Alma Mater Studiorum – Università di Bologna

FACOLTÁ DI SCIENZE MATEMATICHE, FISICHE E NATURALI

Dottorato di Ricerca in Scienze Chimiche Chim/06 – XX Ciclo –

Dipartimento di Chimica «G. Ciamician»

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Sintesi asimmetrica di ammine benziliche ed eterobenziliche

Asymmetric synthesis of benzylic and heterobenzylic amines

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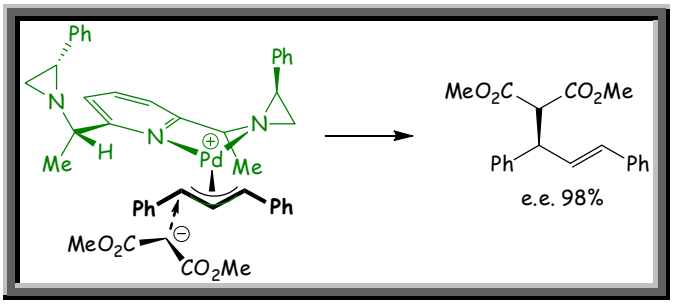
Parole chiave: Ammine, catalisi enantioselettiva, composti eterociclici, composti organometallici, sintesi asimmetrica,

Esame Finale 2008

Chapter Index

Chap. 1 – New chiral ligands featuring two aziridine rings separated by pyridine spacer: Synthesis and applications.



1.1 - Introduction

1.1.1 – N-Ligands in asymmetric synthesis

The enantioselective syntheses of complex chiral molecules, such as those routinely demanded by the pharmaceutical industry, rank among the most important and problematic objectives in all of chemistry. Progress in this area has been greatly accelerated by the development of reliable metal-catalyzed asymmetric reactions that create stereocentres with programmable absolute configurations.[1]

In principle, asymmetric catalytic processes are desirable because they give precise control over chirality and generate maximum complexity in the minimum number of reactions. These efficiencies may dramatically reduce the number of steps required in synthesis and therefore minimize the use of toxic solvents and reagents, labour and cost. Catalyzed reactions may also be conducted under milder conditions that are less energy intensive and that yield fewer undesirable side products than other routes. They may relieve some of the tedium and wastefulness associated with installation and removal of stereodirecting groups, and may provide other synthetic approaches that are much shorter and simpler than convoluted pathways involving lengthy modifications of naturally occurring chiral starting materials.

The discovery of new asymmetric catalysts involves to a great degree the development of new ligands, which support the central metal ions and govern their

enantioselectivity in asymmetric reactions. The development process is the combined result of rational design, intuition, trial and error and serendipity. Often, a chance observation uncovers a lead candidate, which is optimized iteratively in successive improvement cycles. Successful ligand design/synthesis/test cycles are greatly aided by the following guiding principles:

Proposed syntheses should be modular, i.e., it should be possible to generate many different members of a ligand family using the same reaction(s) simply by varying the combination of starting materials.

Ligands should be accessible in only a very few steps, and the diversification step(s) should be placed as close as possible to the end of the synthetic route.

Simple, high-yielding reactions should be used whenever possible.

In order to generate meaningful quantities of material and to avoid enantiomeric and/or diastereomeric separations, the reagents should be readily available and optically pure as both enantiomers. Moreover, the synthetic chemistry should be stereospecific and not affect any of these built-in stereocentres in an unpredictable way.

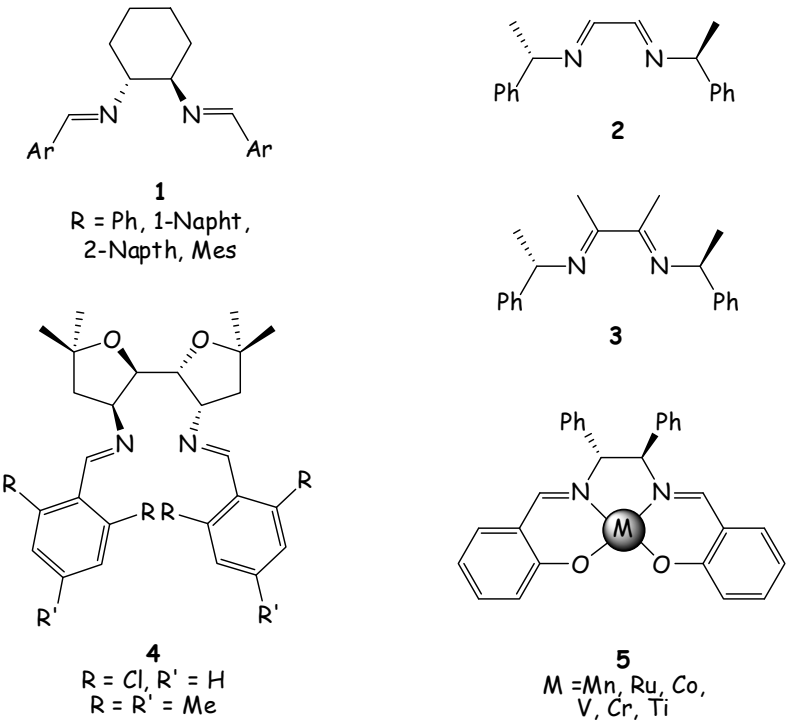
It should be possible to install multiple stereocentres that are independently variable. This in turn should allow for trivial expansion of ligand families.

Basic ligand frameworks should be easily modifiable to allow production of "next generation" ligands of higher complexity.

The ready availability of optically pure amino acids/alcohols from the chiral pool, by resolution processes and in part by stereoselective syntheses, the ease transformation of the amine group to other nitrogen-containing functional groups with different electronic and chemical (acid, base) properties, e.g., amides and imines, and the rapid development of peptide-based synthesis has positioned chiral nitrogen-donor ligands to fullfill the preceding criteria. Although nitrogen-containing ligands were only rarely used in the 1970s and the 1980s, some of the first historic asymmetric catalysts were heterogeneous nitrogen-containing chiral systems. Very early, asymmetric reduction was reported on silk fibroin with palladium[2] and with Raney nickel modified by amino acids. The field has been developed by the pioneering work of Brunner, Pfaltz, Evans and Sharpless, among others.

Nitrogen-containing ligands are increasingly applied in asymmetric catalysis,[3] since they present several advantages with respect to the more conventional phosphorus-containing ligands, even in transition metal-catalyzed reactions. Indeed, the amine functionality can

coordinate any metal species, ranging from lithium and magnesium to zinc, copper, early transition metal complexes and also precious metals.

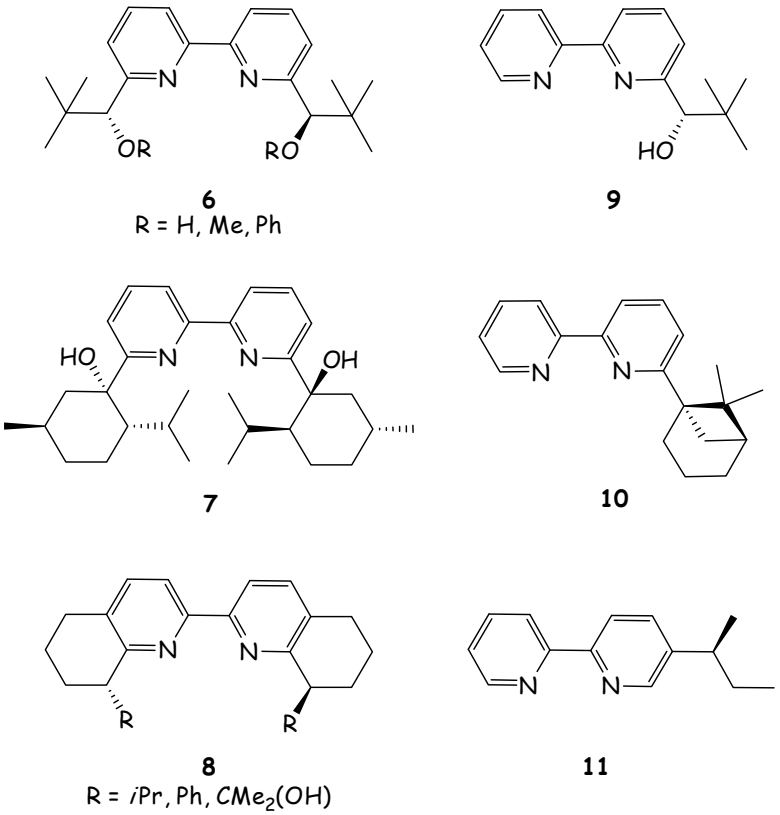


Scheme 1

Diimine-based chiral ligands is easily synthesized via simple base condensation between aldehyde and a chiral amine. The C_2-symmetry, which is commonly displayed by a variety of chiral ligands, limits the number of diastereomeric pathways in the asymmetric reaction can transverse, and also renders the ligands easier to assemble in some cases. A number of chiral diimines have since been developed, some example of which are shown in (Scheme 1). Their simple syntheses by condensation of a chiral diamine, the most common *trans*-1,2-diaminocyclohexane, with two equivalents of an achiral aldehyde (**1**), or by condensation of an achiral dialdehyde (e.g.,glyoxal) with two equivalents of a chiral amine (**2**, **3**), allow quick variation of steric bulk and the incorporation of different chiral elements. The simple C_2-symmetric chiral diimines, show in Scheme 1, present poor or moderate enantioselectivities in the relative asymmetric reactions. A few examples are excluded, e.g. the reduction of ketones by polymethylhydrosiloxane/Et_2Zn in the presence of ligands of type **1**.[4] Enantioselectivities of up to 99% have been achieved using ligands of type **4** in the Cu-catalyzed aziridination of electron deficient olefins.[5]

More popular derivatives of diimine ligands and the most widely and successfully used are the salens.[6] These ligand systems, which employ an O,N,N,O metal coordination mode, were first made by Combes via the condensation of a diamine with two equivalents of salicylaldehyde.[7] Salen complexes of Mn, Ru, Co, V, Cr and Ti (**5**) have been employed in enantioselective aziridinations, oxidations, hydroxylations, cyclopropanations, epoxide ring openings and hetero-Diels–Alder reactions.

In the last years a lot of *N,N'*-bidentate ligands have been development, in particular the 2,2'-bipyridine scaffold with one or more chiral substituent chelates a wide variety of different metals in asymmetric catalysis.[8] The chiral C_2-symmetric bipyridines are primarily made by the Ni-catalyzed coupling of two halopyridines with appended chiral groups. Bolm and coworkers reported one of the first examples of non-racemic chiral 2,2'-bipyridyl ligands, **6** (Scheme 2).[9] Other examples, such as **7** and **8**, that use substituents from the naturally available chiral pool, have been developed by Kwong and coworkers.[10]

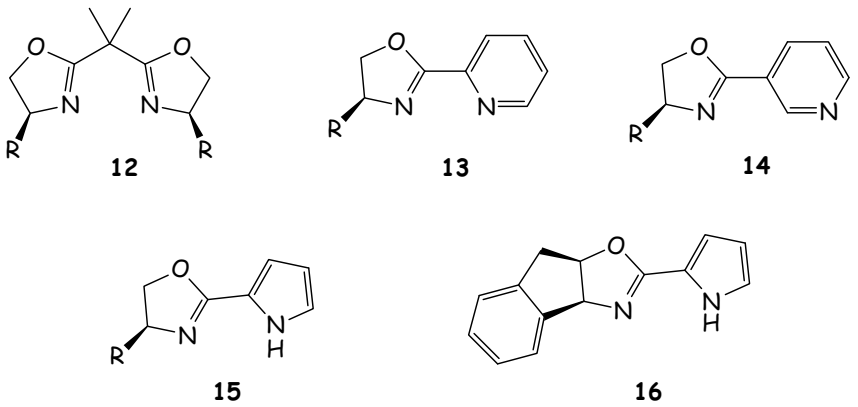


Scheme 2

C_1-symmetric variations on the bipyridine ligand scaffold have also been developed (**9**-**11**, Scheme 2). Standard synthetic protocols are based on cross-coupling reactions between

2-pyridyl derivatives and chirally substituted 6-halopyridines.[9] Another approach employs Co-catalyzed co-cyclotrimerization reactions between 2-cyanopyridines and acetylene.[11] A wide variety of such ligand scaffolds have been used for many asymmetric transformations. These primarily include: Cu-catalyzed cyclopropanations and allylic oxidations, Rh-catalyzed hydrosilylations, and alkylations using R_2Zn.

Other types of nitrogen ligands widely used in asymmetric catalytic transformations are based on the oxazoline (4,5-dihydrooxazole) ring (Scheme 3) discovered by Evans in the 1980s.[12] Oxazoline ligands could easy prepared from readily available enantiopure amino alcohols derived from reduction of naturally occurring amino acids. In this class of bidentate ligands we could found symmetric bis(oxazoline) ligands (box's) (**12**) or C_1-symmetric ligands, where togheter with the oxazoline ring is present another nitrogen heterocycle.



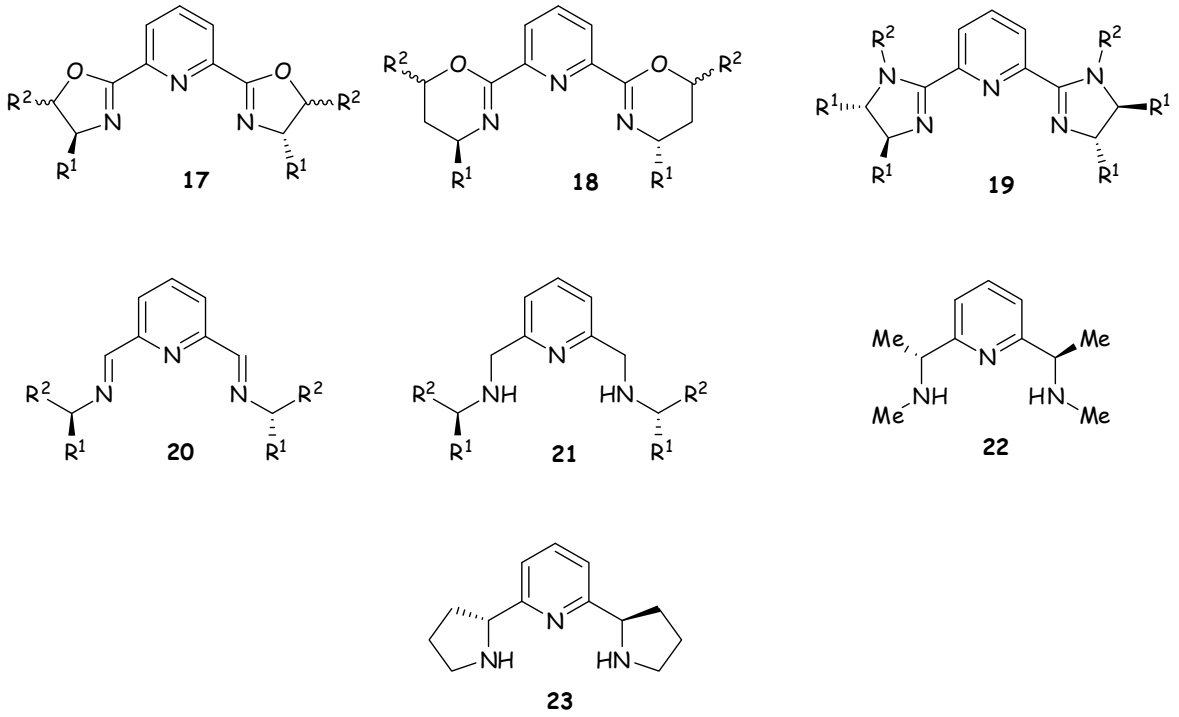
Scheme 3

C_2-symmetric bis(oxazolines) are one of the most popular classes of compounds, which have received a great deal of attention as ligands in coordination chemistry[13] and in asymmetric catalysis.[14] These ligands have two oxazoline rings separated by a spacer, and C_2-symmetric bis(oxazolines) having a single carbon atom with two identical substituents different from hydrogen as the spacer. This ligands have seen widespread and very successful application that is not possible to discuss in this thesis.

Brunner and coworkers developed the first series of pyrrolyl- (**15**, **16**) and pyridyloxazoline (**13**, **14**) ligands for asymmetric catalysis.[15] These ligands are easily and modularly made by $ZnCl_2$-catalyzed condensation of 2-cyanopyrrole (or 2-cyanopyridine) with different amino alcohols,[16] to give a library of ligands with different absolute configurations of the stereocentres and of the ligand's steric bulk. Pyridyl-2-oxazolines (**13**) were first used

as ligands in the asymmetric Cu-catalyzed monophenylation of meso-diols[17] and then more successfully applied in asymmetric Rh-catalyzed hydrosilylations, which gave enantioselectivities as high as 83%.[18] Pyrrolyl oxazoline **15** and **16** are used in the Rh-catalyzed hydrogenation of ketopantolactone[19] with lower e.e..

A significant niche in the domain of nitrogen ligands is hold by N,N',N''-terdentate ligands, especially those having C_2-symmetry (Scheme 4). The pyridine ring is present in most compounds of this type, where it has the role of a spacer between two identical N-containing moieties as in the widely used and highly performing pyridine-bis(oxazolines) **17** (Pybox's)[20] and the more recently developed pyridine-bis(oxazines) (Pyboxazines) **18**[21] and pyridine-bis(imidazolidines) **19**.[22] Both ligands **17** and **18** are readily prepared from 2,6-pyridinedicarboxylic acids and enantiopure β- and γ-aminoalcohols, respectively, without need to construct new stereocenters.



Scheme 4

Pyridinediimines **20**, which are similarly prepared from 2,6-pyridinedicarbaldehyde, have been also used as ligands in metal-catalyzed asymmetric reactions.[23] Moreover, N,N',N''-terdentate ligands **21**[24] bearing two chiral amine functions in the lateral chains of the pyridine ring were prepared from 2,6-di(chloromethyl)pyridine, then used in transamination

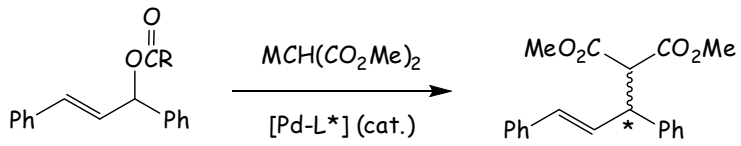
reactions with moderate enantioselectivities. However, only a few compounds with stereocenters at the benzylic positions have been described. The (*R*,*R*)- and (*S*,*S*)-enantiomers of the ligands **22**[25] and **23**[25] were obtained after separation from the *meso*-compounds and resolution of the racemic mixture or copper complex, but no application of these ligands in asymmetric syntheses has been until now described.

1.1.2 – N-Ligands in the Pd catalyzed asymmetric allylic substitution (AAA)

Metal-catalyzed asymmetric allylic substitution, which involves the attack of diverse nucleophiles at an η^3-allylic metal intermediate or S_N2'-type allylic substitution, has been investigated with great intensity.[26] Besides a high level of asymmetric induction, the advantages of this method are its tolerance of a wide range of functional groups and a great flexibility in the type of bonds that can be formed. For example, H-, C-, N-, O-, and S-centered nucleophiles can be employed. Many ligands have been designed for the benchmark allylic alkylation with 1,3-diphenylallyl acetate. It should be noted that the asymmetric alkylation of unsymmetrical allylic substrates was seldom simultaneously regio- and enantioselective. However, useful results have recently been reported because of the availability of many new chiral ligands.

Palladium is the most studied and used metal in the asymmetric allylic substitution. In the last twenty years a wide number of chiral ligands have been designed to chelate the metal for improving the enantioselectiviy of the reaction. Here I give some examples of nitrogen chiral ligands which are used in the Pd-catalyzed allylic substitution reaction and present aziridine or pyridine ring inside.

The prototype reaction to test new chiral ligands is the reaction of 1,3 diphenylpropenyl acetate **24a,b** with the anion of dimethyl malonate, in the presence of a palladium source (complex or salt) to give the substitution product **25** (Scheme 5).



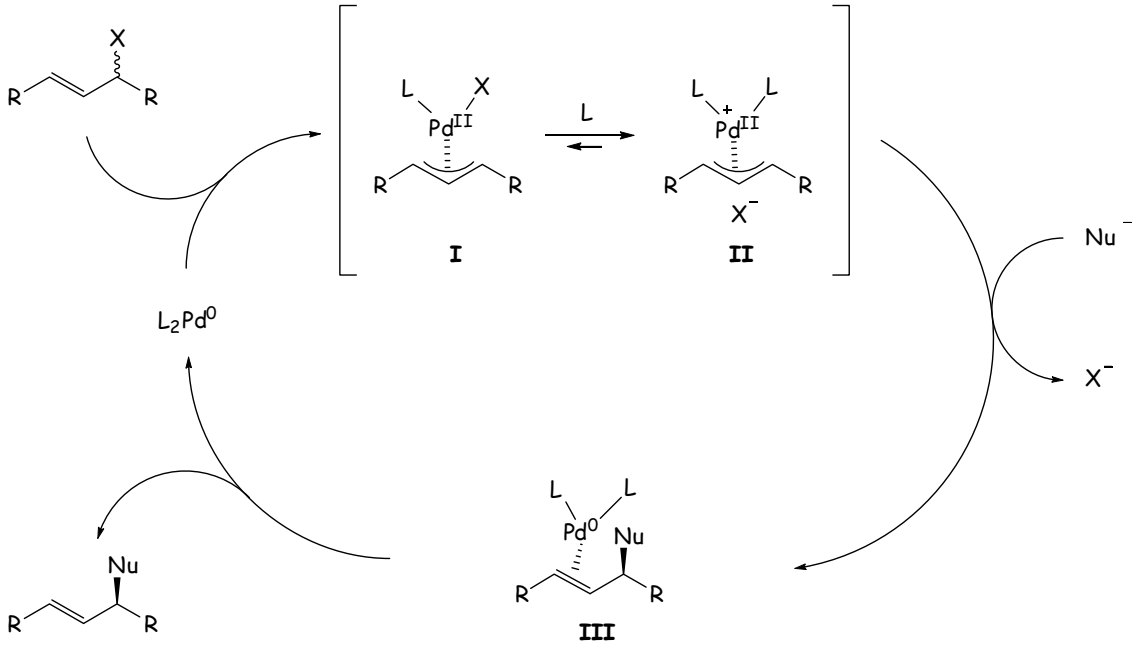
24

a: R = Me
b: R = OEt

25

Scheme 5

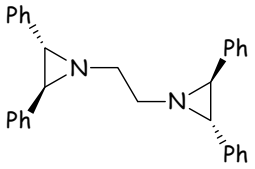
The accepted mechanism for this reaction involves first the oxidative addition of a Pd(0) specie on the allylic substrate to yield an η^3 allyl-Pd(II) complex (Scheme 6). The equilibrium between the neutral complex **I** and the cationic species **II** depends on many factors, e.g. the solvent and the nature of the ligand, but with bidentate ligands it is usually shifted to the side of the cationic complex. This is highly reactive towards soft nucleophiles, which attack at the less substituted allylic terminus leading to a η^2-olefin-Pd(0) complex **III**, then to the final product and a Pd(0) complex that restarts another catalytic cycle.



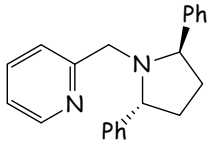
Scheme 6

In the literature are described many examples of ligands which contain the pyridine ring and efficiently catalyse this reaction in an asymmetric fashion. Chiral aziridines have been seldom used in the AAA. It is noteworthy that the C_2-symmetric bis(aziridine) **26**[27] (Scheme 7) afforded a complete enantioselectivity, while the pyridine derivative **27**[28] gave a 64% e.e. and the phenantroline derivate **29**[29] gave a 96% e.e.. In C_1-symmetric 2-(2'-pyridyl)oxazolines **29a,b**[30] and **30**[30c, 31] a remarkable effect of the substituent in both rings was observed; particularly, the substitution of Ph for the *i*-Pr group in the oxazoline was beneficial, as a better e.e. was provided by **30** with the same pyridine substituent (R = H). Most importantly, the presence of a (chiral) bulky substituent at the pyridine-C_6, or the presence of a benzo[*b*]-fused ring as in **31**, caused an increase of the enantioselectivity.[30,31]

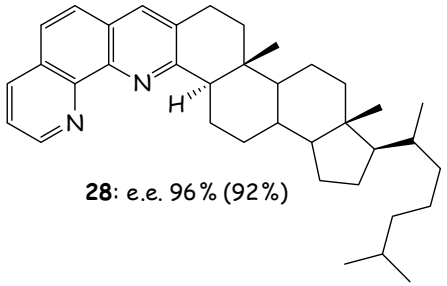
It should be observed that the ligands **30-31** form a rigid five-membered chelation ring in the cationic (η^3-allylic)Pd complexes however, six-membered chelation rings like those derived from the ligands **32-34** have been also studied. In the case of 8-quinoline-oxazolines **32**, an unexpected effect of the substitution was observed, as with R = Me[32] and the benzo[*b*]-derivative[4] the opposite enantiomer of **25** was produced. Similarly, the 2-(quinolylmethyl)oxazoline **34** displayed the opposite enantioselectivity with respect to **33**.[32]



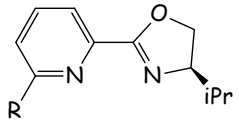
26: e.e. >99%



27: e.e. 64%

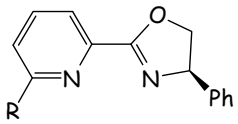


28: e.e. 96% (92%)



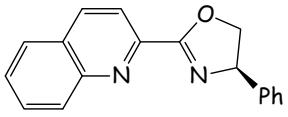
29

a: R = H, e.e. 24% (*R*);
b: R = Me, e.e. 70% (*R*)

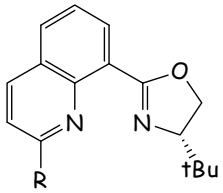


30

a: R = H, e.e. 50% (*R*) (55%);
b: R = Me, e.e. 74% (*R*) (74%);
c: R = CH_2OH, e.e. 88% (*R*);
d: R = (*S*)-CH(*t*Bu)OMe, e.e. >99% (*R*)

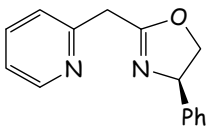


31: e.e. 73% (*R*)

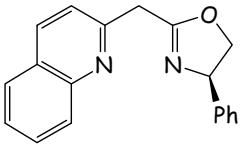


32

a: R = H, e.e. 77% (*S*);
b: R = Me, e.e. 78% (*R*)



33: e.e. 16% (*R*)

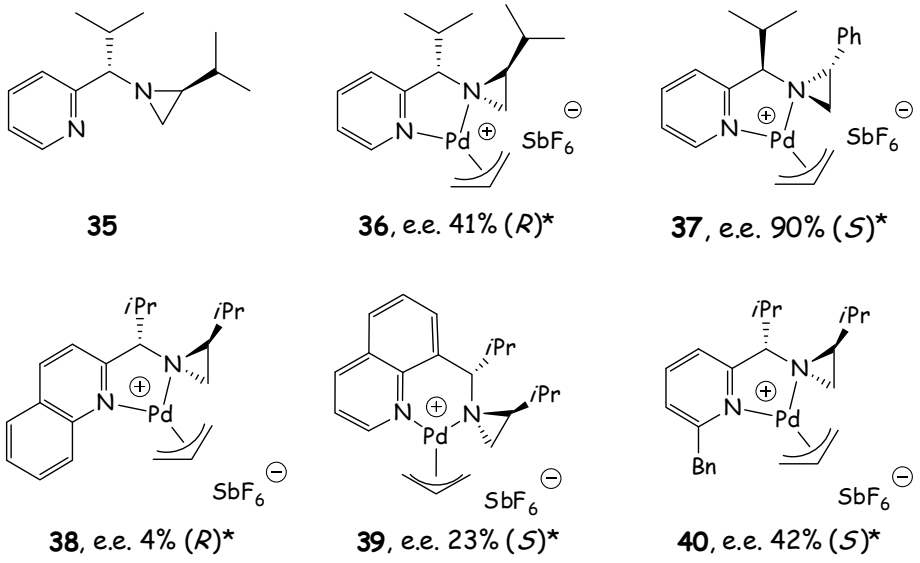


34: e.e. 78% (*S*)

Scheme 7

The Savoia's group has studied (*N*,*N*')* ligands containing both the pyridine and aziridine rings. We have described the preparation of **35** and its cationic η^3-allylpalladium complex **36** (Scheme 8), which is more effective than the free base in the above mentioned Pd-catalysed allylic substitution reaction, providing (*R*)-**25** with moderate yield and 41% e.e..[33] The ligand **35** differs from **26-32** for the presence of a stereocentre in the carbon chain linking the two rings, besides the one present on the aziridine carbon. The two

stereocentres in **35** have a combined role compelling the aziridine nitrogen to assume the *R* configuration when forming the Pd complex, as shown by the X-ray structure analysis of **36**. This happens to avoid the severe interaction of the two *i*Pr substituents, which instead would occur in the alternative complex with the *S* configuration.



35 **36**, e.e. 41% (*R*)* **37**, e.e. 90% (*S*)*

38, e.e. 4% (*R*)* **39**, e.e. 23% (*S*)* **40**, e.e. 42% (*S*)*

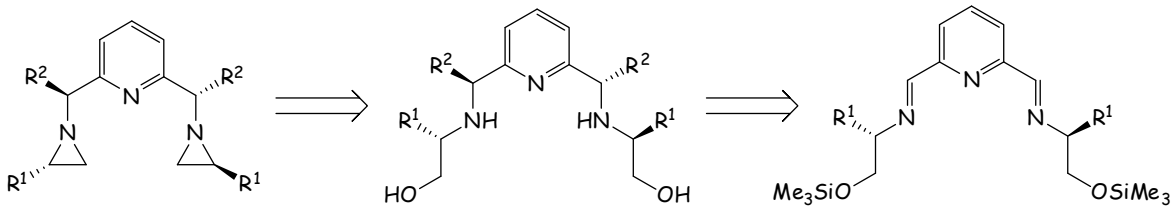
* Product's configuration

Scheme 8

After this first work, we prepared new ligands containing the aziridine and pyridine rings and then converted them to the [(*N*,*N*')*(η^3-allyl)Pd][SbF_6] complexes, which were used as catalysts in the allylic substitution reaction.[34] The ligand prepared from (*R*)-phenylglycinol (**37**) was considerably more enantioselective in the catalytic application (e.e. 90%), as a consequence of the more demanding steric effect of the phenyl substituent in the aziridine ring, which is oriented towards the Pd-allylic ligand. On the other hand, structural variations in the starting heterocyclic aldehyde (**38**-**40**), also allowing the ligand to form either a five- or six-membered chelation ring with palladium, and the substitution pattern in the aza-heteroaromatic ring had relevant effects on both reactivity and stereocontrol. Especially, inversion of enantioselectivity was observed using the ligand bearing a 6-benzyl-substituted pyridine (**40**). The moderate efficiency of the alkylation reactions catalysed by our ligands/complexes can be attributed to the weakness of the Pd-N(pyridine) bond(s), which affects the stability of [(*N*,*N*')*(η^3-allyl)Pd]$^+$ cations. Moreover, the absence of a π-acceptor *N* ligand in (*N*,*N*')* does not allow the effective stabilization/dissolution of the Pd(0) species which are formed by nucleophilic attack to the intermediate cationic complex as a matter of

fact, formation of a black palladium precipitated was observed, after that the reaction stopped.

As an evolution of these chiral pyridine-aziridine chiral ligands we envisioned a similar three step route to enantiopure C_2-symmetrical *N,N',N''*-terdentate ligands[35] involving the addition of organometallic reagents to chiral diimine derived from 2,6-pyridinedicarbaldehyde and (*S*)-valinol and (*S*)-phenylglycinol followed by conversion of the β-aminoalcohols to 2,6-**di**[1-(1-**az**iridinyl)**a**lkyl]**p**yridines (DIAZAP's) was achieved by a Mitsunobu reaction (Scheme 9). By this strategy, the carbon skeleton of the starting chiral aminoalcohol and the absolute configuration of the inherent stereocenters are retained in the final molecule. The new ligands were then used in palladium catalyzed asymmetric allylic alkylation (*AAA*) of stabilized carbanions, where they provided higher enantioselectivity with respect to the analogous, previously described, bidentate pyridine-aziridine ligands.[33,34] Our idea was also based on the report that a higher reaction rate was obtained using a *P,N,N*-terdentate ligand instead of a bidentate *P,N*-ligand in Pd-catalyzed *AAA* reactions;[36] a result that may have been the consequence of the capability of the terdentate ligand to effectively stabilize either Pd(0) or the (allylic)Pd(II)$^+$ complexes involved in the catalytic cycle. However, in the case of our terdentate ligands, taking into account the effects of substituents in the bidentate ligands on enantioselectivity, it was difficult to foresee the importance of the C6 pyridine substituent (aziridine-alkyl group), which could potentially oppose the asymmetric induction of the aziridine substituent.



