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Dipartimento di Chimica Organica e Industriale

Scuola di Dottorato in Scienze e Tecnologie Chimiche

Corso di Dottorato in Chimica Industriale - XXIV Ciclo - CHIM 06

STEREOSELECTIVE SYNTHESIS OF α-AMINO ACIDS β-SUBSTITUTED WITH A 4,5 DIHYDROISOXAZOLE NUCLEUS AND OF TERTIARY AND QUATERNARY ALLYLSILANES

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Anno Accademico 2010-2011

A Mamma e Papà,
con un grande grazie per l'amore, il supporto e l'incoraggiamento in questi tre anni.

PREFACE

During the second year of PhD, I spent six months at Bristol University, in Prof. Varinder Aggarwal's laboratory. In order to broaden my skills and competences in a wide science such as Organic Chemistry, there I developed a topic that was different from the one I was studying in Milan. For this reason, the thesis will be articulated in two principal parts (namely Section A and Section B) corresponding respectively to the work performed in Milan ("Stereoselective synthesis of α-amino acids β-substituted with a 4,5-dihydroisoxazole nucleus") an the one performed in Bristol ("Stereoselective synthesis of tertiary and quaternary allylsilanes").

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ABBREVIATIONS

Ac	acetyl	*J*	coupling constant
AcOEt	ethyl acetate	LDA	lithium di*iso*propylamide
Ar	Aryl	m	multiplet
9-BBN	9-borabicyclo[3.3.1]nonyl	Me	methyl
Boc	*tert*-butoxycarbonyl	mp	melting point
n-BuLi	*n*-butyllithium	MS	mass spectrometry
s-BuLi	*sec*-butyllithium	*n*	normal
t-BuLi	*tert*-butyllithium	NMP	N-Methylpyrrolidone
Cb	*N*,*N*-di*iso*propylcarbamoyl	NMR	nuclear magnetic resonance
δ	chemical shift	pin	pinacolate
D	doublet	PMHS	Polymethylhydrosiloxane
DIBALH	di*iso*butylaluminium hydride	PMP	*p*-methoxyphenyl
d.r.	diastereomeric ratio	ppm	parts per million
equiv.	equivalent	PPTS	Pyridinium *para*-toluene sulfonate
e.r.	enantiomeric ratio	q	quartet
Et	ethyl	rt	room temperature
FAB	fast atom bombardment	*t*	*tert*
HRMS	high resolution mass spectrometry	t	triplet
i	*iso*	THF	tetrahydrofurane
IR	infra-red	TMEDA	tetramethylethylenediamine

SECTION A

1 INTRODUCTION

β-Hydroxy-α-amino acids are an important class of amino acids. They are found within the twenty natural amino acids (threonine, serine, and β-hydroxy proline) and as constituents of more complex natural products. For example, β-hydroxy tyrosine and β-hydroxyphenylalanine derivatives are found in clinically important glycopeptide antibiotics, such as Vancomycin, discovered in 1956 by Eli Lilly, and Teicoplanin (Figure 1).[1, 2]

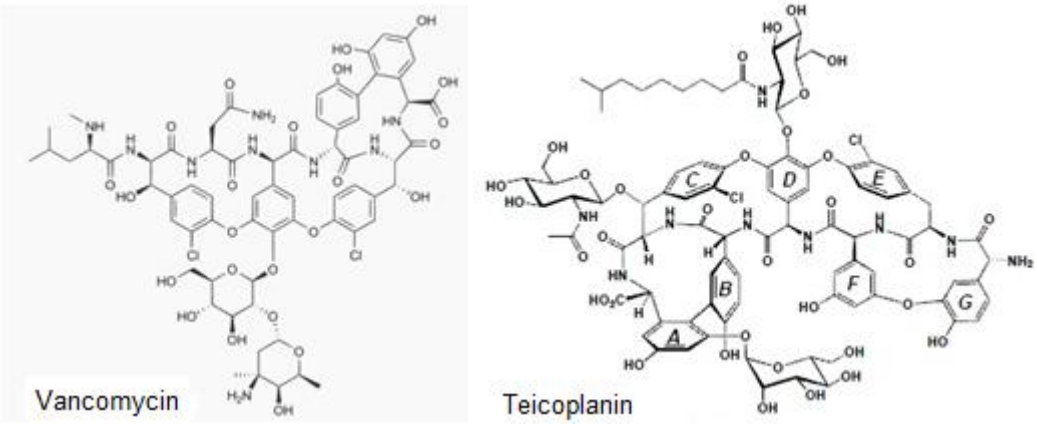


Figure 1: Structure of Vancomycin and Teicoplanin

Vancomycin and Teicoplanin are the progenitors of glycopeptides antibiotics and elucidation of their structures led to the development of new antibiotics.[2] Today, both Vancomycin and Teicoplanin are used in the treatment of patients infected with drug-resistant Gram-positive bacterial strains. Glycopeptides antibiotics are toxic for bacteria because they interfere with the synthesis of peptidoglycan layer of the bacterial cell wall. Peptidoglycan is a polymer consisting of sugars and amino acids that forms a mesh-like layer outside the plasma membrane of eubacteria. The sugar component consists of alternating residues of β-(1,4) linked *N*-acetylglucosamine (NAG) and *N*-acetylmuramic acid (NAMA) residues. Attached to the *N*-acetylmuramic acid is a peptide chain of three to five amino acids. The peptide chain can be cross-linked to the peptide chain of another strand forming the 3D mesh-like layer. Peptidoglycans serve an

important role in the bacterial cell wall, especially in Gram-positive organisms, giving structural strength as well as counteracting the osmotic pressure of the cytoplasm.

In Gram-positive bacteria the glycopeptides antibiotics easily diffuse through the peptidoglycan layer and reach the periplastic space where the peptidoglycan polymerization takes place. By binding onto the L-Lys-D-Ala-D-Ala tails of the monomers the antibiotic positions itself to inhibit the transglycosidase from joining the carbohydrate ends as shown in Figure 2.[2]

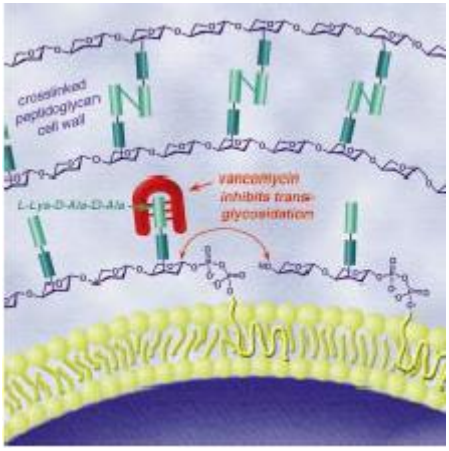


Figure 2: Mechanism of action of Vancomycin

Other β-hydroxy-α-amino acids can be found in antibiotics: D-threonine is present in Katanosins (Figure 3),[3, 4] while β-hydroxyleucine in lysobactin.[5] Both are highly active against Gram-positive bacteria that have shown resistance to Vancomycin.[6]

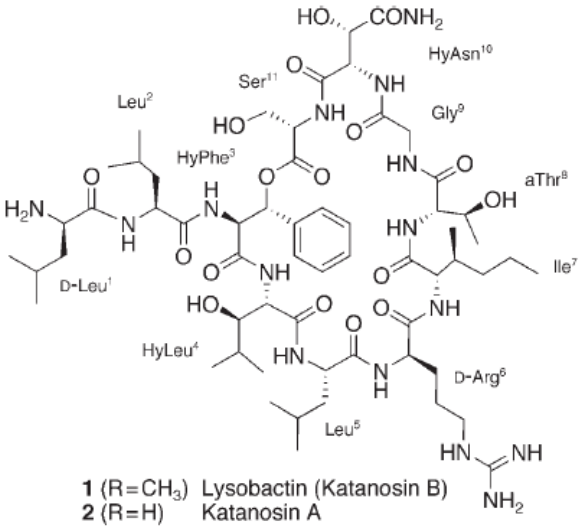


Figure 3: Structure of Katanosins A and B

Another β-hydroxy-α-amino acid, L-threo-β-(3,4 dihydroxyphenyl) serine, acts itself as a drug, being used in the treatment of Parkinson's disease.[7]

β-Hydroxy-α-amino acids have also played a key role in the synthesis of other important compounds. For example, Miller and co-workers[8] used β-hydroxy-α-amino acid **1** in the synthesis of carbacephem **2**, a β-lactam (Figure 4(a)), Vederas and co-workers[9] converted protect β-hydroxy-α-amino acids **3** into β-fluoro amino acids (Figure 4(b)) **4**, and Corey and co-workers[10] used a β-hydroxy-α-amino acids **5** as a chiral building block for the synthesis of α-Methylomuralide (Figure 4(c)).

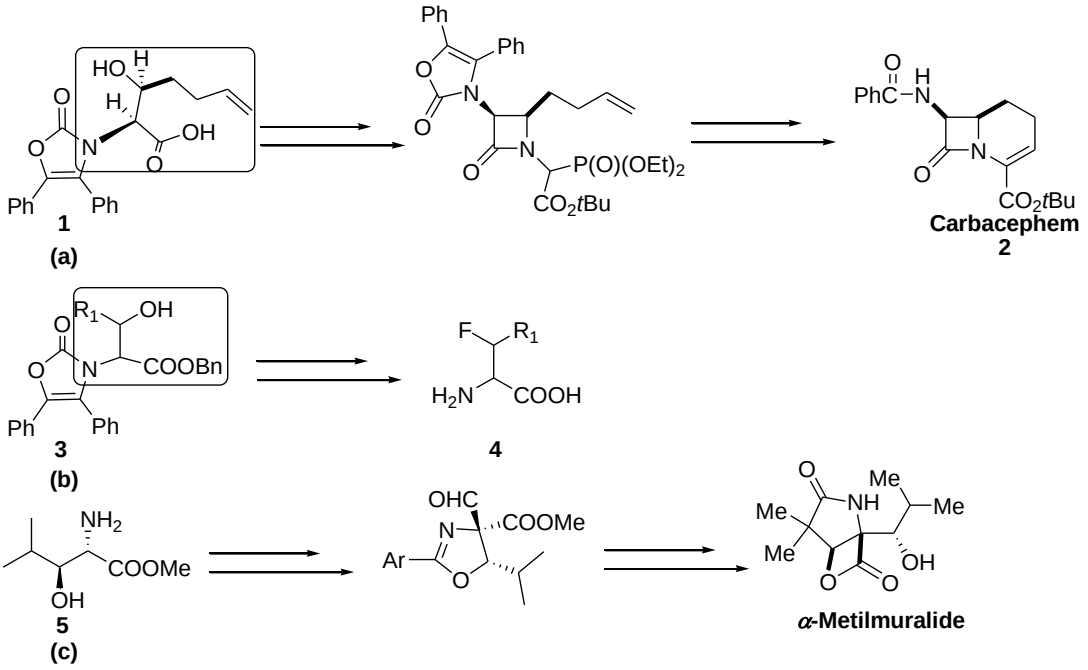


Figure 4: Use of β-Hydroxy-α-amino acids in synthesis

Within the twenty human amino acids, two of them, tryptophan and histidine, are *β*-substituted with an heterocyclic ring (Figure 5). Also in the natural product this is a common scaffold, and amino acid *β*-substituted with an heterocycle can be found, for instance, in the structure of (–)-Kaitocephalin (Figure 5),[11] a molecule active on glutamate receptors.

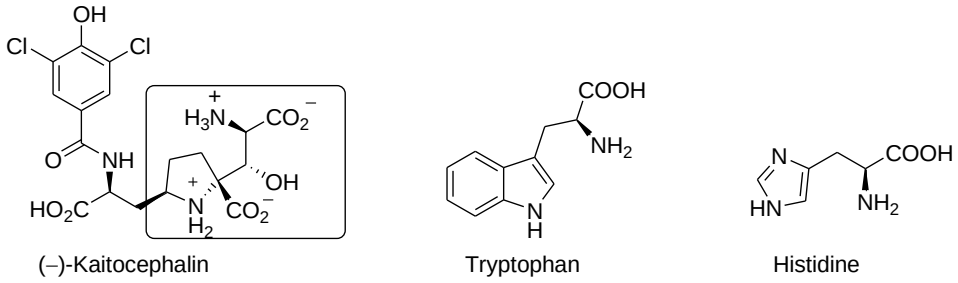


Figure 5: Structures of *α*-amino acids *β*-substituted with an heterocycle

Among the different heterocycles, isoxazole and isoxazoline rings play a pivotal in molecule that show activity towards glutamate receptors.[12-14] As shown in Figure 6, isoxazole ring is found in both agonists and antagonists of AMPA receptor, one of the ionotropic glutamate receptors.

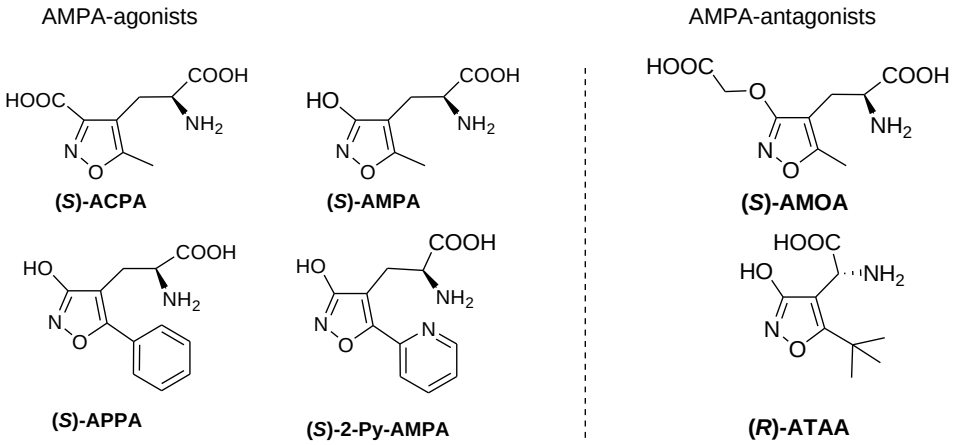


Figure 6: Structures of AMPA agonists and antagonists

The acidic amino acid glutamate (Glu) is the major neurotransmitter of the fast excitatory synapses in the central nervous system (CNS) and plays a key role in physiological processes ranging from learning and memory to control of movements and pain sensitivity.[15,16] Several mental diseases like epilepsy, cerebral ischemia, Parkinson and Alzheimer are due to overstimulation of Glu receptors by endogenous or exogenous substances. Glu activity is mediated by different type of receptor and for this reason it is really important to develop molecules that are selective only towards one type, in order to minimize the side effects. For example compounds **6** and **7** reported in Figure 7 show a neuroprotective activity, due to their action as antagonists of NMDA receptors, one of the ionotropic glutamate receptors.[17] In both molecules it is identifiable the chain of glutamate, one atom longer in the case of **6** and two in the case of **7**.

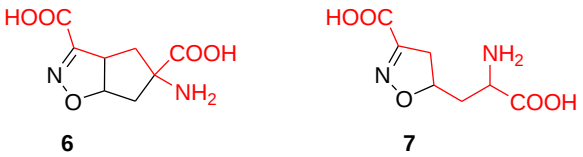


Figure 7: Molecules containing a Δ^2- isoxazoline ring that show activity as NMDA antagonists

1.1 Synthetic Methodologies for the Synthesis of β-Hydroxy-α-amino Acids

As a consequence of the essential role played by β-hydroxy-α-amino in biological systems and their utility as synthetic building blocks, a number of useful strategies have been devised for their preparation in enantiomerically pure form. These include Sharpless asymmetric epoxidation,[18-20] Sharpless asymmetric dihydroxylation,[21-23] electrophilic amination,[24] hydroxylation,[25] stereoselective hydrolysis of aziridine carboxylate esters,[26-30] and the aldol reaction.[31, 32] Among these methods, the focus of this section will be on aldol reactions of glycine equivalents with aldehydes. This reaction, in fact, provides an effective and direct access to β-hydroxy-α-amino acids derivatives, because the process involves the formation of a C-C bond and construction of vicinal stereogenic centres. There are two possible methods to synthesize enantiomerically pure β-hydroxy-α-amino acids through aldol reaction. One utilises a chiral catalyst, whilst the other uses a chiral auxiliary often build into the glycine equivalent.

A few elegant methods for the aldol strategy have been described employing only catalytic amount of chiral sources. In 1999 Corey and co-workers used the cinchonidine-derived bifluoride salt **8**, shown in Figure 8, as catalyst in the reaction between the silyl enol ether **9** and different aldehydes, obtaining the desired β-hydroxy-α-amino acids in good yield, good *d.r.* (up to 13:1 *syn*:*anti*) and excellent enantioselectivity (*e.e.*: 95%).[33]

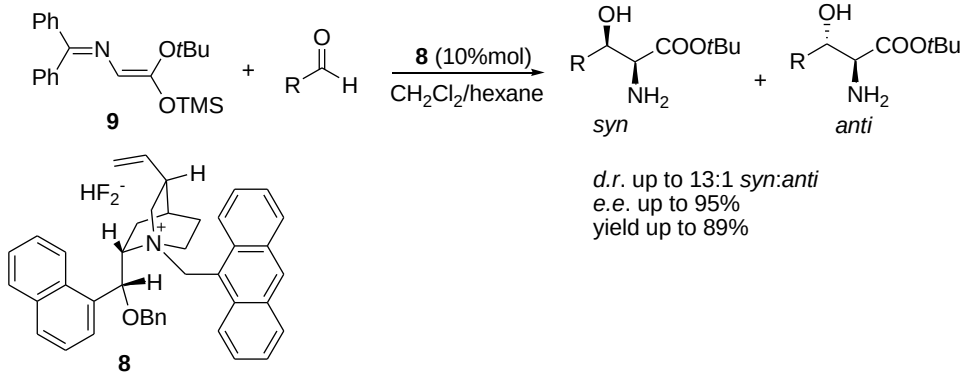


Figure 8: Corey's synthesis of β-hydroxy-α-amino acids

In 2001 Evans and co-workers reported the aldol reaction of aromatic aldehydes and 5-alkoxyoxazoles **10** catalyzed by the chiral aluminium complex **11** shown in Figure 9.[34] This methodology allows the synthesis of masked β-hydroxy-α-amino acids in excellent yield, *d.r.*(up to 99:1 *cis*:*trans*) and *e.e.* (up to 99%).

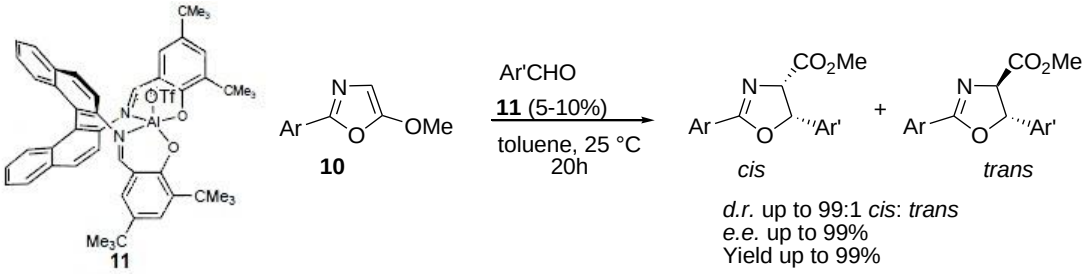


Figure 9: Evan's synthesis of masked β-hydroxy-α-amino acids

The first direct aldol condensation for the synthesis of β-hydroxy-α-amino acids was reported by Shibasaki in 2002.[35] Heterobimetallic asymmetric complex (***S*)-LLB** catalyzed the reaction between glycinate Schiff base **12** with different aliphatic aldehydes with a moderate *d.r.* (up to 86:14 *anti*:*syn*) and *e.e.* (up to 76% of the *anti* diastereoisomer) (Figure 10).

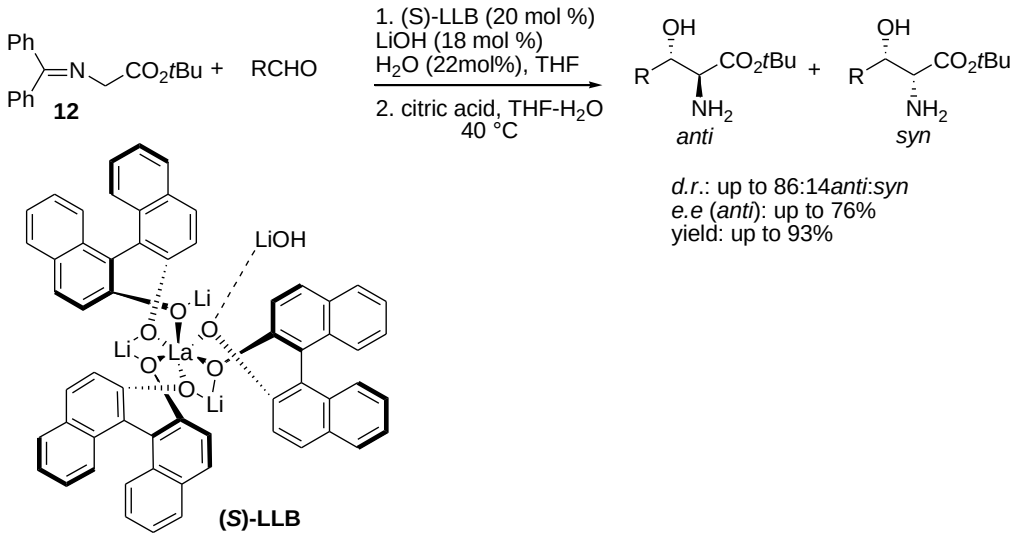


Figure 10: Shibasaki's synthesis of β-hydroxy-α-amino acids

A big improvement in the direct aldol reaction was made in 2004 by Maruoka and co-workers.[36] The use of their chiral phase transfer catalyst **13** under organic/aqueous biphasic conditions (Figure 11), provided the β-hydroxy-α-amino acids in excellent diastereoselectivity (96:4 *anti:syn* ratio) and enantioselectivity (*e.e.* 98%).

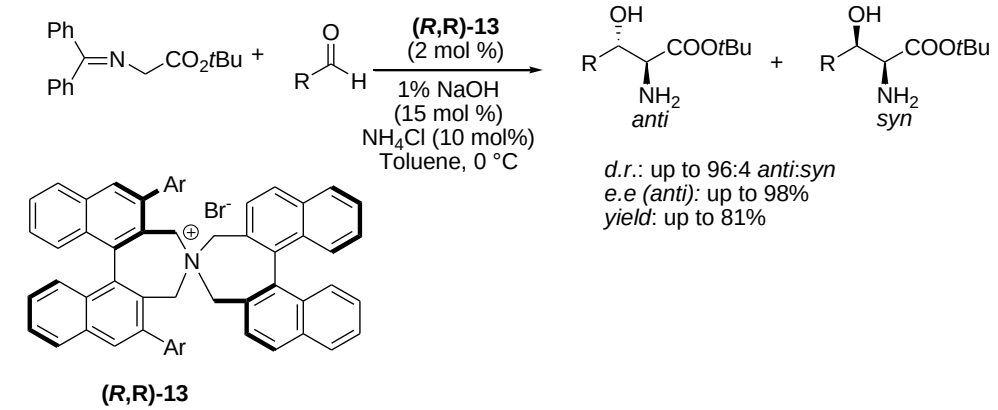


Figure 11: Maruoka's synthesis of β-hydroxy-α-amino acids

Another possibility for synthesizing β-hydroxy-α-amino acids involves an aldol type reaction between a chiral glycine synthon and an aldehyde. Several glycine chiral equivalent have been described in the literature.[37] Evans and co-workers were the first describing the chiral oxazolidinone **14** as a chiral glycine equivalent.[38] The isothiocyanate unit build in the molecule acts as a masked amino group, while the stereochemical control is provided by the oxazolidinone unit. The aldol reaction

between this chiral auxiliary and different aldehydes proved to be highly diastereoselective, providing the desired *syn* adduct in a *d.r.* up to 99:1.[38] Several *β*-hydroxy-*α*-amino acids were synthesized using this useful chiral auxiliary,[39-41] including MeBmt shown in Figure 12.[38]

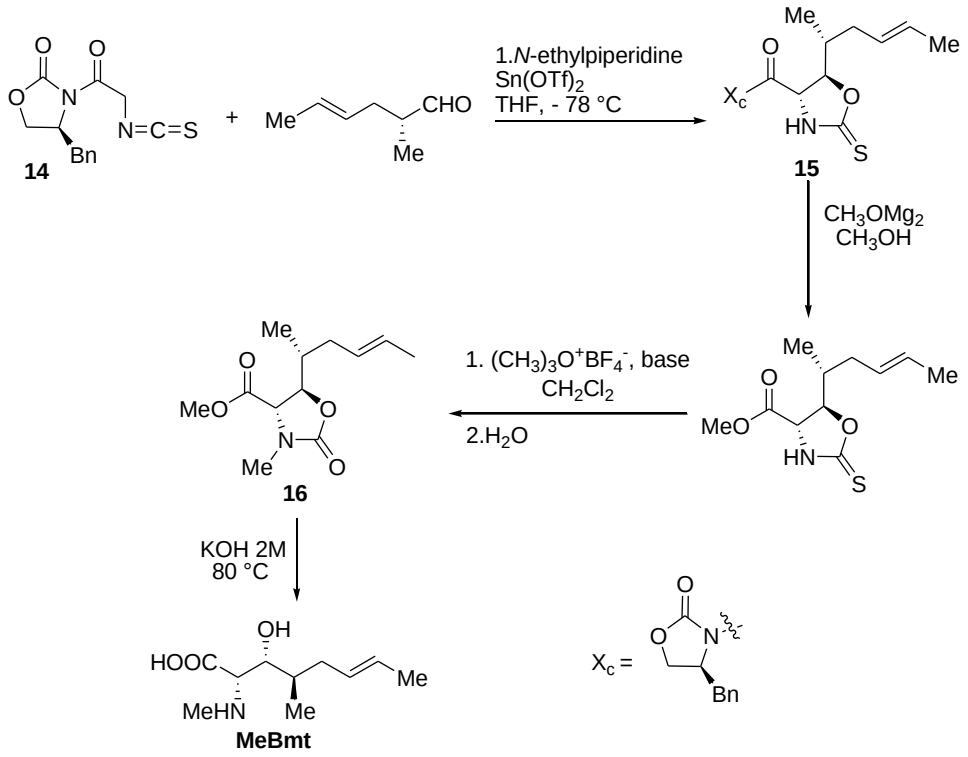


Figure 12: Evan's synthesis of MeBmt

Recently Frank[42] and co-workers proposed a modification of the isothiocyanate unit of oxazolidinone **14**. In fact in the reaction with aldehydes, the isothiocianate group reacts with the newly formed alcolate, providing the oxazolidin-2-thione **15**, that has to be hydrolysed in order to release the free *β*-hydroxy-*α*-amino acids. However hydrolysis is not a straightforward step, as prior transformation of the oxazolidin-2-thione **15** into the more easily hydrolyzed oxazolidin-2-one **16** is needed (Figure 12).[38] For this reason, in order to avoid laborious steps, Frank and co-workers envisaged that the isothiocyanate group could be replaced by an azido group. In particular they showed how the reaction between the enolate derived from azide **17**, and differently substituted aldehydes provided the *syn* aldol products **18** in good yield and diastereoselectivities (Figure 13). The transformation of the *β*-hydoxy-*α*-azido ester into the desired amino esters **19** is

more straightforward, requiring only the removal of thiazolidin-2-thione followed by the reduction of the azido group.

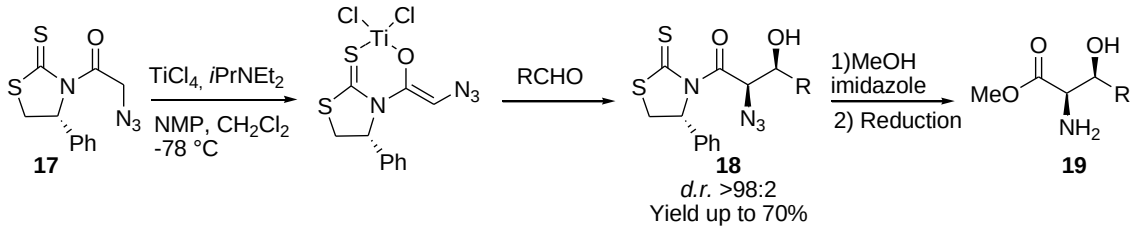


Figure 13: Frank's synthesis of β-hydroxy-α-amino esters

Xu and co-workers[43] developed an aldol reaction between aldehydes and the enolates of tricyclic iminolactones **20** and **21**, which are derived from natural (1*R*)-(+)-camphor as chiral glycine templates to generate optically pure β-hydroxy-α-amino acids in good yield and high diastereoselectivity (*d.r*. up to > 25:1) (Figure 14). The formation of just two of the four possible diastereoisomers is due to the exclusively *endo* addition of the nucleophile to the aldehyde with the C_{12}-methyl blocking the attack from the *exo*-face of the enolate. The β-hydroxy-α-amino acids was then easily released through an acid hydrolysis and the chiral auxiliary recovered in excellent yield.[43]

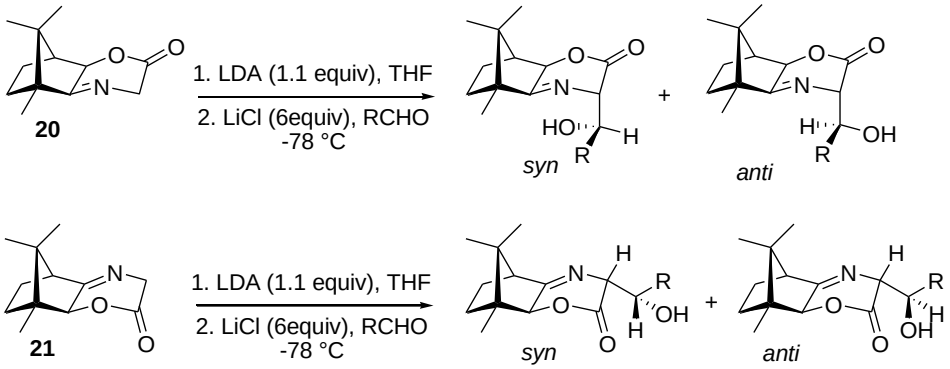


Figure 14: Xu's synthesis of precursors of β-hydroxy α-amino acids

Within the different chiral glycine equivalents, *Schöllkopf*'s bislactim ether **22** is particularly attractive because it has proved to be highly diastereoselective in aldol-type reactions and is commercially available in both enantiopure (*R*)- and (*S*)-forms.[44-46] *Schöllkopf*'s reagent is selectively deprotonated at C-2 providing the azaenolate **23** The attack of this latter to an electrophile compound, such as an alkyl halide, occurs only

from the face opposite to the isopropyl group, leading to products where C-2 and C-5 substituents are in trans relationship (Figure 15).

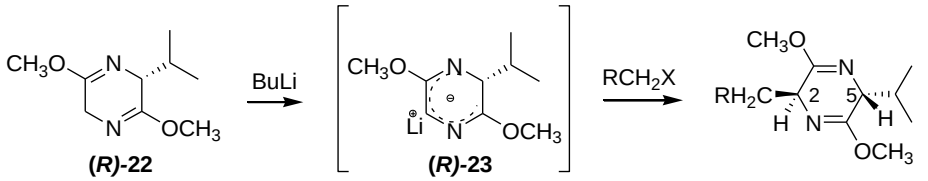


Figure 15: Reaction between *Schöllkopf's* reagent and alkyl halides

When the electrophile is a carbonyl group of an aldehyde, a second stereocenter is formed on C-1'. However, in this case the formation of the epimer 2,5-*trans*-2,1'-*syn* is preferred over the 2,5-*trans*-2,1'-*anti* ones (Figure 16).

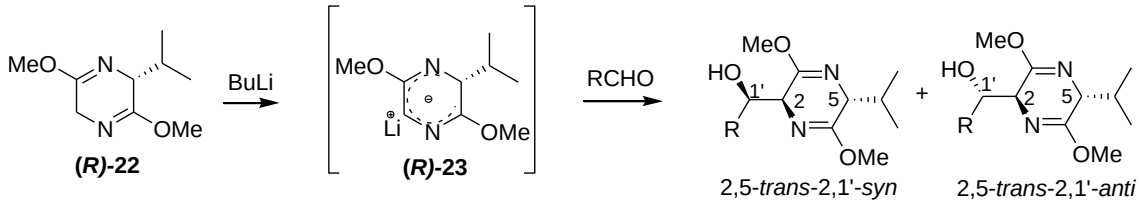


Figure 16: Reaction between *Schöllkopf's* reagent and aldehydes

This is due to a more favourable transition state, in which the aldehyde substituent is far from the methoxy group and from the metal atom (*Schöllkopf's* model) (Figure17).[44]

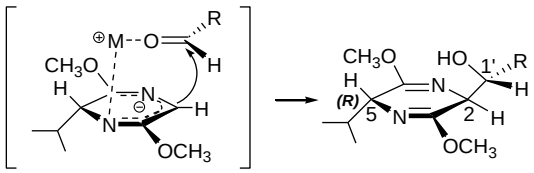


Figure17: *Schöllkopf's* model

The acid catalyzed opening of pyrazine ring leads to the formation of enantiomerically pure amino esters (alanines or serines) in high yields (Figure 18). At this stage the valinate methyl ester can be easily recovered through distillation and used to synthesise new *Shöllkopf's* reagent.

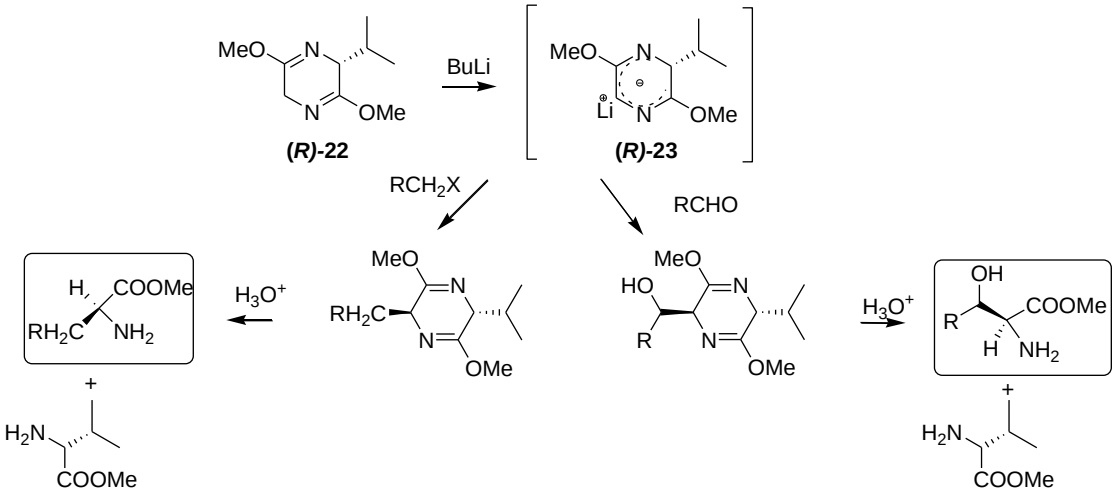
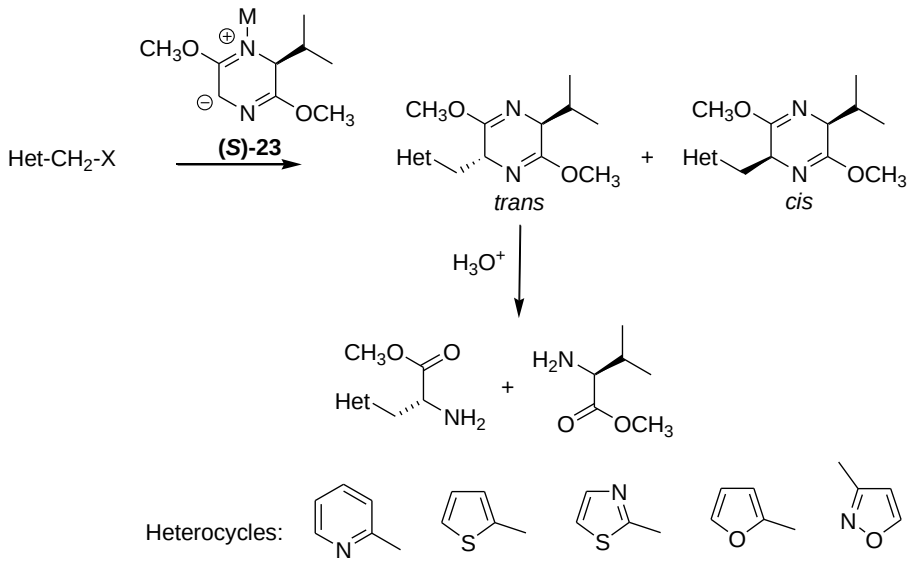


Figure 18: Synthesis of α-amino acids using *Schöllkopf's* reagent

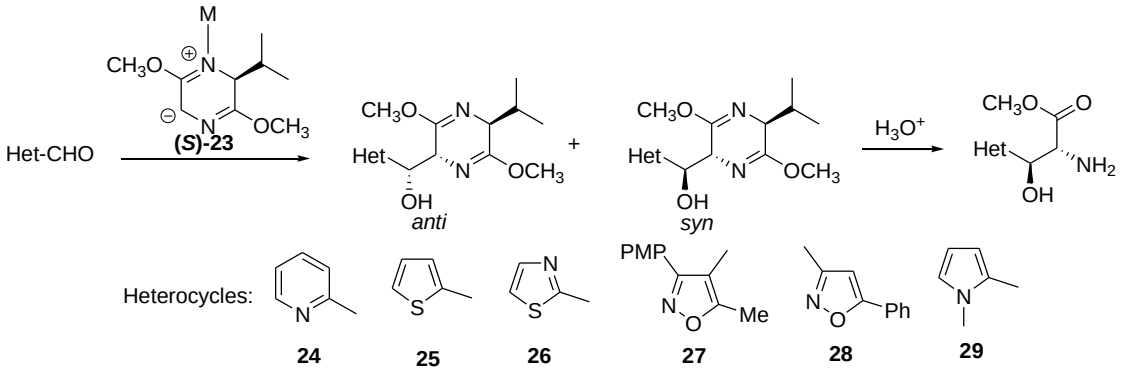
1.2 Previous Work Overview

The research group where I performed the PhD, has been interested for several years in the stereoselective synthesis of non-proteinogenic α-amino acids containing an heterocyclic ring using the *Schöllkopf's* reagent as chiral glycine equivalent. In particular, our early interest concerned the synthesis of alanine and serine type amino acids bearing in position 3 an heteroaromatic ring. Initial studies looked at the reaction between the *Schöllkopf's* reagent and halogenomethyl derivatives of heteroaromatic systems, as shown in Scheme 1.[47] The reaction proved to be highly stereoselective, providing only two of the four possible diastereoisomers with a *anti:syn* ratio of up to 91:9. This stereochemical outcome was explained considering the model shown before (Figure 15). The two adducts were easily separated through chromatographic column, to give, after the hydrolysis of pyrazine ring, enantiomerically pure 3-heteroaromatic-substituted-alanines.



Scheme 1: Synthesis of 3-heteroaromatic-substituted-alanines

In order to synthesise the more synthetically useful β-hydroxy-α-amino acids, we started studying the reaction between heteroaryl aldehydes and *Schöllkopf's* azaenolate **23**. Again just two of the four possible diastereoisomers were formed as shown in Scheme 2.[48] These products were epimers on the newly formed alcoholic carbon, while the C-2 and C-5 substituents maintained a *trans* relationship, as previously described.



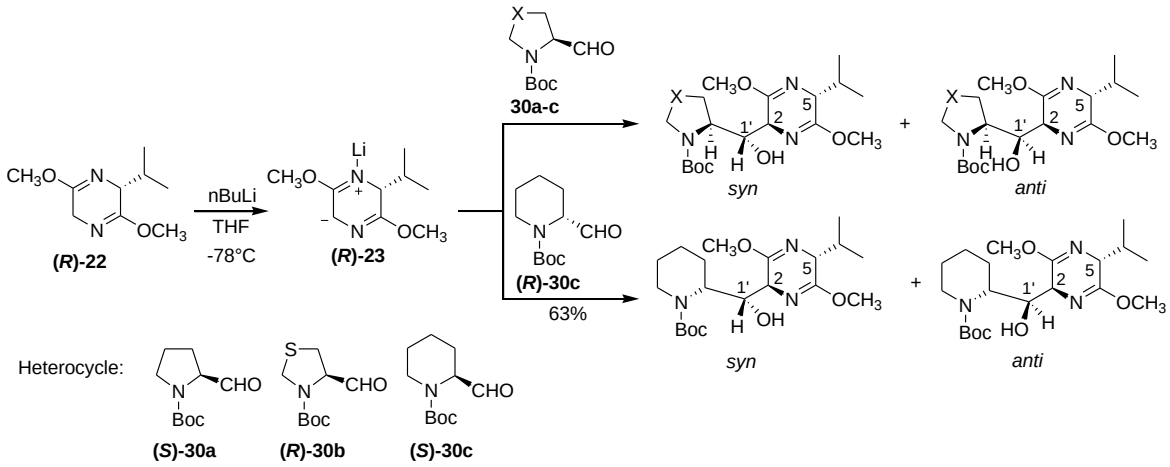
Scheme 2 Synthesis of β-hydroxy-α-amino acids β-substituted with an heterocyclic ring

Heterocycle	*anti*:*syn* ratio	Yield (%)	Counterion
24	90:10	17	Ti
25	65:35	26	Li
26	100:0	43	Ti
27	70:30	87	Ti
28	80:20	60	Ti
29	87:13	95	Ti

Table 1: Optimization of reaction of heteroaldehydes with *Schöllkopf*'s reagent

The *syn*/*anti* ratio depends on the nature of the counterion (Table 1). The titanium derivative of azaenolate **23** reacts with high diastereoselectivity giving a preference for *syn* attack product owing to a tight transition state[44] promoted by coordination of titanium to the aldehyde oxygen. Moreover, the predominance of the (*R*)-epimer of the alcoholic carbon atom comes from an energetically more favored transition state in which the aldehyde substituent R is far from the methoxy group and the metal atom.

To evaluate the effect of a stereocenter at the α position of the aldehyde on the stereochemical course of the reaction, we studied the reaction between *Schöllkopf's* reagent and non-aromatic enantiopure aldehydes **30a-c** (Scheme 3).[49]



Scheme 3: Reaction of *Schöllkopf's* reagent and non-aromatic enantiopure aldehydes

Entry	Aldehyde **30**	Counterion	Yield (%)	Ratio *syn:anti*
1	a	Li	66	75:25
2	a	Ti	31	84:16
3	b	Li	56	61:39
4	b	Ti	--	--
5	**(*S*)-30c**	Li	75	64:36
6	**(*S*)-30c**	Ti	27	51:49
7	**(*R*)-30c**	Li	63	64:36

Table 2: Optimization of the reaction between *Schöllkopf's* reagent and enantiopure aldehydes

Also in these cases both lithium and titanium were used as counterion. However, unlike the previous results,[48, 50] the diastereoselectivity was not enhanced except in one case (Table 2, entry 2) and at the expense of the yield. In the other cases, no reaction occurred in the presence of titanium (Table 2, entry 4), or it occurred with a decreased yield and, surprisingly, also less stereoselectivity (Table 2, entry 6). These findings differ from our previous results obtained using heteroaromatic aldehydes[48] and β-heteroaryl-α,β-unsaturated aldehydes,[50] presumably because, in this case, titanium may competitively interact also with the carbonyl group of the Boc-protecting group.

The stereochemical outcome at the C-1' and C-2 of the pyrazine ring is in line with the previous results[48,50] and the widely accepted model for the aldol-type addition of **22** to aldehydes (Figure17). As chiral aldehydes have diastereotopic carbonyl faces, the reactions of *Schöllkopf's* reagent with aldehydes **30a-c** raise the problem of "double asymmetric induction". In our case, the stereodifferentiation due to the chiral aldehyde (*substrate control*) clearly does not have a greater effect than *Schöllkopf's* pyrazine (*reagent control*) as both **(*S*)-30c** and **(*R*)-30c** lead to similar stereochemical results with a *syn*:*anti* ratio of 1.8:1 (Table 2 entry 5 and 7). This result was quite surprising, because, considering the transition states, we would have presumed a better diastereoselectivity for the reaction between **(*R*)-22** and **(*R*)-30c**. In this case, we predicted the major diastereoisomer would have derived from a positive combination of both Felkinh-Ahn[51] and *Schöllkopf* models (Figure 19, transition state A) whereas the minor diastereoisomer would have been the result of an unfavourable transition state, where the more cumbersome substituent is pseudoaxial (Figure 19, transition state B).

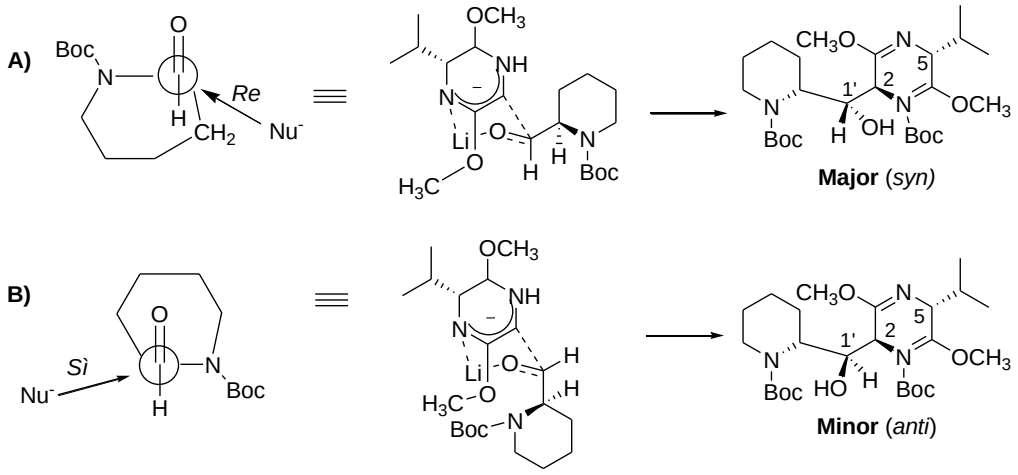


Figure 19: Models for the reaction between aldehyde **(*R*)-30c** and *Schöllkopf's* reagent

Conversely, we expected the reaction between **(*R*)-22** and **(*S*)-30c** should have been less diastereoselective because both the major (Figure 20, transition state A) and the minor (Figure 20, transition state B) diastereoisomers would have derived from *half-matched* transition states.[44]

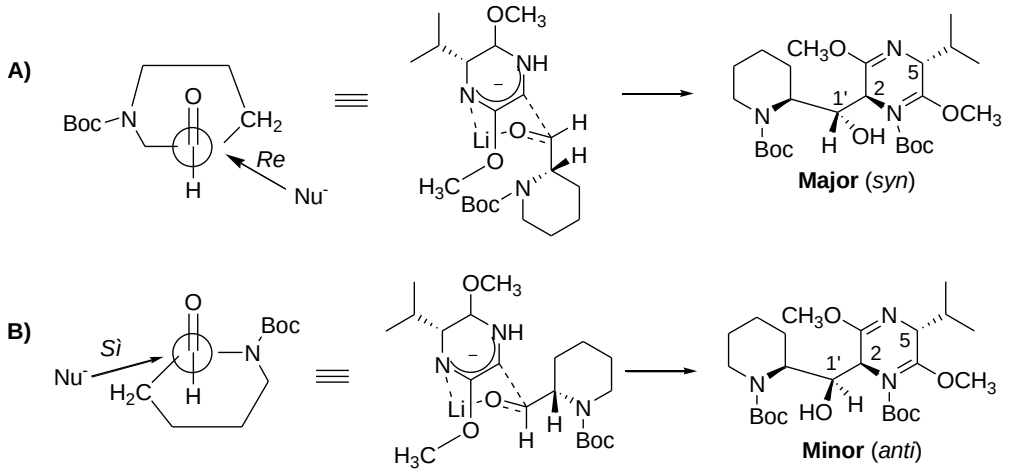
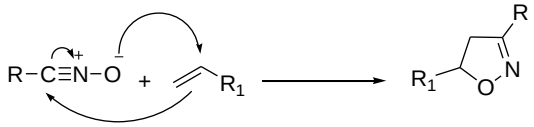


Figure 20: Models for the reaction between aldehyde **(*S*)-30c** and *Schöllkopf's* reagent

However, it is well-known that the lithium salts of the α-azaenolates are generally not very selective.[44,52,53] It is therefore very difficult to rationalise the observed stereochemical results fully. The only clear thing that can be deduced is that the azaenolate reacts through the standard *Schöllkopf* model.

More recently we have focus our attention on 4,5 dihydroisoxazole-3-carbaldehydes. The choice of this heterocycle stems from its peculiar features. In fact it is easy to synthesise through a 1,3-dipolar cycloaddition reaction between nitrile oxides and alkenes (Scheme 4).[54]

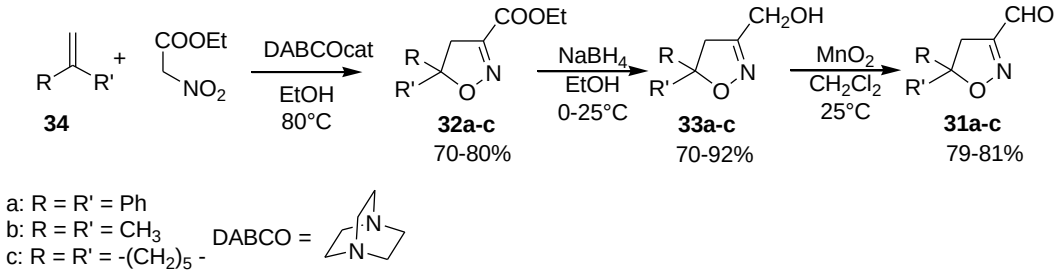


Scheme 4: Synthesis of Δ^2-isoxazolines through 1,3-dipolar cycloaddition

From the synthetic point of view, the 4,5-dihydro-isoxazole ring proves to be a very versatile heterocycle: in fact it can be converted into a number of useful synthetic units, such as *β*-hydroxy ketones[55-57] or *β*-amino alcohols,[58] depending on the experimental conditions used for reductive ring cleavage.

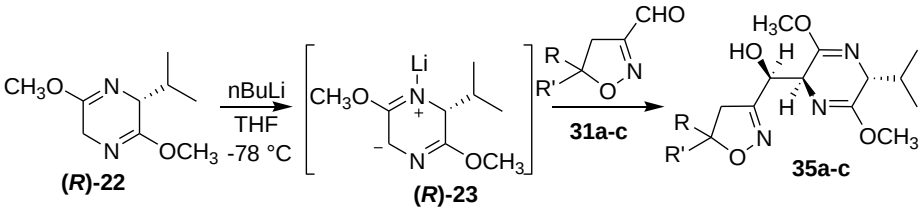
Initial studies concerned the reaction between *Schöllkopf*'s reagent and aldehydes **31a-c** 5,5-disubstituted with two identical groups.[59] The absence of a racemic stereocenter in the isoxazoline ring allowed us to minimise the total number of diastereoisomers that

result from the reaction with *Schöllkopf's* reagent. These substrates were synthesised according to a recently reported method[60] that involves a base-catalysed condensation between ethyl nitroacetate and alkenes **34** (*vide infra*). The methodology was extended to 1,1-disubstituted alkenes in this study.[59] The esters **32a-c** were then converted into the corresponding aldehydes (Scheme 5)



Scheme 5: Synthesis of aldehydes **31a-c**

Aldehydes **31a-c** underwent reaction with *Shöllkopf*'s anion **23** (Scheme 6), providing just two of the possible four diastereoisomers, with an excellent *d.r* as reported in Table 3. The reaction was extremely diastereoselective despite the use of lithium as counterion. The structures of the major diastereoisomers **35** were determined using NMR analysis and on the base of *Schöllkopf* model.

