd, J_1=2.4 Hz, J_2=3.6 Hz, 1H), 6.98 (m, 2H), 5.02 (dd, J_1=3.6 Hz, J_2=10.0 Hz, 1H), 4.87 (d, J=2.4 Hz,1H), 4.25 (dq, J_1=2.4 Hz, J_2=6.4 Hz, 1H), 2.94 (s, 3H), 2.81 (m, 2H), 1.19 (d, J=6.4 Hz, 3H), 1.08 (m, 21H). ^{13}CNMR (100 MHz, $CDCl_3$): 167.32, 142.87, 126.60, 25.48, 123.93, 90.84, 70.56, 68.87, 39.90, 29.43, 18.05, 16.57, 12.46. MS m/z: 397, 354, 216, 137. Anal. Calcd for$C_{23}H_{41}NO_3SSi$: C, 62.82; H, 9.40. Found: C, 62.70; H, 9.38.

(2R,6R)-[(S)-1-(triisopropylsilyloxy)ethyl]-3-methyl-6-(thiophen-2-yl)-1,3-oxazinane 122 (2S,6S)-[(S)-1-(triisopropylsilyloxy)ethyl]-3-methyl-6-(thiophen-2-yl)-1,3-oxazinane 123. Ph_2SiH_2 (0.46 mL, 2.5 mmol) and $RhH(CO)(PPh_3)_3$ (1%)were added to a solution of **120** (or **121**) (1.0 mmol) in THF (10 mL) at room temperature and the stirring maintained for 15 h. Disappearance of starting material was verified by TLC (CH2Cl2/cyclohexane/ethylacetate 50/30/20). An aliquot of the solution was utilized for identification of the reduction product **122** (or **123**) after removing the solvent and fast purification by a short flash chromatography eluting with cyclohexane/ethyl acetate 90:10 (saturated with $NH_{3(g)}$).

Compound **122**: $[\alpha]_D^{20}$ +35.7 (*c* 1.0, $CHCl_3$).IR ($CHCl_3$): 2944, 2865, 1463 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$):7.23 (dd, J_1=1.6 Hz, J_2=4.8 Hz, 1H), 6.96 (m,2H), 4.75 (dd, J_1=2.0 Hz, J_2=11.2 Hz, 1H), 3.99 (m, 1H), 3.92 (d, J=5.2 Hz, 1H), 3.06 (ddd, J_1=2.0 Hz, J_2=4.4 Hz, J_3=12.8 Hz, 1H), 2.88 (dt, J_1=2.8 Hz, J_2=12.8 Hz, 1H),2.40 (s, 3H), 2.13 (m, 1H), 1.64 (m, 1H), 1.28 (d, J=6.8 Hz, 3H), 1.06 (m, 21H). ^{13}C NMR (100 MHz, $CDCl_3$):145.80, 126.12, 124.35, 123.43, 97.06, 75.38, 70.46, 54.80, 36.62, 30.51, 18.78, 18.12, 12.27. MS m/z: 383, 340, 235, 182, 123. Anal. Calcd for $C_{20}H_{37}NO_2SSi$:C, 62.61; H, 9.72. Found: C, 64.49; H, 9.99.

Compound **123**: $[\alpha]_D^{20}$ -17.8 (*c* 2.3,$CHCl_3$). IR ($CHCl_3$): 2944, 2865, 1463 cm^{-1}. ^1H NMR(400 MHz, $CDCl_3$): 7.23 (dd, J_1=2.8 Hz, J_2=3.6 Hz,1H), 6.96 (m, 2H), 4.73 (dd, J_1=2.8 Hz, J_2=11.6 Hz, 1H), 4.15 (m, 1H), 3.92 (d, J=4.0 Hz, 1H), 3.07 (ddd, J_1=1.6 Hz, J_2=4.4 Hz, J_3=14.4 Hz, 1H), 2.88 (dt, J_1=3.2 Hz, J_2=13.2 Hz, 1H), 2.37 (s, 3H), 2.13 (m, 1H), 1.71 (m, 1H), 1.28 (d, J=6.0 Hz, 3H), 1.06 (m, 21H). ^{13}CNMR (100 MHz, $CDCl_3$): 146.17, 126.24, 124.31,122.89, 96.83, 75.32, 68.14, 54.65, 37.22, 29.81, 18.77, 18.17, 12.60. MS m/z: 383, 340, 235, 182, 123. Anal. Calcdfor $C_{20}H_{37}NO_2SSi$: C, 62.61; H, 9.72. Found: C, 64.49; H,9.99.

