REGIO- AND ENANTIOSELECTIVE SYNTHESIS OF UNSATURATED AMINO ALCOHOLS, AMINO KETONES AND DIAMINES AS VALUABLE INTERMEDIATES IN ORGANIC SYNTHESIS.

Joan Guash Savidó

Dipòsit Legal: T 1366-2015

JOAN GUASCH SAVIDÓ

Regio- and Enantioselective Synthesis of Unsaturated Amino Alcohols, Amino Ketones and Diamines as Valuable Intermediates in Organic Synthesis

DOCTORAL THESIS

Supervised by

Prof. Sergio Castillón Miranda and Prof. M. Isabel Matheu Malpartida

Departament de Química Analítica i Química Orgànica

UNIVERSITAT ROVIRA I VIRGILI

Tarragona, 2015

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FAIG CONSTAR que aquest treball, titulat "*Regio and Enantioselective Synthesis of Unsaturated Amino Alcohols, amino Ketones and Diamines as Valuable Synthetic Intermediates in Organic Synthesis*", que presenta **Joan Guasch Savidó** per a l'obtenció del títol de Doctor, ha estat realitzat sota la nostra direcció al Departament Química Analítica i Química Orgànica d'aquesta universitat.

Tarragona, 6 de Maig de 2015

Dr. Sergio Castillón Miranda

Dra. M. Isabel Matheu Malpartida

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Als meus pares i germana

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ABREVIATIONS AND ACRONYMS

A

aq	Aqueous
atm	Atmosphere

B

BHT	2,6-bis(*tert*-butyl)-4-hydroxytoluene
Boc	*tert*-Butylcarbamate
brs	Broad signal

C

conv.	Conversion

D

d	Doublet
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DFT	Density functional theory
DKR	Dynamic kinetic resoltion
DIBAL	Diisobutyl aluminium hydride
DIPEA	*N*,*N*-Diisopropulethylamine
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
d.r.	Diastereomeric ratio

E

equiv.	Equivalent(s)
ESI-HMRS	Electrospray ionization-high mass resolution spectrometry
e.r.	Enantiomeric ratio
ee	Enantiomeric excess
esp	3-[3-(2-Carboxy-2,2-dimethylethylethyl)phenyl]-2,2-dimethylpropanoic acid)

G

g	Gram(s)
GalCer	Galactosyl Ceramide
gCOSY	Gradient correlation spectroscopy
gHMBC	Gradient heteronuclear multiple bond correlation

gHSQC	Gradient heteronuclear single quantum coherence

H

h	Hour(s)
HPLC	High performance liquid chromatography
Hz	Hertz(s)

I

IBX	2-Iodoxybenzoic acid
^{i}Pr	*Iso*-propyl
IR	Infrared

J

J	Coupling constant

K

K	Equilibrium constant

L

L	Litre(s)
LA	Lewis acid
LG	Leaving group

M

m	Meter(s)
m (in NMR)	Multiplet
[M]	Molar
m/z	Mass under charge
min	Minute(s)
m.p.	Melting point
MS	Mass spectrometry

N

NMR	Nuclear magnetic resonance
Nu	Nucleophile

P

P	Product
PG	Protecting group

PhINTs	*N*-Tosyliminophenyl-iodane
Py	Pyridine

Q

q	Quadruplet

R

rac	Racemic
Rf	Retention factor
r.t.	Room temperature

S

s	Singlet
S	Substrate
sat.	Saturated

T

t	Time
t (in NMR)	Triplet
TBA	Tetra-*n*-butylammonium
TBAF	Tetra-*n*-butylammonium fluoride
TBSCl	*tert*-Butyldimethylsilyl chloride
temp.	Temperature
THF	Tetrahydrofuran
TLC	Thin layer chromatography
T_R	Retention time
Tp	Trispyrazolylborate
TPA	Trifluoroacetate
Tpm	Trispyrazolylmethane
Ts	Tosyl
TSA	Toluenesulfonic acid

U

UV	Ultra-violet

V

v	Reaction rate

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SUMMARY

The present PhD work has two different objectives: 1) to develop new synthetic procedures for obtaining distinctly functionalised unsaturated aminoalcohols in a regio- and enentioselective manner, and 2) to prepare enantioenriched α-arylamino ketones and 1,2-diamines from α-arylamino hydrazones synthesised by enantioselective intermolecular nucleophilic α-amination of azoalkenes

1. This objective is part of a more general objective in our group that aims to prepare sphingosine and ceramide analogues as downstream receptor agonists and sphingosine and ceramide-metabolizing enzyme inhibitors.

Ceramide is a central mediator in sphingolipid metabolism being referred to as a 'tumor suppressor lipid', since it powerfully potentiated signaling events that drive to apoptosis, cell cycle arrest and autophagic responses.[i]

The complex regulation of sphingolid metabolism[ia,ii] involves deacylation of ceramide (Cer) by ceramidases to generate sphingosine 1-phosphate (S1P) catalysed by sphingosine kinases (SK) (Scheme I). The dynamic balance between ceramide and SP1 signaling guides the cell towards either an apoptic process or a survival process. For these reasons, several cancer treatments often result in the generation of ceramide, which is implicated in regulating the cell death response.

[i] a) Morad, S. A. F.; Cabot, M. C. *Nat. Rev. Cancer* **2013**, *13*, 51-65. b) Schiffmann, S.; Geisslinger, G. *Progr. Lipid Res.* **2012**, *51*, 50-62. c) Ruvolo, P. P. *Pharmacol. Res.* **2003**, *47*, 383-392. d) Senchenkov, A.; Litvak, D.A.; Cabot, M. C. J. Natl. Cancer Inst. 2001, 93, 347-357.

[ii] a) Orr Gandy, K. A.; Obeid, L. M. *Biochim. Biophys. Acta* **2013**, *1*, 157−166. b) Chalfant, C. E.; Spiegel, S. *J. Cell Sci.* **2005**, *118*, 4605−4612. c) Airola, M.; Hannun, Y.A. *Handb. Exp. Pharmacol.* **2013**, *215*, 57−76. d) Pyne, S.; Pyne, N.J. *Biochem. J.* **2000**, *349*, 385-402.

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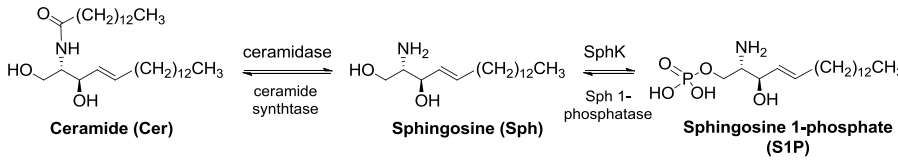


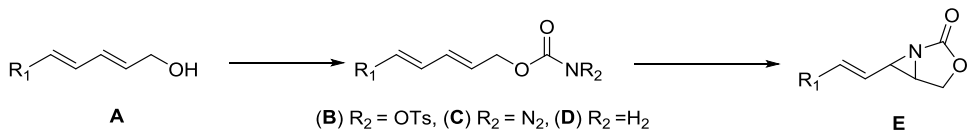
Scheme I

Therefore, with the aim of preparing ceramide analogues, the present work has been oriented towards the development of synthetic routes that provide an easy access to a wide range of distingly functionalized sphingosine derivatives, which then could be acylated and form ceramide analogues. In this regard, two main concrete objectives were aimed:

a) **Regio- and stereoselective synthesis of unsaturated aminoalcohols through intramolecular aziridination and ring opening of substituted dienols.**

b) **Enantioselective synthesis of unsaturated amino alcohols through kinetic resolution of oxazolidinones.**

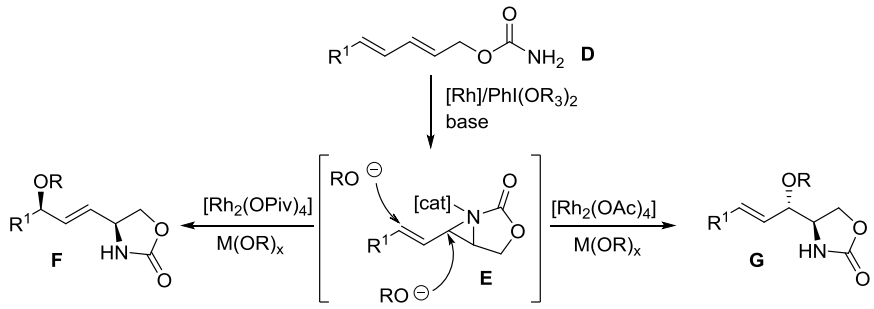
1a. In Chapter 3 we initially studied the intramolecular aziridination of dienols with different nitrogen-donor functional groups, named tosyloxycarbamate (**B**), acyl azide (**C**) and carbamate (**D**) (**Scheme II**).



Scheme II

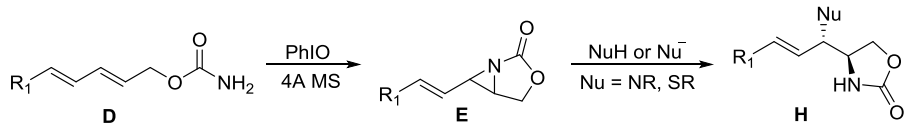
The metal catalysed aziridination of *N*-tosyloxycarbamate (**B**) and acyl azide (**C**) substrates resulted unsuccessful. In the former case, although **E** was generated during the reaction, uncontrollable *in situ* ring opening processes made us to discard this approach.

The intramolecular aziridination of carbamate-modified dienols (**D**) was carried out using hypervalent iodine (III) reagents (PhIR) and the process could be carried out under metal-catalysis, when PhIR = $PhI(OCOR_3)_2$, or under metal-free conditions, when PhIR = PhIO. In the former case, an appropriate choice of the catalyst, iodine(III) reagent and base provided an efficient methodology for the regio- and stereoselective oxyamination of dienols (Scheme III).



Scheme III

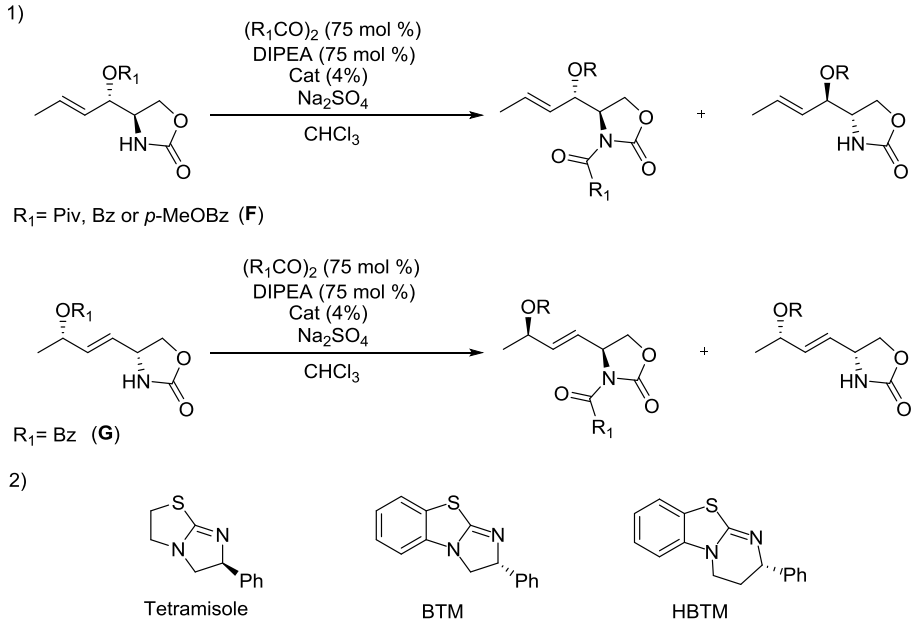
On the other hand, the use of PhIO provided the opportunity to obtain distingly functionalised unsaturated aminoalcohols through a two-step process involving initial carbamate aziridination followed by ring opening of vinyl aziridine **E** with an external nucleophile (Scheme IV).



Scheme IV

1b. In Chapter 4 is presented the study on enantioselective *N*-acylation, through kinetic resolution, of the oxazolidinones obtained in the previous chapter (**F**, **G** and **H**).

Initially, using *O*-substituted oxazolidinones (**F**, **G**), we studied the effect that the acyl substituent, the catalyst (Scheme V, 2), the acylating agent and the position of the substituent, had on the effectiveness of the kinetic resolution (Scheme V, 1).



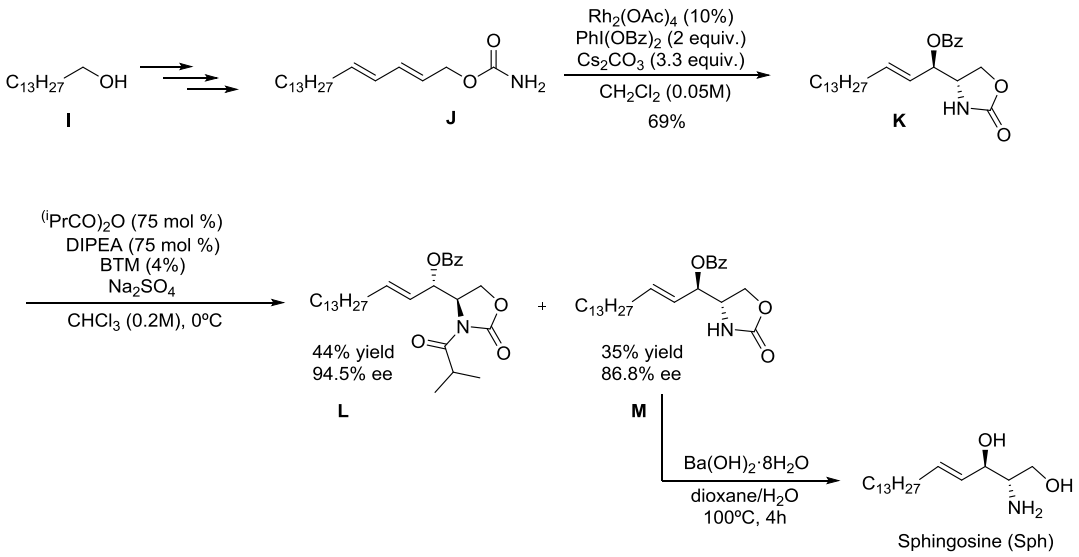
Scheme V

From this study the following was concluded:

a) The presence of aromatic groups on the substituent greatly increases both the activity and enantioselectivity of the process, being benzoate- and *p*-methoxy benzoate-substituted oxazolidinones (*s* up to 118) superior to pivalate (*s* = 31).
b) A sharp decrease on the effectiveness of the kinetic resolution is observed when the substituent is at C-5 instead of C-3.
c) Among the three catalysts tested (BTM, tetramisole, HBTM), BTM resulted remarkably superior. Several recrystalyzations of BTM resulted determining for high selectivities.
d) The best acylating agent was shown to be isobutyric anhydride.

The optimized conditions were used to resolve oxazolidinones bearing *N*- and *S*-substituents. Outstanding resolution of phthalimide-substituted oxazolidinones was achieved with selectivity factors over 500.

The methodologies studied in chapter 3 and 4 were applied to the enantioselective synthesis of sphingosine (Scheme VI). Diene **J** was used as starting material for such purpose. Tandem aziridination / ring opening of **J** with $Rh_2(OAc)_4$, $PhI(OBz)_2$ and Cs_2CO_3 gave **K** as a single regioisomer in 69% yield. Then **K** was reacted under kinetic resolution conditions to afford acylated oxazolidinone **L** which rendered sphingosine after hydrolysis.

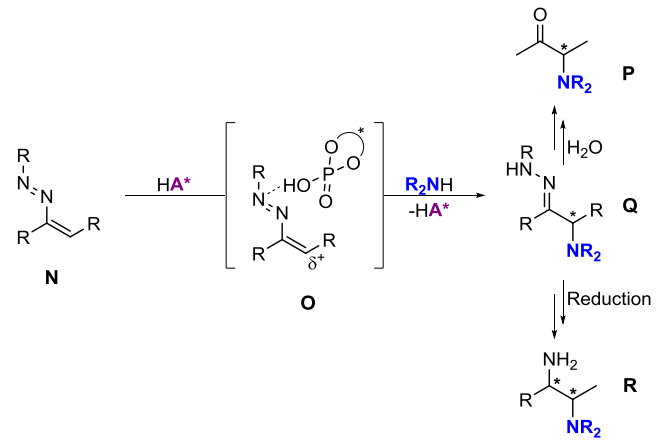


Scheme VI

2. The work developed in this chapter was carried out during a six-month stay at the group of Prof. Dean F. Toste at UC Berkeley.

In this chapter it is described the enantioselective addition of anilines to azoalkenes through the use of a chiral phosphoric acid as catalyst and the

transformation of the resultanting α-arylamino hydrazones to enantioenriched α-arylamino ketones and 1,2-diamines (Scheme VII).



Scheme VII

The methodology for the enantioselective synthesis of α-arylamino hydrazones (**Q**) from azoalkenes (**N**) was conceived and developed by Dillon H. Milles (UC Berkeley). Therefore, the discussion of the results in this chapter will be particulary focused on the conversion of α-arylamino hydrazones (**Q**) into α-arylamino ketones (**P**) and 1,2-diamines (**R**).

In order to demonstrate the synthetic potential of the nucleophilic amination protocol developed, where compound **Q** was obtained with yields of 49-93% and enantioselectivities of 89-94% , it was crucial to transform the obtained aminohydrazones into the corresponding amino ketones. In addition we considered also interesting to transform the amino hydrazones into 1,2-diamines. In both cases it was imperative to avoid enantiopurity loss. Taking into account the propensity towards keto-enol or imine-enamine tautomerism of carbonyl compounds with substituents at the α position, the main efforts in this chapter involve the search for non-racemizing hydrolysis and reduction conditions.

Enantioenriched α-arylamino hydrazones were successfully hydrolysed using Amberlyst-15 and a sacrificial amount of *p*-formaldehyde in water/acetone mixtures. Whereas enantioenriched α-arylamino hydrazones with isopropyl substituents were resistant to racemization under the above mentioned conditions, methyl-substituted and cyclic hydrazones required specifically a 1:1 acetone:water mixture to avoid racemization.

Concerning the reduction of α-arylamino hydrazones, two routes were explored; a) catalytic hydrogenation of hydrazones to amines, and b) initial reduction with metal hydrides followed by catalytic hydrogenolysis of the obtained hydrazines.

a. Catalytic hydrogenation of α-arylamino hydrazones with Raney Nickel provided 1,2-diamines in low yield and with unexpected enantiopurity loss.

b. Sodium cyanoborohydride ($NaCNBH_3$) in the presence of an acid additive was the unique system able to reduce the targeted hydrazones to hydrazines. However, although this route provided moderate yields of diamines, considerable enantiopurity loss was observed. The enantiopurity could be finally preserved carrying out the hydride reduction under the same conditions found for the hydrolysis but in the absence of *p*-formaldehyde. However, the yields obtained were low.

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Joan Guash Savidó
Dipòsit Legal: T 1366-2015

CHAPTER 1

GENERAL INTRODUCTION

UNIVERSITAT ROVIRA I VIRGILI
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1.1. BIOLOGICAL IMPORTANCE OF SPHINGOLIPIDS

Sphingolipid play an important role in the regulation of cell proliferation, differentiation, survival, trafficking and cell death.[1] They are interconvertible by the different metabolic enzymes in a complex lipid signaling system. Modulation of this sphingolipid metabolism is a promising strategy for cancer, having been implemented many connections between cancer therapies and sphingolipid metabolism.[2,3] The complex regulation of sphingolipid metabolism[4] involves deacylation of ceramide (Cer) by ceramidases to generate sphingosine (Sph) and the subsequent conversion of sphingosine to sphingosine 1-phosphate (S1P) catalyzed by sphingosine kinases (SK) (Scheme 1.1).

The dynamic balance between ceramide and S1P signalling guides the cell towards either an apoptotic process or a survival process.[5] Thus, stress signalling such as radiation and chemotherapy treatment or by using sphingosine kinase inhibitors (SKIs) drives cancer cells to undergo apoptosis and antiproliferation.[4a] Several cancer treatments often result in the generation of Cer which is implicated in regulating the

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1 a) Ratajczak, M.Z.; Suszynska, M.; Borkowska, S.; Ratajczak, J.; Schneider, G. *Expert. Opin. Ther. Targets* **2014**, *18*, 95-107. b) Ogretmen, B.; Hannun, Y. A. *Nature Rev. Cancer* **2004**, *4*, 604-616. c) Ogretmen, B. *FEBS Lett.* **2006**, 5467-5476.

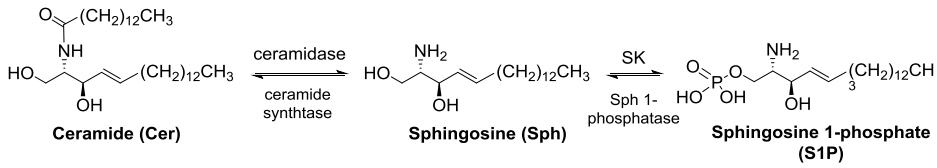
2 "The role of Sphingolipids in Cancer Development and Therapy", Adv. Cancer Res., Norris, J. S. Ed., Academic Press, 2013.

3 a) Truman, J.-P.; García-Barros, M.; Obeid, L.M.; Hannun, Y.A. *Biochim. Biophys. Acta* **2014**, *1841*, 1174-1188. b) Giussani, P.; Tringali, C.; Riboni, L.; Viani, P.;Venerando, B. *Int. J. Mol. Sci.* **2014**, *15*, 4356-4392. c) García-Barros, M.; Coant, N.; Truman, J.-P.; Snider, A.J.; Hannun, Y.A. *Biochim. Biophys. Acta Mol. Cell Biol. Lip.* **2014**, *1841*, 773-782. d) Adan-Gokbulut, A.; Kartal-Yandim, M.; Iskender, G.; Baran, Y. *Curr. Med. Chem.* **2013**, *20*, 108-122. e) Beckham, T. H.; Cheng, J. C.; Marrison, S. T.; Norris, J. S.; Liu, X. *Adv. Cancer Res.* **2013**, *117*, 1-36.

4 a) Morad, S. A.; Cabot, M. C. *Nat. Rev. Cancer* **2013**, *13*, 51-65. b) Orr Gandy, K. A.; Obeid, L. M. *Biochim. Biophys. Acta* **2013**, *1*, 157-166. c) Chalfant, C. E.; Spiegel, S. *J. Cell Sci.* **2005**, *118*, 4605-4612. d) Airola, M.; Hannun, Y.A. *Handb. Exp. Pharmacol.* **2013**, *215*, 57-76. e) Pyne, S.; Pyne, N.J. *Biochem. J.* **2000**, *349*, 385-402.

5 a) Young, M. M.; Kester, M.; Wang, H.-G. *J. Lipid Res.* **2013**, *54*, 5-19. b) Maceyka, M.; Harikumar, K. B.; Milstien, S.; Spiegel, S. *Trends Cell Biol.* **2012**, *22*, 50-60.

cell death response.[6] On the other hand, a shift toward S1P accumulation drives cells to prosurvival, antiapoptosis and/or chemoresistance conditions.[7] In fact, one common survival strategy employed by cancer cells is the synthesis of S1P, formed the phosphorylation of Sph catalised by sphingosine kinases, promoting in this way their growth, survival and metastasis.[8]



Scheme 1.1. General scheme of the sphingolipid metabolism.

Thus, SKs, particularly the SK1 isoform, play a central role as the key enzymes regulating the equilibrium between proapoptotic (Cer/Sph) and promitogenic/prosurvival (S1P), and being responsible for maintaining the balance between these "stop" or "go" signals. This fact makes this kinase an attractive new target in developing effective therapeutics to fight against cancer.[9] Therefore, there has been extensive focus on the development of effective SK inhibitors (SKIs) during the past years. The classes of compounds identified include those derived from sphingolipids, natural products, and nonlipidic small druglike molecules.[10] Mostly, the structural design of SK inhibitors is focused in structure-activity relationship

6 Dimanche-Boitrel, M.-T.; Rebillard, A. *Handb. Exp. Pharmacol.* **2013**, *216*, 73-91.

7 a) Ponnusamy, S.; Meyers-Needham, M.; Senkal, C. E.; Saddoughi, S. A.; Sentelle, D.; Selvam, S. P.; Salas, A.; Ogretmen, B. *Future Oncol.* **2010**, *6*, 1603-1624. b) Jiang, W.; Ogretmen,B. *Biochim. Biophys. Acta Mol. Cell Biol. Lip.* **2014**, *1841*, 783-792.

8 a) Kim, E.S.; Kim, J.S.; Kim, S.G.; Hwang, S.; Lee, C.H.; Moon, A. *J. Cell Sci.* **2011**, *124*, 2220-2230. b) Anelli, V.; Gault, C.R.; Snider, A.J.; Obeid, L.M. *FASEB J.* **2010**, *24*, 2727-2738.

9 a) C.R. Gault, L.M. Obeid, *Crit. Rev. Biochem. Mol. Biol.* **2011**, *46*, 342-351. b) Takabe, K.; Paugh, S. W.; Milstien, S.; Spiegel, S. *Pharmacol. Rev.* **2008**, *60*, 181-195.

10 a) Plano, D.; Amin, S.; Sharma, A.K. J. Med. Chem. **2014**, *57*, 5509-5524. b) Canals, D.; Hannun, Y.A. *Handb. Exp. Pharmacol.* **2013**, *215*, 211-238.

studies using analogues of SK's lipid substrates and is often inspired by the structure of sphingosine.[4b,11]

1.2. VICINAL AMINO ALCOHOLS OVERVIEW

The vicinal aminoalcohol moiety, named also as 1,2-amino alcohol or β-amino alcohol, is among the most important and omnipresent in natural occurring products, synthetic pharmacologically active molecules as well as in ligands for catalytic processes.[12]

Naturally occurring molecules. In this regard, a classification can be made in terms of natural product structure. Thus, naturally occurring amino alcohols can be divided in 1) hydroxy amino acids,[13] such as serine and threonine; 2) lipids and lipid-like molecules[14] as sphingosine and analogues; 3) cyclic amino alcohols,[15] and 4) carbohydrates[16] (Scheme 1.2).

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11 a) Liu, Z.; Macritchie, N.; Pyne, S.; Pyne, N. J.; Bittman, R. *Bioorg. Med. Chem.* **2013**, *21*, 2503-2510. b) Baek, D. J.; MacRitchie, N.; Pyne, N. J.; Pyne, S.; Bittman, R. *Chem. Commun.* **2013**, *49*, 2136-2138. c) Mei, T.-W.; Luo, Y.; Feng, X.-J.; Lu, W.; Yang, B. *Tetrahedron* **2013**, *69*, 2927-2932.

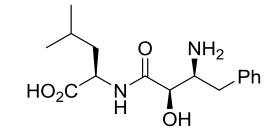
12 Bergmeier, S. C. *Tetrahedron* **2000**, *56*, 2561-2576.

13 a) Bergmeier, S. C.; Stanchina, D. M. *J. Org. Chem.* **1999**, *64*, 2852-2859. b) Stratmann, K.; Burgoyne, D. L.; Moore, R. E.; Patterson, G. M. L. Smith, C. D. *J. Org. Lett.* **1994**, *59*, 7219-7226.

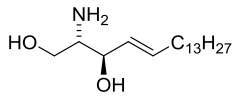
14 a) Morales-Serna, J. A.; Llaveria, J.; Díaz, Y.; Matheu, M. I.; Castillón, S. *Curr. Org. Chem.* **2010**, *14*, 2483-2521. b) Koskinen, P. M.; Koskinen, A. M. P. *Synthesis* **1998**, 1075-1091.

15 a) Kobayashi, J.; Cheng, J.-F.; Ishibashi, M.; Walchii, M. R.; Yamamura, S. Ohizumi, Y. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1135-1137. b) Kobayashi, S.; Ueno, M.; Suzuki, R.; Ishitani, H. *Tetrahedron Lett.* **1999**, *40*, 2175-2178.

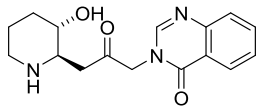
16 a) Beisler, J. A. *Prg. Med. Chem.* **1982**, *19*, 247-268. b) Lown, W. *Anthracycline and Anthracendione-Based Anti-cancer Agents*, Elsevier: Amsterdam, 1988.



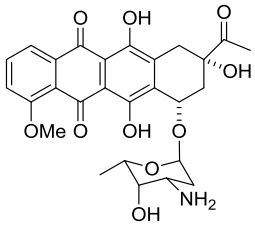
Bestatin (hydroxyl amino acid)



Sphingosine (Lipid-derivative)



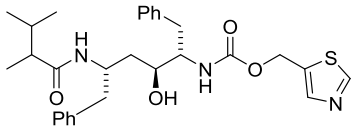
Febrifugine (cyclic amino alcohol)



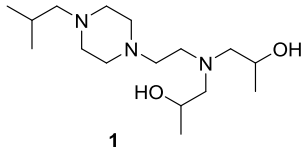
Daunomycin (carbohydrate derivative)

Scheme 1.2. Examples of naturally occurring compounds containing vicinal amino alcohols.

Synthetic pharmacologically active molecules. Typical examples include Saquinavir, a HIV protease inhibitor, and amidine **1**, an inhibitor of nitric oxide synthetase and also important for the treatment of several diseases (Scheme 1.3). The strong relation discovered between the aminoalcohol moiety and the biological activity of such molecules empowered the efforts towards the development of methodologies for the synthesis of vicinal amino alcohols.



Saquinavir



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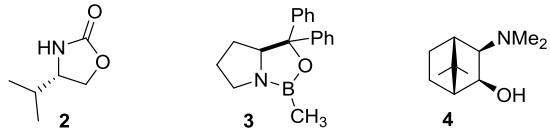
Scheme 1.3. Synthetic pharmacologically active molecules containing vicinal amino alcohols.

Ligands and chiral auxiliaries. Probably the most famous vicinal amino alcohol derived chiral auxiliaries are the Evans auxiliaries such as **2** (Scheme 1.4).[17] Other

[17] Evans, D. A.; Tedrow, J. S.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2002**, *124*, 392-393.

remarkable examples are oxazaborilidines (**3**),[18] used for the asymmetric reduction of carbonyl compounds, and also chiral ligand **4**, developed by Noyori for the enantioselective catalytic organozinc additions to carbonyl compounds.[19]



Scheme 1.4. Common vicinal amino alcohol-based chiral auxiliaries and ligands.

1.3. UNSATURATED AMINO ALCOHOLS

The presence of a double bond in the vicinal amino alcohol moiety is of doubtless repercussion on the synthetic versatility of a compound due to the large derivatisation potential of double bonds. It is important to clarify that the present thesis is focused on the preparation of α,β-unsaturated amino alcohols, which will be named as unsaturated amino alcohols.

Unsaturated vicinal amino alcohols are intermediates in the preparation of a wide range of pharmacologically active compounds. The most relevant examples include the preparation of JNK3 inhibitors,[20] DNJ analogues[21] and Dopamine D2 receptor antagonist[22] among others.[23]

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18 Parker, K. A.; Ledeboer, M. W. *J. Org. Chem.* **1996**, *61*, 3214-3217.

19 a) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757-824. b) Noyori, R.; Suga, S.; Kawai, S. K.; Okada, S.; Kitamura, M. *Pure Appl. Chem.* **1988**, *60*, 1597-1606.

20 Rech, J. C.; Yato, M.; Duckett, D.; Ember, B.; LoGrasso, P. V.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 490-491.

21 a) Pearson, M. S. M.; Mathé-Allainmat, M.; Fargeas, V.; Lebreton, J. *Eur. J. Org. Chem.* **2005**, 2159-2191. b) Afarinkia, K.; Bahar, A. *Tetrahedron: Asymmetry* **2005**, *16*, 1239-1287. c) Pearson, M. S. M.; Saad, R. O.; Dintinger, T.; Amri, H.; Mathé-Allainmat, M.; Lebreton, J. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3262-3267. d) Felpin, F.-X.; Boubekeur, K.; Lebreton, J. *J. Org. Chem.* **2004**, *69*, 1497-1503.

22 Harris, M. C. J.; Jackson, M.; Lennon, I. C.; Ramsden, J. A.; Samuel, H. *Tetrahedron Lett.* **2000**, *41*, 3187-3191.

Due to the biological role of unsaturated vicinal amino alcohols, in addition with the intrinsic potential that possess for drug discovery, developing new methods targeting these type of compounds have attracted the interest of researchers. In this section the most relevant methods will be briefly presented.

One of the most efficient and versatile approaches to unsaturated 1,2-amino alcohols is the intramolecular C-H amination reaction of homoallyl carbamates and *N*-tosylcarbamates. In this sense two main research fields have gained more relevance: metal-catalysed nitrene insertion reactions to C-H sp^3 or sp^2 bonds, and metal-catalysed oxidative cyclisation reactions.

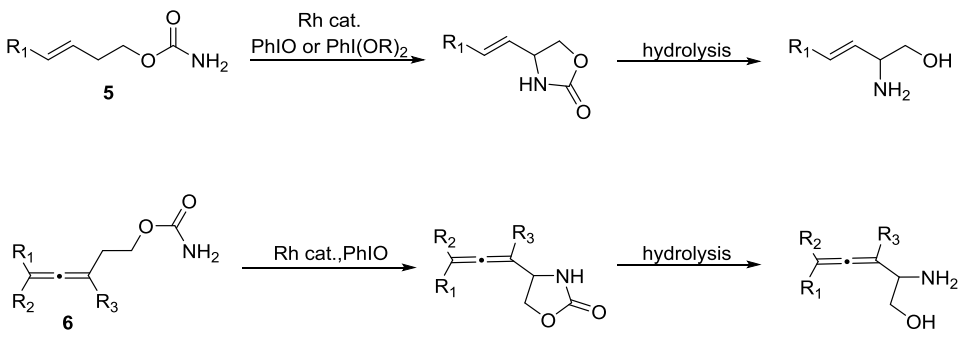
Nitrene insertion reactions will be deeply discussed in Chapter 3, therefore only key examples will be provided as a general overview. In this regard, in 2001, Du Bois and co-workers published the synthesis of oxazolidinones from the rhodium-catalysed intramolecular C-H amination of carbamates.[24] This work became a reference for the following explosion of interest in the development of methods for C-H amination and aziridination reactions. Thus, based on the conditions found by Du Bois, formation of unsaturated 1,2-amino alcohols have been accomplished by the means of metal-catalysed intramolecular C-H amination of homoallylic cabamates (**5**) and intramolecular aziridination of carbamate-derivatised allylic allenes (**6**) (Scheme 1.5).[25]

---

[23] a) Imashiro, R.; Sakurai, O.; Yamashita, T.; Horikawa, H. *Tetrahedron* **1998**, *54*, 10657-10670. b) Felpin, F.-X.; Lebreton, J. *Tetrahedron Lett.* **2003**, *44*, 527-530. c) Felpin, F.-X.; Boubekeur, K.; Lebreton, J. *Eur. J. Org. Chem.* **2003**, 4518-4527.

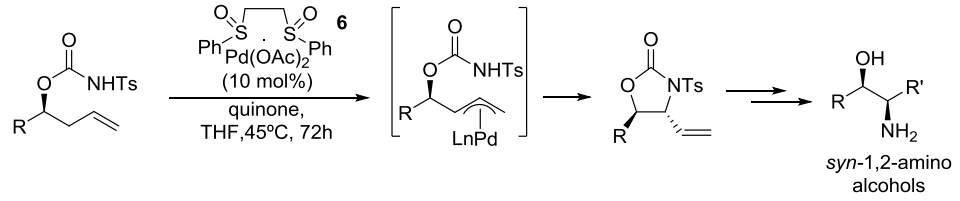
[24] Espino, C. G.; Du Bois, J. *Angew. Chem. Int Ed.* **2001**, *40*, 598-600.

[25] Examples will be provided in Chapter 3.



Scheme 1.5. Obtaintion of unsaturated vicinal amino alcohols by nitrene insertion reactions.

Concerning metal-catalysed oxidative amination reactions, an important contribution was made by White and co-workers (Scheme 1.6).[26] In that work the authors demonstrated that the combination of simple $Pd(OAc)_2$ with sulfoxide ligand **6** enabled the diastereoselective allylic C-H amination of readily available homoallylic *N*-tosylcarbamates to render exclusively *anti*-oxazolidinones which, in turn, can be easily transformed into *syn*-amino alcohols. They also showed the synthetic potential of the obtained oxazolidinones, which can be further elaborated to a wide range of medically and biologically active *syn*-vicinal aminoalcohols.

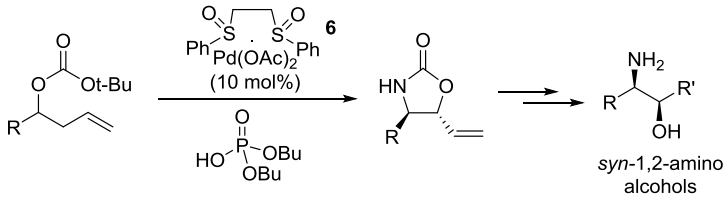


Scheme 1.6. Pd(II)-catalysed diastereoselective intramolecular C-H amination developed by White.

A similar system was used by the same group to obtain regioisomeric oxazolidinones from those obtained in the C-H amination process described in Scheme 1.6. Thus the combination of a Pd(II) catalyst with bis-sulfoxide **6** and a

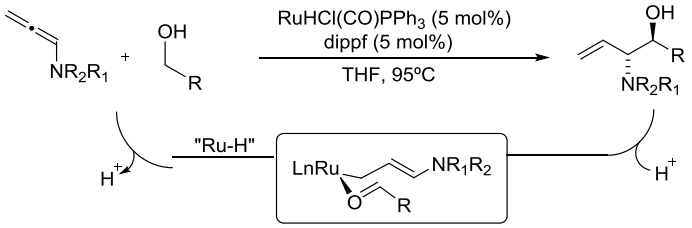
[26] Fraunhoffer, K. J.; White, M. C. *J. Am. Chem. Soc.* **2007**, *129*, 7274-7276.

phosphoric acid derivative allowed to transform unsaturated *N*-Boc amines into oxazolidinones through allylic C-H oxidation (Scheme 1.7).[27]



Scheme 1.7. Pd(II)/Bis-sulfoxide/Bronsted acid co-catalysed allylic C-H oxidation of unsaturated *N*-Boc amines.

Alternatively, *anti*-1,2-amino alcohols can be selectively obtained by the means of a ruthenium-catalysed alcohol-allene C-C coupling under transfer hydrogenation conditions (Scheme 1.8).[28] This procedure developed by Krische and co-workers allowed the direct diastereoselective obtantion of *anti*-amino alcohols from the exposure of alcohols to allenamides in the presence of $RuHCl(CO)(PPh_3)_3$ and dippf.

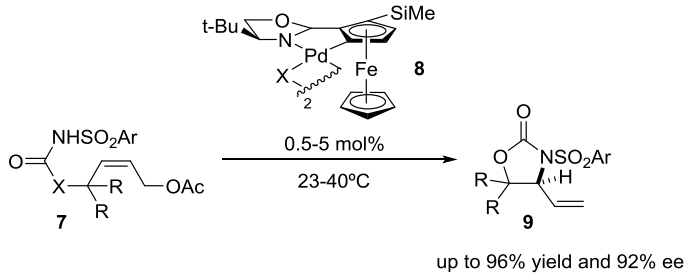


Scheme 1.8. Ru-catalysed carbonyl *anti*-aminoallylation between alcohols and allenamides.

Another widely used strategy towards unsaturated amino alcohols is the intramolecular palladium(II)-promoted addition of nitrogen nucleophiles to olefins (aminopalladation).[29] An example of particular interest is the work by Overman and Remarchuk on the enantioselective synthesis of vinyl-substituted oxazolidinones (**9**)

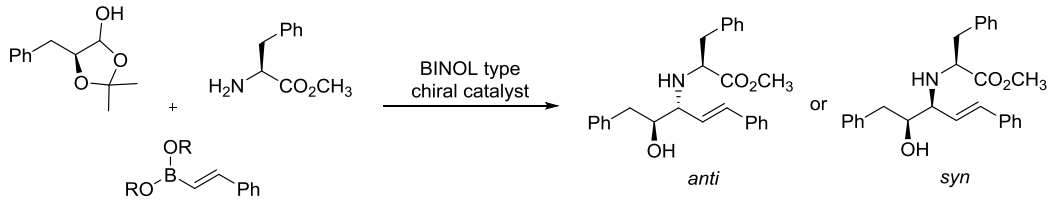
[27] Osberger, J. T.; White, M. C. *J. Am. Chem. Soc.* **2014**, *136*, 11176-11181.
[28] Zbieg, J. R.; Mclnturff, E. L.; Krische, M. J. *Org. Lett.* **2010**, *12*, 2514-2516.
[29] Hirai, Y.; Watanabe, J.; Nozaki, T.; Yokoyama, H.; Yamaguchi,S. *J. Org. Chem.* **1997**, *62*, 776-777 and references therein.

via intramolecular aminopalladation of *N*-tosylcarbamate acetate **7** using ferrocenyloxazoline palladacycle **8** as catalyst (Scheme 1.9).[30]



Scheme 1.9. Enantioselective synthesis of oxazolidinones by Pd-catalysed intramolecular aminopalladation of *N*-tosylcarbamate acetates.

The Petasis Borono-Mannich reaction, a multicomponent reaction of boronic acids, amines and aldehydes, is also an attractive alternative to selectively obtain unsaturated vicinal amino alcohols from a wide range of starting materials.[31] The reaction is intrinsically *anti*-selective, which can be understood as an advantage in terms of selectivity or as a scope limitation.



Scheme 1.10. Diastereoselective Petasis reaction to afford either *anti*- or *syn*-vicinal amino alcohols.

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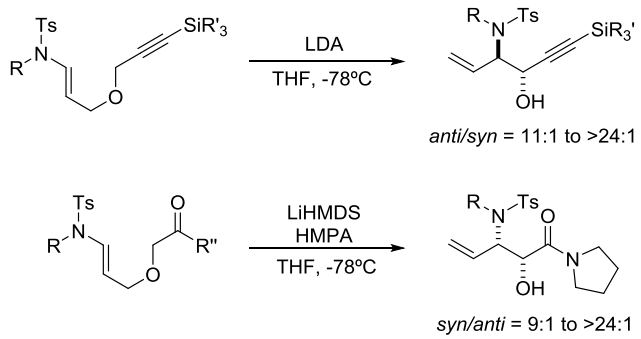
30 Overman, L. E.; Remarchuk, T. P. *J. Am. Chem. Soc.* **2002**, *124*, 12-13.

31 For reference publications see: a) Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1998**, *120*, 11798-11799. b) Candeias, N. R.; Montalbano, F.; Cal, P. M. S. D.; Gois, P. M. P. *Chem. Rev.* **2010**, *110*, 6169-6193.

Scheme 1.10. Diastereoselective Petasis reaction to afford either *anti*- or *syn*-vicinal amino alcohols.

Unsaturated 1,2-amino alcohols have also been prepared by the means of sigmatropic rearrangements.[33] These procedures allow a good control of the diastereoselectivity but require more elaborated starting materials compared to the previously discussed methodologies.

An example of these type of procedures are the [2,3]-Wittig Rearrangements. In this direction, Meyer developed a useful strategy for the stereoselective preparation of unsaturated amino alcohols from 3-aza-allylic alcohol derivatives.[33c,d,e] It was observed that the *anti*- or *syn*-selectivity could be governed depending on whether the anion stabilising group was an alkyne (*anti*) or an amide (*syn*) (Scheme 1.11).

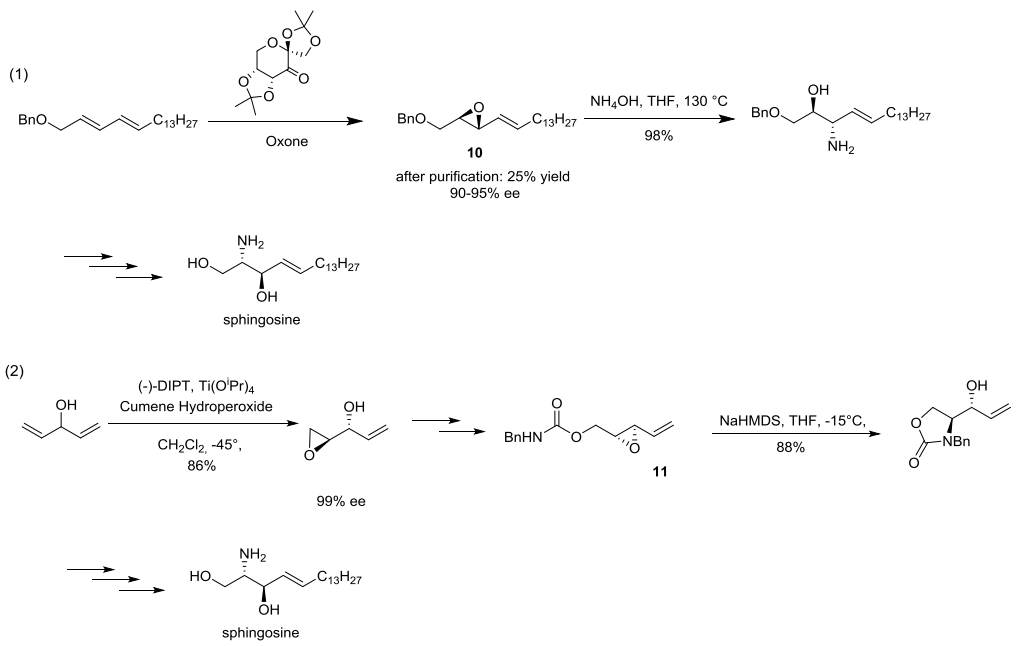


Scheme 1.11. Diastereoselective synthesis of 1,2-amino alcohols by [2,3]-Wittig Rearrangements.

Probably the most classical route towards unsaturated 1,2-amino alcohols is the ring-opening of vinyl epoxides (**10** and **11**, Scheme 1.12) with nitrogen

[33] Aza-Claisen Rearrangement: a) Flanning, K. N.; Jamieson, A. G.; Sutherland, A. *Org. Biomol. Chem.* **2005**, *3*, 3749-3756. b) Swift, M. D.; Sutherland, A. *Tetrahedron Lett.* **2007**, *48*, 3771-3773. [2,3]-Wittig Rearrangements: c) Barbazanges, M.; Meyer, C.; Cossy, J. *Org. Lett.* **2007**, *9*, 3245-3248. d) Barbazanges, M.; Meyer, C.; Cossy *Tetrahedron Lett.* **2008**, *49*, 2902-2906. e) Barbazanges, M.; Meyer, C.; Cossy, J.; Turner, P. *Chem. Eur. J.* **2011**, *17*, 4480-4495.

nucleophiles.[34] This methodology greatly benefits from the development of the asymmetric epoxidation of alkenes by Sharpless[35] and Shi.[36] Concretely, this strategy became a milestone for the fructification of various synthesis of sphingosine derivatives during the past decade, particularly those developed by Somfai and co-workers (Scheme 1.12).[34e,f]



Scheme 1.12. Different routes to D-*erithro*-sphingosine through asymmetric epoxidation followed by ring-opening with *N*-nucleophile. (1) Shi epoxidation. (2) Sharpless epoxidation.

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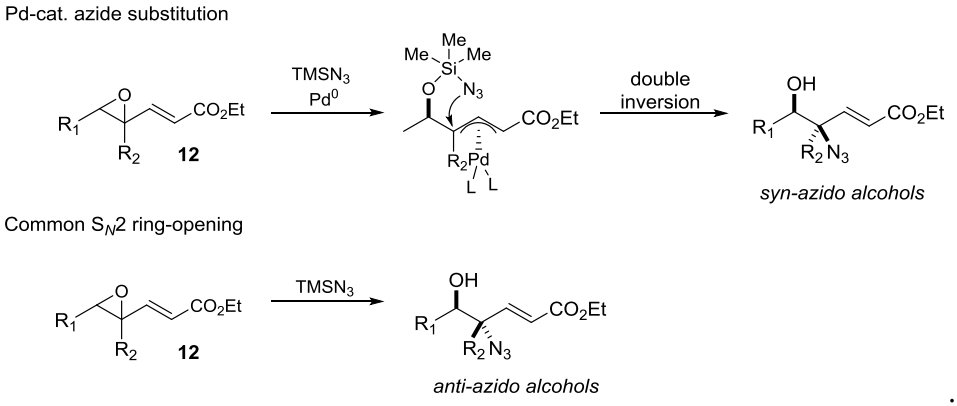
[34] a) Lindstroem, U. M.; Somfai, P. *J. Am. Chem. Soc.* **1997**, *119*, 8385-8386. b) Lindstroem, U. M.; Somfai, P. *Synthesis* **1998**, 109-117. c) Romero, A.; Wong, C.-H. *J. Org. Chem.* **2000**, *65*, 8264-8268. d) Olofsson, B.; Somfai, P. *J. Org. Chem.* **2002**, *67*, 8574-8583. e) Olofsson, B; Somfai, P. *J. Org. Chem.* **2003**, *68*, 2514-2517. f) Torssell, S.; Somfai, P. *Org. Biomol. Chem.* **2004**, *2*, 1643-1646.

[35] a) Gao, Y.; Klunder, J. M.; Hanson, R. M.; Masamune, H.; Ko, S. Y; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765-5780. For a review see: b) Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*, Ojima, I., Ed.; VCH: New York, **1993**, 103-158.

[36] a) Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224-11235. For a review see: b) Wong, O.; Shi, Y. *Chem. Rev.* **2008**, *108*, 3958-3987.

Since the nucleophilic ring-opening of epoxides follows a S_N2 mechanism, the resulting amino alcohols will invariably be obtained as the *anti* isomer. However, some modifications can be added in order to force obtaining the *syn* isomer as in the Pd-catalysed azide substitution of α,β-unsaturated γ,δ-epoxy esters **12** (Scheme 1.13) reported by Miyashita *et al.*[37] This method involves two consecutive S_N2 processes, namely initial π-allyl palladium formation and azide substitution, which allows the stereoselective formation of *syn*-azido alcohols from unsaturated *trans*-epoxy esters, and *anti*-azido alcohols from unsaturated *cis*-epoxy esters.[38]



Scheme 1.13. Comparison of the stereochemical outcome of the normal S_N2 azidolysis of epoxides with the Pd-catalysed process.

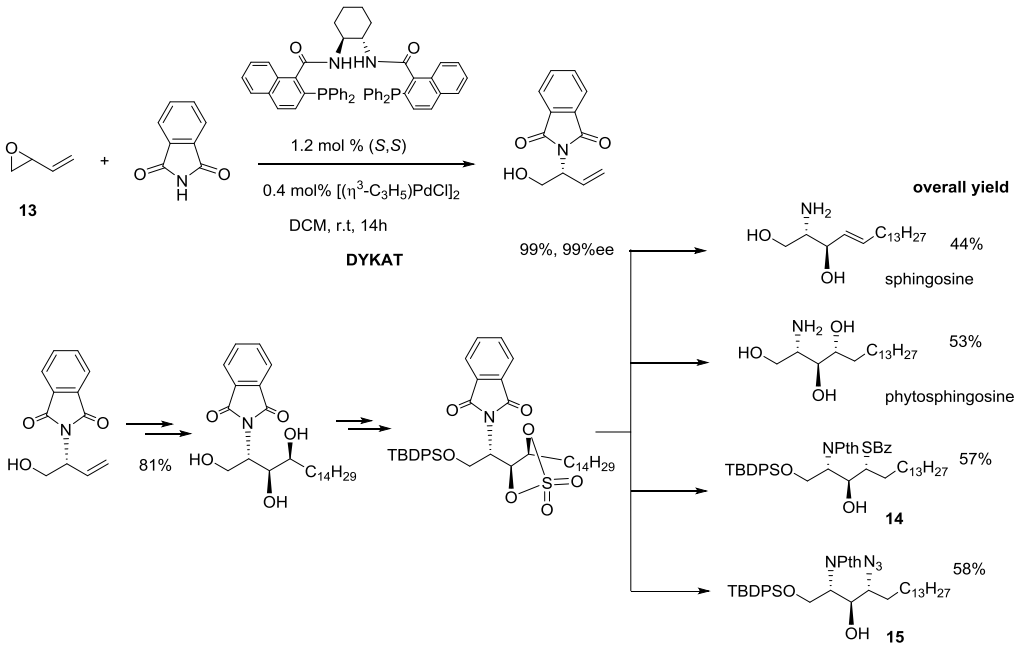
Another key synthetic tool to prepare chiral unsaturated amino alcohols is the Pd-catalysed Dynamic Kinetic Asymmetric Transformation (DYKAT) of butadiene monoepoxide (**13**, Scheme 1.14) in the presence of nitrogen nucleophiles developed by Trost and co-workers.[39] This methodology was implemented in our group for

[37] Miyashita, M.; Mizutani, T.; Tadano, G.; Iwata, Y.; Miyazawa, M.; Tanino, K. *Angew. Chem Int. Ed.* **2005**, *44*, 5094-5097.

[38] Righi, G.; Manni, L. S.; Bovicelli, P.; Pelagalli, R. *Tetrahedron Lett.* **2011**, *52*, 3895-3896.

[39] a) Trost, B. M.; Bunt, R.C.; Lemoine, R.C.; Calkins, T.L. *J. Am. Chem. Soc.* **2000**, *122*, 5968-5976. b) Trost, B. M.; Horne, D. B.; Woltering, M. J. *Angew. Chem. Int. Ed.* **2003**, *42*, 5987-5990.

synthesising sphingosine, phytosphingosine, and 4-substituted derivatives (**14** and **15**).[40]



Scheme 1.14. Synthesis sphingosine, phytosphingosine, and 4-substituted derivatives.

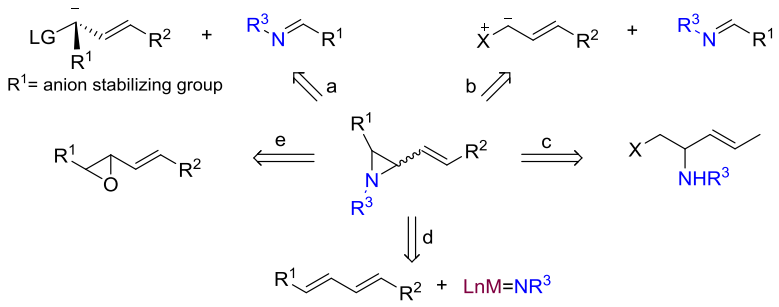
If the ring-opening of vinyl epoxides is a useful way to prepare unsaturated 1,2-amino alcohols, the same should be applicable to the ring-opening of vinyl aziridines with oxygen nucleophiles. The most common family of methods to prepare vinyl aziridines are summarized in Scheme 1.15.[41] One of the oldest and more flexible methods is the Aza-Darzens reaction (path a, Scheme 1.15).[42] Another widely used

[40] Llaveria, J.; Diaz, Y.; Matheu, M. I.; Castillón, S. *Org. Lett.* **2009**, *11*, 205-208.

[41] a) Aziridines and Epoxides in Organic Synthesis; Yudin, A. K., Ed.; Wiley-VCH; Weinheim, Germany, **2006**. b) Ohno, H. *Chem. Rev.* **2014**, *114*, 7784-7814.

[42] a) Sweeney, J. *Eur. J. Org. Chem.* **2009**, 4911-4919. b) Williams, A. L.; Johnston, J. N. *J. Am. Chem. Soc.* **2004**, *126*, 1612-1613. c) Concellón, J. M.; Rodríguez-Solla, H.; Simal, C. *Org. Lett.* **2008**, *10*, 4457-4460.

method is the reaction between an allylic ylide and imines (Scheme 1.15, path b).[43] Generally, these two methods afford the thermodynamically more stable *cis* aziridines[44] although *trans* aziridines can be obtained through the ylide route driving the reaction under kinetic control conditions.[45] Vinyl aziridines can also be prepared from the ring opening of vinyl epoxides with azides (Scheme 1.15, path e) and, in a similar fashion, from 1,2-haloamines (Scheme 1.15, path c).[46]



Scheme 1.15. Methods to synthesise vinylaziridines.

Although in some cases the aforementioned methods resulted highly effective in terms of yield and stereoselectivity, the absence of methods able to provide vinyl aziridines from readily available or commercial starting materials in a stereoselective fashion like Sharpless and Shi epoxidation, is still a handicap for the synthetic usefulness of vinyl aziridines. The addition of nitrenes to dienes (Scheme 1.15, path d) has great potential towards this goal. However, direct aziridination of dienes through addition of nitrenes to alkenes must deal with the troublesome control of the regioselectivity and stereoselectivity of the process. In this regard, as a result of a collaboration between our and Pérez's group, a metal-catalysed aziridination of

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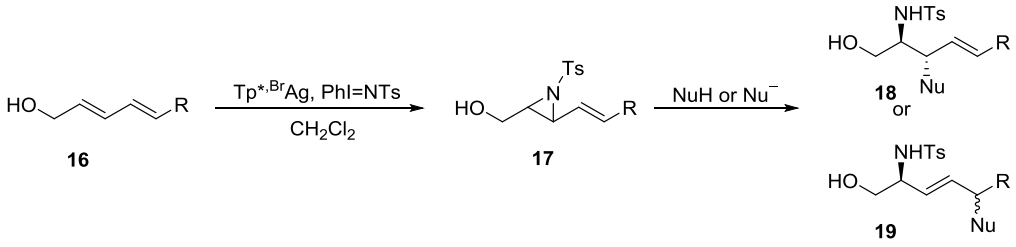
43 a) Zhu, B.-H.; Zheng, J.-C.; Yu, C.-B.; Sun, X.-L.; Zhou, Y.-G.; Shen, Q.; Tang, Y. *Org. Lett.* **2010**, *12*, 504-507. b) Aggarwal, V. K.; Alonso, E.; Fang, G.; Ferrara, M.; Hynd, G., Porcelloni, M. *Angew. Chem. Int. Ed.* **2001**, *40*, 1433-1436.

44 a) Ibuka, T.; Mimura, N.; Ohno, H.; Nakai, K.; Akaji, M.; Habashita, H.; Tamamura, H.; Miwa, Y.; Taga, T.; Fujii, N. Yamamoto, Y. *J. Org. Chem.* **1997**, *62*, 2982-2991. b) Ibuka, T.; Mimura, N.; Aoyama, H.; Akaji, M.; Ohno, H.; Miwa, Y.; Taga, T.; Nakai, K.; Tamamura, H.; Fujii, N. *J. Org. Lett.* **1997**, *62*, 999-1015

45 Yang, X.-F.; Zhang, M.-J.; Hou, X.-L.; Dai, L.-X. *J. Org. Chem.* **2002**, *67*, 8097-8103.

46 Watson, I. D. G.; Yu, L.; Yudin, A. K. *Acc. Chem. Res.* **2006**, *39*, 194-206.

dienols (**16**, Scheme 1.16) was developed, which enabled, using a silver homoscorpionate complex ($Tp^{Br}Ag$) as catalyst, the stereo- and regioselective transformation of various dienols into their corresponding hydroxy vinyl aziridines (**17**).[47] Those vinyl aziridines could then be ring openend with various nucleophiles providing a fast route towards distinctly functionalised racemic unsaturated vicinal amino alcohols (**18** and **19**).



Scheme 1.16. Regio-and stereoselective conversion of allylic dienols into hydroxyl vinyl aziridindes via nitrene addition to alkenes.

[47] a) Llaveria, J., Beltrán, A., Díaz-Requejo, M. M., Matheu, M. I., Castillón, Pérez, P. J. *Angew. Chem. Int. Ed.* **2010**, *49*, 7092-7095. b) Llaveria, J.; Beltran, A.; Sameera, W. M. C.; Locati, A.; Díaz-Requejo, M. M.; Matheu, M. I.; Castillón, S.; Maseras, F.; Pérez, P. J. *J. Am. Chem. Soc.* **2014**, *136*, 5342-5350.

UNIVERSITAT ROVIRA I VIRGILI
REGIO- AND ENANTIOSELECTIVE SYNTHESIS OF UNSATURATED AMINO ALCOHOLS, AMINO KETONES AND DIAMINES AS VALUABLE INTERMEDIATES IN ORGANIC SYNTHESIS.
Joan Guash Savidó
Dipòsit Legal: T 1366-2015

CHAPTER 2

OBJECTIVES OF THIS Ph.D WORK

UNIVERSITAT ROVIRA I VIRGILI
REGIO- AND ENANTIOSELECTIVE SYNTHESIS OF UNSATURATED AMINO ALCOHOLS, AMINO KETONES AND DIAMINES AS VALUABLE INTERMEDIATES IN ORGANIC SYNTHESIS.
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The present PhD work has two different objectives; 1) to develop new synthetic procedures for obtaining distinctly functionalised unsaturated aminoalcohols in a regio- and enentioselective manner, and 2) to synthesise enantioenriched α-arylamino ketones and 1,2-diamines from α-arylamino hydrazones obtained by enantioselective intermolecular nucleophilic α-amination of azoalkenes

1. This first objective is part of a more general objective in our group that aims to prepare sphingosine and ceramide analogues as downstream receptor agonists and sphingosine and ceramide-metabolizing enzyme inhibitors. The results of this work were divided in two parts:

a) Regioselective intramolecular aziridination/ aziridine opening of 2,4-dien-1-ol derivatives (Chapter 3), and

b) Organocatalyzed kinetic resolution of the oxazolidone products obtained in Chapter 3 (Chapter 4).

1a) The research described in Chapter 3 aims to develop a regio- and stereoselective synthesis of unsaturated amino alcohols through intramolecular aziridination and ring opening of substituted dienols. Therefore, the specific objectives of this chapter are:

- Identify the most suitable nitrogen-donor functional group for the intramolecular aziridination of dienols.
- Optimization of the conditions for the intramolecular aziridination of dienols.
- Investigate the aspects that control the regioselectivity in the ring opening of vinyl aziridines.
- Synthesis, on the basis of the intramolecular aziridination protocol, of unsaturated vicinal amino alcohol with *O*-, *N*- and *S*-substituents.
- Explore chiral catalyst for an asymmetric intramolecular aziridination

1b) The research described in Chapter 4 aims to develop an enantioselective synthesis of unsaturated amino alcohols through kinetic resolution of oxazolidinones. Therefore, the specific objectives of this chapter are:

- Explore the enantioselective organocatalysed acylation of oxazolidinones with acyl substituents at position 3 and 5.
- Apply the optimized conditions to the kinetic resolution of oxazolidinones having *N*- and *S*-substituents.
- Apply the before mentioned methodology to the enantioselective synthesis of sphingosine.

2. The research described in Chapter 5 is independent to the general objective presented above and was developed during a doctoral stage at the University of California (Berkeley) under the supervision of Professor Dean F. Toste. It aims to prepare enantioenriched α-arylamino ketones and 1,2-diamines from α-arylamino hydrazones synthesized by enantioselective intermolecular nucleophilic α-amination of azoalkenes. Therefore, the specific objectives of this chapter are:

- To synthesise a set of racemic α-arylamino hydrazones.
- To explore methodologies that provide, in high yield, racemic α-arylamino ketones and diamines from racemic α-arylamino hydrazones.
- To synthesise enantioenriched α-arylamino hydrazones.
- To convert enantioenriched α-arylamino hydrazones into α-arylamino ketones and diamines, avoiding racemization processes.

CHAPTER 3

REGIO- AND STEREOSELECTIVE SYNTHESIS OF UNSATURATED AMINO ALCOHOLS THROUGH INTRAMOLECULAR AZIRIDINATION

UNIVERSITAT ROVIRA I VIRGILI
REGIO- AND ENANTIOSELECTIVE SYNTHESIS OF UNSATURATED AMINO ALCOHOLS, AMINO KETONES AND DIAMINES AS VALUABLE INTERMEDIATES IN ORGANIC SYNTHESIS.
Joan Guash Savidó
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3.1. INTRODUCTION

3.1.1. STUCTURAL AND CHEMICAL PROPERTIES OF AZIRIDINES

Aziridines are three-membered nitrogen containing heterocycles. The aziridine structural motif is present in a number of bioactive compounds such as mitomycin C and azinomycin. However, is their ability to undergo regio- and stereoselective ring opening reactions what makes aziridines attractive for synthetic chemists as invaluable building blocks. Like in all the rich mosaic of chemical entities, their particular structural properties will configure their reactivity pattern.[48]

The main feature affecting the reactivity is the strain associated with their three-membered ring nature. The C-C-N system possesses sp^3 hybridation, therefore the lowest energy conformation would require a 109.5º angle between atoms that is far from the 60º angle present in a three-membered ring. This pronounced strain is behind the susceptibility of aziridines to have the C-N bond cleaved through ring opening or cycloaddition reactions.[49]

Another important factor building the reactivity of aziridines is the nature of the N-substituent. In this sense, aziridines can be divided in two main groups: activated and non-activated towards nucleophilic attack. Thus, activated aziridines are considered those in which the aziridine nitrogen is part of an amide-, carbamate-, sulfamate- or sufonamide-functionality, whereas non-activated are those with either proton-, alkyl or aryl-*N*-substituent (Figure 3.1).

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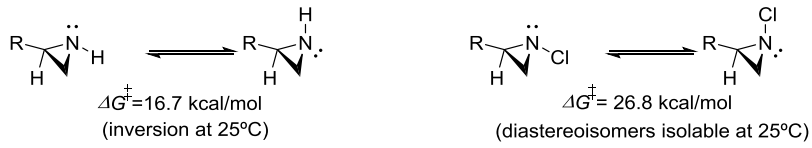
[48] For general books and reviews see: a) *Aziridines and Epoxides in Organic Synthesis;* Yudin, A. K., Ed.; Wiley-VCH: Weinheim, Germany, **2006**. b) Sweeney, J. B. *Chem. Soc. Rev.* **2002**, *31*, 247-258. c) Zwanenburg, B.; ten Holte, P. *Top. Curr. Chem.* **2001**, *216*, 93-124. d) Tanner, D. *Angew. Chem. Int Ed.* **1994**, *33*, 599-619.

[49] Pearson, W. H.; Lian, B. W. ; Bergmeier, S. C. *Aziridines and Azirines: Monocyclic*. Pergamon: Oxford, **1996**; p 1-60.

Figure 3.1. Activated and non-activated aziridines.

The use of the term activated and non-activated is easily rationalised in terms of leaving group ability of the aziridine nitrogen upon nucleophilic attack. Those substituents able to more effectively stabilise the generated negative charge will be the ones rendering more labile aziridines. On the contrary, strong σ-donor alkyl groups clearly destabilise the generation of a negative charge on the nitrogen, making the aziridine considerably resistant to ring opening. In fact these kinds of non-activated aziridines can even behave as nucleophiles.[50] Thus, despite the high ring strain energy, unactivated aziridines are generally not extremely susceptible to ring opening via nucleophilic attack.

Apart from having an effect on the ring opening, the *N*-substituent also plays a role in the inversion barrier of nitrogen being directly proportional to the electronegativity of the substituent. This gives rise to two distinguishable invertomers: one with *cis* disposition of the two substituents, and the other with the substituents in *trans* relationship (Scheme 3.1).[48 b,51]



Scheme 3.1. Nitrogen inversion barrier of aziridine as a function of the N-substituent.

[50] a) Hodgson, D. M.; Humphreys, P. G.; Hughes, S. P. *Pure Appl. Chem.* **2007**, *79*, 269-279. b) Kim, Y.; Ha, H.-J.; Yun, S. Y.; Lee, W. K. *Chem. Commun.* **2008**, 4363-4365.

[51] Deyrup, J. A.. *The Chemistry of Heterocyclic Compounds*, Hassner, A., Ed.; John Wiley and Sons: New York, **1983**, Vol 42, part1, pp 1-215.

3.1.2. NITRENES AND IMINOIODANES

Among all the existing methods for preparing aziridines, the addition of nitrenes to an olefin is the most attractive due to the ready availability of olefinic starting materials and the direct nature of the process.[48a]

Nitrenes are molecular fragments that possess a monovalent nitrogen atom with a sextet of electrons, which makes them electrophilic.[52] The generation of nitrenes is generally accomplished by thermal or photochemical decomposition of azides upon nitrogen loss. They can exist in two possible structures (Figure 3.2), the first with the free electrons paired and a vacant orbital (singlet nitrene) and the other with the free electrons unpaired (triplet nitrene). The triplet state is the ground energy state whereas the singlet is the first excited state.

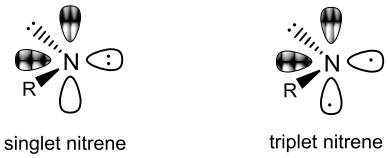
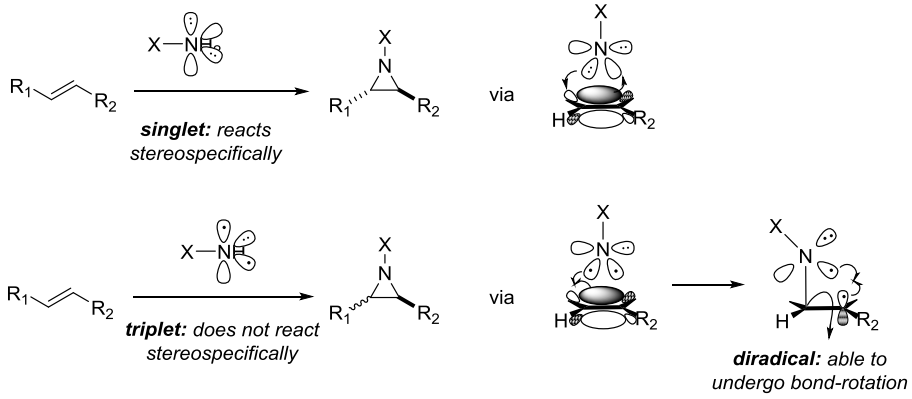


Figure 3.2. Electronic structure of triplet and singlet nitrenes

Nitrenes have become a useful tool for the formation of C-N bonds through either the aziridination of alkenes or the C-H amination of alkanes.[53] In the case of the aziridination reaction, which is classified as a nitrene addition (cycloaddition) to a double bond, a simplified general mechanism is depicted in Scheme 3.2. In this reaction the electronic state (singlet or triplet) is not innocuous, since has an important role on the stereoselective outcome of the reaction. Thus, from the singlet state, the addition takes place in a concerted fashion leading to a stereospecific process. On the other hand, the addition from the triplet state takes place in a two step process involving radicals, which are the responsible for the loss of stereoselectivity

[52] Horner, L.; Christmann, A. *Angew. Chem. Int. Ed.* **1963**, *2*, 599-608.
[53] Dequirez, G.; Pons, V.; Dauban, P. *Angew. Chem. Int. Ed.* **2012**, *51*, 7384-7395.

upon bond rotation (Scheme 3.2). It is worth pointing that this is the general view of the aziridination process and that recent mechanistic studies provided a more complex scenario as it will be discussed further in this introduction section.[48b]

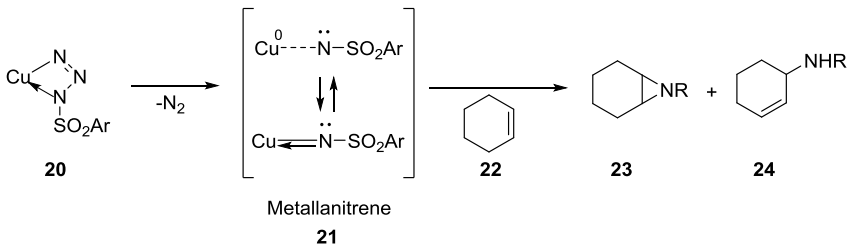


Scheme 3.2. General view of the nitrene addition to a double bond.[48b]

One of the major limitation of working with nitrenes is that free nitrenes are highly unstable. This can be explained taking into account that the nitrogen, as previously pointed, has a sextet of electrons, which makes it prone to react in order to attain the octet of electrons. In this concerns, the common reactions of nitrenes are isomerisation, insertion reactions and additions to nucleophilic reagents. The easiness of nitrenes to react in different manners is responsible for the low yields and selectivities suffered by aziridination based on the addition of nitrenes to olefins. As a matter of fact, in order to take advantage of the synthetic potential of nitrenes, it was necessary to find the way to control their reactivity.

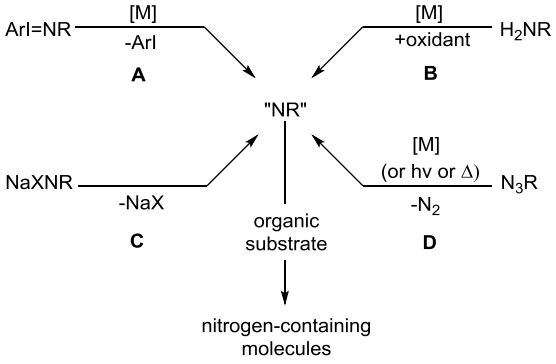
In this sense, Kwart and Kahn, in 1967, showed that copper powder could catalyse the decomposition of benzenesulfonyl azide (**20**) in a cyclohexene (**22**) solution (Scheme 3.3).[54] The products identified (**23** and **24**) suggested the formation of a copper-nitrene complex (**21**), generally known as metallanitrene.

[54] Kwart, H.; Kahn, A. A. *J. Am. Chem. Soc.* **1967**, *89*, 1951-1953.



Scheme 3.3. Aziridination and C-H amination products formed by copper-catalysed decomposition of benzenesulfonyl azide in the presence of cyclohexene.

This initial finding demostrated the possibility to stabilise nitrenes with metals but resulted markedly unselective. From that work different methods have been developed towards a controlled nitrene generation and transfer (Scheme 3.4). Among them, the use of iminoiodanes, either isolated (Scheme 3.4, A) or generated *in situ* (Scheme 3.4, B), resulted the most used and successful strategy. Other methods such as the use of Chloramine-T (TsN(Cl)Na), bromamine-T (TsN(Br)Na) and organic azides (RN_3) have also been successfully employed.[55]

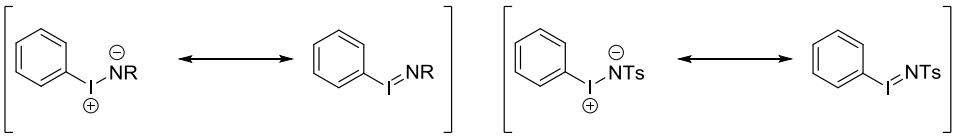


Scheme 3.4. Summary of the methods for the nitrene formation and transfer.[55a]

Iminoiodanes (**25**) are hypervalent iodine (III) reagents. A very simplified explanation of the role of iminoiodanes in nitrene transfer reactions is that, in the

[55] For reviews see: a) Fantauzzi, S.; Caselli, A.; Gallo, E. *Dalton Trans.* **2009**, 5434-5443. b) Driver, T. G. *Org. Biomol. Chem.* **2010**, *8*, 3831-3846.

presence of a metal able to stabilise nitrenes, iminoiodanes can transfer nitrogen, upon loss of iodobenzene, generating a nitrene-metal complex called metallanitrene that then can undergo nitrene transfer reactions to olefins or C-H bonds. The most widely used is [*N*-(*p*-toluenesulfonyl)imino]phenyliodane (PhINTs, **26**, Scheme 3.5).[56]



General structure of iminoiodanes **25** PhINTs **26**

Scheme 3.5. General structure of the iminoiodanes (**25**) and PhINTs (**26**).

The independent works of Breslow and Mansuy, were pioneer showing the ability of iminoiodane reagents as nitrene precursors.[57] They demonstrated that PhINTs could transfer the NTs moiety to Mn(III) and Fe(III) porphyrin complexes. Then the metallanitrenes formed underwent either nitrene insertion to a C-H bond or nitrene addition to a double bond. This initial breakthrough, although lacking of generality, settled the foundation for the reference work by Evans on the copper-catalysed aziridination of alkenes mediated by PhINTs.[58] Evans, and in parallel Jacobsen, identified copper (I) and (II) salts as excellent nitrene deliverers from PhINTs to a double bond. The major contribution from these studies was the scope of substrates that were successfully aziridinated and the stereselectivity of the process in combination with the possibility of an enantioselective approach.[59] From these works it was also drawn the first schematic catalytic cycle for the aziridiantion reaction,

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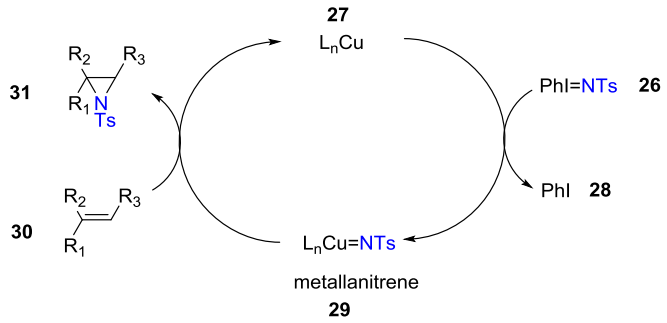
56 Dauban, P.; Dodd, R. *Synlett* **2003**, *11*, 1571-1586.

57 a) Breslow, R.; Gellman, S. H. *J. Chem. Soc. Chem. Commun.* **1982**, 1400-1401. b) Mansuy, D.; Mahy, J.-P.; Dureault, A.; Bedi, G.; Battioni, P. *J. Chem. Soc. Chem. Commun.* **1984**, 1161-1163.

58 a) Evans, D. A.; Faul, M. M.; Bilodeau, M. T. *J. Org. Chem.* **1991**, *56*, 6744-6746.Evans, D. A.; b) Faul, M. M.; Bilodeau, M. T.; Anderson, B. A.; Barnes, D. M. *J. Am. Chem. Soc.* **1993**, *115*, 5328-5329.

59 a) Evans, D. A.; Bilodeau, M. T.; Faul, M. M. *J. Am. Chem. Soc.* **1994**, *116*, 2742-2753. b) Li, Z.; Quan, R. W.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, *117*, 5889-5890.

which is well-accepted as an overview of the process (Scheme 3.6). As commented above, the cycle starts by the interaction between the metal catalyst (**27**) and the iminoiodane **26** (Scheme 3.6). The iminoiodane transfers the NTs moiety to the metal generating a metallanitrene (**29**) and PhI (**28**). This metallanitrene reacts like a nitrene adding to an olefin and releasing an aziridine.



Scheme 3.6. General view of the copper-catalised aziridination using PhINTs

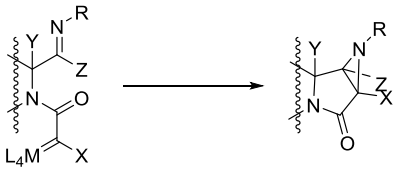
3.1.3. INTRAMOLECULAR AZIRIDINATION

3.1.3.1. BACKGROUND

Intramolecular aziridination has its origin on the initial work of Vedejs in 1987 demonstrating that aziridines could intramolecularly be formed by electrocyclic ring closure of an ester-stabilised azomethine ylide.[60] During the second half of the nineties, McMills and co-workers reported the intramolecular generation of aziridines (**33**, Scheme 3.7) via rhodium(II)-catalysed [2 + 1] cycloaddition reaction of α-diazoamides with tethered oximino-ethers (**32**, Scheme 3.7).[61] The substrate

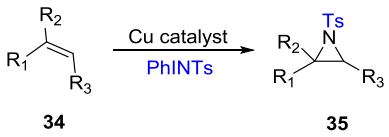
[60] Vedejs, E.; Dax, S.; Martinez, G.R.; McClure, C. K. *J. Org. Chem.* **1987**, *52*, 3470-3472.
[61] McMills, M. C.; Wright, D. L.; Zubkowski, J. D.; Valente, E. J. *Tetrahedron Lett.* **1996**, *37*, 7205-7208.

implications and initial mechanistical considerations were later analysed by the same group.[62]



Scheme 3.7. Aziridine formation *via* metallocarbenoid addition into an imine.

The strategy of metallocarbenoid addition into imine lost prominence, concerning intramolecular aziridination, in favour to the emerging metal-catalysed nitrene addition to alkenes.[59] In this direction, and on the basis of the pioneering parallel work by Jacobsen and Evans on the copper catalysed aziridination of alkenes with iminoiodanes (Scheme 3.8), Dauban and Dodd conceived an intramolecular alternative grounded on the generation of the iminoiodane on the substrate (Scheme 3.9).[63]

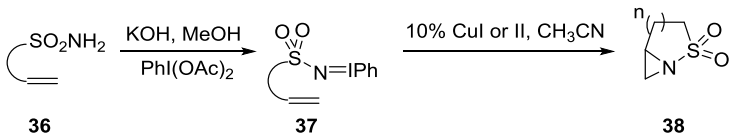


Scheme 3.8. Copper-catalysed olefin aziridination.