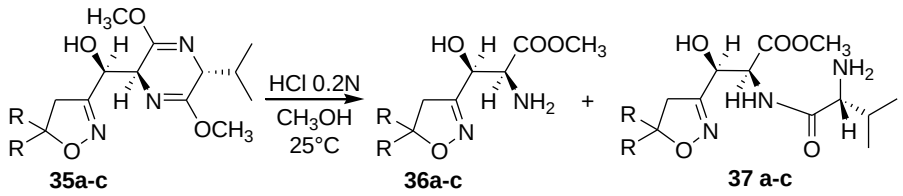


Scheme 6: Reaction between *Schöllkopf's* reagent and aldehydes **31a-c**

Aldehyde 31	Total yield (%)	*d.r.*
a	66	93:7
b	64	90:10
c	68	95:5

Table 3: Yields and *d.r* of the reaction between *Schöllkopf's* reagent and aldehydes **31a-c**

Adducts **35a-c** were hydrolysed under mild conditions, which allowed the isolation of the β-hydroxy-α-amino esters **36a-c** and the dipeptides **37a-c** (Scheme 7 and Table 4).



35a-c **36a-c** **37 a-c**

a: R = R' = Ph
b: R = CH_3
c: R = R' = -$(CH_2)_5$ -

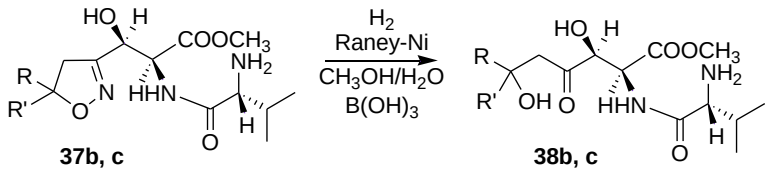
Scheme 7: Hydrolysis of pyrazine ring

35	**R**	Yield (%)	
		36	**37**
a	Ph	20	48
b	CH_3	20	63
c	-$(CH_2)_5$-	28	42

Table 4: Hydrolysis of pyrazine ring

The formation of these dipeptides was due to the partial hydrolysis of the pyrazine ring that often occurs during the hydrolysis reaction.[49,61-63] We were unable to avoid this despite changing solvent (methyl alcohol, acetonitrile or THF), temperature (from 0 °C to room temperature), the acid (HCl or TFA) or its concentration (from 0.2N to 2N). Products **36** and **37** were easily separated by means of column chromatography and their structure was assigned using exhaustive NMR analysis. Finally, we carried out a hydrogenolysis-hydrolysis of the 4,5-dihydroisoxazole ring of the amino esters **36** and of the dipeptides **37** using 1 atmosphere of hydrogen and Raney-Ni as the catalyst.[64] Hydrogenolysis of **36b** and **c**, was not successful due to a complete degradation of the starting material. The same result was observed using HCl instead of $B(OH)_3$ or Pd/C as a catalyst. On the contrary, cleavage of dipeptides **37b** and **c** allowed us to obtain the corresponding β,ε-dihydroxy-γ-oxo α-amino acid derivatives **38b** and **c** in good yields (Scheme 8). In no case we were able to detect any loss of stereochemical purity. These

α-amino acids derivatives have a highly functionalized structure which makes them extremely attractive as potential peptidomimetics.



37b, c

38b, c

68-86%

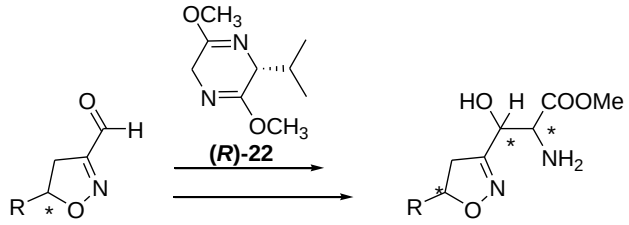
b: R = R' = -$(CH_2)_5$ -
c: R = R' = CH_3

Scheme 8: Synthesis of polifunctionalized dipeptides through Δ^2-isoxazoline ring opening

1.3 PhD Thesis Program

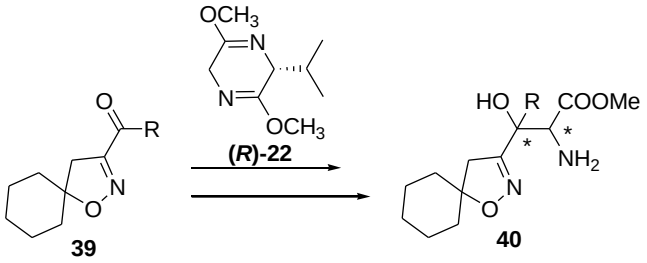
In connection with previous results and with the aim of synthesizing new β-hydroxy-α-amino acids β-substituted with an isoxazoline ring, the program of this PhD thesis tackles the following points:

A) Study of the synthesis of enantiomerically pure 5-substituted-Δ^2-isoxazoline-3-carbaldehydes and of the reaction with *Schöllkopf's* reagent **(*R*)-22** in order to obtain β-hydroxy-α-amino acids with a supplementary stereocenter on isoxazoline ring (Scheme 9).



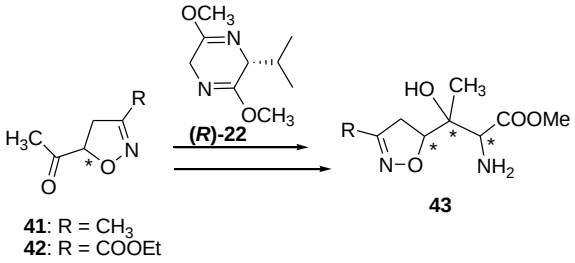
Scheme 9: Reaction between *Schöllkopf's* reagent and 5-substituted-Δ^2-isoxazoline-3-carbaldehydes

B) Extention of the methodology to the more challenging reaction between *Schöllkopf's* reagent **(*R*)-22** and 3-acyl-Δ^2-isoxazolines. In particular initially we will focus our attention on achiral ketones as **39** (Scheme 10). The presence in position 5 of the isoxazoline of two identical groups, avoids the doubling of the number of the stereoisomers in the reaction with *Schöllkopf's* reagent. After reaction with *Schöllkopf's* reagent and hydrolysis of pyrazine ring, β-hydroxy-α-amino acids **40**, with a β quaternary stereocentre, will be obtained (Scheme 10). The choice of different R groups on the ketones is made in order to evaluate the steric encumbrance on diastereoselectivity.



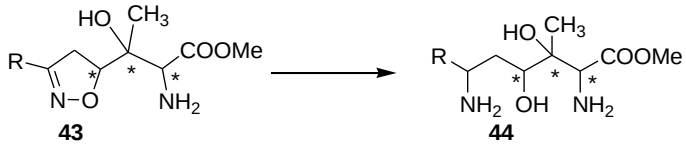
Scheme 10: Synthesis of β-hydroxy-α-amino acids through reaction between *Schöllkopf's* reagent and 3-acyl-Δ^2-isoxazolines

C) Further investigation of the reaction with ketones bearing an acetyl group in position 5 of isoxazoline ring. The presence of a stereocenter in the molecule will require the investigation of a suitable method to obtain 5-acetyl-Δ^2-isoxazolines **41** and **42** as single enantiomers before reaction with *Schöllkopf's* reagent **(*R*)-22** (Scheme 11).



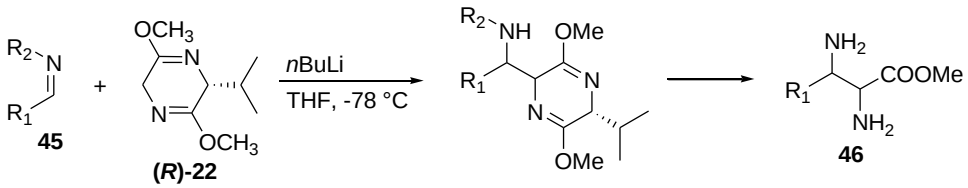
Scheme 11: Synthesis of β-hydroxy-α-amino acids through reaction between *Schöllkopf's* reagent and 5-acetyl-Δ^2-isoxazolines

D) Study of the best cleavage conditions of Δ^2-isoxazolines, in order to use them in the cleavage of more complex substrates as **43** to obtain polifunctionalized β-hydroxy-*a*-amino acids **44** (Scheme 12).



Scheme 12: Synthesis of polifunctionalized β-hydroxy-α-amino acids through isoxazoline ring opening

E) Preliminary study will be run on the reaction between simple imines **45** and *Schöllkopf* reagent (***R*)-22** (Scheme 13). This will allow us to obtain, after pyrazine cleavage, α,β-diamino acids **46**.

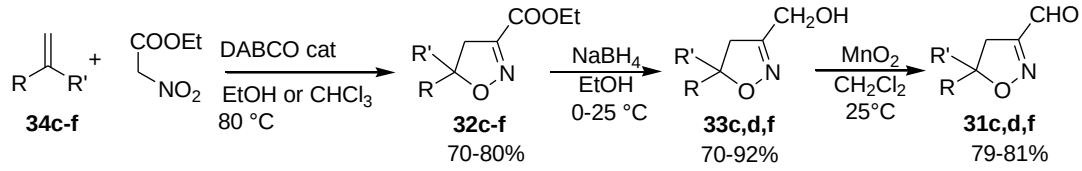


Scheme 13: Study of the reaction between imines and *Schöllkopf's* reagent

2 RESULTS AND DISCUSSION

2.1 Synthesis of 4,5-Dihydroisoxazole-3-carbaldehydes 31c, d, f

As previously mentioned, aldehyde **31c** was synthesised starting from the corresponding ester **32c** obtained by means of a base-catalysed condensation between ethyl nitroacetate and methylencyclohexane in accordance with a recently reported method.[60] The same methodology was also applied in the synthesis of new isoxazolines **31d-f** monosubstituted in position 5. According to the described procedure, a mixture of alkene **34c-f** and ethylnitroacetate reacted in presence of DABCO to give the desired isoxazolines in excellent yields and with total regioselectivity (Scheme 14 and Table 5). The esters **32c, d, f** were converted into the corresponding aldehydes **31** through a reduction[65]-oxidation sequence (Scheme 14 and Table 5).



c: R = R'= -$(CH_2)_5$-
d: R = -C_6H_{11}, R' = H
e: R = Py, R' = H
f: R = Ph, R' = H

DABCO =

Scheme 14 Synthesis of aldehydes **31c,d,f**

	32 (%)	33 (%)	31 (%)
c	70	89	79
d	77	77	60
e	55		
f	84	94	83

Table 5: Yields of esters **32**, alcohols **33** and aldehydes **31**

The proposed mechanism by De Sarlo and co-workers, reported in Figure 21, discards the formation of nitriloxide as intermediate.[60] The tertiary amine, present in the reaction in a catalytic amount, promotes the dehydration of the nitrocompound that is already formed upon addition to alkene (intermediate α).

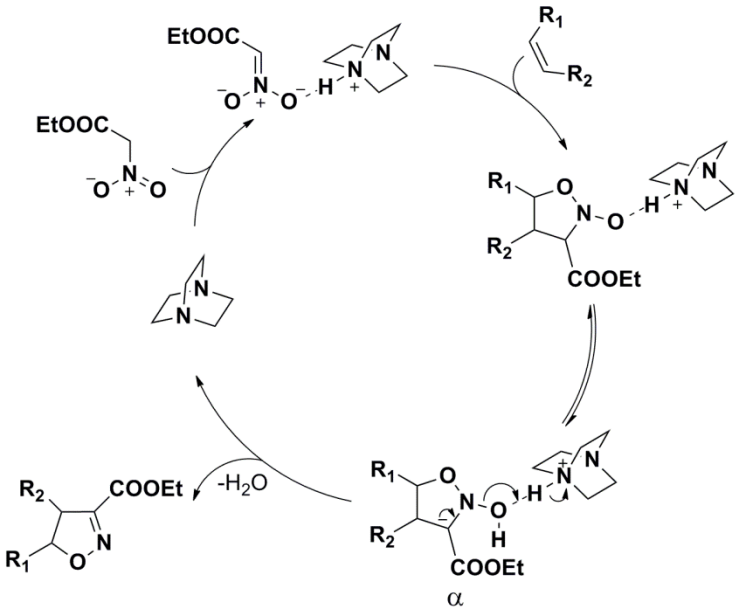
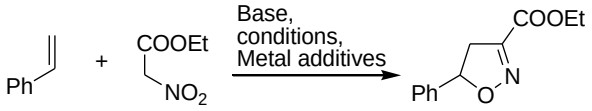


Figure 21 Proposed mechanism for the synthesis of Δ^2-isoxazolines *via* base-catalyzed condensation reaction

2.2 Synthesis of Enantiomerically Pure 5-Phenyl-4,5-dihydroisoxazole-3-carbaldehyde 31f

2.2.1 **Organocatalyzed Synthesis**

In order to minimize the number of diastereoisomers deriving from the reaction between *Schöllkopf's* reagent and aldehyde **31f**, it was necessary to study an enantioselective synthesis of it. Because of the good results obtained with the base catalyzed reaction between styrene and ethyl nitroacetate (Scheme 14), we thought that the use of a chiral tertiary amine could preferentially form a single enantiomer. However the temperature required for this reaction (60-70 °C) doesn't match with a possible organocatalysis. Therefore we started studying the feasibility of the reaction at lower temperature using DABCO as base. As shown in Table 6 the reaction run at room temperature doesn't afford the desired product (Table 6 entry 2), neither when it is carried out using ultrasound or molecular sieves in order to try to shift the dehydration equilibrium (Table 6, entry 3 and 4).



34f **32f**

Entry	Solvent	T(°C)	t (h)	Base (0.2%)	Metal additive	Yield(%)	α_D	Conditions
1	$CHCl_3$	80	72	DABCO	-	70	-	-
2	$CHCl_3$	20	120	DABCO	-	0	-	-
3	$CHCl_3$	30	48	DABCO	-	4	-	ultrasound
4	$CHCl_3$	20	144	DABCO	-	0	-	molecular sieves
5	$CHCl_3$	80	24	Quinine	-	10	0	-
6	$CHCl_3$	20	120	Quinine	-	2	74.5	-
7	$CHCl_3$	20	144	Quinine	$Cu(OAc)_2$	0	-	-

Table 6: Attempts of synthesis of enantiomerically pure **32f** using organocatalysis

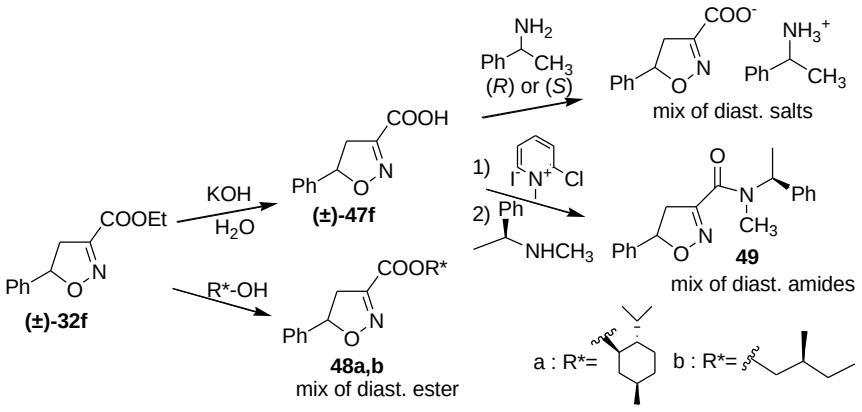
Despite these results, we tried to use quinine as chiral base. When the reaction was

carried out at 80 °C, the product was isolated, racemic, in 10% yield (Table 6, entry 5). The reaction at room temperature led to the formation of trace of product that was optically active (Table 6, entry 6). However because the results were not encouraging we used other approaches to obtain the isoxazoline **31f** as single enantiomer.

2.2.2 **Classical Chemical Resolution**

Our next approach was to use classical chemical resolution. Through the transformation of the two enantiomers into separable diastereoisomers we could obtain the enantiomerically pure **31f**. We tried three different procedures, in order to obtain a mixture of diastereoisomeric salts, amides or esters as shown in Scheme 15. Firstly ester **32f** was hydrolysed to the corresponding carboxylic acid[66] **47** and this was treated with (*R*)- or (*S*)-1-phenyl-ethylamine. However the resulted diastereoisomeric salts were not separable by crystallisation under a number of different solvent condition.

Ester **32f** was then transformed into a couple of diastereoisomeric esters **48a,b** by means of trans-esterification with different chiral alcohols such as L-menthol or (*S*)-2-methyl-1-butanol. However it was not possible to separate the obtained diastereoisomeric mixtures by chromatography. The same problem was encountered in transforming acid **47**, after activation by the *Mukaiyama's* reagent, into a couple of diastereoisomeric amides **49** by means of a reaction with (*S*)-methyl-(1-phenyl-ethyl)-amine.

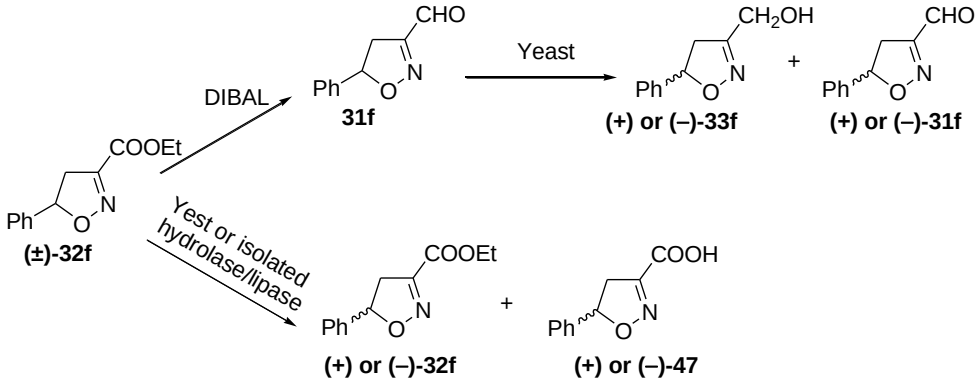


Scheme 15: Attempts of classical chemical resolution of **(±)-32f**

2.2.3 **Enzimatic Resolution**

After these approaches to enantiomers separation, we directed our attention to an enzymatic resolution. This work was conducted in collaboration with Dott.ssa Gandolfi from Dipartimento di Scienze Molecolari Applicate ai Biosistemi that provided us the more suitable microorganisms or enzymes.

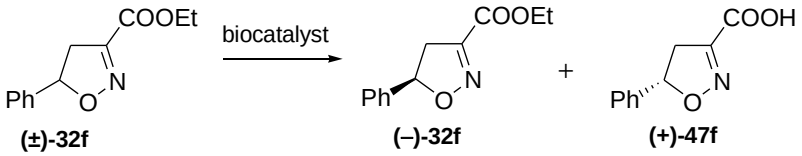
To obtain the enantiomerically pure aldehyde **31f** it is possible to use two different biocatalytical approaches based on kinetic resolution: the reduction of aldehyde **(±)-31f** catalysed by yeasts or the hydrolysis of ester **(±)-32f** operated by the same microorganisms or isolated hydrolases (Scheme 16)



Scheme 16: Enzimatic startegies for resolution of **(±)-32f**

In the case of aldehyde reduction, the fifteen yeasts of different species used showed good activity but the alcohol **33f** was obtained in racemic mixture.

The hydrolysis of ester **(±)-32f** was preliminary screened using different types of microorganism or enzymes known to be able to hydrolyze racemic esters in good selectivity.[67] All the biocatalysts tested hydrolysed the substrate with a good rate, but only pancreatic porcine lipase (PPL), *Pichia etchellsii* MIM and *Saccaromyces cerevisiae* Zeus enantioselectively hydrolysed the ester function of **32f** (Table 7). Evaluation of the progress of the reaction showed that the enantiomerically pure ester could only be obtained by driving the reaction over 50% of molar conversion (Table 7).



(±)-32f **(–)-32f** **(+)-47f**

Biocatalyst	e.e. 32f	e.e. 47f	Molar conversion (%)	E[a]	Time
PPL	60	75	44	12	30 min
PPL	96	52	65	11	45 min
Pichia etchellsii MIM	44	47	48	4.2	2 h
Pichia etchellsii MIM	70	45	61	5.3	3.5 h
Saccharomyces cerevisiae Zeus	23	46	33	3,4	4 h
Saccharomyces cerevisiae Zeus	92	33	74	5.7	24 h

[a] Conversion and enantioselectivity factor (E) were calculated from the ee of the substrate and the product

Table 7: Screening of biocatalysts for enzymatic hydrolysis of **(±)-32f**

The best results were obtained using PPL, which was also most active at a low concentration (5 gL^{-1}).[68] In this case it was possible to obtain the enriched unreacted ester **(–)-32f** with 65% of molar conversion and 96 % *e.e.* The absolute configuration of ester **(–)-32f** was not assigned at this stage, but was determined by means of X-ray analysis of the major adduct obtained after reaction with *Schöllkopf*'s reagent (*vide infra*) and proved to be (5*R*). Ester **(−)-32f** was then reduced by sodium borohydride[65] into the alcohol **(−)-33f**, and oxidation of the latter with manganese dioxide led to aldehyde **(−)-31f** (Scheme 14).

The *e.e.* obtained using PPL was quite surprising, considering that the stereocentre is far from the functionality that is subjected to the action of the enzyme. For this reason we were interested in studying the influence of the substituent in position 5 of isoxazoline. In particular we envisaged to maintain the six member ring and, taking in consideration the commercial availability of alkenes necessary to synthesize the isoxazolines, we prepared the esters **32d** and **32e** (Figure 22) as previously described (see Scheme 14). In

this way we could evaluate the influence of a non planar ring as ciclohexyl and, through the isoxazoline substituted with pyridine, the influence of an heteroatom in the cycle.

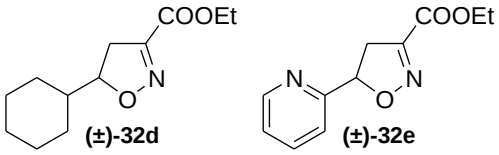
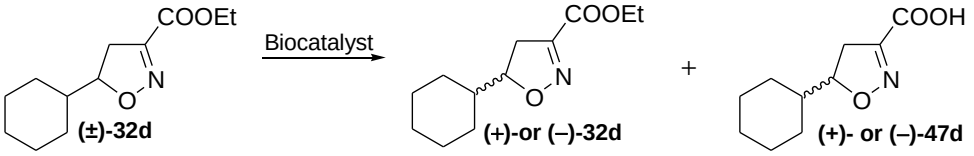


Figure 22: Structure of esters **(±)-32d** and **(±)-32e**

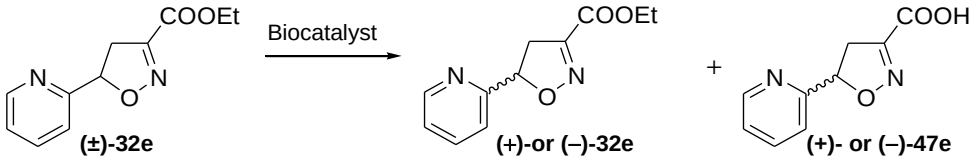
Different microorganisms were used in the hydrolysis of esters **32d**,**e**. Some of them proved to be able to hydrolyze the esters with a high reaction rate, even employing a very low concentration of biocatalyst, but unfortunately without any enantioselectivity. The only positive result in term of racemate resolution was obtained using *Saccharomyces cerevisiae* Zeus. Table 8 and Table 9 show how by using this yeast and stopping the reaction after 50% of molar conversion, we were able to obtain the esters **32d**,**e** and the corresponding acids **47d,e** enantiomerically enriched. The presence of R substituent in position 5 with different geometry and electronic properties than phenyl seems to influence the selectivity. In fact if we consider the *e.e* of the leftover ester after 24 hours, in the case of **32d** and **e**, this is lower than the one of **32f** (see also Table 7). Moreover in the case of ester **32e** we observed a very low hydrolysis rate, presumably due to the presence of the heteroatom in the cycle, that may cause a change in the polarity of the molecule making the substrate less accessible to the enzymes.



Biocatalyst	e.e. 32d	e.e. 47d	Molar conversion[a] (%)	E[a]	Time
S. cerevisiae Zeus	10	37	21	2.4	2.5 h
S. cerevisiae Zeus	12	28	30	2	4 h
S. cerevisiae Zeus	81	37	69	5	24 h

[a] Conversion and enantioselectivity factor (E) were calculated from the ee of the substrate and the product

Table 8: Optimization of hydrolysis reaction of **(±)-32d** with S.*cerevisiae* Zeus



Biocatalyst	e.e. 32e	e.e. 47e	Molar conversion[a] (%)	E[a]	Time
S. cerevisiae Zeus	8	12	14	1.3	2 h
S. cerevisiae Zeus	15	39	28	2.6	17 h
S. cerevisiae Zeus	28	46	38	3.5	24 h
S. cerevisiae Zeus	54	61	47	7.0	48 h
S. cerevisiae Zeus	61	56	52	6.4	72 h

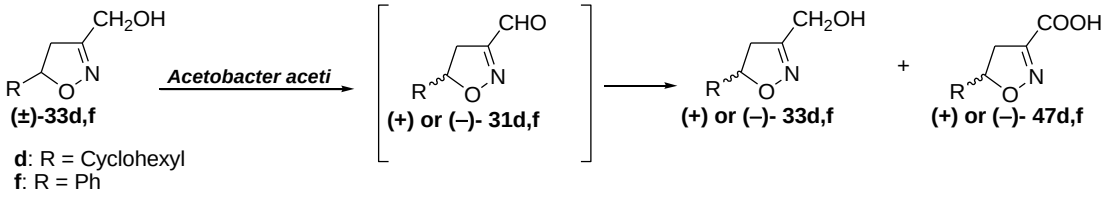
[a] Conversion and enantioselectivity factor (E) were calculated from the ee of the substrate and the product

Table 9: Optimization of hydrolysis reaction of **(±)-32e** with S.*cerevisiae* Zeus

The enantiomeric excess and molar conversion were determined through chiral HPLC.

After having studied the reaction of hydrolase on esters **33d-f**, being again supported by Dott.ssa Gandolfi, we wanted to explore if biocatalysts could selectively oxidize alcohols **33d, f** to the corresponding acids (Scheme 17). In particular we were interested in testing as biocatalyst whole cells of *Acetobacter aceti* MIM 2000/28 In fact this microorganism, isolated in Dott.ssa Gandolfi's laboratories, showed previously a certain efficiency in the transformation of primary alcohols.[69, 70] *Acetobacter aceti* oxidizes the

alcohols into the corresponding acids in two steps: in the first one the enzyme alcohol dehydrogenase (ADH) converts the alcohol into the aldehyde **(+)**- or **(–)-31d,f** that is subsequently transformed into the corresponding acid by aldehyde dehydrogenase (ALDH) (Scheme 17).



Scheme 17: Enzimatic oxidation of **(±)-33d,f**

The reactions were carried out in water using *Acetobacter aceti* grown 48 hours. Table 10 summarizes the results obtained for the oxidation of **33f**: the acid **47f** was obtained with a very high *e.e.*, while the leftover alcohol is racemic. Because, as previously said, the oxidation proceeds through two steps, we can hypothesize that the stereoselective one is the oxidation of the aldehyde to the acid.

Entry	e.e. 33f	e.e. 47f	Time
1	8	98	3 h
2	11	98	6 h
3	17	98	24 h
4	22	98	72 h

Table 10: Optimization of enzymatic oxidation of **(±)-33f**

A similar outcome was observed for the alcohol **33d** bearing a cyclohexyl in position 5. Table 11 shows that also in this case the acid **47d** is obtained with a good e.e (even if lower than the corresponding 5-phenyl-Δ^2-isoxazoline **47f**) while, similarly as before the leftover alcohol is racemic.

Entry	e.e. 33d	e.e. 47d	Time
	3	86	6 h
	4	83	24 h
	2	86	48 h

Table 11: Optimization of enzymatic oxidation of **(±)-33d**

In both cases it was not possible to isolate the intermediate aldehydes **31d,f** and therefore evaluate their *e.e.* For this reason it was not possible to evaluate the conversion of the reaction. However the HPLC traces run after 72 hours and 48 hours, showed a large amount of leftover alcohol, suggesting that the reaction proceded very slowly. This may be due to the accumulation of the intermediate aldehydes **31d,f**, that, even in small amount, are toxic for the microorganism and may cause an inhibition of the enzymatic activity.

2.3 Synthesis of 3-Acyl-4,5-dihydroisoxazoles 39a-d

For the synthesis of compounds **39a-d**, we envisaged three possible retrosynthetic approaches described in Figure 23.

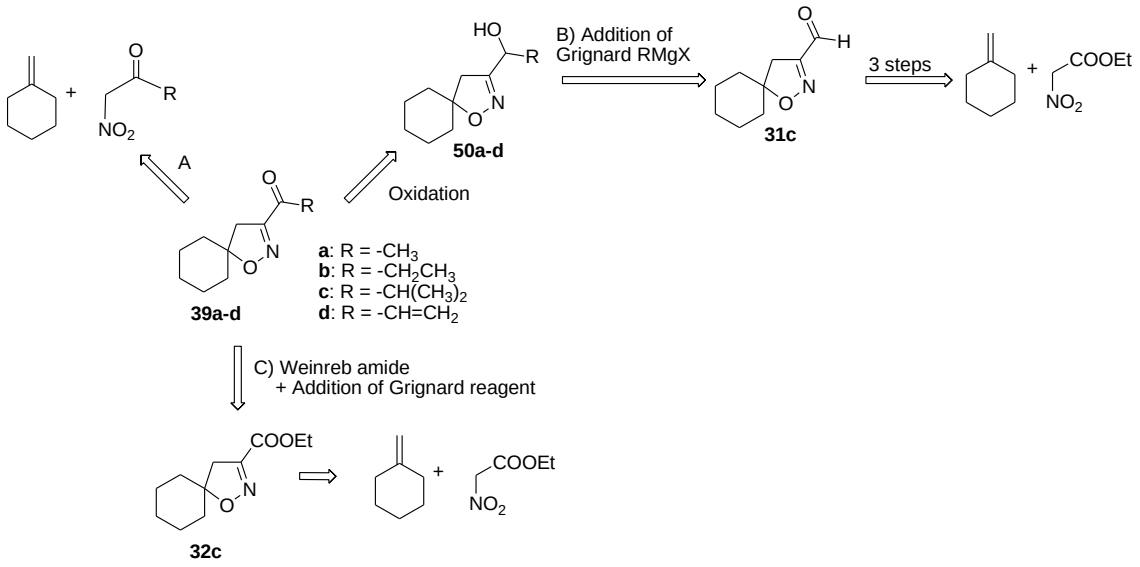
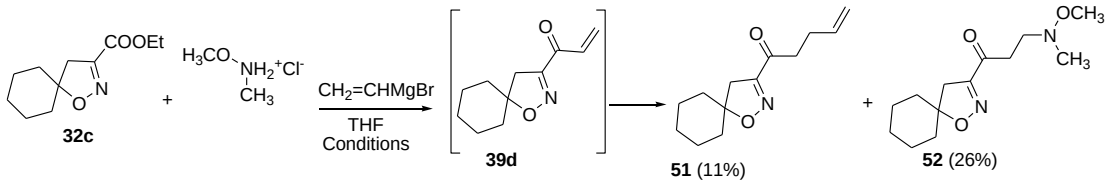


Figure 23: Retrosynthetic approaches for the synthesis **of 39a-d**

The synthesis of **39a-d** by strategy A was based on the cycloaddition between methyleneciclohexane and different nitro ketones. However these latter compounds are not commercially available and requires a four step synthesis to be obtained.[71] In the strategy B the key intermediate aldehyde **31c**, could undergo reaction with various Grignard, providing the alcohols **50a-d** with different R group. Oxidation would give the corresponding ketones. This strategy, however, required 5 steps synthesis. The third possibility (C) envisaged the direct conversion of the ester of the isoxazoline **32c** into the ketone via the corresponding Weinreb amide. This strategy was the more appealing because it would allow the synthesis of ketones **39a-d** in just two steps.

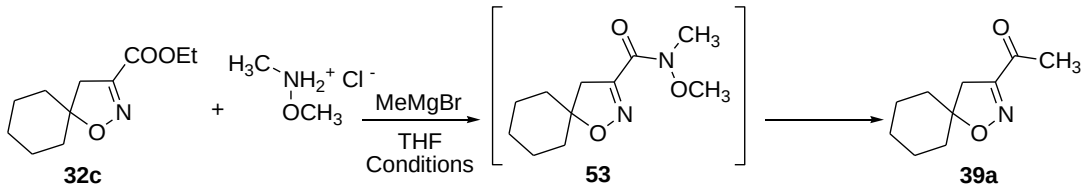
Our investigations started using strategy C with significant results summarized in Table 12. Initially we thought that converting one pot the isoxazoline **32c**, into the corresponding vinyl ketone **39d** without isolating Weinreb amide would have been advantageous. For this reason we used an excess (8.3 equivalents) of vinylmagnesium bromide,[72] which would act to neutralize the HCl salt and to deprotonate the amine

itself, and then act as nucleophile once the intermediate amide as been formed. The desired product **39d** was not formed but instead from the complex reaction mixture, **51** was isolated in 11% yield. This compound derived from the attack of one molecule of vinyl magnesium bromide on the intermediate vinylketone **39d**. In addition, ketone **52** in 26% yield arising again from the attack of the amine on the highly reactive α,β unsaturated ketone (Scheme 18 and Table 12, entry 1).



Scheme 18: Attempted transformation of ester **32c** into vinyl ketone **39d**

We therefore tried to isolate the Weinreb amide, using methylmagnesium bromide as base. In a first attempt we mixed 3.5 equivalents of Grignard's reagent[73] with amine and ester **32c**. However this procedure led to isolation of the corresponding methyl ketone in 70% yield (Table 12 entry 2 and Scheme 19). Given this result, we decrease the equivalent of methylmagnesium bromide to 2.35 and inverted the order of the addition. We sought that allowing the formation of the deprotonated amine by mixing the Grignard reagent and *N*,*O*-dimethylhydroxilamine hydrochloride, would have favoured the formation of the amide. In fact we managed to isolate the desired amide **53** in 49% yield (Table 12 entry 3).



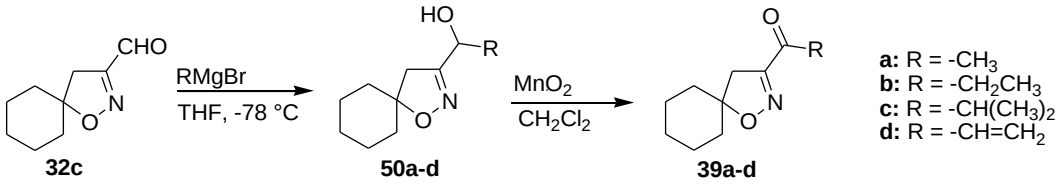
Scheme 19: Synthesis of Weinreb amide **53**

However the subsequent reaction of the amide **53** with vinylmagnesium bromide led to isolation of ketone **52** in 92% yield.

Entry	Equiv of $CH_3NOCH_3 \cdot HCl$	RMgBr (equivalents)	Conditions	Product (%)
1	1.25	CH_2=CHMgBr (8.3 eq)	-5 °C for 45 min 25 °C for 16 h 60 °C for 4 h	11% **51** 26% **52**
2	1.25	CH_3MgBr (3.5 eq)	-30 °C for 2h	70% **39a**
3	1.15	CH_3MgBr (2.35 eq)		49% **53**

Table 12: Results obtained in the synthesis of ketones **39** using strategy C

We then turned our attention to strategy B (Scheme 20). As shown in Table 13 the reaction of **32c** with various Grignard's reagents occurred with moderate to good yields. In particular when ethylmagnesium bromide and *iso*propylmagnesium bromide (Table 13, entry 2 and 3) were used, the Grignard's reagent acted as reducent[74] on the aldehyde and it was possible to isolate the corresponding primary alcohol **33c**, which, in one case, was also the main product. However the two products could be easily separated by column chromatography.



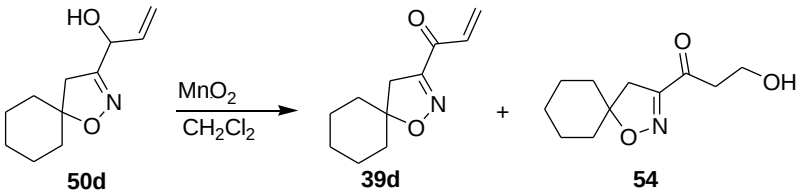
32c **50a-d** **39a-d**

Scheme 20: Synthesis of ketones **39** through strategy B

Entry	RMgBr	Yield (%) 50a-d	Yield (%) 39a-d
1	CH_3MgBr	73%	88 %
2	CH_3CH_2MgBr	46% + 19% **33c**	83%
3	$(CH_3)_2CHMgBr$	25% + 43% **33c**	59%
4	CH_2=CHMgBr	58%	53% + 26% **54**

Table 13: Yields of the reactions shown in Scheme 20

The oxidation was carried out using MnO_2 in good to excellent yield. In the reaction of of **39d** the yield was not as high compared to the other examples due to the formation of side product **54** (Scheme 21 and Table 13, entry 4).

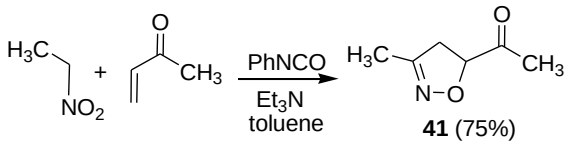


50d **39d** **54**

Scheme 21: Oxidation of **50d**

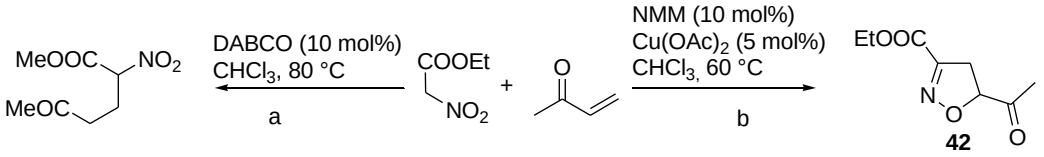
2.4 Synthesis of 3-Substituted-5-Acetyl-4,5-dihydroisoxazoles 41 and 42

The racemic 5-acetyl-3-methyl-2-isoxazoline **41** was regioselectively synthesised by means of the 1,3-dipolar cycloaddition of acetonitrile oxide (generated from nitroethane) with methyl vinyl ketone (Scheme 22).[54]



Scheme 22: Synthesis of **41** through 1,3-dipolar cycloaddition

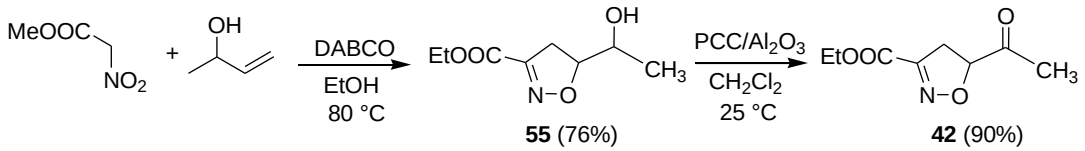
In the case of ketone **42**, as the analogous 1,3-cycloaddition between ethyl nitroacetate and methyl vinyl ketone afforded the desired product in very poor yield, it was necessary to find an alternative route. Initially we tried to use the same base catalyzed methodology[60] described above, between ethyl nitroacetate and methyl vinyl ketone. However the reaction run in presence of DABCO led to the isolation of just the Michael adduct (Scheme 23, pathway a). According to De Sarlo and co-workers, the same reaction carried out in presence of *N*-methyl-morpholine as base and 5% of $Cu(OAc)_2$, shifted the reaction towards the desired isoxazolines (Scheme 23, pathway b).[75] However the autors reported also that the little amount of Michael adduct formed during the reaction proved not to be separable from the desired isoxazoline even after several columns.



Scheme 23: Base catalyzed reaction between ethyl nitroacetate and methyl vinyl ketone

For this reason we discarded this route and we decided to follow the same base catalyzed reaction but using the 3-buten-2-ol instead of the corresponding ketone. This reaction afforded the desired mixture of *syn*/*anti* (57/43) isoxazolines **55** that was then

transformed into racemic 5-acetyl-isoxazoline **42** by oxidation of the alcohol function (Scheme 24).[76]

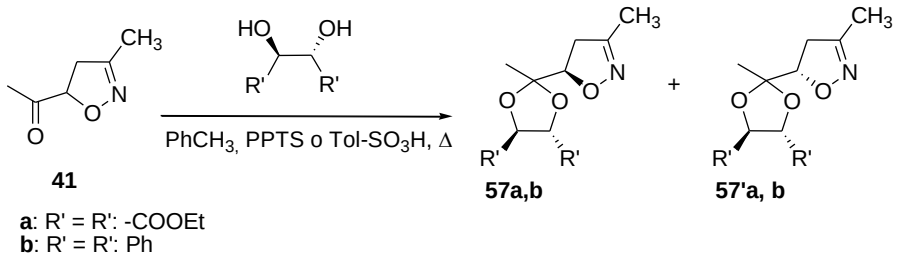


Scheme 24: Synthesis of **42**

2.5 Synthesis of Enantiomerically Pure 3-Substituted-5-Acetyl-4,5-dihydroisoxazoles 41 and 42

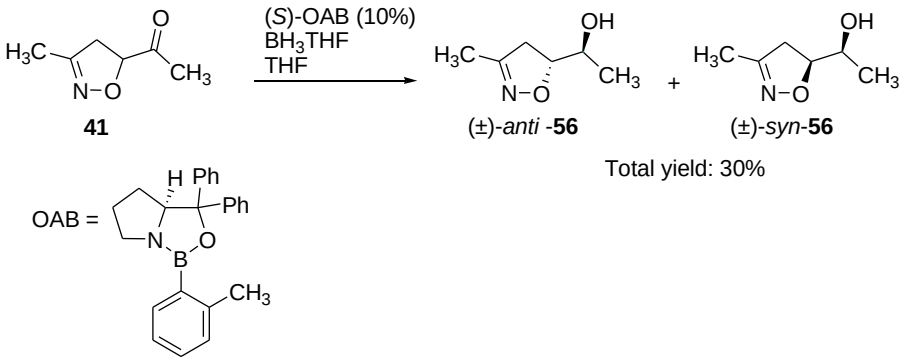
2.5.1 **Chemical Resolution**

Due to the presence of a stereocentre in position 5 of isoxazoline, **41** and **42** needed to be resolved into their enantiomers, in order to minimize the number of stereoisomers after reaction with *Schöllkopf*'s reagent. We envisaged to convert the racemic ketone **41** into a couple of diastereoisomeric ketals that could have been then separated by chromatography (Scheme 25). Ketone **41** was treated with diethyl L-tartrate but no reaction occurred. The reaction with (*R*,*R*)-1,2-diphenyl-1,2 ethandiol gave a mixture of starting material and desired ketals **57b** and **57'b**. Unfortunately the diastereoisomers were not separable by column chromatography.



Scheme 25: Chemical resolution of **41** through formation of diastereoisomeric ketals

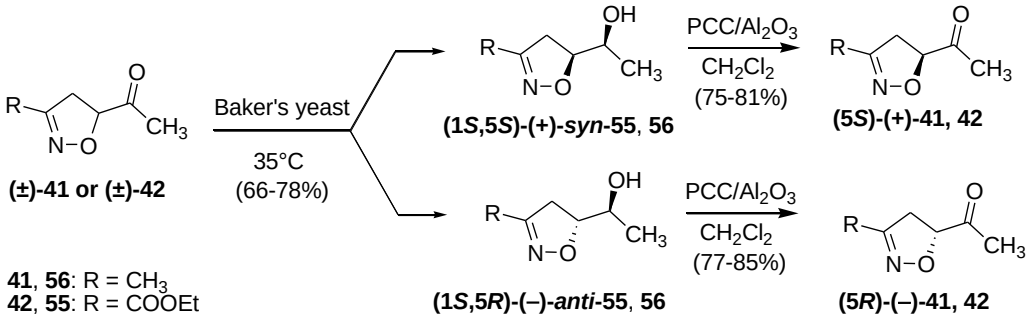
Another chemical method to resolve **41** was attempted using the enantioselective CBS (Corey-Bakshy-Shibata) reduction of ketones.[77,78] This would give *anti*-**56** and *syn*-**56**, which, after chromatographic separation, would have been oxidised into the corresponding enantiomerically pure ketones. However the treatment of **41** with 10 mol % of (*S*)-(–)-*o*-tolyl-CBS-oxazaborolidine and 1.8 equivalent of BH_3·THF led to a mixture of the racemic alcohols *syn* and *anti*-**56** (Scheme 26).



Scheme 26: Attempted enantioselective reduction of **41**

2.5.2 **Enzimatic Resolution**

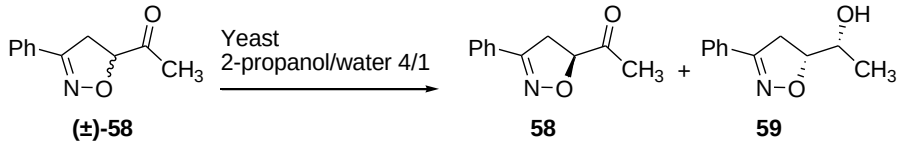
Because of the lack of success using chemical approaches, once again we shifted our attention to the enzymatic resolution. Ticozzi[79] in 1988 reported an enzymatic reduction of **41** and **42** into the corresponding alcohols, though he did not report either the α_D or the enantiomeric excess of the products. Therefore, following their procedure, racemic isoxazolines **41** and **42** were treated with commercial baker's yeast at 35 °C, in phosphate buffer, pH 5.5-6.0, in the presence of glucose. After continuous extraction of the aqueous solution with dichloromethane, 1:1 mixtures of the corresponding *syn*/*anti* diastereoisomeric alcohols **55** and **56** were obtained in 66-78% yield (Scheme 27).[76]



Scheme 27: Enzymatic resolution of **(±)-41** and **(±)-42** using baker's yeast

The two *syn*/*anti* alcohols **55** were separated by means of flash chromatography on silica gel, whereas the two *syn*/*anti* alcohols **56** required flash chromatography and a semi-preparative HPLC separation. Ticozzi reported that, if the reduction of the analogous isoxazoline **58** was performed in a mixture of 2-propanol/water, the kinetics and the stereoselectivity of the reaction was strongly dependent on the alcohol/water

ratio.[80] In particular when the reduction of **58** was performed using a ratio of 2-propanol/water of 4/1, it was possible to obtain the enantiomerically pure *syn* alcohol **59** and the enantiomerically pure leftover ketone **58** (Scheme 28).



(±)-58 **58** **59**

Scheme 28: Kinetic enzymatic resolution proposed by Ticozzi[80]

Based on these results and in order to avoid the laborious purification of *syn*/*anti* **56**, we studied the enzymatic reduction of **41** using different ratio of 2-propanol /water. It was found that depending on the 2-propanol:water ratio used with our substrate, the reactions led either to the unreacted ketone or the completely reduced alcohol (Table 14). However also Bhaduri and co-workers reported that reduction of 5-acetyl-3-phenyl-isoxazoline **58** performed in different 2-propanol/water ratio led to recovery of unreacted starting material .[81]

Entry	H_2O	*i*PrOH	41 recovered	56
1	1	3	100	0
2	1	4	100	0
3	1	5	100	0
4	1	6	100	0
5	3	1	100	0
6	4	1	100	0
7	5	1	0	100

Table 14: Study of the kinetic enzymatic resolution of **(±)-41** using different H_2O/*i*PrOH ratio

The relative *syn*/*anti* configuration of compounds **55** and **56** was assigned using ^{1}H-NMR spectra from the value of the coupling constant between H-5 and H-1 (J = 5.2-5.7 for *syn*-**55** and **56** and 3.3-3.2 Hz for *anti*-**55** and **56**). The enantiomeric excess of each alcohol was determined by HPLC to be > 98%. Absolute configurations were not assigned at this stage, but were determined by means of an X-ray analysis of the adducts

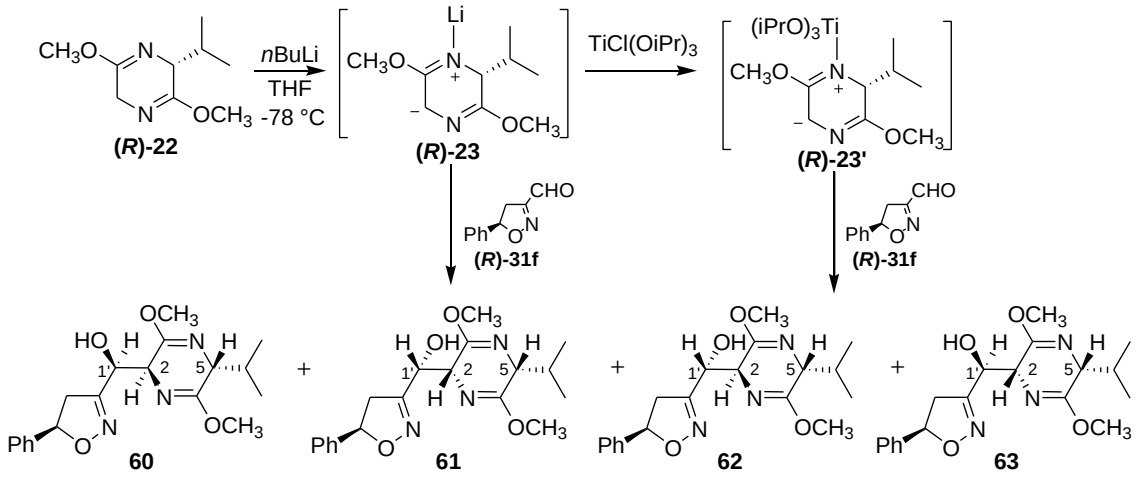
obtained in the following reaction with *Schöllkopf*'s reagent (*vide infra*), which allowed the assignment of configuration (1*S*,5*S*) to alcohols *syn*-**55**, **56** and (1*S*,5*R*) to anti-**55**, **56**. Finally, oxidation of the *syn* and *anti* alcohols **55** and **56** with PCC/Al_2O_3 respectively led to (5*S*)- and (5*R*)- **42** and **41** (Scheme 27). The enantiomeric excess of the final ketones **42** and **41** was confirmed to be respectively > 98% and 92%.

2.6 Study of the Reaction with Schöllkopf's Reagent

2.6.1 **Addition of Schollköpf's Reagent Anion to (*R*)-5-Phenyl-4,5-dihydroisoxazole-3-carbaldehyde (*R*)-31f**

As previously said, after having studied the reaction between *Schöllkopf's* reagent and 5,5-disubstituted-4,5-dihydroisoxazole-3-carbaldehydes (Scheme 6),[59] we decided to extend this protocol to aldehyde **(*R*)-31f**. [68]

In accordance with the general procedure, a solution of aldehyde **(*R*)-31f** was added to *Schöllkopf's* anion **(*R*)-23** generated by *n*BuLi in THF at –78 °C. To evaluate the influence of the counter-ion on diastereoselectivity, the reaction was also performed in a parallel experiment in which the lithium azaenolate **(*R*)-23** was treated with triisopropoxytitanium (IV) chloride[82] to give the corresponding titanium azaenolate **(*R*)-23'** before the addition of aldehyde **(*R*)-31f**. ^{1}H-NMR of the crude showed the presence of a mixture of diastereoisomers **60-63,** whose ratio was determined by means of HPLC analysis (Table 15).



Counterion	Total Yield (%)	Diastereomer Ratios					
		60 (2S,1'S)	**61** (2R,1'R)	**62** (2S,1'R)	**63** (2R,1'S)	**60+62 / 61+63**	**60 / 62**
Li	60	56.8	21.9	19.5	1.8	3/1	3/1
Ti	60	76.8	4.5	18.7	0.0	21/1	4/1

Table 15: Optimization of the reaction between *Schöllkopf's* reagent and aldehyde **(*R*)-31f**

When the reaction temperature was raised to -20 °C, the yield of the adducts **60**-**63** was lower and compound **64**[83] was isolated in 20% yield (Figure 24). Therefore we hypothesised that, similarly to the reported decarboxylative ring-opening reaction of 3-carboxyisoxazolines,[56] the anion of the alcohol evolves and a fragmentation, via ring-opening of the isoxazoline ring, takes place as shown in Figure 24.