(R)-3-(methylamino)-1-(thiophen-2-yl)propan-1-ol 124; (S)-3-(methylamino)-1-(thiophen-2-yl)propan-1-ol 125. Aqueous HCl (1 M, 2.5 mL) was added to the crude THF solution of **122** (or **123**) and the stirring maintained at the same temperature for 4 h. The organic solvent was removed in vacuo and the obtained aqueous solution extracted with Et_2O. The aqueous phase was basified with NH_4OH (pH=10) and then extracted with CH_2Cl_2.The organic phases were dried over Na_2SO_4 and the solvent evaporated. The crude reaction mixture was subjected to column chromatography (ethyl acetate/MeOH/NH_4OH 80/19/1) to give **124** (or **125**).

Compound **124**: Y=68% calculated on product **120**. $[\alpha]_D^{20}$ +13.7 (*c* 2.5, EtOH) [lit. [□]$_D$ +13.3 (c 1.05, MeOH)]. IR ($CHCl_3$): 3302, 3103, 2939, 2853, 2793, 1473, 1315 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): 7.20 (dd, J_1=1.2 Hz, J_2=4.8 Hz, 1H), 6.96 (dd, J_1=4.0 Hz, J_2=5.2 Hz, 1H), 6.91 (d, J=1.2 Hz, 1H), 5.19 (dd, J_1=2.8 Hz, J_2=8.4 Hz, 1H), 2.94 (m, 1H), 2.89 (m, 1H), 2.44 (s, 3H), 1.95 (m, 2H). ^{13}CNMR (100 MHz, $CDCl_3$): 149.64, 126.53, 123.70, 122.31, 71.92, 50.12, 36.73, 35.88. MS m/z: 170, 153, 138, 127, 110, 97, 88. Anal. Calcd for $C_8H_{13}NOS$: C,56.11; H, 7.65. Found: C, 56.21; H, 7.66.

Compound **125**: Y=60% calculated on product **121.** $[\alpha]_D^{20}$ -12.0 (*c* 3.0, EtOH). IR ($CHCl_3$): 3302, 3103, 2939, 2853, 2793, 1473, 1315 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): 7.20 (dd, J_1=1.2 Hz,J_2=4.8 Hz, 1H), 6.96 (dd, J_1=4.0 Hz, J_2=5.2 Hz, 1H), 6.91 (d, J=1.2 Hz, 1H), 5.19 (dd, J_1=2.8 Hz, J_2=8.4 Hz,1H), 2.94 (m, 1H), 2.89 (m, 1H), 2.44 (s, 3H), 1.95 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 149.64, 126.53, 123.70, 122.31, 71.92, 50.12, 36.73, 35.88. MS m/z: 170, 153, 138, 127, 110, 97, 88. Anal. Calcd for $C_8H_{13}NOS$: C,56.11; H, 7.65. Found: C, 57.23; H, 7.88.

6.7 (*R*/*S*)-Venlafaxine preparation

4-(4-methoxy-phenyl)-3-trimethylsilyloxy-2-aza-1-phenylbutan-1,3-diene 127. 1 mL of benzaldehyde **44** (1 mmol) was added to a solution of LiHMDS (1.1 mL of 1 M sol in THF) and hexane (5 mL) at 0°C under inert atmosphere. The reaction mixture was stirred at 0°C for 1 h. IR analysis confirmed the formation of silylimine **45** (ν_{CN}=1655 cm^{-1}). TMSCl (0.14 mL, 1 mmol) was added in one portion and after stirring for 10 min at 0°C the mixture was allowed to stir for 1 h at rt. A white precipitate formed. The mixture was cooled at 0°C, triethylamine (0.3 mL, 2 mmol) was added in one portion and after 5 min a solution of (4-methoxy-phenyl)acetyl chloride **126** (1 mmol) in 5 mL of hexane was added. Stirring was maintained for 2 h and a precipitate appeared. The mixture was filtered through Celite under argon and the solvent was removed in vacuo to afford **127** as an oil, which was analyzed. ^1H NMR (400 MHz $CDCl_3$): 8.45 (s, 1H), 7.83 (m, 2H), 7.57 (d, 2H, J = 8.8), 7.45 (m, 3H), 6.88 (d, 2H, J = 8.8), 5.92 (s, 1H), 3.82 (s, 3H), 0.21 (s, 9H).