In the aforementioned work by Dauban and Dodd,[63] the iminoiodanes (**37**, Scheme 3.9) initially formed were isolated prior to treatment with the appropriate copper catalyst. Iminoiodanes can be unstable depending on their structure, what definitely has an impact on the robustness of the synthetic methodology. For this purpose resulted essential the use of the highly electrophylic iodobenzene diacetate ($PhI(OAc)_2$), which can react with sulphonamides (**36**) in the presence of a base to

[62] Wright, D. L.; McMills, M. C. *Org. Lett.* **1999**, *1*, 667-670.
[63] Dauban, P.; Dodd, R. H. *Org. Lett.* **2000**, *2*, 2327-2329.

form the desired nitrene transfer iminoiodane (**37**) analogously to the preparation of PhINTs.



Scheme 3.9. Imtramolecular copper-catalysed aziridination.[63]

As stated above, the field of intramolecular aziridination would undoubtedly benefit from the existence of methods based on *in situ* formation of the iminoiodane both in terms of reproducible reaction outcomes and practicality.

Before going into further details, it is worth mentioning that the development of the intramolecular aziridination has grown being fed by the findings on intermolecular aziridination and C-H insertion reactions. This sequence of events was clearly reviewed in 2003.[56]

In this regard, Che was the first who directly use the commercially available $PhI(OAc)_2$ in combination with amides (NH_2R) to *in situ* generate iminoiodanes (PhINR) in a C-H amidation reaction catalysed by ruthenium and manganese porphyrins.[64] Shortly afterwards, Du Bois applied the same concept for the transformation of carbamates (**39**) into oxazolidinones (**40**) by the means of rhodium-catalysed intramolecular C-H insertion reaction (Scheme 3.10).[65]

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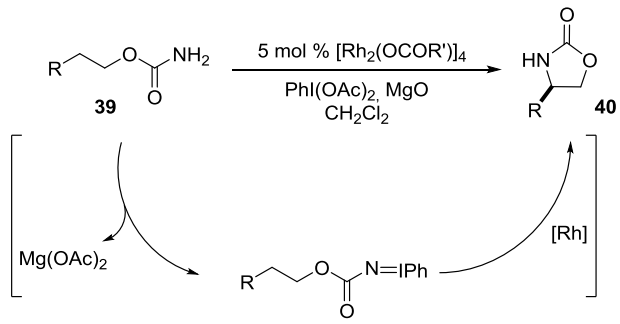
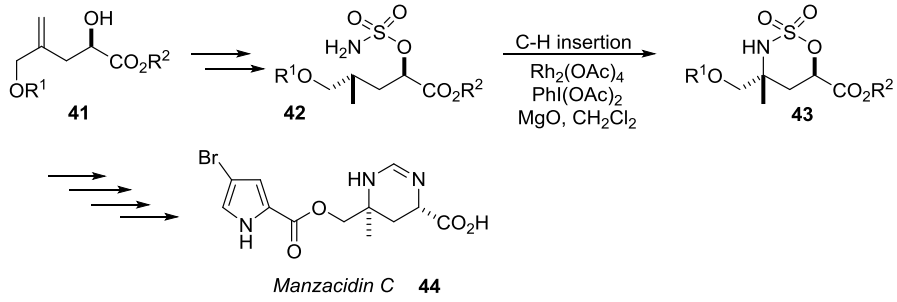
64 a) Yu, X.-Q.; Huang, J.-S.; Zhou, X.-G.; Che, C.-M. *Org. Lett.* **2000**, *2*, 2233-2236. b) Au, S.-M.; Huang, J.-S.; Che, C.-M.; Yu, W.-Y. *J. Org. Chem.* **2000**, *65*, 7858-7864.

65 Espino, C. G.; Du Bois, J. *Angew. Chem. Int Ed.* **2001**, *40*, 598-600.



Scheme 3.10. Rh-catalysed C-H insertion developed by Du Bois.

The accurate choice of MgO as a base to scavenge the acetic acid generated from $PhI(OAc)_2$ during the iminoiodane formation was an important contribution to the field of metal-mediated nitrene transfer reactions. Its utilisation has allowed, from that time on, the use of readily available rhodium and copper catalysts, which were claimed to be deactivated by the acid. The same methodology found success with sulfamate esters, serving as a useful tool to access 1,3-aminoalcohols and being applied to the synthesis of manzacidin A, B and C (**44**) (Scheme 3.11).[66]



Scheme 3.11. Enantioselective synthesis of manzacidin C through stereospecific C-H bond insertion.[66b]

[66] a) Espino, C. G.; Wehn, P. M.; Chow, J.; Du Bois, J. *J. Am. Chem. Soc.* **2001**, *123*, 6935-6936. b) Wehn, P. M.; Du Bois, J. *J. Am. Chem. Soc.* **2002**, *124*, 12950-12951.

The named as Du Bois conditions ($PhI(OAc)_2$, catalytic $Rh_2(OAc)_4$ and MgO) were then satisfactory employed, in addition to C-H insertion, to the intramolecular aziridination of olefinic substrates bearing sulfamate ester,[67] sufonamide-,[68] sulfonimidamide-,[69] and carbamate[70]-functional groups as nitrogen donors.

Owing to the fact that the main body of the present thesis will be focused on the use of copper and rhodium catalyst for the intramolecular aziridination of dienes, we considered adequate to discuss, on the basis of published reports, the different behaviour that both metals have shown depending on the type of nitrogen donor and iminoiodane precursor.

Initial studies by Dauban and Dodd suggested that copper salts were incompatible with acetate salts (See Scheme 3.9). This statement comes from failed attempts on intramolecular aziridination of sulfamates with $PhI(OAc)_2$.[68b] This argument was strengthened by the absence of reports applying the Du Bois conditions together with

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67 a) Duran, F.; Leman, L.; Ghini, A.; Burton, G.; Dauban, P.; Dodd, R. H. *Org. Lett.* **2002**, *4*, 2481-2483. b) Fruit, C.; Müller, P. *Tetrahedron: Asymmetry* **2004**, *15*, 1019–1026. c) Lorpitthaya, R.; Xie, Z.-Z.; Kuo, J.-L.; Liu, X.-W. *Chem. Eur. J.* **2008**, *14*, 1561-1570. d) Malik, G.; Estéoule, A.; Retailleau, P.; Dauban, P. *J. Org. Chem.* **2011**, *76*, 7438-7448. e) Olson, D. E.; Maruniak, A.; Malhorta, S.; Trost, B. M.; Du Bois, J. *Org. Lett.* **2011**, *13*, 3336-3339. f) Mahbubul, H. M.; Miyamoto, K.; Tada, N.; Shiro, M.; Ochiai, M. *Org. Lett.* **2011**, *13*¸ 5428-5431. g) Adams, C. S.; Boralsky, L. A.; Guzei, I. A.; Schomaker, J. M. *J. Am. Chem. Soc.* **2012**, *134*, 10807-10810.

68 a) Dauban, P.; Dodd, R. *Org. Lett.* **2000**, *2*, 2327-2329. b) Dauban, P.; Sanière, L.; Tarrade, A.; T. Dodd, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 7707-7708. c) Liang, J.-L.; Yuan, S.-X.; Chan, P. W. H.; Che, C. M. *Org. Lett.* **2002**, *4*, 4507-4510. d) Liang, J.-L.; Yuan, S.-X.; Huang, J.-S.; Che, C.-M. *J. Org. Chem.* **2004**, *69*, 3610-3619. e) Liu, P.; Wong, E. L.-M.; Yuen, A. W.-H.; Che, C.-M. *Org. Lett* **2008**, *10*, 3275-3278.

69 a) Di-Chenna, P. H.; Peillard, F. R.; Dauban, P.; Dodd, R. H. *Org. Lett.* **2004**, *6*, 4503-4505. b) Peillard, F. R.; Di Chenna, P. H.; Liang, C.; Lescot, C.; Collet, F.; Dodd, R. H.; Dauban, P. *Tetrahedron: Asymmetry* **2011**, *21*, 1447-1457.

70 a) Levites-Agababa; Menhaji, E.; Perlson, L. N.; Rojas, C. M. *Org. Lett.* **2002**, *4*, 863-865. b) Padwa, A.; Stengel, T. *Org. Lett.* **2002**, *4*, 2137-2139. c) Padwa, A.; Flick, A. C.; Leverett, C. A.; Stengel, T. *J. Org. Chem.* **2004**, *69*, 6377-6386. d) Hayes, C. J.; Beavis, P. W.; Humphries, L. A. *Chem. Commun.* **2006**, 4501-4502. e) Gupta, R., Sogi, K. M.; Bernard, S. E.; Decatur, J. D.; Rojas, C. M. *Org. Lett.* **2009**, *11*, 1527-1530. f) Boralsky, L. A.; Marston, D.; Grigg, R. D.; Hershberger, J. C.; Schomaker, J. M. *Org. Lett.* **2011**, *13*, 1924-1927. g) Deng, Q.-H.; Wang, J.-C.; Xu, Z.-J.; Zhou, C.-Y.; Che, C.-M. *Synthesis* **2011**, 2959-2967. h) Rigoli, J. W.; Weatherly, C. D.; Vo, B. T.; Neale, S.; Meis, A. R.; Schomaker, J. M. *Org. Lett.* **2013**, *15*, 290-293.

copper salts. In fact the only examples where copper salts are used in combination with $PhI(OAc)_2$ / NH_2R exclude the use of a base that would generate the corresponding acetate salt. Moreover, the yields afforded are generally low or highly dependent on the substrate and type of nitrene source.[71] Such incompatibility would have deep impact on the forthcoming of intramolecular aziridination owing to the versatility that copper salts provide in terms of ligand complexation. Fortunately though, iodosylbenzene (PhIO), an oxygen transfer reagent,[72] demonstrated excellent behaviour in the copper-catalysed intramolecular aziridination of sulfamates,[68b] becoming from the moment on the oxidant of choice in copper-mediated nitrene addition reactions.[67a, 69b,73] This fact can be explained considering that the formation of an iminoiodane from PhIO generates water as the byproduct instead of acetic acid. The water released is easily trapped adding molecular sieves to the reaction mixture (See section 3.2.7)

On the contrary, rhodium catalysts showed remarkable capacity towards intramolecular aziridination regardless of the hypervalent iodine reagent presumably in connection with a higher tolerance by rhodium to acetate salts.[56] In this direction, Rojas *et al.* reported the metal-catalysed intramolecular aziridination of of allal-3-carbamates (**45**, Scheme 3.12), where $Rh_2(OAc)_4$ provided comparable yields when either $PhI(OAc)_2$ or PhIO were used as oxidant (Scheme 3.12).[70a] An additional point of interest provided in this work, was the possibility of using copper catalysts ($Cu(acac)_2$ and $Cu(MeCN)_4PF_6$) to aziridinate carbamates, since the lack of reports raise a question about its ability to stabilise acyl nitrenoids.

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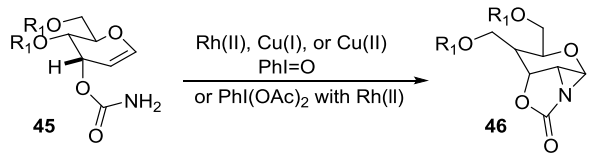
71 a) Kwong, H.-L.; Liu, D.; Chan, K.-Y.; Lee, C.-S.; Huang, K.-H.; Che, C.-M. *Tetrahedron Lett.* **2004**, *45*, 3965-3968. b) Wang, X.; Ding, K. *Chem. Eur. J.* **2006**, *12*, 4568-4575.

72 a) Collman, J. P.; Zhang, X.; Lee, V. J.; Uffelman, E. S.; Brauman, J. I. *Science* **1993**, *261*, 1404-1411. b) Nam, W.; Valentine, J. S. *J. Am. Chem. Soc.* **1990**, *112*, 4977-4979. c) Groves, J. T.; Nemo, T. E. *J. Am. Chem. Soc.* **1983**, *105*, 5786-5791.

73 Estéoule, A.; Durán, F.; Retailleau, P.; Dodd, R. H.; Dauban, P. *Synthesis*, **2007**, 1251-1260.



Scheme 3.12. Metal-catalysed amidoglycosylation of 3-allal-carbamates through intramolecular aziridination.

Almost at the same time, Padwa *et al* applied the Du Bois conditions in the intramolecular aziridination of cyclic carbamates.[74] The use of MgO as a base in this work is probably the reason for the stereoselective ring opening of the tricyclic aziridine formed in opposition with the epimeric mixtures observed in Rojas's work. These mixtures must be the result of a S_N1 mechanism promoted by the presence of acetic acid, which is otherwise neutralised when a base is employed.

In the following sections the basic aspects to be taken into consideration for the intramolecular aziridination reaction will be discussed: mechanistical implications depending on the catalyst used (Cu or Rh) and differences between nitrogen containing functional groups.

3.1.3.2. MECHANISTICAL IMPLICATIONS IN THE COPPER- AND RHODIUM-CATALYSED AZIRIDINATION REACTION MEDIATED BY HYPERVALENT IODINE OXIDANTS

The stabilization of nitrenes with metals was a milestone in the field of C-N bond formation, permitting to amend the high intrinsic reactivity of nitrenes, which is the key for broad scope of selective C-N bond formation methodologies based on nitrene insertion and addition.[75]

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[74] Padwa, A.; Stengel, T. *Org. Lett.* **2002**, *4*, 2137-2139.

[75] Dauban, P.; Lescot, C.; Díaz-Requejo, M. M.; Perez, P. J. (2012) *Rh-, Ag-, and Cu-Catalyzed C-N Bond* Formation, in *Innovative Catalysis in Organic Synthesis: Oxidation*,

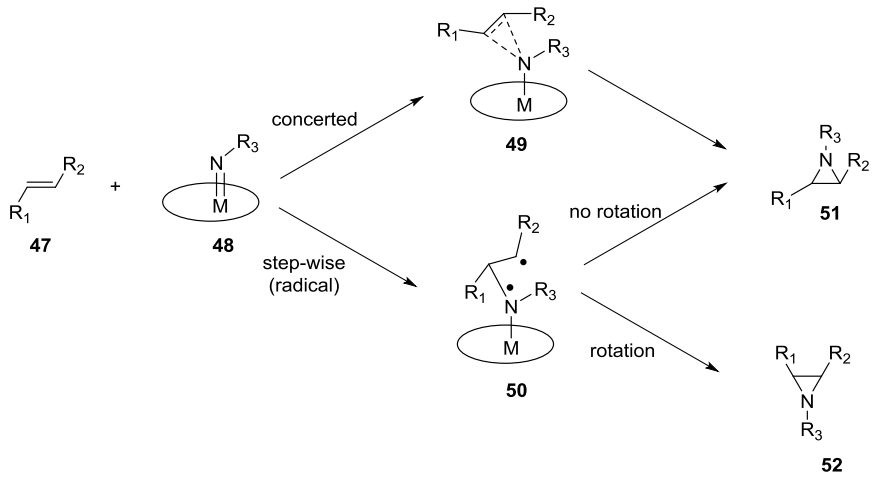
Since most of the work discussed in the present PhD thesis work will deal with copper- and rhodium-catalysed intramolecular aziridination we considered appropriate to discuss the main mechanistic conclusions to date in this regard.

Copper-catalysed nitrene insertions and additions

The ability of copper to promote nitrene insertion reactions was firstly communicated in the aforementioned work by the aforementioned report by Kwart and Kahn in 1967 when copper powder catalysed the amination of cyclohexane with benzenesulfonyl azide.[54]

Almost 30 years later, Evans demonstrated the utility and potential of copper salts for the aziridination of olefins using iminoiodanes.[58a] The mechanistic portrait of the copper-catalysed process is rather complicated and not yet concluded. However, the implication of metallanitrenes intermediates is firmly accepted. The main question resides, as it has been briefly introduced previously, in whether nitrene transfer from the metallanitrene (**48**, Scheme 3.13) to either the olefin or the C-H bond follows a concerted pathway, from a single nitrene intermediate or, on the contrary, involve radical intermediates leading to a step-wise mechanism from triplet nitrenes (Scheme 3.13).

Hydrogentation, and C-X Bond Forming, (ed *Andersson, P. G.*) Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany.



Scheme 3.13. Possible mechanisms for the copper-catalyzed aziridination.[76]

Since the initial insides provided by Evans suggesting a different mechanistic scenario depending on the type of substrate; being concerted for alkyl substituted olefins and step-wise for styrene derivatives, most of the following investigations strengthened the participation of radicals in such process. In this direction a deep theoretical study by Norrby proved the intervention of triplet nitrene species in the aziridination of olefins mediated by PhINTs and introduced the possibility that spin crossing from nitrene triplet state to the singlet state was the reason behind the isomerisation observed in some olefins and not in others.[77] This fact was recently confirmed for the aziridination of dienols catalysed by copper and silver-Tp^x complexes.[78] In the case of silver complexes, the formation of the aziridine products takes place after the spin crossing providing a stereospecific process whereas in the

[76] Simonato, J.-P.; Pécaut, J.; Scheidt, W. R.; Marchon, J.-C. *Chem. Commun.* **1999**, 989-990.

[77] Brandt, P.; Södergren, M. J.; Andersson, P. G.; Norrby, P.-O. *J. Am. Chem. Soc.* **2000**, *122*, 8013-8020.

[78] a) Mestre, L.; Sameera, W. M. C.; Díaz-Requejo, M. M.; Maseras, F.; Pérez, P. J. *J. Am. Chem. Soc.* **2013**, *135*, 1338-1348. b) Llaveria, J.; Beltran, A.; Sameera, W. M. C.; Locati, A.; Díaz-Requejo, M. M.; Matheu, M. I.; Castillón, S.; Maseras, F.; Pérez, P. J. *J. Am. Chem. Soc.* **2014**, *136*, 5342-5350.

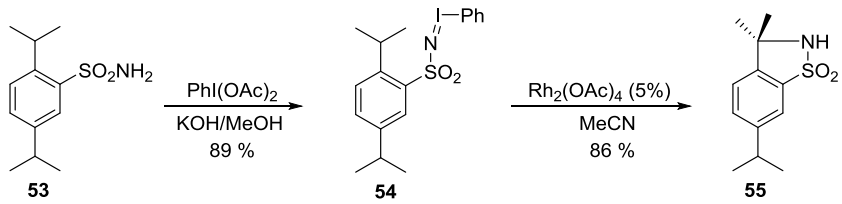
copper case the formation of the aziridine takes place before the spin crossing point from a triplet nitrene state, producing isomerisation.

Currently there is no mechanistic data in the literature related to the copper-catalysed intramolecular aziridination. Therefore we will initially assume that the same type of mechanism is operating.

Finally, it is important to highlight the lesser propensity of copper catalyst to perform C-H insertion in comparison with rhodium catalysts, which becomes relevant when homoallylic substrates are targeted since the allylic C-H amination could compete.[75]

Rhodium-catalysed nitrene insertions and additions

The first demonstration of the utility of rhodium in nitrene insertion reactions was done by Breslow in 1983 when $Rh_2(OAc)_4$ catalysed the amination of benzylic C-H bonds (Scheme 3.14).[79]



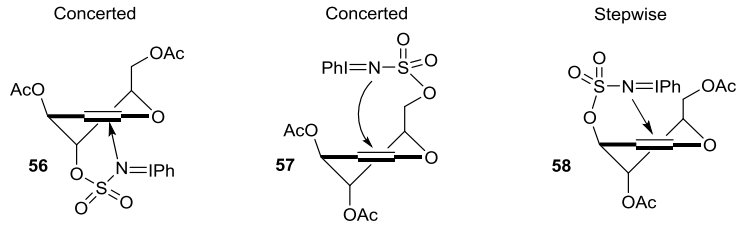
Scheme 3.14. Pioneer $Rh_2(OAc)_4$ catalysed amination of benzylic C-H bonds

The understanding of the nitrene transfer process from a rhodium-based metallanitrene met, initially, more agreement. Several studies on C-H amination and aziridination identified the mechanism as a concerted asynchronous C-H insertion of a rhodium-bound singlet nitrene. This conclusion is grounded on positive results from radical clock experiments, Hammet analysis and Kinetic Isotope Effect

[79] Breslow, R.; Gellman, S. H. *J. Am. Chem. Soc.* **1983**, *105*, 6728-6729.

measurements.[80] Nevertheless some recent contradictory results obtained by Dauban *et al*. opened the door to the possibility of a radical pathway in determinate substrates.[81]

In connection with this, Liu and Kuo investigated the mechanism of the rhodium-catalysed intramolecular aziridination of glycals.[67b,82] They carried out theoretical analysis of the aziridination mechanism on glycals with the sulfamate functionality in different positions. It was concluded that the electronic state of the metallanitrene in the nitrene transfer step depended on the position of the glycal substituted. Therefore, in the case of intermediates **56** and **57** (Scheme 3.15) the aziridine formation took place in a concerted manner from a singlet metallanitrene, whereas for **58** it would be a step-wise addition from a triplet nitrene.



Scheme 3.15. Model compounds adressed for the mechanistic study on rhodium-catalysed aziridination of sulfamate-substituted glycals.

More recently, Zhao and co-workers reported an exhaustive mechanistic investigation of rhodium-catalysed intramolecular allylic C-H amination and aziridination of 4-pentenylsulfamate **59** (Scheme 3.16).[83] In this study it was demonstrated the coexistence of singlet concerted and triplet step-wise pathways for both reactions as a function of the catalyst properties. Thus, aziridination of **59**

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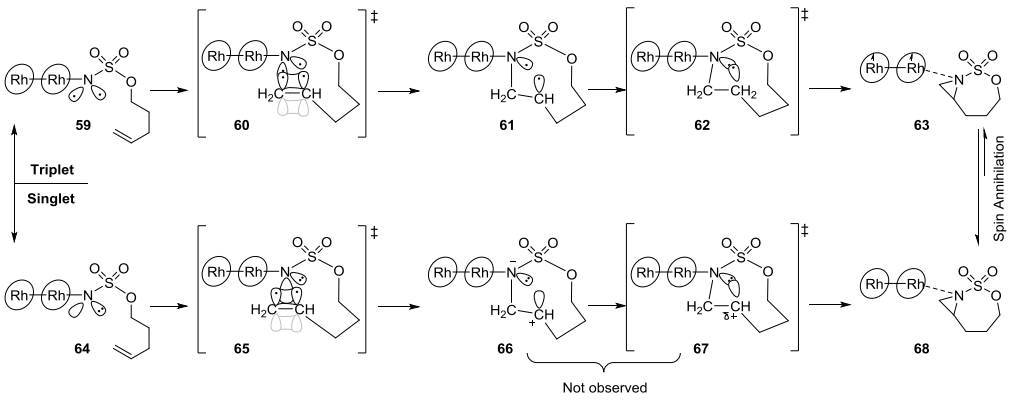
80 a) Müller, P.; Baud, C.; Jacquier, Y.; Moran, M.; Nägeli, I. *J. Phys. Org. Chem.* **1996**, *9*, 341-347. b) Nägeli, I.; Baud, C.; Bernardinelli, G.; Jacquier, Y.; Moran, M.; Müller, P. *Helv. Chim. Acta.* **1997**, *80*, 1087-1105.

81 Collet, F.; Lescot, C.; Liang, C.; Dauban, P. *Dalton Trans.* **2010**, *39*, 10401-10413.

82 Lorpitthaya, R.; Xie, Z.-Z.; Sophy, K. B.; Kuo, J.-L.; Liu, X.-W. *Chem. Eur. J.* **2010**, *16*, 588-594.

83 Zhang, X.; Xu, H.; Zhao, C. *J. Org. Chem.* **2014**, *79*, 9799-9811.

followed a concerted, highly asynchronous singlet nitrene transfer mechanism when the process was catalysed by either $Rh_2(OAc)_4$ or $Rh_2(NHCOCF_3)_4$. On the other hand the same reaction occurs via a triplet stepwise pathway being catalysed by $Rh_2(NCH_3CHO)_4$. The reason is attributed mainly to the electronic properties of the ligands. Thus, the major electrondonating character of carboxiamidates (case of $Rh_2(NCH_3CHO)_4$) increases the backbonding capacity of dirhodium centres to the π-acidic nitrene. This backdonation effect stabilises more triplet nitrene intermediates than singlet, resulting in preference for the stepwise pathway. Conversely, in electronpoorer $Rh_2(OAc)_4$ or $Rh_2(NHCOCF_3)_4$ the energy diference between singlet and triplet states is small allowing a nitrene of singlet nature in the product-determining step.

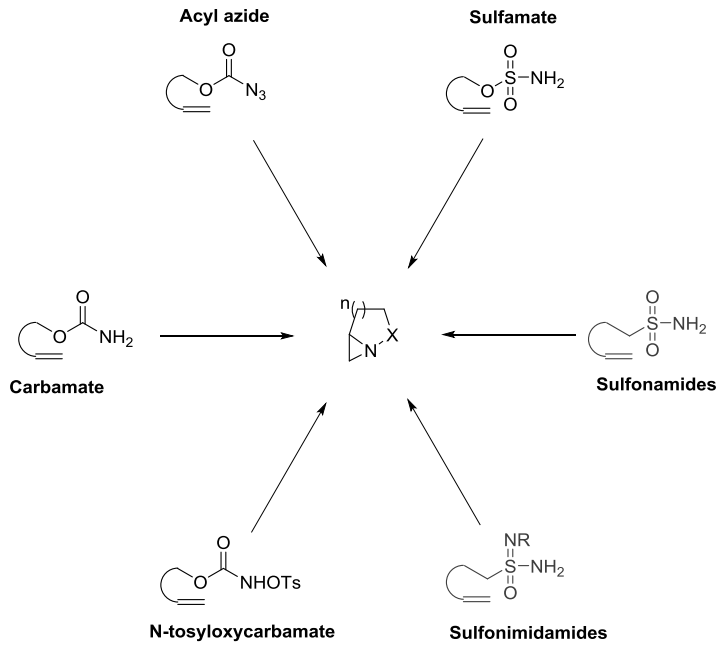


Scheme 3.16. Universal reaction mechanisms of the dirhodium catalysed alkene aziridination reactions proposed by Zhao.[83]

All in all, it appears that contrary to the initial beliefs, both mechanistic pathways must be taken into account since the operation of one or the other is strongly linked to the substrate and catalyst nature.

3.1.3.3. FUNCTIONAL GROUPS USED AS NITRENE PRECURSORS

The choice of one or another source of nitrogen for intramolecular aziridination is normaly determined by either the desire of a particular type of product or by the reactivity of the system. The most commonly used are sulfamates, sufonamides, sulfonimidamides, carbamates, *N*-tosyloxycabamates and acyl azides (Scheme 3.17). In the present work the functional groups employed were sulfamates, carbamates, *N*-tosyloxycabamates and acyl azides therefore, the introduction is only focused on them.



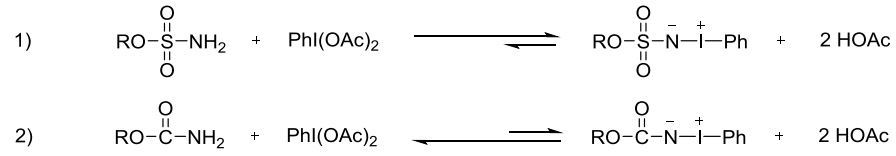
Scheme 3.17. Functional groups used as nitrogen donors in intramolecular aziridination reactions.

Sulfamates

Among all the nitrogen containing functional groups employed for intramolecular nitrene insertion and addition reactions, sulfamates are, by far, the most widely used. The reason is the unique versatility that provides, allowing its use

in uncountable substrate types as well as in combination with different I(III) oxidants and metal catalysts. There are two main points responsible for such versatility: electronic properties and structural features.

Concerning electronic properties, their importance become clear when analysing the proposed mechanism for both intramolecular aziridination and C-H amination. Detailed kinetic studies made by Du Bois and co-workers on the Rh-catalysed intramolecular C-H amination led to the conclusion that the rate-determining step of the process was the formation of the iminoiodane from the sulfamate substrate and the I(III) oxidant.[84] Taking into account that aziridination and C-H amination follow the same mechanism before C-N bond formation, and the lack of mechanistical studies dealing with the entire intramolecular aziridination process,[85] we could consider the iminoiodane formation to be also the slowest step in intramolecular aziridination. Therefore, the superior behaviour of sulfamate compared to carbamate-type nitrogen donors could be explained as a larger charge-stabilisation capacity of (Scheme 3.18).



Scheme 3.18. Equilibrium of iminoiodane formation from sulfamates and carbamates.

Moving to the structural features, the sulfamate has long S-O and S-N bonds (1.58 Å) and an obtuse N-S-O angle (103º).[66a] These geometrical parameters justify the strong preference of sulfamates for six-membered ring formation. Being the six-membered ring optimal, the tolerance is higher for larger rings rather than smaller.

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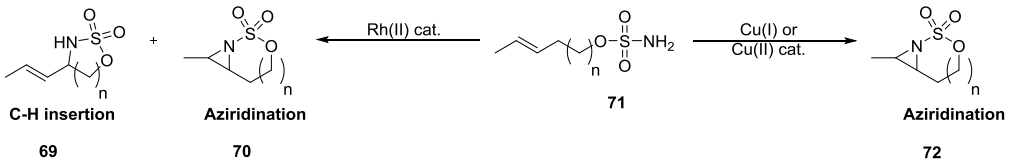
[84] Fiori, K. W.; Espino, C. G.; Brodsky, B. H.; Du Bois, J. *Tetrahedron* **2009**, *65*, 3042-3051.

[85] DFT calculations for the Rh-catalysed aziridination of glycals did not take into consideration the formation of the iminoiodane. However, that was the highest energy state of the proposed mechanism: Lorpitthaya, R.; Xie, Z.-Z.; Kuo, J.-L.; Liu, X.-W. *Chem. Eur. J.* **2008**, *14*, 1561-1570.

This fact is unambiguously demonstrated by the numerous reports where seven-[67a,84,86] and even eight-membered[87] rings are generated from sulfamates, which stands in sharp contrast with the very limited amount of publications facing five-membered compounds.[68c,88] In the 5-membered ring, moreover, the authors take advantage of the close proximity between the sulfamate and the olefin due to the intrinsic substrate rigidity or the presence of more reactive terminal olefins.

It is worth pointing that, even though in the vast majority of publications the intramolecular aziridination is catalysed by rhodium(II) complexes, this is normally treated as a side reaction that competes with the aimed C-H amination. In fact, as pointed in the previous section, the strong preference of copper catalysts to undergo aziridination over C-H amination reactions makes them the catalysts of choice when aiming to aziridinate homoallyl or longer-chain olefinic substrates (**71**) (Scheme 3.19).[89]



Scheme 3.19. Copper-catalysed selective aziridination of sulfamates *vs.* competitive rhodium-catalysed C-H amination and aziridination.

The last differential aspects between nitrogen containing functional groups are the feasibility of their removal and the type of products rendered. The predominance of

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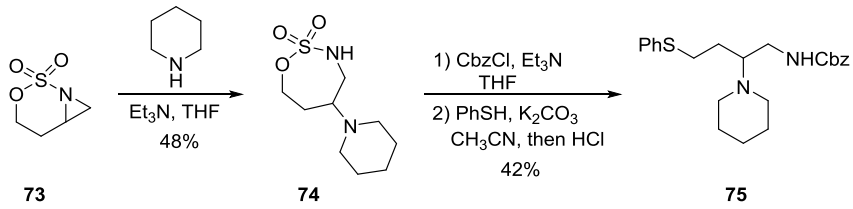
86 a) Olson, D. E.; Maruniak, A.; Malhorta, S.; Trost, B. M.; Du Bois, J. *Org. Lett.* **2011**, *13*, 3336-3339. b) Harvey, M. E.; Musaev, D. G.; Du Bois, J. *J. Am. Chem. Soc.* **2011**, *133*, 17207-17216. c) Duran, F. J.; Ghini, A. A.; Dauban, P.; Dodd, R. H.; Burton, G. *J. Org. Chem.* **2005**, *70*, 8613-8616. d) Wehn, P. M.; Lee, J.; Du Bois, J. *Org. Lett.* **2003**, *5*, 4823-4826.

87 Kornecki, K. P.; Berry, J. F. *Chem. Commun.* **2012**, *48*, 12097-12099.

88 a) Liu, P; Wong, E. L.-M.; Yuen, A. W.-H.; Che, C.-M. *Org. Lett.* **2008**, *10*, 3275-3278. b) Liang, J.-L.; Yuan, S.-X.; Chan, P. W. H.; Che, C.-M. *Tetrahedron Lett.* **2003**, *44*, 5917-5920.

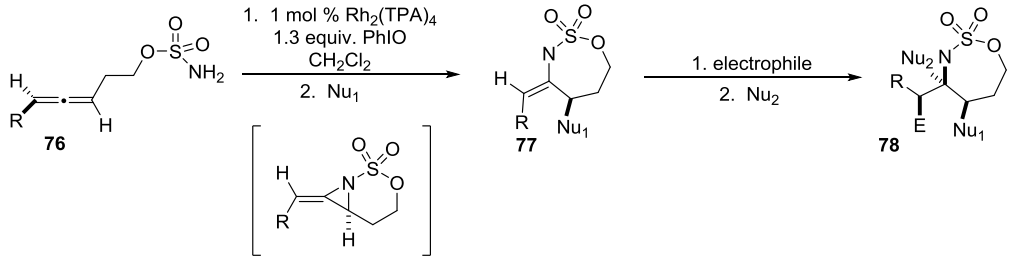
89 *Modern Rhodium-Catalyzed Organic Reactions;* Espino, C. G.; Du Bois, J., Ed.; Wiley-VCH: Weinheim, Germany: **2005**.

publications dealing with aziridination of sulfamates over sulfonamides could be explained on the basis of the previous considerations. Thus, the impossibility to remove the sulfonyl moiety from cyclic sulfonamides diminishes their synthetic attractiveness compared with cyclic sulfamates which, upon aziridine ring opening and acid hydrolysis, led to distinctly functionalised aminoalcohols. In addition, the leaving group character of the cyclic sulfamate allows the introduction of a second nucleophile (Scheme 3.20).[67a,90]



Scheme 3.20. Aziridine ring opening followed by second nucleophilic attack and sulfamate cleavage.

The striking potential of the bicyclic aziridine-sulfamate moiety is especially highlighted in allenes as shown by Schomaker and co-workers in a recent publication (Scheme 3.21).[90]



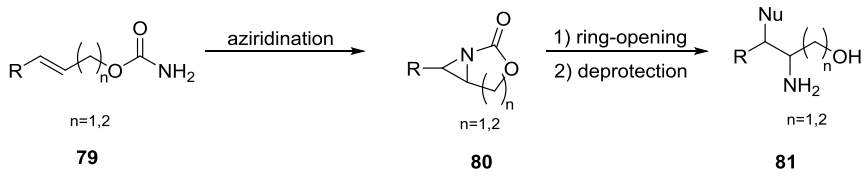
Scheme 3.21. Preparation of triply functionalised amines from sulfamate-derivatised allenes.

[90] Adams, C. S.; Boralsky, L. A.; Guzei, I. A.; Schomaker, J. M. *J. Am. Chem. Soc.* **2012**, *134*, 10807-10810.

They were able to transform substituted allenes (**76**) into triply functionalised amines (**78**) through a sequence involving allene aziridination with $Rh_2(TPA)_4$ (TPA = triphenylacetate), nucleophilic aziridine ring opening, electrophilic addition to the enesulfamate **77** and final nucleophilic addition to the intermediate iminium ion**.**

Carbamates

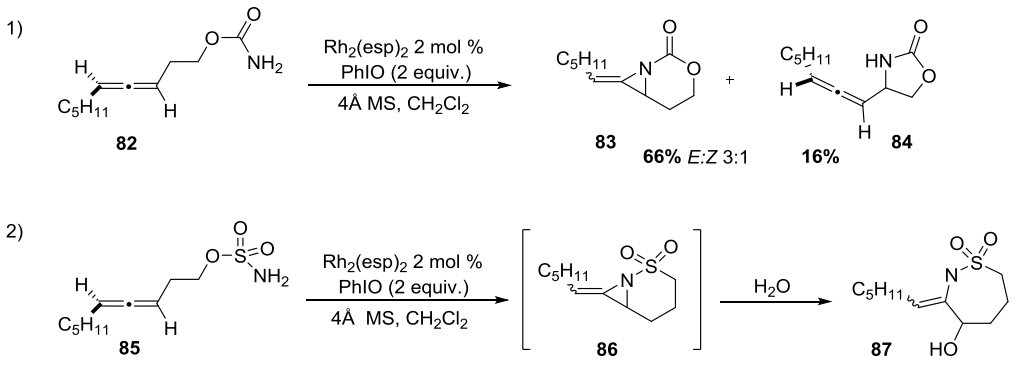
The carbamate functional group would, at the first sight, seem to be overcome by its analogue sulfamate in both electronic and structural properties for intramolecular aziridination concerns. Firstly, the formation of the iminoiodane is less energetically favoured if we take into account the minor charge delocalisation, as depicted in Scheme 3.18, and secondly, the sp^2 hybridisation of the carbonylic carbon is intrinsically associated with an ideal O-C-N angle around 120º. The latter limits the application of carbamates to aziridine products having five-membered or, at last, six-membered oxazolidinone rings. Nevertheless, the easy cleavage of oxazolidinones under acid or basic conditions[91] makes carbamates one of the most attractive precursors for obtaining synthetically and biologically interesting substituted 1,2- and 1,3-aminoalcohols (Scheme 3.22).



Scheme 3.22. Preparation of aminoalcohols via aziridination of substituted carbamates.

[91] Acid oxazolidinone cleavage: a) Sugiyama, S.; Arai, S.; Ishii, K. *Tetrahedron* **2012**, *68*, 8033-8045. b) Avenoza, A.; Busto, J. H.; Corzana, F.; Peregrina, J. M.; Sucunza, D.; Zurbano, M. M. *Tetrahedron:* Asymmetry **2004**, *15*, 719-724. Basic oxazolidinone cleavage: c) Dhar, S.; Kodama, T.; Greenberg, M. M. *J. Am. Chem. Soc.* **2007**, *129*, 8702-8703. d) Pyun, D. K.; Lee, C. H.; Ha, H.-J.; Park, C. S.; Chang, J.-W.; Lee, W. K. *Org. Lett.* **2001**, *3*, 4197-4199. e) Reddy, R. P.; Lee, G. H.; Davies, H. M. L. *Org. Lett.* **2006**, *8*, 3437-3440.

Another advantage of the carbamate functionality respect to the sulfamate is its reduced electrowithdrawing character that results in more estable aziridines. This is of particular importance if we take into consideration the already unstable nature of bicyclic aziridines and even more in the extreme case of methylene aziridines and vinylaziridines. An illustrated example is the study made by Schomaker on the intramolecular aziridination of carbamoyl and sulfamoyl substituted allenes (Scheme 3.23).[92] Whereas carbamate **82** was successfully aziridinated and **83** could be isolated in good yield, the analogous aziridine **86**, generated from sulfamate **85**, underwent *in situ* hydrolysis to afford **87** even in the presence of 4Å molecular sieves.

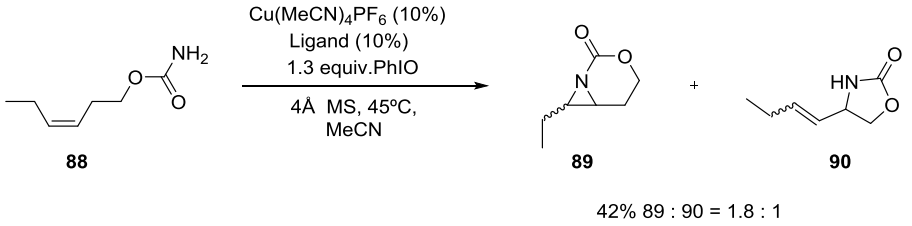


Scheme 3.23. Comparison of the stability between sulfamate- and carbamate-based methylene aziridines.

Probably the major drawback associated with the use of carbamates is their lack of activity in intramolecular copper-catalysed nitrene insertion and addition reactions. To the best of our knowledge there are only two minor examples in the literature. In the most recent one, Schomacker and co-workers screened various metal catalysts looking for selective aziridination over C-H amination in homoallylic allenic carbamates (Scheme 3.24).[70h] Whereas many silver and rhodium catalysts displayed moderate to high activity, copper catalysts rendered exclusively starting carbamate. As an exceptional case, 13% of aziridine was obtained when the carbamate substrate

[92] Boralsky, L. A.; Marston, D.; Grigg, D.; Hershberger, J. C.; Schomaker, J. M. *Org. Lett.* **2011**, *13*, 1924-1927.

was premixed with PhIO before adding $Cu(MeCN)_4PF_6$. This particular copper complex also provided low yields of aziridine from carbamate **88** (Scheme 3.24). It must be stated that $Cu(MeCN)_4PF_6$ is generally the best catalyst for the aziridination of sulfamate-substituted compounds.[93]



Scheme 3.24. Copper-catalysed intramolecular aziridination using carbamate-substituted olefins.

Acyl azides (azidoformates)

The use of acyl azides precludes the use of hypervalent iodane oxidants because the nitrogen is already in the required oxidation state for nitrene transfer reactions. Therefore, nitrenes are commoly generated, upon dinitrogen loss, from acyl azides under thermal or photochemical conditions.[94] The use of acyl azides as nitrogen donors would be, as a concequence, advantageous in terms of atom economy of the process. However, whereas iminoiodanes are excellent nitrene-transfer agents to metals, the direct formation of the metallanitrene by metal activation of the acyl azide moiety is still an unsolved challenge.

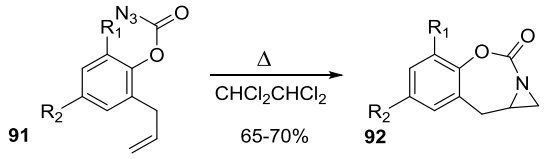
The intramolecular addition of a nitrene from an azidoformate to an olefin was firstly observed by Rhouati and Bernou (Scheme 3.25).[95] In this work, phenyl

[93] Barman, D. N.; Nicholas, K. M. *Eur. J. Org. Chem.* **2011**, 908-911.

[94] For a classic review on the decomposition and addition reactions of organic azides see: a) L'Abbé, G. *Chem. Rev.* **1969**, *69*, 345-363. For a book chapter about properties of acyl nitrenes see: b) Gritsan, N. P. (2013) *Properties of Carbonyl Nitrenes and Related Acyl Nitrenes*, in *Nitrenes and Nitrenium Ions* (eds D. E. Falvey and A. D. Gudmundsdottir), John Wiley & Sons, Inc., Hoboken, NJ, USA.

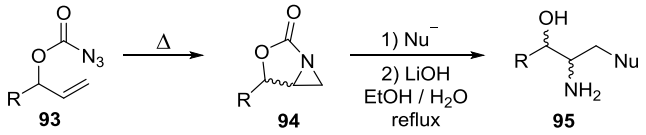
[95] Rhouati, S.; Bernou, A. *J. Chem. Soc. Chem. Commun.* **1989**, 730-732.

azidoformates **91** were subjected to thermolysis in refluxing tetrachloroethane providing good yields of aziridines **92**.



Scheme 3.25. First example of intramolecular aziridination of azidoformates via thermal decomposition.

This finding was later applied by Bergmeier in the preparation of vicinal aminoalcohols **95** from azido derivatives **93** through a tandem thermal aziridination and subsequent ring opening (Scheme 3.26).[96]



Scheme 3.26. Synthesis of 1,2-aminoalcohols **95** by thermolysis of azidoformate **93**.

Bicyclic acyl-aziridines have also been obtained from acylazides through photochemical decomposition.[97] Previously to his work on the intramolecular aziridination of allal-3-carbamates,[70a] Rojas published the amidoglycosylation of allal azidoformates presumably via photo-induced aziridination.[98] These two connected studies serve as a clear example to raise the superiority of metal-nitrenoid-based (more stable and selective) nitrene addition over free-nitrene (more reactive and unselective) processes (Scheme 3.27). Concretely, allopyranoside **98** was selectively

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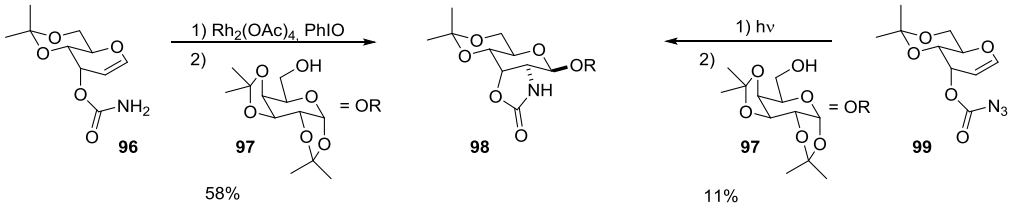
96 a) Bergmeier, S. C.; Stanchina, D. M. *J. Org. Chem.* **1997**, *62*, 4449-4456. b) Bergmeier, S. C.; Stanchina, D. M. *J. Org. Chem.* **1999**, *64*, 2852-2859.

97 Bräse, S.; Gil, C.; Knepper, K.; Zimmermann, V. *Angew. Chem. Int. Ed.* **2005**, *44*, 5188-5240 and references cited therein.

98 Kan, C.; Long, C. M.; Paul, M.; Ring, C. M.; Tully, S. E.; Rojas, C. M. *Org. Lett.* **2001**, *3*, 381-384.

obtained from allal carbamate **96** in 58 % yield. On the contrary, photoactivation of azidoformate **99** rendered **98** in a conspicuously poor 11 % yield. Moreover, other byproducts resulting from low functional group tolerance of free nitrenes were observed.



Scheme 3.27. Synthesis of allopyranoside **98** by either by rhodium-catalysed aziridination of carbamate **96** or by photodecomposition of azidoformate **99**.

Historically speaking, methods based on the decomposition of azides for the formation of C-N bonds are the ancestors of the lately developed iminoiodane-based chemistry for nitrene insertions and additions. In these concerns and as introduced above, the emerging of iminoiodane reagents relegate the use of organic azides to a second line owing to the ability of the formers to interact with metals releasing key metallanitrene intermediates.[99] However, the possibility of achieving a method for nitrene insertion being nitrogen the sole byproduct was appealing.

In this regard, in 2000, Bach tackled the Fe^{II}-catalysed intramolecular nitrogen transfer to alkenes from acyl azides.[100] It was concluded that the chlorinated oxazolidinones **107** (Scheme 3.28) obtained were not the result of nucleophilic ring-opening of a transient aziridine, but the reaction took place through a radical aminochlorination mechanism (Scheme 3.28).[101]

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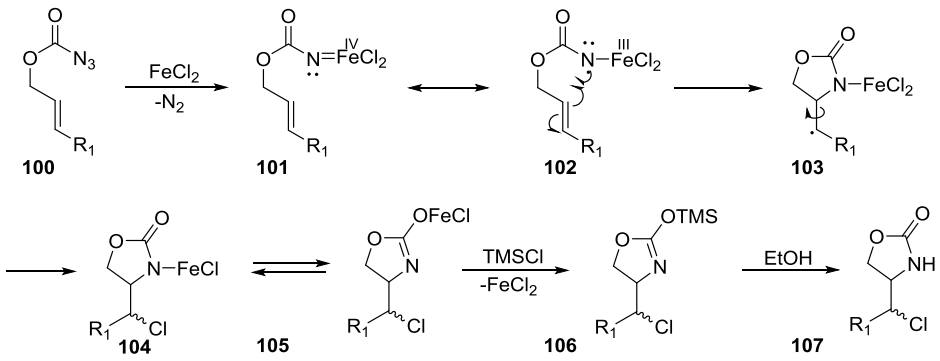
[99] Organic azides have been successfully used in aziridination of terminal alkenes using generally Co and Ru porphyrin complexes as catalysts through a radical mechanism. See for example: Olivos Suárez, A. I.; Jiang, H.; Zhang, X. P.; De Bruin, B. *Dalton Trans.* **2011**, *40*, 5697-5705 and references cited therein.

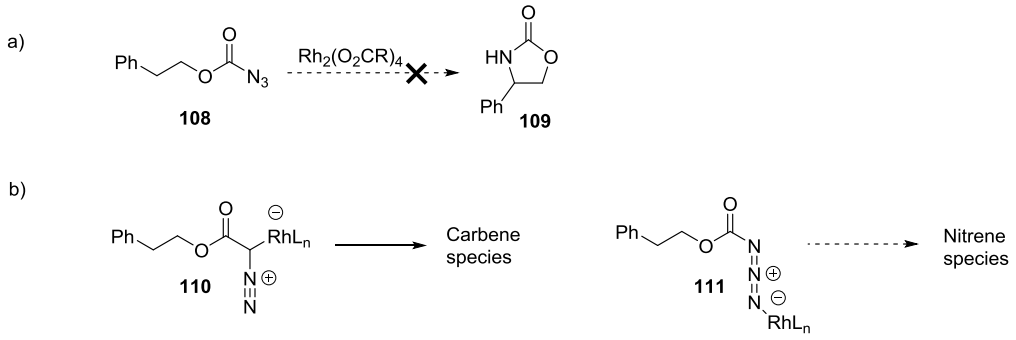
[100] Bach, T.; Schlummer, B.; Harms, K. *Chem. Commun.* **2000**, 287-288.

[101] Bach, T.; Schlummer, B.; Harms, K. *Chem. Eur. J.* **2001**, *7*, 2581-2594.



Scheme 3.28. Proposed mechanism of the Fe^{II}-catalysed intramolecular chloroamination of acyl azides.

Alternatively, and in the context of their studies on catalytic activation of carbonyl azides with transition-metal complexes, Helen Lebel and her collaborators were unsuccessful attempting the decomposition of acyl azide **108** with various rhodium(II) carboxylate catalysts (Scheme 3.29a).[102]



Scheme 3.29. a) Attempts to activate **108** with rhodium catalysts. b) Coordination modes of rhodium to diazonium compounds and acyl azides.

Taking into account that the corresponding rhodium nitrene of **108** was known to easily undergo C-H insertion in combination with the relative weakness of the N=N bond (~100 kcal/mol) of diazo compounds compared to the parent C=N (~150

[102] Lebel, H.; Leogane, O.; Huard, K.; Lectard, S. *Pure Appl. Chem.* **2006**, *78*, 363-375.

kcal/mol), they assumed that the coordination of rhodium took place at the terminal nitrogen of the azide moiety **111** rather than to the desired internal one, which would prevent from nitrogen expulsion and formation of the metallanitrene (Scheme 3.29b).

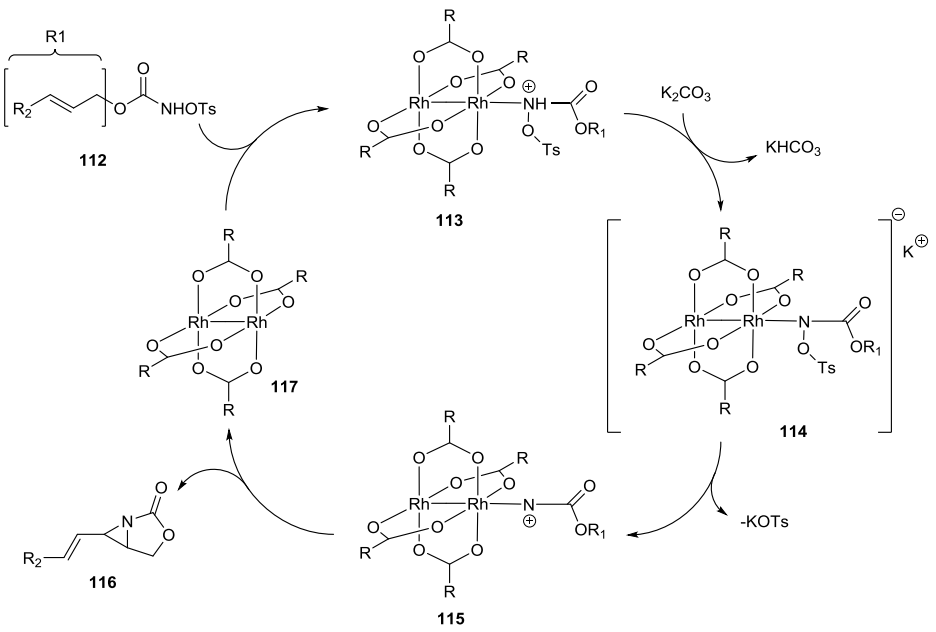
However, it was seeking for better leaving groups than nitrogen that in the same group were identified *N*-tosyloxycarbamates as a new and promising type of nitrogen-containing functional group.

_N_-tosyloxycarbamates

In a seminal work, Lebel *et al.* presented *N*-tosyloxycarbamates as a valuable alternative to iminoiodane-based methods for the insertion of nitrenes to C-H bonds and olefins that avoids the generation of stoichiometric amounts of iodobenzene.[103] Thus, in the presence of a generally high excess of base (K_2CO_3), *N*-tosyloxycarbamates **112** (Scheme 3.30) interact with rhodium carboxylate catalysts **117** generating the metallonitrene **115** upon expulsion of KOTs. This metallanitrene **115**, like in the rest of cases exposed, undergoes either C-H amination or aziridination (Scheme 3.30).[104]

In terms of final product considerations, *N*-tosyloxycarbamates afford cyclic acyl aziridines equivalent to those obtained from carbamates or acyl azides. So that, allylic and homoallylic olefins are preferred due to geometrical limitacions.

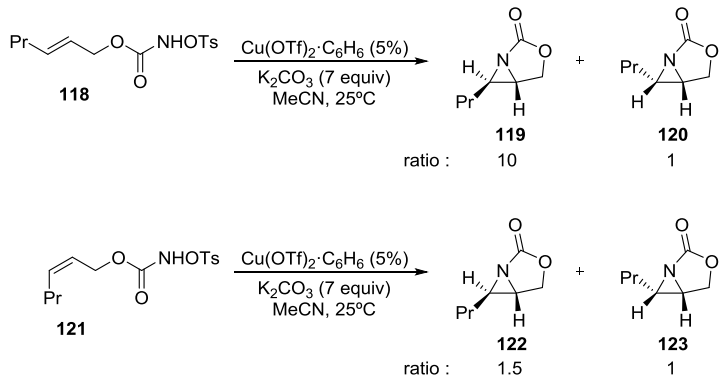
[103] Lebel, H.; Huard, K.; Lectard, S. *J. Am. Chem. Soc.* **2005**, *127*, 14198-14199.
[104] Huard, K.; Lebel, H. *Chem. Eur. J.* **2008**, *14*, 6222-6230.



Scheme 3.30. Lebel's proposed mechanism of the C-H amination using *N*-tosyloxycarbamates adapted to the aziridination reaction.[105]

An advantage respect to analogous carbamates, is that *N*-tosyloxycarbamates can be activated by copper catalysts. In this direction, the groups of Fleming and Lebel published separately and within a short time the copper-catalysed intramolecular aziridination of allylic carbamates.[105] The latter took advantage of the major solubility of a pyridine copper complex $Cu(pyridine)_4(OTf)_2$ to get improved yields. The process resulted stereoselective for *E*-alkenes (**118**, Scheme 3.31), but diastereoisomeric aziridine mixtures resulted from *Z*-alkenes (**121**) in support to the radical nature of the copper-catalysed reaction.

[105] a) Liu, R.; Herron, S. R. ; Fleming, S. A. *J. Org. Chem.* **2007**, *72*, 5587-5591. b) Lebel, H.; Lectard, S.; Parmentier, M. *Org. Lett.* **2007**, *9*, 4797-4800.



Scheme 3.31. Non-stereospecific copper-catalysed intramolecular aziridination of *N*-tosyloxycarbamates.[105a]

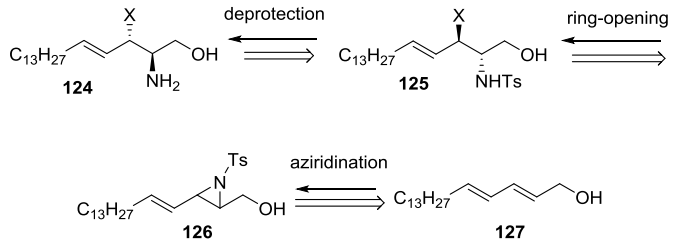
Conversely, Lebel proposed that the rhodium-catalysed aziridination of *N*-tosyloxycarbamates was stereospecific since only one diastereoisomer was observed. However, only examples of di- and tri-substitued *E*-alkenes were provided raising the question if that could be applied to *Z*-alkenes.[103]

As a final remark, the use of *N*-tosyloxycarbamates for the intramolecular aziridination of allenes found low yields of methylene aziridines and limited substrate scope.[106,92]

[106] Robertson, J.; Feast, G. C.; White, L. V.; Steadman, V. A.; Claridge, D. W. *Org. Biomol. Chem.* **2010**, *8*, 3060-3063.

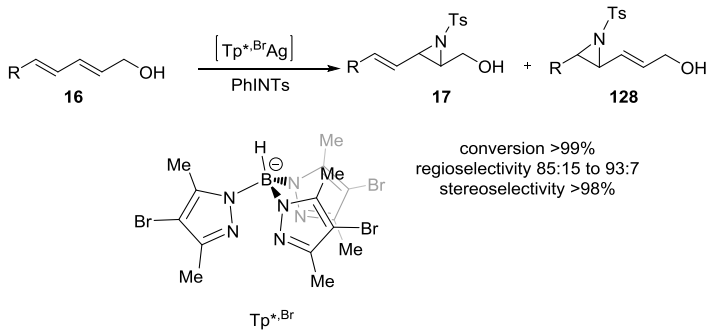
3.2. RESULTS AND DISCUSSION

The present work must be understood in the context of the ongoing efforts made by our group towards the development of new and efficient methodologies for obtaining sphingoid bases to gain access to galactosyl ceramides and analogues thereof. More concretely, we became especially interested on the investigation of methodologies that allowed the introduction of different functionalities on the C-3 position of sphingosine-type compounds **124** (Scheme 3.32). In this sense we designed a synthetic route in which the key element is the regio- and stereoselective aziridination of 2,4-diene-1-ols (**127**). The subsequent ring opening of aziridine **126** with different nucleophiles to give **125** and final deprotection of the amine moiety would render the desired sphingosine derivatives **124** (Scheme 3.32.).



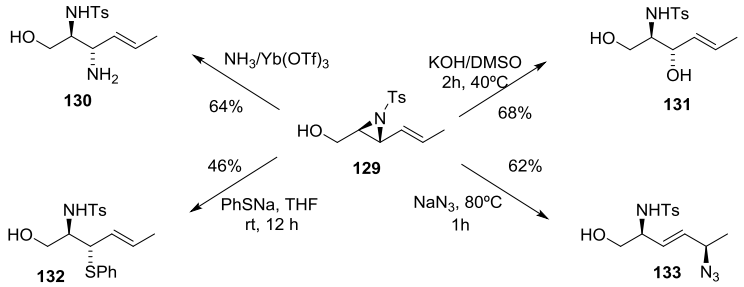
Scheme 3.32. Proposed retrosynthetic sequence for obtaining sphingosine derivatives with different substituents at C-3.

In our group it had been studied the intermolecular aziridination of 2,4-dien-1-ols using Tp*,^{Br}Ag as catalyst.[47] After optimization of the catalytic system full conversion was achieved using 1 mol% of catalyst loading, and the reaction was stereoselective (only *trans* aziridines were obtained from the *trans* alkenes) and regioselective (mixtures of 85:15 to 93:7 of aziridines **17**:**128** were obtained).



Scheme 3.33. Regio- and stereoselective aziridination of dienols catalysed by $Tp^{*,Br}Ag$.

The versatility of this type of vinyl aziridines **(129)** was then proved being readily ring opened with different nucleophiles such as NH_3, KOH, PhSNa or N_3 (Scheme 3.34).[78]

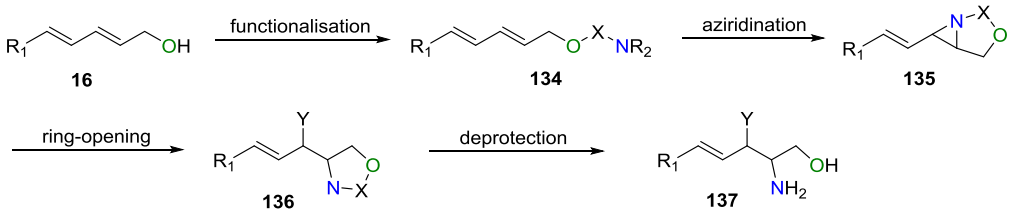


Scheme 3.34. Ring-opening reaction of aziridine **129**.

Tp*^{Br}Ag resulted optimum where the rest of catalyst tried were inferior for this type of transformation.[106] However, this uniquely effective combination of catalyst and substrate type could hamper the development of the enantioselective version of the process. In addition, in this previous work we demonstrated the effect of the hydroxyl group, directing the aziridination process with good, but not complete

[106] Other $Tp^{x}M$ (M = Cu, Ag) provided high to complete conversions and similar levels of regioselectivity than $Tp^{*,Br}Ag$ although without such an excellent stereoselectivity: Llaveria, J. (2011). *Synthesis Of Sphingoid Bases By Transition Metal-Catalised Reactions.* Ph.D. Thesis. Universitat Rovira i Virgili: Spain.

regioselectivity. As a concequence, it was considered that an intramolecular approach for the aziridination of dienols had the potential to overcome the aforementioned limitations of the intermolecular method. Therefore, we decided to investigate the intramolecular aziridination of 2,4-diene-1-ols derivatives **134** (Scheme 3.35).



Scheme 3.35. Proposed synthetic sequence for the preparation of C-3-substituted sphingosine derivatives via intramolecular aziridination of functionalised dienols.

The points considered to address our study in this direction are the following:

1) *Possibility to use copper and rhodium catalysts*. It is well-known the wide scope of commercial chiral bisoxazolines that copper can support and that provided good enantioselectivities in alkene aziridination. On the other hand, Rh(II) dimers, with either readily available chiral carboxylate and carboxiamidate ligands, gave the best enantioselectivities in reported intramolecular aziridinations.

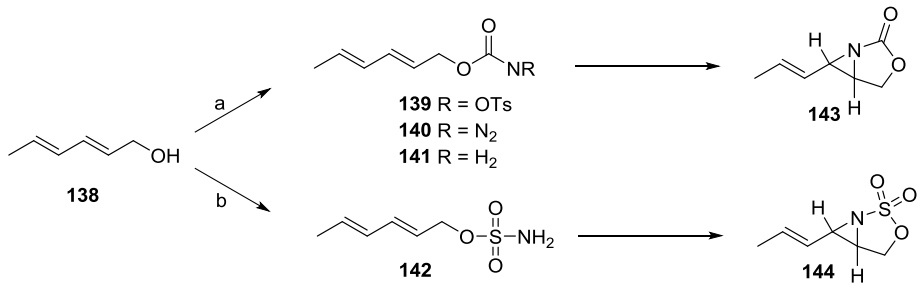
2) *Complete regioselectivity*. The geometrical restrictions present in the intramolecular process clearly should discard the nitrene delivery to the furthest double bond.

3) *Stereoselectivity*. As discussed in the introduction of the present chapter, copper catalyst show preference for a mechanism of aziridination involving radicals. In the case of rhodium, evidences suggest a strong substrate and catalyst-dependence on the mechanism. Mindful of these implications, we could think that the conformational restrictions provided by an intramolecular process could limit the extent of the isomerisation in the case of stepwise radical-based nitrene addition.

4) *Ease to remove protecting groups*.

3.2.1. PREPARATION OF FUNCTIONALISED DIENOLS

To initiate our studies on intramolecular aziridination we first identified the nitrogen-donor groups that would serve to functionalise the standard dienol **138** (Scheme 3.36). As it has been previously described in the above introduction, those functional groups leading to acyl aziridines are the most appropriate for allylic substrates due to geometrical parameters. Thus, studies on the aziridination of *N*-tosyloxycarbamate, acyl azide and carbamate derivatives of **138** to afford **143** will be our initial goal (Scheme 3.36a). In addition, the sulfamate functional group was also considered for comparison purposes (Scheme 3.36b). In this last case aziridine **144** would be expected.



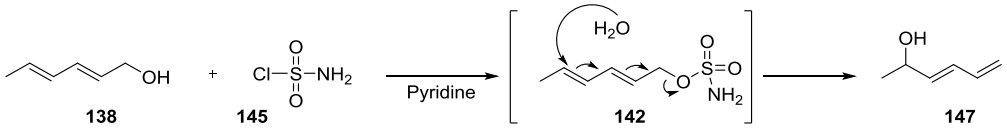
Scheme 3.36. Different nitrogen sources that will be used for the intramolecular aziridination of **138**.

Before going into details with the discussion of the results obtained from each type of functional group, it is important to mention that, unfortunately, all the attempts to prepare sulfamate **143** resulted fruitless. In fact, in most of the cases, the major product isolated was secondary alcohol **147** (Scheme 3.37).

Preparation of sulfamate **142** was attempted accordingly to the procedure described by Du Bois.[107] Sulfamoyl chloride was *in situ* generated from chlorosulfonyl isocyanate and formic acid. Subsequent sulfamoylation reaction of

[107] Espino, C. G.; When, P. M.; Chow, J.; Du Bois, J. *J. Am. Chem. Soc.* **2001**, *123*, 6935-6936.

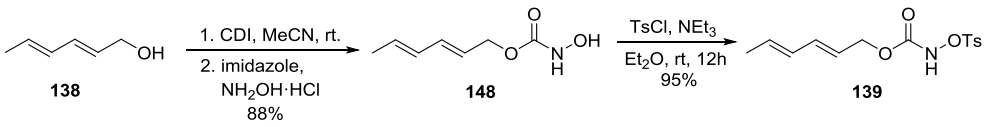
dienol **138** assisted by pyridine should give rise to sulfamate ester **142** (Scheme 3.37). However, unexpectedly compound (*E*)-hexa-3,5-dien-2-ol (**147**) was isolated as the sole product in 41% yield. Such isomerisation could be explained as a matter of the good leaving group ability of the allylic sulfamate, which would allow water (added during the work-up) to undergo conjugate addition. Working at lower temperatures or using other bases such as dimethylacetamide provided mixtures of products which ^{1}H NMR signals suggested the presence of **142**. However **142** could never be isolated by column chromatography.



Scheme 3.37. Possible pathway for the isomerisation of **138** into **147**.

3.2.2. AZIRIDINATION USING *N*-TOSYLOXYCARBAMATES

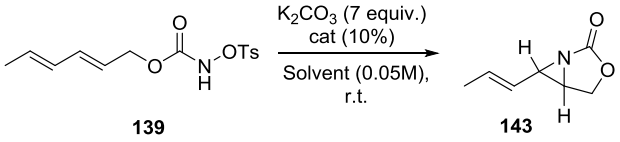
The formation of *N*-tosyloxycarbamates was carried out following the experimental procedures described in the literature (Scheme 3.38).[103,105] Thus, initial carbamoylation of **138** with carbonyl diimidazole (CDI) and further substitution of the restanting imidazole by hydroxylamine led to hydroxycarbamate **148** in 88% yield. Product **148**, after purification, was tosylated affording **139** in 95% yield from **148**. Normally hydroxycarbamate **148** can be used for the tosylation step without purification.



Scheme 3.38. Synthesis of *N*-tosyloxycarbamate derivative of dienol **138**.

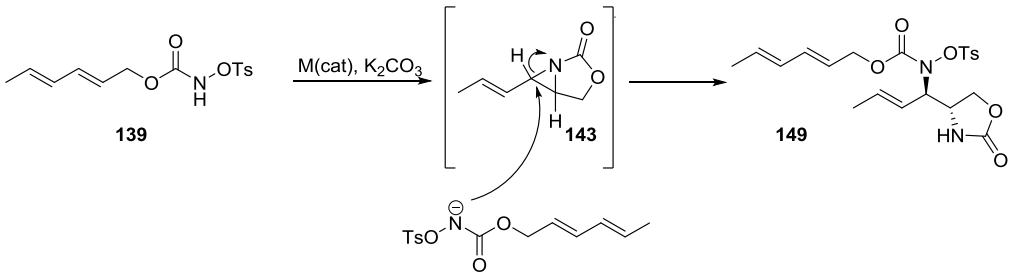
As the starting point for our investigations in aziridination reaction with this type of substrate we decided to reproduce those conditions initially employed by Lebel and

then by others.[103,105b] Therefore, 10% mol of the selected catalyst was used in combination with 7 equivalents of K_2CO_3 and the appropiate solvent (0.05M), runing the reactions at room temperature (Scheme 3.39).



Scheme 3.39. General conditions for the formation of bicyclic aziridine **143** through intramolecular aziridination of *N*-tosyloxycarbamate **139**.

Initially, we tested copper(I) triflate ($[Cu(OTf)]_2 \cdot C_6H_5$) and CuI as the catalyst and the reactions were run in acetonitrile. By using $[Cu(OTf)]_2 \cdot C_6H_5$, the almost complete consumption of the starting material led to a complex mixture of unidentified products not consistent with aziridine **143**. Only when CuI was used, traces of the aziridine **143** were detected. Similarly, $Rh_2(OAc)_4$ –mediated process provided also a complex mixture of products and high starting material conversion. Alternatively, when Tp*^{Br}Ag was tested, neither aziridination product **143** could be obtained. However, in this case we were able to isolate **149** (Scheme 3.40) by column chromatography and sufficient material was obtained to allow for a full spectroscopy characterization in support of this unprecedented structure.



Scheme 3.40. Formation of **149** by nucleophilic ring opening of the vinylaziridine **143**.

Comparison with the crude spectra revealed that **149** was present as the major product in all cases. Formation of **149** was attributed to the initial formation of the desired aziridine **143** followed by ring opening by nucleophilic attack of the deprotonated substrate at the allylic carbon of the aziridine (Scheme 3.40).

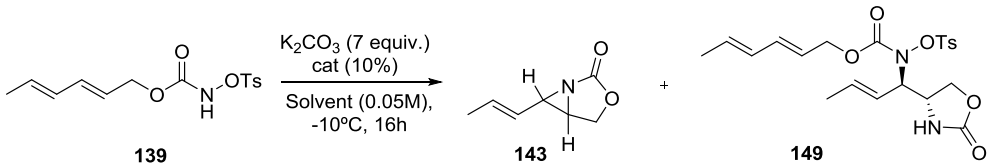
Molecular formula of compound **149** was confirmed by mass spectrometry. ^{1}H NMR showed six signals in the olefinic region consistent with the three double bonds of the molecule. A unique tosyl moiety was also clearly displayed. Moreover, ^{13}C experiment revealed the presence of a pair of carbonyl signals, which was confirmed by IR. Finally full 2D-NMR spectroscopy experiments were in agreement with the proposed product. As a key indicator, gHMBC correlation between the carbonyl of the diene fragment and the proton in α-position to the oxazolidone was observed.

At that point we became aware that the major issue to be concerned about would be the high electrophilicity of the targeted vinylaziridine **143**. As it has been introduced previously, this particularly high reactivity is the result of a combination of factors. Thus the intrinsic conformational strain of the three-membered ring is accentuated taking part on a bicyclic system. However, the most differential element is the presence of a vicinal double bond which would stabilise the formation of a *pseudo* carbocation in the allylic position largely lowering the energy barrier for a nucleophilic attack.

Taking advantage of the celerity of process,[108] we decided to repeat the catalyst screening at -10ºC aiming to obtain a more selective process and to prevent from aziridine ring opening (Table 3.1).

[108] Starting material was generally consumed in less than 3h at room temperature as indicated by TLC.

Table 3.1. Screening of catalyst in the aziridination of *N*-tosyloxycarbamate **139**.



Entry	Catalyst	Solvent	Conv. (%) [a]	143:149 [a],[b]
1	CuI	CH_3CN	>95	64:36
2	$[Cu(OTf)]_2 \cdot C_6H_5$	CH_3CN	>95	22:78
3	$[Cu(CH_3CN)]_4 \cdot PF_6$	CH_3CN	>95	28:72
4 [c]	CuCN	CH_3CN	60-70	0:100
5	$Tp^{*,Br}Cu$	CH_2Cl_2	>95	32:68
6	$Cu(OTf)_2$	CH_3CN	<5	-
7	$Cu(pyridine)_4(OTf)_2$	CH_3CN	>95	0:100
8	$Rh_2(OAc)_4$	Acetone	>95	0:100

[a] Determined by ^1H NMR spectroscopy. [b] The reaction gave mainly **143** and **149** unless otherwise indicated. [c] More unidentified products were obtained others than **143** and **149**.

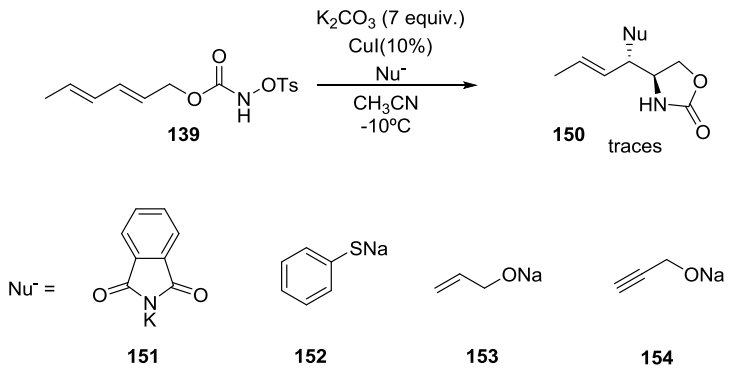
The selectivity of the aziridination of **139** was clearly enhanced at -10ºC since in all the cases with the exception of the poorly soluble CuCN only **143** and its ring opened derivative **149** were identified from the crude ^1H NMR spectra. Simple CuI resulted the most active catalyst (Table 3.1, entry 1). Other commonly employed Cu^I catalyst such as $[Cu(OTf)]_2 \cdot C_6H_5$ and $[Cu(CH_3CN)]_4 \cdot PF_6$ (Table 3.1, entries 2 and 3) gave a slight decrease in the **143**:**149** ratio. Similar activity was observed using complex $Tp^{*,Br}Cu$ (Table 3.1, entry 5). Contrary to those studies where Cu^{II} salts performed similarly to Cu^I, no reaction was observed using $Cu(OTf)_2$ (Table 3.1, entry 6). That apparent inactivity of Cu^{II} salts was solved using $Cu(pyridine)_4(OTf)_2$ (Table 3.1, entry 7). This complex was introduced by Lebel claiming that the better coordinating pyridine ligands would prevent from possible formation of insoluble copper carbonate complexes in such reaction conditions. In fact, in the aforementioned report, this complex displayed higher activity than others even at low catalyst loading (2 mol%).[105b] Using this system, even though aziridination took

place, only undesired ring opening product **149** was observed carrying out the reaction at -10ºC either in acetonitrile or acetone. Only working at -60ºC, in acetone, the aziridine is detected in very small quantities. Finally, $Rh_2(OAc)_4$ led exclusively to **149** suggesting that for this system Cu^I salts are more active (Table 3.1, entry 8).

Although the initial results were unsatisfactory, we were pleased to find that the aziridination process was stereoselective, at least concerning the model *trans*,*trans*-diene substrate **139** leading only the corresponding *trans* aziridine. The *trans* nature of the aziridine was stablished taking into consideration the coupling constants between the aziridine protons determined in the reaction crudes. Coupling constants between protons in *trans* aziridines have a value around 3-4 Hz, whereas in *cis* aziridines this value is higher (6-8 Hz).[105] In the particular case of vinyl aziridine **143**, the coupling constant was 4.1 Hz which matched with the expected *trans* aziridine.

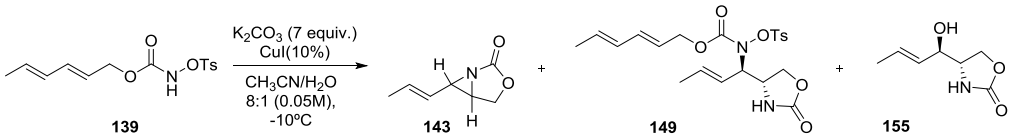
Next, we decided to investigate if further modifications of the reaction conditions could suppress the *in situ* ring opening of vinyl aziridine **143**. The variables taken into consideration were the concentration of the substrate solution and amount of base employed. Thus, the substrate concentration was evaluated in the 0.1M to 0.005M range and the amount of base from 1 to 7 equivalents. CuI was selected as the catalyst and the reactions were carried out in acetonitrile at -10ºC. None of the modifications had any remarkable impact favouring the rate of aziridine formation in detrimental to its ring opening.

We sought to stop the formation of **149** adding a competitive nucleophile in the reaction medium. Nevertheless, when nucleophiles such as potassium phtalamide (**151**), sodium thiophenolate (**152**) and propargylic (**153**) and allylic alcoholates (**154**) were *in situ* added in the reaction mixture, only traces of the ring opening products could be detected from the complex mixture of products obtained (Scheme 3.41).



Scheme 3.41. Attempt to avoid **149** formation by the addition of a competing nucleophile in the aziridination of **139**.

However, an interesting observation was done when the effect of added water was being investigated: a significant amount of hydroxylated compound **155** was isolated when the reaction was carried out in 8:1 acetonitrile/water mixture (Scheme 3.42 and Table 3.2, entry 1). Undoubtedly, **155** comes from the ring opening of **143** by either water or hydroxyl anions.

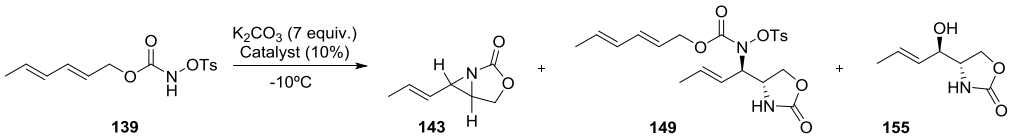


Scheme 3.42. Initial observation of the formation of aminoalcohol **155**.

Since **155** is an analogue of sphingosine, efforts were focussed on its selective formation (Table 3.2). For the optimisation of conditions temperature was maintained at -10ºC and the substrate/K_2CO_3/catalyst ratio at 1:7:0.1. Using CuI as the catalyst, the concentration, the organic solvent / water ratio and the type of solvent were varied without achieving any positive impact on the selectivity towards **155** (Table 3.2, entries 1-4). On the other hand, by using $Rh_2(OAc)_4$ almost complete selectivity for **155** could be obtained simply decreasing the substrate concentration from 0.05M to 0.01M (Table 3.2, entries 5 and 6). That allowed to isolate **155** in 61% yield. Sligh

modification of the temperature to -15ºC (Table 3.2, entry 7) or 0ºC (Table 3.2, entry 8) not only did not provide enhanced selectivity towards **155**, but a sharp decrease, which evidenced the sensibility to the reaction conditions of this transformation.

Table 3.2. Optimisation of conditions for the formation of hydroxylated compound **155**.[a]



Entry	Catalyst	Solvent (M)	**143:149:155**[b] (% **155 yield**)[c]
1	CuI	8:1 CH_3CN/H_2O (0.05)	38:12:50
2	CuI	46:1 CH_3CN/H_2O (0.005)	**149** major
3	CuI	99.5:0.05 CH_3CN/H_2O (0.005)	**149** major
4	CuI	8:1 CH_2Cl_2/H_2O (0.05)	**149** major
5	$Rh_2(OAc)_4$	8:1 CH_2Cl_2/H_2O (0.05)	32:68:N.D.
6	$Rh_2(OAc)_4$	8:1 CH_2Cl_2/H_2O (0.01)	0:10:90 (61)
7[d]	$Rh_2(OAc)_4$	8:1 CH_2Cl_2/H_2O (0.01)	0:28:72
8[e]	$Rh_2(OAc)_4$	8:1 CH_2Cl_2/H_2O (0.01)	0:100:0

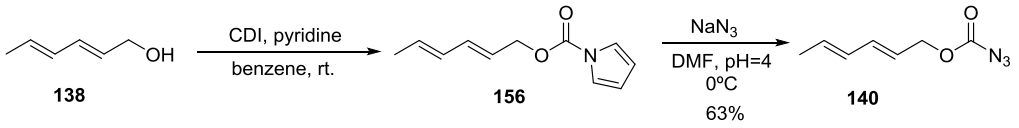
[a] All reactions showed complete starting material consumption in less than 16h. Substrate/K_2CO_3/catalyst: 1:7:0.1 [b] Determined by ^1H NMR spectroscopy. [c] Isolated yield. [d] T = -15ºC. [e] T = 0ºC.

3.2.3. AZIRIDINATION USING ACYL AZIDES

Acyl azide **140** was prepared adapting the procedure described by Hansen[109] in a similar fashion than the preparation of *N*-tosyloxycarbamate **139**. Therefore, dienol **138** was initially carbamoylated using carbonyldiimidazole. The adduct **156** was isolated and then trated at 0ºC with sodium azide at pH = 4 to afford compound **140** in 63% yield. Keeping the temperature at 0ºC was especially important to avoid

[109] Yuan, P.; Plourde, R.; Shoemaker, M. R.; Moore, C. L.; Hansen, D. E. *J. Org. Chem.* **1995**, *60*, 5360-5364.

