
# PALLADIUM-CATALYZED ASYMMETRIC ALLYLIC AMINATION. DEVELOPMENT AND SYNTHETIC APPLICATIONS

**Sebastien Soriano Istat**

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# PALLADIUM-CATALYZED ASYMMETRIC ALLYLIC AMINATION. DEVELOPMENT AND SYNTHETIC APPLICATIONS

DOCTORAL THESIS

Supervised by

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Departament de Química Analítica i Química Orgànica

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HAGO CONSTAR que el presente trabajo, titulado "**Palladium-catalyzed asymmetric allylic amination. Development and synthetic applications**", que presenta **Sébastien Soriano Istat**. para la obtención del título de Doctor, ha sido realizado bajo mi dirección en el Departamento de Química Analítica y Orgánica de esta universidad.

Tarragona, 6 de octubre de 2015

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# PUBLICATIONS BASED ON THE CONTENT OF THE THESIS

Soriano, S.; Azzouz, M.; Llaveria, J.; Marcé, P.; Matheu, M. I.; Díaz, Y.; Castillón, S.

***Enantioselective Formal Synthesis of Nectrisine***

Manuscript in preparation

Soriano, S.; Azzouz, M.; Matheu, M. I.; Díaz, Y.; Castillón, S.

***Palladium-Catalyzed Allylic Amination and Metathesis Reactions Powerfull Tools for the Enantioselective Synthesis of Acyclic Nucleoside Phosphonates Analogues of Cidofovir***

Manuscript submitted

Soriano, S.; Matheu, M. I.; Díaz, Y.; Castillón, S.

***Optimizing Substrate Control of the Regioselectivity of the Palladium-Catalyzed Asymmetric Allylic Amination for the Synthesis of Enantioenriched Branched Allyl Amines. Formal Enantioselective Synthesis of Fagomine.***

Manuscript submitted

## CONGRESSES AND SCIENTIFIC MEETINGS

**2015** Soriano, S; Matheu, M. I.; Díaz, Y.; Castillón, S. **Enantioselective Formal Synthesis of Nectrisine**, *Poster Contribution.* OMCOS, 18th Organometallic Chemistry Directed Towards Organic Synthesis, Sitges-Barcelona, july 2015

**2014** Soriano, S; Matheu, M. I.; Díaz, Y.; Castillón, S. **Enantioselective Formal Synthesis of Nectrisine**, *Poster Contribution.* **IX Jornadas Carbohidratos,** Logroño, Spain, 2014

**2013** Díaz, Y.; Soriano, S; Matheu, M. I.; Castillón, S. **Palladium-catalyzed allylic amination of linear allylic carbonates. Gaining insight in the role of steric and hydrogen-bonding interactions in the control of the regioselectivity.** *Poster Contribution.***ESOC, 18th European Symposium on Organic Chemistry**, Marseilles, France, July 2013

**2013** Soriano, S; Matheu, M. I.; Díaz, Y.; Castillón, S. **Palladium-catalyzed allylic amination of linear allylic carbonates. Gaining insight in the role of steric and hydrogen-bonding interactions in the control of the regioselectivity.** *Poster Contribution.* XXXIV Reunión Bienal de la Real Sociedad de Química Española. Santander, Spain, September 2013.

**2012** Soriano, S; Matheu, M. I.; Díaz, Y.; Castillón, S. **Substrate control of the regioselectivity in Palladium-Catalyzed Allylic Substitution Reaction,** *Poster Contribution.* 18th International Symposium on Homogeneous Catalysis. Toulouse (France), July, 2012 .

**2011** ICIQ Summer School. Tarragona (Spain). July 2011.

**2010** 2nd China-Spain Bilateral Symposium on Catalysis. Tarragona, Spain, November, 2010.

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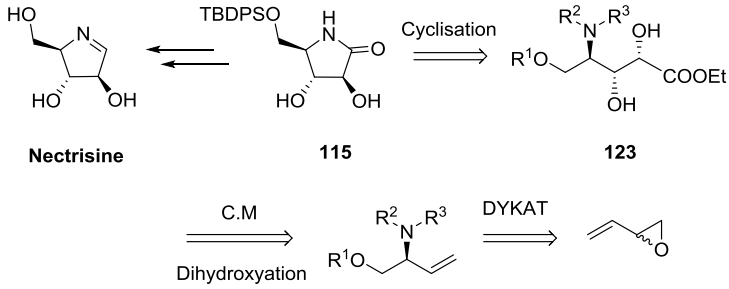
## SUMMARY

Palladium-catalyzed asymmetric allylic alkylation and amination reactions are among the most versatile methods for C-C and C-N bond formation that are widely applied in natural product synthesis. Our research group has acquired an important background in this reaction, and a general objective of this PhD work is to apply it to the synthesis of different natural products or analogues, as well as to enlarge the usefulness of this methodology to new substrates and new nucleophiles. In connection with this purpose, the specific objectives of this thesis was the following:

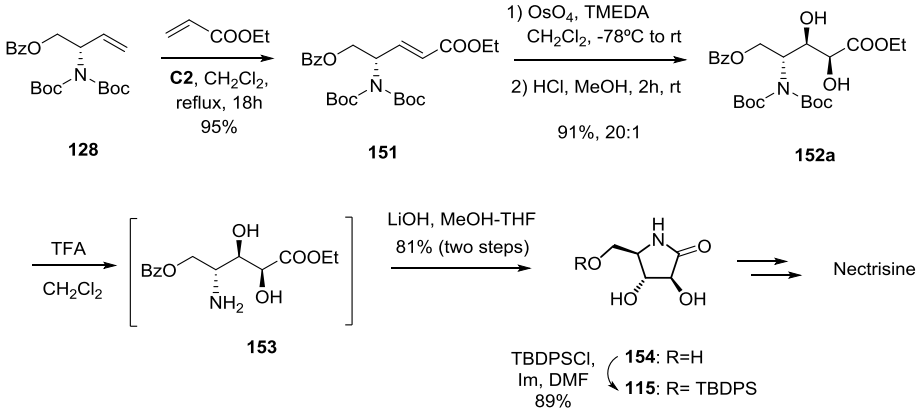
1. ***Enantioselective formal synthesis of nectrisine***: The work presented in this section has as an objective the enantioselective formal synthesis of nectrisine starting from the key synthon allylamine prepared through an palladium-catalyzed Dynamic Kinetic Asymmetric Transformation (DYKAT) of racemic vinyloxirane using imido carboxylate nucleophile. Cross-metathesis would allow the elongation of the chain length and diastereoselective dihydroxylation and cyclization of the corresponding amino-ester **123** could lead to lactam **115**. Nectrisine had been already prepared from compound **115** and consequently this synthesis would involve a formal synthesis of nectrisine.




**Scheme I**

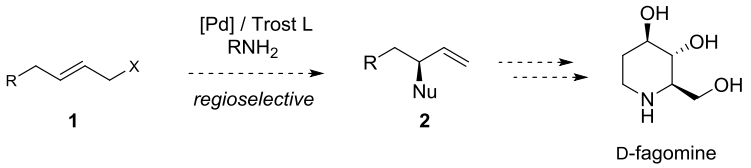
Cross-metathesis reaction of **128** with ethyl acrylate afforded the product **151** in excellent yields (95%) in the presence of Hoveyda-Grubbs catalyst **C2** (5 mol%). Reaction of compound **151** with stoichiommetric $OsO_4$ and TMEDA afforded the osmate ester in excellent stereoselectivity (20:1). Subsequent controlled hydrolysis in the presence of HCl and MeOH (C = 0.24 mol/l) rendered the desired diol **152a** product in 91% overall yield. After hydrolysis of Boc groups in **152a** with TFA, the reaction crude **153** was treated with LiOH to

afford lactam **154** in 81% yield for the two steps. Further protection of primary hydroxyl group by reaction with TBDPSCl provided compound **115** in 89% yield thus completing the first formal synthesis of the glycosidase inhibitor nectrisine in 7 steps and 48% overall yield starting from the commercially available racemic butadiene monoepoxide (Scheme II).



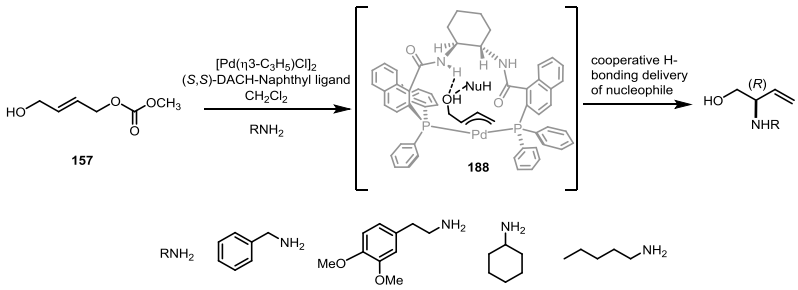

**Scheme II.**

2. ***Enantioselective formal synthesis of* D-*fagomine***: Aiming to explore the synthesis of **2** from **1** using palladium catalysis, and taking into account the role of DACH Trost ligands in the control of the regioselectivity of the reaction, we wondered whether structural elements in the substrate able to provide hydrogen bonding could bias the regiochemistry of palladium-catalyzed allylic amination of allylic carbonates to afford branched derivatives. As an illustration of this methodology we envisioned to apply to a short enantioselective formal synthesis of fagomine, an iminosugar that shows activity against mammalian gut α-glucosidase and β-galactosidases (Scheme III).



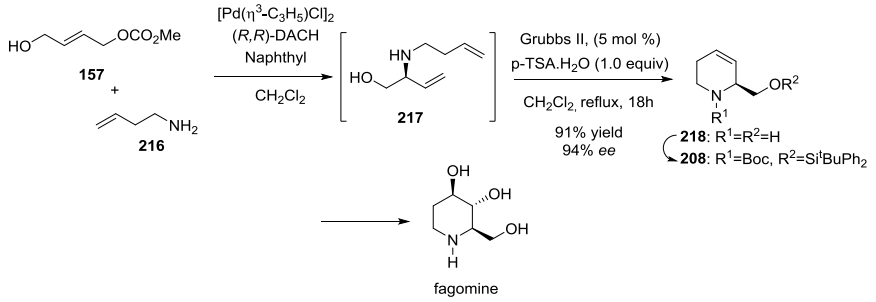

**Scheme III.**

In spite of years of study, controlling regioselectivity in palladium-catalyzed asymmetric allylic amination is a long-established problem that has not found a general solution yet. However, in this Ph.D. thesis we have found that the branched regioisomer could be obtained as the only product in the reaction using palladium/DACH naphthyl Trost ligand and carbonate **157**. Both the yield and enantioselectitity were excellent. We have shown that this system tolerates the use of relatively hard alkylamines as nucleophiles thus widening the synthetic possibilities towards the obtention of enantioenriched allyl amines which are obtained in poor regioselectivity using butadiene monoepoxide (**54**) as electrophile. The excellent control of the regio- and enantioselectivity in this case might be due to hydrogen bonding interactions between the hydroxyl group in the substrate and the diphenylphosphino benzoic acid-derived ligand in the Pd complex, as it can be deduced by the dramatic change in the regioselectivity when the hydroxyl group is protected or replaced by an alkyl chain (Scheme IV). The use of alkylamines as nucelophiles is limited to unhindered primary amines as secondary amines led to a poor regioselectivity. The steric hindrance of the nucleophile could be responsible for the poor regioselectivity observed.



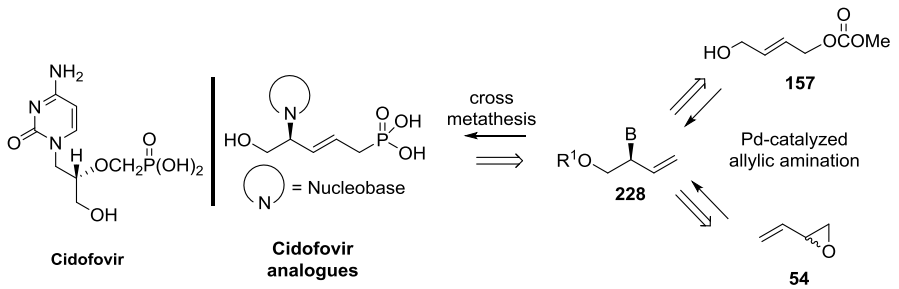

**Scheme IV.**

Based on this protocol a short formal enantioselective synthesis of glycosidase inhibitor D-fagomine is described (V).



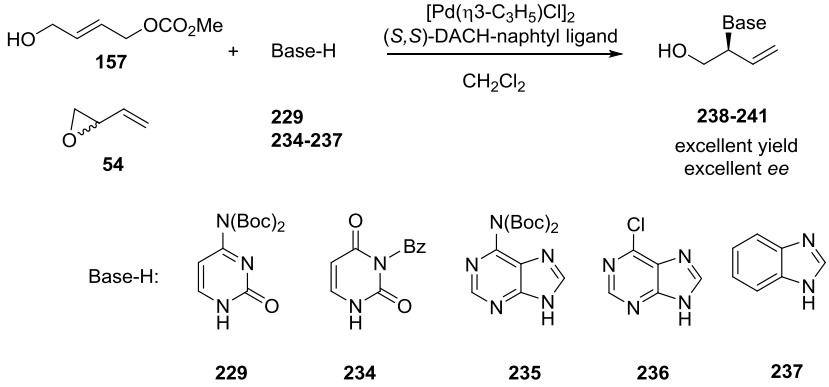

**Scheme V.**

3. ***Enantioselective synthesis of Cidofovir analogues*:** The research described in this part aims to develop an asymmetric and regioselective metal-catalyzed allylic amination process using purinic and pyrimidinic bases and palladium catalysts, and its application to the synthesis of acyclic nucleoside analogues of Cidofovir based on cross metathesis reaction as the second key step (Scheme VI).



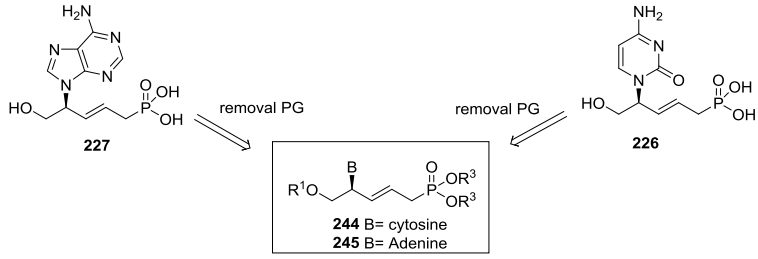

**Scheme VI.**

For this purpose we studied the Pd-catalyzed asymmetric allylic amination of vinyloxirane (**54**) or allylic carbonate **157** with different pyrimidinic and purinic bases as nucleophiles. This method allowed us to obtain compounds **238**-**241** in excellent yields and enantioselectivities (Scheme VII).



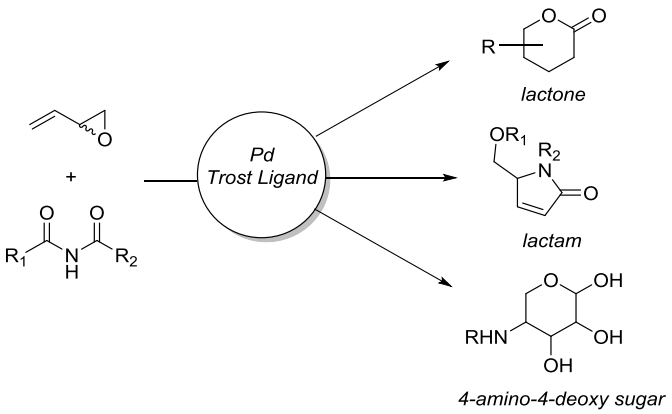

**Scheme VII.**

The allylated nucleobase thus obtained were use to develop a short and efficient enantioselective synthesis of acyclic nucleosides **226** and **227**. After ruthenium-catalyzed cross-metathesis with diethyl allylphosphonate and removal of protecting groups, acyclic nucleosides **226**, **227** were obtained in 66% and 59% yield (Scheme VIII).



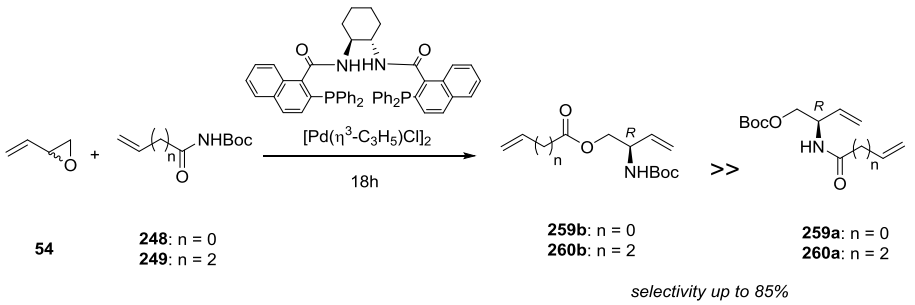

**Scheme VIII.**

4. ***Exploring the use of the catalytic system Pd/ Trost ligand*** with different imido and imidocarboxylate nucleophiles. The different products obtained in this study were used as starting materials in the synthesis of valuable different compounds such as lactam, lactone and 4-amino-4-deoxy sugar (Scheme IX) .



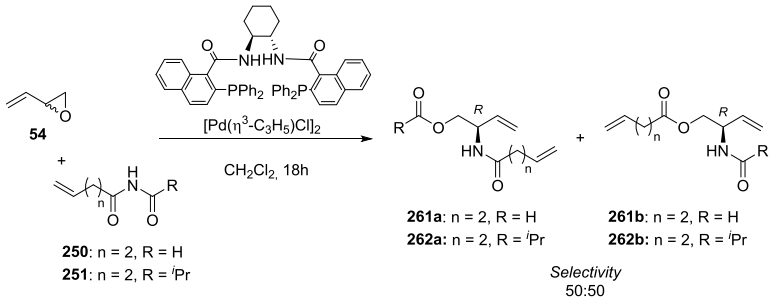

**Scheme IX**

The dynamic kinetic asymmetric transformation (DYKAT) of butadiene monoepoxide (**54**) using the catalytic Pd/Trost ligand system with different imido and imidocarboxylate nucleophiles have been explored. As expected, the resulting allylic imido carboxylate product isomerized through a facile in situ acyl migration. We found that when acryloyl imido carboxylates **248** and **249** were used as nucleophiles, very good to excellent chemoselectivity in the acyl migration wer achieved. This selectivity could be probably explained by both steric and electronic factors of the acyl moiety (Scheme X).



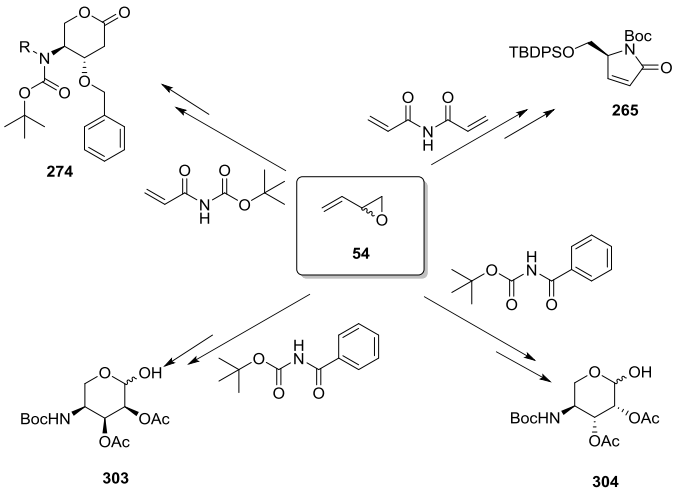

**Scheme X.**

In the case of acryloyl imides **250** and **251** no control of acyl migration was possible and an almost equimolar ratio of both isomers were always obtained (Scheme XI).




**Scheme XI.**

Nevertheless this method allowed us to obtain enantiomerically enriched allylic compounds bearing an acryloyl moiety at *N*, *O* or both positions which in combination with the well known ring-closing metathesis reaction enabled us to obtain very good yield of valuable different compounds such as lactam **265**, lactone **274** and 4-amino-4-deoxy sugars **303** and **304** (Scheme XII).




**Scheme XII.**

# ABBREVIATIONS AND ACRONYMS

## A

| | |
|---|---|
| AAA: | Asymmetric Allylic Alkylation |
| AIDS: | Acquired immune deficiency syndrome |
| ANPs: | Acyclic nucleotide phosphonates |

## B

| | |
|---|---|
| Boc: | *tert*-butoxycarbonyl |
| BzCl: | Benzoyl chloride |

## C

| | |
|---|---|
| c. a.: | Aproximately |
| CM: | Cross-metathesis |
| c.m.: | complexe mixture |
| CMV: | Cytomegalovirus |
| Conv: | Conversion |
| CSA: | Camphorsulfonic acid |

## D

| | |
|---|---|
| DAB: | 1,4-dideoxyimino-D-arabinitol |
| DACH | 1,2-diaminocyclohexane |
| DAST: | Diethylaminosulfur trifluoride |
| DBU: | 1,8-Diazabicyclo[5.4.0]undec-7-ene |
| DCM: | Dichloromethane |
| DDQ: | 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone |
| DEAD: | Diethyl azodicarboxylate |
| DEPC: | Diethyl phosphorocyanidate |

| | |
|---|---|
| DHPA: | 9-(2,3-dihydroxypropyl)adenine |
| DHQ: | Dihydroquinine |
| DIBAL: | Diisobutyl aluminum hydride |
| DHQD: | Dihydroquinidine |
| DMAP: | 4-Dimethylaminopyridine |
| DMF: | *N*,*N*-Dimethylformamide |
| DNA: | Deoxyribonucleic acid |
| dNTPs : | 2'-deoxynucleoside-5'-triphosphates |
| DPPBA: | Diphenylphosphinobenzoic acid |
| DYKAT: | Dynamic Kinetic Asymmetric Transformation |

**E**

| | |
|---|---|
| EWG: | Electron Withdrawing Group |
| e.g.: | for exemple |

**H**

| | |
|---|---|
| HCMV: | Human cytomegalovirus |
| HPLC: | High Performance Liquid Chromatography |
| HPMPA: | (S)-9-(3-hydroxy-2-phosphonylmethoxypropyl)adenine |
| HPMPC: | (*S*)-1-(3-hydroxy-2-phosphonylmethoxypropyl)cytosine |
| HSV: | Herpes simplex virus |

**N**

| | |
|---|---|
| NaHMDS: | Sodium bis(trimethylsilyl)amide |
| NBS: | *N*-Bromosuccinimide |
| NCS: | *N*-Chlorosuccinimide |
| NMO: | *N*-methyl-morpholine-*N*-oxide |
| NMR: | Nuclear Magnetic Resonance |

**P**

| | |
|---|---|
| PHAL: | Phthalazine |
| PHN: | Phenanthryl ether |
| PMB: | *p*-methoxybenzyl |
| PMEA: | 9-(2-phosphonylmethoxyethyl)adenine |
| PMPA: | (*R*)-9-(2-phosphonylmethoxypropyl) adenine |
| PK: | Protein kinase |
| $^{i}$Pr: | *iso*-propyl |
| Py: | Pyridine |

**R**

| | |
|---|---|
| RCM: | Ring-closing metathesis |
| Red-Al: | Sodium bis(2-methoxyethoxy)aluminium hydride |
| RNA : | Ribonucleic acid |

**T**

| | |
|---|---|
| TBAF: | Tetra-*n*-Butylammonium fluoride |
| TBSOTf: | *tert*-Butyldimethylsilyl trifluoromethanesulfonate |
| TBDPSCl: | *tert*-Butyldiphenylsilyl Chloride |
| TDF: | Tenofovir disoproxil fumarate |
| Temp: | Temperature |
| Teoc *:* | 2-trimethylsilylethoxycarbonyl |
| TFA: | Trifluoroacetic acid |
| THF: | Tetrahydrofuran |
| TIPSCl: | Triisopropylsilyl chloride |
| TLC: | Thin Layer Chromatography |
| TMEDA: | Tetramethylethylenediamine |

| | |
|---|---|
| TML: | Trost Modular Ligand |
| TMSBr: | Trimethylsilyl bromide |
| TPAP: | Tetra-*n*-propylammonium perruthenate |
| TK: | Thymidine kinase |

**V**

| | |
|---|---|
| VZV: | Varicella-Zoster Virus |

# CHAPTER 1

*General introduction*

# I. Palladium-catalyzed asymmetric allylic substitution reactions

## I.1. Introduction

Fine chemicals and natural product chemistry rely on enantiomerically pure compounds. The discovery of synthetic routes for preparing these compounds is one of the most persistently pursued goals in chemistry. Asymmetric catalysis is one of the most attractive approaches because it can provide very high reactivity and selectivity, and is environmentally friendly.[1]

Among asymmetric catalytic processes, metal-catalyzed asymmetric allylic alkylations (AAA) are unique in two respects. Firstly, they have multiple mechanisms by which asymmetry can be introduced and secondly, they can form many types of bonds among which are C-H, C-O, C-N, C-S, C-P, and most importantly, C-C using the same catalyst system.[2] Many different metals may be used for such AAA processes including palladium, platinum, gold, rhodium, iridium, molybdenum and ruthenium, which have become more and more interesting during the past few years.[3] At present, palladium has far proven to be the most versatile metal catalyst for its easy manipulation, high catalytic activity and high enantioselectivity and for having the broadest scope.[4]

The first time palladium was used in a commercial homogeneous catalytic process was in the 1950's. The reaction, known as the Wacker process,

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1 (a) Asymmetric Catalysis in Organic Synthesis (Ed. R. Noyori), Wiley, New York, **1994**; (b) Comprehensive Asymmetric Catalysis (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**; (c) Asymmetric Catalysis in Industrial Scale: Challenges, Approaches and Solutions (Eds.: H. U. Blaser, E. Schmidt), Wiley-VCH, Weinheim, **2003**.

2 Reviews: (a) B. M. Trost and D. L. Van Vranken, *Chem. Rev*., **1996**, *96*, 395-422; (b) B. M. Trost and M. L. Crawley, *Chem. Rev*., **2003**, *103*, 2921-2943; (c) Z. Lu and S. Ma, *Angew. Chem., Int. Ed*., **2008**, *47*, 258-297

3 Trost. B. M.; Lee, C. Asymmetric Allylic Alkylation Reactions. In Catalytic Asymmetric Synthesis, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, **2000**; p 593.

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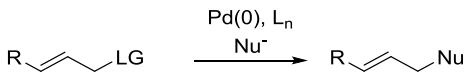
PALLADIUM-CATALYZED ASYMMETRIC ALLYLIC AMINATION. DEVELOPMENT AND SYNTHETIC APPLICATIONS
Sebastien Soriano Istat

produces acetaldehyde from ethylene and water, using $PdCl_2$ as catalyst[5] and marked the beginning of modern palladium chemistry. Later, Smid and Hafner[6] reported the first (π-allyl)Pd complex. In 1965, Tsuji[7] reported a palladium-mediated allylic substitution as a stoichiometric reaction. Thereafter, the reaction was further developed by starting from alkenes and using additional phosphine ligands which accelerate the reaction, and later the asymmetric version of the reaction was reported.[8,9]. Further on the reaction was improved by employing the use of allylic acetates and performing the reaction catalytically (Scheme 1).[10] Since then, palladium-catalyzed allylic substitution reaction has known a remarkable development and today, it has emerged as a powerful methodology in organic synthesis to C-C and C-X bond forming.[2]




**Scheme 1.** Palladium-catalyzed allylic alkylation reaction.

The Pd-catalyzed allylic alkylations are easy to carry out and can be performed under mild conditions at ambient temperature. The most common substrates are allylic acetates, but a variety of leaving groups can be utilized - for example carbonates, phosphates, carbamates or halides. Besides, for the introduction of functionalized allylic side chains, vinyl epoxides[11] or 4-vinyl-1,3-dioxolan-2-ones[12] are also suitable candidates, at least for Pd-catalyzed reactions. For most substrates, the use of a stoichiometric amount of base is necessary to generate the soft nucleophiles. However, allylic carbonates undergo decarboxylation, and since a sufficiently basic alkoxide is formed in the process, no extra base is needed.

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5 Smidt, J.; Sieber, R. *Angew. Chem.* **1959**, *71*, 626.

6 Smid, J.; Hafner, W. *Angew. Chem.* **1959**, *71*, 176-182.

7 Tsuji, J.; Takahashi, H.; Morikawa, M. *Tetrahedron Lett*. **1965**, *6*, 4387-4388.

8 Hata, G.; Takahashi, K.; Miyake, A. *Chem. Commun*. **1970**, 1392-1393.

9 Atkins, K. E.; Walker, W. E.; Manyik, R.M. *Tetrahedron Lett*. **1970**, *11*, 3821-3824.

10 Trost, B. M.; Fullerton, T. J. *J. Am. Chem. Soc*. **1973**, *95*, 292-294.

11 (a) Trost, B. M.; Molander, G. A. *J. Am. Chem. Soc*. **1981**, *103*, 5969-5972. (b) Tsuji, J.; Kataoka, H.; Kobayashi, Y. *Tetrahedron Lett*. **1981**, *22*, 2575-2578. (c) Kimura, M.; Mukai, R.; Tamaki, T.; Horino, Y.; Tamaru, Y. *J. Am. Chem. Soc*. **2007**, *129*, 4122-4123.

12 Kang, S.-K.; Kim, S.-G.; Lee, J.-S. *Tetrahedron: Asymmetry* **1992**, *3*, 1139-1140.

A variety of nucleophiles can be applied in the Pd-catalyzed AAA reaction, such as alkali metal enolates or heteroatom nucleophiles, but the most commonly used are soft stabilized carbon nucleophiles, e.g. malonates.

## I.2. Mechanistic Considerations of Allylic Alkylation

### I.2.1. Catalytic cycle

The allylic alkylation reaction has been the object of numerous investigations, from the scope to the mechanism of the catalytic cycle.[13,14,15] The generally accepted mechanism of palladium-catalyzed allylic substitution is shown in Scheme 2. An allylic substrate **1**, typically an acetate or a carbonate, reacts with the catalyst, which enters the catalytic cycle at the Pd(0) oxidation level. Both Pd(0) and Pd(II) complexes can be used as precatalysts, because Pd(II) is easily reduced *in situ* to the active Pd(0) form by e.g., excess phosphine ligand, certain nucleophiles or other components present in the reaction mixture. Hence, the initial binding of the metal to the olefin forming a $\eta^2$-complex **2** is followed by oxidative addition, leading to an intermediate ($\eta^3$-allyl)Pd(II) complex **3** and **4** with the leaving group as counterion. Structurally, the π-allyl palladium intermediate is a square planar 16-electron complex consisting of ligands and a coordinated allyl unit. The substituents on the allyl unit are defined as *syn* (R *syn* to the substituent on C2 of the allyl) and *anti* (R *anti* to the substituent on C2). The oxidative addition in these types of complexes is also referred to as ionization because it generates ions. Different possible configurations of the allyl ligand are possible when the allyl moiety is substituted at both termini: the *syn,syn* **3** and *syn,anti* **4** and *anti,anti* (not represented in the scheme). The π-allyl intermediate resulting from an *E*-olefin electrophile typically prefers the *syn,syn* configuration, whereas in a cyclic system, the π-allyl is locked in the *anti,anti* configuration. One can think of this step as an $S_N2$-like displacement of the leaving group by the incoming palladium "nucleophile". The electrophilic Pd(II) center activates the allyl system for nucleophilic attack at the allyl termini. Addition of the nucleophile at C1 or C3 generates an unstable

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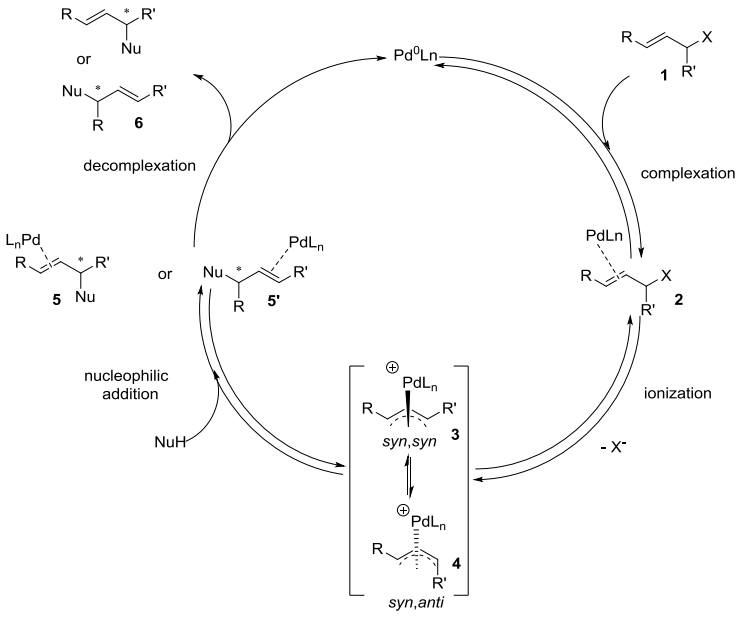
13 Bosnich, B.; Mackenzie, P. B. *Pure & Appl. Chem*., **1982**, *54*, 189-195, and references therein.

14 Consiglio, G.; Waymouth, R. M. *Chem. Rev*. **1989**, *89*, 257-276.

15 Frost, C. G.; Howarth, J.; Williams, J. M. J. *Tetrahedron: Asymmetry*. **1992**, *3*, 1089-1122.

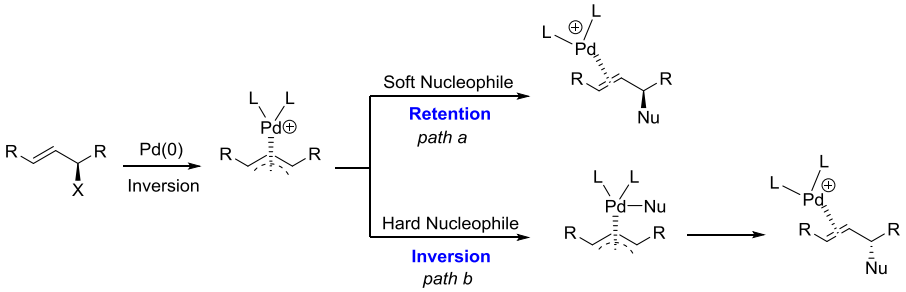
Pd(0)-olefin complex **5** or **5'** which readily releases the final product **6** and a Pd(0) species which undergoes oxidative addition to another substrate molecule. Although attack on the central carbon of the allyl is possible, it is not common and is generally followed by reductive elimination, forming cyclopropanes. The rate-limiting step can be either the oxidative addition or the nucleophilic substitution, depending on the relative height of their respective transition states.




**Scheme 2.** Catalytic cycle in Palladium-catalyzed allylic alkylation.

The oxidative addition process proceeds with inversion of configuration of the initial carbon-leaving group bond, whereas the nucleophilic substitution step in the AAA catalytic cycle can occur through two distinct mechanistic pathways that largely depend on the nature of the metal and nucleophile. Nucleophiles can be qualitatively classified *via* the mechanism by which they attack the $\eta^3$-allyl complex intermediate (Scheme 3). The first mechanistic pathway (path a) is usually attributed to "soft" nucleophiles (stabilized carbon nucleophiles such as carbanions, $pK_a$<20) and involves the external attack at the carbon on the face opposite to the palladium, so the final compound obtained will have overall retention of configuration.

In the case of "hard" nucleophiles (unstabilized carbon nucleophiles such as organometallic reagents), the initial attack proceeds directly at the palladium atom followed by subsequent reductive elimination to form the new bond resulting in overall inversion of configuration (Scheme 3, path b). Heteroatom based nucleophiles such as amines or alcohols[16] are also feasible and they usually react via inversion, as for the stabilized carbon nucleophiles. Carboxylates can react both as soft and hard nucleophiles, depending on the reaction conditions.[17]




**Scheme 3.** Stereochemistry in Pd-AAA reactions.

Because nucleophilic attack is the microscopic reverse of ionization, similar principles govern this step of the catalytic cycle and it could be considered $S_N2$-like, with Pd(II) displaced. To ensure an antiperiplanar trajectory, the nucleophile approaches in an *exo* sense (Figure 1).

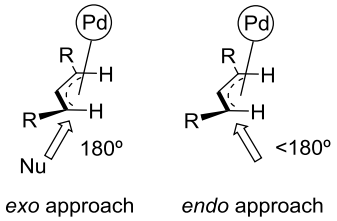



**Figure 1.** Exo approach of the nucleophile.

16 Bäckvall, J.-E.; Andersson, P. G. J. *Am. Chem . Soc*. **1992**, *114*, 6374-6381.
17 Bäckvall, J.-E.; Nordberg, R. E. *J. Am. Chem. Soc*. **1981**, *103*, 4959-4960.

## I.2.2. Dynamic processes in ($\eta^3$-allyl)Pd complexes

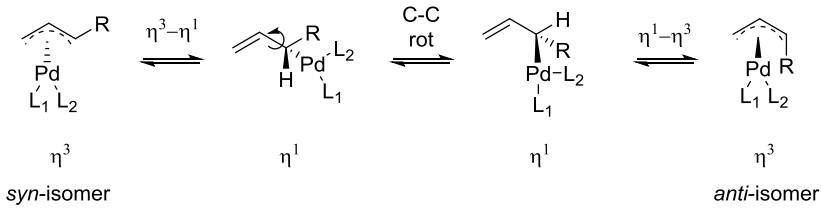
The ($\eta^3$-allyl)Pd intermediates play an important role as key intermediates in the catalytic cycle and since they are often relatively stable, they can be isolated and analyzed both in solution and in solid state. As expected from the strong preference of Pd(II) for a square planar coordination geometry, in most complexes the Pd(II) center is surrounded by the allyl system and two other ligands located in a plane defined by the two allyl termini and the metal center. In solution, several dynamic processes can occur, making the analysis or prediction of the outcome of allylic substitution often difficult. Since the timescale of the relevant dynamic processes is suitable for investigation by coalescence or saturation transfer techniques, dynamic processes in ($\eta^3$-allyl)Pd complexes have been observed and studied using NMR spectroscopy technique. These processes were in fact some of the earliest exchange to be studied by NMR technique, and were reviewed already in 1975 by Vrieze.[18]

### I.2.2.1. *Syn*/*anti* exchange or π-σ-π isomerization

In palladium-catalyzed allylic alkylation reactions, π-allylpalladium complexes are often in a state of dynamic equilibrium. On the time scale of the catalytic cycle, ligands can dissociate, reassociate, and change their conformation and geometry. In a typical alkylation reaction, the *syn*/*anti* substituents in a palladium π-allyl complex can exchange positions hundreds of times faster than alkylation. The palladium can coordinate to the allyl in two different modes, either to all three allylic carbons ($\eta^3$-allyl)Pd, or to one allylic carbon ($\eta^1$-allyl)Pd (Scheme 4). These two isomeric forms are involved in the $\eta^3$-$\eta^1$-$\eta^3$ isomerization of the allyl moiety. The isomerization occurs via a change in coordination of palladium to the allyl from $\eta^3$ to $\eta^1$. The C-C bond in the $\eta^1$-complex can rotate freely and thereafter the ($\eta^3$-allyl)Pd complex can reform, either back to the starting complex or to the complex where one of the termini of the allylic moiety has undergone syn/anti isomerization and the other two carbon atoms in the allylic moiety have been inverted (Scheme 4). The rate of this isomerization is increased in the presence of external ligands such as a halides since these

[18] Vrieze, K. In Dynamic Nuclear Magnetic Resonance Spectroscopy; Jackman, L. M., Cotton F. A., Eds., Academic Press: New York, **1975**, and references therein.

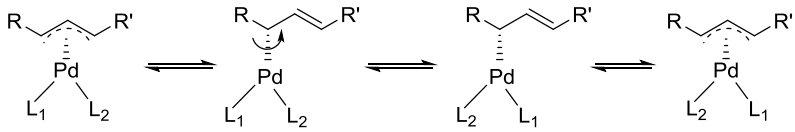
coordinate to Pd and stabilize the $\eta^1$ complex. If the σ complex is formed at a monosubstituted allyl terminus, rotation of 180° about the σ bond and rehybridization results in a π-facial exchange of the coordinated allyl. It is important to point out that the $\eta^3$-$\eta^1$-$\eta^3$ isomerization does not exchange the positions of the ligands in relation to the allyl termini, even in the absence of added ligand and the Pd center stays square planar throughout the process. This equilibrium is very facile when the allyl moiety is monosubstituted, and normally displaced toward the *syn* isomer side in the case of monosubstitution.




**Scheme 4.** π-σ-π isomerization.

## I.2.2.2. Apparent allyl rotation or *syn*/*syn*, *anti*/*anti* isomerization

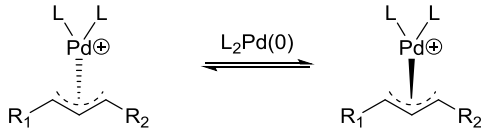
As the name itself reveals, apparent allyl rotation implies the formal rotation of the allyl moiety around the imaginary Pd-allyl bond axis. In this process the two termini of the allyl system switch position with respect to the other two coordination sites (Scheme 5). If the two ligands are different and chiral, this isomerization leads to a diastereomeric complex even if the allyl system has structurally identical termini. These two diastereoisomeric complexes can undergo nucleophilic addition at different rates and different regioselectivity changing the product distribution of the reaction. However, if the ligands are identical, allyl rotation generates two identical structures and therefore has no consequence. Several mechanisms have been proposed, one of them involves π-σ-π isomerization with concomitant rotation around the Pd-C bond in the $\eta^1$-complex.




**Scheme 5.** Allyl rotation.

## I.2.2.3. Pd(0)-catalyzed allyl exchange

Another type of isomerization is shown in Scheme 6. Similarly to the nucleophilic addition step, the electrophilic allyl system bound to Pd(II) can react with Pd(0) complex.[19] The Pd(0) complex adds to the free π-face of the allyl ligand and displaces the Pd(II) complex on the backside. Therefore, this process results in an inversion of configuration at all three carbon atoms. The precise mechanism for this process is unclear at present, but the following conclusions were made. Isomerization can be inhibited by (1) a reactive allylic substrate, (2) a low Pd(0) concentration, (3) bidentate ligands, and (4) halide ions. However, because the concentration of palladium species in catalytic reactions is much lower than that of the substrate and the nucleophile, this isomerization is usually slow compared to product formation (Scheme 6). In contrast to the previously described *syn*/*anti* exchange and apparent allyl rotation that are unimolecular this isomerization is bimolecular. Therefore, as long as the amounts of Pd(0) used are minimized, this isomerization can usually be avoided in catalytic experiments. However, such a process can sometimes become operative, for example when the firstly generated π-allyl complex turns out to be unreactive.




**Scheme 6.** Pd(0)-catalyzed allyl exchange.

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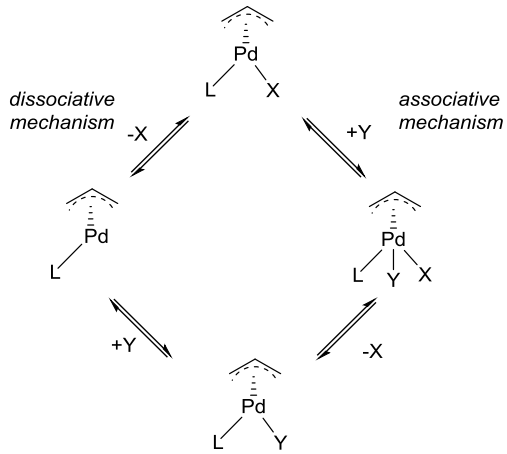
[19] (a) Mackenzie, P. B.; Whelan, J.; Bosnich, B. *J. Am. Chem. Soc*. **1985**, *107*, 2046-2054. (b) Murahashi, S. I.; Taniguchi, Y.; Imada, Y.; Tanigawa, Y. *J. Org. Chem*. **1989**, *54*, 3292-3303. (c) Keinan, E.; Sahai, M.; Roth, Z.; Nudelman, A.; Herzig, J. *J. Org. Chem*. **1985**, *50*, 3558-3566.

## I.2.2.4. Ligand exchange

In solution and in the presence of excess ligands, it is possible to exchange one or both of the ligands L and X in the ($\eta^3$-allyl)PdLX complex. This exchange can proceed either via a dissociative or an associative mechanism (Scheme 7).




**Scheme 7.** Ligand exchange via the dissociative and the associative mechanism**.**

## I.3. Regioselectivity

When the transiently formed π-allyl Pd-complex is unsymmetrically substituted the issue of site-selectivity comes into play. With 1,3-symmetrically disubstituted substrates, various ligands have been synthesized and used in this reaction and high *ee* were obtained.[20] However, in the case of unsymmetrical substrates such as **7** or **8**, the intermediate ($\eta^3$-allyl)palladium(II) complex formed after ionization can be attacked by nucleophiles at both termini of the allylic system, posing the problem of regioselectivity. It is generally accepted that in Pd-catalyzed AAA, the regioselectivity is influenced by opposing steric and electronic effects. Steric factors will direct the nucleophilic attack to the less hindered allylic terminus to

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[20] For examples, see: (a) Trost, B. M. *Acc. Chem. Res*. **1996**, *29*, 355-364. (b) Von Matt, P.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 566-568. (c) Kudis, S.; Helmchen, G. *Angew. Chem., Int. Ed*. **1998**, *37*, 3047-3050.

minimize steric interactions with the nucleophile, yielding to achiral linear product **10** rather than the chiral branched isomer **9**, which is the preferred product for applications in asymmetric synthesis.[21,22] By contrast, electronic factors tend to favor the attack at the more electropositive carbon, usually the more substituted terminus. It is difficult to rationalize the regiochemical outcome of nucleophilic addition on allyl complexes since steric effects are often superimposed with electronic ones. High regio- and enantioselectivity for certain substrates in allylic alkylation reactions were, however, achieved by employing chiral metal complexes other than Pd such as W, Mo, and Ir.[23]

The allylic carbon atoms in the *syn*- and *anti*-isomers of the ($\eta^3$ -allyl)Pd have different reactivity. In monosubstituted allylic substrates, the resulting *anti*-isomer has a moderate preference for internal nucleophilic substitution, whereas the *syn*-isomer has a strong preference for terminal nucleophilic attack. Therefore, by increasing the amount of the desired isomer of the intermediate in the reaction, it is possible to increase the desired selectivity.[24,25] In most cases, the *syn*-isomer is the more stable one.

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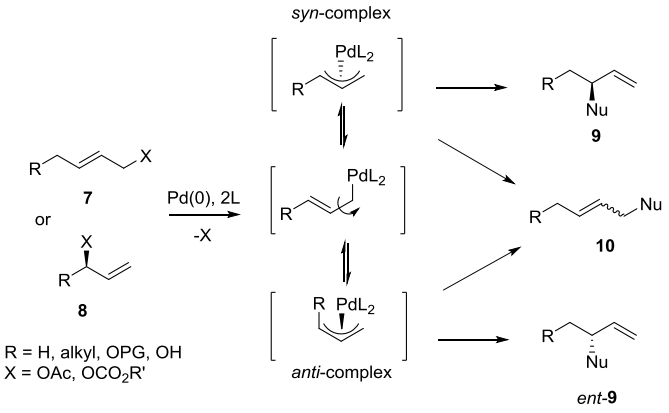
21 (a) Norsikian, S.; Chang, C.-W. *Curr. Org. Synth.* **2009**, *6*, 264-289. (b) Helmchen, G. Dahnz, A. Dbon, P. Schelwies, M.; Weihofen, R. *Chem. Commun.* **2007**, 675-691.

22 Trost, B. M.; Dietsche, T. J.; Fullerton, T. J. *J. Org. Chem*. **1974**, *39*, 737-738.

23 Examples of other metal-catalyzed allylic substitutions: (a) W: Lloyd-Jones, G. C.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl*. **1995**, *34*, 462-464. (b) Mo: Trost, B. M.; Hildbrand, S.; Dogra, K. *J. Am. Chem. Soc*. **1999**, *121*, 10416-10417. (c) Ir: Bartels, B.; Helmchen, G. *Chem. Commun*. **1999**, 741-742. (d) Fe: Xu, Y.; Zhou, B. *J. Org. Chem.* **1987**, *52*, 974-977. (e) Rh: Evans, P. A.; Nelson, J. D. *J. Am. Chem. Soc.* **1998**, *120*, 5581-5582. (f) Ru: Kondo, T.; Ono, H.; Satake, N.; Mitsudo, T.; Watanable, Y. *Organometallics* **1995**, *14*, 1945-1953. (g) Pt: Blacker, A. J.; Clarke, M. L.; Loft, M. S.; Mahon, M. F.; Humphries, M. E.; Williams, J. M. *J. Chem. Eur. J.* **2000**, *6*, 353-360.

24 Sjögren, M.; Hansson, S.; Åkermark, B.; Vitagliano, A. *Organometallics*, **1994**, *13*, 1963-1971.

25 Sjögren, M.; Hansson, S.; Norrby, P.-O.; Åkermark, B.; Cucciolito, M. E.; Vitagliano, A. *Organometallics*, **1992**, *11*, 3954-3964.




**Scheme 8.** Metal-catalyzed allylic substitution reaction with unsymmetrical monosubstituted substrates **7**, **8**.

There are several factors that influence the regioselectivity of the reaction such as steric and electronic effects from both the substrates and the nucleophiles, but also the nature of the metal, the ligands,[2,26] solvent,[27] the nature of the leaving group,[28,29] and the presence of additives, which can interfere and give enhanced or unexpected regiochemistry. Moreover, regioselectivity is also known to be sensitive to the regiochemical memory of the position of the leaving group,[30] the preferred configuration[25,28] and to dynamic exchange in the ($\eta^3$-allyl)Pd intermediate.[31] Recently, control of the regioselectivity in palladium(0)-catalyzed allylic alkylation have been reviewed.[21a]

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26 (a) Hayashi, T.; Yamamoto, A.; Ito, Y.; Nishioka, E.; Miura, H.; Yanagi, K. *J. Am. Chem. Soc*. **1989**, *111*, 6301-6311. (b) Kranenburg, M.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Eur. J. Inorg. Chem*. **1998**, 25-27. (c) Frölander, A.; Lutsenko, S.; Privalov, T.; Moberg, C. *J. Org. Chem*. **2005**, *70*, 9882-9891. (c) Lu, Z.; Ma, S. *Angew Chem., Int. Ed.* **2008**, *47*, 258-297.

27 (a) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 4545-4554. (b) Cook, G. R.; Yu, H.; Sankaranarayanan, S.; Shanker, P. S. *J. Am. Chem. Soc*. **2003**, *125*, 5115-5120. (c) Cook, G. R.; Saraswathiamma, M. *Tetrahedron Lett*. **2005**, *46*, 6491-6494.

28 Fristrup, P.; Jensen, T.; Hoppe, J.; Norrby, P. O. *Chem. Eur. J.* **2006**, *12*, 5352-5360.

29 Kazmaier, U.; Stolz, D.; Krämer, K.; Zumpe, F. L. *Chem. Eur. J.* **2008**, *14*, 1322 -1329.

30 Lloyd-Jones, G. C.; Stephen, S. C. *Chem. Eur. J.* **1998**, *4*, 2539-2549.

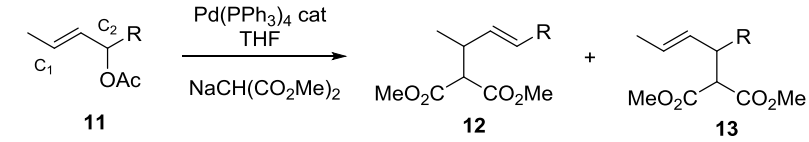
31 Hansson, S.; Norrby, P.-O.; Sjögren, M.; Akermark, B.; Cucciolito, M. E.; Giordano, F.; Vitagliano, A. *Organometallics* **1993**, *12*, 4940-4948.

Herein, we will focus on the regioselectivity obtained with "soft" nucleophiles, since nonstabilized nucleophiles have been shown to present some propensity for attack at the more substituted terminus.[32]

## I.3.1. Effect of the substituent on the allyl moiety

### I.3.1.1. Steric control of the regioselectivity

As said before, soft carbon nucleophiles approach preferentially to the less substituted terminus of the π-allylpalladium complexes with a good level of regioselectivity to minimize the steric interactions between the π-allyl complex and the nucleophile. For example, in the palladium-catalyzed allylic substitution of **11** with sodium dimethyl malonate, a remarkable differentiation was observed between the methyl group at $C_1$ and propyl, *i*-propyl or *i*-butyl substituents at $C_3$ (Scheme 9).[32] In this series, as the difference in the group size increases, the ratio of **12**:**13** varied from 77:23 to >99:1 in favour of the $C_3$-alkylated compound. However, the situation is not so simple and electronic effects are superimposed with steric effects mainly when R in Scheme 9 is a polar group.




R = propyl, *i*-propyl, *i*-butyl

**Scheme 9.** Steric control of the regioselectivity.

[32] Keinan, E.; Sahai, M. *J. Chem. Soc., Chem. Commun*. **1984**, 648-650.

## I.3.1.2. Functional groups effect

### I.3.1.2.1. Electronic control of the regioselectivity

Electron-withdrawing groups on allylic substrate such as R = R'CO- and R'OCO-,[33] NC-,[34, 33d] $PhSO_2$-,[35] $(R'O)_2P(O)$-,[36] PhS-[37]) have been shown to usually direct the nucleophilic attack on π-allyl palladium complex at the more remote side from this group, whereas electron-donating groups such as R = -OR' favor the attack close to this group.[38] For mono- and disubstituted (diphosphino)($\eta^3$-allyl)palladium system, it has been shown by density functional study that the shortest Pd-C(terminal) bond is the one closest to the most electron-withdrawing group. This fact has been rationalized in terms of molecular orbital interactions between the allyl ligand and the metal. The nucleophilic attack takes place at the carbon atom which presents a longer Pd-C bond. For example, the carbonate derivatives of allylic (hydroxy)phosphonates **14** (EWG) underwent palladium catalyzed amination leading to the corresponding allylic amines **15** in high yields[39] whereas the presence of the

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33 (a) Jackson, W. R.; Strauss, J. U. G. *Tetrahedron Lett*. **1975**, 2591-2592. (b) Collins, D. J.; Jackson, W. R.; Timms, R. N. *Tetrahedron Lett*. **1976**, 495-496. (c) Jackson, W. R.; Strauss, J. U. *Aust. J. Chem*. **1977**, *30*, 553562. (d) Tsuji, J.; Ueno, H.; Kobayashi, Y.; Okumoto, H. *Tetrahedron Lett*. **1981**, *22*, 2573-2574. (e) Ognyanov, V. I.; Hesse, M. *Synthesis* **1985**, 645-647. (f) Ono, N.; Hamamoto, I.; Kaji, A. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1439-1443. (g) Tanikaga, R.; Jun, T. X.; Kaji, A. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1185-1191.

34 (a) Keinan, E.; Roth, Z. *J. Org. Chem*. **1983**, *48*, 1769-1772.

35 (a) Ogura, K.; Shibuya, N.; Iida, H. *Tetrahedron Lett*. **1981**, *22*, 1519-1522. (b) Alonso, I.; Carretero, J. C.; Garrido, J. L.; Magro, V.; Pedregal, C. *J. Org. Chem*. **1997**, *62*, 5682-5683.

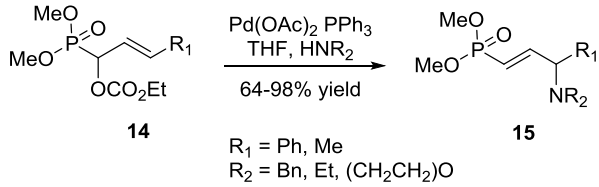
36 (a) Zhu, J.; Lu, X. *Tetrahedron Lett.* **1987**, *28*, 1897-1900. (b) Öhler,E.; Kanzler, S. *Synthesis* **1995**, 539. (c) Principato, B.; Maffei, M.; Siv, C.; Buono, G.; Peiffer, G. *Tetrahedron* **1996**, *52*, 2087-2096.

37 (a) Godleski, S. A.; Villhauer, E. B. *J. Org. Chem*. **1984**, *49*, 2246-2252. (b) Godleski, S. A.; Villhauer, E, B. *J. Org. Chem.* **1986**, *51*, 486-491. (c) Yamamoto, Y.; Al-Masum, M.; Takeda, A. *Chem. Commun*. **1996**, *7*, 831-832.

38 (a) Billups, W. E.; Erkes, R. S.; Reed, L. E. *Synth. Commun*. **1980**, *10*, 147-154. (b) Trost, B. M.; Merlic, C. A. *J. Org. Chem*. **1990**, *55*, 1127-1129. (c) Chaptal, N.; Colovray-Gotteland, V.; Grandjean, C.; Cazes, B.; Goré, J. *Tetrahedron Lett*. **1991**, *32*, 1795-1798. (d) Vicart, N.; Cazes, B.; Goré, J. *Tetrahedron Lett*. **1995**, *36*, 535-538. (e) Yamamoto, Y.; Al-Masum, M. Synlett 1995, 9, 969-970.

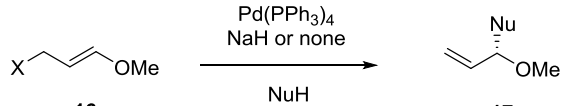
39 De La Cruz, M. A.; Shabany, H.; Spilling, C. D. *Phosphorus Sulfur Silicon Relat. Elem.* **1999**, *144*, 181-184

methoxy group (EDG) in substrate **16**, directed the attack of various carbonucleophiles at the more substituted carbon (Scheme 10).[38]




**14** **15**

$R_1$ = Ph, Me
$R_2$ = Bn, Et, $(CH_2CH_2)O$




**16** **17**

X = OAc, $OCO_2Me$

**Scheme 10.** Electronic control of the regioselectivity.

## I.3.1.2.2. The β-Substituent Effects

With substrates bearing polar substituents such as Z = Cl, OH, OR, OAc, $OCO_2R$, $NR_2$ or $NO_2$ at the homoallylic position, the nucleophilic attack proceeds with high regioselectivity remote from these groups. (Scheme 11).

It has been recognized[40] that the electronic effects of certain β-substituents, such as Z = Cl, OH, OR, OAc, $OCO_2R$, $NR_2$ and $NO_2$,[41] are likely to be transmitted to the allylic moiety, increasing the regioselectivity of the nucleophilic attack remote from these groups. This observed regioselectivity cannot be simply explained by the electron-withdrawing effects of the β-substituent Z (Scheme 11), since the electron deficiency is created at the more substituted terminus of the allyl moiety. This regioselectivity was explained by a

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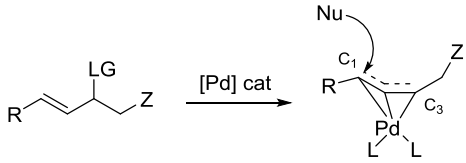
40 S. A. Godleski, Comprehensive Organic Synthesis, eds. B. M. Trost and I. Fleming, New York, vol. 4, ch. 3.3, **1991**.

41 (a) Szabo, K. J. *J. Am. Chem. Soc*. **1996**, *118*, 7818-7826. (b) Szabó, K. J. *Chem. Eur. J.* **1997**, *3*, 592-600. (c) Szabó, K. J.; Hupe, E.; Larsson, A. L. E. *Organometallics* **1997**, 16, 3779-3785. (d) Jonasson, C.; Kritikos, M.; Bäckvall, J.-E.; Szabó, K. J. *Chem. Eur. J*. **2000**, *6*, 432-436. (e) Szabó, K. J. *Chem. Soc. Rev.* **2001**, *30*, 136-143.

new type of σ-π electronic interactions between the β-substituent and the allyl-metal moiety as suggested by some theorical studies. Indeed, these interactions change the structure of the ($\eta^3$-allyl)palladium complex creating an asymmetric distortion of the allylmetal bond. The $C_3$-Pd bond becomes shorter than $C_1$-Pd bond enhancing the reactivity of the less substituted allyl terminus.[42,43,44]




LG = leaving group
Z = Cl, OH, OR, OAc, $OCO_2R$, $NR_2$, $NO_2$
R = Alkyl

**Scheme 11.** The β-Substituent Effects.

β-Silyl-substituted ($\eta^3$-allyl)palladium intermediates have also shown to undergo γ-regioselective nucleophilic substitution with malonates or enolates.[41]

Numerous examples are reported with cyclic or acyclic allylic substrates containing homoallylic free hydroxy,[45,46] ether,[47] acetate,[48,49] benzoate or carbonate and vinyl epoxides.[50] For examples, the use of cyclic or acyclic vinyl epoxide to formation of new C-C bond in high regioselectivity was efficiently

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42 Helmchen, G.; A. Pfaltz, A. *Acc. Chem. Res*., **2000**, *33*, 336-345.

43 Pfaltz, A. *Acc. Chem. Res*., **1993**, *26*, 339-345.

44 P. v. Matt, G. C. Lloyd-Jones, A. B. E. Minidis, A. Pfaltz, L. Macko, M. Neuburger, M. Zehnder, H. Rüegger and P. S. Pregosin, *Helv. Chim. Acta*, **1995**, *78*, 265-284.

45 Genet, J. P.; Balabane, M.; Legras, Y. *Tetrahedron Lett*. **1982**, *23*, 331-334.

46 Deardorff, D. R.; Linde, R. G.; Martin, A. M.; Shulman, M. J. *J. Org. Chem*. **1989**, *54*, 2759-2762.

47 Bäckvall, J. E.; Bystroem, S. E.; Nordberg, R. E. *J. Org. Chem*. **1984**, *49*, 4619-4631.

48 Bäeckvall, J. E. *Acc. Chem. Res*. **1983**, *16*, 335-342.

49 Chapsal, B. D.; Hua, Z.; Ojima, I. *Tetrahedron: Asymmetry* **2006**, *17*, 642-657.

50 Tsuda, T.; Horii, Y.; Nakagawa, Y.; Ishida, T.; Saegusa, T. *J. Org. Chem*. **1989**, *54*, 977-979.

applied to the synthesis of natural molecules such as prostaglandins,[51] side chains of steroids[52] or carbocyclic nucleosides.[53]

### I.3.1.2.3. Intramolecular directing group effect

Efficient approaches to direct the regioselectivity in the palladium-catalyzed allylic substitution reaction have been obtained using substrates capable of coordinating to the metal. Thus, for example Krafft's and Yoshida's groups reported that a regioselective addition to allylic acetates **18**, catalyzed by palladium, can be achieved by incorporation of a thioether or tertiary amine into the substrate in the homoallylic position.[54,5556] It was the first time when heteroatoms capable of coordinating to palladium could change or even reverse the expected regiochemical and stereochemical outcome. Reactions with the malonate anion proceed with high selectivity to provide the product **19** substituted at the terminus of the allyl moiety proximal to the heteroatom, even if that position is more substituted. The selectivity of the reaction is reversed with a homoallylic ether or when the number of methylene units between the heteroatom and the allylic moiety is increased. Potential explanations for the observed high regioselectivity in the presence of the homoallylic tertiary amine or thioether are illustrated in Scheme 12. One possible scenario uses the amine or sulfide as a coordinating group to bring the nucleophile, via coordination to the counterion, to the metal (Scheme 12). Then, the nucleophile could be directed to the metal center followed by reductive coupling of the two carbon ligands on the metal. The stereochemical outcome would be overall inversion of configuration.

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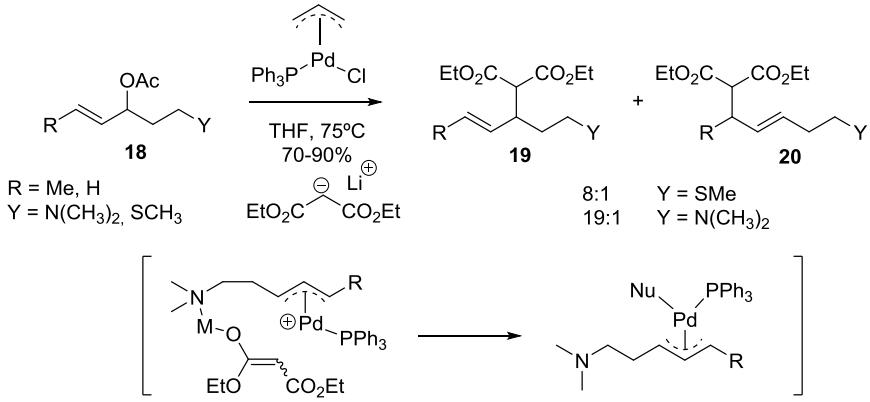
51 Takahashi, T.; Kataoka, H.; Tsuji, J. *J. Am. Chem. Soc*. **1983**, *105*, 147-149.

52 Takahashi, T.; Ootake, A.; Tsuji, J.; Tachibana, K. *Tetrahedron* **1985**, *41*, 5747-5754.

53 Peel, M. R.; Sternbach, D. D.; Johnson, M. R. *J. Org. Chem*. **1991**, *56*, 4990-4993.

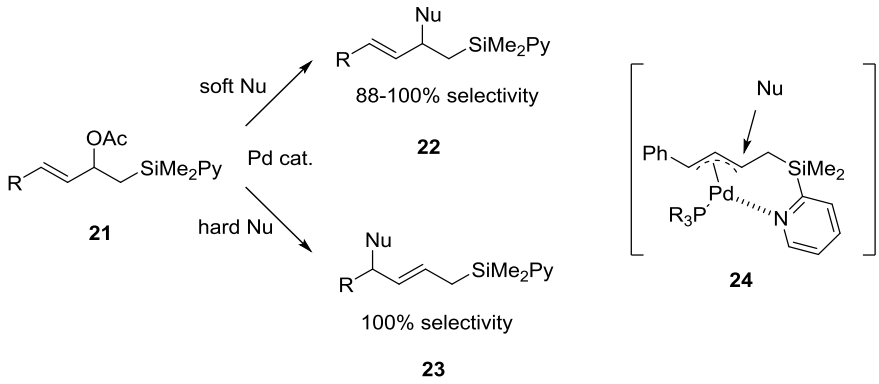
54 Krafft, M. E.; Wilson, A. M.; Fu, Z.; Procter, M. J.; Dasse, O. A. *J. Org. Chem*. **1998**, *63*, 1748-1749.

55 Krafft, M. E.; Fu, Z.; Procter, M. J.; Wilson, A. M.; Dasse, O. A.; Hirosawa, C. *Pure Appl. Chem.* **1998**, *70*, 1083-1090.




**Scheme 12.** Heteroatom-directed palladium-catalyzed allylation.

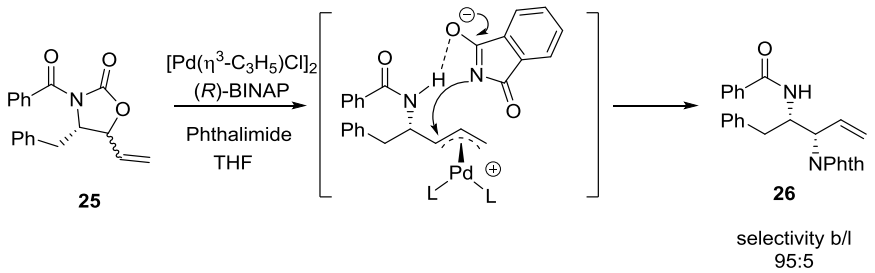
Another interesting example of an intramolecular directing group in palladium-catalyzed allylic alkylation was the 2-pyridyldimethylsilyl (2-PyMe$_2$Si) group which functions as the removable directing group for palladium-catalyzed regioselective allylic alkylation of allylic acetate **21** leading predominantly to **22**.[56] Moreover, it has been shown that the regioselectivity can be completely switched by the type of nucleophile used. The structural analysis of the (π-allyl)palladium complex revealed the distortion of the allyl ligand on palladium **24**, which might be the reason for unusual inner site-selective nucleophilic attack of soft carbon nucleophiles (Scheme 13).




**Scheme 13.** Heteroatom-directed palladium-catalyzed allylation.

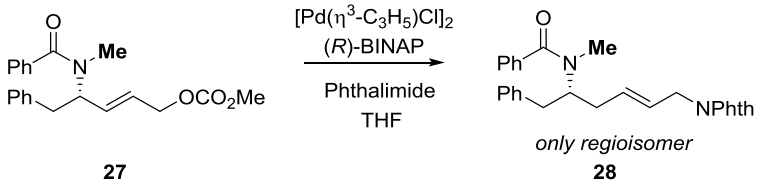
[56] Itami, K.; Koike, T.; Yoshida, J. I. *J. Am. Chem. Soc*. **2001**, *123*, 6957-6958.

Control of the regioselectivity by the substrate has also been observed by Cook and coworkers for the palladium-catalyzed allylic amination of 5-vinyloxazolidinones **25** with imide-type nucleophiles affording the branched product **26**, probably as a consequence of a hydrogen bond directing effect.[27b,57] The regioselectivity was influenced by the type of substrate, the solvents, and the nucleophile reflecting changes in the strength of the hydrogen bond. The use of the protic solvent ethanol induced reversal of the regioselectivity, supporting the hypothesis of a hydrogen bonding between the substrate and nucleophile.




**Scheme 14.** Hydrogen-bond directed palladium-catalyzed allylic substitution.

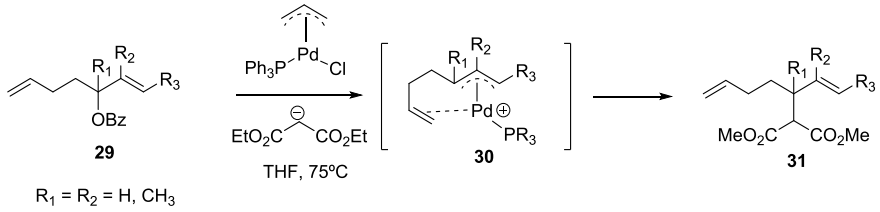
Evidence for direction of the nucleophile via hydrogen bonding was obtained by replacing the hydrogen of the amide with a methyl, resulting in the production of only the normally expected linear product **28** (Scheme 15).




**Scheme 15.** Evidence for direction of the nucleophile via hydrogen bonding.

57 Cook, G. R.; Shanker, P. S.; Pararajasingham, K. *Angew. Chem. Int. Ed.* **1999**, *38*, 110-113.

An unusual use of internal ring strain to drive regioselectivity has also been described. Using a tethered alkene as a nontraditional control element, regioselective addition to π-allyl Pd complexes is possible.[58,59] The directing effect overcomes the normal steric bias, and reaction can occur at the more substituted terminus of a monofunctionalized π-allyl moiety. X-ray diffraction analysis of the alkene-bound intermediate sheds light on the mechanism by providing structural evidence for alkene binding such in intermediate **30**. Thus, allylic benzoates **29** underwent allylation affording only isomers dienes **31** in very good yield (Scheme 16).




**Scheme 16.** Alkene-directed palladium-catalyzed allylation.

## I.3.2. Ligand effect

Over the last decades, an important number of types of ligands have been intensively synthesized and widely investigated. However, the vast majority of the studies published in the field of palladium-catalyzed allylic alkylation have been focused on asymmetric induction, while less attention has been paid to regioselectivity. With soft nucleophiles, the nucleophilic attack is usually produced in the less sterically hindered terminus of the allyl moiety. However, this preference can be overturned by the modification of the ligand associated to the allylpalladium complex and several noticeable achievements concerning the regioselectivity derived from the ligand effects will be discussed herein.

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58 Åkermark, B.; Vitagliano, A. *Organometallics* **1985**, *4*, 1275-1283.

59 Krafft, M. E.; Sugiura, M.; Abboud, K. A. *J. Am. Chem. Soc*. **2001**, *123*, 9174-9175.

## I.3.2.1. Steric and electronic effects of the ligand

Considering sterics, ligands with wider bite angle ($\beta_n$)[60] increasing steric hindrance at the palladium center tend to favor addition to the less substituted allyl terminus. However, it was found that the presence of substituents on one terminus of the allyl moiety distorted the symmetry of the terminal palladium-allyl bonds leading to a notable difference in bonding distance ($C_3$-Pd longer than $C_1$-Pd). As the bite angle increases, it results in more steric hindrance of the allyl moiety, leading to a more pronounced 1,2-type coordination instead of $\eta^3$-type (Figure 2). This distortion induced the favorable formation of the branched product in the nucleophilic attack. Moreover, as the back-bonding to the substituted site of the allyl moiety decreases with wider bite angle, electronic effects must also be taken into account.

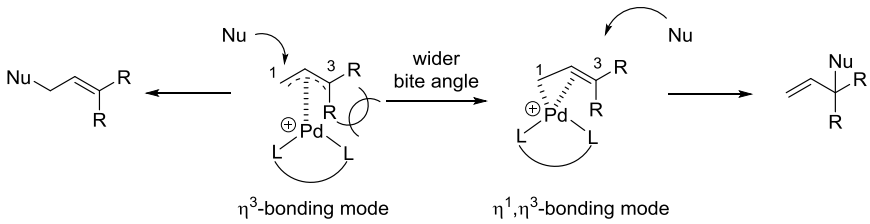


**Figure 2.** Steric effect of the ligand.

The application of ligands in the allylic alkylation reaction has a dual purpose, both the activation of the $\eta^3$-allyl for nucleophilic attack and control of the selectivity in the reaction. Considering electronics, good π-acid ligands increase the cationic character of the allyl through back-bonding[61] and consequently the rate of nucleophilic attack is increased.[62] The increased cationic character makes more stable the substituted allyl terminus and directs nucleophilic addition to that position (path C in Scheme 17). This effect was

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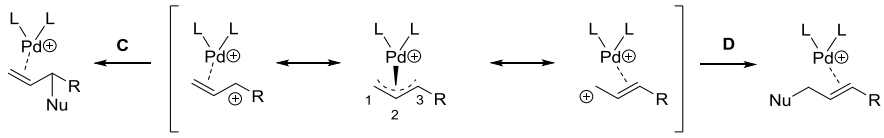
60 The natural bite angle ($\beta_n$) of a bidentate ligand is defined as the preferred chelation angle determined only by ligand backbone constraints

61 Crabtree, R., H. The Organometallic Chemistry of the Transition Metals, John Wiley & Sons, Inc., Hoboken, New Jersey, **2005**.

62 Åkermark, B.; Krakenberger, B.; Hansson, S.; Vitagliano, A. *Organometallics* **1987**, *6*, 620-628.

observed by $^{13}C$ NMR spectroscopy where the $C_3$ is always observed downfield than the $C_1$. In contrast, reactions involving σ-donating ligands promote addition at the less substituted terminus (path D in Scheme 17). The influence from the ligand arises from the bonding via a free electron pair on the ligand to the metal (σ-donation), and the back donation from the metal to the ligand (π-accepting).




**Scheme 17.** Electronic effects of the ligand.

## I.3.2.3. Chiral ligands

As for many other palladium catalyzed reactions, considerable effort has been made in the area of ligand design to afford the desired regio- and stereoselectivity in the asymmetric allylic alkylation reactions.[2,22,63,64,65] Many of the bidentate ligands used in the reaction induce selectivity by both steric and electronic effects. Initially, chiral bidentate phosphines which proved to be so efficient in enantioselective hydrogenation reactions were used as ligands in Pd-AAA reactions. Although high *ee* could be obtained in certain cases, e.g. with the well known $C_2$-symmetric BINAP ligand developed by Noyori et *al*.,[66] the scope of standard diphosphines in allylic substitution seems limited. Indeed, for soft nucleophiles, the nucleophilic addition to the allyl system is taking place outside the coordination sphere and, therefore, cannot be directly controlled by the chiral ligand.

Hayashi et *al*. found a solution to this problem by synthesizing a bifunctional ligand system **L1**. They postulated that the side chain could reach over the allyl system and could interact with the nucleophile by hydrogen bonding, hence, directing nucleophilic attack. This ligand has been used in the

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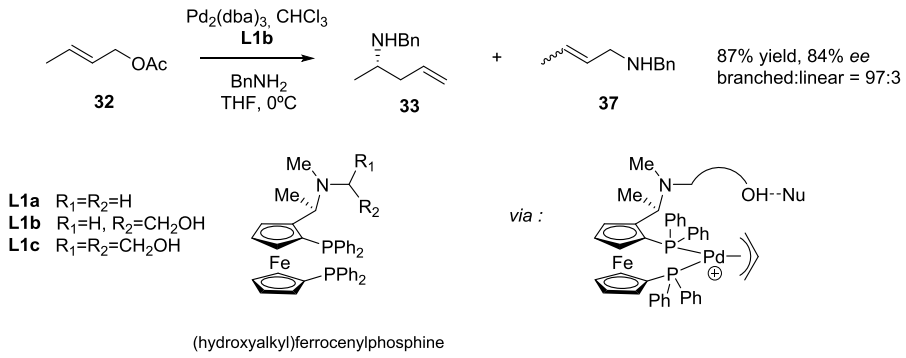
63 Review on P,N-ligands: Guiry, P.; Saunders, C. P. *Adv. Synth. Catal*. **2004**, *346*, 497-537.

64 Review on S,L-ligands: Martin, E.; Diéguez, M. C. *R. Chimie* **2007**, *10*, 188-205.

65 Trost, B. M.; Van Vranken D. L. *Chem. Rev*. **1996**, *96*, 395-422 , and references therein.

66 Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 7932-7934.

asymmetric allylic amination of 2-butenyl acetate **32** with benzylamine (Scheme 18).[26e, 67] The nucleophilic attack occurred selectively at the more substituted position leading to optically active 3-benzyl-amino-1-butene **33** of up to 84% *ee*.




**Scheme 18.** Pd-catalyzed amination of 2-butenyl acetate **32** with benzylamine using **L1**.

Trost's ligands are undoubtedly the most successful in asymmetric allylic substitution reaction. Most of the total synthesis applications using a chiral ligand use $C_2$-symmetric Trost modular ligand **(**TML**)** developed by Trost et *al*. These ligands are derived from chiral diamines and 2-(diphenylphosphino)benzoic acids (DPPBA) (Figure 3).

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[67] (a) Hayashi, T. *Pure & Appl. Chem.*, **1988**, *60*, 7-12. (b) Hayashi, T.; Kishi, K.; Yamamoto, A.; Ito, Y. *Tetrahedron Lett.* **1990**, *31*, 1743-1746.