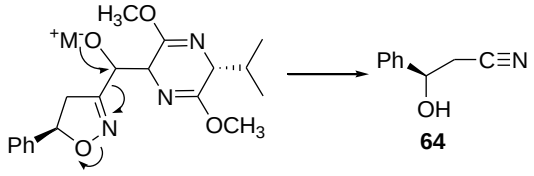


Figure 24: Formation of side product **64**

The structures **60**-**63** were assigned by NMR. The (2*S*)-configuration of compounds **60** and **62** was established using the $^{5}J_{\text{H-2/H-5}}$ coupling constant whose value of 3.6 Hz, corresponds to a *trans* relationship between the 2-H and 5-H protons of the pyrazine ring.[84, 85] The absolute configuration of the major adduct **60** was determined through X-

ray crystallographic analysis (Figure 25). This allowed the assignment of (*R*) configuration to C-5 of isoxazoline ring and therefore the configurations of compounds **32f**, **33f**, **31f** by analogy. The X-ray analysis assigned also the (*S*) configuration to both 1'-C and C-2 of pyrazine ring. As a consequence, the (*R*) configuration was assigned to the 1'-C of the epimer **62**.

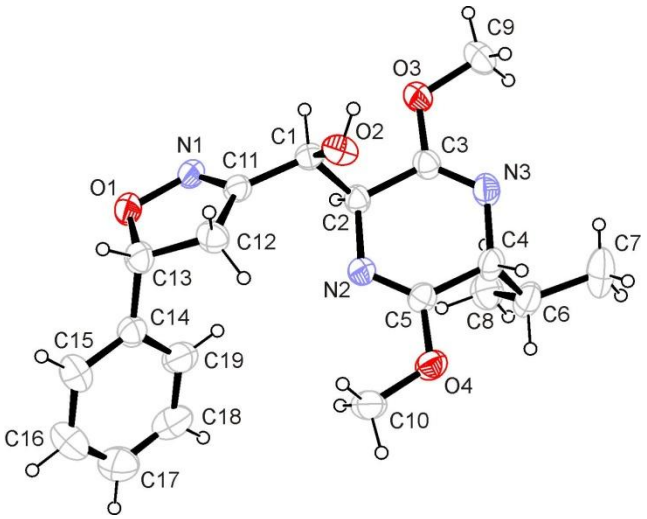


Figure 25: X-ray of **60**

On the contrary, the ^{1}H-NMR spectra of diastereoisomers **61** and **63** showed a $^{5}J_{H\text{-}2/H\text{-}5}$ coupling constant value of 5.6 Hz, which corresponds to a *cis* relationship between the H-2 and H-5 protons of the pyrazine ring. The *cis* relationship was also confirmed by a positive NOE effect between the two protons. The (1'*R*) and (1'*S*) configurations were respectively assigned to diastereoisomers **61** and **63** taking into account the accepted model for the aldol-type addition of *Schöllkopf's* enolate to aldehydes,[44] which has also been extensively confirmed in our previous studies.[49, 59] On the strength of this model, the azaenolate-pyrazine attacks the aldehyde by means of a more favourable transition state in which the aldehyde substituent is far from the methoxy group and the metal atom (Figure 26a). According to this model, the more cumbersome substituent of the aldehyde (the isoxazoline ring) occupies the equatorial position in a six member ring chair like transition state. This led to a predominance of the adduct **(1'*S*)-60** when the attack takes place from the opposite side of the isopropyl group (Figure 26a). On the contrary, when the attack takes place from the same side as the isopropyl group, the most favourable transition state leads to compound **(1'*R*)-61** (Figure 26b). This is the

first time we have observed the formation of products arising from an attack of the aldehyde from the more hindered side of the azaenolate (adducts **61** and **63**).[44, 53] The formation of adduct **61** in a comparable amount to **62** when Li is used as counterion (see Table 15) may be explained taking in consideration the two transition states. As shown in Figure 26c the transition state that leads to the formation of product **62** is more encumbered than the one that leads to **61** (Figure 26b), because of the phenyl pointing toward the pyrazine ring. We hypothesized the two transition states having comparable energy, leading to the formation of the two adducts in the similar amount.

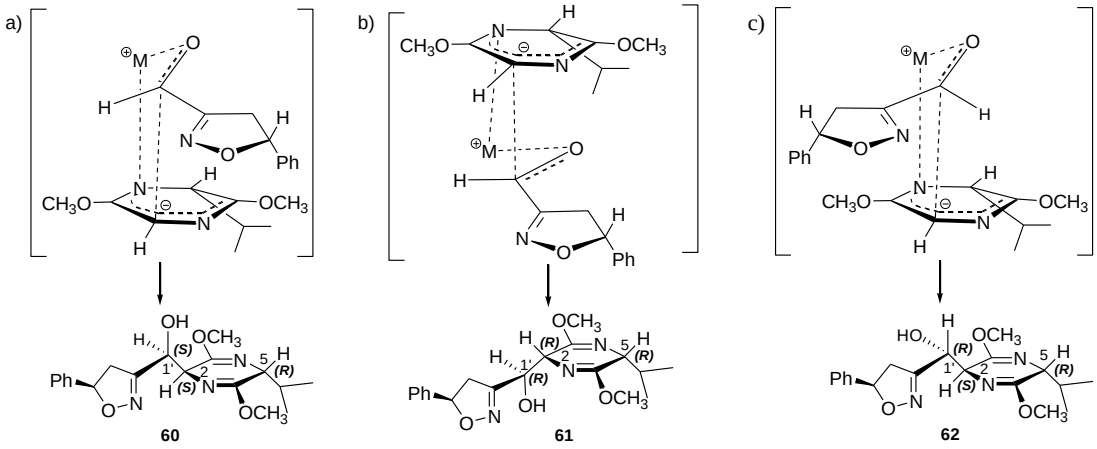


Figure 26: Transition states for the formation of adducts **60**, **61** and **62**

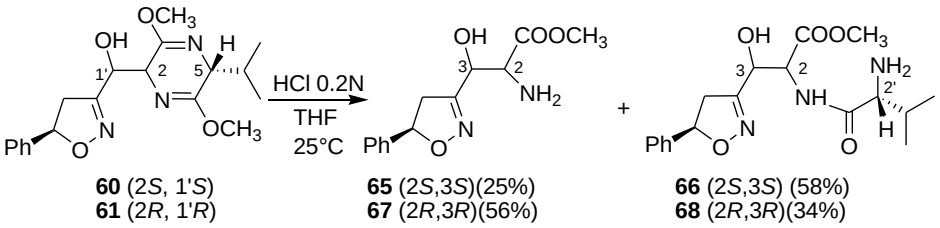
As shown in Table 15 the diastereoisomeric ratio increases when titanium is used as counterion. It is thought that titanium promotes a tight transition state[84] and so the reaction proceeds more selectively than the one using lithium. As shown in Table 15, diastereofacial selectivity with respect to the pyrazine anion is enhanced (Σ(2*S*):Σ(2*R*) = 21:1 *vs* 3:1) as is the facial preference of the carbonyl addition, albeit in a less marked manner (ratios (1'*S*):(1'*R*) = 4:1 *vs* 3:1).

An involvement of the isoxazoline ring in the complex intermediate can be expected especially when $TiCl(OiPr)_3$ is used.[86, 87] However, in this case, the additional coordination of the titanium atom with the isoxazoline nitrogen should involve a less stable *s*-cis O=C-C=N conformation of the aldehyde, as well as a more encumbered transition state with the isoxazoline arrangement on the same side as the methoxy group. If a coordination would have taken place, the yield of **62** would have risen when

titanium was used as counterion. However the amount of product **62** was practically the same with the two counterions (Table 15), suggesting that the potential metal-isoxazolidine coordination had a poor effect.

2.6.2 **Hydrolysis of Adducts 60 and 61 and Isoxazoline Cleavage of 66**

Adducts **60** and **61** were hydrolysed under controlled conditions, leading to the formation β-substituted serine methyl esters **65**, **66** and the dipeptides **66**, **68** (Scheme 29). These dipeptides, formed by a partially hydrolysis of pyrazine ring, were isolated in variable amounts during hydrolysis reaction, independent of the conditions used.[59] However they were separated by means of column chromatography and their structure was assigned using ^{1}H-NMR analysis.[59, 62, 63]



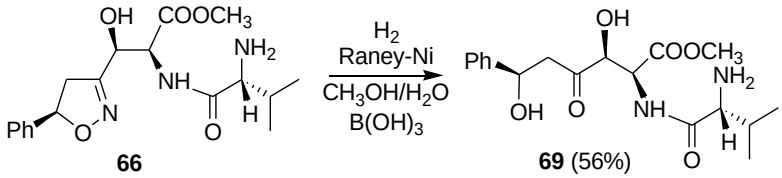
60 (2*S*, 1'*S*)
61 (2*R*, 1'*R*)

65 (2*S*,3*S*)(25%)
67 (2*R*,3*R*)(56%)

66 (2*S*,3*S*) (58%)
68 (2*R*,3*R*)(34%)

Scheme 29: Hydrolysis of adducts **60** and **61**

Finally, the hydrogenolysis-hydrolysis of the 4,5-dihydroisoxazole ring of dipeptide **66** using three equivalents of $B(OH)_3$ in a mixture $MeOH/H_2O$, with H_2 and Raney-Ni as catalyst,[57] led to the corresponding β,ε-dihydroxy-γ-oxo α-amino acid derivative **69** in good yield (Scheme 30). This α-amino acid derivative, like the ε,ε-disubstituted derivatives previously obtained by us, has a highly functionalised structure with a further stereocentre that makes it extremely attractive as a potential peptidomimetic.

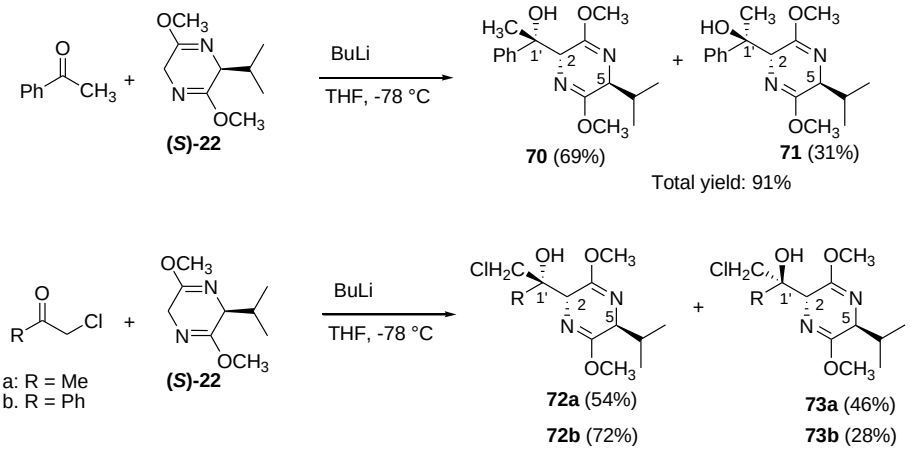


66 **69** (56%)

Scheme 30: Synthesis of polifunctionalized dipeptide **69**

2.6.3 Addition of Schollköpf's Reagent Anion to 3-Acyl-4,5-dihydroisoxazole

With the aim of obtaining new β-hydroxy-α-amino acids, β-substituted with a 2-isoxazoline ring that is potentially susceptible to further transformation, and containing an asymmetric, enantiomerically pure quaternary carbon in the β position, we extended the protocol previously studied for aldehydes, to ketones. One of the most interesting goals of organic synthesis is the asymmetric synthesis of quaternary carbon centres, and one of the most useful means of achieving it is the asymmetric addition of nucleophiles on ketones.[88-90] In particular, the aldol reaction between a glycine equivalent and prochiral ketones provides access to β,β-disubstituted-β-hydroxy-α-amino acids, which are of considerable interest in the synthesis of peptidomimetics because of their sterically constrained structure.[91] There are very few published examples of the reaction between *Schöllkopf*'s reagent and prochiral ketones, most of which have involved acetophenone, chloroacetone and chloroacetophenone (Scheme 31).[92-96] In all cases there is a completely stereocontrol in the formation of the stereocentre at C-2. Moreover when the ketone has two very different size substituents, a good *syn*/*anti* ratio can be achieved, as in the case of products **70**/**71** and **72b**/**73b**.

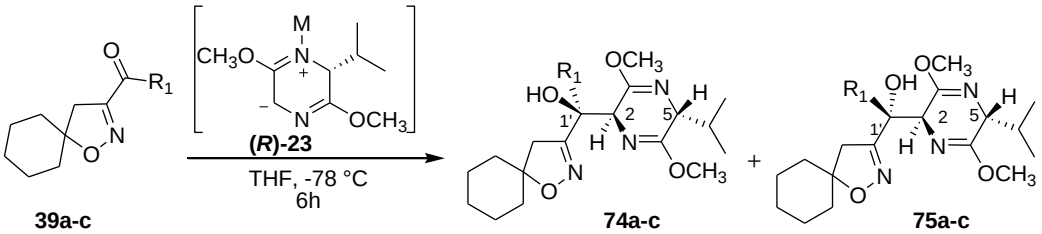


Scheme 31: Literature examples of reaction between *Schöllkopf* 's reagent and ketones

We decided to start our studies using 3-acyl-4,5 dihydroisoxazole **39a-d** 5,5-disubstituted with two identical group, in order to avoid the presence of a stereocentre that would have doubled the number of diastereomers after reaction with the

Schöllkopf's reagent. Therefore compounds **39a-d** were synthesised as previously described**.** We envisaged that having ketones substituted with different *R* groups (eg. methyl, ethyl, *iso*propyl), would give us the possibility of studying the influence of the steric encumbrance on diastereoselectivity. The vinyl ketone **39d** was chosen to allow the synthesis of the pharmacologically interesting vinyl amino acids. Moreover this substrate gave us the possibility of studying the behaviour of *Schollkopf's* reagent in the presence of two electrophilic carbons.

Following the general procedure, a solution of ketone **39a-d** was added to the anion of the bislactim ether **(*R*)-23** generated by *n*BuLi in THF at –78 °C.



39a-c **74a-c** **75a-c**

a: R_1 = -CH_3
b: R_1 = -CH_2CH_3
c: R_1 = $CH(CH_3)_2$

Counterion	R_1	*d.r.*	Yield (%)
Li^+	-CH_3	50:50	61
$(iPrO)_3Ti^+$	-CH_3	—	0
$SnCl_2$	-CH_3	—	0
Li^+	-CH_2CH_3	50:50	34
Li^+	-*i*Pr	—	0

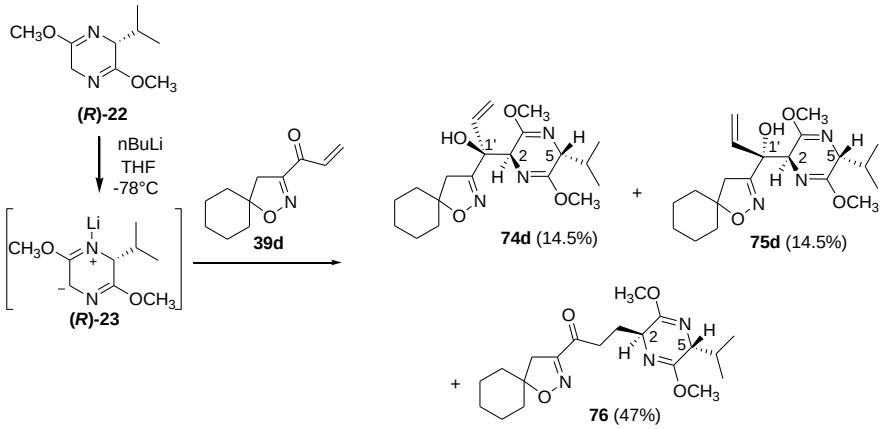
Table 16: Reaction between *Schöllkopf's* reagent and 3-acyl-4,5-dihydroisoxazole **39a-c**

As shown in Table 16, the reaction occurred in good yield in the case of ketone **39a** and in lower yield for compound **39b**. In both cases ^{1}H-NMR analysis of the crude material revealed the presence of two diastereoisomers in 1:1 ratio. However there was not reaction with ketone **39c**. In this case the reaction didn't occur presumably due to the large steric hindrance given by the *iso*propyl group.

The products **74a/75a** and **74b**/**75b** were separated through a chromatographic column and their structures were confirmed by NMR analysis. Through ^{1}H-NMR analysis it was possible to assign the *S* configuration to C-2 of pyrazine. In fact for all the adducts the $^{5}J_{\text{H-2/H-5}}$ coupling constant had a value of 3.5 Hz, that corresponded to a *trans* relationship between the 2-H and 5-H protons of the pyrazine ring.[84, 85] The *Schöllkopf* reagent attacks the carbonyl group exclusively from the opposite side of the *iso*propyl group, however without any stereocontrol of the newly formed tertiary alcohol. Ongoing X-ray analysis will allow to determine the absolute configuration also at C-1'.

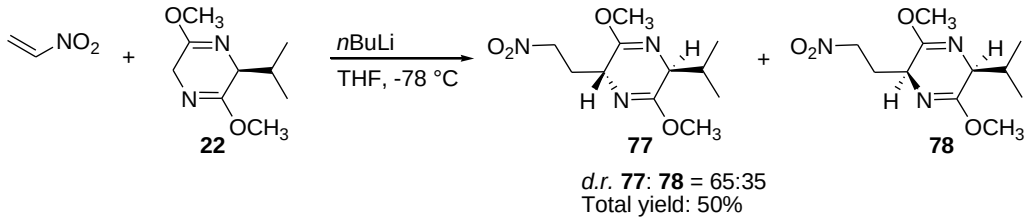
In order to improve the diastereoselectivity, we studied the reaction between ketone **39a** and *Schöllkopf's* azaenolate with counterions other than lithium. Because in the reactions with aldehydes we observed an increased *d.r.* when titanium was used as the counterion,[48, 50] we thought this metal might be suitable also in this case. However, as shown in Table 16, the reaction run with TiCl(*i*PrO)$_3$ led to the recovery of unreacted starting material. The same result was obtained when tin was used as counterion. The lack of reactivity in the reaction with titanium, is presumably due to a too hindered transition state occurring when this metal is used.[44]

The reaction of the vinylketone **39d** led to the formation of inseparable diastereoisomers **74d** and **75d** in a 1:1 ratio and in 29% yield. Together with these two expected adducts, ketone **76** derived from the 1,4 addition of *Schöllkopf's* anion to α,β-unsaturated ketone, was isolated in 47% yield (Scheme 32).



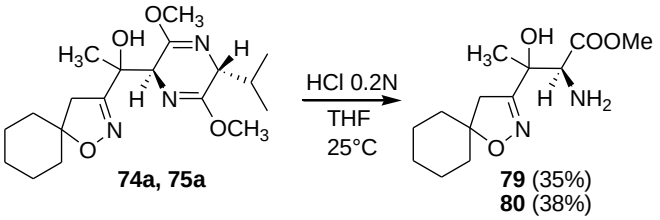
Scheme 32: Reaction between Schöllkopf's reagent and vinyl ketone **39d**

^{1}H-NMR analysis showed that attack of *Schöllkopf's* anion to the carbonyl group of **39d** occurred only *trans* to *iso*propyl group, leading again to the formation of adducts with *S* configuration at C-2 of pyrazine. Similarly, exclusive *trans* attack occurred in the case of 1,4 addition with product **76** having a $^5J_{\text{H-2/H-5}}$ coupling constant of 3.5 Hz, confirming a *trans* relation between the two protons. The only other reported example of a similar 1,4 addition is the reaction of *Schöllkopf's* azaenolate with nitroethylene, described by Schöllkopf himself.[84] However in this case both diastereoisomers **77** and **78** were isolated in a ratio of 65:35, showing that the attack of the anion on the double bond occurred from both sides of the *iso*propyl group (Scheme 33).



Scheme 33: 1,4-addition of *Schöllkopf's* reagent to nitroethylene

Finally the two adducts **74a** and **75a** were separately hydrolyzed with 0.2N HCl in THF providing the corresponding amino esters **79**, **80** in moderate yield (Scheme 34).

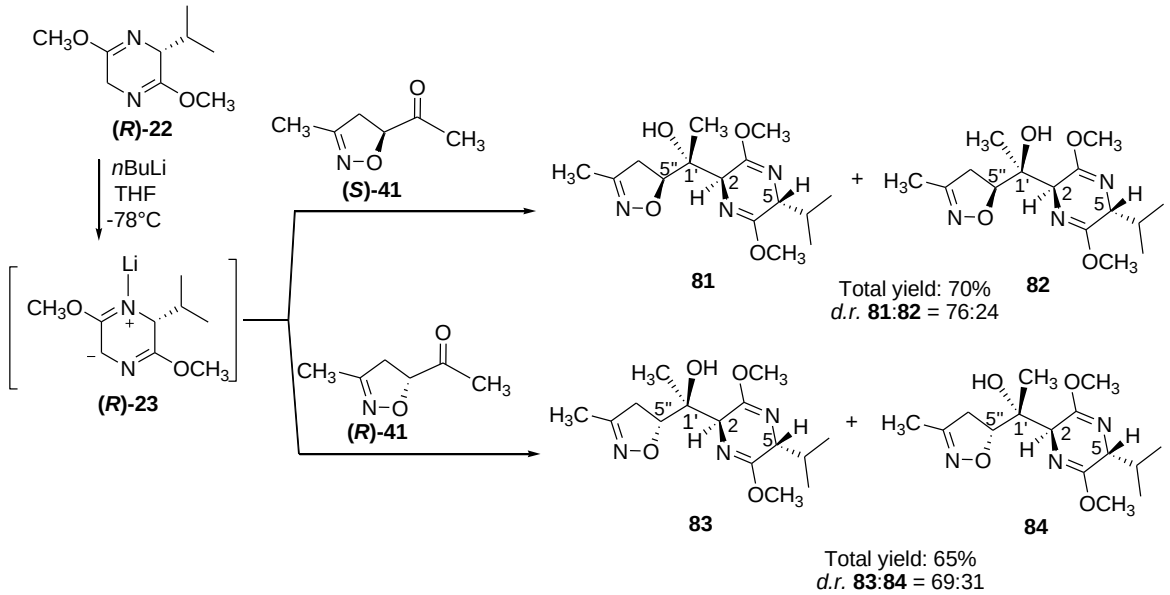


Scheme 34: Hydrolysis of adducts **74a** and **75a**

2.6.4 Addition of Schöllkopf's Reagent Anion to **5-Acetyl-4,5-dihydroisoxazoles**

After we found that the reaction between prochiral ketone **39a-d** and *Schöllkopf's* reagent occurred without any stereocontrol of the newly formed tertiary alcohol, we were interested in studying the influence of a stereocenter α to the ketone on diastereoselectivity.[76] Therefore the keto group was moved from position 3 to position 5 of 2-isoxazolines and the two enantiomerically pure 5-acetyl-4,5-dihydroisoxazoles **(5*R*)**- and **(5*S*)-41** and **(5*R*)**- and **(5*S*)-42** were synthesized as previously described (Scheme 27). The methyl ketone is chosen to minimise the steric hindrance around the carbonyl group. We select the 3-methyl and 3-carbethoxy derivatives because the resolution of their corresponding racemate was approximately described as previously mentioned.[79] Moreover the carbethoxy group, in addition to introducing another important functional group, allow us to consider the possible competition between the two carbonyl groups in the reaction with *Schöllkopf*'s reagent.

Various experimental conditions were examined to optimise yields and evaluate the diastereoselectivity of the addition reaction. Under the best conditions, a THF solution of ketone **41** was added to the anion of the bislactim ether **(*R*)-23** at -78 °C, and maintained at this temperature for four hours. It was found that longer times or higher temperatures led to lower yields due to the reversibility of the addition, as previously observed by ourselves and by Hayashi.[68, 97] With the (5*S*)- or (5*R*)-3-methyl derivatives **41**, the reaction gave mixtures of two diastereoisomeric adducts **81/82** or **83/84** in ratios of respectively 76:24 and 69:31, as determined by integrating the doublet of the isopropyl groups in the ^{1}H-NMR spectra of the crude reaction mixtures (Scheme 35 and Table 17).



Scheme 35: Reaction between *Schöllkopf's* reagent and **(*S*)- or (*R*)-41**

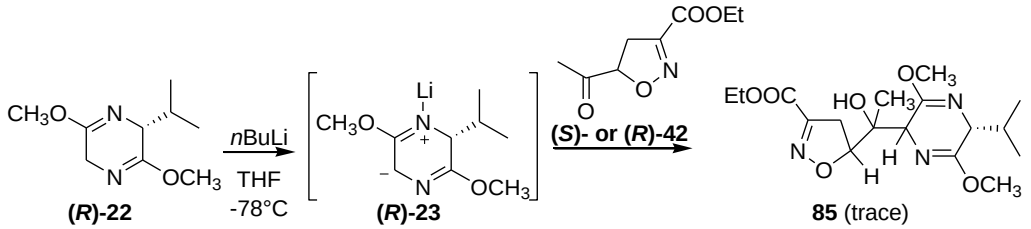
Entry	ketone	counter-ion	total yield (%)	81:82 or 83:84 ratio
1	**(5*S*)-41**	Li^+	70	76 : 24
2	**(5*S*)-41**	$(iPrO)_3Ti^+$	Trace	---
3	**(5*S*)-41**·$TiCl_4$	Li^+	48	87 : 13
4	**(5*R*)-41**	Li^+	65	69 : 31

Table 17: Optimization of the reaction between *Schöllkopf's* reagent and **(*S*)- or (*R*)-41**

To evaluate the influence of the counter-ion on diastereoselectivity, the lithium azaenolate **(*R*)-23** was treated with triisopropoxytitanium (IV) chloride[82] to give the corresponding titanium azaenolate before the addition of **(*S*)-41** (Table 17, entry 2). However a mixture of adducts **81/82** was obtained only in trace amounts. In another experiment in order to make the carbonile more reactive, titanium (IV) chloride was added to a THF solution of ketone **(*S*)-41** before it was added to the anion of the bislactim ether (Table 17, entry 3). Compounds **81/82** were obtained with better diastereoselectivity (87:13) but a lower yield (48%).

A different result was obtained using the (*S*)- and (*R*)- ketone **42** (Scheme 36). In this case, under the best experimental conditions, the reaction led to a mixture of

unidentified compounds and varying amounts (20-40%) of unreacted ketone **42**. The ^{1}H-NMR spectra of this mixture indicated the presence of a pair of adducts **85**, but only in trace amounts. This different behaviour may have been due to competition between different electrophilic carbons, such as the ketone and the carbethoxy group, despite this latter should be less reactive than the ketone group.



Scheme 36 Reaction between *Schöllkopf's* reagent and **(*S*)- or (*R*)-42**

Diastereoisomers **81**/**82** and **83**/**84** were purified by means of flash chromatography on silica gel, and their structures were confirmed on the basis of mono and bi-dimensional ^{1}H-NMR and X-ray analysis. The configuration at C-2 of pyrazine of compounds **82**-**84** was established being *S* using the $^{5}JH_2/H_5$ which was 3.5-4.0 Hz.[84, 85] Adducts **81** and **82** were obtained as crystalline solids and underwent X-ray crystallographic analysis, which made possible to assign the configuration at C-1' and at C-5" of both products and the configuration at C-2 of **81**, which could not be determined through ^{1}H-NMR analysis. As shown in Figure 27, the *S* configuration was assigned at C-5" and C-2 of both **81** and **82**. The configuration at C-1' was found to be *R* for **81** (Figure 27a) and *S* for **82** (Figure 27b), showing that the two diastereoisomers are epimer at C-1'.

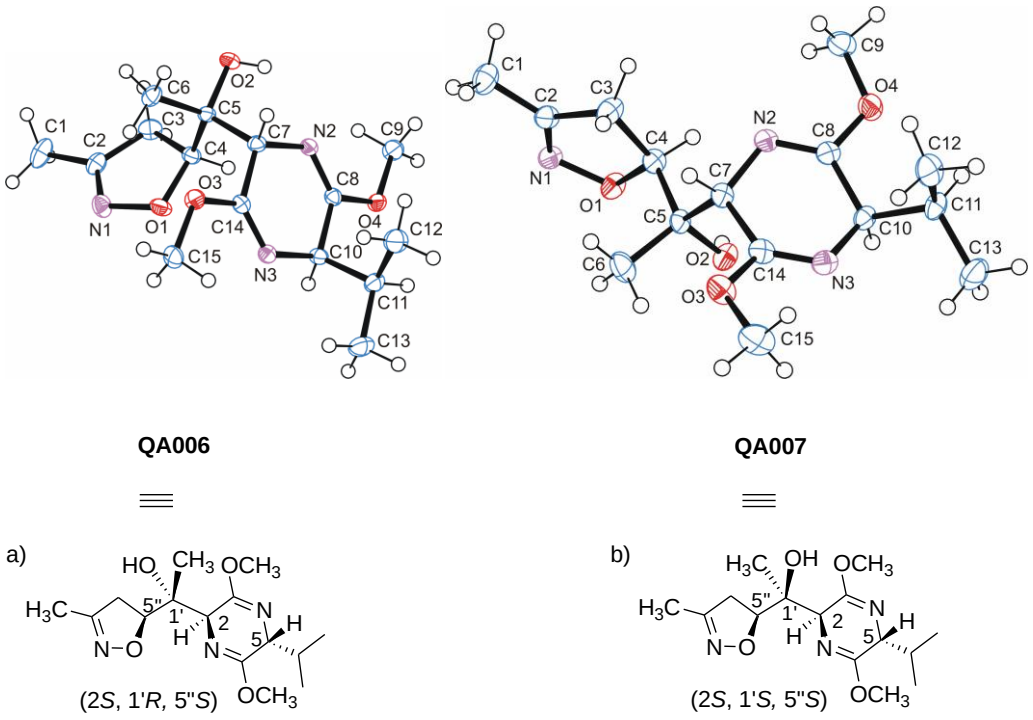


Figure 27: X-ray of adducts **81** and **82**

By analogy, we assigned the same (*S*) configuration to compound **(+)-41** and the (*R*) configuration to **(–)-41** (Figure 28).

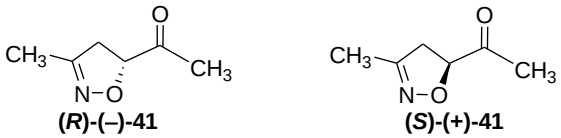


Figure 28: Absolute configurations of **(–)-41** and **(+)-41**

Compounds **83** and **84** couldn't be obtained as suitable crystals for X-ray analysis, and so their absolute configurations at C-1' were assigned by means of exhaustive ^{1}H-NMR spectra and NOESY experiments.

The NOESY spectra of the major diastereoisomer **83** (Figure 29) shows positive effects between H-2 and 1'-CH_3, between isoxazolin H-5 and 1'-CH_3, and between the H-2 and one of the H-4 protons. This last effect suggests an (*S*) configuration at C-1' because, as shown by the Dreiding's[98] molecular models, these positive effects can't all be observed at the same time with the opposite (*R*) configuration at C-1'.

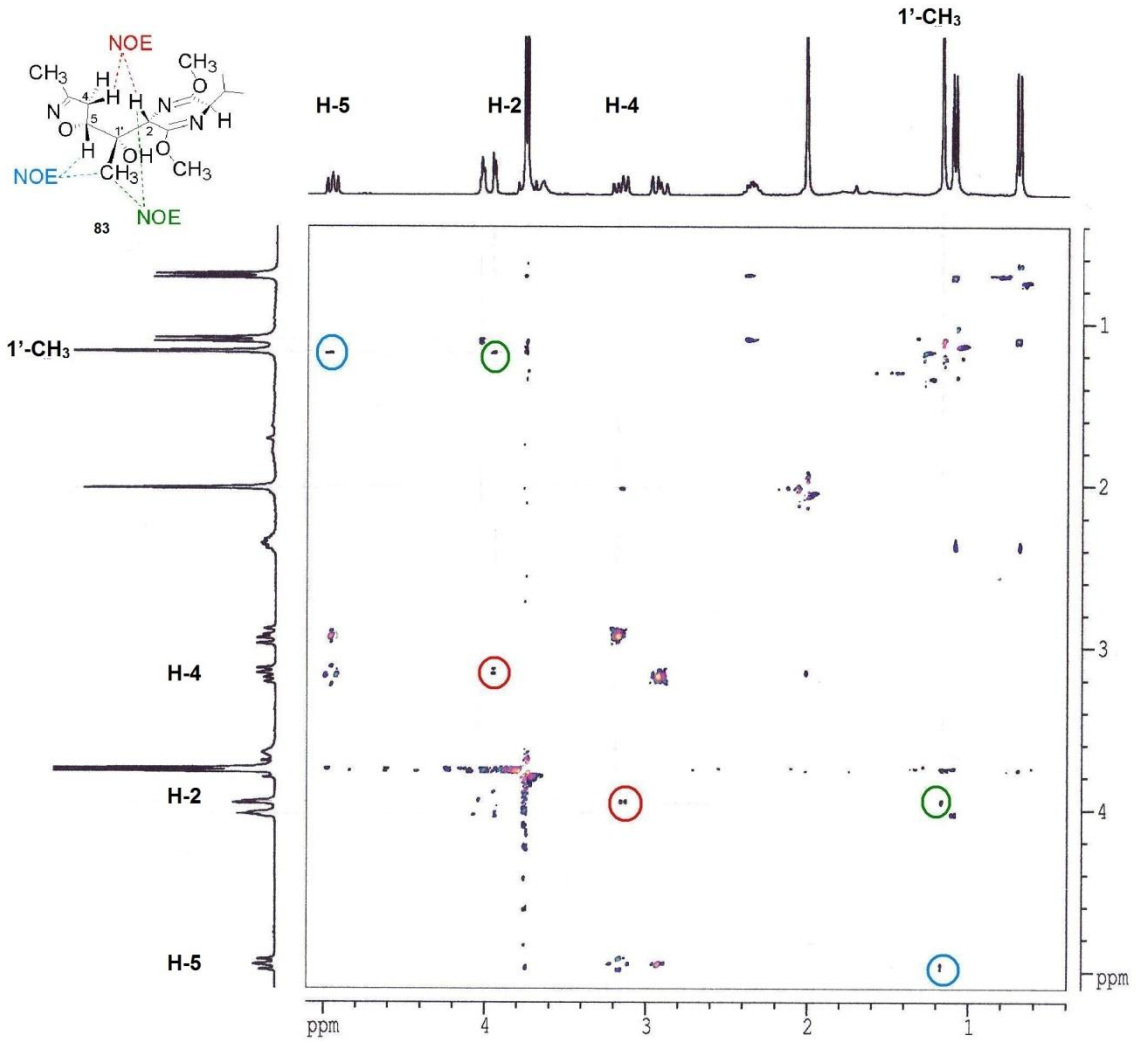


Figure 29: NOESY spectrum of **83**

The NOESY spectra of the minor diastereoisomer **84** (Figure 30), shows positive effects between H-2 and 1'-CH_3, and between isoxazolinic H-5 and 1'-CH_3 but, instead of the positive effect between the H-2 and H-4 proton as in the case of **83**, there is a positive effect between the H-4 protons and the 1'-CH_3, thus confirming a (*R*) configuration for 1'-C.

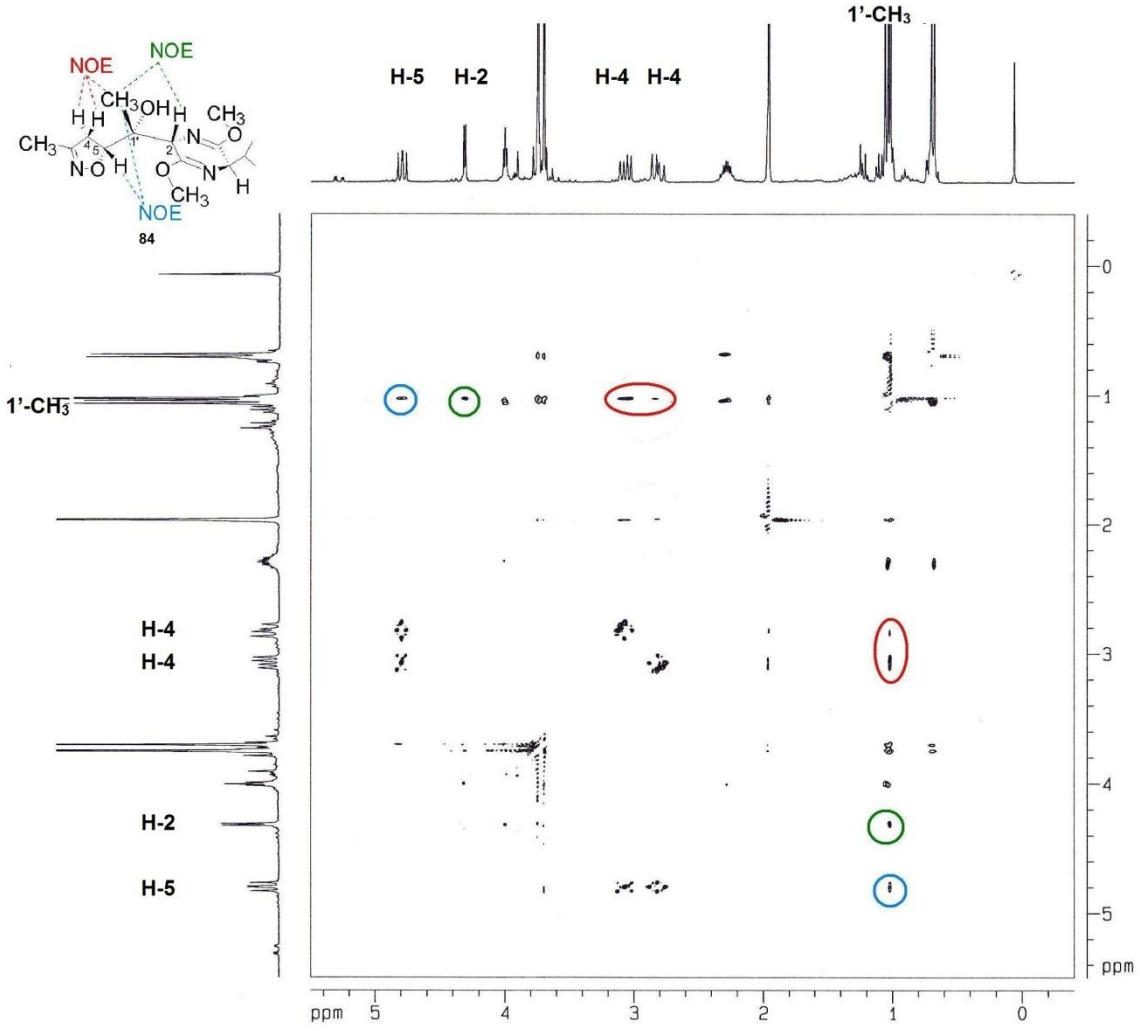
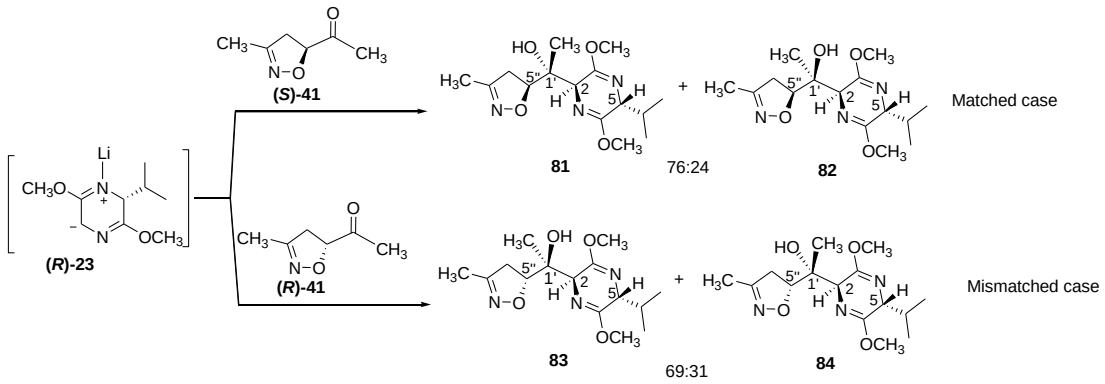


Figure 30: NOESY spectrum of **84**

2.6.5 Models of the Addition of Schöllkopf's Reagent Anion to Ketones (5*S*)- and (5*R*)-41

As previously mentioned, there are just few reported examples of the reaction between *Schöllkopf*'s reagent and ketones and none using prochiral ketones containing stereocenters. The reactions of *Schöllkopf*'s reagent with chiral ketone **41** raises the question of "double asymmetric induction". The use of the enantiomeric forms of ketone **41** led to both *matched* (**(*R*)-22** and **(*S*)-41**) and *mismatched* (**(*R*)-22** and **(*R*)-41**) situations (Scheme 37), allowing us to evaluate the relative influence of both the

carbonyl α-stereocentre (*substrate control*) and the azaenolate-pyrazine (*reagent control*) on reaction stereoselectivity.



Scheme 37: Matched and mismatched cases for reaction between *Schöllkopf's* reagent and **(*S*)-41** /**(*R*)-41**

The reaction between **(*R*)-22** and the ketone **(*S*)-41** was more diastereoselective than the reaction with the ketone **(*R*)-41**, with the ratio of adducts **81**/**82** being 3.2:1 versus 2.2:1 for **83**/**84** (Scheme 37). This result was for us quite surprising, because, considering the transition states, we would have presumed a better *d.r.* for the reaction between **(*R*)-22** and **(*R*)-41**.

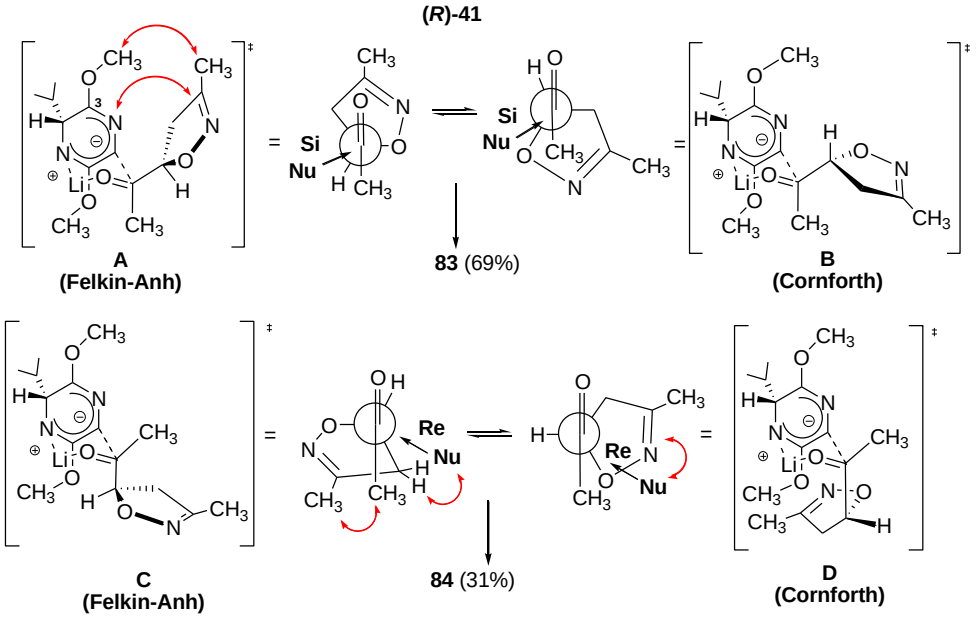


Figure 31: Transition state for reaction between *Schöllkopf's* reagent and **(*R*)-41**

In the reaction between **(*R*)-22** and **(*R*)-41**, we proposed the major diastereoisomer **83** was derived from the preferential attack of the nucleophile from the favoured *Si* face of ketone **(*R*)-41** which is favoured in both the Felkin-Anh[99, 100] and Cornforth[101] models. This situation allowed the less cumbersome methyl group to be in a pseudoaxial position, in agreement with Schöllkopf[44] and Zimmerman- Traxler[102] models (Figure 31, transition state **A** and **B**). Therefore, in this case, the favoured diastereoisomer **83** was a result of a positive combination of both substrate and reagent control. However, this favourable situation may be diminished by a negative steric effect between the 2-isoxazoline ring and the pyrazine 3-methoxy group (Figure 31, transition state **A**), which could give rise to the moderate diastereomeric ratio.

We proposed that in the reaction between **(*S*)-41** and **(*R*)-22**, the major diastereoisomer **81** was derived from the attack of the nucleophile from the *Re* face, favoured in both the Felkin-Anh and Cornforth models. However this approach places the more hindered isoxazoline ring in a pseudoaxial position, which is opposite to that normally observed in reactions using *Schöllkopf's* reagent[44, 49] (Figure 32, transition states **E** and **F**). However, in the Cornforth-like transition state **F**, the unfavourable steric interaction between the pyrazine 6-methoxy and the 2-isoxazolinic ring can be minimised by making this the preferred conformation. The attack from the *Si* face, which puts the more cumbersome isoxazoline ring in a pseudoequatorial position (Figure 32, transition states **G** and **H**), suffers from steric repulsions between the nucleophile and the 2-isoxazoline ring. This negative interaction suggested that the transitions states **E** and **F** were favoured over **G** and **H**, thus explaining the preferential formation of adduct **81** over **82**. In conclusion, the diastereoselectivity of this mismatched case was presumably influenced to a greater effect by the chiral ketone than the *Schöllkopf*'s reagent as the reaction with the ketone **(*S*)-41** leads to the "*substrate control*" adduct **81** as the major diastereomer.

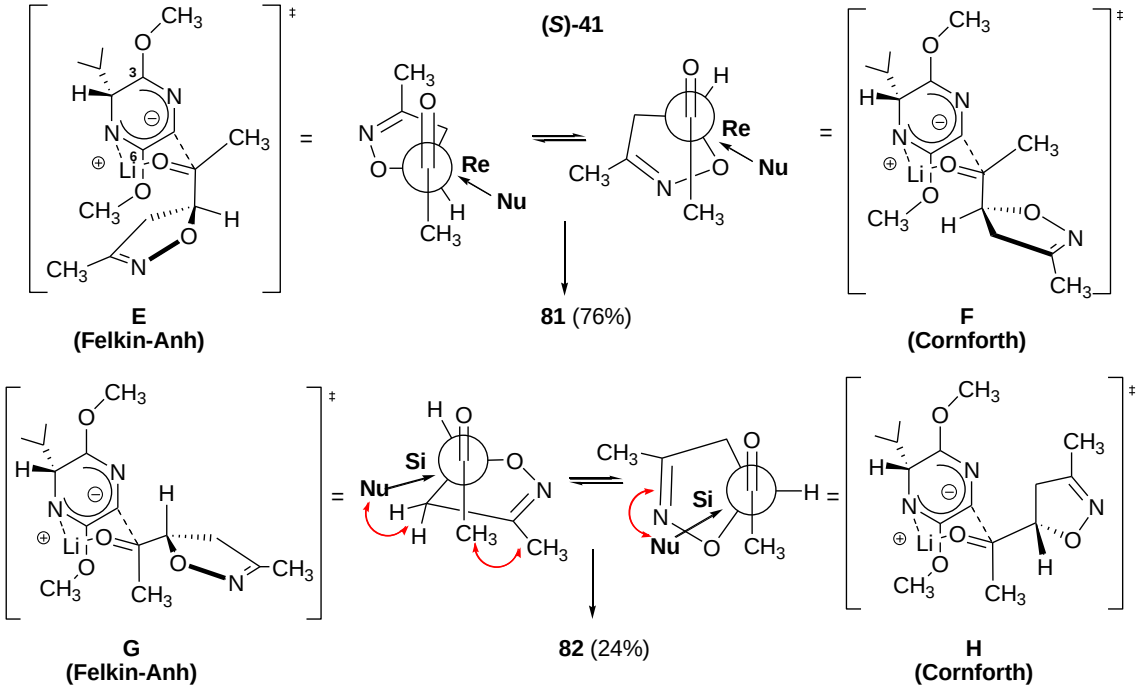
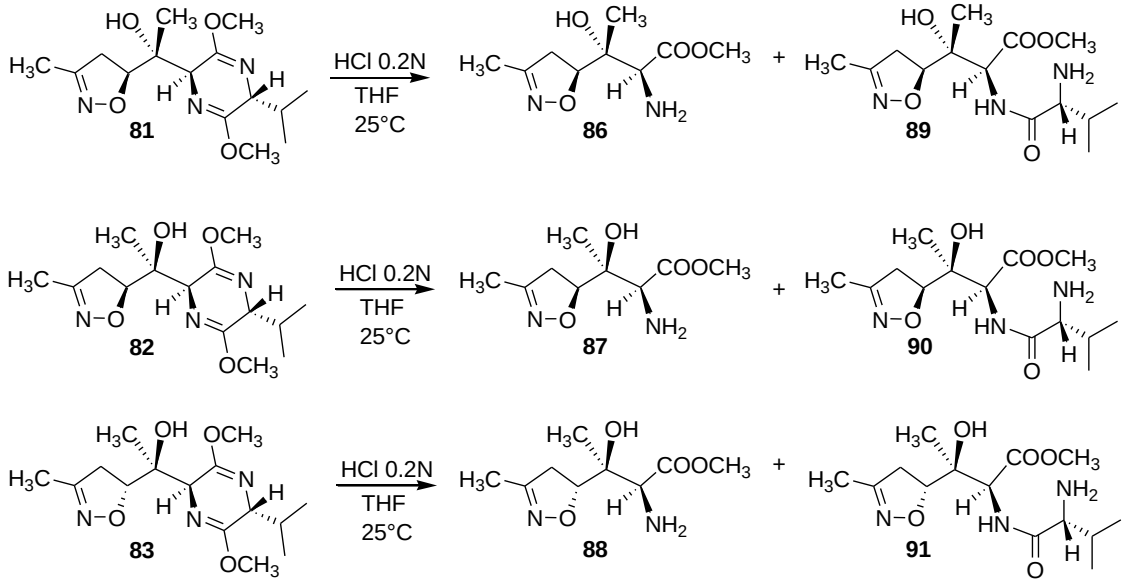


Figure 32: Transition state for reaction between *Schöllkopf's* reagent and **(*S*)-41**

2.6.6 Hydrolysis of Adducts 81-83

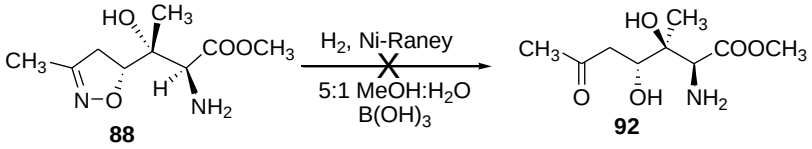
Adducts **81-83** were hydrolysed under mild conditions to give *β*-substituted L-threonines methyl esters **86-88** and the dipeptides **89-91** (Scheme 38). Amino esters **86-88** were easily separated from their corresponding dipeptides **89-91** by means of column chromatography and their structure was assigned using ^{1}H- and ^{13}C-NMR analysis.[59, 62, 63]



Scheme 38: Hydrolysis of adducts **81-83**

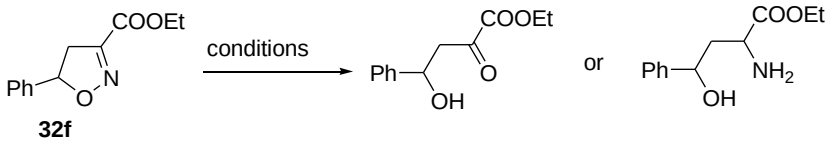
2.7 Study of the Cleavage of 2-Isoxazoline Ring

In order to obtain polyfunctionalyzed β-hydroxy-α-amino acids, we planned to cleave the isoxazoline ring of **88.** Initially Ni-catalyzed hydrogenolysis, that we previously used,[59, 68] run in hydrolytic conditions (a methodology developed by Curran),[64] led to a mixture of undefined products (Scheme 39).