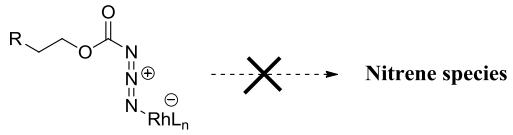
competitive reactions that led to unidentified side products observed when the reaction was conducted at room temperature.



138 **156** **140**

Scheme 3.43. Synthesis of acyl azide **140** from dienol **138**.

As previously mentioned in the introduction, rhodium catalysts have resulted inactive for the aziridination with organic azides. Lebel *et al.* postulated that the later could be attributed to the formation of a stable Lewis acid/Lewis base adduct through the coordination of rhodium to the terminal nitrogen rather than to the internal nitrogen of an acyl azide (Scheme 3.44) which would deactivate the catalyst and prevent from nitrogen expulsion.[102]

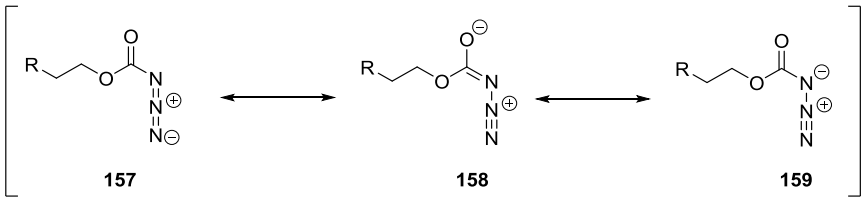


Scheme 3.44. Coordination oh rhodium catalysts to the external nitrogen of an acyl azide moiety as postulated by Lebel.[102]

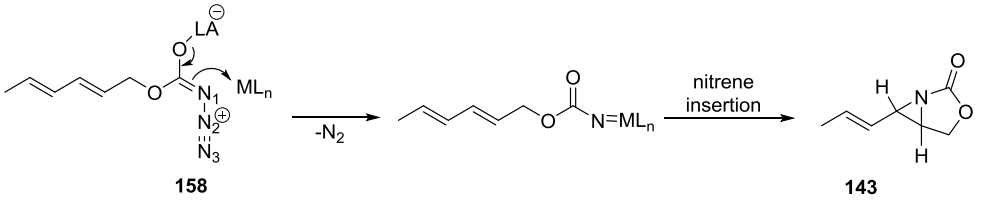
Mindful of this information, our strategy to enhance the feasibility of the reaction was to induce rhodium attachment to the internal nitrogen of the azide. In this regard we had to bear in mind the three possible resonance forms of acyl azides (Scheme 3.45).[110] Our hypothesis was that if we were able to force a greater contribution of either resonance form **157** or **158**, the metal catalyst would coordinate to the internal nitrogen atom producing nitrogen evolution and generating the metallanitrene. It was considered that a possibility would be the addition of equimolar amount of an

[110] Abu-Eittah, R. H.; Mohamed, A. A.; Al-Omar, A. M. *Int. J. Quant. Chem.* **2006**, *106*, 863-875.

oxophilicLewis acid that would coordinate the carbonyl oxygen expecting that the resulting complex would react in an "enolate-manner" with the catalyst (Scheme 3.46).



Scheme 3.45. Ressonance forms of acyl azides.



Scheme 3.46. Strategy to induce metal-catalysed nitrene addition reaction from acyl azides.

Our hypotheses found a theoretical basement in the calculations performed by Zabalov in Lewis acid/carbonyl azide adducts.[111] In the mentioned report it was studied the rate acceleration of the Curtius rearrangement of benzoyl azide into phenyl isocyanate in the presence of Lewis acids. In favor to our purposes, DFT analysis showed that coordination of a Lewis acid to the carbonyl oxygen was energetically more favourable than coordination to any of the azide nitrogens. In addition, such coordination favours resonance form **158** (Scheme 3.46), which results in the lowering of the strength of both the C=O bond and the N_1=N_2 bonds facilitating N_2 evolution. Obviously an expected complication was the competing Curtius rearrangement since, for example, it was reported that BF_3 complexes with acyl azides are already formed at -20ºC and rearrange to the isocyanate by only raising the

[111] Zabalov, M. V.; Tiger, R. P. *J. Mol. Struct.: THEOCHEM*, **2010**, *962*, 15-22.

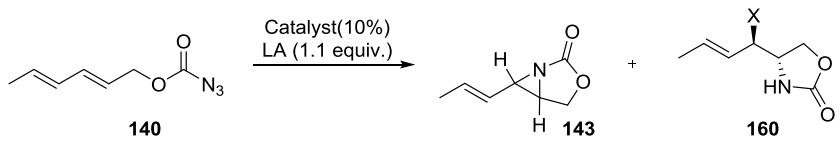
temperature to 0ºC.[112] Therefore our expectations were focused in two directions. Firstly, that the metal interacted in the way displayed in Scheme 3.46 or, alternatively, that the metal could trap an acylnitrene generated upon Lewis acid activation. The latter is based on the evidences supporting a stepwise pathway involving free acyl nitrene in the thermal and photochemical Curtius rearrangement of ethoxycarbonyl azide (structurally similar to our model substrate).[113] The catalysts of choice were rhodium(II) with electrondeficient tetracarboxylates since we were aware of their successful application in the sp^2 C-H amination with conjugated azides developed by Driver.[55b] In these studies a rhodium-nitrenoid was postulated as an intermediate.

Initial reaction of acyl azide **140** with either $Rh_2(OAc)_4$ or $Rh_2(OCOCF_3)_4$ did not provide any conversion (Table 3.3, entries 1 and 2) as it could be expected concerning Lebel's work.[102] It is worth commenting that the catalyst employed in Driver's work was $Rh_2(O_2CC_3F_7)_4$.

Then, we decided to explore the effect of Lewis acids. The procedure followed for this study involved an initial mixing of **140** and the Lewis acid in dichloromethane at the appropriate temperature. After 30 min. the catalyst was added and normally the temperature was raised. Initially TMSOTf was used in combination with $Rh_2(OAc)_4$ providing a very sluggish reaction outcome (Table 3.3, entry 3). The use of the softer TMSCl in combination with more electrondeficient $Rh_2(OCOCF_3)_4$ only led starting azide (Table 3.3, entry 4). To our delight, when $Rh_2(OCOF_3)_4$ was used in combination with $AlCl_3$, compound **160** was isolated even though in low yield (<10%) (Table 3.3, entry 5). Formation of **160** could arise from the nucleophilic ring opening of the strained aziridine **143** by a chloride anion released from $AlCl_3$.

[112] Fahr, E.; Neumann, L. *Angew. Chem.* **1965**, *77*, 591-592.
[113] Mc Conaghy Jr, J. S.; Lwowsky, W. *J. Am. Chem. Soc.* **1967**, *89*, 4450-4456.

Table 3.3. Study of the rhodium-catalysed intramolecular aziridination of acyl azide **140** in the presence of Lewis acids.[a]

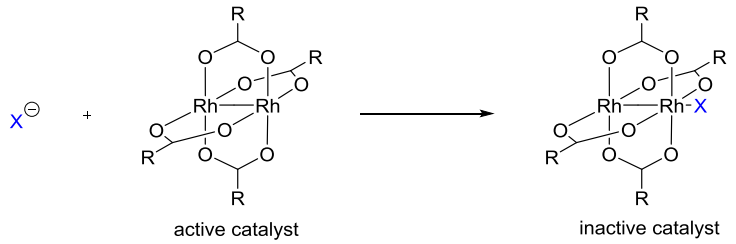


Entry	Catalyst	Lewis acid	Solvent	T(ºC)	Products (% yield) [b]
1	$Rh_2(OAc)_4$	-	toluene	rt	NR
2	$Rh_2(OCOCF_3)_4$	-	toluene	rt to 60	NR
3	$Rh_2(OAc)_4$	TMSOTf	CH_2Cl_2	rt	CM
4	$Rh_2(OCOCF_3)_4$	TMSCl	CH_2Cl_2	0	NR
5	$Rh_2(OCOCF_3)_4$	$AlCl_3$	CH_2Cl_2	-20 to 0	**160 (X=Cl)** (<10)
6	$Rh_2(OAc)_4$	$AlCl_3$	CH_2Cl_2	-20 to 0	NR
7	$Rh_2(OAc)_4$	$BF_3{\cdot}OEt_2$	CH_2Cl_2	-20	CM
8	$Rh_2(OCOCF_3)_4$	TMSOTf	CH_2Cl_2	-40 to 10	CM

[a] **140** (0.1 mmol), catalyst (10%), Lewis acid (0.11 mmol), solvent (0.05M). [b] Isolated yield. NR = no reaction. CM = complex mixture.

A closer monitoring of the reaction course by TLC revealed that formation of **160** is accomplished almost instantaneously after the addition of $Rh_2(OCOCF_3)_4$ in the mixture of **140** and $AlCl_3$ and then the reaction does not go forward. A plausible explanation for that would be the deactivation of the rhodium catalyst by coordination of a Lewis base in one of its acidic sites. A possibility, in this direction, is that the chlorine released by $AlCl_3$ was the deactivating agent had coordinated to the axial acidic sides of $Rh_2(OCOCF_3)_4$ producing the deactivation of the catalyst. An experimental evidence to support this theory was the presence of a singlet at -150 ppm in the ^{19}F NMR spectrum of the recovered catalyst from the reaction employing $BF_3{\cdot}OEt_2$ (Table 3.3, entry 7) and $Rh_2(OAc)_4$. This suggested that the fluorine released from $BF_3{\cdot}OEt_2$ upon coordination to the carbonyl had coordinated to the catalyst analogously to the chlorine. In addition, another experimental evidence is the

concurrent presence of a green precipitate in all the experiments carried out probably as a result of the precipitation of the poorly soluble Rh(II)-Lewis base adduct. Therefore the sharp drop of the reaction rate may be attributed to two effects resulting from Lewis base coordination to the catalyst. The first is the precipitation of the catalyst, and the second the loss of activity of the resting axial site once one is occupied (Scheme 3.47).[114] The need of electrondeficient rhodium catalyst became clear comparing entries 5 and 6 in Table 3.3 since no conversion is obtained by simply shifting from $Rh_2(OCOF_3)_4$ to $Rh_2(OAc)_4$.



Scheme 3.47. Coordination of Lewis bases to the Lewis acidic axial sides of Rh(II) dimers.

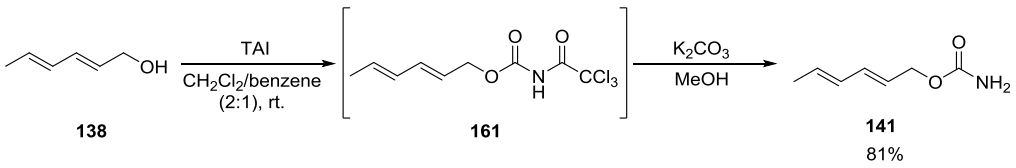
We finally attempted to use again TMSOTf expecting that the non-coordinating triflate anion would not deactivate the catalyst (0, entry 8). The addition of the Lewis acid was done at a lower temperature (-40ºC) than in the case of $AlCl_3$ owing to its markedly higher Lewis acidity. Unfortunately this did not find any success, even increasing the temperature.

The dificulty in finding conditions that meet the activation requirements for such reaction without deactivating the expensive catalysts used made us cease our effords on this approach and shift our attention to carbamate substrates.

[114] It was demostrated that the activity of the axial sites strongly decreases once one is occupied: Trindade, A. F.; Coelho, J. A. S.; Alfonso, C. A. M.; Veiros, L. F.; Gois, P. M. P. *ACS Catal.* **2012**, *2*, 370-383.

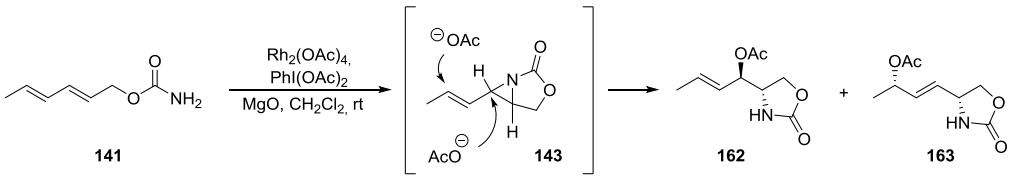
3.2.4. AZIRIDINATION OF CARBAMATES

Model carbamate **141** was easily obtained in 81% upon treatment of dienol **138** with trichloroacetyl isocyanate (TAI) followed by methanolysis of the intermediate trichloroacetyl carbamate **161** in the presence of K_2CO_3 (Scheme 3.48).



Scheme 3.48. Preparation of model carbamate substrate **141** from dienol **138**.

As starting point for the study of the intramolecular aziridination of dienyl carbamate **141** we selected the Du Bois conditions owing to their generality (Table 3.4, entry 1). The reaction proceeds smoothly providing acetates **162** and **163** as the two major products. Similarly to that observed in the study with *N*-tosyloxycarbamate **139**, the vinylaziridine generated easily reacted with any nucleophile present in the reaction medium. In this case, the nucleophiles are the acetate anions released in the formation of the iminoiodane intermediate from carbamate **141** and iodobenzene diacetate (Scheme 3.18 and Scheme 3.49).

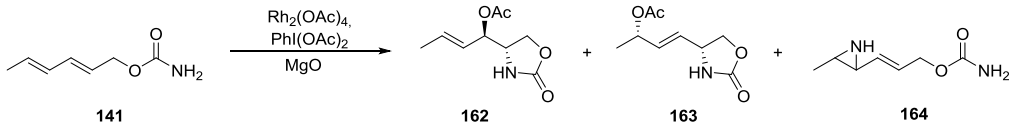


Scheme 3.49. Formation of acetates **162** and **163** by *in situ* ring opening of vinylaziridine **143**.

This phenomenon is well-known as a concurrent side reaction when the aziridine obtained is reactive enough to undergo ring opening with the carboxylate anions

released from $PhI(OCOR)_2$ oxidants. This was initially observed in the aforementioned pioneering works on intramolecular aziridination of carbamates by Rojas and Padwa (Scheme 3.50, a), where the tricyclic aziridines obtained were readily ring opened by acetate anions.[70a-c,e,74] Alternatively, this is also an ongoing issue in the studies on methylene aziridines derived from allenes (Scheme 3.50, b).[70f]

Table 3.4. Initial screening of catalysts for the intramolecular aziridination of **141**.[a]



141 **162** **163** **164**

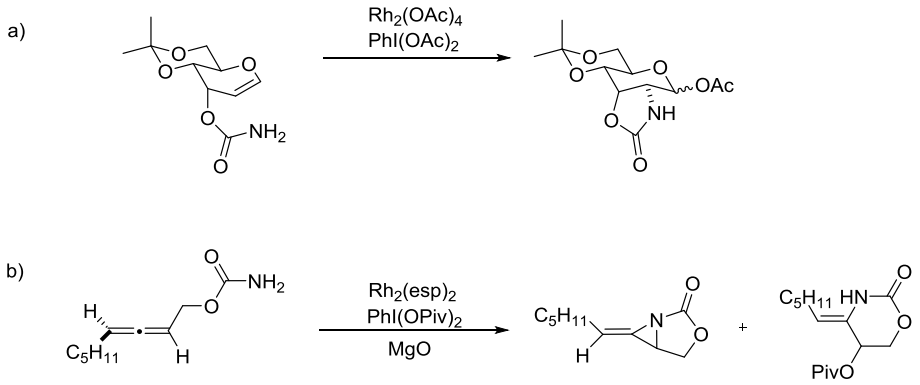
Entry	Catalyst	Solvent	T(ºC)	Conv. (%)[b]	(162/163/164) Ratio[b]
1	$Rh_2(OAc)_4$	CH_2Cl_2	rt	95	75:25:0
2	CuI	CH_3CN	rt	<2	-
3	$Cu(OTf)_2{\cdot}(C_6H_6)$	CH_3CN	rt	<2	-
4	$Cu(CH_3CN)_4PF_6$	CH_3CN	rt	<2	-
5	CuI	CH_3CN	40	>95	CM
6	$Cu(OTf)_2{\cdot}(C_6H_6)$	CH_3CN	40	>95	CM
7	$Cu(CH_3CN)_4PF_6$	CH_3CN	40	>95	CM

[a] **141** (0.1 mmol), catalyst (10%), $PhI(OAc)_2$ (0.2 mmol), MgO (0.33 mmol), solvent (0.05M). [b] Determined by ^1H NMR spectroscopy. CM = complex mixture.

Nevertheless, and contrary to the ring opening product (**149**) obtained from the *N*-tosyloxycarbamate **139**, acetates **162** and **163** were synthetically interesting for our purposes. The results on the selective synthesis of **162** and **163** type compounds will be discussed in section 3.2.5.

Going back to the screening of catalysts, we decided to explore the use of copper despite of being aware of the little activity displayed towards carbamate substrates by copper salts as mentioned in the introduction, apparently due to incompatibility with carboxylate salts. As it could be expected none of the copper catalysts tested in combination with $PhI(OAc)_2$ showed any activity when the reactions were carried out

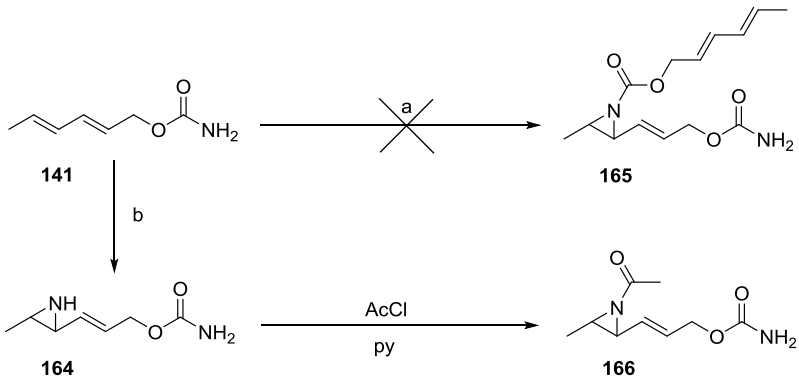
at room temperature (Table 3.4, entries 2-4). When the temperature was raised to 40ºC (Table 3.4, entries 5-7), the result was a complex mixture of products from which we were able to isolate aziridine **164**, the major product in each case concerning the crude ^{1}H NMR spectra.



Scheme 3.50. Examples of ring opening of reactive aziridines by carboxylate anions released from PhI(OCOR)$_2$.

Formation of vinylaziridine **164** was attributed to a non metal-catalysed intermolecular aziridination. Although we did not study the mechanism behind this transformation, our speculations are based in two main points. First of all the confirmation, based on the literature and our experimental results in Table 3.4, that copper salts fail in the catalysis of aziridination in the presence of carboxylate salts. This is strengthened by the good behaviour showed towards *N*-tosyloxycarbamates. The second argument is that the same compound **164** was also detected in the study of the metal-free aziridination of carbamates mediated by iodosylbenzene, which will be discussed later in Chapter 4. Interestingly, **164** was isolated as a diastereoisomeric mixture of aziridines with a 65:35 *trans*:*cis* ratio. Confirmation of the structure was made on the basis of complete NMR characterisation and mass spectroscopy. What was more intriguing of this compound (**164**) was the unprotected aziridine moiety since we would have expected product **165** from an intermolecular process (Scheme 3.51, a). To further confirm the presence of the N-H aziridine moiety, **164** was

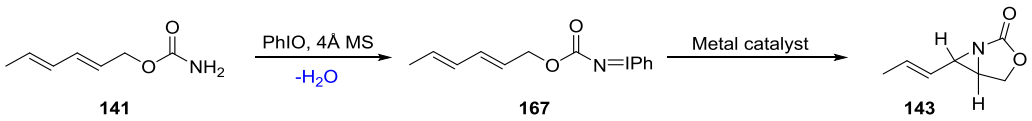
acylated providing the expected aziridine **166** (Scheme 3.51, b), the structure of which was confirmed by NMR spectroscopy.



Scheme 3.51. a) Expected product for the intermolecular aziridination of **141**.
b) Acetilation of **164**.

The good reactivity showed by $Rh_2(OAc)_4$ in this system encouraged us to explore its use in combination with PhIO. This oxidant could be efficiently used with rhodium(II) tetracarboxylate catalysts regardless of the type of nitrogen donor group. In addition, it has also been exposed to promote copper-catalysed aziridinations, banned with $PhI(OCOR)_2$ reagents.

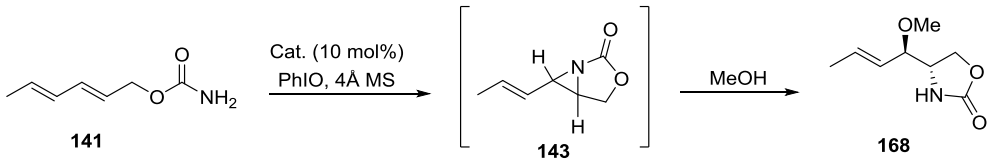
The typical reaction conditions employed in aziridinations mediated by PhIO are of particular interest for our sensitive system since the formation of the intermediate iminoiodane (**167** in Scheme 3.52) from PhIO releases water, which is trapped by molecular sieves. As a consequence we would be able to obtain the targeted vinylaziridine **143** preventing the subsequent ring opening (Scheme 3.52).



Scheme 3.52. General scheme for the metal-catalysed intramolecular aziridination using PhIO.

In order to accurately quantify the yield of the process, methanol was added to the reaction mixture after 16 hours in order to force complete ring opening of vinyl aziridine **143** and form **168** (Table 3.5). This would avoid that highly reactive **143** underwent side reactions during the work-up leading to unrepresentative results.

Table 3.5. Metal-catalysed intramolecular aziridination of **141** using PhIO.[a]



Entry	Catalyst	Solvent	Conv. (%)[b]	Yield (%)[c]
1	$Rh_2(OAc)_4$	CH_2Cl_2	40 c.a.	17
2	CuI	CH_3CN	54 c.a.	32
3	$Cu(CH_3CN)_4PF_6$	CH_3CN	49 c.a.	20
4	$Cu(OTf)\cdot(C_6H_6)^{1/2}$	CH_3CN	<2	0

[a] **141** (0.1 mmol), catalyst (10%), $PhI(OAc)_2$ (0.2 mmol), MgO (0.33 mmol), solvent (0.05M) and T = r.t. [b] Determined by ^1H NMR spectroscopy. [c] Determined by ^1H NMR spectroscopy using 1,3-dinitrobenzene as internal standard.

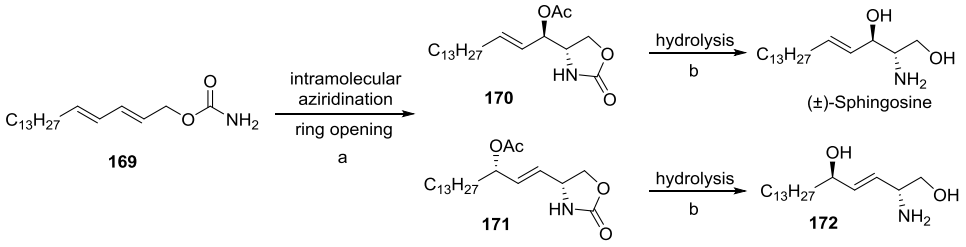
Disappointingly, the use of PhIO instead of $PhI(OCOR)_2$ as oxidant in the $Rh_2(OAc)_4$-catalysed aziridination of carbamate **141** proved to be much less efficient affording compound **168** in low yield (Table 3.5, entry 1). Yields improved slightly when CuI and $Cu(CH_3CN)_4PF_6$ were used (Table 3.5, entries 2 and 3), although the

process resulted unselective. Finally no reaction was observed when was $Cu(OTf)_2 \cdot (C_6H_6)$ was employed (Table 3.5, entry 4).

The low yields provided by this protocol and, even more, the low selectivities observed prompted us to abandon this route.

3.2.5. REGIOSELECTIVE OXYAMINATION OF DIENES

In the previous section it was commented that when carbamate **141** was treated with $Rh_2(OAc)_2$ and $PhI(OAc)_2$ in the presence of MgO a 75:25 mixture of acetates **162** and **163** was smoothly obtained (Table 3.4, entry 1). These types of compounds, considered as side products by others, result interesting for our purposes since by simple hydrolysis could lead to racemic sphingosine and its C-5 hydroxylated analogue **172** (Scheme 3.53). Especially in the case of the latter this would considerably shorten its preparation.[115]



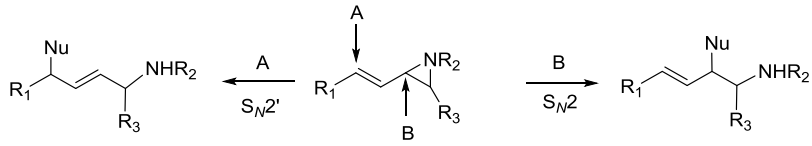
Scheme 3.53. Pathway for the preparation of (±)-sphingosine and its analogue **172**.

3.2.5.1. BACKGROUND

The presence of a double bond vicinal to an aziridine ring provides vinyl aziridines with an attractive reactivity pattern. Concerning the ring opening of vinyl aziridines with nucleophiles, it should be considered that this process can take place following two pathways: 1) by the attack of a nucleophile at the allylic aziridine

[115] Chun, J.; Byun, H.-S.; Arthur, G.; Bittman, R. *J. Org. Chem.* **2003**, *68*, 355-359.

carbon (named S_N2, pathway B in Scheme 3.54) and 2) by attack at the vinyl terminus through a conjugate 1,4-addition (named S_N2', pathway A in Scheme 3.54),[116]as a result of the selective weakening of the allylic C-N bond by πC=C–σ*C–N overlap.[117]



Scheme 3.54. Pathways for the ring opening of vinylaziridines.

Vinylaziridines also undergo isomerization and cycloaddition reactions affording a wide range of heterocycles through tandem opening/cyclization processes usually catalyzed by transition metal complexes.[48a]

A S_N2'path is generally observed with organocopper reagents,[118] whereas oxygen-centered nucleophiles,[119] halogens[120] and sulfur-stabilized carbanions,[121] lead preferentially to S_N2 products. These previous examples suggest that the regioselectivity of the ring opening reactions of vinylaziridines is governed mainly by

[116] Toda, A.; Aoyama, H.; Mimura, N.; Ohno, H.; Fujii, N.; Ibuka, T. *J. Org. Chem.* **1998**, *63*, 7053-7061.

[117] Carballares,S.; Craig, D.; Hyland, C. J. T.; Lu, P.; Mathie, T.; White, A. J. P. *Chem. Commun.* **2009**, 451-453.

[118] a) Ibuka, T.; Nakai, K.; Habashita, H.; Hotta, Y.; Fujii, N.; Taga, T.; Mimura, N.; Miwa, Y.; Yamamoto, Y. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 652-654. b) Fujii, N.; Nakai, K.; Tamamura, H.; Otaka, A.; Mimura, N.; Miwa, Y.; Taga, T.; Yamamoto, Y.; Ibuka, T. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1359-1371. c) Wipf, P.; Fritch, P. C. *J. Org. Chem.* **1994**, *59*, 4875-4886.

[119] a) Davis, F. A.; Reddy, G. V. *Tetrahedron Lett.* **1996**, *37*, 4349-4352. b) Atkinson, R. S.; Ayscough, A. P.; Gatrell, W. T.; Raynham, T. M. *Tetrahedron Lett.* **1998**, *39*, 4377-4380. c) Olofsson, B.; Somfai, P. *J. Org. Chem.* **2002**, *67*, 8574-8583. d) Olofsson, B; Somfai, P. *J. Org. Chem.* **2003**, *68*, 2514-2517. e) Disadee, W.; Ishikawa, T. *J. Org. Chem.* **2005**, *70*, 9399-9406.

[120] a) Righi, G.; Potini, C.; Bovicelli, P. *Tetrahedron Lett.* **2002**, *43*, 5867-5869. b) Righi, G.; Bovicelli, P.; Barontini, M.; Tirotta, I. *Green Chem.* **2012**, *14*, 495-502.

[121] Craig, D.; Lu, P. ; Mathie, T.; Tholen, N. T. H. *Tetrahedron* **2010**, *66*, 6376-6382.

the type of nucleophile. Nevertheless, vinylaziridine substitution, catalysts[122] and solvent also play a role in the regioselective opening control. In this sense, controlling the regioselective opening of vinylaziridines remains an unachieved challenge. The ability to control the regioselectivity would be of particular interest for our purposes since the concrete case of ring-opening reactions of vinylaziridines with oxygen nucleophiles constitutes a useful pathway for the stereoselective synthesis of unsaturated aminoalcohols (sphingosine-type compounds).[123]

3.2.5.2. RESULTS AND DISCUSSION

With this final goal in mind, initially we became interested in optimising the reaction conditions (Table 3.6), especially the catalyst loading taking into account the value of rhodium. Moreover, we would give preference to those conditions favouring the selective formation of one regioisomer over the other.

In a blank experiment we observed that the reaction did not proceed without the presence of $Rh_2(OAc)_4$ and little conversion to aziridine **164** was observed in this case (Table 3.6, entry 1). Keeping the catalyst loading at 10 mol% in a 0.05M substrate concentration, the use of benzene provided similar conversion than dichloromethane although with a decrease in the selectivity towards **162** (Table 3.6, entries 2 and 3). On the other hand, the system resulted sensitive to the catalyst loading. Thus, using 5 mol% of $Rh_2(OAc)_4$ not only the reaction rate experimented a drop but also the reaction resulted less selective as it was observed from the crude ^{1}H NMR spectrums (Table 3.6, entry 4). An increase of the temperature to 40ºC resulted in the increase on intermolecular formation of aziridine **164** (Table 3.6, entry 5). In order to overcome the rate drop, the concentration of the solutes was doubled.

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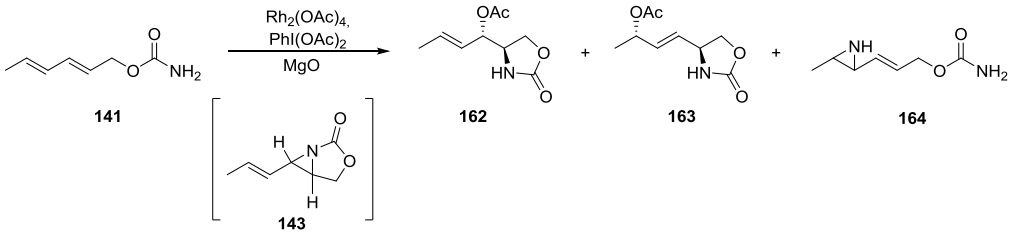
[122] a) Trost, B. M.; Fandrick, D. R.; Brodmann, T.; Stiles, D. T. *Angew. Chem. Int. Ed.* **2007**, *46*, 6123-6125. b) Crotti, S.; Bertolini, F.; Macchia, F.; Pineschi, M. *Org. Lett.* **2009**, *11*, 3762-3765.

[123] For a review about the synthesis of sphingosines see: Morales-Serna, J. A.; Llaveria, J.; Díaz; Y., Matheu, M. I.; Castillón, S. *Curr. Org. Chem.* **2010**, *14*, 2483-2521.

However, this only favoured an additional increase in the formation of **164** as well as providing a more unselective outcome (Table 3.6, entry 6).

Table 3.6. Optimization of the catalyst loading in the rhodium-catalysed aziridination of **141**.[a]

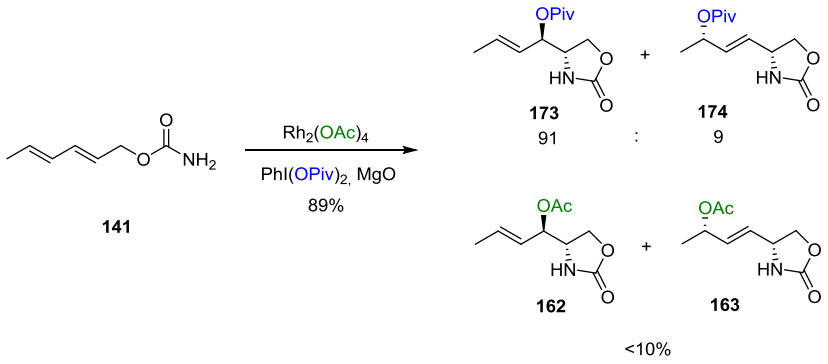


Entry	Catalyst (mol %)	Solvent (M)	T(ºC)	Conv. (%)[b]	(162/163/164) Ratio[b]
1	none	CH_2Cl_2 (0.05)	rt	<10	0:0:100
2	$Rh_2(OAc)_4$ (10%)	CH_2Cl_2 (0.05)	rt	>95	75:25:0
3	$Rh_2(OAc)_4$ (10%)	Benzene (0.05)	rt	73	65:35:0
4	$Rh_2(OAc)_4$ (5%)	CH_2Cl_2 (0.05)	rt	~50	69:31:0
5	$Rh_2(OAc)_4$ (5%)	CH_2Cl_2 (0.05)	40	~50	70:23:7
6	$Rh_2(OAc)_4$ (5%)	CH_2Cl_2 (0.01)	rt	~60	61:20:19

[a] **141**/$PhI(OAc)_2$/MgO (1: 2: 3.3) [b] Determined by ^1H NMR spectroscopy.

With the optimised conditions in hand (Table 3.6, entry 2) we focused our attention on the selective obtention of S_N2-oxyamination products (analogues of **162**). We thought that stronger nucleophile than acetate would preferentially undergo 1,2-addition at the aziridine ring of **143**. Therefore $PhI(OAc)_2$ oxidant was replaced by $PhI(OPiv)_2$ and used in the optimised conditions (Scheme 3.55). Effectively, compounds **173** and **174** bearing a pivaloate group where obtained with and increased regioselectivity (91:9). However, a small amount of **162** and **163** was also

isolated. After checking that $PhI(OPiv)_2$ was pure, the most plausible explanation was that the acetate ligands in the rhodium catalyst were replaced by the more strongly coordinating pivalate anions, and were then involved in the aziridine opening.

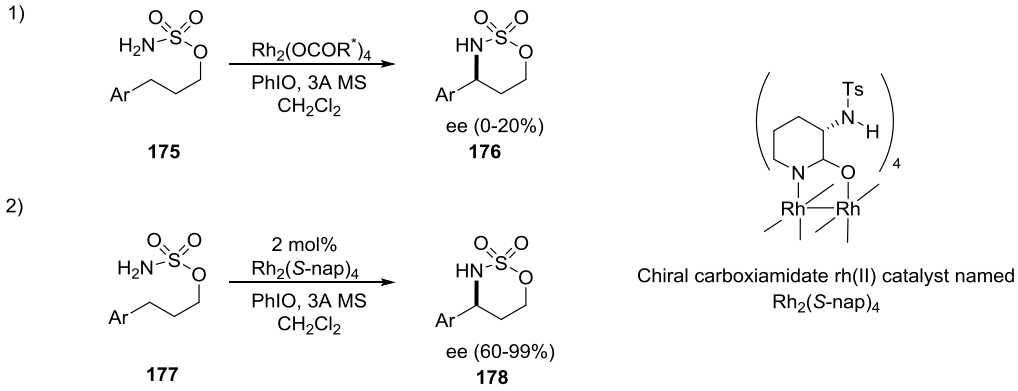


Scheme 3.55. Intramolecular aziridination-ring opening of **141** using $PhI(OPiv)_2$.

This effect is a consequence of the higher lability of carboxylate ligands compared, for example, to carboxiamidate ligands, as a result of a weaker sigma donation from the ligand to the metal centre.[124] An illustrative example of this behaviour in relation to carboxiamidates was provided by Du Bois and Zalatan during the studies on asymmetric C-H amination (Scheme 3.56).[125] They observed that the enantiomeric ratio in the intramolecular amination of **175** was decreasing over the time when the reaction was catalysed by chiral rhodium (II) tetracarboxylate catalysts, which suggested modification of the structure of the catalyst related to the lability of carboxylate ligands (Scheme 3.56, eq. 1). That was further confirmed by the high and robust enantiomeric ratios obtained with chiral carboxiamidate ligands (Scheme 3.56, eq. 2).

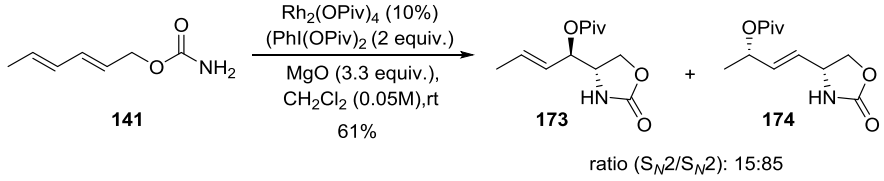
[124] *Progress in Inorganic Chemistry*; Doyle, M. P., Ed.; Wiley: New York, **2001**; vol 49, 113-168.
[125] Zalatan, D. N.; Du Bois, J. *J. Am. Chem. Soc.* **2008**, *130*, 9220-9221.

It was then considered for our purposes was the use $Rh_2(OPiv)_4$ as the catalyst, in combination with $PhI(OPiv)_2$, since it would avoid competition between carboxylate anions in the ring opening (Scheme 3.57).



Scheme 3.56. Varing e.r. during the time in the C-H amination reaction catalysed by chiral rhodium (II) tetracarboxylates and carboxyamidates.

$Rh_2(OPiv)_4$ was prepared heating $Rh_2(OAc)_4$ at 130ºC in pivalic acid following a reported procedure.[126] The use of $Rh_2(OPiv)_4$ in the reaction with **141** provided a notoriuous surprise since a reversion on the regioselectivity was observed. Thus a oxazolidinones **173** and **174** were obtained in 61% yield and with a regioisomeric ratio of 15:85.



Scheme 3.57. Aziridination-ring opening of carbamate **141** using $Rh_2(OPiv)_4$ as the catalyst.

[126] Cotton, F. A.; Felthouse, T. R. *Inorg. Chem.* **1980**, *19*, 323-328.

Encouraged by this unexpected result we decided to study the effect that the nucleophile (modifying the I(III) oxidant) and the catalyst had on the regioselectivity (Table 3.7). For the study of nucleophiles, trifluoroacetate, benzoate and *p*-methoxybenzoate $PhI(OR)_2$ derivatives were chosen, apart from the already used acetate and pivalate.

Iodobenzene dibenzoate and the corresponding *p*-methoxybenzoate are not commercially available. They were prepared by stirring $PhI(OAc)_2$ and either benzoic acid or *p*-methoxybenzoic acid in chlorobenzene at 50ºC at low vacuum to remove the acetic acid generated.[127]

Thus, when the reaction is catalysed by $Rh_2(OAc)_4$, the S_N2 ring opening is the main process, and the extend of the preference towards S_N2 attack can be related to the respective nucleophilicity of the carboxylates used (Table 3.7, entries 1-4). Concretely, the best S_N2 selectivity is obtained when pivalate is the carboxylate released during the iminoiodane formation (Table 3.7, entry 2), whereas the least is observed with benzoate anion (Table 3.7, entry 3). On the other hand, when the reaction was catalysed by the more sterically demanding $Rh_2(OPiv)_4$, the S_N2' attack was preferentially produced, and the character of the nucleophile did not have a significant influence on the regioselectivity (Table 3.7, entries 7-9). In fact, only when $PhI(OAc)_2$ is used a slight increase in the regioselectivity respect to other nucleophiles is achieved (Table 3.7, entry 6). In terms of catalyst activity, $Rh_2(OPiv)_4$ provided complete conversion of starting carbamate **141** in 24 hours, whereas 48 hours were required for $Rh_2(OAc)_4$. This higher activity allowed carrying out the reaction at lower temperature (5ºC) providing almost complete selectivity for the S_N2' attack (Table 3.7, entry 12). Alternatively, rising the temperature to 45ºC rendered a small decrease in the regioselectivity (Table 3.7, entry 11).

From the results collected in Table 3.7 it appeared evident that the catalyst was responsible for the control of the regioselectivity.

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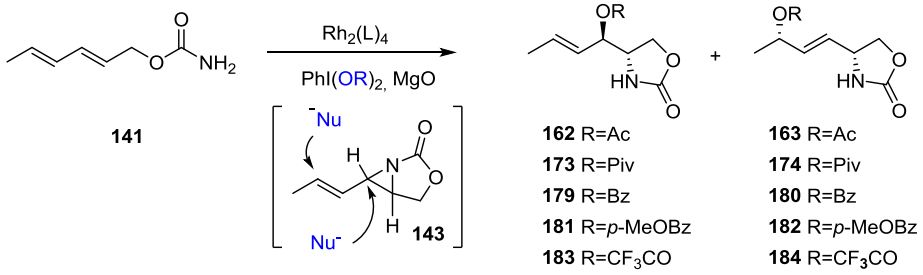
[127] Stang, P. J.; Boehshar, M.; Wingert, H.; Kitamura, T. *J. Am. Chem. Soc.* **1988**, *110*, 3272-3278.

Table 3.7. Tandem intramolecular aziridination/ring opening of **141** with different nitrene sources using Rh(II)carboxylate as catalysts. Optimization of the reaction conditions.[a]



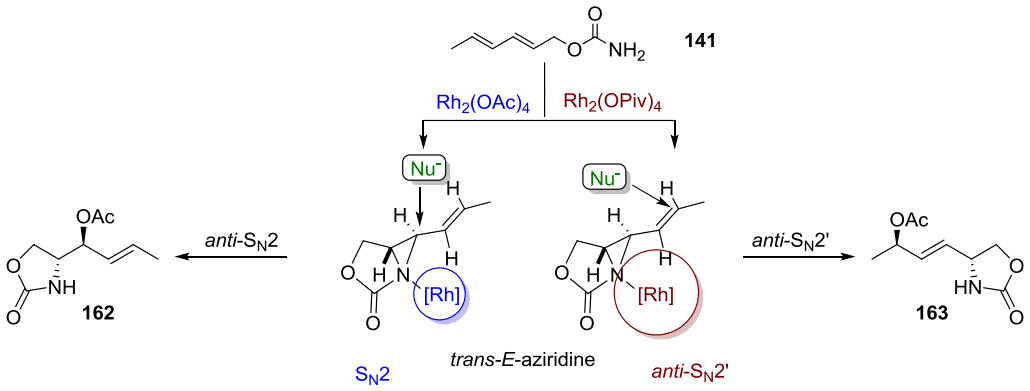
Entry	R	L	Products	Conv.[b] (Yield)[c] (%)	S_N2: S_N2' ratio(%)[b]
1	Ac	OAc	**162,163**	95(87)	75:25
2	Piv	OAc	**173,174**	>99(89)[d]	91:9
3	Bz	OAc	**179,180**	>99(91)	66:34
4	*p*-MeO-Bz	OAc	**181,182**	>99	77:23
5	CF_3CO	OAc	**183,184**	>99(0)	-
6	Ac	OPiv	**162,163**	>99 (82)	10:90
7	Piv	OPiv	**173,174**	>99(61)	15: 85
8	Bz	OPiv	**179,180**	>99(82)	14:86
9	*p*-MeO-Bz	OPiv	**181,182**	>99	15:85
10	CF_3CO	OPiv	**183,184**	>99(0)	-
11[e]	Ac	OPiv	**162,163**	>99	18:82
12[f]	Ac	OPiv	**162,163**	>99(74)	<5:95

[a] Catalyst/**141**/$PhI(OR)_2$/MgO (0.1: 1: 2: 3.3) in a 0.05M substrate solution in CH_2Cl_2, T= 20ºC, t= 24 h for $Rh_2(OAc)_4$ and 48h for $Rh_2(OPiv)_4$. [b]Determined by ^1H NMR. [c] Isolated yields (combination of regioisomers). [d]Compounds **162,163** were also obtained in 8% yield. [e] Temperature 45ºC. [f]Temperature 5ºC.

The use of different $PhI(OR)_2$ oxidants can also be addressed concerning their ability to form a common iminoiodane. In this regard all showed similar behaviour with the exception of $PhI(OCOCF_3)_2$, which led to a complex mixture of unidentificable products (Table 3.7, entries 5 and 10). In all cases, products were obtained after a short filtration in silica gel. It is interesting to note that yields suffered

a sharp drop when longer column chromatography was carried out in order to isolate both regioisomers. Yields are not indicated in cases when it was not possible to completely separate both regioisomers.

Our initial hypothesis to explain the inversion in the regioselectivity (Scheme 3.58), by simply changing the catalyst, was to consider that the rhodium catalyst remained coordinated to the aziridine nitrogen acting as a Lewis acid and activating the opening process. In fact, this coordination is postulated in the vast majority of publications dealing with mechanistic studies on aziridination.[67b,83] Thus, we thought that the more sterically demanding $Rh_2(OPiv)_4$ would hamper the S_N2 ring opening in favour to the S_N2'. On the other hand, smaller $Rh_2(OAc)_4$ would have an innocuous effect in terms of sterics as it was confirmed by the different product distribution as a function of the electronic properties of the nucleophiles (Table 3.7, entries 1-5).

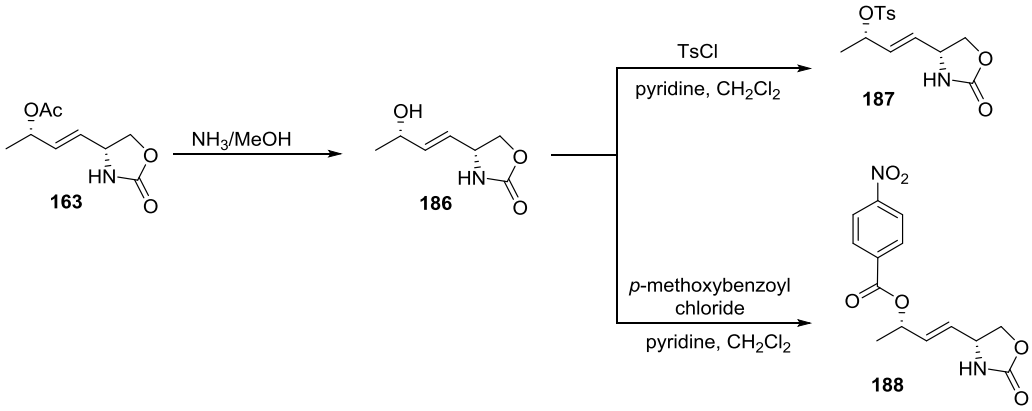


Scheme 3.58. Initial proposal to explain the effect of the catalyst on the regioselectivity of the aziridine ring opening.

Next the relative configuration of the two stereogenic generated was investigated. As it is depicted in Scheme 3.58, and owing to the normal reactivity of vinyl aziridines and vinyl epoxides, we assumed for **162** a *trans*-disposition between the acetate substituent and the oxazolidinone nitrogen as a result of the normal *anti*-S_N2 ring opening. In the case of the S_N2' ring opening, although it could be expected an

anti-S_N2' ring opening,[118] the longer distance between the aziridine leaving group and the carbon attacked raised some doubts that could not be ignored.

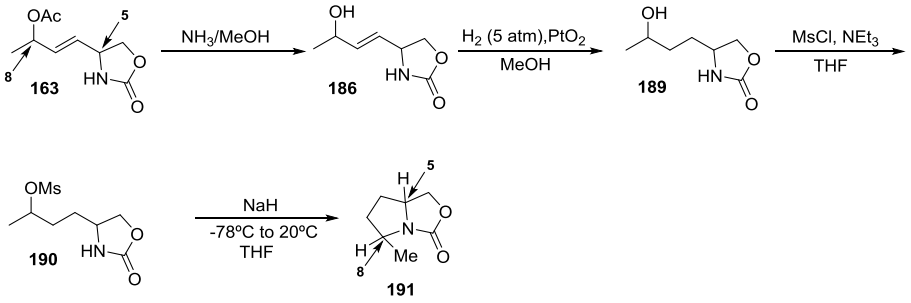
Thus, with the aim of knowing the relative configuration of S_N2' products we tried, at first, to grow a single crystal of **163** without success. The same result was obtained with benzoyl derivative **180**. Then, acetate **163** was then converted into tosyl-derivative **187** after methanolysis of the acetyl group to give **186**, and further tosylation. *p*-Nitrobenzoyl derivative **187** was also obtained although with none of them single crystals were obtained (Scheme 3.59).



Scheme 3.59. Modification of acetate **163** into **187** and **188**.

The lack of known compounds in the literature that could be easily accessed from **163** in order to assign by analogy the relative configuration, prompted as to face the derivatisation of **163** into carbamate **191** (Scheme 3.60), since we expected to determine the relative configuration by a NOE study. Thus, **163** was converted into **186** by aminolisis, and the double bond was reduced to give **189** using hydrogen in the presence of PtO_2 as catalyst. Reaction of **189** with mesyl chloride afforded mesylate **190**, from which compound **191** was obtained by an intramolecular substitution in basic medium.

This product would allow us to carry out NOE experiments from what the relative configuration in **163** could be deduced (Scheme 3.60). Concretely, the relative configuration of carbon 5 and 8 in **191** will provide us the information about the relative configuration between carbon 5 and 8 in **163**.



Scheme 3.60. Synthesis of bicyclic carbamate **191** for the determination of the relative configuration of **163** and its analogues.

A full characterisation of the product **191** was carried out by the means of complete NMR analysis (^{1}H, ^{13}C, gCOSY, gHSQC, gHMBC) that allowed an unambigous assignment of all signals in the ^{1}H NMR spectrum.

From the NOESY spectrum (Figure 3.3 and Figure 3.4), the most determinig information would have been provided by either a correlation between H_8 and H_5 or between H_9 (Me) and H_5. Unfortunately the signals observed in Figure 3.3 and Figure 3.4 between these protons are not conclusive. Alternatively we were able to conclude that H_9 (Me) and H_5 were in a *trans* disposition in compound **191** taking into consideration the observations listed below:

- Absence of correlation between the H_5 and H_7 in combination with the NOE correlation observed between H_5 and $H_{7'}$ (Figure 3.3).
- Intense correlation between $H_{7'}$ and H_8 compared with the little correlation existent between H_7 and H_8 (Figure 3.4).
- H_9 (Me) correlates with H_7 but not with $H_{7'}$ (Figure 3.3).

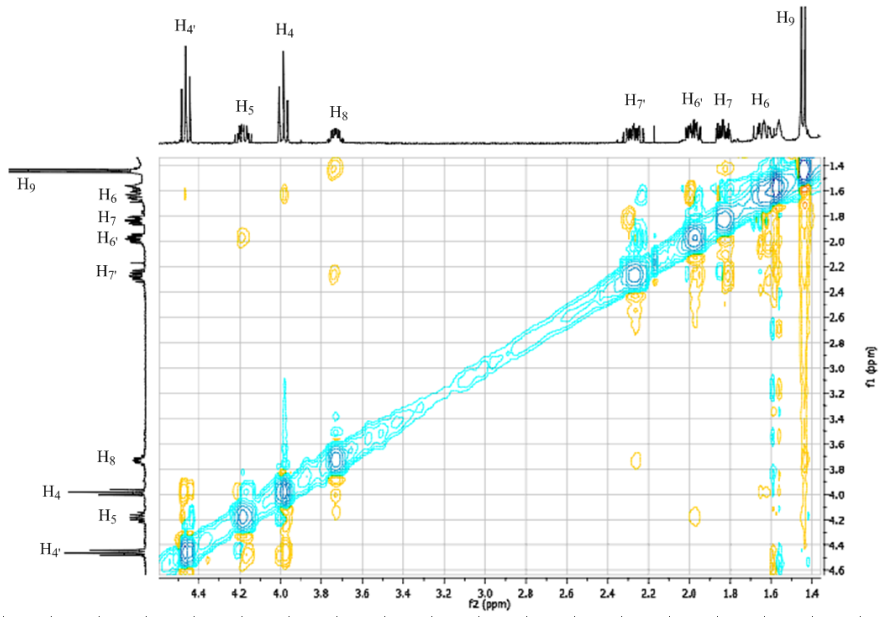


Figure 3.3. Full NOESY spectrum of **191**.

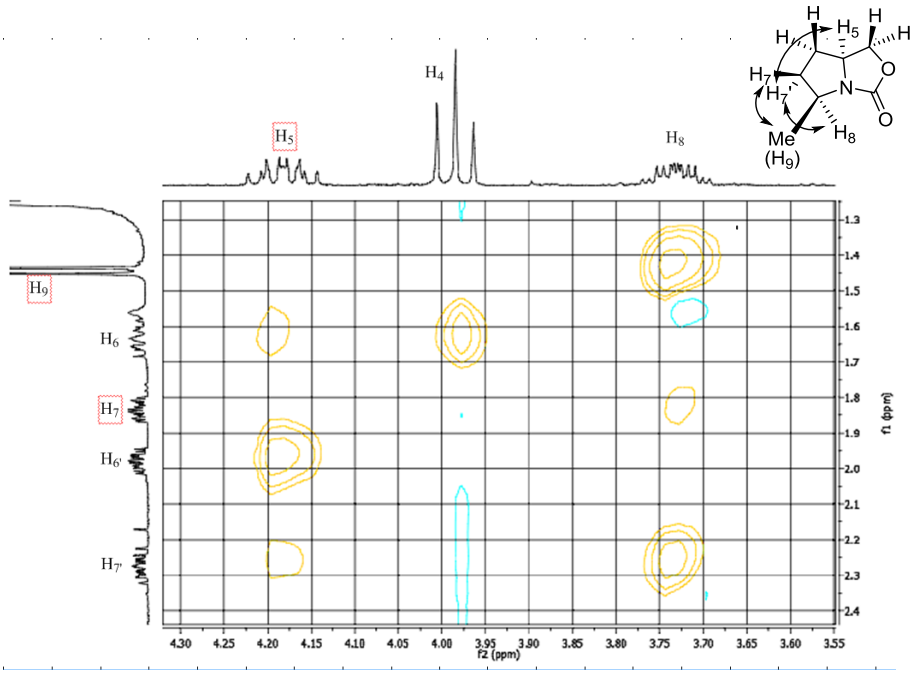
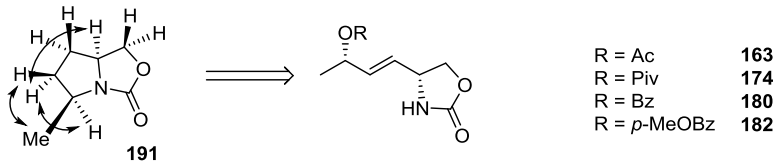


Figure 3.4. Amplified NOESY spectrum of **191**.

Consequently, and taking into consideration the inversion of configuration at C_1 during the synthesis of **191**, the acetate substituent in **163** and the aziridine nitrogen are in a *syn*-disposition and, analogously, the same disposition is attributed to **174**, **180** and **182** (Scheme 3.61). This relative configuration, in turn, implies that the nucleophilic ring opening of vinylaziridine **143** took place throuhg a *syn*-S_N2', which is the opposite configuration than the initially expected.

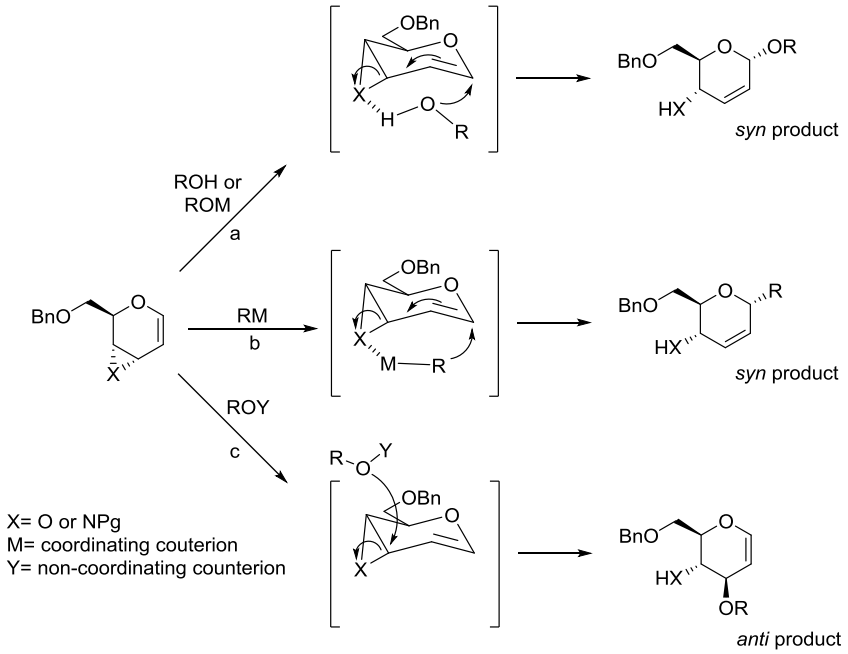


Scheme 3.61. Assignament of the relative configuration in S_N2' products.

In the elaboration of a reasonable explanation to understand this unexpected outcome it was of particular interest the deep study developed by Crotti *et al.* on the synthesis and ring opening of glycal-derived vinyl aziridines and vinyloxiranes with *O*-nucleophiles and *C*-nucleophiles (Scheme 3.62).[128] Concerning the *O*-nucleophiles, they observed that the configuration of the anomeric carbon after the ring opening depended on the configuration of the corresponding aziridine or epoxide. Their experimental results raised the conclusion that the regio- (attack at C_1 or C_3) and the stereoselectivity (attack at C_1 in *anti*- or *syn*-fashion) were related with the capacity of the *O*-nucleophile to coordinate the epoxidic oxigen or the aziridine nitrogen via H-bonding or metal coordination, and direct the alkoxyde towards C_1 in a *syn*-fashion (Scheme 3.62, pathways a and b). Thus, when alcohols (H-bond donors) or metal alcoxydes with a coordinating couterion were used, the nucleophilic attack took place

[128] For vinyl oxiranes see: a) Di Bussolo, V.; Caselli, M.; Pineschi, M.; Crotti, P. *Org. Lett.* **2002**, *4*, 3695-3698. b) Di Bussolo, V.; Caselli, M.; Romano, M. R.; Pineschi, M.; Crotti, P. *J. Org. Chem.* **2004**, *69*, 7383-7386. For vinyl aziridines see: c) Di Bussolo, V.; Romano, M. R.; Pineschi, M.; Crotti, P. *Org. Lett.* **2005**, *7*, 1299-1302. d) Di Bussolo, V.; Romano, M. R.; Favero, L.; Pineschi, M.; Crotti, P. *J. Org. Chem.* **2006**, *71*, 1696-1699. e) Di Bussolo, V.; Fiasella, A.; Favero, L.; Bertolini, F ; Crotti, P. *Org. Lett.* **2009**, *11*, 2675-2678. f) Di Bussolo, V.; Checchia, L.; Romano, M. R.; Favero, L.; Pineschi, M.; Crotti, P. *Tetrahedron* **2010**, *66*, 689-697.

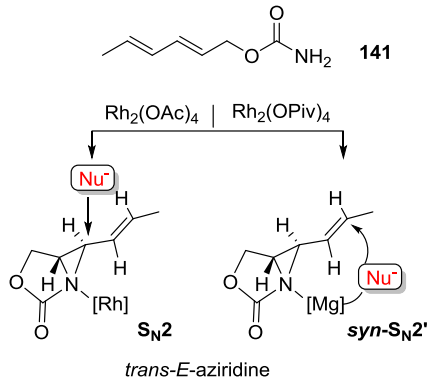
selectively at C_1 with almost complete *syn* selectivity. On the other hand, when *O*-nucleophiles bearing non-coordinating couterions ($TBA^+Me_3SiO^-$ or TBAOMe) were used, the ring opening occurred selectively at the allylic carbon in an *anti* fashion.



Scheme 3.62. Summary of the conclusions of Crotti *et al.* about the regio- and stereoselectivity in the ring opening of vinyl aziridines and vinyl oxiranes with *O*- and *C*-nucleophiles.

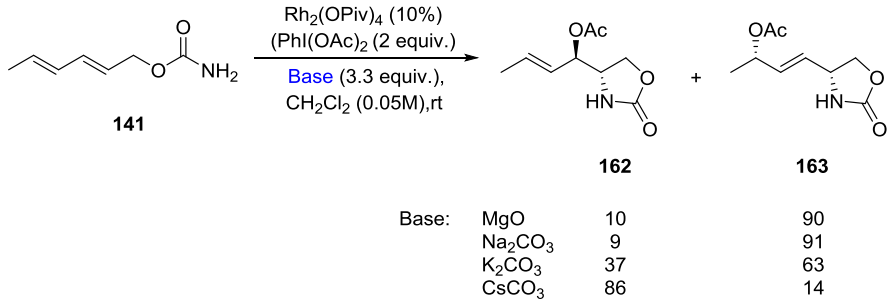
Returning to our work, our proposal had to take into account that, contrary to Crotti's work, in our case the coordination ability of the *O*-nucleophile ($Mg(OR)_2$) did not change since we were dealing always with the same countercation (Mg^{2+}). With all the information from Crotti's work and our experimental evidences we proposed that the strong preference for the S_N2 attack in the $Rh_2(OAc)_4$-catalysed process can be rationalized considering that rhodium remains coordinated to nitrogen, and $Mg(OCOR)_2$ opens the activated aziridine through an *anti*-S_N2 process. Conversely, the sterically more demanding $Rh_2(OPiv)_4$ can be easily released from

the coordination to nitrogen, which enables $Mg(OCOR)_2$ to coordinate the aziridine and direct the *syn*-attack of the carboxylate (Scheme 3.63).



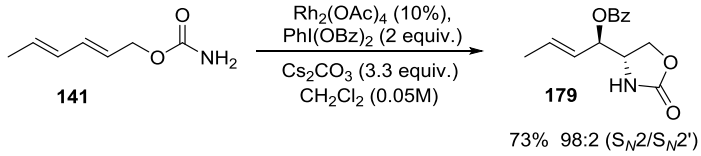
Scheme 3.63. Mechanistic proposal to explain the effect of the catalyst on the regio- and stereoselectivity of the oxyamination of carbamate **141**.

If this hypothesis was correct, we would expect that less coordinating cations than Mg^{2+} such as K^+ and especially Cs^+ would have less tendency to give S_N2' ring opening. Thus, the $Rh_2(OPiv)_4$-catalysed process from of **141** was carried out, in addition to $PhI(OAc)_2$, with Na_2CO_3, K_2CO_3 and Cs_2CO_3. We observed the formation of **162/163** in ratios of 9:91, 37:63 and 86:14, respectively (Scheme 3.64). Particularly illustrative of the effect of the coutercation is the last result in which even using $Rh_2(OPiv)_4$ (initially considered as the main factor favouring S_N2') as the catalyst, a 86% selectivity for the direct S_N2 attack was observed.



Scheme 3.64. Study of the effect of the counteraction in the regioselectivity.

This knowledge about the relevant role of the counteraction was higly useful to obtain almost complete S_N2 selectivity. Therefore, if $Rh_2(OAc)_4$ is used in combination with the weakly coordinating Cs_2CO_3, carbamate **141** could be transformed into benzoate **179** in 73% yield and 98% of regioselectivity (Scheme 3.65), compared to the 66% of regioselectivity obtained when using MgO (entry 3, Table 3.7). The selective preparation of **179** was of particular interest concerning the kinetic resolution experiments discussed in the next chapter.



Scheme 3.65. Highly regioselective synthesis of **179** taking advantage of the low coordinating ability of Cs^+.

This work represented the first synthesis of vinylaziridines via direct intramolecular metal-catalysed aziridination of dienes. It also provides an interesting control on the regioselectivity in the ring-opening determined by the choice of the catalyst and the base. Taking all these facts into account, we considered appropriate to investigate the scope of the process. For this study we prepared different dienyl carbamates shown in Figure 3.5, from which we aimed to obtain information about the effect that different double bond configuration, substitution and chain length have in the reaction.

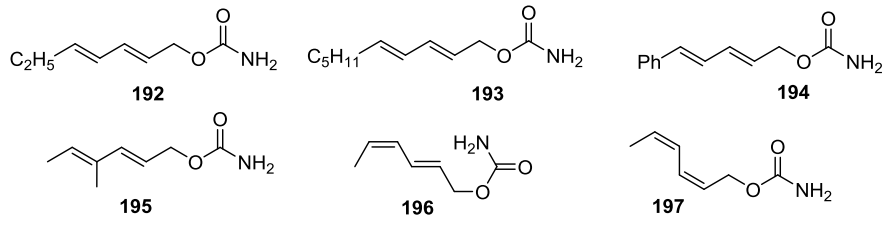


Figure 3.5. Dienes studied in the oxyamination reaction.

Carbamates in Figure 3.5 were synthesised from the corresponding dienols through the same carbamoylation reaction described for **141**. Dienol precursors of **192** and **193** are commercially available, but not those of **194**, **195**, **196** and **197**. In the following pages, thus, preparation of dienols **198**, **199**, **200** and **201** (Figure 3.6) will be discussed.

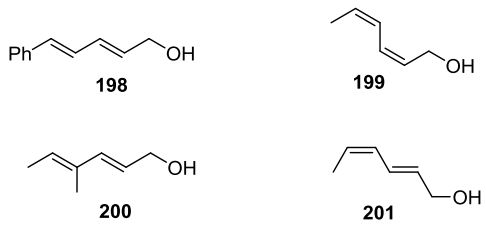
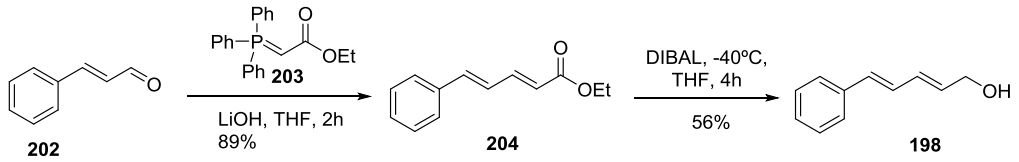


Figure 3.6. Dienol precursors that were prepared for the scope of the reaction.

Preparation of dienol **198** involved an initial Wittig olefination of cinnamaldehyde **202** with the stabilized phosphine ylide **203** providing unsaturated ester **204** in 89% yield. Dienol **198** was obtained in 56% yield after reduction of ester **204** with DIBAL at -40ºC (Scheme 3.66).[129]

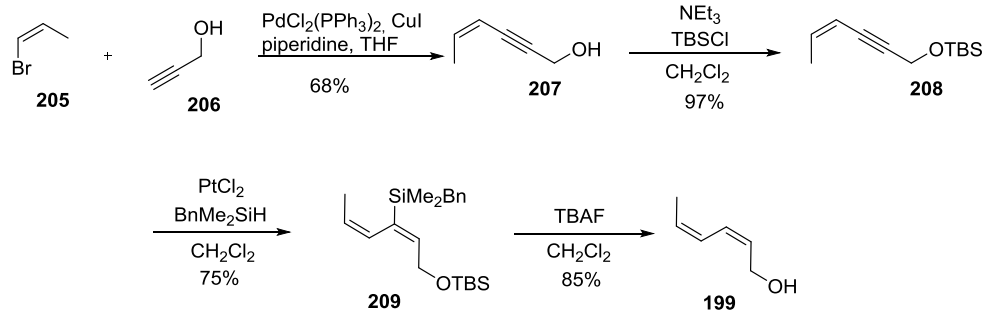


Scheme 3.66. Preparation of dienol **198**.

The synthesis of *cis*,*cis*-configured dienol **199** (Scheme 3.67) started by a Sonogashira cross-coupling reaction between *Z*-bromopropene **205** and propargyl alcohol **206**, which provided enyne **207** in 68% yield.[130] Product **207** was then

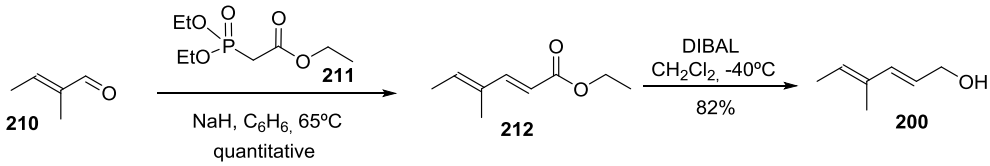
[129] DeBoef, B.; Counts, W. R.; Gilbertson, S. R. *J. Org. Chem.* **2007**, *72*, 799-804.
[130] Egger, M.; Pellett, P.; Nickl, K.; Geiger, S.; Graetz, S.; Seifert, R.; Heilmann, J.; König, B. *Chem. Eur. J.* **2008**, *14*, 10978-10984.

protected as silyl ether to afford compound **208** in 97% yield.[131] Taking advantage of a recent methodology published by Ferreira, enyne **208** was selectively hydrosilylated to give **209** in 75% yield using $PtCl_2$ as the catalyst.[132] Final protodesilylation and cleavage of the silyl ether protecting group with TBAF provided targeted (*Z*,*Z*)-hexadien-1-ol **199**.[133]



Scheme 3.67. Preparation of dienol **199**.

Branched (2*E*,4*E*)-4-methyl-2,4-hexadien-1-ol (**200**) was synthesized in 82% yield by the reduction of the ester **212** with DIBAL. In turn, ester **212** was prepared quantitatively by olefination reaction of *trans*-2-methyl-2-butanal (**210**) using phosphonate **211** (Scheme 3.68).[129]



Scheme 3.68. Preparation of branched dienol **200**.

(2*E*,4*Z*)-2,4-hexadiene-1-ol (**201**) was prepared by reduction of enyne **207** with $LiAlH_4$ in 84% yield (Scheme 3.69).

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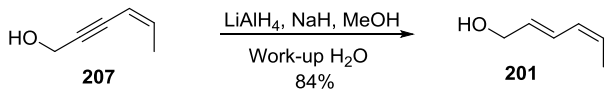
131 Kluge, A. F.; Kertesz, D. J.; O-Yang, C.; Wu, H. Y. *J. Org. Chem.* **1987**, *52*, 2860-2868.
132 Rooke, D. A.; Ferreira, E. M. *Angew. Chem. Int. Ed.* **2012**, *51*, 3225-3230.
133 Suzuki, D.; Nobe, Y.; Watai, Y.; Tanaka, R.; Takayama, Y.; Sato, F.; Urabe, H. *J. Am. Chem. Soc.* **2005**, *127*, 7474-7479.



Scheme 3.69. Preparation of dienol **201**.

Once all the dienols in hand they were transformed into the corresponding carbamates in good yield (Figure 3.7).

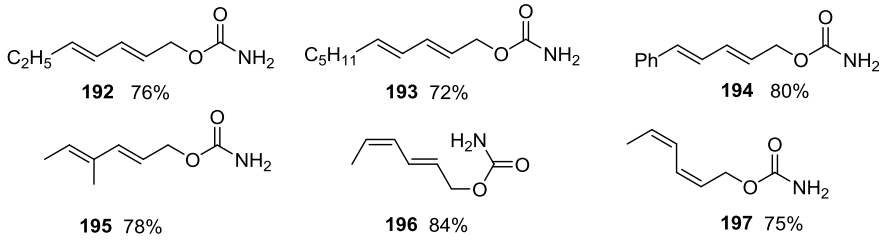
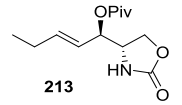
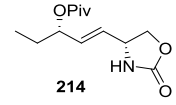
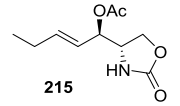
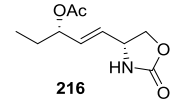
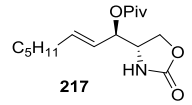
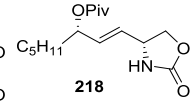
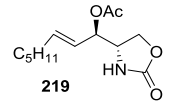
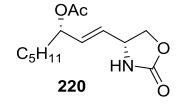
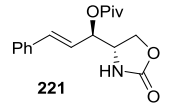
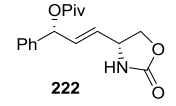
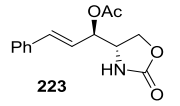
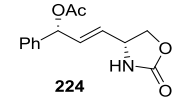
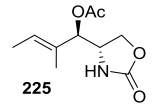
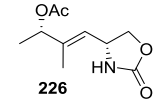
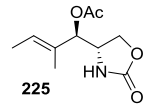
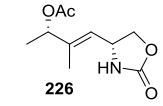
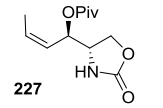
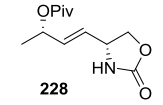
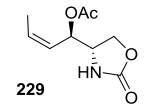
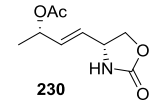
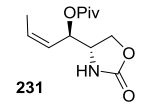
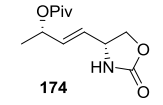
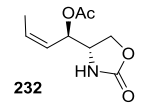
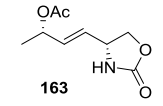


Figure 3.7. Yields obtained in the synthesis of carbamates used for the scope of the reaction from the corresponding dienols.

The scope of the reaction to afford S_N2 or S_N2' opening products was explored using standard conditions (Table 3.8): Conditions A: ($Rh_2(OAc)_4$/PhI$(OPiv)_2$/MgO) for S_N2 products and Conditions B: ($Rh_2(OPiv)_4$/PhI$(OAc)_2$/MgO) for S_N2' products. It is worth pointing that the use of Cs_2CO_3 as optimised base for S_N2 products was discovered at the end of the work, and therefore the scope was made with MgO. Tandem aziridination/opening of substrates **192** and **193** with a *trans/trans* configuration of the double bonds (Table 3.8, entries 1-4) provided an excellent regiocontrol with both catalytic systems affording products resulting from an S_N2 attack under conditions A (**213, 217**), and from a S_N2' attack under conditions B (**216**, **220**). When the diene was substituted by a phenyl group (**194**) (Table 3.8, entries 5, 6) selectivity with both catalytic systems decreased probably due to the high reactivity of the transient phenyl-substituted vinylaziridine. It is worth mentioning the unexpected effect of the methyl substituent at C-4 in the regioselective outcome. Thus, when the reaction was conducted with carbamate **195**, either employing

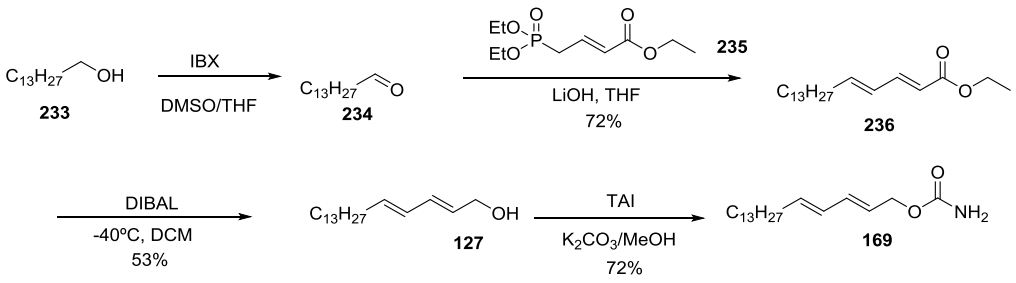
$Rh_2(OAc)_4$, and especially $Rh_2(OPiv)_4$, the S_N2' attack was preferred over the S_N2 (Table 3.8, entries 7, 8). This could probably be explained by the steric congestion provided by the methyl substituent close to the allylic aziridine carbon. We explored next the reaction of *trans-cis* and *cis-cis* dienyl carbamates **196** and **197**, related to carbamate **141** but with different configurations in the double bonds (Table 3.8, entries 9-12). The regioisomers resulting from an S_N2 attack were obtained in selectivities similar to those obtained with the *trans-trans* dienes, while those resulting from S_N2' attack suffered a moderate drop. Compounds obtained from carbamate **197** by aziridination and S_N2' opening proved to be identical to **163** (Table 3.8, entry 12) and **174** (Table 3.8, entry 11), which indicates that the reaction follows a similar stereochemical pathway regardless of the double bond configuration. Products **228** and **230**, obtained from **196**, showed very similar ^{1}H and ^{13}C NMR spectra compared to **174** and **163**, respectively. To elucidate whether related products were configurationally identical, compounds **230** and **163** were hydrolyzed and the resulting products were treated with Mosher acid chloride to give selectively the esters. The NMR spectra of the obtained products showed significant differences, proving that both compounds were different. Since a *syn*-relative configuration was confirmed for product **163** by NOE experiments (Figure 3.3 and Figure 3.4), an *anti*-relative configuration was attributed to compound **230.**

Table 3.8. Scope of the regioselective aziridination/ ring opening reaction of carbamates.

Entry	SM	Cond.[a]	Products	Yield[b](%)	S_N2: S_N2' ratio[c] (%)
1	**192**	A	 **213**  **214**	72	86:14
2	**192**	B	 **215**  **216**	65	10:90
3	**193**	A	 **217**  **218**	71	91:9
4	**193**	B	 **219**  **220**	76	13:87
5	**194**	A	 **221**  **222**	54	70:30
6	**194**	B	 **223**  **224**	60	28:72
7[d]	**195**	A	 **225**  **226**	71	25:75
8	**195**	B[d]	 **225**  **226**	68	10:90
9	**196**	A	 **227**  **228**	56	90:10
10	**196**	B	 **229**  **230**	64	39:61
11	**197**	A	 **231**  **174**	74	90:10
12	**197**	B	 **232**  **163**	71	36:64

[a] Conditions A: $Rh_2(OAc)_4$/**141**/$PhI(OPiv)_2$/MgO (0.1:1:2:3.3) in a 0.05M solution in CH_2Cl_2, T= 20 ºC, t= 48h. Conditions B: $Rh_2(OPiv)_4$/substrate/$PhI(OAc)_2$/MgO (0.1: 1:2:3.3) in a 0.05M solution in CH_2Cl_2, T = 5ºC, t= 24 h.[b] Isolated yields (combination of regioisomers).[c] Determined by ^1H NMR.[d] $PhI(OAc)_2$ was used instead of $PhI(OPiv)_2$ since yields were better and selectivity similar.

Drived by our aforementioned interest in developing new methods for the synthesis of aminoalcohols of biological interest,[134] we applied this methodology to the synthesis of (±)-sphingosine.[135] For this purpose, first we prepared carbamate **169** having the appropiate lipid chain for sphingosine. Preparation of **169** started from 1-tetradecanol (**233**), which was reacted with 2-iodoxybenzoic acid (IBX) in DMSO/THF at room temperature to afford tetradecanal (**234**), which was reacted with the phosphonate **235** in presence of LiOH to provide ester **236** in a 72% yield. Reduction of **236** with DIBAL at -40ºC afforded dienol **127**, from which carbamate **169** was finally obtained following the procedure described before (Scheme 3.70).[136]



Scheme 3.70. Preparation of carbamate **169** for the synthesis of (±)-sphingosine.

Carbamate **169** was reacted under both conditions A and B with excelent regioselectivities in both cases in parallel with the results obtained with the others *trans-trans* dienes (Scheme 3.71). Particularly notorious was the selectivity of the S_N2 ring opening when conditions A were applied, affording oxazolidinone **237** in 79% yield. When the reaction was driven in conditions B, compound **171** was obtained as major isomer in 66% yield, together with a minor amount of compound **170**. Finally, hydrolysis of the ester substituent and the oxazolidinone in **237** rendered (±)-sphingosine in 71% yield.

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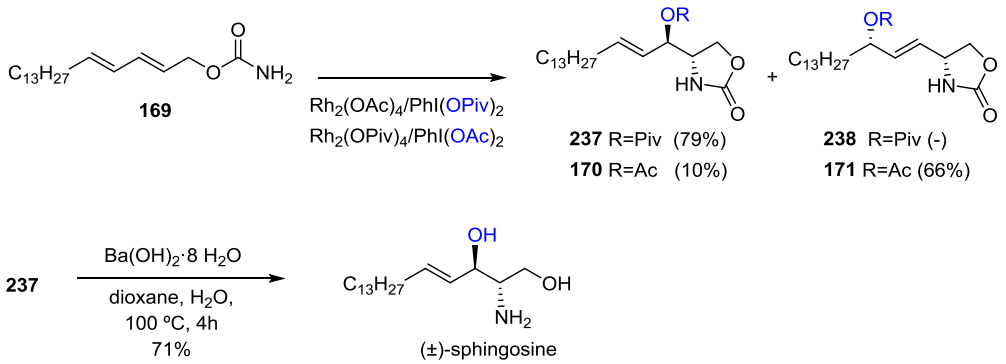
134 a) Llaveria, J.; Díaz, Y.; Matheu, M. I.; Castillón, S. *Org. Lett.* **2009**, *11*, 205-208; b) Morales-Serna, J. A.; Llaveria, J.; Díaz, Y.; Matheu, M. I.; Castillón, S. *Org. Biomol. Chem.* **2008**, *6*, 4502-4504.

135 For a review about the synthesis of sphingosines see: Morales-Serna, J. A.; Llaveria, J.; Díaz, Y.; Matheu, M. I.; Castillón, S. *Curr. Org. Chem.* **2010**, *14*, 2483-2521.

136 Olofsson, B.; Somfai, P. *J. Org. Chem.* **2003**, *68*, 2514-2517.



Scheme 3.71. Synthesis of (±)-sphingosine from carbamate **169**.