Scheme 9

1.2 - Results and discussion

1.2.1 – Preparation of the DIAZAP Ligands

The starting *O*-silylated diimines **41a** and **41b** (Scheme 10) were prepared in almost quantitative yields by the protocol previously described for the analogous monoimines,[33,34,37]

and were used directly in the following step without purification. As stated before, Grignard reagents and allylic zinc reagents were not effective and lead generally to mixture of products coming from the further attack to the pyridine moiety. Organolithium compounds were found to be the reagents of choice to achieve a highly efficient, regio- and diastereoselective double addition to the azomethine groups in anhydrous tetrahydrofuran (THF) at -78 °C (Table 1Table 1). 3,3-Dimethylbutyllithium was prepared by the reaction of *t*-butyllithium (2 equivalents) with THF (solvent) at room temperature, involving the addition of *t*-butyllithium to ethylene, which is formed together with the lithium enolate of acetaldehyde following the initial cleavage of THF by *t*-butyllithium.[38] It is noteworthy that almost all the reactions gave the expected products **42a** and **42b** in high yields and with very high diastereoselectivities (Table 1). As a matter of fact, apart from the addition of *t*-butyllithium to both imines (entries 3 and 8), which provided the corresponding aminoalcohols with low diastereomeric ratios, the reactions of organolithium reagents with the valinol-derived imine **41a** occurred in most cases with higher diastereoselectivities (d.r. of **42a** 94:6) with respect to the phenylglycinol-derived imine **41b** (d.r. of **42b** 91:9). For the imine **41a**, the best result was obtained with phenyllithium, which afforded the aminoalcohol **42ae'** in 95% yield and d.r. 98:2. However, the addition of methyllithium to **41b** (entry 6) was even more diastereoselective, as the pure compound (*S*,*S*)-**41ba'** was obtained in 94% yield after column chromatography of the crude reaction product, no trace of the other diastereomers were detected by ^{1}H NMR spectroscopy.

It should be observed that all the organometallic additions produced only two of three possible diastereomers of the compounds **42**: the prevalent one had C_2-symmetry, as observed by ^{1}HNMR spectroscopy. The *S*,*S* configuration of the two newly formed stereocenters at the benzylic positions was at first assumed considering the sense of asymmetric induction previously observed in the addition of organolithium reagents to the analogous 2-pyridine monoimine,[37] and was then confirmed by the X-ray structure obtained for one palladium complex (see later). Column chromatography of the crude reaction products often allowed isolation of the main diastereomer only, however, enriched chromatographic fractions of the minor diastereomer were obtained, allowing its C_1 symmetry to be determined. In particular, the separation of the diastereomers was difficult for **42aa'** and **42ac'**, and low yields of the pure main (*S*,*S*)-diastereomer were obtained. In these cases, it was preferable to merely filter the crude reaction mixtures through a small pad of silica and use the diastereomeric mixtures in the subsequent step, that is the cyclization to DIAZAP's

43aa' and **43ac'**, since the diastereomers of the latter compounds were more readily separated by chromatography.

Scheme 10

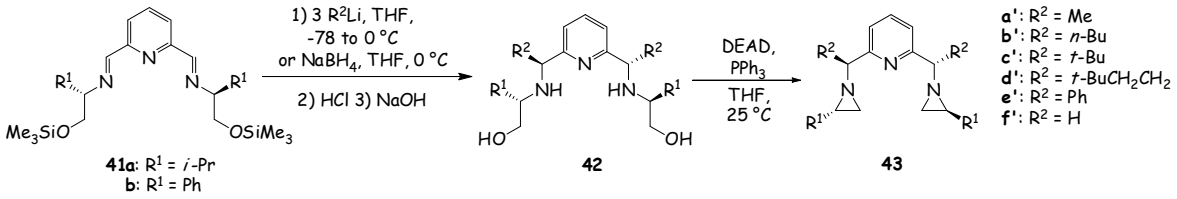


Table 1

Entry	Imine (R1)	R_2Li	Product	D.r.[a]	42, Yield %[b]	43, Yield %[c]
1	**41a** (*i*-Pr)	MeLi	42aa′	95:5	95	**43aa'** (85)
2	"	*n*-BuLi	42ab′	95:5	95 (79)[c]	**43ab'** (87)
3	"	*t*-BuLi[d]	42ac′	84:16	95 (54)[c]	**43ac'** (84)[e]
4	"	*t*-BuCH_2CH_2Li[f]	42ad′	94:6	84 (70)[c]	**43ad'** (86)
5	"	PhLi	42ae′	98:2	95	**43ae'** (90)
6	**41b** (Ph)	MeLi	42ba′	>99:1	94[g]	**43ba'** (85)
7	"	*n*-BuLi	42bb′	91:9	93 (76)	**43bb'** (90)[h]
8	"	*t*-Bu[d]	42bc′	86:14	94(59)	**43bc'** (86)[i]
9	"	PhLi	42be′	92:8	98 (84)	**43be'** (89)[j]

[a] Determined by ^{1}H NMR spectroscopy of the crude reaction products. [b] Yield of the crude reaction product. Unless otherwise indicated, the diastereomers were not separated. [c] Yield of pure (*S,S*)-**42** isolated after column chromatography. [d] The reaction was performed in diethyl ether. [e] The product was obtained after column chromatography as a 89:11 mixture of diastereomers. [f] The reagent was prepared in situ by adding *t*-BuLi to THF (solvent) at 0 °C. [g] The crude product was apparently pure by ^{1}H NMR spectroscopy. [h] The product was obtained after column chromatography as a 91:9 mixture of diastereomers. [i] The product was obtained after column chromatography as a 86:14 mixture od diastereomer. [j] The product was obtained after column chromatography as a a 92:8 mixture of diastereomers.

The reaction protocols that were successful for the construction of the mono-aziridine ligands did not give good results. Instead we found that the Mitsunobu reaction using diethylazadicarboxylate (DEAD) and triphenylphosphine in THF at room temperature gave much better results. DIAZAP's **43a** and **43b** were so obtained with high yields. In the case of phenylglycinol derivatives, the diastereomers of the aminoalcohols **42bb'**, **42bc'** and **42be'** and the corresponding aziridines **43bb'**, **43bc'** and **43be'** could not be separated.

1.2.2 – Pd-Catalyzed AAA in presence of DIAZAP ligand: substituent effects

A number of reactions were carried out on the allylic carbonate **24b** with the anion of dimethyl malonate, generated by treatment of dimethylmalonate with either sodium hydride or bis(trimethylsilyl)amide (BSA) and a catalytic amount of potassium acetate in different solvents (Scheme 11, Table 2). Allylpalladium chloride dimer and the terdentate ligands **43a** and **43b** were used as precursors of the effective enantioselective catalyst. The ligands derived from (*S*)-valinol were examined first. The carbonate **24b** was treated with the pre-formed sodium salt of dimethyl malonate (1.5 molar equivalents) and catalytic amounts of allylpalladium chloride dimer (5 mol%) and ligand **43aa'** (10 mol%) in tetrahydrofuran at room temperature. The course of the reaction was monitored by GC and TLC analysis and an almost complete conversion of the starting compound was observed after 24 h. The product **25** was isolated in high yield and 76% e.e. in favour of the *R* enantiomer (Table 2, entry 1). It should be observed that use of performer palladium salt [(η^3-allyl)(**43aa'**)Pd][SbF_6] was unnecessary. In fact a smooth reaction occurred and the formation of black palladium was observed only when the reaction was almost complete. In a second run (entry 2) at -20 °C, with all the other experimental conditions being unchanged, we observed that the same e.e. was obtained, but a longer reaction time was required to obtain a satisfactory yield of product. Hence, all the successive reactions were carried out at 25 °C.

The role of the solvent was then examined and it was found that the reaction took place also in dichloromethane, despite the poor solubility of sodium dimethyl malonate and the consequent lower reaction rate, but a slightly lower e.e. was obtained (entry 3). The same trend was observed when the *n*-butyl substituted ligand **43ab'** was used in both solvents, but the e.e.'s (60-63%) were lower (entries 4, 5). Similar results were obtained with the *t*-butyl substituted ligand **43ac'** (used as a 84:16 mixture of unseparable diastereomers) and the ligand **43ad'** (R2 = *t*-BuCH_2CH_2) in different experimental conditions. Finally, the phenyl

substituted ligand **43ae'** provided high levels of enantioselectivity with e.e. up to 88% in entry 12.

Scheme 11

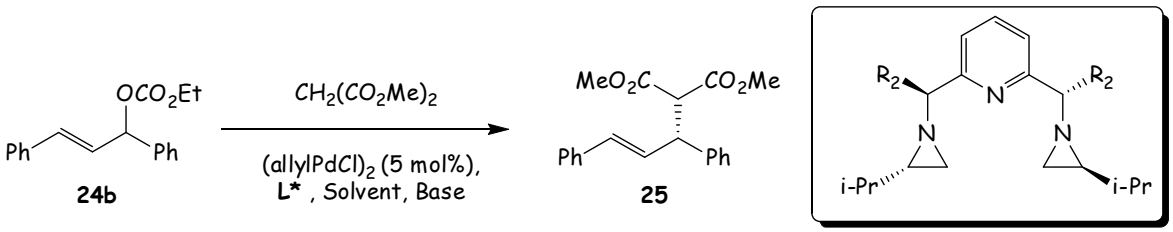


Table 2

Entry	Ligand (mol%)	Base	Solvent	Time (h)	Yield (%)	E.e. (%)
1	**43aa'** (10)	NaH	THF	24	79	76
2	**43aa'** (10) [b]	"	THF	96	69	76
3	**43aa'** (10)	"	CH_2Cl_2	48	85	73
4	**43ab'** (10)	"	THF	24	81	63
5	**43ab'** (10)	"	CH_2Cl_2	48	86	60
6	**43ac'** (10, d.r. 89:11)	BSA/AcOK	CH_2Cl_2	48	84	69
7	**43ad'** (10)	NaH	THF	48	86	70
8	**43ad'** (10)	BSA/AcOK	CH_2Cl_2	16	90	62
9	**43ae'** (10)	NaH	THF	24	85	76
10	**43ae'** (10)	NaH	CH_2Cl_2	18	89	86
11	**43ae'** (10)	BSA/AcOK	CH_2Cl_2	15	90	82
12	**43ae'** (10)	BSA/AcOLi	CH_2Cl_2	24	89	88
13	**43af'** (10)	BSA/AcOK	CH_2Cl_2	24	87	13

Again, we wanted to demonstrate the need of a substituent at the benzylic positions since this would induce the stereoselective formation of the *N*-aziridine stereocenter in the cationic palladium complex. It should be observed that *N*-alkyl aziridines are not pyramidally stable at room temperature, and the bulkiness of the substituent decrease the barrier of inversion.[39] As demonstrated in the previous chapter, all the previously prepared η^3-allylic palladium complexes carrying bidentate (*N,N*)*-ligands displayed a unique configuration of the aziridine nitrogen atoms, that is dictated by the configuration of the benzylic carbon

stereocenters and minimises the steric interactions between the benzylic (R^2) and aziridine (R^1) substituents. To that purpose, we synthesized the ligand **43af'** by reduction of the diimine **41a** to give the intermediate diaminediol **42a,f'**, followed by the usual cyclization step (Scheme 10). The correctness of our hypothesis was demonstrated by the observation that the typical allylic alkylation of sodium dimethyl malonate with the allylic carbonate **24b** in THF at 25 °C in the presence of 10 mol% of ligand **43af'** occurred with very low enantioselectivity (13% e.e., entry 13).

Scheme 12

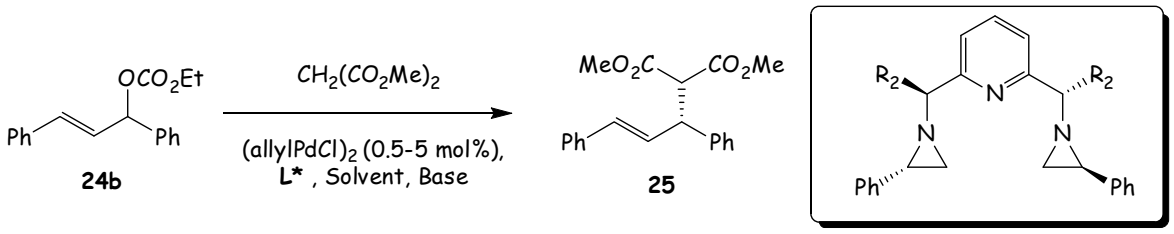


Table 3

Entry	Ligand (mol%)	Base	Solvent	Time (h)	Yield (%)	E.e. (%)
1	**43ba'** (10)	NaH	THF	72	82	82
2	**43ba'** (10)	NaH	CH_2Cl_2	3	90	98
3	**43ba'** (10)	BSA/AcOK	CH_2Cl_2	2	92	98
4	43ba' (3)	BSA/AcOK	CH_2Cl_2	8	87	98
5	43ba' (3)	BSA/AcOLi	CH_2Cl_2	5	90	98
6	43ba' (1)	BSA/AcOK	CH_2Cl_2	38	68	98
7	**43bb'** (10, d.r. 91:9)	NaH	THF	48	77	80
8	**43bb'** (10, d.r. 91:9)	BSA/AcOK	CH_2Cl_2	16	89	81
9	**43bc'** (10, d.r. 86:14)	BSA/AcOK	CH_2Cl_2	48	64	70
9	**43be'** (10, d.r. 92:8)	BSA/AcOK	CH_2Cl_2	16	88	83
10	**43bf'** (10)	BSA/AcOK	CH_2Cl_2	24	92	76

The terdentate ligands **43b**, derived from (*S*)-phenylglycinol and hence carrying phenyl substituents on the aziridine rings, were then examined in the same typical *AAA* reaction (Table 3). (*R*)-**25** was formed in all cases with e.e.'s definitely superior to those

obtained with the corresponding (*S*)-valinol-derived ligands **43a**. For example, using sodium hydride as the base in THF in the presence of allylpalladium chloride dimer (5 mol%) and the ligand **43ba'** (10 mol%) the product (*R*)-**25** was obtained with 82% yield and 82% e.e. after 72h (entry 1,
Table 3). Then, we observed that in dichloromethane, despite the very low solubility of sodium dimethyl malonate, the reaction with the ligand **43ba'** was almost complete after only 3 h and the product was obtained with excellent yield and 98% e.e. (entry 2). The same level of enantioselectivity was obtained by performing the reaction with the same ligand and generating the nucleophile by the alternative protocol (BSA-AcOK in DCM, entry 3), even with reduced amounts of ligand (1 mol%, entries 4 to 6).

It was apparent that an increase in the bulkiness of the R^2 substituents in the ligands **43b** caused a decrease of the reaction rate. The *n*-butyl- and phenyl-substituted ligands **43bb'**, **43bc'** and **43be'** were used as an unseparable mixture of diastereomers, with the (*S*,*S*) and (*S*,*R*) configurations of the two benzylic stereocenters (d.r. 91:9, 86:14 and 92:8, respectively); nevertheless high e.e.'s were obtained (e.e.'s 80, 81, 70 and 83% in entries 7 to 9). Finally, we were surprised to find that the ligand **43bf'** (R2 = H, Scheme 1), in contrast to the analogous (*S*)-valinol-derived **43af'** (13% e.e., entry 13 Table 2), provided a moderate enantioselectivity (76% e.e., entry 10 Table 2).

1.2.3 – Pd-Catalyzed AAA in the presence of DIAZAP ligand: Pd source.

The role of different palladium sources was briefly investigated carrying out the allylation of the malonate anion (BSA, AcOK) with the carbonate **24b** in the presence of the ligand **43ba'** in dichloromethane at 25 °C (Scheme 13). In comparison with the reaction catalyzed by allylpalladium chloride dimer (entry 1, Table 4), which was almost complete after only 3 h, the reactions catalyzed by palladium acetate, palladium chloride and the dibenzylideneacetonate complex required 24 h to give comparable yields and slightly lower e.e.s; up to 85% yield and 96% e.e. were obtained with the latter catalyst (entry 4).

Scheme 13

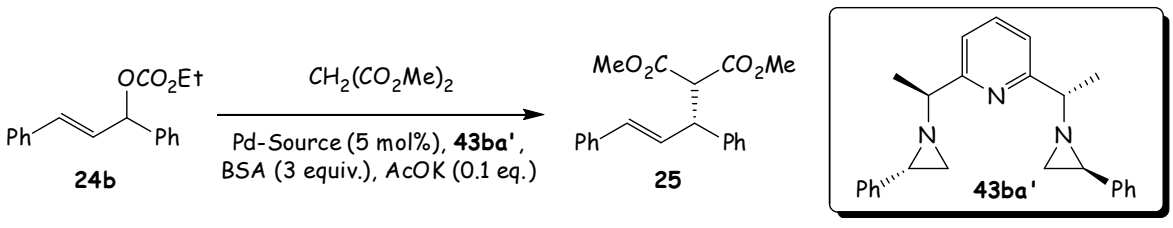
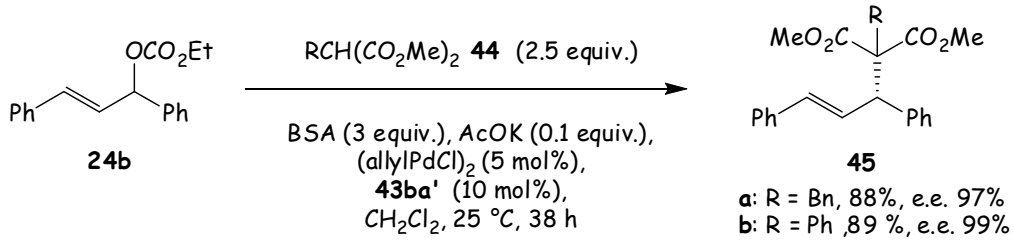


Table 4

Entry	Pd catalyst (5 mol%)	Time (h)	Yield (%) of (*S*)-25	E.e. (%)
1	$(allylPdCl)_2$	3	87	98
2	$Pd(OAc)_2$	24	76	87
3	$PdCl_2$	24	81	94
4	$Pd(dba)_2CHCl_3$	24	85	96

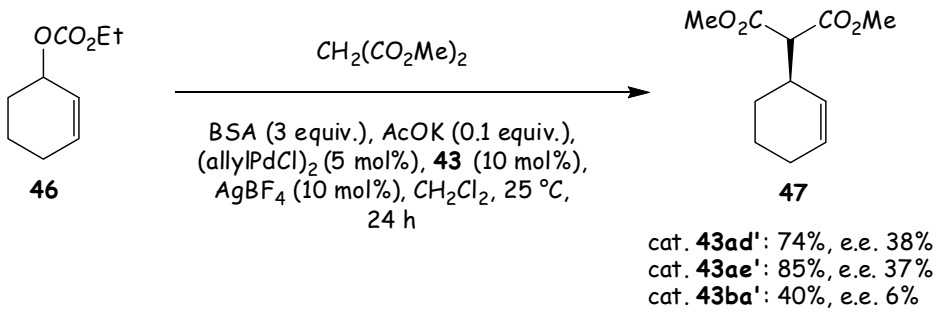
1.2.4 - Pd-Catalyzed AAA in presence of DIAZAP ligand: different nucleophiles and substrates

Then, to extend the scope of our catalytic system, we investigated the AAA reactions of other stabilized enolates as well as diversely substituted allylic carbonates. The enolates derived from substituted malonates have been relatively less employed as nucleophiles, and chiral (*P,P*), (*P,N*) and (*N,P,N*) ligands have been used.[40] We were pleased to find that the alkylations of the benzyl- and phenyl-substituted malonate esters **44a** and **44b**, respectively, proceeded smoothly in the presence of the ligand **43ba'** to give the products **45a** and **45b** in high yields and with 97-99% e.e.'s. The *S* configuration of the stereocenter in **45a** was assigned on the basis of the optical rotation (-)[40c]. Since the new compound **45b** is also levorotatory **45a**, the same configuration is assumed.



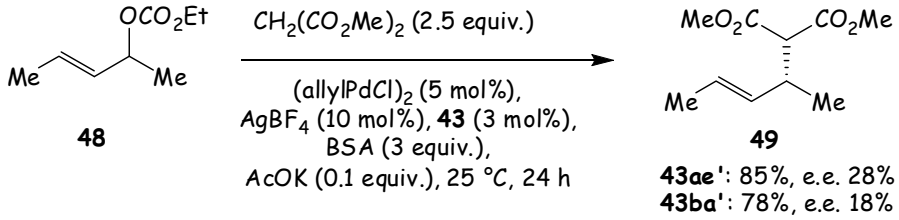
Scheme 14

The cyclohexenyl carbonate **46** was poorly reactive in the usual experimental conditions and the e.e. of the derived product **47**[41] was low. For example, using ligand **43ba'**, a 40% yield and 6% e.e. were achieved, whereas a 68% yield and 37% e.e. were obtained with the ligand **43ae'**, in both cases after 3 days. The reaction rate could be slightly increased in the presence of silver tetrafluoroborate, and good yields of the cyclohexenyl-substituted malonate **19** were obtained after 2 days using either ligand **43ad'** or **43ae'**, but the e.e. did not exceed 38%. Surprisingly, the use of ligand **43ba'** resulted in a low yield of **47** (40%) and very low e.e. (6%).



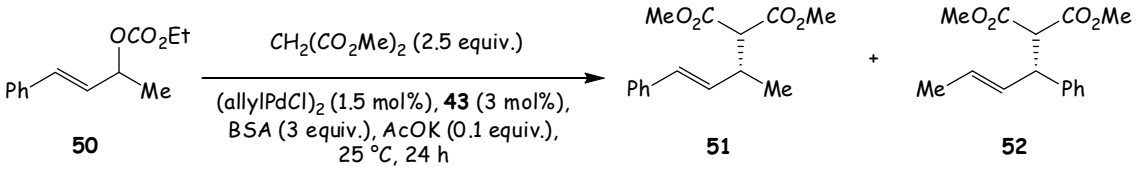
Scheme 15

Similarly, the reaction of dimethyl malonate anion with ethyl 3-penten-2-yl carbonate **48** (Scheme 16) in the presence of the ligands **43ae'** and **43ba'** afforded the substitution product **49** in good yields in the presence of $AgBF_4$, but with low e.e.s (up to 28%).



Scheme 16

Performing the reaction an the unsymmetrically disubstituted allylic carbonate **50** (Scheme 17), a mixture of products (ratio 95:5) was obtained, as usually found with other ligands:[42] the prevalent product **51** was formed by attack at the methyl-substituted allylic terminus with low enantioselectivity (e.e. 14%), whereas the minor regioisomer **52** was obtained with 95% e.e..



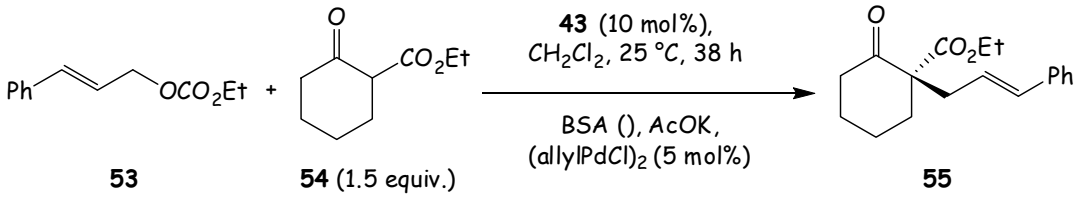
43ba': 88%, **51**/ **52** = 95:5, e.e. **51** 14%, e.e. **52** 95%
43ae': 89%, **51**/ **52** = 85:15, e.e. **51** 10%, e.e. **52** 95%

Scheme 17

Finally, we turned our attention to the capability of our catalytic system to induce enantioselectivity in the formation of a quaternary stereogenic center at the nucleophilic carbon. This goal should be achieved by the discrimination of the two diastereotopic faces of a fully substituted planar enolate attacking the η^3-allylic ligand. This is difficult to realise because the chiral *N,N,N*-ligand does not interfere in any way with the incoming nucleophile,

and the newly formed stereocenter is more remote from the inducing stereocenter(s) than in previous experiments. Hence, we investigated the reaction of (*E*)-cinnamyl ethyl carbonate **53** (Scheme 18) with the anion derived from 2-ethoxycarbonylcyclohexanone **54** under different reaction conditions. The reaction proceeded smoothly to give the linear alkylation product **55** with high yield but only 27% e.e.. An increase in the enantioselectivity was observed when we used a lithium enolate as nucleophile but a decrease of the yield was observed. This result can be compared with the reported Pd-catalyzed enantioselective synthesis of **55** using a *P*-chirogenic diaminophosphine oxide as the ligand, where 92% e.e. was obtained.[43] We assigned the *S* configuration to the major enantiomer of **55** by comparison with the authentic enantiomer.[43]

Scheme 18



53 **54** (1.5 equiv.) **55**

Table 5

Entry	Ligand	Base	Time (h)	Yield (%) of 55	E.e. (%)
1	43ab'	NaH	2	95	13
2	43ae'	BSA/AcOK	24	84	5
3	43ba'	BSA/AcOK	38	83	27
4	43ba'	BSA/AcOLi	72	68	35

1.3 – Tentative explanation of mechanism and enantioselectivity

Aiming to get information on the possible structural factor effecting the enantioselctivity, we prepared different (allyl)- and (1,3-diphenylallyl)Pd^+ salts bearing the (*S*)-valinol- and (*S*)-phenylglycinol-derived ligands, **43ae'** and **43ba'**, with PF_6, SbF_6 or BF_4 counterions, were prepared by standard methodology. These salts were generally obtained as white or yellowish powders, and some of them appeared impure by ^1H NMR analysis. Up till now, we have succeeded to obtain crystals suitable for X-ray crystallographic structure determinations only in the case of the salt [(**43ae'**)(allyl)Pd][PF_6].

The crystal structure is quite similar to those of the previously reported allylic palladium salts with pyridine-aziridine ligands,[37] featuring the bidentate coordination of the ligand to palladium cation and the η^3 hapticity of the *endo*/*exo* allyl ligand. The palladium-aziridine bond is shorter than the palladium-pyridine bond (2.109(3) vs 2.158(3) Å), and the terminal allylic carbon *anti* to the aziridine form a bond with palladium (2.178(4) Å) longer than the allylic terminus *anti* to the pyridine ring (2.126(4) Å). This observation supports the hypothesis that the allylic terminus *anti* to the aziridine has a more electrophilic character. The ^{1}H NMR spectra of the CD_2Cl_2 solutions of this salt and all the other [(allyl)- or (1,3-diphenylallyl)(**43a** or **43b**)]Pd^+ salts with PF_6^-, SbF_6- and BF_4^- counterions were complex and showed broad absorptions, indicating the presence of several species, although the *endo*- and *exo*-(η^3-allyl) (N,N)Pd^+ species were predominant. Most importantly, in the case of the 1,3-diphenylallyl complexes, a higher ratio of rotamers (>3:1) was observed for the complex derived from the ligand **43ba'**, which afforded the highest enantioselectivity. Moreover, the spectra were complicated by the lack of C_2-symmetry of the ligand complex, demonstrating that only one aziridine nitrogen was involved in Pd coordination. For example, for each rotamer, distinct absorptions were observed for the two benzylic protons.

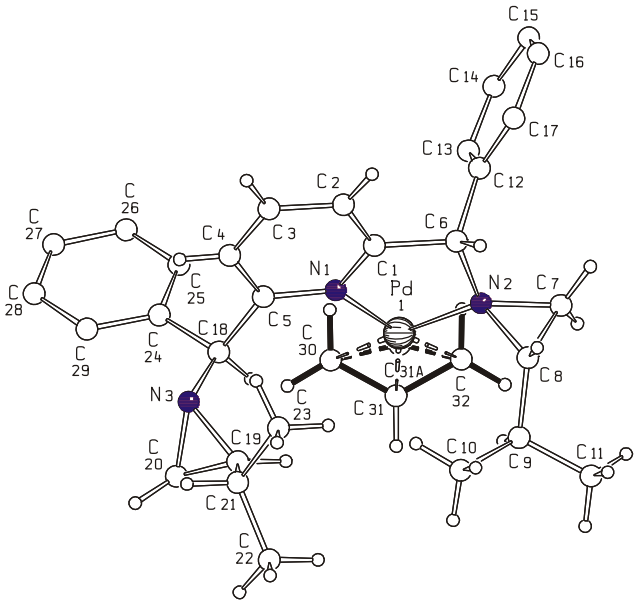
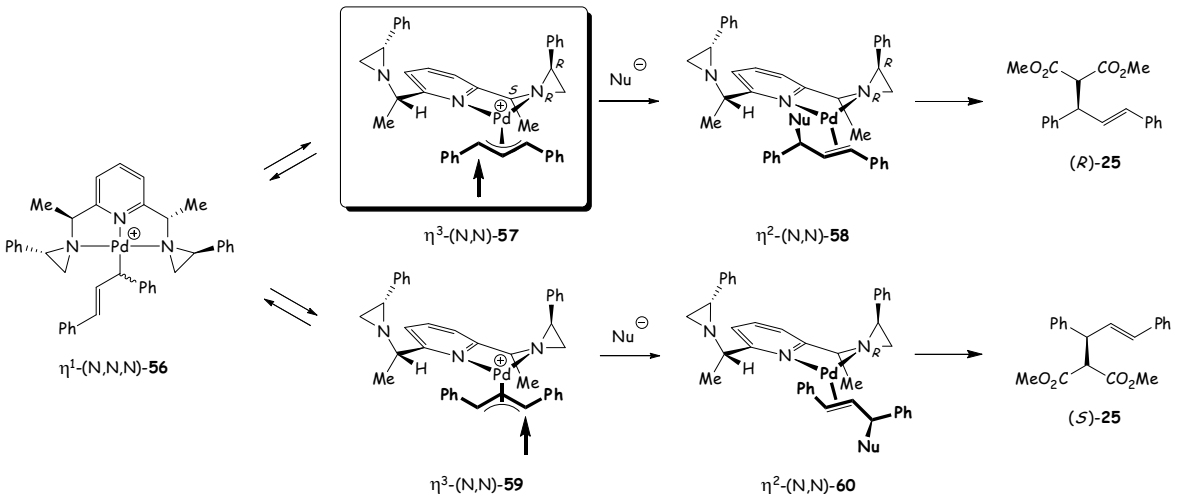


Figure 1

In the absence of information on the reactive intermediate involved in the enantioselective step, we can only speculate on the the origin of the enantioselectivity. We take into account the available structural information of the bidentate complex **40** and the

mechanistic hypothesis that has been suggested to explain the sense of asymmetric induction provided by such ligands.[37] Moreover, several studies on the binding properties of potentially terdentate ligands towards (allyl)Pd(II) cations have been reported.[44,45,46] For example, the X-ray crystal structure of a (terpyridine)(allyl)palladium complex has been determined and its dynamic behaviour in solution has been studied by ^{1}H- and ^{13}C-NMR spectroscopy.[47] It was therein shown that terpyridine binds the (η^1-allyl)Pd^+ fragment in the terdentate fashion and . η^3-allyl)Pd^+ as a bidentate ligand. In fact, the two species are present both in the crystal and in a CD_2Cl_2 solution in a dynamic equilibrium, which is strongly displaced towards the η^3-allyl form at low temperature. On the other hand, the 2,6-bis(diphenylphosphanylmethyl)pyridine (*PNP*) ligand in the complex [(*PNP*)(allyl)Pd][BF_4] adopts the terdentate coordination mode both in the crystal and in solution, where the complex is fluxional through η^1-η^3 equilibrium processes.[45,46] This is in contrast to the behaviour of (*N,P,N*) ligands which act as (*P,N*)-bidentate ligands in (η^3-dimethylallyl)Pd^+ complexes.[48] Similarly, the presence of the pyridine ring in a chiral (*P,N,N*) ligand was unnecessary for high selectivity in the *AAA* reaction, suggesting that the ligand acts in a (*P,N*)-bidentate fashion.[49]



Scheme 19

On the basis of the precedent studies, we believe that the prevalent rotamer of the reactive (η^3-1,3-diphenylallyl)(N,N,N)Pd+ complex is **57** (Scheme 19), featuring the *syn,syn*-configuration of the allylic ligand and reduced interactions of the allylic phenyl groups and the aziridine substituent. Moreover, in solution the chiral aziridinylalkyl substituent not involved in palladium chelation should take the same spatial arrangement as observed in the

crystal structure, with the methine hydrogen oriented towards the allylic ligand in order to reduce the steric interactions. Obviously, owing to the C_2-symmetry of the nitrogen ligand, identical η^3-(N,N)-complexes are formed when one or the other aziridine nitrogen is involved in Pd coordination. The complex **57** is equilibrium with the less stable complex **59** trought the (η^1-1,3-diphenylallyl)(*N,N,N*)Pd+ where all the nitrogen chelating the metal.