Scheme 39: Isoxazoline ring opening using Curran conditions

This result prompted us to study the cleavage on more simple substrates. Although the opening of 2-isoxazolines has been extensively studied,[103] this reaction remains still quite substrate-dependent. As a test substrate we chose the isoxazoline **32f**. Therefore this compound was subjected to different set of reaction conditions as summarized in Table 18.

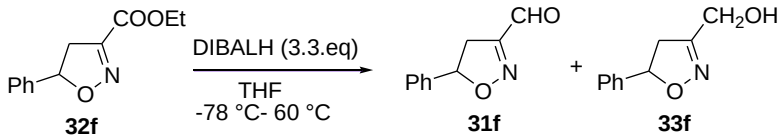


Entry	Conditions	Result
1	H_2/Ni-Raney, MeOH/H_2O 5/1, $B(OH)_3$	Complex mixture
2	$NiSO_4$ (1eq)/$NaBH_4$ (4.5 eq)	Complex mixture
3	$NiCl_2 \cdot 6H_2O$ (3eq), $NaBH_4$ (10eq), Boc_2O (3eq), MeOH/THF 3/1	Complex mixture
4	DIBALH (3.3.eq), THF, -78 °C→60 °C	Mixture of **33f** and **31f**
5	$Mo(CO)_6$ (1 eq), CH_3CN/H_2O, reflux	Decomposition
6	PMHS (4 eq), Boc_2O (1.1 eq), Pd(OH) (cat 2%), EtOH, reflux	Complex mixture
7	H_2/Ni-Raney, AcOEt	**94**+ **95** (~10%)
8	H_2/Ni-Raney, AcOEt, Boc_2O (1.1 eq)	Starting material recovered

Table 18: Attempted cleavage of isoxazoline ring

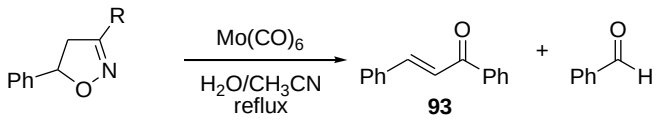
Initially, we tested again the conditions developed by Curran,[64] that lead to *β*-hydroxy-ketone. However, also in this case we isolated a mixture of undefined products (Table 18, entry 1). We therefore thought to change the reductant system, using a nickel salt/borohydride system. Using the conditions previously reported by Lakhvich,[104] we again isolated a mixture of undefined products (Table 18, entry 2). By carrying out the same reaction in the presence of Boc_2O anhydride (Table 18, entry 3)[105] we thought that protection of the newly formed alcohol and amine might prevent subsequent reaction of polymerisation with the ester functionality. Unfortunately also in this case, although the thorough analysis carried out, we were not able to identify any useful product in the reaction mixture.

Scott and co-workers in 2006 reported a very simple method for the cleavage of the N-O bond of isoxazolines.[106] They found that DIBALH could reduce the C-N bond and cleave the N-O one, leading to amino alcohol in high yield and high diastereoselectivity. However when isoxazoline **32f** was subjected to the same conditions, a mixture of aldehyde **31f** and alcohol **33f** was formed from reduction of ester (Scheme 40 and Table 18, entry 4).



Scheme 40: Cleavage of isoxazoline ring using DIBALH

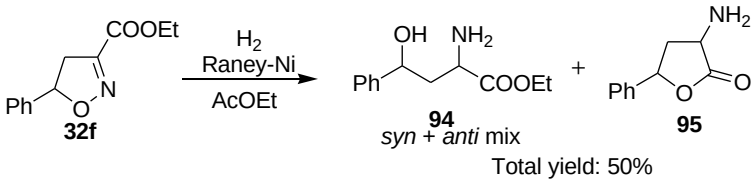
Another reagent widely used and studied for the cleavage of 2-isoxazoline is $Mo(CO)_6$.[107, 108] Treatment of our substrate with $Mo(CO)_6$ in acetonitrile led to decomposition of the starting material (Table 18, entry 5). Kobayashi[109] and co-workers reported some difficulties in the cleavage of 5-phenyl- Δ^2-isoxazolines as well. In fact they only obtained the dehydrated product **93** and the benzaldehyde (Scheme 41) .



Scheme 41: Kobayashi's cleavage of isoxazoline ring with $Mo(CO)_6$

A more recent method used $Pd(OH)_2$ as catalyst and the polimer polymethylhydrosiloxane (PMHS) as the reductant.[110] This methodology is used also in presence of Boc anhydride to protect the newly formed amine. However, when reacting ester **32f** under these conditions, complex mixture was obtained (Table 18, entry 6).

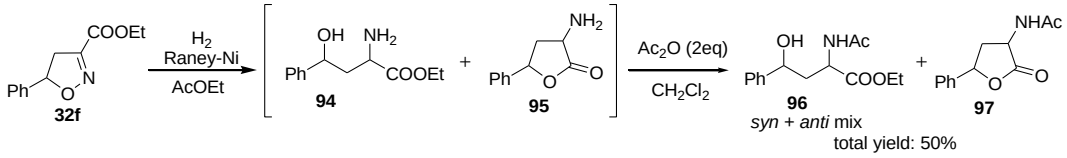
Finally we decided to go back to the Ni-catalyzed hydrogenolysis but run in anhydrous conditions. The reaction afforded a mixture of the two expected *syn* and *anti* amino alcohols **94** together with the two cyclic products **95** deriving from the lactonization between the alcohol and the ester functionality (Scheme 42 and Table 18, entry 7). The amount of **95** rose from 10% to 30% after the column chromatography, due to the acidity of the silica that catalyzed the lactonization.



Scheme 42: Cleavage of isoxazoline ring with H_2/Ni Raney in anhydrous conditions

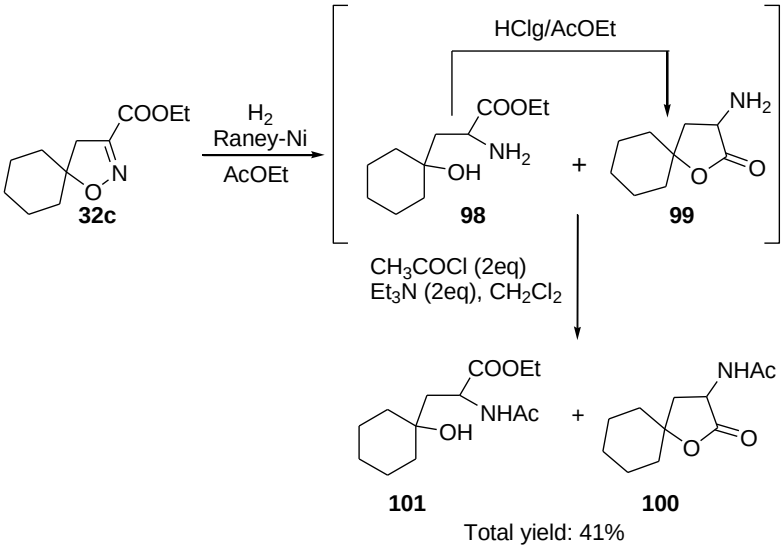
In order to avoid the formation of the close product, we tried running the hydrogenation reaction in presence of Boc anhydride to protect the newly formed alcohol and amine. Unfortunately we were able to recover just the unreacted starting material (Table 18, entry 8).

It was possible to avoid lactonization due to column chromatography by treating the crude material after hydrogenation with two equivalents of acetic anhydride. Surprisingly we obtained the amino alcohol protected just on the amine functionality **96** (Scheme 43). The amount of lactone detected in the crude NMR after hydrogenation (~10%) remained constant after acetylation and column chromatography, despite the alcohol not being protected.



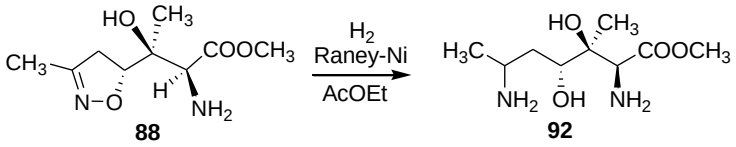
Scheme 43: Hydrogenation of isoxazoline of **32f** ring followed by acetilation

The Ni-catalyzed hydrogenolysis reaction was tested also on isoxazoline **32c** (Scheme 44). Also in this case, together with the expected amino alcohol **98**, it was possible to identify the lactone **99** (~36%) in the crude NMR after hydrogenation. However, in this case, the treatment of the crude mixture with acetyl chloride was less successful. It was possible to isolate the *N*-acetylated lactone **100** and the *N*-acetylated amino ester **101**, thought the latter proved not to be stable and cyclised to give **100**.



Scheme 44: Hydrogenation of isoxazoline of **32c** ring followed by acetilation

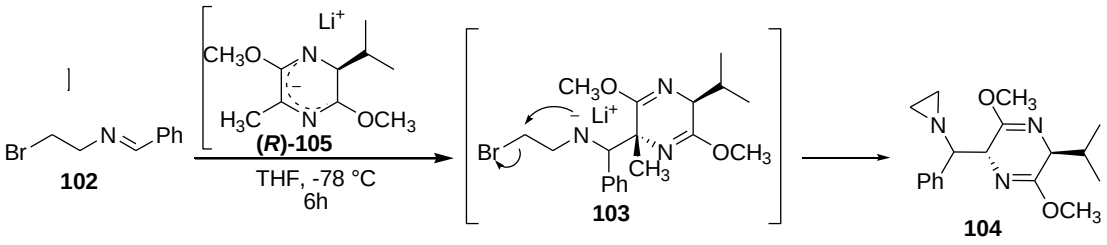
Finally we used Ni-catalyzed hydrogenolysis in anhydrous condition to open the ring of isoxazoline **88**, obtaining *γ*-hydroxy-3-amino-L-threonine derivative **92** in 25% yield (Scheme 45). In the ^{1}H NMR spectra of crude reaction mixture it was possible to detect only one diastereoisomer. Spectroscopic data and HRMS (FT-ICR) confirmed the structure but it was not possible to obtain suitable crystals for X-ray analysis necessary to assign the absolute configuration of the newly formed stereocentre C-6. Despite the low yield of compound **92**, this remains the only method to obtain this highly functionalized molecule.



Scheme 45: Cleavage of isoxazoline ring of amino ester **88** with H_2/Ni Raney in anhydrous conditions

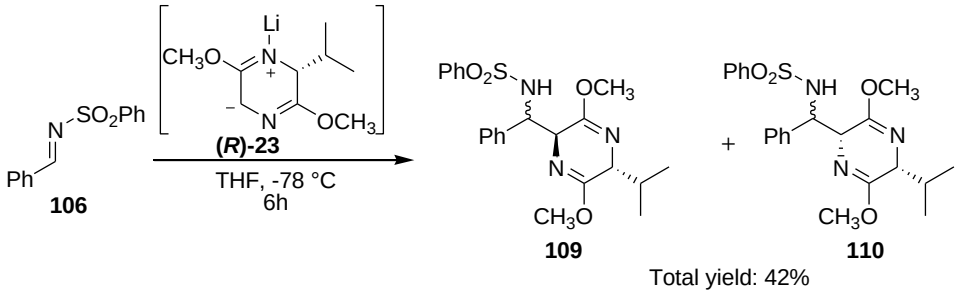
2.8 Preliminary Studies on Addition of Schöllkopf's Reagent Anion to Imines

After having studied the reaction between *Schöllkopf's* reagent and aldehydes and ketones, in the last part of my PhD we focussed our attention on a different electrophile, imines. Only one example has been reported in the literature by *Schöllkopf* himself about this reaction (Scheme 46).[111] In that case azaenaolate **(*S*)-105** reacted with the imine functionality of **102**, providing the intermediate **103**, that cyclised into product **104**. The attack on the imine occurred on the opposite face of *iso*propyl group. However nothing was reported about the diastereoselectivity of the newly formed C-N bond.



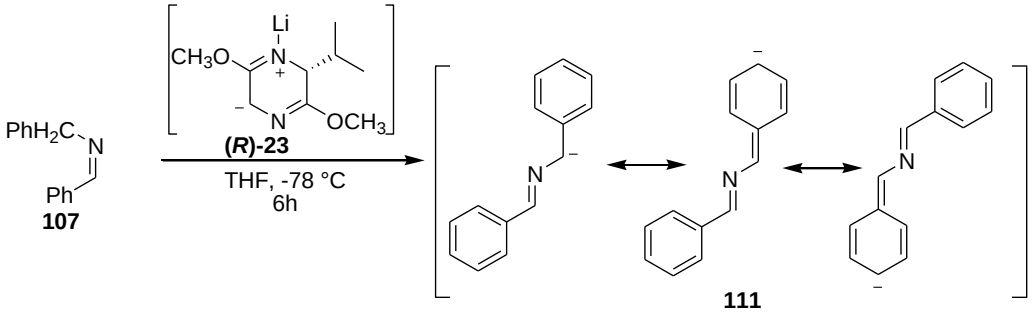
Scheme 46: Reaction of azaenolate **(*S*)-105** with an imine group

In order to do a preliminary screening, we chose three imines **106**-**108**, all commercially available, bearing three different R group on the nitrogen. Following the general procedure, a solution of imine **106** or **107** was added to the anion of the bislactim ether **(*R*)-23** generated by *n*BuLi in THF at –78 °C. In the case of sulphonyl imine **106**, the reaction occured with a low yield and provided all the four possible diastereoisomers (Scheme 47). Adducts **109** derived from the favourite attack of the *Schöllkopf's* azaenolate **(*R*)-23** from the opposite group of isopropyl, while for adducts **110** the attack occurred from the same side of *iso*propyl. However the four products couldn't be separated by column chromatography.



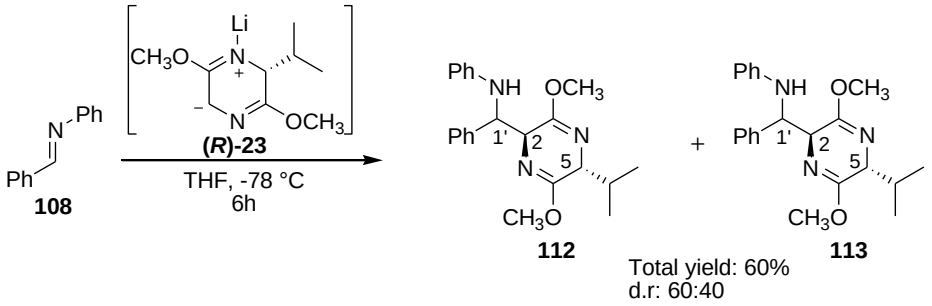
Scheme 47: Reaction between Schöllkopf's reagent and sulphonyl imine **106**

The reaction between benzyl imine **107** and *Schöllkopf's* anion **(*R*)-23** didn't occur because **(*R*)-23** deprotonated the benzylic hydrogen of **107**, providing the unreactive poly-conjugated system **111** (Scheme 48).



Scheme 48: Reaction between Schöllkopf's reagent and sulphonyl imine **107**

The reaction between phenyl imine **108** and *Schöllkopf's* azaenolate **(*R*)-23** occurred in good yield and provided just two of the four possible diastereoisomers, **112** and **113**. ^{1}H-NMR of the products shown a *trans* relationship between H-2 and H-5, confirming the attack of *Schöllkopf's* anion from the side opposite to isopropyl group. However the diastereoselection in the formation of the new stereocenter at C-1' proved to be relatively low, as the two products were formed with a *d.r.* of 60:40. Ongoing X-ray analysis will assign the absolute configuration at C-1'of **112** and **113** allowing to establish which of the two is the major one.



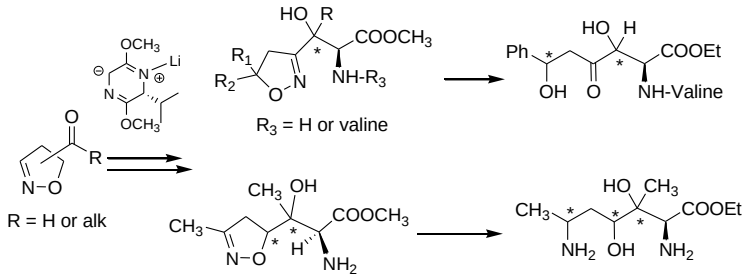
Scheme 49: Reaction between *Schöllkopf's* reagent and phenyl imine **108**

The hydrolysis of pyrazine ring to obtain the desired *a,β*-diamino acids is object of ongoing researches.

3 CONCLUSION

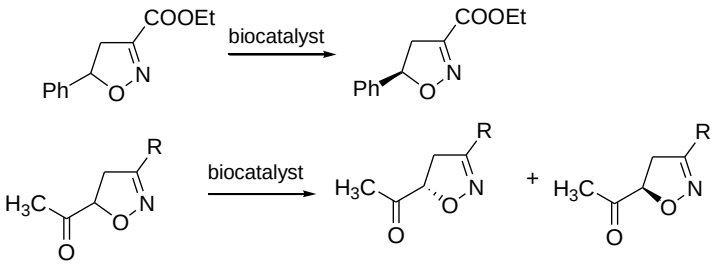
In summary, a simple method to obtain enatiomerically pure β-hydroxy-α-amino acids β-substituted with a 4,5-dihydroisoxazole nucleus was developed. This involved the reaction between *Schöllkopf's* reagent and Δ^2-isoxazoline ring bearing a carbonyl group (aldehyde or ketone) in position 3 or 5 of the ring (Scheme 50). Reaction between *Schöllkopf's* reagent and enantiomerically pure 5-acetil-Δ^2-isoxazolines was throughly studied in order to explain the stereochemical outcome of the reaction.

Δ^2-isoxazoline ring was further exploited and its cleavage led to the formation of polifunctionalized amino acids or dipeptides (see Scheme 50) that can be potentially incorporated in polypeptides with biological interest.



Scheme 50: Transformation of Δ^2- isoxazoline ring bearing a carbonyl group into polifunctionalized amino acids or dipeptides

Moreover strategies to obtain enantiomerically pure 5-substituted isoxazoline through enzymatic resolution were developed (Scheme 51).



Scheme 51: Enzymatic resolution of 5-substituted-Δ^2-isoxazolines

A preliminary study on the synthesis of α,β-diamino acids using the reaction between *Schöllkopf's* reagent and imines was also started. The development of this project, with the aim to extend the methodology to more complex imines, is now ongoing.

4 EXPERIMENTAL

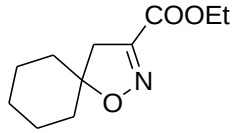
4.1 General informations

Melting points were measured using a *Büchi* B-540 apparatus and are uncorrected. ^{1}H and ^{13}C-NMR spectra were recorded in $CDCl_3$ (unless otherwise specified) on a *Bruker AMX 300* spectrometer; chemical shifts (δ) are given in ppm relative to TMS and all of the coupling constants are in Hertz. Optical rotation values were measured at 25 °C on a *Jasco P-1030* polarimeter. The MS spectra were determined using a *VG Analytical 7070 EQ* mass spectrometer with an attached *VG analytical 11/250* data system. The IR spectra were determined using a *Jasco FT-IR-4100* spectrometer, in cm^{-1}.

4.2 General procedure for the synthesis of compounds 32c-f

A solution of alkene **34c-f** (5 mmol, 1 equiv.), ethyl nitroacetate (10 mmol, 2 equiv.) and DABCO (0.5 mmol, 0.1 equiv.) in ethanol (20 mL) was heated at 80 °C for five days in a sealed tube. The organic solvent was evaporated off and the products were purified by column chromatography on silica gel (hexane/ethyl acetate: 80/20).

4.2.1 **Oxa-2-aza-spiro[4.5]dec-2-ene-3-carboxylic acid ethyl ester 32c**



Colourless liquid (70%);

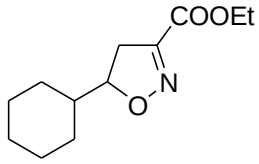
^{1}H NMR: δ 1.37 (3H, t, J = 7.1, CH_3); 1.40-1.90 (10H, m, -$(CH_2)_5$-); 2.89 (2H, s, H-4); 4.31 (2H, q, J = 7.1, CH_2).

^{13}C NMR: δ 13.79 (CH_3); 22.82, 24.48, 35.94 (-$(CH_2)_5$-); 43.0 (C-4); 61.4 (O-CH_2); 90.36 (C-5); 150.48 (C-3); 160.77 (C=O).

MS-EI (m/z): 211 (M^+).

IR (nujol): 1717 ($\nu_{C=N}$, C=N), 1740 ($\nu_{C=O}$, C=O).

4.2.2 **Ethyl 5-cyclohexyl-4,5-dihydroisoxazole-3-carboxylate 32d**



White solid (*n*-hexane) (77%)

m.p.: 48.6 -49.5 °C

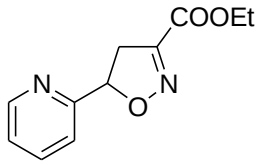
^{1}H NMR: δ 1.38(3H, t, J = 7.1, CH_3); 2.00-2.09 (11H, m, C_6H_{11}); 2.94 (1H, dd, J = 9.2, 17.6 H-4 isox); 3.16 (1H, dd; J = 11.1, 17.6, H-4 isox); 4.35 (2H, q, J = 7.1, OCH_2); 4.59 (1H, ddd, J = 9.2, 11.1, H-5 isox)

^{13}C NMR: δ 14.04 (CH_3); 25.54-26.13-28.02 ($CH_2(C_6H_{11})$); 35.74 (C-4isox); 42.08 ($CH(C_6H_{11})$); 61.78 (OCH_2); 88.19 (C-5 isox); 151.26 (C=N); 160.80 (O-C=O).

MS-EI (m/z): 225 (M^+), 152, 83

IR (nujol) 1711 ($\nu_{C=O}$, C=O).

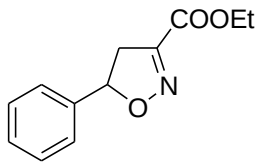
4.2.3 **Ethyl 4,5-dihydro-5-(pyridin-2-yl)isoxazole-3-carboxylate 32e**



Brown solid (di*iso*propyl ether) (55%)

Spectroscopic and analytical data are in agreement with those previously reported. [112]

4.2.4 **5-Phenyl-4,5-dihydroisoxazole-3-carboxylic acid ethyl ester 32f**



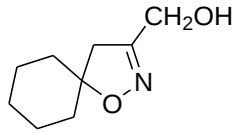
Oil (84%)

Spectroscopic and analytical data are in agreement with those previously reported.[65]

4.3 General procedure for the synthesis of compounds 33c, d, f

A solution of ester **32c, d, f** (10 mmol, 1 equiv.) in ethanol (10 mL) (ethanol/CH_2Cl_2: 1/1 for **32c**) was added dropwise to suspension of $NaBH_4$ (26 mmol, 2.6 equiv.) in ethanol (20 mL) at 0 °C. The reaction was stirred at room temperature for 6 hours. The organic solvent was evaporated off and the residue was poured into water. Acetic acid was added until pH=6, and the mixture was extracted with several portions of ethyl acetate. The combined extracts were dried (Na_2SO_4) and concentrated at reduced pressure. The crude alcohols were purified by column chromatography on silica gel (Hexane/AcOEt 6/4).

4.3.1 **(1-Oxa-2-aza-spiro[4.5]dec-2-en-3-yl)-methanol 33c**



Colourless liquid (89%);

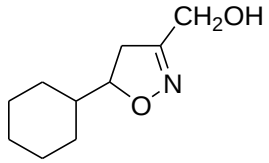
^{1}H NMR: δ 1.46-1.82 (10H, m, -$(CH_2)_5$-); 2.54 (1H, broad, OH); 2.78 (2H, s, H-4 isox); 4.39 (2H, s, CH_2-O).

^{13}C NMR: δ 23.81, 25.4, 36.74 (-$(CH_2)_5$-); 45.33 (C-4 isox); 58.86 (CH_2-O); 87.47 (C-5 isox); 158.51 (C-3).

MS-EI (m/z): 169 (M^+).

IR (nujol): 3374 (ν_{O-H}, OH), 1625 ($\nu_{C=N}$, C=N).

4.3.2 **(5-cyclohexyl-4,5-dihydroisoxazol-3-yl)methanol 33d**



White solid (di*iso*propyl ether) (77%)

m.p: 69.5-70.5 °C

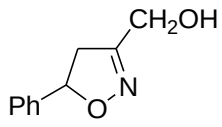
^{1}HNMR: δ 2.0-2.09 (11H, m, -C_6H_{11}); 2.17 (1H, s broad, OH); 2.77 (1H, dd, *J* = 8.9, 17.1, H-4 isox); 3.00 (1H, dd, *J* = 10.5, 17.1, H-4 isox); 4.38 (1H, dd, *J* = 8.9, 10.5, H-5 isox); 4.39 (2H, s, CH_2OH)

^{13}C-NMR: δ 25.65-26.20-28.40 (CH_2 (C_6H_{11})); 37.44 (C-4 isox); 42.21 (CH (C_6H_{11})); 57.96 (CH_2OH); 85.37 (C-5 isox); 158.57 (C=N).

MS-EI (m/z): 183 (M^+).

IR (nujol): 3377 (ν_{O-H}, OH), 1623 ($\nu_{C=N}$, C=N).

4.3.3 **5-Phenyl-4,5-dihydroisoxazol-3-yl]-methanol 33f**

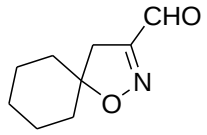


Colourless solid (85%). Spectroscopic and analytical data are in agreement with those previously reported.[65]

4.4 General procedure for the synthesis of compounds 31 c, d, f

Following a reported procedure,[59] MnO_2 (5/1 w/w) was added to a solution of alcohol **33c, d, f** (10 mmol) in CH_2Cl_2 (15 mL), and the reaction mixture was stirred at room temperature for 12 hours. The MnO_2 was filtered through celite, and the organic solvent was evaporated off. The resulting aldehydes were purified through column chromatography (Exane/AcOEt 80/20) to remove MnO_2 residues.

4.4.1 **1-Oxa-2-aza-spiro[4.5]dec-2-ene-3-carbaldehyde 31c**



Colourless liquid (79%);

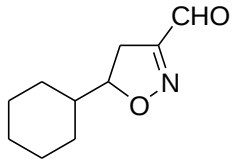
^{1}H NMR: δ 1.50-1.90 (10H, m, -$(CH_2)_5$-); 2.84 (2H, s, H-4 isox); 9.95 (1H, s, CHO).

^{13}C NMR: δ 23.09, 24.71, 36.28 (-$(CH_2)_5$-); 40.13 (C-4 isox); 92.43 (C-5); 158.01 (C-3 isox); 186.43 (CO).

MS-EI (m/z): 167 (M^+).

IR (nujol): 1695 ($\nu_{C=O}$, C=O), 1573 ($\nu_{C=N}$, C=N).

4.4.2 **5-cyclohexyl-4,5-dihydroisoxazole-3-carbaldehyde 31d**



Oil (60%)

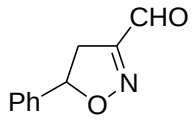
^{1}H NMR: δ 2.00-2.09 (11H, m, C_6H_{11}); 2.83 (1H, dd, *J* = 9.1, 17.5, H-4), 3.07 (1H, dd, *J* = 11.2, 17.5; H-4); 4.61 (1H, ddd, *J* = 9.1, 11.2, H-5), 9.91 (1H, s, C*H*O)

^{13}C-NMR: δ 25.56-26.14-28.09 (CH_2 (C_6H_{11})); 32.51 (C-4 isox); 42.22 (CH (C_6H_{11})); 89.49 (C-5 isox); 159.39 (C=N); 185.84 (CHO).

MS-EI (m/z): 181 (M^+).

IR (nujol): 1669 ($\nu_{C=O}$, C=O)

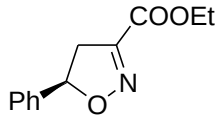
4.4.3 **4,5-dihydro-5-phenylisoxazole-3-carbaldehyde 31f**



Oil (83%). Analytical and spectroscopic data are in agreement with those previously reported.[65]

4.5 Enzimatic resolution of (±)-32f

4.5.1 **(5*R*)-5-Phenyl-4,5-dihydroisoxazole-3-carboxylic acid ethyl ester (*R*)-32f**

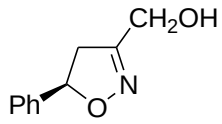


Compound **(*R*)-32f** was obtained by biotransformation, with 3.57 g of ester **(±)-32f** dissolved in DMSO and 3.75 g of Lipase from hog pancreas (PPL) being added to 700 ml of 0.1 M phosphate buffer, pH 7. The biotransformation was carried out at 30°C under magnetic stirring. After 45 min (HPLC monitoring), the reaction was extracted

three times with ethyl acetate to recover ester **(*R*-)-32f**. The aqueous phase was brought to pH 2 with HCl and extracted three times with ethyl acetate to recover the acid **(*S*)-47f**. The organic extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude **(*R*)-32f** was purified by means of flash chromatography on silica gel (hexane/ethyl acetate: 90/10). Colourless oil (30%);

$[\alpha]_D^{25}$ -285.3 (*c* 0.95, $CHCl_3$).

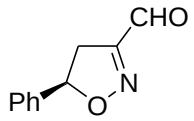
4.5.2 [(5*R*)-5-Phenyl-4,5-dihydroisoxazol-3-yl]-methanol (*R*)-33f



Alcohol **(*R*)-33f** was prepared starting from the ester **(*R*)-32f** as previously described for the racemic compound. Analytical and spectroscopic data are in agreement with those previously reported for the racemic compound.

$[\alpha]_D^{25}$ -166.3 (*c* 1.05, $CHCl_3$)

4.5.3 (5*R*)-4,5-dihydro-5-phenylisoxazole-3-carbaldehyde (5*R*)-31f

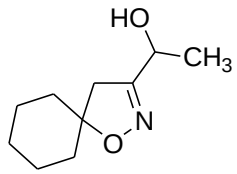


Aldehyde **(*R*)-31d** was prepared the ester **(*R*)-32f** as previously described for the racemic compound. Analytical and spectroscopic data are in agreement with those previously reported for the racemic compound.
Colourless oil (83%);
$[\alpha]_D^{25}$ -459 (*c* 1.29, $CHCl_3$).

4.6 General procedure for the synthesis of compounds 50a-d

A solution of the appropriate Grignard reagent (7.5 mmol, 2.5 equiv) was added dropwise at -78 °C to a solution of aldehyde **31c** (3 mmol) in 5 mL of anhydrous THF. The reaction mixture was stirred for 3 hours and allowed to warm at -20 °C. A saturated solution of NH_4Cl (10 mL) was added to the reaction and the mixture was allowed to warm to room temperature. THF was removed under reduced pressure and the aqueous layer was extracted with AcOEt (3 × 3mL). The combined organic phases were dried (Na_2SO_4) and the solvent removed under reduced pressure. The product were purified by column chromatography (hexane/AcOEt: 75/25) to give alcohols **50a-d.**

4.6.1 **1-(1-oxa-2-azaspiro[4.5]dec-2-en-3-yl)ethan-1-ol 50a**



Oil (73%)

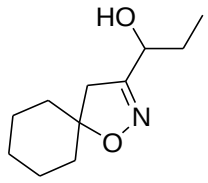
^{1}H NMR δ: 1.4 (3H, d, J = 6.6 CH_3); 1.8-1.4 (10 H, m. cyclohexyl); 2.02 (1H, s broad, OH); 2.68 (1H, d J = 16.97, H-4); 2.75 (1H, d J = 16.97, H-4); 4.65 (1H, q, J = 6.6 CH)

^{13}C NMR δ: 20.70 (CH_3); 23.27, 24.87, 36.10 (-$(CH_2)_5$); 43.12 (C-4); 63.75 (CH); 86.55 (C-5); 161.5 (C=N)

IR (nujol): 3397 (ν_{O-H}, OH), 1624 ($\nu_{C=N}$, C=N).

MS-EI (m/z): 183 (M^+), 166.

4.6.2 **1-(1-oxa-2-azaspiro[4.5]dec-2-en-3-yl)propan-1-ol 50b**



Liquid (46%)

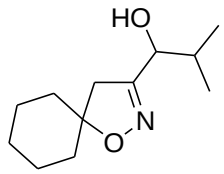
^{1}H NMR δ: 0.95 (3H, t, J = 6.2, CH_3); 1.4-1.8 (10H, m, cyclohexyl); 2.1 (1H, d, J = 4.5, *CH*OH), 2.6 (1H, d, J = 17.0, H-4); 2.75 (1H, d, J = 17.0, H-4); 4.45 (2H, dq, J = 4.5, 6.2 CH_2)

^{13}C NMR δ: 9.32 (CH_3); 23.27, 24.89 (-$(CH_2)_5$); 27.56 (CH_2); 36.20 (-$(CH_2)_5$); 43.14 (C-4); 68.89 (CHOH); 86.29 (C-5); 160.61 (C=N)

IR (nujol): 3394 (ν_{O-H}, OH), 1623 ($\nu_{C=N}$, C=N).

MS-EI (m/z): 197 (M^+), 140

4.6.3 **2-methyl-1-(1-oxa-2-azaspiro[4.5]dec-2-en-3-yl)propan-1-ol 50c**



White solid (25%)

m.p: 54-56 °C

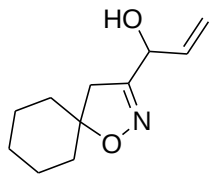
^{1}H NMR δ: 0.85 (3H, d, J = 6.7, CH_3); 0.95 (3H, d, J = 6.7, CH_3); 1.3-1.75 (10H, m, cyclohexyl); 1.75-1.85 (1H, m, *CH*$(CH_3)_2$); 2.55 (1H, d, J = 17.0 , H-4); 2.75 (1H, d, J = 17.0, H-4); 3,3 (1H, s broad, OH); 4.05 (1H, d, J = 7.5, *CH*OH)

^{13}C NMR δ: 17.85 (CH_3); 18.56 (CH_3); 23.33, 24.96 (-$(CH_2)_5$); 31.90 (*CH*$(CH_3)_2$); 36.27, 36.41 (-$(CH_2)_5$); 43.59 (C-4); 73.01 (C*H*OH); 86.31 (C-5); 160.45 (C=N)

MS-EI (m/z): 212 (M^+), 194

IR (nujol): 3394 (ν_{O-H}, OH), 1623 ($\nu_{C=N}$, C=N).

4.6.4 **1-(1-oxa-2-azaspiro[4.5]dec-2-en-3-yl)prop-2-en-1-ol 50d**



Liquid (58%)

^{1}H NMR δ: 1.4-1.8 (10H, m, cyclohexyl); 2.65 (1H, d, J = 17.0, H-4); 2.75 (1H, d, J = 17.0, H-4); 4.95 (1H, d, J = 5.8, CHOH); 5.25 (1H, d, J = 10.4, CH=*CH_2*); 5.45 (1H, d, J = 17.2, CH=*CH_2*); 5.9 (1H, ddd; J = 5.8, 10.4, 17.2, *CH*=CH_2)

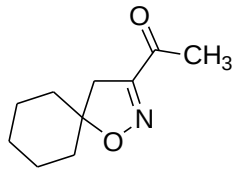
^{13}C NMR δ: 23.38, 25.02, 36.30 (-$(CH_2)_5$); 43.50 (C-4); 69.38 (*CH*OH); 87.14 (C-5); 117.17 (CH=*CH_2*); 136.28 (*CH*=CH_2); 159.13 (C=N)

MS-EI (m/z): 195 (M^+).

4.7 General procedure for the synthesis of compounds 39a-d

Following a reported procedure,[59] MnO_2 (5/1 w/w) was added to a solution of alcohol **39a-d** (2 mmol) in CH_2Cl_2 (5 mL), and the reaction mixture was stirred at room temperature for 12 hours. The MnO_2 was filtered through celite, and the organic solvent was evaporated under reduced pressure. The product was purified by column chromatography (hexane/AcOEt: 90:10) to give ketones **39a-d**.

4.7.1 **1-(1-oxa-2-azaspiro[4.5]dec-2-en-3-yl)ethan-1-one 39a**



White solid (exane) (88%)

m.p.: 55-58 °C

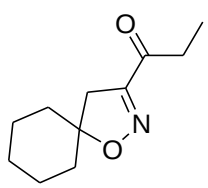
^{1}H NMR δ: 1.4-1.8 (10H, m, cyclohexyl); 2.48 (3H, s, CH_3); 2.81 (2H, s, H-4)

^{13}C NMR δ: 23.12, 24.75 (-$(CH_2)_5$); 26.26 (CH_3); 29.62, 36.31(-$(CH_2)_5$), 41.65 (C-4) 91.46 (C-5) ; 157.89 (C=N); 193.70 (C=O)

IR (nujol): 1679 ($\nu_{C=O}$, C=O).

MS-EI (m/z): 181 (M^+), 164

4.7.2 **1-(1-oxa-2-azaspiro[4.5]dec-2-en-3-yl)propan-1-one 39b**



Liquid (83%)

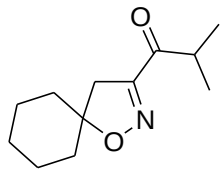
^{1}H NMR δ: 1.13 (3H, t, J = 7.4, CH_3); 1.4-1.8 (10H, m, cyclohexyl); 2.82 (2H,s, H-4); 2.9 (2H, q, J = 7.4, CH_2)

^{13}C NMR δ: 7.60 (CH_3); 22.87, 24.61 (-$(CH_2)_5$); 31.88 (CH_2); 36.53 (-$(CH_2)_5$); 41.77 (C-4); 90,67 (C-5); 157.00 (C=N); 196.43 (C=O)

IR (nujol): 1682 ($\nu_{C=O}$, C=O).

MS-EI (m/z): 195 (M^+), 178

4.7.3 **2-methyl-1-(1-oxa-2-azaspiro[4.5]dec-2-en-3-yl)propan-1-one 39c**



Liquid (59%)

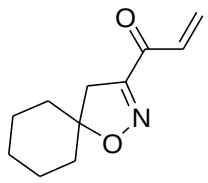
^{1}H NMR δ: 1.15 (6H, d, J = 6.9, 2 CH_3); 1.8-1.4 (10H, m, cyclohexyl); 2.82 (2H, s, H-4); 3.55 (1H, sept, J = 6.9, CH)

^{13}C NMR δ: 18.60 (CH_3), 23.26, 24.77, 36.26 (-$(CH_2)_5$); 36.60 (CH); 42.11 (C-4); 90.80 (C-5); 156.40 (C=N); 299.20 (C=O)

MS-EI (m/z): 209 (M^+), 192

IR (nujol): 1680 ($\nu_{C=O}$, C=O).

4.7.4 **1-(1-oxa-2-azaspiro[4.5]dec-2-en-3-yl)prop-2-en-1-one 39d**



Yellow solid (exane) (53%)

m.p.: 45.2-48.6 °C

^{1}H NMR δ: 1.4-1.8 (10H, m, cyclohexyl); 2.9 (2H, s, H-4), 5.83 (1H, dd, J = 1.6, 10.5, CH=CH_2), 6.5 (1H, dd, J = 1.6, 17.3, CH=CH_2); 7.21 (1H, J = 10.5, 17.3, CH=CH_2)

^{13}C NMR δ: 23.01, 24.62, 36.16 (-$(CH_2)_5$); 41.79 (C-4); 91.12 (C-5); 129.31 (CH=CH_2); 131.33 (CH=CH_2); 157.85 (C=N); 184.01 (C=O)

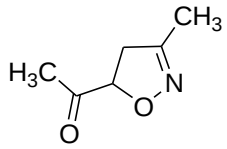
MS-EI (m/z): 193 (M^+), 176

IR (nujol): 1607 ($\nu_{C=N}$, C=N), 1665 ($\nu_{C=O}$, C=O)

4.8 Synthesis of 5-Acetyl-4,5-dihydroisoxazole 41 and 42

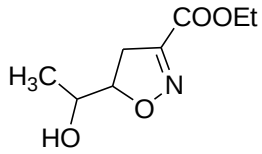
In the case of 5-acetyl-4,5-dihydoisoxazole **41** and **42** a general procedure was not followed. Below are reported the single procedures that have been used in the synthesis of these compounds.

4.8.1 **1-(4,5-dihydro-3-methylisoxazol-5-yl)ethanone (±)-41**



Compound **41a** was prepared starting from 3-buten-2-one and nitroethane, according to the known procedure.[54] Spectroscopic data were in agreement with those reported.

4.8.2 **Synthesis of 5-(1-Hydroxyethyl)-4,5-dihydro-isoxazole-3-carboxylic acid ethyl ester (±)-*synlanti*- 55**



A solution of 3-buten-2-ol (1.04 mL, 12 mmol), ethyl nitroacetate (2.64 mL, 24 mmol, 2 equiv) and DABCO (269 mg, 2.4 mmol, 0.5 equiv) in ethanol (30 mL) was heated at 80 °C for five days in a sealed tube. The organic solvent was evaporated under reduced pressure and the mixture of diastereoisomers was purified and separated by means of flash chromatography (SiO_2, hexane/ethyl acetate: 3/1), affording 1.7 gr of product (76%).

1st diast: *anti*-55

^{1}H NMR: δ 1.16 (d, *J* = 6.5, 3H, CH_3); 1.32 (t, *J* = 7.2, 3H, CH_3); 1.87 (d, *J* = 3.6, 1H, OH); 3.08 (dd, *J* = 17.7, 11.5, 1H, H-4); 3.22 (dd, J = 17.7, 8.9, 1H, H-4); 4.06 (m, 1H, H-1); 4.30 (q, *J* = 7.2, OCH2); 4.68 (ddd, *J* = 11.5, 8.9, 3.3, 1H, H-5).

^{13}C NMR: δ 13.9 (CH_3); 17.8 (CH_3); 32.8 (C-4); 61.95 (CH2); 66.8 (C-1), 87.5 (C-5); 152.0 (C-3); 160.4 (C=O).

IR (Nujol): 3433 (vOH, OH),1722 ($\nu_{C=O}$, C=O),1591 ($\nu_{C=N}$, C=N).

Anal. Calcd for $C_8H_{13}NO_4$: C, 51.33; H, 7.00; N, 7.48. Found: C, 51.19; H, 6.85; N, 7.33.

MS-FAB^{+} (m/z): 188 $[M+H]^{+}$.

2 nd diast: *syn*-55

^{1}H NMR: δ 1.28 (d, *J* = 6.5, 3H, CH_3); 1.37 (t, *J* = 7.1, 3H, CH_3); 1.99 (d, *J* = 6.2, 1H, OH); 3.06 (dd, *J* = 17.8, 8.2, 1H, H-4); 3.24 (dd, *J* = 17.8, 11.2, 1H, H-4); 3.78 (m, 1H, H-1); 4.33 (q, *J* = 7.1,OCH2); 4.67 (ddd, *J* = 11.2, 8.2, 5.2, 1H, H-5).

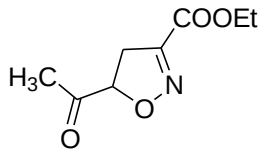
^{13}C NMR: δ 14.1 (CH_3);18.8 (CH_3); 35.6 (C-4); 62.1 (CH_2); 68.9 (C-1), 87.1 (C-5); 152.0 (C-3);160.4 (C=O).

IR (Nujol): 3430 (ν_{OH}, OH), 1720 ($\nu_{C=O}$, C=O), 1593 ($\nu_{C=N}$, C=N).

Anal. Calcd for $C_8H_{13}NO_4$: C, 51.33; H, 7.00; N, 7.48.Found: C, 51.22; H, 6.92; N, 7.38.

MS-FAB^{+} (m/z): 188 $[M+H]^{+}$.

4.8.3 Synthesis of 5-Acetyl-4,5-dihydro-isoxazole-3-carboxylic acid ethyl ester (±)-42



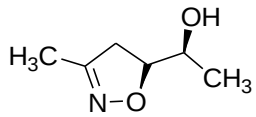
PCC/Al_2O_3 (3 equiv) was added to a solution of *syn*/ *anti*- **55** (1.7 g, 9.1 mmol, 1 equiv) in CH_2Cl_2 (40 mL), and the reaction mixture was stirred at reflux temperature for 24 h. The PCC was filtered through Celite, and the organic solvent was removed under

reduced pressure. The crude ketone was purified by column chromatography (SiO_2, hexane/ethyl acetate: 8/2). Oil (1.5 g, 90%). Spectroscopic data of compound **42** were in accord with those reported.[75]

4.9 Enzymatic resolution of (±)-41 and (±)-42

Ketone **41**[54] or **42** (1 mmol) dissolved in the minimum amount of ethanol, was added to a suspension of commercial fermenting yeast (5 g) in tap water (30 mL) containing KH_2PO_4(60 mg), Na_2HPO_4 (30 mg), $MgSO_4$ (30 mg) and glucose (10 g). If necessary, the pH of the mixture was kept at 5.5-6.0 by addition of diluted aqueous NaOH. The reaction was carried out at 35 °C under magnetic stirring for 24 h and monitored by TLC. The suspension was stirred with celite at 0 °C for 15 min and then filtered. The filtered water was extracted in continuous with CH_2Cl_2. The organic phase was dried over Na_2SO_4 and the solvent was evaporated at reduced pressure. The mixture of *syn*/*anti*-alcohols **56** (78% total yield) was purified by means of flash chromatography (SiO_2, hexane/ethyl acetate: 8/2) and separated by semi-preparative HPLC (Waters-Micropack, 10µ SiO_2, hexane/i-PrOH: 95/5, flow rate: 7 mL/min). The mixture of syn/anti-alcohols **55** (66% total yield) was purified and separated by means of flash chromatography (SiO_2, hexane/ethyl acetate: 85/15).

4.9.1 **(1*S*,5*S*)-1-(3-Methyl-4,5-dihydro-isoxazol-5-yl)-ethanol ((+)-*syn*-56)**



Oil.

^{1}H NMR: δ 1.22 (d, *J* = 6.4, 3H, CH_3); 1.98 (s, 3H, CH_3); 2.09 (broad s, 1H, OH); 2.73 (dd, *J* = 17.1, 7.4, 1H, H-4); 2.98 (dd, *J* = 17.1, 10.6, 1H, H-4); 3.68 (m, 1H, H-1); 4.39 (ddd, *J* = 10.6, 7.4, 5.7,1H, H-5).

^{13}C NMR: δ 12.9 (3-CH_3); 18.7 (CH_3); 40.6 (C-4); 68.9 (C-1), 83.6 (C-5); 155.75 (C-3).

IR (Nujol): 3419 (ν_{OH}, OH),1639 ($\nu_{C=N}$, C=N).

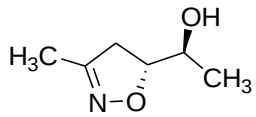
Anal.Calcd for $C_6H_{11}NO_2$: C, 55.80; H, 8.58; N, 10.84. Found: C, 55.62; H, 8.45; N, 10.78.

MS-EI$^+$ (m/z): 129 (M^+).

Chiral HPLC data: *e.e.* >98% (Chiralcel OD analytical column, hexane/*i*PrOH: 98/2, flow rate 1.5 mL/min, retention time: major (1*S*,5*S*) 21.8 min, minor (1*R*, 5*R*) 22.3 min)

$[\alpha]_D^{25}$ +148.2 (*c* 0.51, $CHCl_3$)

4.9.2 **(1*S*,5*R*)-1-(3-Methyl-4,5-dihydro-isoxazol-5-yl)-ethanol (−)-*anti*-56**



Oil.

^{1}H NMR: δ 1.13 (d, *J* = 6.5, 3H, CH_3); 1.85 (broad s, 1H, OH); 1.97 (s, 3H, CH_3); 2.80 (dd, *J* = 17.1,10.7, 1H, H-4); 2.97 (dd, *J* = 17.1, 8.6, 1H, H-4); 4.05 (m, 1H, H-1); 4.46 (ddd, *J* = 10.7, 8.6, 3.2, 1H, H-5).

^{13}C NMR: δ 13.1 (3-CH_3); 17.9 (CH_3); 37.8 (C-4); 67.05 (C-1); 84.1 (C-5); 156.0 (C-3).

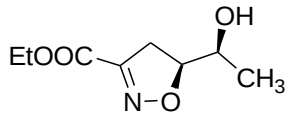
IR (Nujol): 3420 (ν_{OH}, OH), 1641 ($\nu_{C=N}$, C=N).

Anal.Calcd for $C_6H_{11}NO_2$: C, 55.80; H, 8.58; N, 10.84. Found: C, 55.70; H, 8.49; N, 10.74. MS-EI$^+$ (m/z): 129 (M^+).

Chiral HPLC data: *e.e.* >98% (Chiralcel OD analytical column, hexane/*i*PrOH: 98/2, flow rate 1.5 mL/min, retention time: major (1*S*,5*R*)18.5 min and minor (1*R*,5*S*)19.5 min.

$[\alpha]_D^{25}$ −90.0 (*c* 0.54, $CHCl_3$).

4.9.3 **(1*S*,5*S*)-5-(1-Hydroxyethyl)-4,5-dihydro-isoxazole-3-carboxylic acid ethyl ester (+)-*syn*-55.**



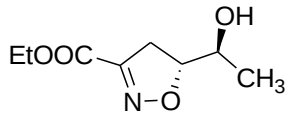
Oil.

Spectroscopic and analytical data are in agreement with those reported for the racemic compound.

Chiral HPLC data: *e.e.* >98% (Chiralcel OD analytical column, hexane/iPrOH: 98/2, flow rate: 1 mL/min, retention time: major (1*S*,5*S*) 56.7 min and minor (1*R*,5*R*) 60.1 min)

$[\alpha]_D^{25}$ +164.1 (*c* 0.39,$CHCl_3$)

4.9.4 (1*S*,5*R*)-5-(1-Hydroxyethyl)-4,5-dihydro-isoxazole-3-carboxylic acid ethyl ester (−)-*anti*-55



Oil.

Spectroscopic and analytical data are in agreement with those reported for the racemic compound.

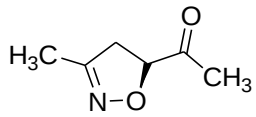
Chiral HPLC data: *e.e.*: 95% (Chiralcel OD analytical column, hexane/i-PrOH: 95/5, and a flow rate: 1 mL/min, retention time: minor (1*R*,5*S*) 20.6 and major (1*S*,5*R*) 22.6 min)

$[\alpha]_D^{25}$ −134.5 (*c* 0.91,$CHCl_3$)

4.10 General procedure for synthesis of (R)- and (S)-41 and (R)- and (S)- 42

PCC/Al_2O_3 (3 equiv) was added to a solution of alcohol (1 equiv) in CH_2Cl_2 (4mL), and the reaction mixture was stirred at reflux temperature for 24 h. The PCC was filtered through celite, and the organic solvent was evaporated off. The crude ketone was purified by column chromatography (SiO_2, hexane/ethyl acetate: 8/2).

(5*S*)-1-(3-Methyl-4,5-dihydro-isoxazol-5-yl)-ethanone (*S*)-41



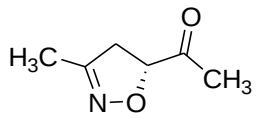
Spectroscopical data were in accord with those reported.[54]

Oil (81%).

Chiral HPLC data: *e.e.*>98% (Chiralcel OD analytical column, hexane/*i*-PrOH: 98/2, flow rate: 1.5 mL/min, retention time: minor (*R*) 10.5 min, major (*S*)11.8 min.

$[\alpha]_D^{25}$ +177.9 (*c* 0.62,$CHCl_3$).

4.10.1 **(5*R*)-1-(3-Methyl-4,5-dihydro-isoxazol-5-yl)-ethanone (*R*)-41**



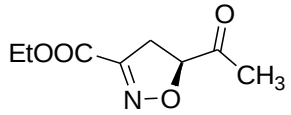
Spectroscopical data were in agreement with those previously reported.[54]

Oil (85%)

Chiral HPLC data: *e.e.*>98% (Chiralcel OD analytical column, hexane/i-PrOH: 98/2, flow rate: 1.5 mL/min, retention time: major (*R*) 10.5 min, minor (*S*)11.8 min.