As concluding remarks for this section, tandem intramolecular aziridination/ring opening of dienol carbamates was regioselectively performed by selecting the rhodium catalysts and the iodine (III) oxidizing reagent. The carboxylate present in the iodine (III) reagent that is released during the reaction behaves as a nucleophile opening the aziridine intermediate in a tandem process. The use of $Rh_2(OAc)_4$ affords products resulting from an S_N2 attack and the rhodium catalysts plays a double role, first promoting the metalonitrene formation and second as a Lewis acid in the S_N2 opening process. On the contrary, when $Rh_2(OPiv)_4$ was used as the catalyst, products resulting from an S_N2' attack were selectively obtained. The bulkiness of $Rh_2(OPiv)_4$ might favor the de-coordination from the aziridinic nitrogen, leaving place for coordination of magnesium, which might direct carboxylate attack in a *syn* S_N2' fashion. The efficiency of the reaction is strongly affected by the presence of substituents in the intermediate framework of the diene system, and the product resulting from S_N2' attack is obtained with both catalytic systems if a methyl group is present at C-4. This procedure permits to obtain unsaturated aminoalcohols with protected alcohols either at C-3 or at C-5 positions from a same starting carbamate. In addition, this work has allowed the synthesis of sphingosine in only two steps from the starting dienyl carbamate.

3.2.6. ENANTIOSELECTIVE INTRAMOLECULAR AZIRIDINATION OF DIENYL CARBAMATES

Having understood how to control the regioselectivity in the intramolecular aziridination/ring opening of dienyl carbamates, we focused our efforts on an asymmetric version of the process. Enantioselective aziridination has found success mainly by the use of copper-bisoxazoline complexes[48b,137] and rhodium (II) catalyst bearing either chiral carboxiamidate or carboxylate ligands.[138] Since copper salts resulted poorly effective in our system, we decided to focus our interest in chiral rhodium complexes.

Among all the ligands used for asymmetric transformations catalysed by chiral rhodium (II) complexes, carboxiamidates have provided the best results in terms of enantioselectivity. Dirhodium(II) carboxyamidate complexes possess a paddlewheel (lantern) structure (Figure 3.8), where the dirhodium (Rh_2^{4+}) core is supported by four monoanionic, three atom, bidentate carboxyamidate bridging ligands. Because the chiral carboxyamidate ligands are unsymmetrical bridges, four different geometries are possible: *cis*-(2, 2) and *trans*-(2, 2), -(3, 1), and –(4, 0) (see Figure 3.8).[138a] However the *cis*-(2, 2) isomer is dominant or exclusive in the preparation, which implies an overall C_2-symmetry.

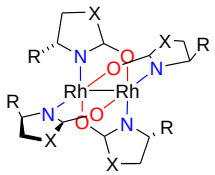
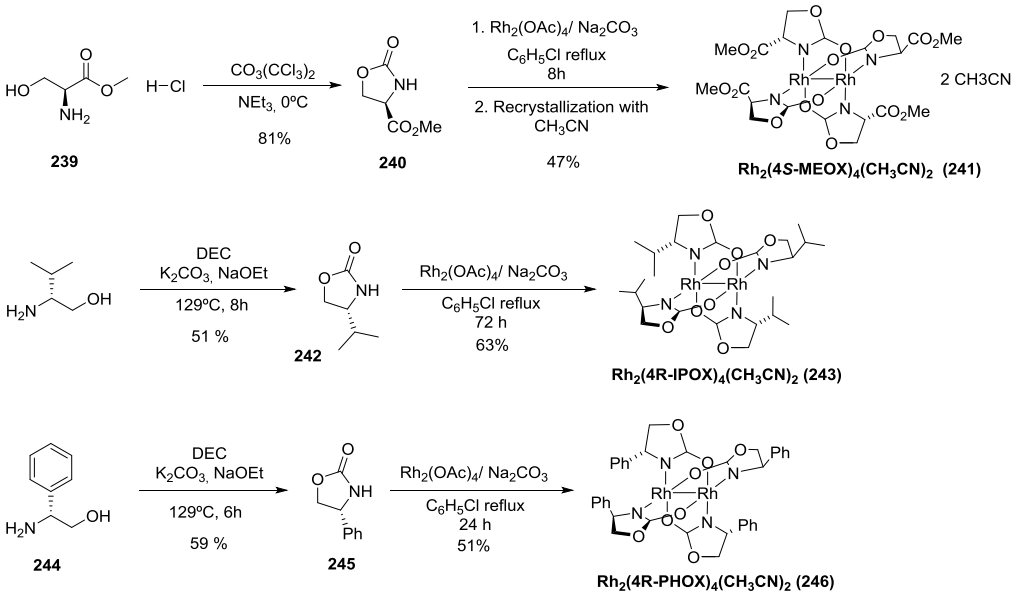


Figure 3.8. Generalized structure for (*cis*-2, 2) dirhodium carboxamides; (*cis*-2, 2) refers to the atomic distribution of N and O on rhodium.

[137] Lebel, H.; Parmentier, M. *Pure Appl. Chem.* **2010**, 1827-1833.
[138] For reviews see: a) Doyle, P. *J. Org. Chem.* **2006**, *71*, 9253-9260. b) Hansen, J.; Davies, H. M. L. *Coord. Chem. Rev.* **2007**, *252*, 545-555. c) El-Deftar, M.; Adly, R. G.; Gardiner, M. G.; Ghanem, A. *Curr. Org. Chem.* **2012**, *16*, 1808-1836.

In this sense we prepared three chiral oxazolidinone ligands from commercial amino alcohols following the reported procedures. The obtained chiral ligands were then reacted in a Soxhlet equipment with $Rh_2(OAc)_4$ in chlorobenzene and in the presence of a Na_2CO_3 cartridge to scavenge the generated acetic acid. This methodology provided chiral catalysts **241**, **243** and **246** in moderate yields (Scheme 3.72).

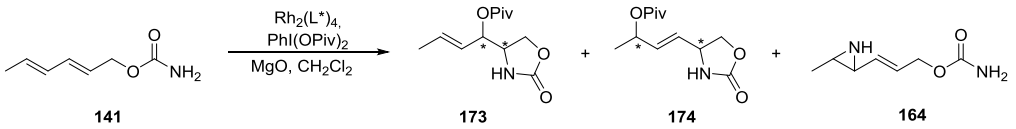


Scheme 3.72. Synthesis of chiral dirhodium(II) carboxyamidate complexes **241**, **243** and **246**.

Unfortunately, the use of the prepared rhodium catalysts **241**, **243** and **246** in the intramolecular aziridination of **141** using $PhI(OPiv)_2$ rendered a sluggish mixture of products from which, looking at the ^1H NMR of the reaction crude, only aziridine **164** could be identified as the major product (Table 3.9). In fact, oxazolidinones **173** and **174** were only detected in a small amount. From our point of view, the reason of the low activity of these catalysts on the intramolecular aziridination was the steric congestion on the axial sites of the rhodium paddlewheel structure effectuated by the

chiral the ligands. In order to overcome this limitation we planned to use commercially available chiral dirhodium tetracarboxylate catalysts.

Table 3.9. Asymmetric intramolecular aziridination of carbamate **141** using chiral dirhodium tetracarboxylate complexes.[a]



141 **173** **174** **164**

Entry	Catalyst	Conc. (M)	T(ºC)	t(h)	Yield (%)[b]	Observations
1	241	0.05	rt	72	C.M.	**164** major product
2	243	0.05	rt	72	C.M.	**164** major product
3	246	0.05	rt	72	C.M.	**164** major product
4	241	0.025	rt	72	C.M.	**164** major product
5	243	0.025	rt	72	C.M.	**164** major product
6	243	0.025	40	48	C.M.	**164** major product

[a]Catalyst/**141**/$PhI(OPiv)_2$/MgO (0.1:1:2:3.3). [b] C.M. = complex mixture.

Chiral carboxylate ligands have the chiral entity further from the axial site than carboxiamidates. This should be advantageous for preventing overcongestion at the reactive axial sites.

With this purpose, comercially available $Rh_2(DOSP)_4$ and $Rh_2(PTAD)_4$ (Figure 3.9) were used in the aziridination of **141** using $PhI(OBz)_2$ (Scheme 3.73). As it was anticipated the reactions were smooth providing 61% and 69% yields of a regioisomeric mixture of **179** and **180**, although with low enantioselectivities, 21% and 17% ee, respectively in compound **179**. It must be pointed that the reason for changing from $PhI(OPiv)_2$ to $PhI(OBz)_2$ as the oxidant was the better resolution and sensitivity of the HPLC detector for **179** and **180** rather than **173** and **174**, even though the regioselectivity was known to be worse.

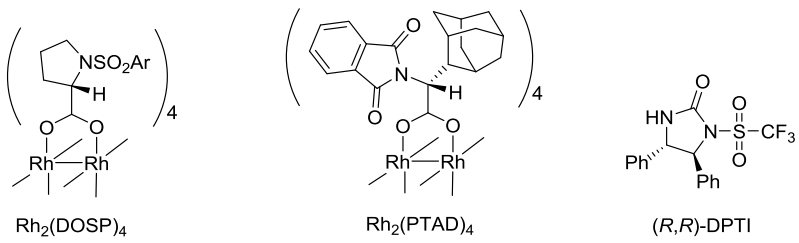
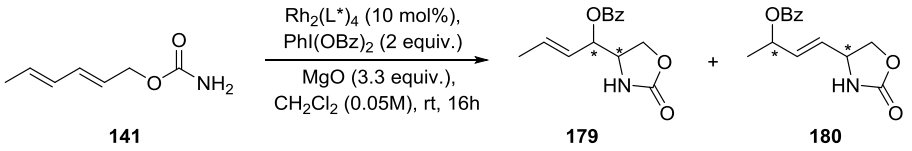


Figure 3.9. Chiral carboxylate rhodium catalysts used in the aziridination of **141**.



$Rh_2(L^*)_4 = Rh_2(DOSP)_4$ 61% yield (**179**+**180**), 21% ee(**179**)

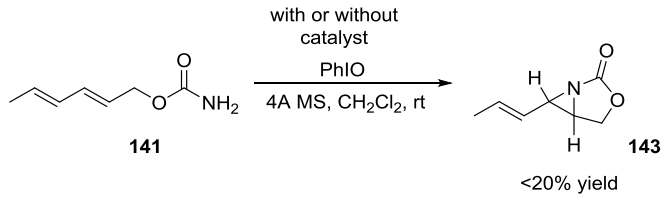
$Rh_2(L^*)_4 = Rh_2(PTAD)_4$ 69% yield (**179**+**180**), 17% ee(**179**)

Scheme 3.73. Asymmetric intramolecular aziridination of **141** using chiral dirhodium carboxylate catalysts.

It is known that carboxyamidate ligands provide higher selectivity but lower activity than carboxylate in nitrene insertion and addition reactions as a result of their more electrondonating character.[114] In this sense we considered that the preparation of a dirhodium catalyst bearing a mixture of carboxiamidate and carboxylate ligands could provide the required equilibrium in the reactivity of the catalyst to afford good yields and enantioselectivities. Thus, $Rh_2(OAc)(DPTI)_3$ (See Figure 3.9 for DPTI), developed by Corey *et al.*, was targeted. However, although the chiral imidazolidinone ligand was successfully synthesized, attempts to form the rhodium complex repeatedly failed.

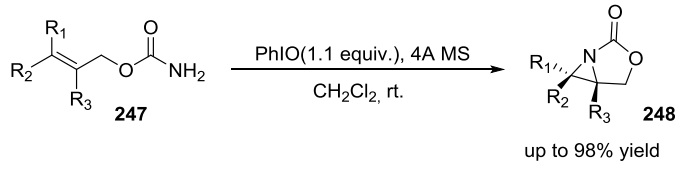
3.2.7. METAL FREE INTRAMOLECULAR AZIRIDINATION

At the outset of our studies on intramolecular aziridination and, in the framework of the initial screening of catalyst, aziridination of carbamate **141** was also attempted with PhIO in the absence of metal catalayst. Our interest was to develop a procedure of aziridine synthesis that avoided spontaneous aziridine ring opening, allowing, therefore, the opening with different nucleophiles. It is worth commenting that reaction of **141** with $PhI(OAc)_2$ in the absence of a metal catalyst did not evolve. Conversively, reaction of carbamate **141** with PhIO in the presence of 4Å MS gave vinyl aziridine **143** although in very low yield (Scheme 3.74).



Scheme 3.74. Initial attempts on the intramolecular aziridination of **141** using PhIO as oxidant.

At that point we focused our efforts on the development of the regioselective oxyamination reaction discussed before. However, the publication by Che of the metal free intramolecular aziridination of allyl carbamates directed again our interest towards this reaction (Scheme 3.75).[139]

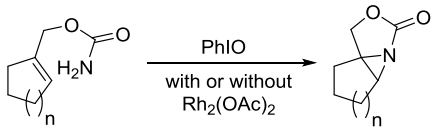


Scheme 3.75. Metal free intramolecular aziridination of allylic carbamates reported by Che *et al.*[139]

[139] Deng, Q.-H.; Wang, J.-C.; Xu, Z.-J.; Zhou, C.-Y.; Che, C.-M. *Synthesis*, **2011**, 2959-2967.

3.2.7.1. BACKGROUND

Aziridination reaction effectiveness has been supported by the use of metals capable of stabilizing nitrenes, especially Rh (II), Cu(I) and Cu(II). The use of these metal-catalysts has been indispensable for the formation of the reactive metallanitrene species in the vast majority of aziridination of alkenes implying hypervalent iodane reagents.[75] In addition, the use of metal catalyst seemed to be indispensable for the development of enantioselective processes. In fact, only those systems with a certain degree of conformational rigidity could prescind from using a metal; at least this was the supposition before the aforementioned report by Che.[139] This peculiarity was firstly reported by Padwa[70b] in the intramolecular aziridination of cyclic carbamates and lately investigated by Moriarty (Scheme 3.76).[140]

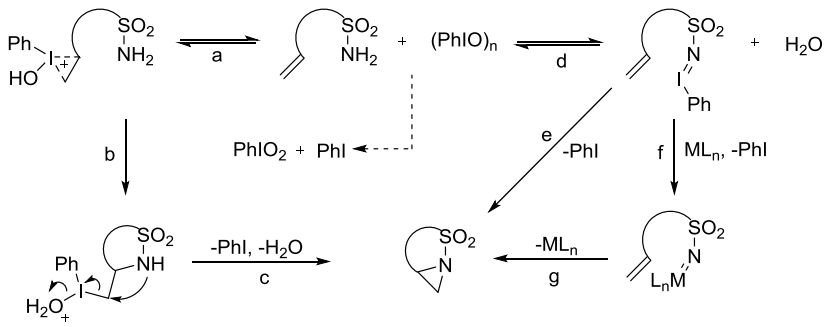


249 **250**

Scheme 3.76. Intramolecular aziridination of cyclic allylic carbamates in the presence or absence of metal catalyst.

The investigation of Moriarty interestingly revealed, contrary to what would be expected, that the aziridination in conformationally rigid systems performs better without the presence of Rh(II) or Cu(I) catalysts what, in his regards, suggested the presence of three competitive mechanisms (Scheme 3.77).

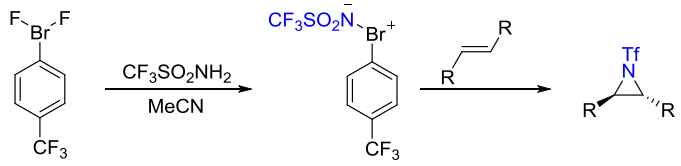
[140] Moriarty, R. M.; Tyagi, S. *Org. Lett.* **2010**, *12*, 364-366.



Scheme 3.77. Patways suggested by Moriarty for the intramolecular aziridination of alkenylsulfonamides with PhIO.

Control experiments rejected the initial double bond hyperiodination as the starting point for the aziridination (**a-b-c** path, Scheme 3.77). In conformationally rigid substrates, aziridination reaction would take place by the reaction of the iminoiodane with the adjacent double bond via a [2+2] cycloaddition from an initial electrophilic addition of the double bond to the I(III) and subsequent reductive elimination of PhI (**a-d-e** path). This was in agreement with the absence of reactivity in more flexible substrates which, in turn, gave good yields if Rh(II) or Cu(I) catalyst were used following the accepted pathway for the metal-catalysed aziridination of alkenes (**d-f-g** path). However, as mentioned before Che and coworkers reported an efficient metal-free aziridination of allylic carbamates using PhIO where even simple akyl-substituted allylic carbamates were aziridinated in high yields (up to 98%) at room temperature.[139] Comparison of Che's results with those previously reported by Moriarty[140] relativizes the importance of the stability of the intermediate iminoiodane, since sulfonamide-derived iminoiodanes are more stable than carbamate-derived due to the better charge stabilization. In that case, the outstanding yields of bicyclic aziridines could be attributed to the shift of the equilibrium to the formation of the iminoiodane (path **d**) in Scheme 3.77 as a result of an efective removal of water and also a faster electrophilic addition to I(III) by the more reactive allylic alkene.

Alternatively, during the last years, the use of hypervalent bromane (III) species is emerging as a powerful tool for the metal free aziridination and C-H amination reactions (Scheme 3.78).[141] These compounds present enhanced hyper leaving group ability compared to their iodane parent compounds probably due to the higher electronegativity and larger ionization potential of bromine respective to iodine.[141b] Some of the relevant benefits that hypervalent bromane (III) species provide for aziridination include ability to perform it with limiting amounts of substrate, stereochemical retention and precluding of the competing C-H amination.[141c] However, the still lack for a straightforward preparation and the instability associated with their high reactivity prevent from a generalized use.



Scheme 3.78. Hypervalent bromane (III) acting as a nitrenoid in the metal-free aziridination of olefins.

3.2.7.2. RESULTS AND DISCUSSION

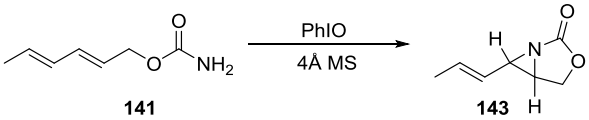
At the beginning of this investigation we adapted the conditions employed for the oxyamination reaction. Therefore, carbamate **141** was reacted with 2 equivalents of PhIO in a 0.05M concentration (Table 3.10). The solvents of choice were dichloromethane, because it is the most widely used in this type of transformation, and also benzene due to the particular efficiency shown in PhIO-mediated aziridination of homoallyl carbamates.[70d]

[141] a) Ochiai, M.; Kaneaki, T.; Tada, N.; Miyamoto, K.; Chuman, H.; Shiro, M.; Hayashi, S.; Nakanishi, W. *J. Am. Chem. Soc.* **2007**, *129*, 12938-12939 b) Ochiai, M.; Miyamoto, K.; Kaneaki, T.; Hayashi, S.; Nakanishi, W. *Science* **2011**, *332*, 448-451. c) Hoque, M. M.; Miyamoto, K.; Tada, N.; Shiro, M.; Ochiai, M. *Org. Lett.* **2011**, *13*, 5428-5431.

Reaction of **141** with PhIO either in dichloromethane or benzene provided low yields of vinylaziridine **143** (Table 3.10). A common feature of those experiments was the apparent selective reaction as it was deduced from the analysis of ^{1}H NMR spectra of the reaction crudes. Especially intringuing was the result in entry 1 of Table 3.10 since even though aziridine **143** was the major product and all carbamate **141** was consumed, the yield was only 16%.

This reaction outcome was attributed to an excessive reaction time, which could allow the highly reactive vinyl aziridine **143** to be involved in side reactions. In order to minimise any type of side reaction before carrying out the ^{1}H NMR spectrum, in the following screening of conditions the aziridine was *in situ* ring opened with sodium thiophenolate (NaSPh) once TLC showed complete starting material consumption (Table 3.11).

Table 3.10. Initial tests on the metal-free intramolecular aziridination of **141** mediated by PhIO.[a]



141 **143**

Entry	Solvent (M)	T(ºC)	Time (h)	Yield (%)[b]
1	CH_2Cl_2 (0.05)	rt	24	16
2	CH_2Cl_2 (0.05)	0	24	4
3	Benzene (0.05)	rt	24	13

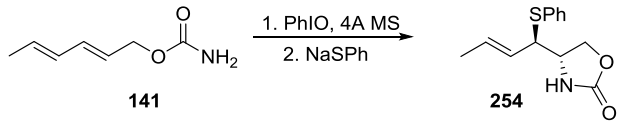
[a] PhIO (2 equiv.), 4Å MS (100 mg per 0.1 mmol carbamate **141**). [b] Determined by ^{1}H NMR spectroscopy using 1,4-dimethoxybenzene as internal standard.

Application of the same conditions than in entry 1 of Table 3.10 provided, after ring opening with NaSPh, 54% yield of **254** (Table 3.11, entry 1), which proved our feeling about the need to *in situ* ring opening these type of reactive aziridines. Dilution of the reaction mixture revealed to be detrimental for the aziridination (Table

3.11, entry 2). Concerning the amount of oxidant employed, 2 equivalents of PhIO resulted optimum since doubling and, especially, dividing by two the amount of PhIO employed (Table 3.11, entries 3 and 4) provided low yields of **254**. Portionwise addition of PhIO, a common requirement in the reactions mediated by PhINTs, neither help on achieving higher yields (Table 3.11, entry 5). Changing the solvent to benzene was also detrimental for the yield (Table 3.11, entry 6). The temperature could be slighly raised without yield loss, what allowed a substantial reaction time shortening (Table 3.11, entry 7) to 3 hours at 35ºC. Finally we found that a small dilution from 0.05M to 0.04M favoured the formation of the aziridine giving an acceptable 62% yield (Table 3.11, entry 8). This was probably as a concequence of an improvement on the system solubility taking into account the low solubility of PhIO in most organic solvents.[142]

[142] Moriarty, R. M.; Kosmeder III, J. W. Iodosylbenzene. *E-EROS Encyclopedia of Reagents for Organic Synthesis.*

Table 3.11. Intramolecular aziridination of **254** with PhIO and *in situ* ring opening with NaSPh.[a]



141 254

Entry	Solvent (M)	PhIO (equiv.)	T(ºC)	Time (h)	Yield (%)[b]
1	CH_2Cl_2 (0.05)	2	rt	5	54
2	CH_2Cl_2 (0.002)	2	rt	7	0
3	CH_2Cl_2 (0.05)	4	rt	8	17
4	CH_2Cl_2 (0.05)	1	rt	24	<5
5	CH_2Cl_2 (0.05)	2	rt	2	30
6	Benzene (0.05)	2	rt	5	14
7	CH_2Cl_2 (0.05)	2	35	3	52
8	CH_2Cl_2 (0.04)	2	35	3	62

[a] 4Å MS (100 mg per 0.1 mmol carbamate **141**), NaSPh (5 equiv.). [b] Determined by ^{1}H NMR spectroscopy using 1,4-dimethoxybenzene as internal standard. [c] Portionwise addition of PhIO over 2h.

The distribution of products obtained include, apart from oxazolidinone **254**, vinyl aziridine **164** and two unidentified compounds, one of them possessing the typical signals of an S_N2 ring opening derivative of **143**.

In order to get more information about the behaviour of the process, the reaction was monitored by ^{1}H NMR. Fortunately, although molecular sieves were essential for the progress of the reaction, if the temperature was set at 35ºC or above, similar yields of **143** were obtained, which allowed to prescind from them, thus making possible a good shiming. Therefore, the reaction was carried out in deuterated dichloromethane (0.04M) inside a NMR tube at 35ºC in the abscense of molecular sieves and with 2 equivalents of PhIO. The ^{1}H NMR was recorded every 15 minutes (Figure 3.10).

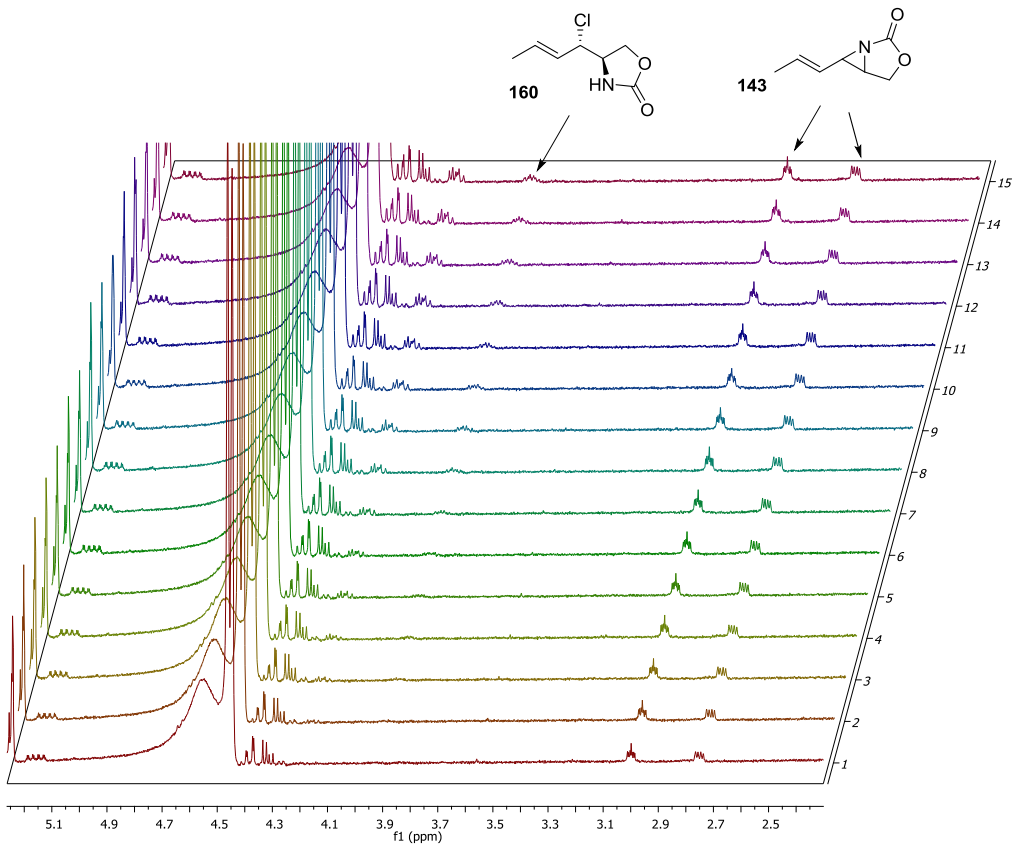


Figure 3.10. ^{1}H NMR monitoring of the aziridination of **141** with PhIO.

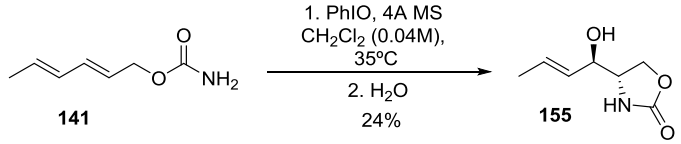
Figure 3.10 shows that the desired aziridine is rapidly generated (signals at 3.01 and 2.76 ppm). However, its intensity is maintained constant while other two independent signals are appearing with a growing intensity (signals at 4.25 and 4.00 ppm). This strongly suggests that once the aziridine is generated, it starts to react with other substances present in the reaction medium. Efforts on increasing the reaction rate by increasing the temperature prevent from a correct monitoring as a result of the interferences provoked by the undissolved PhIO when dichloromethane started to boil. Comparison of the ^{1}H NMR of the side products with alcohol **155** and its S_N2' regioisomer discarded the ring opening by the residual water present in the solvent or

generated as a result of the interaction of PhIO and the carbamate to generate the iminoiodane. Then, the compound that showed a signal at 4.00 ppm was isolated. After full NMR characterization and obtaining the molecular peak by mass spectroscopy, the unknown product was concluded to be **160** (Figure 3.10). The presence of chlorine containing products as a result of aziridine ring opening had already been reported by Bergmeier.[96a]

In that example, the authors associated the formation of chlorinated oxazolidinones with the formation of HCl from water and tetrachloroethane at high temperature (100ºC). However, upon changing the solvent to dichloromethane they were able to suppress this side reaction. An interesting comment in the mentioned report was the formation of polymeric products during the reaction course. That would explain, in our case, why in most cases the integration of the internal standard did not mach the sum of the discrete productes obtained. Further optimisation of the reaction taking into account the formation of polymeric compounds and **160**, are being carried out in our laboratory by Irene Giménez.

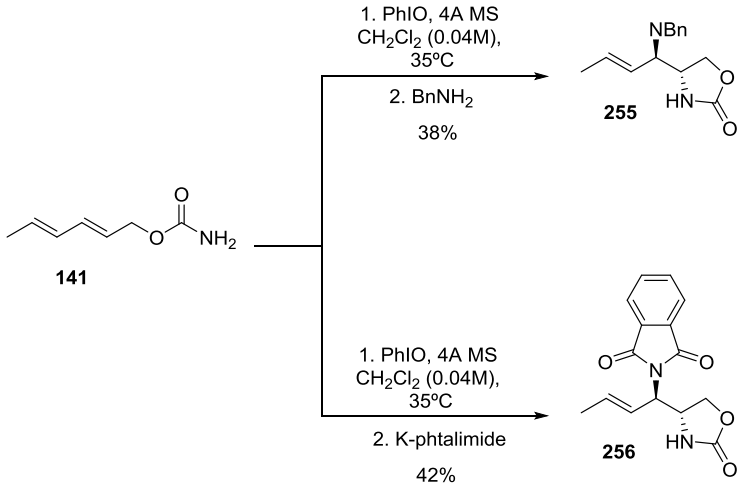
Concerning the present PhD thesis work we had to put the optimisation of this reaction in a second plane, since we were interested on the synthesis of unsaturated oxazolidinones with different substituents at C-3 through aziridination mediated by PhIO and subsequent ring opening. We considered that it would be interesting to carry out the ring opening of vinylaziridines such as **143** with oxygen, nitrogen, fluorine and sulphur-nucleophiles. In this regard, and taking into account that oxygen-substituents can be already successfully installed via the oxyamination process descrived above, the unique *O*-nucleophile that was tried was water. The standard conditions employed for the aziridination were the best from the optimization in Table 3.11 (2 equiv. of PhIO, CH_2Cl_2 0.05M, 35ºC). Then 5 equivalents of the corresponding nucleophile were added. In the case of water a drop was added per 0.1 mmol of starting carbamate.

Alcohol **155** was obtained by this methodology in a surprisingly low 24% yield taking into consideration that we expected the ring opening step to proceed quantitively (Scheme 3.79).



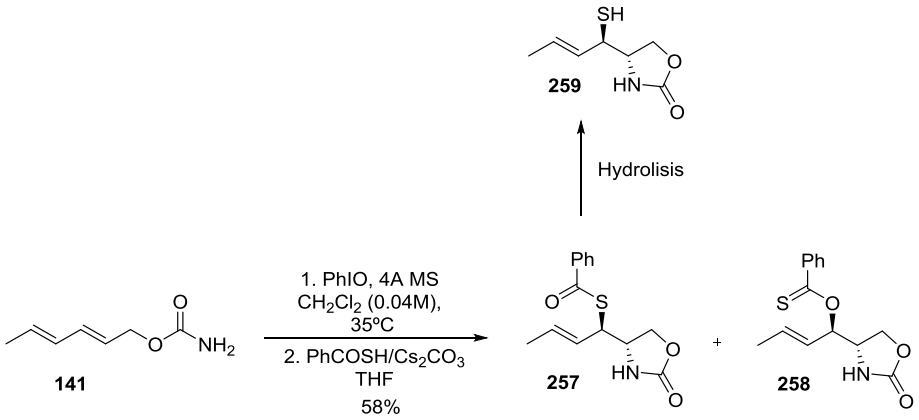
Scheme 3.79. Preparation of alcohol **155** from **141**.

For the addition of *N*-nucleophiles we selected benzylamine, sodium azide and potassium phtalimide. Particularly interesting are the last two reagents in terms of further transformation of the products. The ring opening reaction proceed smoothly when benzylamine and potassium phtalimide were used, providing oxazolidinones **255** and **256** in 38% and 42% yield, respectively (Scheme 3.80). Conversely, the ring opening with sodium azide resulted higly unselective and none of the desired S_N2 or S_N2' products could be isolated.



Scheme 3.80. Preparation of *N*-substituted oxazolidinones **255** and **256**.

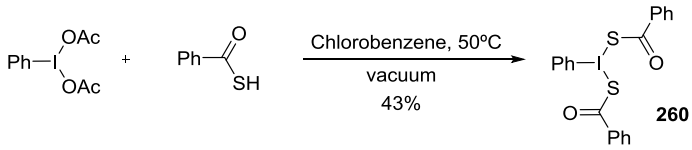
The introduction of *S*-nucleophiles was initially done using the same system than entry 8 in Table 3.11 from where oxazolidinone **254** was isolated in 44% yield. At that point we wondered whether it would be possible to introduce a *S*-nucleophile that could be readily transformed into the more versatile -SH moiety. In this sense and for the expected suitability in the kinetic resolution experiments discussed in the next chapter, thiobenzoate anion was chosen as the nucleophile. Thus, thiobenzoic acid (5 equiv.) was initially treated with equimolar amount of Cs_2CO_3 and added to the solution of preformed vinylaziridine **143**. The crude ^{1}H NMR revealed the formation of two major products, however, attempts to separate them by column chromatography failed. An analysis of the ^{1}H spectrum suggested that a mixture of **257** and **258** (58% yield) was obtained as a result of the ambident nucleophile nature of the thiobenzoic acid/base system (Scheme 3.81).



Scheme 3.81. Attemp to prepare *S*-substituted oxazolidinone **257** from carbamate **141**.

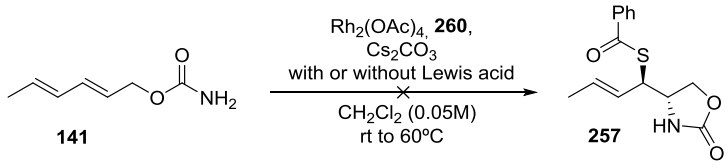
The use of Cs_2CO_3 was in connection to our desire of generating the *S*-centered salt rather than the *O*-centered since we expected the large Cs^+ cation to interact better with the S^- anion. The use of other bases such as K_2CO_3 did not provide improved results. The main reason for the lack of selectivity of the reaction was attributed to the partial deprotonation of the thiobenzoic acid, which would contribute to undesired side reactions such as S_N1 processes. That uncertainty, in addition with the smooth

reactivity encountered with $PhI(OCOR)_2$ reagents, prompted us to prepare thiobenzoate hypervalent (III) iodine oxidant **260** from $PhI(OAc)_2$ and thiobenzoic acid following the same procedure than the preparation of $PhI(OCOR)_2$ derivatives (Scheme 3.82).[127] Following that procedure **260** was obtained as a higly crystalline solid after recrystallisation with a THF/pentane mixture.



Scheme 3.82. Preparation of oxidant **260** for the tandem aziridination/ring opening of **141**.

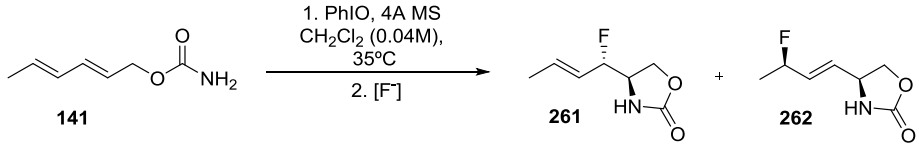
Disappontingly, when carbamate **141** was treated with $Rh_2(OAc)_2$, **260** and Cs_2CO_3 in dichloromethane no reaction was observed even at 60ºC (Scheme 3.83). We think that the strong I-S bond prevented from iminoiodane formation. The use of Lewis acids such as $BF_3{\cdot}OEt$, $Yb(OTf)_3$ and $AlCl_3$ neither help on breaking the I-S bond.



Scheme 3.83. Attempts to prepare **257** from the tandem aziridination/ring opening using **260** as the oxidant.

Finally, some preliminar tests on the tandem aziridination/ring opeing with fluorine were done. It is well known that procedures regarding nucleophilic fluorination must deal with the intrisic tendency of fluorine to be solvated by protic solvents and the basic character of the naked fluoride anion. To overcome this problems associated with the high electronegativity of fluorine, a valuable strategy

has been the *in situ* generation of the fluorine anion.[143] Analogously to the other type of nucleophiles tried, the fluorine source was added after carbamate consumption and the conscequent aziridine formation. However, after tring TBAF, AgF, HF·py, KF and $NEt_3 \cdot 3(HF)$ as fluorine sources, only traces of fluorinated compounds **261** and **262** were detected by ^{19}F NMR (Scheme 3.84).[144]



Scheme 3.84. Attempts to prepare fluoroamines **289** and **290** via tandem aziridination/ring opening with fluoride.

[143] For recent examples on the ring opening of aziridines and epoxides with fluorine see: a) Kalow, J. A.; Doyle, A. G. *J. Am. Chem. Soc.* **2010**, *132*, 3268-3269. b) Zhang, Q.; Nguyen, H. M. *Chem. Sci.* **2014**, *5*, 291-296. c) Kalow, J. A.; Schmitt, D. E.; Doyle, A. G. *J. Org. Chem.* **2012**, *77*, 4177-4183.

[144] Compunds **261** and **262** were obtained during studies on Pd-catalysed fluorination not discussed in the present thesis work.

CHAPTER 4

ENANTIOSELECTIVE SYNTHESIS OF UNSATURATED AMINO ALCOHOLS THROUGH KINETIC RESOLUTION OF OXAZOLIDINONES

UNIVERSITAT ROVIRA I VIRGILI
REGIO- AND ENANTIOSELECTIVE SYNTHESIS OF UNSATURATED AMINO ALCOHOLS, AMINO KETONES AND DIAMINES AS VALUABLE INTERMEDIATES IN ORGANIC SYNTHESIS.
Joan Guash Savidó
Dipòsit Legal: T 1366-2015

4.1. INTRODUCTION

As stated in the objectives chapter, one of the main goals aimed in this thesis work was the enantioselective preparation of unsaturated vicinal amino alcohols from readily available dienols. As a matter of fact, the most effective solution would have been the application of an enantioselective aziridination procedure to either dienols (intermolecular aziridination) or derivatized dienols (intramolecular aziridination). In the former case, the attempts carried out by our group either using metal-bisoxazoline complexes[145] or chiral tripirazolyl borate complexes[146] provide only low enantioselectivities in the aziridination reaction of dienols. Similarly, as discussed in Chapter 3, the use of chiral rhodium (II) catalysts in the intramolecular aziridination of dienyl carbamates did not afford enantiomeric excesses higher than 21%. Mindful of the aforementioned negative results in combination with the lack of general enantioselective aziridination protocols in the literature, we decided to look for an alternative strategy towards the preparation of enantioenriched unsaturated amino alcohols.

After analysing the structure of the oxazolidinone derivatives rendered after aziridination of dienyl carbamates and subsequent ring opening, it was envisaged that the N-H functionality of the oxazolidinone ring had the potential to be acylated under kinetic resolution conditions (Scheme 4.1). This would provide enantioenriched oxazolidinones **(*R*,*S*)-268** and **(*S*,*R*)-264** (Scheme 4.1), which would be easily separated and would give access to the two enantiomeric unsaturated amino alcohols **272** and **273**.

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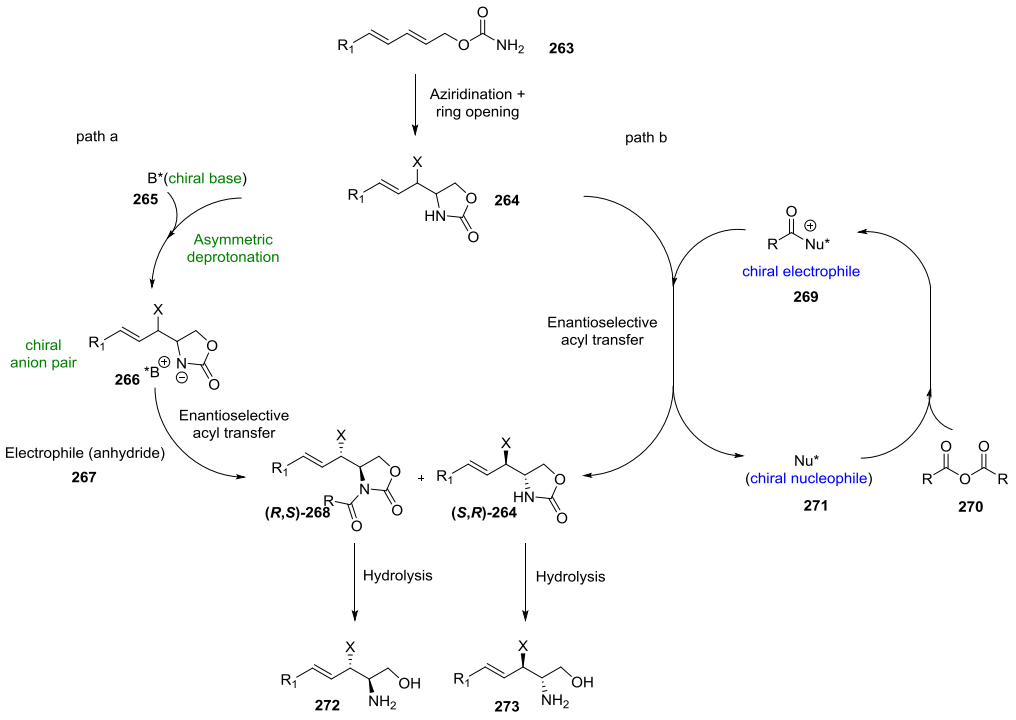
[145] Llaveria, J. (2011). *Synthesis Of Sphingoid Bases By Transition Metal-Catalised Reactions.* Ph.D. Thesis. Universitat Rovira i Virgili, Spain.

[146] Arenas, I. (2014). *Copper, Silver and Ruthenium Complexes with Tridentate Ligands. Application as Catalysts in Aziridination, C-H Insertion and Hydrogenation Reactions.* Ph.D. Thesis. Universitat Rovira i Virgili, Spain.

In this regard, the two scenarios contemplated were: chiral base-induced enantioselective acyl transfer reaction (Scheme 4.1, path a)[147] and chiral nucleophile-induced enantioselective acyl transfer reaction (Scheme 4.1, path b).[148]



Scheme 4.1. Strategies considered towards the enantioselective synthesis of substituted unsaturated aminoalcohols from oxazolidinone compounds obtained in Chapter 3.

In the former, initial deprotonation of the oxazolidinone **264** by a chiral base (**265**) would render a chiral anion pair (**266**), which would be able to react enantioselectively with an added electrophile (presumably an anhydride, **267**). On the other hand, in path b, an initial interaction of a chiral nucleophile (**271**) with an acyl

147 Simpkins, N. S.; Weller, M. D. (2013) *Asymmetric Transformations by Deprotonation Using Chiral Lithium Amides Organic Reactions*. 79:2:317-636.

148 Jarvo, E. R.; Miller, S. J. Asymmetric Acylation. In *Comprehensive Asymmetric Catalysis*, Suplement 1; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. Eds.; Springer-Verag: Berlin, Heidelberg, **2004**; Chapter 43.

transfer agent (**270**) electrophile (generally an anhydride) would generate a chiral electrophile intermediate (**269**), which would be attacked preferentially by one enantiomer of the racemic oxazolidinone. This methodology gives the possibility to work under catalytic regime contrary to what happened in the chiral base method. For this reason and also for the vast amount of publications that use this technique in the kinetic resolution of alcohols and amines, we decided to adopt it for the kinetic resolution of oxazolidinones.

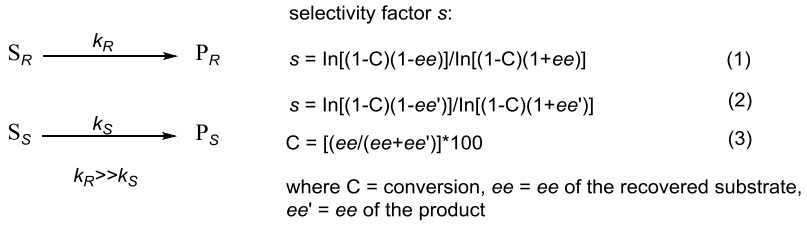
4.1.1. KINETIC RESOLUTION CONCEPT

The importance of asymmetric synthesis nowadays resides, mainly, in the fact that the vast majority of natural products are chiral and their physiological or pharmacological properties are strongly associated with the recognition by chiral receptors, which will only interact with one of the two possible enantiomers of the respective drug.[149] Enantiomerically pure molecules have found, in addition, applicability in other fields such as electronic and optical devices, development of new polymers or as probes of biological function.[150] Although methods of asymmetric synthesis that rely on the use of chiral catalyst or substrates have achieved levels of excellence in recent years, the resolution of racemates still is widely used in the pharmaceutical industry for the synthesis of optically pure compounds.[151]

One of the most common strategies for the resolution of racemates is the kinetic resolution. A kinetic resolution is a process in which the two enantiomers of a racemic mixture are converted into products at a different rate (k_R *vs.* k_S in Scheme 4.2). The efficiency of a kinetic resolution is normally expressed by the selectivity factor *s* or k_{rel} where $s = k_R/k_S$ (Scheme 4.2). The enantiomeric enrichment of substrate (S) and product (P) depends on the conversion because the two enantiomers of the

[149] Pellissier, H. *Adv. Synth. Catal.* **2011**, *353*, 1613-1666.
[150] Noyori, R. *Adv. Synth. Catal.* **2003**, *345*, 15-32.
[151] a) Blaser, H. U.; Schmindt, E. *Assymmetric Catalysis on Industrial Scale*, Wiley-VCH, Weinheim, **2004**. b) Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001**, *343*, 5-26.

starting racemate (S_R and S_S) can react simultaneously with an enantiomerically pure compound at a different rate. The selectivity value (*s*) as a function of the conversion and the enantiomeric excess can be calculated from equations 1 and 2 in Scheme 4.2 when the reaction proceeds irreversibly. In the ideal case, one of the enantiomers of the racemate is transformed into the desired product in 50% yield whereas the other enantiomer remains unreacted. The main strength of the kinetic resolution process is the possibility to obtain both the unreacted starting material and the desired product with high enantiomeric excess.



Scheme 4.2. General concept of the kinetic resolution and selectivity factor.

4.1.2. ENANTIOSELECTIVE ACYL TRANSFER REACTIONS FOR THE KINETIC RESOLUTION OF ALCOHOLS, AMINES AND AMIDES

The kinetic resolution, via acyl transfer reactions of alcohols, amines and amides was traditionally tackled using natural enzymes, generally lipases.[152] The use of enzymes allowed obtaining impressive selectivities in kinetic resolution experiments. However, the intrinsic specificity of enzymes also implies that their application on a broad range of compounds could be difficult and unpredictable.[148]

[152] a) Schmid, R. D.; Verger, R. *Angew. Chem. Ed.* **1998**, *37*, 1608-1633. b) Griffith, D. A.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1996**, *118*, 9526-9538.

In order to overcome the limitations of enzymes, in the mid nineties emerged the interest of many research groups on the development of small molecular catalyst for the enantioselective acylation reaction.[153]

Acyl transfer reactions are widely known to be accelerated by the use of nucleophilic catalyst. The most generally used are *N*,*N*-dimethylaminopyridine (DMAP, **274**), *N*-methyl imidazole (NMI, **275**), 4-pyrrolidinopyridine (PPY, **276**), and phosphines (Figure 4.1).[150]

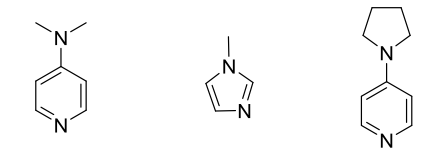
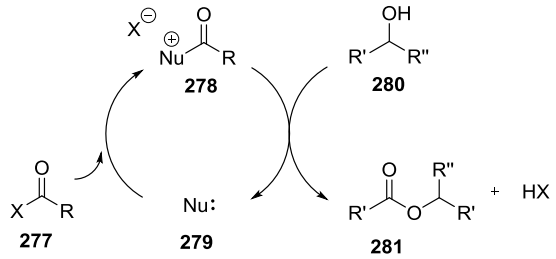


Figure 4.1. Common nucleophilic catalyst used in acylation reactions.

The general catalytic cycle that explains the role of nucleophilic catalyst in the acylation reaction is shown in Scheme 4.3. Thus, initially, the nucleophilic catalyst (**279**), more nucleophilic than the acyl acceptor (**280**) (secondary alcohol in the example), attacks the acyl donor (**277**) generating a *N*-acyl or *P*-acyl intermediate (**278**) that is more electrophilic than the starting acyl donor (**277**), reacting, consequently, faster with the acyl acceptor (**280**).

[153] For reviews see: a) Somfai, P. *Angew. Chem. Int. Ed.* **1997**, *36*, 2731-2733. b) France, S.; Guerin, D. J.; Miller, S. J.; Lectka, T. *Chem. Rev.* **2003**, *103*, 2985-3012. c) Vedejs, E.; Jure, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 3974-4001. d) Taylor, J. E.; Bull, S. D.; Williams, J. M. J. *Chem. Soc. Rev.* **2012**, *41*, 2109-2121.



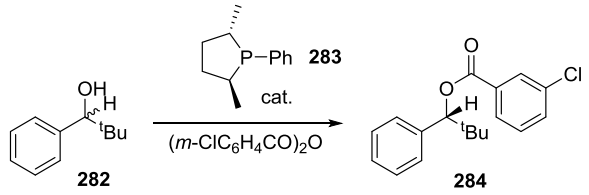
Scheme 4.3. General catalytic cycle for the nucleophilic catalysis of acyl transfer.[149]

Kinetic resolution of alcohols, amines and amides using this strategy is achieved by the generation of chiral acyl donor-nucleophilic catalyst complexes intermediates like **278** from chiral nucleophilic catalysts. The efficiency in which this complex discriminates between the two enantiomers of a racemic acyl acceptor will determine the efficiency of the kinetic resolution. Is important to mention that the aspects discussed below will be focused basically on kinetic resolution of alcohols because most of the work on the literature deals with secondary alcohols. In addition, concerning enantioselective acylation, the reactivity of oxazolidinones is better related to secondary alcohols than to amines, since generally a catalyst is required for reaching good rates in acylation reactions. The problem of primary amines, in this type of kinetic resolution, is connected with their comparable nucleophilicity with the chiral nucleophilic catalyst towards simple acylating agents such as anhydrides. This background reaction notoriously decreases the kinetic resolution effectiveness. Strategies to overcome the racemic background reaction include the use of low-reactive amines (e.g.indolines),[154] the use of reduced-activity electrophiles (e.g. *O*-acylated azalactones)[155] and the use of nitrogen-containing molecules in which the nitrogen atom serves as a spectator group.[156] Finally, an alternative to the previous catalytic methods is the use of stoichiometric amounts of chiral acylating agents as,

[154] Arp, F. O.; Fu, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 14264-14265.
[155] Arai, S.; Bellemin-Laponnaz, S.; Fu, G. C. *Angew. Chem. Int. Ed.* **2001**, *40*, 234-236.
[156] a) Hang, J.; Tian, S.-K.; Tang, L.; Deng, L. *J. Am. Chem. Soc.* **2001**, *123*, 12696-12697. b) Berkessel, A.; Cleemann, F.; Mukherjee, S. *Angew. Chem. Int Ed.* **2005**, *44*, 7466-7469. c) Tokunaga, M.; Kiyosu, J.; Obora, Y.; Tsuji, Y. *J. Am. Chem. Soc.* **2006**, *128*, 4481-4486.

for example, in the kinetic resolution of propargyl amines and allylic amines reported by Cossy *et al.*[157]

The first example of catalytic kinetic resolution of alcohols with *s* >10 was provided by Vedejs and co-workers in 1996.[158] In that work a chiral phosphine catalyst (**283**) was employed in the acylation of benzylic secondary alcohols (**282**) with *m*-chlorobenzoic anhydride (Scheme 4.4).



Scheme 4.4. Kinetic resolution of benzylic secondary alcohols catalysed by chiral phospine **283**.

From the initial finding by Vedejs, several other types of nucleophilic catalyst have been developed (Figure 4.2), being the most widely used, apart from the aforementioned phosphines (**285** and **286**),[159] metallocenes (**287** and **298**),[160] PPY analogues (**288**),[161] peptide-based catalysts (**289**),[162] tertiary diamines (**290**),[163] axially chiral DMAP analogues (**291**),[164] C1-symmetric DMAP analogues (**292**),[165]

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[157] a) Kolleth, A.; Christoph, S.; Arseniyadis, S.; Cossy, J. *Chem. Commun.* **2012**, *48*, 10511-10513. b) Kolleth, A.; Cattoen, M.; Arseniyadis, S.; Cossy, J. *Chem. Commun.* **2013**, *49*, 9338-9340.

[158] Vedejs, E.; Daugulis, O.; Diver, S. T. *J. Org. Chem.* **1996**, *61*, 430-431.

[159] a) Vedejs, E.; Rozners, E. *J. Am. Chem. Soc.* **2001**, *123*, 2428-2429. b) MacKay, J. A.; Vedejs, E. *J. Org. Chem.* **2006**, *71*, 498-503.

[160] a) Fu, G. C. *Acc. Chem. Res.* **2004**, *37*, 542-547. b) Hu, B.; Meng, M.; Wang, Z.; Du, W.; Fossey, J. S.; Hu, X.; Deng, W. P. *J. Am. Chem. Soc.* **2010**, *132*, 17041-17044.

[161] a) Kawabata, T.; Nagato, M.; Takasu, K.; Fuji, K. *J. Am. Chem. Soc.* **1997**, *119*, 3169-3170. b) Kawabata, T.; Yamamoto, K.; Momose, Y.; Yoshida, H.; Nagaoka, Y.; Fuji, K. *Chem. Commun.* **2001**, 2700-2701.

[162] a) Miller, S. J. *Acc. Chem. Res.* **2004**, *37*, 601-610. b) Jarvo, E. R.; Evans, C. A.; Copeland, G. T.; Miller, S. J. *J. Org. Chem.* **2000**, *66*, 5522-5527.

[163] Oriyama, T.; Imai, K.; Sano, T.; Hosoya, T. *Tetrahedron Lett.* **1998**, *39*, 3529-3532.

[164] Spivey, A. C.; Fekner, T.; Spey, S. E. *J. Org. Chem.* **2000**, *65*, 3154-3159.

[165] Yamada, S.; Misono, T.; Iwai, Y. *Tetrahedron Lett.* **2005**, *46*¸ 2239-2242.

bizoxazolines (**293**)[166] and, more recently, amidines (**294**, **295**, **296**, **297** and **298**).[153d,167]

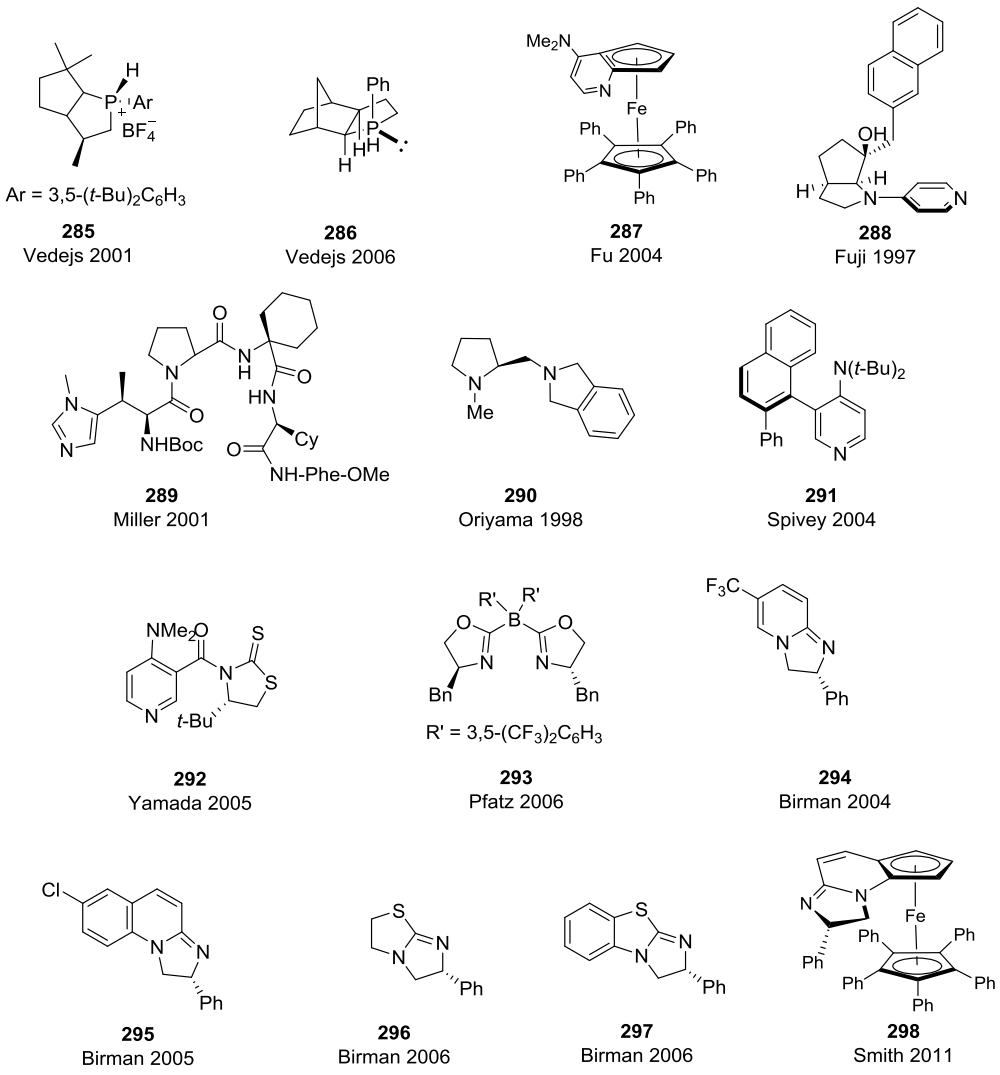

Figure 4.2. Some relevant nucleophilic catalyst used in enantioselective acylations.

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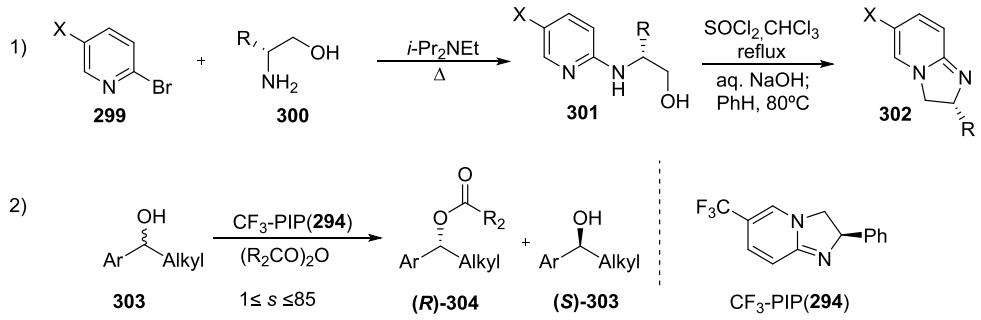
[166] a) Roseblade, S. J.; Pfaltz, A. *Synthesis* **2007**, *23*, 3751-3753. b) Mazet, C.; Roseblade, S.; Kölhler, V.; Pfaltz, A. *Org. Lett.* **2006**, *8*, 1879-1882.

[167] a) Birman, V. B.; Uffman, E. W.; Jiang, H.; Li, X.; Kilbane, C. J. *J. Am. Chem. Soc.* **2004**, *126*, 12226-12227. b) Birman, V. B.; Jiang, H. *Org. Lett.* **2005**, *7*, 3445-3447. c) Birman, V. B.; Li, X. *Org. Lett.* **2006**, *8*, 1351-1354.

The field of asymmetric acylations greatly benefited from the work made by Birman and co-workers towards the development of asymmetric acyl transfer agents easy to prepare. The first breakthrough in this sense was the preparation of a variety of chiral amidines following a simple procedure involving initial condensation of 2-halobromopyridines (**299**) with a chiral aminoalcohol followed by cyclization (Scheme 4.5, eq. 1). Concretely, (*R*)-2-phenyl-6-(trifluoromethyl)-2,3-dihydroimidazo[1,2-*a*]pyridine (CF_3-PIP, **294**) was demonstrated to be active in the kinetic resolution of benzylic alcohols with anhydrides providing *s* values up to 85 (Scheme 4.5, eq. 2).[167b]



Scheme 4.5. 1) General preparation of chiral amidine nucleophilic catalysts. 2) Kinetic resolution of benzylic alcohols via enantioselective acyl transfer reaction catalysed by chiral amidine **294**.

The authors suggested that the enantio-discrimination step would involve cation-π interations between the pyridinium ring of the catalyst and the aryl group of the alcohol substrate (Figure 4.3).[168]

[168] For a review on the role of cation-π interactions in asymmetric organocatalysis see: Yamada, S.; Fossey, J. S. *Org. Biomol. Chem.* **2011**, *9*, 7275-7281.

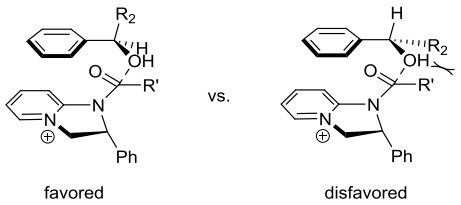
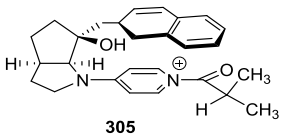


Figure 4.3. Transition state model proposed by Birman for the kinetic resolution using CF_3-PIP (**294**).

The relevance of this type of non bonding interactions in asymmetric acylation reactions was already stated by Fuji *et al.* on the kinetic resolution of alcohols using PPI analogues chiral nucleophilic catalysts.[161a] NOE experiments as well as ^{1}H NMR chemical shifts served to support the π-cation interactions between the electron-rich naphthyl ring and the electron-poor pyridinium ring in the catalyst-acyl donor complex **305** in (Figure 4.4). Such spectroscopic data were in agreement with the enantioselectivity increase as the naphthyl ring bears more electron-donating substituents. Indeed, the more electron-richer the naphthyl ring was, the more robust intermediate **305** would be, and thus, more efficient would be the facial discrimination. In Figure 4.4 the *si* face of the carbonyl group is blocked by the naphthalene whereas the *re* face is available for the addition of an alcohol.

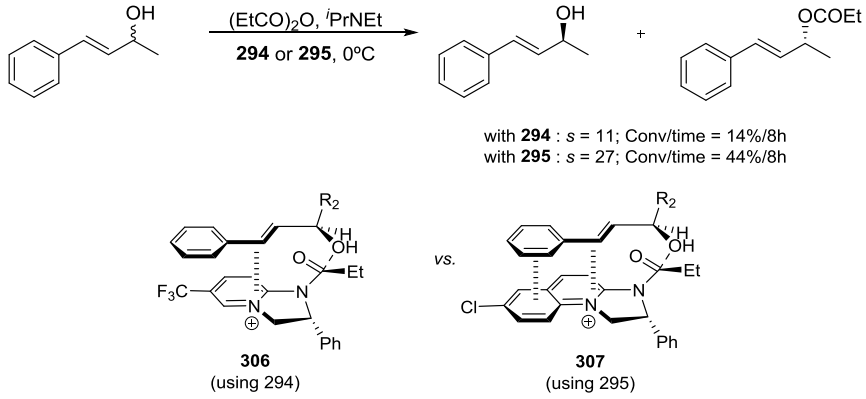


305

Figure 4.4. Closed conformation proposed by Fuji for the *N*-acyliminium ion **305**.

Another example that demonstrates the importance of π-cation interactions in this type of process is the improved behaviour displayed by amidine **295** with respect to its analogue **294** in the acylation of allylic alcohols with propionic anhydride (Scheme 4.6).[167c] The extended aromatic system of **295** would facilitate the interaction between

the alkene of the allylic alcohol and the *N*-acyliminium ion **307**, which, in turn, gave rise to increased activity and enantioselectivity.



Scheme 4.6. Rationalization of the higher activity and selectivity provided by **295** compared with **294** in the acylation of allylic alcohols as a result of the extended aromaticity of the former.

Continuing on their efforts to develop easy-to-make catalysts, Birman and co-workers found that commercially available tetramisole (**296**, Figure 4.2) could catalyse the acylation of secondary benzylic alcohols with up to s = 35. Interestingly, and contrary to previous catalysts, tetramisole does not possess the pyridinium ring in the acylated intermediate, which was considered to be essential for enantioinduction. Owing to the growing consensus about the importance of π-π and cation-π interactions, the same authors prepared a benzannullated derivative of tetramisole, named as benzotetramisole (BTM **297**, Figure 4.2). BTM performed excellently with benzylic secondary alcohols giving up to s = 355. However, the most important feature of this catalyst was the versatility displayed. Thus, a broad range of benzylic alcohols were acylated with BTM giving similar or higher selectivity factors than

when the same substrates were previously tackled separately with different catalysts.[167c,169]

Not only BTM revealed to be optimum for the resolution of alcohols but also resulted to be an appropriate choice for other type of kinetic resolution processes. In this sense it has been successfully applied by Birman's group, and also adopted by others, in the kinetic resolution of α-hydroxy- lactones and lactams (**308**),[170] α-arylalkanoic acids (**309**),[171] 2-hydroxyalkanoates (**310**),[172] lactams and imidazolones (**311**), oxazolidinones (**312**) and oxazolidin-2-thiones (**313**) (Figure 4.5).[173]

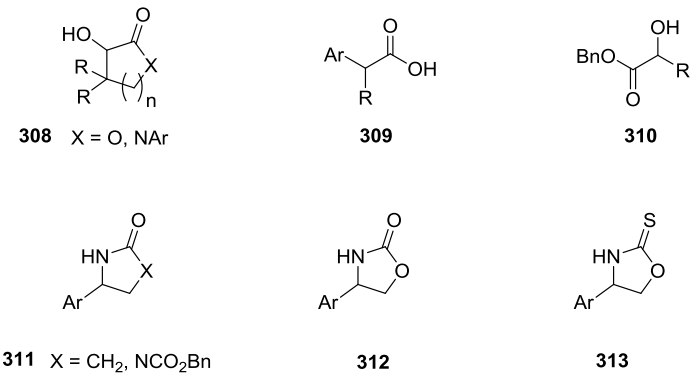


Figure 4.5. Different type of substrates in which BTM has found applicability as chiral acyl transfer agent.

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169 a) Vedejs, E.; Daugulis, O. *J. Am. Chem. Soc.* **2003**, *125*, 4166-4173. b) Kano, T.; Sasaki, K.; Maruoka, K. *Org. Lett.* **2005**, *7*, 1347-1349.

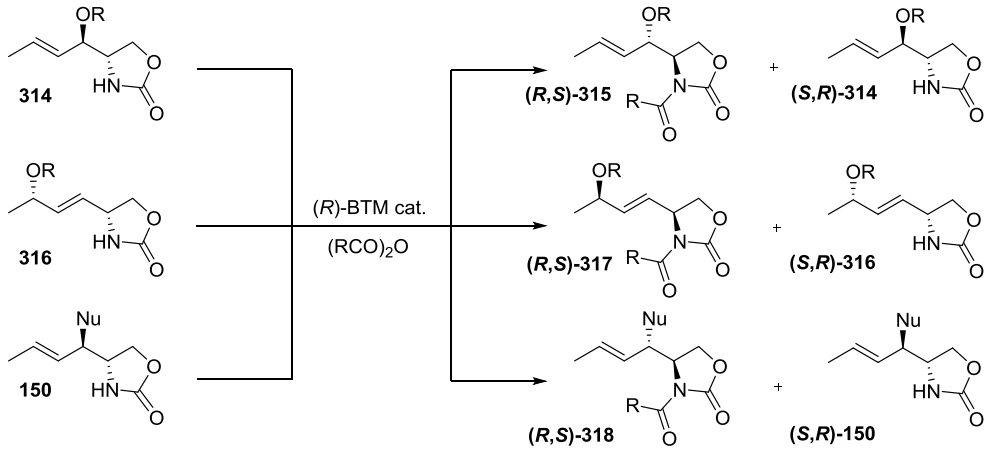
170 Clark, R. W.; Deaton, T. M.; Zhang, Y.; Moore, M. I.; Wiskur, S. L. *Org. Lett.* **2013**, *15*, 6132-6135. b) Nakata, K.; Gotoh, K.; Ono, K.; Futami, K.; Shiina, I. *Org. Lett.* **2013**, *15*, 1170-1173.

171 In that case its analogue (*S*)-*β*-Np-BTM provided better enantioselectivities: a) Shiina, I.; Nakata, K.; Ono, K.; Onda, Y.; Itagaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 11629-11641. b) Nakata, K.; Onda, Y.; Ono, K; Shiina, I. *Tetrahedron Lett.* **2010**, *51*, 5666-5669. c) Shiina, I.; Nakata, K. *Tetrahedron Lett.* **2007**, *48*, 8314-8317.

172 a) Nakata, K.; Sekiguchi, A.; Shiina, I. *Tetrahedron: Asymmetry* **2011**, *22*, 1610-1619. b) Shiina, I.; Nakata, K.; Ono, K.; Sugimoto, M.; Sekiguchi, A. *Chem. Eur. J.* **2010**, *16*, 167-172.

173 a) Yang, X.; Bumbu, V. D.; Liu, P.; Li, X.; Jiang, H.; Uffman, E. W.; Guo, L.; Zhang, W.; Jiang, X.; Houk, K. N.; Birman, V. B. *J. Am. Chem. Soc.* **2012**, *134*, 17605-17612. b) Birman, V. B.; Jiang, H.; Li, X.; Guo, L.; Uffman, E. W. *J. Am. Chem. Soc.* **2006**, *128*, 6536-6537.

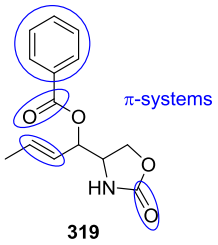
Among all the substrates in Figure 4.5, the demostration of the feasibility to acylate oxazolidinones (**312**) with high selectivity was of valuable interest for our purposes taking into account that the oxazolidinone moiety is present in the products obtained from the oxyamination process and also from the *in situ* ring opening of vinylaziridines with *N*- and *S*-nucleophiles described in Chapter 3 (Scheme 4.7). Thus, the application of Birman's conditions for the enantioselective acylation of oxazolidinones could provide an attractive solution for the preparation of the enantioselective unsaturated aminoalcohols targeted in this thesis work.



Scheme 4.7. Representative scheme for the enantioselective preparation of unsaturated aminoalcohols via kinetic resolution of oxazolidinones.

However, a deep analysis of the aforementioned report by Birman on the acylation of oxazolidinones revealed that the reaction only proceeded with aromatic-substituted oxazolidinones (**312** in Figure 4.5). That evidence raised some doubts about the possibility of achieving success with our substrates taking into consideration that they don't possess aromatic substituents directly attached to the oxazolidinone ring. Conversely, our substrates have alternative π-systems (Figure 4.6) such as the olefin and the carbonyl moieties of the acyl substituents that could also interact with the *N*-acyliminium cation intermediate, although not directly linked to

the oxazolidinones. In addition to these π-systems, in the case of benzoate-, phtalimide- or thiophenolate-substituted substrates, aromatic rings are present.



319

Figure 4.6. Different π-systems present in benzoate substrate **319**.

All in all, if application of Birman's conditions to our system met success, it would demonstrate that the kinetic resolution of oxazolidinones is an attractive alternative for the enantioselective preparation of aminoalcohols not only in simple selected substrates but also in more complex structures.

4.2. RESULTS AND DISCUSSION

As previously commented, we were interested in obtaining enantioselectively 1,2-unsaturated aminoalcohols bearing *O*-, *N*- or *S*-substituents. In the particular case of *O*-substituents our final goal is the alcohol functionality and, as a consequence, the type of ester protecting group precursor is of minor relevance. This openened the possibility to look the ester-protecting group, among those obtained in Chapter 3, that provided the highest selectivity in the kinetic resolution and, afterwards, hydrolyse it.

4.2.1. PREPARATION OF SUBSTRATES FOR THE KINETIC RESOLUTION OF *O*-SUBSTITUTED OXAZOLIDINONES

Initially we planned to prepare the substrates displayed in Figure 4.7. Although some of them were obtained in good yields from the rhodium-catalysed oxyamination

process described in Chapter 3, the requirement of 10% mol of rhodium catalyst prompted us to look for an alternative synthesis.

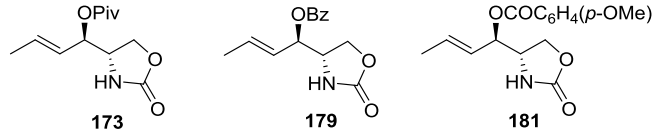


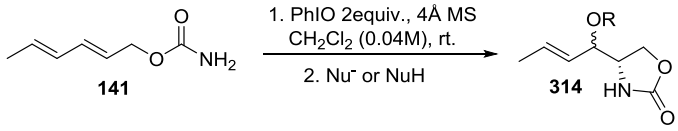
Figure 4.7. Substrates planned to be resolved by enantioselective *N*-acylation.

It was therefore decided to prepare these substrates, analogously to *N*- and *S*-substituted, by metal-free aziridination with PhIO and ring opening with the corresponding salt or acid (Table 4.1).

Addition of 20 equivalents of acetic acid in the reaction vessel containing preformed vinylaziridine **143** from carbamate **141** (See Table 4.1 and Scheme 4.8) provided an epimeric mixture (70:30) of acetylated products (Table 4.1, entry 1).[174] This outcome was attributed to a S_N1 mechanism catalysed by the presence of acid (Scheme 4.8). Similar result was obtained when the acid added was benzoic acid (Table 4.1, entry 2). Vinylaziridine **143** showed to be considerably sensitive to acid conditions since by only adding 2 equivalents of acetic acid epimerization occurred (Table 4.1, entry 3). In an attempt to emulate the conditions of ring opening during oxyamination, a mixture of acetic acid and MgO was added, although, again, epimerization was produced (Table 4.1, entry 4). Finally, the use of ammonium acetate salt neither avoided epimerizaton (Table 4.1, entry 5).

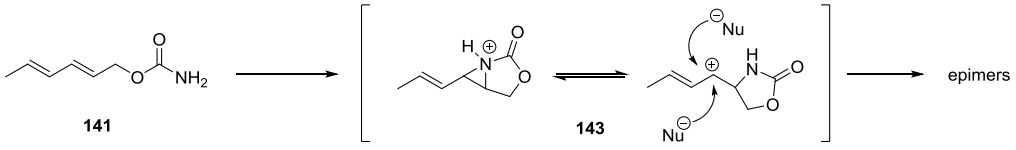
[174] The formation of epimers was already observed in this pioneering work on intramolecular aziridination of carbamates when the reaction was carried out with $PhI(OAc)_2$ in the absence of a base: Levites-Agababa, E.; Menhaji, E.; Perlson, L. N.; Rojas, C. M. *Org. Lett.* **2002**, *4*, 863-865.

Table 4.1. Attempts to prepare ester-substituted oxazolidinone substrates from the metal-free aziridination approach.[a]



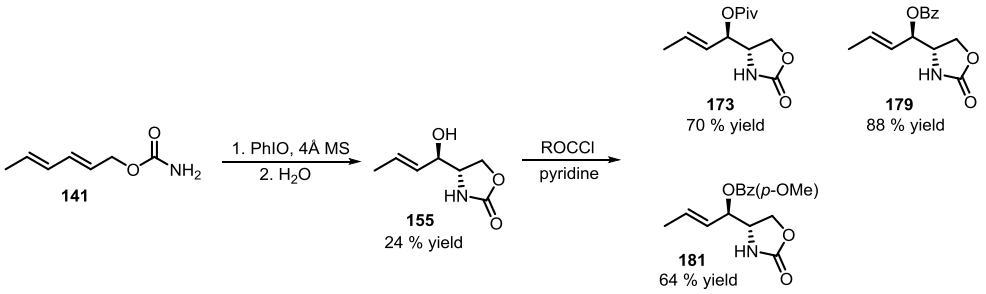
Entry	Nucleophile (equiv.)	Conv. (%)[b]	Products selectivity (%)[b]
1	AcOH (20)	>98	70:30
2	BzOH (20)	>98	60:40
3	AcOH (2)	>98	70:30
4	AcOH/MgO (4/5)	>98	70:30
5	NH_4Ac (2)	>98	65:35

[a] PhIO (2 equiv.), 4Å MS (100 mg per 0.1 mmol carbamate **141**). [b] Determined by ^1H NMR spectroscopy.



Scheme 4.8. Plausible mechanistic scenario for the formation of epimers.

At that point the strategy was changed. We decided to prepare first alcohol **155** and then to acylate it with different acyl chlorides (Scheme 4.9). For the acylation reaction especial care have had to be taken in the use of freshly distilled acyl chlorides since the presence of acid traces produced epimerisation and, of course, in neutralysing the generated HCl. Alcohol **155** was obtained in 24% yield by addition of water to the reaction mixture of carbamate **141** and PhIO once **141** was consumed. Esters **173**, **179** and **181** where obtained in good yields from acylation of alcohol **155** in good yields and, although the overall yields from carbamate **141** resulted low, the method resulted convenient for our purposes.



Scheme 4.9. Preparation of different ester-substituted oxazolidinones from alcohol **155**.

4.2.2. KINETIC RESOLUTION OF ESTER-SUBSTITUTED OXAZOLIDINONES

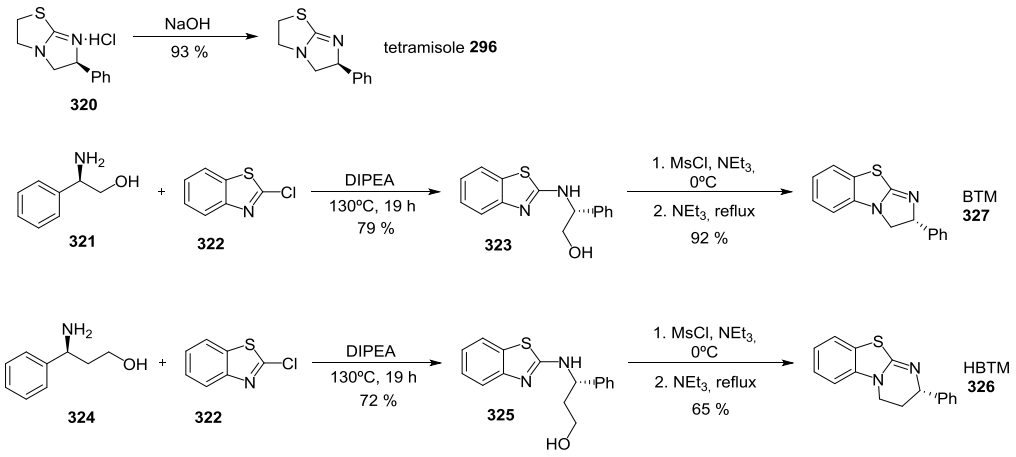
The main factors to be considered in the optimization of the reactions conditions were the acyl protecting group, the catalyst, the acylating agent, the concentration and the temperature.

The catalysts of choice were tetramisole (**296**), benzotetramisole (BTM, **297**) and benzotetramisole (HBTM, **326**). Tetramisole is the non-benzannulated form of BTM, and HBTM is the ring-expanded version. Moreover, HBTM was also chosen as a result of the complementarity shown with BTM in the kinetic resolution of alcohols. Thus, whereas BTM gave high selectivities when the π-system was located α- to a nucleophilic atom but not when in β, HBTM provided an inverse pattern of selectivities.[175] The latter would be convenient for the kinetic resolution of the S_N2'-oxyaminated products, in which the π-system is further away compared to the S_N2-oxyaminated ones.

Concerning the preparation of these catalysts, tetramisole can be readily obtained in 93% yield by the basic hydrolysis of its hydrochloride salt (Scheme 4.10, a). BTM and HBTM were obtained following the reported procedures[167d,175] by the condensation of the respective amino alcohols (*R*)-2-amino-2-phenylethan-1-ol (**321**)

[175] Birman, V. B.; Li, X. *Org. Lett.* **2008**, *10*, 1115-1118.