If this assumption is correct, the sense of enantioselectivity is easily explained by the attack of the nucleophile on the more electrophilic allylic terminus *anti* to the aziridine nitrogen of the more stable intermediate **57** to give the (η^2-alkene)Pd(0) complex η^2-(N,N)-**58**. The regioselectivity of the nucleophilic attack is also favoured by the preferential clock-wise rotation of the hydrocarbon ligand occurring during the formation of the most stable (η^2-alkene)Pd complex **58**, as the steric interactions between the alkene and the nitrogen ligand are reduced concurrently.

1.4 - Conclusion

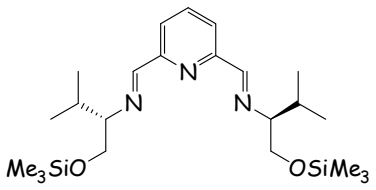
C_2-symmetrical *N,N',N''*-terdentate ligands featuring two aziridine rings in the lateral arms of a pyridine ring are constructed by a short and efficient route starting from commercially available building blocks: 2,6-pyridinedicarbaldehyde, optically pure β-aminoalcohols and organolithium reagents. These ligands (DIAZAP's) induce high levels of enantioselectivity (e.e. up to 98%) in the allylic alkylation of dimethyl malonate anion and analogous C2-substituted anions. Contrary to the corresponding bisdentate ligands derived from 2-pyridinecarbaldehyde, the DIAZAP ligands are capable of stabilizing both cationic and zerovalent palladium, thus avoiding the ready interruption of the catalytic cycle by deposition of Pd black. Unfortunately, application of these ligands in the allylic alkylation of different nucleophiles has met with low enantioselectivity or no success. However, it is expected that they can be used in other transition metal catalyzed reactions.

1.5 – Experimental section

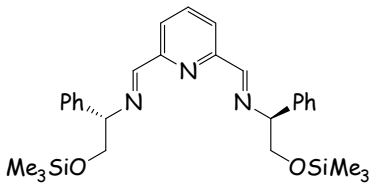
1.5.1 – General protocol for the preparation of Imines ***41***

To a solution of (*S*)-valinol (6 mmol, 0.618 g) or (*S*)-phenylglycinol (6 mmol, 0.823 g) in THF (50 mL) was added anhydrous $MgSO_4$ (5 g), the aldehyde (3 mmol, 0.405 g) and the

mixture was stirred overnight. The solid phase was filtered off on a pad of Celite and the organic solvent was evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 (20 mL) and triethylamine (7 mmol, 0.708 g) and chlorotrimethylsilane (7 mmol, 0.97 mL. 0.760 g) were added at 0 °C. After 3 h the solvent was removed under vacuum. A solution of cyclohexane/diethyl ether 1:1 was added and the solid phase was filtered off on a pad of Celite. The organic solvent was evaporated under reduced pressure to leave the imine in almost quantitative yield; this was used in the following step without further purification.



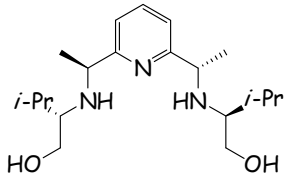
***N,N'*-Bis((*S*)-1-trimethylsilyloxy-3-methyl-butan-2-yl)-2,6-bis(imino)pyridine (41a)**: Yellowish oil; $[\alpha]_D^{25}$ = -19.7 (c 0.7, $CHCl_3$); 1H NMR ($CDCl_3$, 200 MHz): δ = 0.05 (s, 18 H), 0.92 (d, *J* = 6.9 Hz, 6 H), 0.94 (d, *J* = 6.9 Hz, 6 H), 2.0 (sept, *J* = 6.9 Hz, 2 H), 3.1 (m, 2 H), 3.69 (dd, *J* = 7.8 Hz, *J* = 10.3 Hz, 2 H), 3.89 (dd , *J* = 4.3 Hz, *J* = 10.3 Hz , 2 H), 7.76 (t, *J* = 7.6 Hz, 2 H), 8.07 (d, *J* = 7.6 Hz, 1 H), 8.36 (s, 2 H); 13C NMR (CDCl3, 50 MHz): δ = -0.4, 18.5, 20.0, 29.9, 64.3, 78.4, 121.9, 136.7, 154.5, 161.6; IR (neat): ν = 2958, 2872, 1648, 1585, 1569, 1457, 1251, 1107,1077, 877, 841, 746 cm^{-1}; *GC-MS m/z* : 73 (100), 171 (70), 346 (36), 103 (27), 316 (11), 449 (10, M).



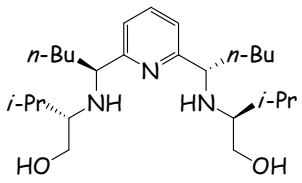
***N,N'*-Bis((*S*)-2-trimethylsilyloxy-1-phenylethyl)-2,6-bis(imino)pyridine (41b)**: white solid; m.p. = 117 °C; $[\alpha]_D^{25}$ = +25.1 (c 0.8, CHCl3); 1H NMR (CDCl3, 200 MHz): δ = 0.02 (s, 18 H), 3.89 (d, *J* = 1.7 Hz, 2 H), 3.91 (s, 2 H), 4.52 (dd, *J* = 5.6 Hz, *J* = 7.8 Hz, 2 H), 7.2-7.4 (m, 7 H), 7.5-7.6 (m, 3 H), 7.81 (t, *J* = 7.6 Hz, 1 H), 8.20 (d, *J* = 7.6 Hz, 2 H), 8.49 (s, 2 H); 13C NMR (CDCl3, 50 MHz): δ = - 0.4, 67.6, 76.7, 122.2, 127.4, 128.4, 136.7, 140.7, 155.4; IR (Nujol): ν = 3067, 3029, 1647, 1364, 1251, 1118, 1081, 1054, 884, 841, 757, 699 cm^{-1}.

*1.5.2 – Preparation of β-Aminoalcols **42** by additin of organolithium reagents ti imines **41**:*

Organolithium reagent (9 mmol) was added to a magnetically stirred solution of the imine **41** (3 mmol) in THF (10 mL) cooled to –78 °C. After 30 minutes, the reaction mixture was slowly warmed at 0 °C, and quenched after 3 h by adding 1 N HCl (10 mL). After 2 h NaOH pellets were added until the solution reached pH 11, and the organic phase was extracted with diethyl ether (3 ×10 mL). The collected ethereal phases were dried over Na_2SO_4 and concentrated to leave the crude products. The diastereomeric ratio was determined by ^1H NMR analysis. Flash column chromatography (SiO_2), eluting with cyclohexane/ethyl acetate mixtures, gave the product which was directly used in the subsequent step.

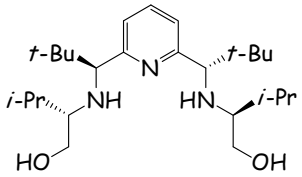


***N,N'*-Bis((*S*)-1-hydroxy-3-methyl-butan-2-yl)-2,6-bis((*S*)-1-aminoethyl)pyridine (42aa')**: White solid; m.p. = 86 °C; $[\alpha]_D^{25}$ = -74.6 (c 0.18, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ = 0.81 (d, *J* = 6.8 Hz, 6H), 0.86 (d , *J* = 6.8 Hz, 6 H), 1.37 (d, *J* = 6.7 Hz, 6 H), 1.65 (sept, *J* = 6.8 Hz, 2 H), 2.19 (dd, *J* = 4.2 Hz, *J* = 4.8 Hz, 2 H), 2.70 (bs, 4 H), 3.38 (dd, *J* = 4.8 Hz, *J* = 10.8 Hz, 2 H), 3.61 (dd, *J* = 4.2 Hz, *J* = 10.8 Hz, 2 H), 3.89 (q, *J* = 6.7 Hz, 2 H), 7.05 (d, *J* = 7.7 Hz, 2 H), 7.57 (t, *J* = 7.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 18.8, 19.6, 23.5, 29.4, 56.2, 60.0, 62.0, 119.8, 136.7, 163.7; IR (KBr): ν = 3404, 3968, 1572, 1449, 1361, 1172, 1074, 834 cm^{-1}; anal. calcd. for $C_{19}H_{35}N_3O_2$: C 67.62, H 10.45, N 12.45; found: C 67.37, H 10.48, N 12.41.

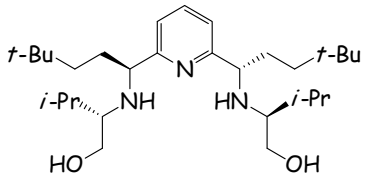


***N,N'*-Bis((*S*)-1-hydroxy-3-methyl-butan-2-yl)-2,6-bis((*S*)-1-aminopentyl)pyridine (42ab')**: Yellowish oil; $[\alpha]_D^{25}$ = -48.5 (c 1.1, CH_2Cl_2); ^1H NMR ($CDCl_3$, 200 MHz): δ = 0.77 (d, *J* = 6.8 Hz, 6 H), 0.79 (d, *J* = 6.8 Hz, 6 H), 0.82 (t, *J* = 6.6 Hz, 6 H), 1.25 (m, 8 H), 1.63 (sept, *J* = 6.8 Hz, 2 H), 1.72 (m, 4 H), 2.08 (dd, *J* = 3.8 Hz, *J* = 6.4 Hz, 2 H), 3.73 (bs, 4 H), 3.39 (dd, *J* = 3.8 Hz, *J* = 10.8 Hz, 2H), 3.61 (dd, *J* = 6.4 Hz, *J* = 10.8 Hz, 2 H), 3.62 (t, *J* = 6.9 Hz, 2 H), 6.97 (d, *J* = 7.6 Hz, 2 H), 7.52 (t, *J* = 7.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$,

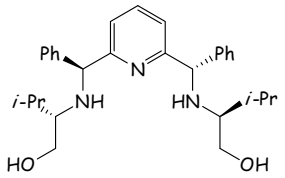
50 MHz): δ = 13.9, 18.8, 19.6, 22.6, 28.7, 29.4, 37.5, 59.5, 61.3, 62.0, 120.9, 136.0, 163.2; IR (neat):ν = 3160, 2957, 2926, 2858, 1590, 1464, 1260, 1089, 801 cm^{-1}; ESI-MS *m/z* : 422.4 [M+ 1], 423.3 [M+ 2]; anal. calcd. for $C_{25}H_{47}N_3O_2$: C 71.21, H 11.23, N 9.97; found: C 71.08, H 11.25, N 9.93.



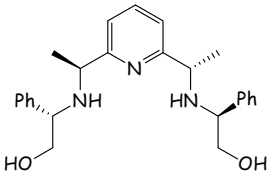
***N,N'*-Bis((*S*)-1-hydroxy-3-methyl-butan-2-yl)-2,6-bis((*S*)-1-amino-2,2-dimethylpropyl)pyridine (42ac')**: Colourless oil; $[\alpha]_D^{25}$ = -82.9 (c 1.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.75 (d, *J* = 6.6 Hz, 6 H), 0.8 (d , *J* = 6.6 Hz, 6 H), 0.93 (s, 18 H), 1.62 (sept, *J* = 6.6 Hz, 2 H), 2.00 (dd, *J* = 3.4 Hz, *J* = 3.9 Hz, 2 H), 2.40 (bs, 4 H), 3.39 (dd, *J* = 3.4 Hz, *J* = 10.9 Hz, 2 H) 3.42 (s, 2 H), 3.62 (dd, *J* = 3.9 Hz, *J* = 10.9 Hz, 2 H), 7.00 (d, *J* = 7.6 Hz, 2 H), 7.50 (t, *J* = 7.6 Hz, 1 H); ^{13}C NMR($CDCl_3$, 50 MHz): δ = 18.7, 19.9, 27.3, 29.6, 35.4, 59.0, 62.4, 69.9, 121.8, 131.0, 161.3; IR (Nujol): ν = 3444, 1644, 1496, 1205, 1090, 933 cm^{-1}; ESI-MS *m/z* : 422.6 [M+ 1], 423.2 [M+ 2]; anal. calcd. for $C_{25}H_{47}N_3O_2$: C 71.21, H 11.23, N 9.97; found: C 71.00, H 11.28, N 9.94.



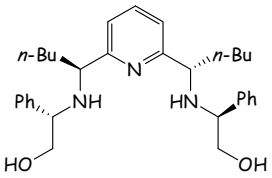
***N,N'*-Bis((*S*)-1-hydroxy-3-methyl-butan-2-yl)-2,6-bis((*S*)-1-amino-4,4-dimethylpentyl)pyridine (42ad')**: Colourless oil; $[\alpha]_D^{25}$ = -47.7 (c 1.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.80 (d, *J* = 6.9 Hz, 6 H), 0.82 (s, 18 H), 0.83 (d , *J* = 6.9 Hz, 6 H), 1.00 (dt, *J* = 4.4 Hz, *J* = 13.1 Hz, 2H), 1.35 (dt, *J* = 4.4 Hz, *J* = 13.1 Hz, 2 H), 1.65 (m, 6 H), 2.12 (dd, *J* = 3.9 Hz, *J* = 6.8 Hz, 2 H), 3.42 (dd, *J* = 3.9 Hz, *J* = 10.8 Hz, 2 H), 3.60 (dd, *J* = 6.8 Hz, *J* = 10.8 Hz, 2 H), 3.63 (t, *J* = 3.9 Hz, 2 H), 7.00 (d, *J* = 7.8 Hz, 2 H), 7.55 (t, *J* = 7.8 Hz, 1 H); ^{13}C NMR($CDCl_3$, 50 MHz): δ = 18.9, 19.8, 29.3, 29.5, 30.1, 32.9, 40.7, 59.5, 62.0, 62.1, 120.7, 136.2, 163.2; IR (neat): ν = 3420, 2925, 1646, 1591, 1376, 1278, 997 cm^{-1}; anal. calcd. for $C_{28}H_{52}N_3O_2$: C 72.68, H 11.33, N 9.08; found: C 72.38, H 11.40, N 9.07.



***N,N'*-Bis((*S*)-1-hydroxy-3-methyl-butan-2-yl)-2,6-bis((*S*)-amino(phenyl)methyl)pyridine (42ae')**: Yellowish oil; $[\alpha]_D^{25}$ = + 95.7 (c 1.6, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.91 (d, J = 6.9 Hz, 6 H), 0.95 (d , J = 6.9 Hz, 6 H), 1.92 (sept, J = 6.9 Hz, 2 H), 2.46 (ddd, J = 3.9 Hz, J = 6.0 Hz, J = 10.2 Hz, 2 H), 2.92 (bs, 2 H), 3.42 (dd, J = 6.6 Hz, J = 10.8 Hz, 2 H), 3.57 (dd, J = 4.2 Hz, J = 10.8 Hz, 2 H), 5.0 (s, 2 H), 6.92 (d, J = 7.8 Hz, 2 H), 7.27-7.42 (m, 11 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 18.2, 19.5, 30.2, 60.5, 62.1, 35.0, 120.8, 127.4, 127.9, 128.5, 136.9, 142.9, 161.2; IR (neat): ν = 3417, 3333, 3061, 3027, 2957, 2872, 1589, 1572, 1448, 1045, 839, 736, 700 cm^{-1}; ESI-MS *m/z* : 462.0 [M+ 1]; anal. calcd. for $C_{29}H_{39}N_3O_2$: *C* 75.45, H 8.52, N 9.10; found: *C* 75.24, H 8.65, N 9.04.

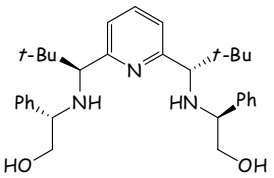


***N,N'*-Bis((*S*)-2-hydroxy-1-phenylethyl)-2,6-bis((*S*)-1-aminoethyl)pyridine (42ba')**: White solid; m.p. = 95 °C; $[\alpha]_D^{25}$ = +30.7 (c 1.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.40 (d, J = 6.6 Hz, 6 H), 3.59 (dd, J = 7.8 Hz, J = 10.8 Hz, 2 H), 3.65-3.88 (m, 6 H), 7.03 (d , J = 7.8 Hz, 2 H), 7.2-7.4 (m, 10 H), 7.81 (t, J = 7.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 21.4, 55.7, 61.8, 66.1, 119.3, 127.5, 127.3, 128.3, 136.8, 141.1, 162.7; IR (KBr):ν= 3383, 3065, 3032, 2973, 2930, 2846, 1577, 1458, 1327, 1233, 1096, 751, 733, 699 cm^{-1}; ESI-MS *m/z* : 406.2 [M+ 1], 428.3 [M+ Na]; anal. calcd. for $C_{25}H_{31}N_3O_2$: *C* 74.04, H 7.70, N 10.36; found: *C* 73.98, H 7.75, N 10. 33.

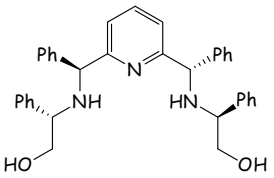


***N,N'*-Bis((*S*)-2-hydroxy-1-phenylethyl)-2,6-bis((*S*)-1-aminopentyl)pyridine (42bb')**: Colourless oil; $[\alpha]_D^{25}$ = +110.3 (c 0.6, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.88 (t, J = 6.7 Hz, 6 H), 1.0-1.4 (m, 8 H), 1.6-1.8 (m, 4 H), 3.1 (bs, 4 H), 3.4-3.6 (m, 4 H), 3.6-3.8 (m, 4 H), 6.88 (d, J = 7.7 Hz, 2 H), 7.1-7.4 (m, 11 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 14.0, 22.7, 28.3,

36.4, 61.4, 62.2, 65.3, 120.2, 127.0, 127.2, 128.2, 136.0, 141.6, 162.5; IR (neat): ν = 3324, 2923, 2853, 1576, 1457, 1366, 1129, 1052, 701 cm^{-1}; anal. calcd. for $C_{31}H_{43}N_3O_2$: C 76.03, H 8.85, N 8.58; found: C 75.75, H 8.87, N 8.55.



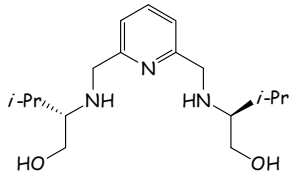
***N,N'*-Bis((*S*)-2-hydroxy-1-phenylethyl)-2,6-bis((*S*)-1-amino-2,2-dimethylpropyl)pyridine (42bc')**: Colourless oil; $[\alpha]_D^{25}$ = +105.0 (c 1.5, $CHCl_3$), ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.84 (s, 18 H), 3.31 (s, 2 H), 3.43 (dd, J = 4.8 Hz, J = 5.1 Hz, 2 H), 3.51 (dd, J = 5.1 Hz, J = 10.6 Hz, 2 H), 3.73 (dd, J = 4.8 Hz, J = 10.6 Hz, 2 H), 6.73 (d, J =7.5 Hz, 2 H), 7.00-7.10 (m, 5 H), 7.15-7.55 (m, 5 H), 7.46 (t, J = 7.4 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 27.1, 35.5, 63.3, 64.9, 70.0, 122.4, 128.2, 134,3, 142.0, 160.9; IR (neat): ν = 3408, 3055, 2952, 2863, 1588, 1576, 1469, 1453, 1395, 1361, 1031, 824, 757, 701 cm^{-1}; ESI-MS *m/z* : 490.4 [M+ 1], 512.3 [M+ Na]; anal. calcd. for $C_{31}H_{43}N_3O_2$: C 76.03, H 8.85, N 8.58; found: C 75.80, H 8.91, N 8.52.



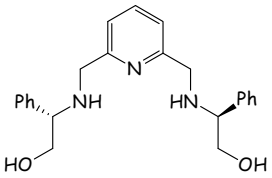
***N,N'*-Bis((*S*)-2-hydroxy-1-phenylethyl)-2,6-bis((*S*)-1-amino(phenyl)methyl)pyridine (42be')**: Colourless oil; $[\alpha]_D^{25}$ = +123.2 (c 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ = 3.00 (bs, 4 H), 3.72 (m, 6 H), 4.78 (s, 2 H), 6.72 (d, J = 7.6 Hz, 2 H), 7.30-7.40 (m, 23 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 61.2, 64.0, 67.0, 120.4, 127.1, 127.5, 127.7, 128.3, 128.6, 128.7, 130.0, 131.5, 133.2, 136.9, 145.0, 141.7, 167.0; IR (neat): ν = 3411, 3060, 3026, 2925, 2850, 1590, 1573, 1493, 1451, 1054, 1027, 700 cm^{-1}; ESI-MS *m/z*: 530.4 [M+ 1], 531.5 [M+ 2], 552.5 [M+ Na]; anal. calcd. for $C_{35}H_{35}N_3O_2$: C 79.37 , H 6.66, N 7.93; found: C 79.00, H 6.71, N 7.90.

*1.5.3 - Preparation of β-Aminoalcohols **42af'** and **42bf'** by Reduction of Imines **41a** and **41b***

To a solution of imine **41a** or **41b** (1 mmol) in methanol (5 mL), $NaBH_4$ (2 mmol, 0.076 g) was added in one portion. After 1 h the reaction was quenched with 1 N HCl (5 mL) and further stirred for 2 h. Then NaOH pellets were added until the solution reached pH 11, and the organic phase was extracted with diethyl ether (3 × 10 mL). The collected ethereal phases were dried over Na_2SO_4 and concentrated to leave the crude product in quantitative yield. Pure compounds were obtained by column chromatography (SiO_2) eluting with cyclohexane/ethyl acetate mixtures.



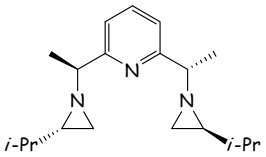
***N,N'*-Bis((*S*)-1-hydroxy-3-methyl-butan-2-yl)-2,6-bis(aminomethyl)pyridine (42af')**: Colourless oil; $[\alpha]_D^{25}$ = +41.6 (c 0.9, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.89 (d, *J* = 6.9 Hz, 6 H), 0.95 (d, *J* = 6.9 Hz, 6 H), 1.89 (sept, *J* = 6.9 Hz, 2 H), 2.43 (dd, *J* = 3.3 Hz, *J* = 7.5 Hz, 2 H), 3.42 (dd , *J* = 7.5, *J* = 11.1 Hz, 2 H), 3.42 (dd , *J* = 3.3, *J* = 11.1 Hz, 2 H), 3.87 (d, *J* = 14.7 Hz, 2 H), 3.97 (d, *J* = 14.7 Hz, 2 H), 7.11 (d, *J* = 7.5 Hz, 2 H), 7.58 (t, *J* = 7.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 18.6, 19.5, 29.5, 52.3, 61.4, 65.0, 120.6, 137.3, 159.5; IR (neat): ν = 3322, 2957, 2866, 1594, 1576, 1455, 1386, 1367, 1155, 1047, 787 cm^{-1}; anal. calcd. for $C_{17}H_{31}N_3O_2$: *C* 65.98, H 10.10, N 13.58; found: *C* 66.01, H 10.11, N 13.54.



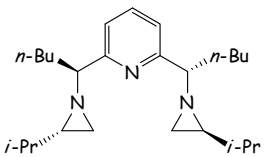
***N,N'*-Bis((*S*)-2-hydroxy-1-phenylethyl)-2,6-bis(aminomethyl)pyridine (42bf')**: Viscous oil; $[\alpha]_D^{25}$ = +106.2 (c 2.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ = 3.67 (m, 4 H), 3.72 (d, *J* = 14.1 Hz, 2 H), 3.80 (d, *J* = 14.1 Hz, 2 H), 3.86 (dd, *J* = 5.3 Hz, *J* = 9.6 Hz, 2 H), 4.1 (bs, 1 H), 7.0 (d , *J* = 7.6 Hz, 2 H), 7.2-7.4 (m, 10 H), 7.52 (t, *J* = 7.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 51.9, 64.6, 67.0, 120.6, 127.4, 127.5, 128.4, 136.8, 140.4, 158.7; IR (Nujol): ν = 3310, 3061, 3028, 2924, 2862, 1594, 1577, 1492, 1452, 1357, 1057, 1027, 759, 702 cm^{-1}; ESI-MS *m/z* : 378.3 [M + 1], 379.4 [M + 2], 400.4 [M + Na]; anal. calcd. for $C_{23}H_{27}N_3O_2$: *C* 73.18; H 7.21, N 11.13; found: *C* 72.83, H 7.24, N 11.10.

1.5.4 - Preparation of Aziridines ***43***

To a solution of β-aminoalcohol **42** (2.8 mmol) in THF (20 mL) was added PPh_3 (6.2 mmol, 1.6 g). To this solution DEAD (6.2 mmol, 1.082 g) was added dropwise. After 4 h, a solution of 2 N KOH (10 mL) was added to the mixture, which was stirred for 3 h. Diethyl ether was added (30 mL) and the organic phase was separated. The aqueous phase was extracted with Et_2O (3 x 20 mL), and the collected organic phase was washed with 2 N KOH (3 x 10 mL), then with brine. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was flash-chromatographed on a SiO_2 column eluting with cyclohexane/ethyl acetate mixtures. In order to obtain analytically pure samples, further purification by chromatography or crystallization was carried out.

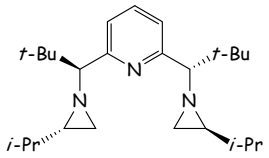


2,6-Bis((*S*)-1-((*S*)-2-isopropylaziridin-1-yl)ethyl)pyridine (43aa'): Colourless oil; $[\alpha]_D^{25}$ = -119.6 (c 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.53 (d, *J* = 6.6 Hz, 6 H), 0.75 (d, *J* = 6.6 Hz, 6 H), 1.10 (sept, *J* = 6.6 Hz, 2 H), 1.22 (m, 2 H), 1.33 (d, *J* = 6.3 Hz, 2 H), 1.38 (d, *J* = 6.6 Hz, 6 H), 1.63 (d, *J* = 3.3 Hz, 2 H), 2.53 (q, *J* = 6.6 Hz, 2 H), 7.37 (d , *J* = 7.6 Hz, 2 H), 7.63 (t, *J* = 7.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 19.5, 20.4, 21.2, 31.4, 32.6, 45.8, 71.6, 119.6, 136.7, 162.7; IR (neat): ν = 3041, 2962, 1591, 1576, 1460, 1327, 1176, 822 cm^{-1}; GC-MS *m/z*: 56 (100), 55 (87), 84 (63), 132 (35), 218 (18), 162 (9); anal. calcd. for $C_{19}H_{31}N_3$: C 75.70, H 10.36, N 13.94; found: C 75.78, H 10.41, N 13.88.

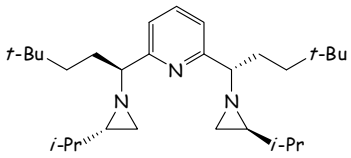


2,6-Bis((*S*)-1-((*S*)-2-isopropylaziridin-1-yl)pentyl)pyridine (43ab'): Colourless oil; $[\alpha]_D^{25}$ = -140.7 (c 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.47 (d, *J* = 6.5 Hz, 6 H), 0.74 (d, *J* = 6.5 Hz, 6 H), 0.78 (t, *J* = 7.0 Hz, 6 H), 0.86 (m, 2 H), 1.04 (m, 2 H), 1.21 (m, 8 H), 1.40 (d, *J* = 6.3 Hz, 2 H), 1.67 (d, *J* = 3.6 Hz, 2 H), 1.88 (q, *J* = 7.6 Hz, 2 H), 2.44 (t, *J* = 7.2 Hz, 2 H), 7.31 (d , *J* = 7.6 Hz, 2 H), 7.63 (t, *J* = 7.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 14.1, 19.9,

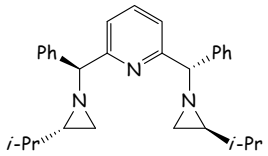
20.6, 22.0, 28.6, 31.9, 34.2, 35.9, 45.0, 77.3, 120.8, 136.7, 162.1; IR (neat): ν = 3040, 2957, 2871, 1591, 1576, 1457, 1364, 1029 cm^{-1}; *GC*-MS *m/z* : 84 (100), 302 (75), 259 (53), 174 (35), 55 (30), 385 (1, M); anal. calcd. for $C_{25}H_{43}N_3$: *C* 77.86, H 11.24, N 10.90; found: *C* 77.58, H 11.26, N 10.85.



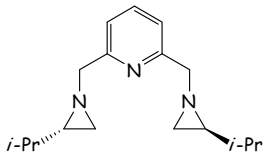
2,6-Bis((*S*)-1-((*S*)-2-isopropylaziridin-1-yl)-2,2-dimethylpropyl)pyridine (43ac'): White solid; m.p. = 84 °*C*; $[\alpha]_D^{25}$ = -18.8 (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.53 (d, *J* = 6.6 Hz, 6 H), 0.72 (d, *J* = 6.6 Hz, 6 H), 0.98 (m, 2 H), 0.99 (*s*, 18 H), 1.18 (*sept*, *J* = 6.6 Hz, 2 H) 1.49 (d , *J* = 6.3 Hz, 2 H), 1.76 (d, *J* = 3.9 Hz, 2 H), 2.73 (*s*, 2 H), 7.33 (d , *J* = 7.5 Hz, 2 H), 7.57 (t, *J* = 7.5 Hz, 1 H); ^{13}*C* NMR ($CDCl_3$, 75 MHz): δ = 19.6, 20.8, 27.8, 30.8, 36.3, 36.7, 42.8, 85.5, 122.4, 134.4, 160.2; IR (KBr): ν = 3064, 2873, 1588, 1571, 1497, 1449, 1286, 1031, 872 cm^{-1}; anal. calcd. for $C_{25}H_{43}N_3$: *C* 77.86, H 11.24, N 10.90; found: *C* 77.91, H 11.28, N 10.86.



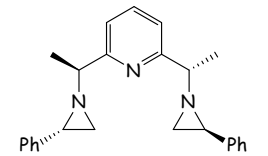
2,6-Bis((*S*)-1-((*S*)-2-isopropylaziridin-1-yl)-4,4-dimethylpentyl)pyridine (43ad'): *C*olourless oil; $[\alpha]_D^{25}$ = -149.5 (c 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.50 (d, *J* = 6.6 Hz, 6 H), 0.79 (d, *J* = 6.6 Hz, 6 H), 0.83 (*s*, 18 H), 1.10 (*sept*, *J* = 6.6 Hz, 2 H), 1.17-1.37 (m, 6 H), 1.43 (d, *J* = 6.5 Hz, 2 H), 1.70 (d, *J* = 3.5 Hz, 2 H), 1.91 (dt, *J* = 7.1 Hz, *J* =9.8 Hz, 4 H), 2.40 (t, *J* = 7.1 Hz, 2 H), 7.36 (d , *J* = 8.0 Hz, 2 H), 7.68 (t, *J* = 8.0 Hz, 1 H); ^{13}*C* NMR ($CDCl_3$, 50 MHz): δ = 19.7, 20.4, 29.2, 30.1, 31.1, 31.7, 34.0, 40.0, 44.7, 77.5, 120.6, 136.6, 161.9; IR (neat): ν = 3060, 2879, 1591, 1568, 1490, 1450, 1281, 1038, 878 cm^{-1}; *GC*-MS *m/z* : 57 (100), 84 (92), 56 (71), 287 (28), 258 (22), 132 (16), 202 (12); anal. calcd. for $C_{29}H_{51}N_3$: *C* 78.85, H 11.64, N 9.51; found: *C* 78.75, H 11.68, N 9.47.



2,6-Bis((*S*)-((*S*)-2-isopropylaziridin-1-yl)(phenyl)methyl)pyridine (43ae'): Yellowish oil; $[\alpha]_D^{25}$ = -158.3 (c 0.6, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ = 0.47 (d, J = 6.6 Hz, 6 H), 0.82 (d, J = 6.6 Hz, 6 H), 1.23 (m, 2 H), 1.44 (d , J = 7.2 Hz, 2 H), 1.54 (dd, J = 3.6 Hz, J = 7.2 Hz, 2 H), 3.78 (s, 2 H), 7.25-7.39 (m, 8 H), 7.54-7.62 (m, 5 H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 19.5, 20.2, 31.4, 46.4, 79.8, 120.9, 126.9, 127.4, 128.1, 137.9, 142.4, 151.0; IR (neat): ν = 3071, 2933, 2862, 1589, 1573, 1455, 1306, 1258, 1029, 699 cm^{-1}; ESI-MS *m/z*: 426.1 [M + 1], 427.2 [M + 2]; anal. calcd. for $C_{29}H_{35}N_3$: *C* 81.84, H 8.29, N 9.87; found: *C* 81.78, H 8.32, N 9.84.