$[\alpha]_D^{25}$ -170.5 (*c* 0.59,$CHCl_3$).

4.10.2 **(5*S*)-5-Acetyl-4,5-dihydro-isoxazole-3-carboxylic acid ethyl ester (*S*)-42**



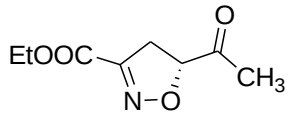
Spectroscopical data were in accord with those reported.[75]

Oil (75%).

Chiral HPLC data:*e.e.*: 92% (Chiralcel AD analytical, hexane/i-PrOH: 95/5, flow rate: 1 mL/min, retention time: major (*S*) 14.0 min, minor (*R*) 15.4 min)

$[\alpha]_D^{25}$ +182.7 (*c* 0.45, $CHCl_3$).

4.10.3 **(5*R*)-5-Acetyl-4,5-dihydro-isoxazole-3-carboxylic acid ethyl ester (*R*)-42**



Spectroscopical data were in accord with those reported.[75]

Oil (75%).

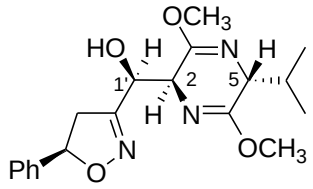
Chiral HPLC data:*e.e.*: 92% (Chiralcel AD analytical, hexane/i-PrOH: 95/5, flow rate: 1 mL/min, retention time: minor (*S*) 14.0 min, major (*R*) 15.4 min)

$[\alpha]_D^{25}$ −187.9 (*c* 0.55, $CHCl_3$).

4.11 General procedure for the synthesis of compounds 60-63

Butyllithium (0.81 mL of a 1.6 N solution in hexane, 1.3 mmol, 1.05 equiv.) was added to a solution of **(2*R*)-22** (0.22 mL, 1.23 mmol, 1 equiv.) in anhydrous THF (5 mL) cooled at –78°C, and the mixture was stirred for 45 min. A solution of triisopropoxytitanium (IV) chloride[82] (1.33 mmol, 1.075 equiv.), prepared by mixing titanium tetraisopropoxyde (1.0 mmol, 0.3 mL) in anhydrous hexane (2 mL) and titanium tetrachloride (0.33 mmol, 0.32 mL of a 1M solution in toluene), was added and stirring was continued for a further 45 min. Aldehyde **(−)-31f** (0.216 g, 1.23 mmol, 1 equiv.) in THF (4 mL) was added, and the mixture was stirred at –78°C for 6 h. The reaction mixture was allowed to warm to -10°C, after which a pH=7 phosphate buffer solution (10 mL) was added, and the mixture was extracted with CH_2Cl_2. The organic phase was separated and dried with Na_2SO_4, and the solvent was evaporated *in vacuo*. Compounds **60-63** were purified by means of flash cromathography on silica gel (hexane/ethyl acetate: 80/20) and subsequently separated by means of flash cromathography on silica gel (Supelco, Versaflash® station, CH_2Cl_2/ethyl acetate: 95/5). The diastereoisomeric ratio of compounds **60-63** was determined by means of HPLC analysis (Supelco Ascentis® Si column, hexane/*iso*PrOH: 95/5, flow: 0.7 mL min^{-1}).

4.11.1 **(*S*)-[(2*S*,5*R*)-5-Isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl]-[(5*R*)-5-phenyl-4,5-dihydroisoxazol-3-yl]-methanol 60**



Colourless solid (di*iso*propyl ether) (77%)

m.p. 92-94 °C

^{1}H NMR: δ 0.75, 1.08 (6H, 2d, *J* = 6.8, CH(CH_3)$_2$); 2.29 (1H, m, CH(CH$_3$)$_2$); 2.84 (1H, d, *J* = 7.5, OH); 3.19 (1H, dd, *J* = 17.0, 8.0, H-4 isox); 3.59 (1H, dd, *J* = 17.0, 10.9, H-4 isox); 3.66 (3H, s, OCH$_3$); 3.77 (3H, s, OCH$_3$); 4.04 (1H, t, *J* = 3.6, H-5 pyraz.); 4.26 (1H, t, *J* = 3.6, H-2); 5.00 (1H, dd, *J* = 7.5, 3.6, H-1'); 5.67 (1H, dd, *J* = 10.9, 8.0, H-5 isox.); 7.34-7.40 (5H, m, Ph); (by deuteration the signal at 2.84 disappeared and the signal at 5.00 turned into a doublet with *J* = 3.6).

^{13}C NMR: δ 16.78, 19.00 (CH(CH_3)$_2$); 31.94 (CH(CH$_3$)$_2$); 43.26 (C-4); 52.78 (3- and 6-OCH$_3$); 59.33, 61.02 (C-2 and C-5 pyr.); 68.90 (1'-C); 82.22 (C-5 isox.); 125.67, 128.09, 128.62, 141.05 (Ph); 159.52, 160.33, 166.60 (C-3 and C-6 pyr., C-3 isox.).

MS-FAB$^+$ (m/z): 360 (MH$^+$).

Anal. Calcd for $C_{19}H_{25}N_3O_4$: C, 63.51; H, 6.96; N, 11.69. Found: C, 63.21; H 6.74; N, 11.49.

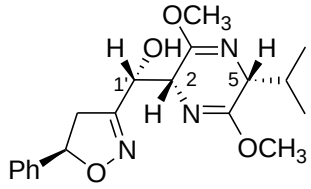
IR (nujol): 3378 (ν_{OH}, OH), 1646 ($\nu_{C=N}$, C=N).

$[\alpha]_D^{25}$ -149.35 (*c* 0.96, $CHCl_3$).

HPLC analysis: retention time: 11.2 min.

Single crystals suitable for X-ray structure determination were obtained by precipitation from CH_2Cl_2/*iso*Pr_2O: 1/1.

4.11.2 **(*R*)-[(2*R*,5*R*)-5-Isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl]-[(5*R*)-5-phenyl-4,5-dihydroisoxazol-3-yl]-methanol 61**



Oil (45%)

^{1}H NMR: δ 0.79, 1.13 (6H, 2d, J = 6.8, CH(CH_3)$_2$); 2.37 (1H, m, CH(CH$_3$)$_2$); 2.79 (1H, d, J = 6.8, OH); 3.20 (1H, dd, J = 16.9, 8.1, H-4 isox); 3.59 (1H, dd, J = 16.9, 11.0, H-4 isox); 3.69 (3H, s, OCH$_3$); 3.78 (3H, s, OCH$_3$); 4.00 (1H, dd, J = 5.6, 3.7, H-5 pyraz.); 4.25 (1H, dd, J = 5.6, 4.0, H-2); 4.97 (1H, dd, J = 6.8, 4.0, H-1'); 5.70 (1H, dd, J = 11.0, 8.1, H-5 isox.); 7.34-7.45 (5H, m, Ph); (by deuteration the signal at 2.79 disappeared and the signal at 4.97 turned into a doublet with J = 4.0).

^{13}C NMR: δ 17.03, 19.48 (CH(CH_3)$_2$); 30.95 (CH(CH$_3$)$_2$); 42.75 (C-4 isox); 52.49,52.58 (3- and 6-OCH$_3$); 58.71, 60.60 (C-2 and C-5 pyr.); 68.92 (1'-C); 82.45 (C-5 isox.); 125.79, 128.06, 128.51, 140.96 (Ph); 159.1, 159.18, 165.79 (C-3 and C-6 pyr., C-3 isox.). MS-FAB$^+$ (m/z): 360 (MH$^+$).

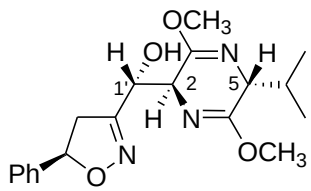
Anal. Calcd for $C_{19}H_{25}N_3O_4$: C, 63.51; H, 6.96; N, 11.69. Found: C, 63.37; H 6.69; N, 11.54.

IR (nujol): 3448 (ν_{OH}, OH), 1696 ($\nu_{C=N}$, C=N).

$[\alpha]_D^{25}$ -78.7 (c 1.41, $CHCl_3$).

HPLC analysis: retention time: 5.8 min.

4.11.3 **(*R*)-[(2*S*,5*R*)-5-Isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl]-[(5*R*)-5-phenyl-4,5-dihydroisoxazol-3-yl]-methanol 62**



Amorphous solid (18.7%)

^{1}H NMR: δ 0.74, 1.05 (6H, 2d, J = 6.8, CH(CH_3)$_2$); 2.28 (1H, m, CH(CH$_3$)$_2$); 2.93 (1H, dd, J = 17.0, 7.5, H-4 isox); 3.33 (1H, dd, J = 17.0, 10.9, H-4 isox); 3.59 (1H, d, J = 7.9, OH); 3.73 (3H, s, OCH$_3$); 3.76 (3H, s, OCH$_3$); 3.90 (1H, t, J = 3.5, H-5 pyraz.); 4.36 (1H, broad t, J = 4.1, H-2); 4.95 (1H, dd, J = 7.9, 4.6, H-1'); 5.58 (1H, dd, J = 10.9, 7.5, H-5 isox.); 7.30-7.45 (5H, m, Ph); (by deuteration the signal at 3.59 disappeared and the signal at 4.95 turned into a doublet with J = 4.6).

^{13}C NMR: δ 16.75, 18.92 (CH(CH_3)$_2$); 32.05 (CH(CH$_3$)$_2$); 43.32 (C-4 isox); 52.60, 52.84 (3- and 6-OCH$_3$); 58.68, 61.26 (C-2 and C-5 pyr.); 69.07 (C-1'); 81.92 (C-5 isox.); 125.67, 128.10, 128.68, 140.99 (Ph); 157.71, 160.22, 165.73 (C-3 and C-6 pyr., C-3 isox.).

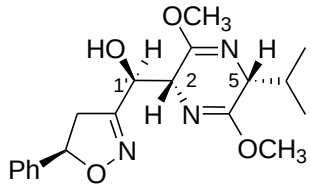
MS-FAB$^+$ (m/z): 360 (MH$^+$).

IR (nujol): 3432 (ν_{OH}, OH), 1642 ($\nu_{C=N}$, C=N).

$[\alpha]_D^{25}$ -51.17 (*c* 0.65, $CHCl_3$).

HPLC analysis: retention time: 14.8 min.

4.11.4 (*S*)-[(2*R*,5*R*)-5-Isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl]-[(5*R*)-5-phenyl-4,5-dihydroisoxazol-3-yl]-methanol 63



This adduct was obtained only in the reaction with Li as counterion.

Amorphous solid (1.8%)

^{1}H NMR: δ 0.68, 1.08 (6H, 2d, J = 6.8, CH(CH_3)$_2$); 2.30 (1H, m, CH(CH$_3$)$_2$); 3.03 (1H, dd, J = 16.8, 8.6, H-4 isox); 3.50 (1H, dd, J = 16.8, 11.2, H-4 isox); 3.54 (1H, broad, OH); 3.59 (3H, s, OCH$_3$); 3.72 (3H, s, OCH$_3$); 3.93 (1H, dd, J = 5.5,3.5, H-5 pyraz.); 4.22 (1H, broad t, J = 6.2, H-2); 4.72 (1H, broad t, J = 5.7, H-1'); 5.57 (1H, dd, J = 11.2, 8.6, H-5 isox.); 7.23-7.40 (5H, m, Ph); (by deuteration the signal at 3.54 disappeared and the signal at 4.72 turned into a doublet with J = 6.6).

^{13}C NMR: δ 17.12, 19.64 (CH(CH_3)$_2$); 30.78 (CH(CH$_3$)$_2$); 42.44 (C-4 isox); 52.75, 52.95 (3- and 6-OCH$_3$); 58.52, 60.87 (C-2 and C-5 pyr.); 70.39 (C-1'); 82.06 (C-5

isox.); 126.02, 128.10, 128.64, 141.26 (Ph); 158.16, 160.18, 164.99 (C-3 and C-6 pyr., C-3 isox.).

MS-FAB$^+$ (m/z): 360 (MH^+).

IR (nujol): 3432 (ν_{OH}, OH), 1640 ($\nu_{C=N}$, C=N).

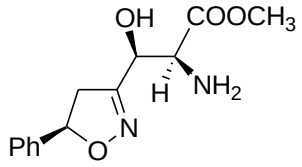
$[\alpha]_D^{25}$ -41.44 (*c* 0.45, $CHCl_3$).

HPLC analysis: retention time: 10.7 min.

4.12 General procedure for the synthesis of compounds 65-68

Adducts **60** and **61** (0.5 mmoli) were dissolved in THF (7.5 mL) and a 0.2 N solution of HCl (7.5 mL, 1.5 mmoli, 3 equiv.) was added. The mixture was stirred for 24 h at room temperature, and then extracted with diethyl ether in order to remove non-basic organic compounds. It was then treated with 25% ammonia solution under stirring until pH=8-10, and extracted with CH_2Cl_2 (5 × 20 mL). The combined organic layers were dried with Na_2SO_4, and the solvent was removed *in vacuo*. Compounds **65**, **66** and **66**, **68** were separated by means of flash chromatography (SiO_2, ethyl acetate:methanol: 98:2, developer: I_2).

4.12.1 **(2S)-Amino-(3S)-hydroxy-3-[(5R)-phenyl-4,5-dihydroisoxazol-3-yl]-propionic acid methyl ester 65**



Oil (25%)

^{1}H NMR: δ 2.30-2.80 (3H, broad, OH, NH_2); 3.16 (1H, dd, *J* = 17.1, 7.9, H-4 isox.); 3.47 (1H, dd, *J* = 17.1, 11.2, H-4 isox); 3.76 (3H, s, OCH_3); 3.98 (1H, m, H-2); 4.72 (1H, m, 3-H); 5.62 (1H, dd, *J* = 11.2, 7.9, H-5 isox.); 7.25-7.45 (5H, m, Ph).

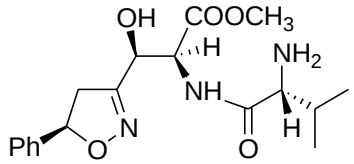
^{13}C NMR: δ 42.42 (C-4-isox.); 52.68 (OCH_3); 56.28 (C-2); 68.42 (C-3); 82.52 (C-5-isox.); 125.90, 128.26, 128.73, 140.55 (Ph); 157.16, 174.35 (C=N, C=O).

MS-FAB$^+$ (m/z): 265 (MH^+).

IR (nujol): 3374 (ν_{OH}, ν_{NH}, OH, NH_2), 1741 ($\nu_{C=O}$, C=O), 1677 ($\nu_{C=N}$, C=N).

$[\alpha]_D^{25}$ -54.09 (*c* 0.77, $CHCl_3$).

4.12.2 **(2*S*)-[(2*R*)-Amino-3-methyl-butyrylamino]-(3*S*)-hydroxy-3-[(5*R*)-5-phenyl-4,5-dihydroisoxazol-3-yl]-propionic acid methyl ester 66**



Amorphous solid (58%);

^{1}H NMR: δ 0.86, 0.99 (6H, 2d, *J* = 6.8, CH(CH_3)$_2$); 2.24 (1H, m, $CH(CH_3)_2$); 2.51-2.70 (3H, broad, OH, NH_2); 2.96 (1H, dd, *J* = 17.0, 9.0, H-4 isox); 3.34 (1H, m, H-2'); 3.62 (1H, dd, *J* = 17.0, 10.7, H-4 isox); 3.77 (3H, s, OCH_3); 4.94 (1H, dd, *J* = 8.4, 2.3, H-2); 5.00 (1H, broad d, *J* = 2.3, H-3); 5.60 (1H, dd, *J* = 10.7, 9.0, H-5 isox.); 7.25-7.50 (5H, m, Ph); 8.21 (1H, d, *J* = 8.4, NH-CO); (by deuteration the signals at 2.51-2.7 and 8.21 disappeared and the signals at 3.34, 4.94 and 5.00 turned into three doublets with *J* = 4.3, 2.3 and 2.3 respectively).

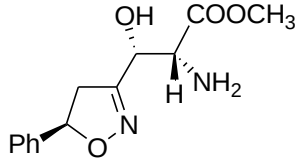
^{13}C NMR: δ 16.13, 19.53 (CH(CH_3)$_2$); 31.01 ($CH(CH_3)_2$); 42.88 (C-4-isox.); 52.87 (OCH_3); 54.66 (C-2'); 60.04 (C-2); 69.46 (C-3); 83.09 (C-5-isox.); 125.87, 128.28, 128.71, 140.13 (Ph); 158.30, 169.89, 175.15 (C=N, C=O ester and amide).

MS-FAB$^+$ (m/z): 364 (MH^+).

IR (nujol): 3340 (ν_{OH}, ν_{NH}, OH, NH_2), 1748 ($\nu_{C=O}$, C=O), 1664 ($\nu_{C=N}$, C=N).

$[\alpha]_D^{25}$ -80.72 (*c* 0.32, $CHCl_3$).

4.12.3 **(2*R*)-Amino-[(3*R*)-hydroxy-3-(5*R*)-5-phenyl-4,5-dihydroisoxazol-3-yl]-propionic acid methyl ester 67**



Oil (56%)

^{1}H NMR: δ 2.45 (3H, broad m, OH, NH_2); 3.03 (1H, dd, *J* = 17.3, 8.5, H-4 isox); 3.58 (1H, dd, *J* = 17.3, 11.0, H-4 isox.); 3.78 (3H, s, OCH_3); 4.03 (1H, m, H-2); 4.71 (1H, d, *J* = 2.9 3-H); 5.60 (1H, dd, *J* = 11.0, 8.5, H-5 isox.); 7.22-7.55 (5H, m, Ph).

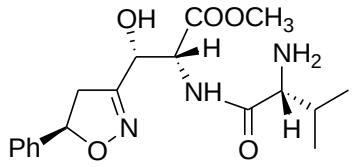
^{13}C NMR: δ 43.13 (C-4 isox.); 52.60 (OCH_3); 56.24 (C-2); 68.55 (C-3); 82.41 (C-5 isox.); 125.83, 128.23, 128.72, 140.57 (Ph); 158.87, 172.84 (C=N, C=O).

MS-FAB$^+$ (m/z): 265 (MH^+).

IR (nujol): 3435 (ν_{OH}, ν_{NH}, OH, NH_2), 1723 ($\nu_{C=O}$, C=O), 1641 ($\nu_{C=N}$, C=N).

$[\alpha]_D^{25}$ -99.74 (*c* 0.30, $CHCl_3$).

4.12.4 **(2*R*)-[(2*R*)-Amino-3-methyl-butyrylamino]-(3*R*)-hydroxy-3-[(5R)-5-phenyl-4,5-dihydroisoxazol-3-yl]-propionic acid methyl ester 68**



Oil (34%)

^{1}H NMR: δ 0.80, 0.97 (6H, 2d, *J* = 6.9, $CH(CH_3)_2$); 2.24 (1H, m, $CH(CH_3)_2$); 2.00-2.40 (3H, broad, OH, NH_2); 3.00-3.60 (3H, m, H-4 isox. and H-2'); 3.80 (3H, s, OCH_3); 4.90 (1H, dd, *J* = 8.7, 3.0, H-2); 4.99 (1H, broad d, *J* = 3.0, 3-H); 5.61 (1H, t, *J* = 10.4, H-5 isox.); 7.25-7.40 (5H, m, Ph); 8.10 (1H, d, *J* = 8.7, NH-CO); (by deuteration the signals at 2.00-2.40 and 8.10 disappeared and the signals at 4.90 and 4.99 turned into two doublets with *J* = 3.0 and 3.0 respectively).

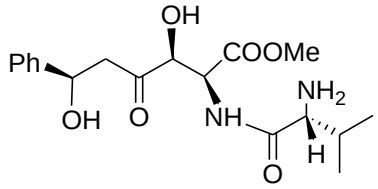
^{13}C NMR: δ 16.15, 19.66 ($CH(CH_3)_2$); 30.84 ($CH(CH_3)_2$); 42.30 (C-4 isox.); 52.98 (OCH_3); 54.63 (C-2'); 60.13 (C-2); 69.44 (C-3); 83.51 (C-5 isox.); 126.31, 128.43, 128.69, 140.22 (Ph); 158.34, 170.07, 175.32 (C=N, C=O ester and amide).

MS-FAB$^+$ (m/z): 364 (MH^+).

IR (nujol): 3387 (ν_{OH}, ν_{NH}, OH, NH_2), 1743 ($\nu_{C=O}$, C=O), 1658 ($\nu_{C=N}$, C=N).

$[\alpha]_D^{25}$ -35.27 (*c* 0.15, $CHCl_3$).

4.13 Synthesis of (2S,3S,6R)-2-[(2R)-2-Amino-3-methyl-butyrylamino]-3,6-dihydroxy-4-oxo-6-phenyl-hexanoic acid methyl ester 69



To a solution of **66** (0.4 mmol, 1 equiv.) in 5/1 methanol/water (10 mL), was added boric acid (1.2 mmol, 3 equiv.) and a spatula tip of Raney-Ni. The mixture was stirred vigorously under hydrogen for 3 hs, then filtered through celite. After evaporation of the solvent, the residue was treated with brine and extracted with ethyl acetate (5×10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Compound **69** were pure enough for the spectroscopic and analytical characterisation.

Amorphous solid (55%);

^{1}H NMR: δ 0.81, 0.96 (6H, 2d, J = 6.9, CH(CH_3)$_2$); 2.25 (1H, m, CH(CH$_3$)$_2$); 2.20-2.70 (4H, broad, 2 OH, NH_2); 3.10-3.21 (3H, m, H-5 and 2'-H); 3.81 (3H, s, OCH_3); 4.79 (1H, broad d, J = 1.8, 3-H); 5.16 (2H, m, H-2 and 6-H); 7.20-7.40 (5H, m, Ph); 7.90 (1H, broad d, J = 9.1, NH-CO).

^{13}C NMR: δ 16.00, 19.54 (CH(CH_3)$_2$); 30.91 (CH(CH$_3$)$_2$); 47.24 (C-5); 53.04 (OCH_3); 53.54 (C-2'); 60.00 (C-2); 70.25 (C-6); 77.56 (C-3); 125.58, 127.86, 128.60, 142.64 (Ph); 169.47, 174.79, 208.51 (C=O ester, ketone and amide).

MS-FAB$^+$ (m/z): 367 (MH^+).

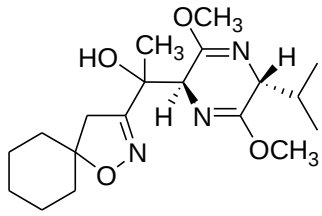
IR (nujol): 3355 (ν_{OH}, ν_{NH}, OH, NH_2), 1744, 1723, 1663 ($\nu_{C=O}$, C=O ketone, ester, amide).

$[\alpha]_D^{25}$ 60.61 (*c* 0.42, $CHCl_3$).

4.14 General procedure for the synthesis of compounds 74a,b and 75a,b and 76

Butyllithium (1.6 N solution in hexane, 1.05 equiv.) was added to a solution of **(*R*)-22** (1 equiv.) in anhydrous THF (5 mL) cooled at –78°C, and the mixture was stirred for 45 min. Ketone **39a** or **b** or **d** (1 equiv.) in THF (4 mL) was added, and the mixture was stirred at –78 °C for 4 h. The reaction mixture was allowed to warm to -10°C, after which a pH=7 phosphate buffer solution (10 mL) was added, and the mixture was extracted with CH_2Cl_2. The organic phase was separated and dried with Na_2SO_4, and the solvent was evaporated *in vacuo*. Compounds **74a/b**, **75a/b** and **76** were purified by means of flash column chromatography**.**

4.14.1 1-[(2*S*,5*R*)- 5-Isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl]-1-(1-oxa-2-azaspiro[4.5]dec-2-en-3-yl) ethan-1-ol 74a/75a



Column chromatography eluent: hexane/AcOEt: 75/25

1st diast.

White solid (hexane)

m.p. 89.8-90.2 °C

^{1}H NMR δ: 0.68 (3H, d, *J* = 6.8 CH(CH_3)$_2$); 1.05 (3H, d, *J* = 6.8 CH(CH_3)$_2$); 1.4 (3H; s, CH_3); 1.4-1.8 (10H, m, cyclohexyl); 2.25-2.36 (1H, m, CH(CH_3)$_2$); 2.72 (1H, d, *J* = 16.5, H-4 isox); 2.87 (1H, d, *J* = 16.5, H-4 isox); 3.7 (3H, s, OCH_3); 3.99 (1H, t, *J* = 3.6, H-5 pyr); 4.12 (1H, d, *J* = 3.6, H-2 pyr)

^{13}C-NMR δ: 16.51, 19.06 (CH(CH_3)$_2$); 22.33 (CH_3COH) 23.48, 25.10 (cyclohexyl); 31.31 (CH(CH_3)$_2$); 36.43, 36.54 (cyclohexyl),); 44.32 (C-4 isox) 52.43, 52.80 (3- and 6-OCH_3); 61.03 61.59 (C-2 and C-5 pyr); 73.93 (C-OH); 86.99 (C-5 isox); 160.39, 161.09, 165.92 (C-3 and C-6 pyr., C-3 isox.).

IR (nujol): 3449 (ν_{OH}, OH), 1694 ($\nu_{C=N}$, C=N).

$[\alpha]_D^{25}$ 40.51 (*c* 0.48, $CHCl_3$).

MS-EI (m/z): 366 (M^+), 141

2nd diast.

White solid (exane)

m.p. 94-95 °C

^{1}H NMR δ: 0.65 (3H, d, *J* = 6.8 $CH(CH_3)_2$); 1.05 (3H, d, *J* = 6.8 $CH(CH_3)_2$); 1.4-1.8 (10H, m, cyclohexyl); 1.45 (3H; s, CH_3); 2.25-2.36 (1H, m, $CH(CH_3)_2$); 2.65 (1H, d, *J* = 16.6, H-4 isox); 2.85 (1H, d, *J* = 16.6, H-4 isox); 3.65 (3H, s, OCH_3); 3.7 (3H, s, OCH_3); 3.95 (1H, t, *J* = 3.7, H-5 pyr); 4.12 (1H, d, *J* = 3.7, H-2 pyr)

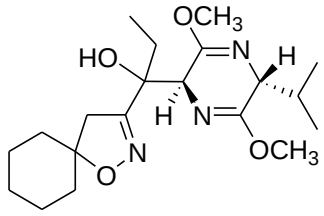
^{13}C-NMR δ: 16.53, 19.06 ($CH(CH_3)_2$); 22.83 (CH_3COH); 23.43, 23.53, 25.11 (cyclohexyl); 31.33 ($CH(CH_3)_2$); 36.39, 36.56 (cyclohexyl),); 44.51 (C-4 isox) 52.51, 52.80 (3- and 6- OCH_3); 60.92, 62.33 (C-2 and C-5 pyr); 74.12 (C-OH); 86.73 (C-5 isox); 160.40, 160.93, 165.09 (C-3 and C-6 pyr., C-3 isox.).

IR (nujol): 3449 (ν_{OH}, OH), 1697 ($\nu_{C=N}$, C=N).

$[\alpha]_D^{25}$ +20.10 (*c* 0.45, $CHCl_3$).

MS-EI (m/z): 366 (M^+), 141

4.14.2 1-[(2*S*,5*R*)-5-(Isopropyl)-3,6-dimethoxy-2,5-dihydropyrazin-2-yl]-1-(1-oxa-2-azaspiro[4.5]dec-2-en-3-yl)propan-1-ol 74b/75b



Column chromatography eluent: hexane/AcOEt 95:5

1st diast.

White solid (exane) (17%)

m.p.: 97-99.5 °C

^{1}H NMR δ: 0.63 (3H, d, *J* = 6.7 $CH(CH_3)_2$); 0.90 (3H, t, *J* = 7.2, CH_2CH_3); 1.05 (3H, d, *J* = 6.7 $CH(CH_3)_2$); 1.4-1.8 (11H, m, cyclohexyl and CH_2CH_3); 2.0 (1H, dq, *J* = 7.2,

14.5, CH_2CH_3); 2.3 (1H, m, $CH(CH_3)_2$); 2.6 (1H, d, J = 16.6, H-4 isox); 2.7 (1H, d, J = 16.6, H-4 isox); 3.65 (3H, s, OCH_3); 3.7 (3H, s, OCH_3); 3.9 (1H, t, J = 3.3, H-5 pyr); 4.1 (1H, d, J = 3.2, H-2 pyr)

^{13}C-NMR δ: 7.60 (CH_2CH_3); 16.37, 19.22 ($CH(CH_3)_2$); 23.45, 25.03 (cyclohexyl); 28.70 (CH_2CH_3); 30.62 ($CH(CH_3)_2$); 36.54, 36.62 (cyclohexyl); 45.03 8C-4 isox); 52.47, 52.82 (3- and 6- OCH_3); 60.64, 61.71 (C-2 and C-5 pyr); 78.07 (C-OH); 87.27 (C-5 isox);160.23, 160.63, 166.07 (C-3 and C-6 pyr., C-3 isox.).

IR (nujol): 3435 (ν_{OH}, OH), 1643 ($\nu_{C=N}$, C=N).

$[\alpha]_D^{25}$ 1.88 (c 0.59, $CHCl_3$).

2nd diast.

White solid (exane) (17%)

m.p.: 137-141 °C

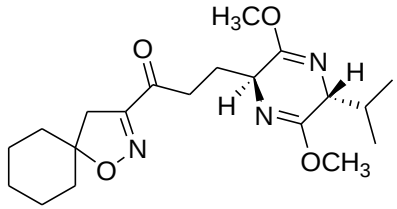
^{1}H NMR δ: 0.7 (3H, d, J = 6.7 $CH(CH_3)_2$); 0.95 (3H, t, J = 7.3, CH_2CH_3); 1.1 (3H, d, J = 6.7 $CH(CH_3)_2$); 1.4-1.8 (10H, m, cyclohexyl);1.9 (1H, dq, J = 7.3, 14.35 CH_2CH_3); 2.1 (1H, dq, J = 7.3, 14.35, CH_2CH_3); 2.3 (1H, m, $CH(CH_3)_2$); 2.6 (1H, d, J = 16.7, H-4 isox); 2.7 (1H, d, J = 16.7, H-4 isox); 3.72 (3H, s, OCH_3); 3.75 (3H, s, OCH_3); 3.98 (1H, t, J = 3.5, H-5 pyr); 4.1 (1H, d, J = 3.5, H-2 pyr)

^{13}C-NMR δ: 7.51 (CH_2CH_3); 16.43, 19.16 ($CH(CH_3)_2$); 23.36, 23.50 25.03 (cyclohexyl); 28.83 (CH_2CH_3); 30.90 ($CH(CH_3)_2$); 36.60, 36.77 (cyclohexyl); 45.56 (C-4 isox); 52.35, 52.80 (3- and 6- OCH_3); 60.71, 61.99 (C-2 and C-5 pyr); 77.40 (C-OH); 87.10 (C-5 isox); 160.41, 165.77 (C-3 and C-6 pyr., C-3 isox.).

IR (nujol): 3435 (ν_{OH}, OH), 1643 ($\nu_{C=N}$, C=N).

$[\alpha]_D^{25}$ 109.48 (c 0.29, $CHCl_3$).

4.14.3 **3-[(2*S*,5*R*)-5-(Isopropyl)-3,6-dimethoxy-2,5-dihydropyrazin-2-yl]-1-(1-oxa-2-azaspiro[4.5]dec-2-en-3-yl)propan-1-one 76**



Yellow oil (47%)

^{1}H NMR δ: 0.68 (3H, d, J = 6.8 CH(CH_3)$_2$); 1.03 (3H, d, J = 6. CH(CH_3)$_2$); 1.4-1.8 (10H, m, cyclohexyl); 2.0 (1H, dt, J = 7.3, 14.35 CH_2-pyr); 2.35-2.2 (2H, m, CH(CH$_3$)$_2$ and CH_2-pyr); 2.8 (2H, s, H-4 isox); 2.95 (2H, t, J = 7.5, CH_2CO); 3.62 (3H, s, OCH$_3$); 3.68 (3H, s, OCH$_3$); 3.96 (1H, t, J = 3.5, H-5 pyr); 4.05 (1H, m, H-2 pyr)

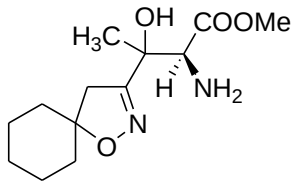
^{13}C-NMR δ: 16.63, 19.00 (CH(CH_3)$_2$); 23.18, 24.80 (cyclohexyl); 28.38 (CH_2-pyr); 31.85 (CH(CH$_3$)$_2$); 34.48 (CH_2CO) 36.35 (cyclohexyl); 41.98 (C-4 isox); 52.42, (OCH$_3$); 54.45, 60.92 (C-2 and C-5 pyr); 91.05 (C-5 isox); 157.47, 163.19, 164.62 (C-3 and C-6 pyr., C-3 isox.), 195.98 (C=O)

$[\alpha]_D^{25}$ -10.93 (c 0.335, CHCl$_3$).

4.15 General procedure for the synthesis of 79 and 80

Adducts **74a** and **75a** (0.2 mmoli) were dissolved in THF (3 mL) and a 0.2 N solution of HCl (3 mL, 1.5 mmoli, 2 equiv.) was added. The mixture was stirred for 24 h at room temperature, and then extracted with diethyl ether in order to remove non-basic organic compounds. It was then treated with 25% ammonia solution under stirring until pH=8-10, and extracted with CH_2Cl_2 (5 × 20 mL). The combined organic layers were dried with Na_2SO_4, and the solvent was removed *in vacuo*. Compounds **79** and **80** were purified by means of flash chromatography (SiO_2, AcOEt/MeOH: 96:4).

4.15.1 **Methyl (2*S*)-2-amino-3-hydroxy-3-(1-oxa-2-azaspiro[4.5]dec-2-en-3-yl)butanoate 79/80**



Amino ester deriving from **74a/75a** (1st diast)

Oil (34%)

^{1}H NMR δ: 1.4-1.8(13H, m, cyclohexyl and CH_3); 2.8 (2H, s, H-4 isox); 3.72 (1H, d, *J* = 2.16 H-2); 3.8 (3H, s, OCH_3)

^{13}C-NMR δ: 22.81 (CH_3); 23.42, 25.06; 36.29 (cyclohexyl); 44.13 (C-4 isox); 55.22 (OCH_3); 60.49 (C-2); 72.65 (C-3); 86.90 (C-5 isox); 161.67 (C-3 isox.); 173.68 (C=O)

$[\alpha]_D^{25}$ 44.75 (*c* 1.04, $CHCl_3$).

MS-EI (m/z):270 (M^+)

Amino ester deriving from **74a/75a** (2nd diast)

Oil (38%)

^{1}H NMR δ: 1.4-1.8(10H, m, cyclohexyl); 1.55 (3H, s, CH_3); 2.7 (2H, s, H-4 isox); 3.55 (1H, s,H-2); 3.75 (3H, s, OCH_3)

^{13}C-NMR δ: 23.42 (cyclohexyl); 23.90 (CH_3): 25.05; 36.24, 36.38 (cyclohexyl); 45.26 (C-4 isox); 52.31 (OCH_3); 61.23 (C-2); 72.10 (C-3); 86.81 (C-5 isox); 161.57 (C-3 isox.); 173.90 (C=O)

$[\alpha]_D^{25}$ -17.57 (*c* 0.57, $CHCl_3$).

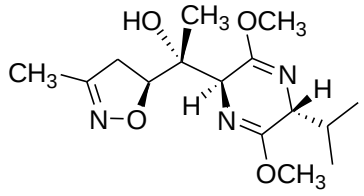
MS-EI (m/z):270 (M^+)

4.16 General procedure for synthesis of compounds 81-84

Butyllithium (1.6 N solution in hexane, 1.05 equiv) was added to a solution of **(2*R*)-22** (1 equiv) in anhydrous THF (5 mL) cooled at -78 °C, and the mixture was stirred for 45 min. Ketone **(5*S*)** or **(5*R*)-41** (1 equiv) in THF (4 mL) was added, and the mixture was stirred at –78 °C for 4 h. The reaction mixture was allowed to warm to –10 °C, after

which a pH 7 phosphate buffer solution (10 mL) was added, and the mixture was extracted with CH_2Cl_2. The organic phase was separated and dried with Na_2SO_4, and the solvent was evaporated in vacuo. Compounds **81** and **82** and **83** and **84** were purified by means of column chromatography (SiO_2, hexane/ethyl acetate: 8/2) and (hexane/ethyl acetate: 7/3), respectively. They were subsequently separated by means of flash chromatography (SiO2, Supelco-Versaflash® station, hexane/ethyl acetate: 75/25).

4.16.1 **(1*R*)-1-[(2*S*,5*R*)-5-Isopropyl-3,6-dimethoxy-2,5-dihydro-pyrazin-2-yl]-1-[(5*S*)-3-methyl-4,5-dihydro-isoxazol-5-yl]ethanol 81**



Colourless solid (hexane). (53%)

m.p.: 79-81 °C

^{1}H NMR: δ 0.67, 1.07 (2d, *J* = 6.8, 6H, CH(*CH*$_3$)$_2$); 1.2 (s, 3H,1-CH$_3$); 1.95 (s, 3H, 3-CH$_3$); 2.29 (m, 1H, *CH*(CH$_3$)$_2$); 2.91 (dd, *J* = 17.0, 10.8, 1H, H-4 isox); 3.12 (dd, *J* = 17.0, 8.9, 1H, H-4 isox); 3.34 (broad, 1H, OH); 3.67 (s, 3H, OCH$_3$); 3.78 (s, 3H, OCH$_3$); 3.99 (broad s, 2H, H-2 and H-5 pyraz.); 4.73 (dd, *J* = 10.8, 8.9, 1H, H-5 isox.).

^{13}C NMR: δ 13.1 (3-CH$_3$); 16.4, 19.0 (CH(*CH*$_3$)$_2$); 19.8 (1-CH$_3$); 31.4 (*CH*(CH$_3$)$_2$); 38.9 (C-4 isox); 52.5 (3- and 6-OCH$_3$); 60.6, 61.6 (C-2 and C-5 pyr.); 75.1 (C-1); 83.5 (C-5 isox.); 155.7 (C-3 isox.); 160.9, 164.7 (C-3 and C-6 pyr.).

IR (Nujol): 3435 (ν_{OH}, OH), 1692($\nu_{C=N}$, C=N).

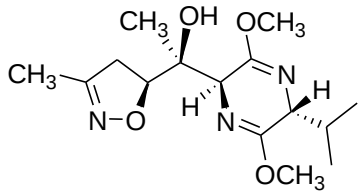
Anal. Calcd for $C_{15}H_{25}N_3O_4$: C, 57.86; H, 8.09; N,13.49. Found: C, 57.67; H, 7.96; N, 13.33.

MS-FAB$^+$ (m/z): 312 $[M+H^+]^+$.

$[\alpha]_D^{25}$ +75.8 (*c* 0.8, $CHCl_3$).

Single crystals suitable for X-ray structure determination were obtained by precipitation from hexane/ethyl acetate: 1/1.

4.16.2 **(1*S*)-1-[(2*S*,5*R*)-5-Isopropyl-3,6-dimethoxy-2,5-dihydro-pyrazin-2-yl]-1-[(5*S*) 3-methyl-4,5-dihydro-isoxazol-5-yl]ethanol 82**



Colourless solid (hexane). (17%);

mp 85-86 °C

^{1}H NMR: δ 0.69, 1.02 (2d, *J* = 6.7, 6H, CH(*CH*$_3$)$_2$); 0.99 (s, 3H, 1-CH$_3$); 1.97 (s, 3H, 3-CH$_3$); 2.23 (m, 1H, *CH*(CH$_3$)$_2$); 2.87 (dd, *J* = 6.7,11.1,1H, H-4 isox); 3.12 (dd, *J* = 16.7, 7.9, 1H, H-4 isox); 3.68 (s, 3H, OCH$_3$); 3.74 (s, 3H, OCH$_3$); 4.02 (t, *J* = 1H, H-5 pyraz.); 4.3 (broad, 1H, OH); 4.33 (d, *J* = 4.1, 1H, H-2 pyraz.); 4.84 (dd, *J* = 11.1, 7.9, 1H, H-5 isox.).

^{13}C NMR: δ 13.0 (3-CH$_3$); 16.7, 19.0 (CH(*CH*$_3$)$_2$); 20.9 (1-CH$_3$); 32.0 (*CH*(CH$_3$)$_2$); 39.4 (C-4 isox); 52.6 (3- and 6-OCH$_3$); 59.0, 61.2 (C-2 and C-5pyr.); 75.3 (C-1); 82.5 (C-5 isox.); 155.5 (C-3 isox.); 161.4,164.7 (C-3 and C-6 pyr.).

IR (Nujol): 3418 (ν_{OH}, OH), 1697 ($\nu_{C=N}$, C=N).

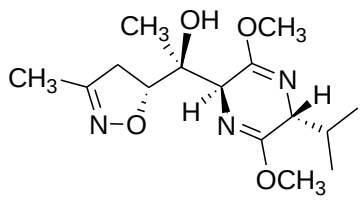
Anal. Calcd for $C_{15}H_{25}N_3O_4$: C, 57.86; H, 8.09; N, 13.49. Found: C, 57.71; H, 7.94; N,13.38.

MS-FAB$^+$ (m/z): 312[M+H]$^+$.

$[\alpha]_D^{25}$ +126.1 (*c* 0.63, $CHCl_3$)

Single crystals suitable for X-ray structure determination were obtained by precipitation from hexane/ethyl acetate: 1/1.

4.16.3 **(1*S*)-1-[(2*S*,5*R*)-5-Isopropyl-3,6-dimethoxy-2,5-dihydro-pyrazin-2-yl]-1-[(5*R*)-3-methyl-4,5-dihydro-isoxazol-5-yl]ethanol 83**



Colourless solid (hexane). (45%);

m.p. 70-72 °C

^{1}H NMR: δ 0.66, 1.06 (2d, *J* = 6.8, 6H, CH(CH_3)$_2$); 1.13 (s, 3H, 1-CH_3); 1.98 (s, 3H, 3-CH_3); 2.32 (m, 1H, C*H*(CH_3)$_2$); 2.92 (dd, *J* = 16.9, 10.9, 1H, H-4 isox); 3.13 (dd, *J* = 16.9, 8.5, 1H, H-4 isox); 3.65 (broad, 1H, OH); 3.7 (s, 3H, OCH_3); 3.73 (s, 3H, OCH_3); 3.91 (d, *J* = 3.9, 1H, H-2 pyraz.); 4.00 (t, *J* = 3.6, 1H, H-5 pyraz.); 4.92 (dd, *J* = 10.9, 8.5, 1H, H-5 isox.).

^{13}C NMR: δ 13.1 (3-CH_3); 16.4, 19.0 (CH(CH_3)$_2$); 19.7 (1-CH_3); 31.3 (*CH*(CH_3)$_2$); 39.0 (C-4 isox); 52.4, 52.8 (3- and 6-OCH_3); 60.6, 60.9 (C-2 and C-5 pyr.); 75.1 (C-1); 84.1 (C-5 isox.); 155.3 (C-3 isox.); 160.4, 165.3 (C-3 and C-6 pyr.).

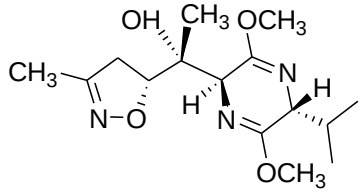
IR (nujol): 3425 (ν_{OH}, OH), 1691 ($\nu_{C=N}$, C=N).

Anal. Calcd for $C_{15}H_{25}N_3O_4$: C, 57.86; H, 8.09; N, 13.49. Found: C, 57.82; H 7.93; N, 13.25.

MS-FAB$^+$ (m/z): 312 $[M+H]^+$.

$[\alpha]_D^{25}$ -38.42 (*c* 0.39, $CHCl_3$).

4.16.4 (1*R*)-1-[(2*S*,5*R*)-5-isopropyl-3,6-dimethoxy-2,5-dihydro-pyrazin-2-yl]-1-[(5*R*)-3-methyl-4,5-dihydro-isoxazol-5-yl]ethanol 84



Amorphous solid (20%).

^{1}H NMR: δ 0.69, 1.07 (2d, *J* = 6.8, 6H, CH(CH_3)$_2$); 1.06 (s, 3H, 1-CH_3); 1.97 (s, 3H, 3-CH_3); 2.3 (m, 1H, *CH*(CH_3)$_2$); 2.82 (dd, *J* = 16.8, 11.0, 1H, H-4 isox); 3.07 (dd, *J* = 16.8, 8.4, 1H, H-4 isox); 3.7 (s, 3H, OCH_3); 3.72 (broad, 1H, OH); 3.75 (s, 3H, OCH_3); 4.00 (t, *J* = 3.7, 1H, H-5 pyraz.); 4.31 (d, *J* = 3.9, 1H, H-2 pyraz.); 4.8 (dd, *J* = 10.9, 8.5, 1H, H-5 isox.).

^{13}C NMR: δ 13.0 (3-CH_3); 16.6, 19.0 (CH(CH_3)$_2$); 20.8 (1-CH_3); 31.5 (CH(CH_3)$_2$); 39.0 (C-4 isox); 52.5, 52.7 (3- and 6-OCH_3); 60.4, 61.1 (C-2 and C-5 pyr.); 75.2 (C-1); 83.0 (C-5 isox.); 155.4 (C-3 isox.); 161.5, 164.2 (C-3 and C-6 pyr.).

IR (nujol): 3446 (ν_{OH}, OH), 1698 ($\nu_{C=N}$, C=N).

Anal. Calcd for $C_{15}H_{25}N_3O_4$: C, 57.86; H, 8.09; N, 13.49. Found: C, 57.76; H 7.91; N, 13.15.

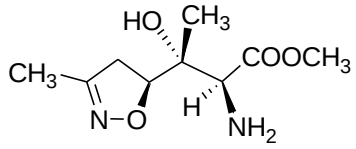
MS-FAB$^+$ (m/z): 312 $[M+H]^+$.

$[\alpha]_D^{25}$ -36.42 (*c* 0.78, $CHCl_3$).

4.17 General procedure for synthesis of compounds 86-88 and 89-91

Aqueous HCl 0.2 N (2.5 mL, 5.5 mmoli, 2 equiv.) was added to a solution of adduct **81, 82, 83** (0.25 mmoli, 1 equiv.) in THF (1.5 mL). The mixture was stirred for 16-24 h at room temperature and then extracted with diethyl ether in order to remove non-basic organic compounds. It was then treated with 25% ammonia solution under stirring until pH=8-10, and extracted with AcOEt (4 × 5 mL). The combined organic layers were dried with Na_2SO_4, and the solvent was removed *in vacuo*. Compounds **86**, **87**, **88** and **89**, **90**, **91** were separated by means of flash chromatography (SiO_2, CH_2Cl_2/MeOH: 98/2, for **86**/**89** and **87**/**90**; AcOEt/MeOH: 98/2, developer: I_2 for **88**/**91**).

4.17.1 **(2*S*)-Amino-(3*R*)-hydroxy-3-[(5*S*)-3-methyl-4,5-dihydro-isoxazol-5-yl]-butyric acid methyl ester 86.**



Amorphous solid (46%).

^{1}H NMR: δ 1.25 (s, 3H, CH_3); 1.95 (s, 3H, 3-CH_3); 2.4 (broad, 3H, OH, NH_2); 2.91 (dd, *J* = 17.6, 11.0, 1H, H-4 isox); 3.07 (dd, *J* = 17.6, 7.5, 1H, H-4 isox); 3.41 (broad s, 1H, H-2); 3.78 (s, 3H, OCH_3); 4.5 (dd, *J* = 11.0, 7.5, 1H, H-5 isox.).

^{13}C NMR: δ 12.9 (3-CH_3); 18.4 (CH_3); 39.7 (C-4 isox); 52.4 (OCH_3); 59.7 (C-2); 73.6 (C-3); 81.6 (C-5 isox.); 155.9 (C-3 isox.); 174.35 (C=O).

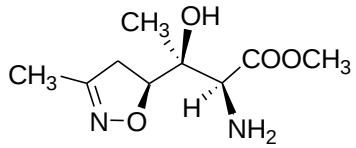
IR (nujol): 3391 (ν_{OH}, ν_{NH}, OH, NH_2), 1735 ($\nu_{C=O}$, C=O), 1637 ($\nu_{C=N}$, C=N).

Anal. Calcd for $C_9H_{16}N_2O_4$: C, 49.99; H, 7.46; N, 12.96. Found: C, 49.87; H 7.28; N, 12.75.

MS-EI$^+$ (m/z): 217 $[M+H]^+$.

$[\alpha]_D^{25}$ +92.8 (*c* 0.9, $CHCl_3$).

4.17.2 (2*S*)-Amino-(3*S*)-hydroxy-3-[(5*S*)-3-methyl-4,5-dihydro-isoxazol-5-yl]-butyric acid methyl ester 87



Amorphous solid (46%).

^{1}H NMR: δ 1.04 (s, 3H, CH_3); 1.98 (s, 3H, 3-CH_3); 2.5 (broad, 3H, OH, NH_2); 2.88 (dd, *J* = 16.8, 10.9, 1H, H-4 isox); 3.12 (dd, *J* = 16.8, 8.2, 1H, H-4 isox); 3.79 (s, 3H, OCH_3); 3.84 (broad s, 1H, H-2); 4.7 (dd, *J* = 10.9, 8.2, 1H, H-5 isox.).

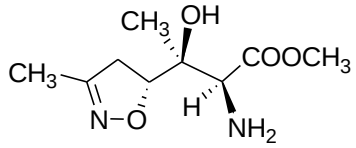
^{13}C NMR: δ 12.9 (3-CH_3); 20.2 (CH_3); 39.4 (C-4); 52.4 (OCH_3); 58.2 (C-2); 73.9 (C-3); 82.7 (C-5 isox.); 155.9 (C-3 isox.); 173.1 (C=O).

IR (nujol): 3379 (ν_{OH}, ν_{NH}, OH, NH_2), 1735 ($\nu_{C=O}$, C=O), 1663 ($\nu_{C=N}$, C=N). Anal. Calcd for $C_9H_{16}N_2O_4$: C, 49.99; H, 7.46; N, 12.96. Found: C, 49.90; H 7.35; N, 12.84.

MS-EI$^+$ (m/z): 217 $[M+H]^+$.

$[\alpha]_D^{25}$ +123.3 (*c* 0.15, $CHCl_3$).

4.17.3 (2*S*)-Amino-(3*S*)-hydroxy-3-[(5*R*)-3-methyl-4,5-dihydro-isoxazol-5-yl]-butyric acid methyl ester 88



Amorphous solid (41%).

^{1}H NMR: δ 1.12 (s, 3H, CH_3); 1.98 (s, 3H, 3-CH_3); 2.3 (broad, 3H, OH, NH_2); 2.95 (dd, *J*=17.4, 10.9, 1H, H-4 isox); 3.06 (dd, *J* = 17.4, 8.0, 1H, H-4 isox); 3.51 (broad s, 1H, H-2); 3.76 (s, 3H, OCH_3); 4.69 (dd, *J* = 10.9, 8.0, 1H, H-5 isox.).

^{13}C NMR: δ 12.9 (3-CH_3); 18.1 (CH_3); 39.2 (C-4 isox); 52.2 (OCH_3); 58.9 (C-2); 73.6 (C-3); 82.4 (C-5 isox.); 155.9 (C-3 isox.); 173.83 (C=O).

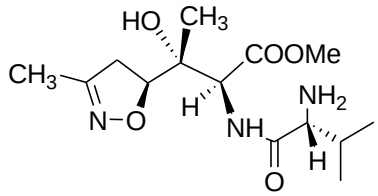
IR (nujol): 3305 (ν_{OH}, ν_{NH}, OH, NH_2), 1736 ($\nu_{C=O}$, C=O), 1631 ($\nu_{C=N}$, C=N).

Anal. Calcd for $C_9H_{16}N_2O_4$: C, 49.99; H, 7.46; N, 12.96. Found: C, 49.89; H 7.37; N, 12.88.