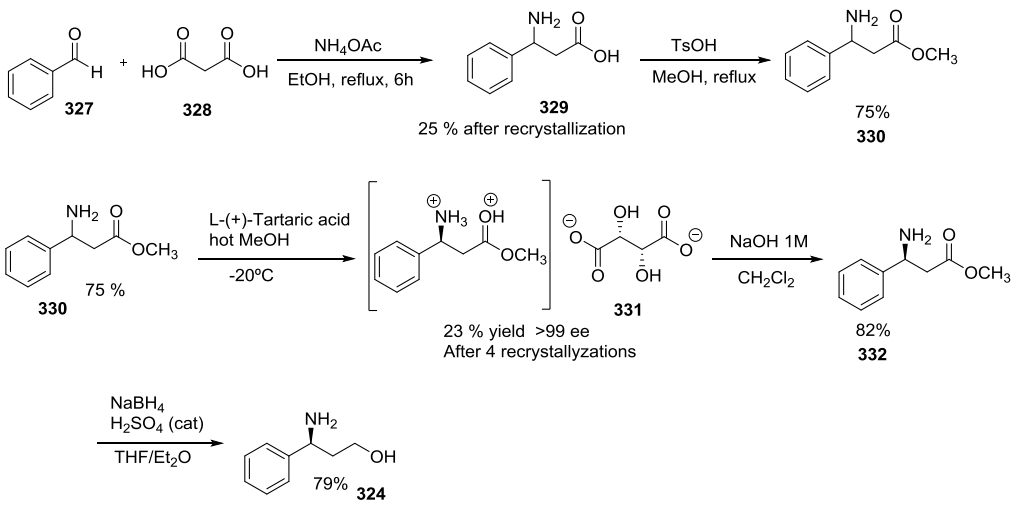
and (*S*)-3-amino-3-phenylpropan-1-ol (**324**) with 2-chlorobenzothiazole (**322**), mesylation of the primary alcohol (**323** and **325**) and final cyclisation (Scheme 4.10, b and c).



Scheme 4.10. Preparation of Tetramisole, BTM and HBTM.

Chiral amino alcohol **321** is commercially available but not **324**. Preparation of the latter was done following the procedure reported by Zehnder[176] via a sequence of transformations starting from benzaldehyde (Scheme 4.11). Initial condensation of benzaldehyde with malonic acid in the presence of ammonium acetate led to (±)-3-amino-3-phenylpropanoic acid **329**. Fisher esterification of **329** provided ester **330**, which was resolved with L-tartaric acid. After being recystallysed 4 times, (*S*)-methyl-3-amino-3-phenylpropanoate L-tartrate salt **331** was obtained in >99% ee. Basification of salt **331** and reduction with $NaBH_4$ with acid catalysis rendered (*S*)-3-amino-3-phenylpropan-1-ol (**324**).

[176] Liu, S.; Müller, J. F. K.; Neuburger, M.; Schaffner, S.; Zehnder, M. *Helv. Chim. Acta* **2000**, *83*, 1256-1267.



Scheme 4.11. Preparation of the chiral aminoalcohol precursor of HBTM.

With the catalysts in hand, the efect of the ester protecting group was analysed using the conditions reported by Birman: 4 mol% of BTM as the catalyst, 75 mol% of isobutyric anhydride, 75 mol% of DIPEA, Na_2SO_4 and chloroform as solvent (0.2M respect the substrate) at room temperature (Table 4.2). The addition of DIPEA was found to be crucial in order to scavenge the acid generated, which reduced the catalyst activity. In the same direction, a desiccating agent (Na_2SO_4) was necessary since water could react with the highly electrophilic *N*-acyliminium intermediate.

As it was expected, considering the importance of π-π interactions between the substrate and the catalyst-acylating agent adduct, benzoyl- and *p*-methoxy benzoyl-substituted substrates showed higher activity and selectivity than the respective pivaloyl-substituted compound (Table 4.2). That confirmed our hypothesis that aromatic rings installed as substituents on the hydroxyl group could have influence in the enantioselective process, presumably through π-π stablilising interactions as it is proposed in the model of (Figure 4.8). Since benzoyl and *p*-methoxybenzoyl groups provided similar results, benzoylated-substrate was chosen as the model substrate for further optimization.

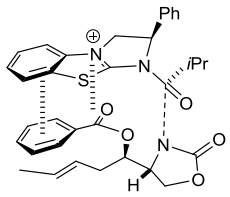
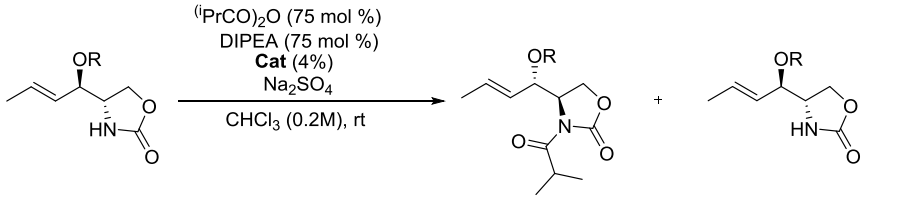


Figure 4.8. Proposed intermediate in the enantioselective acylation of benzoate-substituted oxazolidinones.

Table 4.2. Optimisation of the ester protecting group and catalyst for the kinetic resolution experiments.[a]



173 R=Piv
179 R=Bz
181 R=*p*-MeOBz

(***R***,***S***)-**333** R=Piv
(***R***,***S***)-**334** R=Bz
(***R***,***S***)-**335** R=p-MeOBz

(***S***,***R***)-**173** R=Piv
(***S***,***R***)-**179** R=Bz
(***S***,***R***)-**181** R=p-MeOBz

Entry	R	Cat.	Time (h)	Conv. (%)[b]	Ee (P/S)[c]	Selec. (*s*)
1	Piv	BTM	5.5	43	88/65	31
2	Bz	BTM	4	43	94/72	70
3[d]	*p*-OMeBz	BTM	22	46	92/79	58
4	Bz	Tetramisole	21	10	-	-
5[d]	Bz	HBTM	32	26	86/31	18

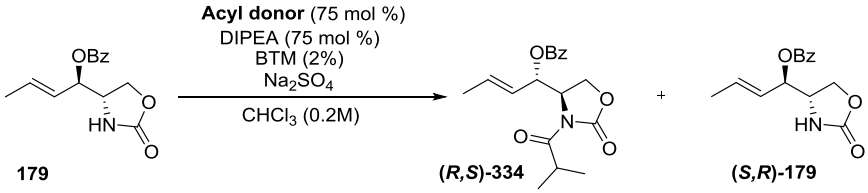
[a] Na_2SO_4 (100mg of per 0.1 mmol of substrate) [b] Determined by ^1H NMR spectroscopy. [c] Enantiomeric excess was determined by chiral HPLC. P = acylated product, S = recovered starting material. [d] The concentration of starting material was 0.1M.

Next, the use of the other previously mentioned catalysts (tetramisole and HBTM) was explored. Tetramisole only provided 10% conversion after 21 hours (Table 4.2, entry 4). On the other hand, HBTM neither showed any improvement, but actually resulted less effective than expected in that particular system with a

selectivity factor of 18 (Table 4.2, entry 5). It is worth mentioning that for practical issues the reaction with HBTM was carried out at 0.1M concentration which later was demonstrated to have a detrimental effect on both the reaction rate and the enantioselectivity.

Another aspect that could play an important role on the enantioselectivity is the choice of the acylating agent. In this sense we tested the most common ones: acyl chlorides, acid anhydrides and carbonate anhydrides. Like in the previous studies by Birman, the use of $(Boc)_2O$ did not display any conversion (Table 4.3, entry 1).[173b] Using benzoyl chloride neither provided conversion of the starting oxazolidinone **179** (Table 4.3, entry 2). Alternatively, and as it could have been anticipated, anhydrides demonstrated to be active for our system. In particular isobutyric anhydride proved to be the best, being even superior to the larger pivalic anhydride (Table 4.3, entries 3 and 4).

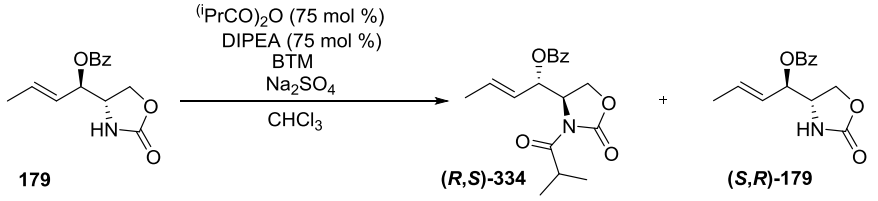
Table 4.3. Kinetic resolution of **179**. Optimisation of the acylating agent.[a]



Entry	Acyl donor	T (ºC)	Conv. (%)[b]	Ee (P/S)[c]	selectivity (*s*)
1[d]	$(Boc)_2O$	20	0	-	-
2	BzCl	20	<5	-	-
3	$(^{i}PrCO)_2O$	0	47	92/80	59
4	$(^{t}BuCO)_2O$	0	28	90/35	28

[a] Using 100mg of Na_2SO_4 per 0.1 mmol oxazolidinone **179** [b] Determined by ^1H NMR spectroscopy. [c] enantiomeric excess was determined by chiral HPLC. [d] 4 mol% of BTM was used.

Table 4.4. Kinetic resolution of **179**. Optimisation of the catalyst loading, concentration and temperature.[a]



Entry	Cat. (%)	Time(h)	Conc.	T(ºC)	Conv. (%)[b]	Ee (P/S)[c]	(*s*)
1	4	4	0.2M	20	43	94/72	70
2	4	10	0.1M	20	37	93/55	48
3	4	2	0.2M	0	48	93/85	75
4	4	7	0.1M	0	28	96/34	68
5	6	10	0.1M	20	51	88/90	48
6	4	21	0.2M	-40	46	92/76	55
7	6	21	0.2M	-40	55	80/97	38
8	8	21	0.2M	-40	53	86/97	55
9	8	21	0.2M	-40	45	92/74	53
10	2	21	0.2M	0	47	92/80	59
11[d]	4	3.5	0.2M	0	37	97/58	118

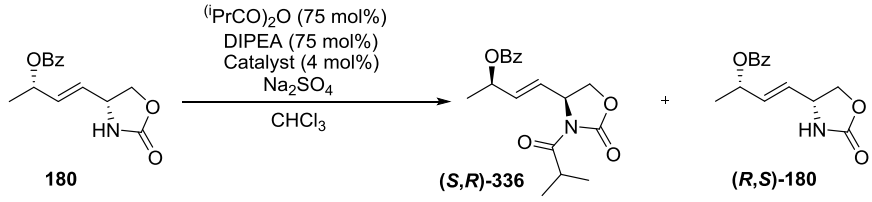
[a] Na_2SO_4 (100mg of per 0.1 mmol of **179**) [b] Determined by ^1H NMR spectroscopy. [c] Enantiomeric excess was determined by chiral HPLC. [d] BTM was recystallysed three times before being used. Product **(*R*,*S*)-334** was isolated in 33% yield and enantioenriched starting material **(*S*,*R*)-179** in 54%.

Finally, the influence of the catalyst loading, concentration and temperature was analysed (Table 4.4). At the first sight, it appears clear that none of the variations on any of the factors had a sharp effect on the reaction outcome. Looking into more detail, dilution from 0.2M to 0.1M provoked a considerable decrease on both the activity and enantioselectivity when the reaction was carried out at room temperature (Table 4.4, entries 1 and 2). Although this effect was less pronounced at 0ºC (Table

4.4, entries 3 and 4). The temperature did not show a clear tendency, thus the best proved to be 0ºC although with only a slight improvement from the results obtained at room temperature. Contrary to what is normally expected, further decrease of the temperature to -40ºC involved a worsening of the selectivity regardless of the catalyst loading which, in turn, was found to be optimum at 4 mol% (Table 4.4, entries 6-10). After becoming aware of the difficulty of improving the already high levels of selectivity obtained modifying common variables, it was decided to recystallise the BTM catalyst several times. To our delight, the use of highly crystalline catalyst allowed to achieve a selectivity factor of 118, almost doubling that achieved previously (Table 4.4, entry 11). From this last reaction acylated oxazolidinone **(*R*,*S*)-334** was isolated in 33% yield whereas the enantioenriched starting material **(*S*,*R*)-179** in 54%.

The high selectivities obtained int he kinetic resolution of the C-3 substituted products encouraged us to explore the resolution of C-5 substituted ones (Table 4.5). For this purpose HBTM, in addition with BTM, was tested as a catalyst due to the aforementioned better results that had showed, compared to BTM, in the kinetic resolution of oxazolidinones bearing the π-system β- to the nucleophilic atom.[1757]

Table 4.5. Kinetic resolution of **180**.[a]

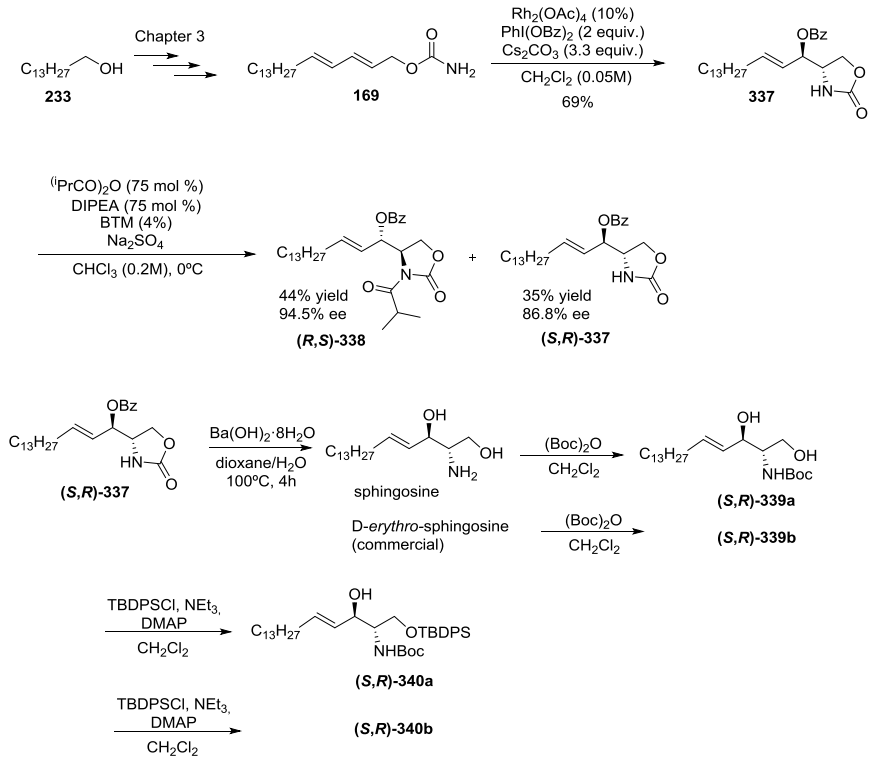


Entry	Catalyst	Time (h)	Conv. (%)[b]	Ee (P/S)[c]	selectivity (*s*)
1	BTM	10	14	78/13	9
2	HBTM	72	16	85/15	10

[a] Na_2SO_4 (100mg of per 0.1 mmol oxazolidinone **180**). [b] Determined by ^1H NMR spectroscopy. [c] Enantiomeric excess was determined by chiral HPLC.

Unfortunately, using either BTM or HBTM the acylation reactions resulted slow and with low enantioselectivity (Table 4.5).

We illustrated the usefulness of the kinetic resolution protocol developed applying it to the enantioselective synthesis of sphingosine. Thus, carbamate **169** was prepared from tetradecanol as described in chapter 3. Rhodium-catalysed oxyamination of **169** using Cs_2CO_3 as the base rendered oxazolidinone **337** as the sole regioisomer in 69% yield. Enantioselective acylation of **337** gave acylated oxazolidinone **(*R*,*S*)-338** in 44% yield and 94.5% ee in combination with unreacted **(*S*,*R*)-337** in 35% yield and 86.8% ee.



Scheme 4.12. Enantioselective synthesis of sphingosine combining the methodologies developed in Chapter 3 and 4.

Unfortunately, we failed in our attempt to hydrolyse acylated oxazolidinone **(*R*,*S*)-338**. At that point it was decided to hydrolyse unreacted oxazolidinone **(*S*,*R*)-337** in

order to obtain sphingosine. Apart from being interesting from a synthetic point of view, obtaining sphingosine and determining which enantiomer we had, was crucial to know which enantiomer of the starting oxazolidinones is acylated faster under the kinetic resolution conditions discussed. In this direction, we planned to derivatise sphingosine obtained from **(*S*,*R*)-337** commercial D-*erythro*-sphingosine and compare the HPLC-MS traces of the obtained derivatives to assign the configuration of our product. Thus, initially sphingosine obtained from **(*S*,*R*)-337** reacted with $(Boc)_2O$ rendering **(*S*,*R*)-339a** and the same was done with commercial D-*erythro*-sphingosine to give **(*S*,*R*)-339b**. Unfortunately we did not manage to resolve the samples by HPLC-MS using normal phase chiral columns. Therefore both samples were silylated with TBSDPCl, which provided **(*S*,*R*)-340a** and **(*S*,*R*)-340b**. Products **(*S*,*R*)-340a,b** were successfully resolved and comparison of the retention times revealed that the unreacted oxazolidinone **(*S*,*R*)-337** after, kinetic resolution, had the same absolute configuration than D-*erythro*-sphingosine.

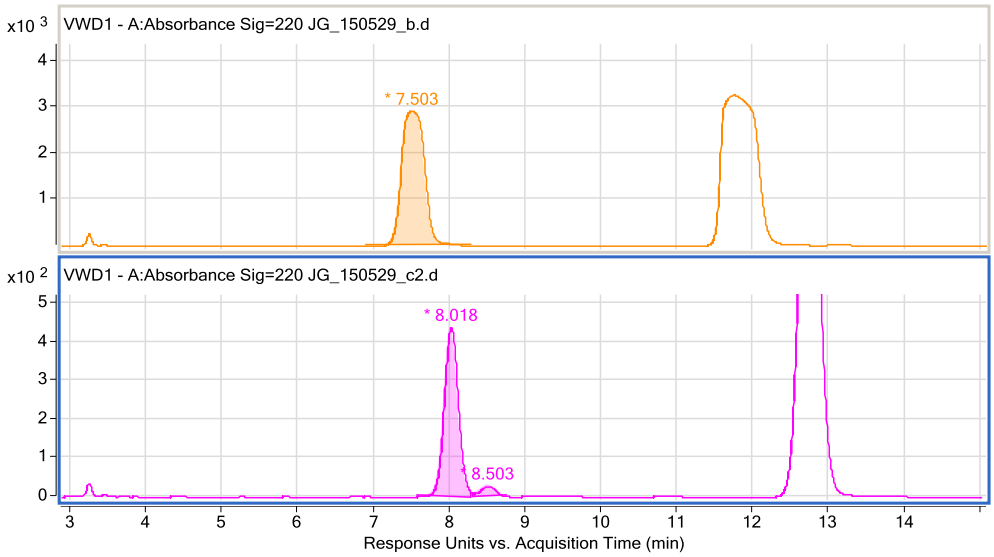
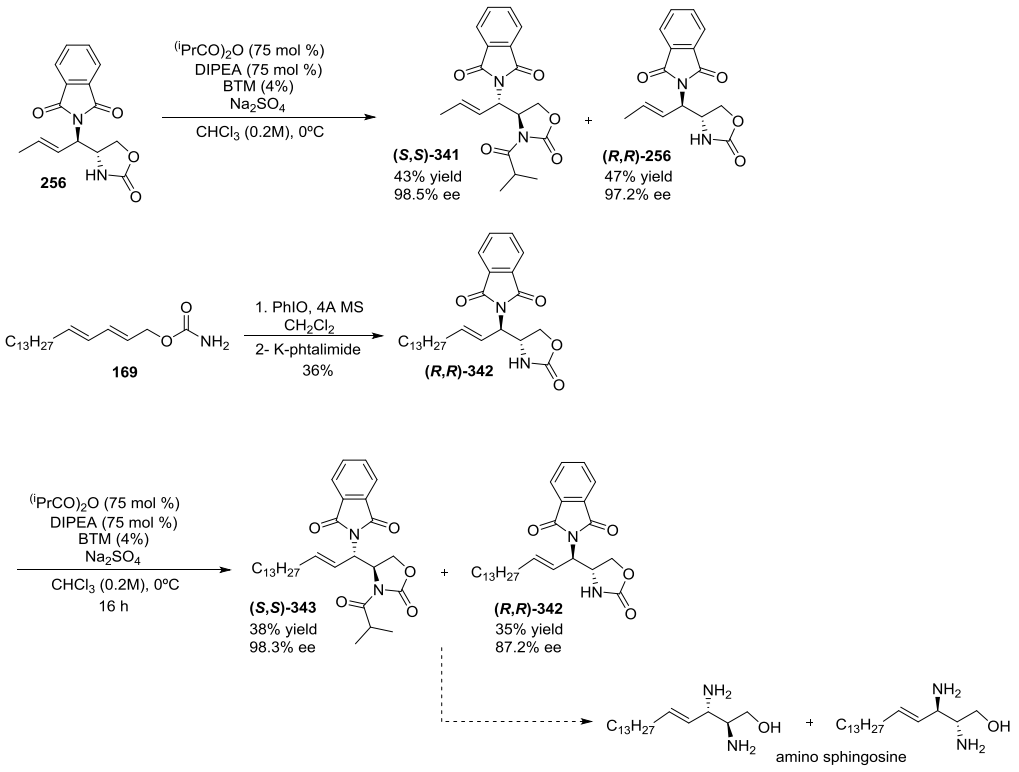


Figure 4.9. Comparison of the HPLC-MS traces of **(*S*,*R*)-340b** (up) and **(*S*,*R*)-340a** (down).

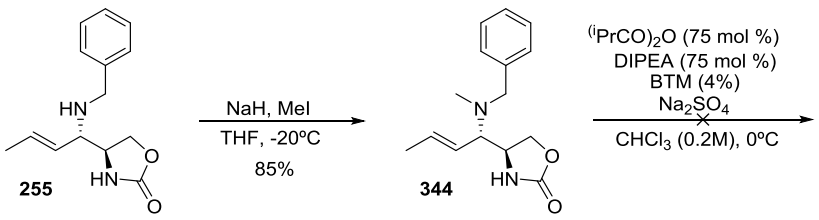
4.2.3. KINETIC RESOLUTION OF *N*- AND *S*-SUBSTITUTED OXAZOLIDINONES

In this section we tackled the kinetic resolution of those oxazolidinones with *N*- and *S*-substituents prepared in chapter 3 using the best conditions found during the optimisation carried out in the previous section. Applying those to phtalimide-substituted oxazolidinone **256** provided an impressive selectivity factor of 570, which allowed to isolate acylated compound **(*S,S*)-341** in 43% yield and 98.5% ee in addition with **(*R,R*)-256** in 47% yield and 97.2% ee (Scheme 4.13). This outstanding level of selectivity could be explained by either the particularly planar nature of phtalimide, or by the presence of numerous π-systems (aromatic ring and two carbonyls) in this substituent. Encouraged by such a positive result the long-chain analogue **342** was prepared from **169** in 36% yield. Product **342** was then resolved providing **(*S,S*)-343** in 38% yield and 98.3% ee, and **(*R,R*)-342** in 52% yield and 87.2% ee, which translated into a *s* value of 335. That opened an efficient route towards a future preparation of the two highly enantioenriched stereoisomers of amino sphingosine.



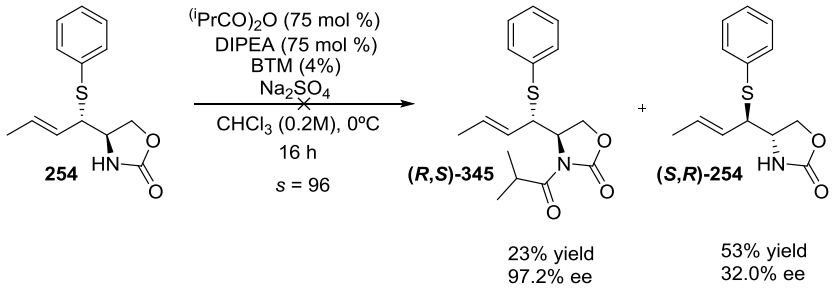
Scheme 4.13. Kinetic resolution of phtalimide-substituted oxazolidinones.

Although the kinetic resolution of *N*-substituted oxazolidinones was already successfully solved, we considered interesting to test the benzylamine-substituted substrate **255** (Scheme 4.14). For this reason the benzylamine was firstly methylated with methyl iodide to avoid the competence of the more nucleophilic secondary amine. Anyway, methylbenzylamine **344** did not react under kinetic resolution conditions.



Scheme 4.14. Attempt to resolve methylbenzylamine substrate **344.**

Finally, the kinetic resolution of thiophenol-substituted oxazolidinone **254** was carried out (Scheme 4.15). The reaction was slower than in the case of OBz- or phtalimide-substituted substrates. However, excellent enantioselectivity (97.2%) was obtained for acylated compound **345**, which was, in addition, isolated in 23% yield. On the other hand, starting thiophenol **254** was isolated in 53% yield and 32% ee, affording a selectivity factor of 96.



Scheme 4.15. Kinetic resolution of thiophenol-substituted oxazolidinone **254**.

As a final remarck, the combination of the intramolecular aziridination/ring opening methodology, described in Chapter 3, with the kinetic resolution methodology, described in the present chapter, represents an attractive approach to highly enantioenriched and distinctly functionalised unsaturated amino alcohols from readily available starting materials. In orther to increase the synthetic value of this methodology, currently, efforts in our group are focused on the optimisation of the metal-free intramolecular aziridination of carbamates.

CHAPTER 5

ENANTIOSELECTIVE SYNTHESIS OF AMINO KETONES AND DIAMINES

UNIVERSITAT ROVIRA I VIRGILI
REGIO- AND ENANTIOSELECTIVE SYNTHESIS OF UNSATURATED AMINO ALCOHOLS, AMINO KETONES AND DIAMINES AS VALUABLE INTERMEDIATES IN ORGANIC SYNTHESIS.
Joan Guash Savidó
Dipòsit Legal: T 1366-2015

5.1. ENANTIOSELECTIVE SYNTHESIS OF α-AMINO KETONES

The formation of amino-containing molecules has been an area of continuous interest in synthetic chemistry since numerous applications exist in the production of both pharmaceuticals and agrochemicals. Over the past decade, the asymmetric *α*-amination of carbonyl moieties has emerged as an area of great interest,[177] with recent examples utilizing chiral Lewis acid complexes,[178] enamine catalysis,[179] and counteranion-directed catalysis[180] as synthetic strategies to achieve high levels of enantioselectivity (Scheme 5.1).

Interestingly, the majority of these approaches utilize electrophilic sources of nitrogen, primarily azodicarboxylates (compounds **346** and **348** in Scheme 5.1) and organonitroso compounds, requiring further derivatization of the amine functionality. Although other efforts have been directed at stereoselectively installing related *α*-amino moieties, these examples also utilize electrophilic nitrogen sources.[181]

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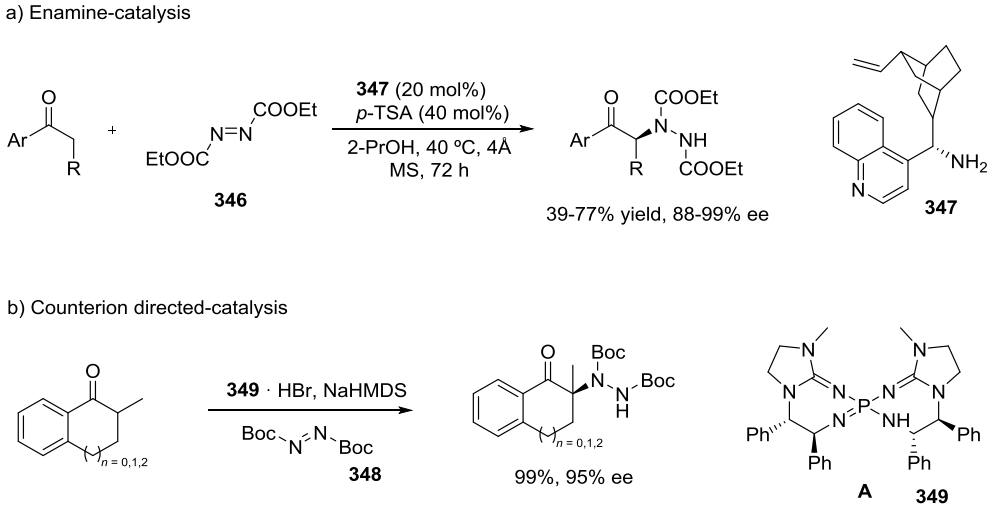
[177] a) Zhou, F.; Liao, F.-M.; Yu, J.-S.; Zhou, J. *Synthesis* **2014**, *46*, 2983-3003. b) Vilaivan, T.; Bhanthumnavin, W. *Molecules* **2010**, *15*, 917-958. c) Marigo, M.; Jørgensen, K. A.; *Chem. Commun.* **2006**, 2001-2011. d) Janey, J. M. *Angew. Chem. Int. Ed.* **2005**, *44*, 4292-4300.

[178] a) Wang, S.-G.; Yin, Q.; Zhuo, C.-X.; You, S.-L. *Angew. Chem. Int. Ed.* **2015**, *54*, 647-650. b) Nan, J.; Liu, J.; Zheng, H.; Zuo, Z.; Hou, L.; Hu, H.; Wang, Y.; Luan, X. *Angew. Chem. Int. Ed.* **2015**, *54*, 2356-2360. c) Yanagisawa, A.; Miyake, R.; Yoshida K. *Org. Biomol. Chem.* **2014**, *12*, 1935-1941. d) Maji, B.; Baidyaab, M.; Yamamoto, H. *Chem. Sci.* **2014**, *5*, 3941-3945. e) Lalli, C.; Dumoulin, A.; Lebée, C.; Drouet, F.; Guérineau, V.; Touboul, D.; Gandon, V.; Zhu, J.; Masson, G. *Chem. Eur. J.* **2014**, *20*, 1704-1712. f) Shen, K.; Liu, X.; Wang, G.; Lin, L.; Feng, X. *Angew. Chem. Int. Ed.* **2011**, *50*, 4684-4688.

[179] a) Maji, B.; Yamamoto, H. *Angew. Chem. Int. Ed.* **2014**, *53*, 8714-8717. b) Kano, T.; Shirozu, F.; Maruoka, K. *Org. Lett.* **2014**, *16*, 1530-1532. c) Xu, C.; Zhang, L.; Luo, S. *Angew. Chem. Int. Ed.* **2014**, *53*, 4149-4153. d) Cecere, G.; König, C. M.; Alleva, J. L.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2013**, *135*, 11521-11524. e) Liu. T.-Y.; Cui, H.-L.; Zhang, Y.; Jiang, K.; Du, W.; He, Z.-Q.; Chen, Y.-C. *Org. Lett.* **2007**, *9*, 3671-3674.

[180] a) Takeda, T.; Terada, M. *J. Am. Chem. Soc.* **2013**, *135*, 15306-15309. b) Konishi, H.; Lam, T. Y.; Malerich, J. P.; Rawal, V. H. *Org. Lett.* **2010**, *12*, 2028-2031. c) Terada, M.; Nakano, M.; Ube, H. *J. Am. Chem. Soc.* **2006**, *128*, 16044-16045.

[181] a) McDonald, S. L.; Wang, Q. *Chem. Commun.* **2014**, *50*, 2535-2538. b) DiRocco, D. A.; Rovis, T. *Angew. Chem. Int. Ed.* **2012**, *51*, 5904-5906. c) Matsuda, N.; Hirano, K.; Satoh,

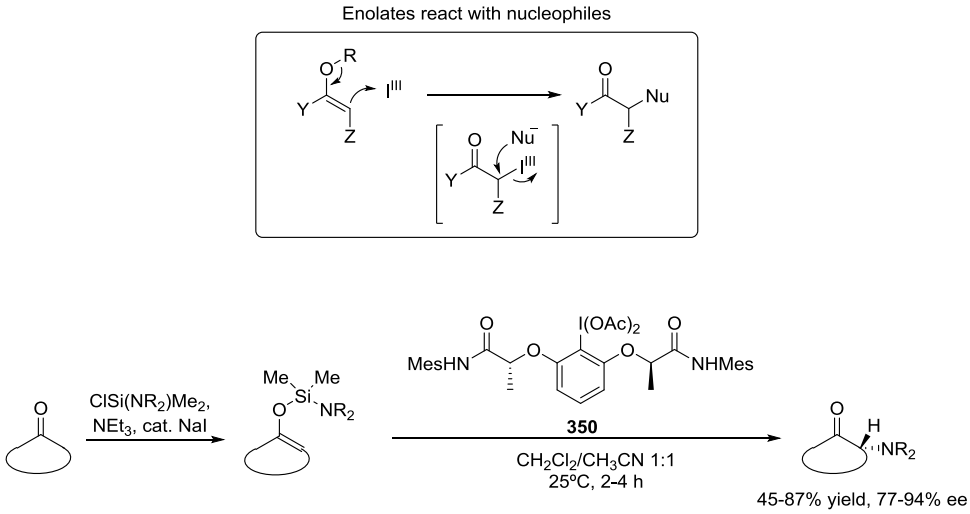


Scheme 5.1. Common strategies used for the enantioselective α-amination of ketones.[179e,180a]

More recently, several clever strategies, although intramolecular, avoid the use of electrophilic nitrogen to form *α*-amino carbonyl compounds in moderate to excellent enantioselectivities (Scheme 5.2 as example).[182]

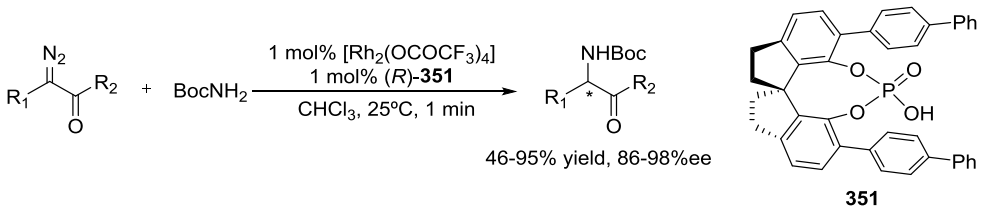
T.; *Angew. Chem. Int. Ed.* **2012**, *51*, 11827-11831. d) Anada, M.; Tanaka, M.; Washido, T.; Yamawaki, M.; Abe, T.; Hashimoto, S. *Org. Lett.* **2007**, *9*, 4559-4562. e) Evans, D. A.; Faul, M. M.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1994**, *116*, 2742. Miura, M. *Angew. Chem. Int. Ed.* Miura, M. *Angew. Chem. Int. Ed.* **2012**, *51*, 11827-11831; d) Anada, M.; Tanaka, M.; Washido, T.; Yamawaki, M.; Abe, T.; Hashimoto, S. *Org. Lett.* **2007**, *9*, 4559. e) Evans, D. A.; Faul, M. M.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1994**, *116*, 2742-2753.

[182] a) Aitken, D. J.; Caboni, P.; Eijsberg, H.; Frongia, A.; Guillot, R.; Ollivier, J.; Piras, P. P.; Secci, F. *Adv. Synth. Catal.* **2014**, *356*, 941-945. b) Mizar, P.; Wirth, T. *Angew. Chem. Int. Ed.* **2014**, *53*, 5993-5997. c) Zhang, X.; Staples, R. J.; Rheingold, A. L.; Wulff, W. D. *J. Am. Chem. Soc.* **2014**, *136*, 13971-13974. d) Frongia, A.; Secci, F.; Capitta, F.; Piras, P. P.; Sanna, M. L. *Chem. Commun.* **2013**, *49*, 8812-8814. e) Tiwari, B.; Zhang, J.; Chi, Y. R. *Angew. Chem. Int. Ed.* **2012**, *51*, 1911-1914.



Scheme 5.2. α-amination of ketones through umpolung with chiral hypervalent iodine reagents.[182b]

An alternative strategy, returning to an intermolecular regime, utilizes N-H insertion to selectively form chiral amino ketones (Scheme 5.3).[183]



Scheme 5.3. α-Amination of ketones through N-H insertion of α-diazoketones using Rh(II) and chiral phosphoric acids as catalysts.

Interestingly, no direct, highly enantioselective *nucleophilic* amination reactions to form *α*-amino carbonyl compounds have been reported to date. Although several

[183] Xu, B. Zhu, S.-F.; Zuo, X.-D.; Zhang, Z.-C.; Zhou, Q.-L. *Angew. Chem. Int. Ed.* **2014**, *53*, 3913-3916

diverse strategies do exist for racemic direct functionalisation of ketones,[184] only moderate[184d] and low[184e] ees are observed.

This problem was sought to be solved through use of electrophilic azoalkenes (1,2-diaza-1,3-dienes), which typically undergo 1,4-addition in the presence of various nucleophiles.[185] Although these compounds are primarily utilized in the synthesis of a diverse array of heterocycles,[186] it was though that their mode of reactivity could help to achieve our goal.

Taking into account the success and diversity of chiral phosphoric acids by the Toste group and others,[187] it was envisioned that the activation of the azoalkene by a chiral phosphoric acid under the appropriate conditions would result in the formation of an activated chiral ion pair. Subsequent nucleophilic attack and deprotonation would yield the desired enantioenriched α-aminated product (Scheme 5.4).

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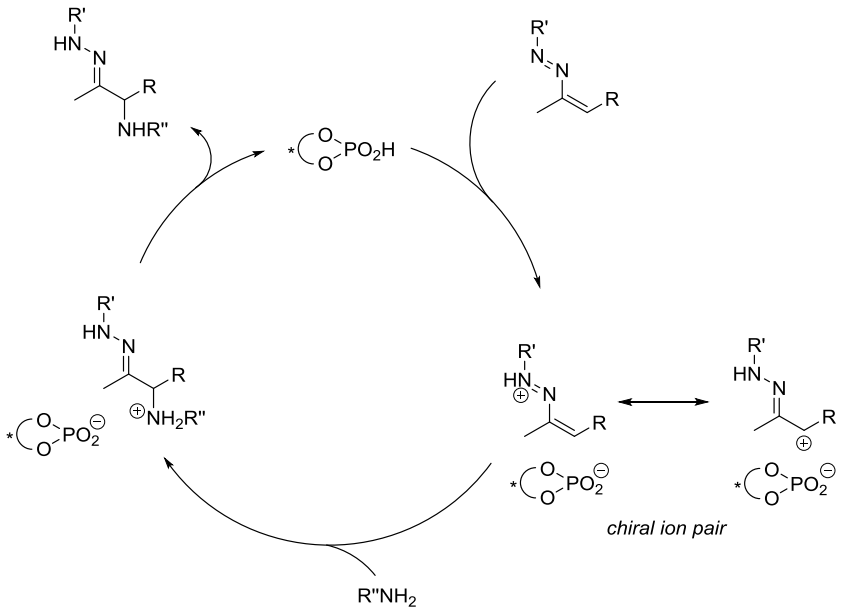
184 a) Sun, C.; O'Connor, M. J.; Lee, D.; Wink, D. J.; Milligan, R. D. *Angew. Chem. Int. Ed.* **2014**, *53*, 3197-3200. b) Jiang, Q.; Xu, B.; Zhao, A.; Jia, J.; Liu, T.; Guo, C. *J. Org. Chem.* **2014**, *79*, 8750-8756. c) Vander Wal, M. N.; Dilger, A. K.; MacMillan D. W. C. *Chem. Sci.* **2013**, *4*, 3075-3079. d) Evans, R. W.; Zbieg, J. R.; Zhu, S.; Li, W.; MacMillan D. W. C. *J. Am. Chem. Soc.* **2013**, *135*, 16074. e) Scarpino Schietroma, D. M.; Monaco, M. R.; Bucalossi, V.; Walter, P. E.; Gentili, P.; Bella, M. *Org. Biomol. Chem.* **2012**, *10*, 4692-4695.

185 a) Juhász-Tóth, E.; Favi, G.; Attanasi, O. A.; Bényei, A. C.; Patonay T. *Synlett* **2014**, *25*, 2001-2004. b) Attanasi, O. A.; Favi, G.; Geronikaki, A.; Mantellini, F.; Moscatelli, G.; Paparisva, A. *Org. Lett.* **2013**, *15*, 2624-2627. c) Attanasi, O. A.; Favi, G.; Filippone, P.; Mantellini F; Moscatelli, G.; Perrulli, F. R. *Org. Lett.* **2010**, *12*, 468-471. d) Kanzian, T.; Nicolini, S.; De Crescentini, L.; Attanasi, O. A.; Ofial, A. R.; Mayr, H. *Chem. Eur. J.* **2010**, *16*, 12008-12016. e) Attanasi, O. A.; Berretta, S.; De Crescentini, L.; Favi, G.; Filippone, P.; Giorgi, G.; Mantellini F. *Tetrahedron*, **2010**, *66*, 6832-6841. f) Bozzini, S.; Felluga, F.; Nardin, G.; Pizzioli, A.; Pitacco, G.; Valentin, E. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1961-1969. g) Attanasi, O.; Filippone, P. *Synthesis* **1984**, 422; h) Bozzini, S.; Gratton, S.; Risaliti, A. *Tetrahedron* **1984**, *40*, 5263-5267.

186 Attanasi, O. A.; De Crescentini, L.; Favi, G.; Filippone, P.; Mantellini F.; Perrulli, F. R.; Santeusanio, S. *Eur. J. Org. Chem.* **2009**, 3109-3127.

187 a) Parmar, D.; Sugiono, E.; Raja, S.; Rueping M. *Chem. Rev.* **2014**, *114*, 9047-9153. b) Mahlau, M.; List, B. *Angew. Chem. Int. Ed.* **2013**, *52*, 518-533. c) Phipps, R. J.; Hamilton, G. L.; Toste, F. D. *Nature Chem.* **2012**, *4*, 603-614.



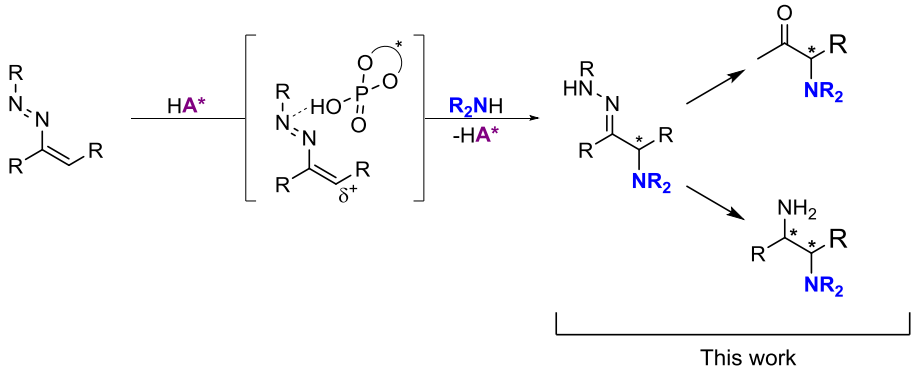
Scheme 5.4. Expected mechanistic scenario for the chiral phosphoric acid-catalysed enantioselective nucleophilic amination of azoalkenes.

It must be highlighted that the methodology for the enantioselective synthesis of α-arylamino hydrazones from azoalkenes was conceived and developed by Dillon H. Milles (UC Berkeley) and the results have been already submited for publication.[188]

The work that will be discussed in the present chapter aims to demostrate that the α-amino hydrazones prepared through the above methodology can provide access to chiral α-amino ketones (Scheme 5.5). Moreover, as an extension of the work, transformation of enantioenriched amino hydrazones into the corresponding vicinal diamines will also be discussed.

[188] Miles, D. H.; Guasch, J.; Toste, F. D. *submitted*.

The preparation of the chiral hydrazones was done using the methodology that was being developed by Dillon H. Milles. In this sense, in the experimental section (Chapter 7), only those compounds that were synthesised by myself are described.



Scheme 5.5. General scheme about the work discussed in the present chapter.

5.2. RESULTS AND DISCUSSION

5.2.1. BACKGROUND

Hydrazones are compounds with the structure $R_1R_2C{=}NNHR_3$ generally obtained by the condensation of hydrazines with aldehydes or ketones.[189] They have found utility in a wide range of fields including organic synthesis, medicinal chemistry, supramolecular chemistry and also as building blocks in metal and covalent organic frameworks, dynamic combinatorial chemistry (DCC) among other applications.[190] Since in this work hydrazones are used as synthetic intermediates, the biological implications will be neglected in the introduction.

[189] Smith, M. B.; March, J. *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 5th Ed., Wiley: New York, **2001**, 1192-1193.

[190] a) Su, X.; Aprahamian, I. *Chem. Soc. Rev* **2014**, *43*, 1963-1981. b) Le Goff, G.; Ouazzani, J. *Bioorg. Med. Chem.* **2014**, *22*, 6529-6544.

The polyfunctionality provided by the triatomic structure C=N-N plays a major role in the understanding of the chemical behaviour of hydrazones. Aprahamian and coworkers showcased in a comprehensive and detailed manner the different applications of hydrazones related to their diverse functionality (Figure 5.1).[190a]

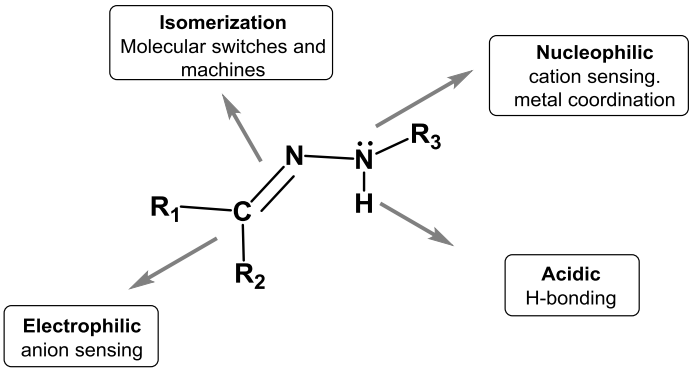


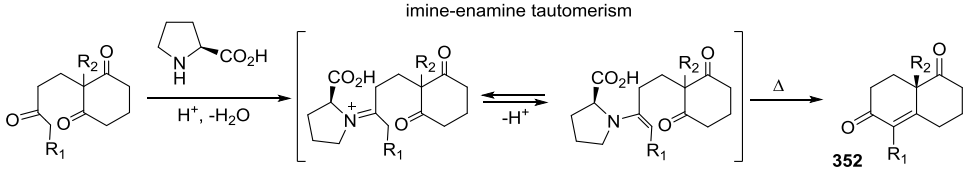
Figure 5.1. Structural and functional diversity of the hydrazone group.[190a]

Therefore, scientist have taken advantage of the nucleophilicity of imine and amino-type nitrogens for both cation sensing and metal coordination applications, whereas anion sensing technology benefites from the electrophilic imine carbon. On the other hand, the hydrazone functional group matches the requirements for being appropriate for molecular switches applications and machines. The reason is the possibility to activate the *E*/*Z* isomerization of the C=N bond by both light and chemical inputs. Finally the N-H acidic proton can be involved in H-bonding.

The nature of the C=N bond, being less polarized than the parent C=O, makes hydrazones less prone to self-condensation and reduces the acidity of the α-carbons in comparison with carbonyl compounds. For these reason, hydrazone have been widely employed as protecting groups for aldehydes and ketones.

5.2.1.1. KETO-ENAMINE TAUTOMERISM IN HYDRAZONES WITH α-HYDROGENS.

In addition to the previous structural features, hydrazones, possessing an α-hydrogen, similarly to imines are capable of existing in tautomeric equilibria with their enamine isomer, named enehydrazine.[191] This tautomerism is the base for the development of methodologies concerning the α-functionalization of carbonyl compounds. In this regard, the seminal work of Stork in enamine chemistry during the 1950s was pioneer in the establishment of this new reactivity.[192] Some years later, in 1971, the development of the proline catalysed asymmetric aldol reaction (named Hajos-Parrish-Eder-Sauer-Wiechert reaction) represented a milestone to illustrate the potencial of enamine catalysis in enantioselective synthesis (Scheme 5.6).[193]



Scheme 5.6. Preparation of enedione **352** through proline-catalysed asymmetric aldol reaction.

However, it was not before 2000 when the term asymmetric enamine catalysis was genaralised due to the publication of the enantioselective intermolecular proline-catalysed aldol reaction by List, Lerner and Barbas (Scheme 5.7).[194]

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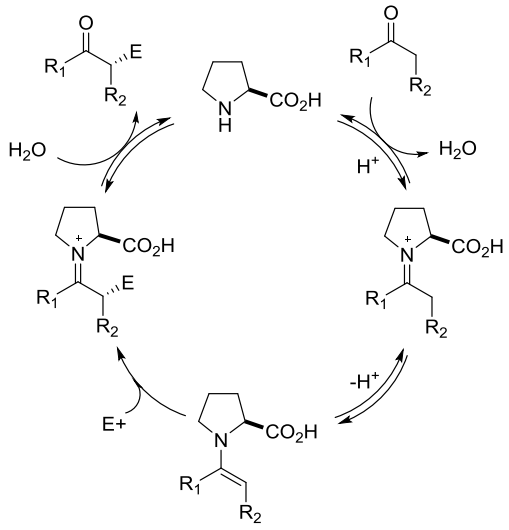
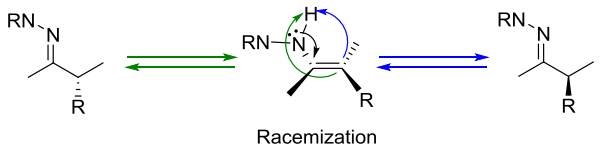
[191] Heindel, N. D.; Kennewell, P. D. *J. Org. Chem.* **1970**, *35*, 80-83.
[192] Stork, G.; Terrel, R.; Szmuszkovicz, J. *J. Am. Chem. Soc.* **1954**, *76*, 2029-2030.
[193] Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem. Int. Ed.* **1971**, *10*, 496-497.
[194] List, B.; Lerner, R. A.; Barbas, C. F. III *J. Am. Chem. Soc.* **2000**, *122*, 2395-2396.



Scheme 5.7. General mechanism of the enamine-catalysed enantioselective α-functionalization.

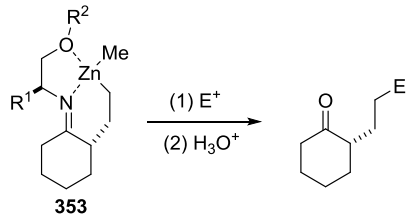
This ability to interconvert two tautomers is, however, no longer a benefit but a real handicap when addressing the chemical modification of carbonyl compounds bearing a chiral entity in the α-position. The racemization in enantioenriched α-substituted ketones, imines and, by analogy, hydrazones, is linked to the above-mentioned tautomerism with the corresponding enol, enamine and enehydrazine isomers (Scheme 5.8).



Scheme 5.8. Racemization of hydrazones through 1,3-proton shift.

In this sense, the transformation of α-amino acids and small peptides into the corresponding terminal C-ketones without epimerization has been an ongoing

challenge.[195] Moreover, the preparation of α-amino acids from enantioenriched α-amido amines has not been exemplified yet probably due to racemization during the hydrolysis of the amide moiety.[196] A clear example appears in the work by Nakamura and coworkers concerning the enantioselective synthesis of α-substituted ketones by asymmetric addition of chiral zinc enamides to 1-alkenes (Scheme 5.9).[197] Compound **353** was obtained with excellent enantioselectivity by addition of ethylene to the corresponding metalloenamine; hovever, the excellent enantioselectivity obtained was partially lost during the hydrolysis process to afford the ketone.



353

Scheme 5.9. Enantioselective synthesis of α-substituted ketones by hydrolysis of chiral zinc imines.

Therefore, to be able to prevent racemization when working with α-substituted carbonyl compounds it is important to understand the factors that govern the tautomerism.

The keto-enol tautomerism has been thoroughly studied experimentally and theoretically.[198] But fewer studies exist in the case of the imine-enamine tautomerism, more closely related to hydrazone-enehydrazine. However, some valuable insights

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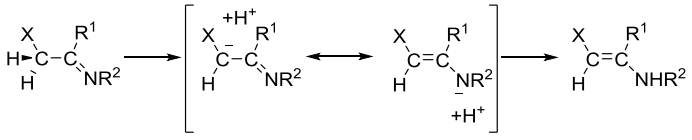
[195] a) Yang, H.; Li, H.;Wittenberg, R.; Egi, F.; Huang, W.; Liebeskind, L. S.; *J. Am. Chem. Soc.* **2007**, *129*, 1132-1140. b) Tokuyama, H.; Yokoshima, S.; Yamashita, T.; Fukuyama, T. *Tetrahedron Lett.* **1998**, *39*, 3189-3192. c) Zhang, Y.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 15964-15965.

[196] a) Lin, S.-Y.; Alper, H. *Angew. Chem. Int. Ed.* **2001**, *40*, 779-781. b) Nanayakara, P.; Alper, H. *Chem. Commun.* **2003**, 2384-2385.

[197] Nakamura, M.; Hatakeyama,T.; Hara, K.; Nakamura, E. *J. Am. Chem. Soc.* **2003**, *125*, 6362-6363.

[198] Toullec, J. *Adv. Phys. Org. Chem.* **1982**, *18*, 1-77.

were provided by Lien *et al*. in an exhaustive theoretical study of the effect on the relative stability between tautomers.[199] In this work, it was shown that among all the possible factors affecting the imine-enamine tautomerism, the nature of the α-substituent resulted to be the most determinant. Therefore, whereas imines are favored by 7.89 kcal/mol with an α-hydrogent substituent, enamines are lower in energy by 5.67 kcal/mol if the substituent is BH_2. In this extreme case, the resonance of the empty 2p orbital of boron with the π orbital of the C=C contributes to the increased stability of the enamine form. Moreover, this theory is strengthened by the close correlation found between the amount of charge transference from the π orbitals of the donor C=C and the acceptor 2p or π* of the α-substituent. This effect gains importance if we take into account the intramolecular 1,3-hydrogen shift mechanism proposed by Poirier for the imine-enamine tautomerism (Scheme 5.10).[200] It can be easily deduced that the rate of imine-enamine tautomerism will strongly depend on the tendency of the α-carbon to be deprotonated. As a consequence, those α-substituents that are able to more effectively delocalize the negative charge of the carbanion will lower the energy barrier for the imine-enamine interconversion.



Scheme 5.10. Mechanism of the imine-enamine tautomerism through a concerted 1,3-intramolecular hydrogen shift.

[199] Lin, J.-F.; Wu, C.-C.; Lien, M.-H. *J. Phys. Chem.* **1995**, *99*, 16903-16908.
[200] Poirier, R. A.; Majlessi, D. *J. Comput. Chem.* **1986**, *7*, 464-475.

On the other hand, theoretical studies on the effect of the solvent concluded that this is small, even though they all agree about the higher the dielectric constant is, the higher the preference for the imine tautomer.[201]

5.2.2. PREPARATION OF THE HYDRAZONE SUBSTRATES

As pointed above, this work aims to demostrate the synthetic potential of the enantioselective nucleophilic amination of azoalkenes developed in the Toste group. The scope of substrates can be divided in three structurally different starting azoalkenes depending on the substitution: cyclic, methyl-substituted or isopropyl-substituted (see Figure 5.2 for the general structures).

Bearing in mind that the search for conditions to hydrolise and reduce α-amino hydrazones would require a deep screening, and in order to avoid unnecessary use of valuable chiral phosphoric acid catalysts, initially, racemic hydrazones were prepared.

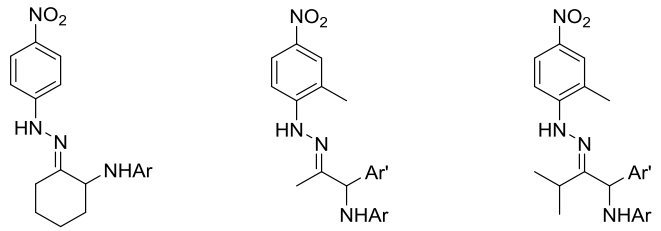
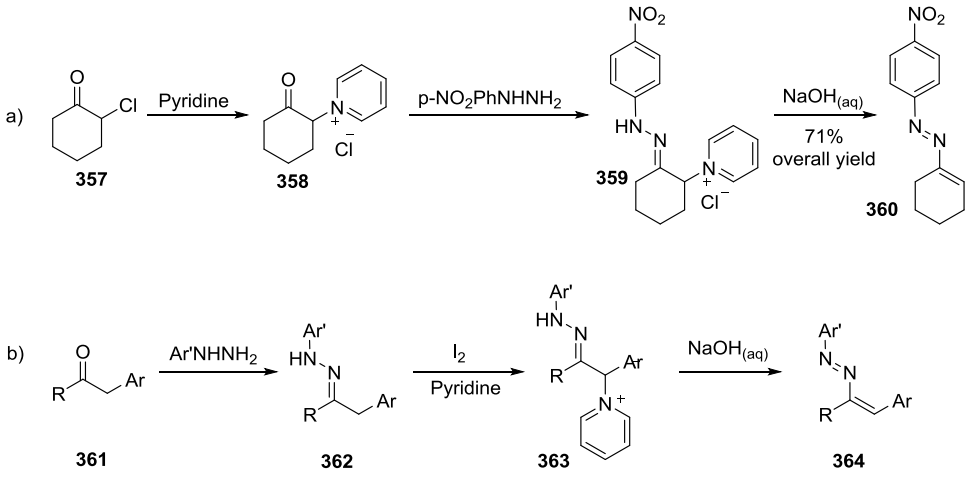


Figure 5.2. Different type of hydrazones prepared for the hydrolysis and reduction studies.

Hydrazones in Figure 5.2 were prepared from the corresponding azoalkenes, which, in turn were prepared from commercially available ketones (Scheme 5.11).

[201] a) Lammertsma, K.; Prasad, B. V. *J. Am. Chem. Soc.* **1994**, *116*, 642-650. b) Kozerski, L.; Kwiecien, B.; Krajewski, P.; Kawecki, R.; Bednarek, E.; Sitkowski, J.; Bocian, W.; Kozmisnki, W.; Hansen, P. E. *J. New. Chem.* **2002**, *26*, 1060-1069.

The synthetic route towards the cyclic azoalkene **360** (Scheme 5.11, eq. a) differs from the route followed to obtain the acyclic azoalkenes **364** (Scheme 5.11, eq. b). Cyclohexanone-derived azoalkene **360** was prepared from chlorocyclohexanone **357**, which upon heating in pyridine affords the pyridinium salt **358**. Condensation of the ketone moiety of **358** with *p*-nitrophenylhydrazine results in the formation of hydrazone **359** that eliminates pyridine·HCl after being treated with base to generate the desired azoalkene **360**.[202] On the other hand, the synthesis of acyclic azoalkenes **364** started with the condensation of the corresponding ketones and hydrazines, forming neutral hydrazones **362**. Those hydrazones were converted into their corresponding hydrazono-pyridinium iodide salts **363** through α-iodination followed by nucleophilic subtitution of the iodide by pyridine. Finally, base induced elimination of pyridine·HI provided azoalkenes of type **364**.[203]



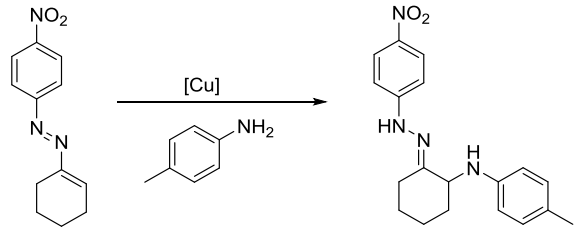
Scheme 5.11. Synthetic pathways towards the azoalkene precursors of hydrazones **354**, **355** and **356**.

The last step involved the conversion of the azoalkenes into the target α-arylamino hydrazones by the means of a 1,4-conjugated addition of the corresponding aniline to the azo-ene system of the arylazoalkenes (See Scheme 5.4 for the

[202] Brodka, S.; Simon, H. *Chem. Ber*. **1969**, *102*, 3647-3655.
[203] Schantl, J. G.; Karpellus, P.; Prean, M. *Tetrahedron* **1982**, *38*, 2647-2652.

mechanism). In this direction, Attanasi, in the mid-80s, had shown that this transformation could be effected in moderate to good yields using $CuCl_2 \cdot H_2O$ as catalyst.[204] At that point we decided to shortly screen some amination conditions based on Attanasi's work. In our hands, $Cu(OTf)_2$ resulted substaintially superior to $CuCl_2 \cdot H_2O$ obtaining yields above 80% (Table 5.1) using the cyclic azoalkene **360** as substrate. Although the yield was slightly increased by the addition of 5Å MS (Table 5.1, entry 3), we decided not to make use of them since (Table 5.1, entry 2) the crude ^{1}H NMR appeared to be cleaner without them.

Table 5.1. Screening of catalysts and conditions for preparing racemic α-arylamino hydrazones from azoalkenes.[a]



360 **354a**

Entry	Catalyst	Additive	Solvent	Yield(%)[b]
1	$CuCl_2 \cdot H_2O$	-	THF	41
2	$Cu(OTf)_2$	-	CH_2Cl_2	80
3	$Cu(OTf)_2$	5Å MS	CH_2Cl_2	88

[a] Catalyst (10 mol%), 0.02 M solution of azoalkene. [b] Determined by ^{1}H NMR spectroscopy.

These conditions allowed preparing all the hydrazones used in our study in up to 5 mmol scale from the corresponding azoalkenes precursors in synthetically acceptable isolated yields (Figure 5.3).

[204] Attanasi, O.; Filippone, P.; Battistoni, P.; Fava, G. *Synthesis*, **1984**, 422-423.

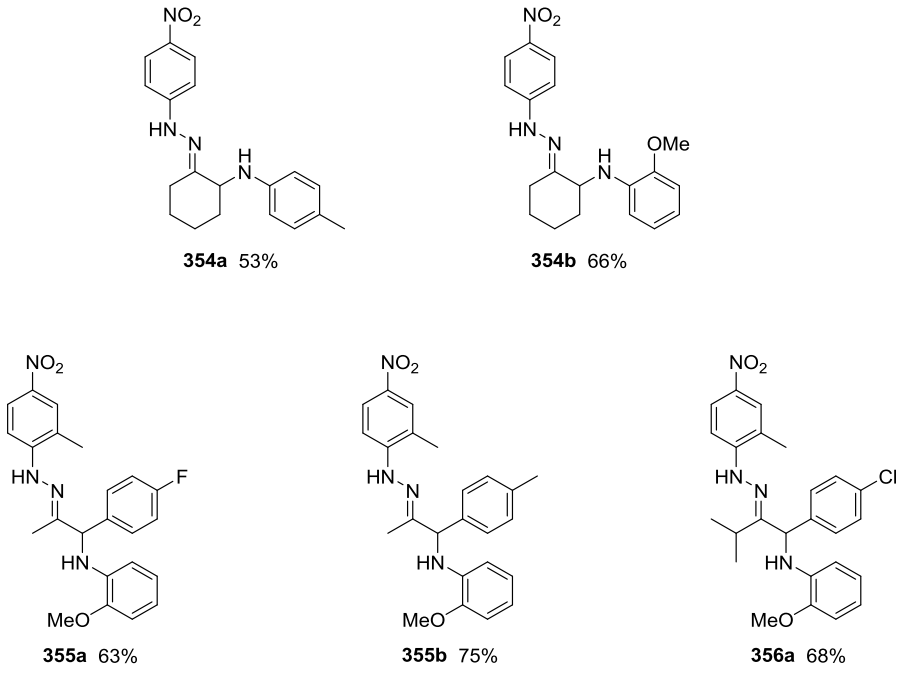


Figure 5.3. Scope of hydrazones prepared by Cu-catalyzed amination of azoalkenes.

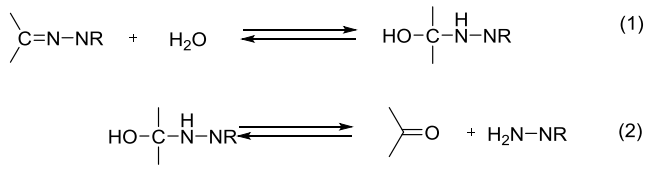
5.2.3. HYDROLYSIS OF α-ARYLAMINO HYDRAZONES

Hydrazones posses a greater hydrolytic stability compared to their parent imines. Practical evidence is that imines are readily hydrolysed in water whereas hydrazones sometimes are formed in its presence.[205]

The invention of the hydrogen electrode supposed a milestone, during the 30s, for the understanding of formation and hydrolysis mechanisms of hydrazones and their parent semicarbazones, oximes and shift bases,[205d,e] which was later thoroughly studied during the 60s and can be summarized by equations 1 and 2 in Scheme 5.12.

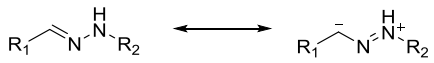
[205] For hydrolysis of imines see: a) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry*, Vol. A, 5th Ed., Springer: New York, **2008**, 645-653. b) Hine, J.; Craig, J. C.; Underwood, J. G., II; Via, F. A. *J. Am. Chem. Soc.* **1970**, *92*, 5194-5199. c) Cordes, E. H.; Jenks, W. P. *J. Am. Chem. Soc.* **1963**, *85*, 2843-2848. For formation of hydrazones see: d) Conant, J. B.; Bartlett, P. D. *J. Am. Chem. Soc.* **1932**, *54*, 2881-2899. e) Ardagh, E. G. R.; Rutherford, F. C. *J. Am. Chem. Soc.* **1935**, *57*, 1085-1088.

The reaction consists on the addition of water to the iminic carbon leading to a carbinolamine, which decomposes in the ketone and the hydrazine.[206] Kinetic studies demonstrated that the rate-determining step of the overall process depends on the pH of the reaction medium. Thus, in acidic conditions, decomposition of the intermediate carbinolamine (eq. 2, Scheme 5.12) results the slowest step whereas in neutral or basic pH, is the addition of water (eq. 1, Scheme 5.12).[207]



Scheme 5.12. Mechanism of the hydrolysis of hydrazones.

The aforementioned hydrolytic stability of hydrazones was initially explained by the additional participation of the nitrogen atom in charge delocalization (Scheme 5.13).[205]



Scheme 5.13. Ressonance forms of the hydrazone functional group.

This argument was later overcome by a study suggesting that the additional stabilisation arises from the reduction of the lone pair repulsion in the conjugate forms.[208]

Nitrophenylhydrazones are a particular case of hydrazones. Concretely, 2,4-dinitrophenylhydrazones have been used to characterize carbonyl compounds due to

[206] Cordes, E. H.; Jenks, W. P. *J. Am. Chem. Soc.* **1963**, *85*, 2843-2848.
[207] Cordes, E. H.; Jenks, W. P. *J. Am. Chem. Soc.* **1962**, *84*, 832-837.
[208] Wiberg, K. B.; Glaser, R. *J. Am. Chem. Soc.* **1992**, *114*, 841-850.

its high crystallinity.[209] Another important feature is their increased hydrolytic stability as a result of the strong electronwithdrawing nature of the nitro group.. The rate of the proton transfer from the hydroxyl group to the hydrazine nitrogen will be influenced by the proton affinity of the latter, which decreases with the presence of electronwithdrawing groups (See eq. 2, Scheme 5.12).[207]

5.2.3.1. HYDROLYSIS OF RACEMIC α-ARYLAMINO HYDRAZONES

Since our major concern was the propensity of α-aminated arylhydrazones to racemize, we initially looked for methods that completely exclude either acid or basic conditions. For the initial studies we chose cyclic hydrazone **354a** (Table 5.2).

The regeneration of the ketone by oxidative cleavage could, in principle, become a suitable alternative to hydrolytic methods. However the use of strong oxidants such as DMDO or oxone, used successfully in related hydrazones, resulted unselective giving overoxidation products (Table 5.2, entries 1 and 2). Later we where encouraged by the remarkable reactivity towards *p*-nitrophenylhydrazones showed by benzyltriphenylphosphonium peroxodisulfate $(BnP(Ph)_3)_2S_2O_8$ on a recent report.[210] Its preparation was easily accomplished from triphenyphosphine after condensation with benzyl chloride and anion exchange between the resulting benzyltriphenylphosphonium chloride and potassium persulfate.[211] However, again oxidation at the aniline nitrogen rapidly occurred (Table 5.2, entry 3). The incompatibility of alfa-amino functionality was confirmed to be the origin of the failure since 76 % yield of cyclohexanone was obtained after applying the same conditions to its *p*-nitrophenyl hydrazone derivative. On the other hand, no reaction was observed when **354a** was treated with either $FeSO_4 \cdot 7H_2O$ or baker's yeast (Table

---

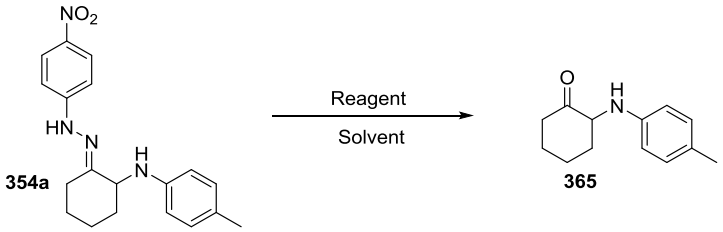
[209] a) Reich, H.; Crane, K. F.; Sanfilippo, S. J. *J. Org. Chem.* **1953**, *18*, 822-832. b) Senapati, M.; Panigrahy, G. P.; Mahapatro, S. N. *J. Org. Chem.* **1985**, *50*, 3651-3655.

[210] Tajbakhsh, M.; Mohammadpoor-Baltork, I.; Ramzanian-Lehmali, F. *Phosphorus, Sulfur, and Silicon* **2003**, *178*, 2621–2625.

[211] Mohammadpoor-Baltork, I; Hajipour, A. R.; Mohammadi, H. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 1649-1653.

5.2, entries 4 and 5).[212] Only the use of sodium periodate in neutral hydrolytic conditions provided the desired aminoketone **365** in low yield (Table 5.2, entry 6).[213] Consequently we considered appropriate to further optimize the conditions aiming to increase the yield. However, it is necessary to take into account that in the hydrolysis of hydrazones under neutral conditions, the inverse reaction, the regeneration of the hydrazone from the resulting ketone and hydrazine, strongly competes (Scheme 5.14).

Table 5.2. Screening of general methods for the hydrolysis of hydrazones.[a]



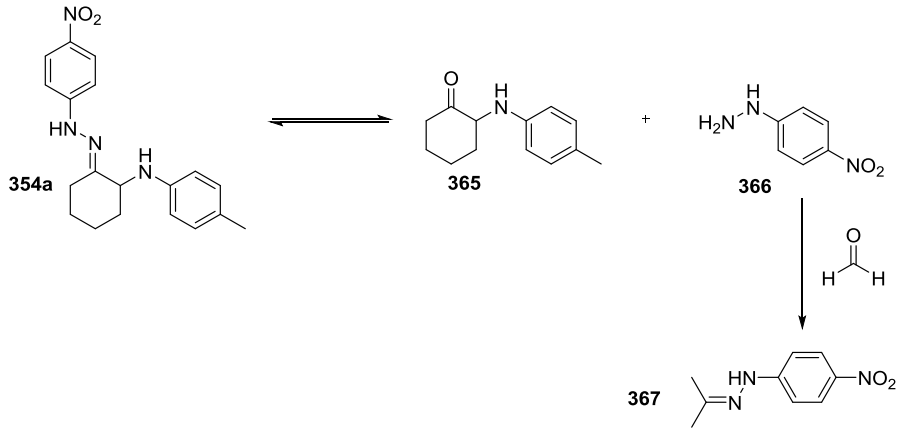
Entry	Reagent (equiv.)	Temp.	Solvent	Conversion	Yield[a]
1	DMDO (3)	r.t.	DCM	>99	0
2	Oxone	r.t.	Toluene	>99	0
3	$(BnP(Ph)_3)_2S_2O_8$ (2)	85ºC	THF	>99	0
4	$FeSO_4 \cdot 7H_2O$ (2)	r.t.	DCM	<5	0
5	Baker's Yeast	r.t.	DCM	<5	0
6	$NaIO_4$ (2.5)	r.t.	Phosphate pH 7 buffer	N.D.	11
7	$NaIO_4$/p-CH_2O (2.5)	r.t.	Acetone:H_2O (10:1)	N.D.	

[a] Determined by ^1H NMR spectroscopy using 1,3-dinitrobenzene as internal standard.

[212] a) Kamal, A.; Rao, M. V.; Meshram, H. M. *Tetrahedron. Lett.* **1991**, *32*, 2657-2658. b) Nasreen, A.; Adapa, S. *Org. Prep. Proc. Int.* **1999**, *31*, 573-575.

[213] Bozzini, S.; Gratton, S.; Pellizer, G.; Risaliti, A.; Stener, A. *J. Chem. Soc. Perkin Trans. I* **1979**, 869-873.

To shield the equilibrium towards the formation of the ketone a more reactive aldehyde, normally paraformaldehyde, can be added to scavenge the hydrazine generated. [214]Indeed, the use of 10 equivalents of paraformaldehyde for the hydrolysis of **354a** in a 10:1 acetone:water mixture afforded ketone **365** in 43 % yield (Table 5.2, entry 7).

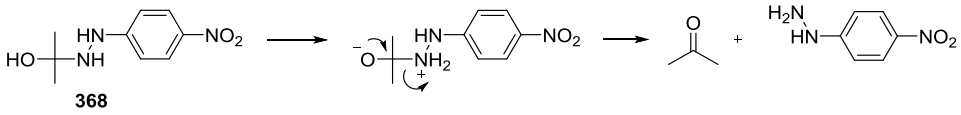


Scheme 5.14. Role of the sacrificial paraformaldehyde to shift the hydrazone-ketone equilibrium.

Further optimization did not lead to improved yields. At that point we turned our attention to reductive hydrolysis methodologies that had been found to be a powerful tool for the conversion of oximes and 2,4-nitrophenylhydrazones into the corresponding ketones (Scheme 5.16).[215] As mentioned previously in the introduction of the present chapter nitrophenylhydrazones are particularly resistant to hydrolytic conditions. This effect can be explanined taking into consideration, as mentioned above, that the rate determining step in the acid hydrolysis of hydrazones is the decomposition of carbinolamine **368** (Scheme 5.15). Thus the rate in the proton transfer from the hydroxyl group of **368** to the hydrazine nitrogen will depend on the

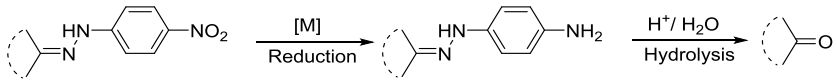
[214] Kalia, J.; Raines, R. T. *Angew. Chem. Int. Ed.* **2008**, *47*, 7523-7526.
[215] a) Shultz, A.; Hagmann, W. K. *J. Org. Lett.* **1978**, *43*, 3391-3393. b) Olah, G. A.; Arvanaghi, M.; Prakash, P. K. S. *Synthesis* **1980**, 220.

basicity of the latter. Therefore, the strong electronwithdrawing character of the nitro group will slow down the reaction rate.



Scheme 5.15. Mechanism for the decomposition of carbinolamine **368** into a ketone and hydrazine.

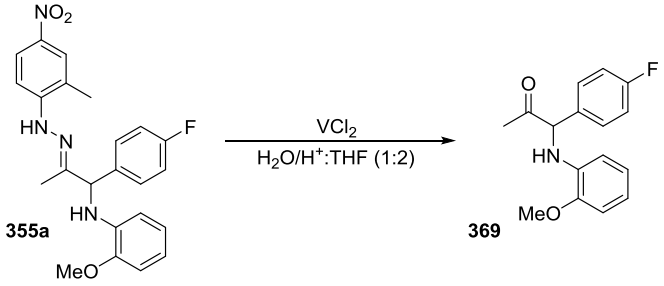
For this reason the reduction of the nitro group into a primary amine activates the hydrazone towards the hydrolysis. The most commonly employed reducing agents are VCl_2 and $TiCl_3$ in aqueous acidic media. VCl_2 can be purchased as a powder allowing us to adjust the pH of the solution to our convenience. On the other hand, $TiCl_3$ is commercialised as a 12 % HCl aqueous solution, which means that it must be basified prior adding the hydrazone.



Scheme 5.16. General scheme of the reductive hydrolysis of nitrophenylhydrazones.

Four aqueous solutions adjusted at different pH values were prepared and degassed before being added to VCl_2 powder. Over this solution, a solution of hydrazone **355a** in degassed THF was added. In all the cases only low yields of desired ketone **369** were obtained. In addition, in most cases almost all starting material remained unreacted meaning that the procedure failed already at the expected initial reduction of the nitro group (Table 5.3).

Table 5.3. Reductive hydrolysis of hydrazone **355a** with VCl_2.[a]



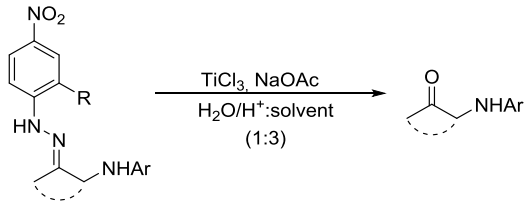
Entry	Conditions	time	Yield (%)[b]
1	pH = 1	16 h	12
2	pH = 2	16 h	5
3	pH = 3	16 h	Traces
4	pH = 7	16 h	11

[a] VCl_2 (1.2 equiv.), 0.015 M of hydrazone. [b] Determined by ^{1}H NMR spectroscopy using 1,3-dinitrobenzene as internal standard.

For the basification of the $TiCl_3$ solution we used sodium acetate. The maximum pH that we were able to achieve was 1 after which a grey precipitate appeared and the solution changed from the common deep purple to dark blue. A selection of results of the reductive hydrolysis of hydrazones **354a**, **355a** and **356a** with $TiCl_3$ are presented in Table 5.4.

As a general trend, the reaction seemed to be selective both regarding TLC and crude ^{1}H NMR analysis. However, the calculated NMR yield was never over 50 % what suggested the formation either of a polar byproduct that would be transferred to the aqueous phase during the work-up, or the formation of a precipitate. In any case all attempts to identify those possible byproducts failed. In terms of conditions optimisation, the reaction could be carried out at room temperature and ideally in a 0.015 M solution of the starting hydrazone. The solvent of choice depended on the

Table 5.4. Reductive hydrolysis of hydrazones **354a**, **355a** and **356a** with $TiCl_3$.[a]



Entry	Substrate	Conditions	Time	Solvent	Yield [b]
1	**354a**	pH < 0	3 h	Acetone	49
2	**354a**	pH = 1	60 h	Acetone	43
3	**355a**	pH = 1	3 h	Acetone	0
4	**355a**	pH = 1	1.5 h	DME	36
5	**356a**	pH = 1	3 h	THF	26
6	**356a**	pH = 1	3 h	DME	32

[a] $TiCl_3$ (3 equiv.), 0.015 M solution of hydrazone. [b] Determined by ^1H NMR spectroscopy using 1,3-dinitrobenzene as internal standard.

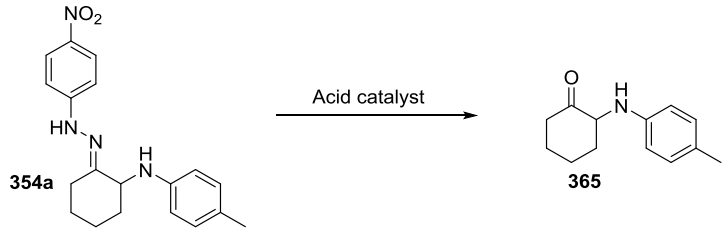
substrate, being acetone the best for cyclic hydrazone **354a** (Table 5.4, entries 1 and 2), but DME for acyclic hydrazones **355a** and **356a** (Table 5.4, entries 3-6).

Despite the little success obtained in the reductive hydrolysis, we were optimistic about the feasibility of a process involving an initial reduction of the nitro group followed by hydrolysis under mild acidic conditions. For this purpose several known methods for the mild reduction of nitro groups were tested such as hydrogenation over Pd/C or by using $SnCl_2 \cdot H_2O$ excluding the common use of strong HCl acid medium. All the attempts, however, were fruitless.

Probably the most relevant information provided by this screening was that under strong acid conditions (pH = 1) enantioenriched hydrazone **(*S*)-354a** was hydrolysed

in just 30 % yield but with only 2 % of enantiomeric loss. Such an unexpected resistance to racemization made us take into consideration other methodologies for the conversion of hydrazones into ketones based on acid catalysed hydrolysis (Table 5.5).

Table 5.5. Hydrolysis of **354a** catalysed by acids.[a]



Entry	Conditions	time	Solvent	Yield (%)[b]
1	TsOH, p-CH_2O	16 h	Acetone:H_2O (4:1) (0.04M)	11
2	Amberyst-15, $HO(CH_2O)_n$	4 h	Acetone:H_2O (10:1) (0.08M)	93

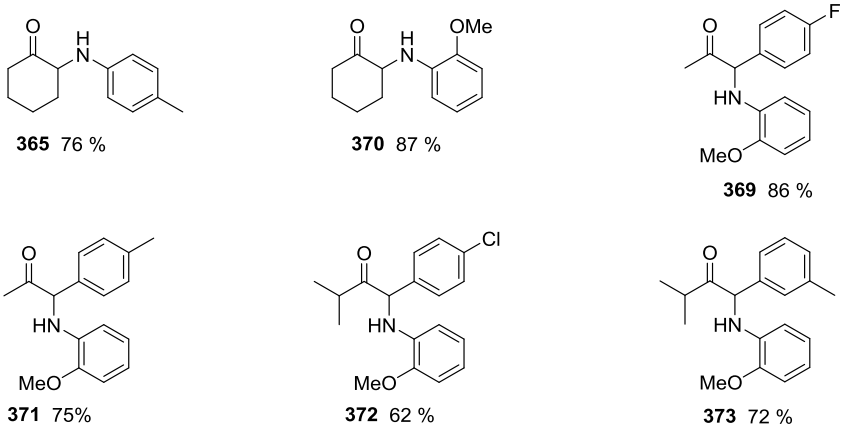
[a] Paraformaldehyde (10 equiv.). [b] Determined by ^{1}H NMR spectroscopy using 1,3-dinitrobenzene as internal standard.