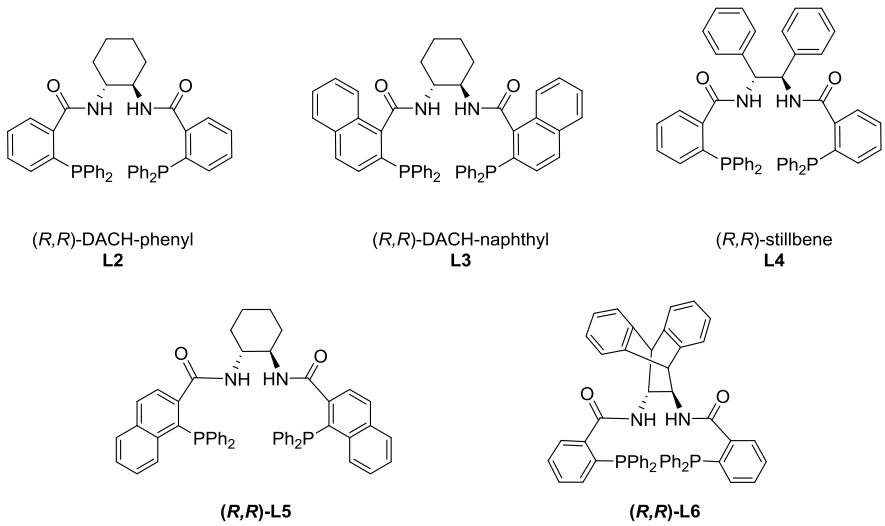



**Figure 3.** Chiral ligands developed by Trost for asymmetric allylic transformations.

The concept of Trost was to increase the bite angle and, as a consequence, create a tight chiral cavity in which the allyl system is embedded. In this case, *trans*-1,2-diaminocyclohexanone is used as a chiral scaffold to induce a specific chiral arrangement of the four P-phenyl groups which are positioned very close to the coordination sites *trans* to the P atoms. Based on molecular modeling and X-ray structural data, Trost and coworkers have devised a cartoon model of the chiral pocket around the allyl ligand for a mnemonic that can be used to predict both regio- and enantioselectivity. The model depicts the more reactive and probably the more stable π-allylpalladium complex. In this model, the walls represent the chiral space created by the propeller-like array of the phenyl rings; the raised flaps represent the phenyls which lie in a plane approximately parallel to the allyl, while the lowered flaps represent phenyls which are somewhat perpendicular to the allyl. Minimizing any steric interactions between the approaching nucleophile and the chiral ligand also directs it to approach from the front left quadrant. While the cartoon depicts the ligand in a $C_2$-symmetric fashion in the allyl complex, the existing structural data

suggest that it does not coordinate in a $C_2$-symmetric manner.[68] The cartoon thus considers only a time-averaged monomeric species in which the ligand coordinates in a $C_2$-symmetric manner.

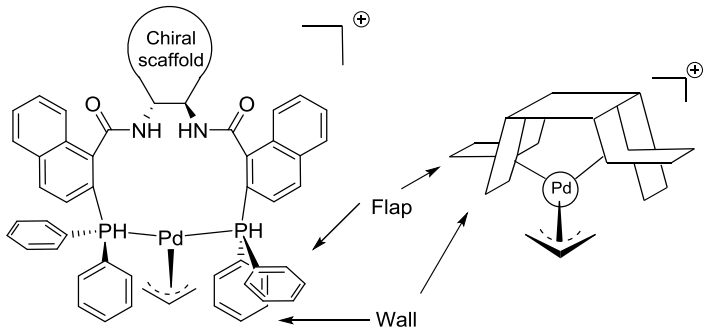



**Figure 4.** Cartoon model to describe the Pd-ligand complex.

Although investigation on the structural features of this system had been precluded by the difficulty to avoid oligomeric species, a very accurate work published in 2009 by Lloyd-Jones and Norrby [69] based on NMR studies, isotopic labeling and computational studies, gave a deeper insight of the key events that occur in the Pd-AAA. In addition to the steric interactions due to the phenyl groups, these authors identified that a hydrogen-bond interaction of one N-H unit in Pd/(*R,R*)-**L2** can substantially accelerate both ionization and nucleophilic attack.The amide bond contained in the chiral ligand facilated pro-*S* delivery of the nucleophile, whereas pro-*R* delivery can be facilitated by an escort counterion $M^+$ binding to the carbonyl of the other amide unit. Thus, selectivity in nucleophilic attack depends identity of escort ion $M^+$, counterion $X^-$, and availability of a hydrogen bond acceptor, in a 1,3-relationship to the nucleophilic site (e.g., malonate, phathalimide, carboxylate, carbonate, etc.). Consequently, both the regio- and stereochemical outcome of the process are influenced (Figure

[68] Lloyd-Jones, G. C.; Stephen, S. C.; Fairlamb, I. J. S.; Martorell, A.; Dominguez, B.; Tomlin, P. M.; Murray, M.; Fernandez, J. M.; Jeffery, J. C.; Riis-Johannessen, T.; Guerziz, T. *Pure. Appl. Chem*. **2004**, *76*, 589-601.

[69] Butts, C.P.; Filali, E.; Lloyd-Jones, G.C.; Norrby, P.-O.; Sale, D.A.; Scramm, Y. *J. Am. Chem. Soc*. **2009**, *131*, 9945-9957

5). This conclusion opens up the possibility for further development of this reaction including design of new ligands.

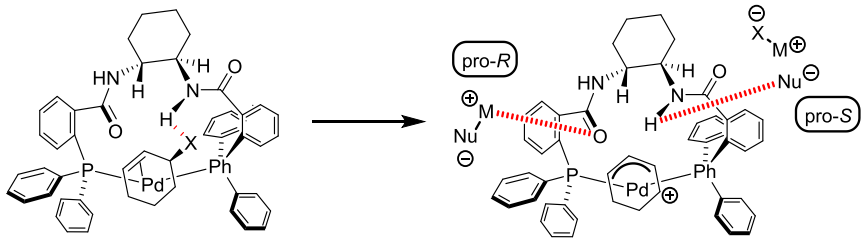
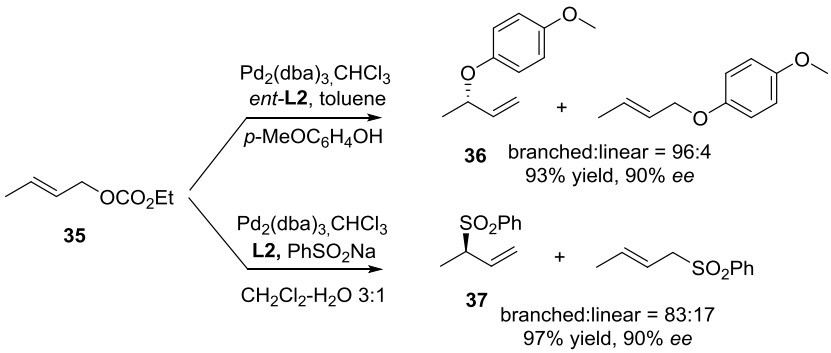



**Figure 5.** Model for ionization in the Pd/(*R*,*R*)-DACH phenyl ligand **L2**-catalyzed reaction of cyclohexenyl esters with nucleophiles; Pro-*S* and pro-*R* nucleophile delivery.

These diphosphine ligands are the most versatile ligands for Pd-catalyzed allylic alkylation available today and have been used with excellent selectivity for many classes of substrates including geminal diacetate, *meso*-substrates, and cycloalkenyl esters. For example, this catalytic system has been used in the preparation of branched allyl aryl ether and branched allyl sulfones. Indeed, with the catalytic system containing ligand ***ent*-L2**, the allylation of *p*-methoxyphenol with (*E*)-crotyl carbonate **35** produced ether **36** with 90% *ee* and a high regioselectivity. With benzenesulfinate as the nucleophile, the reaction also led to the branched regioisomer **37** although with slightly lower regioselectivity.[70]




**Scheme 19.** Allylation of (*E*)-crotyl carbonate **35** using Trost ligand**.**

[70] Trost, B. M.; Krische, M. J.; Radinov, R.; Zanoni, G. *J. Am. Chem. Soc*. **1996**, *118*, 6297-6298.

Vinyl epoxides show a very marked propensity to give 1,4-addition products in Pd-AA with carbon nucleophiles in the presence of an achiral phosphine, which appears to be lower for amines. In case of the former, this could be attributed to the electronic effect of the epoxide oxygen, which directs the attack of the carbanion at the remote side of the allyl termini.[11,71] Asymmetric palladium-catalyzed allylic amination of vinylepoxide, however, leads to the 1,2-adduct in excellent regio- and enantioselectivities using the family of Trost ligand (Figure 3) and with various soft nucleophiles. One example is presented in Scheme 26 and discussed in more details.

It has long been recognized that ligands on Pd can influence the regioselectivity of nucleophilic attack as we have just discussed above. In particular, the large trans effect of phosphorus will enhance reactivity on the allylic terminus *trans* to any phosphine.[72] This phenomenon was utilized in a breakthrough in asymmetric allylic alkylation in the early 1990s, when the research groups of Pfaltz, Helmchen, and Williams independently introduced the phosphino-oxazoline class of ligands now known as PHOX.[20,73] In contrast to allyl complexes with C2-symmetric ligands, complexation of the metal by P,N-ligands results in electronic discrimination of the two allylic termini. This can be explained in terms of orbital overlap, where the ligands in *trans* positions are coordinated to the metal via one common metal orbital. The more strongly one of the ligands binds to the metal, the weaker the bond to the other ligand becomes.[74,75] In these types of hard-soft heterodonor ligands, the steric bulk directs the position of the substrate with respect to the chiral scaffold and thereafter the donor atom with the largest *trans* effect is believed to direct the attack of the nucleophile. For example, special ligands and catalysts have been developed for allylic substitution with 1- or 3-monosubstituted allyl substrates

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71 (a) Trost, B.M.; Cossy, J. *J. Am. Chem. Soc*. **1982**, *104*, 6881-6882; (b) Trost, B.M.; Chen, S.-F. *J. Am. Chem. Soc*. **1986**, *108*, 6053-6054. (c) Trost, B.M.; Kuo, G.-H.; Benneche, T. *J. Am. Chem. Soc*. **1988**, *110*, 621-622

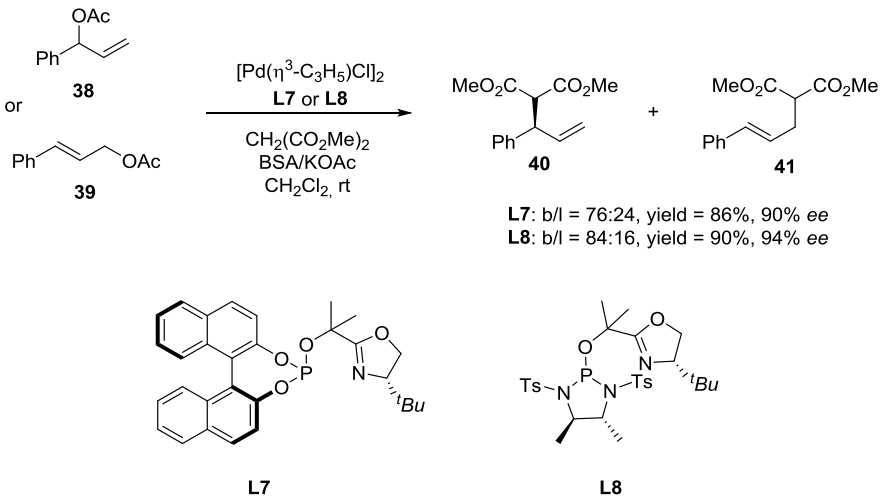
72 Åkermark, B.; Zetterberg, K.; Hansson, S.; Krakenberger, B.; Vitagliano, A. *J. Organomet. Chem*. **1987**, *335*, 133-142.

73 (a) Sprinz, J.; Helmchen, G. *Tetrahedron Lett*. **1993**, *34*, 1769-1773. (b) Allen, J. V.; Coote, S. J.; Dawson, G. J.; Frost, C. G.; Martin, C. J.; Williams, J. M. J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2065-2072.

74 Coe, B. J.; Glenwright, S. J. *Coord. Chem. Rev*. **2000**, *203*, 5-80.

75 Bäcktorp, C.; Norrby, P.-O. *J. Mol.Cat.A*, **2010**, *328*, 108-113.

such as 1- or 3-phenylallyl acetate **38** and **39** (Scheme 20). Normally, most of Pd-catalysts afford mainly the achiral linear **41** product with this kind of substrate. However, in presence of ligands **L7** and **L8**, the opposite regioselectivity was observed, and the chiral branched isomer **40** was obtained as the major isomer of up to 94% *ee*.[42,76]




**Scheme 20.** Allylic substitution of **38** and **39** using chiral ligand developed by Pfaltz et *al.*

The regioselectivity was explained by two factors. Firstly, the phosphite is less electron donating than a phosphine group, inducing a more electrophilic Pd center which should enhance the cationic character of the transition state and thus, facilitate nucleophilic attack at the more substituted allyl terminus. The mechanism of the nucleophilic substitution shifts from a $S_N2$-type to a more cationic $S_N1$-type. Secondly, the hindered binaphthyl system forces the substituted end of the allyl ligand to the less hindered position *trans* to the phosphite group. In this geometry, nucleophilic addition occurred at the substituted terminus for electronic reasons (*trans* to Pd-P bond).

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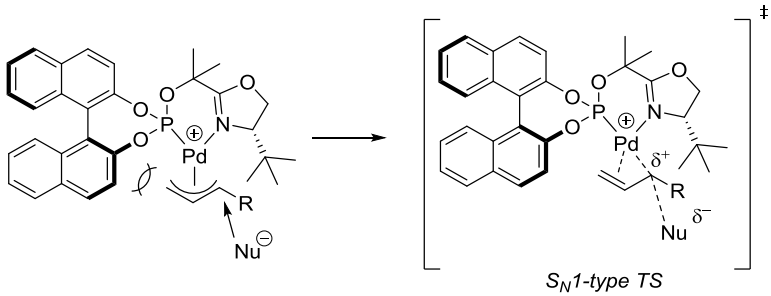
[76] Prétôt, R.; Pfaltz, A. *Angew. Chem., Int. Ed*. **1998**, *37*, 323-325




**Scheme 21.** Shifts from a $S_N2$-type to a more cationic $S_N1$-type mechanism with phosphite-type P,N ligand.

Several other groups developed bidentate ligands with two different coordinating heteroatoms,[2,77] mostly phosphorus and nitrogen, but also, for example, sulfur.[78]

One of these sulfur-containing ligands is BINAP(S), which was used in palladium-catalyzed allylic amination reaction of unsymmetrical substrates such as methyl-monosubstituted allylic carbonates **42**.[79,80,81,82,83] The reaction proceeded with very high regioselectivity in favor of branched isomer **43** although modest enantioselectivities were obtained (Scheme 22).

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77 Lu, Z.; Ma, S. *Angew Chem., Int. Ed*. **2008**, *47*, 258-297.

78 (a) Pellissier, H. *Chiral Sulfur Ligands: Asymmetric Catalysis*; RSC: Cambridge, **2009**. (b) Evans, D. A.; Campos, K. R.; Tedrow, J. S.; Michael, F. E.; Gagné, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 7905-7920.

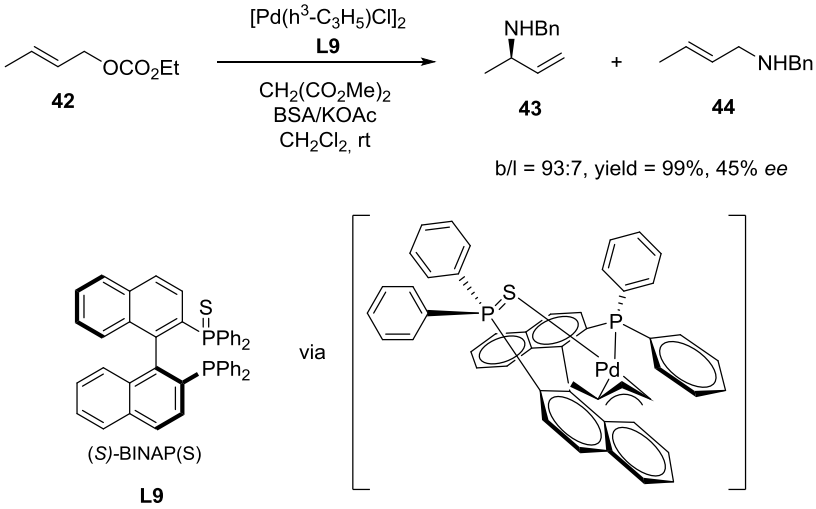
79 Faller, J. W.; Wilt, J. C.; Parr, J. *Org. Lett*. **2004**, *6*, 1301-1304.

80 Selvakumar, K.; Valentini, M.; Pregosin, P. S.; Albinati, A. *Organometallics* **1999**, *18*, 4591-4597.

81 Evans, D. A.; Campos, K. R.; Tedrow, J. S.; Michael, F. E.; Gagne, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 7905-7920.

82 Evans, D. A.; Campos, K. R.; Tedrow, J. S.; Michael, F. E.; Gagne, M. R. *J. Org. Chem.* **1999**, *64*, 2994-2995.

83 Albinati, A.; Pregosin, P. S.; Wick, K. *Organometallics* **1996**, *15*, 2419-2421




**Scheme 22.** Allylic substitution of methyl-monosubstituted allylic carbonates **42** using BINAP(S) as chiral ligand.

In spite of the intense interest in reversing the preferred regioselectivity in the Pd-catalyzed allylic substitution of non-symmetric monosubstituted allylic substrates to favor branched products, the regioselectivity in palladium-catalyzed allylic substitution reaction remains a challenge.

As discussed above, several factors can determine the regiochemical outcome of the addition of soft nucleophiles on π-allylpalladium complexes. Steric and electronic properties of both substrate and catalyst are the two mains factors that dictate the regioselectivity. Steric properties tend to favor the nucleophilic attack to the less substituted allyl terminus and can be generated by the size of the ligand, the steric environement of the allyl moiety and the size of the nucleophile. In contrast, electronic factors tend to help the nucleophilic attack at the more substituted electropositive carbon. Electronic factors in both the substrate and the ligand are able to induce a reversion in the expected regioselectivity, in favor of the branched isomer. Moreover, the nature of the leaving group, the solvent, the presence of additives and little changes in reaction conditions are able to affect the regioselectivity. Above, we have selected different examples that appeared to us to be the most relevant ones.

## I.4. Enantioselectivity

Each step of the AAA catalytic cycle shown in Scheme 2 offers the possibility of controlling absolute stereochemistry. Therefore, several mechanisms for enantiodiscrimination are available in transition-metal-catalyzed AAA reactions. These steps are (a) metal-olefin complexation, (b) ionization, (c) enantioface discrimination of the π-allyl complex, (d) nucleophilic attack at enantiotopic termini, and (e) enantioface discrimination in the nucleophile. The final decomplexation of the metal from the olefinic product cannot change the stereochemistry of the product.

### I.4.1 Metal-olefin complexation as enantiodiscrimination

In many other catalytic asymmetric reactions, differentiation of enantiotopic olefin faces is an operative mechanism of enantioselection. When the olefin is not symmetrically substituted, the metal-ligand complex must distinguish between the two prochiral faces of the olefin. In the first olefin complexation step (Scheme 2), if the rate of ionization of one complex is faster than the other one and nucleophilic attack of that diastereoisomer is faster than π-σ-π isomerization, then enantiotopic olefin face complexation becomes the enantiodetermining step (Scheme 23). The AAA reaction of methyl crotyl carbonate (**45**) with *p*-methoxyphenol (PMP) represents an example of this type of enantiodiscrimination.[84] $Bu_4NCl$ is known to increase the rate of π-σ-π interconversion of the π-allyl Pd-complexes.[85] The fact that addition of 30 mol% of $Bu_4NCl$ reduced the *ee* suggests that enantiotopic face coordination is the enantiodetermining event. The use of a less polar solvent such as toluene increased the enantioselectivity.

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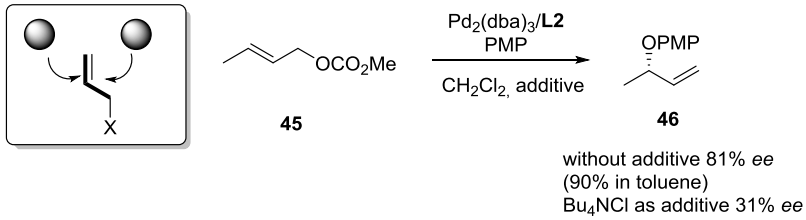
84 Trost, B.M; Crawley, M. L. *Chem. Eur. J.*, **2004**, *10*, 2237-2252.

85 (a) Crociani, B.; Di Biana, F.; Giovenco, A.; Boschi, T. *Inorg. Chim. Acta*, **1987**, 127, 169-182. (b) Trost, B.M; Toste, F. D. *J. Am. Chem. Soc*., **1999**, *121*, 4545-4554.

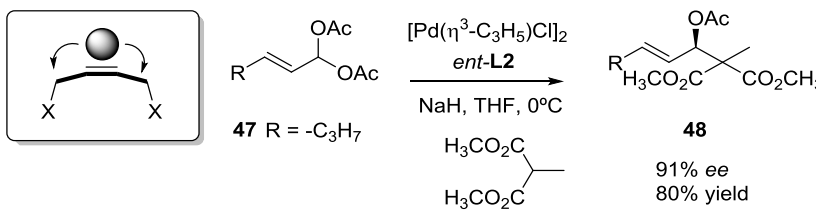



**Scheme 23.** Metal-olefin complexation as enantiodiscrimination process.

## I.4.2. Enantiotopic ionization of leaving groups

Selective ionization of enantiotopic leaving groups has been widely used in total synthesis to induce specific stereochemistry during substitution. There are two types of electrophiles for this mechanistic class: *meso*-1,1-diacyloxy-2-alkenes or an achiral gem-disubstituted allylic substrate. As there are two potential leaving groups on a *meso* or on an achiral gem-disubstituted system, the catalyst has to differentiate two enantiotopic leaving groups in the ionization step. For this kind of enantiodiscrimination, the rate of equilibration of diastereomeric π-allylpalladium complexes must be slower than the rate of nucleophilic addition. Hence, increasing the rate of trapping of the initially formed allyl complex leads to higher enantioselectivity.

One example is the reaction of gem-diacetate **47** with sodium salt of methylmalonate, affording **48** in high yield and excellent enantioselectivity (Scheme 24).[86]




**Scheme 24.** Enantiotopic ionization of leaving groups.

[86] Trost, B. M.; Lee, C. B. *J. Am. Chem. Soc*. **2001**, *123*, 3671-3686.

In this event, the catalyst differentiates between both the prochiral leaving groups and the π faces of the olefin. Ionization of the two prochiral substrates could lead to different complexes; *syn,anti* and *syn,syn* complexes where the latter one is preferred. Then nucleophilic attack onto this diastereomer gave **48** in excellent *ee*.

## I.4.3. Enantiofacial exchange of the ($\eta^3$-allyl)Pd complex

If the diastereomeric π-allylmetal intermediates interconvert faster than nucleophilic attack therefore under Curtin-Hammett conditions (Figure 6) or if the initial olefin coordination is rapid and reversible, then enantiotopic olefin face coordination or enantiotopic ionization are not the enantioselection step in an AAA reaction.

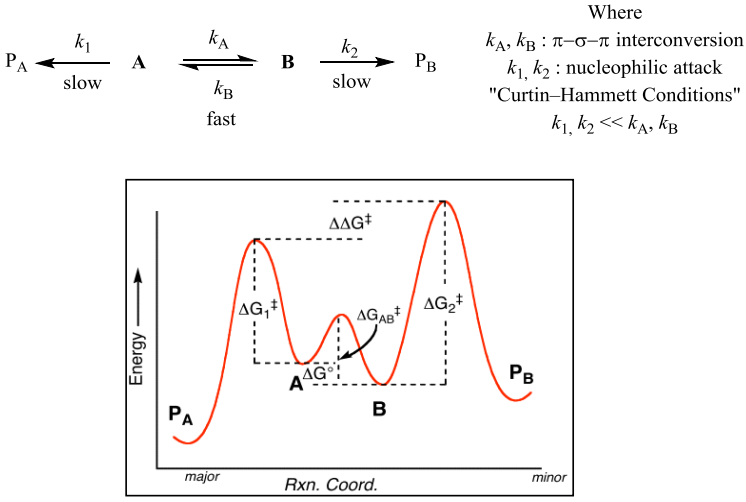
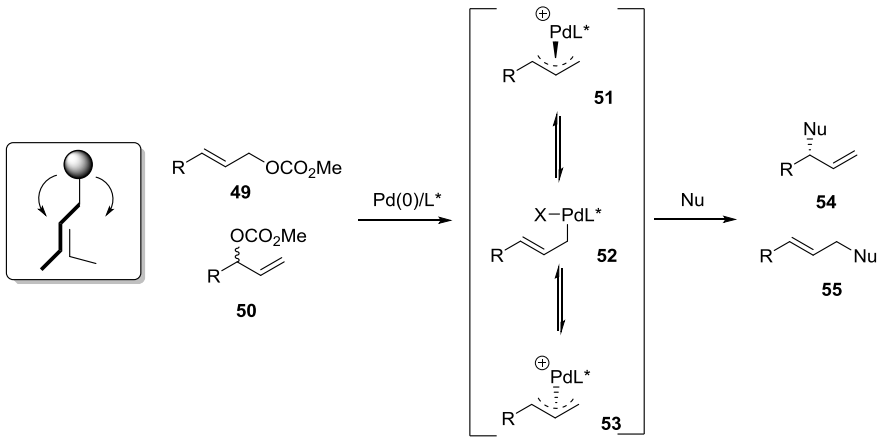



**Figure 6.** Curtin-Hammet principle.

In this type of process, there are several issues that complicate the picture in function of the starting allylic substrate. Not only enantioselectivity but regioselectivity of nucleophilic addition have to be considered with an achiral allylic ester and with a chiral racemic ester. In the reaction depicted in Scheme 25, with linear allylic carbonate **49**, two diastereomeric Pd-complexes (**51** vs. **53**) can be formed after ionization. These two diastereomeric complexes can interconvert through π-σ-π equilibration involving the terminal carbon of the allyl

system. If the more abundant (assuming similar rates of nucleophilic attack) or the more reactive diastereomeric π-allyl complex leads to the product, then high enantioselectivity will be observed assuming that every intermediates gives complementary regioselectivity. In the reaction with the chiral racemic allylic cabonate **50**, the same type of equilibration occurs but in this case a 1:1 mixture of diastereomeric intermediate palladium complexes is initially formed. This constitutes a dynamic kinetic asymmetric transformation (DYKAT). In most cases, the resultant enantiomerically enriched product is structurally different than the starting material and, thus the process is more properly termed an asymmetric transformation rather than a resolution. DYKAT reactions differ from traditional kinetic asymmetric reactions in that both enantiomers of the racemic starting material are converted into a single chiral product. Thus, this allows potential yields of 100% of a particular enantiomer as opposed to only 50 % for a traditional kinetic resolution process.




**Scheme 25.** Enantioselection by discrimination of the π-allyl intermediates.

An example of this class of enantioinduction is the DYKAT of butadiene monoepoxide (**54**) which has been efficiently employed by Trost and co-workers in various total syntheses.[87] C-, O-, as well as *N*-nucleophiles can be used in this transformation. For instance, using phthalimide as a soft nucleophile, with the

[87] Trost, B. M.; Machacek, M. R.; Aponick, A. *Acc. Chem. Res.* **2006**, *39*, 747-760 and references therein.

family of diphenylphosphino benzoic acid-derived ligands developed by Trost, racemic butadiene monoepoxide is readily transformed into a single enantiomer in very good yield.[88] Using the cartoon model developed by Trost, both the regio- and enantioselectivity are rationalized. Indeed, with (*R*,*R*)-Trost ligand **L3**, **(*R*)-54** will ionize via a mismatched pathway to afford **55a**, while **(*S*)-54** undergoes a matched ionization to give **55b** (Scheme 26). The intermediates **55a** and **55b** can readily interconvert by a π-σ-π mechanism on the monosubstituted allyl terminus, a Curtin-Hammett situation being set up in which the more reactive π-allylpalladium complex leads selectively to the product. Phthalimide is directed to react at the more substituted carbon by hydrogen bonding. Nucleophilic approach via **55b** is favored and yields the branched product in 98% *ee*.

However, the use of harder nucleophiles such as alkylamines in the palladium-catalyzed allylic amination still poses a challenge and has not been reported probably because of their low ability for hydrogen bonding involving the amino protons but also due to the faster nucleophilic attack that prevents π-σ-π-isomerization. Pronucleophiles such as alcohols (regiodirected by boron), imides and carbon-nucleophiles such as β-ketoesters, have been employed with success.

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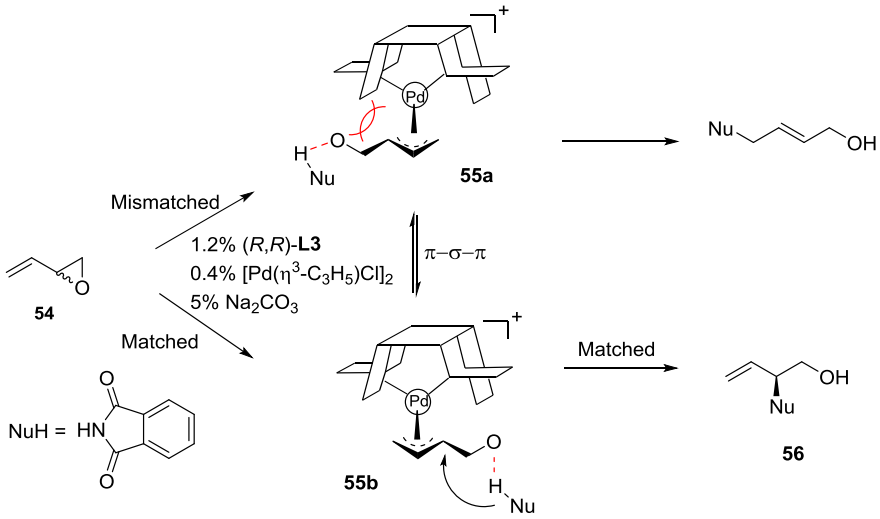
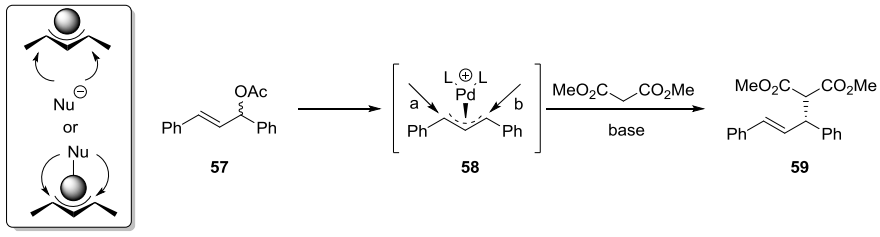
[88] (a) Trost, B. M.; Horne, D. B.; Woltering, M. J. *Angew. Chem. Int, Ed.* **2003**, *42*, 5987-5990. (b) Harris, M. C. J.; Jackson, M.; Lennon, I. C.; Ramsden, J. A.; Samuel, H. *Tetrahedron Lett.* **2000**, *41*, 3187-3191. (c) Trost, B. M.; O'Boyle, B. M. *Org. Lett.* **2008**, *10*, 1369-1372. (d) Trost, B. M.; Lemoine, R. C. *Tetrahedron* **1996**, *37*, 9161-9164.




**Scheme 26.** DYKAT of **54** using phthalimide as nucleophile.

## I.4.4. Enantiotopic allyl termini differentiation

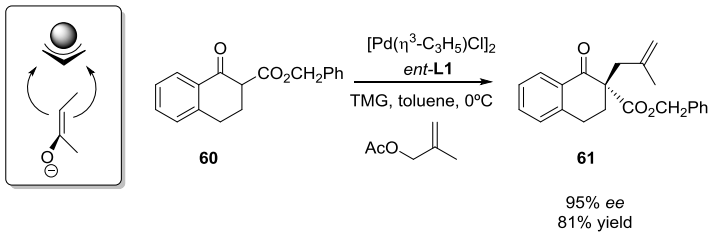
If a chiral allylic substrate generates a *meso* π-allyl intermediate after ionization, then the two allylic termini of the complex are enantiotopic and regioselective addition controlled by the ligand to one of the enantiotopic positions is the enantiodetermining step. The most extensively studied example of such a system is 1,3-diphenylallyl acetate **57**, which on ionization creates a *meso* π-allyl ligand **58**. When a chiral catalyst is employed, one terminus of the π-allyl ligand of **58** can be preferentially attacked by the nucleophile (path a or path b) to afford one enantiomer of product **59** (Scheme 27).




**Scheme 27.** Enantiotopic allyl termini differentiation.

## I.4.5. Prochiral nucleophile face differentiation

There is another way to induce enantioselection, it is the case when the π-allyl-ligand complex can differentiate between the prochiral faces of the nucleophile. This kind of asymmetry appears to be quite challenging. The use of ligands that can impose a good enough chiral environment around prochiral nucleophiles, such as salts of β-diketones and β-diesters, can overcome these demands and give excellent enantioselectivity with allyl acetates. An example of this type of enantiodiscrimination is the alkylation of tetralone **60** with 1-acetoxy-2-methyl-2-propene, to give the quaternary-substituted adduct **61** in high yield and excellent *ee* (Scheme 28).[2]




**Scheme 28.** Prochiral nucleophile face differentiation.

## II. Asymmetric allylic substitution reactions with other transition-metal catalysts

Transition metal-catalyzed asymmetric allylic alkylation reactions have proven to be extremely useful and versatile synthetic transformations. Their enantioselective reactions have witnessed wide applications in the synthesis of numerous pharmaceutical and natural products.[2] Other transition metals than palladium have been applied for this C-C or C-heteroatom coupling reaction, including: iridium,[23,89] iron,[23,90] nickel,[91] ruthenium,[23] rhodium,[23] molybdenum[23,92] and tungsten.[23,93] However, as we have discussed above, unsymmetrical allylic substrates, which form an unsymmetrical π-allyl-complex upon oxidative addition, in the presence of palladium catalyst preferentially lead to achiral linear substitution products. Only in very few cases, the introduction of special ligands or substrates could deliver good levels of both regio- and enantioselectivity.

Rhodium-catalysts have been reported to give excellent level of regioselectivity, although the number of catalytic enantioselective studies is very limited.[80] The air-sensitivity of W- and Mo-catalysts also limited their applications despite their excellent performance in selective allylations of unsymmetrical allylic substrates. In contrast to all the above-mentioned transition metal catalysts, chiral Ir-complexes have been demonstrated to be highly efficient catalysts for regio- and enantioselective allylic substitutions of linear monosubstituted electrophiles. Since the first Ir-catalyzed allylations by Takeuchi

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89 For selected publications see: a) Ohmura, T.; Hartwig, J. F. *J. Am. Chem. Soc*. **2002**, *124*, 15164-15165. b) Takeuchi, R.; Tanabe, K.; Yamashita, K.; Shiga, N. *J. Am. Chem. Soc*. **2001**, *123*, 9525-9534. c) Kiener, C. A.; Shu, C. T.; Incarvito, C.; Hartwig, J. F. *J. Am. Chem. Soc*. **2003**, *125*, 14272-14273. d) Janssen, J. P.; Helmchen, G. *Tetrahedron Lett*. **1997**, *38*, 8025-8026. e) Garcia-Yebra, C.; Janssen, J. P.; Rominger, F.; Helmchen G. *Organometallics* **2004**, *23*, 5459-5-470. f) Lipowsky, G.; Miller, N.; Helmchen G. *Angew. Chem., Int. Ed*. **2004**, *43*, 4595-4597.

90 (a) Plietker, B. *Angew. Chem. Int. Ed*. **2006**, *45*, 1469-1473. (b) Plietker B. *Angew. Chem. Int. Ed*. **2006**, *45*, 6053-6056.

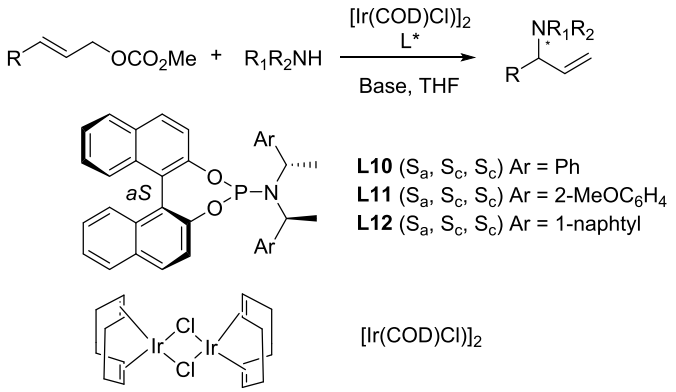
91 (a) Yatsumonji, Y.; Ishida, Y.; Tsubouchi, A.; Takeda, T. *Org. Lett* **2007**, *9*, 4603-4606. (b) Didiuk M.T., Morken J.P., Hoveyda A.H. *J. Am. Chem. Soc*. **1995**, *117*, 7273-7274.

92 Trost, B. M.; Lautens, M. *J. Am. Chem. Soc*. **1982**, *104*, 55435545.

93 Lloyd-Jones, G.C.; Pfaltz A. *Angew. Chem. Int. Ed*. **1995**, *34*, 462-464.

et *al.*[94] and its enantioselective version by Helmchen et *al.*[95] in 1997, many efforts have been made from various research groups, expanding the scope of this reaction. The Hartwig group have extensively studied the mechanistic aspect of this reaction leading to the identification of the active catalysts that further broaden the reaction types. The invariably high regio- and enantioselectivity with predictable product configuration of Ir-catalyzed allylic substitutions makes them extremely attractive in organic synthesis.

For example, Hartwig and co-workers achieved high enantioselectivities (95-99 % *ee*'s) with high branched-to-linear ratios (> 10 : 1) by using a phosphoramidite ligand **L10-12** in iridium-catalyzed allylic amination with monosubstituted allylic carbonates as starting materials.[96, 97, 98] The nucleophile scope is very general, including aromatic and aliphatic primary amines as well as cyclic and acyclic aliphatic secondary amines.




**Scheme 29.** Phosphoramiditesligands used in Iridium-catalyzed allylic amination reaction.

The mechanism for iridium-catalyzed allylic amination was identified by Kiener *et al.* and differs from palladium catalyst.[89]

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94 Takeuchi, R.; Kashio, M. *Angew. Chem. Int. Ed*. **1997**, *36*, 263-265.

95 Janssen, J.P.; Helmchen G. *Tetrahedron Lett*. **1997**, *38*, 8025-8026.

96 Polet, D.; Alexakis, A.; Tissot-Croset, K.; Corminboeuf, C.; Ditrich, K. *Chem. Eur. J.* **2006**, *12*, 3596-3609.

97 Tissot-Croset, K.; Polet, D.; Alexakis, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 2426-2428.

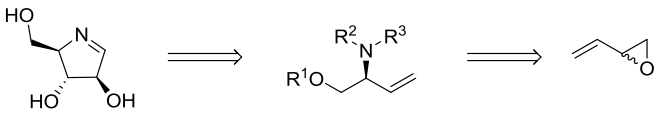
98 Shu, C.; Leitner, A.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2004**, *43*, 4797-4800

# CHAPTER 2

*Objectives*

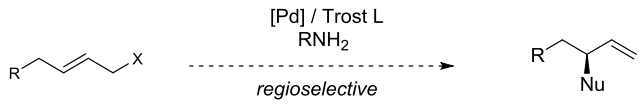
As mentioned in the general introduction, palladium-catalyzed asymmetric allylic alkylation reaction are among the most versatile methods for C-X bond formation widely applied in natural product synthesis. Our research group has acquired an important background in this reaction, and a general objective of this PhD work is to apply it to the synthesis of different natural products and analogues thereof, as well as to broaden the scope of the reaction to new substrates and new nucleophiles. In connection with this purpose, the specific objectives of this thesis are the following:

1. *Enantioselective synthesis of nectrisine*: The work presented in this section has as a final objective the enantioselective synthesis of nectrisine starting from the key synthon allylamine prepared through an palladium-catalyzed Dynamic Kinetic Asymmetric Transformation (DYKAT) of racemic vinyloxirane using imido nucleophiles.



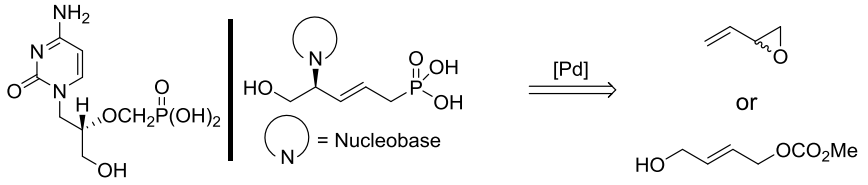

**Nectrisine**

2. *Enantioselective formal synthesis of D-fagomine*: Aiming to explore the synthesis of **2** from **1** using palladium catalysts, and taking into account the role of DACH Trost ligands in the control of the regioselectivity, we wondered whether structural elements in the substrate able to provide hydrogen bonding could bias the regiochemistry of palladium-catalyzed allylic amination of allylic electrophile to afford branched derivatives. As an extension of this methodologic work, we sought to apply this protocol to a short enantioselective formal synthesis of D-fagomine, an iminosugar that shows activity against mammalian gut α-glucosidase and β-galactosidases.

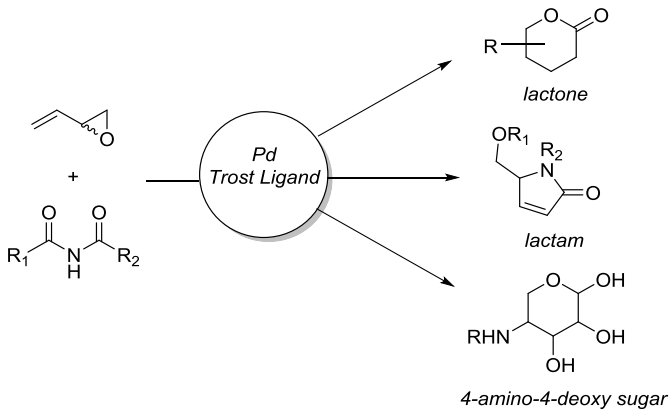



**1** **2**

3. *Enantioselective synthesis of Cidofovir analogues*: The research described in this part aims to develop an asymmetric and regioselective metal-catalyzed allylic amination processes using purinic and pyrimidinic bases and palladium catalysts, and the application of the previous method to the synthesis of acyclic nucleosides analogues of Cidofovir.




4. *A final objective of the Thesis was to explore the use of the catalytic system Pd/ Trost ligand* with different imido and imidocarboxylate nucleophiles. The different products obtained in this study were used as starting materials in the synthesis of valuable different compounds such as lactam, lactone and 4-amino-4-deoxy sugar.



# CHAPTER 3

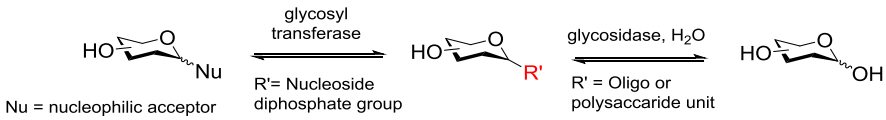
*Enantioselective formal synthesis of nectrisine*

# I. Introduction - Iminosugars

Polyhydroxylated pyrrolidines and piperidines, also called azasugars, represent an interesting class of glycosidase inhibitors that have been widely recognized as potential therapeutic agents for the treatment of diabetes, cancer, and viral infections.

## I.1. Glycosidases and glycosyltransferases

Enzymes are one of the four major classes of nature's biopolymers, playing a fundamental role in life's processes. In particular, glycosyltransferases and glycosidases, also known as glycoside hydrolases, are ubiquitous macromolecules, which catalyze glycosyl group transfer reactions that assemble, trim and shape bioactive glycoprotein and glycolipid conjugates.[1] Overall, these processes involve cleavage of the glycosidic bond linking a sugar's anomeric carbon with an oligo- or polysaccharide, or a nucleoside diphosphate group. The glycosidases transfer the liberated glycosyl group to water, while transferases transfer it to a different nucleophilic acceptor (Scheme 30).




**Scheme 30.** Role of glycosidases and transferases

Glycoside hydrolases are found in essentially all domains of life. In bacteria and prokaryotic cells, they are found as both intracellular and extracellular enzymes that are largely involved in nutrient acquisition. In higher organisms, glycoside hydrolases are located within the endoplasmic reticulum and Golgi apparatus where they mediate quality-control systems and ER-associated degradation mechanisms. In the lysosome, they participate in the degradation of carbohydrate structures. Deficiency in specific lysozomal

[1] (a) Kobata, A. *Anal. Biochem.* **1979**, *100*, 1-14. (b) Kornfeld, R.; Kornfeld, S. *Annu. Rev. Biochem.* **1976**, *45*, 217-237. c) Marshal, J. J. *Ad. Carbohydr. Chem. Biochem.* **1974**, *30*, 257-370. d) Pandey, G. *Proc. Indian Natn. Sci. Acad.* **2005**, *71*, 137-153.

glycoside hydrolases can lead to a range of lysosomal storage disorders that result in developmental problems or death. Glycoside hydrolases are also present in saliva where they degrade complex carbohydrates such as lactose or sucrose. In the gut they are found as glycosylphosphatidyl anchored enzymes on endothelial cells thus involved in intestinal digestion. Moreover, the glycoside hydrolases take part in the biosynthesis and degradation of glycogen in the body. Hence, their function or dysfunction has been implicated in a number of different diseases such as Gauchers and Fabry diseases.[2] In this context, inhibition of these glycosidases can have profound effects in a variety of processes, including viral infection (cell-virus recognition), cancer, and genetic disorders, maturation, transport and secretion of glycoproteins.[3]

The glycosidases are classified based on the stereochemistry of the anomeric glycosidic bond that they cleave. The α-glycosidases (axial glycoside bond) catalyze the cleavage of an α-glycosidic bond whereas β-glycosidases (equatorial glycoside bond) have the same effect on β-glycosidic bonds. Moreover, it has been shown by polarimetry, $^{1}$H-NMR spectroscopy, and product analysis of transglycosylation experiments that glycosidases can be categorized in two groups according to the anomeric configuration of the sugar product relative to the substrate: retaining or inverting glycosidases.

The mechanisms of glycoside cleavage have been reviewed several times.[4,8] In most cases, hydrolysis of the glycosidic bond is catalyzed by two residues of the enzyme: an acid (proton donor) and a base/nucleophile.[5] For both mechanisms the reaction usually proceeds through transition states with significant oxocarbenium ion-like character.[6] Hence, from all compounds that are known to inhibit the action of glycoside hydrolases, the ones that mimic this

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2 (a) Fan, J. Q.; Ishii, S.; Asano, N.; Suzuki, Y. *Nature Medicine* **1999**, *5*, 112-115. (b) Asano, N.; Ishii, S.; Kizu, H.; Ikeda, K.; Yasuda, K.; Kato, A.; Martin, O. R. Fan, J. Q. *Eur. J. Biochem*. **2000**, *267*, 4179-4186. (c) Butters, T. D.; Dwek, R. A.; Platt, F. M. *Chem. Rev.* **2000**, *100*, 4683. (d) Asano, N. *Glycobiology* **2003**, *13*, 93R-104R.

3 Rempel, B. P.; Withers, S. G. *Glycobiology* **2008**, *18*, 570-586.

4 Sinnott, M. L. *Chem. Rev*. **1990**, *90*, 1171-1202.

5 Henrissat, B.; Bairoch, A. *Biochem J.* **1996**, *316*, 695-696.

6 Koshland, D. E. *Biol. Rev.* **1953**, *28*, 416-436.

glycosidase "oxocarbenium-ion-like" transition state are particularly notable (Figure 7).[7]

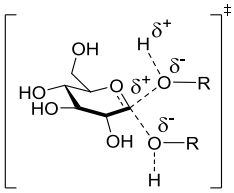


**Figure 7.** Generic glycosidase "oxocarbenium-ion-like" transition state

Any chemical entity that is capable of mimicking either the charge or shape of the substrate or that of any of the transition states, can act as a reversible inhibitor of that particular glycosidase. These entities are termed as *glycosidase inhibitors*.

Glycosyltransferases (GTs) are enzymes that establish natural glycosidic linkages on a wide range of small and macromolecules including cell wall components, natural products, other saccharides, proteins and even nucleic acids. These enzymes are involved in many processes of cellular biochemistry, such as protein and lipid glycosylation, as well as in the synthesis of polysaccharides such as cellulose, the main component of biomass. The role of cell surface oligosaccharides in processes like intercellular recognition, cancer cell metastasis and the immune response to viral and bacterial infection has generated an increased interest in the inhibition of GTs involved in the biosynthesis of oligosaccharides and glycoconjugates, which may lead to the discovery of novel drug therapies. [8]

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[7] a) Withers, S. G.; Namchuk, M.; Mosi R. *Iminosugars as Glycosidase Inhibitors: Nojirimycin and Beyond*, Wiley-VCH, Weinheim, **1999**. b) Bols, M. *Acc. Chem. Res.* **1998**, *31*, 1-8.

[8] (a) Boons, G. J. *Tetrahedron*, **1996,** *52*, 1095–1121. (b) Varki, A. *Glycobiology*, **1993**, *3*, 97-130. (c) Dwek, R. A. *Chem. Rev*., **1996**, *96*, 683-720.

## I.2. Iminosugars and related alkaloids

Alkaloids are nitrogen containing molecules which are widely distributed in nature. They are produced by a wide variety of organisms such as plants, bacteria, fungi, marine animals, some birds and a few mammals.[9] Over the years, the group of polyhydroxylated alkaloids has gained considerable interest as potential therapeutic agents and as tools to gain a better insight in biological processes. This specific group of alkaloids can be considered as carbohydrate mimics in which the endocyclic oxygen is replaced by a nitrogen. The molecules are commonly referred to as azasugars, iminosugars or iminocyclitols. This alteration in combination with their structural resemblance to normal natural sugars is the reason why they are often evaluated as inhibitors of glycosidases[10] and glycosyltransferases.[11]

Over the past 40 years a wide range of iminosugars and related alkaloids were isolated from the leaves, root bark and fruits of the mulberry tree and microorganisms. Although they do not conform to a single structural class, naturally occurring polyhydroxylated alkaloids inhibiting glycosidases are divided into five structural classes: pyrrolidines, piperidines, indolizidines, pyrrolizidines and nortropanes. Some natural occurring emblematic polyhydroxylated alkaloids are depicted in Figure 8.

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9 (a) Roberts, M.; Wink, M. Alkaloids-Biochemistry, Ecological Functions and Medical Applications;Plenum Press, New York, **1998**. (b) Wink, M. The Alkaloids: Chemistry and Biology; Academic Press, San Diego, **1993**; *43*, 1-118. (c) Wink, M. Function of Plant Secondary Metabolites and Their Exploitation in Biotechnology, Annual Plant Reviews; Sheffield Academic Press, Sheffield, **1999**.

10 Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron Asymm.* **2000**, *11*, 1645-1680.

11 Compain, P.; Martin, O. R. *Bioorg. Med. Chem.* **2001**, *9*, 3077-3092.

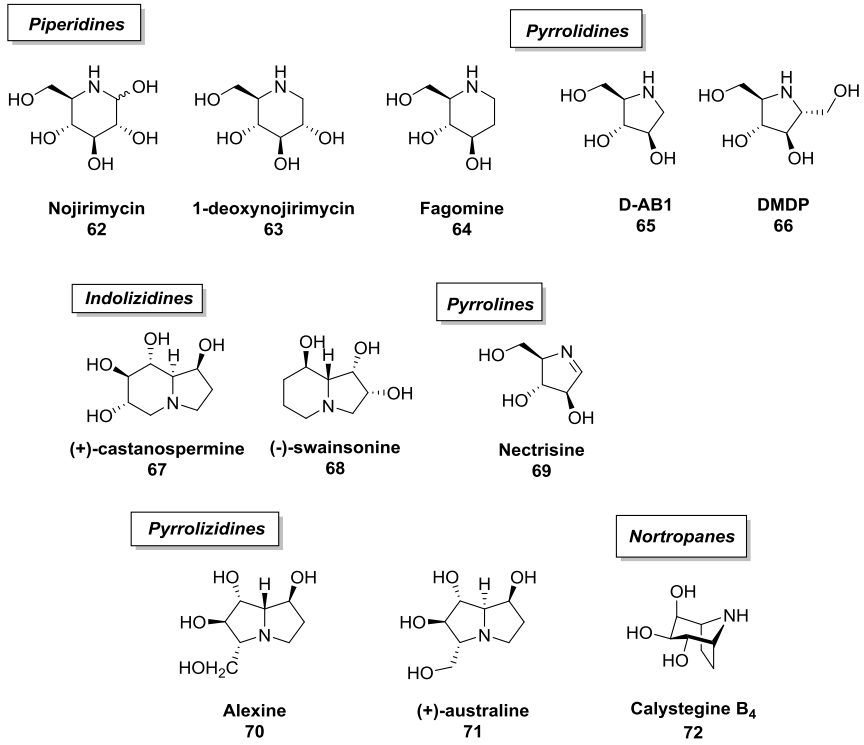


**Figure 8.** Some emblematic natural occurring polyhydroxylated alkaloids.

The scientific history of iminosugars began in the early 1960's with the purely academic exercise of the synthesis of sugar derivatives containing a heteroatom in the ring to form "heteroses".[12,13,14] The first natural occurring iminosugar to be discovered was the 5-substituted amino-glucose (5-amino-5-deoxy-D-glucopyranose) which was isolated in 1965 from *Streptomyces nojiriensis* by Ishida et *al.* and named nojirimycin (NJ **62)**.[15] In addition to

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12 (a) Paulsen, H., *Angew. Chem. Int. Ed. Engl*., **1962**, *1*, 597. (b) Paulsen, H., *Angew. Chem. Int. Ed. Engl.*, **1962**, *1*, 454. (c) Paulsen, H.; Todt, K. Adv. *Carbohydr. Chem. Biochem*. **1968**, *23*, 116.

13 (a) Jones, J. K. N.; Turner, J. C. *J. Chem. Soc*., **1962**, 4699-4703. (b) Jones, J. K. N.; Szarek, W. A. *Can. J. Chem*., **1963**, *41*, 636-640.

14 (a) Hanessian, S.; Haskell, T. H. *J. Org. Chem.*, **1963**, *28*, 2604-2610. (b) Hanessian, S. *Chem. Commun.*, **1966**, 796-798.

15 (a) Nishikawa, T.; Ishida, N. *J. Antibiotics*, **1965**, *18*, 132-133. (b) Inouye, S.; Tsuruoka, T.; Niida, T. *J. Antibiotics*, **1966**, *19*, 288-292. (c) Ishida, N.; Kumagai, K.; Niida, T.; Hamamoto, K.; Shomura, T. *J. Antibiotics*, **1967**, *20*, 62-65.

antimicrobial activity, nojirimycin was found few years later to be a potent inhibitor of α-and β-glucosidases.[16] This finding naturally stimulated further intensive synthetic studies in this area. Alternative deoxynojirimycin syntheses were developed and hundreds of *N*-substituted and C-branched derivatives of deoxynojirimycin were synthesized in the Bayer laboratories among other and screened for their biological activity. Twenty years later, these studies led to the generation of miglitol (2-hydroxyethyldeoxynojirimycin) which was approved for treatment of non-insulin-dependent diabetes in Europe and the USA.

Soon after the discovery of naturally occurring iminosugars in micro-organisms, alkaloid chemists began to isolate multiple hydroxylated piperidine alkaloids from plants. The first to be isolated was fagomine **3** (2-hydroxymethyl-3,4-dihydroxypiperidine) from *Fagopyrum esculentum* (Polygonaceae),[17] followed by 1-deoxynojirimycin (DNJ **63**) which was obtained by Inouye et *al.*[18] by reduction of NJ or by isolation from bacterial culture[19] or mulberries.[20]

Mulberry trees additionally contain the polyhydroxylated pyrrolidine alkaloid, 1,4-dideoxy-1,4-imino-D-arabinitol (DAB1 **65**), which was originally isolated from fruits of *Angylocalyx boutiqueanus* (*Leguminosae*)[21] and found to be a good inhibitor with a broad inhibitory spectrum toward mammalian glycosidases particularly.[22] Almost simultaneously, another pyrrolidine alkaloid, 2,5-dideoxy-2,5-imino-D-mannitol (DMDP **67**), was isolated from a species of the legume genus *Lonchocarpus*. This is a powerful inhibitor of a large range of α-, as well as β-glucosidases, even more potent than 1-deoxynojirimycin which is frequently used as a standard.[23]

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16 Niwa, T.; Inouye, S.; Tsuruoka, T.; Koaze, Y.; Niida, T. *Agric. Biol. Chem*., **1970**, *34*, 966-967.

17 Koyama, M.; Sakamura, S. *Agric. Biol. Chem*, **1974**, *38*, 1111-1112.

18 Inouye, S.; Tsuruaka, T.; Ito, T.; Niida, T. *Tetrahedron* **1968**, *24*, 2125 - 2144.

19 Murro, S.; Miyata, S. *Agric. Biol. Chem*. **1980**, *44*, 219 - 221.

20 Yagi, M.; Kuono, T.; Aoyagi, Y.; Murai, H. *Nippon Nogei Kagaku Kaishi* **1976**, *50*, 571-572.

21 Nash, R. J., Bell, E. A.; Williams, J. M. *Phytochemistry* **1985**, *24*, 1620–1622.

22 Fleet, G. W. J.; Smith, P. W. *Tetrahedron*, **1986**, *42*, 5685–5692.

23 Card, P. J.; Hitz, W. D. *J. Org. Chem*., **1985**, *50*, 891-893.

The first example of polyhydroxylated indolizidine alkaloids discovered was Swainsonine (**68**), isolated from the leaves of *Swainsona canescens*.[24] The latter has received much attention due to an effective lysosomal α-mannosidase and Golgi α-mannosidase II inhibitory action. It was also the first inhibitor selected for being tested as an anticancer drug, reaching phase I clinical trials. The seeds of another Australian legume, *Castanospermum australe* were found to contain another polyhydroxylated indolizidine, castanospermine. It is a potent inhibitor of lysosomal α-glucosidase[25] and disturbs the lysosomal catabolism of glycogen.[26]

In addition to producing indolizidine alkaloids, *Castanospermum australe* coproduces two pyrrolizidine alkaloids, alexine (**70**)[27] and australine (**71**)[28], which were the first two isolated molecules from this category. These alkaloids did not inhibit many glycosidases, but showed some inhibition of lactose, trehalose and cellubiose hydrolysis.

Among the most recently recognized groups of iminosugars are the polyhydroxylated nortropane alkaloids calystegines (A, B and C), which have been isolated from the families *Solanaceae* and *Convolvulaceae*. Calystegines have three structural features in common: a nortropane ring system; two to four secondary hydroxyl groups varying in position and stereochemistry; and, a novel aminoketal functionality, which generates a tertiary hydroxyl group at the bicyclic ring bridgehead.[29] They have shown inhibitory activity toward almond β-glucosidase and β-glucocerebrosidase (GCase).[30]

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24 Colegate, S. M.; Dorling, P. R.; Huxtable, C. R. *Aust. J. Chem*., **1979**, *32*, 2257-2264.

25 Molyneux, R. J., Roitman, J. N., Dunnheim, G., Szumilo, T. and Elbein, A. D., *Arch. Biochem. Biophys.* **1986**, *251*, 450-457.

26 Saul, R., Ghidoni, J., Molyneux, R. J. and Elbein, A. D. *Proc. Natl. Acad. Sci.*, **1985**, 82, 93-97.

27 Nash, R. J.; Fellows, L. E.; Dring, J. V.; Fleet, G. W. J.; Derome, A. E.; Hamor, T. A.; Scofield, A. M.; Watkin, D. J. *Tetrahedron Lett*. **1988**, *29*, 2487-2490.

28 Molyneux, R. J.; Benson, M.; Wong, R. Y.; Tropea, J. E.; Elbein, A. D. *J. Nat. Prod*. **1988**, *51*, 1198-1206.

29 Asano, N; Kato, A.; Oseki, K.; Kizy, H.; Matsui, K. *Eur. J. Biochem.* **1995**, *229*, 369-376. (b) Asano, N; Yokoyama, K.; Sakurai, M.; Ikeda, K.; Kizu, H.; Kato, A.; Arisawa, M.; Höke, D.; Dräger, B.; Watson, A. A.; Nash, J. R. *Phytochemistry* **2001**, *57*, 721-726.

30 Asano, N., Kato, A., Oseki, K., Kizu, H.; Matsui, K. *Eur. J. Biochem*., **1995**, *229*, 369-376.

## I.3. Therapeutic potential - Biological interactions

Given the broad range of biological and pathological processes in which glycosidases and glycosyltransferases are involved, there has been a steadily increasing interest in creating specific inhibitors of these enzymes. The realization that iminosugars might have enormous therapeutic potential in many diseases has led to the development of an impressive number of synthetic routes to create such compounds. The biological activity of iminosugars in relation to their ability to inhibit glycosidases has been widely reviewed.[31]

The use of glycosidase inhibiting sugar mimetics, such as iminosugars, to prevent the formation of the aberrant *N*-linked oligosaccharides and to inhibit catabolic glycosidases in order to stop tumour metastasis has emerged as a new therapeutic strategy against cancer. One of the more widely investigated iminosugars is the swainsonine (**68**). This alkaloid was found to interact with enzymes involved in the metabolic pathway of glycans responsible for tumour cell invasion. By inhibiting Golgi α-mannosidase II, it acts as a competitive inhibitor of *N*-linked glycan processing in the Golgi apparatus, therefore reducing invasion of tumour cells. SW presents low toxicity and was chosen for Phase I human cancer trials, and reached Phase II testing (Figure 9).

The discovery of strong inhibition of digestive α-glucosidases by DNJ attracted an enormous interest of various research groups. Finally, in 1996 an iminosugar-based drug has been approved for treatment of non-insulin-dependent diabetes in Europe and the USA (Glyset$^{TM}$) (Figure 9).

Lysosomal storage disorders are a group of disorders that result from the abnormal metabolism of macro substances such as glycosphingolipids, glycogen,

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[31] For reviews: (a) Molyneux, R. J.; Lee, S. T.; Gardner, D. R.; Panter, K E.; James, L. F. Phytochemistry, **2007**, *68*, 2973-2985. (b) Melo, E. B.; Gomes, A. S.; Carvalho, I. Tetrahedron **2006**, *62*, 10277-10302.(c) Oikonomakos, N. G.; Tiraidis, C.; Leonidas, D. D.; Zographos, S. E.; Kristiansen, M.; Jessen, C. U.; Norskov-Lauritsen, L.; Agius, L. *J. Med. Chem*. **2006**, *49*, 5687-5701. (d) Bellincampi, D.; Camardella, L.; Delcour, J. A.; Desseaux, V.; D'Ovidio, R.; Durand, A.; Elliot, G.; Gebruers, K.; Giovane, A.; Juge, N.; Sorensen, J. F.; Svensson, B.; Vairo, D. *Biochim. Biophys. Acta*, **2004**, 1696, 265-274. (e) N. Asano, *Glycobiology* **2003**, *13*, 93R. (f) Watson, A. A.; Fleet, G. W. J.; Asano, N.; Molyneux, R. J.; Nash, R. J. *Phytochemistry*, **2001**, *56*, 265-295. (g) Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron*: *Asymmetry* **2000**, 11, 1645-1680.

mucopolysaccharides and glycoproteins in lysosomes.[32] This anomalies are caused by deficiencies in lysosomal enzymes.[33,34] Gaucher disease is the most common lysosomal storage disease and results in a deficiency in a specific β-glucosidase (β-glucocerebrosidase). One strategy is to use a small molecule, *N*-butyl-1-deoxynojirimycin (Zavesca™)[35] to inhibit ceramide-specific glucosyltransferase and prevent the lysosomal accumulation of glycosphingolipids (Substrate Reduction Therapy, SRT) (Figure 9).[36]

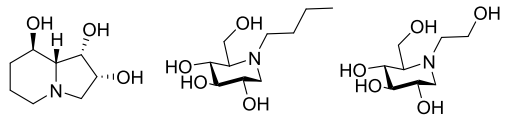


**Figure 9.** Structure of Swainsonine, Zavesca™ and Glyset™.

Various iminosugars have anti-viral activities, in particular, against the Human Immunodeficiency Virus (HIV) which is responsible for the Acquired Immune Deficiency Syndrome (AIDS). This activity is exerted by disrupting the viral envelope and thus preventing further virus-cell contact. It has been shown that castanospermine (**67**) (inhibiting glucosidase I) and DNJ (inhibiting glucosidase I and II ) were active against the virus ($LC_{50}$ 1.2-2.5 μg/mL). As DNJ is cytotoxic,[37] a number of alkyl derivatives of DNJ were tested against HIV and *N*-butyl-deoxynojirimycin (Zavesca™) was found to be the most attractive one.[38] Another example, maybe the most popular one, is the influenza virus which is designated by the viral coat proteins hemagglutinin (H) and neuraminidase (N). Both these viral proteins in fact bind specific carbohydrate sequences on the host cell surface. The glycomimetic drug used for the treatment of Influenza A Virus is the viral neuraminidase inhibitor Tamiflu. This drug

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32 Winchester, B., Vellodi, A. and Young, E. *Biochem. Soc.Trans*. **2000**, *28*, 150-154.

33 Fan, J.-Q. *Trends Pharmacol. Sci*., **2003** , *24*, 355-360.

34 Desnick, R. J. and Schuchman, E. H. *Nat. Rev. Genet*., **2002**, *3*, 954-966.

35 Ojima, I.; Vidal, E. S. *J. Org. Chem*., **1998**, *63*, 7999-8003.

36 Butters, T. D., Dwek, R. A.; Platt, F. M. *Curr. Top. Med. Chem*. **2003**, *3*, 561-574.

37 Ratner, L. *Aids*. Res. *Human Retroviruses*, **1992**, *8*, 165-173.

38 Karpas, A.; Fleet, G. W. J.; Dwek, R. A.; Petursson, S.; Namgoong, S. K.; Ramsden, N. G.; Jacob, G. S.; Rademacher, T. W. *Proc. Natl. Acad. Sci*., **1988**, *85*, 9229-9233.

mimics the transition state of the hydrolysis of the terminal N-acetylneuraminic acid by neuraminidase. Another alkaloid that have antiviral activity is nectrisine (**69**) which has been shown to potentiate the activity of zidovudine (AZT, 3'-azido-3'-deoxythymidine) (Figure 10).[39]

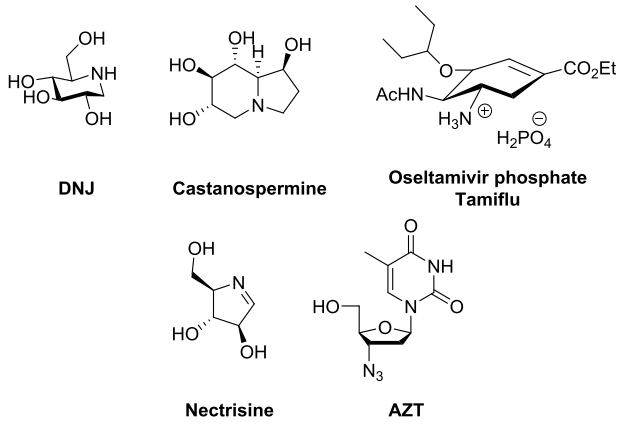


**Figure 10.** Iminosugar-based drugs as antiviral agents.

## I.4. Nectrisine - Chemical synthesis

Dihydro-2-hydroxymethylpyrrole or Nectrisine (**69**), is a fungal metabolite which was isolated from a strain of the fungus *Nectricine lucida* F-4490 as an immunomodulator, and obtained from the fermentation broth of *actinomycete Kitasatosporia kifunense*.[10, 40] It was found to inhibit α-glucosidase, α- and β-mannosidases, β-glucosidase and β-*N*-acetylglucosaminidase, in that order of inhibition strength. Nectrisine enhances the activity of the mouse immune system *in vitro* and exhibits a competitive action against the immunosuppressive factor produced in the serum of tumour-bearing mice.

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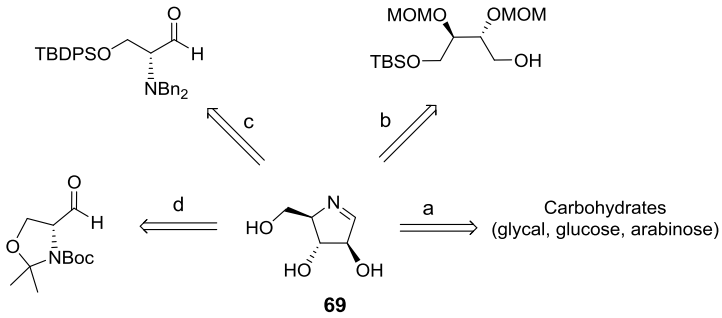
[39] Tatatsuki, K.; Hattori, T.; Kaizu, T.; Okamoto, M.; Yokato, Y.; Nakamura, K.; Kayakiri, H. **1990**. Antiretroviral pyrroline and pyrrolidine sulfonic acid derivatives. European Patent Application, EP O 407 701 A2.

[40] Shibata, T.; Nakayama, O.; Tsurumi, Y.; Okuhara, M.; Terano, H.; Kohsaka, M. *J. Antibiot.* **1988**, *41*, 296-301.

Moreover, nectrisine is involved in the prevention of different diseases such as Newcastle disease virus.[41]

Due to this impressive biological activity many organic chemists are focused on developing new methods to synthesize nectrisine. Several stereoselective syntheses of nectrisine have been reported starting from compounds of the chiral pool like carbohydrates (path a),[42,43] diethyl tartrate (path b),[44,45] aminoacids (path c),[46] and Garner's aldehyde (path d),[47] (Scheme 31).




**Scheme 31:** Nectrisine synthesis. Reported procedures.

41 Tsujii, E.; Muroi, M.; Shiragami, N.; Takatsuki, A. *Biochem. Biophys. Res. Commun*. **1996**, *220*, 459-466.

42 Bosco, M.; Bisseret, P.; Bouix-Peter C.; Eustache, J. *Tetrahedron Lett.* **2001**, 42, 7949-7952.

43 (a) Merino, P.; Delso, I.; Tejero, T.; Cardona, F.; Marradi, M.; Faggi, E.; Parmeggiani, C.; Goti, A. *Eur. Org. Chem.* **2008**, 2929-2947. (b) Kayakiri, H.; Nakamura, K.; Takase, S.; Seloi, H.; Uchida, I.; Terano, H.; Hashimoto, M.; Tada, T.; Koda, S. *Chem. Pharm. Bull*. **1991**, *39*, 2807-2812.

44 Kim, Y. J.; Takatsuki, A.; Kogoshi, N.; Kitahara, T. *Tetrahedron.* **1999**, 55, 8353-8364.

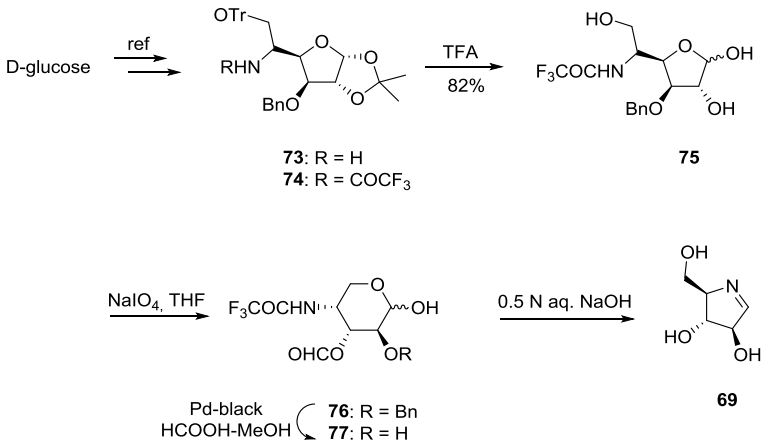
45 Kim, Y. J.; Kitaraha, *T. Tetrahedron Lett*. **1997**, 38, 3423-3426.

46 Hulme, A. N.; Montgomery, C.H. *Tetrahedron Lett*. **2003**, 44, 7649-7653.

47 Ribes, C.; Falomir, E. Carada, M.; Marco, *J. A. J. Org. Chem.* **2008**, 73, 7779-7782.

## I.4.1. Path a: Synthesis from carbohydrates

In 1988, Hashimoto group confirmed the structure of nectrisine by performing a synthesis from D-glucose.[48] (Scheme 32). Thus, compound **73**, already prepared by Niida et *al.* for their synthesis of nojirimycin,[49] was *N*-acylated with trifluoroacetic anhydride and subsequent acidic hydrolysis of resulting **74** with TFA afforded the triol **75**. Oxidative cleavage with $NaIO_4$ gave the pyranose **76**. Although the 2-*O*-benzyl group resisted the usual hydrogenolysis ($H_2$ (5 atm), 10% Pd-C), deprotection was achieved by hydrogenolysis using Pd black in 4.4% HCOOH-MeOH to afford **77** in 98% yield. The two acyl groups in **77** were finally hydrolyzed with a slight excess of 0.5N aqueous NaOH to furnish nectrisine (**69**) in 96% yield.




**Scheme 32.** Synthesis of nectrisine from D-glucose.

Two years later, another synthetic protocol was devised by Samuel J. Danishefsky et *al*.[50] Nectrisine was synthesized from Glycal **78** which was obtained in 40% overall yield from D-glucal (Scheme 33). Treatment of **78** with *m*-CPBA in methanol followed by desilylation (TBAF-THF) and afterwards by selective bromination ($Ph_3P/CBr_4$), afforded compound **79**. Protection of the

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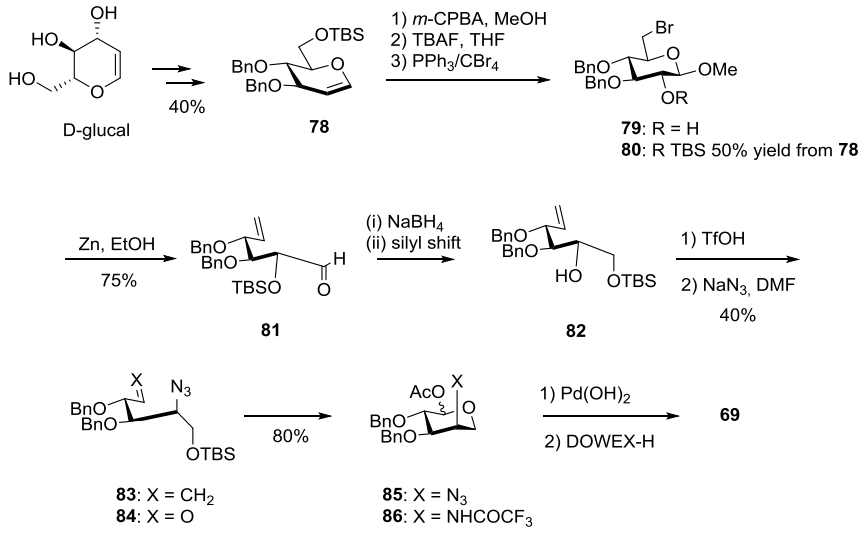
48 Kayakiri, H.; Takase, S.; Seloi, H.; Uchida, I.; Terano, H.; Hashimoto, M. *Tetrahedron Lett.* **1988**, *29*, 1725-1739.

49 Inone, S.; Tsuruoka, T.; Ito, T.; Niida, T. *Tetrahedron* **1968**, *23*, 2125-2144.

50 Chen, S.-H.; Danishefsky, S.J. *Tetrahedron Lett.***1990**, *31*, 2229-2232.

hydroxyl function with TBSCl-imidazole gave the ether **80** (50% from **78**), which was then treated with zinc in aqueous ethanol to afford **81** in 75% yield. Reduction of aldehyde **81** with sodium borohydride and subsequent silyl transfer gave rise to **82**, in 76% yield. Inversion at $C_2$ was accomplished (40% overall) by triflation followed by azidolysis (sodium azide, DMF rt.). Ozonolysis ($O_3$, $CH_2Cl_2$ -78ºC) of **83** gave **84** which, upon desilylation and acetylation generated the pyranosyl acetate **85** in 80% yield. Hydrogenation of the latter ($H_2$/Pd/$Al_2O_3$) followed by acylation with triflouroacetic anhydride afforded a quantitative yield of **86**. Finally, debenzylation using Pearlman's catalyst[51] followed by sequential treatment with 1N sodium hydroxide and Dowex acidic resin provided nectrisine (**69**) in high yield (Scheme 33).




**Scheme 33.** Synthesis of nectrisine from D-glucal.

It seems important to mention the attempt of synthesizing nectrisine from D-glyceraldehyde. Indeed, in 2000, Humphrey and co-workers used D-glyceraldehyde acetonide **87** for the synthesis of protected nectrisine **92** (Scheme 34).[52] Compound **87** was converted into 3,3-diethoxy-2-hydroxypropanal **88**,

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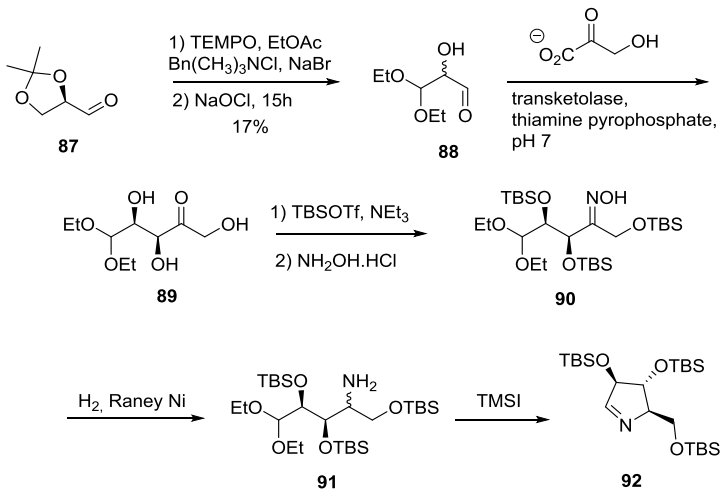
51 Pearlman, W.M. *Tetrahedron Lett.* **1967**, *8*, 1663-1664.