MS-EI$^+$ (m/z): 217 $[M+H]^+$.

$[\alpha]_D^{25}$ -48.9 (*c* 0.76, $CHCl_3$).

4.17.4 (2*S*)-[(2*R*)-Amino-3-methyl-butyrylamino]-(3R)-hydroxy-3-[(5*S*)-3-methyl-4,5-dihydro-isoxazol-5-yl]-butyric acid methyl ester 89



Amorphous solid (28%).

^{1}H NMR: δ 0.85, 0.99 (2d, *J* = 6.8, 6H, CH(CH_3)$_2$); 1.26 (s, 3H, CH_3); 1.96 (s, 3H, 3-CH_3); 2.28 (m, 1H, CH(CH_3)$_2$); 2.65 (broad, 3H, OH, NH_2); 2.97 (dd, *J* = 17.7, 10.7, 1H, H-4 isox); 3.07 (dd, *J* = 17.7, 8.8, 1H, H-4 isox); 3.34 (broad d, *J* = 3.8, 1H, H-2 val.); 3.77 (s, 3H, OCH_3); 4.53 (dd, *J* = 10.7, 8.8, 1H, H-5 isox.); 4.66 (d, *J* = 8.6, 1H, H-2); 8.2 (d, *J*=8.6, 1H, NH).

^{13}C NMR: δ 12.9 (3-CH_3); 16.0 (CH(CH_3)$_2$); 19.6 (CH(CH_3)$_2$) and (CH_3); 30.9 (CH(CH_3)$_2$); 39.8 (C-4 isox); 52.7 (OCH_3); 56.6 (C-2); 59.8 (C-2 val.); 74.8 (C-3); 83.3 (C-5 isox.); 156.4 (C-3 isox.); 171.0, 175.0 (C=O).

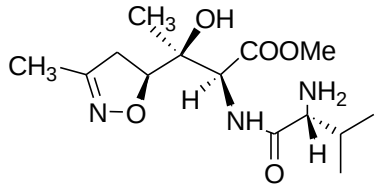
IR (nujol): 3415 (ν_{OH}, ν_{NH}, OH, NH_2), 1734 ($\nu_{C=O}$, C=O), 1647 ($\nu_{C=N}$, C=N).

Anal. Calcd for $C_{14}H_{25}N_3O_5$: C, 53.32; H, 7.99; N, 13.32. Found: C, 53.25; H 7.76; N, 13.21.

MS-FAB$^+$ (m/z): 316 $[M+H]^+$.

$[\alpha]_D^{25}$ +63.1 (*c* 0.77, $CHCl_3$).

4.17.5 **(2*S*)-[(2*R*)-Amino-3-methyl-butyrylamino]-(3*S*)-hydroxy-3-[(5*S*)-3-methyl-4,5-dihydro-isoxazol-5-yl]-butyric acid methyl ester 90**



Amorphous solid (14%).

^{1}H NMR: δ 0.86, 1.0 (2d, J = 6.8, 6H, CH(CH_3)$_2$); 1.13 (s, 3H, CH_3); 1.97 (s, 3H, 3-CH_3); 2.24 (broad m, 4H, CH(CH_3)$_2$ and OH, NH_2); 2.92 (dd, J = 17.1, 10.8, 1H, H-4 isox); 3.02 (dd, J = 17.1, 8.5, 1H, H-4 isox); 3.37 (broad d, J = 3.7, 1H, H-2 val.); 3.79 (s, 3H, OCH_3); 4.63 (dd, J = 10.8, 8.5, 1H, H-5 isox.); 4.85 (d, J = 8.7, 1H, H-2); 8.18 (d, J = 8.7, 1H, NH).

^{13}C NMR: δ 12.9 (3-CH_3); 16.3 (CH(CH_3)$_2$); 19.6 (CH(CH_3)$_2$); 20.2 (CH_3); 29.7 (CH(CH_3)$_2$); 39.6 (C-4 isox); 52.7 (OCH_3); 56.8 (C-2); 59.9 (C-2 val.); 75.4 (C-3); 83.0 (C-5 isox.); 156.1 (C-3 isox.); 170.7, 174.2 (C=O).

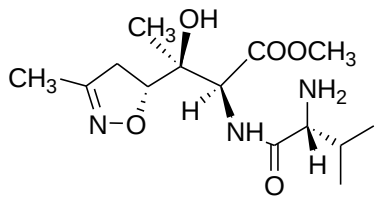
IR (nujol): 3346 (ν_{OH}, ν_{NH}, OH, NH_2), 1740 ($\nu_{C=O}$, C=O), 1655 ($\nu_{C=N}$, C=N).

Anal. Calcd for $C_{14}H_{25}N_3O_5$: C, 53.32; H, 7.99; N, 13.32. Found: C, 53.19; H 7.86; N, 13.24.

MS-FAB$^+$ (m/z): 316 $[M+H]^+$.

$[\alpha]_D^{25}$ +99.0 (*c* 0.2, $CHCl_3$).

4.17.6 **(2*S*)-[(2*R*)-Amino-3-methyl-butyrylamino]-(3S)-hydroxy-3-[(5*R*)-3-methyl-4,5-dihydro-isoxazol-5-yl]-butyric acid methyl ester 91**



Amorphous solid (28%).

^{1}H NMR: δ 0.87, 1.0 (2d, J = 6.9, 6H, CH(CH_3)$_2$); 1.19 (s, 3H, CH_3); 1.98 (s, 3H, 3-CH_3); 2.15 (broad, 3H, OH, NH_2); 2.29 (m, 1H, CH(CH_3)$_2$); 3.0 (m, 2H, H-4 isox); 3.38

(broad d, *J* = 4.0, 1H, H-2 val.); 3.76 (s, 3H, OCH_3); 4.62 (m, 1H, H-5 isox.); 4.67 (d, *J* = 8.3, 1H, H-2); 8.29 (d, *J* = 8.3, 1H, NH).

^{13}C NMR: δ 12.8 (3-CH_3); 16.1 (CH(*CH_3*)$_2$); 19.1 (CH_3); 19.5 (CH(*CH_3*)$_2$); 30.9 (*CH*(CH_3)$_2$); 39.9 (C-4 isox); 52.6 (OCH_3); 58.6 (C-2); 59.9 (C-2 val.); 74.0 (C-3); 82.6 (C-5 isox.); 156.0 (C-3 isox.); 171.4, 174.9 (C=O).

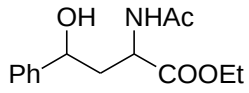
IR (nujol): 3365 (ν_{OH}, ν_{NH}, OH, NH_2), 1739 ($\nu_{C=O}$, C=O), 1658 ($\nu_{C=N}$, C=N). Anal. Calcd for $C_{14}H_{25}N_3O_5$: C, 53.32; H, 7.99; N, 13.32. Found: C, 53.22; H 7.90; N, 13.20.

MS-FAB$^+$ (m/z): 316 $[M+H]^+$.

$[\alpha]_D^{25}$-45.4 (*c* 0.83, $CHCl_3$).

4.18 Δ^2-Isoxazoline ring opening

4.18.1 **2-acetamido-4-hydroxy-4-phenylbutanoate 96**



A spatula of Raney-Ni was added to a solution of compound **31f** (218 mg, 1 mmol) in ethyl acetate (4 mL). The mixture was stirred vigorously under hydrogen at room temperature for 24 h, then filtered through celite. The solvent was removed *in vacuo.* The residue was dissolved in dichloromethane (5 mL) and acetic anhydride (2.2 equiv, 0.22 mL), pyridine (1.5 equiv, 0.13 mL) and 4-dimethylaminopyridine (01.equiv, 12 mgr) were added. The reaction mixture was stirred at room temperature for 12 hours. The reaction mixture was washed with water (3×1.5 mL), dried over Na_2SO_4 and the solvent removed under reduced pressure. Column chromatography (hexane/AcOEt: 30/70) afforded the *syn* and *anti* **96** in 51% total yield.

1st diast

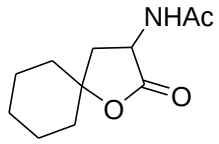
Oil (19%)

^{1}H NMR: δ 1.3 (t, 3H, *J* = 7.1, -OCH_2CH_3); 1.8-1.9 (m, 1H, -CH_2); 2.0 (s, 3H, -$COCH_3$); 2.0-2.1 (m, 1H, CH_2); 4.2 (q, 2H, *J* = 7.1, -OCH_2CH_3); 4.6 (d, *J* = 9.7, -*CH*OH); 4.8-4.9 (m, 1H, *J* = 4.0, 8.8 -*CH*NHAc,); 6.5 (d, 1H, *J* = 7.5, NHAc); 7.2-7.4 (m, 5H, Ph)

^{13}C NMR δ 14.1 (-OCH$_2$*CH$_3$*); 23.1(-CO*CH$_3$*); 43.2 (*CH$_2$*); 50.3 (-*CH*NHAc); 61.8 (-O*CH$_2$*CH$_3$); 69.8 (-*CH*OH); 125.6, 127.4, 128.4, 143.4 (Ph), 171.4, 172.4 (C=O)
MS-EI (m/z): 266, 248 [M-H$_2$O]

2nd diast.
Oil (32%)
^{1}H NMR: δ 1.3 (t, 3H, *J* = 7.1, -OCH$_2$*CH$_3$*); 2.0 (s, 3H, -CO*CH$_3$*); 2.1-2.2 (m, 2H, *CH$_2$*); 4.2 (q, 2H, *J* = 7.1, -O*CH$_2$*CH$_3$); 4.6 (q, 1H, *J* = 5.8, -*CH*NHAc); 4.85 (dd, 1H, *J* = 4.0, 8.8, -*CH*OH); 6.5 (d, 1H, J = 5.8, NHAc); 7.2-7.4 (m, 5H, Ph)
^{13}C NMR δ 14.1 (-OCH$_2$*CH$_3$*); 23.0(-CO*CH$_3$*); 41.2 (*CH$_2$*);50.9(-*CH*NHAc); 61.6 (-O*CH$_2$*CH$_3$); 71.6 (-*CH*OH); 125.8, 127.7, 128.5, 143.9 (Ph), 170.3, 172.5 (C=O)
MS-EI (m/z): 266, 248 [M-H$_2$O]

4.18.2 **N-{2-oxo-1-oxaspiro[4.5]decan-3-yl}acetamide 100**



A spatula of Raney-Ni was added to a solution of compound **31c** (210 mg, 1 mmol) in ethyl acetate (4 mL). The mixture was stirred vigorously under hydrogen at room temperature for 15 hours, then filtered through celite. The solvent was removed *in vacuo.* The residue was dissolved in dichloromethane (5 mL) and acetyl chloride (2 equiv, 0.13 mL), triethylamine (2 equiv, 0.250 mL) were added. The reaction mixture was stirred at room temperature for 12 hours. The reaction mixture was washed with water (3×1.5 mL), dried over Na_2SO_4 and the solvent removed under reduced pressure. Column chromatography (dichloromethane/MeOH: 97/3) afforded **100** in 41% total yield

White solid (dichloromehane)

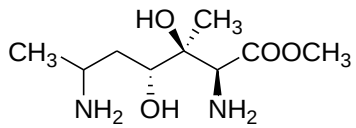
m.p.: 144.5-146 °C

^{1}H NMR: δ 1.4-1.8 (m, 11H, Ciclohexyl and H-4); 2.0 (s, 3H, CH_3); 2.7 (dd, *J* = 9.0, 11.8, H-4); 4.75 (ddd, 1H, *J* = 6.0, 9.0, 11.8, H-3); 6.4 (d, 1H, *J* = 6.0, -*NH*Ac)

^{13}C NMR: d 22.4, 22.6 (Ciclohex); 22.8 (-CH_3); 24.8, 35.9, 38.3 (Ciclohex); 40.8 (C-4); 49.8 (C-3); 84.9 (C-5); 170.48, 174.87 (C=O)

IR (Nujol): 2800 (ν_{OH}, ν_{NH}, OH, NH_2), 1771 ($\nu_{C=O}$, C=O) 1654 ($\nu_{NHC=O}$, C=O).

4.18.3 **(2*S*,3*S*,4*R*))-2,6-Diamino-3,4-dihydroxy-3-methyl-heptanoic acid methyl ester 92**



A spatula of Raney-Ni was added to a solution of compound **88**, (0.1 mmol) in ethyl acetate (4 mL). The mixture was stirred vigorously under hydrogen for 2 h, then filtered through celite. The solvent was removed *in vacuo* and the residue was purified by means of flash chromatography (SiO_2, ethyl acetate/methanol=95/5, developer: I_2).

Waxy solid (25%).

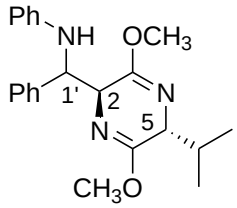
^{1}H NMR: δ 1.15 (d, 3H, J = 6.0, CH_3-7); 1.3 (broad s, 1H, H-5); 1.33 (s, 3H, CH_3-3); 1.63 (broad, 6H, OH, NH_2); 1.87 (broad m, 1H, H-5); 2.74 (m, 1H, H-6); 3.25 (broad s, 1H, H-2); 3.31 (dd, J = 11.4, 4.9, 1H, H-4); 3.76 (s, 3H, OCH_3).

^{13}C NMR: δ 21.1, 21.9 (3-CH_3, C-7); 39.3 (C-5); 49.6 (C-6); 52.1 (OCH_3); 65.9 (C-2); 70.2 (C-3); 73.6 (C-4); 171.3 (C=O).

IR (Nujol): 3350 (ν_{OH}, ν_{NH}, OH, NH_2), 1740 ($\nu_{C=O}$, C=O).

HRMS(FT-ICR)-EI^{+} (m/z): 204.1230 $[M - NH_3 + H]^{+}$.

4.19 Synthesis of N-(((2S,5R)-2,5-dihydro-5-isopropyl-3,6-dimethoxypyrazin-2yl) (phenyl)methyl)benzene amine 112/113



Butyllithium (1.6 N solution in hexane, 1.45 mmol, 0.9 mL, 1.05 equiv.) was added to a solution of **(*R*)-22** (1.4 mmol, 0.25ml, 1 equiv.) in anhydrous THF (3 mL) cooled at –78°C, and the mixture was stirred for 45 min. Imine **108** (1.4 mmol, 0.250 mg, 1 equiv) in THF (3 mL) was added, and the mixture was stirred at –78 °C for 4 h. The reaction mixture was allowed to warm to -20 °C, after which a pH=7 phosphate buffer solution (10 mL) was added, and the mixture was extracted with AcOEt. The organic phase was separated and dried with Na_2SO_4, and the solvent was evaporated *in vacuo*. Adduct **112**/**113** were purified by means of flash column chromatography (hexane/dichloromethane:1/1) and obtained in 60% total yield.

1st diast: Oil (36%)

^{1}H NMR: δ 0.60 (d, 3H, J = 6.8, -CH_3); 0.90 (d, 3H, J = 6.8, -CH_3); 2.1 (m, 1H, *CH*(CH_3)$_2$); 3.1 (t, 1H, J = 3.6, H-5 pyr); 3.7 (s, 3H, -OCH_3); 3.8 (s, 3H, -OCH_3); 4.5 (t, 1H, J = 3.6 H-2 pyr); 5.0 (d, 1H, J = 3.6 *CH*-NHPh); 6.5-6.6 (m, 3H, Ph); 7.05-7.15 (m, 7H, Ph)

^{13}C NMR: δ16.9, 18.8 (CH_3); 31.1 (*CH*(CH_3)$_2$); 52.1, 52.5 (3- and 6 -OCH_3); 58.3 (-*CH*-NHPh) 59.8, 60 (C-2 and C-5 pyr);113.5, 117.1, 127.2, 127.7, 128, 129.1, 138.2, 146.7 (Ph); 160.3, 164.9 (C-3 and C-6 pyr)

$[\alpha]_D^{25}$ 61.8 ($CHCl_3$ *c* 1.04)

2nd diast: White solid (hexane) (24%)

m.p. 88-90 °C

^{1}H NMR: δ 0.65 (d, 3H, *J* = 6.8, -CH_3); 0.95 (d, 3H, *J* = 6.8, -CH_3); 2.2 (m, 1H, *CH*(CH_3)$_2$); 3.55 (t, 1H, *J* = 3.3, H-5 pyr); 3.68 (s, 3H, -OCH_3); 3.72 (s, 3H, -OCH_3); 4.35 (t, 1H, *J* = 3.3 H-2 pyr); 5.0 (d, 1H, *J* = 2.5 *CH*-NHPh); 6.55 (d, *J* = 7.9 2H, Ph); 6.6 (t, 1H, *J* = 7.3 Ph); 7.2-7.4 (m, 7H, Ph)

^{13}C NMR δ16.7, 19.0 (CH_3); 31.7 (*CH*(CH_3)$_2$); 52.6 (3- and 6 -OCH_3); 59.2 (-*CH*-NHPh) 60.6, 60.7 (C-2 and C-5 pyr);113.8, 117.4, 127.2, 127.4, 128, 129.1, 140.4, 146.9 (Ph); 161.4, 165.9 (C-3 and C-6 pyr)

$[\alpha]_D^{25}$92.3 (*c* 1.94, $CHCl_3$).

SECTION B

5 INTRODUCTION

Chiral allylsilanes are very useful intermediates in organic synthesis and they have been used as building blocks and as versatile intermediates for the synthesis of complex molecules.[113-116] Their reactivity is due to the peculiar properties of the C-Si bond. The lower electronegativity of silicon (1.8) compared to carbon (2.5)[117] causes a rise in the HOMO, making the allylsilane reactive nucleophiles. Moreover Si has a large atomic radius (110 pm versus 70 pm of C) and the bulkiness of a silyl group can control the stereochemistry of the reactions occurring in its immediate vicinity. In addition, silicon can be easily removed from the molecule after it exerted its influence on a synthetic sequence. Protodesilylation[118] and oxidation[119, 120] of the C-Si bond occur through initial reaction at silicon by electronegative atoms like oxygen and fluoride, with which it forms very strong bonds.

Chiral allylsilane can react with a broad range of electrophiles leading to the formation of more complex products. Some of the more important and useful reactions are shown in Figure 33.[114] Depending on the experimental conditions, reactions with carbonyl compounds and imines, can lead to the formation of carbocycles and five members ring heterocycles. However reactions with the same electrophiles, under different reaction conditions, provide homoallylic alcohol and amines.

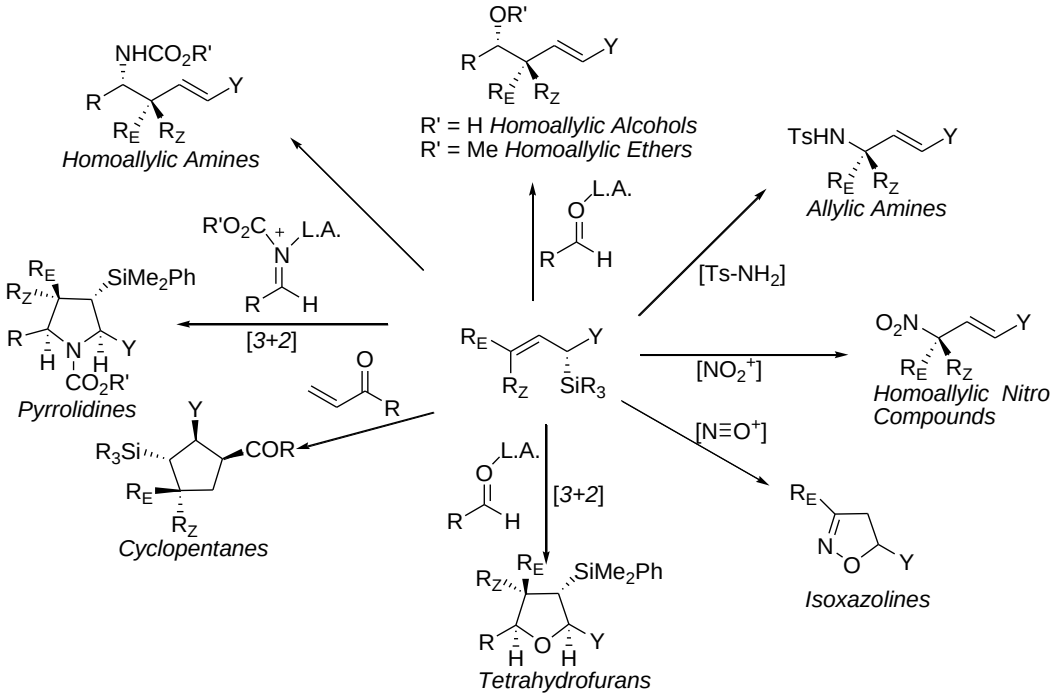
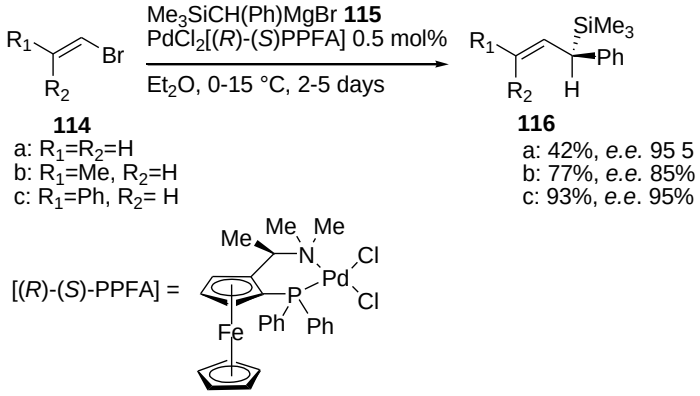


Figure 33: Reactions of allylsilanes

5.1 Synthetic Methodologies for the Synthesis of Chiral Allyl Silanes

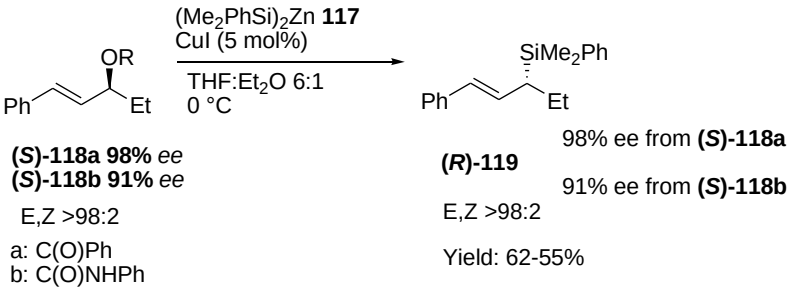
Due to the importance of allylsilanes in organic synthesis, many research groups have studied different approaches to obtain them in high enantiomeric and diastereomeric purity. Hayashi and co workers in 1982 described for the first time an efficient synthesis of enatiomerically pure allylsilanes using a palladium-catalyzed asymmetric Grignard cross-coupling.[121] As shown in Scheme 52, reaction between different allylbromides **114** and Grignard reagent **115** was catalyzed by $PdCl_2$[(*R*)-(*S*)PFA], led to the formation of allylsilanes **116** in moderate to good yields and excellent *e.e*.



Scheme 52: Synthesis of allylsilanes proposed by Hayashi [121]

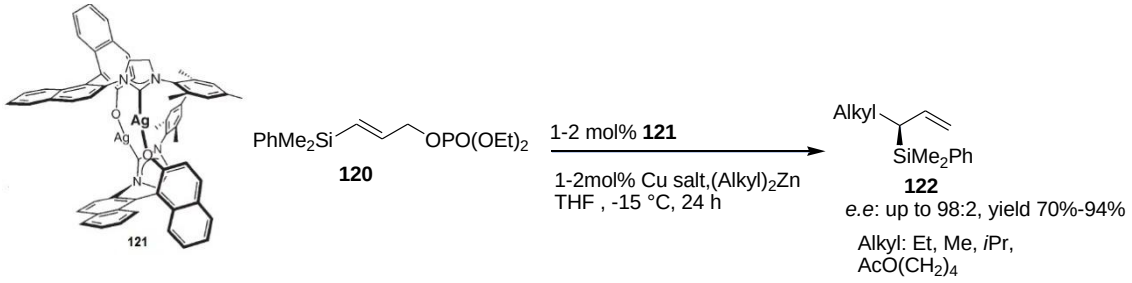
Other Pd catalyzed reaction that have been developed for the synthesis of chiral allylsilanes include the hydrosilalation of 1,3 dienes,[122, 123] silylation of allylic chlorides[124] and silaborations of allenes.[125] However, in many cases products are obtained with less than 90% *e.e.*

More recently, Oestrich described the synthesis of chiral allyl silanes through a copper catalyzed allylic substitution of an enantiomerically pure carbamate or carbonate **118a** or **b** with bis(triorganosilyl) zinc **117** (Scheme 53).[126] Allylsilanes were obtained in moderate to good yield and in high *e.e.*, but this methodology was only applied to a limited number of substrates.



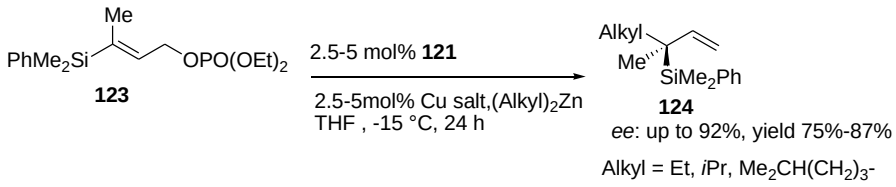
Scheme 53: Syntheis of allylsilanes proposed by Oestrich[126]

Hoveyda and co-workers developed the synthesis of tertiarty and quaternary allylsilanes using catalytic asymmetric allylic alkylation of organozinc reagents to Si substituted allyl phosphates **120**.[127] This transformation is catalyzed by chiral Cu complexes generated *in situ* from *N*-heterocyclic-carbenes ligands **121**(Scheme 54). Tertiary allylsilanes **122** were obtained in high yields and excellent enantioselectivity. Moreover the reaction proved to have a broad scope, with allylsilanes containing different alkyl groups as methyl, ethyl, *iso*propyl, $AcO(CH_2)_4$- formed without any reduction in the enantioselctivity.



Scheme 54: Synthesis of tertiary allylsilanes proposed by Hoveyda[127]

Moreover the same metal-ligand complex can be used for the synthesis of the more challenging quaternary allylsilanes starting from the sterically congested trisubstituted olefin **123**. The quaternary allylsilanes **124** were again obtained in high yields and excellent *e.e.*[127]

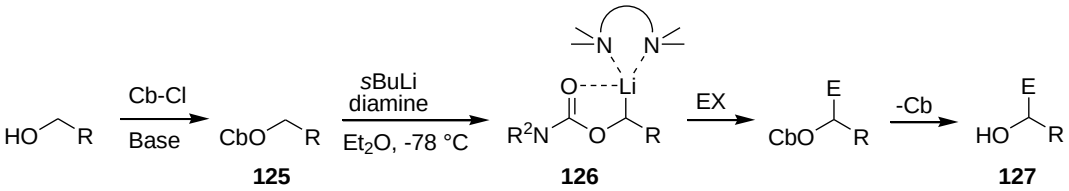


Scheme 55: Synthesis of quaternary allylsilanes proposed by Hoveyda [127]

In this work we aim to study a new route to enantiomerically enriched allylsilanes through the lithiation/borylation reaction developed within the Aggarwal group. The base of lithiation/borylation methodology is the study of the lithiation of carbamates, firstly developed by Hoppe. Therefore in the next section Hoppe's work will be reviewed together with the functionalities allowed by the system.

5.2 Hoppe Carbamates and Functionalities Allowed

Hoppe and co-workers first reported the asymmetric deprotonation of an *O*-alkyl carbamates in 1990.[128] The carbamate **125** is easily synthesised through reaction of the corresponding alcohol with carbamoyl chloride in presence of a mild base as triethylamine[129] or pyridine.[130] The carbamate obtained may be deprotonated using or *s*BuLi at -78 °C, in presence of a diamine ligand. After a four hours deprotonation, the lithiated species **126** can react with a variety of electrophiles. This traps the lithiated intermediate with retention of configuration, providing the corresponding secondary alcohols **127** after deprotection of carbamate group (Table 19).[131]



125 **126** **127**

R	EX	Diamine	Yield (%)	% *e.e.*
Methyl	Me_3SiCl	TMEDA	70	-
Methyl	CO_2	sparteine	75	>95
Methyl	Me_3SnCl	sparteine	73	>95
Hexyl	MeI	sparteine	81	96

Table 19: Examples of the deprotonation of alkyl carbamates followed by trapping with an electrophile [131]

The presence of the carbamate group has two important effects in the deprotonation reaction. Firstly, it acts as an electron withdrawing group making the alpha proton more acidic. Secondly it helps stabilize the lithiated intermediate, through the coordination of oxygen with lithium, as shown in Table 19. The lithiated carbamate is also stabilized by the diamine that chelates with the lithium.

Hoppe and co-workers mainly used two carbamates groups (Figure 34). While the diisopropyl carbamate (OCb) can be removed with $LiAlH_4$ or an excess of DIBALH, the oxazolidines carbamates (OCby and OCbx) can be removed through a easier acid/base hydrolysis using a mixture of $MeSO_3H$ and MeOH followed by $Ba(OH)_2$.[131]

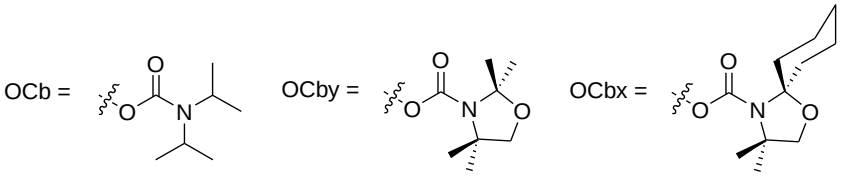


Figure 34: Carbamate groups employed by Hoppe, *et al*.

A wide range of electrophiles have been used in this reaction, as MeI, CH_2N_2, Me_3SiCl, acid chlorides, esters, ketones, aldehydes, allyl bromide an epoxides.[132] In all cases the electrophile traps the lithiated carbamate with retention of configuration (Figure 35).

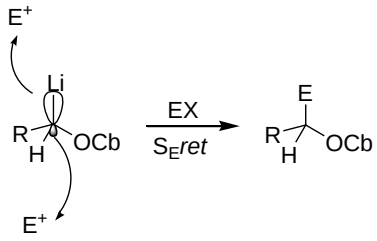


Figure 35: Mechanism of electrophile trapping by lithiated alkyl carbamates

As previously mentioned, the presence of a secondary diamine, such as *N*, *N*, *N*', *N*' tetramethylethyldiamine (TMEDA, Figure 36), is needed for the stabilisation of the intermediate lithiated carabamate. When an achiral amine as TMEDA is used, the product obtained is in racemic form. However when a chiral diamine, like (–)-sparteine (Figure 36) is used, enantioselective deprotonation can be induced.

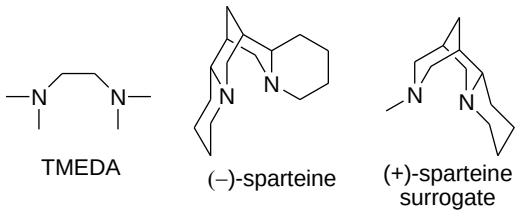
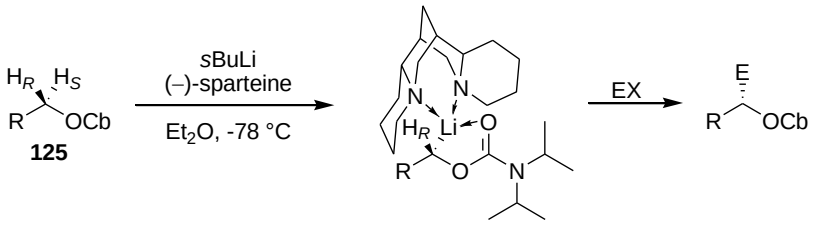


Figure 36: Diamines Employed in the Deprotonation of Alkyl Carbamate

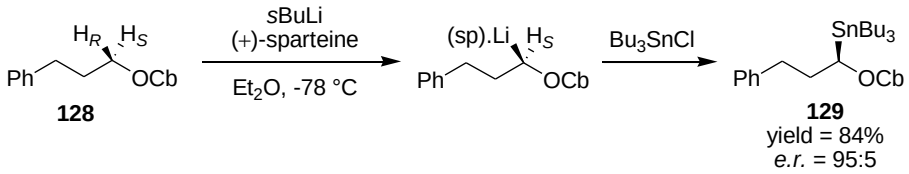
In the case of primary alkyl carabamates, treatment with *s*BuLi in presence of (–)-sparteine, leads to the preferential deprotonation of pro-*S* proton of **125**, affording the product with an *e.r*. up to 99:1 (Scheme 56).[133] Lithiated alkyl carbamates proved to be configurationally stable at -78 °C and so no equilibrium due to racemisation of the

organolithium occurs. Therefore the origin of enantioselectivity is a kinetically controlled process. It has been shown by quantum chemical DFT calculation that the transition state for pro-*S* deprotonation of ethyl carbamate by (–)-sparteine-*s*BuLi complex is 2.75 kcal/mol lower in energy that the transition state fro pro-*R*-H. This difference of energy at – 78 °C corresponds to the observed enantiomeric ratio of 99:1.[134]



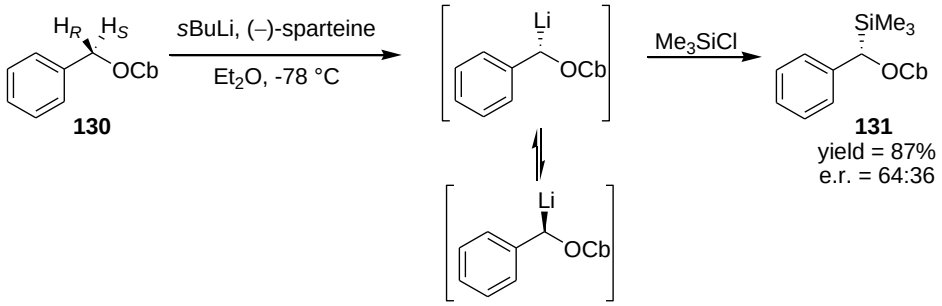
Scheme 56: Enantioselective deprotonation of alkyl carbamates with (–)-sparteine•*sec*-BuLi complex

The synthesis of the opposite enantiomer is achieved using (+)-sparteine surrogate (Figure 36), a ligand developed by O'Brien and co-workers.[135] In fact, while (–)-sparteine is commercially available, its enantiomer is not. The use of (+)-sparteine surrogate in lithiated carbamate reactions leads to the exclusively deprotonation of pro-*R* proton of **128**, affording the product **129** with an *e.r.* of 95:5.[133]



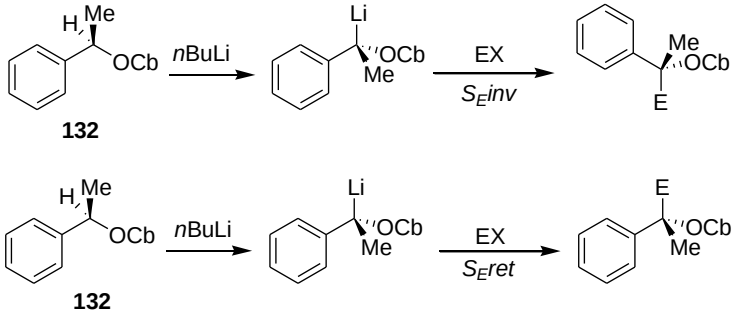
Scheme 57: Use of O'Brien's (+)-sparteine surrogate in lithiated carbamate chemistry

Unlike the case of *O*-alkyl carbamates, the lithiated primary *O*-benzyl ones are not configurationally stable at -78 °C. Therefore when the deprotonation of **130** reaction is run in presence of (–)-sparteine, the product **131** is recovered in racemic form (Scheme 58).[136, 137]



Scheme 58: Deprotonation of benzyl carbamate in the presence of (–)-sparteine[136]

Conversely, secondary benzyl carbamates proved to be configurationally stable at -78 °C.[137] Starting from enantiomerically enriched secondary benzylic carbamates **132**, the electrophiles react with the lithiated form with complete retention or complete inversion of stereochemistry, depending on the nature of the electrophile (Table 20).[130] Electrophiles containing a Lewis basic site usually react with retention of configuration. This is thought to be due to precomplexation between the Lewis basic group and lithium which is Lewis acidic. Electrophiles without a Lewis basic site cannot precomplex with lithium and so reaction occurs with inversion of stereochemistry. In both cases, however, the products are obtained with *e.e.* up to 95%.

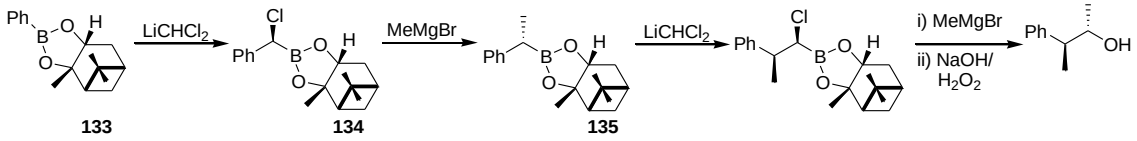


EX	Course	Yield (%)	% *e.e.*
Me_3SiCl	Inversion	94	96
Me_3SnCl	Inversion	92	≥ 95
PrBr	Inversion	77	85
MeOC(O)Cl	Inversion	90	85
$(MeO)_2CO$	Retention	85	94
Me_2CO	Retention	71	54
PhCHO	Retention	69	> 95

Table 20: Electrophiles which react with inversion and retention of configuration[130]

5.3 Lithiation/Borylation Methodology

In 1980 Matteson and co-workers reported a breakthrough in the synthesis of chiral boronic esters.[138] They found that treatment of chiral boronic ester **133** with dichloromethyllithium led to the stereoselective formation of a boron "ate" complex. This intermediate, upon warming to room temperature, underwent a stereospecific 1,2-metallate rearrangement to give α-chloro-boronic ester **134**. When the α-chloro-boronic ester **134** was treated with another nucleophile, such as Grignard reagent, a second homologation occurred, providing **135** (Scheme 59). The presence of a chiral diol (eg. pinane diol) as the ester substituent causes both homologations to proceed in an excellent diasteresoselctivity.[138] The stereochemistry of the "ate" complex is in fact controlled by the chiral environment provided by the boronic ester (substrate control) for the homologation of dichloromethyl lithium. Moreover the diastereomeric ratio can be improved up to >99:1 by adding zinc chloride to the solution.[139, 140]



Scheme 59: Homologation of pinane diol derived boronic esters [138]

The homologation of the α-chloro boronic ester with a nucleophile is a stereospecific reaction. The migrating group in the boron "ate" complex must be antiperiplanar to the leaving group (the chloride) for 1,2-metallate rearrangement to occur (Figure 37).

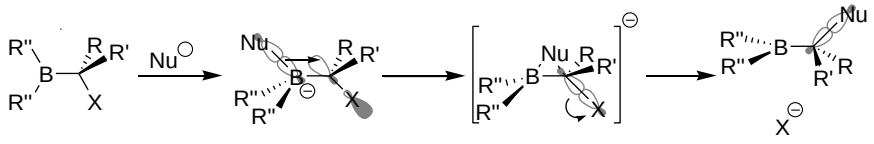
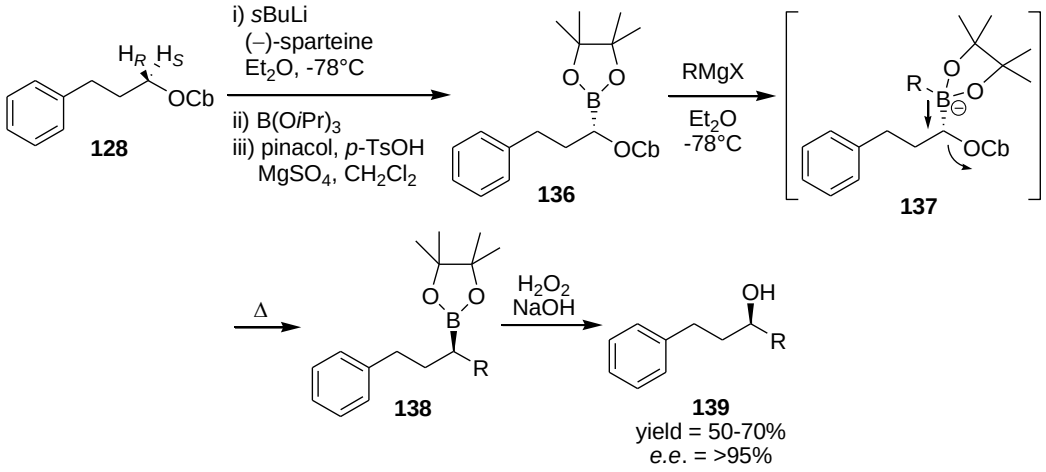


Figure 37: Mechanism of 1,2-metallate rearrangement. X = leaving group

The Matteson homologation has been used in total synthesis to form enantiomerically enriched secondary alcohols[141-146] and allyl boronates for subsequent allylboration.[147-150]

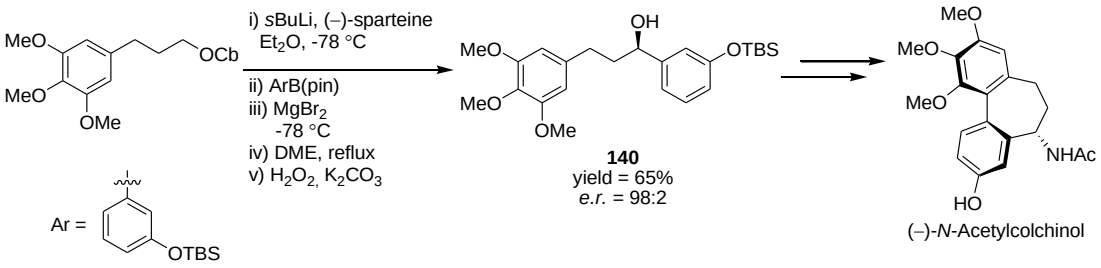
A complementary method to the substrate controlled Matteson homologation, was first developed by Hoppe and co-workers.[151] In this case they obtained the chiral boronic

ester **136** after reacting the chiral lithiated carbamate **128** with triisopropyl borate followed transesterification with pinacol. The lithiated carbamate dictated the stereochemistry of the product. Treatment of the boronic ester with Grignard reagents at -78 °C led to the formation of the "ate" complex **137**. Upon warming at room temperature, this underwent 1,2-metallate rearrangement, with the expulsion of the carbamate moiety, affording to give the secondary boronic ester **138** (Scheme 60).[151] The corresponding alcohol **139** is obtained in excellent yield and *e.r.*



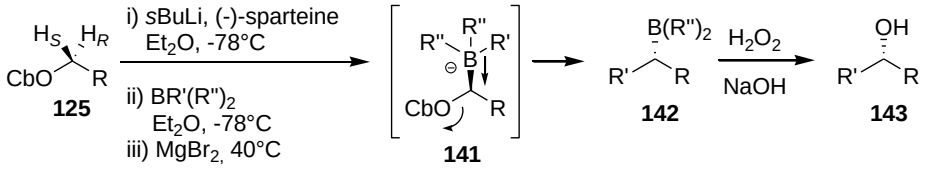
Scheme 60: Formation of secondary boronic ester from chiral lithiated carbamate and subsequent 1,2-metallate rearrangement[151]

This methodology was used in the total synthesis of (–)-*N*-acetylcolchinol by Kocienski and co-workers (Scheme 61).[152] During this work, it was found that the lithiated carbamate could be directly trapped with an aryl boronic ester to form the boron "ate" complex. 1,2-metallate rearrangement, promoted by magnesium bromide in refluxing 1,2-dimethoxyethane (DME) provided the boronic ester, that was oxidized into alcohol **140** in excellent enantioselectivity.



Scheme 61: Synthesis of (–)-*N*-Acetylcolchinol using lithiation/borylation

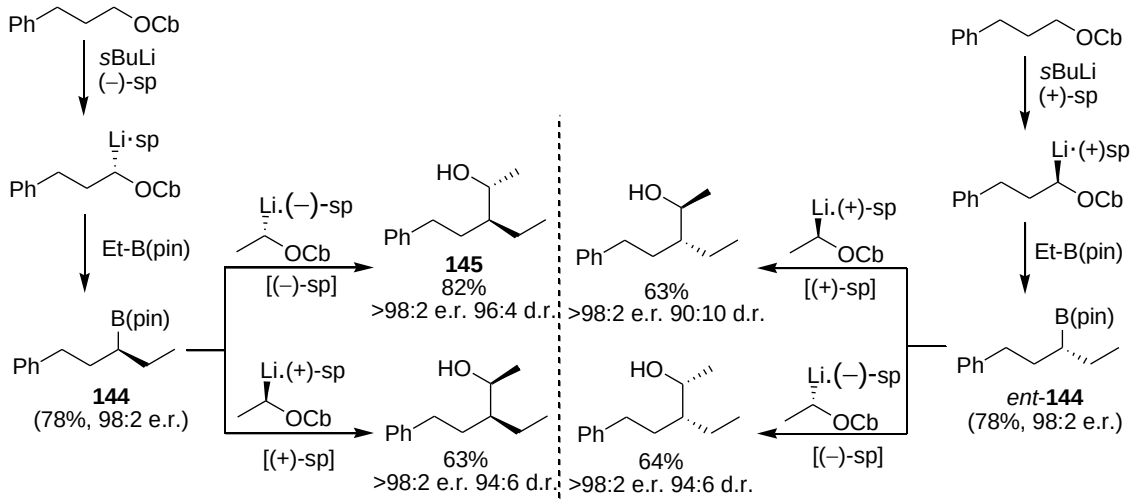
Aggarwal and co-workers generalised this methodology making reactions directly the lithiated carbamates with boranes or boronic esters.[129] Carbamate **125** was enantioselectively deprotonated with *s*BuLi in presence of (–)-sparteine, leading to the formation of the chiral carbenoid **141**. Addition of boranes or boronic esters afforded the boron "ate" complex with retention of configuration which underwent 1,2 metallate rearrangement upon warming. Subsequent oxidation of **142** led to the secondary alcohols **143** in excellent yield and *e.r.* (Table 21) .[129]



R	R'	(R'')$_2$	Yield (%)	*e.r.*
$Ph(CH_2)_2$	Et	Et_2[a]	91	98:2
$Ph(CH_2)_2$	*i*Pr	9-BBN[a]	81	98:2
$Ph(CH_2)_2$	Ph	9-BBN	94	97:3
$Ph(CH_2)_2$	Et	pinacol	94	98:2
$Me_2C{=}CH(CH_2)_2$	Et	Et_2[a]	90	97:3
$Me_2C{=}CH(CH_2)_3$	Ph	9-BBN	71	95:5
$Me_2C{=}CH(CH_2)_4$	Et	pinacol	75	98:2
$Me_2C{=}CH(CH_2)_4$	Ph	pinacol	73	98:2
$TBSO(CH_2)_2C(CH_3)_2CH_2$	Et	Et_2[a]	67	95:5
$TBSO(CH_2)_2C(CH_3)_2CH_2$	Ph	9-BBN	65	97:3
$TBSO(CH_2)_2C(CH_3)_2CH_2$	Ph	pinacol	64	98:2
*i*Pr	Ph	9-BBN	68	96:4
*i*Pr	Ph	pinacol	70	98:2
Me	Ph	pinacol	70	97:3

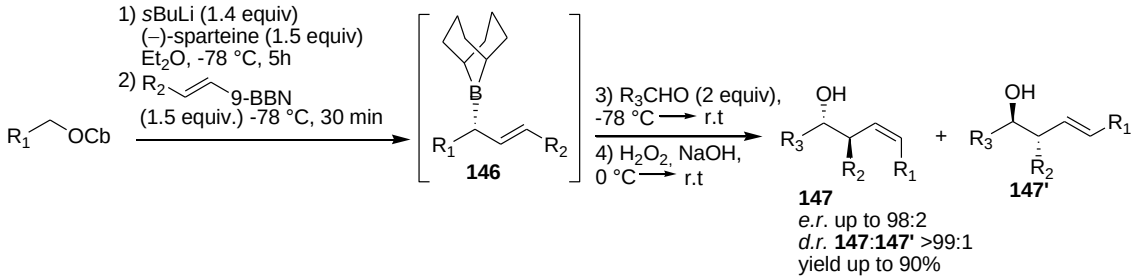
Table 21: Lithiation/Borylation reaction with alkyl carbamates. [a] No $MgBr_2$ added.[129]

As shown in Table 21, a broad range of alkyl carbamates can be employed together with a broad range of aryl and alkyl boronic esters, providing easy access to a wide variety of secondary alcohols. When boronic esters are employed, the addition of $MgBr_2$ in Et_2O at reflux is required to make the 1,2-metallate rearrangement to occur. Moreover it was shown that iterative homologation could be performed, with alcohols **145** obtained in excellent *e.r.* and *d.r.* (Scheme 62). The strength of this methodology lies in the possibility of obtaining all the fours alcohols stereoisomers through the appropriate choice of (–)-sparteine or (+)-sparteine surrogate during deprotonation of the carbamate.