The use of paratoluenesulfonic acid in a acetone:H_2O (4:1) mixture and in the presence of 10 equivalents of paraformaldehyde resulted in a very unselective reaction giving only 11 % yield of the desired ketone. On the contrary, we were pleased to find that if the acid catalysis was provided by Amberlyst-15 resin (p-TsOH based) in a acetone:H_2O (4:1) mixture and again in combination with 10 equivalents of paraformaldehyde, ketone **365** was obtained in an excellent 93 % yield. [216]

This methodology was then successfully applied to a variety of α-aminated hydrazones providing the corresponding ketones **365-373** with isolated yields ranging between 62-91 % (Figure 5.4). Cyclic hydrazones were hydrolysed in almost quantitative NMR yields but 20 % of the ketones were lost in average during

[216] Ballini, R.; Petrini, M. *J. Chem. Soc. Perkin Trans. I* **1988**, 2563-2565.

purification. On the other hand acyclic derivatives **369** and **371** were isolated without significant loss of yield whereas the hydrolysis process affording **372** and **373 was** less selective giving yields ranging between 60 and 70 %. The pH of the reaction mixture was measured to be around 4 confirming the smoothness of this type of hydrolysis and, consequently, becoming a good candidate for the hydrolysis of α-aminated hydrazones under non-racemising conditions.



365 76 %
370 87 %
369 86 %
371 75%
372 62 %
373 72 %

Figure 5.4. Scope of hydrazones transformed into their corresponding ketones by Amberlyst-15-mediated hydrolysis.

5.2.3.2. HYDROLYSIS OF ENANTIOENRICHED α-ARYLAMINO HYDRAZONES

Having found mild high-yielding conditions for the hydrolysis of α-arylamino hydrazones we were optimistic about being able to hydrolyse the enantioenriched ones without racemization.

The preparation of the enantioenriched hydrazones was carried out following the conditions optimised by Dillon Miles. Thus, isopropyl substituted hydrazones **(*S*)-356a** and **356b** were obtained from azoalkenes **364a** and **364b** in 72% and 86% yields, respectively, and both of them in 93% ee using 10 mol% of (*R*)-TCYP (Figure

5.5, **374c**) as the catalyst. Concerning methyl-substituted hydrazone **355b**, it was obtained from azoalkene **364c** in 51% yield and 90% ee using 20 mol% of (*R*)-TRIP (Figure 5.5, **374a**). Finally, cyclic hydrazone **354b** was prepared from alzoalkene **360** also in 51% yield and 90% ee using 5 mol% of (*R*)-TRIP (**374a**).

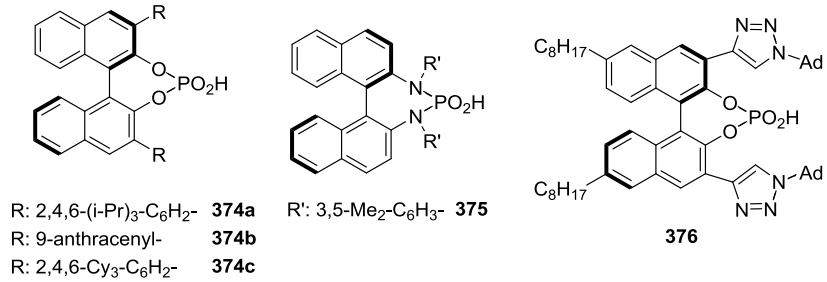
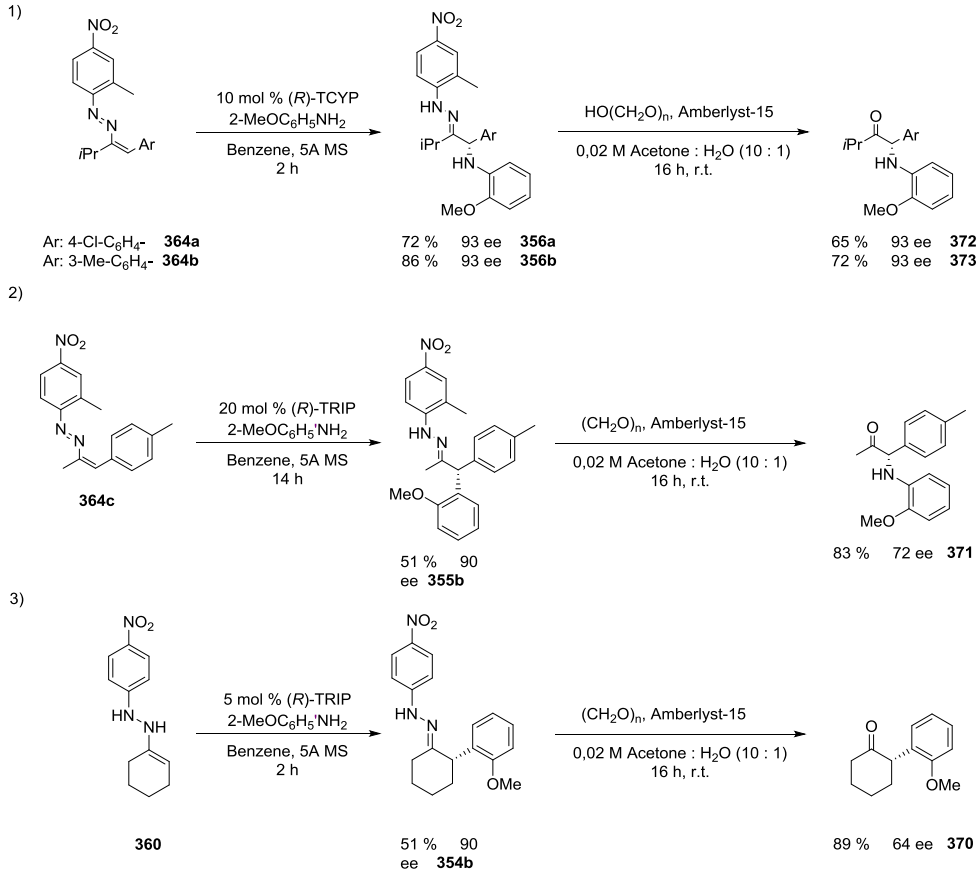


Figure 5.5. Chiral phosphoric acids employed as catalysts in the overall study.

These hydrazones were then subjected to hydrolysis with Amberlyst-15 and in the presence of sacrificial paraformaldehyde (conditions used in Table 5.5, entry 2). Isopropyl-substituted ketones **372** and **373** were obtained in 65% and 72% yields, respectively, with complete preservation of enantiopurity (Scheme 5.17, eq. 1). However, when the same conditions were applied to methyl-substituted and cyclic hydrazones **355b** and **354b** (Scheme 5.17, eq. 2), although the respective ketones **371** and **370** were obtained in superior yields (83% and 89%, respectively) the enantiopurity suffered a sensitive drop **(**20 and 29% drop, respectively).



Scheme 5.17. Preparation of enantioenriched α-arylamino hydrazones and hydrolysis to α-arylamino ketones.

To explain this different behaviour both structural and electronic considerations must be taken into account. From the electronic point of view, the imine-enamine tautomerism would be, in one hand, favoured because the α-hydrogen is at benzylic position. The stabilisation provided by the charge dispersion between the carbanion, after deprotonation, and the "p" orbitals of the aromatic ring would lower the barrier of tautomerization. On the other hand, the lone electron pair of the aniline substituent could slightly distabilise a hypothetical carbanion. In fact, owing to the high acidity of the α-hydrogen in **356a**, **356b**, **372** and **373**, it would be reasonable to expect

racemization in all cases. Therefore, the retention of the enantiopurity in **372** and **373** must be associated with the structure.

On the basis of the numerous and detailed studies on the mechanism of keto-enol tautomerism, and by analogy, it could be concluded that the rate-determining step for the racemization of hydrazones is enolisation.[217] As a general definition, enolisation is a prototropic rearrangement in which a proton is transferred from a carbon to a heteroatom.[198] Considering that enolisation, being acid catalised, involves and initial protonation of the carbonyl nitrogen followed by base abstraction of the α-hydrogen, it would be reasonable that the latter was the limiting step that would explain why racemization occurs in methyl and cyclic hydrazones but not in isopropyl-substituted hydrazones. This supposition is fundamented in the requirement of acid activation of *p*-nitrophenylhydrazones towards hydrolysis. In this regard, conformational aspects must play a decisive role. It is known that enolization is favoured by maximum overlap between the breaking α (C-H) bond and the C-C-X (X=O, N) π system, which occurs when α (C-H) bond breaking takes place perpendicular to the carbonyl plane.[218] Therefore, the energy barrier to adopt this conformation would be higher enough in the isopropyl-subtituted hydrazones to prevent them from racemization. From the models in Figure 5.6 it could be rationalised that the increased steric contribution of isopropyl compared to methyl would raise the energetic demand for the conformation **377** depicted in Figure 5.6. Despite the larger steric hindrance of isopropyl group could be relativized by the free rotation around the C-C single bond of the $(CH_3)_2HC$-C=N system, the confirmed *trans* configuration of the hydrazone (Figure 5.7) would result in a more constrained conformation.

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[217] a) Ingold, C. K.; Wilson, C. L. *J. Chem. Soc.* **1934**, 773-777. b) Bartlett, P. D.; Stauffer, C. H. *J. Amer. Chem. Soc.* **1935**, *57*, 2580-2583. c) Swain, C. G.; Stivers, E. C.; Reuwer Jr., J. F.; Schaad, L. J. *J. Am. Chem. Soc.* **1958**, *80*, 5885-5893.

[218] Corey, E. J.; Sneen, R. A. *J. Am. Chem. Soc.* **1956**, *78*, 6269-6278.

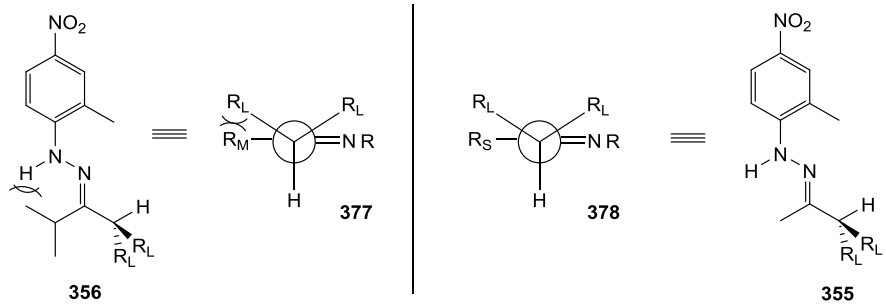


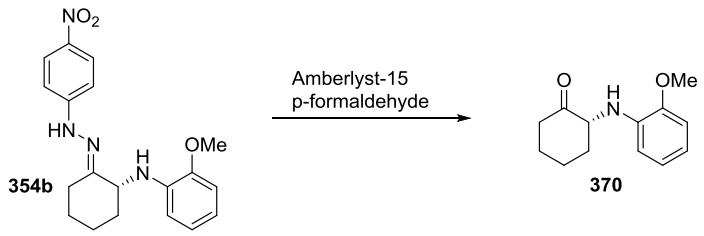
Figure 5.6. The larger isopropyl substituent prevents from racemization as a result of 1,3-allylic strain.

In order to address the racemization problem with the methyl-substituted and cyclic hydrazones little modifications in the system for hydrolysis could be done owing to the high sensitivity of these compounds. However, several studies demonstrated that the keto-enol tautomerism in 1,3-carbonyl compounds is strongly influenced by the nature of the solvent.[219] Thus, since the keto tautomer is stabilized by H-bonding interactions, this is the major tautomer in polar protic solvents. On the other hand, the enol tautomer gains importance in polar aprotic or apolar solvents as a result of intramolecular H-bonding. Concretely Iglesias showed that the rate of tautomerisation between 2-acetylcyclohexanone and 2-acetyl-1-tetralone decreases in water/DMSO mixtures on increasing the water proportion.[219a,b]

These precedents encouraged us to further optimize the hydrolysis of the methyl-substituted and cyclic hydrazones putting the stress on the role of water. The following optimizations were carried with **354b** since enantioenriched cyclic hydrazones required only 5 mol% of chiral phosphoric acid catalyst.

[219] a) Iglesias, E. *New. J. Chem.* **2005**, *29*, 457-464. b) Iglesias, E. *New. J. Chem.* **2005**, *29*, 625-632. c) Iglesias, E. *Curr. Org. Chem.* **1996**, *100*, 1-22.

Table 5.6. Initial screening of conditions to prevent racemization of **354b**.[a]



Entry	Solvent	Amberlyst mg/mmol 354b	Ee (% loss)[b]
1	Acetone:H_2O (10:1) (0.17 M)	20	52 (42)
2	Acetone:H_2O (10:1) (0.17 M)	40	55 (39)
3	Acetone:H_2O (20:1) (0.08 M)	20	55 (39)
4	Acetone:H_2O (10:1) (0.08 M)	20	64 (29)
5	THF:H_2O (10:1) (0.17 M)	20	55 (39)

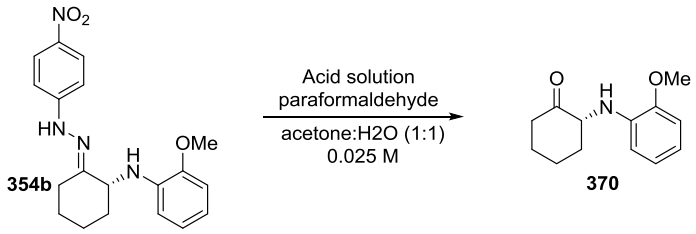
[a] Paraformaldehyde (10 equiv.), T = 22 ºC., t = 11 h. [b] Enantiomeric excess was determined by HPLC (Chiralcel IA column, 3% 2-propanol in hexane, 1.0 ml/min, λ = 235 nm. t_R = 7.8 and 11.0 min.).

The initial test were carried out with the aim of observing if subtile changes on the acetone: H_2O ratio, concentration or in the amount of acid resin employed had any effect on the enantiomeric integrity (Table 5.6). Little differences were appreciated apart from entry 4, where minimum amount of Amberlyst and more diluted conditions were used in combination with the highest proportion of water. Note that in none of the cases the yield was taken into consideration since the celerity on the obtention of non-racemizing condition was priorised.

After such negligible information, we had to move on and apply more drastic changes in the hydrolysis conditions. Combining the knowledge obtained from the

studies mentioned previously on the effect of solvent in tautomerism and the shades from Table 5.6, it was decided to continue the screening using a 1:1 acetone:H_2O mixture. In addition, to the standar procedure (Amberyst-15 / paraformaldehyde, Table 5.7, entries 5 and 6), different aqueous solutions of citric acid (pH = 2,4 and 6, Table 5.7, entries1-3) and also a pH = 1 HCl solution were tested (Table 5.7, entry 4).

Table 5.7. Screening of conditions to prevent racemization of **354b** at different pH levels in a 1:1 acetone:H_2O mixture.[a]



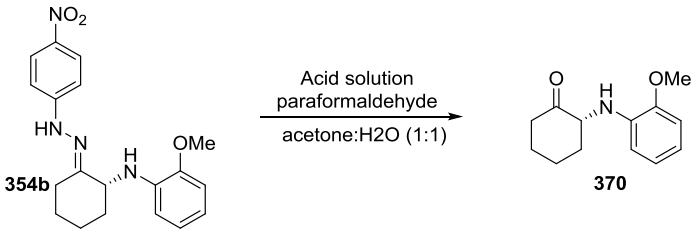
Entry	Conditions	Ee (% loss)[b]
1	aq. citric acid: acetone(1:1), pH = 2	50 (44)
2	aq. citric acid: acetone(1:1), pH = 4	91
3	aq. citric acid: acetone(1:1), pH = 6	90 (0)
4	HCl 2N in acetone: H_2O (1:1), pH = 1	50 (44)
5	Amberlyst-15 in acetone: H_2O (1:1), pH = 6	90 (0)
6	Amberlyst-15 in methanol: H_2O (1:1), pH = 6	88(2)

[a] Paraformaldehyde (10 equiv.), T = 22 ºC., t = 4 h. [b] Enantiomeric excess was determined by HPLC (Chiralcel IA column, 3% 2-propanol in hexane, 1.0 ml/min, λ = 235 nm. t_R = 7.8 and 11.0 min.).

To our delight, working in a 1:1 acetone: H_2O ratio in weakly acidic conditions (Table 5.7, entries 3 and 5) completely suppressed the loss of enantiopurity. The result in entry 2 was not considered valid since in the HPLC chromatogram, the major enantiomer signal appeared overlapped with some impurity. Nevertheless, it is worth pointing again that the enantiopurity using 1:1 acetone: H_2O mixtures could only be kept under strictly soft acidic conditions as it is demonstrated by the sharp drop when solutions at either pH = 1 or 2 are used (Table 5.7, entries 1 and 4). The suppression

of the racemization is connected with a drop in the imine-enamine tautomerism rate as a result, probably, of an increase on the dielectric constant of the solution as it was anticipated in the works cited in reference 201. We thought that the stabilization of the hydrazone tautomer by hydrogen-bonding could slow down the rate of tautomerism.

Table 5.8. Yield optimization for the transformation of **354b** into **370** under non-racemizing conditions.[a]



Entry	Concentration	Time (h)	Yield (%)[b]	Ee (% loss)[c]
1	0,025 M	14	40	90 (0)
2	0,025 M	48	91	90 (0)
3	0,0125 M	14	28	90 (0)
4	$7.5 \cdot 10^{-3}$ M	14	10	90 (0)

[a] Paraformaldehyde (10 equiv.), T = 22 ºC. [b] Determined by ^{1}H NMR spectroscopy using 1,3-dinitrobenzene as internal standard. [c] enantiomeric excess was determined by HPLC (Chiralcel IA column, 3% 2-propanol in hexane, 1.0 ml/min, λ = 235 nm. t_R = 7.8 and 11.0 min.).

To optimize the yield of the reaction the same conditions used in entry 5 of Table 5.7 were choosen as starting point. It this case the only variable examined was the concentration. Ketone **370** was finally obtained, after a long reaction time, with an excellent 91 % yield (Table 5.8, entry 2) and more interestingly, without any loss in enatiopurity.

Finally the optimized conditions served to obtain ketones **370** and **371** in good 84 % and 82 % isolated yield and preserving the enantiopurity.

5.2.3.3. DETERMINATION OF THE ABSOLUTE CONFIGURATION OF α-ARYLAMINOKETONES

We aimed to determine which was the absolute configuration of the three diferent types of α-arylamino ketones prepared (acyclic methyl- and isopropyl-substituted, and cyclic).

All the attempts to obtain single crystals of the ketones failed. Fortunately, we were able to grow a single crystal of hydrazone **356c** what revealed that the aabsolute configuration was (*S*). The X-ray crystallographic data was obtained by Dr. Antonio DiPasquale (UC Berkeley) and show in Figure 5.7.

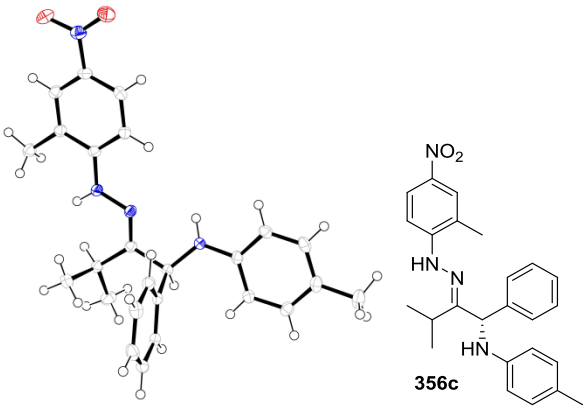
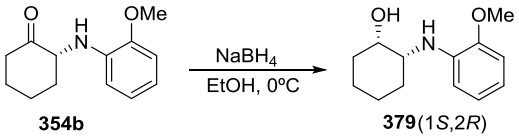


Figure 5.7. X-ray structure of hydrazone **356c**.

Since we were not able to obtain a single crystal of any of the cyclic hydrazones or cyclic ketones prepared, an alternative was to reduce ketone **354b** into amino alcohol **379**, which absolute configuration had been previously stablished by others

(Scheme 5.18).[220] Thus reduction of **354b** with sodium borohydride in ethanol provided *syn*-amino alcohol **379**,[221] which after comparison of the HPLC signals with those reported reveleaded that the absolute configuration of **379** was (1*S*,2*R*). Therefore, the configuration of ketone **354b** was (*R*).



354b **379**(1*S*,2*R*)

Scheme 5.18. Reduction of ketone **354b** to amino alcohol **379** in order to determine the absolute configuration of **354b**.

We assumed that, by analogy, the absolute configuration of the methyl-substituted hydrazones would be (*S*).

As a global conclusion, and as it has been stated in the introduction, the work exposed in this chapter is part of a project that aimed to develop a methodology for the preparation of enantioenriched α-arylamino ketones via a nucleophilic amination approach. In this sense, the nucleophilic amination of a wide range of azoalkenes catalysed by chiral phosphoric acids allowed to obtain the corresponding α-arylamino hydrazones in good yields (49-93%) and excellent enantioselectivities (90-95%) (Figure 5.8). In turn, by the means of the conditions found during the work described in the present chapter, it was demonstrated that these hydrazones can be converted into the corresponding α-arylamino ketones in good yield and, more importantly, preserving the enantiopurity.

[220] Liu, S.; Xie, J.-H.; Li, W.; Kong, W.-L.; Wang, L.-X.; Zhou, Q.-L. *Org. Lett.* **2009**, *11*, 4994-4997.
[221] Hoffman, R. V.; Maslouh, N.; Cervantes-Lee, F. *J. Org. Chem.* **2002**, *67*, 1045-1056.

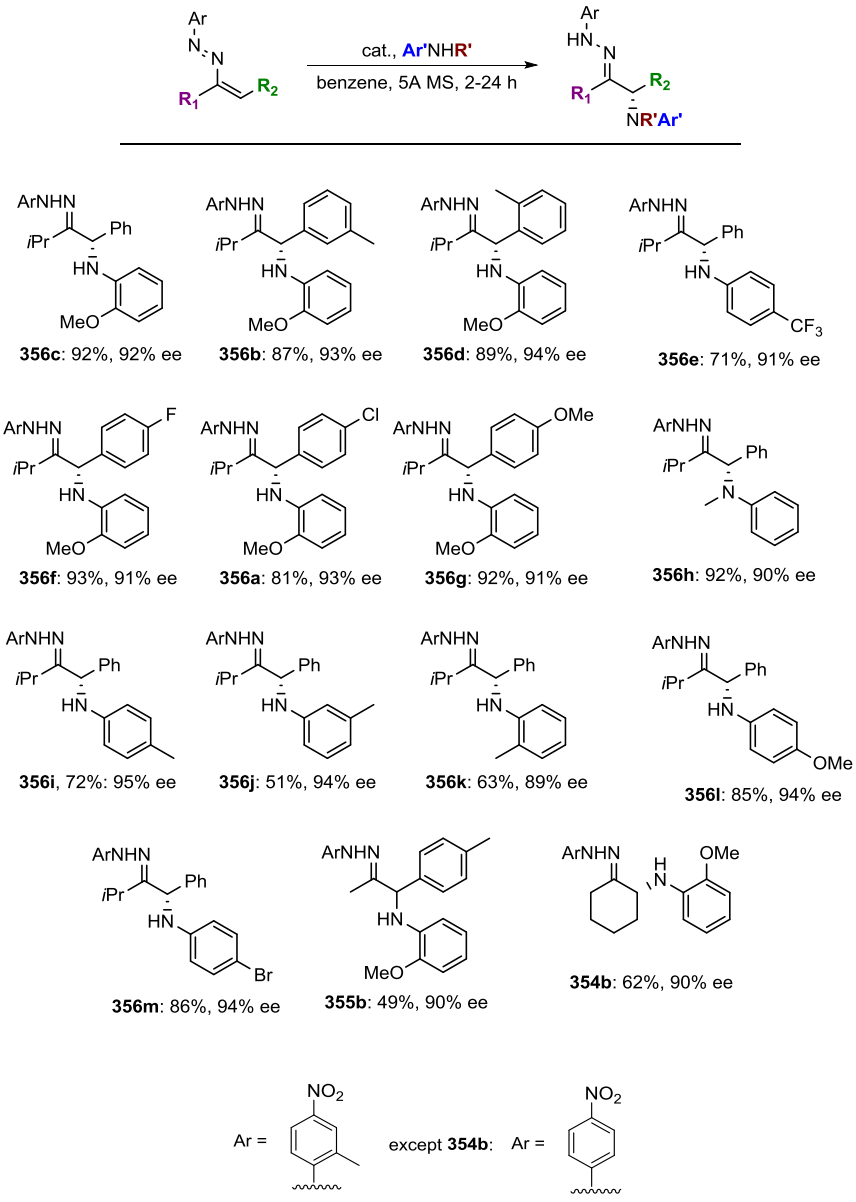
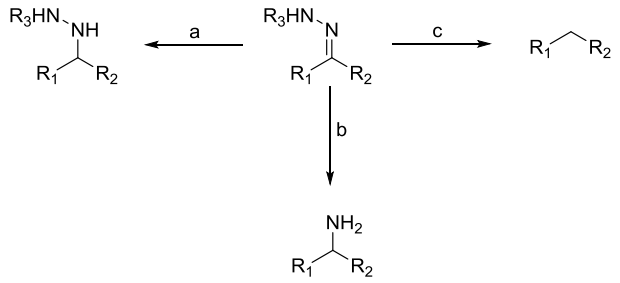


Figure 5.8. Scope of hydrazones prepared by enantioselective α-amination of azoalkenes

5.2.4. REDUCTION OF α-ARYLAMINO HYDRAZONES INTO 1,2-DIAMINES.

The enantioenriched α-arylamino hydrazones obtained can also be modified into another important structural motifs in organic synthesis: enantioenriched vicinal diamines. Vicinal diamines are present in a wide range of biological and pharmaceutical important molecules. In addition, they have found notorious use as ligands for transition metals among other applications.[222]

Concerning the reduction of amino hydrazones into diamines, we must take into account that hydrazones can be partially reduced to hydrazines and amines or completely reduced to hydrocarbons (Scheme 5.19).[223]



Scheme 5.19. Possible reduction products from hydrazones.

a) Reduction to hydrazines: Hydride reagents are able to transform hydrazones into their corresponding hydrazines.[224] However, the efficiency of each reagent strongly depends on the structure of the

[222] For a reference review on the chemistry of 1,2-diamines see: Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem. Int. Ed.* **1998**, *37*, 2580-2627.

[223] Rylander, P. *Catalytic Hydrogenation Over Platinum Metals*; Academic Press: London, **1967**, 134-137.

[224] a) Pratt, J. K.; Donner, P.; McDaniel, K. F.; Maring, C. J.; Warren, M. K.; Mo, J.; Middleton, T.; Liu, Y.; Ng, T.; Xie, Q.; Zhang, R.; Montgomery, D.; Molla, A.; Kempf, D. J.; Kolhbrenner, W. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1577-1582. b) Tiecco, M.; Testaferri, L.; Marini, F.; Santi, C.; Bagnoli, L.; Temperini, A. *Tetrahedron* **1997**, *53*, 10591-10602. c) Hinman, R. L. *J. Am. Chem. Soc.* **1956**, *79*, 414-417.

hydrazone. As an example, sodium borohydride is only effective when dealing with N,N-disubstituted hydrazones[225] and sodium cyanoborohydride normally requires hydrazone preactivation by Bronsted or Lewis acids.[226] Catalytic hydrogenation is an alternative to hydride reagents although in some cases hydrogenolysis of the resulting hydrazine is difficult to avoid. The latter is basically associated with the structure of the hydrazone.

b) Reduction to amines: The most efficient and widely used method is catalytic hydrogenation over palladium, platinum or Raney Nickel.[227] More specifically, Raney Nickel has found broad utility in the obtantion of amino sugars from phenylhydrazones.[228] The main drawback, using either platinum or palladium catalysis, is the need of acidic conditions in order to ensure a complete conversion into the amine.[229]

c) Reduction to hydrocarbons: The Wolf-Kizhner reaction is the most famous method to reduce hydrazones into methylene groups.[230] Hydrazones decompose in alkali medium and at elevated temperature to give dinitrogen and a methylene group. A more particular type of hydrazones, tosylhydrazones, can be converted into hydrocarbons under hydride reduction conditions, such as $LiAlH_4$,[231] $NaBH_4$[232] and $NaCNBH_3$.[233]

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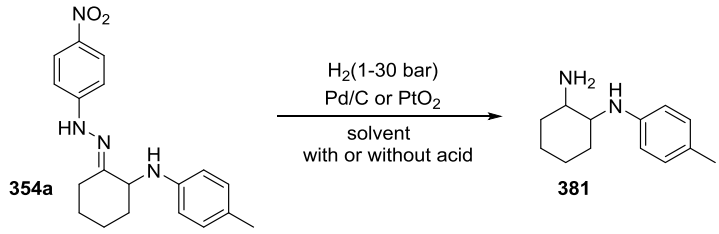
225 Walker, G. N.; Moore, M. A.; Weaver, B. N. *J. Org. Chem.* **1961**, *26*, 2740-2747.
226 Bloodworth, A. J.; Courtneidge, J. L.; Curtis, R. J.; Spencer, M. D. *J. Chem. Soc. Perkin Trans. 1* **1990**, 2951-2955.
227 Rylander, P. *Catalytic Hydrogenation Over Platinum Metals*; Academic Press: London, **1967**, 168.
228 a) Wolfrom, M. L.; Shafizadeh, F.; Werhmüller, J. O.; Armstrong, R. K. *J. Org. Chem.* **1958**, *23*, 571-575. b) Hajivarnava, G. S.; Overend, W. G.; Williams, N. R. *J. Chem. Soc. Perkin Trans. I* **1982**, 205-214.
229 Baldwin, J. E.; Adlington, R. M.; Newington, I. M. *J. Chem. Soc. Chem. Commun.* **1986**, 176-178.
230 a) Kishner, N. J. *Russ. Phys. Chem. Soc.* **1911**, *43*, 582-595. b) Wolff, L. *Justus Liebigs Ann. Chem.* **1912**, *394*, 86-108.
231 Caglioti, L.; Magi, M. *Tetrahedron* **1963**, *19*, 1127-1131.
232 Hutchins, R. O.; Natale, N. R. *J. Org. Chem.* **1978**, *43*, 2299-2301.
233 Hutchins, R. O.; Maryanoff, B. E.; Milewski, C. A. *J. Am. Chem. Soc.* **1971**, *93*, 1793-1794.

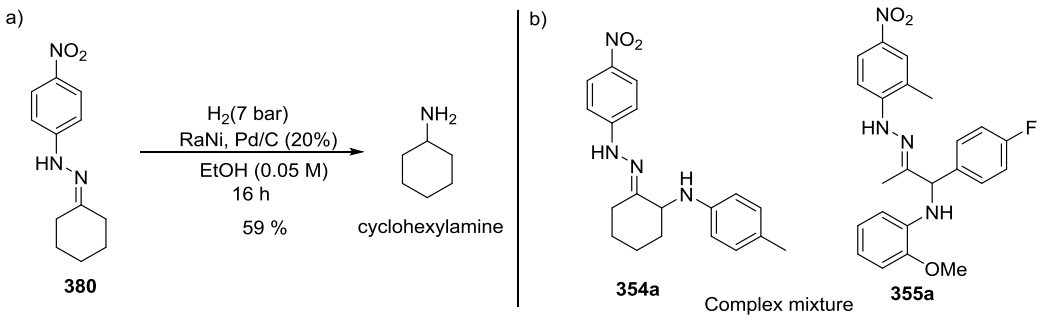
Analogously to the hydrolysis section, firstly the objective was to find an efficient method to reduce hydrazones to amines employing racemic substrates.

At the outset of the reduction studies, the catalytic hydrogenation of α-arylamino hydrazones was sough to be the most attractive route towards diamines (Scheme 5.20). An initial screening of conditions based on the hydrogenation catalyzed by either Pd/C or Adam's catalyst (PtO_2) provided sluggish reaction outcomes for cyclic hydrazone **354a**.



Scheme 5.20. Catalytic hydrogenation of **354a**.

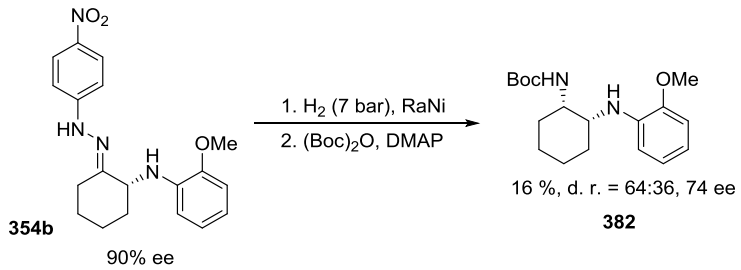
We then turned our attention to the use of Raney Nickel, which, as introduced above, performs well with phenylhydrazones. A cleaner ^1H NMR spectrum was obtained but the identification of the species generated resulted difficult due to troublesome purification. Attempts to isolate the reaction products after derivatization with $(Boc)_2O$ failed repeatedly. In order to overcome the lack of information that we had from this reaction system, the hydrazone of cyclohexanone (**380**) was used as a model substrate since the expected reduction product, cyclohexylamine (**381**), is well known. After an extensive screening of conditions, cyclohexylamine was obtained in 59 % yield using a mixture of Raney Nickel and Pd/C under 7 atm. of H_2 (Scheme 5.21). However, these conditions were unproductive for the more complex hydrazones **354a** and **355a**.



Scheme 5.21. a) Reduction of hydrazone **380** under optimized conditions. b) Result for reduction of hydrazones **354a** and **355a** under optimized conditions of a).

The activity issues that we were having with Raney Nickel were eventually solved using Raney Nickel from a new bottle.[234] Therefore hydrazones **354a** and **355a** were reduced into their corresponding diamines in good NMR yields although with low distereoselectivity.

In addition, when chiral hydrazone **354b** was transformed into Boc-protected diamine **382**, 18 % of the enantiopurity was unexpectedly lost and only 16 % of isolated overall yield was obtained (Scheme 5.22).

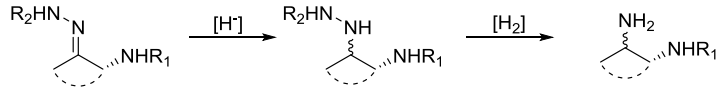


Scheme 5.22. Reduction of (*R*)-**403b** and *in situ* protection of the primary amine with $(Boc)_2O$.

[234] Raney Nickel is known to progressively lose its activity. Ref: Yang, T.-K.; Lee, D.-S.; Haas, J. Raney Nickel. *E-EROS Encyclopedia of Reagents for Organic Synthesis.*

Reduction using hydride reagents.

A second approach to the 1,2-diamines was a two-step process involving initial hydride reduction of the C=N bond followed by catalytic hydrogenolysis of the N-N bond (Scheme 5.23).



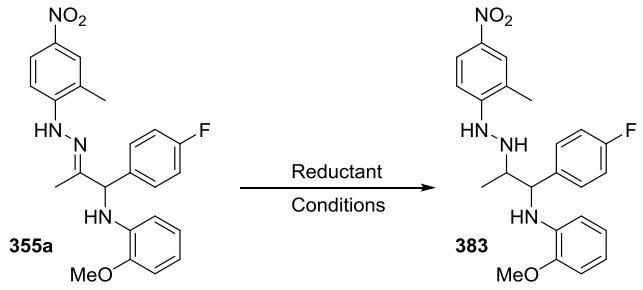
Scheme 5.23. Transformation of α-arylaminohydrazones into their 1,2-diamine derivatives through metal hydride reduction followed by hydrogenolysis.

The model substrate initially chosen in this case was hydrazone **355a**. Surprisingly, although a wide range of common hydride reagents were employed (Table 5.9, entries 1-7), only $NaCNBH_3$ resulted effective upon previous acid activation of the hydrazone by TsOH (Table 5.9, entry 8). The use of TsOH as activating agent was imperative since other Bronsted acids provided sluggish reactions. Even though the yield was moderate (56 %) and the diastereoselectivity resulted low (55:45).

The strategy adopted from that point was to find a combination of conditions that provided the highest diastereselectivity possible while keeping the enantiopurity untouched. The diastereoselectivity of the hydride addition can be greatly affected by the use of chelating Lewis acids that would also provide the required electrophilic hydrazone activation.[235] Cyclic hydrazone **(±)-354b** was used since its cyclic nature makes it more suitable for diastereocontrol (Table 5.10).

[235] a) Coyler, J. T.; Andersen, N. G.; Tedrow, J. S.; Soukup, T. S.; Faul, M. M. *J. Org. Chem.* **2006**, *71*, 6859-6862. b) Hughes, G.; Devine, P. N.; Naber, J. R.; O'Shea, P. D.; Foster, B. S.; McKay, D. J.; Volante, R. P. *Angew. Chem. Int. Ed.* **2007**, *46*, 1839-1842. c) Solé, C.; Whiting, A.; Gulyás, H.; Fernández, E. *Adv. Synth. Catal.* **2011**, *353*, 376-384.

Table 5.9. Screening of hydride reagents for the reduction of hydrazone **355a** into hydrazine **383**.[a]



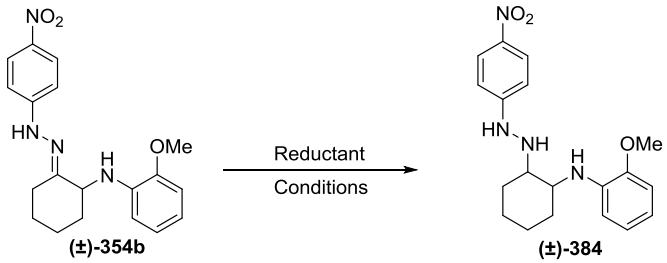
Entry	Reductant	Solvent (M)	Additive[b]	Temp. (ºC)	Time (h)	Yield (%)[c]
1	$NaBH_4$	MeOH (0.05)	-	22	20	N.R.
2	$NaCNBH_3$	THF (0.05)	-	22	20	N.R.
3	DIBAL-H	THF (0.1)	-	-78 to 22	20	N.R.
4	$LiAlH_4$	THF (0.05)	-	-40 to 22	3	C.M.
5	$LiAlH(O^tBu)_3$	EtOH (0.05)	-	0 to 22	24	N.R.
6	L-Selectride	THF (0.08)	-	20	20	C.M.
7	BH_3·THF	THF (0.1)	-	0 to 22	5	C.M.
8	$NaCNBH_3$	THF (0.05)	TsOH	22	4	56

[a] $NaCNBH_3$ (3 equiv.). [b] 2 Equiv. unless otherwise indicated. [c] Determined by ^1H NMR spectroscopy using 1,3-dinitrobenzene as internal standard.

From Table 5.10 the first remarkable information is the confirmation of the excepcionality of $NaCNBH_3$ for this system. Thus, $NaBH_4$ was unable to reduce **(±)-354b** even in the presence of lewis acid additives (Table 5.10, entries 1-3).[236] As a general conclusion, the use of different Lewis acids did not provide sensible changes of the diastereoselectivity of the C=N reduction. The d.r. values ranged from 94:6 when $ZnCl_2$ was used, to 84:16 in the case of using $Zn(OTf)_2$. Larger differences were provided in terms of activity. In one extreme, $Yb(OTf)_3$ (Table 5.10, entry 8) gave a clean reduction of **(±)-354b** giving 76 % yield with a 93:7 d.r.

[236] Liu, S.; Yang, Y.; Zhen, X.; Li, J.; He, H.; Feng, J.; Whiting, A. *Org. Biomol. Chem.* **2012**, *10*, 663-670.

Table 5.10. Screening of Lewis acids additives for the reduction of hydrazone **354b** into hydrazine **384**.[a]

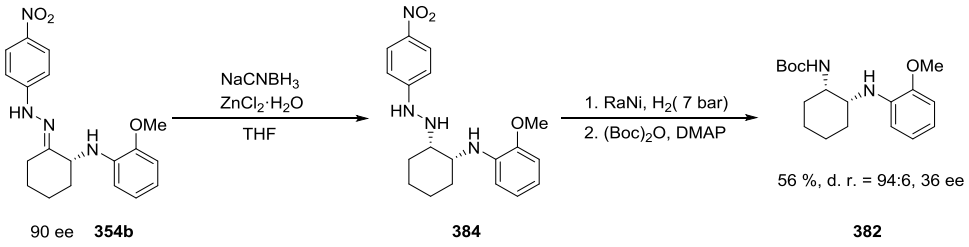


Entry	Reductant	Solvent (M)	Additive[b]	Temp. (ºC)	Time (h)	Yield (%)[c]	d.r. [c]
1[d]	$NaBH_4$	THF (0.1)	$Ti(^iOPr)_4$	22	20	N.R.	-
2	$NaBH_4$	THF:H_2O (98:2) (0.1)	$Zn(OTf)_2$	22	20	N.R.	-
3	$NaBH_4$	THF:H_2O (98:2) (0.1)	$Cu(OTf)_2$	22	20	N.R.	-
4	$NaCNBH_3$	THF (0.05)	$Zn(OTf)_2$	22	5	70	84:16
5	$NaCNBH_3$	THF (0.05)	$Cu(OTf)_2$	22	2.5	51	91:9
6	$NaCNBH_3$	THF (0.05)	$ZnCl_2$	22	2.5	36	94:6
7[d]	$NaCNBH_3$	THF (0.05)	$Ca(OTf)_2$	22	2.5	30	92:8
8	$NaCNBH_3$	THF (0.05)	$Yb(OTf)_3$	22	2.5	76	93:7
9	$NaCNBH_3$	THF (0.05)	$Ti(^iOPr)_4$	22	20	44	89:11
10	$NaCNBH_3$	THF (0.05)	$Zn(OTf)_2$	-40	20	N.R.	-
11	$NaCNBH_3$	THF:H_2O (98:2) (0.05)	$ZnCl_2$	22	20	79	94:6
12	$NaCNBH_3$	THF:H_2O (98:2) (0.05)	$Yb(OTf)_3$	22	3.5	51	91:9
13[d]	$NaCNBH_3$	THF (0.05)	$Yb(OTf)_3$	22	3.5	30	92:8

[a] Reductant. (3 equiv.). [b] 2 Equiv. unless otherwise indicated. [c] Determined by ^1H NMR spectroscopy using 1,3-dinitrobenzene as internal standard. [d] 0.2 Equiv. of additive.

only in 2.5 hours. On the contrary, the use of $Ca(OTf)_2$ and $ZnCl_2$ (Table 5.10, entries 6 and 7) led to the least active system. Although water had helped in raising the diastereoselectivity in some reports,[235] such effect was not observed in this case (Table 5.10, entry 11 and 12).

Finally, decresing the amount of Lewis acid used resulted in a slower reation rate (Table 5.10, entry 13). The best conditions (See Table 5.10, entry 11) were used to reduce **354b** and the obtained hydrazine **384** was hydrogenolysed (1 atm. H_2) over Raney Nickel and *in situ* protected with $(Boc)_2O$ to afford diamine **382** in 56 % yield as a 94:6 mixture of diastereoisomers but with a disappointing 60 % loss of enantiopurity (Scheme 5.24).

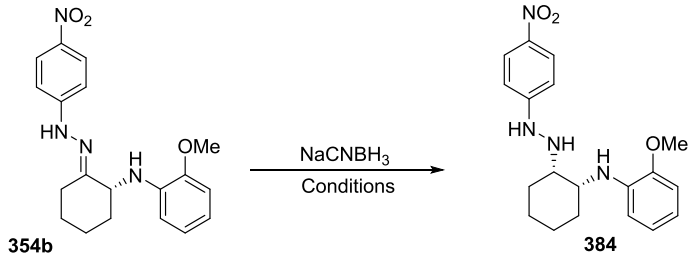


Scheme 5.24. Transformation of hydrazone **354b** into protected 1,2-diamine **382**.

That prompted us to investigate which factors influented the racemization. Initially the effect of the amount of Lewis acid in the $Yb(OTf)_3$-catalysed reduction was checked. The addition of 1, 2 or 3 equivalents of $Yb(OTf)_3$ (Table 5.11, entries 1, 2 and 3) afforded identical diatereo- and enantioselectivities (d.r.= 92:8, ee = 61 (32 % loss)). As in the hydrolysis experiments, the solvent played a determinant role since the replacement of THF by methanol disminished the loss in enantiopurity to 9 % (84% ee) but also reduced the facial selectivity from 93:7 to 82:18 (Table 5.11, entry 4). The reduction of the amount of catalyst used to 0.2 equivalents was only translated into a slower reaction but neither the diastereo- nor the enantioselectivity changed (Table 5.11, entry 5 and 6). The strong effect of the solvent on the diastereo-

and enantioselective outcome of the reaction was confirmed when $Ca(OTf)_2$ was used, although in this case in a lesser extent (Table 5.11, entry 7 and 8).

Table 5.11. Initial screeing of conditions to reduce **354b** into **384** without racemization.[a]



354b **384**

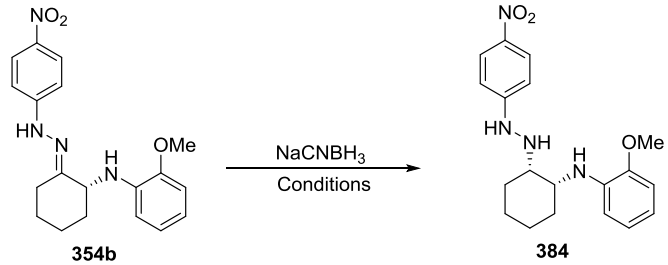
Entry	Solvent (M)	Additive[b]	Time (h)	354:384[c]	d.r. [c]	Ee (%) (% loss)[c]
1	THF (0.05)	$Yb(OTf)_3$	4	1:99	92:8	61(32)
2	THF (0.05)	$Yb(OTf)_3$	4	1:99	92:8	61(32)
3	THF (0.05)	$Yb(OTf)_3$	4	1:99	92:8	61(32)
4	MeOH (0.05)	$Yb(OTf)_3$	4	1:99	82:18	84 (9)
5[d]	MeOH (0.05)	$Yb(OTf)_3$	4	74:26	82:18	84 (9)
6[d]	MeOH:H_2O (10:1) (0.05)	$Yb(OTf)_3$	4	85:15	82:18	84 (9)
7	THF (0.05)	$Ca(OTf)_2$	4	59:41	92:8	72 (20)
8	MeOH (0.05)	$Ca(OTf)_2$	4	72:29	87:13	80 (11)

[a] $NaCNBH_3$ (3 equiv.). [b] 2 Equiv. unless otherwise indicated. [c] Determined by HPLC (Chiralcel AD-H column, 10% 2-propanol in hexane, 1.0 ml/min, λ = 235 nm. t_R = 26.2 and 32.4 min.). [d] 0.2 Equiv. of additive.

Having indentified the solvent and the Lewis acid catalyst as the two variable factors influencing the diastereo- and enantioselectivity, we decided to explore more types of Lewis acids using THF as de solvent (Table 5.12). The reason to use THF is because reaction proceeds with better yields. The strategy was to look firstly for the best enantioselectivity in THF and then try to improve it taking advantage of the positive effect of methanol. As the concentration showed to have no effect and for

practical purposes the following experiments were carried out at a 0.025 M concentration instead of 0.05 M.

Table 5.12. Screening of Lewis acid catalyst in THF as the solvent of choice.[a]



354b 384

Entry	Solvent (M)	Additive[b]	Time (h)	Yield[c] or 354b:384 [d]	d.r. [d]	Ee (% loss)[d]
1	THF (0.025)	CuI	16	78	93:7	68(24)
2	THF (0.025)	CuCN	4	94:6	93:7	66 (27)
3	THF (0.025)	AgOTf	16	80	94:6	76(16)
4	MeOH (0.025)	AgOTf	16	63	84:16	69 (23)
5	THF (0.025)	AgOAc	4	87:13	94:6	68 (24)
6	THF (0.025)	$MnCl_2$	4	79:21	92:8	84 (9)
7	THF (0.025)	$Fe(OTf)_3$	4	N.D.	92:8	60 (34)
8	THF (0.025)	$Sc(OTf)_3$	16	81	94:6	66 (27)
9	THF (0.025)	$B(OMe)_3$	16	50	94:6	65(28)
10	THF (0.025)	TMSCl	16	71	94:6	60(33)

[a] $NaCNBH_3$ (3 equiv.).[b] 2 Equiv. unless otherwise indicated. [c] Determined by ^1H NMR spectroscopy using 1,3-dinitrobenzene as internal standard. [d] Determined by HPLC (Chiralcel AD-H column, 10% 2-propanol in hexane, 1.0 ml/min, λ = 235 nm. t_R = 26.2 and 32.4 min.).

All the catalyst tested in Table 5.12 gave similar values of diastereoselectivity and enantiopurity. CuI, AgOTf and $Sc(OTf)_3$ (Table 5.12, entries 1, 3 and 8) provided

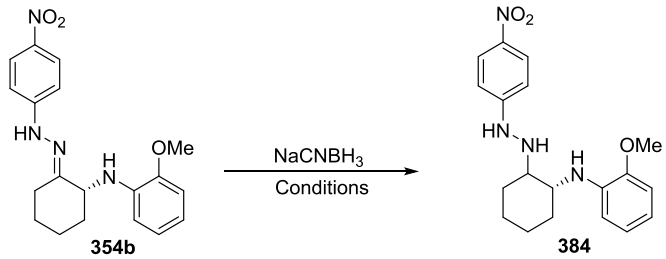
good NMR yields but without preserving the initial enantiopurity. In the case of AgOTf, though, resulted the smaller loss in enantioselectivity using THF observed so long combined with a good yield. However, and contrary to our spectations, when the reaction was carried out in methanol not only the diastereoselectivity dropped but the enantiopurity too (Table 5.12, entry 4). Using $MnCl_2$ the enantiopurity loss was minor (9%), but the slow reaction rate made it unsuitable (Table 5.12, entry 5).

The catalysts commented so long (Table 5.12, entries 1-8) are able to chelate. It was then thought that a possible chelation between the imine nitrogen and the aniline nitrogen could localise the α-(C-H) bond in the appropriate disposition (perpendicular to the C=N bond) for being broken undergoing racemization. To avoid this possible effect weak non-chelating Lewis acids such as $B(OMe)_3$ and TMSCl were tried without fortune since 28 % and 33 % of the enantiopurity was lost, respectively (Table 5.12, entries 9 and 10).

In a final attempt to avoid racemization we took the same non-racemizing conditions that were employed for the hydrolysis of the same hydrazones. Thus 1:1 mixtures of organic solvent and water were used as solvent (Table 5.13). Acetone was, obviously, discarded since it would react with $NaCNBH_3$. In order to fully emulate the non-racemizing conditions applied previously, Amberlyst-15 was used as acid catalyst. In this case, paraformaldehyde was not used in order to avoid the competition of the hydrolysis reaction (See Section 5.2.3.1).

Reduction of **354b** was accomplished without racemization in a 1:1 H_2O:methanol mixture in the presence of Amberlyst-15 (Table 5.13, entry 1). Since the yield was very low after 16 hours, $Yb(OTf)_3$, that resulted the most active catalyst in the previous screenings, was tested although a 9% of enantiopurity loss was produced (Table 5.13, entry 2). In parallel TsOH led to a considerable 22 % of enantiopurity loss (Table 5.13, entry 3). For this reason Amberlyst-15 was kept as catalyst and diferent 1:1 mixtures of water with organic solvent were examined aiming to increase the yield by enhancing the solubility of the system (Table 5.13,

Table 5.13. Reduction of **354b** into **384** using Amberlyst-15 and 1:1 mixtures of water with organic solvent.[a]



354b 384

Entry	Solvent (M)	Additive[b]	Time (h)	Yield (%)[c] or 354:384[d]	d.r. [d]	Ee (% loss)[d]
1	MeOH (0.025)	Amberlyst-15	16	16	84:16	90(0)
2	MeOH (0.025)	$Yb(OTf)_3$	3	14	88:12	84(9)
3	MeOH (0.025)	TsOH	11	79:21	21:79	70 (22)
4	THF (0.025)	Amberlyst-15	16	16	89:11	62(31)
5	dioxane (0.025)	Amberlyst-15	30	12	90:10	81(10)
6[e]	CH_3CN (0.025)	Amberlyst-15	30	6	87:13	90(0)
7	CH_3CN (0.025)	Amberlyst-15	30	7	87:13	90(0)
8[f]	EtOAc (0.025)	Amberlyst-15	30	13	92:8	72(20)
9	MeOH (0.025)	Amberlyst-15	11	C.M.	N.D.	N.D.

[a] $NaCNBH_3$ (3 equiv.). [b] 2 Equiv. unless otherwise indicated. [c] Determined by ^1H NMR spectroscopy using 1,3-dinitrobenzene as internal standard. [d] Determined by HPLC (Chiralcel AD-H column, 10% 2-propanol in hexane, 1.0 ml/min, λ = 235 nm. t_R = 26.2 and 32.4 min.). [e] Using 10 equiv. of $NaCNBH_3$. [f] T = 60ºC.

entries 5-9). As it was expected, organic solvent with higher polarity (dioxane and CH_3CN) preserved better the enantiopurity than the less polar ones (THF and EtOAc). In particular, when the reaction was donducted in CH_3CN the enantiopurity was

completely conserved, although without a remarkable increase in the yield with respect to methanol even using 10 equivalents of $NaCNBH_3$ (Table 5.13, entries 7 and 8). Finally, working at high temperature (60ºC) afforded a complex mixture of unidentified products (Table 5.13, entry 9).

As a last option to reduce **354b** into **384** in good yield and preserving the enantiopurity, $Zn(BH_4)_2$,[237] a well-known chelating-controled reducing agent, was prepared from $NaBH_4$ and $ZnCl_2$ in ether. The obtained solution was directly used affording **(*S*,*R*)-384** in 81% NMR yield, d.r. = 94:6 but ee = 76 (15% loss). The use of methanol as cosolvent provided only starting material recovery presumably due to decomposition of $Zn(BH_4)_2$.

Finally, NOE correlation experiments were carried out with diamine **382** to determine whether the facial selectivity in the C=N bond reduction provides *cis* or *trans* diamines and also to know if the selectivity is the same for the two methods employed. ^{1}H NMR and NOE spectra were identical in both cases, which confirmed that the same product had been obtained. However, the NOE spectra obtained were not conclusive enough for determining the relative configurations in **382**.

Taking into account that the reduction of ketone **354b** afforded unequivocally *cis* amino alcohol **379**, we could consider that, by analogy, reduction of cyclic amino hydrazones give rise to *cis* diamines. For this reason the molecules in the present chapter have been drawn with a *cis* relative configuration.

[237] Deng, Y.; Lee, Y. R.; Newman, C. A.; Wulff, W. D. *Eur. J. Org. Chem.* **2007**, 2068-2071.

UNIVERSITAT ROVIRA I VIRGILI
REGIO- AND ENANTIOSELECTIVE SYNTHESIS OF UNSATURATED AMINO ALCOHOLS, AMINO KETONES AND DIAMINES AS VALUABLE INTERMEDIATES IN ORGANIC SYNTHESIS.
Joan Guash Savidó
Dipòsit Legal: T 1366-2015

CHAPTER 6

GENERAL CONCLUSIONS

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As it was stated in the objectives section the present PhD work has two different goals; 1) to develop new synthetic procedures for obtaining distinctly functionalised unsaturated aminoalcohols in a regio- and enantioselective manner, and 2) the preparation of enantioenriched α-arylamino ketones and 1,2-diamines from α-arylamino hydrazones synthesized by enantioselective intermolecular nucleophilic α-amination of azoalkenes.

1. With the aim of developing new synthetic procedures for obtaining distinctly functionalised unsaturated aminoalcohols in a regio- and enantioselective manner, we envisaged that the intramolecular aziridination of dienols could be an efficient tool for this purpose. The results of this work were divided in two parts:

a) Regioselective intramolecular aziridination/ ariridine opening, and

b) Organocatalyzed kinetic resolution of the products of the former reactions.

1a. Results of this section are collected in Chapter 3. For the study of the regioselective aziridination of dienols 2,4-hexadien-1-ol was selected as model substrate and was modified as *N*-tosyloxycarbamate, acyl azide- and carbamate. These derivatives were studied in the metal-catalysed aziridination reaction with copper and rhodium catalysts. Scope and limitations of this reaction were also studied. The main conclusions are the following:

- *N-tosyloxycarbamate derivative*. Copper- and rhodium-catalysed aziridination of *N*-tosyloxycarbamates in the presence of K_2CO_3 generally rendered a product that resulted from the *in situ* ring opening of the targeted vinyl aziridine by the starting substrate. Efforts on suppressing this side reaction resulted unfruitful. Only the addition of water avoided this reaction, but product of hydroxyl opening was isolated instead.
- *Acyl azide derivative*. Rhodium-catalysed aziridination of acyl azide substrate in the presence of stoichiometric amounts of Lewis acids did not provide the desired vinyl aziridine. Only combining $Rh_2(OAc)_4$ and $AlCl_3$ low yields of

chloride-ring opened vinyl aziridine were achieved. The reaction was probably hampered due to deactivation of the catalyst by halogens released by the Lewis acid.

- <u>*Carbamate derivative*</u>. Aziridination of carbamate substrates was carried out using either rhodium or copper catalyst in combination with $PhI(OAc)_2$ and MgO. Copper catalysts were inefficient for this transformation. However, the use of rhodium catalyst provided a mixture of aziridine ring opening products by the acetate anions released from $PhI(OAc)_2$.
- The regioselectivity of the reaction is governed by the catalysts. Thus, S_N2 ring opening products were preferentially obtained using $Rh_2(OAc)_4$ as the catalyst whereas the use of $Rh_2(OPiv)_4$ gave higher selectivity for S_N2' products.
- The nature of the nucleophile (OR in $PhI(OR)_2$) influenced the regioselectivity when $Rh_2(OAc)_4$ was the catalyst. The stronger the nucleophile, the higher the S_N2 selectivity.
- The best conditions for the selective synthesis of S_N2 and S_N2' products were applied to a scope of carbamate substrates: *trans*, *trans*-substituted dienols provided excellent yields and regioselectivities. However the efficiency of the reaction is strongly affected by the presence of substituents and also in the presence of differently configured double bonds.
- NOE experiments revealed that the S_N2' process takes place in a *syn* fashion. This was explained considering that bulkiness of $Rh_2(OPiv)_4$ might favour the de-coordination of the metal from the aziridinic nitrogen, leaving place for coordination of the base counteranion, which would direct the carboxylate attack in a *syn*-S_N2' fashion.
- The use of low coordinating bases such as Cs_2CO_3 in combination with $Rh_2(OAc)_4$ provided almost complete S_N2 selectivities.
- <u>A chiral version of the reaction</u> was explored using rhodium catalyst with chiral carboxiamidate ligands, which resulted inactive in the aziridination reaction, probably due to steric effects on the dirhodium axial reactive sites.

- Rhodium catalyst with chiral carboxylate ligands were active in the aziridination reaction but the enantioselectivities provided were low (17% ee).
- The reaction was also performed under metal-free conditions using iodosylbenzene (PhIO), although in yields below 50%. Interestingly, the absence of anions in the reaction medium prevented *in situ* ring opening of the vinyl aziridine, which allowed preparing *N*-, and *S*-substituted unsaturated amino alcohols.

1b. As a result of the unsuccessful enantioselective aziridination of dienyl carbamates, we studied the enantioselective synthesis of unsaturated amino alcohols by kinetic resolution through the organocatalyzed acylation of oxazolidinones obtained from the intramolecular aziridination/opening processes described in **1a.** Results are presented in Chapter 4, and the main conclusions are the following:

- The presence of aromatic groups on the neighbouring hydroxyl group greatly increases both the activity and enantioselectivity of the process, being benzoate- and *p*-methoxy benzoate-substituted oxazolidinones (*s* up to 118) superior to pivalate ($s = 31$).
- A sharp decrease on the effectiveness of the kinetic resolution is observed when the substituent is at C-5 instead of C-3.
- Among the three catalysts tested (BTM, tetramisole, HBTM), BTM resulted remarkably superior. Several recrystallizations of BTM resulted determining for high selectivities.
- The best acylating agent was shown to be isobutyric anhydride.
- The optimized conditions were used to resolve oxazolidinones bearing *N*- and *S*-substituents. Outstanding resolution of phthalimide-substituted oxazolidinones was achieved with selectivity factors over 500.
- The methodologies studied in chapter 3 and 4 were efficiently applied to the enantioselective synthesis of sphingosine.

2. The work developed in Chapter 5 aimed at the preparation of enantioenriched α-arylamino ketones and 1,2-diamines from α-arylamino hydrazones synthesized by enantioselective intermolecular nucleophilic α-amination of azoalkenes. The main conclusions of this work are the following:

- Racemic α-arylamino hydrazones were successfully hydrolysed using Amberlyst-15 and sacrificial amount of paraformaldehyde in water/acetone mixtures.
- Enantioenriched α-arylamino hydrazones with isopropyl substituent were resistant to racemization under the above mentioned conditions but not methyl-substituted or cyclic hydrazones.
- Exhaustive adjustment of the water/acetone ratio and concentration eventually allowed suppressing the racemization in methyl-substituted and cyclic hydrazones.
- Catalytic hydrogenation of α-arylamino hydrazones with Raney Nickel provided 1,2-diamines in low yield and with unexpected enantiopurity loss.
- Transformation of hydrazones into diamines through initial metal hydride reduction followed by hydrogenolysis of the obtained hydrazines afforded moderate yields but large enantiopurity loss.
- The enantiopurity could be preserved carrying out the hydride reduction under the same conditions found for the hydrolysis in the absence of paraformaldehyde. However, the yields obtained were low.

CHAPTER 7

EXPERIMENTAL SECTION

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7.1. 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 standard procedure.[238]

^{1}H and ^{13}C NMR spectra were recorded on a Varian® Mercury VX 400 (400 MHz and 100.6 MHz respectively) or Varian 400-MR spectrometer in $CDCl_3$ as solvent, with chemical shifts (δ) referenced to internal standards $CDCl_3$ (7.26 ppm ^{1}H, 77.16 ppm ^{13}C) or Me_4Si as an internal reference (0.00 ppm). 2D correlation spectra (gCOSY, NOESY, gHSQC, gHMBC) were visualized using VNMR program (Varian®). ESI MS were run on an Agilent® 1100 Series LC/MSD instrument. Optical rotations were measured at room temperature in a Perkin-Elmer® 241 MC apparatus with 10 cm cells. Elemental analysis (C, H, N, S) were performed on a Carlo Erba® EA 1108 Analyser in the Servei de Recursos Científics (SRCiT-URV). IR spectra were recorded on a JASCO FT/IR-600 plus Fourier Transform Infrared Spectrometer ATR Specac Golden Gate. Melting points, determined with Reichert apparatus, are uncorrected.

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

[238] Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*, 3rd ed., Pergamon Press, Oxford, **1989**.

7.2. GENERAL PROCEDURES

General procedure for the conversion of allylic dienols to carbamates (Carbamoylation). A solution of trichloroacetyl isocyanate (TAI) (2 equiv.) in dry benzene (1 ml / mmol carbamate) was added to a solution of dienol in dry dichloromethane (2 ml / mmol carbamate). The mixture was left at room temperature until TLC showed complete consumption of the starting dienol. Then a 20% solution of K_2CO_3 in methanol (3 ml / mmol carbamate) was added and the mixture was stirred at room temperature during 3 hours. After solvent evaporation, the residue was dissolved in a 1:1 mixture of dichloromethane and brine. The aqueous phase was extracted with dichloromethane and the combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure.[239]

General procedure for the tandem intramolecular aziridination-ring opening of allyl carbamates (Procedure A). The corresponding carbamate (0.1 mmol), bis(*tert*-butylcarbonyloxy)iodobenzene, $PhI(OPiv)_2$ (0.2 mmol), oven-dried MgO (0.33 mmol) and rhodium(II) dimer, $Rh_2(OAc)_4$ (0.01 mmol) were placed in a 10 ml flame dried Schlenk. Then dichloromethane (2 ml) was added and the mixture was stirred at room temperature until TLC showed complete consumption of the starting material. The reaction mixture was initially purified through a short silicagel column (2-3 cm), washing with hexanes to hexanes/ethyl acetate 1:1, to afford an essentially pure mixture of isomers. Separation of isomers was achieved by column chromatography, although yields dropped significantly after prolonged contact with silicagel.

General for the tandem intramolecular aziridination-ring opening of allyl carbamates (Procedure B). The corresponding carbamate (0.1 mmol), iodobenzene diacetate, $PhI(OAc)_2$ (0.2 mmol), activated MgO (0.33 mmol) and $Rh_2(OPiv)_4$ (0.01 mmol) were placed in a 10 ml flame dried Schlenk. Then dichloromethane (0.05 M solution of the carbamate) was added and the mixture was stirred at 5ºC until TLC showed complete consumption of the starting material. The reaction mixture was initially purified through a short silicagel column (2-3 cm), washing with hexanes to hexanes/ethyl acetate 1:1, to afford an essentially pure mixture of isomers. Separation of isomers was achieved by column chromatography, although yields dropped significantly after prolonged contact with silicagel.

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[239] Espino, C. G.; Du Bois, J. *Angew. Chem. Int. Ed.* **2001**, *40* 598-600.

General method for the BTM-catalysed Kinetic Resolution of oxazolidinones with isobutyric anhydride. The reactions were set at the globe box. The catalyst was used as a solution which was prepared by dissolving (*R*)-BTM (10 mg, 0.04 mmol), DIPEA (0.14 ml, 0.75 mmol) in $CHCl_3$ (4.86 ml). One dram vial was charged with the oxazolidinone substrate (0.10 mmol) and 0.50 ml of the catalyst solution. Then 100 mg of Na_2SO_4 were added and the reaction mixture was magnetically stirred for 5 min before being treated with isobutyric anhydride (0.013 ml, 0.075 mmol). The reaction mixture was kept under stirring and followed by ^1H NMR. Methanol was added to quench the reaction.

General method for the racemic acylation of oxazolidinones. The corresponding oxazolidinone was dissolved in dichloromethane (2 ml per 0.1 mmol oxazolidinone). To this solution is added NaH 60% in mineral oil (1.1. equiv.). After 10 minutes the corresponding anhydride is added and the reaction progress was followed by TLC. Once the starting oxazolidinone was consumed the solvent was evaporated and the crude was directly purified by flash chromatography.

General preparation of racemic α-arylamino hydrazones. To a solution of $Cu(OTf)_2$ (0.1 equiv.) in dichloromethane (0.06 M solution of azoalkene) was added a solution of the corresponding aniline (1.3 equiv.) in dichloromethane (0.06 M solution of azoalkene). The mixture was stirred for 10 minutes turning into a deep green color. Then a solution of the corresponding azoalkene in dichloromethane (0.06 M solution of azoalkene) was added with a Pasteur pipette and the reaction mixture was stirred overnight at room temperature. After solvent removal, the residue was directly purified by column chromatography using hexanes : ethyl acetate as eluent.

General procedure for the hydrolysis of racemic α-arylaminohydrazones. To a 1 dram (3.7 ml) glass vial equipped with a magnetic stir bar was added the corresponding hydrazone (0.05 mmol), paraformaldehyde (15 mg, 0.5 mmol), acetone (0.7 ml) and water (0.07 ml). To the resulting suspension was added Amberlyst-15 ion-exchange resin (10 mg) and the mixture was stirred at room temperature for the required time until TLC showed complete consumption of starting hydrazone. The mixture was then passed through a celite plug and the filtrate was extracted with

DCM (2 x 3ml), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by column chromatography.

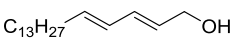
General procedure for the reduction of α-arylamino hydrazones into the corresponding α-aryl amino hydrazines with $NaCNBH_3$ and *p*-toluensulfonic acid. The corresponding hydrazone was dissolved in anhydrous THF (0.5 ml / 0.1 mmol hydrazone). To this solution was added $NaCNBH_3$ (3 equiv.) and then *p*-toluenesulfonic acid (2 equiv.), dissolved also in THF (0.5 ml / 0.1 mmol *p*-TsOH), was slowly added during one hour. When TLC showed complete consumption of starting hydrazone, the reaction mixture was diluted with dichloromethane and a small amount of water was added. The organic phase was separated and the aqueous phase extracted twice with dichloromethane. The combined organic fractions were dried over Na_2SO_4, filtered and, finally the solvent was evaporated.

General procedure for the reduction of α-arylamino hydrazones into the corresponding α-aryl amino hydrazines with $NaCNBH_3$ and Lewis acids or Amberlyst-15. The corresponding hydrazone was dissolved in the appropriate volume of the corresponding organic solvent. To this solution was added $NaCNBH_3$ (3 equiv.) and then the corresponding Lewis acid (2 equiv.). When TLC showed complete consumption of starting hydrazone, the reaction mixture was diluted with dichloromethane and a small amount of water was added. The organic phase was separated and the aqueous phase extracted twice with dichloromethane. The combined organic fractions were dried over Na_2SO_4, filtered and, finally the solvent was evaporated.

General procedure for the reduction of α-arylamino hydrazones into the corresponding α-aryl amino hydrazines with $NaCNBH_3$ and Lewis acids or Amberlyst-15 using water:organic solvent mixtures. The corresponding hydrazone was dissolved in the appropriate volume of organic solvent. Then the appropriate volume of water was added and, to this solution, was added $NaCNBH_3$ (3 equiv.) and then the corresponding Lewis acid (2 equiv.). When TLC showed complete consumption of starting hydrazone, the reaction mixture was diluted with dichloromethane and a small amount of water was added. The organic phase was separated and the aqueous phase extracted twice with dichloromethane. The combined organic fractions were dried over Na_2SO_4, filtered and, finally the solvent was evaporated.

7.3. COMPOUND CHARACTERISATION

(2*E*, 4*E*)-octadeca-2,4-dien-1-ol (127)

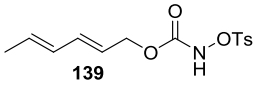


127

Ester **236** (0.4 g, 1.3 mmol) was dissolved in dichloromethane and the solution was cooled at -40ºC. DIBAL (0.66 ml, 3.2 mmol) was added dropwise over 1h and the mixture was stirred at -40ºC for 2 hours. The crude was quenched with methanol, the organic layer was washed with a saturated sodium potassium tartrate solution and the aqueous layer was washed with dichloromethane. The combined organic layers were dried over $MgSO_4$ and the solvent was removed under vacuum. The crude was purified by silica gel chromatography using 7:3 hexanes:ethyl acetate to afford 182 mg of **127** as a white solid (53%).

FT-IR (ATR) ν in cm^{-1}: 3425, 2825, 2750, 1690, 1330, 1230, 1000, 720 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): 6.19 (dd, 1H, *J* = 15.2, 10.8 Hz), 6.01 (dd, 1H, *J* = 15.2, 10.8 Hz), 5.68 (dt, 1H, *J* = 15.2, 7.0 Hz), 5.67 (dt, 1H, *J* = 15.2, 6.0 Hz), 4.13 (t, 2H, *J* = 6.0 Hz), 2.03 (dt, 2H, *J* = 7.2, 7.0 Hz), 1.51 (s, 1H), 1.36-1.22 (m, 22H), 0.85 (t, 3H, *J* = 6.8 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$): δ= 136.0, 132.3, 129.5, 129.5, 63.7, 32.8, 32.1, 29.9, 29.8, 29.7, 29.6, 29.4, 22.9, 14.3. Collected data are in agreement with reported data.[240]

(2*E*, 4*E*)-Hexa-2,4-dienyl tosyloxycarbamate (139).



139

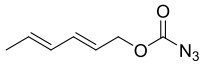
To a solution of hydroxycarbamate **138** (1.20 g , 7.40 mmol) in Et_2O at 0ºC was added *p*-toluensulfonyl chloride (1.60 g, 8.40 mmol). Triethylamine (1.1 ml, 7.79. mmol) was then added slowly and the resulting white suspension was stirred for 12 h at room temperature. The mixture was washed with water and the aqueous phase was extracted with Et_2O (x3). The combined organic layers were washed with brine and then dried over Na_2SO_4. The solvent was removed under reduced pressure, and the

[240] Olofsson, B.; Somfai, P. *J. Org. Chem.* **2003**, *68*, 2514-2517.

tosyloxy carbamate was purified by column chromatography using 25% ethyl acetate – hexane as the eluent to give 2.26 g (95%) of the desired product **139**.

FT-IR (ATR) ν in cm^{-1}: 3065, 2930, 1771, 1375, 1178, 1009, 784 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): 7.86 (d, 2H, *J* = 8.3 Hz), 7.34 (d, 2H, *J* = 8.3 Hz), 6.15 (dd, 1H, *J* = 15.1, 10.3 Hz), 5.99 (ddd, 1H, *J* = 14.9, 10.3, 1.2 Hz), 5.76 (dq, 1H, *J* = 14.9, 6.8 Hz), 5.40 (dt, 1H, *J* = 15.1, 7.2 Hz), 4.48 (d, 2H, *J* = 7.2 Hz), 2.45 (s, 3H), 1.77 (d, 3H, *J* = 6.8 Hz). **^{13}C NMR** ($CDCl_3$, 100 MHz, δ in ppm): 155. 3, 146.1, 136.1, 132.3, 130.2, 130.0, 129.7, 129.6, 122.0, 67.5, 29.7, 22.0, 18.2. **ESI-TOF** [M+NH_4] calc for $C_{14}H_{21}N_2O_5S$: 329.1171, found: 329.1158.

(2*E*,4*E*)-hexa-2,4-dien-1-yl carbonazidate (140).



140

Acyl azide **140** was prepared adapting the procedure described by Hansen.[241] To a solution of dienol **138** (0.72 ml, 6.3 mmol) in 20 ml of dry benzene were subsequently added 1-carbonyldiimidazole (2.05 g, 12.6 mmol) and pyridine (1.15 ml, 18.9 mmol) and the reaction was stirred at room temperature until TLC showed complete consumption of the starting material. Then were added 100 ml of ethyl acetate and the resulting solution was once quickly extracted with 50 ml of brine. Finally the organic layer was evaporated and dried. The clean oil that resulted was dissolved in 30 ml of DMF and cooled to 0ºC. Once at 0ºC, sodium azide (2.05 g, 31.5 mmol) was added and the solution was brought to pH = 4 by the careful addition of HCl (35%). The resulting solution was stirred at 0ºC during 6h and the crude was directly purified using hexanes/ethyl acetate (95:5) to give 660 mg (63 %) of acyl azide **140** as a crystalline solid.

FT-IR (ATR) ν in cm^{-1}: 3028, 2939, 2855, 2131, 1727, 1223, 988 cm^{-1}. **^{1}H NMR** (400 MHz,$CDCl_3$, δ in ppm): 6.30 (dd, 1H, *J* = 15.2, 11.6 Hz), 6.08 (ddd, 1H, *J* = 15.2, 10.4, 1.6 Hz), 5.82 (dq, 1H, *J* = 15.2, 6.8 Hz), 5.62 (dt, 1H, *J* = 15.2, 6.8 Hz), 4.67 (d, 2H, *J* = 6.8 Hz), 1.76 (d, 3H, *J* = 6.8 Hz). **^{13}C NMR** (100MHz, $CDCl_3$, δ in ppm): 157.5, 136.8, 132.8, 130.3, 122.0, 69.2, 18.4.

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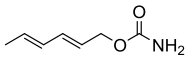
[241] Yuan, P.; Plourde, R.; Shoemaker, M. R.; Moore, C. L.; Hansen, D. E. *J. Org. Chem.* **1995**, *60*, 5360-5364.

(2*E*,4*E*)-Hexa-2,4-dien-1-yl carbamate (141).

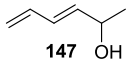


141

The title compound was synthesised following the general carbamoylation procedure starting from **138** (0.78 g, 8.0 mmol) and TAI (1 ml, 8.4 mmol). The crude was purified by flash chromatography (2:8 AcOEt/hexanes) to afford 0.92 g (81 % yield) of pure carbamate **141** as a white powder.

Mp: 86 ºC. **FT-IR (ATR)** ν in cm^{-1}: 3441, 3300, 3212, 2923, 2852, 1663, 1615, 1437, 1354, 1114, 991. **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): 6.24 (dd, 1H, *J* = 15.1, 10.6 Hz), 6.04 (ddd, 1H, *J* = 15.1, 10.6, 1.4 Hz), 5.74 (dq, 1H, *J* = 15.1, 6.8 Hz), 5.62 (dt, 1H, *J* = 15.1, 6.6 Hz), 4.91 (brs, 2H), 4.64 (d, 2H, *J* = 6.6), 1.75 (d, 3H, *J* = 6.8 Hz).**^{13}C NMR** (100MHz, $CDCl_3$, δ in ppm): 157.1, 134.8, 131.4, 130.6, 124.2, 65.7, 18.3. **ESI-TOF** [M+H] calc for $C_7H_{10}O_2$: 142.0790, found: 142.0105.

(*E*)-Hexa-3,5-diene-2-ol (147).



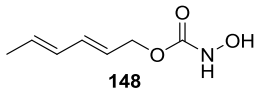
147

Formic acid (1.6ml, 40mmol) was added dropwise to neat chlorosulfonyl isocyanate (3.5 ml, 40 mmol) at 0ºC with rapid stirring. Vigorous gas evolution was observed during the addition process. The resulting viscous suspension was stirred for 5 min at 0ºC during which time the mixture solidified. Dichloromethane (17 ml) was added and the solution was stirred at 0ºC then 8h at 25ºC leading to chlorosulfonamide with total conversion. The reaction mixture was cooled to 0ºC and a solution of **138** (1.96 g, 20 mmol) in dry pyridine (3.4 ml, 40 mmol) in 19 ml of dichloromethane was added dropwise. The contents were warmed to 25ºC and stirred during 4h. The reaction was quenched by the successive addition of 50 ml EtOAc and 30 ml of H_2O. The aqueous phase was extracted with 50 ml of EtOAc (x3). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The oil crude residue was purified by column

chromatography using 10% ethyl acetate-hexane as the eluent to give 0.8 g of **147** (41%). Collected experimental data are in agreement with the reported data.[242]

FT-IR (ATR) ν in cm^{-1}: 3344, 3019, 2971, 2855, 986 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): 6.32 (ddd, 1H, *J* = 16.8, 10.6, 9.8 Hz), 6.19 (dd, 1H, *J* = 15.1, 10.6 Hz), 5.74 (dd, 1H, *J* = 15.1, 6.3 Hz), 5.19 (d, 1H, *J* = 16.8 Hz), 5.08 (d, 1H, *J* = 9.8 Hz), 4.34 (m, 1H), 1.90 (s, 1H), 1.27 (d, 3H, *J* = 6.0 Hz). **^{13}C NMR** (100MHz, $CDCl_3$, δ in ppm): 137.9, 136.6, 130.3, 117.8, 68.6, 23.5.

(2*E*,4*E*)–Hexa-2,4-dienyl hydroxycarbamate (148).



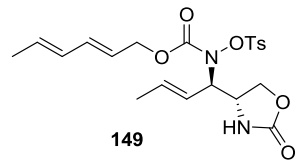
148

1,1'-Carbonyldiimidazole (2.24 g, 13.81 mmol) was added to a solution of *trans, trans*-2,4-hexadien-1-ol (**138**) (1,01 g, 10,29 mmol) in dry acetonitrile (60ml) and stirred at room temperature until TLC indicate complete consumption of the alcohol **138** (4h). Imidazole (3.27 g , 48.03 mmol) and hydroxylamine hydrochloride (4.17 g, 60.00 mmol) were added, and stirring continued until TLC showed complete consumption of the initial alcohol adduct. After removal of the solvent, the residue was partitioned between ethyl acetate and 1 M HCl followed by extraction of the aqueous phase with ethyl acetate (x3). The organic phase was washed with $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to afford the crude product, which was purified by flash column chromatography using 30% ethyl acetate-hexane to give 1.42g (88%) of **148** as a white solid.

FT-IR (ATR) ν in cm^{-1}: 3312, 2936, 2357, 1713, 1116 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): 7.15 (s, 1H), 6.26 (dd, 1H, *J* = 15.5, 10.5 Hz), 6.04 (ddd, 1H, *J* = 15.2, 10.5, 1.6 Hz), 5.76 (dq, 1H, *J* = 15.2, 6.5 Hz), 5.60 (dt, 1H, *J* = 15.5, 6.6 Hz), 4.64 (d, 2H, *J* = 6.6), 1.75 (d, 3H, *J* = 6.5 Hz).**^{13}C NMR** ($CDCl_3$, 100 MHz, δ in ppm): 136.1, 132.2, 130.0, 129.5, 122.0, 67.3, 21.8, 18.1. **ESI-TOF** [M+H] calc for $C_7H_{12}NO_3$: 158.0817, found: 158.0816.