5-(4-methoxy-phenyl)-2-phenyl-1-oxa-3-aza-spiro[5.5]undecan-4-one 128. Azadiene **127** (1 mmol), prepared as reported above, was dissolved in anhydrous CH_2Cl_2 (20 mL) and cooled at -78°C. Cyclohexanone (1 mmol) dissolved in CH_2Cl_2 (2 mL) was added followed by a very slow addition of BF_3 etherate (0.12 mL, 1 mmol) in CH_2Cl_2 (10 mL). The solution was stirred at –78°C for 8 h. The mixture was poured into saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layers were dried and the solvent was removed in vacuo. The reaction mixture was purified by flash chromatography on silica gel, eluting with cyclohexane/ethyl acetate 40/60. Product **128** was obtained with 62%

yield. White solid, mp 186-188 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 7.56 (m, 2H), 7.42-7.46 (m, 3H), 7.34 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 8.8 Hz, 2H), 6.75 (bs, 1H), 5.92 (s, 1H), 3.78 (s, 3H), 3.35 (s, 1H), 2.27 (d, J = 9.2 Hz, 1H), 1.52-1.65 (m, 5H), 1.26-1.39 (m, 3H), 1.08-1.16 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$):171.12, 158.84, 138.30, 130.47, 129.61, 128.98, 126.63, 113.80, 79.52, 56.65, 55.21, 34.92, 33.28, 25.45, 22.08, 21.27.

3-Hydroxymethyl-5-(4-methoxy-phenyl)-1-oxa-3-aza-spiro[5.5]undecan-4-one 130. Cycloadduct **128** (0.3 mmol) was mixed with HCOOH (2.0 mL) and HCHO (4 mL) and put in a flask for microwave oven synthesis (Prolabo). The mixture was submitted to microwave irradiation for 3' at 150 Watt power. The formic acid was removed in vacuo and the mixture was neutralized with $NaHCO_{3\ aq}$. The residue was extracted with ethylacetate, the solvent owas removed in vacuo end the crude reaction mixture was purified by flash chromatography on silica gel, eluting with cyclohexane/ethyl acetate 40/60 to give product **130** in 58% yield.

3-Hydroxymethyl-5-(4-methoxy-phenyl)-2-phenyl–1-oxa-3-aza-spiro[5.5]undecan-4-one 118. If we stopped the transchetalization after 1min, it's possible to isolate and recognize the intermediate **129**. ^{1}H NMR (400 MHz, $CDCl_3$): 7.55-7.58 (m, 2H), 7.47-7.50 (m, 3H), 7.44 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 6.03 (s, 1H), 5.19 (dd, J_1 = 3.2 Hz, J_2 = 10.4 Hz, 1H), 4.16 (pt, J = 10.4 Hz, 1H), 3.94 (bs, 1H), 3.78 (s, 3H), 3.42 (s, 1H), 2.27 (d, J = 11.6 Hz, 1H), 1.46-1.68 (m, 6H), 1.25-1.34 (m, 3H), 1.08-1.16 (m, 1H). ^{13}C NMR (100MHz, $CDCl_3$):172.18, 158.87, 137.12, 130.54, 129.78, 129.06, 128.64, 127.95, 113.83, 83.83, 76.61, 68.42, 56.88, 55.20, 34.58, 32.00, 25.39, 22.12, 21.14.

Compound **130**: ^{1}H NMR (400 MHz, $CDCl_3$): 7.17 (d, J = 8.8 Hz, 2H), 6.83 (d, J = 8.8 Hz, 2H), 5.04 (dd, J_1 = 8.0 Hz, J_2 = 12.8 Hz, 2H), 4.89 (dd, J_1 = 3.6 Hz, J_2 = 11.6 Hz, 1H), 4.67 (dd, J_1 = 6.0 Hz, J_2 = 10.4 Hz 1H), 4.00 (bs, 1H), 3.77 (s, 3H), 3.31 (s, 1H), 1.95 (d, J = 13.6 Hz, 1H), 1.53-1.58 (m, 3H), 1.33-1.48 (m, 3H), 1.17-1.22 (m, 2H), 1.05-1.12 (m, 1H). ^{13}C NMR (100MHz, $CDCl_3$) ppm:170.34, 158.86, 130.66, 128.47, 113.73, 76.54, 72.86, 68.37, 57.10, 55.21, 33.16, 32.77, 25.29, 21.68, 21.11.