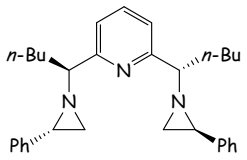


2,6-Bis(((*S*)-2-isopropylaziridin-1-yl)methyl)pyridine (43af'): Colourless oil; $[\alpha]_D^{25}$ = -97.5 (c 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.89 (d, J = 6.6 Hz, 6 H), 0.91 (d, J = 6.6 Hz, 6 H), 1.30 (m, 2 H), 1.37 (dd, J = 3.3 Hz, J = 6.3 Hz, 2 H), 1.41 (d, J = 6.3 Hz, 2 H), 1.69 (d, J = 3.3 Hz, 2 H), 3.48 (d, J = 14.0 Hz, 2H), 3.59 (d, J = 14.0 Hz, 2 H), 7.44 (d, J = 7.7 Hz, 2 H), 7.69 (t, J = 7.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 19.6, 20.6, 31.6, 33.2, 46.7, 66.6, 120.6, 136.9, 158.6; IR (neat): ν = 3044, 2958, 2872, 1592, 1578, 1458, 1363, 1340, 1287, 1035, 896, 829, 783 cm^{-1}; anal. calcd. for $C_{17}H_{27}N_3$: *C* 74.68, H 9.95, N 15.37; found: *C* 74.22, H 9.99, N 15.33.

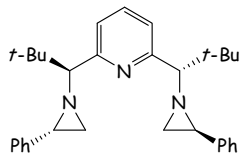


2,6-Bis((*S*)-1-((*S*)-2-phenylaziridin-1-yl)ethyl)pyridine (43ba'): White solid; m.p. = 79 °C; $[\alpha]_D^{25}$ = +176.6 (c 0.4, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.52 (d, J = 6.6 Hz, 6 H), 1.89 (d, J = 6.6 Hz, 2 H), 2.06 (d, J = 3.3 Hz, 2 H), 2.50 (dd , J = 3.3 Hz, J = 6.6 Hz, 2 H), 2.84 (q, J = 6.6 Hz, 2 H), 7.17-7.29 (m, 10H), 7.36 (d, J = 8.1 Hz, 2 H), 7.46 (t , J = 8.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 21.6, 37.3, 40.8, 71.7, 118.8, 126.1, 126.6, 128.1, 137.3, 140.0, 162.5; IR (KBr):ν= 3032, 2972, 1576, 1580, 1459, 1326, 1207, 1095, 815, 698 cm^{-1}; ESI-MS

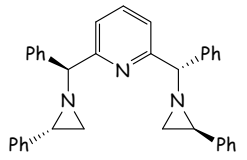
m/z : 370.4 [M+ 1], 371.4 [M + 2], 392.4 [M+ Na]; anal. calcd. for $C_{25}H_{27}N_{25}$: *C* 81.26, H 7.37, N 11.37; found: *C* 81.01, H 7.39, N 11.34.



2,6-Bis((*S*)-1-((*S*)-2-phenylaziridin-1-yl)pentyl)pyridine (43bb'): Yellowish oil; d.r. 91:9; $[\alpha]_D^{25}$ = +124.5 (c 0.9, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ (major diastereomer) = 0.86 (t, *J* = 6.6 Hz, 6 H), 1.2-1.4 (m, 8 H), 1.92 (d, *J* = 6.2 Hz, 2 H), 1.94 (m, 2 H), 2.09 (d, *J* = 3.2 Hz, 2 H), 2.45 (dd, *J* = 3.2 Hz, *J* = 6.2 Hz, 2 H), 2.77 (dd, *J* = 6.2 Hz, *J* = 7.0 Hz, 2 H), 7.07-7.27 (m, 10 H), 7.29 (d, *J* = 7.9 Hz, 2 H), 7.47 (t, *J* = 7.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 14.0, 23.0, 26.9, 28.1, 36.1, 38.4, 39.4, 119.9, 126.3, 126.6, 128.1, 137.0, 146.2, 161.7; IR (neat): ν = 3031, 2978, 1574, 1588, 1454, 1329, 1198, 1092, 818, 701 cm^{-1}; anal. calcd. for $C_{31}H_{39}N_3$: *C* 82.07, H 8.66, N 9.26; found: *C* 82.23, H 8.80, N 9.22.

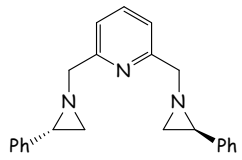


2,6-Bis((*S*)-2,2-dimethyl-1-((*S*)-2-phenylaziridin-1-yl)propyl)pyridine (43bc'): Colourless oil; $[\alpha]_D^{25}$ = +132.6 (c 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ = 1.06 (s, 18 H), 1.97 (d, *J* = 6.4 Hz, 2 H), 2.07 (dd, *J* = 3.2 Hz, *J* = 6.4 Hz, 2 H), 2.14 (d, *J* = 3.2 Hz, 2 H), 2.67 (s, 2 H), 7.07-7.40 (m, 13 H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 27.5, 36.5, 37.6, 42.9, 85.4, 121.6, 126.1, 126.3, 128.0, 141.0, 151.0, 159.4; IR (neat): ν = 3033, 2974, 1572, 1584, 1456, 1323, 1187, 1097, 813, 705 cm^{-1}; anal. calcd. for $C_{31}H_{39}N_3$: *C* 82.07, H 8.66, N 9.26; found: *C* 82.12, H 8.70, N 9.25.



2,6-Bis((*S*)-phenyl((*S*)-2-phenylaziridin-1-yl)methyl)pyridine (43be'): Colourless oil; d.r. 92:8; $[\alpha]_D^{25}$ = +104.5 (c 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) δ (major diastereomer) = 2.00 (d, *J* = 6.4 Hz, 2 H), 2.13 (d, *J* = 3.5 Hz, 2 H), 2.79 (dd, *J* = 3.5 Hz, *J* = 6.4 Hz, 2 H), 4.06 (s, 2 H), 7.17-7.74 (m, 23 H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 38.0, 41.2, 79.5, 120.0, 126.3, 126.6, 126.8, 127.1, 127.7, 128.1, 128.2, 137.3, 140.0, 142.2, 161.3; IR (neat): ν= 3036, 2974,

1575, 1586, 1453, 1324, 1203, 1096, 829, 679 cm^{-1}; ESI-MS *m/z*: 494.5 [M + 1], 495.5 [M + 2]; anal. calcd. for $C_{35}H_{31}N_3$: *C* 85.16, H 6.33, N 8.51; found: *C* 84.92, H 6.35, N 8.48.



2,6-Bis(((*S*)-2-phenylaziridin-1-yl)methyl)pyridine (43bf'): Colourless oil; $[\alpha]_D^{25}$ = +124.3 (c 1.5 $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ = 1.92 (d, *J* = 6.6 Hz, 2 H), 2.03 (d , *J* = 3.2 Hz, 2 H), 7.03 (dd, *J* = 3.2 Hz, *J* = 6.6 Hz 2 H), 3.65 (d, *J* = 15.0 Hz 2 H), 3.91 (d, *J* = 15.0 Hz, 2 H) 7.20-7.74 (m, 13 H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 38.1, 41.6, 66.3, 120.1, 126.1, 126.9, 128.3, 128.4, 128.6, 131.9, 132.0, 132.2, 137.3, 140.1, 158.3; IR (neat): ν = 3031, 2978, 1570, 1586, 1461, 1321, 1204, 1095, 819, 694 cm^{-1}; anal. calcd. for $C_{23}H_{23}N_3$: *C* 80.90, H 6.79, N 12.31; found: *C* 81.15, H 6.83, N 12.30.

*1.5.5 - Preparation of allylic palladium complexes. Typical procedure: [**43ae'**(η^3-allyl)Pd][PF_6].*

Allyl palladium chloride dimer (73 mg, 0.1 mmol) was added to a solution of ligand **43ae'** (80 mg, 0.2 mmol) in CH_2Cl_2 (4 mL) in one portion. After one hour a solution of NH_4PF_6 (39 mg, 0.24 mmol) in THF (1mL) was added. The solution was stirred overnight, then filtered through a HPLC filter (0.45 μm) and the solvent was removed under reduced pressure to give a white solid: 0.130 g, 91%. White crystals, suitable for X-ray diffraction analysis were obtained from a double-layer of CH_2Cl_2 and pentane: white crystals; m.p. 124-126 °C (dec.); $[\alpha]_D^{20}$ = +21.1 (c 1.2, $CHCl_3$); IR (KBr) ν = 3052, 3030, 2882, 1605, 1567, 1496, 1452, 1265, 1014, 840, 732, 701, 553 cm^{-1}.

The ^1H NMR spectra of all the allyl and 1,3-diphenylallyl cationic Pd complexes synthesized showed the presence of different species, but the *exo* and *endo* rotamers were prevalent with variable ratios. Specifically, the spectrum of the complex **43ae'**(1,3-diphenylallyl)$PdPF_6$ (600 MHz, $CDCl_3$) showed a 55:45 ratio of two rotamers, with the following absorptions of the allylic protons: major rotamer, δ = 5.98 (t, *J* =11.4 Hz, 1 H), 4.75 (d, *J* = 11.4 Hz, 1H), 4.67 (d, *J* = 11.4 Hz, 1H) ppm; minor rotamer, δ= 6.13 (t, *J* = 11.4 Hz, 1 H), 5.0 (d, *J* = 11.4 Hz, 1 H), 4.40 (d, *J* = 11.4 Hz, 1 H) ppm. On the other hand, the 1H NMR spectrum (300 MHz, CDCl3) of **43ba'**(1,3-diphenylallyl)$PdPF_6$ showed the presence of a prevalent species (ca 75%) with the *syn,syn* geometry of the allylic ligand, whose protons gave absorptions at δ = 6.16 (t, *J* = 11.4 Hz, 1 H), 4.43 (d, *J* = 11.4 Hz, 1 H) and 3.80 (d, *J* = 11.4 Hz, 1 H).

[(43ae')(allyl)Pd][PF_6]. X-Ray details: Bruker APEX II CCD diffractometer (Mo-Kα radiation λ = 0.71073 Å). Results: $C_{32}H_{40}F_6N_3PPd$, M_r = 718.04, monoclinic *P*2$_1$, *a* = 11.0990(13), *b* = 13.3802(16), *c* = 11.9282(14)Å, β = 112.045(2), V = 1641.9(3)Å^3, Z = 2, ρ_x 1.452 Mgm^{-3}, μ 0.674 mm^{-1}, *F*(000) = 736, *T* = 296(2) K, θ_{max} = 28.51, 13905 reflections collected, 6099 *I*>2σ(*I*). Final R1 = 0.0347, wR2 = 0.0860, GOF = 0.997, absolute structure parameter = 0.04(2).CCD 297723. Crystallographic data (excluding structure factors) for the structure reported in this thesis have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 297723. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: int. code + 44(1223)336-033; E-mail: deposit@ccdc.cam.ac.uk].

1.5.6 - Palladium-Catalyzed Allylic Alkylation

To a solution of DIAZAP **43ba'** (0.03 mmol, 10 mg) in CH_2Cl_2 (2 mL) was added $(allylPdCl)_2$ (0.014 mmol, 5 mg) and the solution was degassed and stirred for 1h. 1,3-diphenyl-2-propenyl ethyl carbonate (**24b**) (0.27 mmol, 76 mg) was then added followed by dimethyl malonate (0.67 mmol, 90 mg), BSA (0.81 mmol, 0.165 g) and KOAc (0.02 mmol, 2 mg) after 10 min. The reaction was monitored by TLC analysis and, when complete, quenched with 1 N HCl solution (1 mL) and the organic phase was extracted with diethyl ether (3 ×10 mL). The organic layer was dried over Na_2SO_4 and the solvents were evaporated to dryness. The crude product was purified by chromatography on a silica gel column (hexane/AcOEt, 75:5) affording methyl (*R*)-(*E*)-3,5-diphenyl-2-methoxycarbonyl-4-pentenoate (**25**): 73 mg, 84%. An e.e. of 99% was determined by chiral HPLC (Chiralpak AD; 2-propanol/hexane 1:9, 1.0 mL/min; 250 nm). retention times: 10.7 min (major enantiomer), 14.9 min (minor enantiomer).

45a: 88%, e.e. 97%; $[\alpha]_D^{25}$ -38.7 (c 2.0, $CHCl_3$). The e.e. was determined by chiral HPLC (Chiralpak AD; 2-propanol/hexane 3:97; 1.0 mL/min, 250 nm); retention times: 16.6 min (major enantiomer), 17.1 min (minor enantiomer). The absolute configuration of the product was determined by comparison of its optical rotation with that of the known compound.[40e]

45b: 89%, e.e. 99%; $[\alpha]_D^{25}$ = -48.4 (c 1.5, $CHCl_3$). The e.e. was determined by chiral HPLC (Chiralpak AD; 2-propanol/hexane 1:99, 0.8 mL/min, 250 nm); retention times: 8.3 min (minor enantiomer), 10.9 min (major enantiomer). The absolute configuration was assumed by analogy with compound **45a**.

47: 40%, e.e. 6%; $[\alpha]_D^{25}$ = +5.0 (c 1.1, $CHCl_3$). The e.e. was determined by chiral GC: Megadex Chiral column (25 m, flow rate: 15mL/min, 50 °C (2 min), then 3 °C/min up to 190 °C,

FID detection): retention times: 27.2 min (minor enantiomer), 27.3 min (major enantiomer). The absolute configuration of the product was determined by comparison of its optical rotation with that of the known compound.

49: 85%, e.e. 28%, $[\alpha]_D^{25}$ = +6.5 (c 1.2, CHCl3). The e.e. was determined by chiral GC (Megadex Chiral column (25 m, flow rate: 15mL/min, isotherm 65 °C, FID detection); retention times: 49.5 min (minor enantiomer), 51.6 min (major enantiomer). The absolute configuration of the product was determined by comparison of its optical rotation with that of the known compound.[42]

51-52: The ratio was determined by GC-MS analysis. The e.e.s of **51** and **52** were determined by chiral HPLC (Chiralpak OD, 2-propanol/hexane 1:99, 0.5 mL/min, 250 nm); retention times of **52**: 14.2 min (major enantiomer), 15.1 min (minor enantiomer); retention times of **51**: 17.9 (minor enantiomer), 18.8 (major enantiomer).

55: 83%, e.e. 27%; $[\alpha]_D^{25}$ = ~-23.5 (c 1.6, $CHCl_3$). The e.e. was determined by chiral HPLC (Chiralpak OD, 2-propanol/hexane 5:95, 0.4 mL/min, 250 nm); retention times: 13.7 min (minor enantiomer), 15.6 min (major enantiomer). The absolute configuration of the product was determined by comparison of its optical rotation with that of the known compound.[43]

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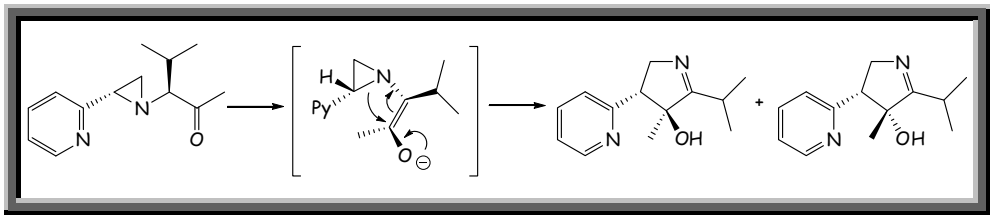
Chapter Index

Chap. 2 – Asymmetric Synthesis of 2-(2-Pyridyl)aziridines from 2-Pyridineimines Bearing Stereogenic *N*-Alkyl Substituents.



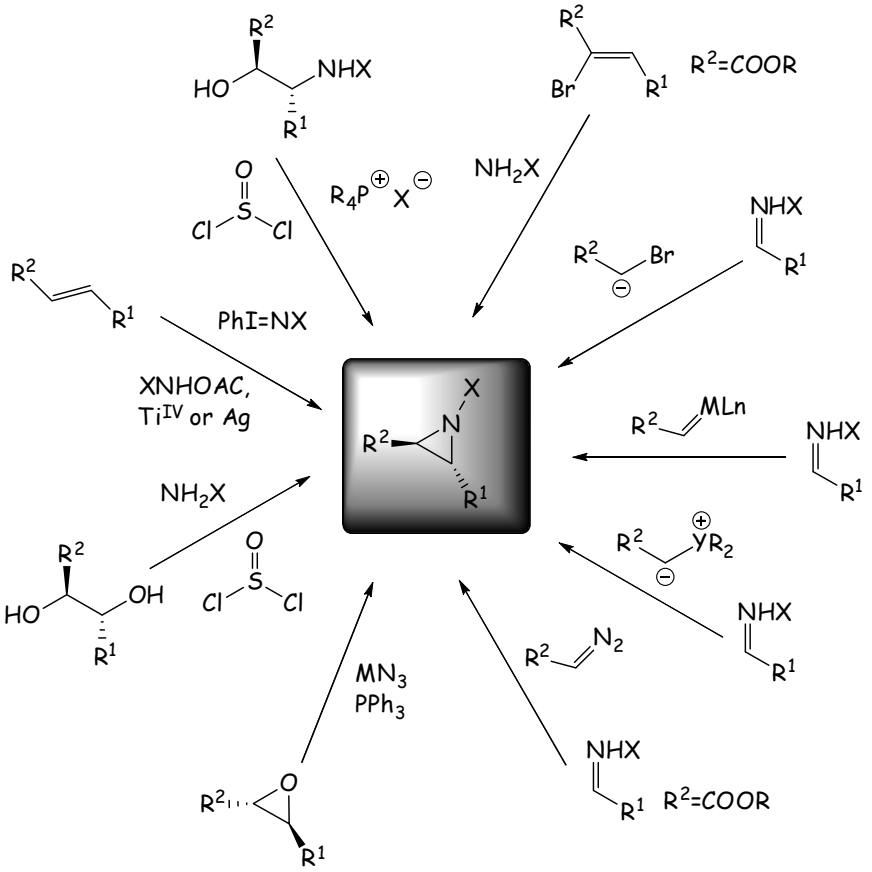
2.1 – Introduction

Aziridine chemistry has indeed been extensively exploited by organic synthetic chemists.[1] In the last several decades, more than 200 research papers have been registered in the Chemical Abstracts database every year, and since 2001 the tally has been more than 350 papers a year, which clearly shows a broad interest in the preparation and utilization of aziridines. Their incorporation into a wide variety of motifs, from drugs and biologically active molecules to ligands for asymmetric catalysis,[2] underlines their importance to modern chemistry.

Aziridines are the nitrogen analogues of epoxides and exhibit similar reactivity patterns as electrophilic reagents. The highly strained three membered ring readily opens with excellent stereo- and regio-control to afford a wide variety of more stable ring opened or ring expanded chiral amines.

2.1.1 – Preparation of aziridine

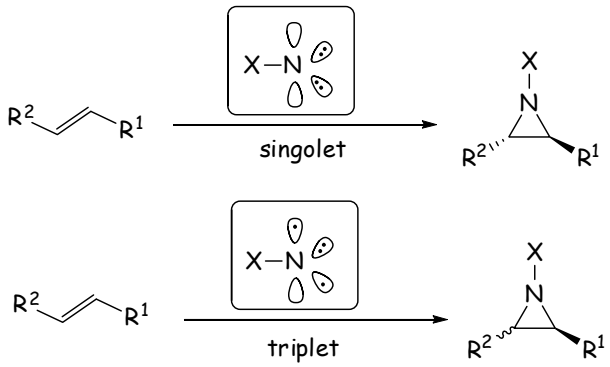
A literature survey reveals an extensive investigation of the synthesis and chemistry of aziridines since the first synthesis by Gabriel in 1888.[3] Numerous methods have been reported for the synthesis of differently substituted aziridines. The range of synthetic methodology available for preparation of aziridines (summarized diagrammatically in Scheme 1) is very wide and include nitrene addition to olefins, carbene and ylide addition to imines, and cyclization of 1,2-amino alcohols, 1,2-aminohalides, and 1,2-azido alcohols.



Scheme 1

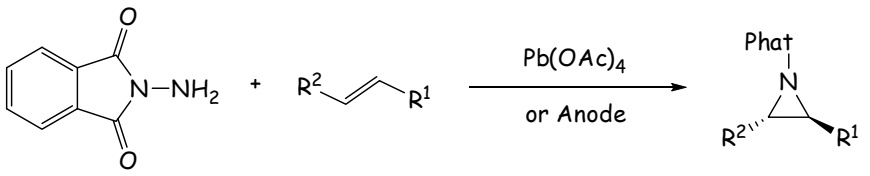
Nitrene methods[4]: 'Classical' methods for direct aziridination of alkenes have traditionally featured addition of nitrenes (reactive intermediates in which nitrogen bears only one substituent, one lone pair and two other electrons) to the unsaturated partner. The limitations to the method (often involving alkoxycarbonylnitrenes) are well-documented, with the necessity for harsh reaction conditions and the lack of stereoselectivity constituting two major factors which have limited the attractiveness of this methodology.

Such nitrenes typically were generated by thermal or photochemical decomposition of the corresponding azides and these methods intrinsically lead to mixtures of (more reactive) singlet and (more stable) triplet nitrenes; only singlet nitrenes may be relied upon to react stereospecifically with 1,2-disubstituted alkenes. Triplet nitrenes react in a two-step process with alkenes (Scheme 2), in which an N–C bond is formed in each step, whereas singlet nitrenes are able to form both new bonds in a concerted process.



Scheme 2

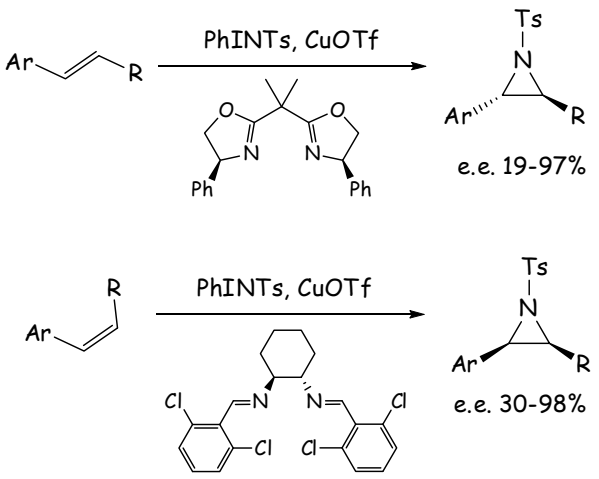
A useful method involves in situ generation of nitrenes, by means of oxidation of hydrazine derivatives. Of particular relevance is the methodology of Rees and his collaborators by which a range of N-amino aziridine derivatives were prepared by reaction of the corresponding hydrazine derivatives with alkenes in the presence of lead tetraacetate (Scheme 3) or with electrochemical processes for oxidation of hydrazine.[5]



Scheme 3

The possibility of transferring nitrenes to olefins by means of transition metal catalysts (Cu, Mn, Rh, Ag) was recognized well before asymmetric catalysis was established. Thus, porphyrin[6] and salen catalysts, known for their ability to aziridinate alkenes in the presence of the nitrene precursor *N*-tosyliminophenyliodinane, provided the inspiration for a new generation of copper-based catalytic processes. In particular, Evans,[7] Jacobsen[8] and Katsuki[9] have described the utility of chiral bis-oxazolines and 1,2-diamines in enantioselective aziridination of a range of alkenes (Scheme 4).

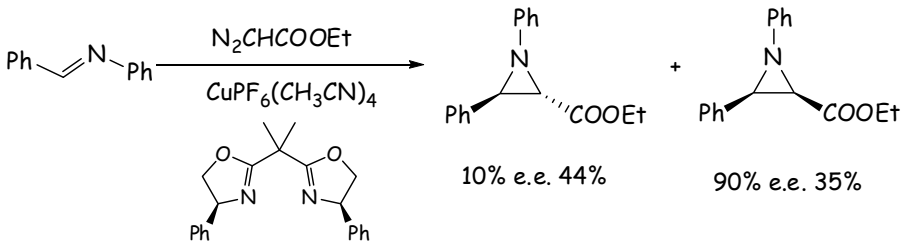
These reactions, though representing a major achievement in the synthesis of enantiopure aziridines, still retain some drawbacks, not least of which is the frequent requirement for the reactions to be conducted using a large excess (often 5 equivalents) of alkene.



Scheme 4

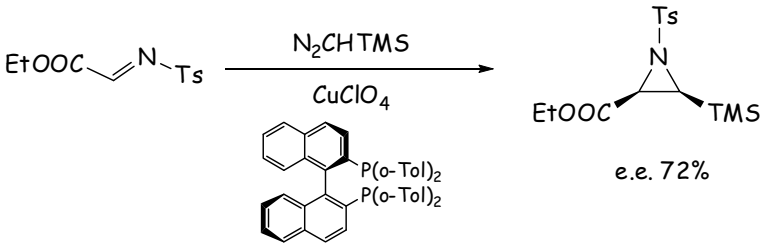
Carbene methods: The synthesis of aziridines by reaction of nitrenes and nitrene equivalents with alkenes involves the roughly simultaneous formation of two new C–N bonds. If one performed an alternative synthetic analysis, one can immediately identify a method which is centred around the simultaneous formation of one C–N bond and one C–C bond. Thus, if a carbene or equivalent thereof (such as an ylid) were to react efficiently with an imine, a useful aziridination protocol would result. This area of research has only recently attracted the attention of synthetic organic chemists.

Thus, Jacobsen and Finney reported that the metallocarbene derived from ethyl diazoacetate and copper(I)hexafluorophosphate adds with mediocre stereoselectivity to *N*-arylaldimines. At best, diasteroeselectivities were acceptable (often > 10:1, in favour of the *cis*-isomers) but enantioselectivity was low (Scheme 5).[10]



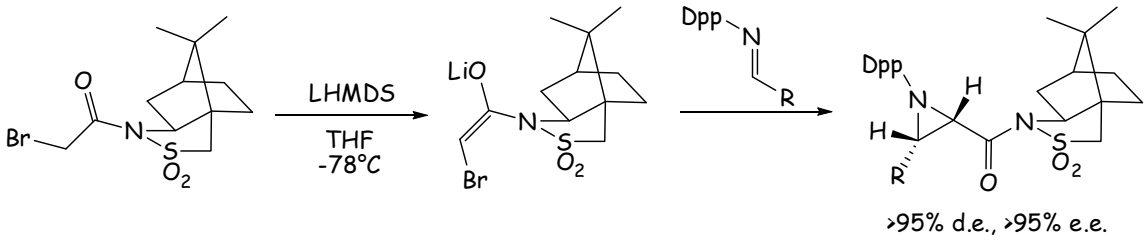
Scheme 5

The similar copper(I)-catalyzed reaction of trimethylsilyldiazomethane with *N*-tosylimines in the presence of (*R*)-Tol-BINAP proceeded with better levels of enantiocontrol, but still falls short of the standards expected of modern asymmetric transformations (Scheme 6).[11]

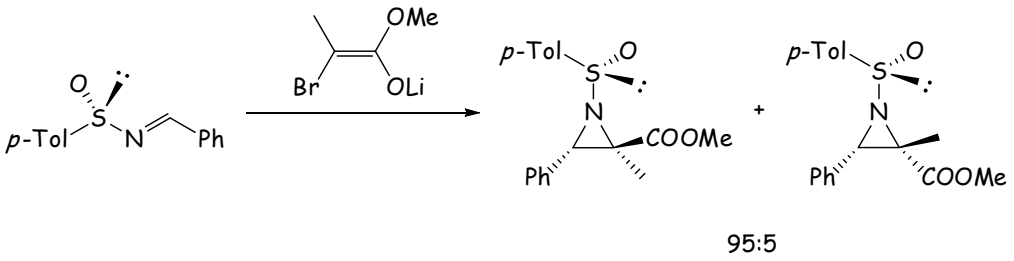


Scheme 6

The aza-Darzens reaction also falls into this category of aziridine-forming reaction. Several groups have investigated this route to aziridines, especially in the asymmetric manifold, in recent years. Thus, reactions of *N*-Dpp imines with (*R*)- and (*S*)-camphorsultam-derived α-bromoenolates[12] (Scheme 7) and of *S*-chiral sulfinylimines with achiral bromoenolates[13] (Scheme 8) have been studied; in both cases, high levels of enantio- and diastereocontrol were observed.



Scheme 7

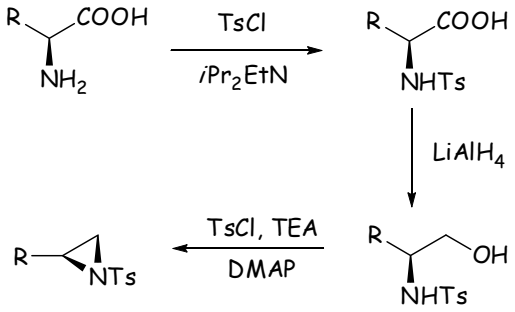


Scheme 8

Rong closure of 1,2-aminoalcohols, 1,2-aminohalides or 1,2-aminoazides: A conceptually obvious synthesis of aziridines utilizes 1,2-amino alcohols as precursors: the reaction can be readily achieved when the hydroxyl functional group is converted to a good leaving group. Intramolecular nucleophilic displacement reaction by the amine lone pair then yields the aziridine ring.

More recent methods exploit the conversion of the alcohol moiety of amino alcohols to oxyphosphonium species. As examples, treatment of an aminoalcohol with Ph_3P plus either Br_2,[14] CCl_4[15] or DEAD,[16] have been widely employed to effect aziridine ring-closure. Other phosphorus reagents employed in such reactions are diphenylphosphinic chloride[17] and diethoxytriphenylphosphine, $[Ph_3P(OEt)_2]$.[18]

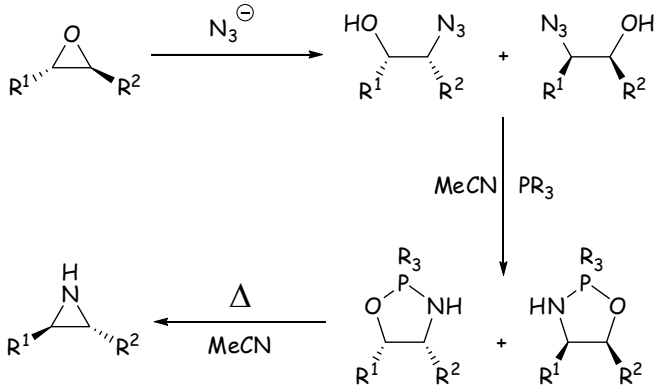
By using enantiopure amino alcohols, enantiopure aziridines are obtained enantiomerically-pure 1,2-amino alcohols required are frequently form via the reduction of enantiopure 2-amino acids, which are commercially available;[19] indeed, in many cases, the aminoalcohols themselves are commercially available. Where only the aminoacid is available, the efficiency of aziridine formation is, in some cases, hampered by the difficulty in isolating the intermediate amino alcohols, due to formation of water soluble metal complexes. To circumvent this problem, the reduction of *N*-Ts amino acids (rather than the aminoacid itself) has been described; this modification allows the synthesis of enantiopure *N*-Ts aziridines in a one-pot reaction.[20] (Scheme 9).



Scheme 9

Given the ready availability of enantiomerically-pure epoxides by a range of asymmetric processes, much use has been made of the multi-step preparation of aziridines from these precursors. In particular, the phosphine-mediated ring-closure of azidoalcohols (a Staudinger reaction), themselves obtained from chiral epoxides by ring-opening reaction using a range of azide sources, has attracted much interest. The pivotal reaction of this particular sequence revolves around the reaction of the hydroxyazide with trialkyl- or triarylphosphine, leading to oxazaphospholidines, which is rapidly formed and may be slowly converted to *N*-unsubstituted aziridine product upon heating in acetonitrile (Scheme 10). The reaction is reliable for a wide range of chiral and achiral epoxides and there is no issue of

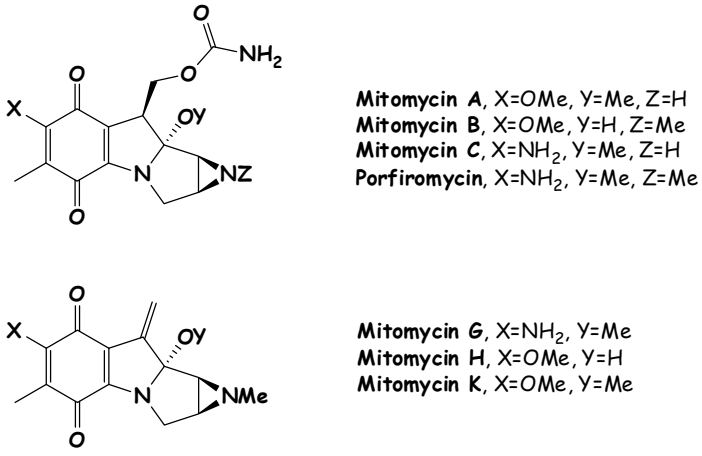
regiochemistry: both asymmetric centres are cleanly and predictably inverted during the process.