52 Humphrey, A.J.; Parsons, S.F.; Smith, M.E.B.; Turner, N.J. *Tetrahedron Lett.* **2000**, *41*, 4481-4485

which then underwent transketolase-mediated condensation with hydroxypyruvate to afford the triol **89** in 56% yield. After silylation of **89** (74%) and treatment with hydroxylamine, oxime **90** was obtained in 82% yield. A diastereomeric mixture of amines **91** (65%) was obtained after reduction of **90** using Raney nickel, which upon cyclization by treatment with iodotrimethylsilane gave a 3:2 mixture of cyclic imines from which the major diastereomer **92**, bearing the stereochemistry found in nectrisine (**69**), was isolated. However, treatment of **92** under a range of desilylation conditions (e.g. TBAF; AcOH–$H_2O$–THF; fluoride resin; HF–acetonitrile) failed to yield a pure sample of nectrisine (**69**).



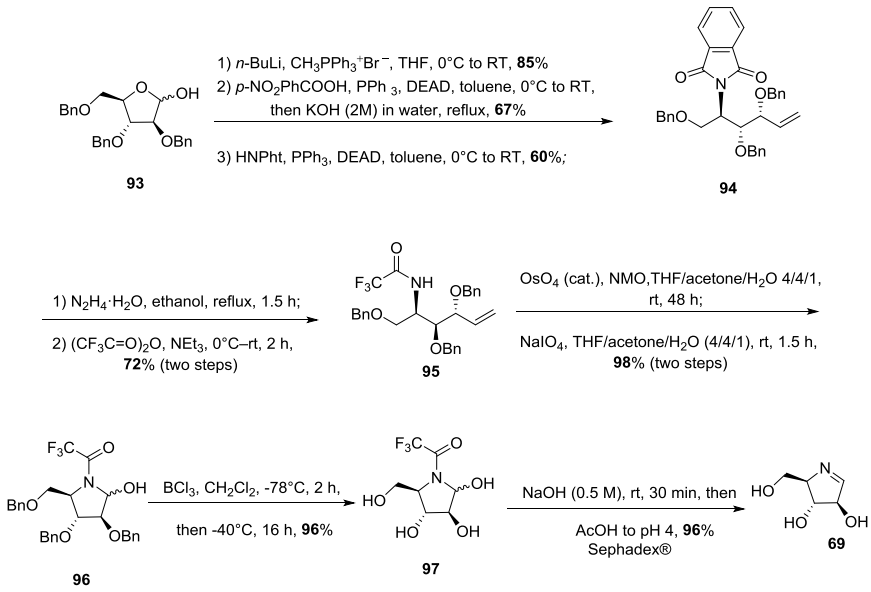

**Scheme 34.** Attempt to synthesis of nectrisine from D-glyceraldehyde.

In 2001, Eustache[42] reported a synthesis of nectrisine from commercially available 2,3,5-tri-*O*-benzyl-D-arabinose (**93**) (Scheme 35) which was first converted to the D-lyxose derivative **94** through a Wittig olefination[53] and two successive Mitsunobu reactions, first with *p*-nitrobenzoic acid, then with phthalimide. Hydrazinolysis of phthalimide **94**[54] (Scheme 35) and treatment of the resulting crude amine with trifluoroacetic anhydride provided the trifluoroacetamide **95**. Dihydroxylation ($OsO_4$/NMO) and oxidative cleavage

53 Freeman, F.; Robarge, R.D. *Carbohydr. Res.* **1986**, *154*, 270-274.

54 Bouix, C.; Bisseret, P.; Eustache, J. *Tetrahedron Lett.* **1998**, *39*, 825-828.

($NaIO_4$) of the resulting diol led to an aldehyde which cyclised to the protected aminal **96** upon standing. Initial attempts to remove the benzyl groups in **96** by hydrogenolysis, using a variety of conditions were disappointing, as the desired deprotected product **97** was obtained only in low yield, always accompanied by substantial amounts of the aminoalcohol arising from reduction of the latent aldehyde function in **97**. Hydrolysis of the trifluoroacetamide with diluted NaOH and concomitant dehydration, followed by ion-exchange chromatography (Sephadex® CM-C-25 ($NH_4^+$), elution with 2% aqueous ammonia) completed their synthesis of nectrisine, thus obtained in nine steps and 18% overall yield starting from commercially available 2,3,5-tri-*O*-benzyl-(D)-arabinose.



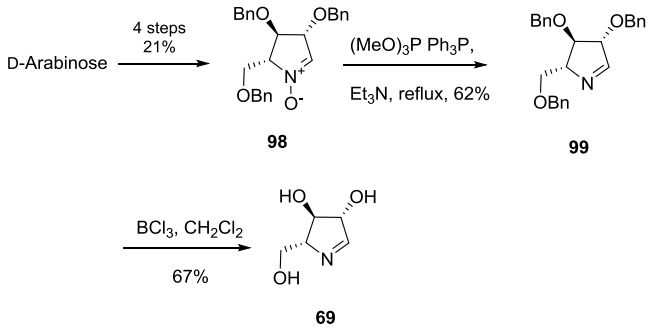

**Scheme 35.** Synthesis of Nectrisine from D-arabinose.

In 2008, Goti[43a] used cyclic nitrone **98** to synthesize nectrisine. They converted D-arabinose into cyclic nitrone **98**[55] in 4 steps and 21% overall yield.

Deoxygenation of nitrone **98** to provide imine **99** was achieved by addition of triphenylphosphine (10 mol%) to trimethylphosphite in triethylamine

55 Cardona, F.; Faggi, E.; Liguori, F.; Cacciarini, M.; Goti, A. *Tetrahedron Lett*. **2003**, *44*, 2315-2318.

affording **99** in good yield. Further debenzylation with $BCl_3$, in order to preserve the imine functionality, gave nectrisine (**69**) in 67 % yield.[43a]




**Scheme 36.** Synthesis of Nectrisine from D-arabinose.

## I.4.2. Path b: Synthesis from D-(-)-diethyl tartrate

Kitahara and co-workers[44,45] reported a synthesis of nectrisine from D-(-)-diethyl tartrate as the starting material in a synthesis that initially had as objective the preparation of aldehyde intermediate **100** (Scheme 37). A modified Strecker reaction[56] of the aldehyde **100**,[57] with *p*-methoxybenzylamine and diethyl phosphorocyanidate (DEPC) in THF gave aminonitrile **101** as an inseparable diastereomeric mixture (2 steps, 96%). Removal of the silyl protecting group from **101** followed by oxidation of the resulting primary hydroxyl group with TPAP[58] afforded the lactam **103**, which was treated with sodium methoxide to produce the methyl ester **104** in 62% yield from **101**. The lactam was then reduced with $LiBH_4$ (lithium borohydride) in THF to form an alcohol as a chromatographically separable mixture of two diastereoisomers *trans-lactam* **105** *and cis-lactam* **106**, in 87% yield, and a ratio of (56:44) (Scheme 37).

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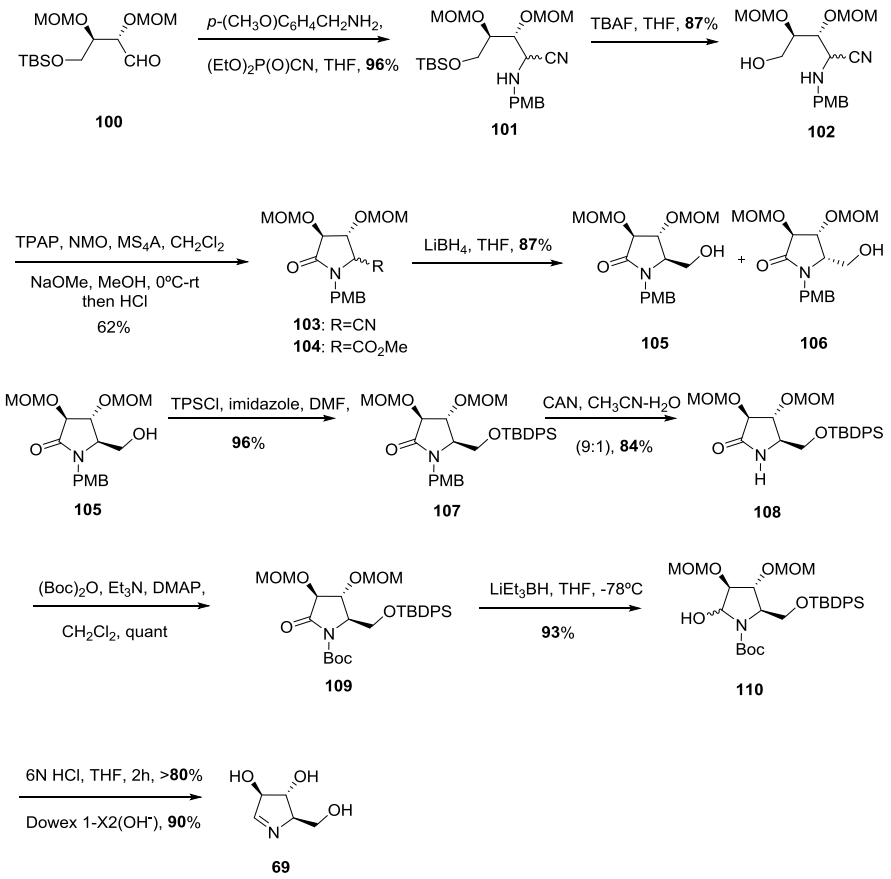
56 Harusawa, S.; Hamada, Y.; Shioiri, T. *Tetrahedron Lett*. **1979**, *20*, 4663-4666.

57 (a) Iida, H.; Yamazaki, N.; Kibayashi, C. *J. Org. Chem.* **1987**, *52*, 3337-3342. (b) Kuwahara, S.; Moriguchi, M.; Miyagawa, K.; Konno, M.; Kodama, O. *Tetrahedron* **1995**, *51*, 8809-8814.

58 Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. J. Chem. Soc., *Chem. Commun.* **1987**, 1625-1627.




**Scheme 37.** Synthesis of nectrisine (**69**) from D-(-)-diethyl tartrate.

Protection of the primary alcohol of *trans-lactam* **105** with *t*-butyldiphenylsilyl chloride (TBDPSCl) and $Et_3N$ gave the silyl ether **107** in 96% yield (Scheme 37). Treatment of **107** with ceric ammonium nitrate (CAN)[59] in $CH_3CN$-$H_2O$ (9:1) at 0ºC afforded lactam **108** in 84% yield. The key step in this synthesis is the reduction of the lactam to the amino alcohol. The reduction of **108** with various reducing reagents (DIBAL-H, $LiEt_3BH$, $NaBH_4$ etc) did not afford the desired product. To face this problem, *N*-protecting group, PMB, was replaced with the more electron-withdrawing and easily removable Boc group. Thus lactam **108** was treated with di-*t*-butyl dicarbonate $(Boc)_2O$ and $Et_3N$ in $CH_2Cl_2$ to give imide **109** in quantitative yield. Reduction of the imide with

59 Kronenthal, D.R.; Han, C.Y.; Taylor, M.K. *J. Org. Chem.* **1982**, *47*, 2765-2768.

$LiEt_3BH$ (Super Hydride®) in THF at -78ºC cleanly afforded the amino alcohol **110** in 93% yield. The final task was the removal of the protecting groups. This was accomplished by treatment of 6N HCI in THF at 50ºC for 2h to give the amino sugar precursor[60] (>80% yield), followed by ion exchange column chromatography (Dowex resin, OH-form) which afforded nectrisine (**69**) in 90% yield (Scheme 37).

## I.4.3. Path c: Synthesis from aminoacids

Few years later, Hulme and co-workers reported an efficient total synthesis of nectrisine from D-Serine as the starting material. [46] Conversion of D-serine to aldehyde intermediate **111** was achieved in five steps with 88% overall yield. Aldehyde **111** was converted to the α,β-unsaturated ester **112** in excellent yield (95%) under Horner–Wadsworth–Emmons conditions using the mild base $Ba(OH)_2$ (Scheme 38).[61] Osmium tetroxide-catalysed dihydroxylation resulted in a moderate yield (59%) of diols **113** and **114** in a 65:35 diastereomeric ratio, favouring the undesired all-*syn* diol **113**. The use of AD-mix-α resulted in a very sluggish reaction and only a modest improvement in yield (65% based on the unrecovered starting material) and no apparent increase in diastereoselectivity. However, the diastereoselectivity could be overturned in favour of the desired *syn* diol **114** by use of AD-mix-β, but again the reaction rate was very slow (7 days) and the diastereoselectivity modest (32:68, **113**:**114**). Separation of the desired *syn* diastereomer **114**, conversion to the corresponding Weinreb amide and removal of the *N*-benzyl protecting groups using $Pd(OH)_2/C$ Pearlman's catalyst resulted in conversion *in situ* to the previously reported lactam **115**.[61]

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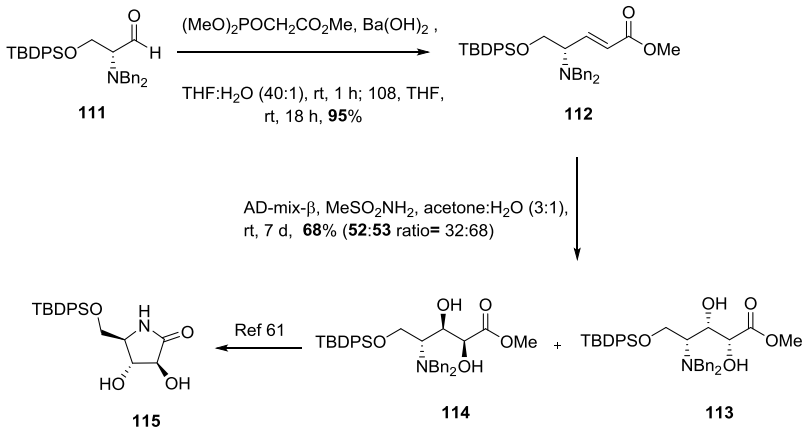
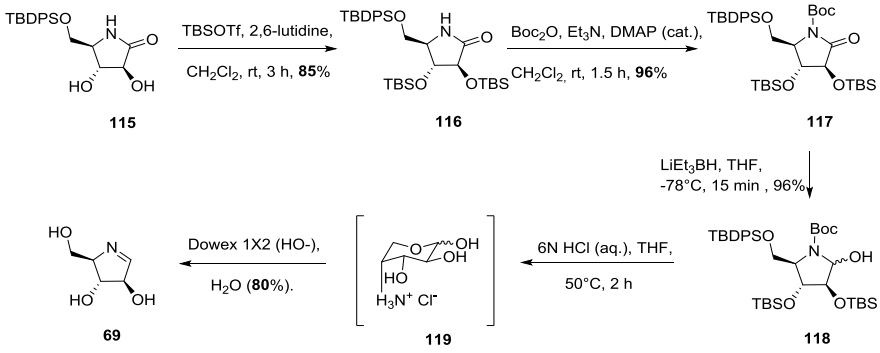
60 Naleway, J. J.; Raetz, C. R. H.; Anderson, L. *Carbohydr. Res.* **1988**, 179, 199-209.

61 Paterson, I.; Yeung. K. S.; Smail, J. B. *Synlett* **1993**, 774-776.




**Scheme 38.** Synthesis of compound **113** and **114**.

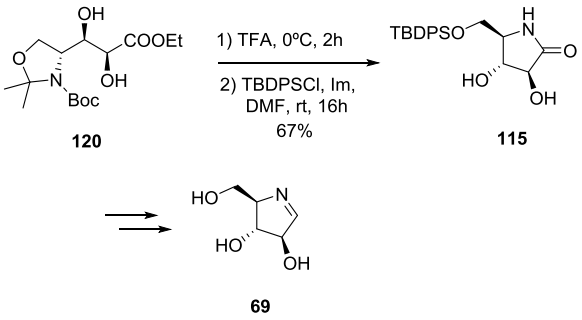
Sequential protection in the hydroxyl and amino functions afforded **117** (Scheme 39). The increased carbonyl electrophilicity resulting from *N*-Boc protection facilitated the smooth reduction of the lactam with Super Hydride® even at −78°C to give **118**. Heating the amino alcohol **118** with 6N HCl at 50°C for 2h led to the clean removal of all of the protecting groups and the formation of an intermediate aminosugar **119**. Neutralisation and purification by ion-exchange chromatography [Dowex 1X2 (HO−)] provided nectrisine (**69**) in excellent yield.[46]




**Scheme 39.** Synthesis of nectrisine from aminoacids.

## I.4.4. Path d: Synthesis from Garner aldehyde

In 2008, a short stereoselective formal synthesis of nectrisine was published by Marco and coworkers.[46] Dihydroxy ester **120** was obtained in two steps and 83% overall yield from Garner's (*R*)-aldehyde via olefination and dihydroxylation.[62] Acidic treatment of **120** caused cleavage of the Boc and acetonide groups, followed by in situ spontaneous formation of the lactam ring (Scheme 40). This gave a crude triol which was then subjected to selective silylation of the primary alcohol group to yield pyrrolidinone **115** in 67% yield. Since **115** was a late intermediate in Hulme's synthesis of **69**[46] this constitutes a formal synthesis of this natural compound.



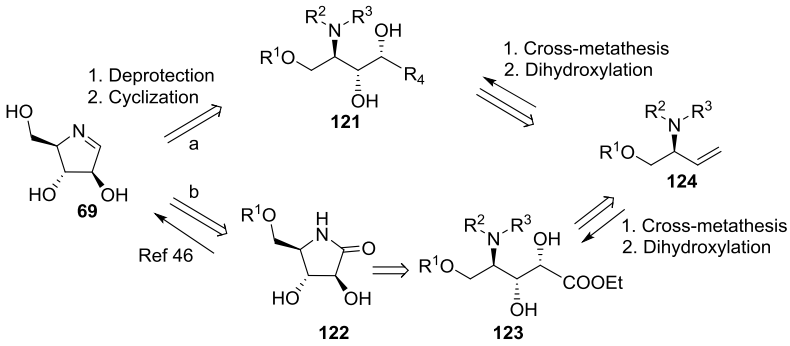

**Scheme 40.** Formal synthesis of nectrisine from Garner aldehyde.

[62] (a) Campbell, A. D.; Raynham, T. M.; Taylor, R. J. K. *Synthesis* **1998**, 1707-1709. (b) Liang, X.; Andersch, J.; Bols, M. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2136-2157.

# II. Results and discussion

## II.1. Retrosynthetic Scheme

Recently, our group described that Trost's DYKAT process in combination with cross-metathesis and dihydroxylation reactions is an efficient strategy for accessing important natural products such as sphingosine[63] and jaspine.[64] A similar protocol has also been described for the synthesis of phytosphingosine.[64,65] We considered that a related procedure could be applied to the synthesis of iminosugars such as nectrisine.




**Scheme 41.** Retrosynthetic scheme proposed.

Our aim at the beginning of this work was to explore a new enantioselective method to obtain nectrisine (**69**) in a short and efficient way. Scheme 41 shows the retrosynthesis proposed where the final step is the formation of the imine bond by two different approaches: a) via intramolecular nucleophilic addition to an aldehyde or surrogate ($R_4$ = CHO or surrogate) from compound **121** or b) from lactam **122** which can be obtained by cyclization of the corresponding amino-ester derivative **123**. Nectrisine had been already prepared from compound **122** and consequently this synthesis would involve a formal synthesis of nectrisine.[46] In our approach compound **121** can be obtained from

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63 Llaveria, J.; Díaz, Y.; Matheu, M. I.; Castillón, S. *Org. Lett*. **2009**, *11*, 205-208.

64 Llaveria, J.; Díaz, Y.; Matheu, M. I.; Castillón, S. *Eur. J. Org. Chem.* **2011**, 1514-1519.

65 Meek S. J.; O'Brien R. V.; Llaveria J.; Schrock R. R.; Hoveyda A. H. *Nature*, **2011**, *471*, 461-466.

the allylamine **124**, which is accesible in high enantiomeric purity from butadiene monoepoxide by using Pd/DACH as the catalytic system. Cross-metathesis would allow the elongation of the chain length. In this case, the choice of the $R_4$ functional group would be critical since it must be compatible with the cross-metathesis reaction and the cyclization process. Configuration of the double bond resulting from cross-metathesis must be *E* in order to provide the correct configuration of the hydroxyl groups in **122** after the dihydroxylation reaction.

## II.2. Approach to enantioselective synthesis of nectrisine

### II.2.1. Synthesis of allyl amines by asymmetric Pd-catalyzed allylic amination of butadiene monoepoxide.

For our purposes, we began with the preparation of the enantioenriched 2-amino-3-butenol by means of a dynamic kinetic asymmetric transformation (DYKAT) consisting in the deracemization of butadiene monoepoxide via asymmetric Pd-catalyzed allylic amination. Thus, reaction of butadiene monoepoxide (**54**) with 2 mol% of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, 6 mol% of (*R*,*R*)-DACH ligand **L3** and imide **125**, which is readily prepared from a reported procedure,[66] afforded allylic carbamate **126** in 95% yield and 99% *ee*. Compound **126** was subsequently treated with di-*t*-butyl dicarbonate and DMAP in $Et_3N$ as solvent for 20h affording the fully protected compound allyl imide **128** in quantitative yield. Deprotection of the benzoyl group of **126** using LiOH in THF furnished the corresponding alcohol **127** in a quantitative yield (Scheme 42).

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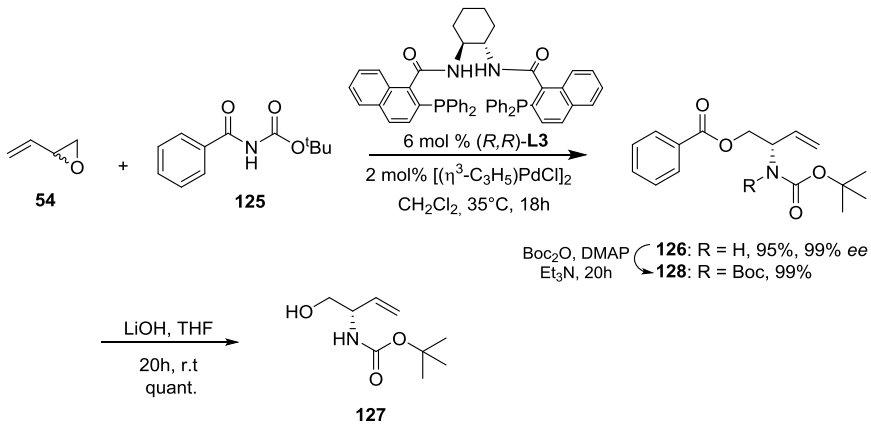
[66] Trost, B.M.; O'Boyle, B. M.; Torres, W.; Ameriks, M. K. *Chem. Eur. J.* **2011**, *17*, 7890-7903.




**Scheme 42.** Synthesis of enantioenriched allylic carbamates **126**, **127** and **128**.

## II.2.2. Synthesis of allyl amine derivatives by Ru-catalyzed cross-metathesis

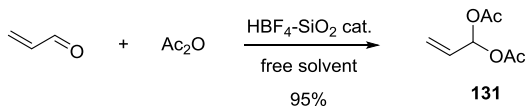
Among the many types of transition-metal-catalyzed C-C bond forming reactions, olefin methatesis has come to the fore in recent years owing to the wide range of transformations that are possible with commercially available and easily handled catalysts. Consequently, olefin metathesis is now widely considered as one of the most powerful synthetic tools in organic chemistry. Until recently the intermolecular variant of this reaction, cross-metathesis, had been neglected despite its potential. With the evolution of new catalysts, the selectivity, efficiency, and functional-group compatibility of this reaction have improved to a level that was unimaginable just a few years ago.

The second generation Grubbs catalyst is compatible with a wide range of functionalities.[67] The generation of olefins with electron-withdrawing functional groups, such as α,β-unsaturated aldehydes, ketones and esters, remains a difficult task in organic synthesis. Other π-conjugated functional groups compatible with alkylidene Schrock catalyst failed to react with first generation of Grubbs catalyst. However, second generation of ruthenium catalyst and, Hoveyda-

[67] (a) Yamamoto, T.; Hasegawa, H.; Hakogi, T.; Katsumura, S. *Org. Lett.* **2006**, *8*, 5569-5572. (b) Chaudhari, V. D.; Kumar, K. S. A.; Dhavale, D. D. *Org. Lett.* **2005**, *7*, 5805-5807. (c) Morales-Serna, J. A.; Llaveria, J.; Díaz, Y.; Matheu, M. I.; Castillón, S. *Org. Biomol. Chem.* **2008**, *6*, 4502-4504. (d) Torsell, S.; Somfai, P. *Org. Biomol. Chem.* **2004**, *2*, 1643-1646.

Grubbs catalysts were found to be very efficient in the reaction with α,β-unsaturated carbonyl compounds.[68]

As mentioned in the retrosynthesis, for the Ru-catalyzed cross-metathesis, different α,β-unsaturated aldehyde surrogates were considered – acrolein (**129**), vinyldioxolane (**130**) and acrolein diacetate (**131**). Gem-diacetate **131** was readily prepared using a known procedure.[69] The corresponding aldehyde was reacted with a stoichiometric amount of acetic anhydride in the presence of fluoroboric acid adsorbed on silica-gel as catalyst to give the diacylated product in 95% yield. The reaction proceeded smoothly at room temperature under solvent-free conditions and was completed within 5 minutes of reaction time without any side reactions (Scheme 43).




**Scheme 43.** Synthesis of gem-diacetates **131**.

In our group the cross metathesis reaction of compound **128** with acrolein and dioxolane had previously been studied.[70] When compound **128** was treated with acrolein in dichloromethane at room temperature (Table 1, entry 1), or in toluene at 80ºC (Table 1, entry 2), in the presence of second generation Grubb's catalyst (**C2**) the reaction did not proceed. Driving the reaction in refluxing dichloromethane, compound **132** was obtained in 34% yield (Table 1, entry 3). Likewise, the use of the Hoveyda-Grubb's catalysts (**C3**) in refluxing dichloromethane did not improve the yield, which poorly equalled 13% (Table 1, entry 4). Furthermore, when an excess of acrolein was used, the yield did not increase either. These results are in agreement with the previously reported

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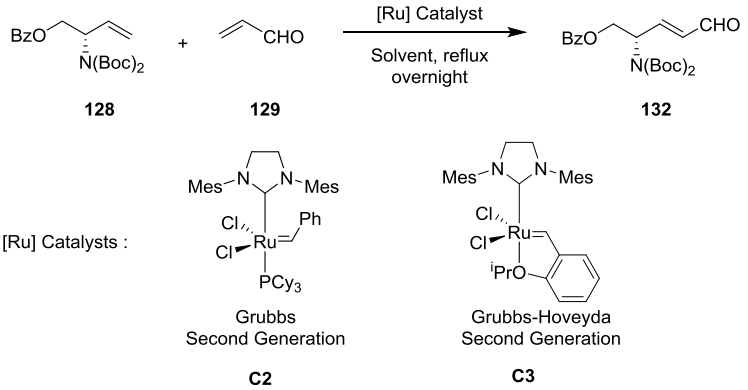
68 (a) Chatterjee, A. K.; Choi. T. L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem.* Soc. **2003**, 125, 11360-11370. (b) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc*. **2000**, *122*, 3783-3784.

69 Kamble, V. T.; Bandgar, B. P.; Joshi, N. S.; Jamode, V. S. *Synlett* **2006**, *17*, 2719-2722.

70 Azzouz, M. (**2012**) *Enantioselective Synthesis of Natural Products.* Ph.D. Thesis. Universitat Rovira i Virgili, Spain.

moderate yields and poor selectivities provided by the cross-metathesis of acrolein and simple alkenes.[69b]

**Table 1.** Cross-metathesis of allylimides **128** with acrolein (**129**).[a][71]

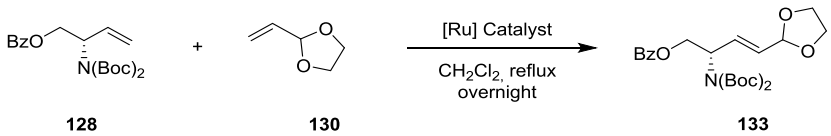



| Entry | Solvent | Temperature (ºC) | Catalyst | Conversion[b] (%) |
|---|---|---|---|---|
| 1 | $CH_2Cl_2$ | rt | **C2** | - |
| 2 | toluene | 80 | **C2** | - |
| 3 | $CH_2Cl_2$ | 40 | **C2** | 34 |
| 4 | $CH_2Cl_2$ | 40 | **C3** | 13 |

[a] Conditions: mixture of allyl imide (1 equiv) , alkene (5 equiv) and catalyst (5 mol%) were stirred for 12h in 0.5M solution. [b] Determined by $^1$H NMR spectroscopy. .

When the reaction between the di-boc derivative **128** and vinyldioxolane (**130**) was performed under similar reaction conditions to those optimized previously – dichloromethane at reflux as solvent, using **C2** (5 mol%) or **C3** (5 mol%) catalysts, afforded **136** in 55% and 54% yields, respectively (Table 2, entries 1, 2). An increase in the number of equivalents of vinyldioxolane (**130**), while working under similar conditions, allowed to increase the yield in compound **136** up to 78% (Table 2, entry 3).

**Table 2.** Cross-metathesis of allylimide **128** with vinyldioxolane (**130**).[a]71



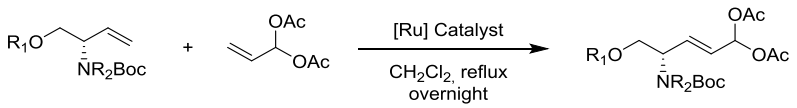

**128** **130** **133**

| Entry | Catalyst | Conversion[b] (%) (Yield)[c] (%) |
|---|---|---|
| 1 | **C2** | 64(55) |
| 2 | **C3** | 64(54) |
| 3[d] | **C2** | 82(78) |

[a]conditions: mixture of allyl imide (1 equiv), alkene (5 equiv) and catalyst (5 mol%) were stirred at reflux for 12h in 0.5M solution of dichloromethane. [b] Determined by $^1$H NMR spectroscopy. [c] Isolated yield. [d] 10 equivalent of vinyldioxolane (**130**) were used.

In this context, we decided to test the allylic carbamate **126**. An initial essay with the allylic carbamate **126** and acroleine diacetate (**131**) did not proceed when the reaction was carried out in dichloromethane at reflux for 12h in the presence of second generation Grubbs **C2** catalyst (5 mol%) (Table 3, entry 1). When the reaction was performed in the presence of Hoveyda-Grubbs catalysts **C3** (5 mol%) the result was also negative (Table 3, entry 2). By contrast, allylic carbamate **127** and acrolein diacetate **131** reacted in presence of 5 mol% of C3 at reflux of dichloromethane affording **134** in a 70% of conversion whereas with second generation of Grubbs catalyst, the reaction did not advance. (Table 2, entries 3, 4). Finally, the conversion was increased to an excellent 98% with 7.5 mol% of C3 catalyst loading (Table 3, entry 5). Then we investigated the cross-metathesis-dihydroxylation sequence with allylimide **128** and alkene **131** (Table 3, entries 6, 7). However, the cross-metathesis reaction of compound **128** with **130** in the presence of **C2** or **C3** catalysts did not provide the desired product **135**. We considered that the high bulkiness of the two reagents could be responsible for the failure of this reaction.

**Table 3.** Cross-metathesis of allylimides **126**, **127** and **128** with acrolein diacetate **131**.[a]




**126**: $R_1$ = Bz, $R_2$ = H
**127**: $R_1$ = H, $R_2$ = H
**128**: $R_1$ = Bz, $R_2$ = Boc

**131**

**134**: $R_1$ = Bz, $R_2$ = H
**135**: $R_1$ = H, $R_2$ = H
**136**: $R_1$ = Bz, $R_2$ = Boc

| Entry | Allylamide | Catalyst | Product | Conversion[b] (Yield)[c] |
|---|---|---|---|---|
| 1 | **126** | **C2** | **134** | - |
| 2 | **126** | **C3** | **134** | - |
| 3 | **127** | **C2** | **135** | - |
| 4 | **127** | **C3** | **135** | 75% (70%) |
| 5[d] | **127** | **C3** | **135** | 98% (95%) |
| 6 | **128** | **C2** | **136** | - |
| 7 | **128** | **C3** | **136** | - |

[a] Conditions: mixture of allylic carbamate (1 equiv), alkene (5 equiv) and catalyst (5 mol%) were stirred at reflux for 12h in 0.5M solution of dichloromethane. [b] Determined by $^1$H NMR spectroscopy. [c] Isolated yield. [d] 7.5 mol% of catalyst was used.

Indeed, the replacement of the acrolein by masked aldehyde **130** and **131** allowed improving the results of the cross-metathesis reaction.

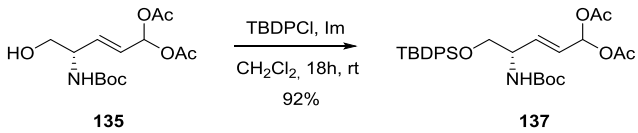
## II.2.3. Dihydroxylation of allyl imides

Bearing in mind the retrosynthetic scheme for the synthesis of nectrisine, the dihydroxylation reaction was subsequently explored. Two possible ways of diastereoselection control could be possible in the dihydroxylation of enantiopure *E*-allylic amines. The presence of a chiral centre in the substrate can control the diastereoselectivity, normally directing the dihydroxylation *anti* to the amine group. Moreover, the use of chiral ligands could allow a double stereodifferentiation stimulated by the substrate and the catalyst control.

However, recent research in dihydroxylation assays of related structurally allyl amides from our group had showed that the reaction works better in an

achiral fashion.[71,71] When the diastereoselective dihydroxylation of di-boc derivative **133** bearing a dioxolane ring was performed using 0.1 equiv. of $OsO_4$ and stoichiometric amounts of oxidant NMO at room temperature. Under these conditions, the desired products **139** was obtained with total conversion but with unsatisfactory selectivity (ratio **139a**/**139b** = 1:1) (Table 4, entry 1). However, when the reaction was performed with an aqueous solution of $OsO_4$ and NMO as oxidant, diastereoselectivity was increased to 5.5:1 (**139a**/**139b**). The mixture was carefully separated obtaining a 70% and 25% yield, respectively, but together with a minor amount of the partially deprotected derivative **139b** (Table 4, entry 2). Previous results on similar systems had shown that running the reaction at low temperature did not improve significantly the diastereoselectivity.

To facilitate the purification of the dihydroxylated product, allylic carbamate **135** was silylated under general conditions affording the *O*-protected allylic carbamate **137** in 92% yield (Scheme 44).




**135** **137**

**Scheme 44.** Synthesis of compound **137**.

Thus, we initially tried the diastereoselective dihydroxylation of compound **137** using $OsO_4$/NMO in dichloromethane at rt. All the starting material was consumed as determined by $^1$H NMR after 24h of reaction (Table 4, entry 3). However, a complex mixture was obtained probably as a result of the acetate hydrolysis. In order to reduce side reactions, we changed the temperature to 0ºC. Unfortunately, the complex mixture was again observed by $^1$H NMR spectroscopy of the crude product (Table 4, entry 4).

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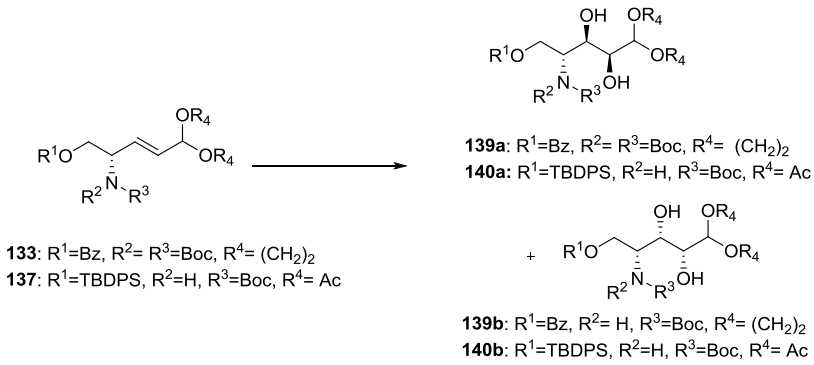
71 (a) Llaveria, J.; Díaz, Y.; Matheu, M. I.; Castillón, S. *Org. Lett.* **2009**, *11*, 205-208. (b) Llaveria, J. (**2011**) *Synthesis of Sphingoid Bases by Transition Metal-Catalyzed Reactions.* Ph.D. Thesis. Universitat Rovira i Virgili, Spain.

**Table 4.** Dihydroxylation reaction of alkenes **133**[b] and **137** using $OsO_4$/NMO.[a]




**133**: $R^1$=Bz, $R^2$= $R^3$=Boc, $R^4$= $(CH_2)_2$
**137**: $R^1$=TBDPS, $R^2$=H, $R^3$=Boc, $R^4$= Ac

**139a**: $R^1$=Bz, $R^2$= $R^3$=Boc, $R^4$= $(CH_2)_2$
**140a:** $R^1$=TBDPS, $R^2$=H, $R^3$=Boc, $R^4$= Ac

**139b**: $R^1$=Bz, $R^2$= H, $R^3$=Boc, $R^4$= $(CH_2)_2$
**140b**: $R^1$=TBDPS, $R^2$=H, $R^3$=Boc, $R^4$= Ac

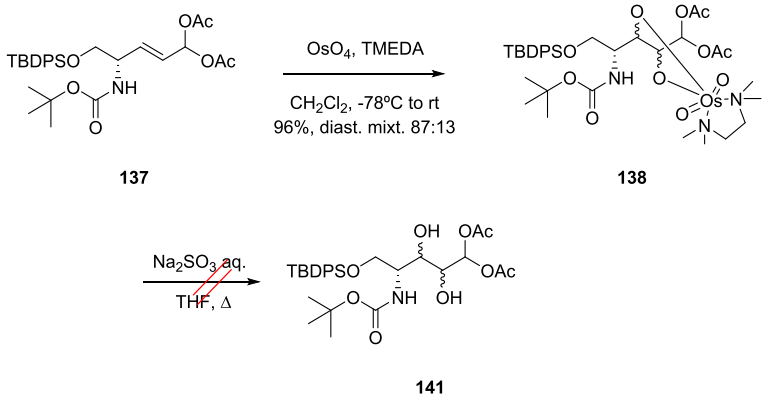
| Entry | Substrate | T (ºC) | t (h) | Product | Ratio a/b | Conversion[c] (%) | Yield[d] (%) |
|---|---|---|---|---|---|---|---|
| 1 | **136** | rt | 24 | **139a**/**139b** | 1:1 | >98 | n.d |
| 2[e] | **136** | rt | 24 | **139a**/**139b** | 5.5:1 | >98 | 95 |
| 3 | **137** | rt | 24 | Complex mixture | - | >98 | - |
| 4 | **137** | 0ºC | 24 | Complex mixture | - | >98 | - |

[a] Conditions: all reactions were stirred in the presence of $OsO_4$ (0.1 equiv.) and NMO (2.5 equiv).[b] Data extracted from Mariam Azzouz Ph.D. Thesis. [c] Determined by $^1$H NMR.[d] Isolated yield. [e] (2.5 mol%) of $OsO_4$ in water were used .

The use of a stoichiometric amount of $OsO_4$ avoided the need of a reoxydant substance such as NMO which could be responsible for the failure of the dihydroxylation reaction of compound **137**. It has been reported that the use of a bidentate amine as an additive in addition to the stoichiometric amount of $OsO_4$ speeded up the reaction and efficiently dihydroxylated alkenes even at -78

°C. Moreover, in many examples, this system has been described to improve diastereoselectivities compared to those of the catalytic $OsO_4$/NMO system.[72]

Thus, the reaction of **137** with stoichiometric $OsO_4$ and TMEDA promoted osmylation in excellent yield (96%) and good selectivity (87:13) to give, however, the expected osmate **138** as an inseparable mixture of diastereoisomers. The ratio of diastereoisomers was determined by $^1H$ NMR spectroscopy of the crude reaction mixtures. This osmate ester should be cleaved during workup to liberate the diol. One method consisted in the use of sodium sulfite as reducing agent to reduce osmium (VI) and thereby facilitate hydrolysis of the glycol ligand from the metal. The osmate ester proved to be inert to hydrolysis under this workup in standard conditions (Scheme 45).




**Scheme 45.** Osmylation of alkenes **137** with $OsO_4$/TMEDA.

At this stage, the relative configuration of the diol moiety is not known. Indeed, configuration assignment of acyclic diastereomeric products obtained from dihydroxylation, is usually achieved by comparison with the spectroscopical data of a further advanced cyclic intermediate, which would be nectrisine, in our case.

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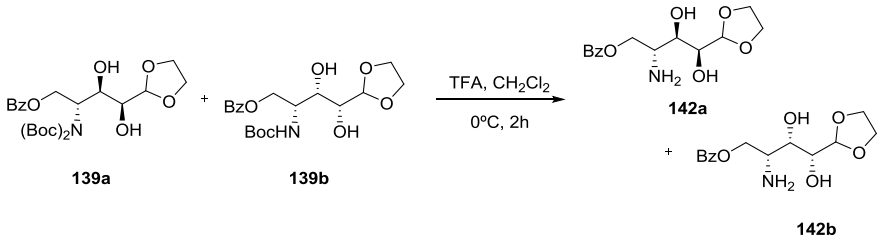
[72] Donohoe, T. J.; Blades, K.; Helliwell, M.; Moore, P. R.; Winter, J. J. G. *J. Org. Chem.* **1999**, *64*, 2980-2981.

## II.2.4. Deprotection and cyclization reactions

### II.2.4.1. Attempt to nectrisine's synthesis from compound **139a**

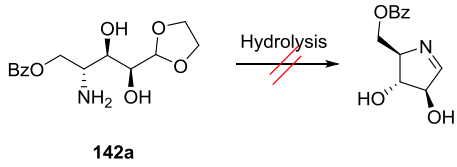
*- Deprotection tests in compound **139**.*

Previous results obtained by our group[71] have demonstrated that trifluoroacetic acid was more efficient than HCl/EtOH for Boc removal.[73] Thus, the treatment of mixture **139a/139b** with TFA[46] afforded a mixture of **142a/142b** with 50% conversion (Scheme 46). This low efficiency was attributed to acetalyzation/hydrolysis processes occurring because of the dioxolane moiety, but no aldehyde product was observed in the reaction crude.




**Scheme 46.** Boc-deprotection reaction.

Removal of the dioxolane protecting group in **142** could directly afford monoprotected nectrisine by releasing the aldehyde group and forming the imine concomitantly. However, any attempt of removing the dioxolane ring to induce the cyclization in **142** by treatment with HCl and *p*-TsOH[74] in THF at 50ºC or rt furnished degradation products only (Scheme 47).




**Scheme 47.** Attempt to cyclization.

73 Bimalendu, R.; Kausikisankar, P.; Balaram, M, *Glycoconj. J* . **2008**, 25, 157-166.
74 Puls, R.; Al-Haras, A.; Rissig, H. U. *Org. Lett.* **2002**, *4*, 2353-2355.

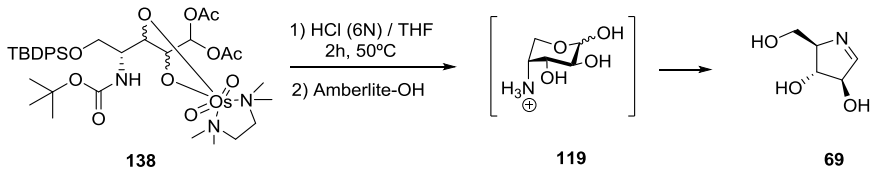
## II.2.4.2. Attempt to nectrisine's synthesis from compound **138**

Due to the difficulty of hydrolysing the dioxolane ring we focused our attention to the di-acetate derivative **138**. All protecting groups (TBDPS, $CH(OAc)_2$, Boc) in compound **138** are acid-labile and could be removed in the same acidic medium. Thus we envisaged that removal of all protecting groups by acid hydrolysis from the mixture of compound **138** could directly afford the unprotected nectrisine by release of the aldehyde and amine groups and concomitant formation of the imine after neutralisation. Indeed, acidic medium is the method of choice to hydrolyse the osmate ester moiety,[75] silyl ether, Boc and acetal groups.

In the first instance, any attempt to remove selectively silyl ether and Boc group (e.g. TBAF, TFA) afforded degradation products or a complex mixture.

Careful hydrolysis of gem-diacetates using Zemplén conditions (MeONa/MeOH) didn't lead to the free aldehyde. Instead, judging by $^1$H NMR spectroscopy, a complex mixture was obtained.

At this stage, we thought that a more drastic acid medium could hydrolyse faster all the protecting groups avoiding side reactions. For this purpose, the mixture **138** was treated with HCl 6N in THF at 50ºC for 2 hours (Scheme 48). After neutralization with Amberlite-OH the crude was washed with EtOAc. The organic phases contained the silyl group and TMEDA. $^1$H NMR spectroscopy of the aqueous phase showed a very complex mixture. However, signals characteristic of a carbohydrate compound were detected.




**138** **119** **69**

**Scheme 48.** Acid-hydrolysis of compound **138**.

[75] Donohoe, T. J. *Synlett* **2002**, *8,* 1223-1232.

We also analyzed the crude product by ESI-mass spectrometry. Nectrisine ( $[M+H]^+$ = 132.0654) was observed as traces whereas one of the most abundant peaks was detected at m/z = 263.1235 m.u. This m/z could correspond to a dimeric form of nectrisine.

It has been reported that nectrisine exists as the imino form, as judged from $^1$H- and $^{13}$C-NMR data, while its stereoisomers such as L-xylo **143** and L-lyxo **144** were reported to adopt mainly the dimeric forms **143c** and **144c**, respectively (Figure 11, A). This was explained by steric factors. Indeed, nectrisine seems to be much more stable than **143b** and **144b** because its three substituents on the pyrroline ring are all in a *trans,* and not eclipsed, relationship while **143b** has one pair and **144b** has two pairs of substituents which are in *cis,* and eclipsed, relationship. On the other hand, the dimeric forms **145** and **146** of nectrisine are likely to be less stable than **143c** and **144c** because of steric hindrance (Figure 11, B)

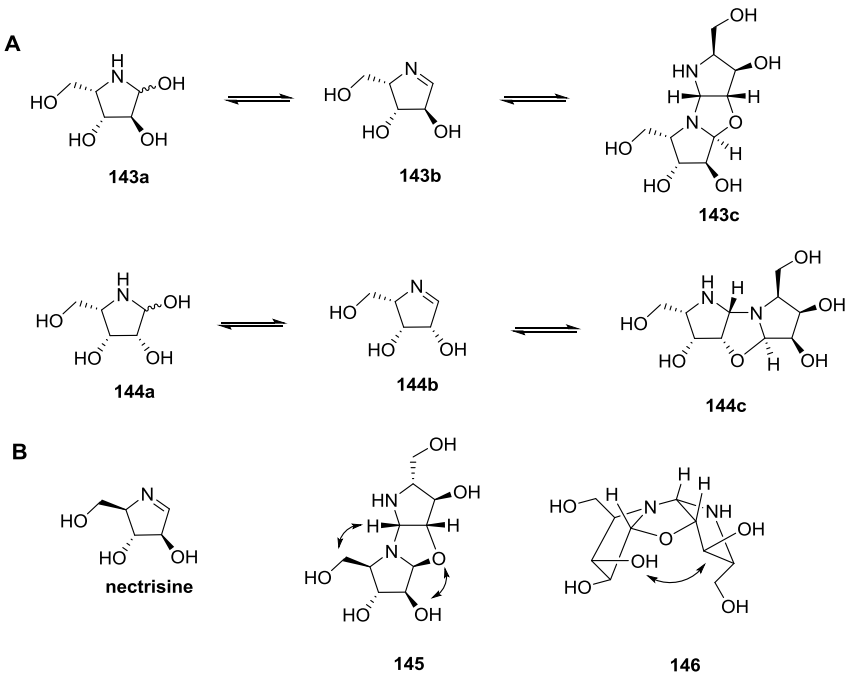



**Figure 11.** Dimeric forms of stereoisomers of nectrisine.

In our case, the possible formation of stereoisomers of nectrisine could arise from the diastereoselective dihydroxylation reaction. Indeed, the non-catalytic system used for the oxidation of alkenes **137** ($OsO_4$/TMEDA) has been reported to give *syn* selectivity for cyclic allylic alcohols and trichloroacetamides.[76] This phenomenon is due to efficient hydrogen bonding between the oxidant and the substrate, thus promoting an oxidation with stereochemistry opposite to that obtained under more standard (e.g. Upjohn) conditions.[77] In our substrate **137** this *syn* selectivity would be explained by hydrogen bonding between the NHBoc group (bearing a fairly acidic proton) as hydrogen bond donor and osmium tetroxide as hydrogen bond acceptor directing the dihydroxylation at the more hindered face (Scheme 49). Indeed, coordination of a Lewis base to the metal increases the electron density on osmium and, in so doing, reduces back-bonding by the oxo ligands, thus making these atoms more electron rich. Electron-rich oxo ligands are prone to efficient hydrogen bonding. TMEDA forms a bidentate complex with osmium tetroxide, making both the metal and oxo groups even more electron-rich again.

The model developed to explain this diastereoselectivity is similar to the one used by others for the epoxidation of acyclic allylic alcohols with peracids.[78] In this model the conformer **B** is energetically favoured relative to conformer **A** (Scheme 49). Indeed, in conformer **A**, the required geometry for hydrogen bond causes more 1,3-allylic ($A^{1,3}$) strain due to the presence of inside alkyl (R = -$CH_2$OTBDPS) group than in conformer **B** although there is some increase in the 1,2-allylic ($A^{1,2}$) strain between the NHBoc group and the vinylic hydrogen atom.

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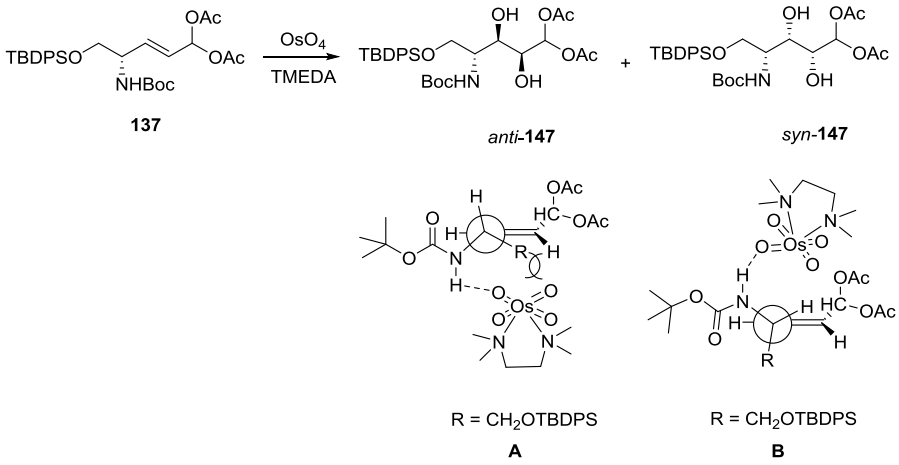
[76] Donohoe, T. J.; Blades, K.; Moore, P. R.; Waring, M. J.; Winter, J. J. G.; Helliwell, M.; Newcombe, N. J.; Stemp, G. *J. Org. Chem.* **2002**, *67*, 7946-7956.

[77] VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett*. **1976**, 1973-1976.

[78] Henbest, H. B.; Wilson, R. A. L. *J. Chem. Soc.*, **1957**, 117, 1958-1965.




**Scheme 49.** Proposed model for the attack of osmium tetroxide on chiral allylic carbamate **137**.

It is noticeable that the stereoselective dihydroxylation reactions of allylic amines have not been studied as thoroughly as those of allylic alcohols.[79] Often, poor or inconsistent stereochemical results have been reported for acyclic allylic amino derivatives with flexible conformation.[80] In several cases, even the well-established Sharpless asymmetric dihydroxylation reactions produced mixed results.[81]

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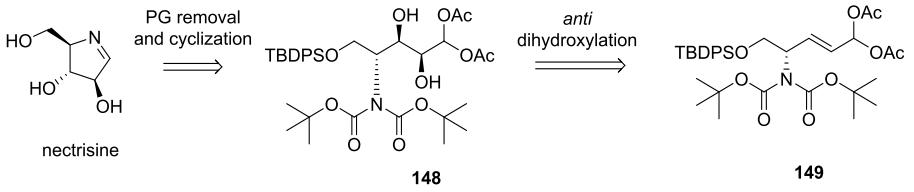
79 For a review, see: (a) Cha, J. K.; Kim, N.-S. *Chem. Rev*. **1995**, *95*, 1761-1795, and references cited therein; (b) Dee, M. F.; Rosati, R. L. *Bioorg. Med. Chem. Lett*. **1995**, *5*, 949-952. (c) Azuma, H.; Tamagaki, S.; Ogino, K. *J. Org. Chem.* **2000**, *65*, 3538-3541. (d) Dolle, R. E.; Herpin, T. F.; Shimshock *Tetrahedron Lett.* **2001**, *42*, 1855-1858. (e) Hulme, A. N.; Montgomery, C. H. *Tetrahedron Lett.* **2003**, 44, 7649-7653.

80 For the stereo-controlled osmylations of cyclic allylic amino derivatives, see: (a) Oh, J. S.; Hong, Y. S.; Kim, Y. G. *J. Ind. Eng. Chem*. **1997**, *3*, 326, *Chem. Abstr*., **1998**, *129*, 202696z; (b) Donohoe, T. J.; Blades, K.; Helliwell, M.; Moore, P. R.; Winter, J. J. G. *J. Org. Chem*. **1999**, *64*, 2980.

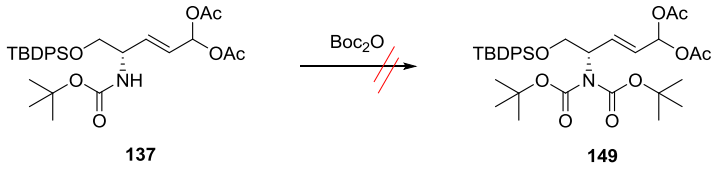
81 (a) Huang, Y.; Dalton, D. R.; Carroll, P. J. *J. Org. Chem*. **1997**, *62*, 372-376. (b) Imashiro, R.; Sakurai, O.; Yamashita, T.; Horikawa, H. *Tetrahedron* **1998**, *54*, 10657-10670. (c) Broady, S. D.; Rexhausen, J. E.; Thomas, E. T. *J. Chem. Soc., Perkin Trans 1* **1999**, 1083-1094. (d) Shirota, O.; Nakanishi, K.; Berova, N. *Tetrahedron* **1999**, *55*, 13643-13658. (e) Thoen, J. C.; Morales-Ramos, A. I.; Lipton, M. A. *Org. Lett*. **2002**, *4*, 4455-4458. (f) Yang, G.; Schmieg, J.; Tsuji, M.; Franck, R. W. *Angew. Chem., Int. Ed.* **2004**, *43*, 3818-3822.

If complexation between the imide group and osmium tetroxide as in compound **149** is not possible, then an *anti* product should be expected, as the well known Kishi model explains the diastereofacial discrimination. As a consequence, correct configuration of the diol moiety should lead to nectrisine after removal of all protecting groups and the cyclization reaction (Figure 13).



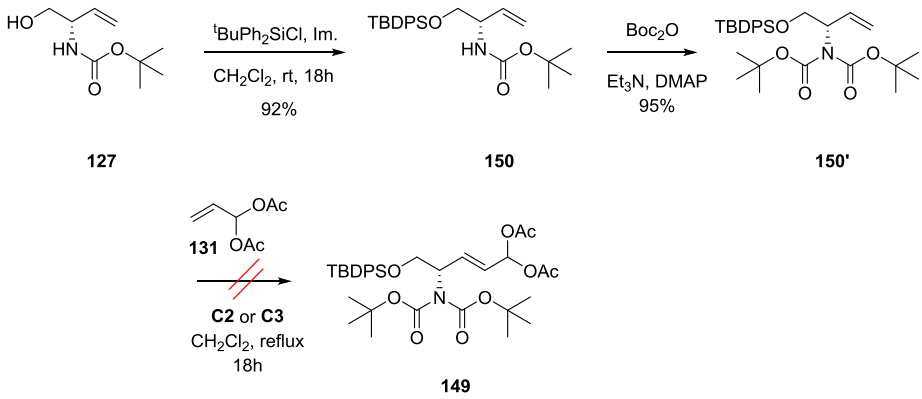

**Scheme 50.** New retrosynthetic scheme to nectrisine synthesis.

In order to confirm this hypothesis, the preparation of a compound such as **149** would be interesting. Therefore, we decided to prepare it from compound **137**. However, any attempt (e.g. $Boc_2O$; $Boc_2O$, DMAP) afforded degradation products or no reaction (Scheme 51).




**Scheme 51.** Attempt at the synthesis of compound **149** from compound **137**.

Considering this result, we envisaged a cross metathesis reaction with alkene **131** and **150'**. The latter was readily prepared from compound **127** by protection of the primary alcohol with TBDPSCl and imidazole in dichloromethane affording compound **150** in 92% yield. Further protection of the carbamate function with $Boc_2O$ in $Et_3N$ furnished **150'** in excellent yield. Unfortunately, no reaction occurred between the two cross partners **131** and **150'**. Once again, the failure of this reaction could be explained by the high bulkiness of the two reagents (Scheme 52).

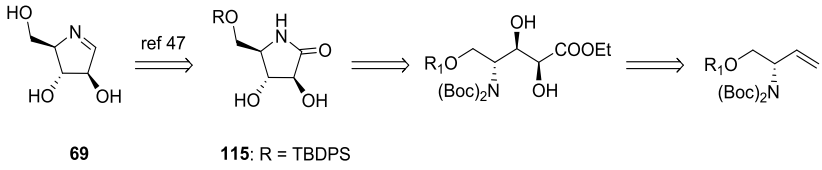



**Scheme 52.** Attempt to synthesise compound **149** from compound **127**.

## II.3. Enantioselective formal synthesis of nectrisine

The synthetic approache to nectrisine discussed above allowed us to prepare the skeleton of this compound incorporating the appropriate functionalities, but failed in the step of removal of protecting groups, providing mixtures of compounds where nectrisine could be detected by mass spectrometry.

In view of the unsuccessful cyclisation using aldehyde surrogates we turned our attention to the synthesis of lactam **115** (R= $SiPh_2{}^tBu$), which had already been transformed into nectrisine (Scheme 53).[46]




**Scheme 53.** Retrosynthetic scheme to lactam **115** synthesis.

Related lactams had been prepared using the chiral-pool approach, and by anchoring allylamines in the amino function of **124**, followed by ring-closing metathesis.[82] That process involved protection and deprotection steps and we considered that it could be accessed through a synthetic sequence similar to the previously discussed one. The only difference consists in the replacement of the previously investigated aldehyde functionality with an ester, and thus the cross-metathesis reaction was studied using ethyl acrylate.

Cross-metathesis reaction of **128** with ethyl acrylate afforded the product **151** in excellent yields (95%) in the presence of Hoveyda-Grubbs catalyst **C2** (5 mol%) (Scheme 54). Similarly to the previous study, reaction of compound **151** with stoichiommetric $OsO_4$ and TMEDA afforded the osmate ester in excellent stereoselectivity (20:1) which, however, was proved to be inert to hydrolysis under the reaction conditions. Subsequent controlled hydrolysis in the presence of HCl and MeOH (C = 0.24 mol/l) rendered the desired diol **152a** product in 91% overall yield. Kishi conducted a comprenhensive investigation about the control of the stereoselectivity in $OsO_4$-catalyzed dihydroxylation of acyclic allylic alcohols and ethers.[83] The observed stereoselectivity trends in dihydroxylations of allylic substrates determined the outlining of an empirical model for predicting the diastereoselectivity. In this case, no complexation with di-Boc group is expected, and therefore we also propose the Kishi model to explain the observed diastereofacial discrimination.

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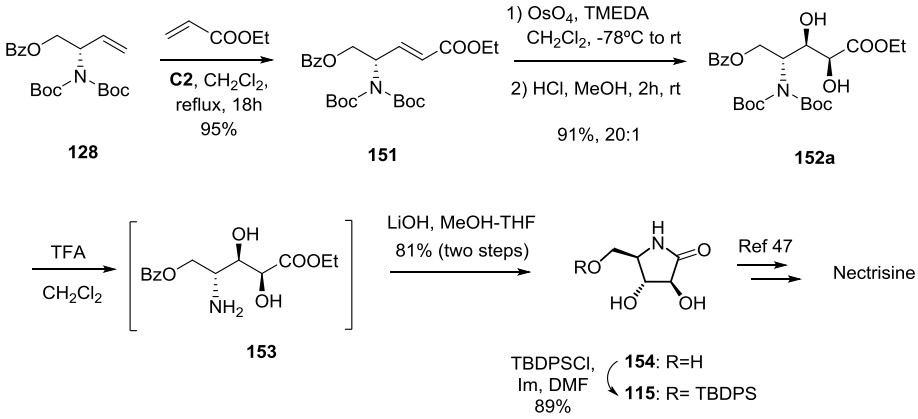
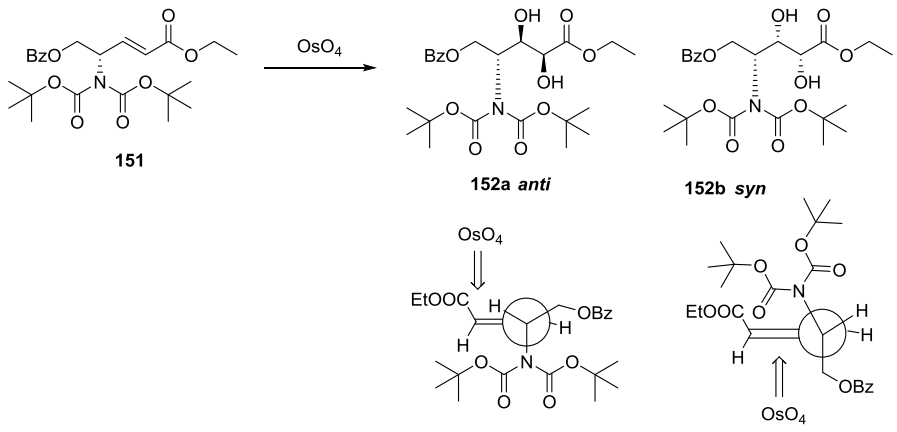
[82] (a) Lee, J. H.; Shin, S.; Kang, J.; Lee, S. *J. Org. Chem*. **2007**, *72*, 7443-7446. (b) Trost, B. M.; Horne, D. B.; Woltering, M. J. *Chem. Eur. J.* **2006**, *12*, 6607-6620.

[83] Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron Lett.* **1983**, *24*, 3943-3946.




**Scheme 54.** Formal synthesis of nectrisine from compound **128**.

In this model, minimization of both the $A^{1,3}$ strain and electrostatic repulsions between Os=O and the C-heteroatom bond are believed to lead to predominant formation of the 1,2-*anti* product.[84] The smallest group at the stereogenic centre is aligned parallel to the double bond and the osmium attacks on the opposite site from the nitrogen of the allylic center (Scheme 55).




**Scheme 55.** Proposed model for the attack of osmium teroxide on chiral allylic amine **151**.

[84] Haller, J.; Strassner, T.; Houk, K. N. *J. Am. Chem. Soc.* **1997**, *119*, 8031-8034.

With compound **152a** in hand, the removal of di-Boc protecting-group was attempted by treatment with chlorhydric acid in THF and with TFA in dichloromethane at 0ºC. It was expected that under these reaction conditions cyclization would be produced. Unexpectedly, the *in situ* spontaneous formation of the lactam ring was not observed under either of the reaction conditions. In the reported formal synthesis of nectrisine, cyclization is produced in a fully deprotected product.[43a] Moreover, in parallel studies with other substrates, we had observed that the benzoate group in **152** prevented cyclization. Thus, after hydrolysis of Boc groups in **152a** with TFA, the reaction crude **153** was treated with LiOH to afford lactam **154** in 81% yield for the two steps. Further selective protection of primary hydroxyl group by reaction with TBDPSCl provided compound **115** in 89% yield. The synthesis of nectrisine from this compound has been previously reported and hence, this approach constituted a formal synthesis.[47]

In summary, the first enantioselective formal synthesis of the glycosidase inhibitor nectrisine has been carried out in 7 steps and 48% overall yield starting from the commercially available racemic butadiene monoepoxide. All spectroscopic data of the obtained compound are in agreement with those reported for the compound **115** and confirmed the assignement of the relative configuration in the dihydroxylation reaction.

# III. Experimental section

## III.1. General Methods

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

$^1H$ and $^{13}C$ NMR spectra were recorded on a Varian® Mercury VX 400 (400 MHz and 100.6 MHz respectively) or Varian 400-MR spectrometer in $CDCl_3$ as solvent, with chemical shifts (δ) referenced to internal standards $CDCl_3$ (7.26 ppm $^1H$, 77.16 ppm $^{13}C$) or $Me_4Si$ as an internal reference (0.00 ppm). $^1H$ NMR spectra are reported as follows (s = singlet, d = doublet, t = triplet, q = quartet, b = broad; coupling constant(s) in Hz; integration). 2D correlation spectra (gCOSY, NOESY, gHSQC, gHMBC) were visualized using VNMR program (Varian®). ESI MS were run on an Agilent® 1100 Series LC/MSD instrument. Optical rotations were measured at room temperature in a Perkin-Elmer® 241 MC apparatus with 10 cm cells. IR spectra were recorded on a JASCO FT/IR-600 plus Fourier Transform Infrared Spectrometer ATR Specac Golden Gate. Reactions were monitored by TLC carried out on 0.25 mm E. Merck® silica gel 60 F254 glass or aluminium plates. Developed TLC plates were visualized under a short-wave UV lamp (250 nm) and by heating plates that were dipped in ethanol/$H_2SO_4$ (15:1) and basic solution of potassium permanganate. Flash column chromatography was carried out using forced flow of the indicated solvent on Fluka® or Merck® silica gel 60 (230-400 mesh). Flash column chromatography (FCC) was performed using flash silica gel (32–63 μm) and using a solvent polarity correlated with TLC mobility.

Compounds *t*-butyl benzoylimido carboxylate,[85] (-)-(*S*)-*tert*-butyl-1-hydroxybut-3-en-2-ylcarbamate **126**,[67] (-)-(*S*)-*tert*-butyl-1-benzoyloxybut-3-ene-2-yl-carbamate **128**,[86] prop-2-ene-1,1-diyl diacetate **131**,[86] (*S*)-*tert*-butyl-(1-((*tert*-

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85 Trost, B. M.; Fandrick, D. R.; Brodmann, T.; Stilles, D. T. *Angew. Chem. Int. Ed.* **2007**, *46*, 6123-6125.

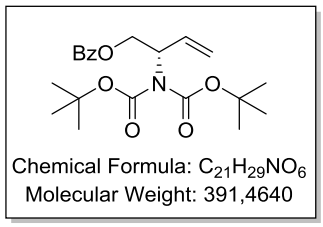
86 Trost, B. M.; Lee, C. B. *J. Am. Chem. Soc.* **2001**, *123*, 3671-3686.

butyldiphenylsilyl)oxy)but-3-en-2-yl)carbamate **150**,[87] were synthesized according to reported procedures. $^{1}$H NMR and $^{13}$C NMR resulted to be identical to the reported ones.

[87] Gärtner, M.; Weihofen, R.; Helmchen, G. *Chem. Eur. J.* **2011**, *17*, 7605-7622.

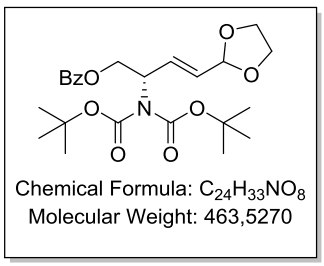
## III.2. Compound characterization

**(*2S*)-2-(bis-(*tert*-Butoxycarbonyl)amino)but-3-en-1-yl benzoate (128)**.[71]




Compound **126** (1.24 g, 3.17 mmol) was dissolved in freshly destilled triethylamine (11 mL) and then DMAP (1.04 g, 8.51 mmol) was added. The mixture was cooled to 0 °C and di-*tert*-butyl dicarbonate (4.9 mL, 16.48 mmol) was added. After 10 minutes the mixture was warmed to room temperature and it was stirred for 20 h. The crude was dissolved in aqueous $NH_4Cl$ and the aqueous phase was extracted with ethyl acetate. The combined organic layers were washed with water and brine and they were dried over $MgSO_4$. The solvent was removed under vacuum and the crude was purified by silica gel chromatography using 97:3 hexanes:ethyl acetate as eluent to afford 1.23 g of product **128** as a colorless oil (99%). $[\alpha]_D^{25}$ −30.5 (*c* 1, $CHCl_3$). **$^1$H NMR (400 MHz, $CDCl_3$):** δ (ppm) 8.06-7.99 (m, 2H), 7.59-7.49 (m, 1H), 7.47-7.36 (m, 2H), 6.01 (ddd, *J* = 17.2, 10.5, 6.1 Hz, 1H), 5.33 (dd, *J* =17.2 Hz, 1.2 Hz, 1H), 5.27 (dd, *J* =10.5 Hz, 1.2 Hz, 1H), 5.22-5.16 (m, 1H), 4.66 (dd, *J* = 11.0 Hz, 8.9 Hz, 1H), 4.60 (dd, *J* = 11.0 Hz, 6.0 Hz, 1H), 1.46 (s, 18H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ (ppm)166.2, 152.8, 133.7, 133.1, 130.1, 129.8, 128.4, 118.4, 82.8, 64.8, 57.2, 28.1. **FTIR-ATR (cm$^{-1}$):** 3094, 2979, 2933, 1723, 1700, 1452, 1367, 1347, 1267, 1112, 855, 710. **HMRS (ESI-TOF) m/*z*:** $[M+Na]^+$ calcd for $C_{21}H_{29}NaNO_6$: 414.1893, Found: 414.1892.

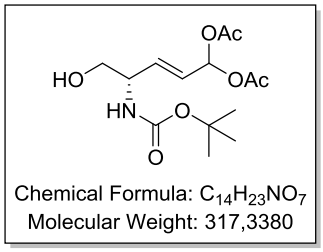
**(2*S*,3*E*)-2-(bis-(*tert*-Butoxycarbonyl)amino)-4-(1,3-dioxolan-2-yl)but-3-en-1-yl benzoate (133)**.[71]




To a solution of product **128** (100 mg, 0.26 mmol) and II generation Grubbs catalyst (11 mg, 0.013 mmol) in dichloromethane (6 mL), 2-vinyldioxolane (**131**) (0.13 mL, 1.3 mmol) was added at reflux. The reaction was stirred at reflux for 12h, and then evaporation of solvent and purification by silica gel chromatography (hexanes:EtOAc, 10:3) provided the desired product **133** (94 mg, 78%). **$^1$H NMR (400 MHz, $CDCl_3$):** δ (ppm) 8.02 (d, *J* =8.4 Hz, 2H),

7.54 (t, *J* =7.6 Hz, 1H), 7.41 (dd, *J* = 8.4 Hz, 7.6 Hz, 2H), 6.11 (dd, *J* = 16.0 Hz, 6.4 Hz, 1H), 5.74 (dd, *J* = 16.0 Hz, 6.0 Hz, 1H), 5.28 (d, *J* = 6.0 Hz, 1H), 5.29-5.23 (m, 1H) , 4.69 (dd, *J* = 11.2 Hz, 10.8 Hz, 1H), 4.58 (dd, *J* = 11.2 Hz, 6.0 Hz, 1H), 3.97-3.91 (m, 4H), 1.45(s, 18H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ (ppm) 166.3, 152.6, 133.3, 131.5, 130.1, 130.0, 128.5, 103.2, 83.1, 65.2, 64.7, 55.9, 28.2. **FTIR-ATR ($cm^{-1}$):** 2979, 2933, 2888, 1721, 1701, 1367, 1348, 1267, 1147, 1113, 968, 712. **HMRS (ESI-TOF) m/*z*:** $[M+Na]^+$ calcd for $C_{24}H_{33}NaNO_8$: 486.2104, Found: 486.2109.

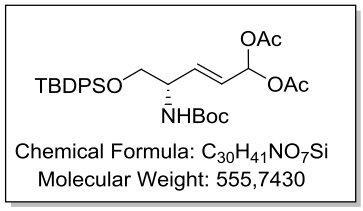
**(+)-(2*S*,3*E*)-4-(*tert*-Butoxycarbonylamino)-5-hydroxypent-2-ene-1,1-diyl diacetate (135).**



Chemical Formula: $C_{14}H_{23}NO_7$
Molecular Weight: 317,3380

Compound **127** (50 mg, 0.267 mmol) and prop-2-ene-1,1-diyl diacetate (157 µL, 1.068 mmol) were dissolved in $CH_2Cl_2$ (2 mL) at room temperature. Second generation Grubbs catalyst (5 mol%) was added to the solution and then the reaction mixture was refluxed under argon for 12 h. After cooling, the reaction mixture was concentrated and purified by column chromatography with hexanes:ethyl acetate (6:4) to afford compound **135** (80 mg, 95%) as a brown oil. **$\alpha_D^{25}$** +175.0 (*c* 7.5, $CHCl_3$). **$^1$H NMR (400 MHz, $CDCl_3$):** δ (ppm) 7.10 (d, *J* = 6.0 Hz, 1H), 5.99 (dd, *J* = 15.7 Hz, 4.8 Hz, 1H), 5.73 (dd, *J* = 15.7 Hz, 6.0 Hz, 1H), 5.05 (bs, 1H), 4.82-4.77 (m, 1H), 3.67-3.62 (m, 2H), 2.70 (bs, 1H), 2.06 (s, 6H), 1.42 (s, 9H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ (ppm) 168.8, 155.8, 134.7, 125.1, 89.0, 80.0, 64.8, 53.3, 28.4 (3C), 21.0 (2C). **FTIR-ATR ($cm^{-1}$):** 3370, 2977, 2931, 1761, 1695, 1521, 1168, 960. **HMRS (ESI-TOF) m/*z*:** $[M+Na]^+$ calcd for $C_{14}H_{24}NO_7Na$: 340.1367, found: 340.1340.

**(+)-(2*S*,3*E*)-4-(*tert*-Butoxycarbonylamino)-5-(*tert*-butyldiphenylsilyloxy) pent-2-ene-1,1-diyl diacetate (137).**

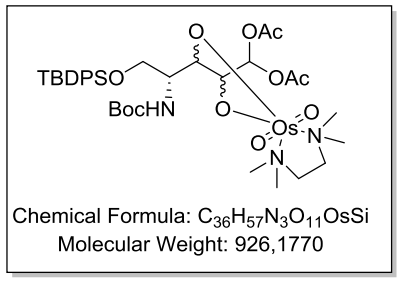


Chemical Formula: $C_{30}H_{41}NO_7Si$
Molecular Weight: 555,7430

Compound **134** (260 mg, 0.82 mmol) was dissolved in dry DMF (1 mL) and treated under argon with *tert*-butylchlorodiphenylsilane (256 µL, 0.98 mmol) and imidazole (112 mg, 1.64 mmol). The mixture was then stirred for 16h at

room temperature. Workup (extraction with $Et_2O$) and column chromatography on silica gel with hexanes:ethyl acetate (9:1) provided **137** (418 mg, 92%) as a colorless oil. $\boldsymbol{\alpha_D^{25}}$ +23.4 (*c* 2.1, $CHCl_3$). **$^1$H NMR (400 MHz, $CDCl_3$):** δ (ppm) 7.72-7.56 (m, 5H), 7.46-7.36 (m, 5H), 7.20 (d, *J* = 6.1 Hz, 1H), 6.04 (dd, *J* = 15.7 Hz, 5.0 Hz, 1H), 5.76 (ddd, *J* = 15.7 Hz, 6.1 Hz, 1.6 Hz, 1H), 4.91 (d, *J* = 8.6 Hz, 1H), 4.35 (bs, 1H), 3.77-3.61 (m, 2H), 2.06 (s, 3H), 2.05 (s, 3H), 1.45 (s, 9H), 1.05 (s, 9H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ (ppm) 168.5, 168.4, 155.1, 135.6, 135.5, 135.2, 133.0, 132.8, 129.9, 129.8, 127.8, 127.7, 124.5, 88.8, 79.6, 65.5, 52.8, 28.3, 26.8, 20.8, 20.7. **FTIR-ATR (cm$^{-1}$):** 3360, 2962, 2931, 2858, 1762, 1716, 1239, 1203, 1112, 1007, 961, 702. **HMRS (ESI-TOF) m/*z*:** $[M+Na]^+$ calcd for $C_{30}H_{41}NNaO_7Si$: 578.2545, found: 578.2546.

**(+)-(2*S*,3*R*,4*R*)-4-(*tert*-Butoxycarbonylamino)-5-(*tert*-butyldiphenylsilyloxy)-2,3-dihydroxy-1,1-diyl diacetate tetramethylethylenediamine osmate derivative (138)**.

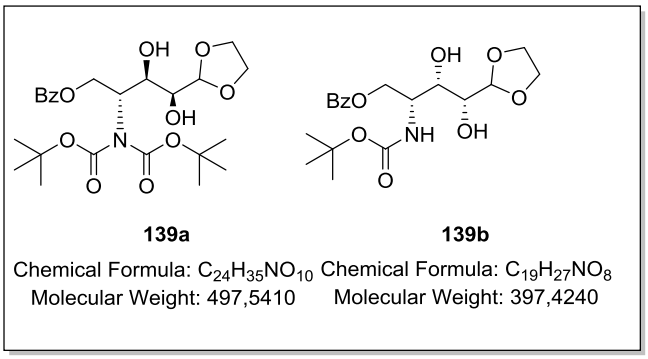



Compound **137** (1.2 g, 2.1 mmol) was dissolved in $CH_2Cl_2$ (2 mL) at -78ºC under dry argon. TMEDA (0.035 mL, 2.3 mmol) was added and the reaction was stirred for 5 minutes before the rapid addition of osmium tetraoxide (0.535 g, 2.1 mmol). The dark coloured solution was stirred for 2 hours at -78ºC before being warmed to room temperature. The solvent was removed *in vacuo* to get a black solid. Purification by silica gel chromatography using ethyl acetate:methanol 8:2 as eluent afforded compound **138** (1.86 g, 96%, inseparable mixture of two diastereoisomers, 87:13) as a dark oil.