(*R*/*S*)-Venlafaxine 131. Compound **130** (0.3 mmol) was dissolved in THF (3 mL) at 0°C and 2 eq of $LiAlH_4$ were added. After 30' at 0°C the mixture was warmed at 40°C for 2 h. After the disappearance of the starting material, controlled by tlc, the rection was

hydrolyzed with HCl 0.1 M at 0°C. THF was removed in vacuo and the residue was extracted twice with ether. The aqueous solution was basified (pH 10) with NH_4OH and ri-extracted with dichloromethane. Compoun **131** was obtained in 66% yield. Spectral data are superimposable with literature data[94].

6.8 5-Unsubstitued-1,3-oxazinan-4-ones preparations

General procedure for the preparation of azadiene 65 and 69. GP8.

1 mL of aldehyde **51** (1 mmol) was added to a solution of LiHMDS (1.1 mL of 1 M sol in THF) and hexane (5 mL) at 0°C under inert atmosphere. The reaction mixture was stirred at 0°C for 1 h. IR analysis confirmed the formation of silylimine **52** (ν_{CN}=1655 cm^{-1}). TMSCl (0.14 mL, 1 mmol) was added in one portion and after stirring for 10 min at 0°C the mixture was allowed to stir for 1 h at rt. A white precipitate formed. The mixture was cooled at 0°C, triethylamine (0.3 mL, 2 mmol) was added in one portion and after 5 min a solution of acetylchloride **64** (1 mmol) in 5 mL of hexane was added. Stirring was maintained for 2 h and precipitate appeared. The mixture was filtered through Celite under argon and the solvent was removed in vacuo to afford azadiene as an oil, which was used for the next step.

Procedure for the preparation of perhydrooxazin-4-ones 67, 68, 71 and 72. GP9.

Azadiene **69** (2 mmol), prepared as reported above, was dissolved in anhydrous chlorobenzene (5 mL) and put in a flask for microwave oven synthesis (Prolabo). Aldehyde (1 mmol) with catalyst (5%) **70** were added and the mixture was submitted to microwave irradiation for the time indicate in Table 3.5 at 300 Watt power. The solvent was evaporated and the mixture was purified by flash chromatography on silica gel, eluting with cyclohexane/ethyl acetate 70/30. Yields and diastereomeric ratio are reported in Tab. 3.6.

(2S*,6S*)-2,6-Diphenyl-[1,3]oxazinan-4-one 67; **(2R*,6S*)-2,6-Diphenyl-[1,3]oxazinan-4-one 68**. Prepared according **GP9** using azadiene **65** and activated benzaldehyde **66**.

Compound **67**: IR: 1653 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 7.51 (m, 2H), 7.43–7.30 (m, 8H), 6.57 (br s, 1H), 5.92 (s, 1H), 5.02 (m 1H), 2.75 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$):168.8, 139.6, 137.7, 129.9, 128.8, 128.7, 128.3, 126.9, 125.6, 85.7, 76.6, 39.1; MS

m/z: 253, 175, 147, 131, 118, 104, 78; E.A. Calcd for $C_{16}H_{15}NO_2$: C 75.87; H 5.97. Found: C 75.96; H 5.98.

Compound **68**: IR: 1653 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 7.60–7.30 (m, 10H), 6.54 (br s, 1H), 5.95 (s, 1H), 5.05 (dd, 1H, J_1=7.2, J_2=5.8), 2.86 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$):169.6, 139.2, 138.4, 129.2, 128.7, 128.6, 128.3, 126.7, 126.1, 81.8, 70.2, 37.6; MS m/z: 253, 175, 147, 131, 118, 104, 78; E.A. Calcd for $C_{16}H_{15}NO_2$: C 75.87; H 5.97. Found: C 75.99; H 5.60.

(2S*,6S*)-6-Phenyl-2-(2-triisopropylsilanyloxy-phenyl)-[1,3]oxazinan-4-one 71a.
(2R*,6S*)-6-Phenyl-2-(2-triisopropylsilanyloxy-phenyl)-[1,3]oxazinan-4-one 72a.
Prepared according **GP9** using azadiene **69a** and activated benzaldehyde **66**.

Compound **71a**: **:** IR: 1663 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): 7.32 (m, 1H), 7.22 (m, 5H), 7.12 (m, 1H), 7.06 (m, 1H), 6.93 (m, 1H), 6.20 (bs, 1H), 6.17 (s, 1H), 5.02 (dd, 1H, J_1=5.4 Hz, J_2=9.6 Hz), 2.76 (m, 2H), 1.15 (s, 3H), 1.12 (s, 9H); 1.08 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$):168.44, 153.04, 139.90, 130.15, 128.57, 128.15, 127.78, 126.88, 125.55, 121.30, 118.15, 80.31, 76.53, 39.29, 17.99, 12.89.