Scheme 10

2.1.2 – Aziridine ring in biologically active compounds

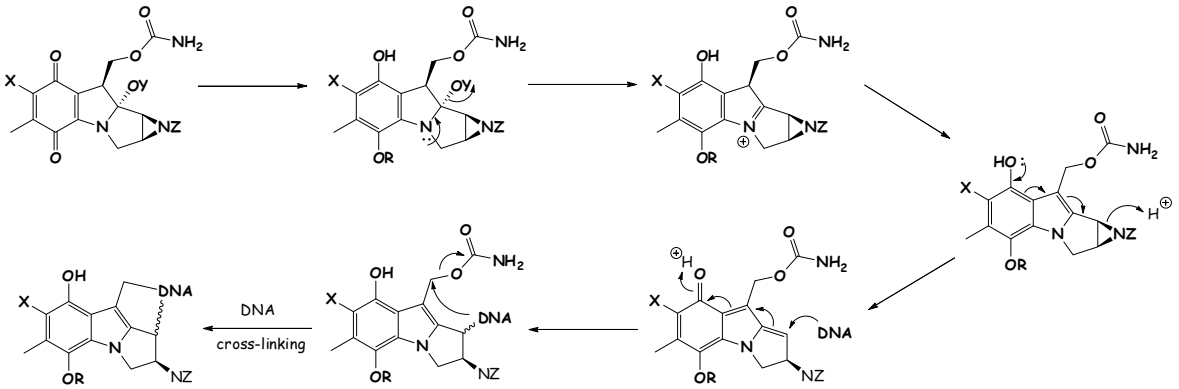
As powerful alkylating agents, aziridines have an inherent in vivo potency, often based primarily on toxicity rather than specific activity. There are, however, several classes of aziridine-containing natural products which marry potency with selectivity, of which perhaps the best-known are the Mitosanes (Scheme 11).[21] The Mitosanes were first isolated from soil extracts of *Streptomyces verticillatus* and they exhibit both anti-tumour and antibiotic activity: structure–activity relationships have identified the aziridine ring as being essential for such anti-tumour activity, and a large amount of work has concentrated on synthesizing derivatives of these natural products with increased potency.



Scheme 11

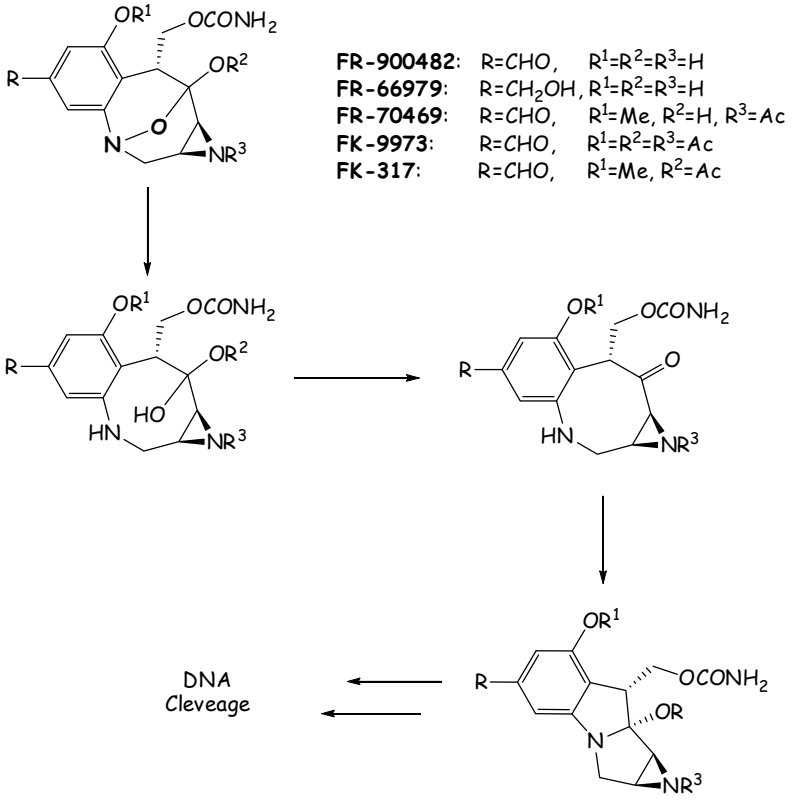
These natural bioactive compounds are powerful DNA alkylating agents. Thus, in the first step of the postulated mechanism of action, the natural products are converted from

the native quinone form to the hydroquinone (Scheme 12); secondly, formation of indoloaziridine occurs. The aziridine ring is next cleaved and DNA is first alkylated and then cross-linking occurs. The Mitosanes are one of the few classes of naturally-occurring antibiotics to exhibit the same mode of action in vivo and in vitro.



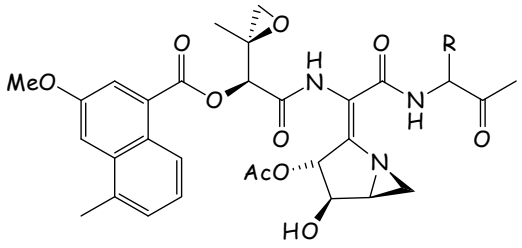
Scheme 12

Related compounds which have also shown similar anti-cancer activity are the FR and FK compounds shown below.[22] Consideration of the acetal-like core of these molecules reveals an intimate relationship with the Mitosanes (Scheme 13).



Scheme 13

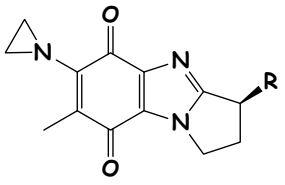
A structurally-distinct class of naturally-occurring aziridine derivatives possessing potent biological activity, isolated from *Streptomyces grieseofuscus* S42227 by Nagaoka and co-workers, is the Azinomycin family (Scheme 14).[23] This class of compounds possesses a wide range of activity against a range of cancers, including solid tumours, and Azinomycin-like structures have been shown to exert cytotoxicity against a variety of human tumour cell lines. The activity of all of these compounds again lies in their ability to act as DNA cross-linking agents, via nucleophilic ring-opening of the aziridine and epoxide moieties by N-7 positions of purines. It is not clear at present which ring-opening reaction takes precedence in the cross-linking event.



R=H, **Azinomycin A**
R=*CHO*, **Azinomycin B**

Scheme 14

The PBI class of natural products (Scheme 15) represents another type of DNA-alkylating aziridinyl quinone species.[24] In these compounds, however, the aziridinenis directly attached to the quinone subunit and undergoes ring-opening by nucleophilic attack of the DNA phosphate backbone, rather than alkylation by a purine nitrogen atom, as in the case of the Mitosane.



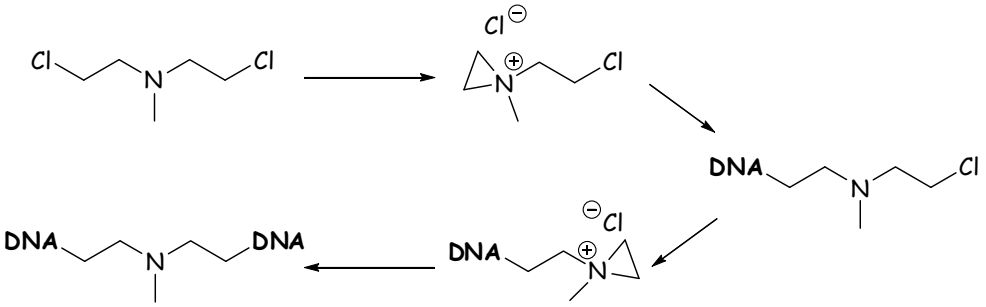
PBI-A R=*OAc*
PBI-B R=*OCONH*$_2$
PBI-C R=H

Scheme 15

Finally, in this section a range of synthetic aziridines has been examined for their suitability as pharmaceutical agents, based on the observations in the 1960s that nitrogen mustards (such as di(2-chloroethyl)methylamine) were able to reduce the rate of tumour growth in mice models. Nitrogen mustards (so-named due to their close structural resemblance to sulfur mustard, di(2-chloroethyl)sulfide, the 'mustard gas' of the First World

War) are very active alkylating agents due to their ability to form aziridinium ions which are rapidly alkylated by DNA (Scheme 16).

In particular, *N*-mustard-based ADEPT (antibody-directed enzyme pro-drug therapy) strategies (in which a protected form of the mustard is directed with high selectivity to a tumour site) have attracted great interest in recent years as potential cancer chemotherapies.[25]



Scheme 16

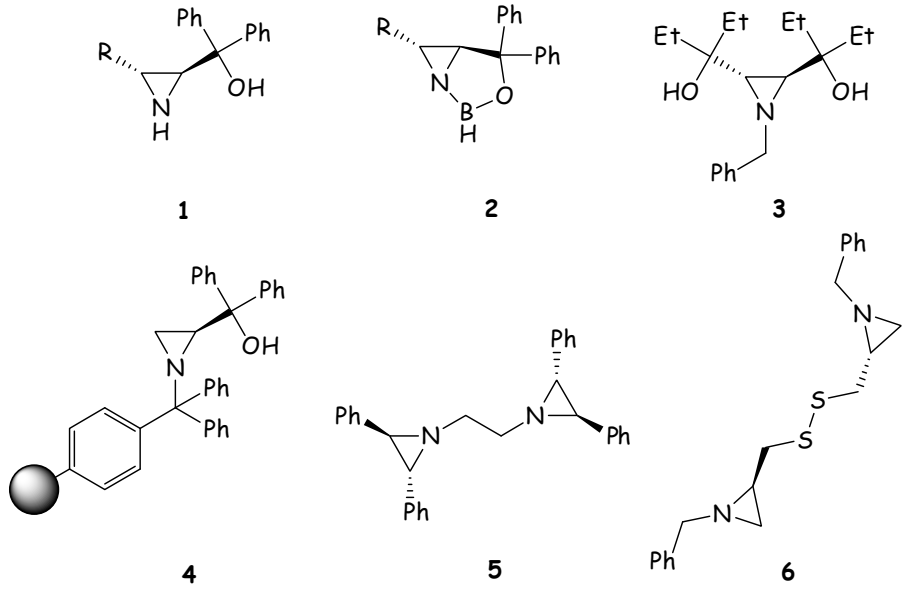
2.1.3 - Aziridines as chiral ligands

Enantiopure aziridines have gained considerable importance over a number of years as chiral ligands in transition metal-catalyzed asymmetric syntheses.[1,2] The concentrated density of stereochemical information located close to a good σ-donor nitrogen makes chiral aziridines attractive ligands for asymmetric catalysis. In an extension of Corey' s chiral oxazaborolidines for the enantioselective reduction of prochiral ketones, aziridine 2-carbinols (2*S*,3*R*)-**1** have been used as precatalysts to prepare oxazaborolidines (2*S*,3*R*)-**2** (Scheme 17).[26] When used with borane-dimethylsulfide complex for the reduction of acetophenone to (*R*)-phenylethyl alcohol, enantioselectivities were greater than 90%.

A range of aziridine 2-carbinols have been screened as catalysts for the enantioselective addition of diethylzinc to aldehydes and aziridine (*S*,*S*)-**3** gave up to 97% ee and good yields.[27] An equally effective *N*-trityl aziridine has been studied and the corresponding polymer supported catalyst (*S*)-**4** prepared.[28,29] High enantioselectivity was retained and the catalyst was recycled without significant loss in enantioselectivity.

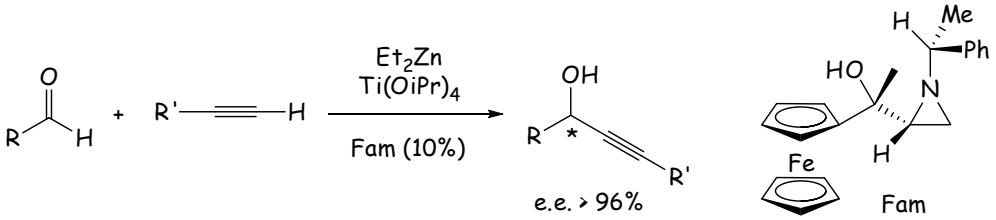
C_2-Symmetric bis-aziridines have been studied as ligands in a number of metal mediated asymmetric reactions.[30] A two carbon tether between the aziridine nitrogens was optimal, regardless of the metal used, to allow five membered chelate formation, and the other aziridine side chains were varied for steric and electronic requirements. Bis-aziridine

(2*S*,3*S*,2'*S*,3'*S*)-**5** generally showed the best performance. This bisaziridine gave good results osmium catalysed asymmetric dihydroxylation of *trans*-stilbene and in the palladium catalysed allylic alkylation. A range of chiral bis-aziridine disulfide as (2*R*,2'*R*)-**6** was prepared by Braga and co-workes[31] and they have been screened as catalysts for the enantioselective addition of diethylzinc to aldehydes with good results (e.e. > 99%).



Scheme 17

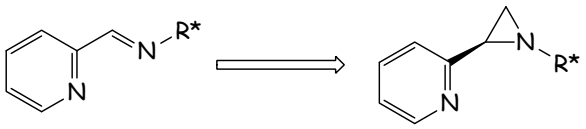
Dogan and co-workes recently developed a new set of chiral ligands, ferrocenyl-substituted aziridinylmethanols (Fam), and used them in diethylzinc addition reactions to aldehydes[32] to obtain secondary alcohols with up to 99% e.e., to enones[33] to obtain β-ethylated ketones in up to 80% e.e. and in alkynylation of aldehyde catalysed by titanium isopropoxyde (Scheme 18).[34]



Scheme 18

2.2 – Asymmetric synthesis of 2-(2'-pyridyl)aziridines

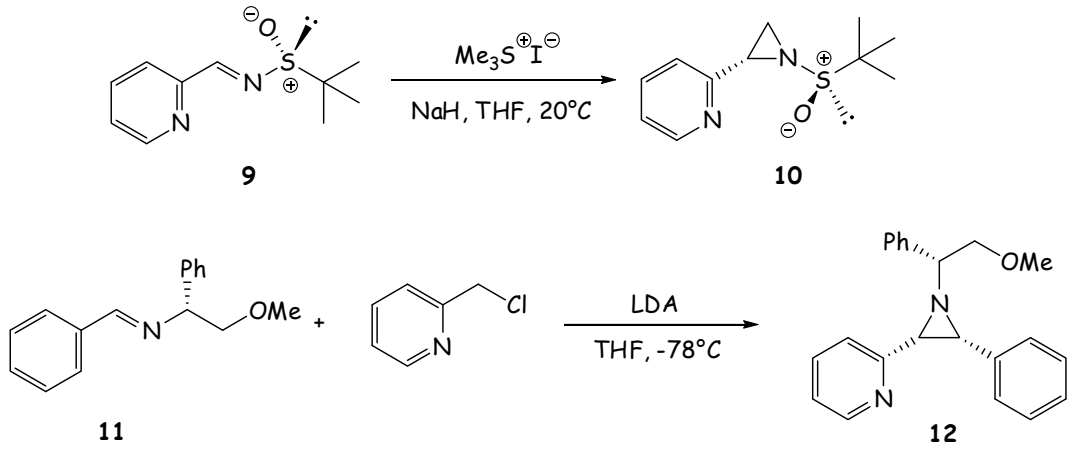
Following our previous studies on enantioselective Pd-catalyzed allylic substitution reactions using 1-(2-pyridyl)alkyl aziridines as ligands (see chapter 1),[35] we directed our interest to the asymmetric synthesis of 2-(2-pyridyl)aziridines **8** from chiral 2-pyridineimines **7** bearing a stereogenic center at the nitrogen atom (Scheme 19), aiming to assess their potential as bidentate ligands in a variety of enantioselective catalytic transformations. The envisioned route involved the addition of halomethylmetal reagents to the imine function.



7 **8**

Scheme 19

The same approach as been recently followed by different authors. The *N*-(*tert*-butylsulfinyl)aziridine **10** (R = (*R*)-*t*-BuSO) has been prepared by the the Corey-Chaykovsky sulfonium ylide aziridination protocol (Scheme 20).[36] Moreover, an *N*-substituted-2-phenyl-3-(2-pyridyl)aziridine was obtained by Darzens-type reaction of lithiated 2-(chloromethyl)pyridine with (*R*)- and (*S*)-*N*-benzylidene-*O*-methyl-phenylglycinol (Scheme 20).[37] However, in both reports removal of the aziridine nitrogen substituent (chiral auxiliary) has not been described. Apparently, this is a difficult task, that should be accomplished by selective procedures to preserve the integrity of the aziridine ring and the configuration of the benzylic stereocenter. In this regard, it should be underlined that the aziridine **8** can easily undergo ring-opening by hydrogenolysis and nucleophilic attack, especially through *N*-activation by protic or Lewis acids. Hence, in order to prepare the *N*-unsubstituted 2-(2-pyridyl)aziridine **8** (R = H), it should be possible to remove the *N*-(*tert*-butyl)sulfinyl substituent R in the aziridine **8** by treatment with methyllithium at low temperature,[38] rather than by the usual treatment with HCl/dioxane or HCl/methanol.



Scheme 20

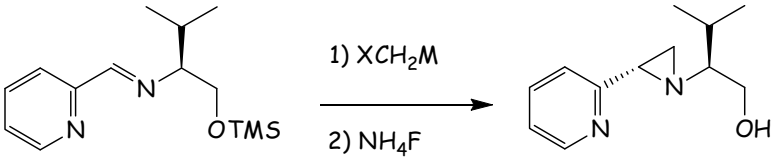
2.2.1 - Addition of "carbenoid" reagents to chiral aromatic imines

Initial reactions were performed on the known imine **13**, which is available by condensation of 2-pyridinecarboxaldehyde with (*S*)-valinol and subsequent protection of the hydroxyl function as its trimethylsilyl ether.[39] As a matter of fact, our previous studies on the asymmetric synthesis of enantiopure 1-(2-pyridyl)alkylamines showed that *O*-trimethylsilyl valinol is the preferred chiral auxiliary for the diastereoselective addition of organometallic reagents to 2-pyridineimines, providing the desired amines with higher diastereoselectivities compared to valine esters and phenylglycinol.[39] Hence, a number of halogenomethylmetal reagents were added to the imine **13** under different experimental conditions, in order to optimize the synthesis of the 1,2-disubstituted aziridine **14**, which was isolated following routine desilylation procedures (Scheme 21).

It should be observed that electron-withdrawing *N*-substituents are generally required to achieve the addition of carbenoid reagents to the azomethine function. We hoped, however, that the electron-withdrawing pyridine ring would provide sufficient activation of the imine **13**. So, in the first experiment, we used the zinc reagent that is formed *in situ* from diethylzinc and chloroiodomethane, and was previously used for the cyclopropanation of alkenes.[40] This reagent was added to the TMSO-protected imine **13** at −30 °C, but no desired product was formed, even allowing the reaction mixture to reach room temperature (Table 1, entry 1). Even replacing chloroiodomethane with diiodomethane no reaction was observed (entry 2). We then moved to reagents that have previously been used for the preparation of halohydrins from aldehydes. We observed that a smooth reaction occurred at room temperature using the samarium reagent formed *in situ* by reaction of

samarium with diiodomethane;[41] the desired aziridine **14** was isolated in good yield but very low diastereoselectivity (entry 3) after desilylation of the crude reaction product with ammonium fluoride and column chromatography. No improvement was achieved by carrying out the reaction at 0 °C, as the yield and diastereomeric ratio (d.r.) were slightly lower (entry 4). The use of chloroiodomethane in place of diiodomethane in the samarium-mediated procedure gave a complex mixture of products (entry 5).

Scheme 21



13 **14**

Table 1

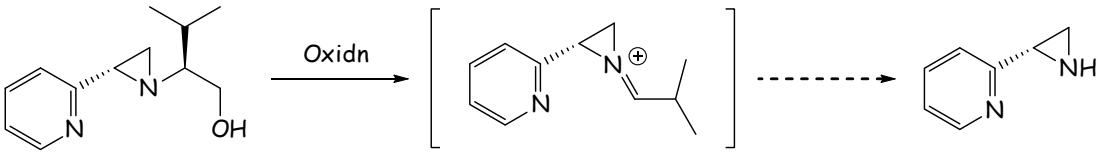
Entry	Reagents (equivalents)	T (°C)	Time (h)	14 (Yield %)[a]	14 (*S,S*):(*R,S*)[b]
1	Et_2Zn (2), CH_2ICl (4)[c]	-30 to 20	3	0[d]	-
2	Sm (3), CH_2I_2 (2)	20	3	72	56:44
3	Sm (3), CH_2I_2 (2)	0	3	70	52:48
4	Sm (3), CH_2ICl (2)	20	3	[e]	-
5	MeLi (2), CH_2I_2 (2)	-78 to 0	4	[e]	-
6	MeLi (1.8), CH_2ICl l (1.8), LiBr (1)	-78 to 20	8	93[f]	87:13
7	MeLi (3.6), CH_2ICl (3.6), LiBr (2)	-78 to 20	8	95[f] (65)[g]	92:8(>99:1)[g]

[a] Yield of the crude reaction product. [b] Determined by GC-MS and 1H NMR analyses. [c] The reaction was performed in toluene. [d] The starting imine was recovered. [e] A complex mixture of products was obtained. [f] The *O*-methyl derivative of **14** (ca 8% yield) was observed by GC-MS analysis in the reaction mixture. [g] Yield and d.r. of **14** after column chromatography (SiO_2).

The reagent formed *in situ*, in the presence of the imine, from diiodomethane and methyllithium[42] also gave a mixture of products, that was abandoned (entry 6). Good results were instead obtained with chloromethyllithium, which was formed *in situ* by the addition of methyllithium to a mixture of chloroiodomethane and lithium bromide in THF at –78 °C in the presence of the imine **13**,[43] then slowly raising the temperature to 20 °C. In this case, the aziridine **14** was obtained with excellent yield and high stereocontrol (d.r. 87:13, entry 7),

following desilylation with ammonium fluoride in a MeOH-H_2O mixture. The positive influence of lithium bromide on the stability of the carbenoid reagent should be similar to that of lithium dialkylamides, which, on the basis of DFT calculations,[44] form mixed dimer aggregates with chloromethyllithium in THF solution. Better diastereoselectivity (d.r. 92:8) was finally obtained by using a greater excess of reagents (3.6 equivalents) with respect to the imine, and the pure diastereomer (*S*,*S*)-**14** was isolated in 65% yield following chromatography on a silica gel column (entry 8). In the latter reactions (entries 7 and 8), small amounts (up to 8%) of the *O*-methyl ether of **14** were detected by GC-MS analysis and this compound was isolated by repeated chromatography of the impure compound obtained by pooling enriched chromatographic fractions coming from different reaction runs.

Unfortunately, removal of the nitrogen substituent from the aziridine **14** to give the 1-unsubstituted aziridine **16** proved to be impossible by the routine procedures generally used to cleave β-aminoalcohols. In fact, the aziridine **14** was unreactive towards oxidizing agents, such as periodic acid/methylamine and lead tetraacetate, in different solvents and experimental conditions (Scheme 22). In our opinion, this failure can be ascribed to the strain associated with the formation of the intermediate iminium ion **15**, which features an exocyclic N=*C* double bond. This hypothesis is supported by the recent observation of the peculiar reactivity of 1-alkenylaziridines, which do not display nucleophilic character at the exocyclic C2-alkenyl carbon as is usually observed in enamines.[45]

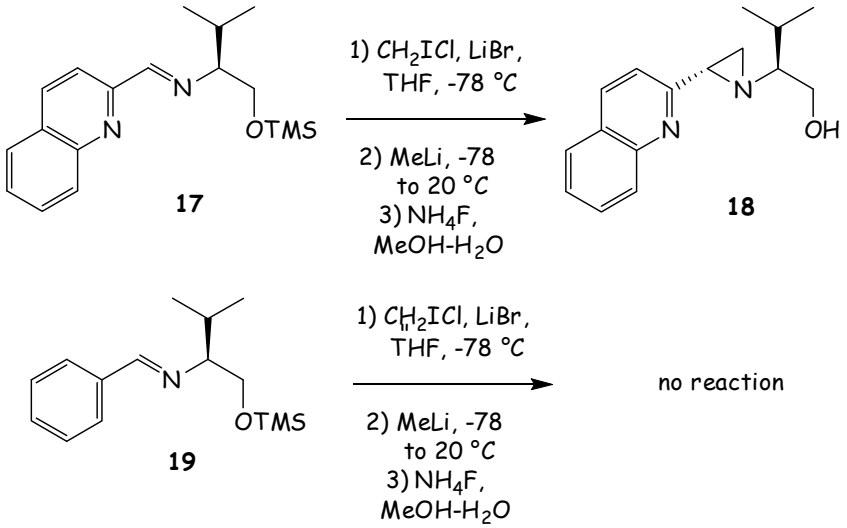


14 **15** **16**

Scheme 22

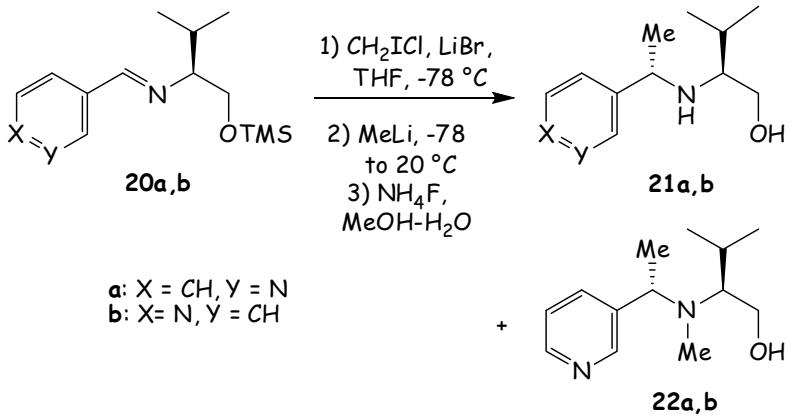
2.2.2 – Variation of aromatic ring

The scope of the described aziridination procedure exploiting chloromethyllithium was then investigated on a range of different aromatic imines derived from the same chiral auxiliary, (*S*)-valinol (Scheme 23). We readily recognized that the presence of the 2-pyridineimine moiety is a requisite for the successful aziridination. As a matter of fact, the 2-quinolineimine **17** proved to be less reactive than the 2-pyridineimine **13**, as the corresponding aziridine **18** was obtained with low yield (51%) and the benzaldimine **19** did not react at all.



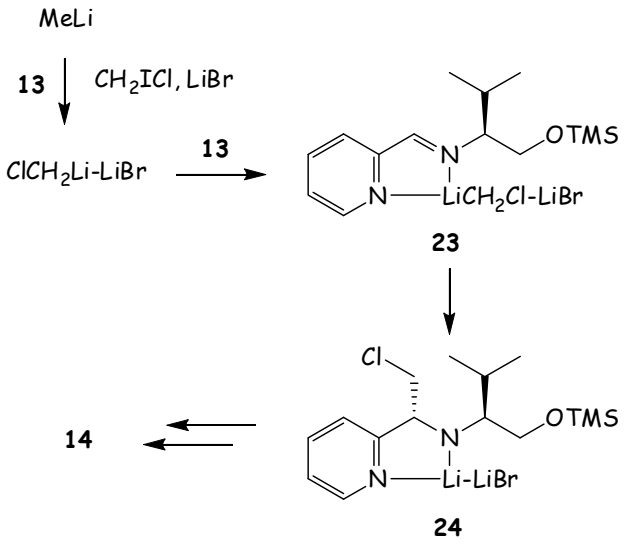
Scheme 23

Surprisingly, the reactions of the 3- and 4-pyridineimines **20a** and **20b**, respectively, lead to the secondary amines **21a,b**, which were isolated in small amounts and identified by comparison with authentic specimen, and mainly the tertiary amines **22a,b**. All the products **21a,b** and **22a,b** were obtained with complete diastereoselectivity.



Scheme 24

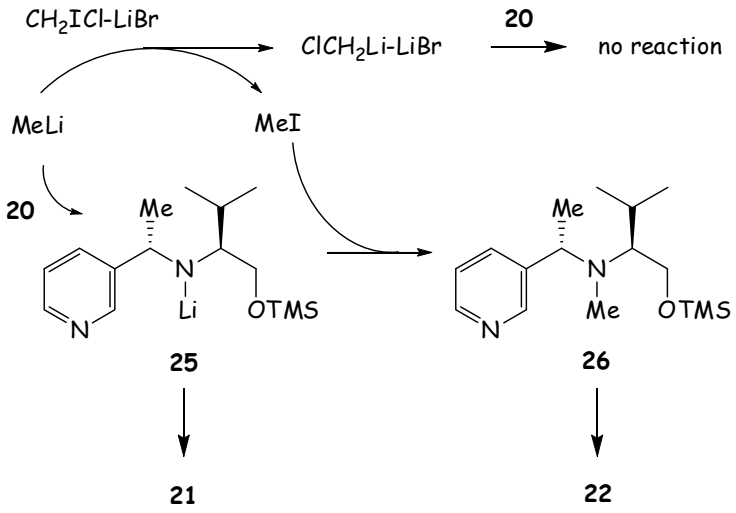
It is noteworthy that the competitive attack of methyllithium on the imine **13** was not observed. Moreover, when quenching the reaction mixture at low temperature, we did not detect the presumed intermediate β-chloro amine. The outcome of a modified experimental procedure was also instructive. When methyllithium was added to the mixture of chloroiodomethane and lithium bromide in THF at −78 °C, then the imine **13** was added to the cold mixture after 15 min, no product was formed after allowing the temperature to slowly reach room temperature. This result demonstrated that the actual reagent must be formed *in situ* in the presence of the imine.



Scheme 25

The proposed rationale for the different behaviour of the 2- and 3-pyridineimines in this reaction is described in Scheme 25. The reactivity of the bidentate imines **13** and **17** can be associated to their chelating ability, allowing formation of the stable chelate complex **23** with the organometallic reagent $ClCH_2Li$ generated *in situ*. At the same time, the bidentate ligand (imine) enhances the nucleophilic character of the organolithium reagent and promotes the intramolecular C-C bond forming reaction leading to the β-chloro lithium amide **24**. Then, this intermediate undergoes intramolecular substitution to give the aziridine **14**, after deprotection of the hydroxyl group.

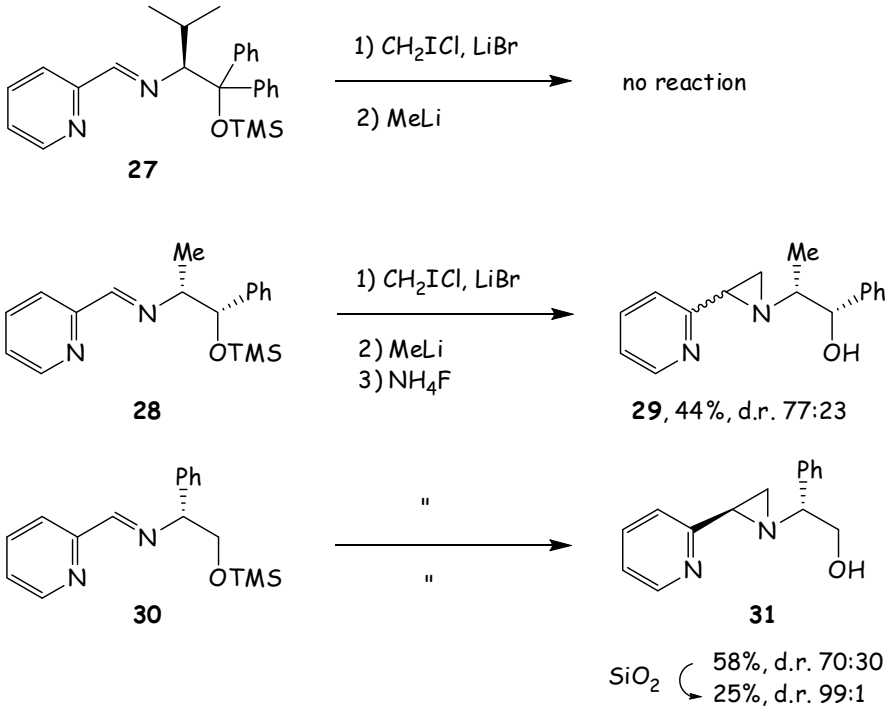
On the other hand, when methyllithium is added to the mixture of chloroiodomethane and 3-pyridineimine **20**, it reacts with both of them at comparable rates. Apparently, the chloromethyllithium generated *in situ* is less reactive or unreactive towards the imine **20**. The amide **25,** formed by attack of methyllithium on the imine **20**, is converted to the secondary amine **21** by proton quenching and desilylation, and to the tertiary amine **22** by reaction with methyl iodide, which is formed in the first halogen-metal exchange step, and desilylation.