**Compound 138 (major)**: **$^1$H NMR (400 MHz, $CDCl_3$):** δ (ppm) 7.70 (m, 5H), 7.42-7.29 (m, 5H), 7.17 (d, *J* = 5.4 Hz, 1H), 5.56 (d, *J* = 9.2 Hz, 1H), 4.77 (dd, *J* = 5.4 Hz, 2.4 Hz, 1H), 4.53-4.44 (m, 1H), 4.27 (t, *J* = 5.4 Hz, 1H), 3.90 (t, *J* = 9.0 Hz, 1H), 3.73 (dd, *J* = 9.0 Hz, 5.5 Hz, 1H), 3.17-2.92 (m, 4H), 2.85-2.70 (m, 12H), 2.10 (s, 3H), 2.03 (s, 3H), 1.37 (s, 9H), 1.04 (s, 9H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ (ppm) 169.1, 168.7, 156.1, 135.8, 135.7, 134.1, 134.0, 129.5, 129.5, 127.6, 127.6, 88.4, 88.2, 85.5, 78.5, 64.3, 63.5, 56.1, 52.4, 51.5, 51.2, 28.5, 26.9, 21.13, 21.09. **FTIR-ATR (cm$^{-1}$):** 3436, 2930, 2857, 1763, 1707, 1474, 1367,

1242, 1112, 1011, 838, 704. **HMRS (ESI-TOF) m/z:** $[M+Na]^+$ calcd for $C_{36}H_{57}N_3NaO_{11}OsSi$: 950.3269, found: 950.3252.

**(2*R*,3*R*,4*S*)-2-((bis-*tert*-butoxy)carbonyl)amino-4-(1,3-dioxolan-2-yl)-3,4-dihydroxybutyl benzoate (139a) and (2*R*,3*S*,4*R*)-2-((bis-*tert*-butoxy)carbonyl)amino-4-(1,3-dioxolan-2-yl)-3,4-dihydroxybutyl benzoate (139b).**[71]

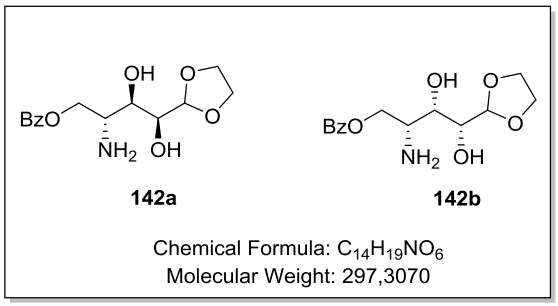



To a solution of product **136** (0.28 g, 0.6 mmol) in dichloromethane (25mL) cooled at 0ºC, NMO (0.38 g, 1.5 mmol) and $OsO_4$ (0.044 mL, 0.015 mmol) were added. The solution was stirred at room temperature for 24h. The reaction mixture was quenched by addition of a solution of $Na_2S_2O_3$ and stirred for 15min. The aqueous layer was extracted with EtOAc three times and the combined organic layers were washed with brine, dried over $MgSO_4$ and concentred in vacuo. Purification of the product (hexanes/EtOAc) provided two products **139a** (0.2 g, 70%) and **139b** (0.06 g, 25%).

**Compound (139a)**:$[\alpha]_D^{25}$ −3.6 (*c* 0.7, $CHCl_3$). **$^1$H NMR (400 MHz, $CDCl_3$):** δ (ppm) 8.02 (d, *J* = 8.0 Hz, 2H), 7.54 (t, *J* = 7.6 Hz, 1H), 7.42 (t, *J* = 8.0 Hz, 2H), 5.04 (d, *J* = 4.0 Hz, 1H), 4.8 (dd, *J* = 6.4 Hz, 2.0 Hz, 2H), 4.58 (ddd, *J* = 8.8 Hz, 4.8 Hz, 1H), 4.32 (t, *J* = 8.0 Hz, 1H), 4.01-3.96 (m, 4H), 3.67 (t, *J* = 4.8 Hz, 1H), 3.07 (bs, 1H), 1.64 (bs, 1H), 1.44 (s, 18H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ (ppm) 166.3, 153.9, 133.1, 130.1, 129.9, 128.4, 104.1, 83.5, 70.5, 69.8, 65.4, 63.3, 58.1, 28.1. **FTIR-ATR ($cm^{-1}$):** 3481, 2978, 2924, 1720, 1702, 1367, 1349, 1269, 1148, 1070, 852, 712. **HMRS (ESI-TOF) m/z:** $[M+Na]^+$ calcld for $C_{24}H_{35}NNaO_{10}$: 520.2159, Found: 520.2131.

**Compound (139b)**: $[\alpha]_D^{25}$ −9.0 (c 0.18,$CHCl_3$). **$^1$H NMR (400 MHz, $CDCl_3$):** δ (ppm) 8.01 (d, *J* = 8.0 Hz, 2H), 7.57 (t, *J* = 7.2 Hz, 1H), 7.44 (t, *J* = 8.0 Hz, 2H), 5.04 (d, *J* = 5.2 Hz, 1H), 4.69-4.60 (m, 3H), 4.4 (dd, *J* = 13.2 Hz, 3.6 Hz, 1H), 4.03-3.95 (m, 4H), 3.66 (bs, 1H), 2.60 (bs, 1H), 1.64 (bs, 1H), 1.52 (s, 9H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ (ppm) 166.2, 149.1, 133.6, 129.9, 129.1, 128.7, 102.0, 84.6, 74.6, 72.6, 65.4, 63.6, 55.6, 28.1. **FTIR-ATR (cm$^{-1}$):** 3339, 2972, 2899, 2357, 1717, 1455, 1378, 1271, 1086, 1046, 880, 668. **HMRS (ESI-TOF) m/*z*:** $[M+Na]^+$ calcld for $C_{19}H_{27}NNaO_8$: 420.1634, Found: 420.1622.

**(2*R*,3*R*,4*S*)-2-Amino-4-(1,3-dioxolan-2-yl)-3,4-dihydroxybutyl benzoate (142a)**
**(2*R*,3*S*,4*R*)-2-Amino-4-(1,3-dioxolan-2-yl)-3,4-dihydroxybutyl benzoate (142b).**[71]

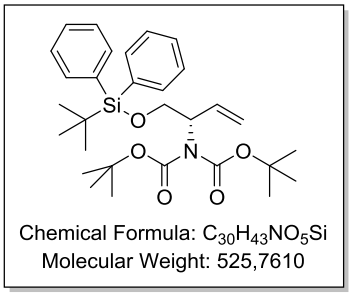



A solution of the mixture **139a**, **139b** (0.1 g, 0.2 mmol) in $CH_2Cl_2$ (1 mL) was treated with triftuoroacetic (1 mL). The reactionmixture was then stirred for 2h at 0ºC. Removal of all volatiles under reduced pressure gave two products one soluble in MeOH (**142a**, 0.024 g, 40%, Maj) and other soluble in $CDCl_3$ (**142b**, 0.018 g , 30 %, Min).

**Compound 142a**: $[\alpha]_D^{25}$ +8.7 (*c* 0.8, $CH_3OH$). **$^1$H NMR (400 MHz, $CDCl_3$):** δ (ppm) 8.13 (d, 2H, *J* = 7.2 Hz), 7.64 (t, *J* = 6.8 Hz, 1H), 7.51 (t, *J* = 8.0 Hz, 2H), 5.06 (d, *J* = 4.4 Hz, 1H), 4.75 (dd, *J* = 12.0 Hz, 3.6 Hz, 1H), 4.56 (dd, *J* = 12.0 Hz, 7.2 Hz, 1H), 4.11 (dd, *J* = 6.0 Hz, 3.6 Hz, 1H), 4.02-3.95 (m, 4H), 3.86-3.79 (m, 1H), 3.72 (t, *J* = 3.6 Hz, 1H). **$^{13}$C NMR (100 MHz, MeOD):** δ (ppm) 158, 125.1, 121.3, 121.1, 120.1, 94.7, 63.6, 59.4, 56.9, 56.8, 53.7, 45.1. **FTIR-ATR (cm$^{-1}$):** 3343, 2922, 1719, 1668, 1540, 1271, 1181, 1131, 1044, 974, 836, 708. **HMRS (ESI-TOF) m/*z*:** [M+H] calcd for $C_{14}H_{20}NO_6$: 298.1285, Found: 298.1288.

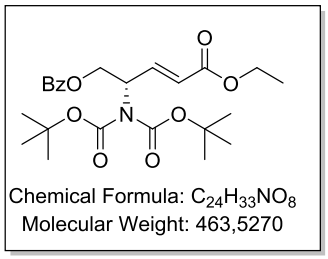
**Compound 142b**: $[\alpha]_D^{25}$ +13.8 (*c*1,$CHCl_3$). **$^1$H NMR (400 MHz, $CDCl_3$):** δ (ppm) 8.01 (d, *J* = 7.6 Hz, 2H), 7.59 (t, *J* = 6.8Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 2H), 5.37(bs, 1H), 5.06 (d, *J* = 4.8 Hz, 1H), 4.64 (dd, *J* = 4.8 Hz, 2.8 Hz, 1H), 4.51 (dd, *J* = 10.8 Hz, 3.2 Hz, 1H), 4.33-4.26 (m, 2H), 4.03-3.95 (m, 4H), 3.68 (bs, 1H), 2.60 (bs, 1H). **FTIR-ATR ($cm^{-1}$):** 3343, 2922, 1750, 1718, 1451, 1394, 1315, 1270, 1114, 1070, 1027, 712. **HMRS (ESI-TOF) m/z:** $[M+Na]^+$ calcd for $C_{14}H_{19}NNaO_6$: 320.1105 , Found: 320.1129.

**(2*S*)-2-(bis-(*tert*-Butoxycarbonyl)amino)-1-*tert*-butyldiphenylsilyl-but-3-en-1-ol (150')**.




Compound **150** (651 mg, 1.53 mmol) was dissolved in freshly destilled triethylamine (11 mL), and then DMAP (187 mg, 1.53 mmol) was added. The mixture was cooled to 0 °C and di-*tert*-butyl dicarbonate (1.33 mL, 6.12 mmol) was added. After 10 minutes the mixture was warmed to room temperature and stirred for 10 h. The crude was dissolved in aqueous $NH_4Cl$ and the aqueous phase was extracted with ethyl acetate. The combined organic layers were washed with brine and water and they were dried over $MgSO_4$. The solvent was removed under vacuum and the crude was purified by silica gel chromatography using 97:3 hexanes:ethyl acetate as eluent to afford 764 mg of product **150'** as a colorless oil (95%). **$[\alpha]_D^{25}$** +12.4 (*c* 1.05, $CHCl_3$). **$^1$H NMR (400 MHz, $CDCl_3$):** δ (ppm)7.71-7.63 (m, 4H), 7.45-7.31 (m, 6H), 5.92 (ddd, *J* = 17.3 Hz, 10.5 Hz, 6.3 Hz, 1H), 5.19 (dt, *J* = 17.3 Hz, 1.4 Hz, 1H), 5.13 (dt, *J* = 10.5 Hz, 1.4 Hz, 1H), 4.98 (dtt, *J* = 8.9 Hz, 6.3 Hz, 1.5 Hz, 1H), 4.09 (dd, *J* = 9.9 Hz, 8.9 Hz, 1H), 3.77 (dd, *J* = 9.9 Hz, 6.3 Hz, 1H), 1.47 (s, 18H), 1.04 (s, 9H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ (ppm) 153.1, 135.6, 135.6, 134.6, 133.6, 133.6, 129.7, 129.6, 127.7, 127.7, 117.5, 81.0, 64.3, 60.6, 28.1, 26.8, 19.3. **FTIR-ATR ($cm^{-1}$):** 3071, 2979, 2931, 2857, 1741, 1701, 1367, 1113. **HMRS (ESI-TOF) m/z:** $[M+Na]^+$ calcd for $C_{30}H_{43}NNaO_5Si$: 548.2803, found: 548.2802.

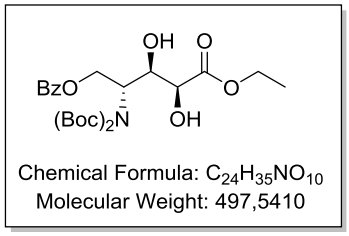
**Ethyl (2*E*,4*S*)-5-benzoyloxy-4-(bis-(*tert*-butoxycarbonyl)amino)-pent-2-enoate (151a)**.



Chemical Formula: $C_{24}H_{33}NO_8$
Molecular Weight: 463,5270

To a solution of product **128** (0.3 g, 0.77 mmol) and (0.024 g, 0.0385 mmol) of Hoveyda-Grubbs catalyst in dichlorometane (2 mL), ethylacrylate (0.41 mL, 3.85 mmol) was added. The reaction mixture was further stirred at reflux for 12h. Evaporation of solvent and purification of the crude by silica chromatography using hexanes/ethyl acetate 90:6 provided the desired product **151a** (339 mg, 95%) as a yellow liquid. $[\alpha]_D^{25}$ +13.8 (*c*1.1, $CHCl_3$). **$^1$H NMR (400 MHz, $CDCl_3$):** δ (ppm) 7.97 (dd, *J* = 8.4, 1.3 Hz, 2H), 7.55-7.47 (m, 1H), 7.41-7.33 (m, 2H), 7.00 (dd, *J* = 16.0 Hz, 5.0 Hz, 1H), 5.97 (dd, *J* = 16.0 Hz, 1.9 Hz, 1H), 5.41-5.30 (m, 1H), 4.69-4.58 (m, 2H), 4.15 (q, *J* = 7.1 Hz, 2H), 1.41 (s, 9H), 1.23 (t, *J* = 7.1 Hz, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ (ppm) 165.9, 165.7, 152.1, 143.5, 133.2, 129.7, 129.7, 128.3, 122.8, 83.3, 64.1, 60.6, 55.3, 27.9, 14.2. **FTIR-ATR (cm$^{-1}$):** 2979, 1720, 1452, 1367, 1350, 1265, 1231, 1149, 1112, 975, 854, 710. **HMRS (ESI-TOF) m/z:** $[M+Na]^+$ calcld for $C_{24}H_{33}NNaO_8$ : 486.2104, Found: 486.2123.

**Ethyl (2*S*,3*R*,4*R*)-5-(benzoyloxy)-4-(bis-(*tert*-butoxycarbonyl)amino)-2,3-dihydroxypentanoate (152a)**.

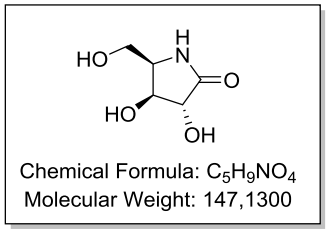


Chemical Formula: $C_{24}H_{35}NO_{10}$
Molecular Weight: 497,5410

Compound **151** (890 mg, 1.92 mmol) was dissolved in $CH_2Cl_2$ (20 mL) under dry argon and the solution was cooled to -78ºC. Then, TMEDA (320 μL, 2.11 mmol) was added and the reaction was stirred for 5 minutes before the rapid addition of osmium tetraoxide (488 mg, 1.92 mmol). The dark coloured solution was stirred for 2 hours at -78ºC before being warmed to room temperature and stirred for 5h. The solvent was removed *in vacuo* and the black solid was dissolved in methanol (5 mL). Concentrated hydrochloric acid (10 drops) was added and the reaction was stirred for 2 hours. The solvent was removed *in vacuo* to afford product **152a** in 91% yield (870 mg) as one diastereoisomer. $[\alpha]_D^{25}$ −6.2 (*c* 10, $CHCl_3$). **$^1$H NMR (400 MHz, $CDCl_3$):** δ (ppm) 8.02-7.91 (m, 2H), 7.47 (t, *J* = 7.5 Hz, 1H), 7.34 (t, *J* = 7.5 Hz, 2H),

4.82-4.62 (m, 3H), 4.46 (t, *J* = 8.8 Hz, 1H), 4.27 (d, *J* = 5.4 Hz, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.55 (d, *J* = 5.4 Hz, 1H), 3.31 (d, *J* = 9.9 Hz, 1H), 1.39 (s, 18H), 1.24 (t, *J* = 7.1 Hz, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ (ppm) 172.9, 166.3, 152.2, 133.1, 130.1, 129.8, 128.3, 83.4, 71.9, 70.9, 63.1, 62.2, 57.8, 27.9, 14.2. **FTIR-ATR (cm$^{-1}$):** 3484, 2979, 2931, 1723, 1452, 1367, 1348, 1268, 1227, 1149, 1114, 711. **HMRS (ESI-TOF) m/z:** $[M+Na]^+$ calcd for $C_{24}H_{35}NNaO_{10}$: 520.2159, Found: 520.2156.

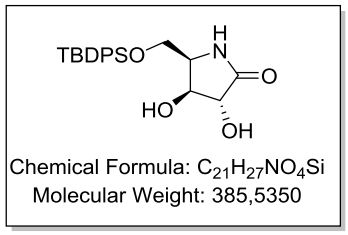
**(3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-(hydroxymethyl)pyrrolidin-2-one (154)**.[88]




An ice-cooled solution of dihydroxy ester **152** (117 mg, 0.2354 mmol) in $CH_2Cl_2$ (1 mL) was treated with trifluoroacetic acid (1 mL). The mixture was then stirred for 2 h at 0°C. Removal of all volatiles under reduced pressure gave crude **153** which was dissolved in THF. An aqueous solution of LiOH (0.4 mL, 0.6 mmol, 1M) was added to that solution and the mixture was stirred at room temperature for 20 h. The crude was diluted with water, and it was washed with dichloromethane. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent was removed under vacuum. The crude was purified by silica gel chromatography using $CHC1_3$/MeOH/$NH_4OH$ (28% aq.), 5:3:1 as a solvent to afford compound **154** (28 mg) in 81% yield. **$[\alpha]_D^{25}$**= +10.4 (*c* 0.12, $H_2O$), ($[\alpha]_D$ $^{20}$= +15.2 (*c* 0.4, $H_2O$) described). **$^1$H NMR (400 MHz, $D_2O$):** δ (ppm) 4.32 (d, *J* = 8.0 Hz, 1H), 4.02 (dd, *J* = 8.0 Hz, 3.1 Hz, 1H), 3.80 (dd, *J* = 12.3 Hz, 3.1 Hz, 1H), 3.63 (dd, *J* = 12.3 Hz, 4.9 Hz, 1H), 3.47 (ddd, *J* = 8.0 Hz, 4.9 Hz, 3.1 Hz, 1H). **$^{13}$C NMR (100 MHz, $D_2O$):** δ (ppm) 175.4, 75.4, 74.2, 59.8, 57.8. **HMRS (ESI-TOF) m/z:** $[M-H]^{+-}$ calcd for $C_5H_9NO_4$: 147.0532, found: 147.0502.

[88] Jeon, J.; Kim, S-H.; Lee, J. H.; Oh, J. S.; Park, D. Y.; Kim, Y. G. *Bull. Korean Chem. Soc*. **2009**, *30*, 1003-1008.

**(3*R*,4*S*,5*R*)-5-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-3,4-dihydroxypyrrolidin-2-one (115)**.[47]




Compound **154** (14 mg, 0.0951 mmol) was dissolved in dry DMF (1mL) and treated under argon with *tert*-butyldiphenylsilyl chloride (29 μL, 0.11 mmol) and imidazole (15 mg, 0.11 mmol). The mixture was then stirred for 16h at room temperature. Workup (extraction with $Et_2O$) and column chromatography on silica gel (ethyl acetate) provided **26** in 89% yield (32 mg). **$^1$H NMR (400 MHz, $CDCl_3$):** δ (ppm) 7.66-7.57 (m, 4H), 7.47-7.33 (m, 6H), 6.07 (bs, 1H), 4.28 (d, *J* = 7.5 Hz, 1H), 4.00 (t, *J* = 7.5 Hz, 1H), 3.89 (dd, *J* = 10.5 Hz, 3.2 Hz, 1H), 3.63 (dd, *J* = 10.5 Hz, 7.4 Hz, 1H), 3.53 (td, *J* = 7.4 Hz, 3.2 Hz, 1H), 1.04 (s, 9H).

# CHAPTER 4

*Enantioselective formal synthesis of D-fagomine*

# I. Introduction

Allylamines are valuable intermediates in organic synthesis and are also present in biologically important natural products (Figure 12).[1] The independent reactivity of the alkene and the amine portions of allylamines allow for the stepwise functionalization of these motifs. Moreover, chiral amines are important compounds in organic chemistry since they have been employed as chiral bases,[2a] nucleophiles,[2b] auxiliaries,[2c] and ligands[2d] for asymmetric synthesis.[3]

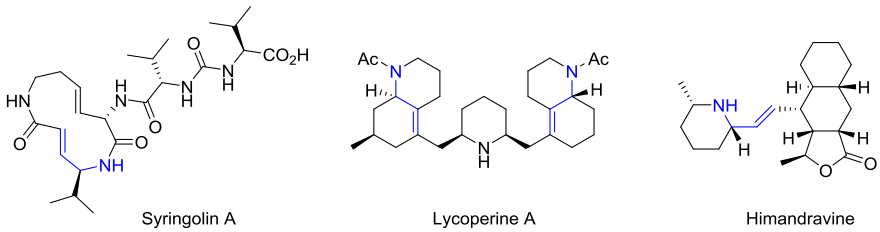



**Figure 12.** Selected natural products containing chiral allylic amine.

Therefore, the development of methods for introducing nitrogen functionality into organic frameworks has been an important research topics in synthetic chemistry and considerable effort has been devoted to the synthesis of chiral allylic amines.[4,5]

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1 (a) Nakamura, Y.; Burke, A. M.; Kotani, S.; Ziller, J. W.; Rychnovsky, S. D. *Org. Lett*. **2009**, *12*, 72-75. (b) Dai, C.; Stephenson, C. R. J. *Org. Lett*. **2010**, *12*, 3453-3455. (c) Clark, R. B.; He, M.; Fyfe, C.; Lofland, D.; O'Brien, W. J.; Plamondon, L.; Sutcliffe, J. A.; Xiao, X.- Y. *J. Med. Chem*. **2011**, *54*, 1511-1528. (d) Chackalamannil, S.; Davies, R.; McPhail, A. T. *Org. Lett*. **2001**, *3*, 1427-1429.

2 For some recent examples see: (a) Graf, C.-D.; Malan, C.; Harms, K.; Knochel, P. *J. Org. Chem*. **1999**, *64*, 5581-5588. (b) Davies, S. G.; McCarthy, T. D. *Synlett* **1995**, 700-702. (c) Choi, I.-Y.; Lee, H. G.; Chung, K.-H. *J. Org. Chem*. **2001**, *66*, 2484-2486. (d) Hashizume, T.; Yonehara, K.; Ohe, K.; Uemura, S. *J. Org. Chem*. **2000**, *65*, 5197-5201.

3 Wei, Z.-Y.; Kraus, E. E. *Synthesis* **1994**, 1463-1466 and references cited therein.

4 (a) Cheikh, R. B.; Chaabouni, R.; Laurent, A.; Mison, P.; Nafti, A. *Synthesis* **1983**, 685-700. (b) Johannsen, M.; Jørgensen, K. A. *Chem. Rev*. **1998**, 98, 1689-1708. (c) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res*. **2002**, *35*, 984-995. (d) Trost, B. M.; Crawley, M. L. *Chem. Rev*. **2003**, *103*, 2921-2944. (e) Burk, M. J.; Allen, J. G.; Kiesman, W. F. *J. Am. Chem. Soc*. **1998**, *120*, 657-663.

General methods for the synthesis of these compounds can be divided into two large categories: nucleophilic allylic substitution and direct allylic amination.[6] Examples of nucleophilic allylic substitution include the Mitsunobu reaction of allyl alcohols,[7] the thermal [3,3]-sigmatropic rearrangement of allylic trichloroacetamides (Overman rearrangement),[8] the Gabriel amination of allyl halides,[9] and palladium-,[10] copper-,[11] iron-,[12] rhodium-[13] catalized allylic aminations. On the other hand, the direct allylic amination methods involve the nitrene addition with allylsilanes and the ene reaction[14] of diimido and aza compounds. In addition to the approaches cited above, other methods have proposed solutions that are yet to gain broad support by the organic chemists. Such methods include indirect approaches such as ring-opening reactions of epoxides,[15] azetidines[16] and aziridines[17] followed by elimination, olefination of

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5 (a) Hili, R.; Yudin, A. K. *Nat. Chem. Biol*. **2006**, *2*, 284-287. (b) Ricci, A. Amino Group Chemistry: From Synthesis to the Life Sciences,1st ed.; Wiley-VCH: Weinheim, Germany, **2007**.

6 (a) Ricci, A. Modern Amination Methods WILEY-VCH, Weinheim (**2000**) (b) For a review of synthetic approaches to allylic amines, see: Johannsen, M; Jørgensen, K.A *Chem. Rev*. **1998**, *98*, 1689-1708.

7 (a) Mitsunobu, O. *Synthesis* **1981**, 1-28 (b) Sen, S.E., Roach, S.L. *Synthesis* **1995**, 756-758.

8 (a) Overman, L. E. *J. Am. Chem. Soc*. **1976**, *98*, 2901-2910. (b) Calter, M.; Hollis, T.K.; Overman, L.E.; Ziller, J.; Zipp, G.G. *J. Org. Chem*. **1997**, *62*, 1449-1456.

9 (a) Gibson, M.S.; Bradshaw, R.W. *Angew. Chem*. **1968**, *80*, 986-996. (b) Osby, J.O.; Martin, M.G.; Ganem, B. *Tetrahedron Lett*. **1984**, *25*, 2093-2096.

10 (a) Togni, A.; Burckhardt, U.; Gramlich, V.; Pregosin, P.S.; Salzmann, R. *J. Am. Chem. Soc.* **1996**, *118*, 1031-1037. (b) Tsuji, J.; Takahashi, H.; Morikawa, M. *Tetrahedron Lett*. **1965**, 6, 4387-4388. (c) Lei, A.; Lu, X. *Org. Lett*. **2000**, *2*, 2357-2360. (d) Trost, B. M.; Krueger, A.C.; Bunt, R.C.; Zambrano, J. *J. Am. Chem. Soc*. **1996**, *118*, 6520-6521.

11 (a) Baruah, J. B.; Samuelson, A.G. *Tetrahedron* **1991**, *47*, 9449-9454. (b) Germon, C.; Alexakis, A.; Normant, J.F. *Tetrahedron Lett*. **1980**, *21*, 3763-3766.

12 (a) Srivastava, R.S.; Nicholas, M. *Tetrahedron Lett*. **1994**, *35*, 8739. (b) Enders, D.; Jandeleit, B.; von Berg, S. *Synlett* **1997**, 421-431.

13 (a) Evans, P. A.; Robinson, J.E.; Nelsen, J.D. *J. Am. Chem. Soc*. **1999**, *121*, 6761-6762. (b) Fagnou, K.; Lautens, M. *Org. Lett*. **2000**, 2, 2319-2321.

14 (a) Loreto, M. A.; Tardella, P. A.; Tofani, D. *Tetrahedron Lett*. **1995**, *36*, 8295-8298. (b) Chanda, B. M.; Vyas, R.; Bedekar, A.V.*J. Org. Chem*. **2001**, *66*, 30-34. (c) Matsumoto, M.; Kitano, Y.; Kobayashi, H.; Ikawa, H. *Tetrahedron Lett*. **1996**, *37*, 8191-8194.

15 Concellón, J. M.; Suarez, J. R.; del Solar, V. *Org. Lett*. **2006**, *8*, 349-351.

16 Ghorai, M. K.; Kumar, A.; Das, K. *Org. Lett*. **2007**, *9*, 5441-5444.

17 (a) Dickinson, J.M.; Murphy, J.A. *Tetrahedron* **1992**, *48*, 1317-1326. (b) Penkett, C. S.; Simpson, I. D. *Tetrahedron Lett*. **2001**, *42*, 3029-3032.

*N*-protected α-aminoaldehydes,[18] as well as reductions of α,β-unsaturated imines, amides or oximes (Figure 13).[19]

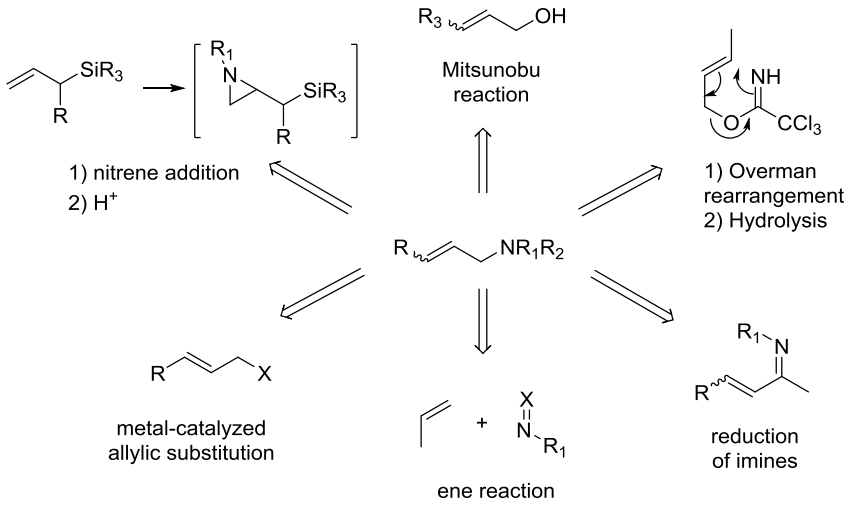


**Figure 13.** Some synthetic approaches to allylamines.

All these methods are constantly improving on the substrate scope, as well as the degree of regio- and stereoselectivity, and each method summarized here has its own advantages and limitations when compared to each other. Transition metal catalysis can be viewed as a superior category of allylic amination methods mostly because they offer the most variability by virtue of having additional parameters to control the fate of reaction intermediates. For this purpose, several transition metals have been used. In particular, palladium has proven to be the most versatile metal catalyst for this reaction, for its high catalytic activity, easy manipulation and high enantioselectivity.[20] Nonetheless, the process is still amenable for further implementation. On one hand, Pd-AAA

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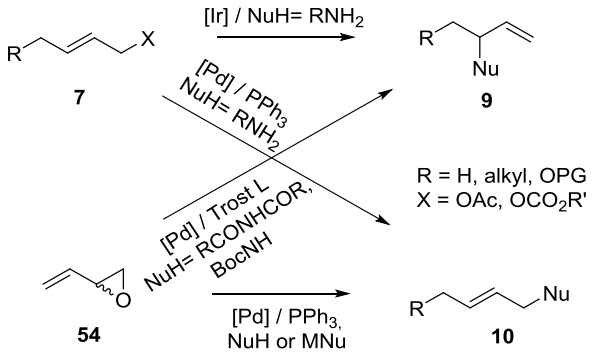
18 (a) Reetz, M. T. *Chem. Rev*. **1999**, *99*, 1121-1162. (b) Wei, Z. -Y.; Knaus, E. E. *Synthesis* **1994**, 1463-1466.

19 (a) Hayashi, T.; Ishigedani, M. *Tetrahedron* **2001**, *57*, 2589-2595. (b) Moody, C.J.; Gallagher, P. T.; Lightfoot, A. P.; Salwin, A. M. Z. *J. Org. Chem*. **1999**, *64*, 4419-4425.

20 For selected publications see a) Trost, B. M. *J. Org. Chem.* **2004**, *69*, 5813-5837. b) Mori, M. *Chem. Pharm. Bull.* **2005**, *53*, 457-70. c) Trost, B. M.; Crawley. *Chem. Rev.* **2003**, *103*, 2921–2943. d) Belda, O.; Moberg, C. *Acc. Chem. Res.* **2004**, *37*, 159-167. e) Sawamura, M.; Ito, Y. *Chem. Rev.* **1992**, *92*, 857-871. f) Trost, B. M. *Pure. Appl. Chem.* **1996**, *68*, 779-784.

typically requires soft nucleophiles such as malonates or imides and application to hard nucleophiles has hardly been reported. On the other hand, only electrophiles with good leaving groups, such as esters or carbonates, have proven efficient in this process. Besides, those with non-stabilized leaving groups have not been reported, with the exception of vinyl epoxides, which due to their ring strain are reactive towards ionization in the Pd-AAA.

The synthesis of allyl amine **9** (R=OH, Nu=NR'$_2$), which is a useful chiral building block in organic synthesis,[21,22,23] is an excellent example for illustrating the regioselectivity problems in palladium allylic amination. Indeed, with the exception of a few examples, the easily accessible allylic electrophiles **7** (Scheme 56), predominantly react at the unsubstituted allyl terminus and consequently, the more thermodynamically stable achiral linear product **10** is formed rather than the chiral branched isomer **9**, which is the preferred product for applications in asymmetric synthesis.[24] Thus, the synthesis of branched allyl amines using this approach has been of little preparative value.




**Scheme 56.** Metal-catalyzed allylic substitution reaction with unsymmetrical monosubstituted substrates **7**, **54**.

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21 (a) Trost, B. M.; Bunt, R. C.; Lemoine, R. C.; Calkins, T. L. *J. Am. Chem. Soc.* **2000**, *122*, 5968-5976. (b) Gnamm, C.; Franck, G.; Miller, N.; Stork, T.; Brödner, K.; Helmchen, G. *Synthesis* **2008**, 3331-3350.

22 Trost, B. M.; Horne, D. B.; Woltering, M. J. *Angew. Chem. Int. Ed.* **2003**, *42*, 5987-5990.

23 Trost, B. M.; Horne, D. B.; Woltering, M. J. *Chem. Eur. J.* **2006**, *12*, 6607-6620.

24 (a) Norsikian, S.; Chang, C.-W. *Curr. Org. Synth.* **2009**, *6*, 264-289. (b) Helmchen, G. Dahnz, A. Dbon, P. Schelwies, M.; Weihofen, R. *Chem. Commun*. **2007**, 675-691.

Judging by the impressive number of publications, controlling regioselectivity in palladium-catalyzed allylic substitution has been an important goal in organic chemistry.

As discussed in the general introduction, there are several factors that influence the regioselectivity of the reaction such as steric and electronic effects from both the substrates and the nucleophiles, but also the nature of the metal, the ligands, the solvent, the presence of additives, etc have a strong influence on the regioselectivity.

For example, substrate **7** affords compound **9** when iridium is used as catalyst, [25,26] while compound **10** is afforded with palladium catalyst limiting the applicability of this latter process in asymmetric processes.[8,9] Vinyl epoxide shows a very marked propensity to give 1,4-addition products in Pd-AA with carbon nucleophiles in the presence of an achiral phosphine, and could be due to the electronic effect of the epoxide oxygen, directing the attack at the remote side of the allyl termini.[27] Asymmetric palladium-catalyzed allylic amination of vinyl epoxide **54**, however, leads to the 1,2-adduct **9** in excellent regio- and enantioselectivities using the family of diphenylphosphino benzoic acid-derived ligands developed by Trost (Scheme 56) and imides as soft nucleophiles. Nevertheless, the use of harder nucleophiles such as amines still poses a challenge, and no examples with this system have been described. A few ligands have also shown to provide an efficient control of regioselectivity in the palladium-catalyzed allylic substitution reaction of unsymmetrical substrates, such as BINAP(S) developped by Faller et *al.*,[28] These ligands direct amines to the more substituted site on the palladium π-allyl complex, which ultimately results in the irreversible formation of branched products **9**. In addition to catalyst modifications, there were also instances when the reactants themselves were biased to give high branched selectivities. Trost and coworkers have shown

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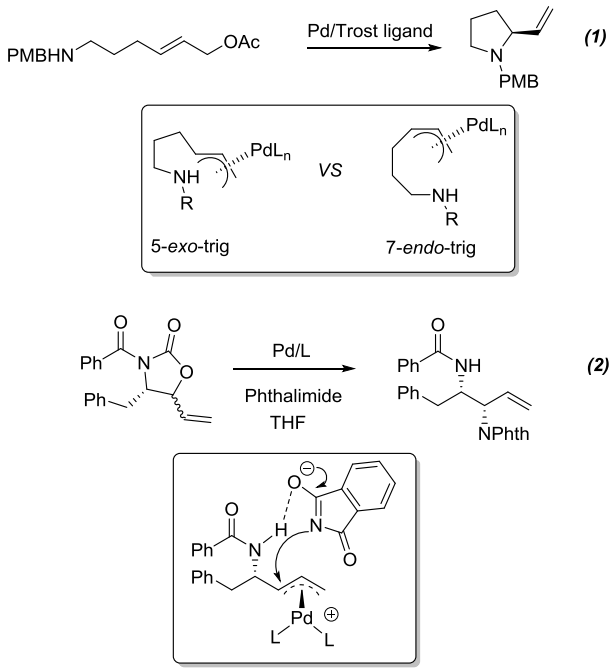
25 Hartwig, J. F.; Stanley, L. M. *Acc. Chem. Res.* **2010**, *43*, 1461-1475

26 Lee, J. H.; Shin, S.; Kang, J.; Lee, S. *J. Org. Chem.* **2007**, *72*, 7443-7446.

27 (a) Trost, B. M.; Molander, G.A. *J. Am. Chem. Soc*. **1981**, *103*, 5969-5972; (b) Trost, B. M.; Cossy, J. *J. Am. Chem. Soc*. **1982**, *104*, 6881-6882; (c) Trost, B. M.; Chen, S.-F. *J. Am. Chem. Soc*. **1986**, *108*, 6053-6054. (d) Trost, B. M.; Kuo, G.-H.; Benneche, T. *J. Am. Chem. Soc*. **1988**, *110*, 621-622

28 (a) Faller, J. W.; Wilt, J. C. *Org. Lett.* **2005**, *7*, 633-636. (b) Faller, J. W.; Wilt, J. C. *Organometallics* **2005**, *24*, 5076-5083.

that ring size could be used to control selectivities in intramolecular allylic amination.[29] Indeed, 2-vinyl pyrrolidines form kinetically faster via a favourable 5-exo-trig transition state, and are more thermodynamically stable than the corresponding allylic tetrahydroazepines (Scheme 57, 1). Certain substituents on the allyl substrates such as trifluoromethyl group may also favor the formation of branched isomers.[30] Another factor that can control regioselectivity is transient intermolecular interactions. Cook showed that the presence of a homoallylic secondary amide directs the approaching phthalimide to the vicinal terminus via a hydrogen bond between the amidic proton and the oxygen of the phthalimide (Scheme 57, 2).[31]




**Scheme 57.** Ring-size control and H-bond-directed control in Pd-catalyzed AAA.

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29 Trost, B. M.; Krische, M. J.; Radinov, R.; Zanoni, G. *J. Am. Chem. Soc.* **1996**, *118*, 6297-6298.

30 Kawatsura, M.; Hirakawa, T.; Tanaka, T.; Ikeda, D.; Hayase, S.; Itoh, T. *Tetrahedron Lett.* **2008**, *49*, 2450-2453.

31 Cook, G. R.; Yu, H.; Sankaranarayanan, S.; Shanker, P. S. *J. Am. Chem. Soc.* **2003**, *125*, 5115-5120.

Control of the regioselectivity by the substrate has also been observed in cases other than vinylepoxide **54**. Thus, palladium-catalyzed allylic amination of 5-vinyloxazolidinones with imide-type nucleophiles affords the branched product probably as a consequence of a hydrogen bond directing effect.[32] Pronucleophiles such as alcohols (regiodirected by boron), imides and carbon-nucleophiles such as β-ketoesters, have been employed with success.

In spite of the intense interest in reversing the preferred regioselectivity in the Pd-catalyzed allylic substitution of non-symmetric monosubstituted allylic electrophiles to favor branched products, the regio- and enantioselectivity of unsymmetrical monosubstituted substrates in palladium-catalyzed allylic substitution reaction remains a challenge.

## II. Results and discusion

The synthesis of chiral allyl amine derivatives is typically carried out using butadiene monoepoxide as the allylic electrophile in a Pd- asymmetric allylic amination using acidic *N*-nucleophiles such as imides or carbamates. The choice of the vinyl epoxide was based on the idea that the alkoxide originated from the ionization of the substrate could direct nucleophilic attack of the acidic nucleophile on the proximal site, probably though hydrogen bonding, thus providing the branched chiral allylic amine. Contrarily, anionic nucleophiles such as malonates furnish linear achiral 1,4-addition products when achiral phosphines are used in achiral reactions. The use of chiral diphenylphosphino ligand, developed by Trost based on a modular concept, provides an excellent control of the regio- and enantioselectivity of the process.

Trying to gain a deeper insight into the key roles of this process, we became interested in exploring the allylic amination of *E*-4-hydroxy-buten-2-yl methyl carbonate derivatives, a linear allylic electrophile that upon ionization under Trost's conditions could formally give the same π-allylpalladium intermediates as those from butadiene monoepoxide. The aim of this work is to explore the effect of installing or not an hydroxyl function on the terminal carbon

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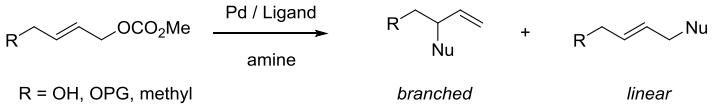
[32] Shanker, P. S.; Pararajasingham, K. *Angew. Chem. Int. Ed.* **1999**, *38*, 110-113.

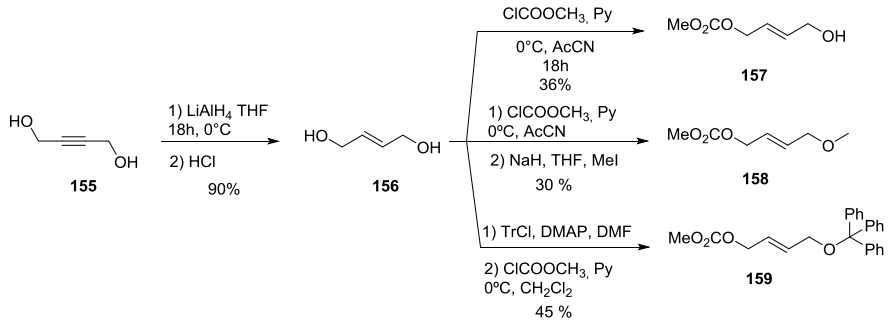
of the allyl carbonate on the regio- or/and enantioselectivty of the process using amines as *N*-nucleophiles and Trost's ligand as a chiral inductor (Scheme 58).




**Scheme 58.** Pd-catalyzed AAA of *E*-4-hydroxy-buten-2-yl methyl carbonate derivatives.

## II.1. Synthesis of starting material allylic carbonates

For our purpose, various derivatives of allylic carbonate were synthesized starting from bis-allylic diol ((*E*)-but-2-ene-1,4-diol **156**). Synthesis of the latter was reported by reduction of but-2-yne-1,4-diol (**155**) (Scheme 59).[33] The reaction was carried out in THF and provided **156** in very good yield (90 %). The reaction proceeds through a *trans*-selective hydrometallation of the triple bond releasing the alkene during the protolytic work-up. Compound **157** was synthesized following standard procedures described in the literature (Scheme 59).[34] Methoxy derivative **158** was obtained from **157** after methylation in basic conditions. We also prepared the very bulky trityl derivative **159** from diol **156** through tritylation followed by carbonatation reaction.




**Scheme 59.** Synthesis of allylic carbonates **157-159**.

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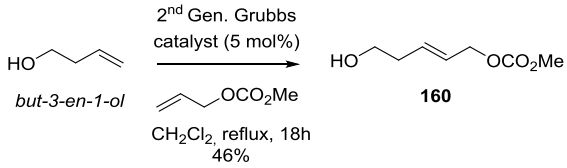
33 McDonald, W. S. Verbicky, C. A.; Zercher, C. K. *J. Org. Chem.* **1997**, *62*, 1215-1222.

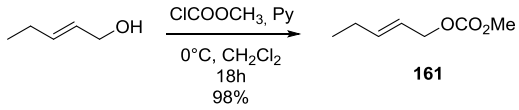
34 Helmchen, G. Dahnz, A. Duebon, P. Schelwies, M.; Weihofen, R. *Chem. Commun*. **2007**, 675-691.

In order to explore if homoallylic alcohols could also play a directing role, we prepared compound **160** via cross metathesis reaction of allyl methyl carbonate and commercially available but-3-en-1-ol (Scheme 60).




**Scheme 60.** Synthesis of allylic carbonate **160** via cross metathesis reaction.

With the aim to determine the effects of oxygen on the regioselectivity, the simple (*E*)-methyl pent-2-enyl carbonate **161** was prepared from (*E*)-pent-2-en-1-ol under similar conditions to those used for for the preparation of **158** (Scheme 61).




**Scheme 61.** Synthesis of allylic carbonate **161**.

## II.2. Palladium-Catalyzed Allylic Amination reaction

*N*-nucleophiles such as imides, purines and pyrimidines contain a relatively acidic proton. Trost and co-workers have rationalized the high branched regioselectivity observed in the reaction of butadiene monoepoxide **54** with imides by the existence of a hydrogen bonding which directs the nucleophilic attack to the more hindered position. As the alkoxide generated in the π-allyl-Pd intermediate is the only base present in the reaction medium able to deprotonate the nucleophile a "proximity effect" might be operative. In the case of allylic carbonate **157** a similar situation could be considered. Indeed, the methoxide anion generated during the oxidative addition step is sufficiently basic to deprotonate these type of *N*-nucleophiles. Consequently the deprotonated form might be involved in a hydrogen-bond with the free hydroxyl group of the π-allyl

complex, directing the nucleophilic attack at the nearest electrophilic carbon leading to the branched regioisomer.

The study was first carried out using *E*-4-hydroxy-buten-2-yl methyl carbonate derivatives **157** and for the sake of comparison, butadiene monoepoxide **54**, two substrates that, upon ionization under Pd-AA, could formally give the same π-allylpalladium intermediate. The latter has been profusely used in the Pd-AAA reaction using relatively acidic soft nitrogenated nucleophiles, but no references have been given with respect to its application with harder amine nucleophiles.[21a,24a,35] In our hands, reaction of butadiene monoepoxide **54** with 4-methoxy-benzylamine **162** in the presence of 2 mol% $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ and 12 mol % of $PPh_3$ in dichloromethane (Table 1, entry 1), afforded a mixture of branched **163** and linear **168** amines in a 24:76 ratio. As expected, the use of chiral (*S*,*S*)-**L3** under similar conditions increased the percentage of the branched product **163** leading, though, to a very poor regioselectivity (44:56) (Table 5, entry 2). The use of a soft nucleophile like phthalimide is described to provide practically exclusively the branched isomer.[35] These results confirm the crucial role of the nucleophile in the regioselectivity control of palladium allylic amination of vinyl epoxide **54**.

We then turned our attention to linear carbonate **157**. Reaction with 4-methoxy-benzylamine **162** in the presence of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2/PPh_3$ in $CH_2Cl_2$ gave a 60:40 mixture of branched product **163** and linear bis-allylated product **173** (Table 5, entry 3). It should be noted that double alkylation processes have already been observed and frequently occur since the product, a secondary amine, is more nucleophilic than the starting material.[21b] Interestingly, the use of Pd/(*S*,*S*)- **L3** as a catalytic system afforded the branched isomer **163** as an only regioisomer (Table 1, entry 4) in an enantiopure form (98% *ee*, (*R*)).[36] To assess the role of hydrogen bonding in the regiochemical outcome of the previous Pd-AAA, the reaction of **157** and **162** was performed in methanol as a solvent, to afford a 20:80 mixture of branched **163**/linear **168** (Table 5, entry 5), thus

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35 Trost, B. M.; Frandick, D. R. *Aldrichim*ica Acta **2007**, *40*, 59-72.

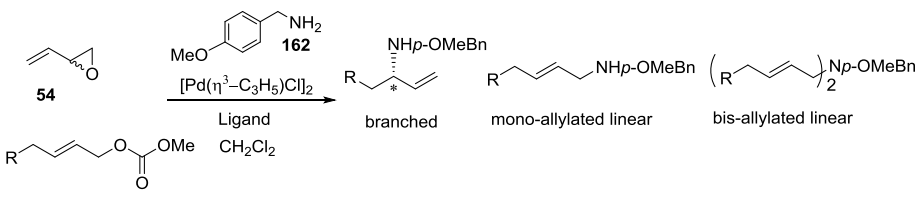
36 Asignment of the absolute configuration was determined by comparison of the otpical rotation with that of the (*S*)-enantiomer described in Gnamm, C.; Franck, G.; Miller, N.; Stork, T.; Brödner, K.; Helmchen, G. *Synthesis* **2008**, 3331-3350.

providing a reverse regioselectivity with respect to that obtained previously in dichloromethane.

Additional evidences of the role of hydrogen bonding were obtained starting from hydroxyl protected derivatives. Thus, the reaction of **158** with amine **162** in the presence of Pd/(*S*,*S*)-**L3** catalytic system afforded a 35:65 mixture of branched **164**/linear **169** (Table 1, entry 6). Furthermore, the Pd-AAA of derivative **159**, with a very bulky trityl group as a protecting group, under standard reaction conditions afforded the linear bis-allylated product **175** in an almost exclusively manner (Table 5, entry 9) without any traces of the branched product. In order to determine the role of electronic effects in the regioselectivity of the process, [31,37] compound **161**, with a methyl group instead of a hydroxyl moiety, was treated with **162** under similar conditions, to furnish a mixture of allyl amines, where the linear isomer was the major one (Table 5, entry 7) in a process which resulted in virtually the same regioselectivity to that observed with **158**. To prove whether homoallylic alcohols could also play a directing role, alcohol **160** was also reacted with amine **162** under similar conditions, but in this case a complex mixture was obtained (Table 5, entry 8).

[37] Catalán, J. *J. Org. Chem.* **1997**, *62*, 8231-8234.

**Table 5.** Palladium-Catalyzed Allylic Amination of **54** and **157-161.**[a]




**157**: R= OH
**158**: R= $OCH_3$
**159**: R= OTr
**160**: R= $CH_2OH$
**161**: R= $CH_3$

**163**: R=OH
**164**: R=$OCH_3$
**165**: R=OTr
**166**: R=$CH_2OH$
**167**: R=$CH_3$

**168**: R=OH
**169**: R=$OCH_3$
**170**: R=OTr
**171**: R=$CH_2OH$
**172**: R=$CH_3$

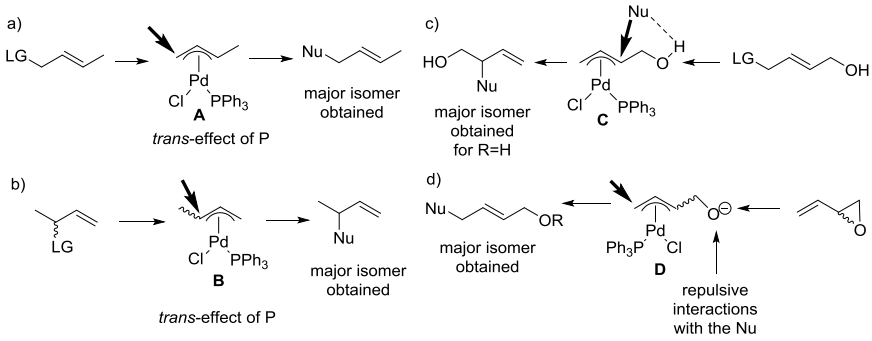
**173**: R=OH
**174**: R=$OCH_3$
**175**: R=OTr
**176**: R=$CH_2OH$
**177**:R=$CH_3$

| Entry | Substrate | Ligand | Products | Conv. (%) | Ratio[b] branched/linear |
|---|---|---|---|---|---|
| 1 | **54** | $PPh_3$ | **163, 168** | >98 | 24:76 [c] |
| 2 | **54** | (*S*,*S*)-**L3** | **163, 168** | >98 | 44:56 |
| 3 | **157** | $PPh_3$ | **163, 173** | >98 | 60:40 [c],[f] |
| 4 | **157** | (*S*,*S*)-**L3** | **163, 168** | >98 | >98:2 [d] |
| 5 [e] | **157** | (*S*,*S*)-**L3** | **163, 168** | >98 | 20:80 |
| 6 | **158** | (*S*,*S*)-**L3** | **164, 169** | >98 | 35:65 |
| 7 | **161** | (*S*,*S*)-**L3** | **167, 172** | >98 | 30:70 |
| 8 | **160** | (*S*,*S*)-**L3** | **166, 171** | >98 | Compl. Mixt. |
| 9 | **159** | (*S*,*S*)-**L3** | **175** | >98 | - [g] |

[a] Conditions: Catalyst $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2 mol%), DACH-naphthyl Trost ligand **L3** (6 mol%) or $PPh_3$ (12 mol%), substrate (1.0 equiv.), nucleophile (1.1 equiv.), reaction time = 16h, concentration = 0.02 M. [b] Ratio of branched /linear has determined by $^1H$ NMR spectroscopy of the crude products. [c] Racemic **163** was obtained. [d] *ee* = 98% (*R*). Detemined by HPLC on chiral columns. Assignment of absolute configuration is determined by comparison of the optical rotation with that described for the (*S*)-enantiomer. Ref 36 [e] The reaction was performed in MeOH. [f] The reaction of amine **162** with the carbonate **157** gave the bis-allylated linear product **173**; the monoallylated linear product **168** was not found. [g] The reaction of amine **162** with the carbonate **159** gave the bis-allylated linear product **175**; the monoallylated linear product **170** and branched product **165** were not found.

Control experiments using $PPh_3$ as a ligand should give us some information on the key issues that govern the regioselectivty of the racemic process in the substrates tested. Comparison of entries 1 and 3 in Table 5 infers that the product distribution depends on the regiochemistry of the starting material.[38]

When $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ is used as a precursor metal complex, high levels of regioretention should be observed starting from either linear or branched substrates (Scheme 62a and Scheme 62b). Under these conditions the highly reactive anionic $[Pd(PPh_3)Cl]^-$ complex is expected to readily ionize the allyl electrophile to give non-symmetric intermediates **A** and **B**. These complexes are preferentially formed by *trans*-effect of phosphorus in the initial ionization step, followed by nucleophilic attack *trans* to the phosphine.[38] The results obtained herein, however, give the opposite trend. Unexpected preferential formation of the branched isomer from linear substrate **157** could be explained from intermediate **C** by directing nucleophilic attack of the hydroxyl group in the substrate (R=H), counteracting the *trans*-effect of phosphine in the nucleophilic addition step (Scheme 62c). More difficult to explain is the relatively high amount of linear isomer from epoxide **54**, which could arise from repulsive interactions of the incoming nucleophile with the alkoxide ion (Scheme 62d).




**Scheme 62.** Repulsive or hydrogen-bondig interactions may counteract the electronic properties of unsymmetrical Pd-allyl complexes.

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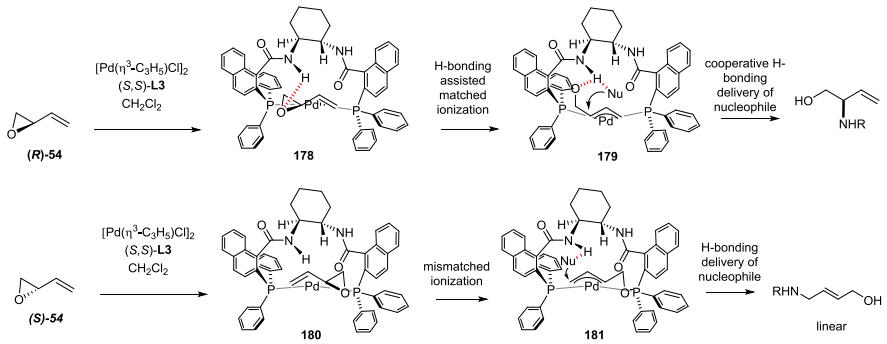
38 (a) Fristrup, P.; Ahlquist, M.; Tanner, D.; Norrby, P.-O. *J. Phys. Chem. A* **2008**, *112*, 12862-12867. (b) Fristrup, P.; Jensen, T.; Hoppe, J.; Norrby, P.-O. *Chem. Eur. J.* **2006**, *12*, 5352-5360. (c) Sjögren, M. P. T.; Hansson, S.; Akermark, B.; Vitagliano, A. *Organometallics* **1994**, *13*, 1963-1971.

Judging by the results, and despite being structurally related, Pd-AAA of vinyl epoxide and allylic carbonate seem to proceed through different reaction paths.

Reaction of a vinyl epoxide **54** with soft nucleophiles is typically described to proceed through a dynamic asymmetric kinetic transformation (DYKAT), where the starting racemate is transformed into an enantioenriched branched product. The key issue for the success of this asymmetric transformation is assuring that the process proceeds under Curtin-Hammet conditions, so that the diastereomeric π-allylpalladium intermediates, which are formed by ionization of the enantiomeric pair by the chiral catalyst, can isomerize by means of a π-σ-π mechanism before being attacked by the nucleophile. In this way, transformation of both enantiomers is eventually biased towards the preferential branched regioisomer in excellent enantioselectivity. A premise for this process to take place is using soft stabilized nucleophiles, where nucleophilic attack is slowed down with respect to π-allylpalladium intermediate interconversion.

In contrast, there is no literature of the application of this DYKAT process with amines as *N*-nucleophiles. With such nonstabilized *N*-nucleophiles, Curtin-Hammet conditions are not likely to be met, probably due to the fact that the rate of nucleophilic attack is very high compared to that of diastereomeric intermediates interconversion. Taking into account that *syn*-allyl Pd complexes are usually the most plausible intermediates when bidentated ligands are used, every enantiomer of **54** is independently transformed into its corresponding π-allylpalladium complex **179** and **181**, which will ultimately react with the nucleophile without any previous interconversion (Scheme 63). This seems to be the case of the reaction of vinyl epoxide with *p*-methoxybenzyl amine, considering the obtention of equimolar ratio of branched and linear aminated products (Table 5, entry 2). The complementary regiochemical outcome of the two intermediates could arise from hydrogen-bonding directed nucleophilic attack of the amine involving the NH amide bond on the concave shape of the ligand, as described by Lloyd-Jones *et al.*[42]

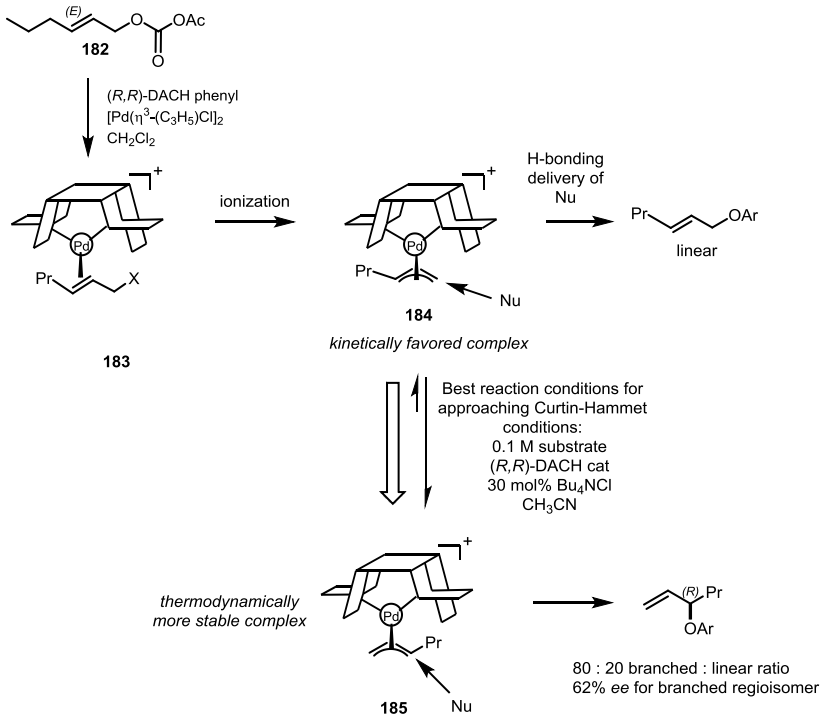



**Scheme 63.** Model which accounts for the regioselectivity and enantioselectivity in the Pd-AAA reaction of **54** with unstabilized hard *N*-nucleophiles.

On the other hand, to understand the behavior of linear allylic carbonate **157**, it could be compared with the Pd-AAA of an analogous substrate, methylhexenyl carbonate **182**, described by Trost.[39] In this study, the typical regioselectivity towards the linear achiral product provided by this non symmetrical allylic electrophile in achiral Pd-AAA was eventually biased towards the branched isomer using Trost's ligand (Scheme 64). The key aspect was optimizing the reaction conditions so that Curtin-Hammet conditions were approached, favoring π–σ–π equilibration of the diastereomeric Pd-π-allyl complexes **184**, **185** and consequently giving reasonably high branched regioselectivities and moderately high enantioselectivities. The reaction conditions were carefully explored to meet Curtin-Hammet requirement, such as: a) large diphenylphosphino benzoic acid-based ligands with a sterically emcubered environment to slow down the rate of nucleophilic attack, increasing the chances for π-σ-π equilibration; b) use of an *O*-nucleophile (4-methoxyphenol) to diminish steric demands of the nucleophile, so that only the steric requirements of the ligand prevail; c) low concentrations to assure the prevalence of monomeric catalytic systems and lower chance of $S_N2$ processes of Pd on the Pd-π-allyl complexes; d) use of $CH_2Cl_2$ as the solvent instead of THF, since the percentage of branched regioisomers is increased with increasing the solvent polarity; and e) use of chloride salts, since they seem to promote

39 Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc*. **1999**, *121*, 4545-4554.

π–σ–π interconversion of the diastereomeric Pd-π-allyl complexes via π-allyl intermediates.

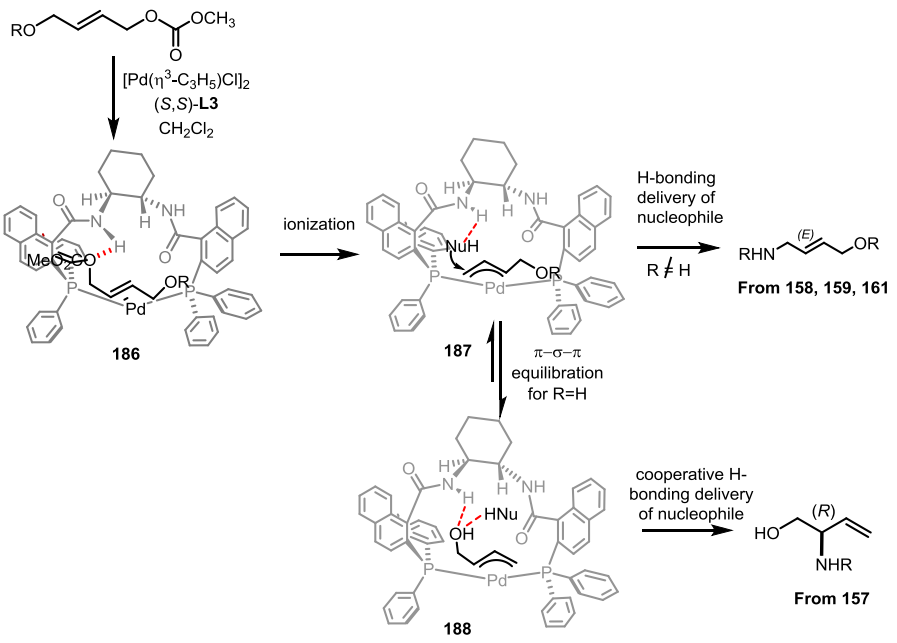



**Scheme 64.** Rationalization of regioselectivity and enantioselectivity in the Pd-AAA reaction of methylhexenyl carbonate with methoxyphenol.

Comparing these results with those obtained by **157**, we should first take into account that in the latter, the reaction parameters towards Curtin-Hammet conditions were not optimized. Consequently, all protected substrates gave predominantly linear achiral regioisomers with a b/l ratio around 1/3, which is virtually the same as that obtained with the unoptimized reaction described by Trost with a phenolate as a nucleophile (b/l 1:4). These results could be explained by direct matched nucleophilic attack on the primarily formed kinetic favored complex **187**, in a process with no π-σ-π equilibration (Scheme 65). Worthy of note is that the trityl protected substrate **159**, which could have had more chances to equilibrate to give a thermodynamically more stable complex by releasing steric strain, gave the best linear:branched ratio. This means that, indeed, the

process is far away from Curtin-Hammet conditions, probably due to the high reactivity of the nucleophile used. Furthermore, in light of the similar performance of the substrates **158** and **159**, the steric encumbrance of the protecting group does not appear to be a determining issue in the regioselectivity of the process. It is, therefore, surprising to see that the unprotected substrate **157** is able to reverse the regiocontrol of the process. Sterics, as we have pointed out, does not seem to be the reason, since ionization of **157** to give the kinetically favored complex, followed by direct nucleophilic attack would give the linear regioisomer. Another mechanism must be operating.

Based on the work by Lloyd-Jones *et al*,[42] we hypothesized that the initial kinetically favored ionization of the electrophile, where departure of the leaving group is assisted by hydrogen bonding interaction with the N-H amide bond in the chiral catalyst, is followed by a fast π–σ–π interconversion of the π-allylpalladium complex to render the diastereomeric intermediate **188** (Scheme 65). The driving force for this isomerization could be explained by some degree of stabilization of the latter complex with respect to **187** due to hydrogen bonding interactions between the N-H bond and the hydroxyl group in the substrate (Scheme 65), an interaction which is not present when this unit is protected. Along these lines, the regioselectivity obtained from reaction of **157** and *p*-methoxybenzylamine in methanol as a solvent (Table 5, entry 5, b/l ratio of 20:80), similar to those obtained with the protected substrates, underlines the importance of hydrogen-bonding interactions, disrupted when the solvent is protic.




**Scheme 65.** Rationalization of regioselectivity and enantioselectivity in the Pd-AAA reaction of allylic carbonate with *N*-nucleophile.

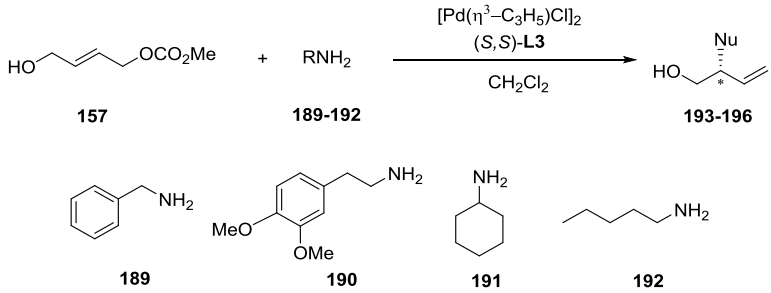
Another very important issue is, if the model based on steric deactivation of the nucleophile by the pendant phenyl groups of the ligand is object of question, how can we explain the regioselectivity (and the enantioselectivity) in the nucleophilic attack? Lloyd-Jones and collaborators showed that the approach of *an anionic nucleophile* may be guided by two opposing interactions: either H-bonding assisted delivery of the nucleophile by the N-H amide bond of the concave surface or alternatively by dipole-ion interactions between the escort counterion of the nucleophile and the concave orientated adjacent amide carbonyl group in close proximity with the allyl group. The selectivity of the process appears to be a result of the coordinating properties of the escort ion, so that with weakly coordinating escort ions the hydrogen bond will dominate, whereas with strong coordinating escort ions hydrogen bonding will be attenuated and interactions with the carbonyl group will be more important.

Attempting to search for an analogous situation for reaction of **157** with 4-methoxybenzylamine, several comments have to be taken into account. First amines are not expected to be in an anionic form in the presence of carbonate or

alternatively, methoxide anion, plausibly formed by decomposition of the carbonate leaving group after ionization. Secondly, if they were in some degree, there are no escort anions in the medium. Be that as it may, the most plausible directing mechanism active in our case should be hydrogen bonding delivery of the amine or amide nucleophile by the N-H bond present in the catalyst. H-Bonding delivery of the nucleophile by the hydroxylic function in the substrate could also be regarded, although it does not appear to be a dominant process, judging by the regioselectivity obtained in the racemic reaction (Table 5, entry 3).

The excellent regio- and enantioselectivity obtained in the preliminary results of allylic amination of substrate **157** with common amines using Pd/(*S*,*S*)-**L3** catalytic system prompted us to investigate the generalization of this reaction. The tolerance of various functional groups under the optimized reaction conditions such as substrates with C-C double bond, aromatics, and cycloalkyl groups, have been examined. Thus we studied the reaction of carbonate **157** with a range of nitrogen-nucleophiles **189-192** to give the corresponding allylic amines **193-196** in excellent yields (up to 96%) (Table 6, entries 1–5). Moreover, in all cases, excellent enantioselectivities were obtained (90 to 98%). These results reveal the scope and generality of the protocol with respect to various primary amines.

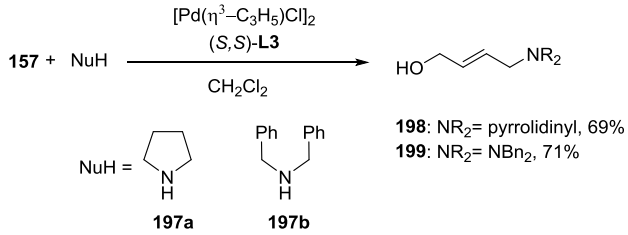
**Table 6**. Palladium-Catalyzed Allylic Amination of **157** with nitrogen-nucleophiles **189-192**.[a]




| Entry | R-$NH_2$ | Products | Conversion (Yield)[b] | b/l Ratio[c] | *ee* % [d] |
|---|---|---|---|---|---|
| 1 | **189** | **193** | >98 (93) | >98:2 | 90 (*R*) |
| 2 | **190** | **194** | >98 (96) | >98:2 | 95 (*R*) |
| 3 | **191** | **195** | >98 (91) | >98:2 | 98 (*R*) |
| 4 | **192** | **196** | >98 (90) | >98:2 | 96 (*R*) |

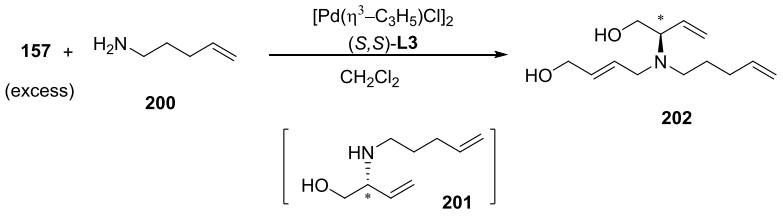
[a] Conditions: Catalyst $[\eta^3\text{-}(C_3H_5)PdCl]_2$ (2 mol%), (*S*,*S*)-**L3** (6 mol%), carbonate (1 equiv), nucleophile (1.1 equiv.), reaction time = 16h, concentration = 0.02 M. [b] Isolated yield of branched regioisomer[c] Ratio of branched /linear has determined by $^1$H NMR spectroscopy of the crude products. [d] Determined by HPLC on chiral columns. Assignment of absolute configuration is given for cases in which it was indenpendently confirmed, determined by comparison of the optical rotation with that described for (*S*)-enantiomer. (Ref. 36).

The reaction with secondary amines was next explored. The treatment of **157** with pyrrolidine **197a** and dibenzylamine **197b** using Pd/(*S*,*S*)-**L3** as catalyst under the optimized reaction conditions, afforded in both cases principally the linear isomers **198** and **199** with a branched/linear ratio of 33:67 and 15:85, respectively (Scheme 66). These results clearly show the sensibility of the regioselectivity of this reaction to the steric hindrance of the nucleophile, so that the steric requirements of secondary amines outweigh the restrictions imposed by the DACH Naphthyl ligand, with a sterically encumbered environment.



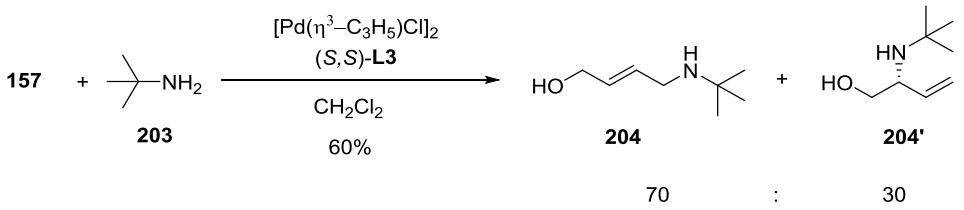

**Scheme 66.** Palladium-catalyzed allylic amination of **157** with nitrogen-nucleophiles **197a** and **197b**.

Similarly, when the reaction of amine **200** was carried out with an excess of **157**, compound **202** was obtained (Scheme 67). The outcome of this reaction can be explained by the initial formation of the branched derivative **201** via an initial Pd-catalyzed allylic amination, which will act as a nucleophile in a second allylic amination of **157** in excess to afford the tertiary amine **202** as a consequence of the attack on the terminal position (linear isomer).




**Scheme 67.** Exploring the regioselectivity of the process using carbonate **157** in excess.

The use of *tert*-butylamine (**203**) as a bulky primary amine nucleophile furnished linear amine **204** as the major regioisomer (ratio linear/branched 70:30), thus underscoring the importance of the bulkiness of the nucleophile to control the regioselectivity of the process (Scheme 68).




**Scheme 68**. Palladium-catalyzed allylic amination of **157** with bulky amine **203**.

## II.3. Attempts of synthesis of Pd((*S*,*S*)-**L3**) complex bearing $\eta^3$-($C_4H_7O$) moiety

The study of the structure and reactivity of the transition metal allyl complexes is an important issue in the coordination chemistry and controlled catalytic synthesis. In allylic substitution reaction, the substituted $\eta^3$-allyl Pd complexes play a key role in the catalytic processes.

The mechanism of asymmetric Tsuji-Trost allylation reaction has, generally, been explored in great depth.[40] However, for the case of Pd/Trost ligand system there has been a near-complete lack of structural detail[41] until the recent, very accurate work by Lloyd-Jones and Norrby.[42] Before that, the interpretation was based only on an empirical "cartoon model" in which the time-averaged structure of coordinated ligand is represented by a $C_2$-symmetric folded surface (Figure 14).[41]

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40 Evans, L. A.; Fey, N.; Harvey, J. N.; Hose, D.; Lloyd-Jones, G. C.; Murray, P.; Orpen, A. G.; Osborn, R.; Owen-Smith, G. J. J.; Purdie, M. *J. Am. Chem. Soc*., **2008**, *130*, 14471-14473.

41 Trost, B. M.; Machacek, M. R.; Aponick, A. *Acc. Chem. Res*., **2006**, *39*, 747-760.

42 Butts, C. P.; Filali, E.; Lloyd-Jones, G. C.; Norrby, P.-O.; Sale, D. A.; Schramm, Y. *J. Am.Chem. Soc*., **2009**, *131*, 9945-9957.

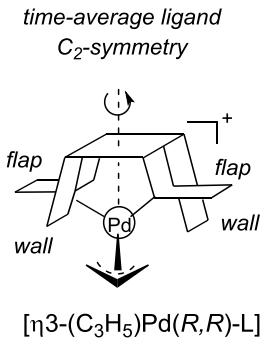



**Figure 14.** Wall-and-flap cartoon model involving Pd complexes of (*R,R*)-L.

In the course of our studies aimed at understanding which factors control the regioselectivity of the Pd-catalyzed allylic amination reaction, we decided to synthesize such complex **205** (Figure 15).

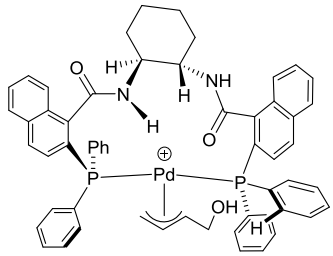
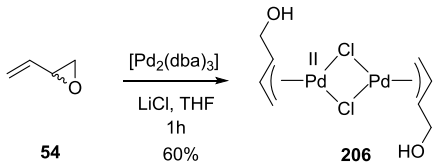



**Figure 15.** Cationic Pd-allyl complex **205**.

Thus, for our purpose, we prepared complex **206** by mixing [$Pd_2(dba)_3$] with butadiene monoepoxide (**54**) in THF in the presence of LiCl. The color of the solution rapidly turned from purple to yellow and the $^1$H NMR spectrum showed formation of ($\eta^3$-allyl)palladium complex **206**, which could be isolated (Scheme 69). The application of chloride salts has been reported to be necessary

to form a stable complex, such as **206**, otherwise the ($\eta^3$-allyl)-palladium complex formed from **54** and $[Pd_2(dba)_3]$ easily decomposes.[43]




**Scheme 69.** Synthesis of complex **206**.

Reaction of complex **206** with (*S*,*S*)-**L3** (Pd/L = 1:2) in $CD_2Cl_2$ or $d_8$-THF and in presence of $NaPF_6$ or $NaBF_4$ as a counterion results in the generation of a mixture of complexes whose $^1H$ and $^{13}C$ NMR spectra are essentially unassignable due to the broad and overlapping nature of the signals arising from numerous species (Figure 16).

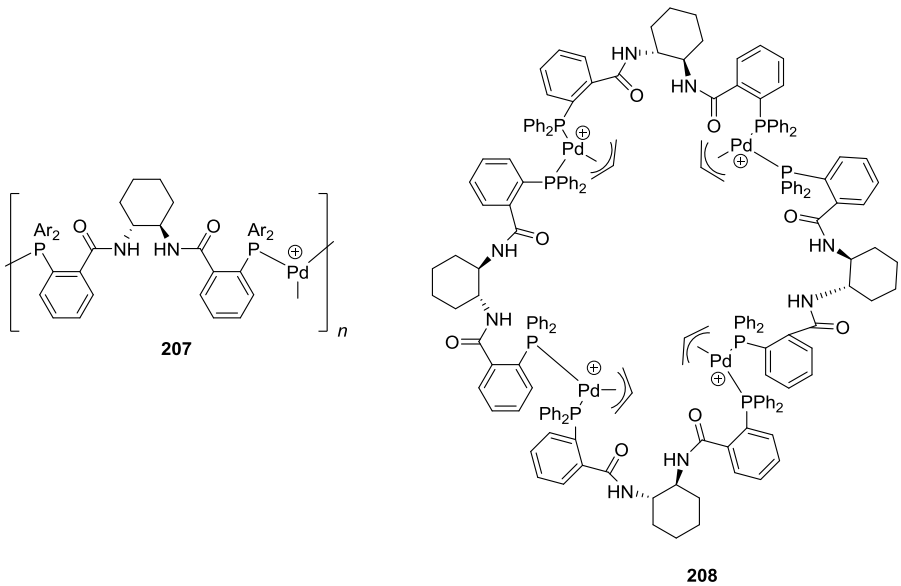



**Figure 16.** Linear and cyclic oligomer complex **207** and **208**.

[43] Kjellgren, J.; Aydin, J.; Wallner, O. A.; Saltanova, I. V.; Szabó, K. J. *Chem. Eur. J.* **2005**, *11*, 5260-5268.