Compound **72a**: IR: 1663 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): 7.50 (m, 1H), 7.17 (m, 5H), 7.11 (m, 1H), 6.98 (m, 1H), 6.80 (m, 1H), 6.40 (bs, 1H), 6.19 (s, 1H), 5.20 (dd, 1H, J_1=5.4 Hz, J_2=6.6 Hz), 2.93 (dd, 1H, J_1=5.4 Hz, J_2=17.2 Hz), 2.79 (dd, 1H, J_1=6.8 Hz, J_2=17.2 Hz), 1.01 (s, 3H), 0.98 (s, 9H), 0.80 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): 168.84, 153.48, 138.90, 131.00, 131.62, 128.54, 128.24, 127.90, 127.21, 126.60, 120.89, 118.47, 76.81, 71.26, 37.14, 17.89, 12.82.

(2S*,6S*)-2-(2-Methoxy-phenyl)-6-Phenyl-[1,3]oxazinan-4-one 71b; (2R*,6S*)-2-(2-Methoxy-phenyl)-6-Phenyl-[1,3]oxazinan-4-one 72b; Prepared according **GP9** using azadiene **69b** and activated benzaldehyde.

Compound **71b**: IR: 1661 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): 7.7 (m, 1H), 7.4 (m, 6H), 6.90 (m,2H), 6.58 (bs, 1H), 6.25 (s, 1H), 5.04 (dd, 1H, J_1=5.6 Hz, J_2=9.4 Hz), 3.87 (s, 3H), 2.76 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$):168.43, 155.89, 139.99, 130.23, 130.17, 128.67, 128.23, 126.24, 126.0, 120.86, 110.32, 80.13, 71.41, 55.38, 39.32.

Compound **72b**: IR: 1661 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): 7.2-7.5 (m, 7H), 7.0 (m, 2H), 6.758 (bs, 1H), 6.19 (s, 1H), 5.21 (t, 1H, J=6.4 Hz), 3.83 (s, 3H), 2.84 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$):169.10, 156.41, 139.51, 130.11, 128.69, 127.08, 126.36, 126.33, 125.94, 120.63, 110.18, 80.07, 71.36, 55.26, 39.12.

(2S*,6S*)-2-(4-Methoxy-phenyl)-6-Phenyl-[1,3]oxazinan-4-one 71c; (2R*,6S*)-2-(4-Methoxy-phenyl)-6-Phenyl-[1,3]oxazinan-4-one 72c; Prepared according **GP9** using azadiene **69c** and activated benzaldehyde.

Compound 71c mp: 138-142°C; IR: 1653, cm^{-1};^{1}H NMR (300 MHz, $CDCl_3$): 7.43-7.31 (m, 7H), 6.89 (d, J=8.8 Hz, 2H), 5.91 (s, 1H), 4.99 (dd, J_1=9.9Hz, J_2=5.1Hz, 1H), 3.80 (s, 3H), 2.75(m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): 169.0, 159.6, 137.7, 131.7, 129.9, 128.9, 127.2, 126.9, 114.0, 85.7, 76.4, 55.3, 39.0, 1.1; Ms (m/z): 283, 176, 161, 147, 118, 104, 91, 77, 65.

Compound **72c**: mp: 138-142°C ; IR: 1653, cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): 7.54-7.28 (m, 7H), 6.91 (d, J = 8.8 Hz, 2H), 6.55 (s, 1H), 5.87 (s, 1H), 4.99 (t, J=6.6Hz, 1H), 3.81 (s, 1H), 2.85 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): 169.2, 159.9, 138.3, 130.8, 129.5, 128.8, 127.9, 126.8, 114.1, 81.4, 70.6, 55.3, 37.1, 1.01; Ms (m/z): 283, 176, 161, 147, 118, 104, 91, 77, 65.

(2S*,6S*)-6-(4-Methoxy-phenyl)-2-Phenyl-[1,3]oxazinan-4-one 71d; (2R*,6S*)-6-(4-Methoxy-phenyl)-6-Phenyl-[1,3]oxazinan-4-one 71d; Prepared according **GP9** using azadiene **69d** and activated 4-Methoxy-benzaldehyde.

Compound 71d: ^{1}H NMR (400 MHz $CDCl_3$): 7.41 (m, 7H) 6.89(m, 2H), 6.46 (bs, 1H), 5.91 (s , 1H), 4.89 (dd J_1=4.8 J_2=10.4 Hz, 1H) 3.79 (s, 3H) 2.75 (m, 2H).^{13}C NMR (100 MHz $CDCl_3$): 168.9, 159.6, 137.8, 131.8, 129.9, 128.8, 127.2, 126.9, 114.1, 85.7, 76.4, 55.3, 39.0.