[242] Tufarielo, J. J.; Meckler, H.; Senaratne, K. P. A. *Tetrahedron* **1985**, *41*, 3447-345.

Compound 149.

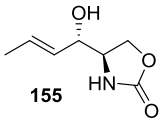


149

Product **149** was synthesised following the general aziridination procedure A. The reaction was carried out with $Rh_2(OAc)_4$ as the catalyst, in acetone and with vigorous stirring at -20ºC during 16h. The reaction crude was purified by flash chromatography on neutralized silica using 4: 6 (hexanes: ethyl acetate) to afford 14 mg of a yellowish oil (62%).

FT-IR (ATR) ν in cm^{-1}: 3359, 3198, 2922, 2851, 1720, 1604, 1329 cm^{-1}. **^{1}H NMR** (600 MHz, $CDCl_3$, δ in ppm): 6.07 (dd, 1H, *J*= 15.2, 10.6Hz), 5.97 (dd, 1H, *J*= 14.6, 10.6Hz), δ= 5.85 (brs, 1H), 5.77 (dq, 1H, *J*= 15.2, 6.7), 5.54 (m, 1H), 5.22 (m, 1H), 4.61 (brs, 2H), 4.31 (m, 4H), 2.46 (s, 3H), 1.79 (d, 3H, *J*= 6.7 Hz), 1.72 (d, 3H, *J*= 6.1Hz). **^{13}C NMR** (150MHz, $CDCl_3$, δ in ppm): 158.8, 146.4, 136.3, 132.6, 130.8, 130.1, 129.9, 129.6, 121.8, 68.4, 29.7, 21.8, 18.7. **ESI-TOF** [M+Na] calc for $C_{24}H_{22}N_2O_7Na$: 473.1358, found: 473.1334.

4-(*E*)-(1-Hydroxybut-2-en-1-yl)oxazolidin-2-one (155).



155

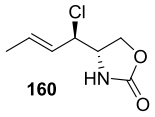
Procedure 1. In a 10 ml Sclenck flask charged with a magnetic stir bar were added *N*-tosylcarbamate **139** (31 mg, 0.1 mmol), $Rh_2(OAc)_4$ (4.5 mg, 0,01 mmol). Then 4.5 ml of dichloromethane and 0.5 ml of water were added and the mixture was cooled to -5ºC when finally K_2CO_3 (96 mg, 0.7 mmol) was added. The reaction mixture was stirred at this temperature since TLC showed complete carbamate consumption. Then the organic layer was separated and the aqueous phase extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$ and the solvent removed by rotatory evaporation. Final purification was efected by column chromatography (1:1 ethyl acetate/hexanes) affording **155** (9.6 mg, 61%) as a colorless film.

Procedure 2. A flame dried 250 ml Schlenk containing a magnetic stirring bar was charged with activated 4 Å MS (10.00 g), carbamate **141** (1.42 g, 10 mmol) and PhIO (4.40 g, 20 mmol) under argon. Then distilled CH_2Cl_2 (200 ml) was added and the hetereogeneous mixture was stirred at 20ºC until TLC shows complete consumption of the carbamate (normaly between 5 and 10 hours). At that point water (5 ml) was added and the reaction mixture was led under stirring for 5 hours. The crude solution was filtered and abundantly washed with methanol. The obtained crude solid after evaporation of the solvent was directly purified by column chromatography employing hexanes: ethyl acetate: methanol (80:15:5) as the eluent. Alcohol **155** was obtained in 24% yield as a white solid.

Collected experimental data are in agreement with the reported data.[243]

^{1}H NMR (400 MHz, $CDCl_3$, δ in ppm): 5.85 (dq, 1H, *J* = 15.2, 6.8 Hz), 5.72 (brs, 1H), 5.42 (dd, 1H, *J* = 15.2, 7.2 Hz), 4.39 (t, 1H, *J* = 8.8 Hz), 4.29 (dd, 1H, *J* = 8.8, 4.8 Hz), 4.07 (m, 1H), 3.83 (m, 1H), 2.61 (brs, 1H), 1.73 (d, 3H, *J* = 6.8 Hz). **^{13}C NMR** (100MHz, $CDCl_3$, δ in ppm): 160.4, 131.6, 128.8, 74.0, 67.1, 56.7, 18.2. **ESI-TOF** [M+H] calc for $C_7H_{12}NO_3$: 158.0739, found: 158.0809.

(*R*/*S*)-4-(((*R*/*S*),*E*)-1-Chlorobut-2-en-1-yl)-oxazolidin-2-one (160).



160

Oxazolidinone **160** can be isolated as a non desired product during the aziridination reaction of carbamate **141** using PhIO as the oxidant under metal free conditions.

^{1}H NMR (400 MHz, $CDCl_3$, δ in ppm): 5.91 (dq, *J*= 15.0, 6.6 Hz, 1H), 5.46 (ddq, *J*= 15.0, 9.4, 1.6 Hz, 1H), 5.35 (s, 1H), 4.51 (dt, *J* = 12.0, 6.0 Hz, 1H), 4.32 (dd, *J* = 9.4, 4.7 Hz, 1H), 4.25 – 4.19 (m, 1H), 4.02 – 3.94 (m, 1H), 1.78 (dd, *J* = 6.6, 1.6 Hz, 2H). **^{13}C NMR** (100MHz, $CDCl_3$, δ in ppm): 158.6, 134.2, 126.47, 68.0, 63.5, 57.1, 18.0. **ESI-TOF** [M+Na] calc for $C_{10}H_{10}ClNO_2Na$: 198.0400, found: 198.0292.

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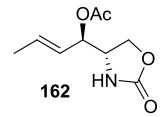
[243] White, J. D.; Hrnciar, P. *J. Org. Chem.* **2000**, *65*, 9129-9142.

(*S*/*R*)-4-(((*S*/*R*),*E*)-1-Acetyloxybut-2-en-1-yl)-oxazolidin-2-one (162).



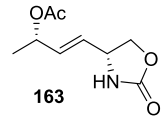
162

Procedure 1. Compound **(162** was synthesised from carbamate **141** according to the general procedure A. Starting from 14 mg (0.1 mmol) of carbamate **141**, products **162** and **163** (17 mg, 87%) were obtained as a 75:25 mixture of regioisomers. The mixture was further purified for characterisation purposes, using 10% ethyl acetate-hexanes to 40% ethyl acetate–hexanes as the eluent. The title compound **162** was isolated as colorless oil.

Procedure 2. Compound **162** was synthesised from alcohol **155**. To a solution of alcohol **155** (71 mg, 0.42 mmol) in anhydrous pyridine (1.0 ml) was added acetyl chloride (0.05 ml, 0.64 mmol) at 0ºC. The reaction mixture was allowed to warm to room temperature and was stirred for 2 hours and then poured into a saturated aqueous $CuSO_4$ solution. The organic layer was washed several times with the $CuSO_4$ solution. Finally, the combined organic layers were washed with brine and dried over Na_2SO_4. Purification was effected by flash chromatography using 50% ethyl acetate-hexanes as the eluent. Acetylated compound **162** was obtained as a colorless syrup in 76% yield (65 mg).

FT-IR (ATR) ν in cm^{-1}: 3297, 2922, 2851, 1741, 1229. **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): 5.92 (dq, 1H, *J* = 14.8, 6.5 Hz), 5.37 (ddq, 1H, *J* = 14.8, 7.6, 1.8 Hz), 5.24 (dd, 1H, *J* = 7.6, 5.0 Hz), 5.16 (brs, 1H), 4.44 (t, 1H, *J* = 8.9 Hz), 4.23 (dd, 1H, *J* = 8.9, 5.0 Hz), 3.99 (m, 1H), 2.09 (s, 3H), 1.75 (dd, 3H, *J* = 6.5, 1.8 Hz). **^{13}C NMR** (100MHz, $CDCl_3$, δ in ppm): 170.2, 157.1, 134.4, 123.6, 74.8, 66.3, 54.7, 29.9, 18.2. **ESI-TOF** [M+Na] calc for $C_9H_{12}NO_4Na$: 222.0845, found: 222.0733.

(*R*/*S*)-4-(((*S*/*R*),*E*)-3-Acetyloxybut-1-en-1-yl)-oxazolidin-2-one (163).



163

Compound **163** has been synthesised from two different carbamates according to the general procedure B.

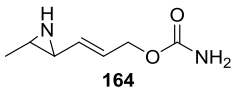
a) Starting from 14 mg (0.1 mmol) of carbamate **141**, compounds **162** and **163** (15 mg, 74 %) were obtained as a <5:>95 mixture.

b) Starting from 14 mg (0.1 mmol) of carbamate **196**, compound **162** and **163** (13 mg, 64 %) were obtained as a 39:61 mixture of regioisomers.

The purification was accomplished by means of column chromatography employing hexanes 10% ethyl acetate-hexanes to 40% ethyl acetate–hexanes as the eluent. The title compound **163** was isolated as colorless oil.

FT-IR (ATR) ν in cm^{-1}: 3295, 2922, 1733, 1371, 1234, 1022 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): 5.76 (dd, 1H, *J* = 15.6, 5.4 Hz), 5.67 (ddd, 1H, *J* = 15.6, 7.3, 1.0 Hz), 5.39 (brs, 1H), 5.35 (m, 1H), 4.54 (t, 1H, *J* = 8.8 Hz), 4.39 (m, 1H), 4.06 (dd, 1H, *J* = 8.8, 6.4 Hz), 2.07 (s, 3H), 1.31 (d, 3H, *J* = 6.7 Hz). **^{13}C NMR** (100MHz, $CDCl_3$, δ in ppm): 170.0, 159.1, 134.1, 128.7, 69.9, 69.3, 54.1, 21.2, 20.0. **ESI-TOF** [M+23] calc for CH_9NO_4Na: 222.0845, found: 222.0731.

(*E*)-3-(3-methylaziridin-2-yl)allyl carbamate (164).



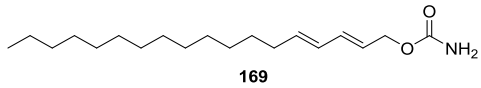
164

Aziridine **164** is generated as a side product in the aziridination of **141**. Purification was carried out by flash chromatography silica using 4:6 (hexanes: ethyl acetate) as eluent affording product **164** as a mixture of diastereoisomers.

FT-IR (ATR) ν in cm^{-1}: 3355, 2924, 2849, 1716, 1605, 1329. **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): 5.98 (dt, 1H, *J*= 15.2, 6.0 Hz, 5.50 (dd, 1H, *J*= 15.2, 7.6 Hz), 4.57

(d, 2H, *J*= 6.0 Hz), 3.07 (dd, 1H, *J*= 7.6, 2.0 Hz), 2.91 (dq, 1H, *J*= 5.2, 2.0 Hz), 1.35 (d, 3H, *J*= 5.2 Hz). **^{13}C NMR** (100MHz, $CDCl_3$, δ in ppm): 156.5, 131.6, 129.2, 64.6, 58.7, 56.7, 30.8, 17.7.

(2*E*,4*E*)-Octadeca-2,4-dien-1-yl carbamate (169).

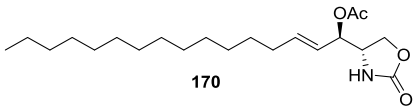


169

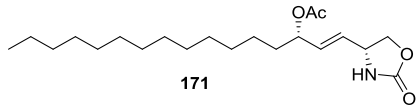
The title compound was synthesised following the general carbamoylation procedure starting from **127** (0.57 g, 2.2 mmol) and TAI (0.29 ml, 2.4 mmol). The crude was purified by flash chromatography (2:8 AcOEt/hexanes) to afford 0.50 g (72 % yield) of pure carbamate **169** as a white crystalline solid.

Mp: 87 ºC. **FT-IR (ATR)** ν in cm^{-1}: 3435, 3289, 3018, 2954, 2917, 2848, 1691, 1606, 1472, 1461, 1438, 1073, 982. **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): 6.26 (dd, 1H, *J* = 15.2, 10.4 Hz), 6.03 (dd, 1H, *J* = 15.2, 10.4 Hz), 5.74 (dt, 1H, *J* = 15.2, 6.8 Hz), 5.64 (dt, 1H, *J* = 15.2, 6.4 Hz), 4.57 (d, 2H, *J* = 6.4 Hz), 4.56 (brs, 2H), 2.07 (q, 2H, *J* = 7.2 Hz), 1.42-1.15 (m, 22H), 0.88 (t, 3H, *J* = 6.4 Hz). **^{13}C NMR** (100MHz, $CDCl_3$, δ in ppm): 156.9, 137.1, 135.0, 129.2, 124.3, 65.8, 32.8, 32.1, 29.9, 29.9, 29.9, 29.8, 29.7, 29.6, 29.4, 29.3, 22.9, 21.3, 14.3. **ESI-TOF** [M+Na] calc for $C_{19}H_{35}NO_2Na$: 332.2668, found: 332.2575.

(*S*/*R*)-4-(((*R*/*S*),*E*)-1-Acetoxyhexadeca-2-en-1-yl)-oxazolidin-2-one (170) and (*R*/*S*)-4-(((*S*/*R*),*E*)-3-Acetyloxyhexadeca-1-en-1-yl)-oxazolidin-2-one (171).



170



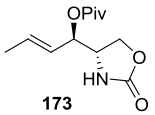
171

Compounds **170** and **171** were obtained from carbamate **169** according to general procedure A. Starting from 31 mg (0.1 mmol) of carbamate **169**, products **170** and **170** (28 mg, 76%) were obtained as a 13:87 mixture. Purification of the tittle products for characterisation purposes was accomplished by means of column chromatography employing 10% hexanes–ethyl acetate-hexanes to 20% ethyl acetate–hexanes as the eluent to afford **170** and **171** as colorless oils.

170 (minor): FT-IR (ATR) ν in cm^{-1}: 3278, 2923, 2853, 1763, 1466, 1399, 1234, 1032 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): 5.90 (dt, 1H, *J* = 15.6, 6.8 Hz), 5.27 (ddt, 1H, *J* = 15.6, 7.2, 1.6 Hz), 5.26 (brs, 1H), 5.16 (t, 1H, *J* = 7.2 Hz), 4.41 (t, 1H, *J* = 9.2 Hz), 4.16 (dd, 1H, *J* = 9.2, 4.8 Hz), 3.95 (m, 1H), 2.10 (s, 3H), 2.05 (m, 2H), 1.48-1.16 (m, 22H), 0.88 (t, 3H, *J* = 7.2 Hz). **^{13}C NMR** (100MHz, $CDCl_3$, δ in ppm) : 170.0, 159.0, 139.6, 122.5, 76.0, 66.5, 54.6, 32.6, 32.1, 29.9, 29.9, 29.9, 29.8, 29.6, 29.6, 29.4, 28.9, 22.9, 21.3, 14.4. **ESI-TOF** [M+23] calc for $C_{21}H_{37}NO_4Na$: 390.2723, found: 390.2631.

171 (major): FT-IR (ATR) ν in cm^{-1}: 3295, 2922, 2853, 1739, 1466, 1399, 1370, 1235, 1023, 969 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): 5.71 (dd, 1H, *J* = 15.6, 5.2 Hz), 5.65 (dd, 1H, *J* = 15.6, 6.0 Hz), 5.23 (q, 1H, *J* = 6.0 Hz), 5.13 (brs, 1H), 4.53 (t, 1H, *J* = 8.4 Hz), 4.37 (m, 1H), 4.03 (dd, 1H, *J* = 8.4, 6.4 Hz), 2.07 (s, 3H), 1.59 (m, 2H), 1.39-1.18 (m, 22H), 0.88 (t, 3H, *J* = 6.2 Hz). **^{13}C NMR** (100MHz, $CDCl_3$, δ in ppm): 170.5, 159.1, 133.4, 129.6, 73.3, 70.2, 54.4, 34.4, 32.1, 29.9, 29.9, 28.9, 28.9, 29.7, 29.6, 29.5, 25.6, 25.3, 22.9, 21.4, 14.4. **ESI-TOF** [M+23] calc for $C_{21}H_{37}NO_4Na$: 390.2723, found: 390.2633.

(*S*/*R*)-4-(((*R*/*S*),*E*)-1-Pivaloyloxybut-2-en-1-yl)-oxazolidin-2-one (173).



173

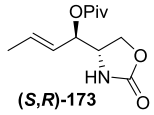
Procedure 1. Compound **173** was synthesised from carbamate **141** according to general procedure A. Starting from 14 mg (0.1 mmol) of carbamate **141**, products **173** and **174** (21 mg, 89%) were obtained as a 91:9 mixture of regioisomers. A small fraction was further purified by column chromatography using 40% ethyl acetate-hexanes to 30% ethyl acetate–hexanes as the eluent for characterisation purposes. The title compound **173** was isolated as colorless oil.

Procedure 2. Compound **173** was synthesised from alcohol **155**. To a solution of alcohol **155** (120 mg, 0.72 mmol) in anhydrous pyridine (1.2 ml) was added freshly distilled pivaloyl chloride (0.225 ml, 1.73 mmol) at 0ºC. Then the reaction mixture was allowed to warm to room temperature and was stirred for 5 hours. After evaporation of pyridine under high vacccum, the crude was directly purified by the

means of a short filtration in silica. 121 mg (70 % yield) of compound **173** were obtained as a colorless syrup.

FT-IR (ATR) ν in cm^{-1}: 3288, 2971, 2936, 2920, 2893, 1753, 1727, 1480, 1398, 1278, 1229, 1148. **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): 5.88 (dq, 1H, *J* = 15.2, 6.5 Hz), 5.35 (ddq, 1H, *J* = 15.2, 7.0, 1.7 Hz), 5.26 (dd, 1H, *J* = 7.0, 4.4 Hz), 4.42 (t, 1H, *J* = 8.9 Hz), 4.27 (dd, 1H, *J* = 8.9, 4.4 Hz), 3.99 (m, 1H), 1.75 (dd, 3H, *J* = 6.5, 1.7 Hz), 1.21 (s, 9H). **^{13}C NMR** (100MHz, $CDCl_3$, δ in ppm): 177.8, 159.1, 133.4, 123.8, 73.9, 66.1, 54.9, 27.3, 18.3. **ESI-TOF** [M+Na] calc for $C_{12}H_{19}NO_4Na$: 264.1314, found: 264.1205.

(*S*)-4-((*R*,*E*)-1-Pivaloyloxybut-2-en-1-yl)-oxazolidin-2-one ((*S*,*R*)-173).

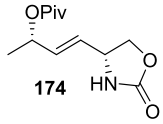


(*S*,*R*)-173

Ozaxolidinone **(*S*,*R*)-173** was synthesised from **173** according to the general method for the kinetic resolution of oxazolidinines. Preparative TLC was used to separate (**(*S*,*R*)-173** from its acylated derivative (**(*R*,*S*)-333**). Therefore the yield obtained was not taken into consideration.

HPLC Chiralpak IC column (80:20 hexanes:isopropanol, 1.0 ml/min, 205 nm); major enantiomer t_r = 25.34 min, minor enantiomer t_r = 21.67 min, 65% ee.

(*R*/*S*)-4-(((*S*/*R*),*E*)-3-Pivaloyloxybut-1-en-1-yl)-oxazolidin-2-one (174).



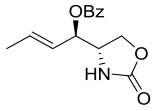
174

Compound **174** was synthesised from carbamate **141** according to general procedure B substrates and employing $PhI(OPiv)_2$ instead of $PhI(OAc)_2$. Starting from 14 mg (0.1 mmol) of carbamate **141**, products **173** and **174** (14 mg, 61%) were obtained as a 15:85 mixture of regioisomers. A small fraction was further purified by column chromatography using 10% ethyl acetate-hexanes to 30% ethyl acetate–

hexanes as the eluent for characterisation purposes. The title compound **174** was isolated as colorless oil.

FT-IR (ATR) ν in cm^{-1}: 3319, 2978, 1756, 1725, 1480, 1398, 1281, 1230, 1164, 1041 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): 5.77 (dd, 1H, *J* = 15.3, 5.2 Hz), 5.65 (ddd, 1H, *J* = 15.3, 7.7, 1.2 Hz), 5.32 (m, 1H), 4.53 (t, 1H, *J* = 8.6 Hz), 4.39 (m, 1H), 4.03 (dd, 1H, *J* = 8.6, 6.7 Hz), 1.29 (d, 3H, *J* = 6.7 Hz), 1.20 (s, 9H). **^{13}C NMR** ($CDCl_3$, 100 MHz, δ ppm): 177.8, 159.2, 134.8, 128.4, 70.2, 69.1, 54.4, 23.7, 20.2. **ESI-TOF** [M+H] calc for $C_{12}H_{19}NO_4Na$: 242.1314, found: 242.2855.

(*S*/*R*)-4-(((*R*/*S*),*E*)-1-Benzoyloxybut-2-en-1-yl)-oxazolidin-2-one (179).



179

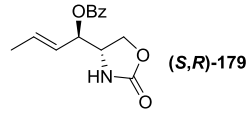
Procedure 1. Compound **179** was synthesised from carbamate **141** according to general procedure A employing $PhI(OCOPh)_2$ instead of $PhI(OPiv)_2$. Starting from 14 mg (0.1 mmol) of carbamate **141**, product **179** (24 mg, 91% yield) was obtained as a 66:34 mixture of regioisomers. The mixture was further purified using 20% ethyl acetate – hexanes as the eluent for characterisation purposes. The title compound **179** was isolated as colorless oil.

Procedure 2. Compound **179** was synthesised from alcohol **155**. To a solution of alcohol **155** (167 mg, 1 mmol) in anhydrous pyridine (3 ml) and dichloromethane (9 ml) was added freshly distilled benzoyl chloride (0.135 ml, 1.2 mmol) at 0ºC. Then the reaction mixture was allowed to warm to room temperature and was stirred 3 hours. After evaporation of pyridine under high vacccum, the crude was directly purified by the means of a short filtration in silica. 230 mg (88 % yield) of compound **179** were obtained as a colorless oil that turned into a white solid after being refrigerated.

FT-IR (ATR) ν in cm^{-1}: 3292, 2922, 2853, 1754, 1720, 1267, 1109, 712 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): 8.02 (d, 2H, *J* = 7.2Hz), 7.60 (t, 1H, *J* = 7.2 Hz), 7.46 (t, 2H, *J* = 7.2 Hz), 6.00 (dq, 1H, *J* = 14.0, 6.8 Hz), 5.44 (m, 2H), 5.33 (brs, 1H), 4.91 (t, 1H, *J* = 8.8 Hz), 4.26 (dd, 1H, *J* = 8.8, 4.8 Hz), 4.10 (m, 1H), 1.75 (d, 3H, *J* = 6.8 Hz). **^{13}C NMR** (100MHz, $CDCl_3$, δ in ppm): 165.6, 160.2, 134.0, 133.5, 129.9,

128.6, 123.6, 75.4, 66.3, 55.0, 18.1. **ESI-TOF** [M+H] calc for $C_{12}H_{20}NO_4$: 242.1314, found: 242. 2831.

(*S*)-4-((*R*,*E*)-1-Benzoyloxybut-2-en-1-yl)-oxazolidin-2-one (***S*,*R*)-179.**

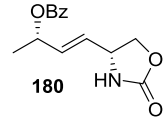


(*S*,*R*)-179

Benzoate **(*S*,*R*)-179** was synthesised from **179** according to the general method for the kinetic resolution of oxazolidinines. Starting from 26 mg (0.1 mmol) of **(±)-207**, **(*S*,*R*)-179** was recovered after 3.5 h in 54% yield and 58% ee after flash chromatography employing 30% ethyl acetate-hexanes as the eluent.

HPLC Chiralpak IC column (80:20 hexanes:isopropanol, 1.0 ml/min, 220 nm); major enantiomer t_r = 15.45 min, minor enantiomer t_r = 13.32 min, 58% ee.

(*R*/*S*)-4-(((*S*/*R*),*E*)-3-Benzoyloxybut-1-en-1-yl)-oxazolidin-2-one (180).

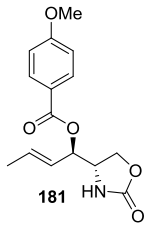


180

Compound **180** was synthesised from carbamate **141** according to the general procedure B employing $PhI(OCOPh)_2$ instead of $PhI(OAc)_2$. Starting from 14 mg (0.1 mmol) of carbamate **141**, product **180** (21 mg, 82% yield) was obtained as a 14:86 mixture of regioisomers. The mixture was further purified using 20% ethyl acetate – hexane as the eluent for characterisation purposes. The title compound **180** was isolated as colorless oil.

FT-IR (ATR) ν in cm^{-1}: 3324, 2923, 2852, 1753, 1716, 1272, 1113, 712 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): 8.05 (d, 2H, *J* = 7.9 Hz), 7.58 (t, 1H, *J* = 7.3 Hz), 7.46 (dd, 2H, *J* = 7.9, 7.3 Hz), 5.98 (dd, 1H, *J* = 15.3, 5.2 Hz), 5.76 (dd, 1H, *J* = 15.3, 7.3 Hz), 5.62 (m, 1H), 5.37 (brs, 1H), 4.54 (t, 1H, *J* = 8.6 Hz), 4.41 (m, 1H), 4.06 (dd, 1H, *J* = 8.6, 6.8 Hz), 1.45 (d, 3H, *J* = 6.7 Hz). **^{13}C NMR** (100MHz, CDCl3, δ in ppm): 165.1, 159.3, 134.5, 133.4, 130.3, 129.8, 129.0, 128.7, 70.2, 70.1, 54.5, 20.4. **ESI-TOF** [M+Na] calc for $C_{12}H_{19}NO_4Na$: 284.1001, found: 284.0845.

(*S*/*R*)-4-(((*R*/*S*),*E*)-1-*p*-Methoxybenzoyloxybut-2-en-1-yl)-oxazolidin-2-one (18).

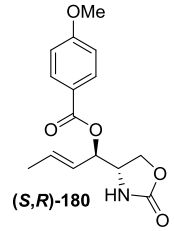


181

Compound **180** was synthesised from alcohol **155**. To a solution of alcohol **155** (90 mg, 0.54mmol) in anhydrous pyridine (1 ml) and dichloromethane (3 ml) was added freshly distilled *p*-methoxy benzoyl chloride (0.146 ml, 1.1 mmol) at 0ºC. Then the reaction mixture was allowed to warm to room temperature and was stirred overnight. After evaporation of pyridine under high vacccum, the crude was directly purified by the means of a short filtration in silica. 100 mg (64 % yield) of compound **180** were obtained as a colorless oil that turned into a white solid after being refrigerated.

FT-IR (ATR) ν in cm^{-1}: 3292, 2938, 2916, 2844, 1756, 1711, 1606, 1510, 1257, 1168, 1102, 1026, 769. **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): 7.97 (d, 2H, *J* = 8.8 Hz), 6.90 (d, 2H, *J* = 8.8 Hz), 6.18 (brs, 1H), 5.95 (dq, 1H, *J* = 14.4, 6.4 Hz), 5.45 (m, 2H), 4.47 (t, 1H, *J* = 8.8 Hz), 4.33 (dd, 1H, *J* = 8.8, 4.8 Hz), 4.08 (m, 1H), 3.84 (s, 3H), 1.73 (d, 3H, *J* = 6.8 Hz). **^{13}C NMR** (100MHz, $CDCl_3$, δ in ppm): 165.4, 163.9, 159.8, 133.9, 132.0, 123.8, 122.0, 114.0, 75.1, 66.4, 55.7, 55.0, 18.2. **ESI-TOF** [M+H] calc for $C_{15}H_{17}NO_5Na$: 291.1107, found: 314.0984.

(*S*)-4-((*R*,*E*)-1-*p*-Methoxybenzoyloxybut-2-en-1-yl)-oxazolidin-2-one ((*S*,*R*)-181).



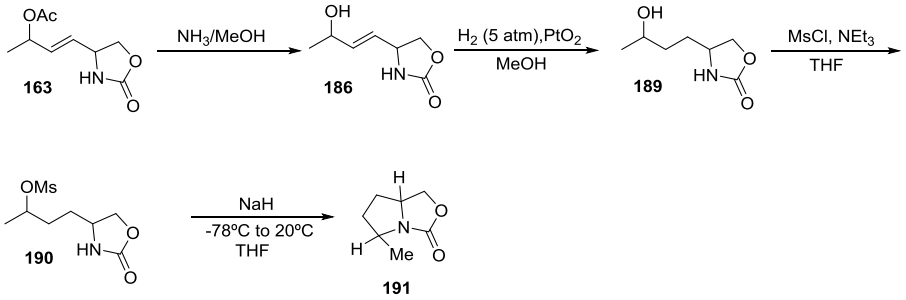
(*S*,*R*)-180

p-methoxybenzoate (***S*,*R*)-181** was synthesised from **181** according to the general method for the kinetic resolution of oxazolidinines. Preparative TLC was used to

separate (***S,R*)-181** from its acylated derivative (***R,S*)-335**. Therefore the yield obtained was not taken into consideration.

HPLC Chiralpak ID column (50:50 hexanes:isopropanol, 1.0 ml/min, 254 nm); major enantiomer t_r = 38.39 min, minor enantiomer t_r = 25.47 min, 68% ee.

Compound 191.



A 10 ml Shlenk was charged with acetate **163** (30 mg, 0.15 mmol) and was dissolved in a 7N solution of NH_3 in methanol under argon. The solution was stirred at room temperature overnight resulting in full conversion to the hydrolyzed compound **186**, which easily decomposes in either silica or alumina. Therefore the crude product was used directly in the hydrogenation step. Thus, alcohol **186** dissolved in methanol (2 ml) and PtO_2 (2.3 mg, 0.01 mmol) were introduced in an autoclave, which was then pressurized with hydrogen (5 atm) and the raction mixture was stirred for 5 h at room temperature. After filtration and evaporation of the solvent under vacuum, the saturated alcohol **189** was obtained as the sole product, pure enough to be used directly in the next reaction.

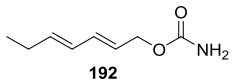
To a stirred solution of **189** and triethylamine (26 µL, 0.18 mmol) in THF (0.5 ml), methanesulfonyl chloride (14 µl, 0.18 mmol) was added at 0ºC. The solution was stirred 2h maintaining the temperature at 0ºC. The reaction was quenched adding a drop of water to eliminate the excess of methanesulfonyl chloride. The solvent was removed and ethyl acetate (1 ml) and water (1 ml) were added. The organic layer was separated and the aqueous phase was extracted repeatedly with 1 ml of ethyl acetate. The combined organic layers were dried with Na_2SO_4, filtered and evaporated to give the mesylated coumpound **190**.

Finally, compound **190** was dissolved in anhydrous THF (2 ml), cooled to -78ºC and NaH (6 mg, 0.15 mmol, as a 60% mixture in mineral oil) was added to the solution. The solution was allowed to warm to room temperature and stirred overnight. A drop of water was added and the solvent evaporated. Afterwards, 1ml of CH_2Cl_2 and 1 ml of water were added, the organic layer was separated and the aqueous phase extracted with CH_2Cl_2 (3x1 ml). The organic layers were dried and evaporated under vacuum. Final purification was effected by column chromatography employing 20% ethyl acetate–hexanes as the eluent obtaining product **191** as a colorless oil in a 56 % (13 mg) overall yield.

FT-IR (ATR) ν in cm^{-1}: 3346, 2959, 2922, 2853, 2361, 1746, 1456, 1399, 1259, 1024. **^{1}H NMR** (400 MHz,$CDCl_3$, δ in ppm): 4.46 (t, 1H, *J* = 8.0 Hz), 4.18 (m, 1H), 3.98 (t, 1H, *J* = 8.4 Hz), 3.73 (m, 1H), 2.27 (m, 1H), 1.98 (m, 1H), 1.83 (m, 1H), 1.62 (m, 1H), 1.44 (d, 3H, *J* = 6.8 Hz). **^{13}C NMR** (100MHz, $CDCl_3$, δ in ppm): 69.5, 61.2, 52.1, 36.5, 29.3, 18.1. **ESI-TOF** [M+23] calc for $C_7H_{11}NO_2Na$: 164.0790, found: 164.0684.

Signal of CO group was not observed in the ^{13}C NMR. However, the presence of a CO band (1746 cm^{-1}) in the FT-IR spectra in combination with the ESI-TOF, undoubtedly confirm the proposed structure.

(2*E*,4*E*)-Hepta-2,4-dien-1-yl carbamate (192).



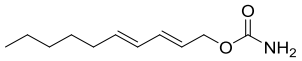
192

The title compound was synthesised following the general carbamoylation procedure starting from (2*E*,4*E*)-hepta-2,4-dien-1-ol (1.0 g, 8.9 mmol) and TAI (1.17 ml, 9.8 mmol). The crude was purified by flash chromatography (1:9 AcOEt/hexanes to 2:8 AcOEt/hexanes) to afford 1.04 g (76 % yield) of pure carbamate **192** as a white powder.

Mp: 70 ºC. **FT-IR (ATR)** ν in cm^{-1}: 3437, 3334, 3273, 3215, 3021, 2966, 2935, 2875, 1687, 1606, 1461, 1415, 1342, 1321, 1047, 984. **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): 6.25 (dd, 1H, *J* = 14.0, 10.4 Hz), 6.02 (dd, 1H, *J* = 15.2, 10.4 Hz), 5.77 (dt, 1H, *J* = 14.0, 6.0 Hz), 5.63 (dt, 1H, *J* = 15.2, 7.2 Hz), 4.92 (brs, 2H), 4.55 (d, 2H, *J* = 6.0

Hz), 2.09 (qt, 2H, *J* = 7.6 Hz), 0.99 (t, 3H, *J* = 7.6 Hz). **^{13}C NMR** (100MHz, $CDCl_3$, δ in ppm): 157.1, 138.4, 134.9, 128.3, 124.4, 65.7, 25.8, 13.5. **ESI-TOF** [M+Na] calc for $C_8H_{13}NO_2Na$: 178.0946,found: 178.0875.

(2*E*,4*E*)-Deca-2,4-dien-1-yl carbamate (193).

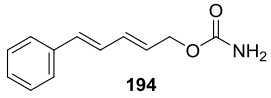


193

The title compound was synthesised following the general carbamoylation procedure starting from (2*E*,4*E*)-deca-2,4-dien-1-ol (1.0 g, 6.4 mmol) and TAI (0.85 ml, 7.1 mmol). The crude was purified by flash chromatography (1:9 AcOEt/hexanes to 2:8 AcOEt/hexanes) to afford 0.92 g (72 % yield) of pure carbamate **193** as a white powder.

Mp: 61 ºC. **FT-IR (ATR)** ν in cm^{-1}: 3432, 3322, 3258, 3198, 3020, 2952, 2923, 2870, 2852, 1687, 1606, 1465, 1416, 1338, 1319, 1053, 986. **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): 6.24 (dd, 1H, *J* = 15.2, 10.4 Hz), 6.02 (dd, 1H, *J* = 15.2, 10.4 Hz), 5.73 (dt, 1H, *J* = 15.2, 6.8 Hz), 5.63 (dt, 1H, *J* = 15.2, 6.4 Hz), 4.81 (brs, 2H), 4.56 (d, 2H, *J* = 6.8 Hz), 2.06 (q, 2H, *J* = 6.8 Hz), 1.44-1.20 (m, 6H), 0.87 (t, 3H, *J* = 6.8 Hz). **^{13}C NMR** (100MHz, $CDCl_3$, δ in ppm): 156.8, 136.9, 134.8, 129.0, 124.1, 65.6, 32.6, 32.3, 28.8, 22.5, 14.0. **ESI-TOF** [M+Na] calc for $C_{11}H_{19}NO_2Na$: 220.1416, found: 220.1317.

(2*E*,4*E*)-5-Phenylpenta-2,4-dien-1-yl carbamate (194).



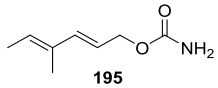
194

The title compound was synthesised following the general carbamoylation procedure starting from **198** (0.20 g, 1.3 mmol) and TAI (0.17 ml, 1.4 mmol). The crude was purified by flash chromatography (2:8 AcOEt/hexanes) to afford 0.21 g (80 % yield) of pure carbamate **194** as a white powder.

Mp: 137 ºC. **FT-IR (ATR)** ν in cm^{-1}: 3445, 3345, 3282, 3031, 2920, 2853, 2364, 1646, 1608, 1426, 1353, 1096, 1052, 990. **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm):

7.40 (d, 2H, *J* = 7.4 Hz), 7.32 (t, 2H, *J* = 7.4 Hz), 7.24 (t, 1H, *J* = 7.4 Hz), 6.78 (dd, 1H, *J* = 15.6, 10.4 Hz), 6.59 (d, 1H, *J* = 15.6 Hz), 6.46 (dd, 1H, *J* = 15.2, 10.4 Hz), 5.89 (dt, 1H, *J* = 15.2, 6.2 Hz), 4.69 (brs, 2H, $CONH_2$), 4.67 (d, 2H, *J* = 6.2 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$, δ in ppm): 156.9, 137.1, 134.4, 133.9, 128.8, 128.0, 127.9, 127.5, 126.7, 65.6.

(2*E*,4*E*)-4-Methylhexa-2,4-dien-1-yl carbamate (195).

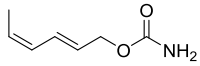


195

The title compound was synthesised following the general carbamoylation procedure starting from **200** (0.45 g, 4.0 mmol) and TAI (0.53 ml, 4.4 mmol). The crude was purified by flash chromatography (2:8 AcOEt/hexanes) to afford 0.492 g (78 % yield) of pure carbamate **195** as a white solid.

FT-IR (ATR) ν in cm^{-1}: 3421, 3343, 3260, 3208, 2359, 1684, 1615, 1426, 1126, 1069, 1350, 963 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): 6.31 (d, 1H, *J* = 15.6 Hz), 5.62 (m, 2H), 4.66 (brs, 2H), 4.61 (d, 2H, *J* = 6.8 Hz), 1.74 (s, 3H), 1.73 (d, 3H, *J* = 6.4 Hz). **^{13}C NMR** (100MHz, $CDCl_3$, δ in ppm): 157.1, 139.6, 133.8, 128.8, 119.9, 66.3, 14.1, 12.1.

(2*E*,4*Z*)-Hexa-2,4-dien-1-yl carbamate (196).



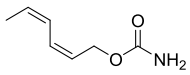
196

The title compound was synthesised following the general carbamoylation procedure starting from **201** (0.24 g, 2.5 mmol) and TAI (0.33 ml, 2.8 mmol). The crude was purified by flash chromatography (1:9 AcOEt/hexanes) to afford 0.29 g (84 % yield) of pure carbamate **196** as a white solid.

Mp: 67 ºC. **FT-IR (ATR)** ν in cm^{-1}: 3429, 3337, 3275, 3212, 3022, 2947, 2915, 2855, 1681, 1610, 1427, 1405, 1346, 1103, 1066, 988 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): 6.59 (ddt, 1H, *J* = 15.2, 12.3, 1.2 Hz), 6.00 (t, 1H, *J* = 10.8 Hz), 5.73 (dt, 1H, *J* = 15.2, 6.4 Hz), 5.57 (dq, 1H, *J* = 10.8, 6.8 Hz), 4.61 (d, 2H, *J* = 6.4

Hz), 1.76 (d, 3H, *J* = 6.8 Hz). **^{13}C NMR** (100MHz, $CDCl_3$, δ in ppm): 156.9, 129.5, 128.4, 128.3, 126.5, 65.8, 13.6. **ESI-TOF** [M+H] calc for $C_7H_{10}NO_2$: 142.0790, found: 142.0129.

(2*Z*,4*Z*)-Hexa-2,4-dien-1-yl carbamate (197).

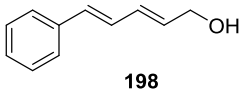


197

The title compound was synthesised following the general carbamoylation procedure starting from **199** (0.10 g, 1.0 mmol) and TAI (0.14 ml, 1.1 mmol). The crude was purified by flash chromatography (2:8 AcOEt/hexanes) to afford 0.11 g (75 % yield) of pure carbamate **197** as a white solid.

FT-IR (ATR) ν in cm^{-1}: 3422, 3332, 3267, 3211, 3044, 2914, 2855, 1684, 1612, 1408, 1355, 1321, 1082. **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): 6.47 (t, 1H, *J* = 11.4 Hz), 6.26 (t, 1H, *J* = 11.4 Hz), 5.66 (dq, 1H, *J* = 10.8, 7.2 Hz), 5.54 (dt, 1H, *J* = 10.8, 6.8 Hz), 4.95 (brs, 2H), 4.72 (d, 2H, *J* = 6.8 Hz), 1.75 (d, 3H, *J* = 7.2 Hz). **^{13}C NMR** (100MHz, $CDCl_3$, δ in ppm): 157.2, 129.6, 127.4, 124.1, 123.7, 61.1, 13.4. **ESI-TOF** [M+Na] calc for $C_7H_{11}NO_2Na$: 164.0790, found: 164.0688.

(2*E*,4*E*)-5-phenylpenta-2,4-dien-1-ol (198).[246]

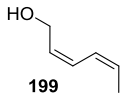


198

Acetate **204** (2.64g, 13 mmol) was disolved in anhydrous CH_2Cl_2 (60 ml) and the solution was cooled at -40ºC before DIBAL (33 ml, 33 mmol, 1M) was added drop wise. After one hour to stir at that temperature the solution was warmed at 0ºC and it was stirred 2h before the mixture was carefully pure into ice-water saturated Rochelle salt solution and the suspension was vigorously stirred for 2h. The phases were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were washed with brine and then dryed over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (8 Hexane: 2 AcOEt) to afford product **198** as a white solid in 56% yield. Collected experimental data are in agreement with the reported data.

^{1}H NMR (400 MHz, $CDCl_3$, δ in ppm): 7.39 (d, *J* = 7.4 Hz, 1H), 7.31 (t, *J* = 7.5 Hz, 1H), 7.22 (t, *J* = 7.3 Hz, 1H), 6.79 (dd, *J* = 15.6, 10.5 Hz, 1H), 6.55 (d, *J* = 15.7 Hz, 1H), 6.42 (dd, *J* = 15.2, 10.5 Hz, 1H), 5.96 (dt, *J* = 15.2, 5.9 Hz, 1H), 4.25 (d, *J* = 5.0 Hz, 1H), 1.36 (s, 1H). **^{13}C NMR** ($CDCl_3$, 100 MHz, δ in ppm): 137.3, 133.0, 132.7, 131.9, 128.8, 128.3, 127.8, 126.6, 63.7.

(2*Z*,4*Z*)-2,4-Hexadiene-1-ol (199).

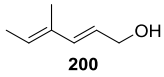


199

Compound **209** (600 mg, 1.6 mmol) was disolved in anhydrous THF (25 ml). The solution was cooled at 0ºC before TBAF (3.8 ml, 1.9 mmol, 1M) was added and the solution was heated to 40ºC for 3h. Then the solvent was removed under vaccum and the residue was directly purified by flash chromatography using 7:3 hexanes:ethyl acetate as eluent to afford a yellowish oil in 85% yield.[244]

FT-IR (ATR) ν in cm^{-1}: 3272, 3064, 2924, 1326, 1158, 1091 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): 6.39 (tq, 1H, *J* = 11.6, 1.2 Hz), 6.29-6.21 (m, 1H), 5.66-5.59 (m, 2H), 4.31 (d, 2H, *J* = 7.0 Hz), 1.72 (dd, 3H, *J* = 5.6, 1.6), 1.72 (1H, overlap). **^{13}C NMR** ($CDCl_3$, 100 MHz, δ in ppm): δ = 129.3, 128.7, 125.6, 123.9, 58.8, 13.3. **ESI-TOF** [M+Na] calc for $C_6H_{10}ONa$: 121.0629, found: 121.0600.

(2*E*,4*E*)-4-Methyl-2,4-hexadien-1-ol (200).[245]



200

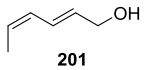
DIBAL solution in dichloromethane (77 ml, 77 mmol 1M) was slowly added dropwise to a solution of ester **212** (31 mmol) in dichloromethane at -40ºC. Then, the mixture was stirred at -20ºC until complete reaction of starting material by TLC (5 h). The mixture was carefully pure into ice-water saturated Rochelle salt solution and the suspension was vigorously stirred for 2h. The phases were separated and the aqueous phase was extracted with dichloromethane (2x30 ml). The combined organic layers

[244] Suzuki, D.; Nobe, Y.; Watai, Y.; Tanaka, R.; Takayama, Y.; Sato, F.; Urabe, H. *J. Am. Chem. Soc.* **2005**, *127*, 7474-7479.
[245] DeBoef, B.; Counts, W. R.; Gilbertson, S. R. *J. Org. Chem.* **2007**, *72*, 799-804.

were washed with brine and then they were dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by flash chromatography using 8:2 to 7:3 hexanes:ethyl acetate to afford a colorless oild (82%).

FT-IR (ATR) ν in cm^{-1}: 3399, 2979, 2934, 1171, 1671, 1456, 1375, 1074 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): 6.25 (d, 1H, *J* = 15.6 Hz), 5.70 (dt, 1H, *J* = 15.6, 6.3 Hz), 4.18 (d, 2H, *J* = 6.3 Hz), 1.74 (s, 3H), 1.69 (s, 3H), 1.32 (brs, 1H). **^{13}C NMR** ($CDCl_3$, 100 MHz, δ in ppm): 136.9, 134.0, 127.7, 124.9, 64.2, 14.0, 12.2. **ESI-TOF**[M+Na] calc for $C_7H_{12}ONa$: 135.0786, found 135.0740.

(2*E*,4*Z*)-2,4-Hexadiene-1-ol (201).[247]

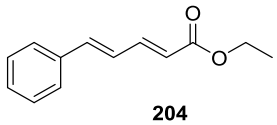


201

Enyne **207** (760 mg, 7.9 mmol) was added to a suspension of NaH (630 mg, 15.8 mmol, 60%) in THF (100 ml) at 0ºC. The suspension was stirred 2h at room temperature before $LiAlH_4$ (600 mg, 15.8 mmol) was added and it was stirred at 20 min at that temperature before it was refluxed for 10h. Then, the reaction was cooled at room temperature and H_2O was carefully added dropwise before the gas evolution ceased. The crude was extracted with ethyl acetate and the combined organic layers were dried over $MgSO_4$ and the solvent was removed under vacuum. The residue was purified by flash chromatography using hexanes:ethyl acetate 8:2 to afford the desired product (84%).

FT-IR (ATR) ν in cm^{-1}: 3330, 3028, 2971, 2912, 1438, 1399, 1139, 1075, 1005, 719 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): 6.57 (dd, 1H, *J* = 15.4, 10.0 Hz), 6.02 (td, 1H, *J* = 10.8, 1.8 Hz), 5.80 (dt, 1H, *J* = 15.4, 5.2 Hz), 5.53 (dq, 1H, *J* = 10.8, 7.2 Hz), 4.21 (d, 2H, *J* = 5.2 Hz), 1.76 (dd, 3H, *J* = 7.0, 1.8 Hz), 1.47 (brs, 1H). **^{13}C NMR** ($CDCl_3$, 100 MHz, δ in ppm): 131.6, 128.7, 127.3, 126.8, 63.8, 13.6. **ESI-TOF** [M+Na] calc for $C_7H_{12}ONa$: 121.0786, found: 121.0799.

Ethyl (2*E*,4*E*)-5-phenylpenta-2,4-dienoate (204)[246]

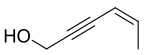


204

To a clean, dry 100 ml round bottom flask equipped with a stir bar was added (carbethoxymethylene) triphenylphosphorane **203** (5g, 14.35 mmol). The flask was seeded under Ar and CH_2Cl_2 (6 ml) was added to the flask while stirring at room temperature. Cinnamaldehyde (2.7 ml, 17.22 mmol) was added drop rise over 10 minutes and the flask was fitted under reflux condenser and placed in an oil bath at 60ºC and refluxed for 3 h. The flask was then removed from the oil bath and concentrated to half its original volume. To the flask was then added petroleum ether (7ml) and the solution was then filtered to remove the triphenylphosphine oxide. The solid was washed with additional petroleum ether, and the solution was once again concentrated. The residue was purified by column chromatography (Hexane 9: AcOEt 1) to afford product **204** as a colorless oil in 89% yield. Collected experimental data are in agreement with the reported data.

^{1}H NMR (400 MHz, $CDCl_3$, δ in ppm): 7.50 – 7.41 (m, 1H), 7.39 – 7.27 (m, 1H), 6.89 (s, 1H), 6.89 – 6.87 (m, 1H), 5.99 (d, *J* = 15.3 Hz, 1H), 4.23 (q, *J* = 7.1 Hz, 1H), 1.32 (t, *J* = 7.1 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 100 MHz, δ in ppm): 167.1, 144.7, 140.5, 136.0, 129.2, 127.6, 126.3, 121.6, 60.6, 14.6.

(*Z*)-Hex-4-en-2-yn-1-ol (207).[247]



207

$PdCl_2(PPh_3)_2$ (300 mg, 0.42 mmol) was dissolved in freshly distilled piperidine (40 ml) and THF (40 ml) and *Z*-bromopropene (2 ml, 23.5 mmol) was added. The solution was stirred at room temperature for 30 minutes and then, propargyl alcohol (1.23 ml, 21.4 mmol) and CuI (164.7 mg, 0.86 mmol) were added. The yellow solution was stirred at room temperature for 10 h. The crude was diluted with diethyl

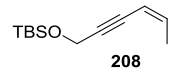
[246] a) Kim, D. D.; Lee, S. J.; Beak, P. *J. Org. Chem.*, **2005**, *70*, 5376-5386. b) Drew, J.; Letellier, M.; Morand, P.; Szabo, A. G. *J. Org. Chem.* **1987**, *52*, 4047-4052.

[247] Egger, M.; Pellet, P.; Nickl, K.; Geiger, S.; Graetz, S.; Seifert, R.; Heilmann, J.; Köing *Chem. Eur. J.* **2008**, *14*, 10978-10984.

ether (50 ml) and water (20 ml). The layers were separated and the aqueous phase was extracted with diethyl ether (2x 20 ml). The combined organic layers were washed with 10% HCl aqueous solution (20 ml), saturated $NaHCO_3$ solution (20 ml) and brine. Then, it was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by flash chromatography using hexanes:AcOEt (9:1 to 8:2) to afford product **207** as a beige oil in a 68% yield.

FT-IR (ATR) ν in cm^{-1}: 3336, 3029, 2915, 2856, 1438, 1399, 1362, 1139, 1075, 1006, 924, 719 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): 5.98 (dq, 1H, *J* = 10.6, 6.8 Hz), 5.48 (dq, 1H, *J* = 10.6, 2.0 Hz), 4.40 (s, 2H), 2.21 (brs, 1H), 1.85 (d, 3H, *J* = 6.8 Hz). **^{13}C NMR** ($CDCl_3$, 100 MHz, δ in ppm): 139.4, 109.5, 91.9, 82.4, 51.7, 16.1. **ESI-TOF** [M+H] calc for C_6H_9O: 97.0653, found: 97.0659.

(*E*)-1-(Dimethyl-tertbutylsilyloxy)-2hex-2-yn-4-ene (208). [248]



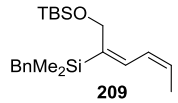
208

Alcohol **207** (10 mmol) was dissolved in dichloromethane (50 ml) and *tert*-butyldimethylsilyl chloride (1.6 g, 11 mmol), triethylamine (3 ml, 22 mmol) and DMAP (10%) were successively added. The mixture was stirred at room temperature overnight. The crude was quenched with saturated NH_4Cl aqueous solution and the aqueous phase was extracted with dichloromethane. The combined organic layers were dried over anhydrous $MgSO_4$ and then, the solvent was removed under vacuum. The residue was purified by flash chromatography using hexanes as a solvent (97%).

^{1}H NMR (400 MHz, $CDCl_3$, δ in ppm): 5.97 (dq, 1H, *J* = 10.6, 6.8 Hz), 5.49 (dq, 1H, *J* = 10.6, 1.6 Hz), 4.47 (s, 2H), 1.86 (d, 3H, *J* = 6.8 Hz). 0.91 (s, 12H), 0.14 (s, 3H), 0.13 (s, 3H). **^{13}C NMR** ($CDCl_3$, 100 MHz, δ in ppm): δ = 138.8, 109.9, 52.5, 26.1, 25.9, 18.6, 16.1, -4.9.

[248] Kluge, A. F.; Kertesz, D. J.; O-Yang, C.; Wu, H. Y. *J. Org. Chem.* **1987**, *52*, 2860-2868.

Benzyl((2*E*,4*Z*)-1-tert-butyldimethylsilyl)oxy)hexa-2,4-dien-1-yl)dimethylsilane (209)[249].

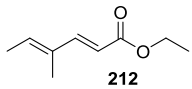


209

To a solution of alkyne **208** (1.4 g, 6.4 mmol) and benzyldimethylsilane (1.2 ml, 7.7 mmol) was added $PtCl_2$ (0.16 g, 0.6 mmol) and the solution was stirred overnight at 25ºC. The solvent was removed under vacuum and the residue was purified by flash chromatography using hexanes as a solvent to afford **209** as a clear oil in 75% yield.

FT-IR (ATR) ν in cm^{-1}: 3029, 2054, 2929, 2895, 1363, 1254, 1141, 1086, 1067, 834, 776 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): 7.21 (t, 2H, *J* = 7.6 Hz), 7.07 (t, 1H, *J* = 7.6 Hz), 7.01 (d, 2H, *J* = 7.6 Hz), 5.87 (m, 2H), 5.55 (dq, 1H, *J* = 11.2, 6.8 Hz), 4.14 (d, 2H, *J* = 5.6 Hz), 2.17 (s, 2H), 1.47 (dd, 3H, *J* = 6.4, 1.2 Hz), 0.92 (s, 9H), 0.06 (s, 6H), 0.05 (s, 6H). **^{13}C NMR** (100MHz, $CDCl_3$, δ in ppm): 140.5, 140.1, 138.1, 128.7, 128.5, 128.3, 125.5, 124.2, 62.4, 26.2, 25.1, 18.6, 14.5, -3.8, -4.8. **ESI-TOF** [M+Na] calc for $C_{21}H_{36}OSi_2Na$: 383.2212, found 383.2154.

Ethyl (2*E*,4*E*)-4-Methylhexa-2,4-dienoate (212).[245]


212

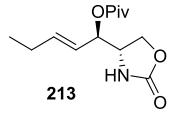
Triethyl phosphonoacetate (16.5 ml, 100 mmol) was added dropwise over a suspensión of NaH (3.1 g, 77 mmol, 65%) in benzene (75 ml) at 0ºC, then the mixture was warmed at room temperature and it was stirred for 1h before *E*-2-methyl-2-butenal (5.7 ml, 60 mmol) was added dropwise over 30 minutes. Then, the mixture was heated at 60ºC for 30 minutes. Ice water (50 ml) was carefully added at 0ºC and the layers were separated. The aqueous phase was extracted with hexanes (3x25 ml) and the combined organic layers were washed with brine and then they were dried over anhydrous $MgSO_4$. The pure unsaturated ester (**212**) was recovered in a quantitative yield as a yellowish liquid.

FT-IR (ATR) ν in cm^{-1}: 2989, 2952, 2955, 1712, 1621, 1300, 1259, 1165, 1038 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): 7.31 (d, 1H, *J* = 15.6 Hz), 5.98 (q, 1H, *J* =

[249] Rooke, D. A.; Ferreira, E. M. *Angew. Chem. Int. Ed.* **2012**, *51*, 3225-3230.

7.2 Hz), 5.78 (d, 1H, *J* = 15.6 Hz), 4.20 (q, 2H, *J* = 6.8 Hz), 1.81 (d, 3H, *J* = 7.2 Hz), 1.77 (s, 3H), 1.28 (t, 3H, *J* = 6.8 Hz). **^{13}C NMR** ($CDCl_3$, 100 MHz, δ in ppm): 167.9, 149.7, 136.5, 133.9, 128.5, 115.6, 60.3, 14.8, 14.6, 12.0. **ESI-TOF** [M+Na] calc for $C_9H_{14}O_2Na$: 177.0891, found: 200.0888.

(*S*/*R*)-4-(((*R*/*S*),*E*)-1-Pivaloyloxypent-2-en-1-yl)-oxazolidin-2-one (213).

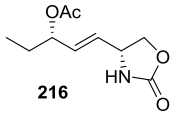


213

Compound **213** was synthesised from carbamate **192** according to general procedure A. Starting from 16 mg (0.1 mmol) of carbamate **192**, products **213** and **214** (19 mg, 72%) were obtained as a 86:14 mixture of regioisomers. The mixture was further purified by column chromatography using 10% ethyl acetate-hexanes to 30% ethyl acetate–hexanes as the eluent for characterisation purposes. The title compound **213** was isolated as colorless oil.

FT-IR (ATR) ν in cm^{-1}: 3289, 2967, 2933, 2873, 1756, 1733, 1480, 1398, 1279, 1229, 1031, 970. **^{1}H NMR** (400 MHz,$CDCl_3$, δ in ppm): 5.91 (dt, 1H, *J* = 14.4, 10.4 Hz), 5.38 (brs, 1H), 5.36-5.26 (m, 2H), 4.42 (t, 1H, *J* = 8.8 Hz), 4.27 (dd, 1H, *J* = 8.8, 4.8 Hz), 3.99 (m, 1H), 2.09 (q, 2H, *J* = 7.6 Hz), 1.21 (s, 9H), 0.99 (t, 3H, *J* = 7.6 Hz). **^{13}C NMR** (100MHz, $CDCl_3$, δ in ppm): 177.5, 158.9, 139.7, 121.3, 73.7, 65.8, 54.7, 39.0, 27.0, 25.4, 13.0. **ESI-TOF** [M+23] calc for $C_{13}H_{21}NO_4Na$: 278.1471, found: 278.1384.

(*R*/*S*)-4-(((*S*/*R*),*E*)-3-Acetoxypent-1-en-1-yl)-oxazolidin-2-one (216).



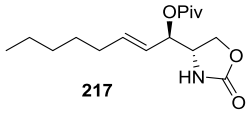
216

Compound **216** was synthesised from carbamate **192** according to general procedure B. Starting from 16 mg (0.1 mmol) of carbamate **192**, products **215** and **216** (14 mg, 65%) were obtained as a 10:90 mixture. A small fraction was further purified by column chromatography using 10% ethyl acetate-hexanes to 30% ethyl

acetate–hexanes as the eluent for characterisation purposes. The title compound **216** was isolated as colorless oil.

FT-IR (ATR) ν in cm^{-1}: 3305, 2968, 2928, 1735, 1588, 1423, 1372, 1238, 1024, 968. **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): 5.72 (dd, 1H, *J* = 15.6, 5.6 Hz), 5.67 (dd, 1H, *J* = 15.6, 6.0 Hz), 5.25 (brs, 1H), 5.18 (m, 1H), 4.55 (t, 1H, *J* = 8.8 Hz), 4.40 (m, 1H), 4.06 (dd, 1H, *J* = 8.8, 6.4 Hz), 2.08 (s, 3H), 1.63 (m, 2H), 0.89 (t, 3H, *J* = 7.2 Hz). **^{13}C NMR** (100MHz, $CDCl_3$, δ in ppm): 170.4, 159.4, 132.9, 74.3, 70.2, 54.3, 27.3, 21.3, 9.5. **ESI-TOF** [M+23] calc for $C_{10}H_{15}NO_4Na$: 236.1001, found: 236.0907.

(*S*/*R*)-4-(((*R*/*S*),*E*)-1-Pivaloyloxyoct-2-en-1-yl)-oxazolidin-2-one (217).

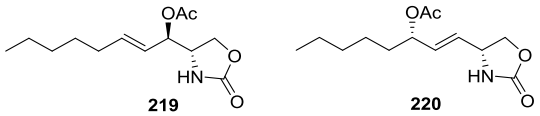


217

Compound **217** was synthesised from carbamate **193** according to general procedure A. Starting from 20 mg (0.1 mmol) of carbamate **193**, products **217** and **218** (21 mg, 71%) was obtained as a 91:9 mixture of regioisomers. The mixture was further purified by column chromatography using 10% ethyl acetate-hexanes to 30% ethyl acetate–hexanes as the eluent for characterisation purposes. The title compound **217** was isolated as colorless oil.

FT-IR (ATR) ν in cm^{-1}: 3273, 2958, 2928, 2857, 1757, 1732, 1480, 1399, 1279, 1231, 1152, 1034. **^{1}H NMR** (400 MHz,$CDCl_3$, δ in ppm): 5.86 (dt, 1H, *J* = 15.6, 7.2 Hz), 5.36-5.24 (m, 3H), 4.42 (t, 1H, *J* = 8.8 Hz), 4.27 (dd, 1H, *J* = 8.8, 5.2 Hz), 3.99 (m, 1H), 2.05 (q, 2H, *J* = 7.2 Hz), 1.44-1.09 (m, 16H), 0.88 (t, 3H, *J* = 5.6 Hz). **^{13}C NMR** (100MHz, $CDCl_3$, δ in ppm): 177.7, 159.2, 138.7, 122.4, 73.9, 66.0, 54.9, 39.2, 32.5, 31.5, 28.6, 27.3, 22.6, 14.2. **ESI-TOF** [M+23] calc for $C_{16}H_{27}NO_4Na$: 320.1940, found: 320.1839.

(*S*/*R*)-4-(((*R*/*S*),*E*)-1-Acetoxyoct-2-en-1-yl)-oxazolidin-2-one (219) and (*R*/*S*)-4-(((*S*/*R*),*E*)-3-Acetoxyoct-1-en-1-yl)-oxazolidin-2-one (220).

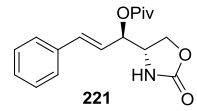


Compounds **219** and **220** have been synthesised from carbamate **193** according to the general procedure B. Starting from 20 mg (0.1 mmol) of carbamate **193**, products **219** and **220** (20 mg, 76 %) were obtained as a 13:87 mixture of regioisomers. Purification of the tittle products was accomplished by means of column chromatography employing hexanes 10% ethyl acetate-hexanes to 30% ethyl acetate–hexanes as the eluent **219** and **220** were isolated as colorless oils.

219 (minor): FT-IR (ATR) ν in cm^{-1}: 3306, 2956, 2924, 2853, 1766, 1403, 1243, 1028 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): 5.90 (dt, 1H, *J* = 15.6, 6.8 Hz), 5.27 (dd, 1H, *J* = 15.6, 6.8 Hz), 5.21-5.08 (m, 2H), 4.42 (t, 1H, *J* = 8.8 Hz), 4.17 (dd, 1H, *J* = 8.8, 4.8 Hz), 3.95 (m, 1H), 2.09 (s, 3H), 2.06 (q, 2H, *J* = 6.4 Hz), 1.42-1.19 (m, 6H), 0.88 (t, 3H, *J* = 6.8 Hz). **ESI-TOF** [M+23] calc for $C_{13}H_{21}NO_4Na$: 278.1451, found: 278.1375.

220 (major): FT-IR (ATR) ν in cm^{-1}: 3298, 2929, 2856, 2361, 2342, 1741, 1466, 1399, 1370, 1237, 1021, 971. **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): 5.71 (dd, 1H, *J* = 15.6, 5.6 Hz), 5.66 (dd, 1H, *J* = 15.6, 6.4 Hz), 5.23 (m, 1H), 5.08 (brs, 1H), 4.54 (t, 1H, *J* = 8.8 Hz), 4.38 (m, 1H), 4.04 (dd, 1H, *J* = 8.8, 6.4 Hz), 2.07 (s, 3H), 1.37-1.21 (m, 8H), 0.88 (t, 3H, *J* = 6.4 Hz). **^{13}C NMR** (100MHz, $CDCl_3$, δ in ppm): 170.3, 154.3, 133.2, 129.3, 70.0, 65.2, 54.1, 34.1, 31.4, 24.7, 22.5, 21.2, 14.0. **ESI-TOF** [M+23] calc for $C_{13}H_{21}NO_4Na$: 278.1451, found: 278.1364.

(*S*/*R*)-4-(((*R*/*S*),*E*)-1-Pivaloyloxy-3-phenylprop-2-en-1-yl)-oxazolidin-2-one (221).

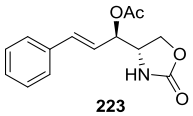


221

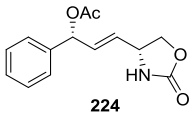
Compound **221** was synthesised from carbamate **194** according to general procedure A. Starting from 19 mg (0.1 mmol) of carbamate **194**, product **221** and **222** (16 mg, 54%) were obtained as a 70:30 mixture of regioisomers. The mixture was further purified by column chromatography using 10% ethyl acetate-hexanes to 20% ethyl acetate–hexanes as the eluent for characterisation purposes. The title compound **221** was isolated as colorless oil.

FT-IR (ATR) ν in cm^{-1}: 3270, 3060, 3026, 2973, 2933, 2873, 1753, 1725, 1586, 1480, 1398, 1276, 1144, 1065, 1033, 968. **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): 7.41-7.25 (m, 5H), 6.74 (d, 1H, *J* = 16.0 Hz), 6.02 (dd, 1H, *J* = 16.0, 7.2 Hz), 5.67 (brs, 1H), 5.41 (m, 1H), 4.41 (t, 1H, *J* = 8.8 Hz), 4.23 (dd, 1H, *J* = 8.8, 4.4 Hz), 4.1 (m, 1H), 1.25 (s, 9H). **^{13}C NMR** (100MHz, $CDCl_3$, δ in ppm): 177.5, 159.0, 135.9, 135.4, 129.0, 127.0, 121.7, 74.9, 66.7, 54.9, 39.3, 27.3. **ESI-TOF** [M+23] calc for $C_{17}H_{21}NO_4Na$: 326.1471, found: 326.1369.

(*S*/*R*)-4-(((*R*/*S*),*E*)-1-Acetoxy-3-phenylprop-2-en-1-yl)-oxazolidin-2-one (223) and (*R*/*S*)-4-(((*S*/*R*),*E*)-3,3'-Acetoxyphenylprop-1-en-1-yl)-oxazolidin-2-one (224).



223



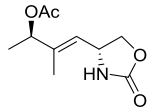
224

Compounds **223** and **224** were obtained from carbamate **194** according to general procedure B. Starting from 19 mg (0.1 mmol) of carbamate **194**, products **223** and **224** (16 mg, 60%) were obtained as a 28:72 mixture of regioisomers. Unfortunately all attempts to separate the regioisomeric mixture resulted in no success. Therefore the spectroscopic data was obtained from the mixture.

223: ^{1}H NMR (400 MHz,$CDCl_3$, δ in ppm): 7.42-7.27 (m, 5H), 6.76 (d, 1H, *J* = 15.6 Hz), 6.00 (dd, 1H, *J* = 15.6, 7.6 Hz), 4.46 (t, 1H, *J* = 9.2 Hz), 4.23 (dd, 1H, *J* = 9.2, 4.8 Hz), 4.14-4.09 (m, 1H), 2.14 (s, 3H).

224: ^{1}H NMR (400 MHz,$CDCl_3$, δ in ppm): 7.42-7.27 (m, 5H), 6.25 (d, 1H, *J* = 5.6 Hz), 5.93 (dd, 1H, *J* = 15.2, 5.6 Hz), 5.71 (dd, 1H, *J* = 15.2, 6.4 Hz), 5.39 (brs, 1H), 5.52 (t, 1H, *J* = 8.4 Hz), 4.40 (m, 1H), 4.05 (dd, 1H, *J* = 8.4, 6.4 Hz), 2.12 (s, 3H).

(*R*/*S*)-4-(((*S*/*R*),*E*)-3-Acetoxy-2-methylprop-1-en-1-yl)-oxazolidin-2-one (226).

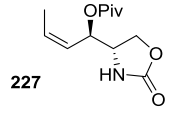


226

Compound **226** was synthesised from carbamate **195** according to general procedure B. Starting from 16 mg (0.1 mmol) of carbamate **195**, products **225** and **226 (**14 mg, 68%) were obtained as a 10:90 mixture. A small fraction was further purified by column chromatography using 10% ethyl acetate-hexanes to 40% ethyl acetate–hexanes as the eluent for characterisation purposes. The title compound **226** was isolated as colorless oil.

FT-IR (ATR) ν in cm^{-1}: 3309, 2981, 2929, 1732, 1675, 1370, 1239, 1075, 1023, 944, 768. **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): 5.48 (d, 1H, *J* = 8.8 Hz), 5.21 (q, 1H, *J* = 6.6 Hz), 5.10 (brs, 1H), 4.68 (m, 1H), 4.53 (t, 1H, *J* = 8.4 Hz), 3.98 (dd, 1H, *J* = 8.4, 6.8 Hz), 2.07 (s, 3H), 1.70 (d, 3H, *J* = 1.6 Hz), 1.30 (d, 3H, *J* = 6.6 Hz). **^{13}C NMR** (100MHz, $CDCl_3$, δ in ppm): 170.3, 159.3, 141.0, 123.9, 73.8, 70.4, 50.2, 21.5, 19.3, 13.2. **ESI-TOF** [M+23] calc for $C_{10}H_{15}NO_4Na$: 236.1001, found: 236.0909.

(*S*/*R*)-4-(((*R*/*S*),*Z*)-1-Pivaloyloxybut-2-en-1-yl)-oxazolidin-2-one (227).



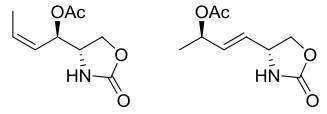
227

Compound **227** was synthesised from carbamate **196** according to the general procedure A. Starting from 14 mg (0.1 mmol) of carbamate **196**, products **227** and **228** (13 mg, 56%) were obtained as a 90:10 mixture. The reaction mixture was not separable and the spectroscopic data were extracted from the spectrum of the mixture.

^{1}H NMR (400 MHz, $CDCl_3$, δ in ppm): 5.88 (dq, 1H, *J* = 10.4, 7.2 Hz), 5.52 (dd, 1H, *J* = 9.2, 4.8 Hz), 5.23 (dd, 1H, *J* = 10.4, 9.2 Hz), 4.97 (brs, 1H), 4.40 (t, 1H, *J* = 8.8

Hz), 4.19 (dd, 1H, *J* = 8.8, 5.2 Hz), 3.96-3.89 (m, 1H), 1.72 (d, 3H, *J* = 7.2 Hz), 1.20 (s, 9H).

(*S*/*R*)-4-(((*R*/*S*),*Z*)-1-Acetyloxybut-2-en-1-yl)-oxazolidin-2-one (229) and (*R*/*S*)-4-(((*R*/*S*),*E*)-3-Acetyloxy-but-1-en-1-yl)-oxazolidin-2-one (230).



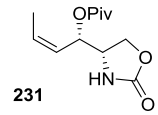
229 **230**

Compounds **229** and **230** have been synthesised from carbamate **196** according to the general procedure B. Starting from 14 mg (0.1 mmol) of carbamate **196**, products **229** and **230** (13 mg, 64%) were obtained as a 39:61 mixture. Purification of the title products was accomplished by means of column chromatography employing hexanes 10% ethyl acetate-hexanes to 40% ethyl acetate–hexanes as the eluent. Compounds **229** and **230** were isolated as colorless oils.

229: FT-IR (ATR) ν in cm^{-1}: 3269, 2961, 2922, 1756, 1735, 1482, 1407, 1371, 1227, 1034, 968. **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): 5.88 (dqd, 1H, *J* = 10.8, 6.8, 0.8 Hz), 5.56 (brs, 1H), 5.49 (ddd, 1H, *J* = 9.6, 7.2, 0.8 Hz), 5.21 (ddq, 1H, *J* = 10.8, 9.6, 2.0 Hz), 4.41 (t, 1H, *J* = 9.0 Hz), 4.10 (dd, 1H, *J* = 9.0, 4.8 Hz), 3.96 (m, 1H), 2.08 (s, 3H), 1.82 (dd, 3H, *J* = 6.8, 2.0 Hz). **^{13}C NMR** (100MHz, $CDCl_3$, δ in ppm): 170.0, 159.1, 133.7, 123.3, 71.5, 66.4, 54.9, 21.2, 14.2. **ESI-TOF** [M+23] calc for CH_9NO_4Na: 222.0845, found: 222.0753.

230: FT-IR (ATR) ν in cm^{-1}: **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): 5.76 (dd, 1H, *J* = 15.6, 5.2 Hz), 5.67 (dd, 1H, *J* = 15.6, 7.2 Hz), 5.35 (m, 1H), 5.34 (brs, 1H), 4.54 (t, 1H, *J* = 8.8 Hz), 4.39 (m, 1H), 4.07 (dd, 1H, *J* = 8.8, 6.8 Hz), 2.06 (s, 3H), 1.31 (d, 3H, *J* = 6.8 Hz). **^{13}C NMR** (100MHz, $CDCl_3$, δ in ppm): δ = 170.4, 159.2, 134.4, 129.1, 70.2, 69.6, 54.4, 21.5, 20.2. **ESI-TOF** [M+23] calc for CH_9NO_4Na: 222.0845, found: 222.0712.

(*S*/*R*)-4-(((*S*/*R*),*Z*)-1-Pivaloyloxybut-2-en-1-yl)-oxazolidin-2-one (231).

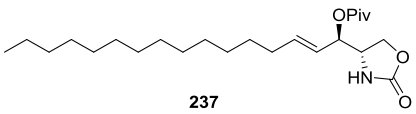


231

Compound **231** was synthesised from carbamate **197** according to the general procedure A. Starting from 14 mg (0.1 mmol) of carbamate **197**, products **231** and **174** (18 mg, 74%) were obtained as a >90:<10 mixture. The mixture was further purified by column chromatography using 10% ethyl acetate-hexanes to 20% ethyl acetate–hexanes as the eluent for characterisation purposes. The title compound **231** was isolated as colorless oil.

FT-IR (ATR) ν in cm^{-1}: 3274, 2962, 2916, 2849, 1757, 1728, 1480, 1398, 1281, 1152, 1036, 937 cm^{-1}. **^{1}H NMR** (400 MHz,$CDCl_3$, δ in ppm): 5.87 (dq, 1H, *J* = 10.8, 7.2 Hz), 5.46 (dd, 1H, *J* = 9.6, 6.8 Hz), 5.30 (brs, 1H), 5.21 (ddd, 1H, *J* = 10.8, 9.6, 1.6 Hz), 4.43 (t, 1H, *J* = 8.8 Hz), 4.11 (dd, 1H, *J* = 8.8, 4.8 Hz), 3.38 (m, 1H), 1.82 (dd, 3H, *J* = 7.2, 1.6 Hz), 1.21 (s, 9H). **^{13}C NMR** (100MHz, $CDCl_3$, δ in ppm): 177.6, 159.0, 133.4, 123.4, 66.5, 64.9, 55.0, 39.1, 27.3, 14.2. **ESI-TOF** [M+23] calc for $C_{12}H_{19}NO_4Na$: 264.1314, found: 264.1207.

(*S*/*R*)-4-(((*R*/*S*),*E*)-1-Pivaloyloxyhexadeca-2-en-1-yl)-oxazolidin-2-one (237).



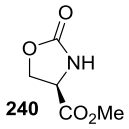
237

Compound **237** was synthesised from carbamate **169** according to general procedure A. Starting from 31 mg (0.1 mmol) of carbamate **169**, product **237** (32 mg, 79%) of the product were obtained as a >98:<2 mixture. It was further purified by column chromatography using 10% ethyl acetate-hexanes to 20% ethyl acetate–hexanes as the eluent for characterisation purposes. The title compound **237** was isolated as colorless oil.

FT-IR (ATR) ν in cm^{-1}: 3277, 2956, 2923, 2853, 1760, 1732, 1480, 1398, 1279, 1149, 1034 cm^{-1}. **^{1}H NMR** (400 MHz,$CDCl_3$, δ in ppm): 5.87 (dt, 1H, *J* = 14.4, 6.8 Hz), 5.30 (m, 2H), 5.02 (brs, 1H), 4.42 (t, 1H, *J* = 8.8 Hz), 4.27 (dd, 1H, *J* = 8.8, 5.2

Hz), 3.99 (m, 1H), 2.05 (q, 2H, *J* = 6.8 Hz), 1.35 (m, 2H), 1.25 (brs, 20H), 1.21 (s, 9H), 0.88 (t, 3H, *J* = 7.2 Hz). **^{13}C NMR** (100MHz, $CDCl_3$, δ in ppm): 177.7, 159.0, 138.8, 122.3, 73.9, 66.0, 58.9, 54.8, 41.6, 39.2, 37.7, 32.6, 32.1, 29.9, 29.9, 29.9, 29.8, 29.6, 29.6, 29.3, 29.0, 28.4, 27.3, 22.9, 20.6, 14.4. **ESI-TOF** [M+23] calc for $C_{24}H_{43}NO_4Na$: 432. 3192, found: 432.3098.

Methyl (4*S*)-2-oxo-1,3-oxazolidine-4-carboxylate (240).



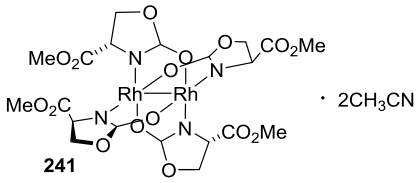
240

The oxazolidone was synthesised according to literature procedure.[250] Triethylamine (13.4 ml, 96.3 mmol) was added at 0ºC to a stirred suspension of serine methyl ester hydrochloride (5.0 g, 32.1 mmol) in dichloromethane (75 ml). The reaction mixture was stirred for 10 min before a solution of triphosgene (3.2 g, 10.9 mmol) in dichloromethane was added dropwise over 2h with the aid of a syringe pump. The reaction was stirred for additional 30 min, diluted with diethyl ether (75 ml) and cooled to -78ºC to precipitate all the Et_2NH_2Cl salts. The mixture was filtrered and then concentrated to approx. 15 ml when it was applied carefully to a 2.5 cm depth column of silica (prepacked with ethyl acetate) in a 100 ml sinter funnel. The solution was washed through the column with ethyl acetate (400 ml) and the filtrate was concentrated to give **240** as a white solid (3.75 g, 81%).

^{1}HMR (400 MHz, $CDCl_3$, δ in ppm): 6.40 (brs, 1H), 4.61 (t, 1H, *J* = 9.2 Hz), 4.52 (dd, 1H, *J* = 9.2, 4.6 Hz), 4.4 (dd, 1H, *J* = 9.2, 4.6 Hz). **^{13}C NMR** ($CDCl_3$, 100 MHz, δ in ppm): 170.5, 159.0, 66.7, 53.7, 53.1.

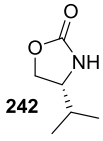
[250] Fürstner, A.; Kirk, D.; Fenster, M. D. B.; Aïssa, C.; De Souza, D.; Nevado, C.; Tuttle, T.; Thiel, W.; Müller, O. *Chem. Eur. J.* **2007**, *13*, 135-149.

Rh_2(4*S*-MEOX)$_4$(CH_3CN)$_2$ (241).



Rh_2(4*S*-MEOX)$_4$(CH_3CN)$_2$ (**241**) was prepared adapting the procedure described by Doyle *et al.*[251] A mixture of $Rh_2(OAc)_4$ (87 mg, 0.196 mmol) and oxazolidone **240** (235 mg, 1.62 mmol) were added under argon in a flame dried round bottom flask fitted with a Soxhlet extractor apparatus. To the mixture was added 12 ml of dry chorobenzene and the thimble in the Soxhlet body was charged with 5g of an overdried mixture of two parts Na_2CO_3 and one part of sand and filled with 15 ml of dry chorobenzene. Then the solution in the round bottom flask was heated at reflux for 8 h under argon. The resulting blue solution was cooled and the solvent was removed under reduced pressure to leave a purple solid. Methanol (1 ml) was added to the residue; the solid was filtered and washed with cold methanol (3x1.5 ml) and pentane. Recrystallization from anhydrous acetonitrile provided 80 mg (47%) of an orange solid as the pure bisacetonitrile rhodium complex **241**. **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): 4.49-4.22 (m, 4H), 4.24 (dd, 1H, *J* = 8.0, 5.2 Hz), 4.09 (dd, 1H, *J* = 8.8, 4.0 Hz), 3.78 (s, 3H), 3.71 (s, 3H), 2.29 (s, CH_3CN).

(*S*)-4-Isopropyloxazolidin-2-one (242).