Scheme 26

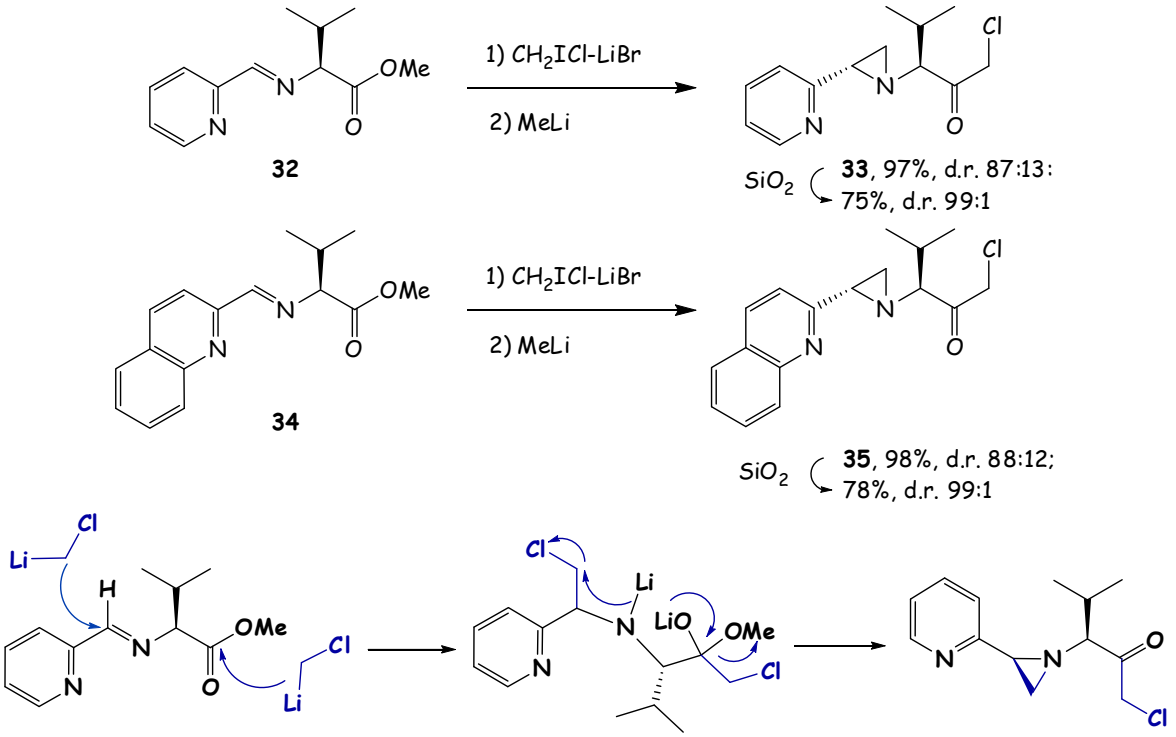
2.2.3 – Different chiral auxiliaries

We also examined the effect of different chiral auxiliaries, either β-aminoalcohols or α-aminoesters available from the "chiral pool", on the reactivity/diastereoselectivity of the corresponding 2-pyridineimines (Scheme 27). The imine **27** derived from 1,1-diphenylvalinol was found to be unreactive, presumably owing to the bulkiness of the *N*-substituent, and the (+)-norephedrine-derived imine **28** reacted sluggishly to give a mixture of products containing the diastereomeric aziridines **29** in 44% yield and 77:23 ratio (GC-MS). Moreover, the imine **30** prepared from (*R*)-phenylglycinol, gave the expected aziridine **31** with low diastereoselectivity and the major (*R*,*R*)-diastereomer was isolated in 25% yield after column chromatography. As found for aziridine **16**, the *N*-substituent in **30** could not be removed by oxidative procedures, and hydrogenolysis over different Pd-catalysts was unsatisfactory due to concomitant cleavage of the pyridyl-substituted aziridine C-N bond.



Scheme 27

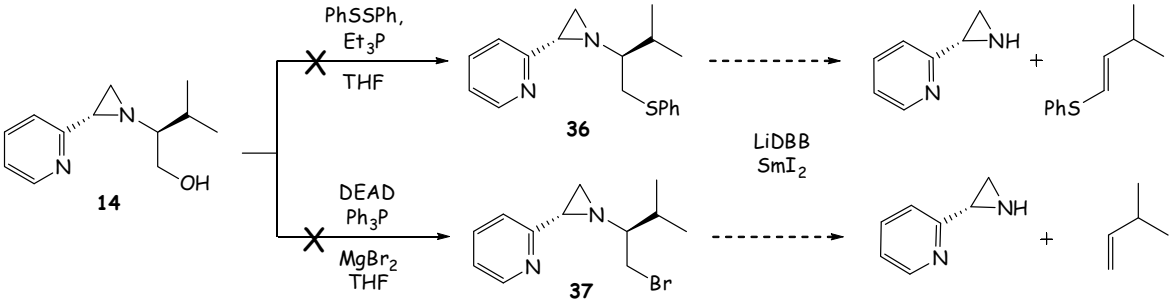
Then we checked (*S*)-valine methyl ester as the chiral auxiliary and carried out the aziridination procedure on the derived imine **32** (Scheme 28). In this way, we obtained the product **33**, coming from organometallic additions to both the imine and ester functions, in good yield and d.r. 87:13. Selective attack to the azomethine functionality could not be accomplished by working with equimolar amounts of reagents (imine, chloroiodomethane and methyllithium), as the same product **33** was formed, albeit in low yield. This result apparently demonstrates that chloromethyllithium, rather than a carbene, is the active intermediate in the reaction. Moreover, products coming from the attack of methyllithium to the ester function were not observed either in the crude reaction mixture or in chromatographic fractions. Similarly, the 2-quinolineimine **34** gave the corresponding aziridine-α-chloroketone **35**, in comparable yield and d.r. 88:12.



Scheme 28

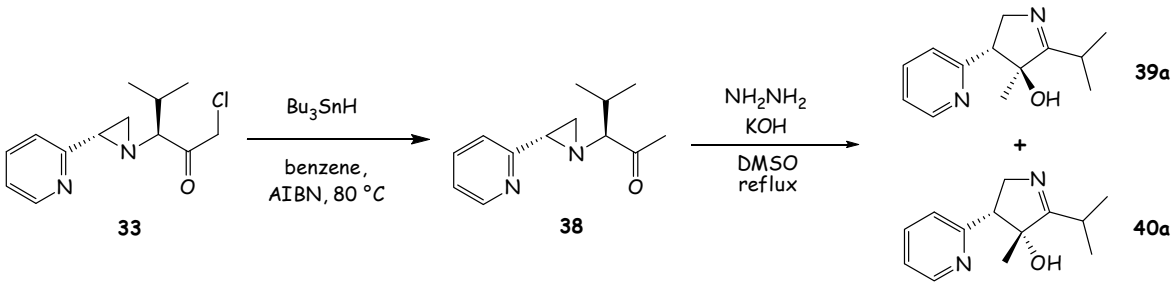
2.2.4 – Removal of N-substituent

Further efforts were devoted to find alternative procedures for the removal of the *N*-substituent in the aziridine **14**, through modification of the hydroxyl functionality. Initial attempts were directed to the transformation of the primary alcohol to halides (**36**) or phenylsulfide (**37**) by Mitsunobu procedures, because these compounds were expected to undergo β-amide elimination by treatment with a metal or a reducing agent (e.g. LiDBB and SmI_2).[46] Unfortunately, we met with no success, because the reaction mixtures were generally complex and the desired product was never isolated by column chromatography. Even the preparation of the bromide via the tosylate in different experimental conditions failed, probably because of the instability of any eventual bromide formed.



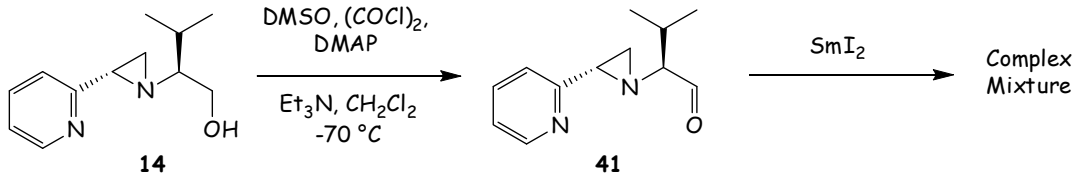
Scheme 29

Treatment of the chloroketone **33** with tributylstannyl hydride in refluxing benzene in the presence of AIBN gave the ketone **38** (Scheme 30), on which Wolff-Kishner reactions with hydrazine or phenylhydrazine and KOH in ethylene glycol or dimethylsulfoxide at high temperature were carried out; however, the expected fragmentation of the hydrazones to give the free aziridine we did not occur contrary to previous reports of α-heterosubstituted hydrazones.[47] Instead, new isomeric products (**39a** and **40a**) were formed by rearrangement of **38** in the basic medium (vide supra).



Scheme 30

Swern oxidation of the aziridine-alcohol **14** smoothly led to the aziridine-aldehyde **41** (Scheme 31), which was reduced with SmI_2 at low temperature. β-Fragmentation of the intermediate ketyl radical anion was expected to occur, thus giving the desired NH-aziridine. Instead, several unidentified products were observed by TLC analysis, presumably due to competitive side reactions, probably including pinacol coupling and most likely cleavage of the aziridine C-N bond. Indeed, it has been reported that acetoxymethylpyridine can be coupled with carbonyl compounds through cleavage of the benzylic C-O bond, driven by chelation of samarium to the pyridine nitrogen and the acetate.[48]

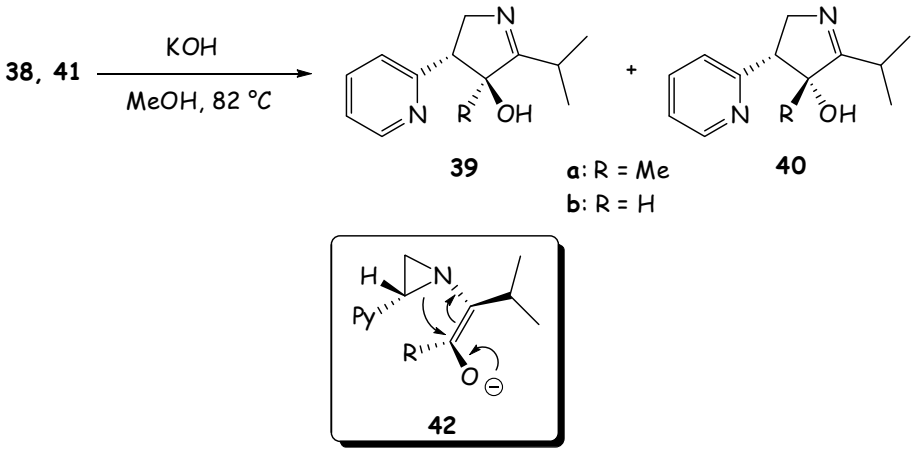


Scheme 31

The aziridine-ketone **38** reacted in basic medium (methanolic KOH at the reflux temperature of methanol) to give a highly prevalent compound, to which the structure **39a** (Scheme 32) was tentatively assigned on the basis of mass-spectrometric and spectroscopic analyses, as a matter of fact, only the depicted structure fits with all the analytical data. In

particular, the stereochemistry of the two ring stereocenters was determined by a NOE experiment: irradiation of the pyridyl-substituted ring proton only caused a response of the adjacent methylene hydrogen, not the ring methyl substituent. Although another compound, probably the diastereomer **40a**, was present (ca 15% by ^{1}H NMR) in the crude reaction mixture, it was not isolated by column chromatography, perhaps because it underwent dehydration more readily.

We suggest that compound **39a** is formed by the concerted mechanism depicted in structure **42**, featuring the cleavage of the aziridine C-N bond, wherein the two electrons unusually move from nitrogen to carbon. We assume that the configuration of the pyridyl-substituted stereocenter is maintained throughout this rearrangement. This supposition is in agreement with the reported stereoselective rearrangement of a 1,2,3-trisubstituted aziridine to 1-pyrroline by generation of a carbanion at the propargyl *N*-substituent.[49] Analogously, when aldehyde **41** was subjected to the same conditions a 55:45 mixture of two compounds was observed, presumably the diastereomers **39b** and **40b**, as evidenced by the ^{1}H NMR spectrum of the crude reaction mixture. However, only the major product was isolated by column chromatography, as the minor one probably decomposed by dehydration. Conversely, no product was formed by heating the sodium alkoxide derived from the aziridine-alcohol **14** in THF.



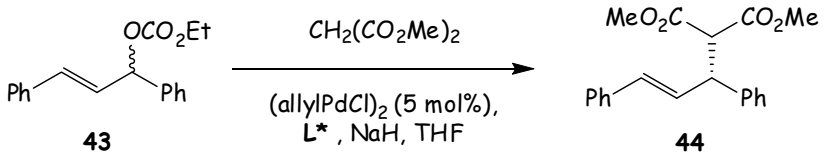
Scheme 32

2.2.5 – Use of the 2-(2-pyridyl)aziridines as chiral ligand

We thought that the new 2-(2-pyridyl)aziridines synthesed in this work could be used a chiral ligands in asymmetric catalysis. We tested them in standard palladium catalyzed

Asymmetric Allylic Alkylation (*AAA*) reaction of the carbonate **43** (Scheme 33), and found that the reactions with dimethyl malonate proceed with in the standard reaction conditions (BSA, allylpalladium chloride dimer, tetrahydrofuran). However with our great disappointment, low to moderate levels of enantioselectivity where obtained (Table 2). The ligand **14** with the *S,S* configurations of the two stereocenter showed the higher enantioselectivity (e.e. 62%) and its diasteroisomer gave the product with the same configuration but with only the 20% of e.e.. This results indicated that the configuration of stereocenter in the benzylic position is more important for the stereocontrol, we also tested the aziridine **18** and **31** but with low e.e..

Scheme 33



43 **44**

Table 2

L*	Yield 44 (%)	e.e. 44 (%)
14 (*S, S*)	85	62 (*R*)
14 (*R, S*)	89	20 (*R*)
18 *(S, S)*	82	33 (*R*)
31 *(R, R)*	85	20 (*S*)

Finally we tested the 2-(2-pyridyl)aziridine **14** in the enantioselective addition of dietylzinc to aromatic aldehydes (Scheme 34). The reaction proceeded very smoothly, and was complete in only 2.5 hours at room temperature (Table 3), affording the addition product with 50% e.e.. Increasing the realative amount of the chiral ligand did not increase the enantioselectivity.

Scheme 34

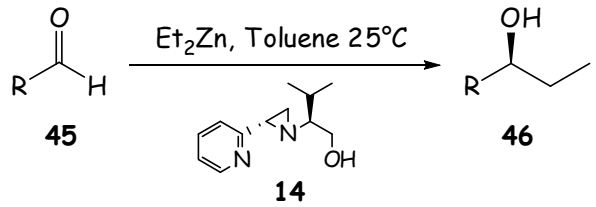


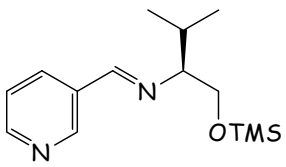
Table 3

R	L (mol%)	Conversion 46 (%)	e.e. 46 (%)
Ph	5	100	50
Ph	10	100	51
2-Naphtyl	5	100	47
4-Br-Ph	5	100	50

2.3 – Experimental section

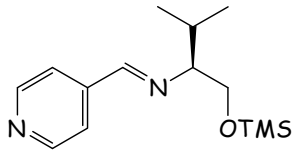
2.3.1 – General protocol for the preparation of Imines

The imines **20a**, **20b**, **28** and **34** were prepared from the corresponding aldehydes and enantiopure amines in almost quantitative yield by the procedures previously described for the preparation of the 2-pyridineimines **14**, **17**, **30** and **32**.[35,39] All the crude imines >95% pure by 1H NMR analysis) and were used immediately as obtained avoiding purification. However, the imine **34**, being obtained as a solid, could be easily purified for analytical purpose by crystallization from Et_2O-pentane mixture.

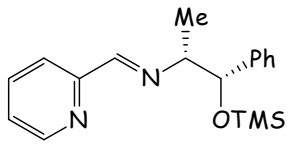


***N*-(3-Pyridylmethylidene)-*O*-trimethylsilyl-(*S*)-valinol (20a)**: Yellow oil; $[\alpha]_D^{20}$ = -20.8 (*c* 1.0, $CHCl_3$); IR (neat): ν = 2958, 2929, 2868, 1646, 1591, 1575, 1470, 1422, 1388, 1250, 1026, 839, 805, 708; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.87 (s, 1 H), 8.63 (d, *J* = 4.7 Hz, 1 H), 8.24 (s, 1 H), 8.12 (dt, *J* = 1.8 Hz, *J* = 7.9 Hz, 1 H), 7.33 (dd, *J* = 4.8 Hz, *J* = 7.8 Hz, 1 H), 3.87 (dd, *J* = 3.9 Hz, *J* = 10.3 Hz, 1 H), 3.66 (dd, *J* = 8.2 Hz, *J* = 10.3 Hz, 1 H), 3.02 (m, 1 H), 1.95 (sept, *J* =

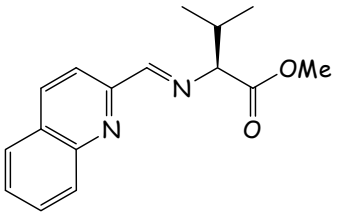
6.8 Hz, 1 H), 0.93 (d, *J* = 6.8 Hz, 3 H), 0.92 (d, *J* = 6.8 Hz, 3 H), 0.03 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.8 (*C*=N), 151.2, 150.2, 134.5, 134.5, 131.9, 123.5, 78.8, 64.2, 29.9, 20.0, 18.6, −0.4; MS (EI): *m/z* = 264 (M^+, 6), 249 (5), 221 (4), 161 (100), 73 (27), 55 (16).



***N*-(4-Pyridylmethylidene)-*O*-trimethylsilyl-(*S*)-valinol (20b)**: Yellow oil; $[\alpha]_D^{20}$ = −43.0 (*c* 0.4, $CHCl_3$); IR (neat): *ν* = 3081, 3032, 2958, 2872, 1650, 1593, 1462, 1405, 1251, 1115, 882, 841; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.67 (dd, *J* = 1.6 Hz, *J* = 4.5 Hz, 1 H), 8.18 (s, 1 H), δ = 7.60 (dd, *J* = 1.6 Hz, *J* = 4.5 Hz, 1 H), 3.86 (dd, *J* = 3.6 Hz, *J* = 10.5 Hz, 1 H), 3.64 (dd, *J* = 7.8 Hz, *J* = 10.5 Hz, 1 H), 3.03 (dd, *J* = 3.6 Hz, *J* = 7.8 Hz, 1 H), 1.95 (sept, *J* = 6.9 Hz, 1 H), 0.93 (d, *J* = 6.9 Hz, 3 H), 0.91 (d, *J* = 6.9 Hz, 3 H), 0.02 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.8, 150.3, 143.1, 121.9 (PyH), 78.7, 64.0, 29.9, 19.9, 18.6, −0.4; MS (EI): *m/z* = 264 (M^+, 11), 249 (10), 221 (3), 161 (100), 131 (4), 103 (9), 73 (35).



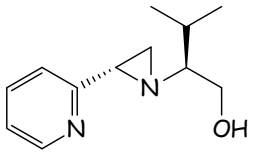
***N*-(2-Pyridylmethylidene)-*O*-trimethylsilyl-1(*R*),2(*S*)-norephedrine (28)**: Colourless oil; $[\alpha]_D^{20}$ +98.0 (*c* 1.9, $CHCl_3$); IR (neat): *ν* = 3054, 2958, 2872, 1650, 1588, 1568, 1468, 1436, 1367, 1251, 1107, 973, 878, 774; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.64 (ddd, *J* = 0.9 Hz, *J* = 1.7 Hz, *J* = 4.9 Hz, 1 H), 8.08 (s, 1 H), 7.90 (dt, *J* = 1.0 Hz, *J* = 7.9 Hz, 1 H), 7.69 (ddt, *J* = 1.0 Hz, *J* = 1.7 Hz, *J* = 7.9 Hz, 1 H), 7.15-7.33 (m, 6 H), 4.78 (d, *J* = 6.4 Hz, 1 H), 7.90 (quint, *J* = 6.4 Hz, 1 H), 1.33 (d, *J* = 6.4 Hz, 3 H), 0.07 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.4, 153.6, 150.1, 138.0, 136.8, 128.4, 128.0, 127.2, 126.5, 123.8, 78.5, 65.8, 16.2, 2.1; MS (EI) *m/z* = 297 (6), 179 (100), 133 (44), 92 (19), 73 (48).



***N*-(2-Quinolylmethylidene)-(*S*)-valine Methyl Ester (34)**: White powder; m.p. = 57-58 °*C* (Et_2O-pentane); $[\alpha]_D^{20}$ –113.7 (*c* 1.1, $CHCl_3$); IR (Nujol): *v* = 1735, 1639, 1595, 1463, 1376, 1193, 1142, 975, 842, 760, 734; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.52 (s, 1 H), 8.28 (d, *J* = 8.5 Hz, 1 H), 8.21 (d, *J* = 8.6 Hz, 1 H), 8.14 (d, *J* = 8.5 Hz, 1 H), 7.87 (d, *J* = 8.0 Hz, 1 H), 7.77 (dt, *J* = 1.4 Hz, *J* = 8.1 Hz, 1 H), 7.77 (dt, *J* = 1.4 Hz, *J* = 8.0 Hz, 1 H), 3.86 (d, *J* = 7.0 Hz, 1 H), 3.78 (s, 3 H), 2.45 (dsept, *J* = 6.8 Hz, *J* = 7.0 Hz, 1 H), 1.01 (d, *J* = 6.8 Hz, 3 H), 0.98 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.0, 164.7, 154.2, 147.7, 136.4, 129.7, 129.5, 128.8, 127.6, 127.5, 118.6, 79.8, 51.9, 31.8, 19.4, 18.5; MS (EI): *m/z* = 270 (M^+, 2), 255 (2), 238 (3), 227 (14), 212 (15), 211 (100), 195 (30), 169 (28), 168 (25), 142 (42), 128 (13), 115 (15). Anal. Calcd for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36. Found C, 71.15; H, 6.73; N, 10.34.

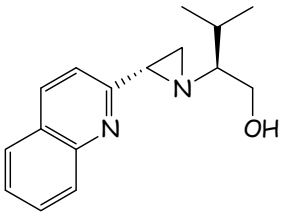
2.3.2 - Reaction of imines with methyllithium/chloroiodomethane.

General procedure: Lithium bromide (0.66 g, 7.6 mmol) and chloroiodomethane (0.99 mL, 13.6 mmol) were added to the solution of the imine **13** (1.00 g, 7.6 mmol) in anhydrous THF (20 mL) under an inert atmosphere. The magnetically stirred mixture was cooled at ~78 °C and MeLi (1.6 M in Et_2O, 8.5 mL, 13.6 mmol) was slowly added, meanwhile the mixture assumed a dark red colour. The temperature was allowed to rise to 20 °C over 6 h, then the mixture was quenched with saturated aqueous sodium hydrogen carbonate (20 mL). The organic phase was extracted with Et_2O (3 x 20 mL), and the combined organic layers were concentrated at reduced pressure. For reactions of imines derived from *O*-TMS-β-aminoalcohols, the residue was taken up in MeOH-H_2O (1:1, 20 mL) and NH_4F (2.5 g) was added, the mixture was stirred overnight, then NaOH pellets were added until pH 11 was achieved, MeOH was removed at reduced pressure, and the organic phase was extracted with Et_2O (3 x 20 mL). The combined organic layers was washed with brine (20 mL), dried (Na_2SO_4) and concentrated at reduced pressure. The dark oily residue was purified via SiO_2 column chromatography eluting with 20:80 cyclohexane/EtOAc, then with 90:10 EtOAc /MeOH mixtures.

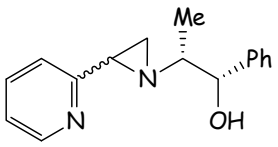


3-Methyl-2(*S*)-[2(*S*)-(2-pyridyl)-1-aziridinyl]-1-butanol (14): 0.509 g, 65%, red oil; $[\alpha]_D^{20}$ –105.6 (*c* 0.5, $CHCl_3$); IR (neat): *ν* = 3373, 2960, 1595, 1570, 1479, 1436, 1387, 1077, 762; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.54 (ddd, *J* = 1.0 Hz, *J* = 1.8 Hz, *J* = 4.8 Hz, 1 H), 7.63 (dt, *J* = 1.2 Hz, *J* = 7.8 Hz, 1 H), 7.24 (dt, *J* = 0.9 Hz, *J* = 7.8 Hz, 1 H), 7.16 (ddd, *J* = 1.2 Hz, *J* = 4.9 Hz, *J* = 7.5 Hz, 1 H), 3.83 (d, *J* = 3.6 Hz, 2 H), 2.69 (dd, *J* = 3.2 Hz, *J* = 6.6 Hz, 1 H), 2.07 (d, *J* = 3.2 Hz, 1 H), 2.04 (sept, *J* = 6.9 Hz, 1 H), 1.95 (d, *J* = 6.5 Hz, 1 H), 1.66 (bs, 1 H), 1.50 (q, *J* = 3.6 Hz, 1 H), 0.98 (d, *J* = 6.9 Hz, 3 H), 0.96 (d, *J* = 6.9 Hz, 6 H); ^{13}*C* NMR (75 MHz, $CDCl_3$): δ = 159.5, 149.9, 136.5, 121.9, 120.3, 75.6, 63.3, 42.9, 35.6, 29.9, 19.5, 19.4; MS (ES): *m/z* = 207.3 $(M + H)^+$, 229.2 $(M + Na)^+$, 413.3 [$(2\ M + H)^+$], 435.3 $(2\ M + Na)^+$. Anal. Calcd for $C_{12}H_{18}N_2O$: *C*, 69.87; H, 8.80; N, 13.58. Found *C*, 69.60; H, 8.85; N, 13.28.

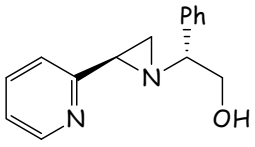
Whereas the minor diastereomer of **14** was not isolated by column chromatography, a sample of the *O*-methyl ether of **14** was obtained by column chromatography of several pooled fractions containing it, coming from different reaction runs: red oil; $[\alpha]_D^{20}$ –82.6 (*c* 4.6, $CHCl_3$); IR (neat): *ν* = 2968, 1590, 1578, 1482, 1431, 1391, 1075, 767; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.49 (ddd, *J* = 0.7 Hz, *J* = 1.6 Hz, *J* = 4.9 Hz, 1 H), 7.59 (dt, *J* = 1.4 Hz, *J* = 7.9 Hz, 1 H), 7.24 (d, *J* = 7.9 Hz, 1 H), 7.12 (ddt, *J* = 0.9 Hz, *J* = 4.7 Hz, *J* = 7.9 Hz, 1 H), 3.55 (d, *J* = 6.7 Hz, 1 H), 3.54 (d, *J* = 4.5 Hz, 1 H), 3.38 (s, 3 H), 2.56 (dd, *J* = 3.3 Hz, *J* = 6.5 Hz, 1 H), 2.02 (d, *J* = 3.3 Hz, 1 H), 2.00 (d, *J* = 6.5 Hz, 1 H), 1.94 (sept, *J* = 6.9 Hz, 1 H), 1.65 (dd, *J* = 4.5 Hz, *J* = 6.7 Hz, 1 H), 0.95 (d, *J* = 6.9 Hz, 3 H), 0.94 (d, *J* = 6.9 Hz, 6 H); ^{13}*C* NMR (75 MHz, $CDCl_3$): δ = 160.1, 148.9, 136.4, 120.7, 120.0, 74.4, 73.8, 59.0, 41.9, 30.1, 19.2, 18.9; MS (EI): *m/z* = 220 (M, 1), 219 (2), 175 (31), 145 (22), 133(10), 119 (100), 106 (69), 92 (55), 79 (21), 65(16). Anal. Calcd for $C_{13}H_{20}N_2O$: *C*, 70.87; H, 9.15; N, 12.72. Found *C*, 70.58; H, 9.18; N, 12.42.



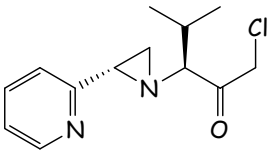
3(*S*)-Methyl-2-[2(*S*)-(2-quinolyl)-1-aziridinyl]-1-butanol (18): it was obtained from the imine **17** (1.1 g, 3.5 mmol), 0.457 g (51%); red oil; $[\alpha]_D^{20}$ –115.7 (*c* 1.6, $CHCl_3$); IR (neat): *ν* = 3370, 2964, 1589, 1574, 1428, 1388, 1070, 770; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.10 (d, *J* = 8.5 Hz, 1 H), 8.07 (d, *J* = 8.5 Hz, 1 H), 7.80 (d, *J* = 8.1 Hz, 1 H), 7.71 (ddd, *J* = 1.5 Hz, *J* = 6.9 Hz, *J* = 8.4 Hz, 1 H), 7.52 (ddd, *J* = 1.2 Hz, *J* = 7.0 Hz, *J* = 8.5 Hz, 1 H), 7.36 (d, *J* = 8.5 Hz, 1 H), 3.86 (d, *J* = 3.9 Hz, 2 H), 2.92 (dd, *J* = 3.3 Hz, *J* = 6.8 Hz, 1 H), 2.13 (sept, *J* = 6.9 Hz, 1 H), 2.10 (d, *J* = 3.3 Hz, 1 H), 2.05 (d, *J* = 6.8 Hz, 1 H), 1.58 (q, *J* = 4.0 Hz, 1 H), 0.98 (d, *J* = 6.9 Hz, 3 H), 0.96 (d, *J* = 6.9 Hz, 3 H); ^{13}*C* NMR (75 MHz, $CDCl_3$): δ = 160.4, 147.6, 136.8, 129.5, 128.8, 127.6, 127.5, 126.0, 117.9, 75.4, 63.5, 42.7, 35.7, 30.1, 19.7, 19.4; MS (ES): *m/z* = 256.4 $(M + H)^+$, 279.3 $(M + Na)^+$, 535.6 $(2\ M + Na)^+$. Anal. Calcd for $C_{16}H_{20}N_2O$: C, 74.97; H, 7.86; N, 10.93. Found C, 74.71; H, 7.88; N, 10.90.



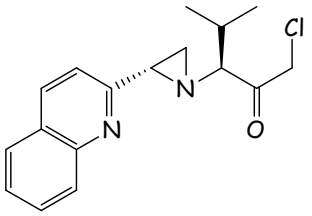
1(*R*)-Phenyl-2(*S*)-[2(*R*)- and 2(*S*)-(2-pyridyl)-1-aziridinyl]-1-propanol 29: The reaction of the imine **28** (0.936 g, 3 mmol) gave a mixture of the diastereomeric aziridines **29** (0.335 g, 44%) with a 77:23 ratio (^{1}H NMR), which could not be separated by column chromatography. The different absorptions for the two diastereomers were evidenced from enriched chromatographic fractions. Major diastereomer: yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.49 (m, 1 H), 7.60 (m, 2 H), 7.38-7.12 (m, 6 H), 4.95 (d, *J* = 3.9 Hz, 1 H), 4.55 (d, *J* = 6.3 Hz, 1 H,), 2.82 (dd, *J* = 3.9 Hz, *J* = 6.3 Hz, 1 H), 2.61 (dd, *J* = 3.3 Hz, *J* = 6.4 Hz, 1 H), 2.06 (d, *J* = 3.3 Hz, 1 H), 1.86 (d, *J* = 6.6 Hz, 1 H), 1.00 (d, *J* = 6.4 Hz, 1 H). Minor diastereomer: yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.60 (m, 1 H, PyH), 7.66 (m, 2 H), 7.38-7.12 (m, 6 H), 4.88 (d, *J* = 3.9 Hz, 1 H), 4.39 (d, *J* = 6.5 Hz, 1 H), 2.84 (dd, *J* = 3.9 Hz, *J* = 6.5 Hz, 1 H), 2.61 (dd, *J* = 3.2 Hz, *J* = 6.6 Hz, 1 H), 2.17 (d, *J* = 3.3 Hz, 1 H), 1.91 (d, *J* = 6.6 Hz, 1 H), 0.88 (d, *J* = 6.5 Hz, 1 H). Anal. Calcd for $C_{16}H_{18}N_2O$: C, 75.56; H, 7.13; N, 11.01. Found C, 75.98; H, 7.17; N, 10.98.



2(*R*)-Phenyl-2-[2(*R*)-(2-pyridyl)-1-aziridinyl]ethanol (31): it was obtained from the imine **30** (1.04 g, 3.5 mmol), 0.210 g (25%); red oil; $[\alpha]_D^{20}$ –87.3 (*c* 0.7, $CHCl_3$); IR (neat): *v* = 3365, 3052, 3019, 2933, 2853, 1595, 1570, 1480, 1389, 1354, 1216, 1150, 1067, 756, 701; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.51 (ddd, *J* = 0.9 Hz, *J* = 1.7 Hz, *J* = 4.9 Hz, 1 H), 7.61 (dt, *J* = 1.9 Hz, *J* = 7.7 Hz, 1 H), 7.38 (dd, *J* = 1.6 Hz, *J* = 7.9 Hz, 1 H), 7.34-7.10 (m, 6 H), 4.01 (dd, *J* = 5.5 Hz, *J* = 11.3 Hz, 1 H), 3.94 (dd, *J* = 5.5 Hz, *J* = 11.3 Hz, 1 H), 2.95 (t, *J* = 5.5 Hz, 1 H); 2.72 (bs, 1 H), 2.61 (dd, *J* = 3.2 Hz, *J* = 6.6 Hz, 1 H), 2.39 (d, *J* = 3.3 Hz, 1 H), 2.19 (d, *J* = 6.6 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.1, 149.1, 139.9, 136.4, 128.3, 127.5, 127.4, 121.9, 120.7, 75.6, 67.6, 39.7, 38.6; MS (EI): *m/z* = 312 (M^+, 1), 297 (5), 177 (10), 144 (31), 119 (63), 106 (100), 92 (30), 73 (43). Anal. Calcd for $C_{15}H_{16}N_2O$: C, 74.97; H, 6.71; N, 11.66. Found C, 75.12; H, 6.88; N, 11.48.