The $^{31}P$ is somewhat simpler but even here, we can distinguish, in Figure 17, three major environments appearing as broad singlets (21-30 ppm).

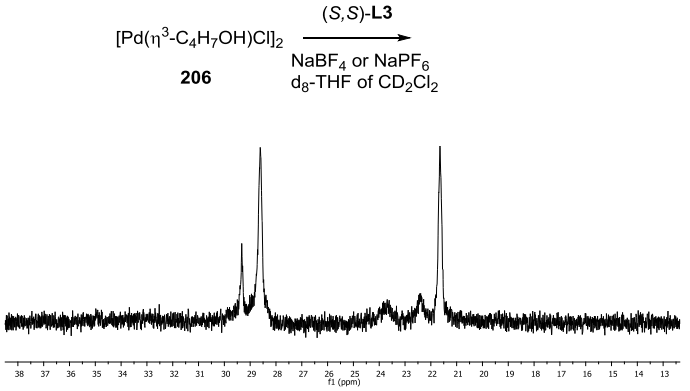



**Figure 17.** $^{31}P\{1H\}$ NMR spectra of complexes generated in situ from (*S,S)*-**L3** and $[Pd(\eta^3\text{-}C_4H_7OH)Cl]_2$ complex.

In fact, it has been reported that this system has a high propensity for reversible oligomerization which depends on both temperature and concentration.[44] Oligomerization occurs at higher concentrations and at lower temperatures. It was also noted that the counterion of the complex was also important so that more coordinating counterions favor the oligomerization process. These aggregates could be either linear such as **207** or cyclic such as **208** and are interconverting reasonably rapidly in solution (Figure 16).

The use of very low interacting $[B((3,5\text{-}(CF_3)_2)C_6H_3)_4]^-$ (BAr'F) for stabilizing cationic electrophilic Pd complex, and keeping a relatively low concentration of $[Pd]_{Total}$, however, did not allow us to prepare monomeric complexes relatively free of oligomer, as judged by the complexity of NMR spectra. Moreover, despite many attempts, we have been unable to crystallize any

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44 (a) Fairlamb, I. J. S.; Lloyd-Jones, G. C. *Chem. Commun*. **2000**, 2447-2448. (b) Lloyd-Jones, G. C.; Stephen, S. C.; Fairlamb, I. J. S.; Martorell, A.; Dominguez, B.; Tomlin, P. M.; Murray, M.; Fernandez, J. M.; Jeffery, J. C.; Riis-Johannessen, T.; Guerziz, T. *Pure. Appl. Chem*. **2004**, *76*, 589-601.

complex from the mixture of monomeric and oligomeric complexes generated by reaction of enantiomerically pure ligand **L3** with $[Pd(\eta^3\text{-}C_4H_7OH)Cl]_2$.

## II.4. Enantioselective formal synthesis of D-fagomine.

Discovery of polyhydroxylated piperidines (iminosugars) is one of the most notable achievements in the field of natural products. They are produced as secondary metabolites in a vast array of different organisms, although the majority originate in plants.[45] Their structural similarity to monosaccharides confers these compounds the inhibition properties of carbohydrate-processing enzymes and therefore they are used in a wide range of potential therapeutic strategies including the treatment of viral infections, cancer, diabetes etc.[46,47,48] For this reason, both the synthesis of polyhydroxylated piperidines and their application as therapeutic agents have been spurred.

As it was discussed in chapter 3, 1,2-Dideoxy azasugars are a representative example of naturally occurring polyhydroxylated piperidines and represent an important class of glycosidase inhibitors. (*2R,3R,4R*)-2-hydroxymethylpiperidine-3,4-diol, D-fagomine is representative of this class of natural products since its first isolation from the seeds of Japanese buckwheat *Fagopyrum esculentum* Moench in 1974.[49] Fagomine and its epimers have been reported to have some activity against mammalian gut α-glucosidase and β-galactosidase. Moreover, D-Fagomine has a potent antihyperglycemic effect in streptozocin-induced diabetic mice and markedly potentiates immunoreactive insulin release.[50] In addition to that, it also lowers postprandial blood glucose concentration and modulates bacterial adhesion. To date, a number of synthetic

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45 Magalhaes, A. F.; Santos, C. C.; Magalhaes, E. G.; Noguiera, M. A. *Phytochem. Anal*. **2002**, *13*, 215-221.

46 Heightman, T. D.; Vasella, A. T. *Angew. Chem., Int. Ed*. **1999**, *38*, 750-770.

47 Zechel, D. L.; Withers, S. G. *Acc. Chem. Res*. **2000**, *33*, 11-18.

48 Stütz, A. E. Iminosugars as glycosidase inhibitors: nojirimycin and beyond; Wiley-VCH: Weinheim, Germany, **1999**.

49 Amézqueta, S.; Galán, E.; Fuguet, E.; Carrascal, M.; Abián, J.; Torres, J. L. *Anal. Bioanal. Chem*., **2012**, *402*, 1953-1960 and references herein.

50 (a) Nojima, N; Kimura, I.; Chen, F. J.; Sugihara, Y.; Haruno, M. *J. Nat. Prod*., **1998**, *61*, 397-400. (b) Taniguchi,S; Asano, N.; Tomino, F.; Miwa, I. *Horm. Metab. Res*., **1998**, *30*, 679-683.

methods for the preparation of fagomine have been reported.[51] The majority of synthetic approaches have involved asymmetric synthesis for the construction of stereogenic centers, chemical and enzymatic resolution, and synthetic strategy from a readily available chiral pool.

In this context, hydroxymethylpiperidene **208** has proven to be an ideal precursor for the synthesis of D-fagomine and all its isomers **209-211** (Figure 18).[51h]

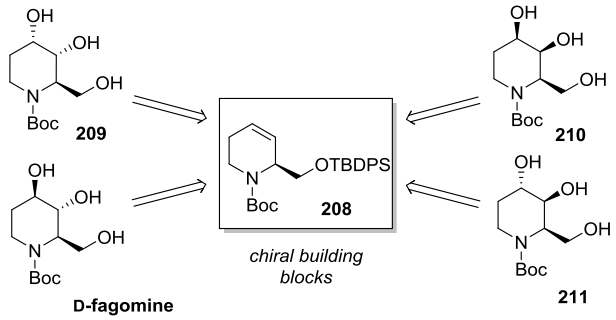


**Figure 18.** Fagomine and its all isomers **209-211**.

This key intermediate was prepared in a stereoselective manner from Garner aldehyde in 7 steps and 26% overall yield (Scheme 70). After Wittig

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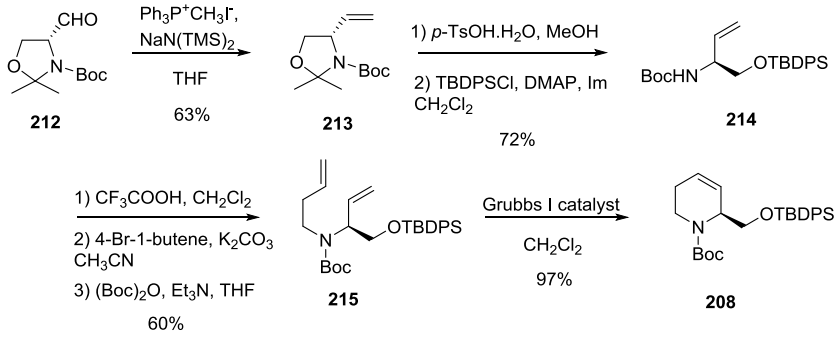
51 (a) Babich, L.; van Hemert, L. J. C.; Bury, A.; Hartog, A. F.; Falcicchio, P.; van der Oost, J.; van Herk, T.; Wever, R.; Rutjes, F. P. J. T. *Green Chem*., **2011**, *13*, 2895-2900. (b). Kim, J. Y.; Mua, Y.; Jin, X.;. Park, S. H.; Pham, V. T.; Song, D. K.; Lee, K. Y.; Ham, W. H. *Tetrahedron*, **2011**, *67*, 9426-9432. (c) Bartali, L.; Casini, A.; Guarana, A.; Occhiato, E. G.; Scarpi, D. Eur. *J. Org. Chem*. **2010**, 5831-5840. (d) Bartali, L.; Scarpi, D.; Guarna, A.; Prandi, C.; Occhiato, E. G. *Synlett* **2009**, 913-916. (e) Kumari, N.; Reddy, B. G.; Vankar, Y. D. *Eur. J. Org. Chem*. **2009**, *1*, 160-169. (f) Yokoyama, H.; Ejiri, H.; Miyazawa, M.; Yamaguchi, S.; Hirai, Y. *Tetrahedron: Asymmetry* **2007**, *18*, 852-856. (g) Castillo, J. A.; Calveras, J.; Casas, J.; Mitjans, M.; Vinardell, M. P.; Parella, T.; Inoue, T.; Sprenger, G. A.; Joglar, J.; Clapés, P. *Org. Lett*. **2006**, *8*, 6067-6070. (h) Takahata, H.; Banba, Y.; Ouchi, H.; Nemoto, H.; Kato, A.; Adachi, I. *J. Org. Chem*. **2003**, *68*, 3603-3607. (i) Lindsay, K. B.; Pyne, S. G. *J. Org. Chem*. **2002**, *67*, 7774-7780. (j) Désiré, J.; Dransfield, P. J.; Gore, P. M.; Shipman, M. *Synlett* **2001**, 1329-1331. (k) Banba, Y.; Abe, C.; Nemoto, H.; Kato, A.; Adachi, I.,; Takahata, H. *Tetrahedron: Asymmetry* **2001**, *12*, 817-819. (l) Degiorgis, F.; Lombardo, M.; Trombini, C. *Synthesis* **1997**, 1243-1245. (m) Fleet, G. W. J.; Smith, P. W. *Tetrahedron Lett*. **1985**, *26*, 1469-1472.

olefination, subsequent hydrolysis and *O*-silylation, compound **214** was subjected to a three-step sequence (deprotection, *N*-Alkylation, *N*-protection) to afford the diene **215**. Ring-closing metathesis (RCM) of **215** furnished the chiral building block **208** in a very good yield.




**Scheme 70.** Reported synthesis of piperidine **208**.

In this context, we thought that the usefulness of our synthetic protocol could be illustrated by the enantioselective preparation of piperidine **208** in a two-step procedure from carbonate **157**.

Our synthetic strategy is based on the utilization of the optically active (*R*)-3-amino-1-butene-4-ol (**217**) as a key intermediate and ring-closing alkene metathesis (RCM) (Scheme 71).[52,53] This efficient approach could give access to enantiomerically pure, stereochemically defined, five, six- and seven-membered heterocyclic scaffolds by just changing the *N*-nucleophile in the palladium-catalyzed AAA. These substituted *N*-heterocyclic compounds, endowed with an internal double bond, are versatile precursors suitable for further functionalization. Asymmetric syntheses employing such intermediates could

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52 For a review on olefin metathesis, see: (a) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.*, 2001, **34**, 18-29. (b) Fürstner, A. *Angew. Chem.* 2000, **112**, 3140-3172.

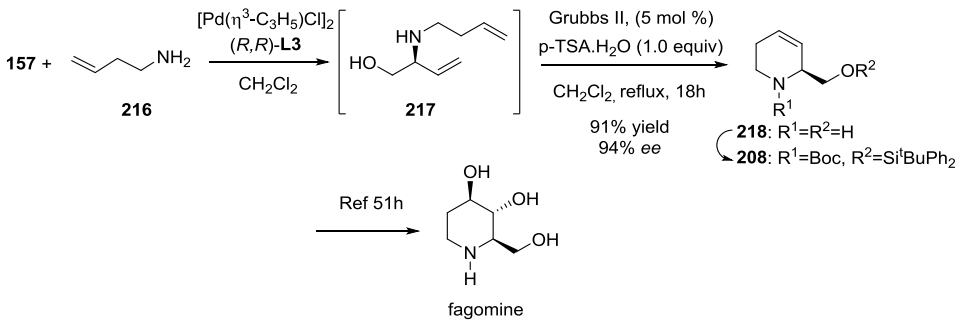
53 For a recent review on the use of RCM in the synthesis of iminosugars see: Dragutan, I.; Dragutan, V.; Demonceau, A. *RSC Advances*, **2012**, *2*, 719-736.

lead to disclosure of further biologically relevant piperidine/azepane alkaloids and iminosugars.[54]

Thus, reaction of allylic carbonate **157** with amine **216** in the presence of Pd/(*R,R*)-**L3** catalytic system afforded crude **217**. This product was directly subjected to ring-closing metathesis using Wright's conditions,[55] which uses 5 mol% of Grubbs' second generation catalyst in the presence of one equivalent amount of *p*-toluenesulfonic acid (*p*-TsOH.$H_2O$) to produce the azacycloalkene **218** in excellent 91% yield and 94% *ee* (Scheme 71). Indeed, RCM of compounds containing basic amines may poison the catalyst and have some limitations. However, it has been reported that these limitations can be overcome by protection or protonation of the amine. In this case, treatment of the secondary amine with *p*-TSA was necessary as the RCM with the free base of the amine did not proceed at all.

*O*-silylation and *N*-Boc protection of compound **218** (87% yield over the two steps) completed the synthesis of the piperidine intermediate **208** described by Takahata, H. et al. in the total synthesis of D-Fagomine.[51h] The spectroscopic ($^1$H and $^{13}$C NMR) data for synthetic **208** was identical to those reported.

As compound **208** has been used as a synthetic intermediate in the synthesis of D-fagomine, it involves a formal synthesis of this natural product.




**Scheme 71.** Formal synthesis of D-fagomine.

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54 Dragutan, I.; Dragutan, V.; Mitan, C.; Vosloo, H. C. M.; Delaude, L.; Demonceau, A. *Beilstein J. Org. Chem.* **2011,** *7*, 699-716

55 Wright, D. L.; Schulte, J. P. II; Page, M. A. *Org. Lett.* **2000**, *2*, 1847-1850.

In conclusion, palladium/DACH Naphtyl-catalyzed allylic amination of carbonate **157** affords compounds chiral branched amines **163**, **192-195**, intermediates for the preparation of biologically important compounds, in high yields and regio- and enantioselectivities. Amines can be used as nucleophiles, differently than when butadiene monoepoxide (**54**) was used. In this case the use of amines as nucleophiles mainly afforded the linear product. We hypothesized that the excellent control of the regio- and enantioselectivity in this situation could be due to hydrogen bonding interactions between the hydroxyl group in the substrate and the diphenylphosphino benzoic acid-derived ligand in the Pd complex, it can be deduced by the dramatic change in the regioselectivity when the hydroxyl group is protected or replaced by an alkyl chain. Maybe future works could focus on computational calculations of the proposed interactions in order to support the hypothesis as it seems to be dificult to see further experiments to confirm these.

These results enlarge the application of the palladium-DACH Naphtyl system for the preparation of the type **163** allyl amines, and based on this protocol a short formal enantioselective synthesis of glycosidase inhibitor D-fagomine is reported.

# III. Experimental Section

## III.1. General Methods.

All chemicals including DACH-naphthyl ligand and $[Pd(C_3H_5)Cl]_2$ used were reagent grade and used as supplied unless otherwise specified. HPLC grade dichloromethane ($CH_2Cl_2$), tetrahydrofuran (THF) and dimethylformamide (DMF) were dried using a solvent purification system (Pure SOLV system-4®).

$^1H$ and $^{13}C$ NMR spectra were recorded at 400 MHz and 101 MHz, respectively, in $CDCl_3$ as solvent unless stated, with chemical shifts (δ) referenced to internal standards $CDCl_3$ (7.26 ppm $^1H$, 77.16 ppm $^{13}C$) or $Me_4Si$ as an internal reference (0.00 ppm). $^1H$ NMR spectra are reported as follows (s = singlet, d = doublet, t = triplet, q = quartet, b = broad; coupling constant(s) in Hz; integration). 2D correlation spectra (gCOSY, NOESY, gHSQC, gHMBC) were visualized using VNMR program (Varian®). ESI MS were run on an Agilent® 1100 Series LC/MSD instrument. Optical rotations were measured at room temperature in a Perkin-Elmer® 241 MC apparatus with 10 cm cells. IR spectra were recorded on a JASCO FT/IR-600 plus Fourier Transform Infrared Spectrometer ATR Specac Golden Gate. Reactions were monitored by TLC carried out on 0.25 mm E. Merck® silica gel 60 F254 glass or aluminium plates. Developed TLC plates were visualized under a short-wave UV lamp (250 nm), by heating plates that were dipped in ethanol/$H_2SO_4$ (15:1), or in a basic solution of potassium permanganate. Flash column chromatography was carried out using forced flow of the indicated solvent on Fluka® or Merck® silica gel 60 (230-400 mesh) and was performed using flash silica gel (32–63 μm) and using a solvent polarity correlated with TLC mobility.

Absolute configurations for new nonracemic chiral compounds were assigned on the basis of a general rule concerning the steric course of the Pd-catalyzed allylic substitution.[41] This rule was found to be correct for all cases that were verified. Configuration of compounds obtained from carbonate **157** was identical to those obtained from **54**. Allylic carbonates **157**, **159** and **161** were synthesized according to reported procedures. [56]

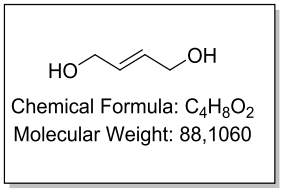
[56] Levi M. Stanley and John F. Hartwig; *J. Am. Chem. Soc.*, **2009**, *131*, 8971–8983; Gnamm, C.; Franck, G.; Miller, N.; Stork, T.; Brödner, K.; Helmchen, G. *Synthesis* **2008**, 3331-3350.

## III.2. Compound characterization

*General Procedure for the Palladium-catalyzed Asymmetric Allylic Amination of Allylic Carbonates.*

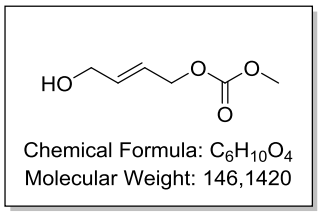
In a Schlenk tube under argon atmosphere were introduced $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (1 mg, 2 mol%), the (*S*,*S*)-DACH Naphthyl ligand **L3** (5.5 mg, 6 mol%) and $CH_2Cl_2$ (10 mL). The resulting solution was stirred for 20 minutes. Then, the carbonate (0.115 mmol) and nucleophile (0.127 mmol) were successively introduced. The mixture was stirred at room temperature for 18h. The reaction mixture was then diluted with $H_2O$. The phases were separated and the aqueous phase was extracted with $CH_2Cl_2$. The combined organic phases were dried over $MgSO_4$, filtered, and concentrated in vacuum. The resulting crude was purified by flash chromatography to afford the pure product. The enantiomeric excess was determined by- HPLC analysis using a DAICEL CHIRALCEL OD-H column. Initially a racemic mixture was prepared and separated in order to confirm signals of both enantiomers.

**(*E*)-But-2-ene-1,4-diol (156)**



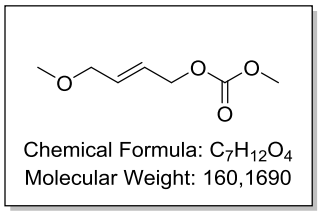

A suspension of $LiAlH_4$ (9.7g, 255.5 mmol) in anhydrous THF (100 mL) was cooled to 0°C, in an ice bath. A solution of 2-butyne-1,4-diol (10g, 116.2 mmol) in THF (20 mL) was added dropwise over 30 minutes and the resulting suspension was refluxed for 20h. The mixture was let to return at room temperature and was cooled to 0°C. Then, it was hydrolyzed by addition of aqueous solution of HCl 10% (50mL) until no gas was developed. Removal of the salts by filtration, washing the filter cake with $Et_2O$ and evaporation of the solvent afforded a yellow oil. Silica was added to the residue and the solvents were removed under reduced pressure. The residue was loaded into a chromatographic column and purified using Hexanes / ethyl acetate 30:70 as eluent which gave the title compound as a colorless oil (9.2 g, 90%). **$^1$H NMR (400 MHz, DMSO-d6):** δ (ppm) 5.67 (td, *J* = 2.5 Hz, 1.4 Hz, 2H), 4.67 (td, *J* = 2.5 Hz, 1.4 Hz, 2H), 3.93-3.90 (m, 4H). **$^{13}$C NMR (100 MHz, DMSO-d6):** δ (ppm) 130.1 (2C), 61.2 (2C).

**(*E*)-4-Hydroxybut-2-en-1-yl methyl carbonate (157)**



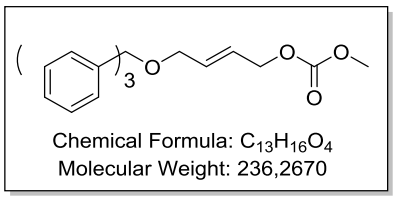

A solution of (*E*)-but-2-ene-1,4-diol (**156**) (1 g, 11.35 mmol) and pyridine (1.3 mL, 15.89 mmol) in anhydrous AcCN (10 mL) was cooled to 0°C and methyl chloroformate (0.964 mL, 12.48 mmol) was added dropwise. The mixture was stirred at 0°C for 1h, allowed to warm up to room temperature, and then stirred for 18 h. Water (10 mL) was added, the phases were separated, and the aqueous layer was extracted with $CH_2Cl_2$ (3 x 10 mL). The combined organic phases were washed with a saturated solution of $CuSO_4$ (10 mL) and $NH_4Cl$ (2 x 10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuum. Crude product was purified by flash chromatography on silica (Hexanes / ethyl acetate 8:2) to afford **157** as a colored oil (0.6 g, 36 %). **$^1$H NMR (400 MHz, $CDCl_3$):** δ (ppm) 5.93 (dtt, *J* = 15 Hz, 4 Hz, 1.4 Hz, 1H), 5.80 (dtt, *J* = 15 Hz, 6 Hz, 1.4 Hz, 1H), 4.60 (dq, *J* = 6.0 Hz, 1.5 Hz, 2H), 4.13 (d, *J* = 4.0 Hz, 2H), 3.75 (s, 3H), 2.21 (bs, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ (ppm) 155.7, 134.5, 124.2, 67.7, 62.5, 54.9.

**(*E*)-4-Methoxybut-2-enyl methyl carbonate (158)**




To a solution of (E)-4-Hydroxybut-2-enyl methyl carbonate **157** (0.6 mg, 4.1 mmol) in THF (25 mL) at room temperature, NaH (0.2 g, 8.2 mmol) was added. After 15 min., $CH_3I$ (1.02 mL, 16 mmol) was added dropwise to the reaction mixture and stirred for four hours. Then, sat. $NH_4Cl/H_2O$ was added to the reaction mixture and the organic layer was separated. The aqueous layer was extracted three times with dichloromethane. The combined organic layer was washed with brine and dried over magnesium sulfate. After removal of the solvents with a rotary evaporator, the residue was purified by column chromatography ($SiO_2$, hexane : ethyl acetate =8:3) to give **158** as an uncolorless oil (558 mg, 85%). **$^1$H NMR (400 MHz, $CDCl_3$):** δ (ppm) 5.92-5.71 (m, 2H), 4.58 (dd, *J* = 3.4, 2.3 Hz, 2H), 3.95-3.81 (m, 2H), 3.73 (s, 3H), 3.28 (s, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ (ppm) 155.6, 131.6, 125.8, 71.9, 67.6, 58.1, 54.9. **HMRS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_7H_{13}O_4$ 161.0808, found: 161.0826.

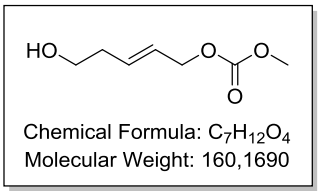
**(*E*)-Methyl 4-(trityloxy)but-2-enyl carbonate (159)**



Chemical Formula: $C_{13}H_{16}O_4$
Molecular Weight: 236,2670

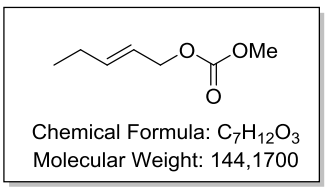
A solution of trityl chloride (1.42 g, 5.11 mmol), triethylamine (1 mL), and DMAP (0.03 g, 0.23 mmol) in 5 mL of DMF was added slowly to a solution of (*E*)-but-2-ene-1,4-diol (**156**) (0.5 g, 5.68 mmol) in DMF (2 mL). The reaction mixture was stirred at room temperature under nitrogen. The reaction mixture was poured in ice water and extracted with $CH_2Cl_2$ (4 x 20 mL). The organic phases were combinated and washed with saturated aqueous $NH_4Cl$ (30 mL) and water and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the resulting orange oil was purified using flash chromatography on silica (Hexanes / ethyl acetate 3:1) to provide 0.99 g of a white solid (59%). A solution of the freshly prepared (*E*)-4-(trityloxy)but-2-en-1-ol (0.99 g, 3.0 mmol) and pyridine (0.4 mL, 4.2 mmol) in anhydrous $CH_2Cl_2$ (10 mL) was cooled to 0°C and methyl chloroformate (0.35 mL, 4.5 mmol) was added dropwise. The mixture was stirred at 0°C for 1h, allowed to warm up to room temperature, and then stirred for 18 h. Water (20 mL) was added, the phases were separated, and the aqueous layer was extracted with $CH_2Cl_2$ (3 x 20 mL). The combined organic phases were washed with a saturated solution of $CuSO_4$ (20 mL) and $NH_4Cl$ (2 x 30 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified by flash chromatography on silica (Hexanes / ethyl acetate 95:5) to afford **159** as uncolored oil (0.89 g, 77 %). **$^1$H NMR (400 MHz, $CDCl_3$):** δ (ppm) 7.46-7.43 (m, 6H), 7.32-7.27 (m, 6H), 7.26-7.21 (m, 3H), 6.00 (dtt, $J$ = 15.7 Hz, 5.5 Hz, 1.8 Hz, 1H), 5.892 (dtt, $J_s$ = 15.7 Hz, 5.0 Hz, 1.8 Hz, 1H), 4.664 (dd, $J$ = 5.2 Hz, 1.0 Hz, 2H), 3.802 (s, 3H), 3.638 (dd, $J$ = 5.2 Hz, 1 Hz, 2H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ (ppm) 155.743, 144.1 (3C), 132.5, 128.7 (6C), 128.0 (6C), 127.2 (3C), 124.0, 87.0, 68.2, 63.8, 55.0.

**(*E*)-5-Hydroxypent-2-enyl methyl carbonate (160).**




A solution of allyl alcohol (11.7 mL, 172 mmol) and pyridine (15.2 mL, 189 mmol) in dry ether (100 mL) was cooled to 0°C under nitrogen. To this solution, methyl chloroformate (14.6 mL, 189 mmol) was added dropwise over 30 minutes. A white precipitate appeared and the resulting suspension was stirred for 18 h at room temperature. After the reaction was complete, the suspension was filtered through celite and the filtrate was washed with saturated $CuSO_4$ (20 mL) to remove excess pyridine. The layers were separated and the aqueous phase was extracted with diethyl ether (3 x 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered and distilled (59-60°C at 35 mmHg) to obtain pure allyl methyl carbonate (19.3 g, 98 %). But-3-en-1-ol (30mg, 0.40 mmol) and freshly prepared allyl methyl carbonate (47 mg, 0.40 mmol) were added via syringe to a stirred solution of 2$^{nd}$ generation Grubbs catalyst (0.02 mmol, 5 mol%) in $CH_2Cl_2$ (2 mL). The flask was fitted with a condenser and refluxed under argon for 12h. The reaction mixture was then reduced in volume to 0.5 mL and purified directly on a silica gel column, eluting with hexanes : ethyl acetate (6:4) to give **160** as a brown oil (30 mg, 46%). **$^1$H NMR (400 MHz, $CDCl_3$):** δ (ppm) 5.79 (dtt, *J* = 15.3 Hz, 6.7 Hz, 1.0 Hz, 1H), 5.68 (dtt, *J* = 15.3 Hz, 6.1 Hz, 1.0 Hz, 1H), 4.57 (dd, *J* = 6.1 Hz, 1.0 Hz, 1H), 3.76 (s, 3H), 3.66 (pseudo q, *J* = 6.1 Hz, 2H), 2.32 (pseudo q, *J* = 6.1 Hz, 2H), 1.73 (t, *J* = 5.2 Hz, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ (ppm) 155.7, 132.9, 126.2, 68.4, 61.6, 54.9, 35.7. **HMRS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_7H_{13}O_4$ 161.0808, found: 161.0786.

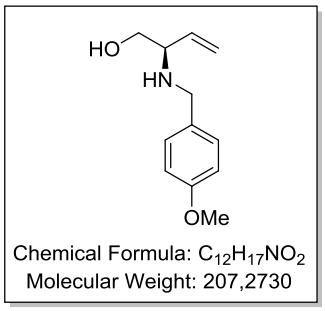
**(*E*)-methyl pent-2-enyl carbonate (161)**




A solution of the (*E*)-pent-2-en-1-ol (1 g, 11.6 mmol) and pyridine (1.3 mL) in anhydrous $CH_2Cl_2$ (12 mL) was cooled to 0°C and methyl chloroformate (1.0 mL, 13.9 mmol) was added dropwise. The mixture was stirred at 0°C for 1h, allowed to warm up to room temperature, and then stirred for 18 h. Water (20 mL) was added, the phases were separated, and the aqueous layer was extracted with $CH_2Cl_2$ (3 x 30 mL). The combined organic phases were washed with a

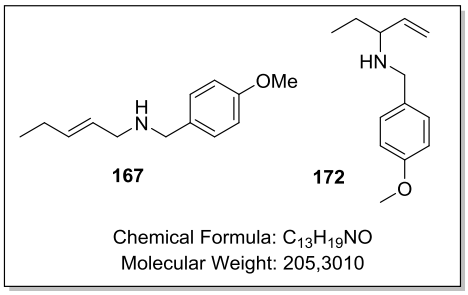
saturated solution of $CuSO_4$ (20 mL) and $NH_4Cl$ (2 x 30 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. Crude product was purified by flash chromatography on silica (Hexanes / ethyl acetate 90:10) to afford **161** as uncolored oil (1.64 g, 98 %).

**(-)-(2*R*)-2-(4-Methoxybenzylamino)but-3-en-1-ol (163).**




Following the general procedure carbonate **157** was treated with (4-methoxyphenyl)methanamine **162** in the presence of the Pd catalysts. The reaction crude was purified by flash column chromatography (silica gel, hexanes-EtOAc, 1:1) to give **163** as a colorless oil (23 mg, 96%). **HPLC** [Daicel Chiralcel OD-H, *n-hexane-*$^{i}$*PrOH, 85:15*, flow = 0.5 mL/min, detection, UV 210 nm; retention times (min), 12.68 (99.0 %), 16.57 (0.96 %) 98 % *ee*. $[\alpha]_D^{25}$ −6.9 (*c* 0.41, $CHCl_3$). **$^1$H NMR (400 MHz, $CDCl_3$):** δ (ppm) 7.24 (d, *J* = 8.4 Hz, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 5.68 (ddd, *J* = 17.0 Hz, 10.8 Hz, 7.4 Hz, 1H), 5.25 (d, *J* = 10.8 Hz, 1H), 5.23 (d, *J* = 17.0 Hz, 1H), 3.81 (d, *J* = 13.0 Hz, 1H), 3.80 (s, 3H), 3.61 (d, *J* = 13.0 Hz, 1H), 3.60 (dd, *J*= 10.5 Hz, *J* = 6.0 Hz, 1H), 3.38 (dd, *J* = 10.5 Hz, 7.9 Hz, 1H), 3.28-3.13 td, *J* = 7.8, 4.6 Hz, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ (ppm) 158.9, 137.5, 132.3, 129.5 (2C), 117.9, 114.0 (2C), 64.7, 62.0, 55.4, 50.4. **FTIR-ATR (cm$^{-1}$):** 3297, 2924, 1512, 1247. **HMRS (ESI-TOF) m/z:** $[M+H]^+$ calcd for $C_{12}H_{18}NO_2$: 208.1332, found: 208.1184.

***N*-(4-methoxybenzyl)pent-1-en-3-amine (167) and (*E*)-*N*-(4-methoxybenzyl)pent-2-en-1-amine (172).**

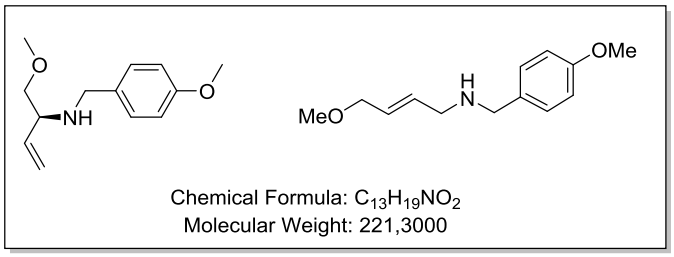



Carbonate **161** was treated with (4-methoxyphenyl)methanamine **162** and following the general procedure. The reaction crude was purified by flash column chromatography (silica gel, hexanes-EtOAc, 9:1) to give **167** (3 mg, 12%) and **172** (16 mg, 68% )as a colorless oil (19 mg, 80%) (ratio 30:70).

**Compound 167: $^{1}$H NMR (400 MHz, $CDCl_3$):** δ (ppm) 7.25-7.19 (m, 2H), 6.89-6.83 (m, 2H), 5.61 (ddd, *J* = 17.1, 10.3, 8.2 Hz, 1H), 5.19-5.07 (m, 2H), 3.79 (s, 3H), 3.76 (d, *J* = 12.9 Hz, 1H), 3.59 (d, *J* = 12.9 Hz, 1H), 2.93 (td, *J* = 8.2, 5.4 Hz, 1H), 1.61-1.36 (m, 2H), 0.87 (t, *J* = 7.5 Hz, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ (ppm) 158.6, 141.2, 132.9, 129.5, 116.347, 113.9, 62.8, 55.4, 50.7, 28.5, 10.5. **HMRS (ESI-TOF) m/z:** $[M+H]^+$ calcd for $C_{13}H_{20}NO$: 206.1539, found: 206.1542.

**Compound 172: $^{1}$H NMR (400 MHz, $CDCl_3$):** δ (ppm) 7.25-7.19 (m, 2H), 6.87-6.80 (m, 2H), 5.66-5.55 (m, 1H), 5.52-5.42 (m, 1H), 3.80 (s, 3H), 3.48 (s, 2H), 2.99 (dd, *J* = 1.0 Hz, *J* = 6.5 Hz, 2H), 2.09-1.99 (m, 2H), 0.99 (t, *J* = 7.8 Hz, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ (ppm) 158.7, 136.3, 131.2, 130.5 (2C), 125.7, 113.6 (2C), 56.6, 55.4, 55.3, 25.6, 13.8. **FTIR-ATR ($cm^{-1}$)**: 2961, 2932, 1511, 1247, 969. **HMRS (ESI-TOF) m/z:** $[M+H]^+$ calcd for $C_{13}H_{20}NO$: 206.1539, found: 206.1531.

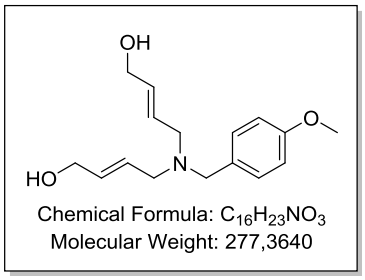
**(*R*)-1-Methoxy-N-(4-methoxybenzyl)but-3-en-2-amine (164) and (*E*)-4-methoxy-N-(4-methoxybenzyl)but-2-en-1-amine (169).**




To a solution of (*E*)-4-hydroxybut-2-enyl methyl carbonate (**157**) (0.6 mg, 4.1 mmol) in THF (25 mL) at room temperature, NaH (0.2 g, 8.2 mmol) was added. After 15 min., $CH_3I$ (1.02 mL, 16 mmol) was added dropwise to the reaction mixture and stirred for four hours. Then, sat. $NH_4Cl/H_2O$ was added to the reaction mixture and the organic layer was separated. The aqueous layer was extracted three times with dichloromethane. The combined organic layers was washed with brine and dried over magnesium sulfate. After removal of the solvents with a rotary evaporator, the residue was purified by column chromatography (hexanes: ethyl acetate =8:3) to give **158** as an colorless oil that appeared slightly contaminated with 1,4-dimethoxybutane, which could not be separated and the mixture was directly used in the next reaction. Following the general procedure carbonate **158** was treated with (4-

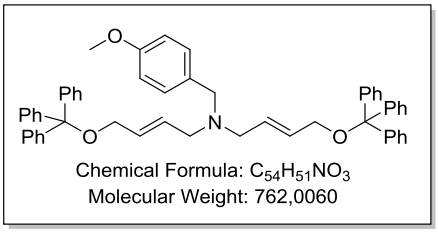
methoxyphenyl)methanamine **162** in the presence of the Pd catalyst. The reaction crude was purified by flash column chromatography (silica gel, Hexanes-EtOAc, 1:1) to give an inseparable mixture of regioisomers **164** and **169** (15 mg, 60% yield; ratio 35:65). Spectroscopical data extracted from the spectrum of the mixture. **164: $^1$H NMR (400 MHz, $CDCl_3$):** δ (ppm) 7.25-7.17 (m, 2H), 6.89-6.78 (m, 2H), 5.80-5.63 (m, 1H), 5.27 (dd, *J* = 17.0, 1.7 Hz, 1H), 5.21 (dd, *J* = 10.1, 1.7 Hz, 1H), 3.79 (s, 3H), 3.78 (d, *J* = 12.8 Hz, 1H), 3.58 (d, *J* = 12.8 Hz, 1H), 3.38-3.32 (m, 3H), 3.32 (s, 3H). **169: $^1$H NMR (400 MHz, $CDCl_3$):** δ (ppm) 7.25-7.17 (m, 2H), 6.89-6.78 (m, 2H), 5.80-5.63 (m, 2H), 3.94-3.87 (m, 2H), 3.51 (s, 3H), 3.52 (s, 2H), 3.31 (s, 3H), 3.07 (d, *J* = 5.3 Hz, 2H). **HMRS (ESI-TOF) m/z:** $[M+H]^+$ calcd for $C_{13}H_{20}O_2$: 222.1489, found: 222.1480.

**Bis-allylated linear product (173).**



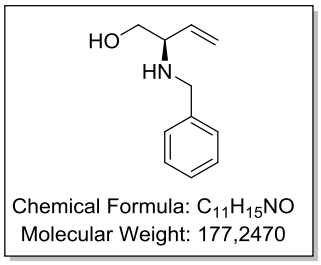

Following the general procedure carbonate **157** was treated with (4-methoxyphenyl)methanamine **162** in the presence of the $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ and $PPh_3$ as ligand. The product ratio was determined by $^1$H NMR spectroscopy (branched **163**/bis-allylated linear **173**, 60:40). **$^1$H NMR (400 MHz, $CDCl_3$):** δ (ppm) 7.19-7.12 (m, 2H), 6.84-6.71 (m, 2H), 5.79-5.59 (m, 4H), 4.10-4.02 (m, 2H), 3.73 (s, 3H), 3.47 (s, 2H), 3.07-2.96 (m, 4H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ (ppm) 158.8, 132.3, 130.3, 129.6, 129.5, 113.7, 63.5, 57.6, 55.4, 55.4. **FTIR-ATR ($cm^{-1}$):** 3297, 2924, 1512, 1247. **HMRS (ESI-TOF) m/z:** $[M+H]^+$ calcd for $C_{16}H_{24}NO_3$: 278.1751, found: 278.1736.

**Bis-allylated linear product (175).**



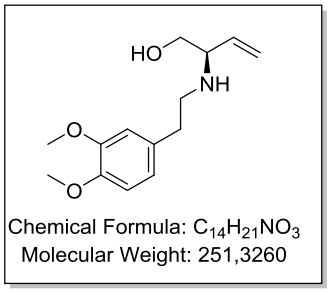

Following the general procedure carbonate **159** was treated with (4-methoxyphenyl)methanamine **162** in the presence of the Pd catalysts. The reaction crude was purified by flash column chromatography (silica gel, hexanes-EtOAc, 95:05) to give **175** as a colorless oil. **$^1$H NMR (400 MHz, $CDCl_3$):** δ (ppm) 7.50-7.41 (m, 12H), 7.32-7.19 (m, 22H), 5.93-5.61 (m, 4H), 3.79 (s, 3H), 3.64-3.62 (m, 6H), 3.18-3.02 (m, 4H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ (ppm) 158.7, 144.4, 131.3, 130.4, 130.3, 129.0, 128.8, 127.9, 127.1, 113.7, 86.9, 64.7, 57.0, 55.4, 55.3. **HMRS (ESI-TOF) m/z:** $[M+H]^+$ calcd for $C_{54}H_{52}NO_3$: 762.3942, found: 762.3951.

**(-)-(2*R*)-2-(Benzylamino)but-3-en-1-ol (193).**



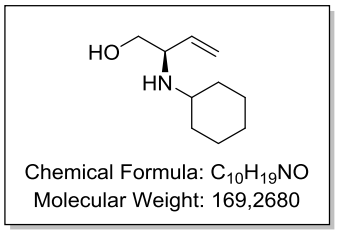

Carbonate **157** was treated with benzylamine **189** following the general procedure. The reaction crude was isolated by flash column chromatography (silica gel, Hexanes-EtOAc, 1:1) to give **193** as a colorless oil (18 mg, Yield: 93%). HPLC [Daicel Chiralcel OD-H, *n-hexane-$^i$PrOH, 85:15*, flow = 0.5 mL/min, detection, UV 210 nm; retention times (min), 11.67 (95.18 %), 14.89 (4.82 %) 90 % *ee*. **$[\alpha]_D^{25}$** −6.8 (*c* 0.6, $CHCl_3$). **$^1$H NMR (400 MHz, $CDCl_3$):** δ (ppm) 7.36-7.30 (m, 3H), 7.29-7.24 (m, 2H), 5.75-5.64 (m, 1H), 5.29-5.20 (m, 2H), 3.89 (d, *J* = 13.0 Hz, 1H), 3.69 (d, *J* = 13.0 Hz, 1H), 3.63 (dd, *J* = 10.6, 4.5 Hz, 1H), 3.40 (dd, *J* = 10.6, 7.9 Hz, 1H), 3.24 (ddd, *J* = 7.7, 7.7, 4.5 Hz, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ (ppm) 140.0, 137.2, 128.6, 128.4, 127.3, 118.1, 64.7, 62.2, 51.0. **FTIR-ATR ($cm^{-1}$):** 3303, 2926, 2851. **HMRS (ESI-TOF) m/z:** $[M+H]^+$ calcd for $C_{11}H_{16}NO$: 178.1226, found: 178.1082.

**2-(3,4-Dimethoxyphenethylamino)but-3-en-1-ol (194).**



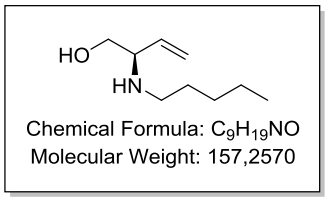

Carbonate **157** was treated with 2-(3,4-dimethoxyphenyl)ethanamine **190** following the general procedure. The reaction crude was purified by flash column chromatography (silica gel, hexanes-EtOAc, 1:1) and gave **194** as a colorless oil (28 mg, 96%). HPLC [Daicel Chiralcel OD-H, *n*-hexane-$^{i}$*PrOH, 90:10*, flow = 0.5 mL/min, detection, UV 210 nm; retention times (min), 25.97 (97.3 %), 29.11 (2.7 %) 95 % *ee*. **$[\alpha]_D^{25}$** −15.5 (*c* 0.18, $CHCl_3$). **$^1$H NMR (400 MHz, $CDCl_3$):** δ (ppm) 6.75 (m, 3H), 5.62 (ddd, *J* = 17.0 Hz, 10.7 Hz, 7.6 Hz, 1H), 5.17 (d, *J* = 10.7 Hz, 1H), 5.15 (d, *J* = 17.0 Hz, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.58 (dd, *J* = 10.4 Hz, 4.5 Hz, 1H), 3.33 (dd, *J* = 10.4 Hz, 7.9 Hz, 1H), 3.22-3.15 (m, 1H), 3.00-2.67 (m, 4H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ (ppm) 149.0, 147.6, 137.5, 132.5, 120.7, 117.5, 112.0, 111.4, 64.6, 62.8, 56.0, 56.0, 48.5, 36.2. **FTIR-ATR ($cm^{-1}$):** 3297, 2927, 1514, 1260, 1026. **HMRS (ESI-TOF) m/z:** $[M+H]^+$ calcd for $C_{14}H_{22}NO_3$: 252.1594, found: 252.1592.

**(-)-(2*R*)-2-(Cyclohexylamino)but-3-en-1-ol (195).**



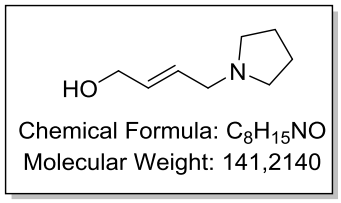

Carbonate **157** was treated with pentan-1-amine **191** following the general procedure. The reaction crude was purified by flash column chromatography (silica gel, EtOAc-MeOH, 9:1) to give **195** as a white foam (18 mg, 91%). HPLC [Daicel Chiralcel OD-H, *n-hexane-*$^{i}$*PrOH, 85:15*, flow = 0.5 mL/min, detection, uv 306 nm; retention times (min), 6.54 (99.14%), 5.59 (0.86%) 98 % *ee*. **$[\alpha]_D^{25}$** −25 (*c* 0.72, $CHCl_3$). **$^1$H NMR (400 MHz, $CDCl_3$):** δ (ppm) 5.71-5.60 (m, 1H), 5.20-5.14 (m, 2H), 3.59-3.53 (m, 1H), 3.36-3.25 (m, 2H), 2.52 (tt, *J* = 10.3 Hz, *J* =3.8 Hz, 1H), 2.32 (bs, 1H), 1.94-1.86 (m, 1H), 1.82-1.67 (m, 3H), 1.63-1.54 (m, 1H), 1.33-1.09 (m, 4H), 1.07-0.94 (m, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ (ppm) 138.1, 117.0, 64.7, 59.1, 53.6, 37.7, 33.3, 26.2, 25.2, 24.8. **FTIR-ATR ($cm^{-1}$):** 3248, 2923, 2855, 1088. **HMRS (ESI-TOF) m/z:** $[M+H]^+$ calcd for $C_{10}H_{20}NO$: 170.1539, found: 170.1600.

**(-)-(2*R*)-2-(Pentylamino)but-3-en-1-ol (196).**




Carbonate **157** was treated with pentan-1-amine **192** following the general procedure. The reaction crude was purified by flash column chromatography (silica gel, EtOAc-MeOH, 9:1) to give compound **196** as a colorless oil (16 mg, 90%). HPLC [Daicel Chiralcel OD-H, *n-hexane-*$^{i}$*PrOH, 85:15*, flow = 0.5 mL/min, detection, uv 313 nm; retention times (min), 6.23 (98.18%), 7.81 (1.82%) 96 % *ee*. **$[\alpha]_D^{25}$** −9.9 (*c* 1.15, $CHCl_3$). **$^1$H NMR (400 MHz, $CDCl_3$):** δ (ppm) 5.73-5.61 (m, 1H), 5.26-5.17 (m, 2H), 3.62 (dd, *J* = 10.6 Hz, *J* = 4.7 Hz, 1H), 3.39 (dd, *J* = 10.6 Hz, *J* = 7.8 Hz, 1H), 3.20 (tdt, *J* = 7.8 Hz, *J* = 4.7 Hz, *J* = 0.9 Hz, 1H), 2.85 (bs, 1H), 2.71 (ddd, *J* = 11.4 Hz, *J* = 8.1 Hz, *J* = 6.6 Hz, 1H), 2.50 (ddd, *J* = 11.4 Hz, *J* = 8.1, *J* = 6.4 Hz, 1H), 1.58-1.41 (m, 2H), 1.37-1.23 (m,4H), 0.95-0.85 (m, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ (ppm) 137.1, 118.0, 64.3, 63.0, 47.0, 29.7, 29.6, 22.6, 14.2. **FTIR-ATR ($cm^{-1}$):** 3298, 2927, 2857, 1457, 1048. **HMRS (ESI-TOF) m/z:** $[2M+Na]^+$ calcd for $C_{18}H_{38}N_2NaO_2$: 337.2831, found: 337.2885.

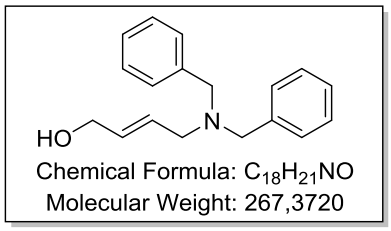
**(*E*)-4-(pyrrolidin-1-yl)but-2-en-1-ol (198).**[57]




Carbonate **157** was treated with pyrrolidine **197a** following the general procedure. The reaction crude was purified by flash column chromatography (silica gel, EtOAc) to give compound **198** as a colorless oil (11 mg, 69%). **$^1$H NMR (400 MHz, $CDCl_3$):** δ (ppm) 5.91-5.72 (m, 2H), 4.15-4.09 (m, 2H), 3.15-3.09 (m, 2H), 2.57-2.50 (m, 4H), 1.83-1.76 (m, 4H). **$^{13}$C NMR (100 MHz, $CDCl_3$)**: δ (ppm) 133.5, 127.8, 59.8, 53.8, 52.4, 23.5.

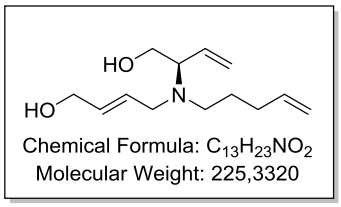
[57] Hennequin, L.F.; Stokes, E.S.E.; Thomas, A.P.; Johnstone, C.; Plé, P.A.; Ogilvie, D.J.; Dukes, M.; Wedge, S.R.; Kendrew, J.; Curwen, J.O. *J. Med. Chem.* **2002,** *45*, 1300-1312.

**(*E*)-4-(Dibenzylamino)but-2-en-1-ol (199).**[58]




Carbonate **157** was treated with dibenzylamine **197b** following the general procedure. The reaction crude was purified by flash column chromatography (silica gel, Hexanes-EtOAc, 1:1) to give compound **199** as a colorless oil (21 mg, 71%). **$^1$H NMR (400 MHz, $CDCl_3$):** δ (ppm) 7.43-7.16 (m, 10H), 5.83-5.71 (m, 2H), 4.10 (d, *J* = 4.3 Hz, 2H), 3.81 (s, 4H), 3.58 (s, 4H), 3.07 (d, *J* = 4.8 Hz, 2H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ (ppm) 139.7, 131.9, 129.8, 128.9, 128.5, 128.3, 126.94, 63.4, 58.1, 55.3.

**(*E*)-4-((1-Hydroxybut-3-en-2-yl)(pent-4-enyl)amino)but-2-en-1-ol (202).**




Carbonate **157** (2 equiv.) was treated with pentan-1-amine **200** (1equiv.) following the reaction conditions. The reaction crude was purified by flash column chromatography (silica gel, EtOAc-MeOH, 9:1) to give **202** as a colorless oil (45 mg, 86%).**$^1$H NMR (400 MHz, $CDCl_3$):** δ (ppm) 5.86-5.62 (m, 4H), 5.27 (ddd, *J* = 10.5 Hz, *J* = 1.7 Hz, *J* = 0.6 Hz, 1H), 5.15 (ddd, *J* = 17.2 Hz, *J* = 1.7 Hz, *J* = 0.9 Hz, 1H), 4.16-4.12 (m, 2H), 4.14 (d, *J* = 5.4 Hz, 2H), 3.49-3.44 (m, 2H) 3.38-3.26 (m, 2H), 2.95 (dd, *J* = 14.4 Hz, *J* = 7.5 Hz, 1H), 2.63-3.53 (m, 1H), 2.33 (ddd, *J* = 13.0 Hz, *J* = 8.3 Hz, *J* = 4.6 Hz, 1H), 2.14-1.96 (m, 2H), 1.64-1.47 (m, 2H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ (ppm) 138.4, 132.6, 132.2, 130.1, 120.1, 114.9, 63.6, 63.3, 60.8, 51.7, 48.7, 31.5, 27.6. **FTIR-ATR ($cm^{-1}$):** 3366, 2924, 1418, 997, 912. **HMRS (ESI-TOF) m/z:** $[M+H]^+$ calcd for $C_{13}H_{24}NO_2$: 226.1802, found: 226.1859.

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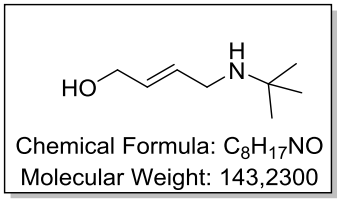
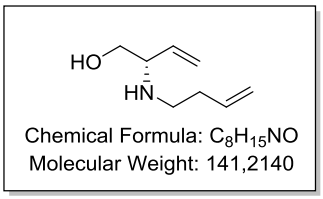
58 Cresswell, A. J.; Davies, S. G.; Lee, J. A.; Morris, M. J.; Roberts, P. M.; Thomson, J. E. *J. Org. Chem*., **2012**, *77*, 7262–7281.

**(*E*)-4-(*tert*-Butylamino)but-2-en-1-ol (204)**



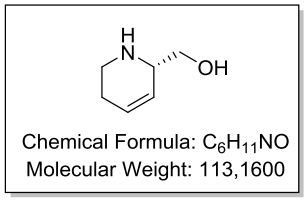

Carbonate **157** was treated with tert-butylamine **203** following the general procedure. The reaction crude was purified by flash column chromatography (silica gel, $CH_2Cl_2$/MeOH) to give compound **204** as a colorless oil (11 mg, 69%). **$^1$H NMR (400 MHz, $CDCl_3$):** δ (ppm) 5.83-5.79 (m, 2H), 4.13-4.08 (m, 2H), 3.21 (d, *J* = 4.6 Hz, 2H), 2.30 (bs, 1H), 1.13 (s, 9H). **$^{13}$C NMR (100 MHz, $CDCl_3$)**: δ (ppm) 131.4, 130.1, 77.5, 77.2, 76.8, 63.0, 51.1, 44.3, 28.8. **HMRS (ESI-TOF) m/*z*:** $[M+Na]^+$ Calcd for $C_8H_{17}NNaO$: 166.1202, found: 166.1225.

**(+)-(2*S*)-2-(But-3-enylamino)but-3-en-1-ol (217).**



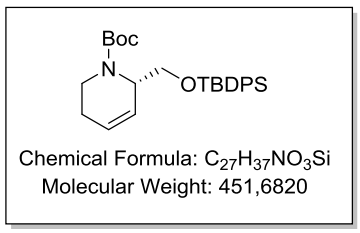

Carbonate **157** was treated with but-3-en-1-amine **216** in the presence of (*R*,*R*)-DACH Naphtyl or (*R*,*R*)-**L3** ligand following the general procedure. The reaction crude was purified by flash column chromatography (silica gel, EtOAc-MeOH, 9:1) to give **217** as a colorless oil (14 mg, 89%). HPLC [Daicel Chiralcel OD-H, *n-hexane-$^i$PrOH, 85:15,* flow = 1 mL/min, detection, uv 309 nm; retention times (min), 4.0 (97%), 4.4 (3%) 94 % *ee*. **$[\alpha]_D^{25}$** +12.1 (*c* 4.1, $CHCl_3$). **$^1$H NMR (400 MHz, $CDCl_3$):** δ (ppm) 5.78 (tdd, *J* = 17.0 Hz, *J* = 10.1 Hz, *J* = 6.8 Hz, 1H), 5.64 (ddd, *J* = 17.2 Hz, *J* = 10.6 Hz, *J* = 7.6 Hz, 1H), 5.23-5.17 (m, 2H), 5.14-5.01 (m, 2H), 3.59 (dd, *J* = 10.5 Hz, *J* = 4.5 Hz, 1H), 3.35 (dd, *J* = 10.5 Hz, *J* = 8.0 Hz, 1H), 3.22-3.13 (m, 1H), 2.76 (td, *J* = 11.2 Hz, *J* = 7.0 Hz, 1H), 2.56 (td, *J* = 11.2 Hz, *J* = 6.7 Hz, 1H), 2.30-2.19 (m, 2H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ (ppm) 137.7, 136.5, 117.5, 116.7, 64.6, 62.8, 46.1, 34.6. **FTIR-ATR ($cm^{-1}$):** 3277, 3075, 2919, 2849, 1455, 1101. **HMRS (ESI-TOF) m/*z*:** $[M+H]^+$ calcd for $C_8H_{16}NO$: 142.1226, found: 141.1241.

**(-)-(1*S*) (1,2,5,6-Tetrahydropyridin-2-yl)methanol (218).**




In a Schlenk tube under argon atmosphere [Pd($\eta^3$-$C_3H_5$)Cl]$_2$ (1 mg, 2 mol%), the (*R*,*R*)-DACH Naphthyl ligand or (*R*,*R*)-**L3** (5.5 mg, 6 mol%) and $CH_2Cl_2$ (10 mL), were introduced. The resulting solution was stirred for 20 minutes, and then, the carbonate **157** (0.115 mmol) and but-3-en-1-amine **216** (0.127 mmol) were successively introduced. The mixture was stirred at room temperature for 18h. Then, *p*-toluenesulfonic acid monohydrate (22 mg, 0.115 mmol) was added to the solution and the mixture was stirred for 30 min at room temperature until the solution became homogeneous. Grubbs' second-generation catalyst (5 mg, 0.0058 mmol, 5 mol %) was added, and the solution was stirred under reflux for 18h. Water (20 mL) was added, the phases were separated, and the aqueous layer was extracted with $CH_2Cl_2$ (3 x 10 mL). The aqueous phase was concentrated under vacuum. The residue was dissolved in MeOH and Amberlite$^{TM}$-OH was added. The heterogeneous solution was stirred for 2 hours and then, filtered, and concentrated to afford pure product **218** (12 mg, 92%) as a colorless oil. **$[\alpha]_D^{25}$** −50.6 (*c* 3.2, MeOH). **$^1$H NMR (400 MHz, $CD_3OD$):** δ (ppm) 5.92-5.82 (m, 1H,), 5.63 (ddd, *J* = 10.3, *J* = 4.2 Hz, *J* = 2.2 Hz, 1H), 3.50 (dd, *J* = 6.2, 3.1 Hz, 2H), 3.41-3.33 (m, 1H), 3.05 (ddd, *J* = 12.1 Hz, *J* = 5.5 Hz, *J* = 3.9 Hz, 1H), 2.81 (ddd, *J* = 12.1 Hz, *J* = 8.8, *J* = 4.9 Hz, 1H), 2.24-2.11 (m, 1H), 2.10-1.96 (m, 1H). **$^{13}$C NMR (100 MHz, $D_2O$):** δ (ppm) 128.0, 124.4, 63.1, 54.4, 39.9, 23.4. **FTIR-ATR ($cm^{-1}$):** 3301, 3027, 2922, 2852, 1636, 1454. **HMRS (ESI-TOF) m/z:** $[M+H]^+$ calcd for $C_6H_{12}NO$: 114.0913, found: 114.0908.

**(*S*)-*tert*-Butyl 2-((tert-butyldimethylsilyloxy)methyl)-5,6-dihydropyridine-1(2H)-carboxylate (208).**




Compound **218** (0.010g, 0.088 mmol) was dissolved in dry $CH_2Cl_2$ (1 mL) and treated under argon with *tert*-butyldiphenyl chloride (0.03 mL, 0.1 mmol) and imidazole(0.01 g, 0.2 mmol).The mixture was then stirred for 16h at room temperature. The reaction mixture was

then diluted with $H_2O$. The phases were separated and the aqueous phase was extracted with $CH_2Cl_2$. The combined organic phases were dried over $MgSO_4$, filtered, and concentrated in vacuum. To stirred solution of crude mixture (0.088 mmol), $Et_3N$ (0.019 mL, 0.13 mmol) and DMAP (catalytic amount) in $CH_2Cl_2$ (2 mL) was added $(Boc)_2O$ (0.03mL, 0.13 mmol) at room temperature. After being stirred for overnight, the solvents were removed under reduced pressure. The residue was then partitioned with $H_2O$ and EtOAC. The aqueous layer was extracted with EtOAC (3 times) and the combined organic layers were washed with saturated aqueous $NaHCO_3$, brine, dried ($MgSO_4$) and concentrated in *vacuo*. The reaction crude was purified by flash column chromatography (4% EtOAc in hexanes) and gave **208** as a colorless oil (25 mg, 87%). $\mathbf{[\alpha]_D^{25}}$ –132.4 (*c* 0.94, $CDCl_3$), ($\mathbf{[\alpha]_D^{27}}$ –150.0 (*c* 1.04, $CDCl_3$) described). **$^1$H NMR (400 MHz, $CDCl_3$)**: δ (ppm) 1.04 (s, 9H), 1.32-1.50 (m, 9H), 1.81-2.03 (m, 1H), 2.10-2.27 (m, 1H), 2.81-3.08 (m, 1H), 3.61-3.81(m, 2H), 4.09-4.26 (m, 0.5H), 4.35-4.51 (m, 0.5H), 5.62-5.85 (m, 1H), 5.88-6.01 (m,1H), 7.33-7.44 (m, 6H), 7.63-7.70 (m, 4H). **$^{13}$C NMR (100 MHz, $CDCl_3$)**: δ (ppm) 162.4, 135.5, 135.5, 133.4, 129.6, 127.6, 127.5, 126.8, 79.9, 66.7, 55.55, 41.0, 36.4, 31.3, 26.8, 26.0, 19.2.

*Stoichiometric reaction of [$Pd_2$(dba)$_3$] and vinyl epoxide **54** affording complex **206***

[$Pd_2dba_3$] (94 mg, 0.1640 mmol) was mixed with vinyl epoxide **8** (23 mg, 0.3281 mmol,) and LiCl (35 mg, 0.8203 mmol,) in THF (10 mL). The progress of the reaction was followed by $^1$H NMR spectroscopy. After 60 min the product was purified by column chromatography by using $CH_2Cl_2$ until all dibenzylidene acetone was eluted and then $CH_2Cl_2/Et_2O$ 1:1 to get pure complex **206**. **$^1$H NMR (400 MHz, $CDCl_3$)**: δ (ppm) 5.84-5.36 (m, 1H), 4.06 (d, *J* = 6.8 Hz, 1H), 3.97 (dt, *J* = 11.0, 4.0 Hz, 1H), 3.80 (dd, *J* = 15.0, 2.5 Hz, 1H), 3.58 (dd, *J* = 15.0, 4.0 Hz, 1H), 3.00 (d, *J* = 12.1 Hz, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$)**: δ (ppm) 108.4, 83.1, 60.8, 59.7.

# CHAPTER 5

*Synthesis of acyclic nucleoside analogues*

# I. Introduction

## I.1. Acyclic Nucleoside Analogue

The "normal" and more abundant viral life cycle, such in the case of herpesviruses, replicates their genome and expresses their genes autonomously, independent of the host cell metabolism. Unlike retroviruses as the HIV virus, herpesviruses do not have a reverse transcription step in their replicative cycle, so that their DNA genome must be replicated by the viral DNA polymerase.[1]

At present, the drugs prescribed for the treatment of herpesvirus infections are nucleoside analogues like acyclic guanosine analogues (acyclovir, penciclovir, ganciclovir) and their oral prodrug forms (valaciclovir, famciclovir and valganciclovir, respectively) (Figure 19).[2] A prodrug is a compound that has to undergo transformation within the body before eliciting its therapeutic action. This strategy is based on chemically modifying an active substance by attaching pro-moieties to pharmacophores.[2] Ideally, it should overcome the biochemical and physical barriers impeding drug transport of the parent substance. All of the nucleoside analogues presented before, target the viral DNA polymerase. Nonetheless, in order for this to happen, they have to interact with viral DNA synthesis. For this reason, they need to be phosphorylated intracellularly to form sequentially the mono-, di-, and triphosphate nucleoside.[3]

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1 De Clercq, E. *Nat. Rev. Drug Disc.* **2002**, *1*, 13-25.

2 McKenna, C. E.; Kashemirov, B. A.; Eriksson, U.; Amidon, G. L.; Kish, P. E.; Mitchell, S.; Kim, J.-S.; Hilfinger, J. M. *J. Organomet. Chem.* **2005**, *690*, 2673-2678.

3 Votruba I.; Bernaerts R.; Sakuma T.; De Clercq E.; Merta A.; Rosenberg I.; Holý A. *Mol. Pharmacol.* **1987**, *32*, 524-529.

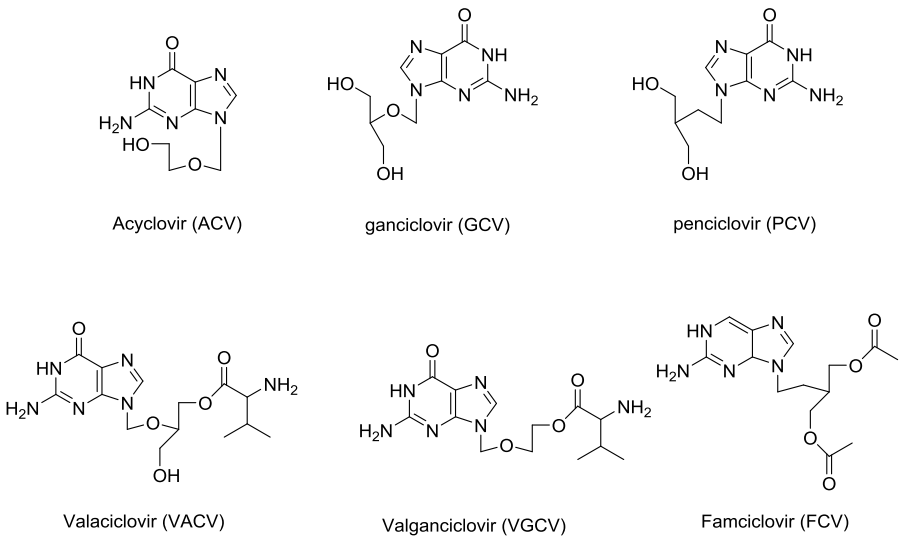


**Figure 19.** Antiviral agents available for the treatment of herpesvirus infections.

In their triphosphate form, these nucleoside analogues can interact with the viral DNA polymerase as competitive inhibitors or as alternative substrates. In the last case, the incorporation of these compounds can prevent further chain elongation. The first phosphorylation step is crucial for the antiviral activity of the acyclic nucleoside analogues. In fact, this step confines the effectiveness of the compounds to viruses that do induce a specific kinase phosphorylating of the compounds while making them inactive against viruses that either do not induce a specific TK (thymidine kinase) or PK (protein kinase) or have developed resistance to the compounds through mutations in these enzymes. Thus, acyclovir, penciclovir, and ganciclovir are ineffective against $TK^-$ HSV (herpes simplex virus), $TK^-$ VZV (varicella-zoster virus), $PK^-$ CMV (cytomegalovirus), and any other DNA viruses (polyomavirus, papillomavirus, adenovirus, and poxvirus) that fail to ensure phosphorylation of the nucleoside to the nucleoside monophosphate (nucleotide).[2, 4, 5, 6]

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4 De Clercq, E.; Field, H. J. *Br. J. Pharmacol.* **2006**, *147*, 1-11.

5 Bronson, J. J.; Ghazzouli, I.; Hitchcock, M. J. M.; Webb, R. R.; Martin, J. C. *J. Med. Chem.* **1989**, *32*, 1457-1463.

6 De Clercq, E. *Clin. Microbiol. Rev.* **2003**, *16*, 569-596.

## I.2. Acyclic Nucleoside Phosphonates (ANPs)

There is another related class of compounds that shows the same biological activities: the acyclic nucleoside phosphonates (ANPs). The ANPs are nucleotide analogues in which a phosphonate group is linked to a purine or pyrimidine through an aliphatic chain via an ether linkage. The phosphonate group (with a stable P-C bond) is equivalent to a phosphate group, but, unlike phosphate, phosphonate can no longer be cleaved by the esterases or any catabolic enzymes at large. These esterases would normally convert nucleoside monophosphates back to their nucleoside form. For this reason, ANPs show a broader antiviral activity spectrum than acyclic nucleoside analogues such as ACV.[7]

There are three ANPs that have been formally licensed for the treatment of severe viral infections: (i) Cidofovir, Vistide® for HCMV (Human Cytomegalovirus) infections (i.e. HCMV retinitis) in AIDS patients, (ii) adefovir dipivoxil, Hepsera® for chronic HBV (hepatitis B virus) infections, and (iii) tenofovir disoproxil fumarate (TDF), Viread® for HIV (Human Immunodeficiency virus) infections AIDS(Figure 20).[5,8,9,10]

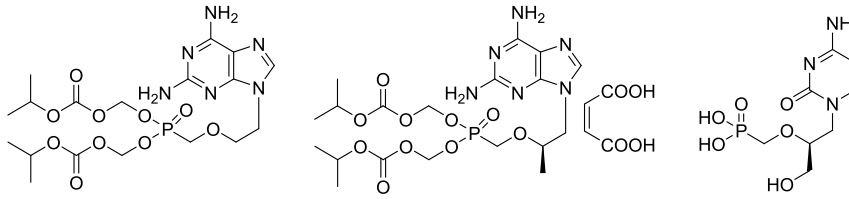


**Figure 20.** Structure of the principal ANPs.

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7 Topalis, D.; Pradère, U.; Roy, V.; Caillat, C.; Azzouzi, A.; Broggi, J.; Snoeck, R.; Andrei, G.; Lin, J.; Eriksson, S.; Alexandre, J. A. C.; El-Amri, C.; Deville-Bonne, D.; Meyer, P.; Balzarini, J.; Agrofoglio, L. A. *J. Med. Chem.***2011**, *54*, 222-232.

8 Balzarini, J.; Pannecouque, C.; De Clercq, E.; Aquaro, S.; Perno, C.-F.; Egberink, H.; Holy, A. *Antimicrob. Agents Chemother.* **2002**, *46*, 2185-2193.

9 Webb II, R. R.; Wos, J. A.; Bronson, J. J.; Martin, J. C. *Tetrahedron Lett.* **1988**, *29*, 5475-5478.

10 Declercq, E. *Biochem. Pharmacol.* **2007**, *73*, 911-922.

Among ANPs, the cytosine derivative (*S*)-1-(3-Hydroxy-2-phosphonylmethoxypropyl)cytosine (HPMPC) is one of the most active ones. The antiviral properties of Cidofovir, now on the market as Vistide® (Figure 20) were first described in 1987 by De Clercq *et al*. This compound and its cyclic analogue have demonstrated *in vitro* (and *in vivo* in some cases) activity against a wide range of DNA viruses including polyoma-, papilloma-, adeno-, herpes-, and pox-viruses. Among the family of herpesviridae, all eight human herpesviruses have proved to be susceptible to the inhibitory effects of cidofovir. The same applies to vaccine, variola, cowpox and monkeypox among the poxviruses. The human cytomegalovirus (HCMV) figures among the members of herpesviruses that can cause severe complications in immunocompromised patients. Actually, cidofovir is the first acyclic nucleoside phosphonate licensed for the intravenous treatment of HCMV retinitis in AIDS patients.[10]

This short introduction on the acyclic nucleoside analogues shows us that antiviral chemotherapy is well established for the prevention and treatment of many important virus infections. Until the 1950s, the kind of viruses discussed here was widely believed not to be susceptible to "antibiotic" therapy. The belief was based on the notion that a virus inhibitor must inevitably be toxic for the host cell. Acyclic nucleoside analogues have been the drugs that changed this concept. The prodrug concept is now an integral part of the drug discovery process and it will continue to be widely exploited by the medicinal chemist.

## I.3. Acyclic nucleoside analogues synthesis

Due to the relevant biological properties of acyclic nucleosides, a high number of analogues have been prepared and tested as antiviral compounds, containing modifications in any part of the Cidofovir structures.[11] Indeed, such

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[11] (a) Krečmerová, M.; Holý, A.; Pískala, A.; Masojídkova, M.; Andrei, G.; Naesens, L.; Neyts, J.; Balzarini, J.; De Clercq, E.; Snoeck, R. *J. Med. Chem*. **2007**, *50*, 106910-1077. (b) Holý, A. *Curr. Pharm. Des*. **2003**, *9*, 2567-2592. (c) De Clercq, E. *Antiviral Res*. **2007**, *75*, 1-13. (d) Holý, A. *Antiviral Res*. **2006**, *71*, 248-253. (e) Ruiz, J. C.; Beadle, J. R.; Aldern, K. A.; Keith, K. A.; Hartline, C. B.; Kern, E. R.; Hostetler, K. Y. *Antiviral Res*. **2007**, *75*, 87-90. (f) Ciesla, S. L.; Trahan, J.; Wan, W. B.; Beadle, J. R.; Aldern, K. A.; Painter, G. R.; Hostetler, K. Y. *Antiviral Res*. **2003**, *59*, 163-171. (g) Keith, K. A.; Hitchcock, M. J.; Lee, W. A.; Holý, A.; Kern, E. R. Antimicrob. *Agents Chemother*. **2003**, *47*, 2193-2198. (h) Bindanset, D. J.; Beadle, J. R.; Wan, W. B.; Hostetler, K. Y.; Kern, E. R. *J. Virol*. **2004**, *190*, 499-503.

modifications can assist in several ways, including modification of the heterocyclic base, carbon chain and phosphonate moiety. The former is somewhat limited, taking into account that the ability to form hydrogen bonds must be retained in order to achieve some biological activity. Accordingly, the number of heterocycles that can be used as alternative bases is limited even though there is a considerable catalogue of possibilities. Figure 21 collects some of these analogues with modifications in the carbon chain.

Most of the modifications involve the hydroxymethyl chain (**220**), which has been removed or replaced by series of methyl and ethyl derivatives including the corresponding unsaturated fragments. The alkyl chain has also been replaced by a triethylenglycol unit (**221**). Another modification involves the exchange of atoms at positions 4 and 5 giving rise to the replacement of the phosphonate by a phosphate unit (**222**)**,** (**223**). Vinyl ANP (**224**) and their allyl (**225**) analogues have also been described.[12]

It is particularly noticeable that the only access to these nucleoside analogues is chemical synthesis, and a great effort is still necessary to develop new routes to a wide variety of modified nucleosides.

[12] Hiroki, K.; Topalis, D.; Broggi, J.; Pradere, U.; Roy, V.; Berteina-Raboin, S.; Nolan, P. S.; Deville-Bonne, D.; Andrei, G.; Snoeck, R.; Garin, D.; Crance, J. M.; Agrofolio, L. A. *Tetrahedron* **2008**, *64* 3517-3526.

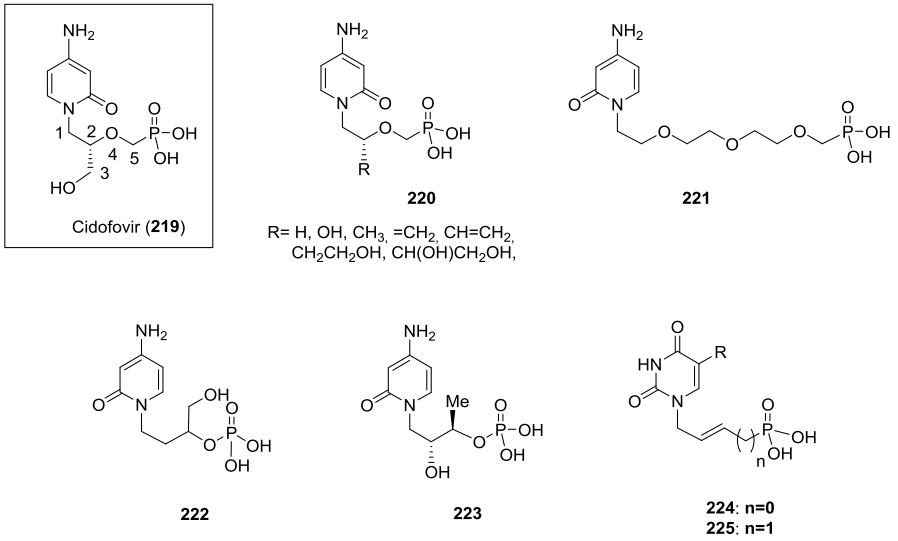


**Figure 21.** Several Cidofovir analogues.

Based on the nucleophilicty of nucleic bases, acyclic nucleosides are commonly synthesized by alkylation with halogenated hydrocarbons, aza-Michael addition-reduction sequence with Michael acceptors such as α,β-unsaturated aldehydes or ring-opening reaction with propylene oxides or pyranoid ring (Scheme 72).[13] More recently, Mitsunobu coupling[14] and the addition of different nucleophiles to 9-allenyl-9H-purines, catalyzed by silver, have been reported.[15] However, many of these procedures afford achiral compounds or racemic mixtures, although antiviral activity depends on the configuration of the nucleoside, both enantiomers showing very different activities.

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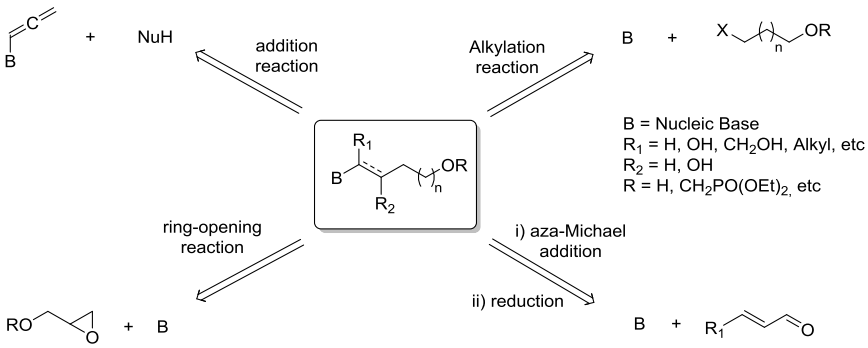
13 For a recent review about chemical synthesis of acyclic nucleosides see: Guo, H.-M.; Wu, Y.-Y.; Niu, H.-Y.; Wang, D.-C.; Qu, G.-R. in *Chemical Synthesis of Nucleoside Analogues*, Merino, P. ed., Wiley, p. 103-162, **2013**.