Compound 72d: ^{1}H NMR (400 MHz $CDCl_3$): 7.43 (m, 7H) 6.90 (m, 2H), 6.73 (bs, 1H), 5.85 (s, 1H), 4.99 (m, 1H) 3.81 (s, 3H) 2.83 (m, 2H).^{13}C NMR (100MHz $CDCl_3$): 168.9, 159.6, 137.8, 131.8, 129.9, 128.8, 127.2, 126.9, 114.1, 85.7, 76.4, 55.3, 39.0.

(2S*,6S*)-2,6-Di-(2-Methoxy-phenyl)-[1,3]oxazinan-4-one 71e; (2R*,6S*)-2,6-Di-(2-Methoxy-phenyl)-6-Phenyl-[1,3]oxazinan-4-one 72e; Prepared according **GP9** using azadiene **69e** and activated 2-Methoxy-benzaldehyde.

Compound **71e**: IR: 1661 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 7.70 (m, 2H), 7.32 (m, 2H), 7.03 (m, 2H), 6.90 (m, 2H), 6.48 (bs, 1H), 6.25 (s, 1H), 5.40 (dd, 1H, J_1=3.4 Hz, J_2=11.4 Hz), 3.89 (s, 3H), 3.84 (s, 3H), 2.90 (dd, 1H, J_1=3.4 Hz, J_2=17.4 Hz), 2.51 (dd, 1H, J_1=11.4 Hz, J_2=17.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$):169.10, 155.85, 155.37, 130.06, 129.54, 129.12, 128.72, 126.27, 125.54, 120.87, 120.80, 110.26, 110.14, 80.00, 71.34, 55.30, 55.20, 38.32.

Compound **72e**:IR: 1661 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 7.50 (, 2H), 7.29 (m, 2H), 7.10-6.90 (m, 4H), 6.65 (bs, 1H), 6.35 (s, 1H), 5.45 (dd, 1H), 3.83 (s, 3H), 3.85 (s, 3H), 2.90 (m, H), 2.60 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 169.95, 156.64, 156.14, 134.15, 129.80, 128.71, 128.53, 126.44, 126.39, 120.80, 110.19, 78.15, 66.50, 55.14, 37.65.

(2S*,6S*)-2-(4-Nitro-phenyl)-6-Phenyl-[1,3]oxazinan-4-one 71g; (2R*,6S*)-2-(4-Nitro-phenyl)-6-Phenyl-[1,3]oxazinan-4-one 72g; Prepared according **GP9** using azadiene **69g** and activated 2-Methoxy-benzaldehyde.

Compound **71g**: ^{1}H NMR (200 MHz, $CDCl_3$): 8.30 (d, 2H), 7.73 (d, 2H), 7.48 (m, 5H), 7.34 (bs, 1H), 6.07 (s, 1H), 5.07 (t, 1H, J=3.4 Hz), 2.79 (d, 2H, J=3.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$):169.04, 148.43, 144.07, 139.06, 128.40, 127.92, 126.55, 125.61, 124.13, 84.39, 76.89, 39.11.

Compound **72g**:^{1}H NMR (200 MHz, $CDCl_3$): 8.13 (d, 2H), 7.68 (d, 2H), 7.35 (m, 5H), 7.10 (bs, 1H), 6.03 (s, 1H), 4.97 (t, 1H, J=6.6 Hz), 2.85 (d, 2H, J=6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 168.46, 148.62, 144.72, 138.35, 129.63, 128.89, 127.82, 126.55, 126.19,124.21, 122.61, 81.42, 71.15, 37.56.

6.9 Piperidinones preparation

General procedure for the preparation of 5-sulfonyl-piperidinones GP8.

Azadiene (1 mmol) was dissolved in 5 mL of anhydrous chlorobenzene (or solvent indicates in Par.3.3) and put in a flask for microwave oven synthesis (Prolabo). Phenyl vinylsulphone **73** (1 mmol) was added and the mixture was submitted to microwave irradiation for 30' at 300 Watt power. The solvent was evaporated and the mixture was purified by flash chromatography on silica gel, eluting with dichloromethane/ethylacetate 70/30.