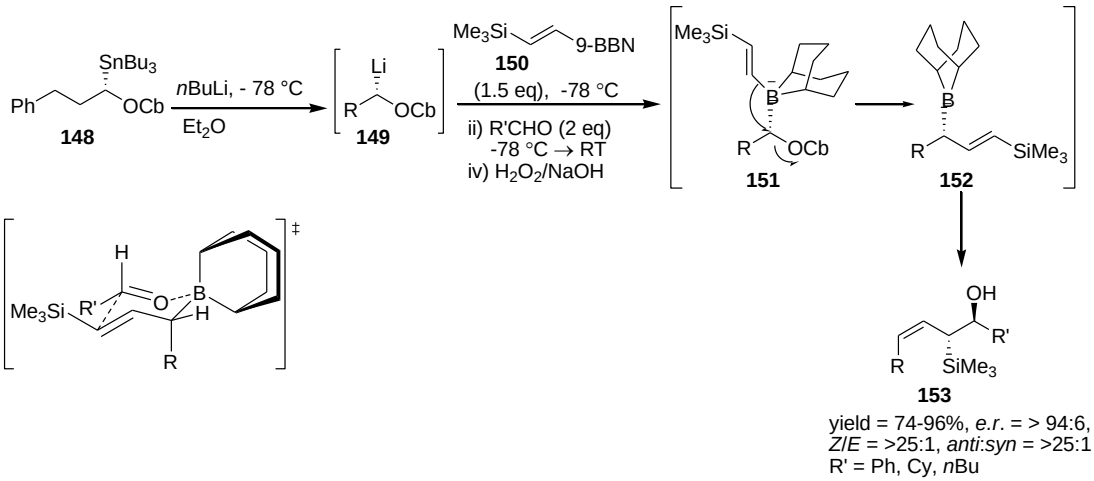
Scheme 62: Iterative homologation reaction of boronic esters **144** and *ent*- **144**

The lithiation/borylation of primary *O*-alkyl carbamates methodology was then applied in the synthesis of enantioenriched allyl boranes **146** (Scheme 63). These, however, were not isolated but underwent an *in situ* allylboration with aldehydes providing homoallylic alcohols **147** in high *e.r.* and *d.r.*[153]



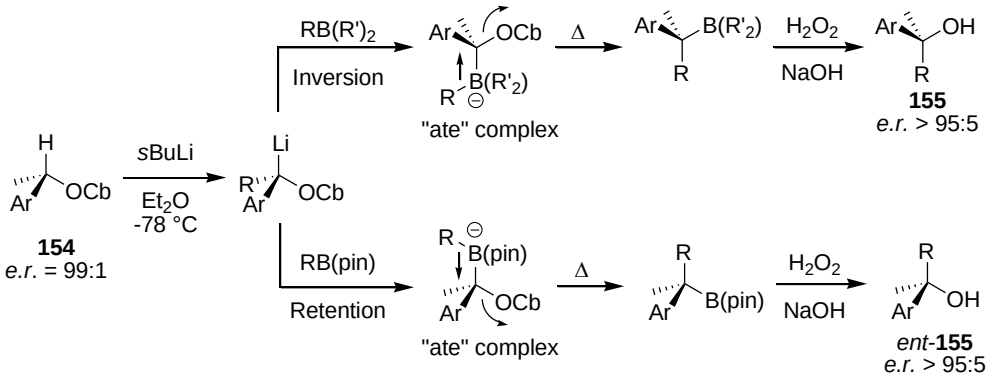
Scheme 63: Lithiation/borylation/allylboration methodology to form homoallylic alcohols[153]

A further application of this methodology was found in the synthesis of *β*-hydroxy allysilanes **153**.[154] Lithium-tin exchange of stannane **148** afforded the lithiated carbamate **149**. This reacted with retention of configuration with *β*-silyl vinyl borane **150** giving the "ate" complex **151**, that upon warming underwent 1,2- metallate rearrangement. However, because the allyl boranes were not stable, **152** was trapped with aldehyde *in situ*, affording *β*-hydroxy allysilanes **153** (Scheme 64).[154] This versatile methodology has been applied in the formal synthesis of (–)-decarestrictine D [154] and the total synthesis of solandelactone E.[155]



Scheme 64: Lithiation/borylation to form β-hydroxy-allylsilanes [154]

The lithiation/borylation methodology was also extended to the use of secondary benzylic *O*-lithiated carbamate.[156] Reaction of the lithiated carbamate **154** with boron reagents formed the corresponding boron "ate" complex. Upon warming to room temperature 1,2-metallate rearrangement occurred to give the tertiary borane or boronic ester. Oxidative workup afforded tertiary alcohols **155** in excellent yields and *e.r* (Table 22). The secondary alcohols, precursors of the carbamate, were easily made enantioselectively by Noyori transfer hydrogenation[157] of the corresponding ketones or by enzymatic resolution[158] of the racemic alcohols in an *e.r.* of up to >99:1.[156]



Ar (*e.r.* of carbamate)	R'	$(R'')_2$	Yield (%)	*e.r.*
Ph (99:1)	Et	Et_2	91	99:1
Ph (99:1)	Et	pinacol	95	1:99
Ph (99:1)	*i*Pr	9-BBN	91	98:2
Ph (99:1)	*i*Pr	pinacol	70	4:96
Ph (99:1)	Hexyl	9-BBN	60	98:2
Ph (99:1)	Hexyl	pinacol	85	4:96
Ph (99:1)	Cyclopropyl	pinacol	85	3:97
Ph (99:1)	vinyl	pinacol	75	2:98
Ph (99:1)	allyl	pinacol	95	1:99
Ph (99:1)	*p*Cl-C_6H_4	pinacol	97	1:99
Ph (99:1)	*p*MeO-C_6H_4	pinacol	92	2:98
Ph (99:1)	*m*CF_3-C_6H_4	pinacol	92	1:99
Ph (99:1)	2-furyl	pinacol	94	2:98
*p*Cl-C_6H_4- (98:2)	Et	Et_2	82	95:5
*p*Cl-C_6H_4- (98:2)	Et	pinacol	92	4:96
*p*Cl-C_6H_4- (98:2)	Ph	pinacol	89	4:96
*p*MeO-C_6H_4- (98:2)	Et	Et_2	87	96:4
*p*MeO-C_6H_4- (98:2)	Et	pinacol	97	2:98
*p*MeO-C_6H_4- (98:2)	Ph	pinacol	81	4:96

Table 22: Lithiation/Borylation of secondary aryl carbamates[156]

The lithiation/borylation methodology proved to be even more useful, because starting from the same enantioenriched carbamate, both enantiomers of the tertiary alcohol can be obtained. The reaction of boronic esters proceeded with retention of configuration of the lithiated carbamate whereas when boranes were used, the reaction occurred with

inversion of stereochemistry. This stereochemical outcome can be so explained: in the case of boronic ester, the oxygen of the ester complexes with the lithium of the metallated carbamate and so it is delivered from the same face as the carbanion (Figure 38). In case of borane, precomplexation cannot occur and so the electrophile attack the face opposite to the lithium where there is significant electron density owing to the nature of the carbanion being between tetrahedron and trigonal biplanar (Figure 38).[156]

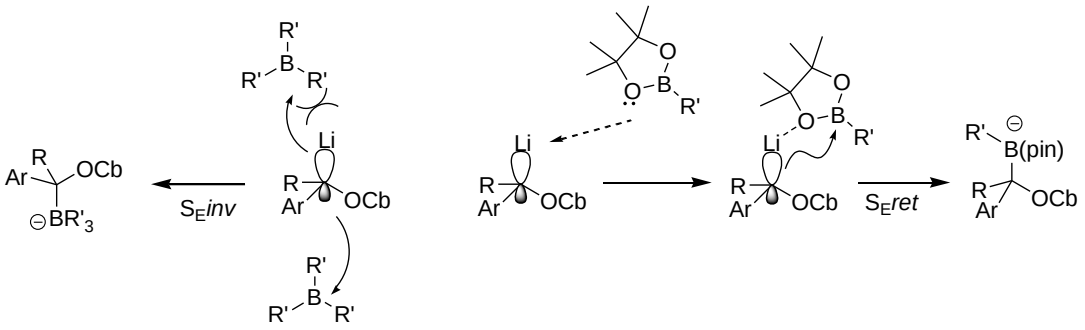
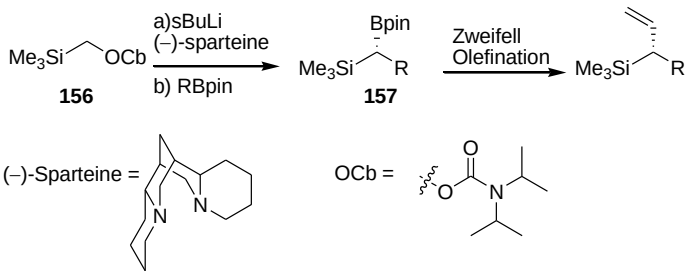


Figure 38: Explanation of whether electrophile reacts with retention or inversion of stereochemistry [156]

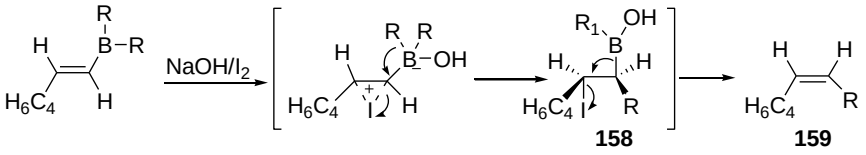
5.4 Aim of the Work

On the base of the results previously obtained with lithiation-borylation methodology, we envisaged to extend it in the synthesis of tertiary and quaternary allylsilanes with high *d.r.* and *e.r.* In particular we thought that the lithiation-borylation of carbamate **156** could afford intermediate **157**, that could have been transformed into allylsilanes by means of Zweifel olefination (Scheme 65).



Scheme 65: Proposed used of lithiation/borylation in the synthesis of chiral allylsilanes

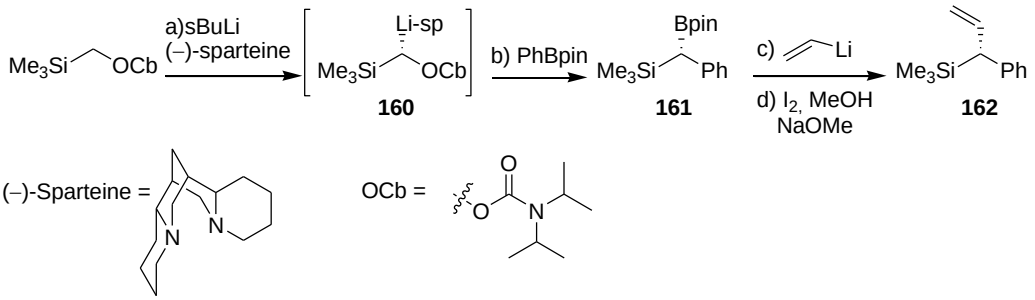
Zweifel and co-workers in 1967 described the synthesis of substituted alkenes *via* iodination of vinylboranes.[159] It was proposed that initial addition of iodine to the double bond was followed by the migration of a R-group from the boron to the adjacent carbon atom to provide organoborane **158** (Scheme 66). Elimination to give alkene **159** proved to be highly stereoselective and occurred when the boron group and the iodine were in a *trans* relationship .



Scheme 66: Zweifel olefination mechanism [159]

6 RESULTS AND DISCUSSION

The first attempt in using lithiation/borylation methodology for the synthesis of allylsilanes envisaged the use of an α-silyl carbamate.[a] We thought that trapping the enatioenriched lithiathed carbamate **160** with a boronic ester would have given, after formation of "ate" complex and 1,2-metallate rearrangement, the product **161** (Scheme 67). Zweifel olefination of the newly formed boronic ester would have provided the allysilane **162**. However this strategy proved unrewarding, because the intermediate lithiated silyl carbamate **160** was configurationally unstable,[160] even when the reaction was performed at -100 °C, and led to racemic **161**.

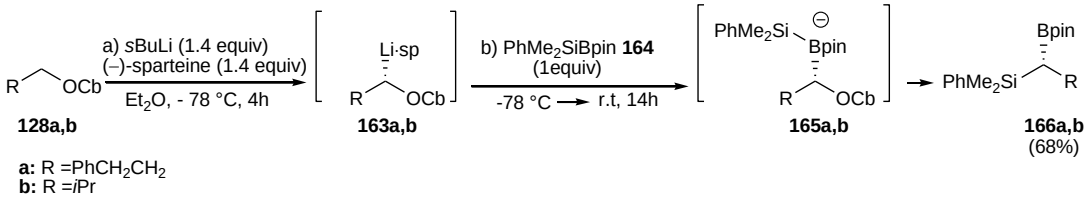


Scheme 67: Lithiation/borylation of silyl carbamate to synthesise chiral allylsilanes **162**

We therefore considered an alternative approach. The lithiation of alkylcarbamate **128a**,**b** was carried out in the presence of chiral diamine (−)-sparteine and provided the enantioenriched lithiated carbamate **163a**,**b** configurationally stable at -78 °C. The subsequent addition of the silaboronate **164** as the electrophile led to the formation of a boron "ate" complex" **165a**,**b**, that upon warming underwent 1,2-metallate

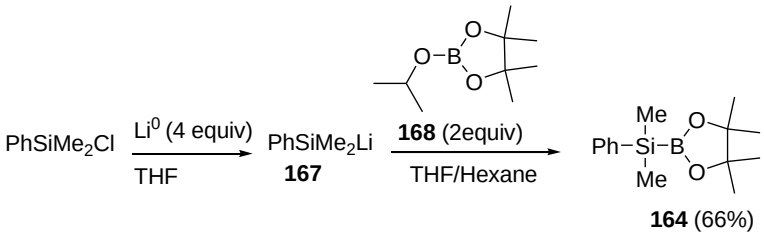
[a] This work was published in *Org. Lett.* **2011**, *13*, 1490 by Aggarwal, V. K.; Binanzer, M.; De Ceglie, M. C.; Gallanti, M.; Glasspoole, B. W.; Kendrick, S. J. F.; Sonawane, R. P.; Vazquez-Romero, A.; Webster, M. P. Therefore this section is the result of the work of several persons. To be complete I included it all, even if I focused my attention on the derivatization of the allylsilanes and on their cyclization

rearrangement with migration of the silyl group and the expulsion of the carbamate group, providing the 1,1-silaboronates **166a**,**b** (Scheme 68). Despite there being few reported examples[161-163] of the migration of a silyl group in the literature, this strategy proved to be successful.



Scheme 68: Synthesis of silaboronates **166a**,**b** through lithiation/borylation of carbamates **128a**,**b**

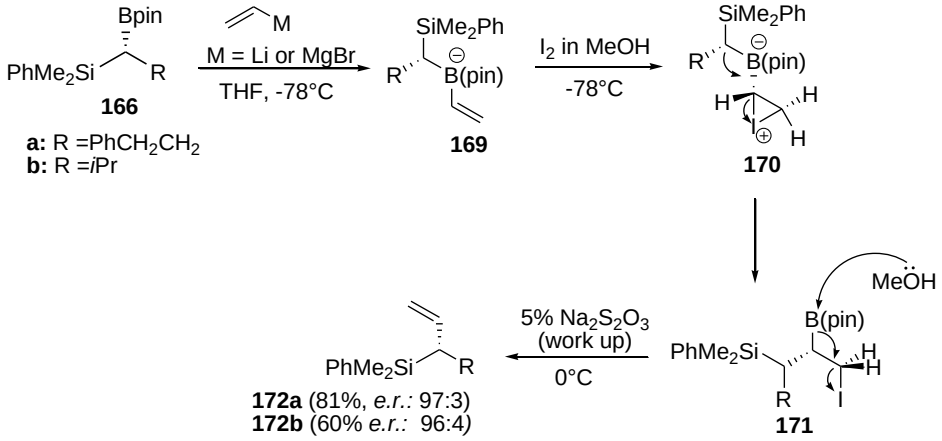
The reaction was performed using two different R groups, the *iso*propyl group and the phenylethyl group. In both cases **166** was obtained in very good yields. Despite the silaboronate **164** being commercially available, we found that when the reactions were carried out using freshly synthesised **164** the yields were dramatically improved (from 26% to 68%). Silaboranate **164** was synthesised according to the procedure reported by Suginome and co-workers (Scheme 69).[164] Silyllithium **167** was prepared treating the corresponding chlorosilane with lithium. The resulting solution was then added to borane **168** and the desired silaboronate **164** was obtained in good yield after distillation.



Scheme 69: Synthesis of silaboronate **164** [164]

In order to synthesise the desired allylsilanes, we applied modified condition of Zweifel olefination.[159, 165, 166] It was found that I_2/MeOH was superior to the more commonly employed conditions I_2/MeONa/MeOH. Initially we focused our attention on the synthesis of vinylsilanes **172a**,**b**. Treatment of silaboronates **166a**,**b** with vinlyllithium

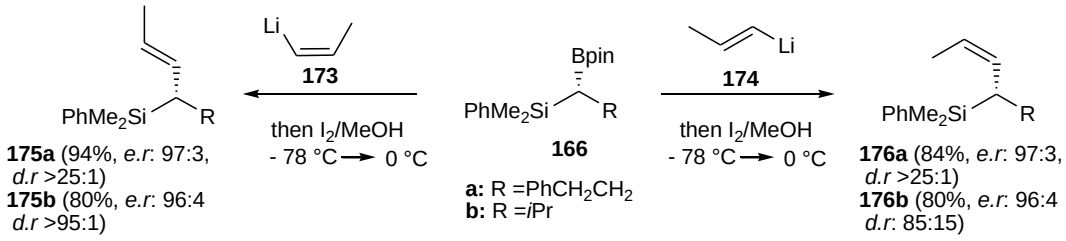
led to the formation of "ate" complex **169a,b** (Scheme 70). The addition of iodine in methanol provided iodonium intermediate **170**. This, upon warming, rearranged into intermediate **171.** *Anti* elimination led to the formation of **172a**,**b** in good yield and excellent *e.r*.



Scheme 70: Synthesis of allysilanes **172a**,**b** through Zweifel olefination

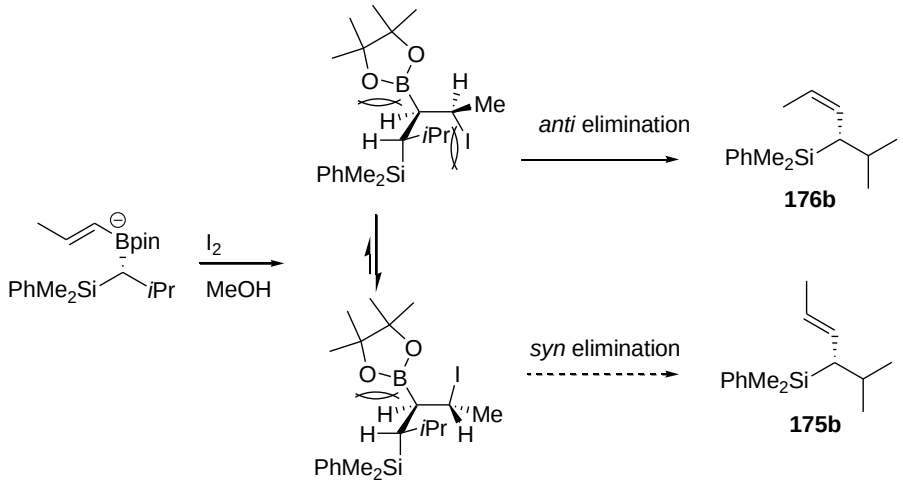
It should be noted that, in the case of boronate ester **166a**, vinylmagnesium bromide was sufficiently nucleophilic to effect the "ate" complex formation but for the more hindered **166b** vinyllithium was required.

Encouraged by this result we directed our attention on the synthesis of more challenging crotylsilanes. Therefore silaboronates **166a**,**b** were treated with *Z*-propenyllithium **173** or *E*-propenyllithium **174** providing, respectively *E*-crotylsilanes **175a,b** and *Z*-crotylsilanes **176a,b** in excellent yields, *e.r* and *d.r.*(Scheme 71).



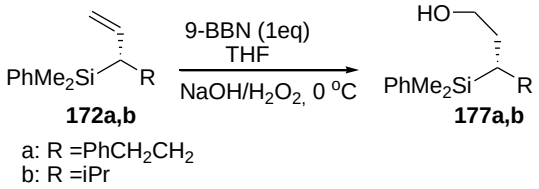
Scheme 71: Synthesis of crotylsilanes **175a,b** and **176a,b** through Zweifel olefination

In the case of the crotylsilanes, the fact that the elimination occurred exclusively when boron and iodine are in *anti* was important as it prevents the formation of a mixture of *cis* and *trans* isomers. Only in the synthesis of highly hindered *Z*-crotylsilane **176b** was the *E* isomer visible in the crude NMR (*d.r.*: 85:15). In this case, the minor *E*-olefin presumably arose due to the severe steric clash in the conformation required for *anti*-elimination which gives the *Z*-olefin. Therefore some *syn*-elimination occurs, providing the small amount of *E*-isomer (Scheme 72).



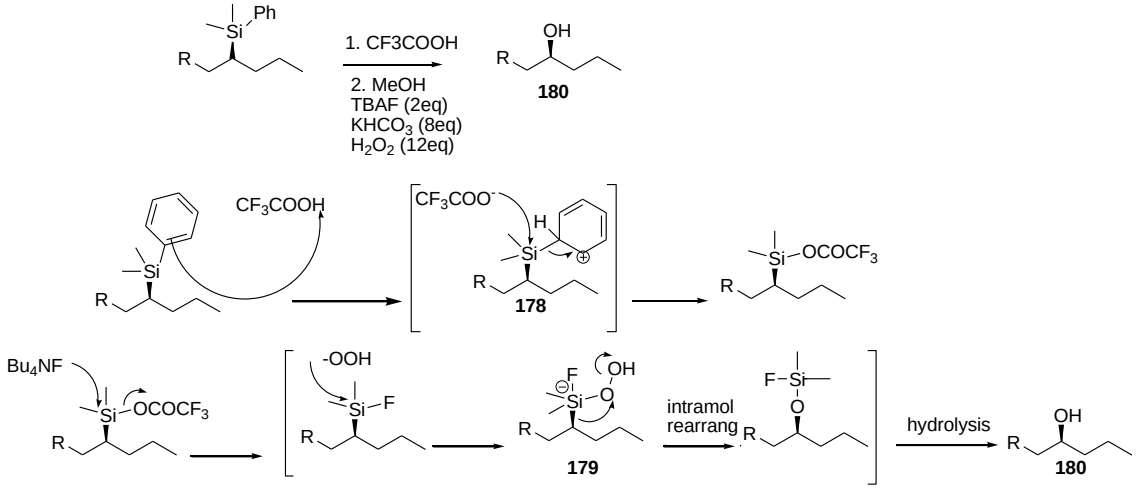
Scheme 72: Conformations that lead to the formation of *cis*-crotylsilane **176a** and *trans* crotylsilane **175b**

All of the allysilanes synthesized were not able to be analyzed by chiral HPLC or chiral GC. Therefore, it was necessary to derivatize them without losing the *e.r.* achieved in the previous steps. While hydroboration[154] and oxidation of the allyl silanes to the alcohol **177a**,**b** (Scheme 73) proved to be a successful strategy for determine the *e.r.* of allilsilanes **172a**,**b**, this was not the case for crotylsilanes **175a**,**b** and **176a,b**.



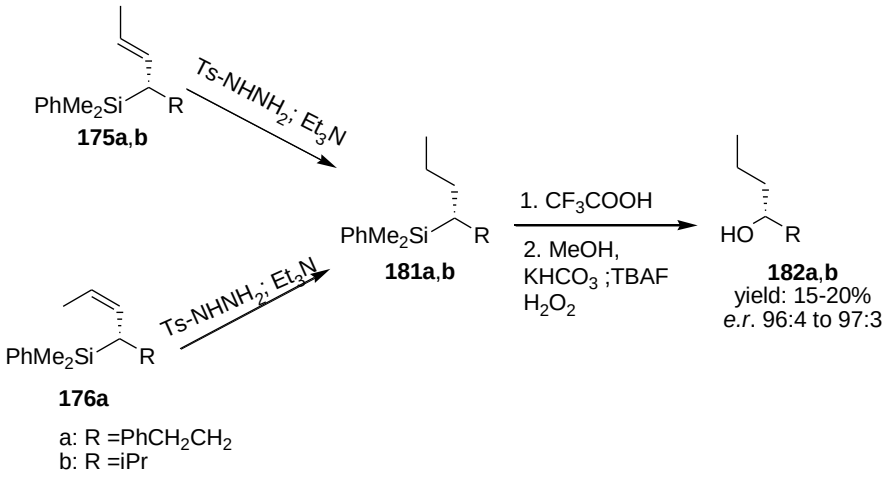
Scheme 73: Hydroboration of allylsilanes **172a, b**

Therefore, we applied the Tamao-Fleming oxidation of organosilane.[119, 167] This reaction allows the conversion of the dimethylphenylsilyl group to an alcohol functionality with retention of configuration (Scheme 74). The authors propose that the phenyl ring is protonated giving the intermediate **178** and the trifluoroacetate anion attacks the silicon leading to the expulsion of benzene. Subsequently, fluorine attacks silicon kicking out the trifluoroacetate anion. Oxidation occurs when the peroxide anion attacks silicon providing the intermediate **179**. This undergoes a stereospecific intramolecular rearrangement with retention of configuration which, after hydrolysis gives alcohol **180**.



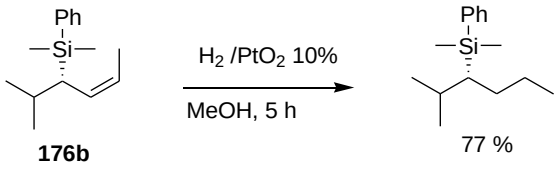
Scheme 74: Mechanism of Tamao-Fleming oxidation [119, 167]

All the crotylsilanes previously synthesized were separately reduced to the saturated organosilanes **181a**,**b** in presence of tosylhydrazide and triethylamine,[164] before oxidation to the corresponding alcohols **182a, b** (Scheme 75). The yields of these reactions were not optimised.



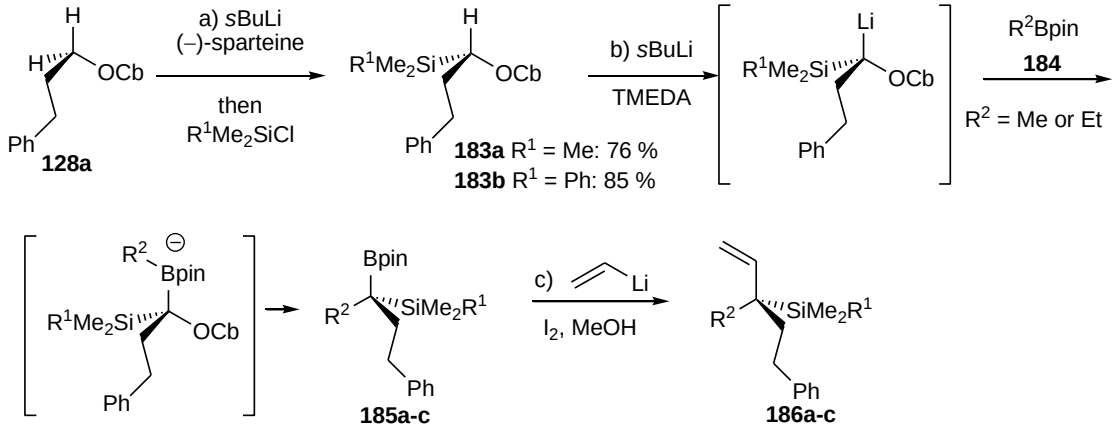
Scheme 75: Tranformation of allysilanes **175a**,**b** and **176a** into alcohols **182a**,**b**

In case of the more encumbered crotylsilane **176b**, hydrogenation reaction using PtO_2 as catalyst was carried out (Scheme 76).[168] All of the allylsilanes synthesised proved to have an excellent *e.r* as shown in Scheme 71.



Scheme 76: Reduction of allylsilane **176b**

Two PhD students in the group, Dr. Binanzer and Dr. De Ceglie, proved that the lithiation-borylation methodology could be extended to the synthesis of the more challenging quaternary allylsilanes. In this case, the sequence started with lithiation and silylation of carbamate **128a** in presence of (–)-sparteine as previously described by Hoppe,[169,170] providing intermediates **183a,b** (Scheme 77). Subsequent deprotonation with *s*BuLi/TMEDA followed by the addition of boronic ester **184** gave intermediate **185**. This intermediate was converted to the corresponding quaternary allylsilane **186,** using the modified Zweifel olefination (see Scheme 70) in good yields and excellent *e.r.* (Table 23). The *e.r.* was determined by HPLC analysis, of the product derived from hydroboration/oxidation of **186a-c**. The absolute configuration was assigned by X-ray analysis of the alcohol obtained from **186c** by hydroboration/oxidation. All other assignments were made by analogy.

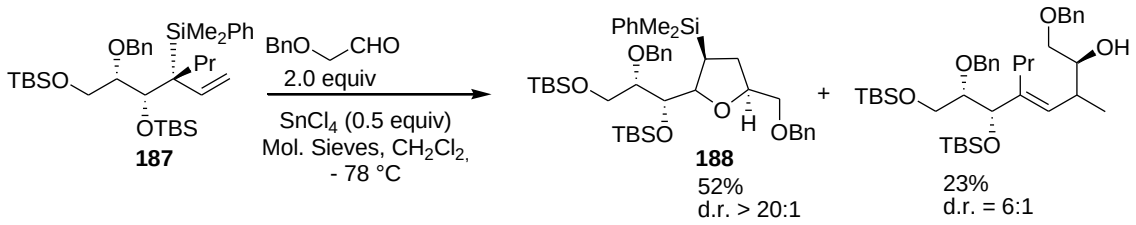


Scheme 77: Lithiation/borylation followed by Zweifel olefination for the synthesis of quaternary allylsilanes **186a-c**

	R^1	R^2	Yield of **185**	Yield of **186**	*e.r.* of **186**
a	Me	Et	94%	73%	97:3
b	Ph	Me	52%	73%	97:3
c	Ph	Et	76%	60%	97:3

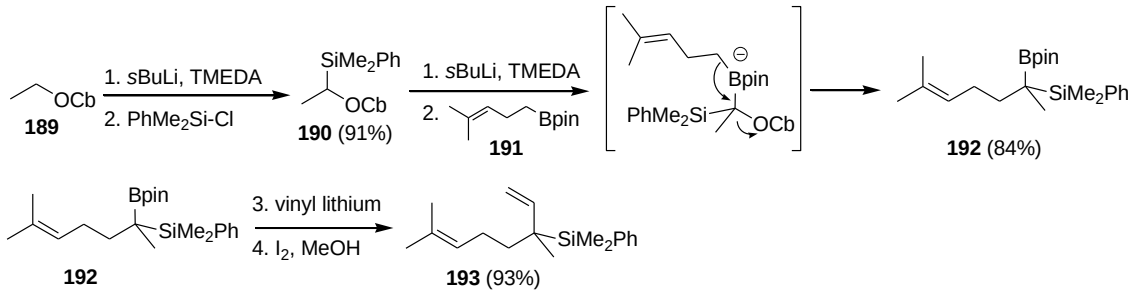
Table 23: Yields and *e.r* for lithiation/borylation/Zweifell olefination sequence

Roush previously showed that quaternary allylsilane **187** can react with aldehydes through a [3+2] cycloaddition reaction, leading to the formation of a tetrahydrofuran **188** in good yield and excellent diastereoselctivity (Scheme 78).[171]



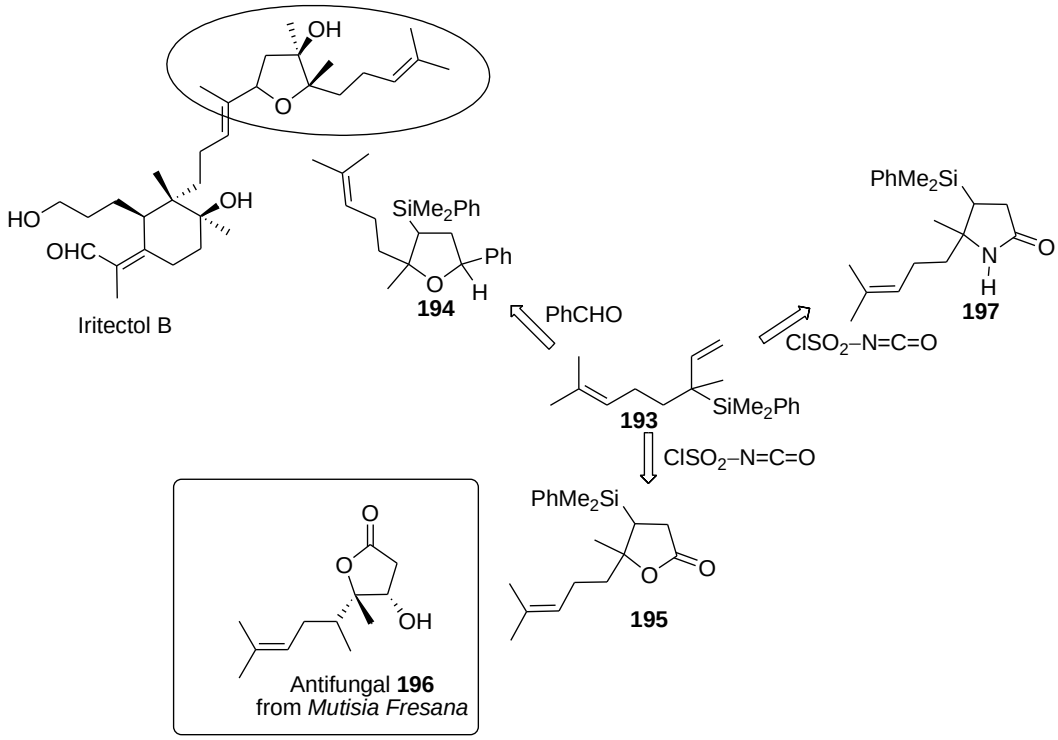
Scheme 78: Cyclization of quaternary allilsilane[171]

This prompted us to synthesise quaternary allylslilane **193** (Scheme 79), according to the methodology shown in Scheme 77. Quaternary allylsilane **193** was obtained racemically starting from carbamate **189** (using TMEDA instead of (–)-sparteine in the deprotonation step) in very good yield.



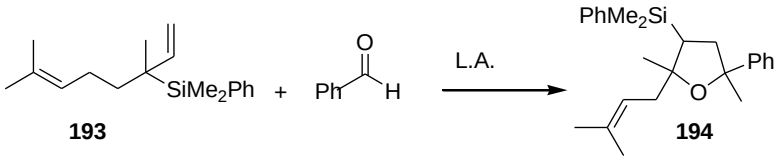
Scheme 79: Synthesis of quaternary allylsilane **193** through lithiation/borylation/Zweifel olefination sequence

We thought that allylsilane **193** could undergo cyclization[114, 172, 173] reaction with different electrophiles, providing natural product precursors (Scheme 80). For instance, reaction of **193** with benzaldehyde would provide **194**, a motif that is found in the molecule of Iritectol B. Reaction with chlorosulphonyl isocyanate would lead to the formation of **195** that could be oxidized to the antifungal compound **196** or to lactam **197**.



Scheme 80: Cyclization of allysilane **193** to provide useful molecules

Therefore, we reacted allysilane **193** with benzaldehyde in presence of different Lewis acids[171,172,174] to obtain **194**. However when $BF_3 \cdot OEt_2$ or tris(pentafluorophenyl)borane were used, the reaction didn't occur at low temperature and led to a mixture of undefined products when the temperature was raised (Table 24).

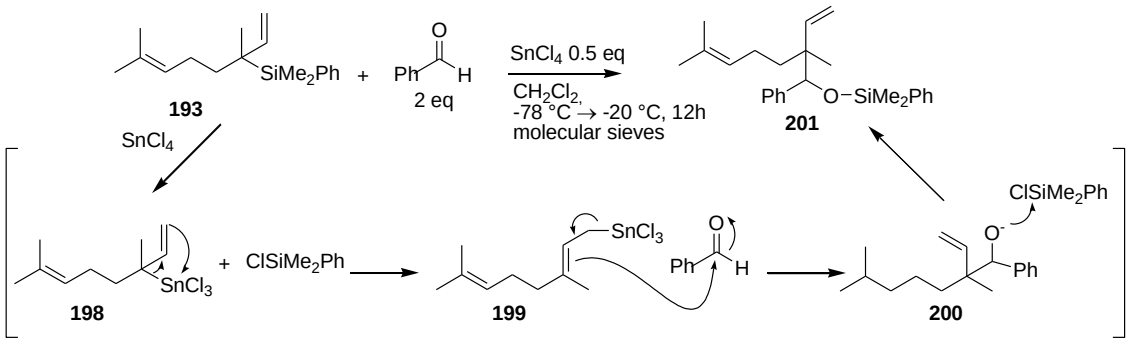


193 **194**

Lewis Acid	PhCHO	Solvent	Temperature	Time	Comment
BF_3OEt_2 (1.3 eq)	1.3 eq	DCM	-78 °C	2 h	No reaction
BF_3OEt_2 (1.3 eq)	1.3 eq	DCM	-45 °C	3 h	No reaction
BF_3OEt_2 (1.3 eq)	1.3 eq	DCM	-30 °C	24 h	No reaction
BF_3OEt_2 (1.3 eq)	1.3 eq	DCM	-20 °C	20 h	Complex reaction mixture
tris(pentafluorophenyl)borane	1.3 eq	DCM	-78 °C	3 h	No reaction
tris(pentafluorophenyl)borane	1.3 eq	DCM	-30 °C	12 h	No reaction
tris(pentafluorophenyl)borane	1.3 eq	DCM	-20 °C →0 °C	8 h	Complex reaction mixture

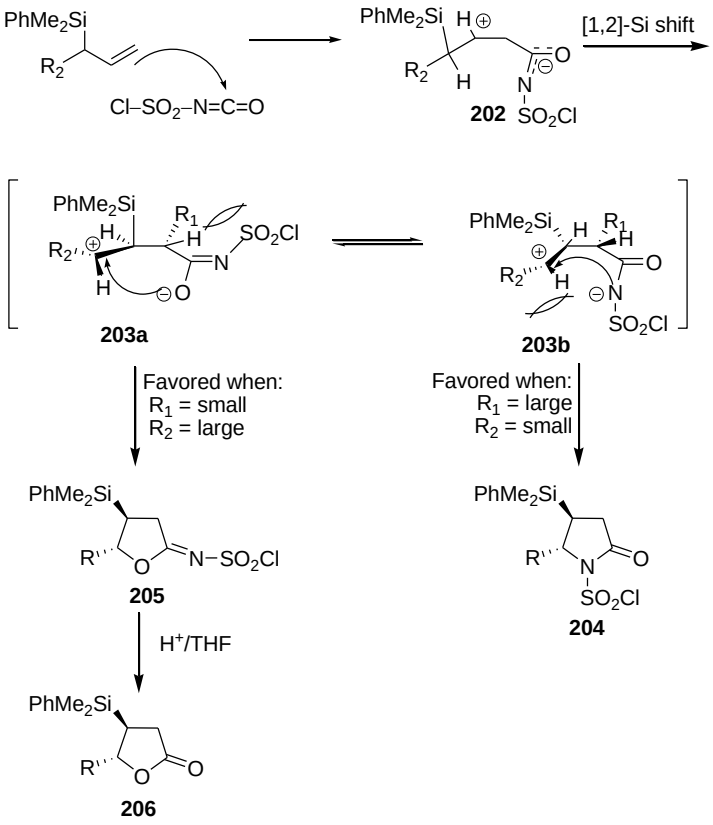
Table 24: Attempted cyclization of **193** with benzhaldehyde using different Lewis acids

Using $SnCl_4$, the only product recovered from the complex reaction mixture was **201** (Scheme 81). This product presumably derives from an initial Si-Sn exchange.[175] The allylstannane **198** undergoes an internal rearrangement, providing **199.** This latter reacts with benzaldehyde providing **200** and the alkoxide is trapped by silylchloride, giving **201**.



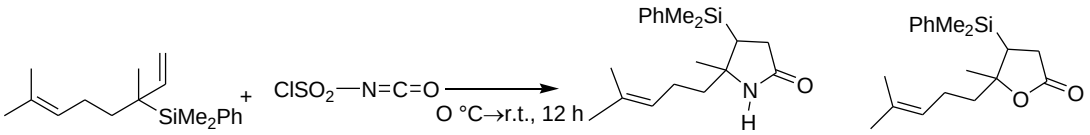
Scheme 81: Proposed mechanism for the formation of **201**

We then turned our attention to the reaction with chlorosulphonyl isocyanate (CSI). This reaction between an allylsilane and CSI can give two possible products: the lactam **204,** if annulation occurred across the C=N bond of CSI, and the lactone **206** if cyclization occurred across the C=O bond (Scheme 82). Woerpel and co-workers proposed that electrophilic attack by CSI occurs antiperiplanar to the silyl group of allylsilane leading to β-silyl carbocation **202**.[173] A subsequent 1,2-silyl migration occurs providing intermediate **203**, that cyclises *anti* to the silyl group to give 4,5-*trans*-**204** or **205**. According to Woerpel and co-workers,[176] the steric size of the α-substituent of the allylsilane exerts a strong influence on the annulations. The steric interaction between the α-substituent R_2 and the NSO_2Cl group disfavours the *N*-cyclization intermediate **203b**. However, intermediate **203b** is favoured by repulsion between NSO_2Cl and R_1. On the other hand, *O*-cyclization intermediate **203a** is favoured by steric repulsion between the α-substituent R_2 and the NSO_2Cl group but disfavoured by interaction of NSO_2Cl and R_1. Therefore an allyl silane with a large R_2 group and a small R_1 group prefers the *O*-cyclization pathway, leading to lactone precursor **205.** In contrast, an allylsilane with a small R_2 group and a large R_1 group favours the *N*-cyclization pathway, to provide the lactam **204**.



Scheme 82: Proposed mechanism of annulation and origin of the competion between C=N and C=O annulations[176]

On the basis of this consideration, we reacted allylsilane **193** with CSI, expecting the lactone **208** as the main product. Instead, a mixture of lactam **207** and lactone **208** were formed. However, although different reaction conditions were tested[176, 177] it was not possible to direct the reaction towards just one of the two products (Table 25). In all the reactions, the crude weight was less than the theoretical yield, suggesting that protodesilylation may have occurred in the reaction.



193 **207** **208**

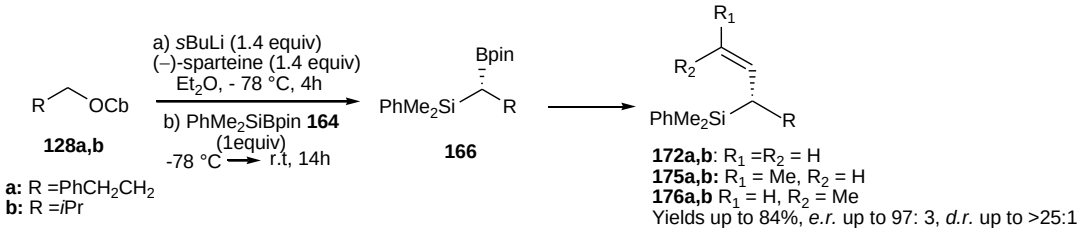
Conditions	**207**	**208**
1) DCM, 1.2 eq CSI 0°C→r.t. 12 h 2) Na_2SO_3 25%, r.t. 20 h	20%	16%
1) toluene, 1.5 eq CSI, 2.5 eq $NaHCO_3$ 0°C→r.t. 12 h 2) $NaHSO_3$ std r.t. 20 h	28%	18%
1) toluene, 1.5 eq CSI 0°C→r.t. 12 h 2) $NaHSO_3$ std, r.t. 20 h	15%	13%

Table 25: Attempted cyclization with CSI

At this point, my stay in Bristol ended. Due to the highly challenging nature of the cyclisation reactions investigated, no further work was carried out on this project.

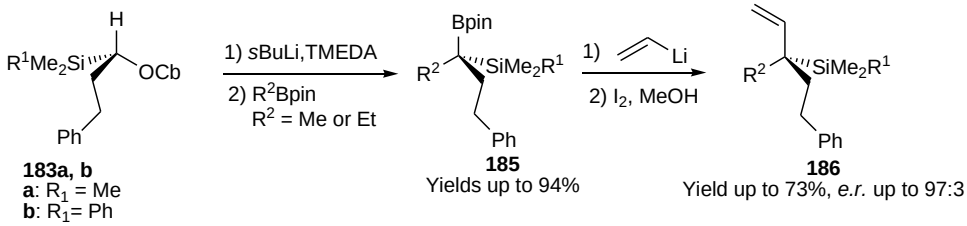
7 CONCLUSION

In summary, a simple method to obtain tertiary allyl- or crotyl silanes in excellent *e.r* and *d.r* was developed. This involved the extension of the lithiation borylation reaction developed within the Aggarwal group through reaction of primary lithiated alkyl carbamates with silaboronate **164** (Scheme 83). Zweifel olefination of the intermediate secondary silaboronate led to allyl and crotyl silanes. It was found necessary to derivatise the allyl silanes using either hydroboration/oxidation or Fleming-Tamao oxidation to obtain material which could be analysed by chiral HPLC.



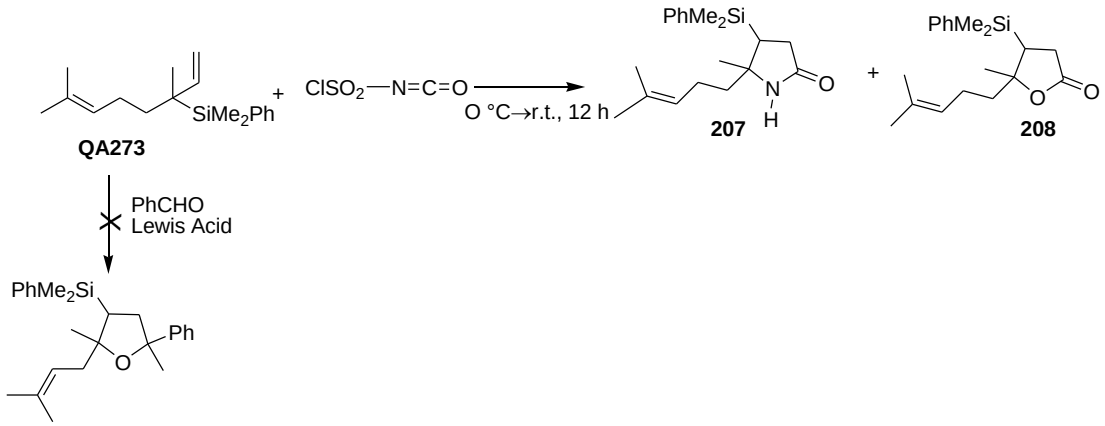
Scheme 83: Synthesis of tertiary allyl- and crotylsilanes through lithiation/borylation/Zweifel olefination

Using a related strategy, a unique reaction sequence that leads to quaternary allylsilanes in similarly high *e.r.* was developed. This involved reaction of lithiated silacarbamate **183a,b** with alkyl boronic esters to give tertiary boronic esters (Scheme 84). Zweifel olefination led to quaternary allylsilanes in excellent *e.r*. and yield.



Scheme 84: Synthesis of quaternary allylsilanes through lithiation/borylation/Zweifel olefination

Attempts to react quaternary allyl silane **193** with aldehydes in the presence of a Lewis acid were unsuccessful. The allyl silane **193** did react with CSI, however, to give a mixture of lactam and lactone products.



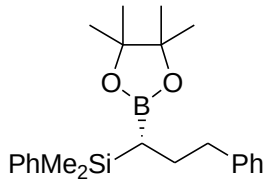
Scheme 85: Attempted cyclization with benzaldehyde and with CSI

8 EXPERIMENTAL

8.1 General information

All reactions were carried out in oven-dried (180 ºC) glassware and under an Ar atmosphere using standard Schlenk techniques. Anhydrous solvents were prepared using anhydrous solvent drying columns. ^{1}H- and ^{13}C-NMR spectra were acquired at various field strengths as indicated, and were referenced to $CHCl_3$ or TMS. ^{11}B NMR spectra were recorded with complete proton decoupling using $BF_3 \cdot Et_2O$ as an external standard. Low- and high-resolution mass spectra were recorded using Electron Impact (EI), Chemical Ionization (CI) or Electron-Spray Ionization (ESI) techniques. For CI, methane or NH_4OAc/MeOH were used. Analytical TLC: aluminium backed plates pre-coated (0.25 mm) with silica gel 60 F 254. Compounds were visualized by exposure to UV-light or by staining with 5% solution of $(NH_4)_2Mo_7O_{24} \cdot 4H_2O$ in EtOH followed by heating. Flash chromatography was carried out using Merck silica gel 60, 0.040–0.063 mm particle size. Melting points were determined with a Boetius hot stage apparatus and were not corrected. All IR data were obtained on a Perkin-Elmer Spectrum One FT-IR spectrometer. *N,N,N',N'*-Tetramethylethylenediamine (TMEDA) was purchased from Aldrich and (–)-sparteine was purchased from Alfa Aesar or Aldrich. Both were distilled under reduced pressure over CaH_2 prior to use. Anhydrous methanol was purchased from Acros and used without further purification. *s*BuLi was purchased from Acros or Aldrich.

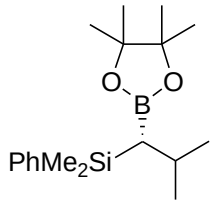
8.2 (R)-Dimethyl(phenyl)(3-phenyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propyl)silane 166a



Phenylpropyldi*iso*propylcarbamate **128a** (0.50 mL, 1.89 mmol) and (–)-sparteine (0.45 mL, 1.89 mmol) were dissolved in diethyl ether (8 mL) and cooled to –78 °C. *s*BuLi (1.4 mL, 1.3 M solution in cyclohexane/hexane (92:8), 1.89 mmol) was added dropwise and the mixture was stirred at –78 °C for 5 hours. Silylboronic ester **164** (0.35 mL, 1.32 mmol) was added dropwise and the resulting mixture was stirred at –78 °C for 1 hour, allowed to warm to 23 °C and stirred for an additional 18 hours. Water was added, the phases were separated, the aqueous phase was extracted three times with diethyl ether and the combined organic phases were washed with brine, dried (Na_2SO_4), filtered and concentrated. Column chromatography (silica gel, 5 % diethyl ether in petroleum ether) gave boronic ester **166a** (344 mg, 69 %) as a colourless oil. The racemate was obtained with TMEDA instead of (–)-sparteine.

R_f (5 % diethyl ether in petroleum ether): 0.2; $[\alpha]_D^{23}$ = +24.0 (*c* = 1.0, CH_3Cl); ^{1}H NMR ($CDCl_3$, 500 MHz): δ [ppm] 7.51–7.10 (m, 10 H), 2.70 (ddd, *J* = 13.4, 9.7, 5.0 Hz, 1 H), 2.46 (ddd, *J* = 13.4, 9.7, 6.8 Hz, 1 H), 1.89 (dddd, *J* = 13.1, 12.0, 9.7, 5.0 Hz, 1 H), 1.64 (dddd, *J* = 13.1, 9.7, 6.8, 2.9 Hz, 1 H), 1.23 (s, 6 H), 1.20 (s, 6 H), 0.71 (dd, *J* = 12.0, 2.9 Hz, 1 H), 0.32 (s, 3 H), 0.31 (3 H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ [ppm] = 142.6, 138.8, 133.8, 128.8, 128.5, 128.2, 127.6, 125.6, 82.8, 39.4, 28.0, 25.2, 24.7, –2.3, –3.4; ^{11}B ($CDCl_3$, 96 MHz) δ [ppm] = 33.7; HRMS (ESI): calculated for $C_{23}H_{33}BO_2Si$ ($[M+Na]^+$): m/z = 403.2235, found: m/z = 403.2224; MS (ESI): m/z = 221.1, 303.2, 373.2, 403.2; IR ($\tilde{\nu}$ /cm^{-1}, neat): 3026, 2977, 2927, 2858, 1350, 1306, 1248, 1143, 1111.

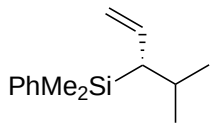
8.3 (R)-Dimethyl(2-methyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propyl)(phenyl)silane 166b



*Iso*butyl di*iso*propylcarbamate **128b** (1.41 g, 2.03 mmol) and (−)-sparteine (0.46 mL, 2.03 mmol) were dissolved in diethyl ether (30 mL) and cooled to at −78 °C. *s*BuLi (1.56 mL, 1.3 M solution in cyclohexane/hexane (92:8), 2.03 mmol) was added dropwise and the mixture was stirred at −78 °C for 5 h. Boronic ester **164** (0.45 mL, 1.57 mmol) was added dropwise and the resulting mixture was stirred at –78 °C for 1 hour, allowed to warm to 23 °C and stirred for an additional 18 hours. Water was added, the phases were separated and the aqueous phase was extracted three times with diethyl ether. The combined organic phases were washed with brine, dried ($MgSO_4$), filtered and concentrated. Column chromatography (silica gel, 4 % diethyl ether in pentane) gave boronic ester **166b** (339 mg, 68 %) as a colourless oil. The racemate was obtained with TMEDA instead of (–)-sparteine.

R_f (4 % diethyl ether in pentane): 0.4; $[\alpha]_D^{23}$ –5.0 (c = 0.63, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ [ppm] = 7.57–7.32 (m, 5 H), 1.91 (dqq, *J* = 7.8, 6.7, 6.6 Hz, 1 H), 1.20 (s, 6 H), 1.15 (s, 6 H), 0.99 (d, *J* = 6.7 Hz, 3 H), 0.89 (d, *J* = 6.7 Hz, 3 H), 0.66 (d, *J* = 7.8 Hz, 1 H), 0.36 (s, 3 H), 0.34 (s, 3 H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ [ppm] = 140.0, 133.9, 128.5, 127.5, 82.6, 27.0, 26.4, 25.2, 24.9, 24.8, –1.3, –1.5; ^{11}B ($CDCl_3$, 96 MHz): δ [ppm] = 32.6; HRMS (CI): calculated for $C_{18}H_{31}BO_2Si$ ($[M+H]^+$): 319.2265, Found: 319.2257; MS (CI): *m/z* = 303.3 (85), 241.3 (100), 157.1 (80); MS (CI): m/z = 157.1, 241.3, 303.3; IR ($\tilde{\nu}$ /cm^{-1}, neat): 2977, 1304, 1247, 1142, 1110, 836, 815.