14 Guo, H.-M.; Wu, Y.-Y.; Niu, H.-Y.; Wang, D.-C.; Qu, G.-R. *J. Org. Chem.* **2010,** *75*, 3863-3866.

15 Wei, T.; Xie, M-S.; Qu, G-R.; Niu, H-Y.; Gou, H-M. *Org. Lett.* **2014**, *16*, 900-903.




**Scheme 72.** General methods to synthesize acyclic nucleosides analogues.

Consequently, the development of methods allowing the synthesis of both enantiomers with high optical purity is highly desirable.

# II. Results and Discussion

## II.I. Retrosynthetic scheme

In this context, our aim is to propose a new enantioselective method to obtain structurally related Cidofovir (**224**) and allyl ANP (**225**) (Figure 22). From a structural point of view, the target compounds present a structure where the nucleic base is directly connected to a stereocenter, whose stereochemistry was chosen according to that present in Cidofovir.

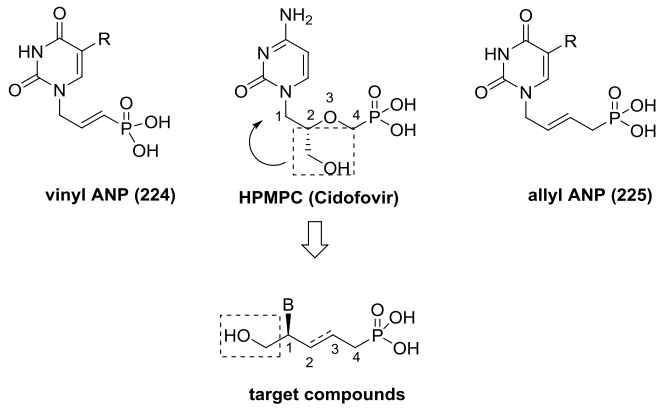
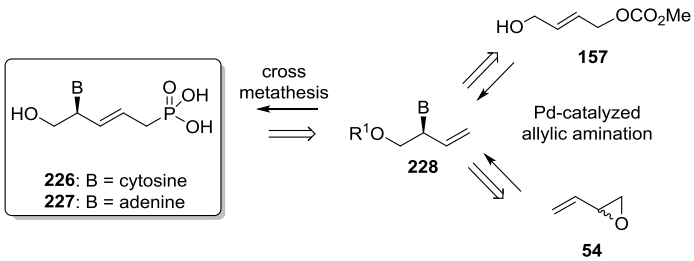



**Figure 22.** Structural relationship between Cidofovir and the target compounds.

Based on a similar strategy to that used in the synthesis of nectrisine, we thought that starting from carbonate **157**, or from vinyl epoxide **54**, compound **226** and **227** could be easily prepared through a palladium-catalyzed allylic substitution reaction, using nucleic bases as nucleophiles followed by cross-metathesis reaction with allyl diethylphosphonate (Scheme 73). This strategy would afford unsaturated compounds related to that of the allyl ANP analogues. Moreover, other purine and pyrimidine bases could be also considered in order to afford a small library of acyclic nucleotide phosphonate analogues.




**Scheme 73.** Retrosynthesis of ANPs **226** and **227**.

## II.2. Synthesis of allyl amines by a Pd-catalyzed allylic amination reaction.

As already discussed in the introduction and in the previous chapter, Pd-catalyzed asymmetric allylic substitution has become a powerful tool for the construction of C-C, C-N, C-O and C-S bonds of defined configuration with high enantioselectivity. Particularly, Pd-catalyzed deracemization of vinyl epoxide is an efficient procedure for preparing 2-amino-3-buten-1-ol derivatives,[16] which are versatile staring materials for the synthesis of natural products. We have recently shown that this type of amino-alcohol derivatives can also be efficiently obtained from methyl 2-buten-1,4-diol-carbonate.

The use of nucleobases[17,18] as nucleophiles in asymmetric Pd-catalyzed allylic alkylation[19] is not trivial. These molecules have been shown to behave

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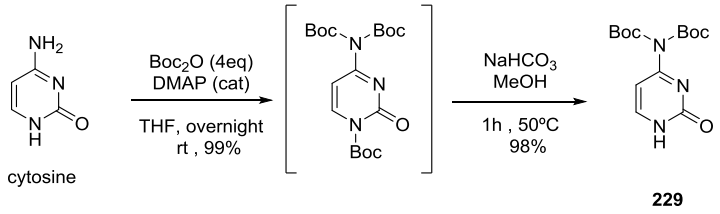
16 Trost, B. M.; Home, D. B.; Weltering, M. J. *Chem. Eur. J*. **2006**, *12*, 6607-6620.
17 Trost, B. M.; Kuo, G. H.; Benneche, T. *J. Am. Chem. Soc*. **1988**, *110*, 621-622.
18 Trost, B. M.; Madsen, R.; Guile, S, D. *Tetrahedron Lett*. **1997**, *38*, 1707-1710.

differently to other simple nucleophiles[20,21] such as malonates, sulfinates, azides and amines in desymmetrization processes. Thus, nucleobases displayed a remarkable effect on the catalytic turnover and the enantioselectivity of desymmetrization reactions, probably because the nucleophile plays a role, and also due to their ability to serve as competitive ligands, and thereby disrupt the normal coordination of palladium.

In order to avoid selectivity problems, and/or bis-alkylation, the process demands previous protection of the secondary amino functionalities other than $N^1$. Furthermore, protection would increase the lipophilicity of the compounds, allowing for the use of common organic solvents in the Pd-catalyzed asymmetric allylic amination.

Thus, reaction of cytosine with Boc anhydride in the presence of DMAP and THF at room temperature afforded the full protected product after 12h, which was treated with $NaHCO_3$ and MeOH at 50ºC for 1h to give the desired product **229** in 98% yield (Scheme 74).[22]




**Scheme 74.** Synthesis of starting material **229**.

Thus, we initially tested the reaction of vinyl epoxide **54** with di-Boc-cytosine **229** in the presence of 2 mol% of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ associated with 6 mol% of (*R*,*R*)-**L3** in dichloromethane at reflux for 18 h. These conditions led to the desired product as a single regioisomer in 87 % yield, but with a moderate

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19 Trost, B. M. *Acc. Chem. Res.* **1996**, *29*, 355-364.

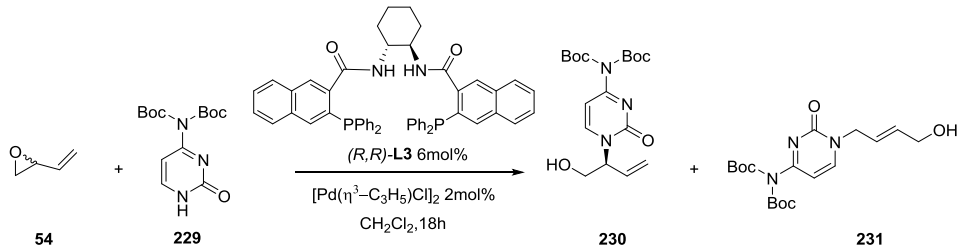
20 Trost, B. M.; Madsen, R.; Guile, S. D.; Brown, B. *J. Am. Chem. Soc.* **2000**, *122*, 5947-5956.

21 Trost, B.M.; Madsen, R.; Guile, S.G.; Elia, A. E. H. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1569-1572.

22 Andrea, P.; Giampaolo, G.; Ivana, P.; Mariolino, C.; Giammario, N. *Eur. J. Org. Chem.* **2008**, *34*, 5786-5797.

enantiomeric excess of 79% *ee* (Table 7, entry 1). When the reaction was conducted at room temperature, product **230** was obtained in an excellent 94% yield and 90% *ee* (Table 7, entry 2). However, decreasing the temperature to -10ºC was detrimental for the enantioselectivity, which decreased to 85% (Table 7, entry 3).

**Table 7**. Influence of temperature on allylic amination of butadiene monoepoxide using **229** as nucleophiles, and $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$/(*R*,*R*)-**L3** as catalytic system.[a]

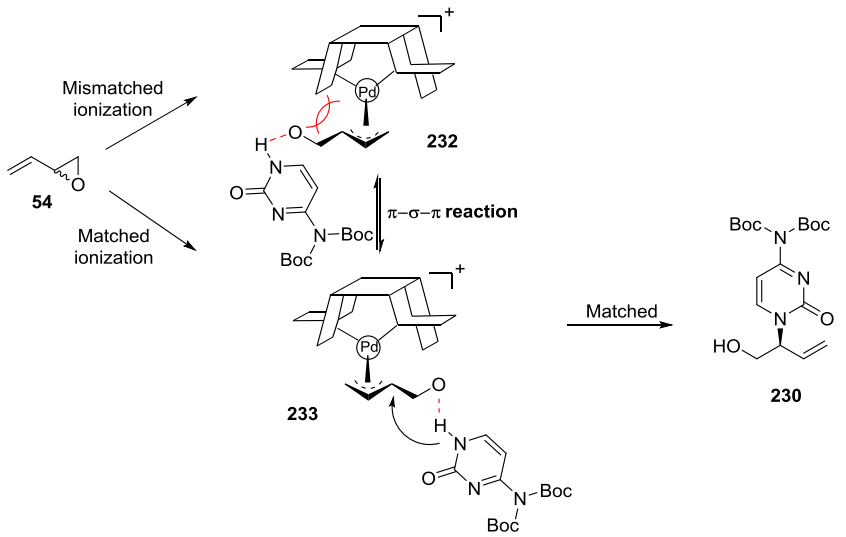



| Entry | Temp. (ºC) | Conversion (%)[b] | Yield of 230 (%)[c] | *ee* (%)[e] |
|---|---|---|---|---|
| 1 | reflux | >98 | 87 | 79 |
| 2 | rt | >98 | 94 | 90 |
| 3 | -10 | >98 | 91 | 85 |

[a] Conditions: catalyst (2 mol%), (*R*,*R*)-**L3** (6 mol%), butadiene monoepoxide (**54**) (1 equiv), **229** (2.0 equiv.), 18h, room temperature, concentration: 0.01M. [b] Determined by $^1$H NMR. Only branched regioisomer was observed. [d] Isolated yield of branched **230** compound. [e] determined by chiral HPLC OD-H Column.

In order to obtain high enantioselectivities, in addition to a selective alkylation of one diastereomeric intermediate over the other, a Curtin-Hammett condition must be established, wherein interconversion of Pd-allyl intermediates is rapid and successfully competes with nucleophilic addition. In this regard, heating can favor equilibration of the π-allyl intermediates, but at the same time, can also balance the rates of corresponding nucleophilic additions, leading to decreased enantioselectivities, as it happens to be the case. On the other hand, lower enantioselectivities when the reaction was performed at lower temperatures may be attributed to the rate of π-allyl complex equilibration being slower than the rate of nucleophilic attack.

Both the regio- and enantioselectivity are rationalized with the cartoon model of Trost (Scheme 75).[23] (*S*)-**54** will ionize via a matched pathway to afford **233**, while (*R*)-**54** undergoes a mismatched ionization to give **232**. The intermediate **232** and **233** can readily interconvert by a π-σ-π mechanism about the allyl terminus. Protected cytosine **229** is directed to react at the more substituted carbon by hydrogen bonding. Nucleophilic approach via **233** is favored because the nucleophile enters under a raised flap, while in the **232** mode the nucleophile encounters a lowered flap.[45]




**Scheme 75.** Model developed by Trost explaining both the regio- and the steroselectivity of the reaction.

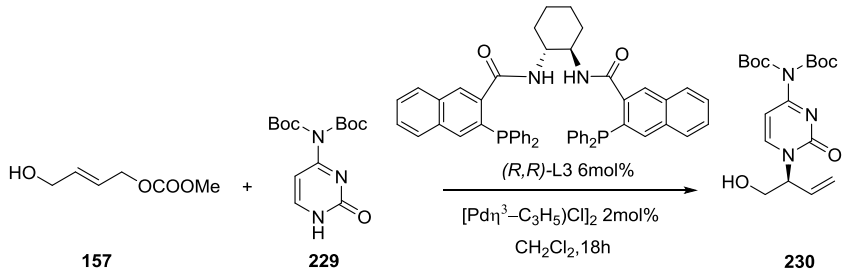
We then tested the reaction of carbonate **157** directly with di-Boc-cytosine (**229**). Results are collected in Table 8. Initially, carbonate **157** was reacted with **229** in the presence of 2 mol% of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ and 6 mol% of (*S*,*S*)-**L3** in dichloromethane (Table 8, entry 1). The branched product **230** was obtained in 94% yield and 87% *ee*. The use of BSA-KOAc did not improve the results (Table 8, entry 2). Lowering the temperature raised the enantioselectivity from 87% to 91.5% (Table 8, entry 3). Further optimization focused on catalyst loading. When the catalysts loading was decreased from 2 mol% to 0.5 mol% a

[23] Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc*. **1999**, *121*, 4545-4554.

drastic drop in the enantioselectivity was produced (Table 8, entries 1, 5 and 6). Similarly, raising the catalyst to 3 mol% had not significant influence on *ee*.

It has been shown that this reaction is fairly sensitive to concentration effects and enantioselectivity was altered by minor concentration changes. Indeed, the interconversion between the two diastereoisomeric intermediates is a unimolecular process; therefore, its rate should be unaffected by concentration of nucleophile. On the other hand, nucleophilic attack is bimolecular, and its rate depends both on the concentration of the nucleophile and of the palladium π-allyl intermediate. Thus, the rate of nucleophilic attack in more concentrated media increases and consequently occurs before π-σ-π equilibration of the π-allyl intermediate is produced. Thus, decreasing the concentration to 0.01M, *ee* was raised to >99% (Table 8, entry 7).

**Table 8.** Influence of Pd loading and temperature on allylic amination of carbonate **157** with cytosine derivative **229** affording **230** using Pd/ (*R,R*)-**L3** as catalytic system.[a]




**157** **229** **230**

| Entry | Pd (mol %) | T (°C) | Conversion (%)[b] (Yield) (%)[c] | *ee* (%)[d] |
|---|---|---|---|---|
| 1 | 2 | rt | >98 (94) | 87 |
| 2[e] | 2 | rt | >98 (95) | 83 |
| 3 | 2 | -10 | >98 (92) | 92 |
| 4 | 1 | rt | >98 (90) | 47 |
| 5 | 0.5 | rt | >98 (92) | 22 |
| 6 | 3 | rt | >98 (93) | 83 |
| 7[f] | 2 | rt | >98 (92) | 99 |

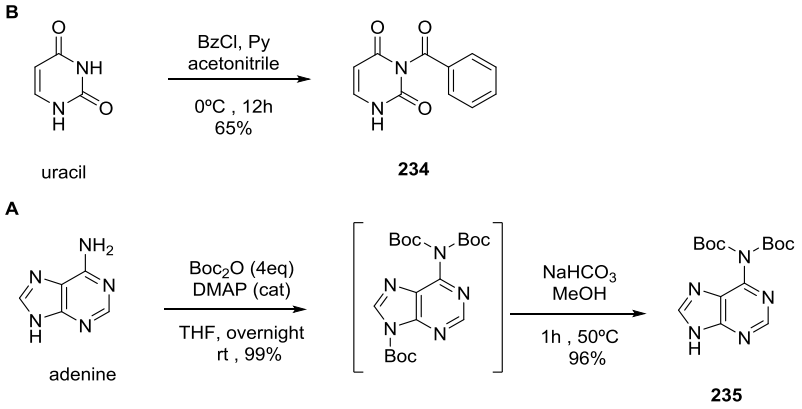
[a]Conditions: Catalyst [Pd($\eta^3$-$C_3H_5$)Cl]$_2$ / (*R,R*)-**L3** (1:3), **157** (1 equiv.), **229** (2.0 equiv.), reaction time = 16-48h, concentration = 0.02 M. [b] A branched/linear ratio > 98:<2 was observed in all cases. [c] Isolated yield of branched regioisomer. [d] Determined by HPLC (see experimental section). [e] 3 equiv. of BSA, and 4 mol% of KOAc were added [f] Concentration = 0.01 M.

Under all the conditions evaluated, the branched *N*-alkylated product was observed exclusively, demonstrating the high regioselectivity of the transformation.

From Table 8, it can be concluded that substrate **157** provides excellent yields and regio- and enantioselectivities in the reaction with di-boc-cytosine (**229**) using Pd/ (*R,R*)-**L3** as the catalytic system. We then decided to extend this

comparative study to other pyrimidinic and purinic bases. Results are collected in Table 9.

In the case of uracil, in order to avoid the reactivity through $N^3$, this group was protected as $N^3$-benzoyl derivative (**234)** with an excess of benzoyl chloride, in the presence of pyridine as base (Scheme 76, A).[24] Adenine was also protected using the same methodology as in the case of cytosine protection (Scheme 76, B) yielding to the *N,N*-diboc adenine (**235**) in very good yield.

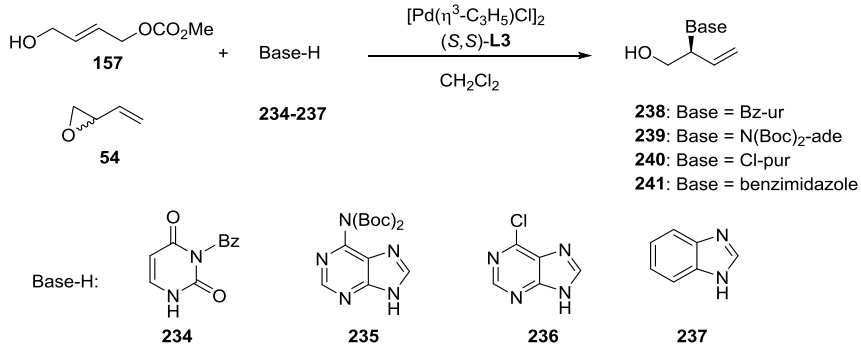



**Scheme 76.** Synthesis of starting material **234** and **235**.

Thus, when **234** was treated with carbonate **157** or epoxide **54**, in the presence of Pd/(*R,R*)-DACH-naphtyl, compound **238** was obtained with a similar enantioselectivity in both cases (Table 9, entries 1, 2).

[24] Kwon, S, C.; Gi Jeong, C.; Sang Moo L.; Gwang Il, A.; Hakjune, R. *J. Med. Chem.* **2007**, *50*, 6032-6038.

**Table 9**. Palladium-Catalyzed Allylic Amination of carbonate **157** and epoxide **54** with pyrimidinic and purinic bases **234-237**.[a]




| Entry | Starting material | Nucleophile | Product | Conv.[b] (Yield)[c] | *ee* %[d] |
|---|---|---|---|---|---|
| 1 | **157** | **234** | **238** | >98 (92) | 84 |
| 2 | **54** | **234** | **238** | >98 (83) | 84 |
| 3 | **157** | **235** | **239** | >98 (92) | >99 |
| 4 | **54** | **235** | **239** | >98 (92) | 94 |
| 5[e] | **157** | **236** | **240** | >98 (96) | 95 |
| 6[e] | **54** | **236** | **240** | >98 (89) | 96 |
| 7[e] | **157** | **237** | **241** | >98 (92) | 90 |
| 8[e] | **54** | **237** | **241** | >98(89) | 90 |

[a] Conditions: Catalyst $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2 mol%), (*R*,*R*)-**L3** (6 mol%), **157** or **54** (1.0 equiv.), nucleophile (2.0 equiv.), rt, time = 16h, concentration = 0.01 M. [b] Isolated yield of branched regioisomer. [c] Ratio of branched /linear has been determined by $^1$H NMR spectroscopy of the crude products. [d] Determined by HPLC (see experimental section). [e] (*S*,*S*)-**L3** (6 mol%) was used.

Then, purinic bases were tested. Di-boc-adenosine (**235**) reacted with carbonate **157** in the presence of (*R*,*R*)-**L3** to provide **239** in an excellent 96% yield and 99% *ee* (Table 9, entry 3). When the reaction was conducted with epoxide **54** yield was also excellent and enantioselectivity achieved 92% (Table 9, entry 4). 6-Chloropurine (**236**) is a versatile starting material in nucleoside synthesis since it allows a set of useful and well known transformations for synthesizing nucleoside derivatives. When carbonate **157** was treated with **236** in

the presence of (*R,R*)-**L3** under similar conditions, enantioselectivity decreased slightly in comparison with the case when **235** was used, achiving 94% *ee* (Table 9, entry 5), while reaction with monoepoxide **54** furnished **240** in lower *ee*, 89% (Table 9, entry 6). When the reaction was driven using carbonate **157** or monoepoxide **54** and benzimidazole (**8e**) as nucleophile, the yield was also excellent but enantioselectivity was a bit lower, achieving 90% *ee* in both cases (Table 9, entries 7, 8).

## II.3. Synthesis of allyl amines derivatives by Ru-catalyzed cross-metathesis[25]

Bearing in mind the retrosynthetic scheme for the synthesis of cidofovir analogues, the cross metathesis reaction was subsequently explored. Over the past decade, the olefin metathesis reaction has become a most powerful tool for advanced organic synthesis, mainly due to the introduction of various ruthenium catalysts such as those developed by Grubbs,[26] Hoveyda,[27] Nolan.[28] The ring-closing metathesis reactions have been already utilized in the construction of a variety of phosphorus containing organic molecules.[29] In 2003, Grubbs *et al.*[30] reported a general model for selectivity in cross-metathesis (CM), in which they ranked olefin reactivity in CM and categorized these olefins by their abilities to undergo homodimerization via CM and by the stability of those homodimers.

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25 Azzouz, M. (**2012**) *Enantioselective Synthesis of Natural Products.* Ph.D. Thesis. Universitat Rovira i Virgili, Spain.

26 (a) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc*. **1992**, *114*, 5426-5427. (b) Fu, G. C.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc*. **1993**, *115*, 9856-9857. (c) Scholl, M.; Trnka, T. M.; Morgan, J. P.; Grubbs, R. H. *Tetrahedron Lett*. **1999**, *40*, 2247-2250.

27 (a) Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791-799. (b) Harrity, J. P. A.; Visser, M. S.; Gleason, J. D.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1997**, *119*, 1488-1489. (c) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc*. **2000**, *122*, 8168-8179.

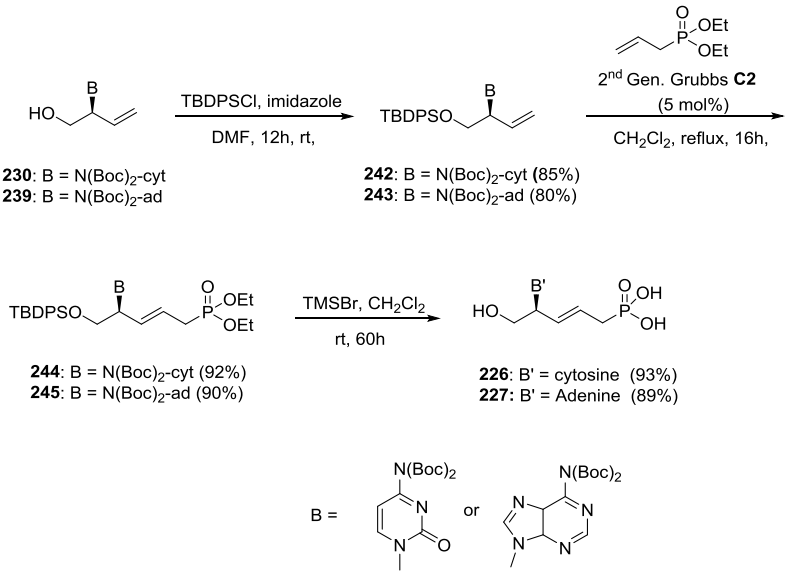
28 Hang, J.; Stevens, E. D.; Nolan, S. P.; Peterson, J. L. *J. Am. Chem. Soc*. **1999**, *121*, 8168-8179.

29 (a) Hanson, P. R.; Stoianova, D. S. *Tetrahedron Lett*. **1998**, *39*, 3939-3942. (b) Hanson, P. R.; Stoianova, D. S. *Tetrahedron Lett*. **1999**, *40*, 3297-3300. (d) Bujard, M.; Gouverneur, V.; Mioskowski, C. *J. Org. Chem*. **1999**, *64*, 2119-2123. (e) Schuman, M.; Trevitt, M.; Redd, A.; Gouverneur, V. *Angew. Chem., Int. Ed*. **2000**, *39*, 2491-2493.

30 (a) Chatterjee, A. K.; Choi. T. L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem.* Soc. **2003**, *125*, 11360-11370. (b) Chatterjee, A. K. Morgan, J. P. Scholl, M. Grubbs, R. H . *J. Am. Chem.* Soc. **2000**, *122*, 3783-3784

Based on this model, H. Kumamoto et *al.*[12] described the syntheses of various acyclic nucleoside phosphonates via alkene cross-metathesis. They established the reactivity and stereochemistry of the cross-coupling metathesis of various C5-substituted crotylated uracil with vinyl(and allyl) phosphonates.

As model substrates for synthesizing acyclic nucleosides containing pyrimidinic and purinic bases we selected compounds **230** and **239**, containing cytosine and adenine moieties, respectively. The primary hydroxyl group was initially protected by reaction with *tert*-butyldiphenylsilyl chloride in DMF in the presence of imidazole to afford compounds **242** and **243** in 85% and 80% yield respectively (Scheme 78). According to the retrosynthetic scheme and following previous works in this field,[12] compounds **242** and **243** were then treated with diethyl allylphosphonate in the presence of Grubbs second-generation catalyst (**C2**) to afford compounds **244** and **245**, in an excellent 92% and 90% yield, respectively, as a result of the cross-metathesis reaction. Compounds with *E* configuration were exclusively obtained as judged by $^{1}$H NMR spectroscopy of the crude product. Removal of protecting groups in both nucleic bases and phosphonate moieties was carried out by treatment of compounds **244** and **245** with TMSBr in dichloromethane,[12] to afford the target acyclic nucleosides **226** and **227** in excellent yields.[71]




**Scheme 77.** Synthesis of target compound **226** and **227**.

In conclusion, acyclic nucleosides **226** and **227** were successfully prepared in high yields and enantioselectivities, by palladium-catalyzed allylic substitution of compounds **157** and **54**, using pyrimidinic and purinic bases as nucleophiles, followed by ruthenium-catalyzed cross-metathesis diethyl allylphosphonate and removal of protecting groups.

Biological evaluation of these nucleosides analogues as chemotherapeutic and anti-viral agents is currently in progress in the Laboratory of Virology and Chemotherapy of Prof. Jan Balzarini (University of Leuven, Belgium), and therefore due activity profiles of these compounds will be presented when provided.

# III. Experimental Section

## III.1. General Methods

All chemicals used were reagent grade and used as supplied unless otherwise specified. HPLC grade dichloromethane ($CH_2Cl_2$), tetrahydrofuran (THF) and dimethylformamide (DMF) were dried using a solvent purification system (Pure SOLVsystem-4®). Toluene was purified using standard procedure.[31]

$^1H$ and $^{13}C$ NMR spectra were recorded on a Varian® Mercury VX 400 (400 MHz and 100.6 MHz respectively) or Varian 400-MR spectrometer in CDCl3 as solvent, with chemical shifts (δ) referenced to internal standards $CDCl_3$ (7.26 ppm $^1H$, 77.23 ppm $^{13}C$) or $Me_4Si$ as an internal reference (0.00 ppm). $^1H$ NMR spectra are reported as follows (s = singlet, d = doublet, t = triplet, q = quartet, b = broad; coupling constant(s) in Hz; integration). 2D correlation spectra (gCOSY, NOESY, gHSQC, gHMBC) were visualized using VNMR program (Varian®). ESI MS were run on an Agilent® 1100 Series LC/MSD instrument. Optical rotations were measured at room temperature in a Perkin-Elmer® 241 MC apparatus with 10 cm cells. IR spectra were recorded on a JASCO FT/IR-600 plus Fourier Transform Infrared Spectrometer ATR Specac Golden Gate. Optical rotations were measured at 598 nm on a Jasco DIP-370 digital polarimeter using a 100 mm cell. The enantiomeric excess was determined by an HPLC analysis using a DAICEL CHIRALCEL OD-H column.

Reactions were monitored by TLC carried out on 0.25 mm E. Merck® silica gel 60F254 glass or aluminium plates. Developed TLC plates were visualized under a short-wave UV lamp (250 nm) and by heating plates that were dipped in ethanol/$H_2SO_4$ (15:1) and basic solution of potassium permanganate. Flash column chromatography was carried out using forced flow of the indicated solvent on Fluka® or Merck® silica gel 60 (230-400mesh). Radial chromatography was performed on 1 or 2 mm plates of Kieselgel 60 PF254 silica gel, depending on the amount of product. Flash column chromatography (FCC) was performed using flash silica gel (32–63 μm) and employed a solvent polarity correlated with TLC mobility.

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[31] Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*, 3rd ed., Pergamon Press, Oxford,**1989**.

## III.2. Compound characterization

*General Procedure 1. Palladium-catalyzed allylic amination from butadiene monoepoxide.*

In a Schlenk tube under argon atmosphere $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2 mol%), the DACH naphthyl Trost Ligand **L3** (6 mol%), the nucleophile (1.1 equiv.) and $CH_2Cl_2$ (*c* = 0.01M) were introduced. The resulting solution was stirred for 20 minutes. Then, butadiene monoepoxide (1.0 equiv.) is added in one portion. The mixture was stirred at room temperature for 18h. The reaction mixture was then diluted with $H_2O$. The phases were separated and the aqueous phase was extracted with $CH_2Cl_2$. The combined organic phases were dried over $MgSO_4$, filtered, and concentrated in vacuum. The resulting crude was purified by flash chromatography to afford the pure product.

*General Procedure 2. Palladium-catalyzed allylic amination from (E)-4-Hydroxybut-2-en-1-yl methyl carbonate in basic medium.*

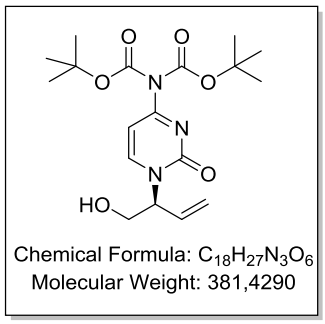
In a Schlenk tube under argon atmosphere $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2 mol%), the DACH naphthyl Trost ligand (**L3**) (6 mol%) and $CH_2Cl_2$ (*c* = 0.01 M). The resulting solution was stirred for 20 minutes. Then, the carbonate (1.0 equiv.), nucleophile (2.0 equiv.), BSA (3.0 equiv.) and KOAc (4 mol %) were successively introduced. The mixture was stirred at room temperature for 18h. The reaction mixture was then diluted with $H_2O$. The phases were separated and the aqueous phase was extracted with $CH_2Cl_2$. The combined organic phases were dried over $MgSO_4$, filtered, and concentrated in vacuum. The resulting crude was purified by flash chromatography to afford the pure product.

*General Procedure 3. Palladium-catalyzed allylic amination from (E)-4-Hydroxybut-2-en-1-yl methyl carbonate in absence of base.*

In a Schlenk tube under argon atmosphere $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2 mol%), the DACH naphthyl Trost ligand **L3** (6 mol%) and $CH_2Cl_2$ (*c* = 0.01M) were introduced. The resulting solution was stirred for 20 minutes. Then, the carbonate (1.0 equiv.) and the nucleophile (2.0 equiv.) were successively introduced. The mixture was stirred at room temperature for 18h. The reaction mixture was then diluted with $H_2O$. The phases were separated and the aqueous phase was

extracted with $CH_2Cl_2$. The combined organic phases were dried over $MgSO_4$, filtered, and concentrated in vacuum. The resulting crude was purified by flash chromatography to afford the pure product.

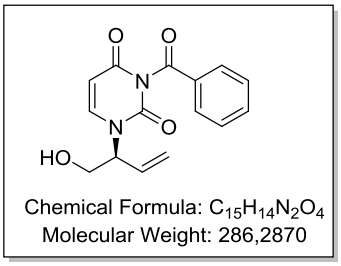
**4-((bis(*tert*-Butoxycarbonyl)amino)-1-((*2S*)-1-hydroxybut-3-en-2-yl)-1,2-dihydropyrimidine-2-one (230).**




**Following the general procedure 1**, compound **230** was prepared from butadiene monoepoxide (**54**) (0.015mL), **229** (0.06 g, 0.231 mmol), $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (1 mg, 0.003 mmol) and (*R,R*)-**L3** (5.5 mg, 0.008 mmol) in dichloromethane (6 mL). Purification by silica chromatography (10:2 hexanes/EtOAc) provided the desired product **230** as a yellow syrup (41 mg, 94%) and 90 % *ee*. **Following the general procedure 3**, compound **230** was prepared from carbonate **157** (17 mg, 0.116 mmol), compound **229** (72 mg, 0.231 mmol), $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (1 mg, 0.003 mmol) and the (*R,R*)-**L3** (5.5 mg, 0.008 mmol) in dichloromethane (12 mL). Purification by silica gel chromatography (10:2 hexanes/EtOAc) provided the desired product **230** as a yellow syrup (40 mg, 92%) and 99% *ee* determined by chiral HPLC (Daicel Chiralcel OD-H, *n-hexane-$^i$PrOH, 85:15*, flow = 0.5 mL/min, detection, uv 254 nm; retention times $t_R$(R) = 16.8 min and $t_R$(S) = 19.2 min).

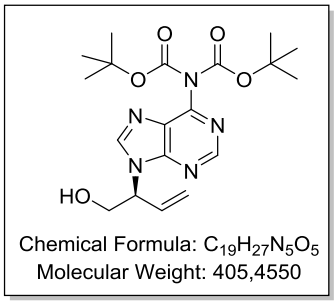
**$[\alpha]_D^{25}$** −7.13 (*c* 1.06, $CHCl_3$) for *ee* = 99%. **$^1$H NMR (400 MHz, $CDCl_3$):** δ (ppm) 7.67 (d, *J* = 7.5 Hz, 1H), 7.05 (d, *J* = 7.5 Hz, 1H ), 6.0 (ddd, *J* = 17.0 Hz, 10.6 Hz, 5.9 Hz, 1H), 5.42 (dd, *J* = 10.6 Hz, 1.5 Hz, 1H), 5.30 (dd, *J* = 17.0 Hz, 1.5 Hz, 1H), 5.28-5.23 (m, 1H), 4.00-3.94 (m, 2H), 3.15 (bs, 1H), 1.55 (s, 18H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ (ppm) 161.9, 155.8, 149.7, 147.2, 132.7, 120.5, 96.2, 85.1, 62.7, 61.2, 27.8. **FTIR-ATR ($cm^{-1}$):** 2918, 2849, 1775, 1741, 1665, 1460, 1369, 1313, 1253, 1154, 1131, 788. **HMRS (ESI-TOF) m/z:** $[M+H]^+$ calcd for $C_{18}H_{28}N_3O_6$: 382.1973, found: 382.1946.

**(*S*)-3-Benzoyl-1-(1-hydroxybut-3-en-2-yl)pyrimidine-2,4(1H,3H)-dione (238).**



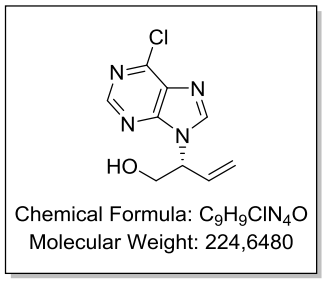

**Following the general procedure 1**, compound **238** was prepared from butadiene monoepoxide (**54**) (0.03 mL), 3-benzoylpyrimidine-2,4(1H,3H)-dione **234** (0.1 g, 0.46 mmol), $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (3 mg, 0.008 mmol) and the (*R*,*R*)-**L3** (0.02 g, 0.025 mmol) in dichloromethane (30 mL). Purification by silica chromatography (1:1 hexanes/EtOAc) provided the desired product as a yellow syrup (27 mg, 83%) and 84% *ee*. **Following the general procedure 2**, compound **238** was prepared from carbonate **157** (17 mg, 0.116 mmol), **234** (72 mg, 0.2312 mmol), BSA (85μL, 0.3469 mmol), KOAc (0.5 mg) $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (1 mg, 0.003 mmol) and the (*R*,*R*)-**L3** (5.5 mg, 0.008 mmol) in dichloromethane (12 mL). Purification by silica gel chromatography (1:1 hexanes/EtOAc) provided the desired product **238** as a yellow oil (30 mg, 90%) and 96 % *ee*. **Following the general procedure 3**, compound **9b** was prepared from carbonate **157** (17 mg, 0.116 mmol), product **234** (72 mg, 0.231 mmol), $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (1 mg, 0.3 mmol) and the (*R*,*R*)-**L3** (5.5 mg, 0.008 mmol) in dichloromethane (12 mL). Purification by silica chromatography (1:1 hexanes/EtOAc) provided the desired product **238** as a yellow syrup (30 mg, 92%) and 84% *ee* determined by chiral HPLC (Daicel Chiralcel OD-H, *n-hexanes-$^i$PrOH, 85:15*, flow = 0.5 mL/min, detection, uv 254 nm; retention times (min), 83, 100, $t_R$(R) = 83 min and $t_R$(S) = 100 min).
**$[\alpha]_D^{25}$** −3.7(*c* 1.8, $CHCl_3$) for *ee* = 96%. **$^1$H NMR (400 MHz, $CDCl_3$):** δ (ppm) 7.94-7.91 (m, 2H), 7.65 (tt, *J* = 7.4 Hz, 1.2 Hz, 1H), 7.50-7.46 (m, 2H), 7.42 (d, *J* = 8.0 Hz, 1H), 5.9 (ddd, *J* = 17.0 Hz, 10.6 Hz, 6.3 Hz, 1H), 5.77 (d, *J* = 8.0 Hz, 1H), 5.42 (dd, *J* = 10.6 Hz, 1.5 Hz, 1H), 5.35 (dd, *J* = 17.0 Hz, 1.5 Hz, 1H), 5.23-5.07 (m, 1H), 3.90-3.79 (m, 2H), 2.38 (bs, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ (ppm) 169.1, 162.4, 150.4, 142.9, 135.3, 131.8, 131.5, 130.6 (2C), 129.3 (2C), 120.9, 101.8, 62.6, 59.2. **FTIR-ATR ($cm^{-1}$):** 3481, 1743, 1699, 1649, 943. **HMRS (ESI-TOF) m/*z*:** $[M+H]^+$ calcd for $C_{15}H_{15}N_2O_4$: 287.1026, found: 287.1015.

**6-(bis-*tert*-Butoxycarbonyl)amino)-9-((*2S*)-1-hydroxybut-3-en-2-yl)-9H-purine (239).**


Chemical Formula: $C_{19}H_{27}N_5O_5$
Molecular Weight: 405,4550

**Following the general procedure 1**, compound **239** was prepared from butadiene monoepoxide (**54**) (0.02 mL), **235** ( 0.1 g, 0.3 mmol), $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2 mg, 0.006 mmol) and the (*R*,*R*)-**L3** (13 mg, 0.019 mmol) in dichloromethane (27 mL). Purification by silica gel chromatography (1:1 hexanes/EtOAc) provided the desired product **239** as a yellow syrup (0.101 g, 92%) and 94 % *ee* determined by chiral HPLC (Daicel Chiralcel OD-H, *n-hexanes-$^i$PrOH* 90:10, 1 mL/min$^{-1}$, $t_R$(R) = 15.4 min and $t_R$(S) = 18.2 min). **Following the general procedure 3**, compound **239** was prepared from carbonate **157** (17 mg, 0.116 mmol), **235** (72 mg, 0.2312 mmol), $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (1 mg, 0.003 mmol) and the (*R*,*R*)-**L3** (5.5mg, 0.008 mmol) in dichloromethane (12 mL). Purification by silica chromatography (1:1 hexanes/EtOAc) provided the desired product **239** as a yellow oil (43 mg, 92%) and 99% *ee*. **$[\alpha]_D^{25}$** −15.80 (*c* 0.92, $CHCl_3$) for *ee* = 99%. **$^1$H NMR (400 MHz, $CDCl_3$):** δ (ppm) 8.84 (s, 1H), 8.17 (s, 1H), 6.20 (ddd, *J* = 17.1 Hz, 10.5 Hz, 6.4 Hz, 1H), 5.40 (d, *J* = 10.5 Hz, 1H), 5.30-5.18 (m, 1H), 5.14 (d, *J* = 17.1 Hz, 1H), 4.26-4.10 (m, 2H), 3.80 (bs, 1H), 1.47 (s, 18H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ (ppm) 153.0, 151.7, 150.8, 150.6, 145.1, 132.7, 129.1, 119.7, 84.1, 63.8, 61.3, 27.9. **FTIR-ATR (cm$^{-1}$):** 3347, 2979, 2926, 1787, 1600, 1107. **HMRS (ESI-TOF) m/z:** $[M+H]^+$ calcd for $C_{18}H_{28}N_5O_5$: 406.2085, found: 406.2073.

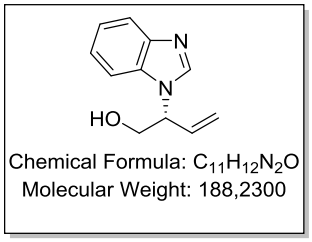
**(2*R*)-(6-Chloro-9H-purin-9-yl)but-3-en-1-ol (240).**


Chemical Formula: $C_9H_9ClN_4O$
Molecular Weight: 224,6480

**Following the general procedure 1**, compound **240** was prepared from butadiene monoepoxide (**54**) (0.024 mL), **236** (0.05 g, 0.3235 mmol), $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2 mg, 0.006 mmol) and the (*S*,*S*)-**L3** (14 mg, 0.017 mmol ) in dichloromethane (30 mL). Purification by silica chromatography (1:1 hexanes/EtOAc) provided the desired product **240** as a colorless oil (60 mg, 89%) and 96% *ee* determined by chiral HPLC.

**Following the general procedure 3**, Compound **240** was prepared from carbonate **157** (17 mg, 0.116 mmol), **236** (72 mg, 0.231 mmol), $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (1 mg, 0.003 mmol) and the (*S*,*S*)-**L3** (5.5 mg, 0.0069 mmol) in dichloromethane (12 mL). Purification by silica gel chromatography (1:1 hexanes/EtOAc) provided the desired product **240** as a colorless oil (25 mg, 96%) and 95% *ee* determined by chiral HPLC (Daicel Chiralcel OD-H, *n-hexanes-$^i$PrOH, 90:10,* flow = 1 mL/min, detection, uv 254 nm; retention times (min), 18.31, 19.30, $t_R$(R) = 19.30 min and $t_R$(S) = 18.31 min). **$[\alpha]_D^{25}$** +10.8 (*c* 1.23, $CHCl_3$) for *ee* = 96%. **$^1$H NMR (400 MHz, $CDCl_3$):** δ (ppm) 8.70 (s, 1H), 8.23 (s, 1H), 6.21 (ddd, *J* = 17.0 Hz, 10.4 Hz, 6.4 Hz, 1H), 5.43 (dd, *J* = 10.4 Hz, 1.4 Hz, 1H), 5.30-5.25 (m, 1H), 5.24 (dd, *J* = 17.0 Hz, 1.4 Hz, 1H), 4.28-4.15 (m, 2H), 3.86 (t, *J* = 6.3 Hz, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ (ppm) 151.8, 151.5, 151.4, 145.5, 132.2, 131.2, 120.4, 63.7, 61.0. **FTIR-ATR ($cm^{-1}$):** 3347, 2927, 1591, 1561, 1337. **HMRS (ESI-TOF) m/z:** $[M+H]^+$ calcd for $C_9H_{10}ClN_4O$: 225.0538, found: 225.0494.

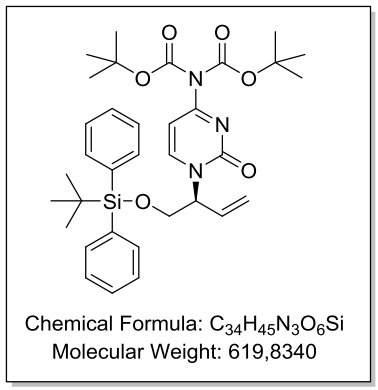
**(*R*)-2-(1H-Benzo[d]imidazol-1-yl)but-3-en-1-ol (241).**




**Following the general procedure 1**, compound **241** was prepared from butadiene monoepoxide (**54**) (0.03 mL), **237** (0.05 g, 0.42 mmol), $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (3 mg, 0.009 mmol) and the (*S*,*S*)-**L3** (16 mg, 0.023 mmol) in dichloromethane (39 mL). Purification by silica gel chromatography (1:1 hexanes/EtOAc) provided the desired product **241** as a colorless oil (62 mg, 89%) and 90% *ee* determined by chiral HPLC. **Following the general procedure 3**, compound **241** was prepared from carbonate **157** (17 mg, 0.116 mmol), **237** (72 mg, 0.2312 mmol), $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (1 mg, 0.003 mmol) and the (*S*,*S*)-**L3** (5.5 mg, 0.008 mmol) in dichloromethane (12 mL). Purification by silica gel chromatography (1:1 hexanes/EtOAc) provided the desired product **241** as a colorless oil (20 mg, 92%) and 90% *ee* determined by chiral HPLC (Daicel Chiralcel OD-H, *n-hexanes-$^i$PrOH, 92:08,* flow = 0.5 mL/min, detection, uv 254 nm; retention times (min), 28.61, 30.24, $t_R$(R) = 30.24 min and $t_R$(S) = 28.61 min). **$[\alpha]_D^{25}$** +26 (*c* 0.80, $CHCl_3$) for *ee* = 90%. **$^1$H NMR (400 MHz, $CDCl_3$):** δ (ppm) 7.84 (s, 1H), 7.53 (d, *J* = 7.7 Hz, 1H), 7.36 (d, *J* = 7.7 Hz, 1H), 7.21 (d, *J* = 7.7 Hz, 1H), 7.14 (d, *J* = 7.7 Hz, 1H), 6.11 (ddd, *J* = 17.0 Hz, 10.8 Hz, 5.7 Hz,

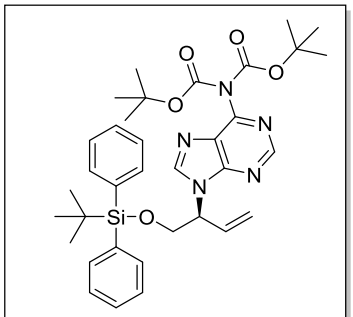
1H), 5.37 (d, *J* = 10.8 Hz, 1H), 5.20 (d, *J* = 17.0 Hz, 1H), 5.05-4.97 (m, 1H), 4.22-4.10 (m, 2H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ (ppm) 143.1, 142.1, 140.7, 132.9, 123.0, 122.5, 119.9, 119.4, 110.6, 63.3, 60.6. **FTIR-ATR ($cm^{-1}$):** 3089, 2922, 1492, 1457. **HMRS (ESI-TOF) m/z:** $[M+H]^+$ calcd for $C_{11}H_{13}N_2O$: 189.1022, found: 189.1005.

***tert*-Butyl *N*-[(*tert*-butoxy)carbonyl]-*N*-{1-[(*2S*)-1-[(*tert*-butyldiphenylsilyl) oxy]but-3-en-2-yl]-2-oxo-1,2-dihydropyrimidin-4-yl}carbamate (242).**



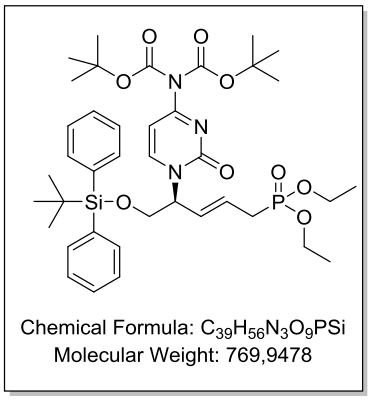

Compound **230** (0.1 g, 0.26 mmol) was dissolved in dry DMF (3 mL) and treated under argon with *tert*-butyldiphenyl chloride (0.08 mL, 0.3 mmol) and imidazole (0.04 g, 0.6 mmol). The mixture was then stirred for 16h at room temperature. Workup (extraction with $Et_2O$) and column chromatography on silica gel (10:2) hexanes/EtOAc provided **242** as a colorless oil (137 mg, 85%). **$[\alpha]_D^{25}$** −13.5 (*c* 1.27, $CHCl_3$). **$^1$H NMR ($CDCl_3$, 400 MHz)**: δ (ppm) 7.75 (d, *J* = 8.0 Hz, 1H), 7.57 (ddd, *J* = 6.0 Hz, 3.2 Hz, 1.6 Hz, 2H), 7.48 (ddd, *J* = 6.4 Hz, 2.8 Hz, 1.2 Hz, 2H), 7.49-7.30 (m, 6H), 6.98 (d, *J* = 7.2 Hz, 1H), 6.01 (ddd, *J* = 17.6 Hz, 10.4 Hz, 6 Hz, 1H), 5.38 (dd, *J* = 10.4, 0.8 Hz, 1H), 5.37-5.34 (m, 1H), 5.32 (dd, *J* = 17.6 Hz, 0.8 Hz, 1H), 3.97 (d, *J* = 3.6 Hz, 2H), 1.57 (s, 18H), 1.02 (s, 9H). **$^{13}$C NMR ($CDCl_3$, 100 MHz)**: δ (ppm) 161.9, 155.1, 149.8, 147.1, 135.7, 135.5, 133, 132.6, 130.1, 128, 120.6, 95.6, 84.9, 63.9, 59.6, 27.9, 26.7, 19.3. **FTIR-ATR ($cm^{-1}$):** 2931, 2857, 1742, 1671, 1524, 1455, 1370, 1319, 1256, 1137, 1110, 784, 701. **HMRS (ESI-TOF) m/z:** $[M+H]^+$ calcd for $C_{34}H_{46}N_3O_6Si$: 620.3156, found 620.3171.

**_tert_-Butyl _N_-[(_tert_-butoxy)carbonyl]-_N_-{9-[(2_S_)-1-[(_tert_-butyldiphenylsilyl) oxy]but-3-en-2-yl]-9H-purin-6-yl}carbamate (243).**




Compound **239** (0.25 g, 0.6 mmol) was dissolved in dry DMF (7 mL) and treated under argon with *tert*-butyldiphenyl chloride (0.18mL, 0.66mmol) and imidazole (0.09 g, 1.32 mmol). The mixture was then stirred for 16h at room temperature. Workup (extraction with $Et_2O$) and column chromatography on silica gel (10:2) hexanes/EtOAC provided **243** (309 mg, 80%). **$[\alpha]_D^{25}$** −0.93 (*c* 1.13, $CHCl_3$). **$^1$H NMR ($CDCl_3$, 400MHz)**: δ (ppm) 8.79 (s, 1H), 8.26 (s, 1H), 7.48 (td, *J* = 8.0 Hz, 1.6 Hz, 4H), 7.39 (tt, *J* = 9.6 Hz, 1.2 Hz, 2H), 7.32 (t, *J* = 7.2 Hz, 4H), 6.02 (ddd, *J* = 17.2 Hz, 10.4 Hz, 6.4 Hz, 1H), 5.34 (dd, *J* = 11.6 Hz, 0.8 Hz, 1H), 5.30-5.20 (m, 1H), 5.17 (dd, *J* = 17.2 Hz, 0.8 Hz, 1H), 4.16(dd, *J* = 11.2 Hz, 6.8 Hz, 1H), 4.05 (dd, *J* = 10.8 Hz, 4 Hz, 1H), 1.43 (s, 18H), 0.94 (s, 9H). **$^{13}$C NMR ($CDCl_3$, 100 MHz)**: δ (ppm) 153.3, 151.8, 150.5, 150.3, 144.5, 135.5, 135.4, 132.5, 130.1, 128.9, 127.9, 119.8, 83.7, 64.8, 59.4, 27.9, 26.8, 19.1. **FTIR-ATR ($cm^{-1}$):** 2987, 2362, 1733, 1716, 1558, 1540, 1507, 1456, 1395, 1259, 1066, 749. **HMRS (ESI-TOF) m/*z*:** $[M+Na]^+$ calcd for $C_{35}H_{45}N_5NaO_5Si$: 666.3088, found 666.3073.

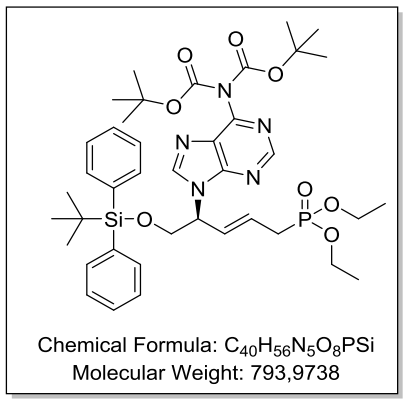
**_tert_-Butyl _N_-[(_tert_-butoxy)carbonyl]-_N_-{1-[(2_S_,3_E_)-1-[(_tert_-butyldiphenyl silyl)oxy]-5-(diethoxyphosphoryl)pent-3-en-2-yl]-2-oxo-1,2-dihydropyrimidin-4-yl}carbamate (244).**




To a solution of **242** (0.05 g , 0.08 mmol) and II generation Grubbs catalyst (0.004 g, 0.004 mmol) in dichloromethane (4 mL), diethylallylphosphonate (0.06 mL, 0.32 mmol) was added. and the solution was heated to reflux for 16h. After evaporation of the solvent purification by silica gel chromatography hexanes/EtOAc (1:2) provided the desired product **244** as yellow liquid (57 mg, 92%).

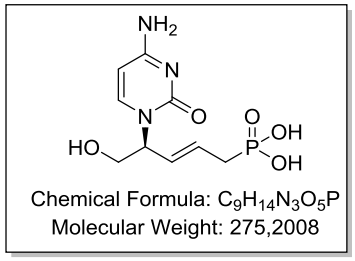
**$[\alpha]_D^{25}$** −21.4 (*c* 1.2, $CHCl_3$). **$^1$H NMR ($CDCl_3$, 400 MHz)**: δ (ppm) 7.68 (d, *J* = 7.6Hz, 1H), 7.56 (dd, *J* = 6.8Hz, 0.8Hz, 2H), 7.45 (dd, *J* = 6.4 Hz, 1.2 Hz, 2H), 7.38 (m, 6H), 6.97 (d, *J* = 7.2Hz, 1H), 5.87-5.80 (m, 2H), 5.29 (brs, 1H), 4.15-4.00 (m, 4H), 3.96 (d, *J* = 4Hz, 2H), 2.62 (d, *J* = 6.4Hz, 1H), 2.58 (d, *J* = 6Hz, 1H), 1.57 (s, 18H), 1.27 (t, *J* = 6.8Hz, 6H), 1.03 (s, 9H). **$^{13}$C NMR ($CDCl_3$, 100 MHz)**: δ (ppm) 161.7, 154.6, 149.5, 146.9, 135.5, 132.5, 130.0, 129.9, 129.5, 128.5, 127.8, 126.5, 95.4, 84.7, 63.6, 62.1, 59.4, 30.6 (d, *J* = 140 Hz), 27.7, 26.8, 19.1, 16.4. **FTIR-ATR ($cm^{-1}$):** 2969, 2931, 1741, 1671, 1455, 1370, 1319, 1255, 1111, 1024, 735, 701**. HMRS (ESI-TOF) m/*z*:** $[M+H]^+$ calcd for $C_{39}H_{57}N_3O_9PSiP$: 770.3602, found 770.3628.

***tert*-Butyl *N*-[(*tert*-butoxy)carbonyl]-*N*-{9-[(*2S*,*3E*)-1-[(*tert*-butyldiphenyl silyl)oxy]-5-(diethoxyphosphoryl)pent-3-en-2-yl]-9H-purin-6-yl}carbamate (245).**



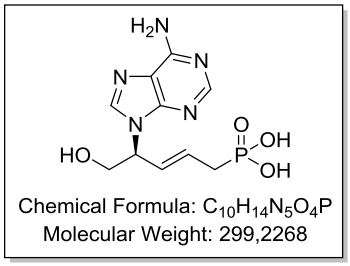

To a solution of product **243** (0.14 g, 0.22 mmol) and II generation Grubbs catalyst (0.009 g, 0.011 mmol) in dichlorometane (11 mL) at reflux was added diethylallylphosphonate (0.16 mL, 0.88 mmol). The reaction was maintained at reflux for 16h. Then, solvent was evaporated and the resulting crude was purified by silica gel chromatography hexanes/EtOAc (2:1) to afford the desired product **245** as a greenish liquid (157 mg, 90%). **$[\alpha]_D^{25}$** −14.6 (*c* 1.36, $CHCl_3$). **$^1$H NMR ($CDCl_3$, 400 MHz)**: δ (ppm) 8.77 (s, 1H), 8.20(s, 1H), 7.42-7.29 (m, 10H), 6.15-6.02 (m, 1H), 5.76 (ddd, *J* = 15.6 Hz, 14.4 Hz, 7.6 Hz, 1H), 5.25 (bs, 1H), 4.16(dd, *J* = 10.4, 6.4 Hz, 2H), 4.07-3.95 (m, 4H), 3.61 (d, *J* = 7.2 Hz, 2H), 2.56 (d, *J* = 7.6 Hz, 1H), 1.43 (s, 18H), 1.22 (t, *J* = 6.8 Hz, 6H), 0.93 (s, 9H). **$^{13}$C NMR ($CDCl_3$, 100 MHz)**: δ (ppm) 153.2, 151.9, 150.6, 150.4, 144.5, 132.5,132.4, 130.1, 129.1, 129, 128, 126.2, 126.1, 83.8, 64.8, 62.2, 62.1, 59.2, 30.6 (d, *J* = 140 Hz), 28.0, 26.9, 19.2, 16.6. **FTIR-ATR ($cm^{-1}$):** 2929, 2856, 1788, 1599, 1452, 1369, 1252, 1139, 1111, 1026, 704. **HMRS (ESI-TOF) m/*z*:** $[M+H]^+$ calcd for $C_{40}H_{57}N_5O_8$ PSi: 794.3714, found 794.3701.

**[(*2E,4S*)-4-(4-amino-2-oxo-1,2-dihydropyrimidin-1-yl)-5-hydroxypent-2-en-1-yl]phosphonic acid (226).**




Compound **244** (0.08 g, 0.1 mmol), was solubilized in $CH_2Cl_2$ (7 mL), and treated with TMSBr (0.08 mL, 0.6 mmol). The reaction mixture was stirred for 60 h at room temperature. The reaction was quenched by adding MeOH (3 mL) and then the reaction mixture was evaporated to dryness by heating at 60ºC. this process was repeated three times. Then the resulting residue was extracted with $H_2O$ and $CH_2Cl_2$, and the inorganic phase was evaporated to dryness to afford the desired compound **226** (25 mg, 93%) as yellow liquid. **$[\alpha]_D^{25}$** −1.2 (*c* 2.89, MeOH). **$^1$H NMR ($D_2O$, 400 MHz):** δ (ppm) 7.85 (d, *J* = 7.8 Hz, 1H), 6.16 (d, *J* = 7.8 Hz, 1H), 5.75-5.56 (m, 2H), 5.16 (bs, 1H), 3.88 (d, *J* = 6.0 Hz, 2H), 2.65 (d, *J* = 7.0 Hz, 1H), 2.61 (d, *J* = 7.0 Hz, 1H). **$^{13}$C NMR ($D_2O$, 100 MHz)**: δ (ppm) 158.8, 149.0, 147.0, 127.5, 127.4, 94.6, 60.9, 59.8, 31.1 (d, *J* = 130 Hz). **FTIR-ATR ($cm^{-1}$):** 2969, 1715, 1669, 1540, 1394, 1043, 973, 872, 793, 762, 748, 702. **HMRS (ESI-TOF) m/z:** $[M+H]^+$ calcd for $C_9H_{14}N_3O_5P$: 276.0749 , found 276.0760.

**[(*2E,4S*)-4-(6-amino-9H-purin-9-yl)-5-hydroxypent-2-en-1-yl]phosphonic acid (227).**




Compound **245** (0.05 g, 0.06 mmol), was solubilized in $CH_2Cl_2$ (4 mL), and treated with TMSBr (0.64 mL, 0.36 mmol). The reaction mixture was stirred for 60 h at room temperature. The reaction was quenched by adding MeOH (3 mL) and then the reaction mixture was evaporated to dryness by heating at 60ºC. this process was repeated three times. Then the resulting residue was extracted with $H_2O$ and $CH_2Cl_2$, and the inorganic phase was evaporated to dryness to afford the desired compound **227** (16 mg, 89%) as a yellow liquid**. $[\alpha]_D^{25}$** −12.4 (*c* 1.93, MeOH). **$^1$H NMR ($D_2O$, 400MHz)**: δ (ppm) 8.44 (s, 1H), 8.40 (s, 1H), 6.02(m, 1H), 5.76 (m, 1H), 5.35 (bs, 1H), 4.11(dd, *J* = 12.0 Hz, 8.4Hz, 1H), 4.05 (dd, *J* = 12.0 Hz, 5.2 Hz, 1H), 2.65 (d, *J* = 7.0 Hz, 1H),

2.59 (d, *J* = 7.0 Hz, 1H). **$^{13}$C NMR ($D_2O$, 100 MHz)**: δ (ppm) 149.6, 148.3, 143.9, 143.6, 127.8, 127.6, 127, 126.9, 118.1, 62.3, 59.2, 31.1 (d, *J* = 130 Hz). **FTIR-ATR ($cm^{-1}$):** 3070, 2325, 1691, 1609, 1531, 1496, 1425, 1387, 1224, 1107, 937, 770. **HMRS (ESI-TOF) m/z:** $[M+Na]^+$ calcd for $C_{10}H_{15}N_5NaO_4P$: 323.0759, found 323.0770.

# CHAPTER 6

*Exploring synthetic applications of Pd-catalyzed DYKAT process*

# I. Introduction

## I.1. Dynamic Kinetic Asymmetric Transformation of butadiene monoepoxide with imido carboxylates as *N*-nucleophiles

Efficient synthetic methods required to assemble complex molecules include reactions that are both selective (chemo-, regio-, diastereo-, and enantio-) and economical in atom count (maximum number of atoms of reactants appearing in the products). Transition metal-catalyzed methods that are both selective and economical for formation of cyclic structures, of great interest for biological purposes, represent an important starting tool for this goal. [1]

In the previous chapters, we have seen that dynamic kinetic asymmetric transformations (DYKAT) of racemic compounds is an efficient and atom economic reaction that allows to convert a racemic starting material into an enantioenriched product.[2] Moreover, it has been proven to be a versatil method towards the synthesis of useful chiral and biologically important target molecules.[3]

Butadiene monoepoxide has become readily available as a cheap raw material now commercially available on large scale.[4] The functional versatility of this four-carbon building block makes it an interesting synthon if the racemic starting material can be directly converted into enantiomerically pure products.

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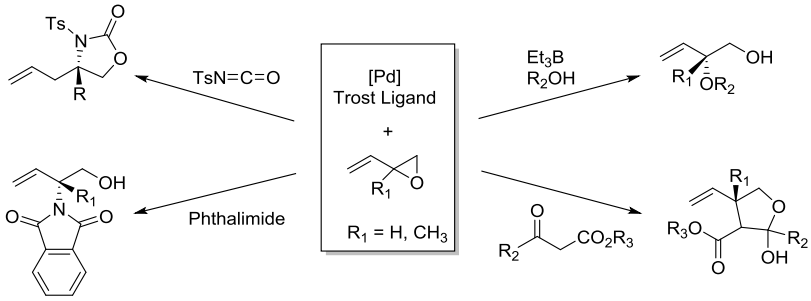
1 (a) Trost, B. M. *Science* **1991**, *254*, 1471. (b) Trost, B. M. *Acc. Chem.Res*. **2002**, *35*, 695-705. (c) Trost, B. M. *Chem. Pharm. Bull*. **2002**, *50*,1-14. (c) Trost, B. M., Fandrick, D. *J. Am. Chem. Soc*. **2003**, *125*, 11836-11837.

2 (a) Trost, B. M.; McEachern, E. J.; Toste, F. D. *J. Am. Chem. Soc*. **1998**, *120*, 12702-12703. (b) Trost, B. M.; Calkins, T. L.; Oertelt, C.; Zambrano, J. *Tetrahedron Lett*. **1998**, *39*, 1713-1716. (c) Trost, B. M.; Jiang, C. *J. Am. Chem. Soc.* **2001**, *123*, 12907-12908.

3 (a) Trost, B. M. *Acc. Chem. Res*. **1996**, *29*, 355-364. (b) Trost, B. M.; Crawley, M. L. *Chem. Rev*. **2003**, *103*, 2921-2944. (c) Trost, B. M. *J. Org. Chem.* **2004**, *69*, 5813-5837.

4 Both butadiene and isoprene monoepoxides are commercially available. Such epoxides are available by the direct epoxidation of the corresponding dienes. For butadiene monoepoxide from diene and oxygen, see: (a) Monnier, J. R. In 3rd World Congress on Oxidation Catalysis, **1997**. (b) Grasselli, R. K., Oyama, S. T., Gaffney, A. M., Lyons, J. E., Eds.; Elsevier: New York, **1997**, 135-149. For isoprene monoepoxide, see: (a) Eletti-Bianchi, G.; Centini, F.; Re, L. *J. Org. Chem*. **1976**, *41*, 1648-1650. (b) Fransen, M. R.; Palings, I.; Lugtenberg, J. *Recl. Trav . Chim. Pays-Bas* **1980**, *99*, 384.

Trost group, which has been one of the most active one in related Pd-catalyzed AAA through DYKAT using its own family of chiral ligands, has extensively and succesfully employed vinyl epoxide as electrophile in Pd-catalyzed AAA by taking advantage of ring strain to facilitate ring-opening. The effect of substitution on the epoxide, to create a quaternary center asymmetrically, has also been studied by the use of isoprene monoepoxide. They have shown that racemic vinyl epoxides undergo a regio- and enantioselective Pd-catalyzed DYKAT with a number of carbon nucleophiles[2c] as well as heteroatom nucleophiles such as alcohol[2a] and phthalimide (Scheme 78). [2b, 5]




**Scheme 78.** Pd-catalyzed DYKAT of vinyl epoxide with various nucelophiles.

The analogous vinyl aziridines have remained a challenge in this transformation since they are normally less reactive toward nucleophilic additions. [6] Indeed, vinyl aziridines require a strong electron-withdrawing group on the nitrogen atom to increase the electrophilicity of the adjacent carbon atoms.[7] Nevertheless Trost *et al*. have successfully employed vinyl aziridines in

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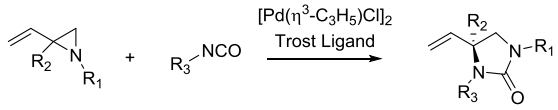
5 Trost, B. M.; Bunt, R. C.; Lemoine, R. C.; Calkins, T. L. *J. Am. Chem. Soc.* **2000**, *122*, 5968-5976.

6 (a) Trost, B. M.; Fandrick, D. R. *J. Am. Chem. Soc*. **2003**, *125*, 11836-11837. (b) Trost, B. M.; Fandrick, D. R.; Brodmann, T.; Stiles, D. T. *Angew. Chem., Int. Ed.* **2007**, *46*, 6123-6125.

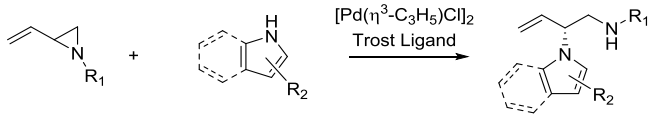
7 For Pd catalysis with vinyl aziridines, see: (a) Butler, A. C. D.; Inman, G. A.; Alper, H. *J. Org. Chem*. **2000**, *65*, 5887-5890. (b) Dong, C.; Alper, H. *Tetrahedron: Asymmetry* **2004**, *15*, 1537-1540. (c) Sebelius, S.; Olsson, V. J.; Szabó, K. *J. Am. Chem. Soc*. **2005**, *127*, 10478-10479. (d) Fontana, F.; Tron, G. C.; Barbero, N.; Ferrini, S.; Thomas, S. P.; Aggarwal, V. K. *Chem. Commun*. **2010**, *46*, 267-269.

dynamic kinetic asymmetric cycloaddition of isocyanates leading in high yields and enantioselectivity to a broad array of imidazolidin-2-ones (Scheme 79).[1c]




**Scheme 79.** DYKA cycloaddition of isocyanates to vinyl aziridines.

Nitrogen heterocycles, such as pyrrole and indole have also been employed in Pd-catalyzed DYKAT of vinyl aziridines. This process provides ready good access to useful, enantioenriched, heterocycle-bearing diamine products, which comprise the core of several biologically relevant compounds (Scheme 80).[8]




**Scheme 80.** Pd-catalyzed DYKAT of nitrogen heterocycles to vinyl aziridines.

In 2007, Trost et *al*. discovered and developed an atom-economical DYKAT of vinyl aziridines and vinyl epoxides for the efficient preparation of useful orthogonally protected chiral vicinal diamines and amino alcohols through use of imido carboxylates as nucleophiles. Surprisingly, the resulting allylic imido carboxylate product isomerized through a facile *in situ* acyl migration (Scheme 81).[9] They applied this methodology to the formal synthesis of balanol and analogues.

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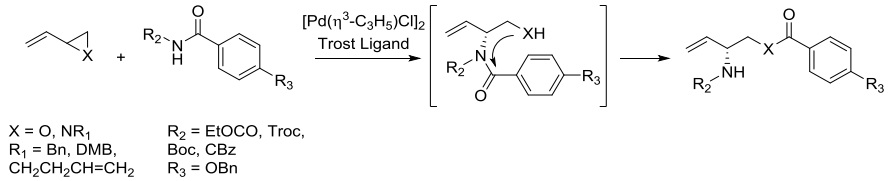
8 Trost, B. M.; Osipov, M.; Dong, G. *J. Am. Chem. Soc*. **2010**, *132*, 15800-15807.

9 Trost, B. M.; Fandrick, D. R.; Brodmann, T.; Stiles, D. T. *Angew. Chem. Int. Ed*. **2007**, *46*, 6123-6125.




**Scheme 81.** Dynamic kinetic asymmetric allylic amination with benzoyl imido carboxylates.

They found that when benzoyl imido carboxylates were used as nucleophiles, Boc acyl migration product was not observed resulting in a high preferance for migration of the more electrophilic benzoyl group. When imido dicarboxylates were used as nucleophiles, the yields were slightly lower. They attributed it to the possible formation of a small amount of a by-product that might be the cyclic urea derived from loss of the alkoxy group in the tetrahedral intermediate of the isomerization step. Considering the preferred migration of the ethyl carbamate functionality over the Boc functionality, in the case of *tert*-butyl-ethyl-imido dicarboxylate, chemoselectivity of the acyl migration seems to be also controlled by steric factors, since electrophilicity of the two carbonyls are fairly similar.

On the other hand, the high regioselectivity in favor of the branched isomer can be rationalized again by an analogous hydrogen bonding interaction between the HN group of the imide nucleophile and the amide of the ligand in the $\eta^3$-allyl Pd intermediate, as well as the directing effect of the ligand.

# II. Results and discussion

## II.1. Synthesis of imido carboxylates

In this context, we planned to synthesize various imide and imido carboxylate type nucleophiles in order to study their reactivity in Pd-catalyzed DYKAT of butadiene monoepoxyde. In particular, imido carboxylates bearing a C=C double bond would provide an excellent access to chiral allylic amides or carbamates for further easy transformation (Figure 23).

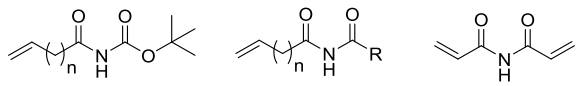



**Figure 23.** Imidocarboxylates **248**-**252** prepared in this work.

Imides are versatile intermediates in the synthesis of nitrogen-containing heterocycles.[10] While cyclic imides reactivity and synthesis are much more documented,[11] only few methods have been reported for the construction of acyclic unsymmetrical imides.[12] Classically, imides are prepared by the reaction of amides with acyl chlorides, anhydrides and carboxylic esters or acids.[13] However, these methods have been reported to suffer from low yields, long reaction time, high temperature, the use of toxic and corrosive reagents, side reactions such as elimination to nitriles, formation of triacyl amides, or acyl group transfer to give symmetrical imides.[14]

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10 Flitsch, W.; Hohenhorst, M. *Liebigs Ann. Chem*. **1990**, *4*, 397-399.

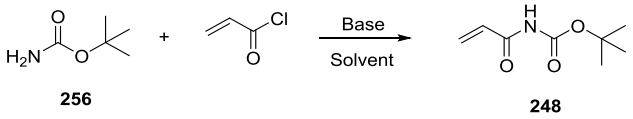
11 Hargreaves, M. K.; Pritchard, J. G.; Dave, H. R. *Chem. Rev*. **1970**, 70, 439-469.

12 Habibi, Z.; Salehi, P.; Zolfigol, M.; Yousefi, M. *Synlett* **2007,** 812-814.

13 (a) Wheeler, O. H.; Rosado, O. in The Chemistry of Amides, Zabicky, J., Ed., John Wiley and Sons: New York, **1970**, 335. (b) Challis, B. C.; Challis, J. in The Chemistry of Amides, Zabicky, J., Ed., John Wiley and Sons: New York, **1970**, 759.

14 (a) Davidson, D.; Skovronek, H. *J. Am. Chem. Soc*. **1958**, *80*, 376-379. (b) Zil'berman, E. N. *Russ. Chem. Rev.* **1960**, *29*, 331-344. (c) Durrell, W. S.; Young, J. A.; Dresdner, R. D. *J. Org. Chem*. **1963**, *28*, 831-833. (d) Bowser, J. R.; Williams, P. J.; Kurz, K. *J. Org. Chem.* **1983**, *48*, 4111-4113.

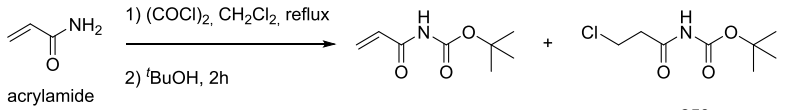
We decided to prepare first the *tert*-butyl acryloylcarbamate **248** according to a general method (Scheme 82). Initially, the reaction of commercially available *tert*-butyl carbamate **256** with acryloyl chloride in THF in the presence of sodium hydride afforded the desired compound in very low yield (~5%). Several bases such as BuLi, *s*-BuLi or *t*-BuLi at low temperature were tested in order to increase the yield but in all cases, only traces of the desired product were obtained in combination with a complex mixture. We thought that the very reactive acryloyl chloride could be the responsible for the failure of the reaction.




**256** **248**

**Scheme 82.** Synthesis of imido carboxylate **248**.

From these results, it is apparent that the desired mono-protected compound **248** could not be obtained efficiently under this methodology. We therefore decided to explore another reported procedure.[15] Thus, acrylamide was reacted with oxalyl chloride to give the corresponding isocyanate *in situ* which upon reaction with *t*-butyl alcohol gave a unseparable mixture of desired product **248** and compound **253** which resulted from conjugate addition of HCl to the electrodeficient double bond (Scheme 83).




acrylamide **248** **253**

**Scheme 83.** Synthesis of imido carboxylate **3** via isocyanate formation.

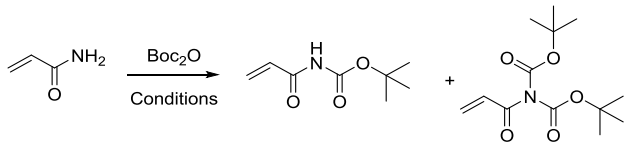
The efficiency of the $Boc_2O$/DMAP couple in amines or alcohols protection prompted us to study reaction of acrylamide with this system under

[15] Wietert, R.J.; Bingham, S.; Emanuel, M.A.; Fraser-Smith, E.B.; Loughhead, P.H.; Nelson, P.H.; Poulton, A.L. *J. Med. Chem*. **1991**, *34*, 1630-1933.

different reaction conditions (Table 10). Initially, the reaction of commercially available acrylamide with di-*tert*-butyl dicarbonate in presence of a catalytic amount of 4-(dimethylamino)pyridine (DMAP) (0.01 equiv) in tetrahydrofuran at room temperature afforded compound **248** in only 10 % yield in combination with the unexpected di-protected acrylamide **254** as the major product in a complex mixture (Table 10, entry 1). Reaction in more polar solvents at room temperature did not proceed and only starting material was recovered (Table 10, entries 2 and 3) while in dichloromethane the result was similar than those obtained in THF (Table 10, entry 4) even at lower temperature (Table 10, entry 5). Lowering to 0.5 equivalents of $Boc_2O$ did not prevent the formation of diprotected compound **254** (Table 10, entry 6). In fact, after 5 min of reaction, TLC showed the rapid formation of compound **254**. When reaction was performed without catalyst, only starting material was recovered (Table 10, entry 7). As a substitute for DMAP, we also tested *N*-methylimidazole (MeIm), a known catalyst in acylation reactions.[16] Reaction of acrylamide with $Boc_2O$ in the presence of MeIm furnished a complex mixture (Table 10, entry 8).

[16] (a) Kamijo, T.; Yamamoto, R.; Harada, H.; Iizuka, K. *Chem. Pharm. Bull.* **1983**, *31*, 3724-3727. (b) Harváth, A. *Synthesis* **1994**, 102. (c) Pavlik, J. W.; Kurzweil, E. M. *J. Org. Chem.* **1991**, *56*, 6313-6320. (d) Shapiro, G.; Gomez-Lor, B. *Heterocycles* **1995**, *41*, 215-218 and references therein.

**Table 10.** Synthesis of compound **248**.[a]




**248** **254**

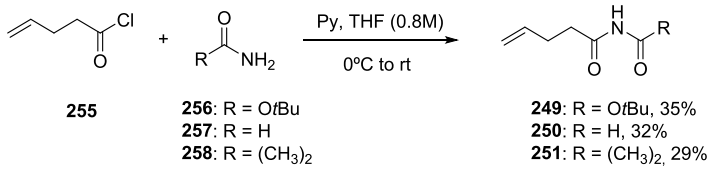
| Entry | $Boc_2O$ equiv. | Additive | Solvent | T (ºC) | Yield of 248[b] (%) |
|---|---|---|---|---|---|
| 1 | 1 | DMAP | THF | rt | 10 |
| 2 | 1 | DMAP | $THF/H_2O$ | rt | - |
| 3 | 1 | DMAP | AcCN | rt | - |
| 4 | 1 | DMAP | $CH_2Cl_2$ | rt | 10 |
| 5 | 1 | DMAP | $CH_2Cl_2$ | 0 | 12 |
| 6 | 0.5 | DMAP | $CH_2Cl_2$ | 0 | - |
| 7 | 0 | DMAP | $CH_2Cl_2$ | 0 to rt | - |
| 8 | 1 | MeIm | $CH_2Cl_2$ | 0 to rt | - |
| 9 | 1 | DMAP/$Et_3N$ | $CH_2Cl_2$ | rt | n.d |
| 10 | 1 | DMAP/NaH | THF | 0 | 42% |

[a] Conditions: 1equiv. of acrylamide; reaction time = 16h.[b] Isolated yield of **248**.