(5*R,6*R**)-5-Benzenesulfonylmethyl-6-phenyl-piperidin-2-one 74.** Prepared according GP8 using azadiene **65.** Yields are reported in Tab. 3.7. IR: 1668 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 7.81 (m, 2H), 7.62 (m, 1H), 7.16 (m, 2H), 7.27 (m, 3H), 7.12 (m, 2H), 5.73 (bs, 1H), (dd, 1H, J_1=3.2 Hz, J_2=4.4 Hz), 3.42 (m, 1H), 2.79 (m, 1H), 2.48 (m, 1H), 2.22 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 170.54, 139.77, 137.62, 134.09, 129.41, 129.11, 126.87, 128.53, 126.44, 63.76, 55.20, 28.05, 18.47; MS m/z: 316, 173, 172, 158, 144, 130, 118, 104, 91, 77.

(3*S,5*R**,6*R**)-5-Benzenesulfonylmethyl-3-chloro-6-phenyl-piperidin-2-one 75.** Prepared according GP8 using azadiene **47a.** ^{1}H NMR (400 MHz, $CDCl_3$): 7.69 (m, 2H), 7.57 (m, 1h), 7.43 (m, 2H), 7.25 (m, 3H), 7.16 (m, 2H), 5.98 (bs, 1H), 5.03 (dd, 1H, J_1=1.6 Hz, J_2=7.2 Hz), 4.71(t, 1H, J=5.2 Hz), 3.87 (dd, 1H, J_1=4.4 Hz, J_2=7.2 Hz, J_3= 8.8Hz), 2.67 (m,2H); ^{13}C NMR (100 MHz, $CDCl_3$): 166.03, 138.39, 137.42, 134.14, 129.34, 129.11, 129.05, 128.33, 127.13, 61.05, 56.42, 51.16, 29.43.

(5R,6R)-6-[(S)-1-Triisopropylsilyloxyethyl]-5-benzenesulfonyl-piperidin-2-one 78; (5S,6S)-6-[(S)-1-Triisopropylsilyloxyethyl]-5-benzenesulfonyl-piperidin-2-one 79. Prepared accordino GP8 using azadiene **77**. Yields and diastereomeric ratio are reported in Table 3.8.

Compound **78:**$[\alpha]_D^{20}$ –19.2 (*c* 0.90, $CHCl_3$). IR: 1669 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 7.88 (m, 2H), 7.69 (m, 1H), 7.29 (m, 2H), 6.51 (bs, 1H), 3.96 (dq, 1H, J_1=3.2 Hz, J_2=6.0 Hz), 3.82 (ddd, 1H, J_1=2.8 Hz, J_2=3.2 Hz, J_3=5.2 Hz), 3.82 (ddd, 1H, J_1=5.2 Hz, J_2=5.6 Hz, J_3=8.8 Hz), 2.43 (m, 1H), 2.21 (m, 1H), 2.01 (m, 2H), 1.13 (d, 3H, J=6.0 Hz), 0.84 (s, 9H),

0.06 (s, 3H), 0.5 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 172.51, 137.00, 134.28, 129.49, 128.80, 70.47, 59.20, 55.44, 28.77, 25.73, 21.10, 20.15, 17.84, -4.30, -4.63; MS m/z: 398, 382, 340, 212, 198, 180, 93, 75.

Compound **79**: $[\alpha]_D^{20}$ –13.2 (*c* 1.06, $CHCl_3$); IR: 1664 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 7.89 (m, 2H), 7.72 (m, 1H), 7.61 (m, 2H), 6.25 (bs, 1H), 4.21 (dq, 1H, J_1=4.0 Hz, J_2=6.0 Hz), 3.88 (ddd, 1H, J_1=2.0 Hz, J_2=4.0 Hz, J_3=5.2 Hz), 3.17 (ddd, 1H, J_1=5.2 Hz, J_2=5.2 Hz, J_3=6.8 Hz), 2.56 (m, 1H), 2.25 (m, 1H), 2.06 (m, 2H), 1.10 (d, 3H, J=6.0 Hz), 0.86 (s, 9H), 0.073 (s, 3H), 0.069 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$):170.89, 136.88, 134.42, 129.56, 128.88, 69.48, 58.57, 56.08, 28.68, 25.71, 21.11, 17.86, 17.12, -4.65, -4.90; MS m/z: 398, 382, 340, 240, 212, 198, 168, 93, 75.

General procedure for the preparation of 5-bis-sulfonyl-piperidinones GP9.

Azadiene (1 mmol) was dissolved in 5 mL of anhydrous toluene and put in a flask for microwave oven synthesis Microsynth-Milestone. 1,1-Bis(phenylsulfonyl)ethylene **82** (1 mmol) was added and the mixture was submitted to microwave irradiation for 30' at 500 Watt power. The solvent was evaporated and the mixture was purified by flash chromatography on silica gel, eluting with dichloromethane/ethylacetate 90/10.