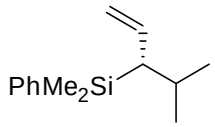
8.4 (S)-Dimethyl(phenyl)(5-phenylpent-1-en-3-yl)silane 172a



Vinylmagnesium bromide (2.1 mL of 1 M solution in tetrahydrofuran, 2.1 mmol) was added dropwise to a stirred solution of boronic ester **166a** (0.19 g, 0.5 mmol) in tetrahydrofuran (4 mL) at −78 °C. The reaction mixture was stirred for 30 minutes at −78 °C, and then a solution of iodine (0.54 g, 2.1 mmol) in methanol (4 mL) was added dropwise. The mixture was stirred for a further 30 minutes, and then allowed to warm to 0 °C. Sodium thiosulfate (15 mL of 5% aqueous solution) was added, and the solvents were removed from the reaction mixture *in vacuo*. The mixture was then extracted with diethyl ether (3 × 20 mL) and the combined organic phases were washed with brine (60 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography (100 % petroleum ether)) to give allylsilane **172a** (0.114 g, 81 %) as a colourless oil.

R_f (100 % petroleum ether): 0.16; $[\alpha]_D^{23}$ = +12.0 (*c* = 0.5, CH_3Cl); ^{1}H NMR ($CDCl_3$, 500 MHz): δ [ppm] =7.49–7.10 (m, 10 H), 5.67 (ddd, *J* = 17.1, 10.3, 9.2 Hz, 1 H), 5.00 (dd, *J* = 10.3, 1.9 Hz, 1 H), 4.89 (dd, *J* = 17.1, 1.9 Hz, 1 H), 2.75 (ddd, *J* = 13.9, 9.5, 4.6 Hz, 1 H), 2.44 (ddd, *J* = 13.9, 9.5, 7.6 Hz, 1 H), 1.82–1.74 (m, 2 H), 1.72–1.62 (m, 1 H), 0.28 (s, 3 H), 0.27 (s, 3 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 142.6, 139.4, 137.6, 134.0, 128.9, 128.5, 128.2, 127.6, 125.6, 113.1, 35.3, 33.9, 30.4, –4.4, –5.3; HRMS (EI, $C_{19}H_{24}Si$): calculated for ($[M]^+$): m/z = 280.1647, Found: m/z = 280.1652; MS (EI): *m/z* = 135.1 (100), 83.9 (45); IR ($\tilde{\nu}$ /cm^{-1}, neat): 2956, 2924, 2855, 1248, 1113, 895, 828, 810. The enantiomeric purity of **172a** was determined by HPLC analysis on a chiral stationary phase of the alcohol obtained by hydroboration with 9-BBN, followed by oxidation with H_2O_2/NaOH.[178] Daicel Chiralpak IA column (25 cm), 1.0 % *iso*propanol in hexane, 0.7 mL/min, room temperature, 210.8 nm, t_R = 26.0 minutes (minor), 27.5 minutes (major), *er* = 97:3.

8.5 (S)-Dimethyl(4-methylpent-1-en-3-yl)(phenyl)silane 172b

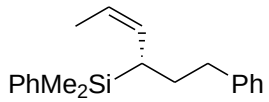


*n*BuLi (1.35 ml, 1.6 M in hexanes, 2.12 mmol) was added dropwise to tetravinyltin (0.20 ml, 1.07 mmol) at 23 °C. The mixture was stirred for 30 minutes during which white vinyllithium precipitated. The hexane was removed carefully by syringe, the solid was washed three times with hexane, dissolved in tetrahydrofuran (0.5 mL) and cooled to –78 °C. Then a solution of **166b** (170 mg, 0.53 mmol) in tetrahydrofuran (4 mL) was added dropwise and the reaction mixture was stirred for one hour. Iodine (538 mg, 2.12 mmol) in methanol (5 mL) was added dropwise, the reaction mixture was stirred for an additional 30 minutes at –78 °C and then warmed to 0 °C. The reaction was quenched by the dropwise addition of a 5 % aqueous solution of $Na_2S_2O_3$ until the solution became colourless. The solvent mixture was removed *in vacuo* and the resulting residue was dissolved in ethyl ether. Water was added, the phases were separated and the aqueous layer was extracted three times with diethyl ether. The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography (100 % petroleum ether) to give **172b** (69 mg, 60 %) as a colourless oil.

R_f = 0.8 (100% petroleum ether); $[\alpha]_D$ = +14 (c 1.0, $CHCl_3$); lit. $[\alpha]_D^{20}$ = +8.33 (c 0.840, $CHCl_3$);[127] ^{1}H (400 MHz, $CDCl_3$): δ [ppm] = 7.56–7.49 (m, 2 H), 7.37–7.33 (m, 3 H), 5.71 (apparent dt, *J* = 16.9, 10.3, 10.3 Hz, 1 H), 4.93 (dd, *J* = 10.3, 2.2 Hz, 1 H), 4.81 (dd, *J* = 16.9, 2.2 Hz, 1 H), 1.93–1.80 (m, 1 H), 1.67 (dd, *J* = 10.3, 5.1 Hz, 1 H), 0.84 (d, *J* = 6.9 Hz, 6 H), 0.30 (s, 3 H), 0.27 (s, 3 H); ^{13}C (100 MHz, $CDCl_3$): δ [ppm] = 138.8, 137.0, 134.0, 128.7, 127.6, 114.2, 42.7, 28.1, 23.8, 20.6, –3.0, –3.7; HRMS (CI, $C_{14}H_{22}Si$): calculated: m/z = 218.1491; found: m/z = 218.1483; MS (CI, $C_{14}H_{22}Si$): 84.0, 135.1, 203.2; IR ($\tilde{\nu}$ /cm^{-1}, neat): 2956, 1427, 1248, 1111; All data was consistent with that reported in the literature.[127] The enantiomeric purity was determined by chiral HPLC analysis of the alcohol obtained by hydroboration of olefin with 9-BBN, followed by oxidation with H_2O_2/NaOH). [178] Daicel Chiralpak IB column (25 cm), 1.0

% *iso*propanol in hexane, 0.8 mL/min, room temperature, 210.8 nm, t_R = 13.6 minutes (major), 15.3 minutes (minor): *er* = 96:4.

8.6 (S,Z)-Dimethyl(phenyl)(1-phenylhex-4-en-3-yl)silane 176a

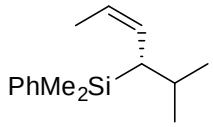


*t*BuLi (1.25 mL of 1.6 M in pentane, 2.0 mmol) was added dropwise to a stirred solution of *trans*-1-bromo-1-propene (0.09 mL, 1.0 mmol) in tetrahydrofuran (2.0 mL) at −78 °C. The mixture was allowed to stir at −78 °C for 30 min, and then a solution of boronic ester **166a** (0.099 g, 0.26 mmol) in tetrahydrofuran (1 mL) was added dropwise. The reaction mixture was stirred at −78 °C for a further 30 min, and then iodine (0.254 g, 1.0 mmol) in methanol (4 mL) was added dropwise. The reaction mixture was stirred at −78 °C for another 30 min, and then warmed to 0 °C and stirred for 1 h. Sodium thiosulfate (10 mL of a 5 % aqueous solution) was added and the mixture was allowed to warm to ambient temperature. The reaction mixture was concentrated *in vacuo* and then extracted with diethyl ether (3 × 10 mL). The combined organic phases were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography (100 % petroleum ether) to give allylsilane **176a** as a colourless oil (0.064 g, 84 % yield);

R_f (100 % petroleum ether): 0.25; $[\alpha]_D^{23}$ = +33.0 (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ [ppm] = 7.49–7.09 (m, 10 H), 5.49 (dqd, *J* = 10.8, 6.8, 1.0 Hz, 1 H), 5.21 (ddq, *J* = 11.0, 10.8, 1.7 Hz, 1 H), 2.71 (ddd, *J* = 13.7, 9.2, 4.5 Hz, 1 H), 2.39 (ddd, *J* = 13.7, 9.2, 7.6 Hz, 1 H), 2.04 (dddd, *J* = 11.9, 11.0, 2.7, 1.0 Hz, 1 H), 1.81 (dddd, *J* = 13.7, 9.4, 7.6, 2.7 Hz, 1 H), 1.56 (dddd, *J* = 13.7, 11.9, 9.4, 4.5 Hz, 1 H,), 1.45 (dd, *J* = 6.8, 1.7 Hz, 3 H), 0.28 (s, 3 H), 0.27 (s, 3 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ [ppm] = 142.6, 137.9, 134.0, 131.8, 128.8, 128.6, 128.1, 127.6, 125.5, 122.7, 35.6, 31.8, 27.2, 13.3, –4.4, –5.2; HRMS (EI, $C_{20}H_{26}Si$): calculated for ($[M]^+$): m/z = 294.1798, found: m/z = 294.1796; MS (EI): *m/z* = 294.1 (25), 135.1 (100); IR ($\tilde{\nu}$ /cm^{-1}, neat): 3002, 2957, 2913, 1427, 1247, 1111; The enantiomeric purity of **176a** was determined by HPLC analysis

of the corresponding unsaturated alcohol, obtained by reduction of the double bond of the olefin with tosylhydrazide followed by oxidation of C-Si bond.[164] Daicel Chiralpak IB column; hexane:*i*PrOH 95:5; flow: 0.7 ml/min; t^1 = 10.1 min (major), t^2 = 12.7 min (minor): *er* = 98:2.

8.7 (S,Z)-Dimethyl(2-methylhex-4-en-3-yl)(phenyl)silane 176b

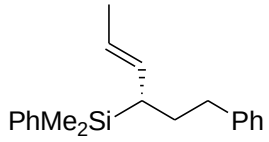


*t*BuLi (1.25 mL of 1.6 M in pentane, 2.0 mmol) was added dropwise to a stirred solution of *trans*-1-bromo-1-propene (0.09 mL, 1.0 mmol) in tetrahydrofuran (2 mL) at −78 °C. The mixture was allowed to stir at −78 °C for 30 min, and then a solution of boronic ester **166b** (0.114 g [70% pure by NMR], 0.25 mmol) in tetrahydrofuran (1 mL) was added dropwise. The reaction mixture was stirred at −78 °C for an hour, and then kept at –45 °C for an hour, before being cooled back to −78 °C. Iodine (0.254 g, 1.0 mmol) in methanol (4 mL) was added dropwise to the reaction mixture. The mixture was stirred at −78 °C for another 30 min, and then warmed to 0 °C and stirred for 1 hour. Sodium thiosulfate (10 mL of a 5 % aqueous solution) was added and the mixture was allowed to warm to ambient temperature. The reaction mixture was concentrated *in vacuo* and extracted with diethyl ether (3 × 10 mL). The combined organic phases were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography (1 % ethyl acetate in pentane) to give **176b** (47 mg, 80 %) as a colourless oil.

R_f (1 % ethyl acetate in pentane): 0.6; $[\alpha]_D^{23}$ = +22.5 (c = 0.71, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ [ppm] 7.47–7.25 (m, 5 H), 5.42 (dqd, *J* = 11.2, 6.7, 0.7 Hz, 1 H), 5.28 (m, 1 H), 1.94 (ddqd, *J* = 11.8, 5.2, 0.9, 0.7 Hz, 1 H), 1.78 (qqd, *J* = 6.8, 6.7, 5.2 Hz, 1 H), 1.38 (ddd, *J* = 6.7, 1.7, 0.9 Hz, 3 H), 0.77 (d, *J* = 6.7 Hz, 3 H), 0.76 (d, *J* = 6.7 Hz, 3 H), 0.24 (s, 3 H), 0.20 (s, 3 H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ [ppm] 139.2, 134.0, 128.8, 128.7, 127.5, 123.0, 35.0, 28.9, 23.9, 20.6, 13.0, –2.9, –3.7; HRMS (EI, $C_{15}H_{24}Si$): calculated: m/z = 232.1647 ($[M]^+$), found: m/z = 232.1657; MS (EI): m/z =

232.1 (35), 135.0 (100), 83.9 (20); IR ($\tilde{\nu}$ /cm^{-1}, neat): 3011, 2955, 2865, 1427, 1247, 1111, 826, 812; The enantiomeric purity was determined by chiral GC analysis of the unsaturated alcohol, obtained by reduction of the double bond of **176b** with H_2/PtO_2 [168] followed by oxidation of C-Si bond.[119, 167] (Supelco Betadex 120 column, 30.0 m × 250 μm × 0.30 μm, 35 °C for 1 min, then 1.5 °C/min. Pressure: 20 psi. Flow rate: 2.1 ml/min. t^1 = 65.2 min (minor), t^2 = 67.5 min (major): *er* = 96:4.

8.8 (S,E)-Dimethyl(phenyl)(1-phenylhex-4-en-3-yl)silane 175a

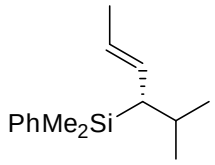


*t*BuLi (1.25 mL of 1.6 M in pentane, 2.0 mmol) was added dropwise to a stirred solution of *cis*-1-bromo-1-propene (0.09 mL, 1.0 mmol) in tetrahydrofuran (2.0 mL) at −78 °C. This mixture was allowed to stir at −78 °C for 30 min, and then a solution of boronic ester **166a** (0.099 g, 0.26 mmol) in tetrahydrofuran (1 mL) was added dropwise. The reaction mixture was stirred at −78 °C for a further 30 min, and then iodine (0.254 g, 1.0 mmol) in methanol (4 mL) was added dropwise. The reaction mixture was stirred at −78 °C for another 30 min, then warmed to 0 °C and stirred at 0 °C for 1 hour. Sodium thiosulfate (10 mL of a 5 % aqueous solution) was added and the mixture was allowed to warm to ambient temperature before being concentrated *in vacuo* and extracted with diethyl ether (3 × 10 mL). The combined organic phases were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography (silica gel, 1 % ethyl acetate in petroleum ether) to give allylsilane **175a** (0.072 g, 94 %) as a colourless oil.

R_f (1 % ethyl acetate in petroleum ether): 0.20; $[\alpha]_D^{23}$ = +8.0 (c 1.63, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ [ppm] 7.47–7.10 (m, 10 H), 5.30 (dq, *J* = 15.1, 4.8 Hz, 1 H), 5.25 (dd, *J* = 15.1, 4.8 Hz, 1 H), 2.74 (ddd, *J* = 13.8, 9.4, 4.7 Hz, 1 H), 2.41 (ddd, *J* = 13.8, 9.4, 7.1 Hz, 1 H), 1.74 (dddd, *J* = 13.0, 9.4, 7.1, 2.5 Hz, 1 H), 1.71 (d, *J* = 4.8 Hz, 3 H), 1.69 (ddd, *J* = 11.4, 7.8, 2.5 Hz, 1 H), 1.59 (dddd, *J* = 13.0, 11.4, 9.6, 4.7 Hz, 1 H), 0.28

(s, 3 H), 0.27 (s, 3 H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ [ppm] = 142.8, 138.0, 134.0, 131.5, 128.8, 128.5, 128.1, 127.5, 125.5, 123.8, 35.4, 32.2, 31.0, 18.2, –4.2, –5.2; HRMS (EI, $C_{20}H_{26}Si$): calculated for: m/z = 294.1798 ($[M]^+$), found: m/z = 294.1800; MS (EI): *m/z* = 294.1 (30), 135.1 (100); IR ($\tilde{\nu}$ /cm^{-1}, neat): 3024, 2958, 2916, 2854, 1427, 1247, 1111, 810; The enantiomeric purity of **175a**was determined by HPLC analysis of the unsaturated alcohol, obtained by reduction of the double bond of the olefin with tosylhydrazide followed by oxidation of C-Si bond.[164] Daicel Chiralpak IB chiral column; hexane:*i*PrOH 95:5; 0.7 ml/min; t^1 = 10.1 min (major), t^2 = 12.9 min (minor): *er* = 97:3.

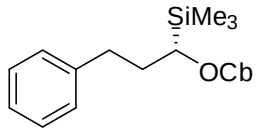
8.9 (S,E)-Dimethyl(2-methylhex-4-en-3-yl)(phenyl)silane 175b



*t*BuLi (1.25 mL of 1.6 M in pentane, 2.0 mmol) was added dropwise to a stirred solution of *cis*-1-bromo-1-propene (0.09 mL, 1.0 mmol) in tetrahydrofuran (2 mL) at −78 °C. The mixture was allowed to stir at −78 °C for 30 min, and then a solution of boronic ester **166b** (0.118 g [70 % pure by NMR], 0.26 mmol) in tetrahydrofuran (1 mL) was added dropwise. The reaction mixture was stirred at −78 °C for an hour, and then kept at –45 °C for an hour, before being cooled back to −78 °C. Iodine (0.254 g, 1.0 mmol) in methanol (4 mL) was added dropwise and the reaction mixture was stirred at −78 °C for another 30 min, warmed to 0 °C and stirred at 0 °C for 1 h. Sodium thiosulfate (10 mL of a 5 % aqueous solution) was added and the mixture was then allowed to warm to ambient temperature. The reaction mixture was concentrated *in vacuo* and extracted with diethyl ether (3 × 10 mL). The combined organic phases were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography (1 % ethyl acetate in pentane) to give allylsilane **175b** (0.048 g, 80 %) as a colourless oil;

R_f (1 % ethyl acetate in pentane): 0.6; $[\alpha]_D^{23}$ = −12.7 (c = 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 301 MHz): δ [ppm] = 7.45–7.24 (m, 5 H), 5.25 (ddq, *J* = 15.0, 10.1, 1.1 Hz, 1 H), 5.14 (dq, *J* = 15.0, 6.0 Hz, 1 H), 1.72 (qqd, *J* = 6.9, 6.7, 4.9 Hz, 1 H), 1.59 (dd, *J* = 6.0, 1.1 Hz, 3 H), 1.51 (dd, *J* = 10.1, 4.9 Hz, 1 H), 0.74 (d, *J* = 6.9 Hz, 3 H), 0.75 (d, *J* = 6.9 Hz, 3 H), 0.21 (s, 3 H), 0.18 (s, 3 H); ^{13}C NMR ($CDCl_3$, 76 MHz): δ [ppm] = 139.5, 134.0, 128.9, 128.6, 127.5, 124.8, 40.7, 28.4, 23.8, 20.7, 18.2, –2.8, –3.6; HRMS (EI, $C_{15}H_{24}Si$): calculated: m/z = 232.1647 ($[M]^+$), found: m/z = 232.1641; MS (EI): *m/z* = 232.1 (35), 135.0 (100), 83.9 (35); IR ($\tilde{\nu}$ /cm^{-1}, neat): 2956, 1428, 1247, 1111, 970, 848, 812; The enantiomeric purity of **175b** was determined by chiral GC analysis of the corresponding unsaturated alcohol, obtained by reduction of the double bond of the olefin with tosylhydrazide followed by oxidation of C-Si bond. [164] Supelco Betadex 120 column, 30.0 m × 250 μm × 0.30 μm, 35 °C for 1 min, then 1.5 °C/min. Pressure: 20 psi. Flow rate: 2.1 ml/min, t^1 = 65.1 min (minor), t^2 = 67.8 min (major): *er* = 96:4.

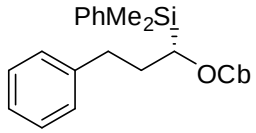
8.10(1S)-3-Phenyl-1-(trimethylsilyl)propyl diisopropylcarbamate 183a



3-Phenylpropyl di*iso*propylcarbamate **128a** (1.16 g, 4.4 mmol) and (–)-sparteine (1.31 mL, 5.72 mmol) were dissolved in diethyl ether (25 mL) and the solution was cooled to–78 °C. sBuLi (4.4 mL, 5.72 mmol, 1.3 M in cyclohexane) was added dropwise and the reaction mixture was stirred for 5 h at –78 °C before TMSCl (0.73 mL, 5.72 mmol) was added dropwise. The mixture was allowed to warm to room temperature, stirred overnight and water (20 mL) was added. The layers were separated and the aqueous layer was extracted with diethyl ether (3 x 20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography (silica gel, 5 % ethyl acetate in petroleum ether) to give **183a** (1.12 g, 76 %) as a colourless oil. The racemate was obtained with TMEDA instead of (–)-sparteine.

R_f = 0.7 (10 % diethyl ether in pentane); $[\alpha]_D^{25}$ = –5 (c = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.30–7.26 (m, 2 H); 7.19–7.16 (m, 3 H); 4.80 (dd, *J* = 10.8, 3.5 Hz, 1 H); 4.16 (br s, 1 H); 3.76 (br s, 1 H), 2.75 (ddd, *J* = 13.6, 11.3, 4.8 Hz, 1H); 2.61 (ddd, *J* = 13.6, 10.8, 5.9 Hz, 1 H); 2.01–1.80 (m, 2H), 1.25 (br s, 12 H), 0.07 (s, 9 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ [ppm]: 156.3, 142.4, 128.3, 125.7, 68.5, 46.5, 44.9, 33.9, 33.8, 21.8, 20.6, –3.3; HRMS (CI, $C_{19}H_{34}NO_2Si$): calculated: m/z = 336.2359 $(M–H)^+$, Found: 336.2347; MS (CI): m/z = 336 (64), 320 (97), 292 (70), 244 (22), 218 (59), 202 (83), 191 (21), 146 (86), 128 (44), 93 (25), 86 (26), 73 (100); IR ($\tilde{\nu}$ /cm^{-1}, neat): 2965, 1682, 1430, 1331, 1298, 1281, 1248, 1219, 1157, 1132, 1048, 1034, 871, 745, 697; The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IB column; hexane:*i*PrOH = 99.5:0.5, 0.3 mL/min; t^1 = 16.2 min (minor), t^2 = 18.1 min (major): *er* > 99:1. All spectroscopic data was consistent with that reported in the literature.[170]

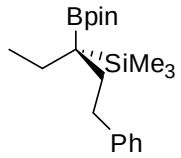
8.11 (1S)-1-[Dimethyl(phenyl)silyl]-3-phenylpropyl diisopropylcarbamate 183b



3-phenylpropyl di*iso*propylcarbamate **128a** (1.24 g, 4.7 mmol) and (–)-sparteine (1.4 mL, 6.11 mmol) were dissolved in diethyl ether (25 mL) and colled cooled to –78 °C. *s*BuLi (4.7 mL, 6.11 mmol, 1.3 M in cyclohexane) was added dropwise and the resulting reaction mixture was then stirred at –78 °C for 5 h before chlorodimethylphenylsilane (1.03 mL, 6.11 mmol) was added. The mixture was allowed to warm to room temperature, stirred overnight and then quenched with water (20 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography (silica gel, 5 % ethyl acetate in petroleum ether) to give **183b** (1.59 g, 85 %) as a colourless oil. The racemate was obtained with TMEDA instead of (–)-sparteine.

R_f = 0.6 (10 % diethyl ether in pentane); $[\alpha]_D^{25}$ = +2 (c = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ [ppm] 7.55–7.53 (m, 2 H), 7.37–7.32 (m, 3 H), 7.26–7.22 (m, 2 H), 7.17–7.14 (m, 1 H), 7.11–7.09 (m, 2 H), 5.00 (dd, *J* = 10.7, 3.7 Hz, 1 H), 4.04 (br s, 1 H), 3.79 (br s, 1 H), 2.69 (ddd, *J* = 13.6, 11.2, 4.8 Hz, 1 H), 2.53 (ddd, *J* = 13.7, 10.9, 5.9 Hz, 1H), 2.00–1.78 (m, 2 H), 1.22–1.19 (m, 12 H), 0.37 (s, 3 H), 0.35 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ [ppm] 155.9, 142.2, 36.4, 134.1, 129.2, 128.3, 127.7, 125.7, 67.8, 46.3, 45.1, 33.7, 21.6, 20.6, –4.5, –5.0; HRMS (CI, $C_{24}H_{35}NO_2Si$): calculated: m/z = 398.2515 ($M\text{-}H^+$), found: m/z = 398.2516; MS (CI, $C_{24}H_{35}NO_2Si$): m/z = 398 $(M)^+$ (4), 382 (29), 354 (28), 320 (100), 278 (10), 264 (14), 253 (10), 202 (98), 146 (11), 135 (44), 128 (16), 114 (4), 91 (8), 86 (11); IR ($\tilde{\nu}$ /cm^{-1}, neat): 3026, 2966, 2932, 1682, 1428, 1331, 1298, 1282, 1249, 1156, 1132, 1114, 1047, 1033, 829, 811, 776, 732. The enantiomeric purity was determined by HPLC analysis; Daicel Chiralpak IB column; hexane:*i*PrOH 99.5:0.5, 0.3 ml/min, t^1 = 19.0 min (major), t^2 = 22.0 min (minor): *er* > 99:1.

8.12 (1S)-1-Ethyl-3-phenyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propyl]-(trimethyl)silane 185a

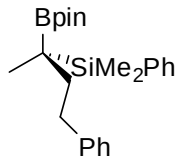


(1*S*)-3-phenyl-1-(trimethylsilyl)propyl di*iso*propylcarbamate **183a** (400 mg, 1.19 mmol), and TMEDA (0.25 mL, 1.67 mmol) were dissolved in diethyl ether (6 mL) and cooled to –78 °C. *s*BuLi (1.28 mL, 1.67 mmol, 1.3 M in cyclohexane) was added dropwise and the reaction mixture was stirred at –78 °C for 5 h before EtBpin (0.30 mL, 1.67 mmol) was added dropwise. After an additional hour at –78 °C, the mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with water (5 mL), the layers were separated, the aqueous layer was extracted with diethyl ether (3 × 5 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography (silica

gel, 5 % ethyl acetate in petroleum ether) to give boronic ester **185a** (390 mg, 94 %) as a colourless solid.

R_f = 0.7 (5 % ethyl acetate in petroleum ether); $[\alpha]_D^{25}$ = –17 (c = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.30–7.26 (m, 2 H), 7.23–7.15 (m, 3 H), 2.67 (dt, *J* = 12.6, 5.3 Hz, 1 H), 2.56 (dt, J = 12.6, 4.8 Hz, 1 H), 1.88–1.62 (m, 4 H), 1.25 (s, 12 H), 1.01 (t, *J* = 7.4 Hz, 3 H), 0.07 (s, 9 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ [ppm] = 144.1, 128.4, 128.2, 125.5, 82.6, 34.3, 33.3, 25.2, 25.1, 23.1, 12.0, 1.0. ^{11}B NMR ($CDCl_3$, 96 MHz): δ [ppm]: 34.4; HRMS (CI, $C_{20}H_{35}BO_2Si$): calculated: m/z = 346.2499, found: m/z = 346.2500; MS (CI): 347 (2), 331 (39), 275 (8), 255 (16), 249 (25), 247 (45), 245 (34), 231 (15), 203 (9), 173 (29), 155 (46), 145 (14), 117 (19), 85 (100), 73 (22). IR ($\tilde{\nu}$ /cm^{-1}, neat): 3027, 2954, 2869, 1453, 1368, 1341, 1297, 1260, 1245, 1143, 1123, 872, 855, 740, 698; mp: 34–35 °C.

8.13 Dimethyl[(1S)-1-methyl-3-phenyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-propyl]phenylsilane 185b

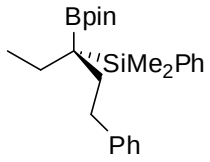


(1*S*)-1-[Dimethyl(phenyl)silyl]-3-phenylpropyl di*iso*propylcarbamate **183b** (996 mg, 2.0 mmol) and TMEDA (0.42 mL, 2.8 mmol) were dissolved in diethyl ether (10 mL) and cooled to –78 °C. *s*BuLi (1.3 M in cyclohexane, 2.1 mL, 2.8 mmol) was added dropwise and the mixture was stirred for 5 hours at –78 °C. MeBpin (398 mg, 2.8 mmol) was added dropwise and the reaction mixture was stirred for 1 hour at –78 °C, allowed to warm to 23 °C, and stirred for an additional hour. Then magnesium bromide diethyl etherate (prepared by stirring 144 mg magnesium and 0.34 mL dibromoethane in 10 mL diethyl ether for 4 hours) was added dropwise and the reaction mixture was stirred overnight. Saturated ammonium chloride was added, the phases were separated and the aqueous phase was extracted with diethyl ether (3 × 50 mL). The combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*.

Flash column chromatography (silica gel, 10 % ethyl acetate in pentane) gave boronic ester **185b** (410 mg, 52 %) as a colourless oil.

$[\alpha]^{23}_{D}$ (c = 1.7, CH_2Cl_2) = –8; ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.54–7.50 (m, 2 H), 7.36–7.22 (m, 5 H), 7.18–7.12 (m, 3 H), 2.66 (td, *J* = 12.7, 5.0 Hz, 1 H), 2.41 (td, *J* = 12.7, 4.2 Hz, 1 H), 2.03 (td, *J* = 12.7, 4.2 Hz, 1 H), 1.40 (td, *J* = 12.7, 5.0 Hz, 1 H), 1.24 (s, 6 H), 1.22 (s, 6 H), 1.11 (s, 3 H), 0.34 (s, 3 H), 0.32 (s, 3 H);^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm] = 134.6, 137.5, 134.8, 128.7, 128.5, 128.2, 127.3, 125.5, 82.9, 36.2, 34.3, 25.3, 24.9, 15.6, –4.5, –4.7; ^{11}B NMR (128 MHz, $CDCl_3$): δ [ppm] = 34.5; HRMS (CI, $C_{24}H_{35}BO_2Si$): calc.: m/z = 417.2397 [M+Na^+], found: m/z = 417.2400 [M+Na^+]; MS (CI, $C_{24}H_{35}BO_2Si$): m/z = 84.0 (35), 93.1 (40), 135.1 (50), 202.1 (50), 235.1 (50), 303.2 (40), 317.2 (100), 320.2 (95), 379.2 (30); IR ($\tilde{\nu}$ /cm^{-1}, in $CDCl_3$) = 3675, 2988, 2901, 1393 1250, 1066; mp: 78–79 °C (EtOAc).

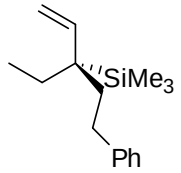
8.14[(1S)-1-Ethyl-3-phenyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propyl]- (dimethyl)phenylsilane 185c



1-(Dimethyl(phenyl)silyl)-3-phenylpropyl di*iso*propylcarbamate **183b** (150 mg, 0.38 mmol) and TMEDA (79 μL, 0.53 mmol) were dissolved in diethyl ether (2 mL) and cooled to –78 °C. *s*BuLi (0.41 mL, 0.53 mmol, 1.3 M in cyclohexane was added dropwise and the resulting reaction mixture was stirred at –78 °C for 5 h before EtBpin (95 μL, 0.53 mmol) was added dropwise. The mixture was stirred for an additional hour at –78 °C and then allowed to warm to room temperature and stirred overnight. The reaction was quenched with water (5 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 5 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography (silica gel, 5 % ethyl acetate in petroleum ether) to give the product **185c** (390 mg, 76 %) as a colourless oil.

R_f = 0.6 (5 % ethyl acetate in petroleum ether); $[\alpha]_D^{25}$ = +11 (c = 1.0, $CHCl_3$); ^{11}B NMR ($CDCl_3$, 96 MHz): δ [ppm] = 30.3; ^1H NMR ($CDCl_3$, 400 MHz): δ [ppm] 7.65–7.62 (m, 2 H); 7.38–7.35 (m, 3 H), 7.31–7.27 (m, 2 H), 7.21–7.16 (m, 3 H), 2.65–2.51 (m, 2 H), 1.98–1.81 (m, 3 H), 1.76–1.67 (m, 1 H), 1.26 (s, 12 H); 0.98 (t, *J* = 7.4 Hz, 3 H), 0.43 (2 × s overlapping, 6 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ [ppm] = 144.0, 138.9, 134.7, 128.7, 128.4, 128.2, 127.4, 125.4, 82.8, 33.9, 33.2, 25.2, 23.2, 118, -2.8, -2.9; HRMS (CI, $C_{25}H_{37}BO_2Si$): calculated m/z = 408.2656 (M^+), found: 408.2651; MS (CI, $C_{25}H_{37}BO_2Si$): 408 (4), 393 (32), 331 (88), 308 (93), 293 (10), 277 (4), 259 (25), 249 (100), 231 (81), 217 (95), 185 (8), 175 (15), 145 (69), 135 (96), 131 (29), 117 (11), 105 (9), 91 (18), 85 (39), 83 (30), 69 (6); IR ($\tilde{\nu}$ /cm^{-1}, neat): 2976, 1454, 1427, 1370, 1338, 1298, 1248, 1143, 1109, 964, 852, 812, 769, 735.

8.15(1S)-1-Ethyl-1-(2-phenylethyl)prop-2-en-1-yl](trimethyl)silane 186a



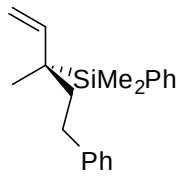
Boronic ester **185a** (50 mg, 0.14 mmol) was dissolved in tetrahydrofuran (1 mL) and cooled to 0 °C. A freshly made solution of vinyllithium (see below) was added dropwise. After stirring for 30 minutes at 0 °C, a solution of I_2 (179 mg, 0.70 mmol) in methanol (6 mL) was added dropwise over 10 minutes. The mixture was then allowed stirred at 0 °C for 20 min before a 5 % aqueous solution of $Na_2S_2O_3$ was added until the red colour disappeared. The reaction mixture was concentrated *in vacuo* and the residue was taken up into diethyl ether (25 mL) and washed with H_2O (3 × 10 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography (silica gel, 100% petroleum ether) to give **186a** (25 mg, 73 %) as a yellow oil.

Preparation of vinyllithium solution: *n*BuLi (1.6 M in hexane, 350 µL, 0.56 mmol) was added dropwise at room temperature to tetravinyltin (51 µL, 0.28 mmol). After stirring

for 30 minutes, the liquid was removed and the white solid was dissolved in tetrahydrofuran.

R_f = 0.6 (100 % pentane); $[\alpha]_D^{25}$ = –28 (c = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ [ppm] = 7.32–7.28 (m, 2H), 7.21–7.17 (m, 3 H), 5.81 (dd, *J* = 17.6, 11.0 Hz, 1 H), 5.02 (dd, *J* = 11.0, 1.5 Hz, 1 H), 4.80 (dd, *J* = 17.6, 1.5 Hz, 1 H), 2.55-2.51 (m, 2 H), 1.92-1.84 (m, 1 H), 1.80-1.57 (m, 3 H), 0.95 (t, *J* = 7.5 Hz, 3 H), 0.02 (s, 9 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ [ppm] = 144.9, 143.6, 128.4, 128.3, 125.6, 110.8, 34.2, 30.8, 24.2, 9.2, –2.9; HRMS (CI, $C_{16}H_{26}Si$): 246.1804 (M^+), found: 246.1807; MS (CI, $C_{16}H_{26}Si$): 246 (7), 231 (48), 173 (5), 155 (26), 191 (6), 73 (100); IR ($\tilde{\nu}$ /cm^{-1}, neat): 3083, 3027, 2962, 2863, 1619, 1454, 1247, 895, 749, 699; The enantiomeric purity was determined by HPLC analysis of the alcohol, obtained by hydroboration of the olefin with 9-BBN, followed by oxidation with H_2O_2. Daicel Chiralpak IB column, hexane:*i*PrOH = 95:5; 0.7 ml/min, t_1 = 13.9 min (minor), t_2 = 15.8 min (major): *er* = 98:2.

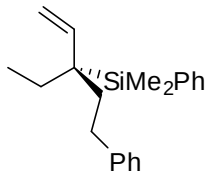
8.16 Dimethyl[(1S)-1-methyl-1-(2-phenylethyl)prop-2-en-1-yl]phenylsilane 186b



Boronic ester **185b** (34 mg, 0.09 mmol) was dissolved in tetrahydrofuran (1 mL) and cooled to 0 °C. A freshly made solution of vinyllithium (see above) was added dropwise. After stirring for 30 minutes the mixture, a solution of I_2 (140 mg, 0.54 mmol) in methanol (3 mL) was added dropwise over 10 minutes. The mixture was stirred for an additional 20 min before $Na_2S_2O_3$ (5 % in water) was added dropwise until the red colour disappeared. The reaction mixture was concentrated *in vacuo* and the residue was taken up into water (5 mL) and extracted with diethyl ether (3 × 25 mL). The combined organic layer was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography (silica gel, 100% pentane) to give **186b** (19 mg, 73 %) as a colourless oil.

R_f = 0.3 (100% petroleum ether); $[\alpha]_D^{25}$ = –30 (c = 1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.41–7.39 (m, 2 H), 7.29–7.22 (m, 3 H), 7.20–7.15 (m, 2H), 7.11–7.01 (m, 3 H), 5.75 (dd, *J* = 17.4, 10.8, Hz, 1 H), 4.97 (dd, *J* = 10.8, 1.5 Hz, 1 H), 4.69 (dd, *J* = 17.4, 1.5 Hz, 1 H), 2.41 (dt, *J* = 13.3, 5.5, Hz, 1 H), 2.32 (dt, *J* = 13.3, 4.5, Hz, 1 H), 1.70 (dt, *J* = 13.3, 4.5 Hz, 1 H), 1.59 (dt, *J* = 13.4, 5.5 Hz, 1 H), 1.02 (s, 3 H), 0.20 (2 × s, overlapping, 6 H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ [ppm] = 144.2, 143.4, 136.7, 134.8, 128.9, 128.4, 128.3, 127.4, 125.5, 111.4, 37.8, 31.0, 30.0, 17.1, –6.11, –6.12; HRMS (CI, $C_{20}H_{26}Si$): calculated m/z = 294.1804 (M^+); found: 294.1796; MS (CI, $C_{20}H_{26}Si$): 294 (22), 279 (66), 217 (94), 203 (44), 201 (8), 189 (3), 135 (100), 91 (3), 84 (6); IR ($\tilde{\nu}$ /cm^{-1}, neat): 3069, 3025, 2952, 2863, 1620, 1496, 1454, 1427, 1248, 1114, 1004, 894, 829, 809, 772, 735, 699, 655; The enantiomeric purity was determined by HPLC analysis of the alcohol, obtained by hydroboration with 9-BBN, followed by oxidation with H_2O_2/NaOH. Daicel Chiralpak IB column; hexane:*i*PrOH 95:5; 0.5 ml/min; t^1 = 18.2 minutes (major), t^2 = 22.1 min (minor); *er* = 97:3.

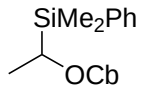
8.17(1S)-1-Ethyl-1-(2-phenylethyl)prop-2-en-1-yl](dimethyl)phenylsilane 186c



Boronic ester **185c** (100 mg, 0.24 mmol) was dissolved in tetrahydrofuran (1 mL) and cooled to 0 °C. A freshly prepared solution of vinyllithium (see above) was added dropwise and after 30 minutes at 0 °C, a solution of I_2 (305 mg, 1.20 mmol) in methanol (10 mL) was added dropwise over 10 minutes. The mixture was then stirred at 0 °C for 20 min before a 5 % aqueous $Na_2S_2O_3$-solution was added dropwise until the red colour disappeared. The reaction mixture was concentrated *in vacuo* and the residue was taken up with diethyl ether (25 mL), washed with H_2O (3 × 10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica gel, 100 % petroleum ether) to give the product (44 mg, 60 %) as a yellow oil.

Rf = 0.3 (100 % pentane); $[\alpha]_D^{25}$ = –6 (c = 1.0, CHCl3); 1H NMR (CDCl3, 400 MHz): δ [ppm] = 7.57–7.55 (m, 2 H), 7.42–7.35 (m, 3 H), 7.32–7.29 (m, 2 H), 7.23–7.19 (m, 1 H), 7.17–7.15 (m, 2 H), 5.77 (dd, J = 17.6, 11.0, Hz, 1 H), 5.08 (dd, J = 11.0, 1.3 Hz, 1 H), 4.80 (dd, J = 17.6, 1.3 Hz, 1 H), 2.53–2.48 (m, 2 H), 1.97–1.89 (m, 1 H), 1.83–1.60 (m, 3 H), 0.93 (t, J = 7.5 Hz, 3 H), 0.38 (s, 6 H); 13C NMR (CDCl3, 100 MHz): δ [ppm] = 144.7, 143.5, 137.7, 134.7, 128.9, 128.31, 128.27, 127.4, 125.6, 111.5, 34.9, 34.0, 30.7, 24.2, 8.9, –4.3; –4.5; HRMS (CI, C21H28Si): calculated m/z = 308.1960 (M+), found: 308.1950; MS (CI, C21H28Si): 308 (6), 293 (16), 231 (22), 217 (12), 209 (8), 135 (100), 91 (8), 85 (10), 75 (4); IR ($\tilde{\nu}$ /cm-1, neat): 3068, 3026, 2961, 1619, 1496, 1454, 1428, 1250, 1118, 1051, 829, 809, 790, 770, 735. The enantiomeric purity was determined by HPLC analysis of the alcohol obtained by hydroboration with 9-BBN, followed by oxidation with H_2O_2/NaOH. Daicel Chiralpak IB column; hexane:*i*PrOH 95:5, 0.7 ml/min: t^1 =15.2 min (major), t^2 = 18.2 min (minor); *er* = 97:3.

8.18 1-[Dimethyl(phenyl)silyl]ethyl diisopropylcarbamate 190

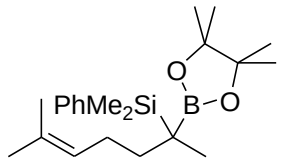


Ethyl di*iso*propylcarbamate **189** (1.88 mL, 10.0 mmol) and TMEDA (1.97 mL, 13.0 mmol) were dissolved in diethyl ether (50 mL) and cooled to –78 °C. *s*BuLi (10.0 mL, 13 mmol, 1.3 M in hexane/cyclohexane) was added dropwise and the reaction mixture was stirred at –78 °C for 5 hours. Then $PhMe_2SiCl$ (2.85 mL, 17.0 mmol) was added dropwise and the mixture was allowed to warm to 23 °C overnight. After the addition of saturated aqueous ammonium chloride solution the phases were separated and the aqueous phase was extracted with diethyl ether (3 × 25 mL). The combined organic layers were washed with brine, dried (magnesium sulfate) and concentrated *in vacuo*. Flash column chromatography (short silica plug, 100 % pentane) gave carbamate **190** (2.971 g, 91 %) as a colourless oil.

The silane was dissolve in dry toluene and the solvent was removed *in vacuo* to remove traces of water. This process was repeated two times and then a 0.2 M solution in dry diethyl ether was prepared and stored over activated 4 Å molecular sieves.

R_f = 0.2 (5 % ethyl acetate in pentane); $[\alpha]^{22}_D$ = –24 (c = 3.2, CH_2Cl_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm] = 155.9, 136.3, 134.0, 129.2, 127.2, 63.6, 46.0 (br), 45.1 (br), 21.1 (br), 16.3, –5.0, –5.4; ^1H NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.56–7.50 (m, 2 H), 7.38–7.50 (m, 3 H), 4.88 (q, *J* = 7.4 Hz, 1 H), 4.01 (br, 1 H), 3.72 (br, 1 H), 1.24 (d, *J* = 7.4 Hz, 3 H), 1.16 (d, *J* = 1.0 Hz, 6 H), 1.14 (d, *J* = 1.0 Hz, 6 H), 0.35 (s, 3 H), 0.34 (s, 3 H); HRMS (CI, $C_{17}H_{29}NO_2Si$): calc. [M+H$^+$]: m/z = 308.2046, found: m/z = 308.2032; MS (CI, $C_{17}H_{29}NO_2Si$): 39.1 (15), 128.1 (15), 220.1 (20), 230.2 (100), 292.2 (30), 308.2 (20); IR ($\tilde{\nu}$ /cm^{-1}, neat) = 2965, 1683, 1428, 1288, 1046, 771, 699;

8.19[1,5-Dimethyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hex-4-en-1- yl](dimethyl)phenylsilane 192

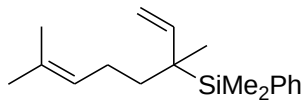


A mixture of (1*S*)-1-[dimethyl(phenyl)silyl]ethyl di*iso*propylcarbamate (0.2 M in diethyl ether, 10 mL, 2.0 mmol) **190** and TMEDA (0.43 mL, 2.8 mmol) was cooled to –78 °C, *s*BuLi (1.3 M in cyclohexane, 2.15 mL, 2.8 mmol) was added dropwise and the mixture was stirred for 5 hours at –78 °C. Boronic ester **191** (1.0 M in diethyl ether, 2.8 mL, 2.8 mmol) was added dropwise and 5 minutes after the end of the addition the reaction mixture was allowed to warm to 23 °C and was stirred overnight. Water was added and the aqueous phase was extracted with diethyl ether (3 × 25 mL). The combined organic layers were washed with brine, dried (magnesium sulfate) and concentrated *in vacuo*. Flash column chromatography (silica gel, 5 % ethyl acetate in pentane) gave the title compound (610 mg, 84 %) as a colourless oil.

R_f = 0.4 (5 % ethyl acetate in pentane); ^{11}B NMR (128 MHz, $CDCl_3$): δ [ppm] = 35.0; ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm] = 137.7 (C), 134.8 (CH), 130.9 (CH), 128.7 (CH), 127.3 (CH), 125.3 (Me_2C=*C*H), 82.8 (BOC), 33.6 (CH_2), 26.1 (CH_2), 25.7 (CH_3), 25.2 (CH_3), 25.0 (CH_3), 17.6 (CH_3), 15.5 (CH_3), –4.5 (CH_3), –4.7 (CH_3); ^1H NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.54–7.50 (m, 2 H, Ph), 7.34–7.30 (m, 3 H, Ph), 5.10–5.04 (m,

1 H, Me_2C=C*H*), 2.09–1.96 (m, 1 H, CH_2), 1.84–1.69 (m, 2 H, CH_2), 1.65 (s, 3 H, CH_3), 1.56 (s, 3 H, CH_3), 1.20 (s, 6 H, 2 × CH_3), 1.17 (s, 6 H, 2 × CH_3), 1.14–1.06 (m, 1 H, CH_2), 1.02 (s, 3 H, CH_3), 0.32 (s, 3 H, $SiMe_3$), 0.31 (s, 3 H, $SiMe_3$); HRMS (ESI, $C_{22}H_{37}BO_2Si$): calc.: m/z = 395.2548 [M+Na^+], found: 395.2559 [M+Na^+]; MS (CI, $C_{22}H_{37}BO_2Si$): 93.1 (100), 135.1 (80), 203.2 (75), 303.3 (60), 357.4 (20), 371.4 (15); m. p.: 60–62 °C (EtOAc); IR ($\tilde{\nu}$ /cm^{-1}, in $CDCl_3$) = 3067, 2975, 2945, 2862, 1449, 1371, 1336, 1297, 1143, 1109;

8.203,7-Dimethylocta-1,6-dien-3-yl)dimethyl(phenyl)silane 193



Tetravinyl tin (0.15 mL, 0.84 mmol) was cooled to 0 °C and *n*BuLi (1.6 M in hexane, 1.05 mL, 1.68 mmol) was added dropwise. After 30 minutes the precipitating vinyl lithium was dissolved in tetrahydrofuran (1 mL) and added dropwise to a solution of [(1*R*)-1,5-dimethyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hex-4-en-1-yl](dimethyl)phenylsilane **192** (100 mg, 0.28 mmol) in tetrahydrofuran (2 mL) at 0 °C. After stirring for 40 minutes at 0 °C, a solution of I_2 (426 mg, 1.68 mmol) in MeOH (4 mL) was added dropwise over 10 minutes. The mixture was then allowed to stir at 0 °C for 25 min and $Na_2S_2O_3$-solution (5 % in water) was added dropwise until the red colour disappeared. The organic solvents (hexane, tetrahydrofuran and methanol) were removed *in vacuo* and the concentrate was taken up into diethyl ether (25 mL). The aqueous phase was extracted with diethyl ether (3 × 25 mL). The combined organic layers were washed with brine, dried (magnesium sulfate) and concentrated *in vacuo*. Flash column chromatography (silica gel, pentane) gave the title compound 63 mg, 93 %) as a colourless oil.

R_f = 0.3 (100 % pentane); ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm] = 144.4 (CH), 137.0 (C), 134.8 (CH), 131.1 (C), 128.9 (CH), 127.3 (CH), 125.1 (Me_2C=*C*H), 110.9 (H_2C=CH), 35.4 (CH_2), 30.8 (C), 25.7 (CH_3), 22.2 (CH_2), 17.6 (CH_3), 16.9 (CH_3), –6.1 (2 × CH_3); ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.51–7.46 (m, 2 H, Ph), 7.38–7.30 (m, 3 H, Ph), 5.74 (dd, *J* = 17.4, 10.7 Hz, 1 H, H_2C=C*H*), 5.02 (dd, *J* = 7.2, 7.2 Hz, 1 H,

Me*2*C=C*H*), 4.97 (dd, *J* = 10.7, 1.5 Hz, 1 H, H_2C=C*H*), 4.69 (dd, *J* = 17.4, 1.5 Hz, 1 H, H_2C=C*H*), 1.92–1.70 (m, 2 H, Me_2C=CHCH_2), 1.65 (d, *J* = 0.9 Hz, 3 H, CH_3CCH_3), 1.53 (s, 3 H, CH_3CCH_3), 1.52–1.44 (m, 1 H, Me_2C=CHCH_2CH_2), 1.36 (ddd, *J* = 13.3, 11.7, 5.5 Hz, 1 H, Me_2C=CHCH_2CH_2), 1.01 (s, 3 H, CH_3CSi), 0.263 (s, 3 H, $SiMe_3$), 0.260 (s, 3 H, $SiMe_3$); **HRMS** (CI, $C_{18}H_{28}Si$): calc. [M^+]: m/z = 272.1960, found: m/z = 272.1948; **MS** (CI, $C_{18}H_{28}Si$): 39.1 (20), 135.1 (100), 203.2 (60), 257.2 (25), 272.2 (25); **IR** ($\tilde{\nu}$ /cm^{-1}, in $CDCl_3$) = 3675, 2967, 2902, 1620, 1409, 1248, 1066;

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ACKNOLEDGEMENT

Giunta alla fine di questi tre anni, desidero ringraziare le persone che mi hanno seguita più da vicino.

Innanzi tutto un grazie a Tina, per avermi guidata e sostenuta con pazienza, per avermi dato suggerimenti ma anche per essere stata aperta al dialogo e avermi lasciata libera di "sperimentare". Un grande grazie anche per avermi permesso di trascorrere sei mesi, davvero decisivi per la mia formazione, a Bristol, città che ora posso un po' considerare la mia seconda casa.

Grazie anche al Prof. Dalla Croce, per essere stato al mio fianco in laboratorio davvero fino all'ultimo secondo. Penso davvero che i "trucchetti" imparati nell'osservarla lavorare siano qualcosa di prezioso che porterò con me.

Grazie anche ai ragazzi con cui ho condiviso il laboratorio: Beppe, per avermi introdotto nel mondo della chimica organica pura, per i consigli e la PAZIENZA! Ciccio, per le risate e per aver reso davvero indimenticabili alcuni momenti trascorsi in labo. Enrica, con cui ho condiviso studio e labo in questo ultimo anno e mezzo, per tutte le chiacchierate, dalle reazioni che non venivano alle ricette di cucina! Grazie anche Giacomo e Marta. In particolare un grazie speciale a Marta per l'aiuto in questi ultimi due mesi e un in bocca la lupo per il proseguimento dello studio sulle immine: sono sicura che farai un ottimo lavoro!

Un grande grazie anche al Prof. Varinder Aggarwal, per avermi accolta nel suo gruppo e avermi dato la possibilità di ampliare le mie conoscenze nella chimica organica. E grazie anche a tutto il VKA group, persone davvero speciali, che hanno reso i miei sei mesi a Bristol davvero indimenticabili.

Questa tesi è dedicata a loro, ma desidero rivolgere un pensiero e un ringraziamento ai miei genitori e alla mia famiglia. Grazie per il sostegno in ogni mia decisione, davvero prezioso in ogni momento, specialmente in quelli più difficli.

A last big thank goes to Ben. We both “delivered our babies” this year and I think I couldn’t be more lucky to have by my side someone who really understand what the all PhD process and writing up mean. I really want to thank you for having been so encouraging, for having motivated me not to give up, for having helped me face the reality being un po’ more positive, showing that every problems can be solved. I really thank you for your love and support, that I can feel so close despite the Ocean or the English Channel between us.