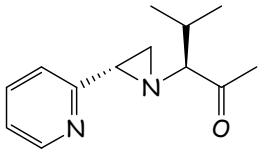


(*S*)-1-Chloro-4-methyl-3-[2(*S*)-(2-pyridyl)-1-aziridinyl]-2-pentanone (33): it was obtained from the imine **32** (0.792 g, 3.6 mmol): 0.60 g (75%); red oil; $[\alpha]_D^{20}$ –59.3 (*c* 1.2, $CHCl_3$); IR (neat): *v* = 2967, 2865, 1734, 1593, 1465, 1436, 1389; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.44 (dd, *J* = 0.9 Hz, *J* = 4.8 Hz, 1 H), 7.58 (tt, *J* = 1.7 Hz, *J* = 7.8 Hz, 1 H), 7.19 (dd, *J* = 0.9 Hz, *J* = 7.8 Hz, 1 H), 7.14 (ddt, *J* = 1.2 Hz, *J* = 4.8 Hz, *J* = 7.8 Hz, 1 H), 4.60 (d, *J* = 17.0 Hz, 1 H), 4.51 (d, *J* = 17.0 Hz, 1 H), 2.68 (dd, *J* = 3.4 Hz, *J* = 6.7 Hz, 1 H), 2.25 (d, *J* = 6.5 Hz, 1 H), 2.06 (dsept, *J* = 6.5 Hz, *J* = 6.6 Hz, 1 H), 2.00 (d, *J* = 3.4 Hz, 1 H), 1.68 (d, *J* = 6.7 Hz, 1 H), 0.91 (d, *J* = 6.6 Hz, 3 H), 0.85 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 202.0, 158.1, 148.9, 136.5, 122.2 , 119.9, 83.9, 47.6, 43.6, 34.9, 32.1, 19.1, 19.0; MS (ES) *m/z* = 253.2 $(M + H)^+$, 275.1 $(M + Na)^+$. Anal. Calcd for $C_{13}H_{17}ClN_2O$: C, 61.78; H, 6.78; Cl, 14.03; N, 11.08; Found C, 61.48; H, 6.88; Cl, 13.99; N, 11.03.



(*S*)-1-Chloro-4-methyl-3-[2(*S*)-(2-quinolyl)-1-aziridinyl]-2-pentanone (35): It was obtained starting from of the imine **34** (0.621 g, 2.3 mmol): 0.514 g (78%); red oil; $[\alpha]_D^{20}$ −71.2 (*c* 1.2, $CHCl_3$); IR (neat): *ν* = 3052, 2964, 2926, 2875, 1733, 1618, 1600, 1505, 1430, 1428, 1389, 1313, 1030, 829, 756, 628; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.13 (d, *J* = 8.6 Hz, 1 H), 8.04 (d, *J* = 8.4 Hz, 1 H), 7.80 (d, *J* = 8.1 Hz, 1 H), 7.71 (dt, *J* = 1.4 Hz, *J* = 8.4 Hz, 1 H), 7.57 (dt, *J* = 1.4 Hz, *J* = 8.0 Hz, 1 H), 7.35 (d, *J* = 8.5 Hz, 1 H), 4.68 (d, *J* = 16.7 Hz, 1 H), 4.60 (d, *J* = 16.7 Hz, 1 H), 2.99 (dd, *J* = 3.3 Hz, *J* = 6.7 Hz, 1 H), 2.42 (d, *J* = 6.3 Hz, 1 H), 2.19 (dsept, *J* = 6.3 Hz, *J* = 6.8 Hz, 1 H), 2.12 (d, *J* = 3.3 Hz, 1 H), 1.79 (d, *J* = 6.7 Hz, 1 H), 1.00 (d, *J* = 6.8 Hz, 3 H), 0.96 (d, *J* = 6.8 Hz, 3 H); ^{13}*C* NMR (75 MHz, $CDCl_3$): δ = 201.1, 158.9, 147.4, 136.9, 129.6, 128.6, 127.5, 127.4, 126.1, 117.0, 83.7, 47.7, 44.2, 35.2, 32.4, 19.2, 19.1; MS (ES): *m/z* = 303.1 $(M + H)^+$, 325.0 $(M + Na)^+$. Anal. Calcd for $C_{17}H_{19}ClN_2O$: *C*, 67.43; H, 6.32; *Cl*, 11.71; N, 9.25. Found *C*, 67.40; H, 6.36; *Cl*, 11.67; N, 9.20.

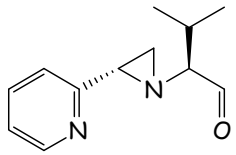
*2.3.3 – Dehalogenation of ketone **33***



(*S*)-4-Methyl-3-[2(*S*)-(2-pyridyl)-1-aziridinyl]-2-pentanone (38): A solution of compound **33** (0.102 g, 0.4 mmol), tri(*n*-butyl)tin hydride (0.12 mL, 0.6 mmol) and AIBN (10 mg) in benzene (5 mL) was heated at the reflux temperature under an inert atmosphere for 3 h. Evaporation of the solvent at reduced pressure gave an oily residue that was subjected to chromatography on a SiO_2 column eluting with cyclohexane-ethyl acetate (70:30) to obtain **28** as a red-brown oil: 0.076 g (88%); red-brown oil: $[\alpha]_D^{20}$ −20.2 (*c* 1.0, $CHCl_3$); IR (neat): *ν* = 2936, 2932, 2874, 1710, 1594, 1565, 1436, 1353, 1212, 996, 776, 748; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.50 (ddd, *J* = 1.0 Hz, *J* = 1.7 Hz, *J* = 4.9 Hz, 1 H), 7.62 (dt, *J* = 1.7 Hz, *J* = 7.7 Hz, 1 H), 7.21 (td, *J* = 1.0 Hz, *J* = 7.7 Hz, 1 H), 7.14 (ddd, *J* = 1.2 Hz, *J* = 4.9 Hz, *J* = 7.7 Hz, 1 H), 2.68 (dd, *J* = 3.3 Hz, *J* = 6.6 Hz, 1 H), 2.31 (s, 3 H), 2.12 (dsept, *J* = 6.2 Hz, *J* = 6.6 Hz, 1 H), 2.07 (d, *J* = 6.2 Hz, 1 H), 2.02 (d, *J* = 3.3 Hz, 1 H), 1.69 (d, *J* = 6.6 Hz, 1 H), 0.97 (d, *J* = 6.6

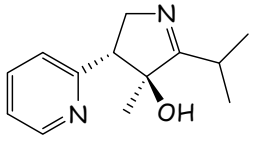
Hz, 3 H), 0.90 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 210.1, 159.0, 149.0, 136.6, 122.1, 120.0, 85.9, 44.0, 34.7, 31.7, 27.1, 19.4, 19.2; MS (ES): *m/z* = 219.4 (M + H)+, 241.4 (M + Na)$^+$Anal. Calcd for $C_{13}H_{18}N_2O$: C, 71.53; H, 8.31; N, 12.83. Found C, 71.21; H, 8.38; N, 12.64.

2.3.4 – Oxidation of aziridine ***14***

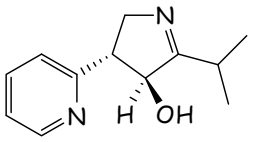


(*S*)-3-Methyl-2-[2(*S*)-(2-pyridyl)-1-aziridinyl]butanal (41): To a solution of oxalyl chloride (68 mg, 45 µL, 0.53 mmol) in CH_2Cl_2 (2 mL) at −60 °C was added dropwise a solution of DMSO (83 mg, 76 µL, 1.1 mmol) in CH_2Cl_2 (2 mL). After 10 min, a solution of aziridine **14** (100 mg, 0.49 mmol) in CH_2Cl_2 (2 mL) was added dropwise, followed, after 15 minutes, by triethylamine (246 mg, 0.34 mL, 2.4 mmol). The temperature was slowly raised to 20 °C and the mixture was further stirred for 2 h, then quenched with H_2O (5 mL). The organic phase was extracted with CH_2Cl_2 (3 x 10 mL), and the combined organic phases was concentrated. The residue was subjected to chromatography on a SiO_2 column eluting with EtOAc to give **29** as a red oil: 74 mg (74%); $[\alpha]_D^{20}$ −24.6 (*c* 0.33, $CHCl_3$); IR (neat): *v* = 3059, 2964, 2919, 2868, 1733, 1669, 1592, 1572, 1472, 1436, 1260, 1079, 804, 753; ^1H NMR (300 MHz, $CDCl_3$): δ = 9.78 (d, *J* = 2.8 Hz, 1 H), 8.48 (ddd, *J* = 0.9 Hz, *J* = 1.8 Hz, *J* = 4.9 Hz, 1 H), 7.61 (dt, *J* = 1.8 Hz, *J* = 7.6 Hz, 1 H), 7.32 (d, *J* = 8.7 Hz, 1 H), 7.21 (ddd, *J* = 0.9 Hz, *J* = 3.9 Hz, *J* = 7.6 Hz, 1 H), 2.64 (dd, *J* = 3.5 Hz, *J* = 6.7 Hz, 1 H), 2.25 (dsept, *J* = 5.7 Hz, *J* = 6.6 Hz, 1 H), 2.23 (d, *J* = 3.5 Hz, 1 H), 2.08 (dd, *J* = 2.8 Hz, *J* = 5.7 Hz, 1 H), 1.82 (d, 1 H, *J* = 6.7 Hz), 0.98 (d, *J* = 6.8 Hz, 3 H), 0.95 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 202.9, 158.8, 149.2, 136.6, 122.2, 120.2, 83.1, 42.3, 35.1, 30.6, 19.2, 18.9; MS (ES): *m/z* = 205.4 (M + H)$^+$, 227.3 (M + Na)$^+$. Anal. Calcd for $C_{12}H_{16}N_2O$: C, 70.56; H, 7.90; N, 13.71; Found C, 70.32; H, 7.93; N, 13.66.

2.3.5 – Tratament in basic mediun of ketone ***38*** *and aldehyde* ***41***



3(*S*),4(*S*)-3-Hydroxy-2-isopropyl-3-methyl-4-(2-pyridyl)-1-pyrroline (39a): To a solution of **38** (300 mg, 1.4 mmol) in MeOH (10 mL) was added KOH (0.118 g, 2.1 mmol). The mixture was heated at the reflux temperature for 2 h, then the solvent was evaporated at reduced pressure, H_2O (5 mL) was added, and the organic phase was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers was washed with brine (10 mL), dried (Na_2SO_4) and concentrated at reduced pressure. The dark oily residue was subjected to chromatography on a SiO_2 column eluting with EtOAc, then with a 90:10 EtOAc/MeOH mixture, to give **39a** as a yellowish oil: 0.186 g (61%); $[\alpha]_D^{20}$ –120.2 (*c* 0.9, $CHCl_3$); IR (neat): ν = 3245, 2967, 2931, 2871, 1641, 1594, 1569, 1473, 1436, 1370, 1151, 1112, 987, 788, 751; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.49 (d, *J* = 4.3 Hz, 1 H), 7.66 (t, *J* = 7.7 Hz), 7.19 (dd, *J* = 4.3 Hz, *J* = 7.7 Hz, 2 H), 6.22 (bs, 1 H), 4.17 (dd, *J* = 7.9 Hz, *J* = 15.5 Hz, 1 H), 3.82 (dd, *J* = 6.9 Hz, *J* = 15.5 Hz, 1 H), 3.22 (dd, *J* = 6.9 Hz, *J* = 7.9 Hz, 1 H), 2.82 (sept, *J* = 6.6 Hz, 1 H), 1.43 (s, 3 H), 1.29 (d, *J* = 6.9 Hz, 3 H), 1.22 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 185.3, 160.1, 148.4, 137.1, 124.7, 121.8, 84.6, 64.0, 53.4, 28.0, 24.6, 21.8, 21.3; MS (EI): *m/z* = 218 (M, 4), 175 (5), 149 (6), 120 (3), 121 (10), 106 (100), 92 (8), 78 (15); MS (ES): *m/z* = 219.3 $(M + H)^+$, 241.4 $(M + Na)^+$. Anal. Calcd for $C_{13}H_{18}N_2O$: C, 71.53; H, 8.31; N, 12.83. Found C, 71.56; H, 8.34; N, 12.80.



3(*S*),4(*S*)-3-Hydroxy-2-isopropyl-4-(2-pyridyl)-1-pyrroline (39b): this was obtained from **41** (0.300 g, 1.45 mmol) by the same procedure used for **39a**: 148 mg (52%); yellowish oil; $[\alpha]_D^{20}$ –98.7 (*c* 1.4, $CHCl_3$); IR (neat): ν = 3241, 2977, 2927, 2864, 1647, 1597, 1578, 1471, 1430, 1378, 1141, 988, 784, 757; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.54 (dt, *J* = 1.7 Hz, *J* = 4.6 Hz, 1 H), 7.64 (td, *J* = 1.9 Hz, *J* = 7.7 Hz, 1 H), 7.17 (m, 2 H), 5.14 (d, *J* = 8.3 Hz, 1 H), 4.30 (dt, *J* = 8.3 Hz, *J* = 14.9 Hz, 1 H), 3.76 (dt, *J* = 8.6 Hz, *J* = 14.9 Hz, 1 H), 3.50 (dt, *J* = 8.3 Hz, *J* = 8.4 Hz, 1 H), 2.87 (sept, *J* = 6.8 Hz, 1 H), 1.26 (d, *J* = 6.8 Hz, 3 H), 1.22 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 183.4, 160.4 (Py), 149., 136.7, 123.9, 122.5, 83.0, 61.7, 55.6, 29.4, 20.0, 19.0; the product decomposed during GC-MS analysis. Anal. Calcd for $C_{12}H_{16}N_2O$: C, 70.56; H, 7.90; N, 13.71; Found C, 70.54; H, 7.93; N, 13.77.

2.3.6 – Catalysis reactions

The reactions of AAA are conducted as see in the Chapter 1.

General procedure for the addition of diethylzinc to aldehydes: To a solution of the ligand **14** (0.1 mmol, 0.021 g) in anhydrous toluene (5 ml) at 0°C a solution of diethylzinc (1 M in hexane, 2 mL) was added. After 30 minutes the benzaldehyde (1 mmol, 101 μL) was added and the temperature was rising at 25°C. After 2.5 hour the reaction mixture was cooled at 0°C and 1N HCl (5 ml) was added. The organic phase was extracted with CH_2Cl_2 (3 x 10 mL), and the combined organic phases was concentrated. The residue was subjected to chromatography on a SiO_2 column eluting column eluting with cyclohexane-ethyl acetate (90:10) to obtain **46** as oil.

The enantiomeric eccess of the benzylic alcohols and their absolute configuration were determined as reported in literature.[50]

2.4 - References

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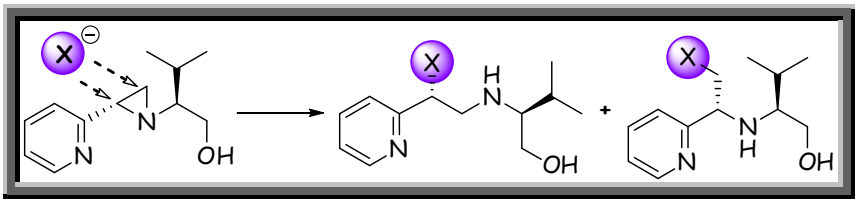
Chapter Index

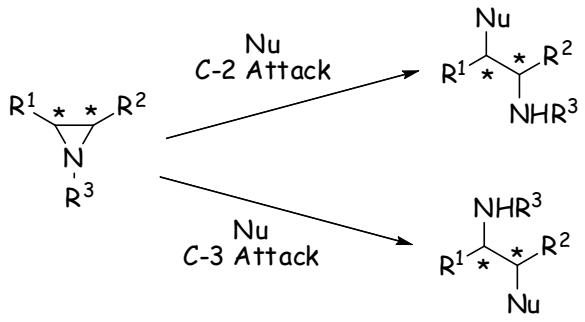
Chap. 3 – Asymmetric Route to Pyridines Bearing a Highly Functionalized 2-Alkyl Substituent by Aziridine Ring Opening Reactions



3.1 – Introduction

The aziridine ring is one of the most valuable building blocks in modern synthetic chemistry,[1] because of its widely recognized versatility for chemical bond elaborations and functional group transformations. Its reactivity is dominated by the electrophilic nature at carbon atoms and generally involves cleavage of the strained three-membered ring, by a wide range of nucleophiles to give β-substituted amines. Its potency is the combination of Bœyer strain (estimated around 111 kJ/mol, comparable with that of oxirane) and the electronegativity of the heteroatom: this means that aziridines are willing to undergo ring-cleavage reactions under relatively mild conditions. As might be expected, due to the diminished electronegativity of nitrogen compared to oxygen, ring-opening reactions of these hetero-cycles are less facile than the corresponding reactions of epoxides, but there is still a wealth of examples of such chemistry. There are several features of these reactions which are worthy of consideration.

Where an aziridine is unsymmetrically-substituted (as would typically be the situation), reaction with a nucleophile can lead to two products of ring-opening (Scheme 1): one derived from nucleophilic attack at C2-carbon and one from the attack to C3-carbon. As would be expected most nucleophiles preferentially direct their attack to the site of lesser substitution, though electronic considerations (for instance in the ring-opening of 2-arylaziridines) may perturb this preference.



Scheme 1

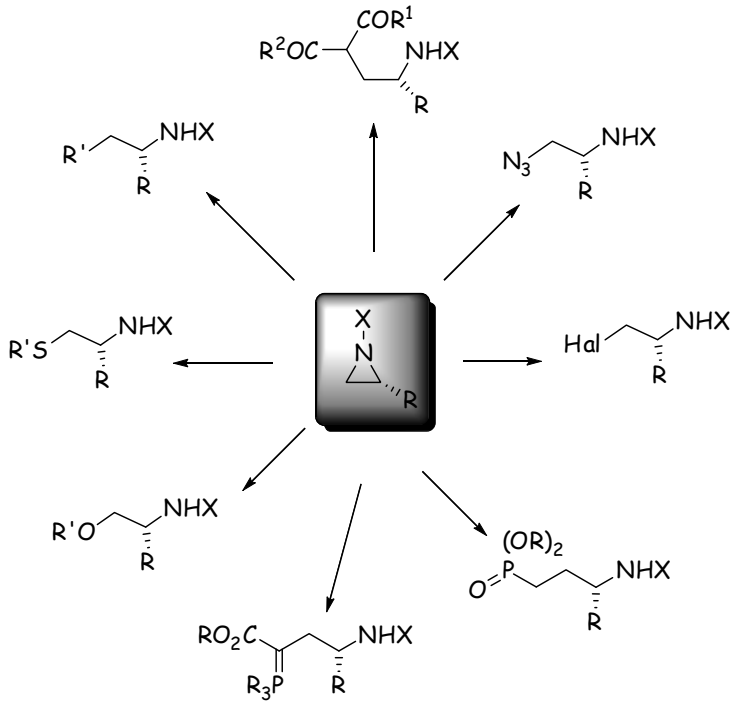
Chiral aziridines undergo regio- and stereoselective ring opening to access to chiral amines with predictable α and β stereochemistry. The increasing synthetic accessibility of chiral aziridines[2] has propelled their use in ring opening reactions in asymmetric organic synthesis. In general, two types of aziridine can be considered: activated and unactivated (Scheme 2). The former contain substituents capable of stabilising by coniugation the developing negative charge on nitrogen during nucleophilic ring opening. The latter, also known as simple aziridines are generally unsubstituted or with alkyl substitution on nitrogen and usually require acid catalysis (protonation or Lewis acid) to facilitate ring opening.

"nonactivated" "activated"

R = H, alkyl, aryl R = COR', CO_2R', SO_2R'

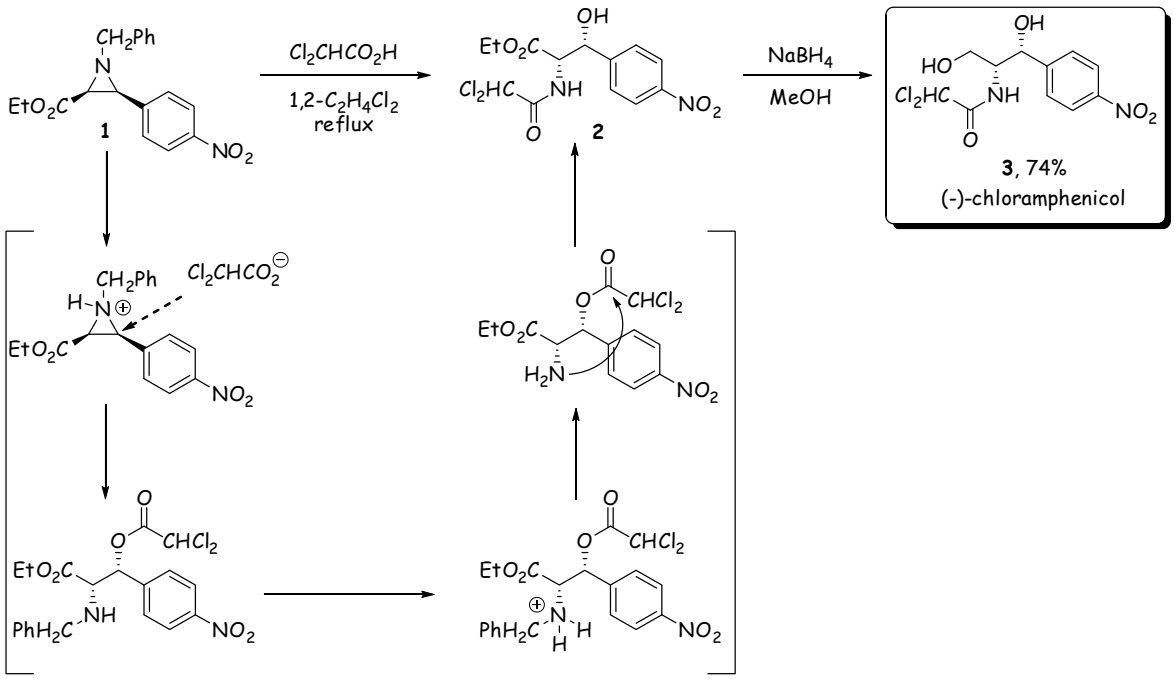
Scheme 2

A large variety of nucleophiles have been employed successfully in asymmetric ring-opening (ARO) reactions, with the majority of these being heteroatom-based such as azide, alcohols, thiols, amines, halides or carbon-based nucleophiles (Scheme 3). Nucleophilic ring opening of aziridine cover examples of broad applications for the synthesis of amino acids, aza-sugars, chiral ligands, biologically active compounds, natural products and other synthesis. In this introduction I desire to report some applications of chiral aziridine's ring opening in the synthesis of chiral organic compounds.



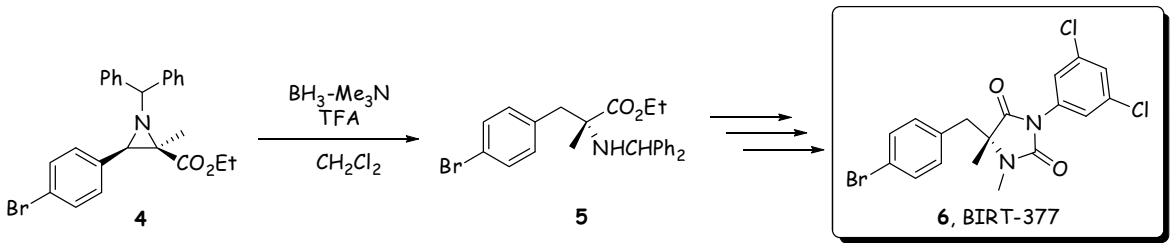
Scheme 3

Chloramphenicol (**3**) is one of the oldest antibacterial agents and only its (2*R*,3*R*) enantiomer is active. Wulff and co-workers reported the synthesis of this important antibiotic in enantiomerically pure form in only four steps,[3] where one step consist in the regio- and stereoselective opening of the aziridine ring by heating with dichloroacetic acid (Scheme 4). The enantiopure aziridine (**1**) was synthetized by the reaction of ethyldiazoacetate and the *N*-benzyl-*p*-nitrobenzaldimine in the presence of the chiral catalyst prepared from tiphenylborate and (*R*)-VAPOL. The treatment of **1** with an excess of dichloroacetic acid under forcing condition resulted in the ring opening of the the protonated aziridine by the dichloroacetate anion with complete inversion of configuration. Under the reaction conditions the benzyl protecting group was removed and the amine was chloroacetilated to give the amide (**2**). Finally the ester function was reduced with sodium borohydride to give the (-)-chloramphenicol (**3**) with good yield.



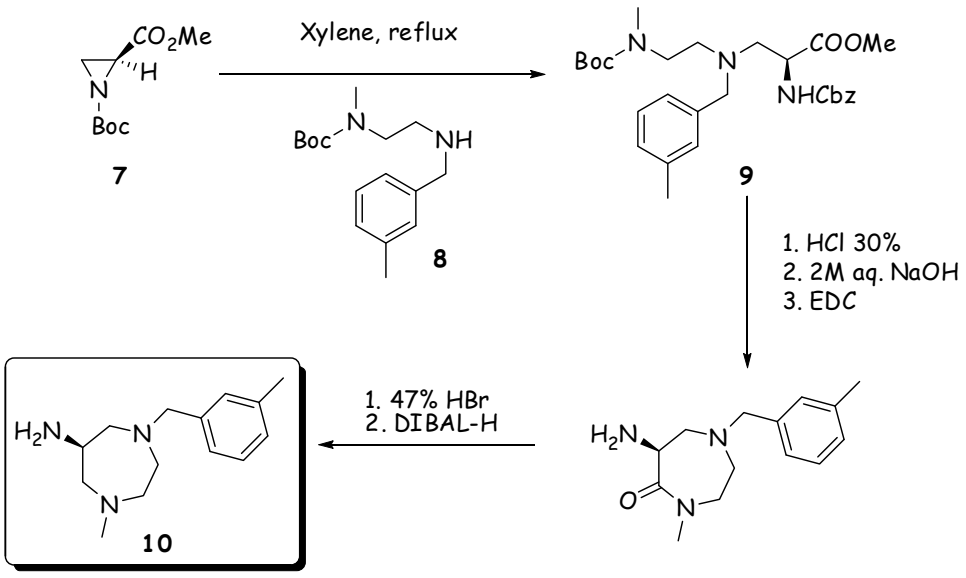
Scheme 4

The same author[4] described the reductive ring opening of the aziridine **4** (Scheme 5) with borane-trimethylamine complex in the presence of TFA to give the amino ester **5**. The amine **5** was converted into the compound **6** (BIRT-377), an antagonist of the leukointegrin LFA-1.



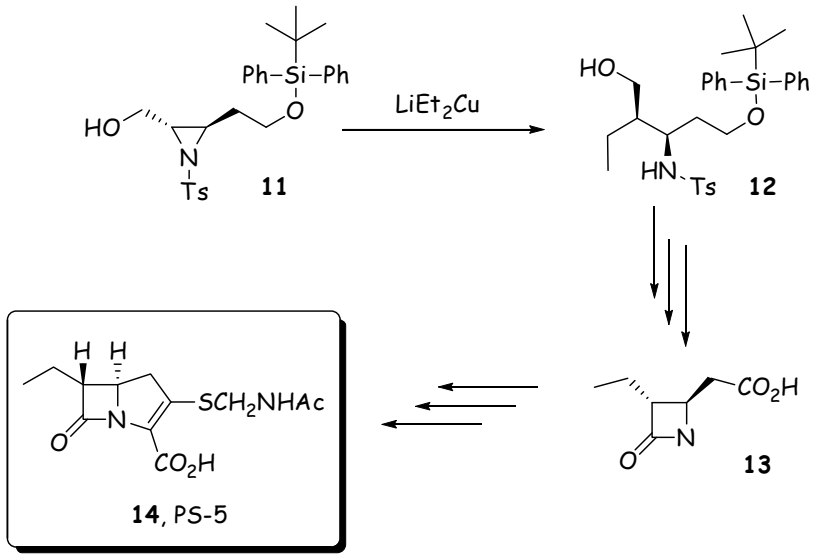
Scheme 5

An interesting example of application of aziridine's ring opening is found in the Harada's preparation of chital diazepines **10** possessing highly potent 5-HT3 receptor antagonist activity (Scheme 6)[5]. The activated aziridine **7**, derived from serine, was opened by the diamine **8** to give the aminoester **9**, which was converted trought deprotection, cyclization and reduction to the diazepine **10**.



Scheme 6

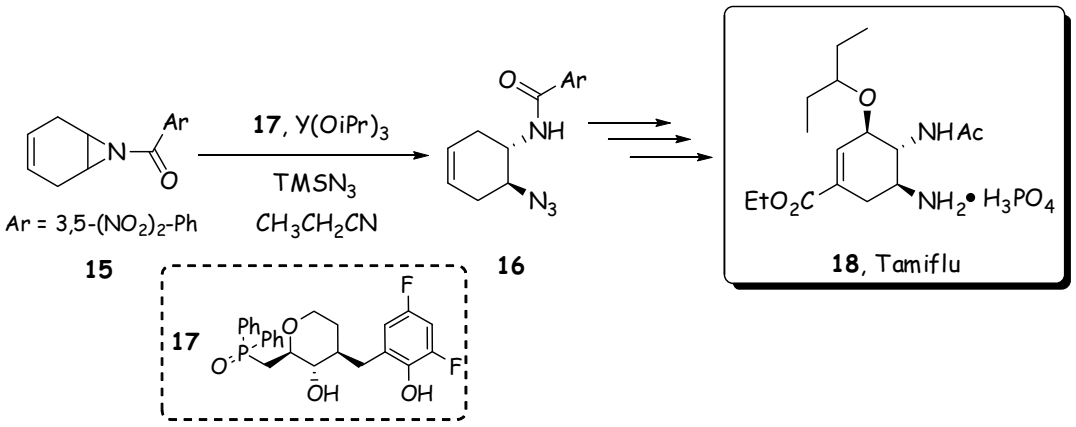
The opening of chiral aziridino alcohols was applied to the enantioselective synthesis of some members of the important class of carbapenem antibiotics. For example the regio- and steroselective opening of the aziridino alcohol **11** (Scheme 7)[6] by lithium diethylcuprate give the amino alcohol **12**, precursor of the β-lactams **13**, a intermediate of the PS5 carbapenem **14**.



Scheme 7

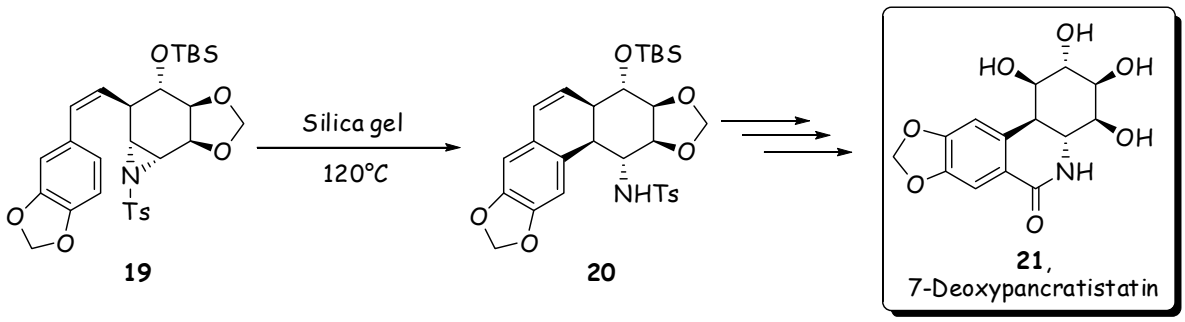
Shibasaki and co-workers[7] developed a new synthesis of Tamiflu (oseltamivir phosphate **18**) an orally active anti-influenza drug that potently inhibits neuramidase, an enzyme crucial for the release and spread of the avian influenza virus from infected cells.[8] One of the first step of the synthesis consists of catalytic desymmetrization of meso-

aziridine (**15**) with $TMSN_3$ using a Yittrium complex of chiral ligand **17** to give the azido amine **16** with 96% of yield and 91% of e.e. (e.e. 99% after recrystalization).