Addition of triethylamine to the reaction miture did not improve the yield and very little conversion of starting material was observed (Table 10, entry 9). Gratifyingly, we found that the portionwise addition of sodium hydride to acrylamide in THF at 0ºC gave the desired compound **248** in a moderate 42% yield (Table 10, entry 10).

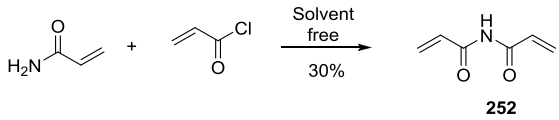
While acrylamide is a cheap commercially available starting material, pent-4-enamide is not and has to be prepared. Thus, we thought that the synthesis of imido carboxylate **249**, **250** and **251** should be shorter using pent-4-enoyl chloride (**255**) with *tert*-butyl carbamate (**256**), formamide (**257**) and

isobutyramide (**258**) respectively. According to a general procedure,[17] reaction of acyl chloride **255** with *tert*-butyl carbamate in presence of pyridine in THF at 0ºC afforded the desired compound in moderate 35% yield (Scheme 84). Similary, imido carboxylate **250** and **251** were obtained in 32% and 29% yield, respectively (Scheme 84).




**Scheme 84.** Synthesis of imido carboxylate **249**, **250** and **251**.

We focused on the synthesis of symmetric imide **252**. Reaction of acrylamide with acryloyl chloride in the presence of a base at low temperature furnished the desired product in very low yield. The best conditions were found to be reacting the two reactants at reflux without a base and under solvent free. In these conditions, imide **252** was obtained in 30% yield (Scheme 85).




**Scheme 85.** Synthesis of symmetric imide **252**.

## II.2. DYKAT of monoepoxide butadiene with imido carboxylate nucleophiles

With various imide type nucleophiles in hand, we next explored the DYKAT of monoepoxide butadiene (**54**). We started with substrates **248** and **249** bearing the Boc functionality. Thus, when butadiene monoepoxide (**54**) was treated with imide nucleophile **248** in the presence of 2 mol % of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ and 6 mol % of (*S*,*S*)-**L3** in dichloromethane at room temperature for

[17] Trost, B. M.; Hirano, K. *Angew. Chem. Int. Ed.* **2012**, *51*, 6480-6483

18h, a mixture of 2 regioisomers was obtained with a poor selectivity (Table 11, entry 1). As expected, a facile *in situ* acyl migration occurred, furnishing both the *O* and *N*-Boc- allyl amine **259a** and **259b** in a ratio 31:69 respectively. The ratio of isomers was determined by NMR spectroscopy of the reaction crude. Indeed, by $^{1}H$-$^{13}C$ HMBC experiments it was possible to unambigously diferentiate these two isomers (Figure 24). The key HMBC correlations between the two diastereotopic protons $H_{4/4'}$ of methylene and the carboxylic carbon of acryloyl moiety $C_3$ were key to identify compound **259b**.

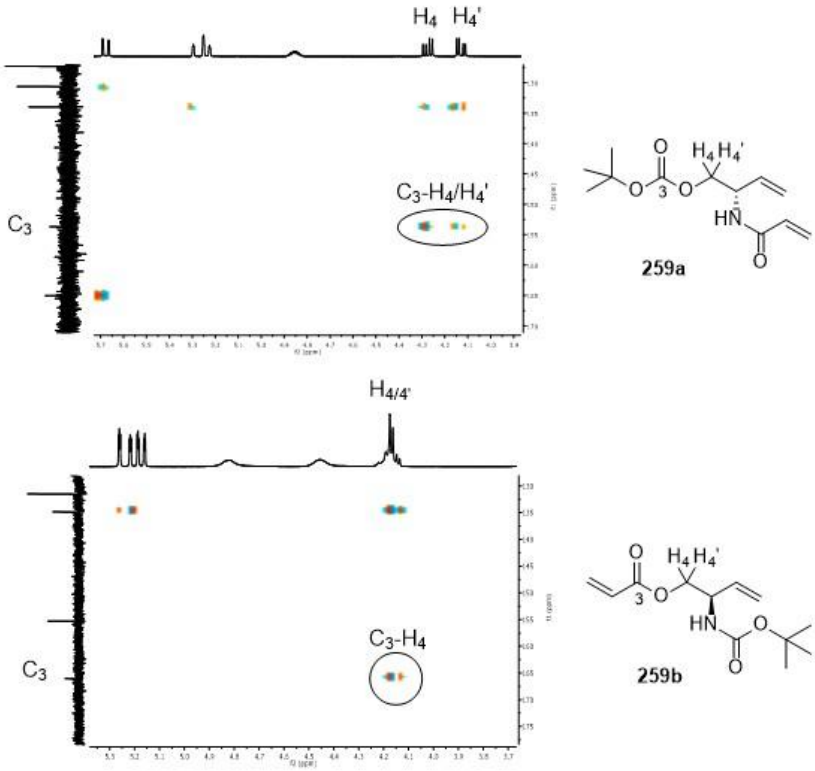
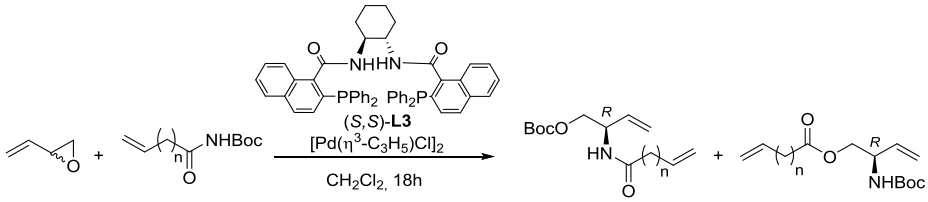



**Figure 24.** Key HMBC correlations for products **259a** and **259b**.

A similar behavior was previously reported by Trost in vinyl aziridines which observed a high selectivity for migration of the more electrophilic benzoyl group (Scheme 81). In our case, the more electrophilic acryloyl group is transfered preferentially than Boc group.

When the reaction was carried out at reflux of dichloromethane, selectivity increased to 10:90 (Table 11, entry 2).

**Table 11.** DYKAT of butadiene monoepoxide (**54**) with imide nucleophiles **248** and **249**.[a]




**54** — **248**: n = 0; **249**: n = 2 — **259a**: n = 0; **260a**: n = 2 — **259b**: n = 0; **260b**: n = 2

| Entry | Nucleophile | Temperature | Product | Ratio (a/b)[b] | Yield (%)[c] |
|---|---|---|---|---|---|
| 1 | **248** | rt | **259a, 259b** | 31:69 | 90 |
| 2[d] | **248** | 35ºC | **259a, 259b** | 10:90 | 92 |
| 3[e] | **248** | 80ºC | **259a, 259b** | 10:90 | n.d |
| 4 | **249** | 35ºC | **260a, 260b** | 5:95 | 94 |

[a] Conditions: Catalyst $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2 mol%), (*S*,*S*)-**L3** (6 mol%), **54** (1 equiv.), nucleophile (1.1 equiv.), reaction time = 16h, concentration = 0.01 M.[b] Ratio of regioisomers has been determined by $^1$H NMR spectroscopy of the crude products. [c] Isolated yield. [d] 97% enantiomeric excess was detemined by HPLC on chiral columns. [e] The reaction was performed in dichloroethane.

When the reaction was carried out at 80ºC in dichloroethane, the selectivity did not change and a ratio 10:90 was obtained (Table 11, entry 3). When *tert*-butyl pent-4-enoyl carbamate **249** was used in the allylic amination reaction, the selectivity increased to 95:5 toward the *N*-Boc allyl amine **260b** (Table 11, entry 4).

The electrophilicity can be evaluated on the basis of the chemical shift of the carbonyl moiety in $^{13}$C NMR spectrum. Indeed, the more deshielded the $^{13}$C signal of carbonyl moiety is, the more electrophilic is the carbonyl moiety. Usually, electron withdrawing groups deshield the signal due to the removal of

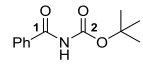
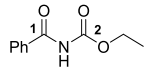
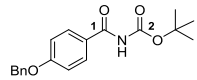
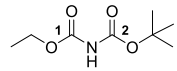
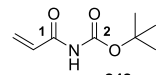
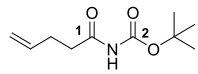
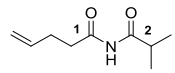
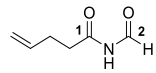
electron density. Surprinsingly, in the case of imides, it does not appear to be the case taking into account the values of chemical shifts in $^{13}C$ NMR spectrum (Table 12).

Table 12 collects the values of $^{13}C$ NMR chemical shift of carbonyl groups in different imide nucleophiles. The yield and selectivity in the acyl migration during the DYKAT process was also reported.

As observed from the results obtained using *tert*-butyl imido carboxylates **248** ($\Delta\delta$ = 15.5 ppm, Table 12, entry 5) and **249** ($\Delta\delta$ = 23.8 ppm, Table 12, entry 6), for a similar steric hindrance, the higher is the difference between the $\delta$ of C=O ($\Delta\delta$) the better the selectivity in acyl transfert is.

We next decided to explore the effect of steric hindrance. Trost reported that steric hindrance also plays an important role in acyl migration. With *tert*-butyl ethyl imido dicarboxylate, where the less hindered ethyl carbamate functionality selectively migrated over the Boc, the difference between the $\delta$ of C=O ($\Delta\delta$) is not significant ($\Delta\delta$ = 1.6, Table 12, entry 4) and good selectivity was obtained judging by the 71% yield achieved.

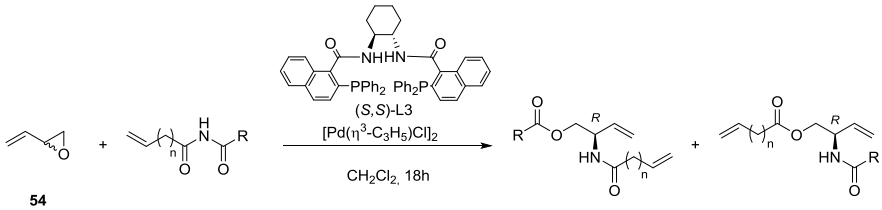
**Table 12.** Values of $^{13}C$ NMR chemical shift of carbonyl groups in imides.

| Entry | δ $^{13}C$ (ppm) C=O 1 | δ $^{13}C$ (ppm) C=O 2 | Δ δ (ppm) | Imido carboxylates | Yields (C=O 1/ C=O 2 migration) |
|---|---|---|---|---|---|
| 1 | 166 | 155 | 10 |  | 98% (>95:5)[6] |
| 2 | 166 | 151 | 15 |  | 90% (n.c.)[6] |
| 3 | 163 | 149.7 | 13.3 |  | 97% (>95:5)[6] |
| 4 | 151.1 | 149.5 | 1.6 |  | 70% (n.c.)[6] |
| 5 | 165.9 | 150.4 | 15.5 |  **248** | 90:10 |
| 6 | 174.3 | 150.6 | 23.8 |  **249** | 95:5 |
| 7 | 175.7 | 178.0 | 2.3 |  **251** | 50:50 |
| 8 | 173.4 | 163.8 | 9.6 |  **250** | 50:50 |

Imide **251** bears a bulky isobutiryl group and the Δδ is only 2.3 (Table 12, entry 7). So we expected that the less hindered would preferentially migrate with high selectivity. Surprisingly, when the same reaction conditions were applied to imide **251** and epoxide **54**, an almost equivalent mixture of both regioisomers **262a** and **262b** was obtained (Table 13, entry 3). Increasing the temperature had no effect on the selectivity (Table 13, entry 4).

We next tested imide **250** bearing the less hindered formyl group althought being the less electrophilic one (Table 12, entry 8) in order to evaluate the influence of both the steric and electronic effects. Thus, when the reation was carried out with imide **250** in the presence of a 2 mol % $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ and 6 mol % of (*S*,*S*)-**L3** in dichloromethane at room temperature, a mixture in almost 50:50 of both regioisomers **261a**, **261b** was obtained (Table 13, entry 1). New attempt to increase selectivity of acyl transfer by carrying out the reactions at higher temperature did not improve the selectivity of the process (Table 13, entry 2).

**Table 13.** DYKAT of butadiene monoepoxide (**54**) with imide nucleophiles **250** and **251**.




54

**250**: n = 2, R = H
**251**: n = 2, R = $^i$Pr

**261a**: n = 2, R = H
**262a:** n = 2, R = $^i$Pr

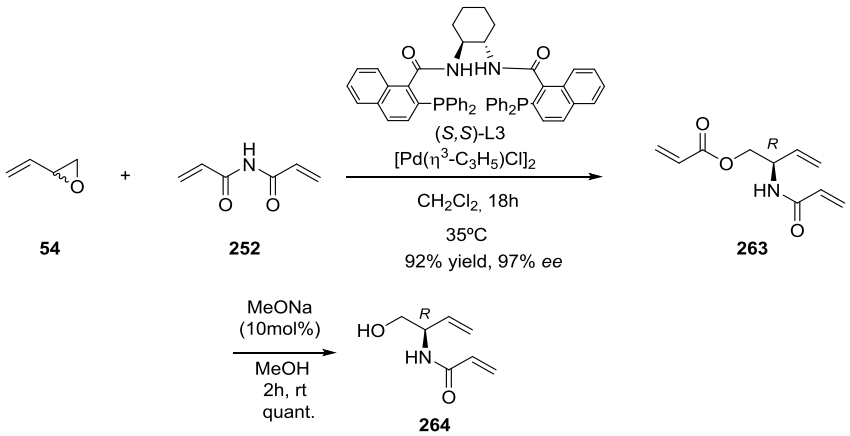
**261b**: n = 2, R = H
**262b:** n = 2, R = $^i$Pr

| Entry | Nucleophile | Temp. | Product | Ratio (a/b)[b] | Yield (%)[c] |
|---|---|---|---|---|---|
| 1 | **250** | rt | **261a, 261b** | 45:55 | 90 |
| 2 | **250** | 35ºC | **261a, 261b** | 43:57 | 94 |
| 3 | **251** | rt | **262a, 262b** | 50:50 | nd |
| 4 | **251** | 35ºC | **262a, 262b** | 50:50 | nd |

[a] Conditions: Catalyst $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2 mol%), (*S*,*S*)-**L3** (6 mol%) **54** (1 equiv.), nucleophile (1.1 equiv.), reaction time = 16h, concentration = 0.01 M. [b] Ratio of regioisomers has determined by $^1$H NMR spectroscopy of the crude products. [c] Isolated yield.

It seems that this system has some limitations. With *tert*-butyl acryloyl imido carboxylates **248** and **249** very good to excellent selectivity were achieved. This chemoselectivity could be probably explained by both steric and electronic factors which matched over those of the acryloyl moiety. In the case of imides, no control of acyl migration was possible.

Therefore symmetric imido nucleophiles are needed to avoid the competition between the two acyl groups. We proceeded then to the DYKAT of butadiene monoepoxide (**54**) with imide **252**. As expected, the *O*-protected **263** product was obtained in very good yield (92%) and excellent enantioselectivity (97%). The ester was then readily hydrolyzed in MeOH with a catalytic amount of methoxide (10 mol%) to furnish quantitatively the alcohol **264** (Scheme 86).




**Scheme 86.** DYKAT of butadiene monoepoxide (**54**) with imide **252**.

## II.3. Transformation of hydroxyamino alkenes

At this stage, we thought that the hydroxyamino alkenes **259b** and **264** obtained in excellent yield and enantioselectivity could be easily transformed via ring-closing metathesis reaction leading to α,β-unsaturated lactam and lactone respectively.

One one hand, lactam **265** has been used as a chiral building block in the synthesis of several natural products such as 3'-Deoxy-4'-azathymidine and 4'-Azauridine,[18] proline derivatives,[51,19] or (2*S*,3*S*)-4-fluorovaline[20] (Scheme 87). It is noteworthy than **265** is usually synthesized from L-pyroglutamic acid.[21]

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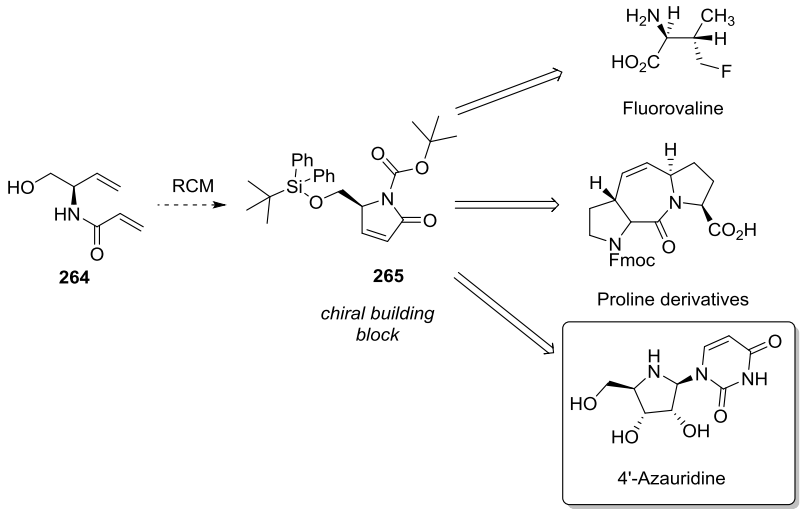
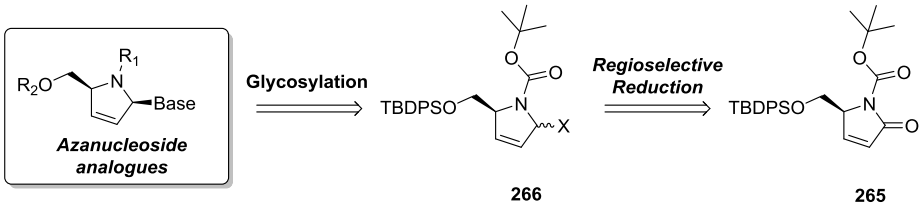
[18] Rassu, G.; Pinna, L.; Spanu, P.; Ulgheri, F.; Casiraghi, G. *Tetrahedron Letters* **1994**, *35*, 4019-4022.




**Scheme 87.** Some relevant biological compound synthesis which used **265** as chiral building block.

We then hypothesized that azanucleoside analogues could be obtained from **264** through ring-closing metathesis reaction, regioselective reduction of the resulting α,β-unsaturated lactam **265** followed by glycosylation reaction (Scheme 88).




**Scheme 88.** Retrosynthesis to azanucleoside analogues.

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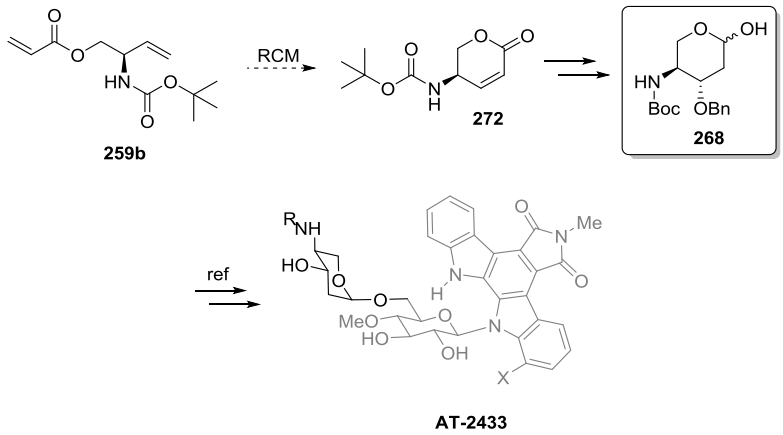
19 Hanessian, S.; Gauchet, C.; Charron, G.; Marin, J.; Nakache, P. *J. Org. Chem*. **2006**, *71*, 2760-2778.

20 Charrier, J. D.; Hitchcock, P. B.; Young, D. W. *Org. Biomol. Chem*. **2004**, *2*, 1310-1314.

21 Acevedo, C. M.; Kogut, E. F.; Lipton, M. A. *Tetrahedron* **2001**, *57*, 6353-6359.

On the other hand, lactone **272** could be an ideal chiral synthon for the preparation of the 2,4-dideoxy-4-amino-xyloside moiety of antitumor antibiotic AT-2433, a L-tryptophan-derived bisindole class of natural products, which has attracted much attention of many researchers from different disciplines because of the variety of chemical structures and the interesting biological activities showed by this family of compounds (Scheme 89).[22] Indeed, this family of compounds display a wide range of biological activities, including antibacterial, antifungal, antiviral, hypotensive, antitumour or neuroprotective properties, but their greatest interest is based on their antitumor properties.

We envisioned that starting from lactone **272**, the 2,4-dideoxy-4-amino-xyloside **268** could be prepared via the stereoselective installation of hydroxyl group followed by lactone reduction. As AT-2433 has been synthesized from **268**, it will constitute a formal synthesis of this biological compound (Scheme 89).[23]



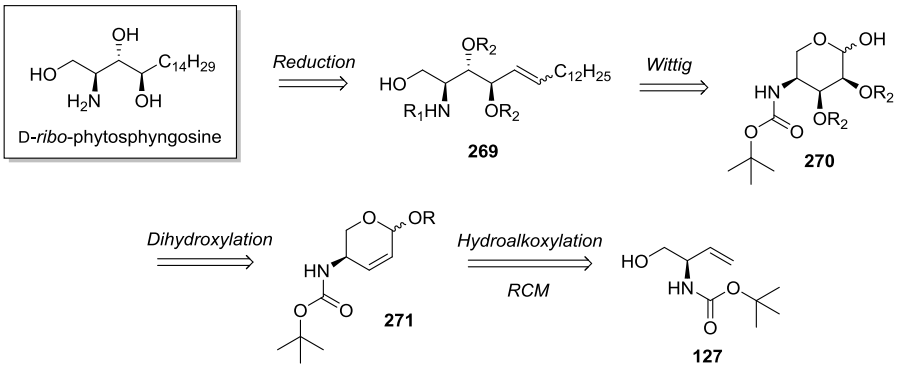

**Scheme 89.** Proposed formal synthesis of AT-2433**.**

[22] Salas, J.A.; Méndez, C. *Curr. Opin. Chem. Biol.*,**2009**,*13*, 152-160.

[23] Chisholm, J. D.; Van Vranken, D. L. *J. Org. Chem*. **2000,** *65*, 7541-7553.

CHAPTER 6

Another hydroxyalkene previously synthesized could be served as chiral synthon in the synthesis of D-*ribo*-phytosphyngosine. Indeed, the latter could be prepared from **269** by C-C double bond hydrogenation followed by deprotection. Alkene **269** in turn could be prepared via Wittig olefination from **270** which can be synthesized from the key synthon **127** by alkoxypalladation, ring-closing metathesis and diastereoselective dihydroxylation reactions (Scheme 90).




**Scheme 90.** Proposed synthesis of D-*ribo*-phytosphingosine.

## II.3.1. Lactone synthesis

### II.3.1.1. Ring-closing metathesis

Since its accidental discovery about sixty years ago, the ring-closing olefin metathesis (RCM) reaction has become one of the most important and effective procedures for the formation of carbon-carbon double bonds, replacing and complementing more traditional C-C bond formations, such as the Wittig olefination or reductive couplings.[24,25,26,27,28,29,30,3132]

Having secured good access to key intermediate, the substrate **259b**, we attempted the cyclization of the allylic carbamate entity by a ruthenium-catalyzed ring-closing olefin metathesis reaction. An initial essay to attempt the cyclization did not proceed when the reaction was carried out in dichloromethane at 35ºC for 12h in the presence of the first generation Grubbs catalyst **C1** (5 mol%) (Table 14, entry 1). When the reaction was performed in dichloromethane at reflux in the presence of catalysts **C2** (5 mol%) the reaction proceeded moderately and the cyclic product **272** was obtained in 45% yield. Increasing catalyst loading to 10 mol% did not increase the yield (Table 14, Entries 2-3). With catalyst **C3** (5 mol%) the yield raised up to 69% but led to a complex mixture of oligomers (Table 14, entry 4). Catalyst loading was then increased to 10 mol% without affecting the effectiveness of the reaction (Table 14, Entries 5).

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24 Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 5426-5427.

25 Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc*. **1992**, *114*, 7324-7325.

26 Schrock, R. R. *Acc. Chem. Res*. **1990**, *23*, 158-165.

27 Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. *J. Am. Chem. Soc*. **1990**, *112*, 3875-3886.

28 Fu, G. C.; Nguyen, S. B.; Grubbs, R. H. J. Am. Chem. Soc. **1993**, *115*, 9856-9857.

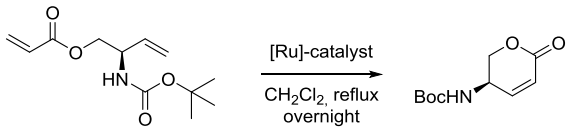
29 Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 1751-1753.

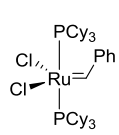
30 Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus Jr., P. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791-799.

31 Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168-8179.

32 (a) Hoveyda, A. H.; Zhugralin, A. R. *Nature* **2007**, *450*, 243-251. (b) Handbook of Metathesis, Vol. 1-3, 1st ed. (Ed.: R. H. Grubbs),Wiley-VCH, Weinheim, **2003**.

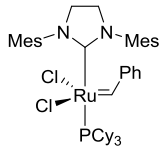
**Table 14**: Ruthenium-Catalyzed ring-closing metathesis of **259b**.[a]



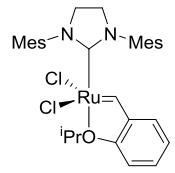

Grubbs
First Generation

**C1**




Grubbs
Second Generation

**C2**



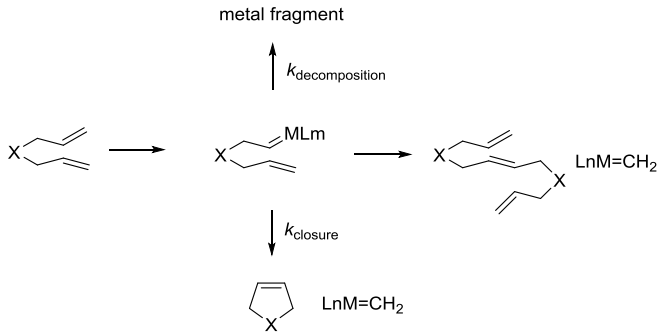

Grubbs-Hoveyda
Second Generation

**C3**

| Entry | Catalyst (mol%) | Additive | Yield (%)[b] |
|---|---|---|---|
| 1 | C1 | - | - |
| 2 | C2 (5) | - | 45 |
| 3 | C2 (10) | - | 45 |
| 4 | C3 (5) | - | 69 |
| 5 | C3 (10) | - | 70 |
| 6[c] | C3 (5) | $Ti(O^iPr)_4$ (30 mol%) | 93 |

[a] Conditions: Catalyst [Ru] (5-10 mol%), reaction time = 18h, concentration = 0.01 M. [b] Isolated yield. [c] The reaction mixture was refluxed for 92h in presence of 0.3 eq of $Ti(OiPr)_4$, concentration = 0.003 M

It has been reported that the rate of oligomerization can be decreased by lowering the concentration of the diene or by using slow addition of the substrates.[32] Higher temperature also favors ring closure; however, it also promote catalyst decomposition (Scheme 91).




**Scheme 91.** Competing reactions between ring-closing metathesis and oligomerization.[32]

It has been described that the RCM of diene substrates bearing a γ,δ- or β,γ-unsaturated carbonyl moiety does not proceed at all. This functional groups was found to be of utmost importance, as well as the proper distance between this key substituent and the alkenes to be metathesized.[33] These results are interpreted in terms of ligation, with the polar group acting as a relay for the evolving carbene species which assembles the reacting sites within the coordination sphere of the metal (e.g., complexes of type A or similar in Figure 25). However, if such an array becomes too stable, as might be the case in certain 5- or 6-membered chelate structures (e.g., B and C in Figure 25), the catalyst can be sequestered in the form of unproductive complexes and cyclization will not take place.[34]

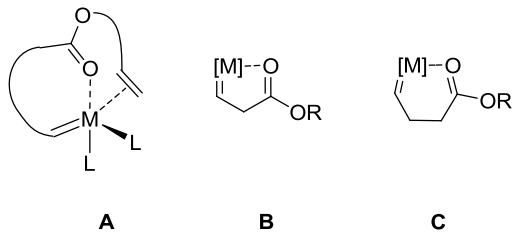



**Figure 25.** Chelate structures that lead to unproductive complexes **A**, **B** and **C**.

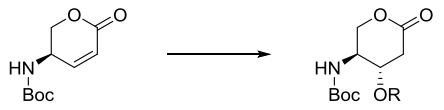
33 Fürstner, A.; Langemann, K. *J. Am. Chem. Soc.* **1997**, *119*, 9130-9136.

34 Andreana, P. R.; McLellan, J. S.; Chen, Y.; Wang, P. G. *Org. Lett*. **2002**, *4*, 3875-3878.

In order to destabilize a presumably unproductive chelate, we ran the cyclization of **259b** in the presence of a Lewis acid, which may compete with the ruthenium carbene for the coordination onto the ester group. Thus, the reaction was carried out in dichloromethane with 30 mol% of $Ti(O^iPr)_4$ as additive in high dilution (c 0.003M) for 92 hours. We were pleased to obtain the β,γ-unsaturated δ-lactone **272** in a very good 93% yield (Table 14, entry 6). No oligomers were observed by $^1H$ NMR spectroscopy.

## II.3.1.2. Further functionalization of δ-lactone **272**.

Bearing in mind the retrosynthetic scheme for the synthesis of **268**, stereoselective installation of hydroxyl group was subsequently explored (Scheme 92).




**272**

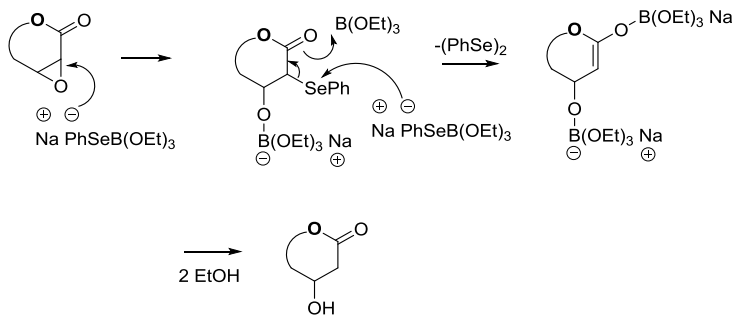
**273**: R = H
**274**: R = Bn

**Scheme 92.** Functionalization of δ-lactone **272.**

For this purpose, we envisioned a diastereoselective epoxydation/regioselective ring opening reaction sequence over the α,β-lactone. Indeed, a highly regioselective organoselenium-mediated reduction of α,β-epoxy lactone to β-hydroxy lactone was reported by Miyashita and co-workers.[35] The reduction is belived to proceed through a sodium phenylseleno(triethyl)borate complex $Na[PhSeB(OEt)_3]$, easily prepared by reduction of $(PhSe)_2$ with $NaBH_4$ in EtOH and benzeneselenol PhSeH generated *in situ* from the borate complex by addition of acetic acid (Scheme 93).

---

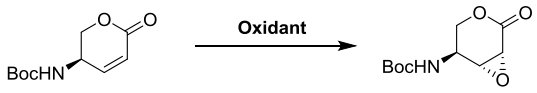
35 (a) Takano, S.; Shimazaki, Y.; Sekiguchi, Y.; Ogasawara, K. *Synthesis* **1989**, 539-541. (b) Miyashita, M.; Suzuki, T.; Yoshikoshi, A. *Tetrahedron Lett.* **1987**, *28*, 4293-4296. (c) Miyashita, M.; Suzuki, T.; Hoshino, M.; Yoshikoshi, A. *Tetrahedron* **1997**, *53*, 12469-12486.




**Scheme 93.** Regiospecific reduction of α,β-Epoxy lactone to β-Hydroxy lactone by organoselenium reagents.

Thus, first attempt towards epoxide formation from compound **272** with hydrogen peroxide and sodium hydroxide in methanol/THF (1:1) at 0ºC affording an unidentified complex mixture and the desired α,β-*trans*-epoxy lactone **275** in diastereomerically pure form but in only 12% isolated yield (Table 15, entry 1). High diastereoselectivities in these types of epoxidations have already been reported.[36] In $^1$H NMR spectrum of **275** the characteristic signals of the double bond (6.8 and 6.1 ppm) disappeared and multiplets appeared in the region of 3-4 ppm indicating protons close to oxygen.

**Table 15.** Epoxidation of lactone **272**.[a]




**272** ***anti*-275**

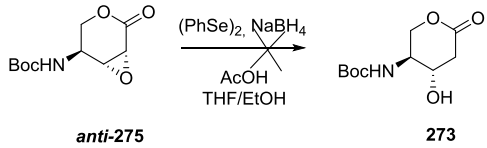
| Entry | Oxidant | Temperature (ºC) | Yield (%)[b] |
|---|---|---|---|
| 1 | $H_2O_2$/NaOH | 0ºC | 12% |
| 2 | TBHP | 0º to rt | - |
| 3 | *m*-CPBA | 0º to rt | - |

[a] Conditions: reaction time = 30 min, concentration = 0.2 M.

[36] Takano, S.; Shimazaki, Y.; Sekiguchi, Y.; Ogasawara, K. *Synthesis*, **1989**, 539-541.

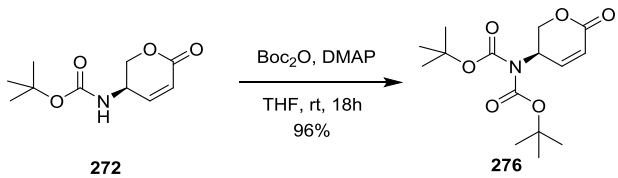
The use of other oxidant which do not need a strong base to be activated like *tert*-butyl hydroperoxide (TBHP) or *meta*-chloroperbenzoic acid (m-CPBA) reacts preferentially with electron rich carbon-carbon double bonds and did not afford the desired epoxy lactone **275** and only starting material was recovered (Table 15, entries 2, 3).

In spite of the fact that the yield obtained was very low, we tried to reduce the epoxide using sodium phenylseleno(tri-ethoxy)-borate ($NaBH_4$ and PhSeSePh in acetic acid) but these conditons did not allow us to obtain the desired β-hydroxy lactone **273** and a complex mixture was obatined (Scheme 94).




**Scheme 94.** Attempt to synthesis of β-hydroxy lactone **273**.

Thus, taking into account these results, lactone **272** was *N*-acylated with di-*tert*-butyl anhydride and DMAP in dichloromethane leading to **276** in very good yield (Scheme 95).




**Scheme 95.** *N*-acylation of lactone **272**.

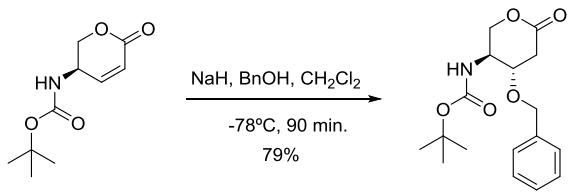
Compound **276** was then subjected to epoxidation reaction under similar conditions. Unfortunately, a complex mixture was obtained after 10 minutes of reaction judging by $^1$H NMR spectroscopy of crude reaction.

At this point, we reconsidered our synthetic strategy and we decided to explore alternative route to the diastereoselective installation of hydroxyl moiety at $C_3$ position. It is well-known that α,β-unsaturated carbonyl compounds have

propensity to participate in Michael addition reactions with nucleophiles. For this reason, we decided to consider a stereoselective 1,4-addition of alkoxide to the unsaturated γ-lactone **272**.

In this regard, Mulzer and co-workers reported diastereoselective conjugate addition reactions of sodium alkoxides to enoates.[37] However, the corresponding alcohols were employed as solvents in all cases, and the reaction with a less reactive alkoxide (sodium benzylate) resulted in only modest diastereoselectivity due to the relatively high temperature (-10 ºC) that was required for the reaction to take place. Indeed, diastereoselectivity depends in the first instance on the reaction temperature; appreciable selectivities occur below -50°C. The difficulty of using solid benzyl alcohol as a solvent together with the lack of sufficient reactivity of the alkoxide derived from benzyl alcohol for the reaction at low temperatures prompted us to explore other conditions reaction.

Gratifyingly, initial attempts to made the reaction using NaH as a base in dichloromethane (C = 0.05M) at -78ºC gave the conjugate adduct **274** with complete stereodifferentiation and good yield (79%) (Scheme 96).[38]




**272** **274**

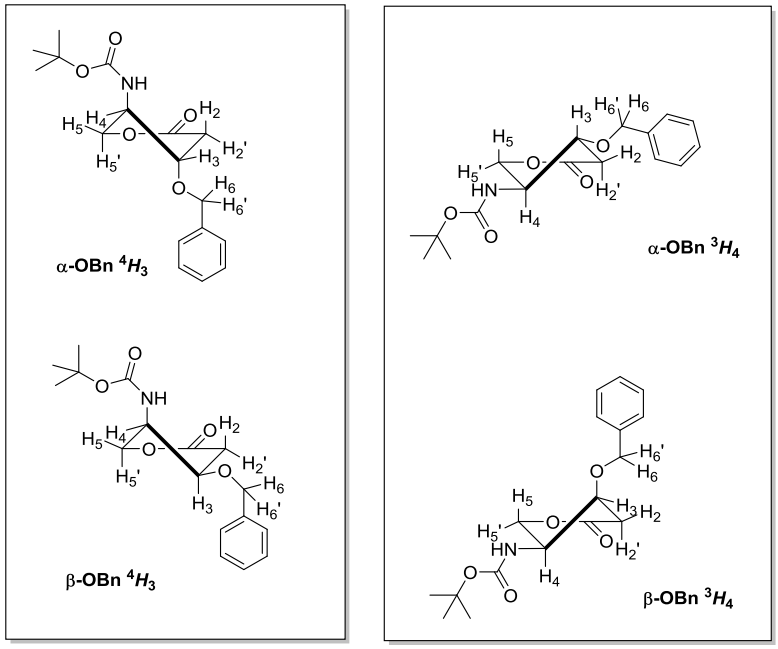
**Scheme 96.** Synthesis of compound **274** by conjuguate addition to lactone **272**.

37 Mulzer, J.; Kappert, M.; Huttner, G.; Jibril, I. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 704-705.

38 Hirata, Y.; Nakamura, S.; Watanabe, N.; Kataoka, O.; Kurosaki, T.; Anada, M.; Kitagaki, S.; Shiro, M.; Hashimoto, S. *Chem. Eur. J.* **2006**, *12*, 8898-8925

The stereochemistry of the γ-lactones **274** was explored by $^{1}$H NMR experiments estimating the vicinal coupling constants.[39]

It should be worthy to note that ORTEPs of δ-lactones have been described showing that their $C_{sp}{}^{3}$-O-$C_{sp}{}^{2}$(=O)-$C_{sp}{}^{3}$ moieties are essentially planar.[40] The $sp^2$ centers establish a planar segment and the remainder of the ring arranges around this segment to form half-chair and/or (twist-)boat conformers. Here, we will consider the 4 half-chair conformations as they are more stable than the boat (*c.a* 1 kcal mol$^{-1}$) conformations (Scheme 97).[41]




**Scheme 97.** Selected conformations of δ-lactone **274** and their interrelation due to ring inversion.

39 Allinger, N. L. *J. Am. Chem. Soc*. **1977**, *99*, 8127-8134.

40 (a) Axiotis, S.; Druex, J.; Perrin, M. Royer, J. *Tetrahedron* **1982**, *38*, 499-504. (b) Avery, M. A.; Gao, F.; Chong, W. K. M.; Hendrickson, T. F.; Inman, W. D.; Crews, P. *Tetrahedron* **1994**, *50*, 957-972.

41 Weber, F.; Brückner, R. *Chem. Eur. J.* **2013**, *19*, 1288-1302.

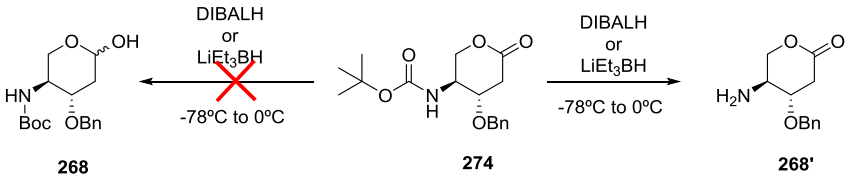
Table 16 shows the coupling constants obtained from the $^{1}$H NMR spectrum. $^{3}\boldsymbol{H_4}$ would be expected to have big value for one $^{3}J_{4\text{-}5}$, as judged by their *trans*-diaxial arrangement. The small value of constants $^{3}J_{4\text{-}5}$ (6.4 Hz and 3.8 Hz) are more in agreement with a *cis* axial/equatorial and *trans*-diequatorial disposition. Furthemore, the small values of constant $^{3}J_{2\text{-}3}$ (4.1 Hz and 7.1 Hz) are more in agreement with a *trans*-diequatorial and *cis* axial/equatorial disposition than a *trans*-diaxial disposition discarding **β-OBn** $^{4}\boldsymbol{H_3}$ and confirming a *trans*-configuration of carbamate and benzyloxy group of **274**. From these results, we suggested that compound **274** may adopt a conformation such as **α-OBn** $^{4}\boldsymbol{H_3}$ This conformation, with substituents in *trans*-diaxial disposition could be the result of steric repulsion of the neighboring substituents (Scheme 97). The small value of constant $^{3}J_{3\text{-}4}$ also match with this proposal.

**Table 16.** Spectrosccopic NMR data of compound **274**.

| Proton | Multiplicity | *J*-value (Hz) | $^{1}$H δ (ppm) | $^{13}$C δ (ppm) |
|---|---|---|---|---|
| 1 | - | - | - | 175 |
| 2 | dd | $^{2}J_{2\text{-}2'}$ = 17.4Hz<br>$^{3}J_{2\text{-}3}$ = 4.1Hz | 2.44 | 37 |
| 2' | dd | $^{3}J_{2'\text{-}3}$ = 7.1Hz | 2.66 | |
| 3 | m | $^{3}J_{3\text{-}4}$ = 3.5Hz | 4.05 | 75 |
| 4 | m | - | 3.88 | 59 |
| 5 | dd | $^{2}J_{5\text{-}5'}$ = 10.8Hz<br>$^{3}J_{4\text{-}5}$ = 6.4Hz | 3.93 | 67 |
| 5' | dd | $^{3}J_{4\text{-}5'}$ = 3.8Hz | 4.20 | |
| 6 | d | $^{2}J_{6\text{-}6'}$ = 11.7Hz | 4.50 | 71 |
| 6 | d | $^{2}J_{6'\text{-}6}$ = 11.7Hz | 4.56 | |
| NH | bs | - | 5.96 | - |

Bearing in mind the retrosynthetic scheme for the formal synthesis of AT-2433, lactone reduction was subsequently explored. Attempts to reduce the lactone moiety in **274** with diisobutylaluminum hydride or Super Hydride™ using a variety of conditions were disappointing, as the desired product **268** was not observed (Scheme 98). Surprisingly, at -78ºC, we observed by $^{1}$H NMR spectroscopy of reaction crude the reduction of the more basic carbamate group leading to compound **268'**. More surprisingly, when compound **274** was reacted with two equivalents of reducing agent, compound **268'** was again observed in the reaction crude (Scheme 98). At this stage, the reasons why lactone reduction did not proceed still remains unknown.

In our hands, the final reduction step has proven troublesome by lack of selectivity so that in the future a synthetic solution for this step should be provided to assure completion of the AT-2433 formal synthesis proposed.



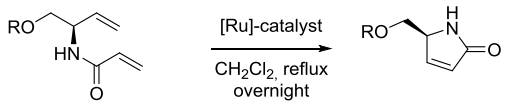

**Scheme 98.** Attempts to reduction of lactone **274**.

## II.3.2. Lactam synthesis

### II.3.2.1. Ring-closing metathesis

In the same way as for lactone synthesis, we decided to subject hydroxyalkene **264** to ring-closing metathesis reaction in order to obtain lactam **277** in enantiomerically pure form. Thus, attempts to perform the ring-closing metathesis (RCM) reaction on the unprotected homoallylic alcohol **264** with Grubbs first- (**C1**) or second-generation catalyst (**C2**) failed to yield any product **277** (Table 17, entries 1, 2). We attributed this to the possible coordination of the pendant free alcohol to the intermediate ruthenium carbene which could shut down the catalytic cycle. Then, we protected the free alcohol as a *tert*-butyldiphenylsilyl ether to obtain **278** in an excellent 95% yield. With this substrate, the metathesis reaction was complete in two hours and half in presence of 5 mol% of **C2** catalyst loading providing 86% yield of pyrrolidone **279**. Unlike RCM of compound **259b**, no interference from the amide oxygen must have taken place judging by the good yield obtained.[42]

**Table 17.** Ruthenium-catalyzed ring-closing metathesis of **264** and **278**.[a]




**264:** R = H
**278:** R = TBDPS

**277:** R = H
**279:** R = TBDPS

| Entry | Substrate | Catalyst (mol%) | Product | Yield (%)[b] |
|---|---|---|---|---|
| 1 | **264** | **C1** (5) | - | - |
| 2 | **264** | **C2** (5) | - | - |
| 3[c] | **278** | **C2** (5) | **279** | 86 |

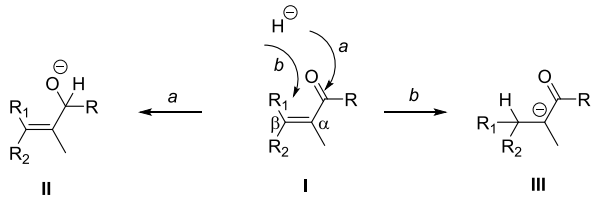
[a] Conditions: Catalyst [Ru] (5 mol%), reaction time = 18h., concentration = 0.01 M. [b] Isolated yield. [c] Catalyst [Ru] (5 mol%); Reaction time = 2.5 h; Concentration = 0.005 M.

42 For examples, see: Rodríguez, S.; Castillo, E.; Carda, M.; Marco, J. A. *Tetrahedron* **2002**, *58*, 1185-1192.

## II.3.2.2. Regioselective reduction of α,β-unsaturated lactam

With pyrrolidinone **279** in hand, the regioselective lactam reduction reaction was next studied. It is well known that lithium aluminum hydride rapidly reduces most carbonyl compounds, including lactones, amides, carbamates, imides, and lactams.[43]

Reduction of α,β-unsaturated carbonyl derivatives poses a potential problem of regioselectivity. Indeed, reduction could lead to either the allylic alcohol (**II**) via normal 1,2-addition of hydride to the carbonyl (Scheme 101, path a), or to the enolate (**III**) via 1,4-addition and delivery of hydride to the alkenyl carbon (Scheme 101, path b).




**Scheme 99.** Regioselectivity problem in reduction of α,β-unsaturated compound.

DIBAL-H, a strong reducing reagent which has been extensively used in the 1,2-reduction of lactones to give lactols, was first employed to attempt the regioselective reduction of lactam **279** (Table 18, entry 1). Unfortunately, no reaction occurred and only starting material was observed by TLC and $^{1}$H NMR spectroscopy.

We therefore presumed that introduction of an electron withdrawing protecting group on the nitrogen atom, which has been used in the reduction of other lactams,[44] might improve the yield of the desired pyrrolidinol. As a *N*-substituent that could be readily cleaved, we opted for a *tert*-butyloxycarbonyl

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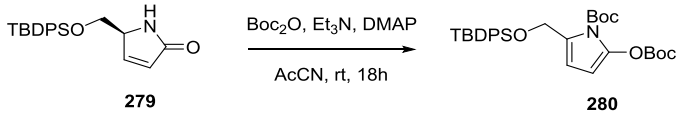
[43] Larock, R.C. Comprehensive Organic Transformations, 2nd ed, Wiley-VCH, New York, **1999**, p 1077-1273.

[44] For recent examples of the use of this strategy see: (a) Zhang, J.; Xiong, C.; Wang, W.; Ying, J.; Hruby, V. J. *Org. Lett*. **2002**, 4, 4029-4032. (b) Mulzer, J.; Schülzchen, F.; Bats, J.-W. *Tetrahedron* **2000**, 56, 4289-4298. (c) Oba, M.; Miyakawa, A.; Nishiyama, K. *J. Org. Chem*. **1999**, 46, 9275-9278. (d) Langlois, N. *Tetrahedron*: *Asymmetry* **1998**, 9, 1333-1336.

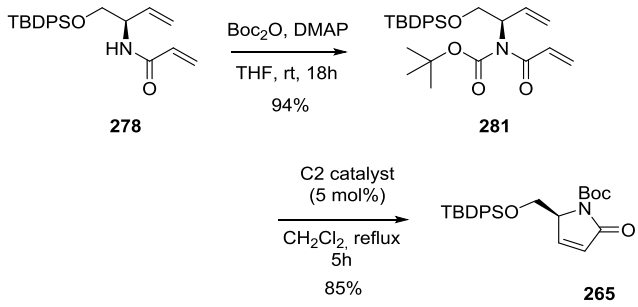
(Boc) protection. Indeed, the increased carbonyl electrophilicity resulting from N-Boc protection should facilitate the reduction of the lactam.[45]

Thus, initial attempts to effect a Boc protection of lactam **279** resulted in the isolation of a compound which was assigned as the pyrrole derivative **280** (Scheme 100).




**Scheme 100.** Unexpected formation of pyrrole **280**.

Protection of the amino moiety in compound **278** was then explore at an earlier stage before RCM (Scheme 101). Allylic amide **278** was then protected under standart conditions using $Boc_2O$ and DMAP in THF affording in very good yield allylic imide **281** which was subjected to ring-closing metathesis under similar conditions to those previously used for compound **278**. The fully protected lactam **265** was obtained in 85% yield.




**Scheme 101.** Synthesis of lactam **265**.

[45] Hulme, A. N.; Montgomery, C. H. *Tetrahedron Lett.* **2003**, 44, 7649-7653.

However, direct reduction of **265** with DIBAL-H gave no reaction either (Table 18, entry 3). Therefore, we decided to carry out the reduction reaction with lithium triethylborohydride ($LiBHEt_3$), which is referred to as Super Hydride™, an extremely useful reducing agent which usually give 1,2-reduction of conjugated carbonyl compounds.[46] Since alkyl groups are electron donating relative to boron, when alkyl groups are attached to the boron of a borohydride reagent the reducing power of that reagent is enhanced.[47] The reaction was monitored by NMR spectroscopy. When the reaction was carried out with substrate **279** a complex mixture was obtained, from which it was not possible to isolate any product (Table 18, entry 2). Reduction of compound **265** conducted under the same conditions gave a complex mixture in which both the C-C double bond and the carbonyl moiety seemed to be reduced (Table 18, entry 3). Indeed, in $^1H$ NMR spectrum of the reaction crude the characteristic signals of the double bond (7.2 and 6.1 ppm) disappeared and multiplets appeared in the region of 2-3 ppm indicating methylene protons close to oxygen and/or nitrogen.

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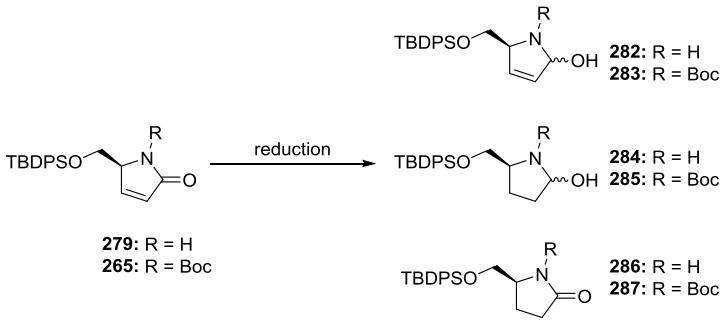
46 Perron F.; Albizati, K.F. *J. Org. Chem.* **1989**, 54, 2044-2047.

47 Brown, H.C.; Krishnamurthy, S. *Aldrichimica Acta* **1979**, *12*, 3-29.

**Table 18.** Reduction of lactam **279** and **265**.




| Entry | Substrate | Reductant | T (ºC) | Time | Product | Conversion (Yield %)[b] |
|---|---|---|---|---|---|---|
| 1 | **279** | DIBAL-H | -78 to rt | 1h | - | <2 |
| 2 | **279** | $LiBHEt_3$ | -78 | 1h | c.m. | >98 |
| 3 | **265** | DIBAL-H | -78 to rt | 1h | - | <2 |
| 4 | **265** | $LiBHEt_3$ | -78 | 1h | c.m. | >98 |
| 5 | **265** | $NaBH_4$ / $CeCl_3$ | -20 | 1h | **288** | >98 (60%) |
| 6 | **265** | $NaBH_4$ / $CeCl_3$ | -40 | 1h | **288** | >98 (n.c) |
| 7 | **265** | Red-Al® | -78 | 1h | **287** | >98 (n.c) |

[a] Conditions: substrate (1.0 equiv.), reductor (1.0 equiv.). [b] Isolated yield.

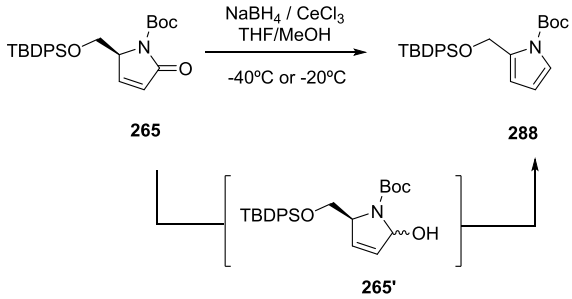
It has been reported that several metals can modify the course of the reduction. For example, addition of cerium salts to the soft reducing agent sodium borohydride leads to a reagent, presumably cerium borohydride (known as the Luche reagent),[48] that gives very selective 1,2-reduction of conjugated aldehydes and ketones.[49] The active species during the Luche reduction is believed to be an alkoxyborohydride, which in combination with the cerium cation acts as a hard reducing agent. The role of the cerium is believed to 1)

48 Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, **2005**, p. 805.

49 Crimmins, M.T.; O'Mahoney, R. *J. Org. Chem*. **1989**, 54, 1157-1161.

catalyze the formation of alkoxyborohydrides; and 2) increase the electrophilicity of the carbonyl carbon atom. By coordinating to the oxygen atom of the solvent, cerium helps activating the carbonyl of the enone indirectly and selective 1,2-reduction takes place.

When the reduction was performed on substrate **265** in methanol in the presence of $NaBH_4$ and $CeCl_3$ at -20ºC (Table 18, entry 5), the corresponding pyrrole **288** was recovered in 60% yield (Scheme 102). Running the reaction at lower temperature (-40 ºC) gave the same result (Table 18, entry 6). In both cases, product **287** was not detected by $^1H$ NMR spectroscopy of reaction crude.




**Scheme 102.** Luche reduction of **265** leading to pyrrole **288**.

Aromatization to pyrrole could certainly take place after initial 1,2-reduction to a " carbinolamine species **265'** " via a elimination reaction (Scheme 102).[50]

[50] Kochhar, K. S.; Pinnick, H. W. *J. Org. Chem*. **1984**,*49*, 3224-3226.

Sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al®, Vitride®) has been also described to give primarily 1,2-reduction in reduction of conjugated carbonyls.[51] However, when the reduction was carried out with Red-Al® at -78ºC, only C-C double bond reduction product **287** was observed by $^{1}$NMR spectroscopy and the carbonyl was not affected under these reaction conditions (Table 18, entry 7).[52]

To the best of our knowledge, no α,β-insaturated lactams have been described to be regioselectively reduced. In spite of the fact that we were not able to reduce selectively lactam **265**, this was obtained in an enantioselective manner in 63 % overall yield (5 steps).

---

51 (a) Markezich, R.L.; Willy, W.E.; McCarry, B.E.; Johnson, W.S. *J. Am. Chem Soc* **1973**, *95*, 4414-4418. (b) McCarry, B.E.; Markezich, R.L.; Johnson, W.S. *Ibid.* **1973**, *95*, 4416-4424.

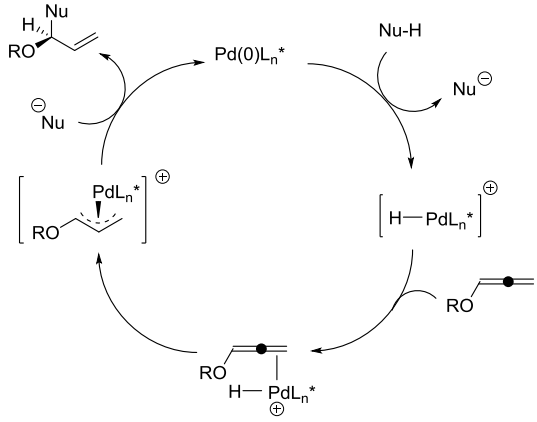
52 Zaminer, J; Brockmann, C.; Huy, P.; Opitz, R.; Reuter, C.; Beyermann, M.; Freund, C.; Mller, M.; Oschkinat, H.; Khne, R.; Schmalz, H. G. *Angew. Chem. Int. Ed*. **2010**, *49*, 7111-7115.

## II.3.3. Approach to synthesis of D-*ribo*-phytosphyngosine

### II.3.3.1. Pd-catalyzed α-addition to allenes (hydroalkoxylation)

As it was previously commented another synthetic approach that we envisaged to explore was the palladium-catalyzed addition to allenes[53] for developing a stereoselective synthesis of phytosphingosine.

In this process, an acid cocatalyst is used in conjunction with the Pd(0) catalyst to generate a Pd(II) hydride intermediate that reacts with the allene and generates an analogous Pd(π-allyl) complex to that formed in the AAA reaction. This intermediate can then be attacked by NuH to generate the formal AAA product while regenerating the acid cocatalyst (Scheme 103).[54,55]




**Scheme 103.** General Pd-catalyzed addition of nucleophiles to allenes.

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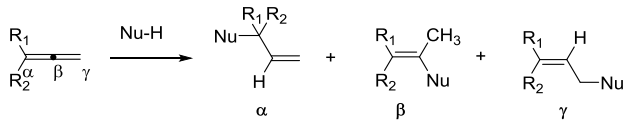
53 Review: Zimmer, R.; Dinesh, C. U.; Nandanan, E.; Kahn, F. A.*Chem. Rev.* **2000**, *100*, 3067-3125.

54 (a) Trost, B. M.; Gerusz, V. J. *J. Am. Chem. Soc.* **1995**, *117*, 5156-5157. (b) Trost, B. M.; Simas, A. B. C.; Plietker, B.; Jäkel, C.; Xie, J. *Chem. Eur. J.* **2005**, *11*, 7075-7082. (c) Trost, B. M.; Xie, J. *J. Am. Chem. Soc*. **2006**, *128*, 6044-6045. (d) Trost, B. M.; Xie, J. *J. Am. Chem. Soc.* **2008**, *130*, 6231-6242. (e) Trost, B. M.; Jäkel, C.; Plietker, B. *J. Am. Chem. Soc*. **2003**, *125*, 4438-4439.

55 For nonenantioselective variants, see: (a) Yamamato, Y.; Al-Masum, M.; Asao, N. *J. Am. Chem. Soc*. **1994**, *116*, 6019-6020. (b) Yamamoto, Y. *Tetrahedron Lett*. **1995**, *36*, 2811-2814.

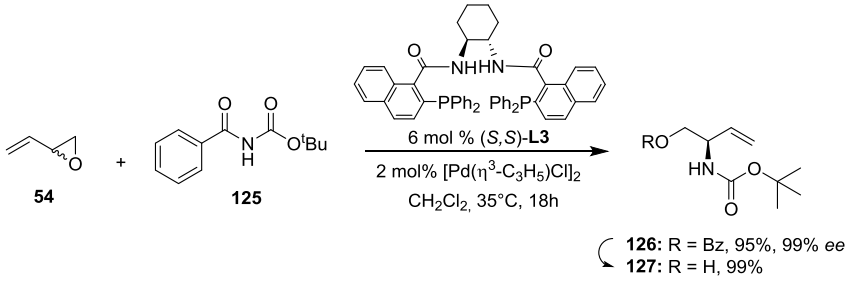
With unsymmetrical allenes, regioselectivity and enantioselectivity issues arises. A nucleophilic addition on allene can occur on three carbon atoms depending on its substituents at the termini. All three possible regioisomers can be selectively produced by properly substituting the allene at the terminal carbon (Scheme 104).




**Scheme 104.** Regioselectivity in nucleophilic addition on allene.

Early work established that alkoxy (aryloxy) allenes gave an electronic bias to afford α-adducts. This is reasonable, since an alkoxy group stabilizes the positive charge formed at the α-position of the π-allyl moiety and hereby a nucleophilic attack (carbonucleophiles) at the α-position becomes more favorable.[56]

In this context, we decided to explore the reactivity of allylic carbamate **127**, in Pd-catalyzed α-addition to allenes. The allylic carbamate was previously synthesized by Pd-catalyzed DYKAT of butadiene monoepoxide (**54**) followed by ester hydrolysis (Scheme 105, see also Scheme 42).



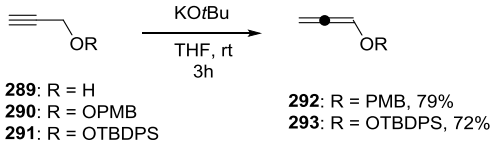

**Scheme 105.** Synthesis of enantioenriched allylic imide **127**.

[56] Yamamoto, Y.; Al-Masum, M. *Synlett* **1995**, 969-970.

As allene derivatives we selected *p*-methoxy-benzyloxyallene **290** and *tert*-butyldiphenylsilyloxyallene **291**.

Alkynes, isomers of allenes, are probably the most widely used starting materials for the synthesis of allenes. Isomerization or prototropic rearrangements of the FG–$CH_2$-C≡C moiety in the presence of a base is one of the earliest methods for access to allenes.[57] Simple alkynes are usually treated with strong bases such as alkali metal amide ($NaNH_2$) at a high temperature. For alkynes with activated α-hydrogen, weaker bases such as NaOH, KO*t*Bu and TBAF are enough to facilitate the isomerization.[58]

The formation of the benzyl and allenyl silyl ethers is summarized in Scheme 106. The reaction sequence involves protection of propargyl alcohol **289** as a benzyl and silyl propargyl ether **290** and **291** respectively,[59] which are subsequently isomerized to the corresonding allene **292** and **293** with catalytic potassium *tert*-butoxide.[60]




**Scheme 106.** Synthesis of alkoxyallenes **292** and **293**.

Compound **127** bearing hydroxyl and carbamate functionality poses the problem of selectivity. Indeed, reaction as *N*-nucleophile with alkoxyallenes would provide a catalytic way to synthesize *N*,*O*-acetal such as **294** or **296** through amidopalladation whereas reaction at the hydroxyl moiety would lead to

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57 (a) Jacobs, T. L.; Akawie, R.; Cooper, R. G. *J. Am. Chem.Soc*., **1951**, *73*, 1273-1275. (b) Enchev, D. D.; *Phosphorus, Sulfur Silicon Relat. Elem*. **2005**, *180*, 2127-2130. (c) Fenández, I.; Monterde, M. I.; Plumet, J.; *Tetrahedron Lett*. **2005**, *46*, 6029-6031. (d) Fotsing, J. R.; Banert, K. *Eur. J. Org. Chem*. **2005**, *17*, 3704-3714. (e) Lepore, S. D.; Khoram, A.; Bromfield, D. C.; Cohn, P.; Jairaj, V.; Silvestri, M. A. *J. Org. Chem*. **2005**, *70*, 7443-7446. (f) Brossat, M.; Heck, M.-P.; Mioskowski, C. *J. Org. Chem*. **2007**, *72*, 5938-5941.

58 (a) Kuhn, R.; Rewicki, D. *Chem. Ber*., **1965**, *98*, 2611-2618. (b) Franck-Neumann, M.; Brion, F. *Angew. Chem. Int. Ed. Engl*., **1979**, *18*, 688-689.

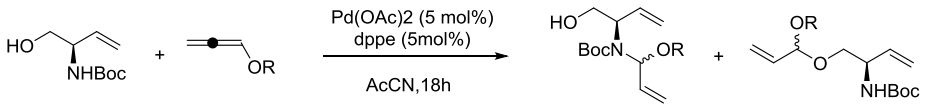
59 Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc*. **1972**, *94*, 6190-6191.

60 Hoff, S.; Brandsma, L.; Arens, J. F. *Recl. Trav. Chim. Pays-Bas* **1968**, *87*, 916-924.

the corresponding *O,O*-acetal such as **295** or **297** via oxypalladation reaction (Table 19).

Thus, initial experiments with alkoxy allene **292** were performed under neutral conditions using 5 mol % of $Pd(OAc)_2$ and 5 mol% of dppe as a bidentate ligand at either room temperature or 80ºC in acetonitrile (Table 19, entries 1, 2). Intriguingly, allylic carbamate did not react under these conditions either at the *O*- or at the *N*-position.

**Table 19.** Pd-catalyzed addition of carbamate **127** to allene **292** and **293**.[a]




**127**

**292**:R = PMB
**293**:R = OTBDPS

**294:** R = PMB
**296**: R = OTBDPS

**295:** R = PMB
**297**: R = OTBDPS

| Entry | Allene | T(ºC) | Additive | Time | Product | Conversion (%) (Yield %)[b] |
|---|---|---|---|---|---|---|
| 1 | **292** | rt | - | 12h | - | <2 |
| 2 | **292** | 80 | - | 12h | - | <2 |
| 3 | **292** | rt | DBU | 12h | - | <2 |
| 4 | **292** | 80 | DBU | 12h | **295** | >98 (86)[c] |
| 5 | **293** | 80 | DBU | 12h | - | <2 |

[a] Conditions: substrate (1.0 equiv), allene (1.2 equiv), $Pd(OAc)_2$ (5 mol%), dppe (5 mol%), DBU (1.5 equiv.), concentration : 0.1M in MeCN [b] Isolated yield. [c] a 1:1 mixture of diastereoisomers was obtained.

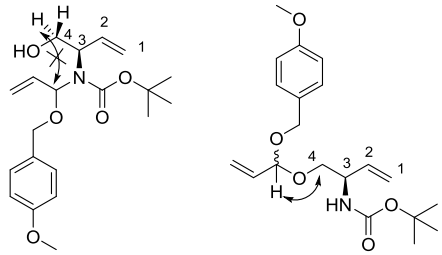
Since it has been recognized that the acidity of the nucleophile, especially for the less acidic amides, might be a key factor in the amidopalladation,[61] DBU ($pK_{aH}$ 24 -25 in MeCN)[62] was used as the base. However, reaction of allylic

61 Trost, B. M. *Chem. Eur. J.* **1998**, *4*, 2405-2412.

62 Kaljurand, I.; Rodima, T.; Leito, I.; Koppel, I. A.; Schwesinger, R. *J. Org. Chem.* **2000**, *65*, 6202-6208.

carbamate with allene **292** in the presence of a catalytic amount of $Pd(OAc)_2$/dppp under basic conditions in dry acetonitrile at room temperature did not afford any product and only starting material was recovered (Table 19, entry 3). The reaction was then carried out in refluxing MeCN for 12 hours using DBU as the base (Table 19, entry 4). Under these conditions, the corresponding *O*,*O*-acetal **295** was formed exclusively. The product **295** was obtained as a *ca*. 1:1 mixture of diastereoisomers which was impossible to separate by column chromatography.

Similary to the acyl migration in Pd-catalyzed AAA, the structure of the products (**294** or **295**) was determined by NMR spectroscopy of reaction crude. Indeed, $^{1}H$-$^{13}C$ HMBC experiments could differentiate these two isomers. The key HMBC correlations was between the carbon $C_4$ which bears the diastereotopic protons (67.0 ppm) and the characteristic proton of acetal (4.9 ppm) (Figure 26). Moreover, a broad signal at 4.8 ppm in the $^{1}H$ NMR spectrum attributed to a labil proton (no correlation in HSQC experiment) fits better to a carbamate than an alcohol.

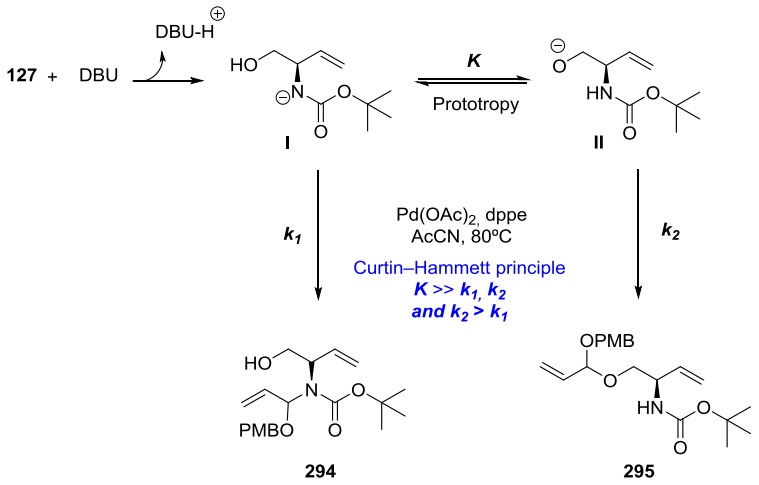



**294** **295**

**Figure 26.** Key HMBC correlations to confirm the structure of compound **295**.

When the reaction was carried out with the sterically bulky alkoxyallene **293** under the optimized reaction conditions, no product was observed by TLC or $^{1}H$ NMR after 12h of reaction and only starting material was recovered (Table 19, entry 5).

Mechanistically, the results obtained under neutral conditions suggested that the base (DBU) deprotonates the more acidic carbamate proton of **127** leading to the corresponding anion **I** (Scheme 107). The protonated tertiary amine generated (DBU-$H^+$) may be oxidatively added to Pd(0), followed by reaction with the allene to give the π-allyl complex. The *O*,*O*-acetal **295** was the unique isomer formed during the reaction. This suggested that alcoholate **II** is formed (via prototropy, *K*) before the nucleophilic attack to the π-allyl complex ($k_1$) (Scheme 107).

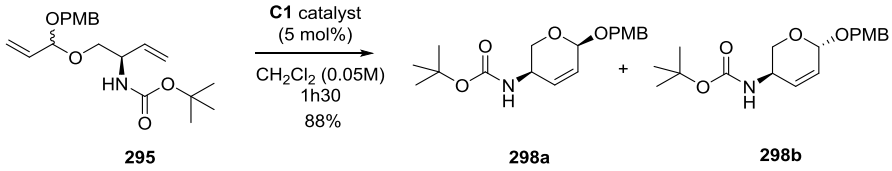



**Scheme 107.** Formation of *O*,*O*-acetal **295** under basic condition.

## II.3.3.2. Further transformations to 4-amino-4-deoxy sugar

Cyclic *O,O*-acetals represent a class of compounds that are rather sensitive and would be especially well suited for construction via a ring-closing metathesis process. In fact, the usefulness of this method for the construction of such acetals has already been illustrated in publications from the group of Rutjes et *al.*[63,64]

Thus, having compound **295** in hand, we explored the ring-closing metathesis reaction. Using the first-generation Grubbs catalyst **C1** (5 mol%) in reflux of dichloromethane smoothly gave the cyclic acetal **298** in a good 88% yield as a 1:1 mixture of diastereoisomers (Scheme 108). Unfortunately, the two diastereoisomers obtained were inseparable using flash column chromatography.




**Scheme 108.** Synthesis of compound **298** via RCM.

The configuration of both isomers was assigned by X-ray diffraction analysis of a single cristal of the mixture **298a**/**298b** (Figure 27). Table 20 and Table 21 show the readable coupling constants obtained from the spectra.

In compound **298a**, the small value of constants $^{3}J_{4\text{-}5}$ (2.9 Hz and 0 Hz) is in agreement with a *cis* pseudo axial/equatorial and *trans* pseudo diequatorial disposition as drawn in Figure 27.

In compound **298b**, the OPMB group has to be the opposite configuration since **298a** and **298b** are diastereoisomers. The relative high value of constant $^{3}J_{4\text{-}}$

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63 Tjen, K. C. M. F.; Kinderman, S. S.; Schoemaker, H. E.; Hiemstra, H.; Rutjes, F. P. J. T. *Chem. Commun*. **2000**, 699-700.

64 Kinderman, S. S.; Doodeman, R.; van Beijma, J. W.; Russcher, J. C.; Tjen, K. C. M. F.; Kooistra, T. M.; Mohaselzadeh, H.; van Maarseveen, J. H.; Hiemstra, H.; Schoemaker, H. E., Rutjes, F. P. J. T. *Adv. Synth. Catal*. **2002**, *344*, 736-748.

$_5$ (8.9 and 5.5 Hz) are in agreement with a *trans* pseudo diaxial and *cis* pseudo axial/equatorial disposition.

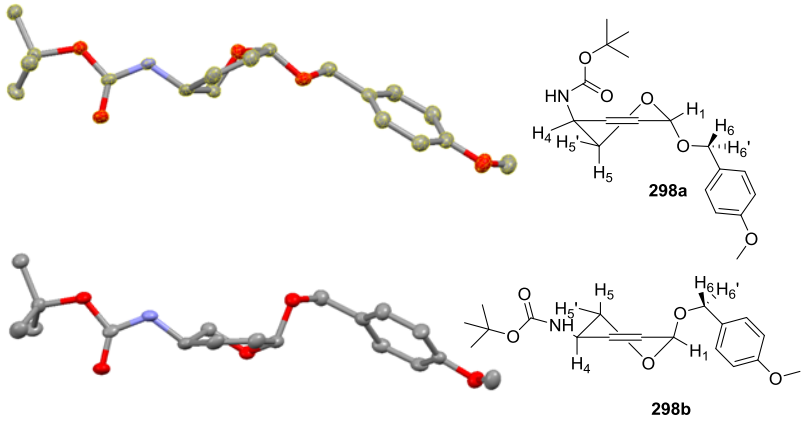



**Figure 27.** X-ray structures of **298a** and **298b**.

**Table 20.** Spectrosccopic data of compound **298a.**

| Proton | Multiplicity | $J_{H-H}$ value (Hz) | δ (ppm) $^1$H | δ (ppm) $^{13}$C |
|---|---|---|---|---|
| 1 | d(d) | 3 (1.1) | 4.96 | 93 |
| 2 | ddd | 10/3/1.1 | 5.84 | 128.8 |
| 3 | dd | 10/5.5 | 6 | 127.9 |
| 4 | m | - | 3.95-3.84 | 43 |
| 5 | dd | 11.8/2.9 | 4.13 | 62.9 |
| 5' | d | 11.8 | 3.74 | |
| 6 | d | 11.6 | 4.70 | 69.7 |
| 6' | d | 11.6 | 4.49 | |
| NH | d | 8.6 | 4.88 | - |

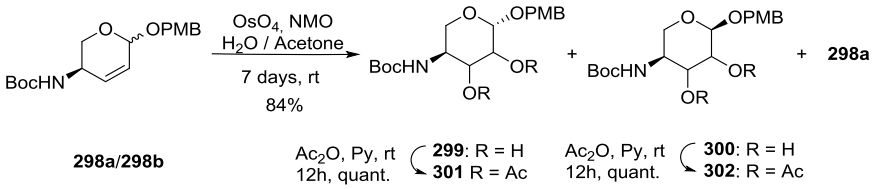
**Table 21.** Spectrosccopic data of compound **298b.**

| Proton | Multiplicity | $J_{H-H}$ value (Hz) | δ (ppm) $^1$H |
|---|---|---|---|
| 1 | d | 2.8 | 4.84 |
| 2 | m | - | 5.82-5.75 |
| 3 | m | - | 5.82-5.75 |
| 4 | bs | - | 4.25 |
| 5 | dd | 10.7/5.5 | 3.77 |
| 5' | dd | 10.7/8.9 | 3.55 |
| NH | d | 9.5 | 4.5 |

Dihydroylation of compounds **298** could afford a compound having the hydroxyl and amino groups with the configuration of D-*ribo*-phytosphyngosine.[65]

Catalytic dihydroxylation using osmium tetroxide and stoichometric amounts of *N*-methylmorpholine *N*-oxide in aqueous acetone[66] at room temperature afforded two diastereoisomers **299** and **300** in 84% yield. A 4% of starting material **298a** was also recovered (Scheme 109). The excellent diastereoselectivity of dihydroxylation reaction have already been observed with various unsaturated cyclic acetals, and it has been shown that the stereoselectivity of dihydroxylation was controlled by the *p*-MeOBn group and proceeded *trans* to it.[66] Although extensive NOE and multinuclear NMR spectroscopy studies were performed, it was not possible to established the relative stereochemistry of **299** and **300** due to the overlapping of the signals. Therefore, hydroxyl groups were readly protected as acetate derivatives under standard conditions affording **301** and **302** respectively in quantitative yields. (Scheme 109).

[65] Yu, X. M.; Han, H.; Blagg, B. S. J. *J. Org. Chem*. **2005**, *70*, 5599-5605.
[66] Yokoyama, M.; Ikenogami, T.; Togo, H. *J. Chem. Soc., Perkin Trans. 1*, **2000**, 2067-2071.




**Scheme 109.** Diastereoselective dihydroxylation of compound **298a** and **298b**.

The configuration of compound **301** and **302** was unambiguously assigned as drawn in Figure 28 by NMR spectroscopy.