(*R)-6-Phenyl-5,5-bis(phenylsulfonyl)piperidin-2-one 83**. Prepared according GP9 using azadiene **65**. Y=65%; ^{1}H NMR (400 MHz $CDCl_3$): 8.20 (m, 2H) 7.75 (m, 1H), 7.66 (m, 2H), 7.54 (m, 1H), 7.48 (m, 2H), 7.30 (m, 7H), 6.23 (bs, 1H), 5.27 (s , 1H), 2.91 (m, 4H).^{13}C NMR (100 MHz $CDCl_3$): 169.5, 138.4, 137.1, 136.2, 135.2, 134.1, 131.3, 130.7, 130.2, 129.3, 129.2, 128.5, 128.3, 90.3, 58.6, 27.8, 23.5.

(3*S,6*R**)-3-Chloro-6-phenyl-5,5-bis(phenylsulfonyl)piperidin-2-one 84**. Prepared according GP9 using azadiene **47a**. Y=70%; IR: 1687 cm^{-1}; ^{1}H NMR (400 MHz $CDCl_3$): 8.20 (m, 2H) 7.80 (m, 1H), 7.64 (m, 2H), 7.58 (m, 2H), 7.50 (m, 2H), 7.40 (m, 2H),7.32 (m, 2H), 7.22 (,2H) 6.68 (bs, 1H), 5.14 (dd, 1H, J_1=1.2 Hz, J_2=3.6 Hz), 4.99 (dd, 1H, J_1=8.0 Hz, J_2=10.4 Hz),3.50 (ddd, 1H, J_1=1.2 Hz, J_2=8.0 Hz, J_3=14.8 Hz), 3.30 (dd, 1H, J_1=10.4 Hz, J_2=14.8 Hz),.^{13}C NMR (100 MHz $CDCl_3$):166.30,137.91, 135.61, 135.13, 134.45,131.34, 130.64, 130.15, 129.38, 128.64, 128.53

(6*R*)-6-[(S)-1-(Triisopropylsilyloxy)ethyl]-5,5-bis(phenylsulfonyl)piperidin-2-one 85; (6*S*)-6-[(S)-1-(Triisopropylsilyloxy)ethyl]-5,5-bis(phenylsulfonyl)piperidin-2-one 86. Prepared according GP9 using azadiene **77**. Y=82% diastereomeric ratio 60/40 respectively.

Compound **85**: IR ($CHCl_3$): 1668 cm^{-1}; ^1H NMR (400 MHz $CDCl_3$) ppm: 8.05 (m, 4H), 7.75 (m, 2H), 7.58(m, 4H), 5.93 (bs, 1H), 4.75 (dq, J_1=6 J_2=2 Hz, 1H), 3.73 (d J=2 Hz, 1H), 3.05 (m, 1H), 2.76 (m, 2H), 2.57 (m, 1H), 1.22 (d J=6 Hz, 3H), 0.75 (s, 9H), -0.03 (s, 3H) –0.09 (s, 3H).^{13}C NMR (100MHz $CDCl_3$) ppm: 170.5, 138.6, 135.4, 135.1, 134.7, 130.9, 130.7, 129.0, 128.5, 88.6, 69.6, 59.7, 27.0, 25.5, 22.1, 18.1, -4.9, -5.5.

Compound **86**: IR ($CHCl_3$): 1668 cm^{-1}; ^1H NMR (400 MHz $CDCl_3$) ppm: 8.83 (bs, 1H) 8.05 (m, 4H), 7.77 (m, 2H), 7.60(m, 4H), 5.01 (q, J=6.4, 1H), 3.47 (s , 1H), 3.33 (m, 1H), 2.62 (m, 3H), 1.15 (d J=6.4 Hz, 3H), 0.83 (s, 9H), 0.14 (s, 3H) 0.05 (s, 3H).^{13}C NMR (100MHz $CDCl_3$) ppm: 173.9, 139.6, 135.3, 135.2, 134.3, 131.1, 130.8, 129.2, 128.4, 89.8, 68.1, 58.5, 28.3, 26.0, 22.8, 18.1, -3.9, -5.7.

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- V Giornata della Chimica dell'Emilia Romagna, Bologna, 2 dicembre 2005.
- ISAOC 2004, Ischia Advanced School of Organic Chemistry, Ischia, 18 – 23 settembre 2004.