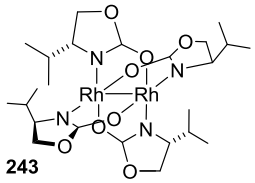


The oxazolidone was synthesised according to literature procedure.[253] To a 100 ml one-neck round bottom flask, (*S*)-valinol (4.0g, 38.8 mmol), diethyl carbonate (20 ml, 160 mmol), K_2CO_3 (0.80 g, 5.82 mmol) and sodium ethoxide (50 mg, 0.7 mmol) were added under argon atmosphere. The mixture was heated at 129ºC for 8 hours and during this period, ethanol generated was removed from the system by

[251] Doyle, M.P.; Dyatkin, A. B.; Proropopova, M. N.; Yang, C. I.; Miertschin, C. S.; Winchester, W. R.; Simonsen, S. H.; Lynch, V.; Ghosh, R. *Trav. Chim. Pays-Bas* **1995**, *115*, 163-170.

distillation. Then, the reaction mixture was cooled down to room temperature and concentrated under vacuum. The residue was dissolved in EtOAc (50 ml) and the solution was washed with saturated NH_4Cl solution (30 ml). The aqueous phase was then further extracted with EtOH (3 x 40 ml), the combined organic phases were dried over anhydrous $MgSO_4$, and the solvent was evaporated under reduced pressure resulting in a impure orange solid. The product **242** was purified by crystallization using EtOAc and *n*-hexane to give a white solid (2.2 g, 51%). **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): 7.14 (brs, 1H), 4.40 (t, 1H, *J* = 8.9 Hz), 4.06 (t, 1H, *J* = 6.9 Hz), 3.58 (q, 1H, *J* = 7.4), 1.68 (m, 1H), 0.93 (d, 3H, *J* = 6.7 Hz), 0.86 (d, 3H, *J* = 6.7 Hz). **^{13}C NMR** ($CDCl_3$, 100 MHz, δ in ppm): δ = 161.0, 68.9, 58.6, 32.9, 18.2, 17.9.

Rh_2(4*R*-IPOX)$_4$ (243).

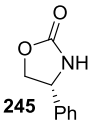


243

Rh_2(4*R*-IPOX)$_4$ (**243**) was prepared adapting the procedure described by Doyle *et al.*[252] A mixture of $Rh_2(OAc)_4$ (87 mg, 0.196 mmol) and oxazolidone **242** (300 mg, 2.32 mmol) were added under argon in a flame dried round bottom flask fitted with a Soxhlet extractor apparatus. To the mixture was added 15 ml of dry chorobenzene and the thimble in the Soxhlet body was charged with 5g of an overdried mixture of two parts Na_2CO_3 and one part of sand and filled with 17 ml of dry chorobenzene. Then the solution in the round bottom flask was heated at reflux for 72 h under argon. The resulting blue solution was cooled and the solvent was removed under reduced pressure to leave a purple solid. ^{1}H NMR spectra revealed the presence of complex **243** as the unique product in addition to a great excess of the ligand. Elimination of the ligand in excess was effectuated by means of column chromatography employing cyano-caped silica gel providing **243** in 63% yield.

[252] Doyle, M. P.; Winchester, W. R.; Hoorn, J. A. A.; Lynch, V.; Simonsen, S. H.; Ghosh, R. *J. Am. Chem. Soc.* **1993**, *115*, 9968-9978.

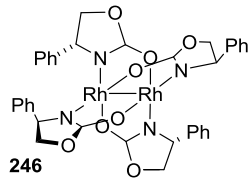
(*R*)-4-Phenyloxazolidin-2-one (245).



245

The oxazolidone was synthesised according to literature procedure.[253] To a twoneck round bottom flask, (*R*)-(+)-2-phenylglycinol (4.0g, 38.8 mmol), diethyl carbonate (20 ml, 160 mmol), K_2CO_3 (0.80 g, 5.82 mmol) and sodium ethoxide (50 mg, 0.7 mmol) were added under argon atmosphere. The mixture was heated at 129ºC for 8 hours and during this period, ethanol generated was removed from the system by distillation. Then, the reaction mixture was cooled down to room temperature and concentrated under vacuum. The residue was dissolved in EtOAc (50 ml) and the solution was washed with saturated NH_4Cl solution (30 ml). The aqueous phase was then further extracted with EtOH (3 x 40 ml), the combined organic phases were dried over anhydrous $MgSO_4$, and the solvent was evaporated under reduced pressure resulting in a impure orange solid. The product **245** was purified by crystallization using EtOAc and *n*-hexane to give a white solid (2.8 g, 59%). **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): 7.44-7.30 (m, 5H), 5.63 (brs, 1H), 4.96 (t, 1H, *J* = 7.8 Hz), 4.74 (t, 1H, *J* = 8.5 Hz), 4.20 (dd, 1H, *J* = 8.5, 7.8 Hz).

Rh_2(4*R*-PHOX)$_4$ (246).



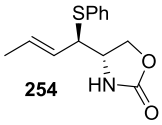
246

Rh_2(4*R*-PHOX)$_4$ (**246**) was prepared adapting the procedure described by Doyle *et al.*[254] A mixture of $Rh_2(OAc)_4$ (87 mg, 0.196 mmol) and oxazolidone **245** (321 mg, 1.96 mmol) were added under argon in a flame dried round bottom flask fitted with a Soxhlet extractor apparatus. To the mixture was added 15 ml of dry chorobenzene and the thimble in the Soxhlet body was charged with 5g of an overdried mixture of

[253] Lang, K.; J. Park, S. Hong. *J. Org. Chem.* **2010**, *75*, 6424-6435.
[254] Doyle, M. P.; Winchester, W. R.; Proropopova, M. N.; Müller, P.; Bernardinelli, D. E.; Motallebi. *Helv. Chim. Acta* **1993**, *76*, 2227-2235.

two parts Na_2CO_3 and one part of sand and filled with 15 ml of dry chorobenzene. Then the solution in the round bottom flask was heated at reflux for 24 h under argon. The resulting blue solution was cooled and the solvent was removed under reduced pressure to leave a purple solid. ^{1}H NMR spectra revealed the presence of complex **246** as the unique product in addition to a great excess of the ligand. Elimination of the ligand in excess was effectuated by means of column chromatography employing cyano-caped silica gel providing **246** in 51% yield.

(*S*/*R*)-4-(((*R*/*S*),*E*)-1-Phenylthiobut-2-en-1-yl)oxazolidin-2-one (254).

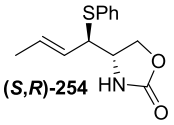


254

A flame dried Schlenk containing a magnetic stirring bar was charged with activated 4 Å MS (500 mg), then 14 ml of dichloromethane were added. After stirring 20 min., carbamate **141** (71 mg, 0.5 mmol) and PhIO (220 mg, 1.0 mmol) were added under argon and the reaction mixture was stirred at 35ºC untill all carbamate **141** was consumed. Then sodium thiophenolate (330 mg, 2.5 mmol) was added and the mixture was stirred overnight at room temperature. After being filtrate, the recovered homogeneous solution was dry loaded on silica gel and purified by flash chromatography (30% to 40% ethyl acetate-hexanes) providing thiophenol derivative **254** in 44% yield (55 mg) as a yellowish foam.

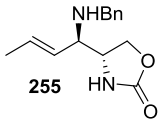
FT-IR (ATR) ν in cm^{-1}: 3278, 3055, 2965, 2916, 2854, 1747, 1582, 1475, 1438, 1403, 1304, 1231, 1067, 1024, 966, 937, 749, 691. **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): 7.44 – 7.36 (m, 2H), 7.34 – 7.28 (m, 3H), 5.56 (dq, *J* = 15.1, 6.5 Hz, 1H), 5.41-5.28 (m, 2H), 4.49 (t, *J* = 8.8 Hz, 1H), 4.31 (dd, *J* = 8.8, 5.3 Hz, 1H), 3.86 (td, *J* = 7.6, 5.3 Hz, 1H), 3.50 (dd, *J* = 8.8, 7.6 Hz, 1H), 1.68 (dd, *J* = 6.5, 1.1 Hz, 3H). **^{13}C NMR** (100MHz, $CDCl_3$, δ in ppm): 158.9, 134.2, 132.2, 132.0, 129.3, 128.5, 126.0, 68.6, 55.9, 54.6, 18.1. **ESI-TOF** [M+Na] calc for $C_{13}H_{15}NO_2SNa$: 272.0823, found: 272.0714.

(*S*)-4-((*R*,*E*)-1-Phenylthiobut-2-en-1-yl)oxazolidin-2-one ((*S*,*R*)-254).



Ozaxolidinone (***S,R*)-254** was synthesised from **254** according to the general method for the kinetic resolution of oxazolidinines. Starting from 20 mg (0.08 mmol) of **254**, **(*S,R*)-254** was recovered after 16 h in 53% yield (14 mg) and 86.8% ee after flash chromatography employing 40% ethyl acetate-hexanes as the eluent. **HPLC-MS** Chiralpak IA column (90:10 hexanes:ethanol, 1.0 ml/min); major enantiomer t_r = 6.77 min, minor enantiomer t_r = 8.09 min, 32.0% ee.

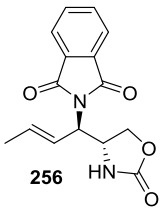
(*R*/*S*)-4-(((*R*/*S*),*E*)-1-Benzylaminobut-2-en-1-yl)oxazolidin-2-one (255).



A flame dried Schlenk containing a magnetic stirring bar was charged with activated 4 Å MS (1.5 g), then 75 ml of dichloromethane were added. After stirring 20 min., carbamate **141** (426 mg, 3 mmol) and PhIO (1.32 g, 6.0 mmol) were added under argon and the reaction mixture was stirred at 35ºC untill all carbamate **141** was consumed. Then benzylamine (1.7 ml, 15 mmol) was added and the mixture was stirred overnight at room temperature. After being filtrate, the recovered homogeneous solution was dry loaded on silica gel and purified by flash chromatography (50% ethyl acetate-hexanes to 100% ethyl acetate) providing benzylamine derivative **255** in 38% yield (300 mg) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$, δ in ppm): 7.40–7.24 (m, 1H), 6.26 (s, 1H), 5.71 (dq, *J* = 15.2, 6.5 Hz, 1H), 5.30–5.18 (m, 1H), 4.42 (t, *J* = 8.8, 1H), 4.27 (dd, *J* = 8.8, 5.9 Hz, 1H), 3.86 (d, *J* = 13.2 Hz, 1H), 3.74 (dt, *J* = 8.8, 5.9 Hz, 1H), 3.63 (d, *J* = 13.2 Hz, 1H), 2.96 (dd, *J* = 8.8, 6.4 Hz, 1H), 1.79 (dd, *J* = 6.5, 1.6 Hz, 1H). **ESI-TOF** [M+1] calc for $C_{12}H_{19}NO_4Na$: 284.1001, found: 284.0845.

(*R*/*S*)-4-(((*R*/*S*),*E*)-1-Phthalimidobut-2-en-1-yl)-oxazolidin-2-one (256).

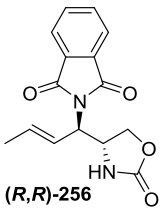


256

A flame dried Schlenk containing a magnetic stirring bar was charged with activated 4 Å MS (1.5 g), then 38 ml of dichloromethane were added. After stirring 20 min., carbamate **141** (213 mg, 1.5 mmol) and PhIO (660 mg, 3 mmol) were added under argon and the reaction mixture was stirred at 35ºC untill all carbamate **141** was consumed. Then potassium phtalimide (2.8 g, 15.0 mmol) was added and the mixture was stirred overnight at room temperature. After being filtrate, the recovered homogeneous solution was dry loaded on silica gel and purified by flash chromatography (50% ethyl acetate-hexanes) providing pure oxazolidinone pure **256** in 42% yield (180 mg) .

FT-IR (ATR) ν in cm^{-1}: 3304, 2357, 1744, 1120, 723 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): 7.70-7.43 (m, 4H), 5.85 (dq, 1H, *J* = 15.2, 6.8 Hz), 5.54 (brs, 1H), 5.43 (ddd, 1H, *J* = 15.2, 7.2, 1.2 Hz), 4.43 (t, 1H, *J* = 8.8 Hz), 4.32 (dd, 1H, *J* = 8.8, 4.8 Hz), 4.10 (t, 1H, *J* = 6.8 Hz), 3.83 (m, 1H), 1.73 (d, 3H, *J* = 6.8 Hz). **^{13}C NMR** (100MHz, $CDCl_3$, δ in ppm): 159.4, 132.1, 132.0, 128.6, 128.4, 128.2, 74.1, 66.8, 55.9, 17.9. **ESI-TOF** [M+Na] calc for $C_{15}H_{14}N_2O_4Na$: 309.0954, found: 309.0846.

(R)-4-((*R*,*E*)-1-Phthalimidobut-2-en-1-yl)oxazolidin-2-one ((*R*,*R*)-256)).

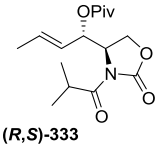


(*R*,*R*)-256

Ozaxolidinone (***R*,*R*)-256** was synthesised from **256** according to the general method for the kinetic resolution of oxazolidinines. Starting from 23 mg (0.08 mmol) of **256**, (***R*,*R*)-256** was recovered after 16 h in 54% yield (13 mg) and 97.2% ee after flash chromatography employing 20% to 30% ethyl acetate-hexanes as the eluent.

HPLC Chiralpak ODH column (80:20 hexanes:ethanol, 1.0 ml/min, 210 nm); major enantiomer t_r = 21.34 min, minor enantiomer t_r = 25.98 min, 97.2% ee.

(*R*)-4-((*S*,*E*)-1-(Pivaloyloxybut-2-en-1-yl)-3-isobutyryloxazolidin-2-one ((*R*,*S*)-333).

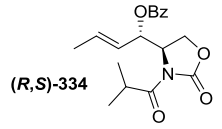


(*R*,*S*)-333

Acylated oxazolidinone **(*R*,*S*)-333** was synthesised from **173** according to the general method for the kinetic resolution of oxazolidinines. Preparative TLC was used to separate **(*R*,*S*)-333**) from unreacted **(*S*,*R*)-173**. Therefore the yield obtained was not taken into consideration.

FT-IR (ATR) ν in cm^{-1}: 2973, 2936, 2875, 1780, 1732, 1702, 1480, 1387, 1276, 1239, 1202, 1144, 1095. **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): 5.82 (ddq, 1H, *J* = 15.2, 6.8, 1.2 Hz), 5.75 (m, 1H), 5.34 (ddq, 1H, *J* = 15.2, 5.6, 1.6 Hz), 4.59 (ddd, 1H, *J* = 9.0, 2.8, 2.0 Hz), 4.45 (dd, 1H, *J* = 9.0, 2.8 Hz), 4.30 (t, 1H, *J* = 9.0 Hz), 4.67 (m, 1H), 1.73 (dt, 3H, *J* = 6.8, 1.2 Hz), 1.20 (s, 9H), 1.16 (d, 3H, *J* = 6.8 Hz), 1.15 (d, 3H, *J* = 6.8 Hz). **^{13}C NMR** (100MHz, $CDCl_3$, δ in ppm): 177.5, 177.2, 153.2, 131.2, 124.4, 70.9, 62.6, 56.5, 39.2, 32.7, 27.3, 19.5, 18.5, 18.2. **ESI-TOF** [M+Na] calc for $C_{16}H_{25}NO_5Na$: 334.1733, found: 334.1618. **HPLC** Chiralpak ID column (90:10 hexanes:isopropanol, 1.0 ml/min, 205 nm); major enantiomer t_r = 6.03 min, minor enantiomer t_r = 6.58 min, 88% ee.

(*R*)-4-((*S*,*E*)-1-(Benzyloxy)but-2-en-1-yl)-3-isobutyryloxazolidin-2-one ((*R*,*S*)-334).



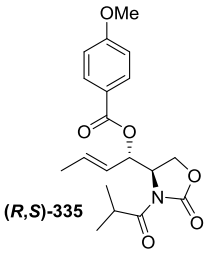
(*R*,*S*)-334

Benzoate **(*R*,*S*)-334** was synthesised from **179** according to the general method for the kinetic resolution of oxazolidinines. Starting from 26 mg (0.1 mmol) of **179**,

(*R*,*S*)-334 was recovered after 3.5 h in 33% yield and 97% ee after flash chromatography employing 30% ethyl acetate-hexanes as the eluent.

FT-IR (ATR) ν in cm^{-1}: 2964, 2922, 2854, 1780, 1724, 1701, 1451, 1387, 1265, 1239, 1200, 1096, 711. **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): 7.99 (dd, 2H, *J* = 8.2, 1.2 Hz), 7.58 (dt, 1H, *J* = 7.2, 1.2 Hz), 7.45 (dd, 2H, *J* = 8.2, 7.2 Hz), 6.00-5.89 (m, 2H), 5.46 (ddq, 1H, *J* = 15.6, 6.0, 1.6 Hz), 4.71 (ddd, 1H, *J* = 9.0, 3.2, 2.0 Hz), 4.62 (dd, 1H, *J* = 9.0, 2.8 Hz), 4.40 (t, 1H, *J* = 9.0 Hz), 3.67 (m, 1H), 1.75 (dt, 3H, *J* = 6.4, 1.2 Hz), 1.14 (d, 3H, *J* = 6.8 Hz), 1.08 (d, 3H, *J* = 6.8 Hz). **^{13}C NMR** (100MHz, $CDCl_3$, δ in ppm): 177.7, 165.5, 163.2, 133.7, 132.1, 129.8, 129.5, 128.8, 124.1, 72.2, 62.9, 56.5, 32.8, 19.5, 18.5, 18.2. **ESI-TOF** [M+Na] calc for $C_{18}H_{21}NO_5Na$: 354.1420, found: 354.1307. **HPLC** Chiralpak OD-H column (90:10 hexanes:isopropanol, 1.0 ml/min, 220 nm); major enantiomer t_r = 14.01 min, minor enantiomer t_r = 12.42 min, 97% ee.

(*R*)-4-((*S*,*E*)-1-(*p*-Methoxybenzoyloxybut-2-en-1-yl)-3-isobutyryloxazolidin-2-one ((*R*,*S*)-335).

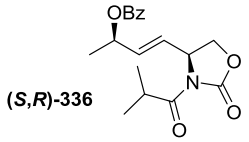


Acylated oxazolidinone **(*S*,*R*)-335** was synthesised from **(±)-181** according to the general method for the kinetic resolution of oxazolidinines. Preparative TLC was used to separate **(*S*,*R*)-335** from unreacted **(*R*,*S*)-181**. Therefore the yield obtained was not taken into consideration.

FT-IR (ATR) ν in cm^{-1}: 2965, 2932, 2874, 2849, 2361, 2339, 2329, 1780, 1717, 1606, 1510, 1387, 1257, 1202, 1168, 1098. **NMR** (400 MHz, $CDCl_3$, δ in ppm): 7.96 (d, 2H, *J* = 8.8 Hz), 6.92 (d, 2H, *J* = 8.8 Hz), 5.93 (m, 2H), 5.45 (ddq, 2H, *J* = 15.2, 6.0, 1.6 Hz), 4.70 (ddd, 1H, *J* = 8.8, 2.8, 2.4 Hz), 4.60 (dd, 1H, *J* = 8.8, 2.8 Hz), 4.38 (t, 1H, *J* = 8.8 Hz), 3.86 (s, 3H), 3.66 (m, 1H), 1.74 (dd, 3H, *J* = 6.0, 2.4 Hz), 1.13 (d, 3H, *J* = 5.8 Hz), 1.07 (d, 3H, *J* = 5.8 Hz). **^{13}C NMR** (100MHz, $CDCl_3$, δ in ppm):

177.6, 165.2, 163.9, 131.9, 124.3, 121.8, 114.1, 71.8, 62.9, 56.5, 55.7, 32.8, 27.3, 19.5, 18.4, 18.2. **ESI-TOF** [M+Na] calc for $C_{18}H_{21}NO_5Na$: 354.1420, found: 354.1307. **HPLC** Chiralpak IC column (80:20 hexanes:isopropanol, 1.0 ml/min, 220 nm); major enantiomer t_r = 12.79 min, minor enantiomer t_r = 10.20 min, 92% ee.

(*S*)-4-(((*R*),*E*)-3-Benzoyloxybut-1-en-1-yl)-3-isobutyryloxazolidin-2-one ((*S*,*R*)-336).

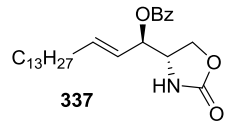


(*S*,*R*)-336

Acylated oxazolidinone **(*S*,*R*)-336** was synthesised from **180** according to the general method for the kinetic resolution of oxazolidinines. Preparative TLC was used to separate **(*S*,*R*)-336** from its unreacted **(*R*,*S*)-180**). Therefore the yield obtained was not taken into consideration.

NMR (400 MHz, $CDCl_3$, δ in ppm): 8.06 – 8.00 (m, 2H), 7.60 – 7.53 (m, 1H), 7.47 – 7.41 (m, 2H), 5.92 (ddd, *J* = 15.5, 5.5, 0.8 Hz, 1H), 5.77 (ddd, *J* = 15.5, 7.1, 1.3 Hz, 1H), 5.62 (m, 1H), 5.01 – 4.94 (m, 1H), 4.45 (t, *J* = 8.9 Hz, 1H), 4.16 – 4.09 (m, 1H), 3.73 (dt, *J* = 13.6, 6.8 Hz, 1H), 1.43 (d, *J* = 6.5 Hz, 3H).

(*R*/*S*)-4-(((*S*/*R*),*E*)-1-Benzoyloxyhexadeca-2-en-1-yl)-oxazolidin-2-one (337).



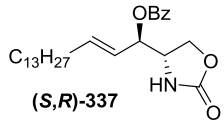
337

Compound **337** was synthesised from carbamate **169** according to general procedure A employing $PhI(OCOPh)_2$ instead of $PhI(OPiv)_2$ and Cs_2CO_3 instead od MgO as the base. Starting from 83 mg (0.27 mmol) of carbamate **169**, product **337** (79 mg, 69% yield) was obtained after short flash chromatography using 10% ethyl acetate – hexanes as the eluent.

FT-IR (ATR) ν in cm^{-1}: 2921, 2851, 1755, 1720, 1601, 1451, 1407, 1314, 1264, 1177, 1109, 1069, 1025, 970, 936, 765, 709, 666, 616. **^{1}H NMR** (400 MHz, $CDCl_3$,

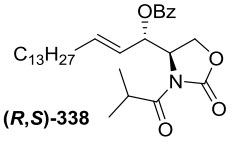
δ in ppm): 8.03 (d, *J* = 8.1 Hz, 2H), 7.57 (dd, *J* = 10.6, 4.2 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 2H), 6.01 (brs, 1H), 5.96 (dt, *J* = 13.9, 6.8 Hz, 1H), 5.53 – 5.36 (m, 2H), 4.48 (t, *J* = 8.9 Hz, 1H), 4.35 (dd, *J* = 9.0, 4.8 Hz, 1H), 4.15-4.06 (m, 1H), 2.06 (dd, *J* = 14.3, 6.9 Hz, 2H), 1.43 – 1.13 (m, 23H), 0.87 (t, *J* = 6.8 Hz, 3H). **^{13}C NMR** (100MHz, $CDCl_3$, δ in ppm): 165.6, 159.6, 139.5, 133.5, 129.8, 129.6, 128.7, 122.0, 75.4, 66.3, 54.9, 32.6, 32.1, 29.8, 29.8, 29.7, 29.6, 29.5, 29.3, 28.9, 22.9, 14.3. **ESI-TOF** [M+23] calc for $C_{26}H_{39}NO_4Na$: 452.2879, found: 452.2769.

(*S*)-4-((*R*,*E*)-1-Benzoyloxyhexadeca-2-en-1-yl)-oxazolidin-2-one ((*S*,*R*)-337).



Ozaxolidinone **(*S*,*R*)-337** was synthesised from **337** according to the general method for the kinetic resolution of oxazolidinines. Starting from 43 mg (0.1 mmol) of **337**, **(*S*,*R*)-337** was recovered after 16 h in 35% yield (15 mg) and 86.8% ee after flash chromatography employing 10% ethyl acetate-hexanes as the eluent. **HPLC** Chiralpak IC column (90:10 hexanes:ethanol, 1.0 ml/min, 220 nm); major enantiomer t_r = 18.60 min, minor enantiomer t_r = 14.73 min, 86.8% ee.

(*R*)-4-((*S*,*E*)-1-Benzyloxyhexadeca-2-en-1-yl)-3-isobutyryloxazolidin-2-one ((*R*,*S*)-338).



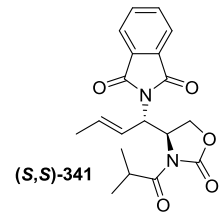
Acylated oxazolidinone **(*R*,*S*)-338** was synthesised from **337** according to the general method for the kinetic resolution of oxazolidinines. Starting from 43 mg (0.1 mmol) of **337**, **(*R*,*S*)-338** was obtained after 16 h in 44% yield (22 mg) and 94.5% ee after flash chromatography employing 5% ethyl acetate-hexanes as the eluent.

FT-IR (ATR) ν in cm^{-1}: 2922, 2853, 1781, 1708, 1480, 1462, 1385, 1320, 1281, 1235, 1194, 1152, 1087, 969, 803, 759, 688, 666. **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): 8.00 (d, *J* = 7.8 Hz, 2H), 7.58 (t, *J* = 7.8 Hz, 2H), 7.45 (t, *J* = 7.8 Hz, 2H), 6.00

(d, *J* = 5.8 Hz, 1H), 5.91 (dt, *J* = 15.6, 6.8 Hz, 1H), 5.42 (dd, *J* = 15.6, 5.9 Hz, 1H), 4.72 (d, *J* = 9.0 Hz, 1H), 4.61 (dd, *J* = 9.0, 2.9 Hz, 1H), 4.39 (t, *J* = 9.0 Hz, 1H), 3.72-3.61 (m, 1H), 2.06 (dd, *J* = 13.7, 6.7 Hz, 2H), 1.14 (d, *J* = 6.4 Hz, 3H), 1.08 (d, *J* = 7.2 Hz, 3H), 0.88 (dd, *J* = 7.0, 5.9 Hz, 3H). **^{13}C NMR** (100MHz, $CDCl_3$, δ in ppm): 219.6, 137.3, 133.4, 129.8, 128.8, 122.6, 72.0, 62.6, 56.3, 32.8, 32.6, 32.1, 29.9, 29.9, 29.9, 29.8, 29.8, 29.8, 29.7, 29.6, 29.5, 29.3, 29.9, 22.9, 19.3, 18.4, 14.3. **HPLC** Chiralpak ODH column (95:5 hexanes:ethanol, 1.0 ml/min, 230 nm); major enantiomer t_r = 9.30 min, minor enantiomer t_r = 7.97 min, 94.5% ee.

HPLC Chiralpak IC column (90:10 hexanes:isopropanol, 1.0 ml/min, 210 nm); major enantiomer t_r = 18.60 min, minor enantiomer t_r = 14.73 min, 87% ee.

(*S*)-4-((*S*,*E*)-1-Phthalimidobut-2-en-1-yl)-3-isobutyryloxazolidin-2-one ((*S*,*S*)-341).



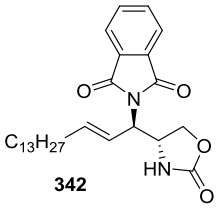
(*S*,*S*)-341

Acylated oxazolidinone **(*S*,*S*)-341** was synthesised from **256** according to the general method for the kinetic resolution of oxazolidinines. Starting from 43 mg (0.1 mmol) of **256**, **(*S*,*S*)-341** was obtained after 16 h in 43% yield (13 mg) and 98.5% ee after flash chromatography employing 20% to 30% ethyl acetate-hexanes as the eluent.

FT-IR (ATR) ν in cm^{-1}: 2963, 2922, 2853, 1776, 1710, 1611, 1467, 1384, 1358, 1330, 1259, 1236, 1196, 1076, 1017, 968, 931, 873, 798, 759, 717. **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): 7.83 (dd, 2H, *J* = 5.6, 3.2 Hz), 7.73 (dd, 2H, *J* = 5.6, 3.2 Hz), 6.13 (ddd, 1H, *J* = 15.2, 8.8, 1.6 Hz), 5.87 (dq, 1H, *J* = 15.2, 6.4 Hz), 5.14 (dd, 1H, *J* = 8.8, 5.2 Hz), 4.99-4.93 (m, 1H), 4.41 (t, 1H, *J* = 8.8 Hz), 3.95 (dd, 1H, *J* = 6.8, 2.4 Hz), 3.79-3.66 (m, 2H), 1.42 (d, 3H, *J* = 7.2 Hz), 1.15 (d, 6H, *J* = 5.2 Hz). **^{13}C NMR** (100MHz, $CDCl_3$, δ in ppm): 177.5, 168.5, 134.6, 133.8, 131.7, 123.8, 122.9, 65.1, 56.8, 54.8, 32.8, 19.3, 18.9, 18.1. **ESI-TOF** [M+Na] calc for $C_{15}H_{14}N_2O_4Na$: 379.1372, found: 379.1263. **HPLC** Chiralpak IA column (80:20 hexanes:ethanol, 1.0

ml/min, 210 nm); major enantiomer t_r = 21.34 min, minor enantiomer t_r = 25.98 min, 98.5% ee.

(*R*/*S*)-4-(((*R*/*S*),*E*)-1-Phthalimidohexadeca-2-en-1-yl)-oxazolidin-2-one (342).

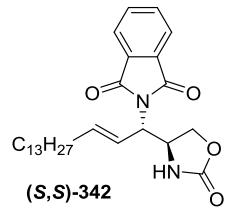


342

A flame dried Schlenk containing a magnetic stirring bar was charged with activated 4 Å MS (400 mg), then 14 ml of dichloromethane were added. After stirring 20 min., carbamate **169** (176 mg, 0.56 mmol) and PhIO (246 mg, 1.12 mmol) were added under argon and the reaction mixture was stirred at 35ºC untill all carbamate **169** was consumed. Then potassium phtalimide (518 mg, 2.8 mmol) was added and the mixture was stirred overnight at room temperature. After being filtrate, the recovered homogeneous solution was dry loaded on silica gel and purified by flash chromatography (10% ethyl acetate-hexanes) providing pure oxazolidinone pure **342** in 36% yield (92 mg) .

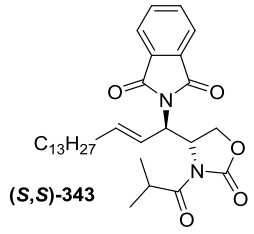
FT-IR (ATR) ν in cm^{-1}: 2957, 2923, 2851, 1757, 1710, 1467, 1379, 1329, 1259, 1028, 801, 718. **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): 7.86 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.76 (dd, *J* = 5.5, 3.0 Hz, 2H), 5.94 – 5.75 (m, 3H), 4.65 (dd, *J* = 8.3, 5.2 Hz, 1H), 4.50 (dd, *J* = 11.7, 5.7 Hz, 1H), 4.36 (dt, *J* = 8.8, 5.2 Hz, 1H), 4.15 (dd, *J* = 8.8, 5.7 Hz, 1H), 2.10 – 2.01 (m, 2H), 1.60 (s, 2H), 1.45 – 1.01 (m, 23H), 0.88 (dd, *J* = 7.5, 6.3 Hz, 3H). **^{13}C NMR** (100MHz, $CDCl_3$, δ in ppm): 220.0, 168.3, 140.3, 134.7, 131.7, 123.9, 121.00, 67.9, 57.0, 54.5, 32.6, 32.1, 29.9, 29.9, 29.9, 29.8, 29.6, 29.6, 29.4, 29.0, 22.9, 14.3. **ESI-TOF** [M+Na] calc for $C_{27}H_{38}N_2O_4Na$: 477.2832, found: 477.2723. **HPLC** Chiralpak IA column (90:10 hexanes:ethanol, 1.0 ml/min, 210 nm); major enantiomer t_r = 21.34 min, minor enantiomer t_r = 25.98 min, 86% ee.

(*R*)-4-((*R*,*E*)-1-Phthalimidohexadeca-2-en-1-yl)oxazolidin-2-one ((*R*,*R*)-342).



Ozaxolidinone (***R*,*R*)-342** was synthesised from **342** according to the general method for the kinetic resolution of oxazolidinines. Starting from 37 mg (0.08 mmol) of **342**, (***R*,*R*)-342** was recovered after 16 h in 47% yield (17 mg) and 87.2% ee after flash chromatography employing 10% ethyl acetate-hexanes as the eluent. **HPLC** Chiralpak IA column (90:10 hexanes:ethanol, 1.0 ml/min, 210 nm); major enantiomer t_r = 21.34 min, minor enantiomer t_r = 25.98 min, 87.2% ee.

(*S*)-4-((*S*,*E*)-1-Phthalimidohexadeca-2-en-1-yl)-3-isobutyryloxazolidin-2-one ((*S*,*S*)-343).

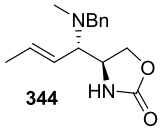


Acylated oxazolidinone (***S*,*S*)-343** was synthesised from **342** according to the general method for the kinetic resolution of oxazolidinines. Starting from 37 mg (0.1 mmol) of **342**, (***S*,*S*)-343** was obtained after 16 h in 38% yield (15 mg) and 98.2% ee after flash chromatography employing 10% ethyl acetate-hexanes as the eluent. **HPLC** Chiralpak IA column (90:10 hexanes:ethanol, 1.0 ml/min, 210 nm); major enantiomer t_r = 7.92 min, minor enantiomer t_r = 9.63 min, 98.2% ee.

FT-IR (ATR) ν in cm^{-1}: 2923, 2852, 1779, 1715, 1467, 1385, 1330, 1265, 1195, 1109, 976, 718. **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): 7.83 (dd, *J* = 5.6, 3.0 Hz, 2H), 7.73 (dd, *J* = 5.6, 3.0 Hz, 2H), 6.11 (ddt, *J* = 15.1, 8.9, 1.4 Hz, 1H), 5.86 (ddd, *J* = 15.1, 7.0, 6.3 Hz, 1H), 5.17 (dd, *J* = 8.9, 4.7 Hz, 1H), 4.92 (ddd, *J* = 8.1, 4.7, 2.0 Hz, 1H), 4.85 (dd, *J* = 9.2, 2.0 Hz, 1H), 4.31 (dd, *J* = 9.2, 8.1 Hz, 1H), 3.67 – 3.56 (m,

1H), 2.03 (dt, *J* = 8.0, 4.0 Hz, 2H), 1.42 – 1.17 (m, 23H), 1.14 (d, *J* = 6.8 Hz, 2H), 0.91 – 0.82 (m, 3H). **^{13}C NMR** (100MHz, $CDCl_3$, δ in ppm): 177.5, 168.5, 153.2, 139.1, 134.5, 131.7, 123.7, 121.3, 65.0, 57.1, 54.7, 32.1, 29.9, 29.9, 29.9, 29.9, 29.9, 29.9, 29.9, 28.9, 22.9, 19.2, 18.9, 14.3. **ESI-TOF** [M+Na] calc for $C_{27}H_{38}N_2O_4Na$: 477.2832, found: 477.2723.

(*R*/*S*)-4-(((*S*/*R*),*E*)-1-Benzyl(methyl)amino)but-2-en-1-yl)oxazolidin-2-one (344).

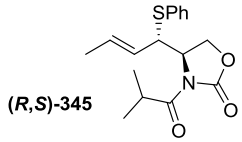


344

A solution of oxazolidinone **255** (90 mg, 0.41 mmol) in THF (8 ml) was cooled to -20ºC and then NaH (60% in mineral oil, 36 mg, 0.9 mmol) was added. After 1 hour, a solution of MeI (0.018 ml, 0.41 mmol) in THF (2 ml) was added during 1 hour. Once TLC showed complete consumption of **255** the solution is slightly concentrated and dichloromethane and water were added. The organic phase was separated and the aqueous phase was extracted three times with dichloromethane. The combined organic layers were dired over $MgSO_4$, filtrated and the the solvent was evaporated. Finally, pure **344** (81 mg, 85% yield) was obtained after flash chromatography employing 30% ethyl acetate-hexanes as the eluent

FT-IR (ATR) ν in cm^{-1}: 3321, 3027, 2912, 2849, 1779, 1495, 1477, 1452, 1428, 1406, 1308, 1265, 1126, 1038, 966, 752, 739, 701 **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): 7.35 – 7.21 (m, 5H), 5.75 (dqd, *J* = 15.2, 6.5, 0.6 Hz, 1H), 5.20 (ddq, *J* = 15.2, 8.2, 1.6 Hz, 1H), 4.33 (dd, *J* = 8.8, 6.9 Hz, 1H), 4.23 (t, *J* = 8.8 Hz, 1H), 3.86 (d, *J* = 13.6 Hz, 1H), 3.65 – 3.60 (m, 1H), 3.57 (d, *J* = 13.6 Hz, 1H), 3.23 (dd, *J* = 8.2, 3.6 Hz, 1H), 2.72 (s, 3H), 1.75 (dd, *J* = 6.5, 1.6 Hz, 3H).). **^{13}C NMR** (100MHz, $CDCl_3$, δ in ppm): 159.2, 140.2, 131.1, 128.6, 128.3, 128.1, 127.27, 63.7, 61.4, 58.9, 50.8, 30.1, 18.1. **ESI-TOF** [M+Na] calc for CH_9NO_4Na: 222.0845, found: 222.0731.

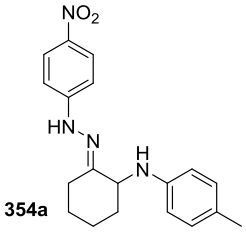
(*R*)-4-((*S*,*E*)-1-Phenylthiobut-2-en-1-yl)-3-isobutyryloxazolidin-2-one ((*R*,*S*)-345)



Acylated oxazolidinone (***R,S*)-345** was synthesised from **254** according to the general method for the kinetic resolution of oxazolidinines. Starting from 20 mg (0.08 mmol) of **254**, (***R,S*)-345** was obtained after 16 h in 23% yield (6 mg) and 97.2% ee after flash chromatography employing 10% ethyl acetate-hexanes as the eluent.

FT-IR (ATR) ν in cm^{-1}: 2962, 2921, 2852, 1779, 1698, 1582, 1467, 1439, 1386, 1358, 1234, 1090, 1024, 964, 753, 690. **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): 7.39-7.35 (m, 2H), 7.29 – 7.20 (m, 3H), 5.65 (dq, *J* = 15.2, 6.5 Hz, 1H), 5.39 (dd, *J* = 15.2, 7.8 Hz, 1H), 4.77 – 4.66 (m, 1H), 4.44 (dd, *J* = 9.1, 3.3 Hz, 1H), 4.40 – 4.28 (m, 1H), 3.52 – 3.40 (m, 1H), 1.68 (dd, *J* = 6.5, 0.8 Hz, 3H), 1.07 (d, *J* = 6.8 Hz, 3H), 0.93 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR** (100MHz, $CDCl_3$, δ in ppm): 177.8, 153.2, 133.6, 132.9, 130.6, 129.2, 127.9, 126.9, 64.4, 57.5, 53.6, 32.6,19.0, 18.8, 18.1. **ESI-TOF** [M+Na] calc for $C_{17}H_{21}NO_3SNa$: 342.1242, found: 342.113. **HPLC** Chiralpak IC column (95:5 hexanes:ethanol, 1.0 ml/min, 220nm); major enantiomer t_r = 8.02 min, minor enantiomer t_r = 7.12 min, 97.2% ee.

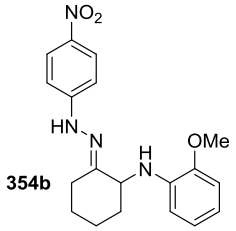
(*E*)-4-methyl-*N*-(2-(2-(4-nitrophenyl)hydrazono)cyclohexyl)aniline (354a).



Hydrazone **354a** was synthesised following the general method for the preparation of racemic α-arylamino hydrazones. Starting from 650 mg (2.8 mmol) of azoalkene **360**, 389 mg (3.64) toluidine and 101 mg of $Cu(OTf)_2$ (3.6 mmol) hydrazone **354a** (421 mg, 53 %) was obtained as a yellow solid after column chromatography using 20 % ethyl acetate-hexanes as the eluent.

^{1}H NMR (400 MHz, $CDCl_3$, δ in ppm): 8.11 (dd, *J* = 9.4, 2.6 Hz, 2H), 8.00 (s, 1H), 7.04-6.92 (m, 4H), 6.64 (dd, *J* = 8.6, 2.6 Hz, 2H), 4.00 (dd, *J* = 9.6, 4.5 Hz, 1H), 2.82-2.71 (m, 1H), 2.43-2.33 (m, 1H), 2.22 (s, 3H), 2.12-2.00 (m, 1H), 1.95-1.82 (m, 2H), 1.78- 1.44 (m, 4H). **^{13}C NMR** ($CDCl_3$, 100 MHz, δ in ppm): 152.4, 150.5, 145.1, 140.0, 129.8, 126.9, 126.3, 113.7 111.7, 57.1, 35.3, 26.4, 24.9, 23.5, 20.5. **ESI-TOF** [M+H] calc for $C_{19}H_{23}N_4O_2$: 339.1814 found: 338.1743.

(*E*)-2-methoxy-N-(2-(2-(4-nitrophenyl)hydrazono)cyclohexyl)aniline (354b).

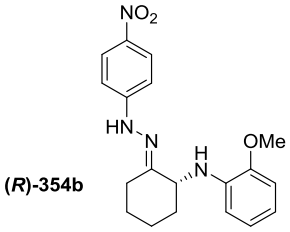


354b

Hydrazone **354b** was synthesised following the general method for the preparation of racemic α-arylamino hydrazones. Starting from 46 mg (0.2 mmol) of azoalkene **360**, 32 mg (0.26) of 2-methoxyaniline and 7.2 mg of $Cu(OTf)_2$ (0.02 mmol) hydrazone **354b** (47 mg, 66 %) was obtained as a yellow solid after column chromatography using 20 % ethyl acetate-hexanes as the eluent.

^{1}H NMR (500 MHz, $CDCl_3$, δ in ppm): 10.21 (s, 1H), 8.11 (d, *J* = 9.0 Hz, 2H), 7.14 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.0 Hz, 1H), 6.77 (t, *J* = 7.5 Hz, 1H), 6.66 (d, *J* = 7.7 Hz, 1H), 6.58 (t, *J* = 7.5 Hz, 1H), 5.61 (br s, 1H), 4.06 – 3.95 (m, 1H), 3.89 (s, 3H), 3.04 (d, *J* = 14.0 Hz, 1H), 2.40 – 2.27 (m, 1H), 2.15 – 2.03 (m, 1H), 1.93 – 1.62 (m, 3H), 1.54 – 1.33 (m, 2H). **^{13}C NMR** ($CDCl_3$, 126 MHz, δ in ppm): 152.7, 151.8, 146.5, 138.0, 137.2, 125.9, 121.0, 116.0, 111.0, 110.2, 109.8, 56.1, 55.5, 35.2, 26.0, 25.8, 23.3; **EI** $[M]^+$ calc for $C_{19}H_{22}N_4O_3$: 354.1692, found: 354.1693.

(*R*,*E*)-2-methoxy-*N*-(2-(2-(4-nitrophenyl)hydrazono)cyclohexyl)aniline ((*R*)-354b).

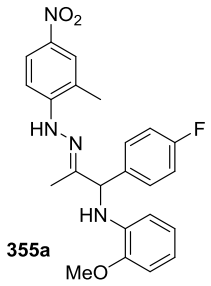


(*R*)-354b

To a 2 dram (7.4 ml) glass vial equipped with a magnetic stir bar was added **360** (46.3 mg, 0.20 mmol), (*R*)-TRIP (**374a**) (7.5 mg, 0.010 mmol), and 5Å molecular sieves (400 mg). A solution of 2-methoxyaniline (29.6 mg, 0.24 mmol) in benzene (4 ml) was added, the vial capped with a PTFE screw cap, protected from ambient light, and stirred at r.t. for 2 h. The reaction mixture was loaded directly onto the column and purified by column chromatography (petroleum ether:acetone 4:1) and additional column chromatography (1:1 petroleum ether:ether) to afford **(*R*)-354b** (44.1 mg, 51%) as a yellow foam.

HPLC Chiralpak AD-H column (90:10 hexanes:isopropanol, 1.0 ml/min, 259 nm); major enantiomer t_r = 21.37 min, minor enantiomer t_r = 18.73 min, 90% ee; absolute configuration tentatively assigned as (*R*) by analogy to **(*S*,*R*)-379**.

(*E*)-*N*-(1-(4-fluorophenyl)-2-(2-(2-methyl-4-nitrophenyl)hydrazono)propyl)-2-methoxyaniline (355a).



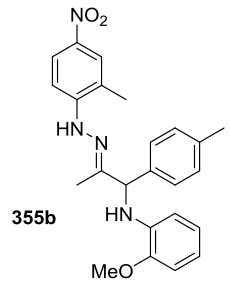
355a

Hydrazone **355a** was synthesised following the general method for the preparation of racemic α-arylamino hydrazones. Starting from 400 mg (0.95 mmol) of azoalkene **364d**, (132 mg, 81.24 mmol) toluidine and 34 mg (0.095 mmol) of

$Cu(OTf)_2$ hydrazone **355a** (355 mg, 63 %) was obtained as a yellow solid after column chromatography using 20 % ethyl acetate-hexanes as the eluent.

^{1}H NMR (500 MHz, $CDCl_3$, δ in ppm): 8.15 (dd, *J* = 9.1, 2.6 Hz, 1H), 8.08-7.99 (m, 1H), 7.61 (d, *J* = 9.1 Hz, 1H), 7.51-7.39 (m, 2H), 7.34 (s, 1H), 7.06 (t, *J* = 8.8 Hz, 2H), 6.81 (dd, *J* = 7.8, 1.4 Hz, 1H), 6.76 (td, *J* = 7.6, 1.5 Hz, 1H), 6.68 (td, *J* = 7.7, 1.6 Hz, 1H), 6.53 (dd, *J* = 7.7, 1.6 Hz, 1H), 5.83 (s, 1H), 5.10 (s, 1H), 3.94 (s, 3H), 2.25 (s, 3H), 1.87 (s, 3H). **^{13}C NMR** ($CDCl_3$, 126 MHz, δ in ppm): 148.9, 148.1, 147.1, 140.1, 136.7, 136.0, 129.2, 129.1, 126.5, 124.3, 121.3, 120.0, 117.4, 116.1, 115.9, 111.7, 111.0, 109.6, 63.4, 55.8, 17.0, 12.5. **ESI-TOF** [M+Na] calc for $C_{23}H_{23}FN_4O_3Na$: 445.1754, found: 445.1646.

(*E*)-2-methoxy-*N*-(2-(2-(2-methyl-4-nitrophenyl)hydrazono)-1-(*p*-tolyl)propyl)aniline ((±)-355b).

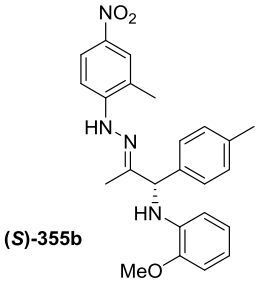


355b

Hydrazone **355b** was synthesised following the general method for the preparation of racemic α-arylamino hydrazones. Starting from 250 mg (0.85 mmol) of azoalkene **392b**, 135 mg (1.1 mmol) of 2-methoxyaniline and 31 mg (0.85 mmol) of $Cu(OTf)_2$ hydrazone **355b** (266 mg, 75 %) was obtained as a yellow solid after column chromatography using 20 % to 30% ethyl acetate-hexanes as the eluent.

^{1}H NMR (400 MHz, $CDCl_3$, δ in ppm): 8.15 (dd, *J* = 9.1, 2.5 Hz, 1H), 8.02 (d, *J* = 2.1 Hz, 1H), 7.64 (d, *J* = 9.2 Hz, 1H), 7.41 – 7.32 (m, 3H), 7.19 (d, *J* = 7.9 Hz, 2H), 6.83 – 6.74 (m, 2H), 6.68 (td, *J* = 7.7, 1.6 Hz, 1H), 6.60 (dd, *J* = 7.8, 1.5 Hz, 1H), 5.83 (br s, 1H), 5.09 (s, 1H), 3.94 (s, 3H), 2.35 (s, 3H), 2.23 (s, 3H), 1.88 (s, 3H). **^{13}C NMR** ($CDCl_3$, 100 MHz, δ in ppm): 149.8, 148.2, 147.1, 139.8, 137.8, 137.1, 136.8, 129.7, 127.4, 126.4, 124.2, 121.3, 119.9, 117.2, 111.6, 111.1, 109.6, 63.8, 55.7, 21.2, 16.9, 12.3. **EI** $[M]^+$ calc for $C_{24}H_{26}N_4O_3$: 418.2005, found: 418.2004.

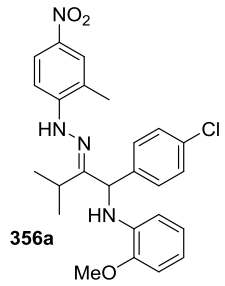
(*S*,*E*)-2-methoxy-*N*-(2-(2-(2-methyl-4-nitrophenyl)hydrazono)-1-(*p*-tolyl)propyl)aniline (*S*)-355b.



(*S*)-355b

To a 2 dram (7.4 ml) glass vial equipped with a magnetic stir bar was added **364c** (58.9 mg, 0.20 mmol), (*R*)-TRIP (**374a**) (30.1 mg, 0.040 mmol), and 5A molecular sieves (400 mg). A solution of 2-methoxyaniline (74 mg, 0.60 mmol) in benzene (4 ml) was added, the vial capped with a PTFE screw cap, protected from ambient light, and stirred at r.t. for 14 h. The reaction mixture was loaded directly onto the column and purified by column chromatography (hexanes:ether 3:1 to 2:1) to afford **(*S*)-355b** (41.0 mg, 51%) as a yellow film. **HPLC** Chiralpak AD-H column (80:20 hexanes:isopropanol, 1.0 ml/min, 356 nm); major enantiomer t_r = 8.22 min, minor enantiomer t_r = 14.30 min, 90% ee; absolute configuration tentatively assigned as (*S*) by analogy to **(*S*,*R*)-379** and **(*S*)-356c**.

(*E*)-*N*-(1-(4-chlorophenyl)-3-methyl-2-(2-(2-methyl-4-nitrophenyl)hydrazono)butyl)-2-methoxyaniline (356a).



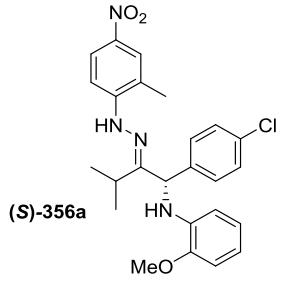
356a

Hydrazone **356a** was synthesised following the general method for the preparation of racemic α-arylamino hydrazones. However, for practical purposes during purification the ratio between azoalkene **364a** and 2-methoxyaniline was inverted. Starting from 400 mg (1.2 mmol) of azoalkene **364a**, 57 mg (0.45 mmol) of

2-methoxyaniline and 16 mg (0.045 mmol) of $Cu(OTf)_2$, hydrazone **356a** (147 mg, 68%) was obtained as a yellow solid after flash chromatography using 10 % to 20% ethyl acetate-hexanes as the eluent.

^{1}H NMR (400 MHz, $CDCl_3$, δ in ppm): 8.14 (dd, *J* = 9.1, 2.5 Hz, 1H), 8.03 (d, *J* = 2.0 Hz, 1H), 7.74 (s, 1H), 7.52 (d, *J* = 9.1 Hz, 1H), 7.43 (d, *J* = 8.5 Hz, 2H), 7.32 (d, *J* = 8.5 Hz, 2H), 6.83 – 6.73 (m, 2H), 6.67 (td, *J* = 7.7, 1.5 Hz, 1H), 6.58 – 6.51 (m, 1H), 5.92 (br s, 1H), 5.19 (s, 1H), 3.94 (s, 3H), 2.88 (hept, *J* = 6.8 Hz, 1H), 2.26 (s, 3H), 1.22 (d, *J* = 7.1 Hz, 3H), 1.10 (d, *J* = 7.2 Hz, 3H). **^{13}C NMR** ($CDCl_3$, 100 MHz, δ in ppm): 154.6, 148.1, 147.2, 140.0, 139.1, 136.4, 133.6, 129.5, 128.9, 126.5, 124.3, 121.2, 119.9, 117.4, 111.3, 110.9, 109.7, 59.8, 55.8, 28.7, 18.7, 18.6, 17.0 **ESI-TOF** [M+H] calc for $C_{25}H_{28}ClN_4O_3$: 467.1844, found: 467.1850.

(*S*,*E*)-*N*-(1-(4-chlorophenyl)-3-methyl-2-(2-(2-methyl-4-nitrophenyl)hydrazono)butyl)-2-methoxyaniline ((*S*)-356a).

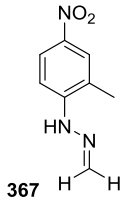


(*S*)-356a

To a 1 dram (3.7 ml) glass vial equipped with a magnetic stir bar was added the arylazoalkene **364a** (103mg, 0.30 mmol), (*R*)-TCYP (**374c**) (9.9 mg, 0.010 mmol), and 5A molecular sieves (100 mg). A solution of 2-methoxyaniline (12 mg, 0.10 mmol) in benzene (1 ml) was added, the vial capped with a PTFE screw cap, protected from ambient light, and stirred at r.t. for 24 h. The reaction mixture was loaded directly onto the column and purified by column chromatography (4:1 to 2:1 hexanes:ether) affording **(*S*)-356a** (38.9 mg, 87%) as a yellow film.

HPLC Chiralpak AD-H column (80:20 hexanes:isopropanol, 1.0 ml/min, 356 nm); major enantiomer t_r = 10.39 min, minor enantiomer t_r = 15.78 min, 93% ee; absolute configuration assigned as (*S*) by analogy to **(*S*)-356c**

1-(2-methyl-4-nitrophenyl)-2-methylenehydrazine (367).



367

Hydrazone **367** was isolated as a brown solid from the hydrolysis reactions where paraformaldehyde is used to trap the hydrazine generated in order to shift the equilibrium towards the ketone product. See section 5.2.3.1.

^{1}H NMR (500 MHz, $CDCl_3$, δ in ppm): 8.09 (dd, *J* = 9.6, 1.6 Hz, 1H), 8.02 (s, 1H), 7.74 (s, 1H), 7.47 (d, *J* = 9.1 Hz, 1H), 6.91 (d, *J* = 10.9 Hz, 1H), 6.46 (d, *J* = 10.9 Hz, 1H), 2.26 (s, 3H). **^{13}C NMR** ($CDCl_3$, 126 MHz, δ in ppm): 147.7, 131.1, 126.6, 124.2, 119.5, 111.8, 17.1. **ESI-TOF** [M+H] calc for $C_8H_9N_3O_2$: 180.0695, found: 180.0768

Preparation of azoalkenes

The azoalkenes usen as precursors of α-arylamino hydrazones are shown in Figure 7.1. In this experimental section only those prepared by myself will be described (**360** and **364d**).

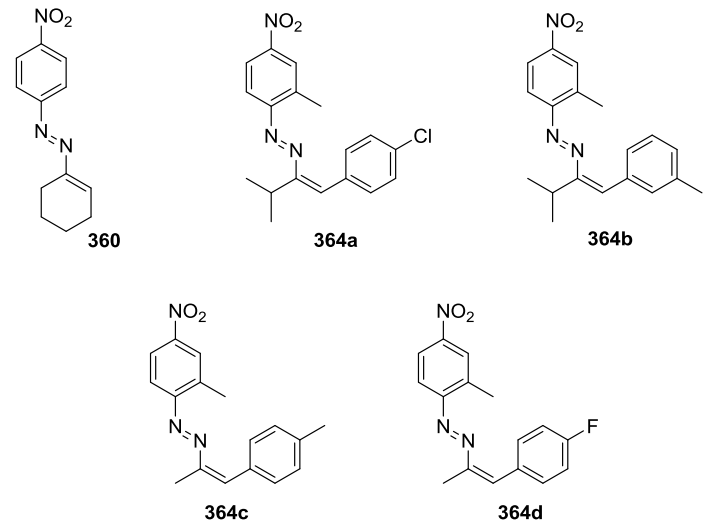
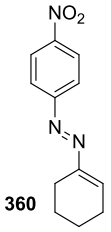


Figure 7.1. Azoalkenes prepared for the synthesis of α-arylamino hydrazones.

(*E*)-1-(cyclohex-1-en-1-yl)-2-(4-nitrophenyl)diazene (360).



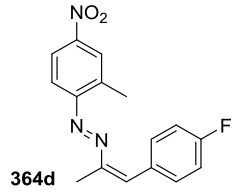
360

Adapted from a published procedure.[255] To a 50 ml round bottom flask with a magnetic stir bar was added 2-chlorocyclohexanone (1.37 g, 10.0 mmol) and pyridine (1.22 ml, 15.1 mmol). The reaction mixture was heated to 100 °C (pre-heated oil bath) and stirred at this temperature for 5 min. The reaction mixture was cooled and THF (2 ml) was added (named solution **A**). In a separate 250 ml round bottom flask with a magnetic stir bar was added 4-nitrophenyl hydrazine and THF (10 ml). The reaction mixture was cooled to 0 °C and solution **A** was added dropwise. After addition, the reaction mixture was stirred at 0 °C for 2 h at which point ice water (140 ml) was added. A 1M NaOH(aq.) solution (16 ml) was then added dropwise and the reaction mixture extracted with DCM (3 x 50 ml). The combined organic phases were washed with NaCl(sat., aq.), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by column chromatography (19:1 hexanes:ethyl acetate) to afford **360** (1.65 g, 71%) as a orange solid.

^{1}H NMR (500 MHz, $CDCl_3$, δ in ppm): 8.29 (d, *J* = 9.0 Hz, 2H), 7.82 (d, *J* = 9.0 Hz, 2H), 7.13 (t, *J* = 4.4 Hz, 1H), 2.57 – 2.47 (m, 2H), 2.45 – 2.36 (m, 2H), 1.83 – 1.69 (m, 4H). **^{13}C NMR** ($CDCl_3$, 126 MHz, δ in ppm): 156.3, 156.3, 148.1, 146.5, 124.7, 123.0, 26.9, 22.8, 22.2, 21.9. **EI** $[M]^+$ calc for $C_{12}H_{13}N_3O_2$: 231.1008, found: 231.1008

[255] Brodka, S; Simon, H. *Chem. Ber.* **1969**, *102*, 3647-3655.

(*E*)-1-((*Z*)-1-(4-fluorophenyl)prop-1-en-2-yl)-2-(2-methyl-4-nitrophenyl)diazene (364d).



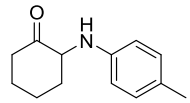
364d

To a 250 ml round-bottom flask equipped with a magnetic stir bar was added 1-(4-fluorophenyl)propan-2-one (1.62 g, 10.0 mmol), 2-methyl-4-nitrophenylhydrazine hydrochloride (2.44 g, 12.0 mmol), anhydrous sodium acetate (8.20 g, 100 mmol), and ethanol (50 ml). The reaction mixture was heated to 60 °C and stirred at this temperature for 14 h. The reaction mixture was cooled, dichloromethane (50 ml) was added, and filtered. The filtrate was concentrated under reduced pressure and passed through a plug of silica (dry load, 9:1 to 4:1 hexanes:ethyl acetate), collecting the first yellow band to afford the crude hydrazone (1.92 g, 6.39 mmol; mixture of both (*E*) and (*Z*) isomers). To a 100 ml round-bottom flask equipped with a magnetic stir bar and containing the crude hydrazone was added pyridine (3.6 ml). The flask was protected from light and a solution of iodine (1.62 g, 6.39 mmol) in pyridine (7.1 ml) was added dropwise to the hydrazone solution. The reaction mixture was then stirred in the absence of light at r.t. for 14 h. The reaction mixture was then cooled to 0 °C and a 1M $NaOH_{(aq)}$ solution (19 ml) was added dropwise. After addition, ether (50 ml) and water (50 ml) were added, the mixture was filtered to remove any solids, the filtrate layers were separated, and the aqueous layer extracted with ether (2 x 50 ml). The combined organic phases were washed with 2M HCl(aq.) (3 x 50 ml), $NaHCO_3$(sat., aq), and NaCl(sat., aq.), dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by column chromatography using 19:1 hexanes:ether as the eluent to afford 281 mg, (9%, two steps) of **364d** as a brown solid.

^{1}H NMR (500 MHz, $CDCl_3$, δ in ppm): 8.21 (d, *J* = 2.1 Hz, 1H), 8.09 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.73 (d, *J* = 7.2 Hz, 2H), 7.50 (d, *J* = 8.8 Hz, 1H), 7.45 – 7.33 (m, 3H), 7.12 (s, 1H), 3.41 (hept, *J* = 6.8 Hz, 1H), 2.76 (s, 3H), 1.27 (d, *J* = 6.8 Hz, 6H). **^{13}C NMR** ($CDCl_3$, 126 MHz, δ in ppm): 160.2, 154.5, 148.2, 139.2, 135.8, 135.2, 132.3, 128.7,

128.3, 126.4, 122.1, 116.5, 27.1, 21.7, 17.9. **ESI-TOF** [M+H] calc for $C_{16}H_{15}FN_3O_2$: 300.1070, found: 300.1143.

2-(*p*-tolylamino)cyclohexan-1-one (365).

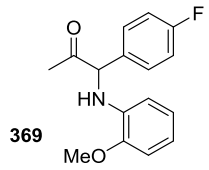


365

Ketone **365** was synthesised from hydrazone **354a** following the general method for the hydrolysis of racemic α-arylamino hydrazones. Starting from 68 mg (0.20 mmol) of hydrazone **354a**, Amberlyst-15 (40 mg), paraformaldehyde (60 mg, 2 mmol), acetone (2.8 ml) and water (0.28 ml), ketone **365** (31 mg, 76 %) was obtained as a colorless foam after flash chromatography using 10 % ethyl ether-hexanes as the eluent.

^{1}H NMR (500 MHz, $CDCl_3$, δ in ppm): 7.02-6.92 (m, 2H), 6.53 (dd, *J* = 8.7, 2.4 Hz, 2H), 4.75 (brs, 1H), 3.97 (ddd, *J* = 12.1, 5.8, 1.5 Hz, 1H), 2.69-2.62 (m, 1H), 2.61-2.53 (m, 1H), 2.42 (tdd, *J* = 13.3, 6.2, 1.5 Hz, 1H), 2.23 (s, 3H), 2.19-2.11 (m, 1H), 1.98-1.88 (m, 1H), 1.88-1.76 (m, 1H), 1.76-1.63 (m, 1H), 1.44 (qd, *J* = 12.8, 3.6 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 126 MHz, δ in ppm): 208.9, 144.5, 130.0, 127.0, 113.4, 100.2, 62.4, 41.4, 36.1, 28.4, 24.3, 20.6.

1-(4-fluorophenyl)-1-((2-methoxyphenyl)amino)propan-2-one (369).

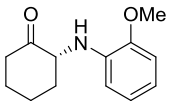


369

Ketone **369** was synthesised from hydrazone **355a** following the general method for the hydrolysis of racemic α-arylamino hydrazones. Starting from 84 mg (0.20 mmol) of hydrazone **355a**, Amberlyst-15 (40 mg), paraformaldehyde (60 mg, 2 mmol), acetone (2.8 ml) and water (0.28 ml), ketone **369** (47 mg, 86 %) was obtained as a beige solid after flash chromatography using 10 % ethyl ether-hexanes as the eluent.

^{1}H NMR (400 MHz, $CDCl_3$, δ in ppm): 7.57- 7.37 (m, 2H), 7.07 (t, *J* = 8.6 Hz, 2H), 6.78 (dd, *J* = 7.7, 1.6 Hz, 1H), 6.68 (ddd, *J* = 14.4, 7.6, 1.7 Hz, 1H), 6.30 (dd, *J* = 7.6, 1.7 Hz, 1H), 5.91 (d, *J* = 4.0 Hz, 1H), 4.99 (d, *J* = 3.7 Hz, 1H), 3.90 (s, 3H), 2.15 (s, 3H). **^{13}C NMR** ($CDCl_3$, 100 MHz, δ in ppm): 203.9, 163.9, 161.4, 147.2, 135.9, 134.0, 134.0, 129.5, 129.4, 121.0, 117.3, 116.4, 116.3, 110.7, 109.6, 67.5, 55.6, 26.7. **ESI-TOF** [M+H] calc for $C_{16}H_{17}FNO_2$: 274.1165, found: 274.1238.

(*R*)-2-((2-methoxyphenyl)amino)cyclohexan-1-one ((*R*)-370).



(*R*)-370

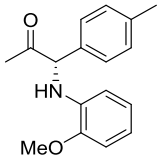
To a 1 dram (3.7 ml) glass vial equipped with a magnetic stir bar was added **(*R*)-354b** (25 mg, 0.07 mmol), paraformaldehyde (10 mg, 0.35 mmol), acetone (1.4 ml) and water (1.4 ml). To the resulting suspension was added Amberlyst-15 ion-exchange resin (7.3 mg) and the mixture was stirred at room temperature for 40 h until TLC showed complete consumption of starting hydrazone **(*R*)-354b**. The mixture was then passed through a celite plug and the filtrate was extracted with DCM (2 x 3ml), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by column chromatography (hexanes:ether 9:1) to afford **(*R*)-370** (13 mg, 84%) as a colorless film.

^{1}H NMR (500 MHz, $CDCl_3$, δ in ppm): 6.83 (td, *J* = 7.6, 1.4 Hz, 1H), 6.78 (dd, *J* = 7.9, 1.4 Hz, 1H), 6.67 (td, *J* = 7.7, 1.5 Hz, 1H), 6.50 (dd, *J* = 7.9, 1.5 Hz, 1H), 5.34 (br s, 1H), 4.05-3.95 (m, 1H), 3.87 (s, 3H), 2.70-2.63 (m, 1H), 2.63-2.56 (m, 1H), 2.43 (tdd, *J* = 13.4, 6.2, 1.4 Hz, 1H), 2.20-2.11 (m, 1H), 1.99-1.95 (m, 1H), 1.88-1.78 (m, 1H), 1.73 (qt, *J* = 13.0, 4.0 Hz, 1H), 1.51 (dq, *J* = 12.5, 3.5 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 126 MHz, δ in ppm): 208.5, 147.2, 136.6, 121.2, 116.9, 109.8, 109.8, 61.8, 55.6, 41.3, 35.8, 28.3, 24.2; **ESI-TOF** [M+H] calc for $C_{13}H_{18}NO_2$: 220.1331, found: 220.1332; **HPLC**: Chiralpak IA column (97:03 hexanes:isopropanol, 1.0 ml/min, 285 nm); major enantiomer t_r = 7.76 min, minor enantiomer t_r = 12.00 min, 90% ee;

absolute configuration tenatively assigned as (*R*) by an ethanolic sodium borohydride reduction and subsequent comparison previously reported HPLC retention times.[256]

1-((2-methoxyphenyl)amino)-1-(*p*-tolyl)propan-2-one ((*S*)-371).

(*S*)-371

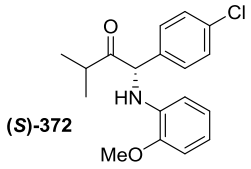


To a 1 dram (3.7 ml) glass vial equipped with a magnetic stir bar was added **(*S*)-355b** (34 mg, 0.08 mmol), paraformaldehyde (11 mg, 0.4 mmol), acetone (1.7 ml) and water (1.7 ml). To the resulting suspension was added Amberlyst-15 ion-exchange resin (8.3 mg) and the mixture was stirred at room temperature for 48 h until TLC showed complete consumption of starting hydrazone **(*S*)-355b**. The mixture was then passed through a celite plug and the filtrate was extracted with DCM (2 x 3ml), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by column chromatography (hexanes:ether 9:1) to afford **(*S*)-371** (18.9 mg, 82%) as a colorless film.

^{1}H NMR (500 MHz, $CDCl_3$, δ in ppm): 7.35 (d, *J* = 8.1 Hz, 2H), 7.17 (d, *J* = 7.8 Hz, 2H), 6.75 (dd, *J* = 7.9, 1.4 Hz, 1H), 6.69 (td, *J* = 7.6, 1.4 Hz, 1H), 6.62 (td, *J* = 7.7, 1.6 Hz, 1H), 6.33 (dd, *J* = 7.7, 1.6 Hz, 1H), 5.86 (br d, *J* = 4.3 Hz, 1H), 4.95 (d, *J* = 4.2 Hz, 1H), 3.89 (s, 3H), 2.33 (s, 3H), 2.14 (s, 3H). **^{13}C NMR** ($CDCl_3$, 126 MHz, δ in ppm): 204.5, 147.1, 138.3, 136.2, 135.2, 130.0, 127.8, 121.1, 117.0, 110.7, 109.5, 68.0, 55.6, 26.8, 21.3. **ESI-TOF** [M+H] calc for $C_{17}H_{20}NO_2$: 220.1331, found: 220.1332. **HPLC**: Chiralpak IA column (97:03 hexanes:isopropanol, 1.0 ml/min, 285 nm); major enantiomer t_r = 7.33 min, minor enantiomer t_r = 8.81 min, 90% ee; absolute configuration assigned as (*S*) by analogy to **(*S*,*R*)-379** and **(*S*)-356c**.

[256] a) Gao, B.; Wen, Y.; Yang, Z.; Huang, X.; Liu, X.; Feng, X. *Adv. Synth. Catal.* **2008**, *350*, 385. b) Bao, H.; Wu, J.; Li, H.; Wang, Z.; You, T.; Ding, K. *Eur. J. Org. Chem.* **2010**, 6722. c) Bao, H.; Wang, Z.; You, T.; Ding, K. *Chin. J. Chem.* **2013**, *31*, 67.

(*S*)-1-(4-chlorophenyl)-1-((2-methoxyphenyl)amino)-3-methylbutan-2-one ((*S*)-372).

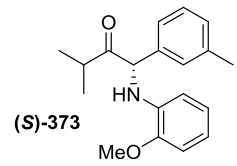


(*S*)-372

To a 1 dram (3.7 ml) glass vial equipped with a magnetic stir bar was added the hydrazone **(*S*)-356a** (27 mg, 0.06 mmol), paraformaldehyde (18.0 mg, 0.6 mmol), acetone (0.45 ml) and water (0.05 ml). To the resulting suspension Amberlyst-15 ion-exchange resin (12 mg) was added and the mixture was stirred at room temperature until TLC showed complete consumption of starting hydrazone **(*S*)-356a**. The mixture was then passed through a celite plug and the filtrate was extracted with DCM (2x3ml), dried over Na_2SO_4 and concentrated. After flash chromatography (9:1 hexanes:ether) ketone **(*S*)-(372)** (15.3 mg, 82%) was obtained as a pale yellow film.

^{1}H NMR (500 MHz, $CDCl_3$, δ in ppm): 7.40 (d, *J* = 8.5 Hz, 2H), 7.33 (d, *J* = 8.5 Hz, 2H), 6.76 (dd, *J* = 7.8, 1.5 Hz, 1H), 6.69 (td, *J* = 7.6, 1.5 Hz, 1H), 6.63 (td, *J* = 7.7, 1.6 Hz, 1H), 6.30 (dd, *J* = 7.7, 1.6 Hz, 1H), 5.98 (d, *J* = 4.8 Hz, 1H), 5.10 (d, *J* = 4.7 Hz, 1H), 3.89 (s, 3H), 2.82 (hept, *J* = 6.8 Hz, 1H), 1.16 (d, *J* = 7.0 Hz, 3H), 0.83 (d, *J* = 6.6 Hz, 3H). **^{13}C NMR** ($CDCl_3$, 126 MHz, δ in ppm): 209.6, 147.2, 136.8, 135.8, 134.2, 129.5, 121.0, 117.3, 110.6, 109.6, 65.5, 55.6, 37.2, 19.6, 18.5. **ESI-TOF** [M+H] calc for $C_{28}H_{21}NO_2Cl$: 318.1252, found: 318.1255. **HPLC**: Chiralpak IA column (97:3 hexanes:isopropanol, 1.0 ml/min, 215 nm); major enantiomer t_r = 7.33 min, minor enantiomer t_r = 8.81 min, 90% ee; absolute configuration assigned as (*S*) by analogy to **(*S*)-356c**.

(*S*)-1-(4-chlorophenyl)-1-((2-methoxyphenyl)amino)-3-methylbutan-2-one ((*S*)-373).

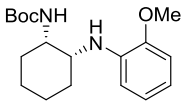


(*S*)-373

To a 1 dram (3.7 ml) glass vial equipped with a magnetic stir bar was added **(*S*)-356b** (26 mg, 0.058 mmol), paraformaldehyde (14 mg, 0.47 mmol), acetone (0.7 ml) and water (0.07 ml). To the resulting suspension was added Amberlyst-15 ion-exchange resin (10 mg) and the mixture was stirred at room temperature for 16 h until TLC showed complete consumption of starting hydrazone **(*S*)-356b**. The mixture was then passed through a celite plug and the filtrate was extracted with DCM (2 x 3ml), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by column chromatography (hexanes:ether 19:1) to afford **(*S*)-373** (12.5 mg, 72%) as a pale yellow film.

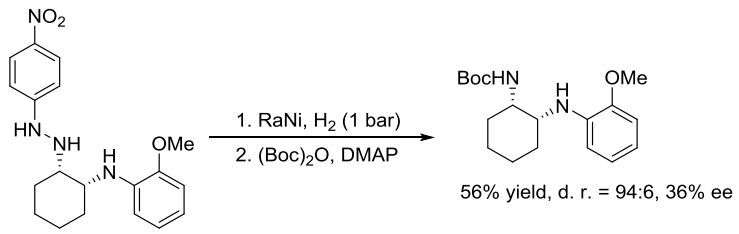
^{1}H NMR (500 MHz, $CDCl_3$, δ in ppm): 7.30 – 7.22 (m, 3H), 7.10 (d, *J* = 7.5 Hz, 1H), 6.76 (d, *J* = 7.8 Hz, 1H), 6.71 (td, *J* = 7.6, 1.1 Hz, 1H), 6.62 (td, *J* = 7.7, 1.5 Hz, 1H), 6.39 (dd, *J* = 7.8, 1.2 Hz, 1H), 5.99 (br d, *J* = 4.4 Hz, 1H), 5.08 (d, *J* = 4.7 Hz, 1H), 3.90 (s, 3H), 2.85 (hept, *J* = 7.0 Hz, 1H), 2.34 (s, 3H), 1.16 (d, *J* = 7.0 Hz, 3H), 0.82 (d, *J* = 6.6 Hz, 3H). **^{13}C NMR** ($CDCl_3$, 126 MHz, δ in ppm): 210.4, 147.1, 138.9, 138.1, 136.3, 129.2, 129.0, 128.6, 125.4, 121.0, 116.9, 110.6, 109.5, 66.3, 55.6, 37.0, 21.6, 19.7, 18.5; **ESI-TOF** [M+H] calc for $C_{19}H_{24}NO_2$: 298.1802, found: 298.1804. **HPLC**: Chiralpak AD-H column (98:02 hexanes:isopropanol, 1.0 ml/min, 285 nm); major enantiomer t_r = 9.24 min, minor enantiomer t_r = 6.10 min, 93% ee; absolute configuration assigned as (*S*) by analogy to **(*S*)-356c**.

***tert*-butyl ((1*S*,2*R*)-2-((2-methoxyphenyl)amino)cyclohexyl)carbamate ((1*S*,2*R*)-382).**



(1*S*,2*R*)-382

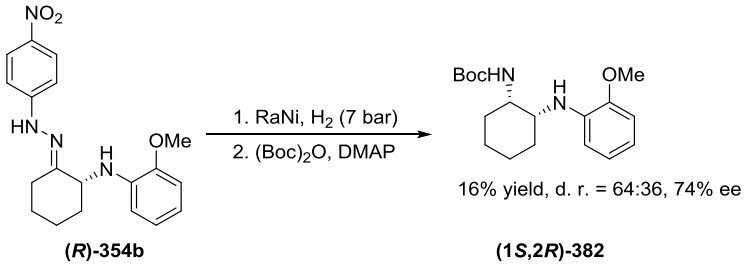
Procedure 1. Boc-protected diamine **(1*S*,2*R*)-382** was obtained from the unpurified α-arylamino hydrazine **(1*S*,2*R*)-384**. Thus, the quantities of each reagent and solvent will be calculated assuming a quantitative yield from the initial amount of hydrazone used. Hydrazine **(1*S*,2*R*)-384** (36 mg, 0.1 mmol) was dissolved in ethanol (2 ml) in a flask containing a magnetic stirrer. Then an excess of Raney Nickel in ethanol was added. A balloon filled with hydrogen was adapted to the flask and it was flushed three times before leaving the mixture with vigorous stirring overnight. After this time the heterogeneous mixture was filtered through a celite plug and the solvent was evaporated. Then, the unprotected diamine was dissolved in dichloromethane (2 ml) and di-*tert*-butyl dicarbonate ($(Boc)_2O$, 0.031 ml, 0.12 mmol) and DMAP (1.2 mg, 0.01 mmol) were added. When the reaction was completed the solvent was evaporated and directly purified by flash chromatography using 20 % ethyl acetate-hexanes as the eluent. Diamine **(1*S*,2*R*)-382** was obtained as a white solid in 56% yield from hydrazone **(*R*)-354b** with 36% ee and 94:6 d.r.



(1*S*,2*R*)-384 **(1*S*,2*R*)-382**

Procedure 2. Boc-protected diamine **(1*S*,2*R*)-382** was obtained from hydrazone **(*R*)-354b**. Hydrazone **(*R*)-354b** (36 mg, 0.1 mmol) was dissolved in ethanol (2 ml) in a flask containing a magnetic stirrer. Then an excess of Raney Nickel in ethanol was added. The mixture was stirred overnigh in a parr reactor under 7 atm of hydrogen. After this time the heterogeneous mixture was filtered through a celite plug and the solvent was evaporated. Then, the unprotected diamine was dissolved in dichloromethane (2 ml) and di-*tert*-butyl dicarbonate ($(Boc)_2O$, 0.031 ml, 0.12 mmol)

and DMAP (1.2 mg, 0.01 mmol) were added. When the reaction was completed the solvent was evaporated and directly purified by flash chromatography using 20 % ethyl acetate-hexanes as the eluent. Diamine **424** was obtained as a white solid in 16% yield from hydrazone **(*R*)-354b** with 74% ee and 64:36 d.r.



(*R*)-354b **(1*S*,2*R*)-382**

Diastereomerically pure *cis*-diamine **(1*S*,2*R*)-382** was obtained after recystallization in chloroform.

APPENDIX

UNIVERSITAT ROVIRA I VIRGILI
REGIO- AND ENANTIOSELECTIVE SYNTHESIS OF UNSATURATED AMINO ALCOHOLS, AMINO KETONES AND DIAMINES AS VALUABLE INTERMEDIATES IN ORGANIC SYNTHESIS.
Joan Guash Savidó
Dipòsit Legal: T 1366-2015

PUBLICATIONS

Guasch, J.; Díaz, Y.; M. M.; Matheu, M. I.; Castillón. S. "**Rhodium-catalyzed regio- and stereoselective oxyamination of dienes *via* tandem aziridination/ring-opening of dienyl carbamates.**" *Chem. Commun.* **2014**, *50*, 7344-7347

Miles, D. H.; Guasch, J.; Toste, F. D. "**A nucleophilic strategy for enantioselective intermolecular α-amination: access to enantioenriched α-arylamino ketones."** *Submitted.*

Guasch, J.; Díaz, Y.; M. M.; Matheu, M. I.; Castillón. S. "**A rapid access to highly enantioenriched distinctly functionalised unsaturated amino alcohols.**" *in preparation.*

Guasch, J.; Díaz, Y.; M. M.; Matheu, M. I.; Castillón. S. "**Intramolecular aziridination of dienols**" *in preparation.*

SCIENTIFIC MEETINGS

Guasch, J.; Díaz, Y.; M. M.; Matheu, M. I.; Castillón. S. **Rhodium-catalyzed regio- and stereoselective oxyamination of dienes via tandem aziridination-ring-opening of dienyl carbamates. Scope and Mechanism.** *Flash Communication*. XXV Reunión Bienal de Química Orgánica. Alicante (Spain), June 2014.

Guasch, J.; Díaz, Y.; M. M.; Matheu, M. I.; Castillón. S. **Regiocontrolled consecutive intramolecular aziridination/ring-opening of diennyl carbamates.** *Poster Contribution.* XXXIV Reunión Bienal de la Real Sociedad de Química Española. Santander (Spain), September 2013.

Guasch, J.; Díaz, Y.; M. M.; Matheu, M. I.; Castillón. S. **Intramolecular aziridination of non-symmetric dienols using carbamates as nitrene source.** *Poster Contribubution (P065).* 18th International Symposium on Homogeneous Catalysis. Toulouse (France), July, 2012 .

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

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