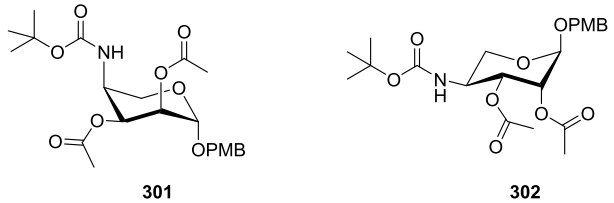



**Figure 28.** Conformation of compound **301** and **302**.

In compound **301**, the small value of constant $^{3}J_{5'\text{-}4}$ (2.3 Hz) suggested a *trans* diequatorial disposition and consequently the carbamate group is in an axial position. HSQC experiment obtained without $^{13}C$ decoupling is commonly used to assign the anomeric configuration. A value of ~170 Hz for $^{1}J_{\text{C-1,H-1}}$ indicates an equatorial proton at C-1, while $^{1}J_{\text{C-1,H-1}}$ ~160 Hz indicates an axial proton, which has been rationalized in terms of stereoelectronic factors.[67] In our case, HSQC-$^{13}C$ without decoupling experiment indicates that the $H_1$ is in equatorial position ($^{1}J_{\text{C-1,H-1}}$ ~174 Hz). The NOESY experiment (Figure 29) showed interactions between $H_3$ and $H_{5'}$ which indicates that the acetoxy group is equatorial and consequently both acetoxy groups are in the same face than the carbamate (Figure 28).

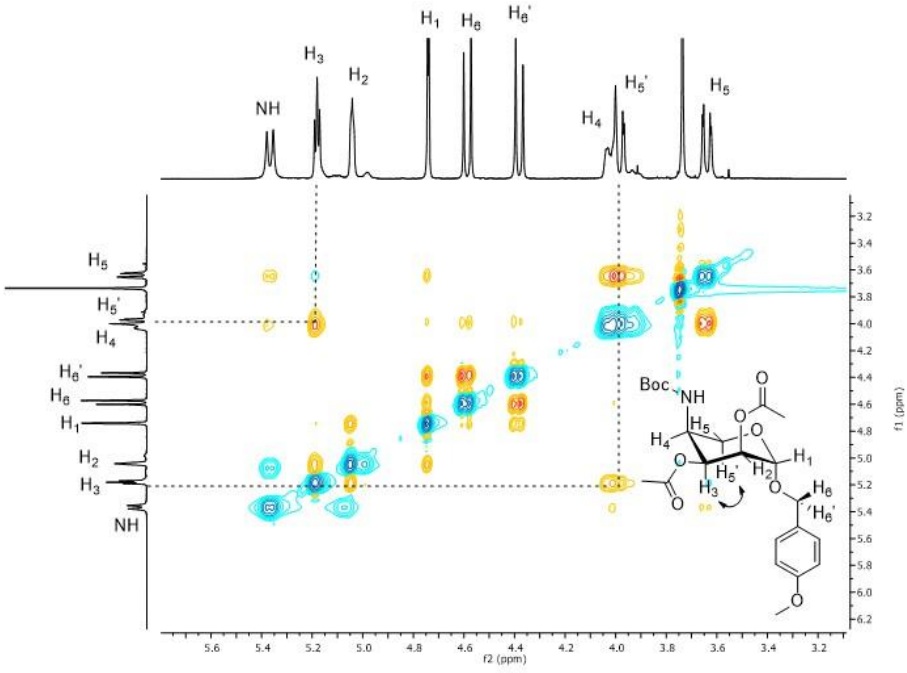



**Figure 29.** Relevant NOE contacts from NOESY experiment of compound **301.**

67 Tvaroska I.; Taravel, F.R. *Adv. Carbohydr. Chem. Biochem.* **1995**, *51*, 15-61.

In compound **302**, the value of constant $^{3}J_{4\text{-}5'}$ of 11 Hz indicates that these two protons are in a *trans* diaxial disposition. The value of $^{1}J_{C\text{-}1,H\text{-}1}$ ~174 Hz indicates that $H_1$ is equatorial. A NOE interaction (Figure 30) between $H_3$ and $H_{5'}$, indicates that 3-OAc group is *trans* to the carbamate group and consequently both acetoxy groups are *trans* to that group as well as to the benzyloxy group (Figure 28). These results confirmed that the *p*-MeOBn group control the stereoselectivity of the process

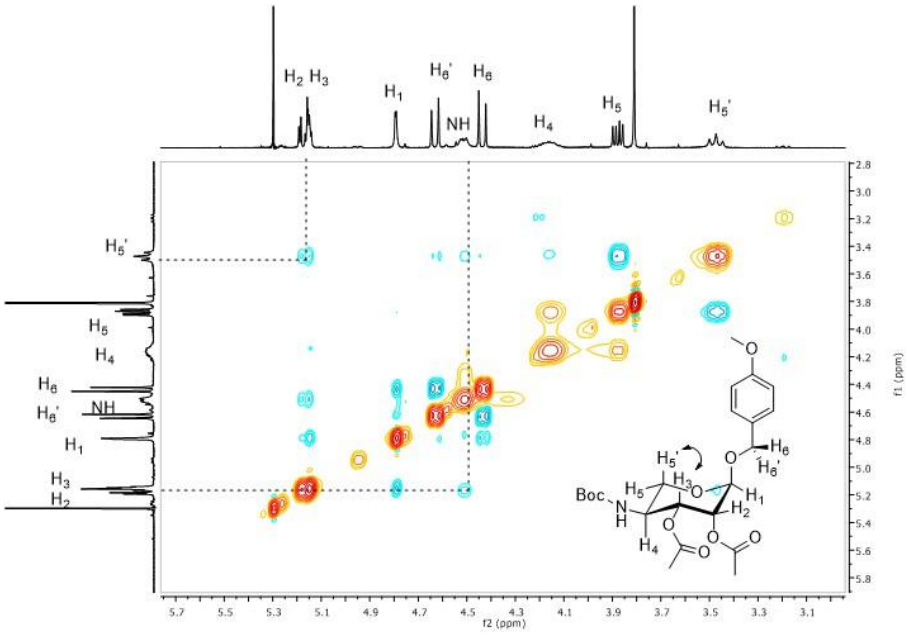
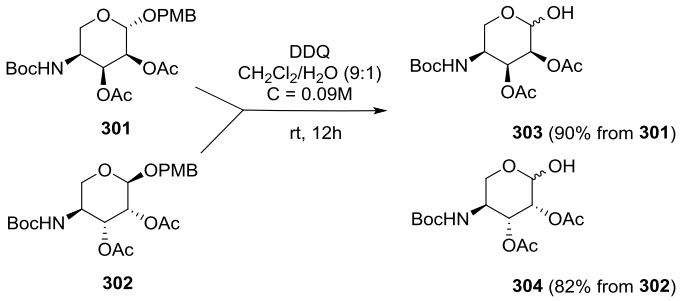



**Figure 30.** Relevant NOE contacts from NOESY experiment of compound **302**.

Once the structure of compound **301** and **302** was confirmed and accordingly to the retrosynthetic proposal, the metoxy benzyl protecting group was removed using oxidative conditions.[68]

Thus, deprotection of the PMB group of **301** and **302** was achieved in the presence of DDQ in dichloromethane and water at room temperature. In these conditions, the corresponding cyclic hemiacetal **303** was obtained in 90% yield (Scheme 110).




**Scheme 110.** Deprotection of the PMB group of **301** and **302** with DDQ.

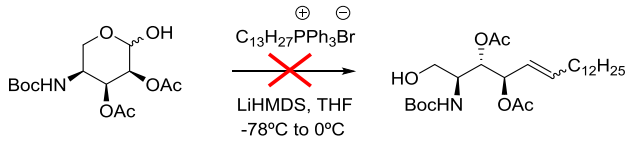
Similary, compound **302** was treated under the same oxidative conditions and alcohol **304** was obtained in 82 % yield (Scheme 110).

[68] (a) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett*. **1982**, *23*, 3253-3256. (b) Horita, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron* **1986**, *42*, 3021-3028.

With the aim of synthesizing D-*ribo*-phytosphyngosine and since the Wittig reaction applied to reducing sugars has been routinely used in glycochemistry,[69] Wittig olefination of hemiacetal **303** was subsequently explored.

It has been reported for related compounds that among several conditions attempted for Wittig reaction, the *in situ* generation of the phosphorane via a slow addition of the base to the well-stirred suspension of hemiacetal and the phosphonium salt at 0ºC worked the best to afford the desired Wittig product stereoselectively.[70]

Unfortunately, attempts of reacting **303** with phosphoranes **305** generated *in situ*, from its phosphonium salts precursor using $LiN(SiMe_3)_2$ in anhydrous THF at -78ºC did not furnish any product and applying heat to the reaction only resulted in complex mixtures of products (Scheme 113).




**303** **305**

**Scheme 113.** Attempt to Wittig reaction on compound **304**.

We hypothesized that the acetoxy protecting group in **303** should be the responsible of the failure of the reaction looking the basic conditions used. Futur work may involve changing protecting group in **300** such as benzyl ether which should not be so sensitive to Wittig conditions. Moreover, as the last step is a hydrogenolysis, both protecting goups and the C-C double bond could be removed in one step.

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69 (a) Zhdanov, Y. A.; Alexeev, Y. E.; Alexeeva, V. G. *Adv. Carbohydr. Chem. Biochem*. **1972**, *27*, 227-299. (b) Postema,M. H. *C-glycosides synthesis*; Wiley: London, **1995**; 91-110.

70 Yen, Y. F.; Kulkarni, S. S.; Chang, C. Y.; Luo, S. Y. *Carbohydr. Res.* **2013**, *368*, 35-39.

# III.Experimental section

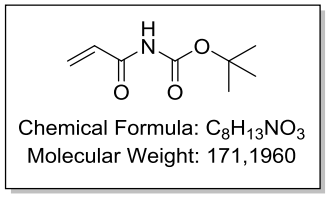
## III.1. General Methods

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

$^1H$ and $^{13}C$ NMR spectra were recorded on a Varian® Mercury VX 400 (400 MHz and 100.6 MHz respectively) or Varian 400-MR spectrometer in $CDCl_3$ as solvent, with chemical shifts (δ) referenced to internal standards $CDCl_3$ (7.26 ppm $^1H$, 77.16 ppm $^{13}C$) or $Me_4Si$ as an internal reference (0.00 ppm). $^1H$ NMR spectra are reported as follows (s = singlet, d = doublet, t = triplet, q = quartet, b = broad; coupling constant(s) in Hz; integration). 2D correlation spectra (gCOSY, NOESY, gHSQC, gHMBC) were visualized using VNMR program (Varian®). ESI MS were run on an Agilent® 1100 Series LC/MSD instrument. Optical rotations were measured at room temperature in a Perkin-Elmer® 241 MC apparatus with 10 cm cells. IR spectra were recorded on a JASCO FT/IR-600 plus Fourier Transform Infrared Spectrometer ATR Specac Golden Gate. Reactions were monitored by TLC carried out on 0.25 mm E. Merck® silica gel 60 F254 glass or aluminium plates. Developed TLC plates were visualized under a short-wave UV lamp (250 nm) and by heating plates that were dipped in ethanol/$H_2SO_4$ (15:1) and basic solution of potassium permanganate. Flash column chromatography was carried out using forced flow of the indicated solvent on Fluka® or Merck® silica gel 60 (230-400 mesh). Flash column chromatography (FCC) was performed using flash silica gel (32–63 μm) and using a solvent polarity correlated with TLC mobility.

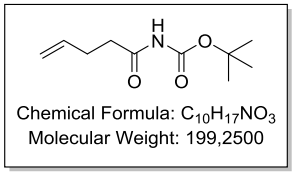
## III.2. Compound characterization

### *N-tert*-Butoxycarbonylacrylamide (NBocAAm) (248).[1]




The THF (250 mL) solution of acrylamide (5.0 g, 70 mmol) was placed in a 250 mL round-bottom flask equipped with a condenser and was magnetically stirred at 0 ºC for 30 min. After the addition portionwise of NaH dispersed in paraffin liquid (60%, 2.8 g, 70 mmol), the solution was stirred for further 10 min under Ar. To the resulting solution was added di-*tert*-butyl dicarbonate (15.2 g, 70 mmol) and the mixture was stirred at 0 ºC for 3 h and at room temperature overnight. After the solvent was evaporated, the mixture was dissolved in ethyl acetate, washed with HCl and water, dried over $MgSO_4$, filtered and the solvent was removed under vacuum. The crude was purified by flash chromatography using hexanes: ethyl acetate (9:1) to give the NBocAAm **248** as a crystalline solid (5.0 g, 42%). All spectroscopic data are in good accordance with reported data.[71]

### *tert*-Butyl pent-4-enoylcarbamate (249).

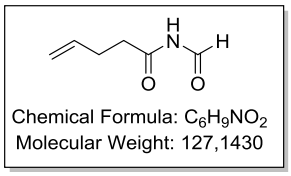



To a solution of $BocNH_2$ (110 mg, 0.939 mmol) and pyridine (75 µL, 0.939 mmol) in THF (0.8 M) was added pent-4-enoyl chloride (103 µL 0.939 mmol) dropwise over 5 min at 0 ˚C. The resulting suspension was stirred overnight at rt and diluted with EtOAc. The mixture was acidified to *ca*. pH 2 with 1N HCl aq. and the phases were separated. The aqueous phase was extracted with EtOAc (x3) and the combined organic layers were washed with water (x3) and brine, dried over $MgSO_4$, and filtered. Volatiles were removed under reduced pressure. The crude material was purified by column chromatography on silica gel using 8:2 hexanes:ethyl acetate as a solvent to afford **249** as a white solid (65 mg, 35%). **$^1$H NMR (400 MHz, $CDCl_3$):** δ (ppm) 7.55 (s, 1H), 5.84 (ddt, *J* = 16.8 Hz, 10.2 Hz, 6.5 Hz, 1H), 5.06 (dq, *J* = 17.1 Hz, 1.7 Hz, 1H), 4.98 (ddd, *J* = 10.2 Hz, 3.0 Hz, 1.7 Hz, 1H), 2.82 (t, *J* = 7.5 Hz, 2H), 2.46-2.32 (m, 2H), 1.47 (s, 9H). **$^{13}$C NMR (100 MHz,**

[1] Hirano, T.; Miyazaki, T.; Ute, K. *J. Polym. Sci. Part A: Polym. Chem* **2008**, *46*, 5698-5701.

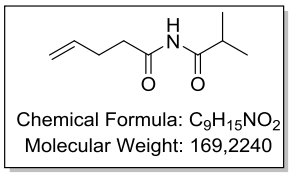
**$CDCl_3$):** δ (ppm) 174.3, 150.7, 137.0, 115.6, 82.6, 35.5, 28.2, 28.1. **FTIR-ATR ($cm^{-1}$):** 3272, 2980, 2359, 1787, 1698, 1146. **HMRS (ESI-TOF) m/z:** $[M+Na]^+$ calcd for $C_{10}H_{17}NNaO_3$: 222.1101, found: 222.1116.

***N*-Formylpent-4-enamide (250).**




To a solution of formamide **257** (0.5 g, 11.10 mmol) and pyridine (0.896 mL, 11.10 mmol) in THF (0.8 M) was added pent-4-enoyl chloride (1.2 mL, 11.10 mmol) dropwise over 5 min at 0 ˚C. The resulting suspension was stirred overnight at rt and diluted with EtOAc. The mixture was acidified to ca. pH 2 with 1N HCl aq. and the phases were separated. The aqueous phase was extracted with EtOAc (x 3) and the combined organic layers were washed with water (x 3) and brine, dried over $Na_2SO_4$, and filtered. Volatiles were removed under reduced pressure. The crude material was purified by column chromatography on silica gel using 9:1 hexanes:ethyl acetate as a solvent to afford **250** as a yellow oil (450 mg, 32%). **$^1$H NMR (400 MHz, $CDCl_3$):** δ (ppm) 9.86 (bs, 1H), 9.02 (d, *J* = 9.8 Hz, 1H), 5.72 (ddt, *J* = 16.7, 10.2, 6.4 Hz, 1H), 5.03-4.88 (m, 2H), 2.44 (dd, *J* = 10.9 Hz, 4.1 Hz, 2H), 2.37-2.25 (m, 2H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ (ppm) 173.41, 163.85, 135.77, 115.96, 35.39, 27.79. **FTIR-ATR ($cm^{-1}$):** 3275, 1745, 1690, 1201. **HMRS (ESI-TOF) m/z:** $[M+Na]^+$ calcd for $C_6H_9NNaO_2$: 150.0525, found: 150.0528.

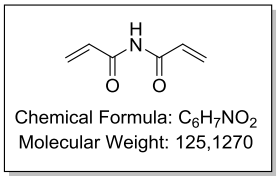
***N*-Isobutyrylpent-4-enamide (251).**




To a solution of isobutyramide **258** (0.5 g, 5.74 mmol) and pyridine (0.47 mL, 5.74 mmol) in THF (0.8 M) was added pent-4-enoyl chloride (0.62 mL, 5.74 mmol) dropwise over 5 min at 0 ˚C. The resulting suspension was stirred overnight at rt and diluted with EtOAc. The mixture was acidified to ca. pH 2 with 1N HCl aq. and the phases were separated. The aqueous phase was extracted with EtOAc (x 3) and the combined organic layers were washed with water (x 3) and brine, dried over $Na_2SO_4$, and filtered. Volatiles were removed under reduced pressure. The crude material was purified by column chromatography on silica gel using 9:1 hexanes:ethyl acetate as a solvent to afford **251** as a white solid (280 mg, 29%).

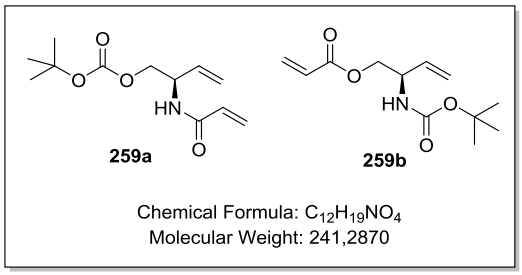
**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ (ppm) 9.65 (bs, 1H), 5.86-5.60 (m, 1H), 5.06-4.77 (m, 2H), 2.85-2.65 (m, 3H), 2.36-2.19 (m, 2H), 1.07 (dd, *J* = 6.9 Hz, 2.8 Hz, 6H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ (ppm) 178.0, 175.7, 136.7, 115.4, 36.5, 35.6, 28.0, 18.7. **FTIR-ATR ($cm^{-1}$):** 3267, 3178, 1732, 1512, 1170. **HMRS (ESI-TOF) m/z:** $[M+H]^+$ calcd for $C_9H_{16}NO_2$: 170.1176, found: 170.1152.

***N*-Acryloylacrylamide (252).**




A mixture of acrylamide (1.0 g, 14.06 mmol) and acryloyl chloride (1.2 g, 14.06 mmol) was stirred at 75 °C without solvent for 2 h. Then the mixture was dissolved in EtOAc (100 mL) and washed with $H_2O$ (30 mL x3). The organic layer was dried over $Na_2SO_4$ and filtered. The evaporation of the filtrate gave a colorless oil, which was purified by flash column chromatography on silica gel (7:3 hexanes:ethyl acetate as eluent) to give **252** (527 mg, 30%). **$^{1}$H NMR (400 MHz, $CDCl_3$):** δ (ppm) 9.11 (bs, 1H), 6.85 (dd, *J* = 17.0, 10.4 Hz, 2H), 6.54 (dd, *J* = 17.0, 0.9 Hz, 2H), 5.92 (dd, *J* = 10.4, 0.9 Hz, 2H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ (ppm) 166.17, 131.85, 130.06. **HMRS (ESI-TOF) m/z:** $[M+H]^+$ calcd for $C_6H_8NO_2$: 126.0550, found: 126.0581.

**(*R*)-2-Acrylamidobut-3-en-1-yl *tert*-Butyl carbonate (259a).**
**(*R*)-*tert*-Butyl acryloyl(1-hydroxybut-3-en-2-yl)carbamate (259b).**



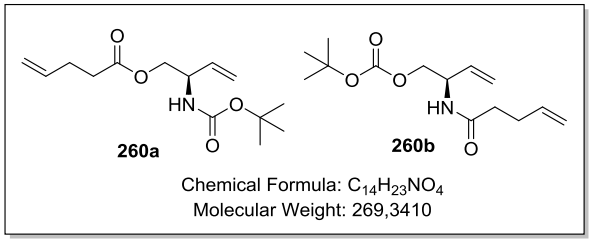

In a 50 mL flamed-dried flask under vacuum, **248** (0.15 g, 0.876 mmol), $[(\eta^3\text{-}C_3H_5)PdCl]_2$ (5 mg, 0.015 mmol) and (*S*,*S*)-**L3** (35 mg, 0.044 mmol) were added under argon and the flask was purged three times with argon. Then dry dichloromethane (45 mL) was added to the mixture and the solution was stirred 30 min at rt. Butadiene monoepoxide (**54**) (60 μl, 0.73 mmol) was added in one portion and the resulting mixture was stirred at room temperature for 18h. The resulting mixture was concentrated and purified by flash chromatography using 8:2 hexanes:ethyl acetate as a solvent to afford products **259b** (140 mg, 80%) and **259a** (21 mg, 12%) as a colorless oil (ratio 85:15). The enantiomeric excess of

**259b** was 97% *ee* determined by chiral HPLC (chiralpack OD-H, hexanes : $^{i}$PrOH 90:10, 1 mlmin$^{-1}$, $t_R$(S) = 4.4 min and $t_R$(R) = 4.9 min).

**Compound 259a: $[\alpha]_D^{25}$** +10.1 (*c* 0.9, $CHCl_3$). **$^1$H NMR (400 MHz, $CDCl_3$):** δ (ppm) 6.38 (dd, *J* = 17.3, 1.4 Hz, 1H), 6.08 (dd, *J* = 17.3, 10.4 Hz, 1H), 5.82 (dd, *J* = 10.4, 1.4 Hz, 1H), 5.80-5.72 (m, 1H), 5.24 (ddd, *J* = 17.2, 1.7, 1.0 Hz, 1H), 5.17 (ddd, *J* = 10.5, 1.6, 1.0 Hz, 1H), 4.8 (bs, 1H), 4.5 (bs, 1H), 4.23-4.13 (m, 2H), 1.41 (s, 9H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ (ppm) 166.0, 155.3, 134.9, 131.5, 128.1, 116.7, 83.0, 66.0, 51.8, 28.4. **FTIR-ATR (cm$^{-1}$):** 3356, 2979, 1712, 1514, 1407, 1366, 1163, 809. **HMRS (ESI-TOF) m/z:** $[M+Na]^+$ calcd for $C_{12}H_{19}NNaO_4$: 264.1206, found: 264.1222.

**Compound 259b: $[\alpha]_D^{25}$** +34.5 (*c* 1.2, $CHCl_3$). **$^1$H NMR (400 MHz, $CDCl_3$):** δ (ppm) 6.31 (dd, *J* = 17.0, 1.4 Hz, 1H), 6.12 (dd, *J* = 17.0, 10.3 Hz, 1H), 5.99 (d, *J* = 7.8 Hz, 1H), 5.83 (ddd, *J* = 17.2, 10.5, 5.3 Hz, 1H), 5.68 (dd, *J* = 10.2, 1.4 Hz, 1H), 5.32-5.20 (m, 2H), 4.91-4.80 (m, 1H), 4.27 (dd, *J* = 11.3, 5.3 Hz, 1H), 4.13 (dd, *J* = 11.3, 3.9 Hz, 1H), 1.47 (s, 9H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ (ppm) 165.0, 153.7, 134.0, 130.6, 127.3, 117.4, 83.0, 68.0, 50.9, 27.8. **FTIR-ATR (cm$^{-1}$):** 3263, 3201, 2980, 1764, 1746, 1529, 1143, 803. **HMRS (ESI-TOF) m/z:** $[M+H]^+$ calcd for $C_{12}H_{20}NO_4$: 264.1206, found: 264.1208.

**(*R*)-2-(*tert*-Butoxycarbonylamino)but-3-enyl pent-4-enoate (260a).**
**(*R*)-*tert*-Butyl 2-pent-4-enamidobut-3-enyl carbonate (260b).**



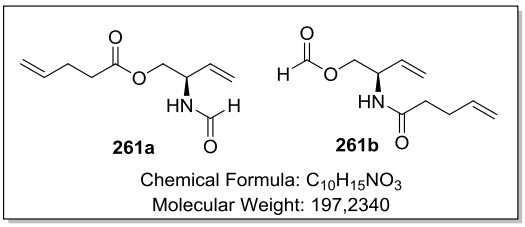

In a 50 mL flamed-dried flask under vacuum, tert-butyl pent-4-enoylcarbamate (150 mg, 0.7528 mmol), $[(\eta^3\text{-}C_3H_5)PdCl]_2$ (4.6 mg, 0.01 mmol) and (*S*,*S*)-**L3** (30 mg, 0.04 mmol) were added under argon and the flask was purged three times with argon. Then dry dichloromethane (30 mL) was added to the mixture and the solution was stirred 30 min at rt. Butadiene monoepoxide (51 μl, 0.6274 mmol) was added in one portion and the resulting solution was stirred at room temperature for 18h. The resulting mixture was concentrated and purified by flash chromatography using

70:30 hexanes:ethyl acetate as a solvent to afford products **260a** (154 mg, 91%) and **260b** (5 mg, 3%) as a colorless oil (ratio 95:05).

**Compound 260a. $[\alpha]_D^{25}$** +80 (*c* 1, $CHCl_3$). **$^1$H NMR (400 MHz, $CDCl_3$):** δ (ppm) 5.87-5.68 (m, 2H), 5.22 (ddd, *J* = 17.2 Hz, 1.7 Hz, 1.0 Hz, 1H), 5.16 (ddd, *J* = 10.5 Hz, 1.7 Hz, 1.1 Hz, 1H), 5.07-4.93 (m, 2H), 4.83 (d, *J* = 8.6 Hz, 1H), 4.41 (bs, 1H), 4.16-4.04 (m, 2H), 2.79 (t, *J* = 7.5 Hz, 2H), 2.43-2.28 (m, 2H), 1.41 (s, 9H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ (ppm) 172.9, 155.3, 136.9, 134.9, 116.6, 115.5, 82.4, 65.7, 51.7, 35.4, 33.4, 28.8. **FTIR-ATR ($cm^{-1}$):** 3343, 2979, 2933, 1740, 1696, 1503, 1367, 1148, 917. .**HMRS (ESI-TOF) m/z:** $[M+Na]^+$ calcd for $C_{14}H_{23}NNaO_4$: 292.1519, found: 292.1525.

**Compound 260b. $[\alpha]_D^{25}$** +6 (*c* 0.8, $CHCl_3$). **$^1$H NMR (400 MHz, $CDCl_3$):** δ (ppm) 5.90-5.74 (m, 2H), 5.30-5.17 (m, 2H), 5.07 (dq, *J* = 17.1 Hz, 1.6 Hz, 1H), 5.00 (ddd, *J* = 10.1 Hz, 2.8 Hz, 1.2 Hz, 1H), 4.84-4.70 (m, 1H), 4.21 (dd, *J* = 11.2 Hz, 5.1 Hz, 1H), 4.09 (dd, *J* = 11.2 Hz, 4.0 Hz, 1H), 2.45-2.34 (m, 2H), 2.34-2.27 (m, 2H), 1.47 (s, 9H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ (ppm) 171.9, 153.3, 137.0, 134.3, 117.1, 115.8, 82.8, 68.1, 50.6, 36.0, 29.7, 28.4. **FTIR-ATR ($cm^{-1}$):** 3286, 2980, 1740, 1641, 1540, 1276, 1253, 1156. .**HMRS (ESI-TOF) m/z:** $[M+Na]^+$ calcd for $C_{14}H_{23}NNaO_4$: 292.1519, found: 292.1523.

**(*R*)-2-Formamidobut-3-enyl pent-4-enoate (261a).**
**(*R*)-2-Pent-4-enamidobut-3-enyl formate (261b).**

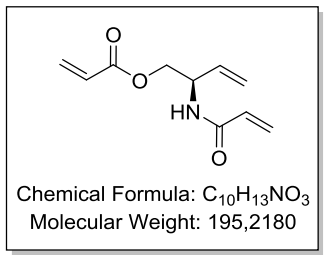



In a 50 mL flamed-dried flask under vacuum, N-formylpent-4-enamide (150 mg, 1.18 mmol), $[(\eta^3\text{-}C_3H_5)PdCl]_2$ (7.2 mg, 0.02 mmol) and (*S*,*S*)-**L3** (47 mg, 0.06 mmol) were added under argon and the flask was purged three times with argon. Then dry dichloromethane (50 mL) was added to the mixture and the solution was stirred 30 min at rt. Butadiene monoepoxide (80 µl, 0.9831 mmol) was added in one portion and the resulting solution was stirred at room temperature for 18h. The resulting mixture was concentrated and purified by flash chromatography using 80:20 hexanes:ethyl acetate as a solvent to afford products **261a** (104 mg, 54%) and **261b** (77 mg, 40%) as a colorless oil (ratio 57:43).

**Compound 261a. $[\alpha]_D^{25}$** +40 (*c* 1.5, $CHCl_3$). **$^1$H NMR (400 MHz, $CDCl_3$):** δ (ppm) 8.16 (s, 1H), 6.44 (d, *J* = 6.5 Hz, 1H), 5.85-5.66 (m, 2H), 5.36-5.13 (m, 2H), 5.06-4.90 (m, 2H), 4.86-4.71 (m, 1H), 4.27-4.01 (m, 2H), 2.46-2.24 (m, 4H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ (ppm) 173.0, 160.9, 136.4, 133.6, 118.2, 115.7, 65.6, 49.2, 33.3, 28.7. **FTIR-ATR ($cm^{-1}$):** 3284, 3078, 2932, 1725, 1640, 1538, 920. **ESI-HRMS** $[M+Na]^+$ calcd for $C_{10}H_{15}NnaO_3$: 220.0944, found: 220.0962.

**Compound 261b. $[\alpha]_D^{25}$** +15 (*c* 1, $CHCl_3$). **$^1$H NMR (400 MHz, $CDCl_3$):** δ (ppm) 8.03 (s, 1H), 6.08 (d, *J* = 7.9 Hz, 1H), 5.86-5.68 (m, 2H), 5.29-5.16 (m, 2H), 5.09-4.93 (m, 2H), 4.86-4.74 (m, 1H), 4.25 (ddd, *J* = 11.2, 5.7, 0.8 Hz, 1H), 4.17 (ddd, *J* = 11.2, 4.5, 0.8 Hz, 1H), 2.42-2.24 (m, 4H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ (ppm) 172.0, 160.8, 136.9, 134.0, 117.3, 115.7, 64.9, 50.1, 35.7, 29.6. **FTIR-ATR ($cm^{-1}$):** 3295, 3079, 2983, 1739, 1667, 1528, 1169, 919. .**HMRS (ESI-TOF) m/z:** $[M+Na]^+$ calcd for $C_{10}H_{15}NnaO_3$: 220.0944, found: 220.0955.

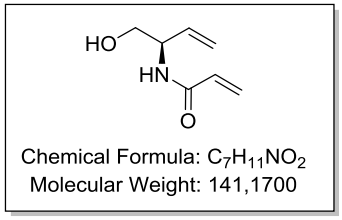
**(*R*)-2-Acrylamidobut-3-enyl acrylate (263).**




In a 50 mL flamed-dried flask under vacuum, *N*-acryloylacrylamide **252** (0.110 g, 0.8779 mmol), $[(\eta^3\text{-}C_3H_5)PdCl]_2$ (6 mg, 0.0175 mmol) and *S*,*S* **L3** (38 mg, 0.0526 mmol) were added under argon and the flask was purged three times with argon. Then dry dichloromethane (45 mL) was added to the mixture and the solution was stirred 30 min at rt. Butadiene monoepoxide (64 μl, 0.7992 mmol) was added in one portion and the resulting solution was stirred at reflux for 18h. The resulting mixture was concentrated and purified by flash chromatography using 7:3 hexanes:ethyl acetate as a solvent to afford **263** as white solid (92%). The enantiomeric excess was 97% *ee* determined by chiral HPLC (chiralpack OD-H, hexanes : $^i$PrOH 90:10, 1 $mlmin^{-1}$, $t_R(S)$ = 14.2 min and $t_R(R)$ = 17.4 min). **$[\alpha]_D^{25}$** +28.4 (*c* 1.3, $CHCl_3$). **$^1$H NMR (400 MHz, $CDCl_3$):** δ (ppm) 6.44 (d, *J* = 7.9 Hz, NH), 6.37 (dd, *J* = 17.3 Hz, 1.3 Hz, 1H), 6.25 (dd, *J* = 17.0 Hz, 1.7 Hz, 1H), 6.18-6.02 (m, 2H), 5.85-5.73 (m, 2H), 5.61 (dd, *J* = 10.1 Hz, 1.7 Hz, 1H), 5.28-5.21 (m, 1H), 5.19 (ddd, *J* = 10.5 Hz, 1.6 Hz, 1.0 Hz, 1H), 4.90-4.81 (m, 1H), 4.27 (dd, *J* = 11.3 Hz, 6.3 Hz, 1H), 4.19 (dd, *J* = 11.3 Hz, 4.7 Hz, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ (ppm) 166.2, 165.3, 134.0, 131.7, 130.7, 127.9, 127.0, 117.3, 65.5,

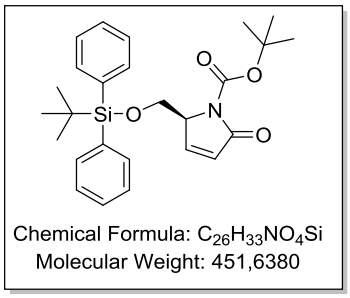
50.7. **HMRS (ESI-TOF) m/z:** $[M+H]^+$ calcd for $C_{10}H_{14}NO_3$: 196.0968, found: 196.0982.

**(*R*)-*N*-(1-Hydroxybut-3-en-2-yl)acrylamide (264).**




Sodium methoxide (8 mg, 0.09 mmol) was added at room temperature to an stirred solution of **263** (90 mg, 0.46 mmol) in methanol (5 mL). Upon completion of the reaction, the solvent was removed *in vacuo*. Workup (extraction with $CH_2Cl_2$) and column chromatography on silica gel (1:9 hexanes:ethyl acetate) provided the desired compound **264** as a colorless oil in quantitative yield (65 mg). **$[\alpha]_D^{25}$** +9.1 (*c* 0.6, $CHCl_3$). **IR** (neat): 3356, 2979, 1712, 1514, 1407, 1366, 1163, 809 $cm^{-1}$. **$^1$H NMR (400 MHz, $CDCl_3$):** δ (ppm) 6.32 (dd, *J* = 17.2 Hz, 1.4 Hz, 1H), 6.15 (dd, *J* = 17.0 Hz, 10.2 Hz, 1H), 6.09 (bs, 1H), 5.86 (ddd, *J* = 17.2 Hz, 10.6 Hz, 5.4 Hz, 1H), 5.69 (dd, *J* = 10.2 Hz, 1.4 Hz, 1H), 5.32-5.22 (m, 2H), 4.70-4.59 (m, 1H), 3.82-3.66 (m, 2H), 2.65 (t, *J* = 5.3 Hz, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ (ppm) 165.3, 134.8, 130.6, 127.4, 117.3, 65.1, 53.8. **FTIR-ATR ($cm^{-1}$):** 3365, 2975, 1715, 1514, 1391, 1163, 985. .**HMRS (ESI-TOF) m/z:** $[M+Na]^+$ calcd for $C_7H_{11}NNaO_2$: 164.0682, found: 164.0698.

**(*S*)-*tert*-Butyl-2-(((*tert*-butyldiphenylsilyl)oxy)methyl)-5-oxo-2,5-dihydro-1H-pyrrole-1-carboxylate (265).**[2]

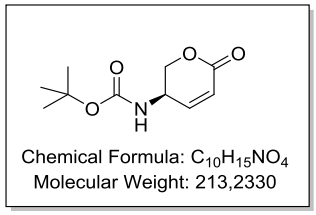



Compound **281** (1.2 g, 1.581 mmol) was dissolved in $CH_2Cl_2$ (410 mL) at room temperature. Second generation Grubbs catalyst (106 mg, 0.125 mmol) was added to the solution and then the reaction mixture was refluxed under argon for 5 h. After cooling the reaction mixture was concentrated and purified by column chromatography with hexane:ethyl acetate (8:2)

[2] Zaminer, J.; Brockmann, C.; Huy, P.; Opitz, R.; Reuter, C.; Beyermann, M.; Freund, C.; Müller, M.; Oschkinat, H.; Kühne, R.; Schmalz, H.-G. *Angew. Chem. Int. Ed.* **2010**, *49*, 7111-7115.

to afford compound **265** (477 mg, 85%) as a colorless oil. $\alpha_D^{25}$ −112.6 (*c* 0.27, $CHCl_3$). $\alpha_D^{25}$ (reported) −121.1 (*c* 0.63, $CHCl_3$). **$^1$H NMR (400 MHz, $CDCl_3$):** δ (ppm) 7.64-7.55 (m, 4H), 7.45-7.33 (m, 6H), 7.29-7.23 (m, 1H), 6.16 (dd, *J* = 6.1 Hz, 1.6 Hz, 1H), 4.65 (m, 1H), 4.11 (dd, *J* = 9.8 Hz, 3.5 Hz, 1H), 3.85 (dd, *J* = 9.8 Hz, 6.2 Hz, 1H), 1.43 (s, 9H), 1.02 (s, 9H). **$^{13}$C NMR (100 MHz, $CDCl_3$)** δ (ppm) 169.5, 149.4, 149.2, 135.5, 135.5, 132.9, 132.6, 129.9, 127.9, 127.8, 127.3, 82.9, 63.5, 62.9, 28.0, 26.7, 19.2. **FTIR-ATR (cm$^{-1}$):** 3072, 2931, 2857, 1780, 1742, 1710, 1354, 1321, 1160, 1112, 705. **HMRS (ESI-TOF) m/z:** $[M+Na]^+$ calcd for $C_{26}H_{33}NNaO_4Si^+$: 474,2071, found: 474.2075.

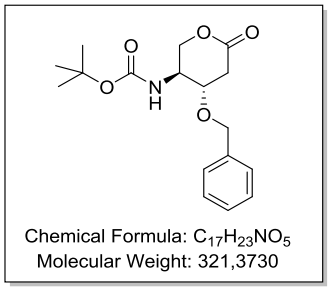
**(*R*)-*tert*-Butyl 6-oxo-3,6-dihydro-2H-pyran-3-ylcarbamate (272).[3]**




Compound **259b** (50 mg, 0.20 mmol) and $Ti(OiPr)_4$ (17.6 mg, 0.062 mmol, 18 μL, 0.3 equiv) were dissolved in $CH_2Cl_2$ (70 mL, c 0.003M), and the mixture was refluxed for 1 h. A solution of second generation Grubbs-Hoveyda catalyst (6.5 mg, 0.01 mmol, 2 mol %) in $CH_2Cl_2$ (2 mL) was added, and reflux was continued for 96 h, after which all of the starting material was consumed as indicated by TLC. After cooling the reaction mixture was concentrated and purified by column chromatography with hexane:ethyl acetate (8:2) to afford compound **272** (41mg, 93%) as a colorless oil. $\alpha_D^{25}$ −101.0 (*c* 0.5, $CHCl_3$). $\alpha_D^{25}$ (reported for (*S*)-enantiomer) +113.0 (*c* 1.07, $CHCl_3$). **$^1$H NMR** (400 MHz, $CDCl_3$): δ (ppm) 6.88 (dd, *J* = 9.7 Hz, 4.8 Hz, 1H), 6.09 (dd, *J* = 9.7 Hz, 1.1 Hz, 1H), 4.83 (bs, 1H), 4.52-4.40 (m, 2H), 1.45 (s, 9H). **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ (ppm) 162.8, 155.0, 145.1, 122.3, 80.3, 70.3, 42.7, 28.2. **FTIR-ATR (cm$^{-1}$):** 3336, 2977, 2933, 1721, 1684, 1519, 1244, 1165. **HMRS (ESI-TOF) m/z:** $[M+Na]^+$ calcd for $C_{10}H_{15}NNaO_4$: 236.0893, found: 236.0892.

[3] (a) Shimamoto, K.; Ishida, M.; Shinozaki, H.; Ohfune, Y. *J. Org. Chem*. **1991**,*56*,4176-4181. (b) Risgaard, R.; Nielsen, S. D.; Hansen, K. B.; Jensen, C. M.; Nielsen, B.; Traynelis, S. F.; Clausen, R. P. *J. Med. Chem*. **2013**, *56*, 4071-4081.

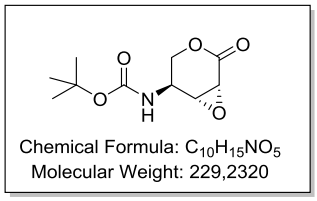
**_tert_-Butyl ((*3S,4S*)-4-(benzyloxy)-6-oxotetrahydro-2H-pyran-3-yl)carbamate (274).**[4]




To a stirred solution of benzyl alcohol (8 mg, 0.0703 mmol) in $CH_2Cl_2$ (1 mL) at 0 °C, NaH (14 mg, 0.1055 mmol) was added. After stirring at room temperature for 30 min, the mixture was cooled to –78 °C, and a solution of lactone **272** (15 mg, 0.0703 mmol) in $CH_2Cl_2$ (0.5 mL) was added. After stirring at this temperature for 1.5h, the reaction mixture was poured into a two-layer mixture of $Et_2O$ (5 mL) and saturated aqueous $NH_4Cl$ (5 mL), and was extracted with EtOAc (10 mL). The organic extract was washed with brine (2 × 5 mL) and dried over anhydrous $Na_2SO_4$. Filtration and evaporation in vacuo furnished the crude product, which was purified by column chromatography (*n*-hexanes/EtOAc 1:1) to give **274** (17.8 mg, 79%) as a colorless oil. $\boldsymbol{\alpha_D^{25}}$ −32 (*c* 1.0, $CHCl_3$). $\boldsymbol{\alpha_D^{25}}$ (litterature) −25.8 (*c* 1.24, $CHCl_3$). **$^1$H NMR (400 MHz, $CDCl_3$):** δ (ppm) 7.41-7.27 (m, 5H), 5.96 (bs, NH), 4.56 (d, *J* = 11.7 Hz, 1H), 4.50 (d, *J* = 11.7 Hz, 1H), 4.20 (dd, *J* = 10.8 Hz, 3.8 Hz, 1H), 4.08-4.03 (m, 1H), 3.93 (dd, *J* = 10.8 Hz, 6.4 Hz, 1H), 3.90-3.84 (m, 1H), 2.66 (dd, *J* = 17.4 Hz, 7.3 Hz, 1H), 2.44 (dd, *J* = 17.4 Hz, 4.1 Hz, 1H), 1.48 (s, 9H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ (ppm) 175.0, 153.3, 137.2, 128.7 (2C), 128.2, 127.9 (2C), 83.2, 75.7, 71.5, 67.2, 59.4, 37.0, 27.8 (3C). **FTIR-ATR (cm$^{-1}$):** 3235, 2977, 2926, 2851, 1741, 1700, 1455, 1368, 1274, 1253, 1159, 858. **HMRS (ESI-TOF) *m/z*:** $[M+Na]^+$ calcd for $C_{17}H_{23}NNaO_5$: 344.1468, found: 344.1462. $[2M+Na]^+$ calcd for $C_{34}H_{46}N_2NaO_{10}$: 665.3045, found: 665.3042.

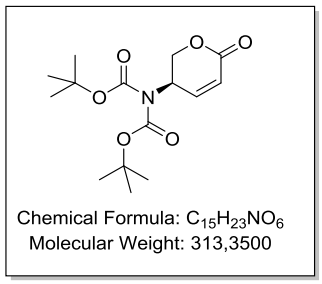
[4] Yoda, H.; Shirai, T.; Katagiri, T.; Takabe, K.; Hosoya, K. *Chem. Express* **1992**, *7*, 477-80.

**_tert_-Butyl ((1R,5S,6R)-2-oxo-3,7-dioxabicyclo[4.1.0]heptan-5-yl)carbamate (275).**




To a solution of the lactenone **272** (50 mg, 0.2345 mmol) in MeOH (1.2 mL) was added an aqueous $H_2O_2$ solution (30%, 69 μL, 0.7973 mmol). The solution was cooled to 0°C, and an aqueous NaOH solution (6.0 M, 23 μL, 0.1407 mmol) was added dropwise and stirred for 10 min. The reaction mixture was then warmed to rt and kept stirring for 0.5 h, before being diluted with $Et_2O$ (10 mL) and $H_2O$ (10 mL).Concentrated aqueous HCl solution was added to adjust the pH to 5. The aqueous layer was extracted with $Et_2O$ (2×15 mL), and the combined organics were washed with brine (10 mL). After being dried over $Na_2SO_4$, the organic solution was concentrated under reduced pressure. The residue was redissolved in toluene (3.4 mL),and the resultant solution was refluxed for 15 min using a Dean - Stark apparatus to remove water. After solvent evaporation, flash silica gel column chromatography (10% EtOAc in hexanes) afforded the epoxide **275** ($R_f$ = 0.4, 20% EtOAc in hexanes) as a colorless oil. $\boldsymbol{\alpha_D^{25}}$ −19.0 (*c* 0.8, $CHCl_3$). **$^1$H NMR (400 MHz, $CDCl_3$):** δ (ppm) 5.00 (bs, 1H), 4.56 (dd, *J* = 11.8 Hz, 2.7 Hz, 1H), 4.48 (d, *J* = 8.4 Hz, 1H), 4.15 (dt, *J* = 11.8 Hz, 1.4 Hz, 1H), 3.76-3.73 (m, 1H), 3.60 (d, *J* = 3.8 Hz, 1H), 1.46 (s, 9H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ (ppm) 166.3, 155.0, 81.1, 67.8, 53.3, 49.1, 45.2, 28.4. **FTIR-ATR ($cm^{-1}$):** 3332, 2976, 1745, 1687, 1519, 1248, 1159, 1038, 780. **HMRS (ESI-TOF) m/*z*:** $[M+H]^+$ calcd for $C_{10}H_{16}NO_5$: 230.1023, found: 230.1048.

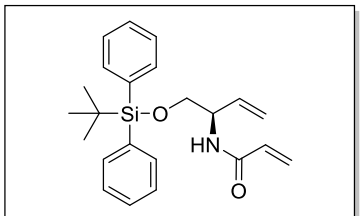
**(*R*)-_tert_-Butyl 6-oxo-3,6-dihydro-2H-pyran-3-ylcarbamate (276).**




A mixture of **272** (106 mg, 0.4971 mmol), 4-(dimethylamino)pyridine (6 mg,0.0491 mmol), and di-tert-butyl dicarbonate (300 mg, 1.3745 mmol) in THF (6 mL) was stirred at room temperature for 12 h. Evaporation of the solvent followed by column chromatography (eluent: hexanes/ethyl acetate, 8:2) afforded **276** as a colorless oil (150 mg, 96%). $\boldsymbol{\alpha_D^{25}}$ −6.5 (*c* 0.8, $CHCl_3$). **$^1$H NMR (400 MHz, $CDCl_3$):** δ (ppm) 6.83 (dt, *J* = 10.1 Hz, 2.0 Hz, 1H), 5.91 (dd, *J* = 10.1 Hz, 2.8 Hz, 1H), 5.25 (dddd, *J* = 11.1 Hz, 6.1 Hz,

2.8 Hz, 2.3 Hz, 1H), 4.57 (dd, *J* = 11.1 Hz, 10.2 Hz, 1H), 4.34 (ddd, *J* = 10.2 Hz, 6.1 Hz, 1.9 Hz, 1H), 1.48 (s, 18H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ (ppm) 162.6, 151.8, 148.7, 118.4, 84.3, 67.3, 49.7, 28.0. **FTIR-ATR ($cm^{-1}$):** 2979, 2934, 1731, 1457, 1366, 1234, 1144, 1114. **HMRS (ESI-TOF) m/z:** $[M+Na]^+$ calcd for $C_{15}H_{23}NNaO_6$: 336.1418, found: 336.1422.

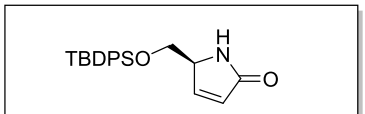
**(*R*)-*N*-(1-((*tert*-Butyldiphenylsilyl)oxy)but-3-en-2-yl)acrylamide (278).**



Chemical Formula: $C_{23}H_{29}NO_2Si$
Molecular Weight: 379,5750

Compound **264** (240 mg, 1.7 mmol) was dissolved in dry THF (6 mL) and treated under argon with *tert*-Butylchlorodiphenylsilane (546 μL, 2.1 mmol) and imidazole (231 mg, 3.4 mmol).The mixture was then stirred for 18h at room temperature. Workup (extraction with $CH_2Cl_2$) and column chromatography on silica gel (9:1) hexanes/EtOAc provided **278** as colorless oil (613 mg, 95%). **$\alpha_D^{25}$** +76.0 (*c* 2.6, $CHCl_3$). **$^1$H NMR (400 MHz, $CDCl_3$):** δ (ppm) 7.72-7.66 (m, 4H), 7.47-7.36 (m, 6H), 6.49 (d, *J* = 8.4 Hz, 1H), 6.29 (dd, *J* = 17.0 Hz, 1.6 Hz, 1H), 6.15 (dd, *J* = 17.0 Hz, 10.1 Hz, 1H), 5.91 (ddd, *J* = 17.2 Hz, 10.4 Hz, 5.5 Hz, 1H), 5.59 (dd, *J* = 10.1 Hz, 1.6 Hz, 1H), 5.25 (d, *J* = 17.3 Hz, 1H), 5.18 (d, *J* = 10.5 Hz, 1H), 4.80-4.66 (m, 1H), 3.79 (d, *J* = 4.7 Hz, 2H), 1.11 (s, 9H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ (ppm) 164.9, 135.5, 135.5, 135.4, 133.1, 132.9, 130.9, 129.8, 129.8, 127.7, 126.3, 116.1, 65.6, 52.8, 26.8 (3C), 19.2. **FTIR-ATR ($cm^{-1}$):** 3267, 3070, 2931, 2857, 1656, 1543, 1428, 1264, 1112, 736, 703. **HMRS (ESI-TOF) m/z:** $[M+H]^+$ calcd for $C_{23}H_{30}NO_2Si^+$: 380.2040, found: 380.2038.

**(*S*)-5-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-1H-pyrrol-2(5H)-one (279).[5]**



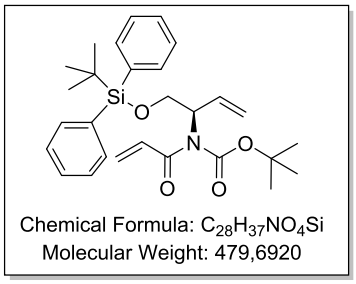
Chemical Formula: $C_{21}H_{25}NO_2Si$
Molecular Weight: 351,5210

Compound **278** (600 mg, 1.581 mmol) was dissolved in $CH_2Cl_2$ (320 mL) at room temperature. Second generation Grubbs catalyst (67 mg, 0.0790 mmol) was added to the solution and then the reaction mixture was

5 Hanessian, S.; MacKay, D. B.; Moitessier, N. *J. Med. Chem*. **2001**, *44*, 3074-3082.

refluxed under argon for 2.5h. After cooling the reaction mixture was concentrated and purified by column chromatography with hexanes:ethyl acetate (1:1) to afford compound **279** (477 mg, 86%) as a brown oil. $\alpha_D^{25}$ −22.0 (*c* 2.1, $CHCl_3$). $\alpha_D^{25}$ (reported for (*S*)-enantiomer) +14.1 (*c* 1.0, $CHCl_3$). **$^1$H NMR (400 MHz, $CDCl_3$):** δ (ppm) 7.73 (bs, 1H), 7.68-7.62 (m, 4H), 7.46-7.35 (m, 6H), 7.06 (dt, *J* = 5.8 Hz, 1.5 Hz, 1H), 6.12 (dt, *J* = 5.8 Hz, 1.4 Hz, 1H), 4.34 (t, *J* = 6.6 Hz, 1H), 3.78-3.63 (m, 2H), 1.07 (s, 9H). **$^{13}$C NMR (100 MHz, $CDCl_3$)** δ (ppm) 174.4, 147.4, 135.4, 135.4, 132.8, 132.7, 129.9, 128.3, 127.8, 64.9, 61.7, 26.7, 19.1. **FTIR-ATR (cm$^{-1}$):** 3072, 1730, 1597, 1498. **HMRS (ESI-TOF) m/z:** $[M+H]^+$ calcd for $C_{21}H_{26}NO_2Si^+$: 352.1727, found: 352.1701.

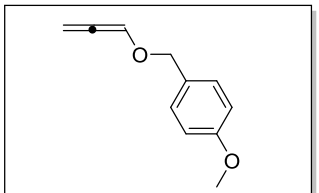
**(*R*)-*tert*-Butyl acryloyl(1-((tert-butyldiphenylsilyl)oxy)but-3-en-2-yl)carbamate (281).**



Chemical Formula: $C_{28}H_{37}NO_4Si$
Molecular Weight: 479,6920

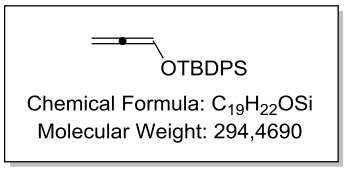
Compound **281** (820 mg, 2.16 mmol) and DMAP (105 mg, 0.86 mmol) was dissolved in dry THF (20 mL) and treated under argon with di-*tert*-butyl dicarbonate (1.242 mL, 5.4 mmol). The mixture was then stirred for 18h at room temperature. Workup (extraction with $CH_2Cl_2$) and column chromatography on silica gel (9:1) hexanes/EtOAc provided **281** as colorless oil (973 mg g, 94%). $\alpha_D^{25}$ +140 (*c* 2.7, $CHCl_3$). **$^1$H NMR (400 MHz, $CDCl_3$):** δ (ppm) 7.70-7.60 (m, 4H), 7.46-7.33 (m, 6H), 6.82 (dd, *J* = 16.9 Hz, 10.3 Hz, 1H), 6.30 (dd, *J* = 16.9 Hz, 1.7 Hz, 1H), 5.92 (ddd, *J* = 17.4 Hz, 10.5 Hz, 6.2 Hz, 1H), 5.67 (dd, *J* = 10.3 Hz, 1.7 Hz, 1H), 5.41-5.28 (m, 1H), 5.15 (ddt, *J* = 10.5 Hz, 6.1 Hz, 1.4 Hz, 2H), 4.06 (dd, *J* = 9.9 Hz, 8.7 Hz, 1H), 3.81 (dd, *J* = 9.9 Hz, 6.4 Hz, 1H), 1.44 (s, 9H), 1.01 (s, 9H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ (ppm) 168.8, 153.2, 135.6, 135.5, 134.4, 133.4, 133.3, 132.1, 129.7, 129.7, 127.7, 127.7, 127.0, 117.7, 83.4, 63.84, 58.9, 27.9, 26.7, 19.3. **FTIR-ATR (cm$^{-1}$):** 2978, 2931, 1731, 1682, 1142, 1112. .**HMRS (ESI-TOF) m/z:** $[M+H]^+$ calcd for $C_{28}H_{37}NNaO_4Si$: 502.2384, found: 502.2401

**1-methoxy-4-((propa-1,2-dien-1-yloxy)methyl)benzene (292).** [6]




At room temperature, KO$^t$Bu (38 mg, 0.34 mmol) was added into the solution of *p*-methoxybenzyl propargyl ether (200 mg, 1.13 mmol) in 0.5 mL THF. The suspension was stirred at room temperature for 3 hours, then filtered through a celite pad and was washed with 50 mL $Et_2O$. Combined solution was concentrated in vacuo and purified by flash chromatography (1% diethyl ether in petroleum ether) to afford **292** as a light yellowish liquid (158 mg, 79%). All spectroscopic data are in good accordance with reported data.[76]

***tert*-Butyldiphenyl(propa-1,2-dien-1-yloxy)silane (293).**[7]




At room temperature, KO$^t$Bu (38 mg, 0.34 mmol) was added into the solution of *tert*-Butyldiphenyl(prop-2-yn-1-yloxy)silane (**291**) (330 mg, 1.13 mmol) in 0.5 mL THF. The suspension was stirred at room temperature for 3 hours, then filtered through a celite pad and was washed with 50 mL $Et_2O$. Combined solution was concentrated in vacuo and purified by flash chromatography (1% diethyl ether in petroleum ether) to afford **293** as a light yellowish liquid (240 mg, 72%). All spectroscopic data are in good accordance with reported data.

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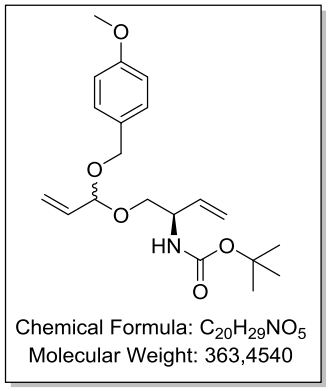
6 Trost, B. M.; Xie, J. *J. Am. Chem. Soc*. **2008** , *130*, 6231-6242.

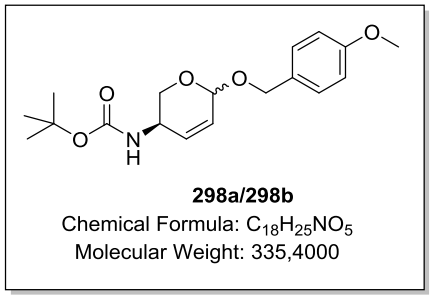
7 Suarez-Pantiga, S.; Hernandez-Diaz, C.; Piedrafita, M.; Rubio, E.; Gonzalez, J. M. *Adv. Synth. Catal*. **2012**, *354*, 1651-1657.

**_tert_-Butyl ((2*R*)-1-((1-((4-methoxybenzyl)oxy)allyl)oxy)but-3-en-2-yl) carbamate (295).**




To a 0.1 M solution of the amide **127** in dry acetonitrile was added DBU (95.2 mg, 0.6252 mmol), $Pd(OAc)_2$ (5 mg, 5 mol%), dppe (11 mg, 5 mol%) and the alkoxyallene **292** (78 mg, 0.4168 mmol). After the reaction mixture was stirred at 80ºC for 12h and the solvent was removed under reduced pressure. After purification by flash chromatography (hexanes/EtOAc = 95/5) (130 mg, 86%) **295** was obtained as colourless oil. $\boldsymbol{\alpha_D^{25}}$ = +56 (*c* 1.3, $CHCl_3$). **$^1$H NMR (400 MHz, $CDCl_3$)** both diastereoisomers: δ (ppm) 7.22-7.14 (m, 2H), 6.82-6.75 (m, 2H), 5.83-5.70 (m, 2H), 5.34 (ddd, *J* = 17.4 Hz, 2.3 Hz, 1.3 Hz, 1H), 5.27-5.21 (m, 1H), 5.21-5.12 (m, 1H), 5.08 (ddd, *J* = 10.5 Hz, 2.9 Hz, 1.5 Hz, 1H), 4.91 (dt, *J* = 4.7 Hz, 1.1 Hz, 1H), 4.49 (d, *J* = 11.4 Hz, 1H), 4.38 (d, *J* = 11.4 Hz, 1H), 4.23 (bs, 1H), 3.69 (s, 3H), 3.61-3.39 (m, 2H), 1.36 (s, 9H). **$^{13}$C NMR (100 MHz, $CDCl_3$)** both diastereoisomers: δ (ppm) 159.2, 155.3, 136.4, 136.4, 134.6, 129.4 (2C), 119.0, 115.7, 113.8 (2C), 100.5, 79.3, 67.3, 66.9, 55.2, 52.5, 28.4 (3C). **FTIR-ATR (cm$^{-1}$):** 3363, 2977, 2935, 1712, 1514, 1247, 1171, 1033. **HMRS (ESI-TOF) m/z:** $[M+Na]^+$ calcd for $C_{20}H_{29}NNaO_5^+$: 386.1938, found: 386.1910.

**_tert_-Butyl 2-(hydroxymethyl)-5-((4-methoxybenzyl)oxy)-2,5-dihydro-1H-pyrrole-1-carboxylate** (**298a)** and (**298b).**

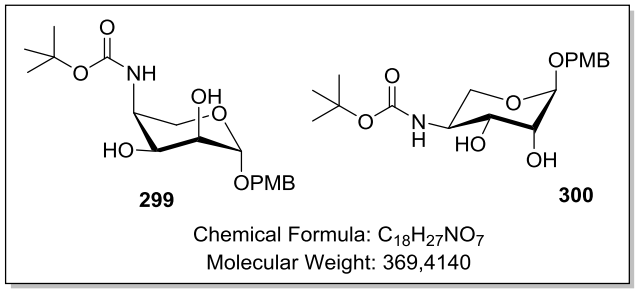



Compound **295** (130 mg, 0.3577 mmol) was dissolved in $CH_2Cl_2$ (7 mL, C = 0.05M) at room temperature. First generation Grubbs catalyst (15 mg, 5 mol%) was added to the solution and then the reaction mixture was refluxed under argon for 1h. After cooling the reaction mixture was concentrated and purified by column chromatography with hexane:ethyl acetate (9:1) to afford a diastereoisomeric mixture **298** (106 mg, 88%) as a brown oil. $\boldsymbol{\alpha_D^{25}}$ +48 (*c* 0.45, $CHCl_3$). **$^1$H NMR (400 MHz, $CDCl_3$)** both diastereoisomers: δ (ppm) 7.23-7.17

(m, 4H), 6.83-6.77 (m, 4H), 5.93 (dd, *J* = 9.9 Hz, 5.6 Hz, 1H), 5.82-5.75 (m, 2H), 5.71 (dt, *J* = 10.2 Hz, 2.3 Hz, 1H), 4.93 (s, 1H), 4.91-4.88 (m, 1H), 4.83 (d, *J* = 8.9 Hz, 1H), 4.64 (dd, *J* = 11.4 Hz, 8.6 Hz, 2H), 4.49 (d, *J* = 9.0 Hz, 1H), 4.42 (dd, *J* = 11.4 Hz, 1.7 Hz, 2H), 4.25 (s, 1H), 4.11-4.03 (m, 1H), 3.89 (m, 1H), 3.77 (dd, *J* = 10.8 Hz, 5.5 Hz, 1H), 3.72 (s, 6H), 3.66 (d, *J* = 11.9 Hz, 1H), 3.55 (dt, *J* = 9.0 Hz, 5.0 Hz, 1H), 1.37 (s, 18H). **$^{13}$C NMR (100 MHz, $CDCl_3$)** both diastereoisomers: δ (ppm) 159.4, 155.18, 131.3, 129.9, 129.9, 129.8, 128.7, 128.3, 127.9, 113.9, 113.9, 93.0, 92.0, 79.9, 79.7, 69.7, 69.3, 62.9, 62.0, 55.3, 44.4, 43.0, 28.5, 28.4. **FTIR-ATR ($cm^{-1}$):** 3253, 2976, 1711, 1513, 1247, 1029.

**Compound 298b: $^1$H NMR (400 MHz, $CDCl_3$):** δ (ppm) 7.25-7.17 (m, 2H), 6.85-6.76 (m, 2H), 5.94 (dd, *J* = 10.0 Hz, 5.6 Hz, 1H), 5.78 (ddd, *J* = 10.0 Hz, 3.0 Hz, 1.0 Hz, 1H), 4.90 (dd, *J* = 3.0 Hz, 0.8 Hz, 1H), 4.79 (d, *J* = 8.8 Hz, 1H), 4.64 (d, *J* = 11.5 Hz, 1H), 4.43 (d, *J* = 11.5 Hz, 1H), 4.06 (dd, *J* = 11.9 Hz, 2.9 Hz, 1H), 3.94-3.84 (m, 1H), 3.73 (s, 1H), 3.67 (d, *J* = 11.9 Hz, 1H), 1.37 (s, 9H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ (ppm) 159.4, 155.3, 129.9, 129.8, 128.8, 128.0, 114.0, 92.0, 79.8, 69.4, 63.0, 55.4, 43.0, 28.5. **HMRS (ESI-TOF) m/z:** $[M+Na]^+$ calcd for $C_{18}H_{25}NNaO_5$: 358.1625, found: 358.1629

***tert*-Butyl ((*3S,4S,5S,6S*)-4,5-dihydroxy-6-((4-methoxybenzyl)oxy) tetrahydro-2H-pyran-3-yl)carbamate (299) and *tert*-Butyl ((*3S,4R,5R,6R*)-4,5-dihydroxy-6-((4-methoxybenzyl)oxy)tetrahydro-2H-pyran-3-yl)carbamate (300).**



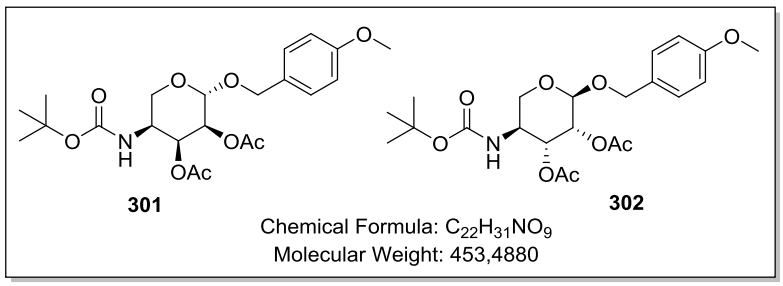

To a cooled solution of compounds **298** (140 mg, 0.42 mmol) and 4-methylmorpholine N-oxide monohydrate (NMNO) (110 mg,0.63 mmol) in acetone (6.4 mL) and $H_2O$ (1.7 mL) was added $OsO_4$ (5 mg, 0.021 mmol). The resulting mixture was stirred at room temperature for 7 days.The reaction was quenched with $Na_2S_2O_3$ and the mixture was stirring for 15 min. The aqueous layer was extracted with ethyl acetate (3 times). The combined organic phases were washed with brine and dried over anhydrous $Na_2SO_4$. After filtration and removal of the solvent, the resulting

residue was purified by flash chromatography (hexane/ethyl acetate, 6:4) to afford **299** and **300** as a colorless oil (130 mg,84%) and the starting material (6 mg).

**Compound 299.** $[\alpha]_D^{25}$ +19.2 (*c* 2.0, $CHCl_3$). **$^1$H NMR (400 MHz, $CDCl_3$):** δ (ppm) 7.24-7.14 (m, 2H), 6.80 (d, *J* = 8.5 Hz, 2H), 5.55 (d, *J* = 8.6 Hz, 1H), 4.68 (d, *J* = 3.1 Hz, 1H), 4.64 (d, *J* = 11.4 Hz, 1H), 4.37 (d, *J* = 11.4 Hz, 1H), 3.94 (s, 1H), 3.88-3.75 (m, 2H), 3.73 (s, 3H), 3.60 (bs, 1H), 3.52 (dd, *J* = 11.6 Hz, 5.8 Hz, 1H), 3.22 (bs, 2H), 1.36 (s, 9H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ (ppm) 159.5, 156.3, 129.9, 129.2, 114.0, 99.1, 80.0, 70.6, 69.7, 66.9, 62.6, 55.4, 49.8, 28.5. **FTIR-ATR ($cm^{-1}$):** 3399, 2976, 2937, 1685, 1513, 1366, 1249, 1172. **HMRS (ESI-TOF) m/*z*:** $[M+Na]^+$ calcd for $C_{18}H_{27}NNaO_7$: 392.1680, found: 392.1680.

**Compound 300.** $[\alpha]_D^{25}$ −38.0 (*c* 0.9, MeOD). **$^1$H NMR (400 MHz, MeOD):** δ (ppm) 7.29-7.23 (m, 2H), 6.93-6.86 (m, 2H), 4.76 (d, *J* = 2.3 Hz, 1H), 4.62 (d, *J* = 11.4 Hz, 1H), 4.41 (d, *J* = 11.4 Hz, 1H), 3.90-3.79 (m, 1H), 3.78 (s, 3H), 3.77-3.65 (m, 3H), 3.44 (t, *J* = 10.6 Hz, 1H), 1.43 (s, 9H). **$^{13}$C NMR (100 MHz, MeOD):** δ (ppm) 160.9, 158.4, 130.9, 130.8, 114.7, 100.7, 80.2, 71.28, 70.2, 69.8, 62.8, 55.7, 55.7, 50.3, 28.7. **FTIR-ATR ($cm^{-1}$):** 3397, 2973, 2938, 1684, 1510, 1361, 1252, 1171. **HMRS (ESI-TOF) m/*z*:** $[M+Na]^+$ calcd for $C_{18}H_{27}NNaO_7$: 392.1680, found: 392.1674.

**(*2S,3S,4S,5S*)-5-((*tert*-Butoxycarbonyl)amino)-2-((4-methoxybenzyl)oxy) tetrahydro-2H-pyran-3,4-diyl diacetate (301) and (*2R,3R,4R,5S*)-5-((*tert*-Butoxycarbonyl)amino)-2-((4-methoxybenzyl)oxy)tetrahydro-2H-pyran-3,4-diyl diacetate (302).**



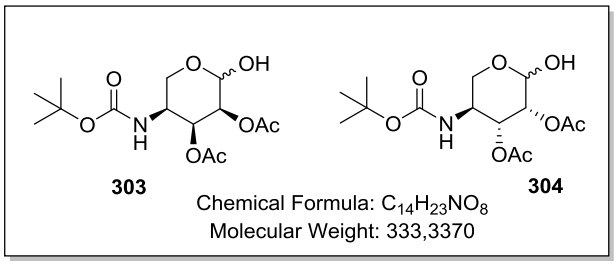

To a solution of compound **299** and **300** (140 mg, 0.42 mmol) in pyridine (2 mL) was added acetic anhydride ( 5 drops). The mixture was stireed 18h at room temperature. Water was added to the reaction mixture and it was extracted

with dichloromethane. The combined organic layers were washed with aqueous $CuSO_4$ sat., $NH_4Cl$, brine and dried over anhydrous $MgSO_4$, filtered and the solvent was removed under vacuum to give pure product **301** and **302** in a quantitative yield (188 mg).

**Compound 301. $[\alpha]_D^{25}$** +14 (*c* 1.0, $CHCl_3$). **$^1$H NMR (400 MHz, $CDCl_3$):** δ (ppm) 7.22-7.14 (m, 2H), 6.86-6.78 (m, 2H), 5.37 (d, *J* = 10.0 Hz, 1H), 5.18 (t, *J* = 3.9 Hz, 1H), 5.04 (bs, 1H), 4.74 (d, *J* = 2.0 Hz, 1H), 4.59 (d, *J* = 11.5 Hz, 1H), 4.38 (d, *J* = 11.5 Hz, 1H), 4.08-3.94 (m, 2H), 3.74 (s, 3H), 3.64 (dd, *J* = 11.9 Hz, 2.0 Hz, 1H), 2.08 (s, 3H), 1.94 (s, 3H), 1.38 (s, 9H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ (ppm) 169.7, 169.3, 159.6, 155.8, 129.8, 128.5, 114.0, 96.9, 79.4, 69.5, 69.2, 65.7, 62.5, 55.3, 47.7, 29.8, 28.4, 20.9, 20.8. **FTIR-ATR (cm$^{-1}$):** 3450, 2974, 2931, 1750, 1716, 1514, 1243, 1068. **HMRS (ESI-TOF) m/*z*:** $[M+Na]^+$ calcd for $C_{22}H_{31}NNaO_9$: 476,1891, found: 476.1879.

**Compound 302. $[\alpha]_D^{25}$** −80.0 (*c* 1, $CHCl_3$). **$^1$H NMR (400 MHz, $CDCl_3$):** δ (ppm) 7.21-7.13 (m, 2H), 6.86-6.74 (m, 2H), 5.12 (d, *J* = 3.3 Hz, 1H), 5.11-5.06 (m, 1H), 4.72 (d, *J* = 1.5 Hz, 1H), 4.56 (m, 2H), 4.36 (d, *J* = 11.5 Hz, 1H), 4.17-4.03 (m, 1H), 3.80 (dd, *J* = 11.1 Hz, 5.4 Hz, 1H), 3.73 (s, 3H), 3.41 (t, *J* = 10.9 Hz, 1H), 2.15 (s, 3H), 2.05 (s, 3H), 1.96 (s, 9H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ (ppm) 171.0, 170.1, 159.5, 155.3, 129.8, 128.6, 114.0, 96.5, 79.9, 69.3, 69.1, 69.0, 61.8, 55.3, 47.4, 28.3, 21.0, 20.9. **FTIR-ATR (cm$^{-1}$):** 3344, 2975, 2932, 1748, 1712, 1514, 1244, 1066. **HMRS (ESI-TOF) m/*z*:** $[M+Na]^+$ calcd for $C_{22}H_{31}NNaO_9$: 476,1891, found: 476.1881.

**(*3S,4S,5S*)-5-((*tert*-Butoxycarbonyl)amino)-2-hydroxytetrahydro-2H-pyran-3,4-diyl diacetate (303) and (*3R,4R,5S*)-5-((*tert*-Butoxycarbonyl)amino)-2-hydroxytetrahydro-2H-pyran-3,4-diyl diacetate (304).**




To a stirred solution of PMB protected alcohol **301** or **302** generated above (60 mg, 0.1323 mmol) in $CH_2Cl_2$ (1.3 mL) and water (0.2 mL) was added DDQ (36 mg, 0.16 mmol) and the reaction mixture was stirred at rt for 12h. Saturated $NaHCO_3$ aqueous solution was added, and the mixture was extracted with $CH_2Cl_2$ (3x). The extract was washed with saturated $NaHCO_3$ and brine, and dried over anhydrous $Na_2SO_4$. The solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column with 40% EtOAc in hexanes to yield the desired alcohol as a white foam (40 mg, 90%).

**Compound 303: $^1$H NMR (400 MHz, $CDCl_3$):** δ (ppm) 5.31-5.19 (m, 1H), 5.11 (bs, 2H), 4.89 (bs, 1H), 4.21-3.96 (bs, 2H), 3.86 (dd, *J* = 11.2 Hz, 4.7 Hz, 1H), 3.71 (appt, *J* = 10.8 Hz, 1H), 2.12 (s, 3H), 2.05 (s, 3H), 1.41 (s, 9H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ (ppm) 170.6, 155.5, 92.6, 80.1, 69.9, 69.0, 62.0, 47.7, 28.4, 21.0 (2C). **FTIR-ATR (cm$^{-1}$):** 3369, 2972, 1744, 1513, 1364, 1220, 730. **HMRS (ESI-TOF) m/*z*:** $[M+Na]^+$ calcd for $C_{14}H_{23}NNaO_8$: 356,1316, found: 356,1317.

**Compound 304: $^1$H NMR (400 MHz, $CDCl_3$):** δ (ppm) 5.41 (bs, 1H), 5.35-5.22 (m, 2H), 5.23-5.10 (m, 2H), 5.05 (bs, 1H), 4.97 (bs, 1H), 4.25-3.75 (m, 5H), 3.76-3.39 (m, 3H), 2.08 (s, 3H), 2.05-1.95 (m, 9H), 1.43 (s, 9H), 1.38 (s, 9H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ (ppm) 171.0, 170.6, 155.6, 92.5, 80.1, 69.9, 69.0, 61.9, 60.6, 47.6, 28.4,21.0 (2C), 14.3. **FTIR-ATR (cm$^{-1}$):** 3370, 2980, 1746, 1510, 1367, 1227, 732. **HMRS (ESI-TOF) m/*z*:** $[M+Na]^+$ calcd for $C_{14}H_{23}NNaO_8$: 356,1316, found: 356,1314.

# CHAPTER 7

*Conclusions*

In this thesis, we have studied the palladium-catalyzed asymmetric allylic amination reaction with two different orientations:

- To provide some methodological improvements in order to enlarge the usefulness of the reaction
- To apply this methodology as the key step in the synthesis of natural products analogues

In this context the main conclusion derived of this work are the following:

1. We have been able to obtain the branched regioisomer as the only product in the reaction using palladium/DACH naphthyl Trost ligand **L3** and carbonate **157**. Both the yield and enantioselectitity were excellent.

2. We have shown that this system tolerates the use of relatively hard alkylamines as nucleophiles thus widening the synthetic possibilties towards the obtention of enantioenriched allyl amines, which typically provide poor regioselectivity using butadiene monoepoxide (**54**) as electrophile.

3. The excellent control of the regio- and enantioselectivity in this case might be due to hydrogen bonding interactions between the hydroxyl group in the substrate and the diphenylphosphino benzoic acid-derived ligand in the Pd complex, as it can be deduced by the dramatic change in the regioselectivity when the hydroxyl group is protected or replaced by an alkyl chain.

4. The use of alkylamines as nucleophiles is limited to unhindered primary amines. Bulkyl primary or secondary amines lead to a poor regioselectivity. We have hypothesized that steric hindrance of the nucleophile could be responsible for the poor regioselectivity observed.

5. Based on this protocol a short formal enantioselective synthesis of glycosidase inhibitor D-fagomine is reported.

6. Acyclic nucleosides analogues **226** and **227** were successfully prepared in high yields and enantioselectivities, by palladium-catalyzed allylic substitution of allylic carbonate **157** or butadiene monoepoxide (**54**), using pyrimidinic and purinic bases as nucleophiles, followed by ruthenium-catalyzed cross-metathesis with diethyl allylphosphonate and removal of protecting groups.

7. The first enantioselective formal synthesis of the glycosidase inhibitor nectrisine has been carried out in 7 steps and 48 % overall yield starting from the commercially available racemic butadiene monoepoxide (**54**) as electrophile and imidocarboxylate **125** as nucleophile through a synthetic scheme that involves regioselective palladium-catalyzed asymmetric allylic amination reaction, cross metathesis and diastereoselective dihydroxylation reactions as key steps.

8. The DYKAT of butadiene monoepoxide (**54**) using the catalytic system Pd/ Trost ligand with different imido and imidocarboxylate nucleophiles have been explored. As expected, the resulting allylic imido carboxylate product isomerized through a facile *in situ* acyl migration. We found that when acryloyl imido carboxylates **248** and **249** were used as nucleophiles, very good to excellent selectivity in the acyl migration can be achieved. This selectivity could be probably explained by both steric and electronic factors of the acyl moiety. In the case of imides **250** and **251** no control of acyl migration was possible and an almost equivalent ratio of both isomers were always obtained.

9. This method allowed us to obtain enantiomerically enriched allylic compounds **259b**, **263** and **264** bearing an acryloyl moiety at *N*, *O* or both positions which in combination with the well known ring-closing metathesis reaction enabled us to obtained in very good yield valuable different synthetic scaffold such as lactam **265**, lactone **274** and 4-amino-4-deoxy sugars **303** and **304**.