Scheme 8

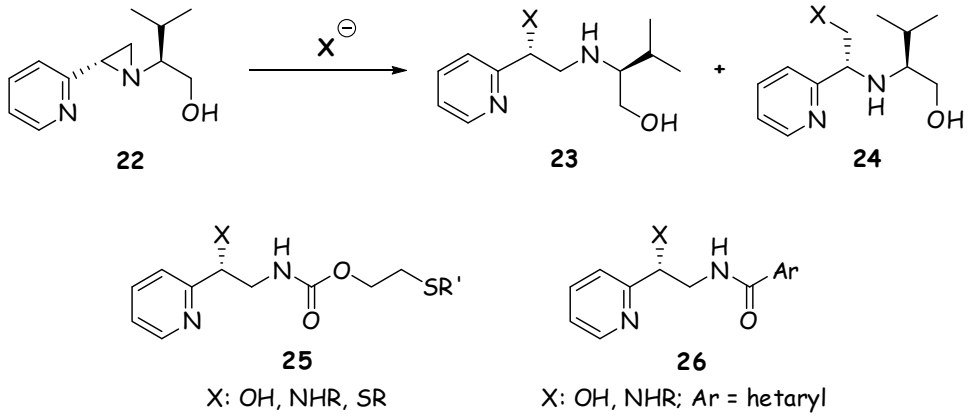
Finally Hudlicky[9] studied a new synthesis of 7-deoxypancratistatin (**21**), a compound highly active against many cancer cell lines, *via* region- and stereoselective intramolecular ring opening of the chiral aziridine **19** in presence of silica gel as Lewis acid.



Scheme 9

I have reported in the Chapter 2 the synthesis of the 2-(2-pyridyl)-substituted aziridine **22** by the addition of chloromethyllithium to the pyridineimine derived from (*S*)-valinol.[10] Stimulated by the plethora of reports describing the ring-opening of unactivated aziridines by hetero-nucleophiles, we applied a few such procedures to the aziridine **22**, aiming to assess the factors controlling the regioselectivity of the nucleophilic attack, providing the polyfunctional compounds **23** and/or **24** (Scheme 10). In particular, we planned to prepare the compounds **23**, whose stuctural features are the homobenzylic amine moiety and the benzylic stereocenter. We envisaged that these compounds and those obtained by removal or transformation of the *N*-substituent can find use as chiral non-racemic polydentate ligands in enantioselective catalytic reactions. Moreover, this skeleton is present

in a number of compounds, e.g. **25**[11] and **26**[12], which have been described in recent patents reporting their herbicide and fungicide properties.

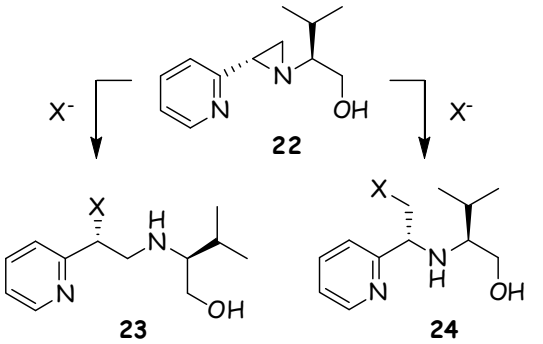


Scheme 10

3.2 - Results and discussion

The protocols for the Lewis acid-promoted nucleophilic ring opening of analogous substituted aziridines, as described by other groups, were taken into account. A series of reactions with several hetero-nucleophiles in different experimental conditions demonstrated that it is possible to activate the aziridine ring and control the regioselectivity of the ring-opening process by the proper choice of the reagent, Lewis acid and solvent.

The reactions gave the products **23** (Scheme 11), coming from nucleophilic attack at the more substituted aziridine carbon, either exclusively or together with the alternative product **24** (Table 1). Initial attempts involved water as the nucleophile in the presence of a protic[13] or Lewis acid catalyst.[14] Heating a mixture of aziridine **22** and *p*-toluenesulfonic acid (20 mol%) in 9:1 acetonitrile-water at the reflux temperature for 6 h gave a mixture of the regioisomeric ring-opening products **23a** and **24a** (82:18), which were separated by column chromatography. Slightly better results were obtained using cerium trichloride heptahydrate (30 mol%) with other experimental conditions remaining constant; by this manner an improved regioselectivity (86:14) was obtained.



a: X = OH
b: X = N_3
c: X = $NHCH_2Ph$
d: X = NHC_6H_4-4-OMe
e: X = $N(CH_2Ph)_2$
f: X = S-2-Naphthyl
g: X = SPh
h: X = SCH_2Ph
i: X = S-*n*-Bu

Scheme 11

Then, efforts were devoted to optimize the reaction with sodium azide, with the aim of preparing the benzylic azide **23b**. By using sodium azide as the nucleophile source, an acetonitrile-water mixture (9:1) was used as the solvent. Having observed no reactivity at the reflux temperature in the absence of a Lewis acid, we evaluated ceric ammonium nitrate (CAN) and cerium trichloride heptahydrate,[15] which were both found to be effective catalysts in the same solvent mixture either at room temperature or at the reflux temperature.

In both cases we obtained good results. As a matter of fact, the benzylic azide **23b** was formed exclusively and isolated in high yield. A slightly lower yield of **24b** was obtained using sodium azide (2 equivalents) and aluminum trichloride[16] (10 mol%) in 1:1 EtOH-H_2O after 24 h at 25 °C. On the other hand, trimethylsilyl azide,[17] when used in aprotic solvents (THF, CH_2Cl_2), gave a mixture of the azides **23b** (prevalent) and **24b**. The reaction rate increased in the presence of tetrabutylammonium fluoride;[17c,d] in this case, the amount of the benzylic amine **24b** was also increased, such that this compound could be isolated by column chromatography.

Table 1

Reagent (eq.)	Additive (mol %)	Solvent, T, t	Ratio 23/24[a]	23, yield (%)[b]	24, yield (%)[b]
H_2O	*p*-TsOH (20)	CH_3CN-H_2O (9:1), reflux, 6 h	82:18	**23a**, 77	**24a**, 14
H_2O	$CeCl_3 \cdot 7H_2O$ (30)	CH_3CN-H_2O (9:1), reflux, 8 h	86:14	**23a**, 71	**24a**, 8
NaN_3 (1.5)	-	CH_3CN-H_2O (9:1), reflux, 6 h	-	-	-
NaN_3 (1.1)	CAN (10)	CH_3CN-H_2O (9:1), 25 °C, 24 h	100:0	**23b**, 91	-
NaN_3 (1.1)	CAN (10)	CH_3CN-H_2O (9:1), reflux, 5 h	100:0	**23b**, 94	-
NaN_3 (1.1)	$CeCl_3 \cdot 7H_2O$ (10)	CH_3CN-H_2O (9:1), 25 °C, 18 h	100:0	**23b**, 92	-
NaN_3 (1.1)	$CeCl_3 \cdot 7H_2O$ (10)	CH_3CN-H_2O (9:1), reflux, 4 h	100:0	**23b**, 91	-
NaN_3 (2)	$AlCl_3$ (10)	EtOH-H_2O (1:1), 25 °C, 24 h	100:0	**23b**, 62	-
$TMSN_3$ (2)	-	CH_3CN , 25 °C, 20 h	91:9	**23b**, 87	**24b**[c]
$TMSN_3$ (2)	-	CH_2Cl_2 , 25 °C, 48 h	80:20	**23b**, 73	**24b**, 16
$TMSN_3$ (2)	*n*-Bu_4NF (20)	THF, 25 °C, 20 h	65:35	**23b**, 58	**24b**, 31

[a] Determined by ^{1}HNMR analysis of the crude product. [b] Yield of product isolated by column chromatography (SiO_2). [c] The product was not isolated.

The reactions with the primary amines benzylamine and *p*-anisidine in different conditions always gave mixtures of the isomeric products **23c,d** and **24c,d**. The best ratio in favour of **23c** (75:25) and **24d** (71:29) was obtained in the presence of the hydrated ceric salt in acetonitrile-water. In comparison the use of anhydrous zinc triflate[18] or lithium perchlorate[18,19] in acetonitrile led to lower selectivities. Moreover, no reaction was observed with benzylamine and zinc triflate in dichloromethane. All the four compounds **23c,d** and **24c,d** could be isolated, preferably from the properly enriched reaction mixtures. Similarly, the reaction with dibenzylamine in the optimal reaction coditions gave the two products **23e** and **24e** in almost 1:1 ratio, and they were separated chromatographically with some difficulty.

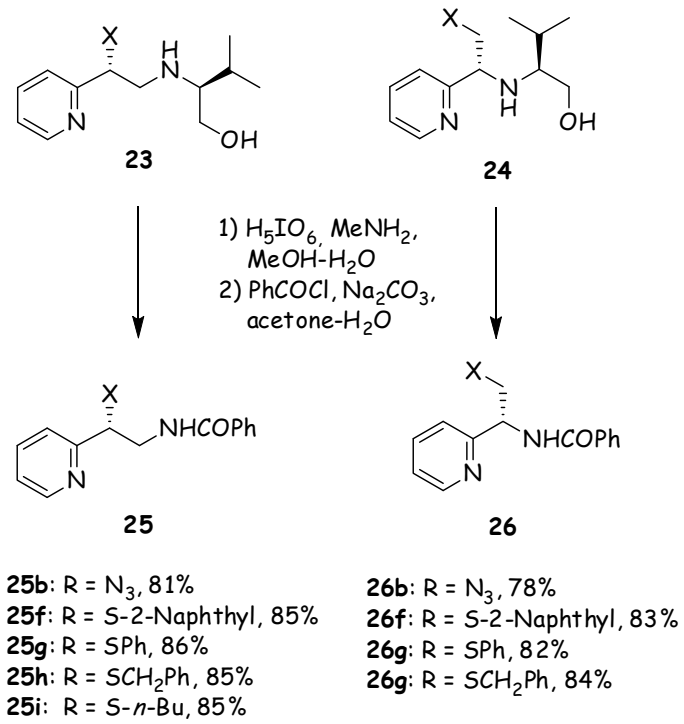
Table 2

Reagent (eq.)	Additive (mol %)	Solvent, T, t	Ratio 23/24[a]	23, yield (%)[b]	24, yield (%)[b]
$PhCH_2NH_2$ (2)	$CeCl_3 \cdot 7H_2O$ (50)	CH_3CN-H_2O (9:1), reflux, 6 h	75:25	**2c**, 67	24c[c]
$PhCH_2NH_2$ (2)	$Zn(OTf)_2$ (10)	CH_3CN, reflux, 8 h	51:49	**23c**, 38	**24c**, 40
$PhCH_2NH_2$ (2)	$Zn(OTf)_2$ (10)	CH_2Cl_2, reflux, 6 h	-	-	-
$PhCH_2NH_2$ (2)	$LiClO_4$ (10)	CH_3CN, reflux, 8 h	40:60	**23c**[c]	24c[c]
4-$CH_3OC_6H_4NH_2$ (1.2)	$LiClO_4$ (10)	CH_3CN, reflux, 24 h	69 :31[d]	**23d**, 62	**24d**, 27
4-$CH_3OC_6H_4NH_2$ (1.2)	$CeCl_3 \cdot 7H_2O$ (50)	CH_3CN, reflux, 24 h	71 :29	**23d**, 51	**24d** , 24
$(PhCH_2)_2NH$ (2)	$CeCl_3 \cdot 7H_2O$ (50)	CH_3CN-H_2O (9:1), reflux, 5 h	53:47	**23e**, 48	24e, 41
2-NaphthylSH (1.1)	$CeCl_3 \cdot 7H_2O$ (30)	CH_3CN-H_2O (9:1), reflux, 2 h	100:0	**23f**, 92	-
2-NaphthylSH (3)	-	CH_3CN-H_2O (9:1), reflux, 5 h	75:25	**23f**, 57	**24f**, 18
2-NaphthylSH (3)	-	CH_2Cl_2, 25 °C, 24 h	70:30	**23f**, 54	**24f**, 19
PhSH (1.1)	$CeCl_3 \cdot 7H_2O$ (30)	CH_3CN-H_2O (9:1), reflux, 4 h	96:4	**23g**, 84	**24g**, 3
PhSH (3)	-	CH_2Cl_2, 25°C, 2 h	50:50	**23g**, 42	**24g**, 45
$PhCH_2SH$ (1.1)	$CeCl_3 \cdot 7H_2O$ (30)	CH_3CN-H_2O (9:1), reflux, 2 h	70:30	**23h**, 65	**24h**, 23
n-BuSH (1.1)	$CeCl_3 \cdot 7H_2O$ (30)	CH_3CN-H_2O (9:1), reflux, 4 h	-[e]	**23i**, 57; **23a**, 12	-
t-BuSH (1.1)	$CeCl_3 \cdot 7H_2O$ (30)	CH_3CN-H_2O (9:1), reflux, 4 h	81:19	**23a**, 62	**24a**, 9
t-BuSH (1.1)	*p*-TsOH (50)	CH_3CN-H_2O (9:1), reflux, 4 h	85:15	**23a**, 79	**24a**, 11

[a] Determined by ^{1}HNMR analysis of the crude product. [b] Yield of product isolated by column chromatography (SiO_2). [c] The product was not isolated. [d] The reaction was incomplete (about 60% conversion of **1c**). [e] A complex mixture of products was observed, only **23i** and **23a** were isolated by column chromatography (SiO_2).

The positive effect of both the protic solvent and the cerium salt was particularly evident in the reactions of the aziridine **22** with aromatic thiols. In the case of 2-naphthalenethiol (1.1 equiv.), the benzylic sulfide **23f** was obtained exclusively with high yield

after heating in the presence of the hydrated ceric salt in 9:1 acetonitrile-H_2O at the reflux temperature for 2 h.[20] On the other hand, lower reaction rates and mixtures of **23f** and **24f** were observed in the absence of the catalyst in the same solvent mixture and in dichloromethane.[21] Similar results were obtained in the case of thiophenol, whereas the reaction with benzylthiol gave a mixture of the products **23h** and **24h** (70:30) in the optimized conditions. The reaction with *n*-butylthiol was even less satisfactory, as it afforded a mixture, from which only the prevalent sulfide **23i** and the alcohol **24a** were isolated by column chromatography. Finally, *t*-butylthiol was ineffective, as we only obtained the alcohols **23a** and **24a**, coming from the competitive ring opening by water.



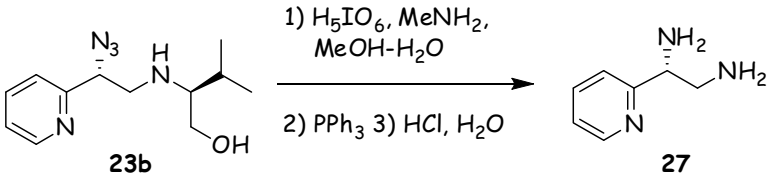
25b: R = N_3, 81%
25f: R = S-2-Naphthyl, 85%
25g: R = SPh, 86%
25h: R = SCH_2Ph, 85%
25i: R = S-*n*-Bu, 85%

26b: R = N_3, 78%
26f: R = S-2-Naphthyl, 83%
26g: R = SPh, 82%
26g: R = SCH_2Ph, 84%

Scheme 12

A few of the compounds **23** and **24** were subjected to routine oxidative cleavage of the *N*-substituent to obtain the corresponding homobenzylic and benzylic amines, which were immediately converted to the benzamides **25** and **26** with good overall yields (Scheme 12). Moreover, the azide **23b** was converted to the 1-(2-pyridyl)-1,2-diamine **27** by the three-step sequence described in Scheme 13, avoiding purification of the intermediates. In particular, after the usual oxidative cleavage of the *N*-substituent, we tried the reduction of the azide group with lithium aluminum hydride at 0 °C, but a complex mixture of products was obtained. Alternatively, the β-azido amine was treated with triphenylphosphine, then hydrolysis of the

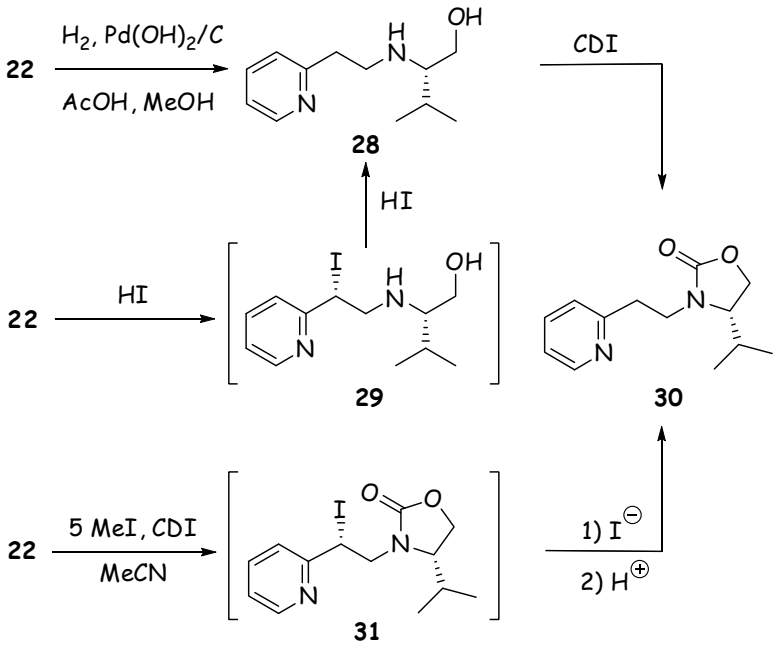
intermediate ylide gave the primary diamine **27**. It should be observed that the analogous process carried out on the isomeric azide-amine **24b** would give the enantiomer of the amine **27**.



23b **27**

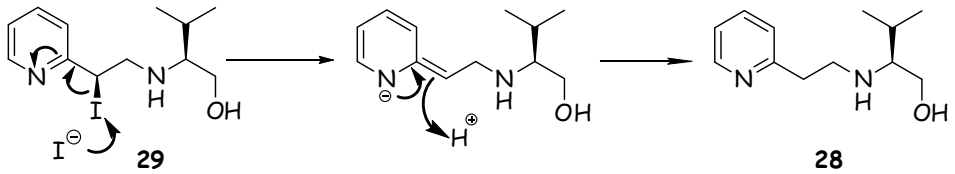
Scheme 13

Other methodologies to achieve ring opening reactions of the aziridine ring in the aziridine-alcohol **22** were then studied (Scheme 14). The secondary amine **28** was obtained by hydrogenolysis of the more substituted C-N bond of the aziridine-alcohol **22** in the presence of $Pd(OH)_2/C$. Surprisingly, treatment of **22** with an excess of hydroiodic acid gave the same amine **28**. A literature survey showed that hydroiodic acid displays reducing properties towards many organic compounds.[22] In particular, reductions of α-halo ketones by iodide ion and hydroiodic acid have been reported.[23] Based on these reports, we propose that ring-opening occurs first to give the iodide **29**, which is then reduced by iodide attack (Scheme 15).



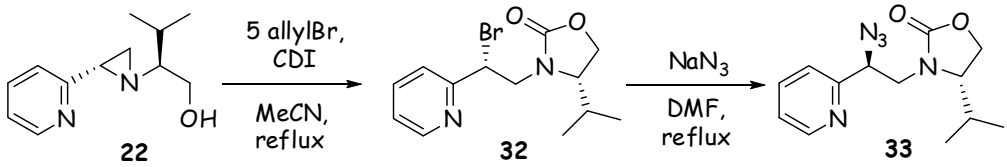
Scheme 14

The reactions of aziridine-alcohol **22** with an excess of both carbonyldiimidazole (CDI) and reactive alkyl halides were then carried out, as these reactions were expected to give halogenated products coming from the ring opening of the aziridine by halide ion.[24] Presumably, the halide ion is generated by *N*-alkylation of one imidazole ring of CDI or a reaction intermediate.[25] However, when methyl iodide was used the only product observed was the imidazolidinone **30**, which was also prepared by reaction of the amino alcohol **28** with CDI. In order to account for this result, the iodide **31** is proposed as an intermediate in the formation of **30** from **22**.



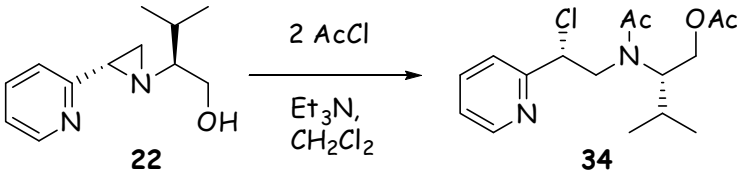
Scheme 15

The bromide **32** was obtained by reaction of **22** with CDI and an excess of allyl bromide in acetonitrile at room temperature (Scheme 16). The diastereomeric bromide was detected in 10% in the crude reaction mixture. It showed the ^{1}H NMR absorption of the CHBr proton at lower field with respect to the major diastereomer, and its amount increased to 33% when the reaction was carried out at reflux temperature. Interestingly, analogous reactions of 2-(2-hydroxyalkyl)aziridines described in the literature gave compounds coming from attack of halide ions to the unsubstituted aziridine carbon.[24] The bromine in **32** could be easily substituted by reaction with sodium azide in refluxing DMF to give the azido-oxazolidinone **33** as a single stereoiosomer. The complete or very high stereoselectivity observed in the described transformations of both the aziridine **22** and the bromide **32** involving cleavage of the benzylic C-N and C-Br bonds, respectively, points to an S_N2 mechanism operating with inversion of configuration.



Scheme 16

Finally, reaction of **22** with two equivalents of acetyl chloride gave the polyfunctional compound **34** by *N,O*-diacetylation and concomitant aziridine ring-opening by chloride ion (Scheme 17).



22 **34**

Scheme 17

In conclusion, the ring-opening reaction of the 2-(2-pyridyl)aziridine **22** with hetero-nucleophiles in optimized experimental conditions, i.e. in acetonitrile-water mixture as the solvent, and in the presence of a catalytic amount of ceric trichloride heptahydrate, proved to be a useful route to a variety of laterally di-functionalized pyridines.

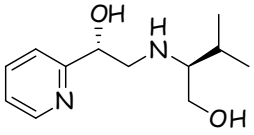
3.3 – Experimental section

*3.3.1 – General protocol for ring opening reaction of **22***

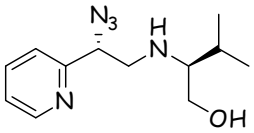
$CeCl_3 \cdot 7H_2O$-catalyzed hydrolytic ring-opening of aziridine 22. Preparation of pyridine-amine-diols 23a and 24a. $CeCl_3 \cdot 7H_2O$ (0.054 g, 0.15 mmol) was added to the solution of the aziridine **22** (0.100 g, 0.48 mmol) in 1:1 CH_3CN-H_2O mixture (20 mL). The mixture was stirred at the reflux temperature for 8 h: T.L.C. analysis showed that the starting material was totally consumed and two products were formed. Saturated aqueous solution of $NaHCO_3$ (10 mL) was added and the organic materials were extracted with Et_2O (3 x 20 mL). The collected ethereal layers were dried over Na_2SO_4 and concentrated to leave a brown oily residue which was subjected to chromatography eluting with EtOAc/MeOH/30% NH_4OH (98:2:1) mixture.

$CeCl_3 \cdot 7H_2O$-Catalyzed ring-opening of the aziridine 1 by hetero-nucleophiles. Preparation of laterally poly-functionalized pyridines 23b-i and 24b-d,f-h. Typical procedure: Sodium azide (0.034 g, 0.52 mmol) and $CeCl_3 \cdot 7H_2O$ (0.090 g, 0.24 mmol) were added to the solution of the aziridine 22 (0.100 g, 0.48 mmol) in a 9:1 CH_3CN-H_2O mixture (20 mL). The mixture was stirred at the reflux temperature for 2 h: T.L.C. analysis showed that the starting material was totally consumed. The organic materials were extracted with

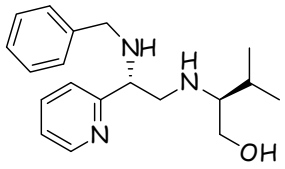
EtOAc (3 × 20 mL). The collected ethereal layers were dried over Na_2SO_4 and concentrated to leave 23a as a yellowish oil: Pure 23b (0.109 g, 71%) was obtained by column chromatography on a short SiO_2 column eluting with cyclohexane/EtOAc mixture.



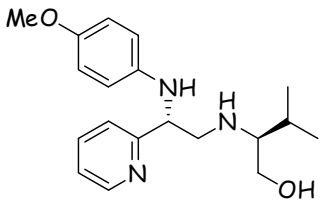
(*S*)-2-[(*R*)-2-Hydroxy-2-(2-pyridyl)ethylamino]-3-methyl-1-butanol (23a): Yellow oil; $[\alpha]_D^{20}$ +24.2 (*c* 1.3, $CHCl_3$). IR (neat): *v* = 3406, 2962, 2925, 1658, 1597, 1413, 1260, 1049, 794, 751. ^{13}H NMR (300 MHz, $CDCl_3$): δ = 8.55 (ddd, *J* = 0.7, *J* = 1.3, *J* = 4.7, 1 H), 7.72 (dt, *J* = 1.7, *J* = 7.6, 1 H), 7.38 (dt, *J* = 0.9, *J* = 7.9, 1 H), 7.23 (ddd, *J* = 0.7, *J* = 4.7, *J* = 7.6, 1 H), 4.86 (dd, *J* = 3.6, *J* = 7.5, 1 H), 3.65 (dd, *J* = 4.1, *J* = 10.8, 1 H), 3.38 (dd, *J* = 7.7, *J* = 10.8, 1 H), 3.06 (dd, *J* = 3.6, *J* = 12.0, 1 H), 2.97 (bs, 3 H), 2.90 (dd, *J* = 7.5, *J* = 12.0, 1 H), 2.43 (ddd, *J* = 4.1, *J* = 6.7, *J* = 7.7, 1 H), 1.81 (sept, *J* = 6.9, 1 H), 0.97 (d, *J* = 6.8, 3 H), 0.90 (d, *J* = 6.8, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.3, 148.3, 136.9, 122.6, 120.6, 72.3, 64.8, 61.0, 54.0, 29.1, 19.5, 18.5. GC-MS *m/z* 207 (2), 193 (26), 181(8), 175 (10), 121(44), 116 (60), 109 (100), 108 (24), 94 (25), 79 (19), 69 (11); MS (ES) *m/z* 225.4 $(M + H)^+$. Anal. Calcd for $C_{12}H_{20}N_2O_2$: C, 64.26; H, 8.99; N, 12.49. Found C, 64.06; H, 9.01; N, 12.44.



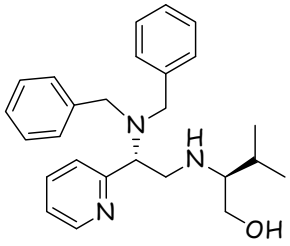
(*S*)-2-[(*R*)-2-Azido-2-(2-pyridyl)ethylamino)-3-methyl-1-butanol (23b): Red oil; $[\alpha]_D^{20}$ +76.8 (*c* 1.7, $CHCl_3$). IR (neat): *v* = 3380, 2956, 2922, 2102, 1592, 1472, 1436, 1155, 1117. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.61 (ddd, *J* = 0.9, *J* = 1.8, *J* = 4.7, 1 H), 7.74 (dt, *J* = 1.8, *J* = 7.7, 1 H), 7.38 (dt, *J* = 0.9, *J* = 7.7, 1 H), 7.26 (ddd, *J* = 1.1, *J* = 4.7, *J* = 7.5, 1 H), 4.64 (dd, *J* = 5.0, *J* = 7.6, 1 H), 3.59 (dd, *J* = 4.1, *J* = 10.8, 1 H), 3.31 (dd, *J* = 7.7, *J* = 10.8, 1 H), 3.30 (dd, *J* = 5.0, *J* = 12.5, 1 H), 3.19 (dd, *J* = 7.6, *J* = 12.5, 1 H), 2.39 (dd, *J* = 4.1, *J* = 7.7, 1 H), 2.14 (bs, 2 H) 1.77 (sept, *J* = 6.9, 1 H), 0.94 (d, *J* = 6.9, 3 H), 0.88 (d, *J* = 6.9, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.5, 149.6, 137.0, 123.2, 121.9, 66.7, 64.8, 61.0, 51.1, 29.2, 19.4, 18.4. MS (ES) *m/z* 250.2 $(M + H)^+$, 272.1 $(M + Na)^+$. Anal. Calcd for $C_{12}H_{19}N_5O$: C, 57.81; H, 7.68; N, 28.09; O, 6.42. Found C, 57.55; H, 7.70; 27.99.



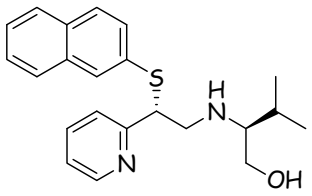
(*S*)-2-[(*R*)-2-(Benzylamino)-2-(2-pyridyl)ethylamino]-3-methy-1-lbutanol (23c): Yellow oil; $[\alpha]_D^{20}$ +30.8 (*c* 1.7, $CHCl_3$); IR (neat): ν = 3308, 3061, 3028, 2956, 2921, 2864, 1591, 1570, 1454, 1434, 1366, 1121, 1048, 749, 699. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.63 (ddd, J = 0.8, J = 1.8, J = 4.8, 1 H), 7.63 (td, J = 1.8, J = 7.7, 1 H), 7.35 (m, 5 H), 7.28 (m, 1 H), 7.23 (ddd, J = 1.2, J = 4.8, J = 7.5, 1 H), 3.87 (dd, J = 5.9, J = 7.2, 1 H), 3.72 (d, J = 12.9, 1H), 3.61 (d, J = 12.9, 1 H), 3.59 (dd, J = 4.0, J = 10.7, 1 H), 3.35 (dd, J = 7.8, J = 10.7, 1 H), 2.91 (m, 2 H), 2.53 (bs, 3 H), 2.39 (dd, J = 4.0, J = 7.8, 1 H), 1.78 (sept, J = 6.8, 1 H), 0.86 (d, J = 6.8, 3 H), 0.88 (d, J = 6.8, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.7, 149.5, 140.1, 136.4, 128.3, 128.2, 126.9, 122.7, 122.3, 64.6, 63.2, 52.8, 51.6, 29.4, 19.5, 18.7. MS (ES) *m/z* 314.3 $(M + H)^+$. Anal. Calcd for $C_{19}H_{27}N_3O$: C, 72.81; H, 8.68; N, 13.41. Found C, 72.88; H, 8.71; N, 13.37.



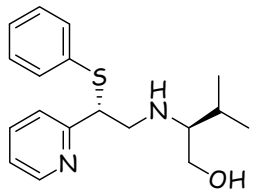
(*S*)-2-[(*R*)-2-(4-Methoxyphenylamino)-2-(2-pyridyl)ethylamino]-3-methyl-1-butanol (23d): Red oil; $[\alpha]_D^{20}$ +21.1 (*c* 1.3, $CHCl_3$). IR (neat): ν = 3333, 2957, 2928, 2872, 2828, 1592, 1512, 1465, 1435, 1239, 1039. ^{13}H NMR (300 MHz, $CDCl_3$): δ = 8.58 (ddd, J = 0.8, J = 1.7, J = 4.8, 1 H), 7.63 (dt, J = 1.7, J = 7.6, 1 H), 7.36 (dt, J = 0.8, J = 7.8, 1 H), 7.18 (ddd, J = 1.2, J = 4.8, J = 7.6, 1 H), 6.72 (d, J = 9.1, 2 H), 6.60 (d, J = 9.1, 2 H), 4.54 (dd, J = 4.8, J = 7.1, 1 H), 3.78 (s, 3 H), 3.62 (dd, J = 4.1, J = 10.8, 1 H), 3.38 (dd, J = 7.5, J = 10.8, 1 H), 3.13 (dd, J = 4.8, J = 11.9, 1 H), 3.05 (dd, J = 7.1, J = 11.9, 1 H), 2.73 (bs, 2 H), 2.43 (ddd, J = 4.1, J = 6.5, J = 7.5, 1 H), 1.81 (sept, J = 6.8, 1 H), 0.93 (d, J = 6.8, 3 H), 0.87 (d, J = 6.8, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.2, 152.4, 149.3, 141.4, 136.8, 122.4, 121.8, 115.5, 114.7, 64.8, 60.9, 60.3, 55.6, 52.4, 28.9, 19.4, 18.4; MS (ES) *m/z* 330.2 $(M + H)^+$. Anal. Calcd for $C_{19}H_{27}N_3O_2$: C, 69.27; H, 8.26; N, 12.76. Found C, 69.52; H, 8.30; N, 12.71.



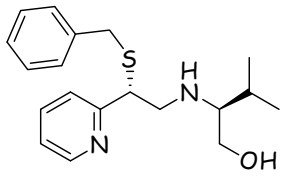
(*S*)-2-((*R*)-2-(dibenzylamino)-2-(pyridin-2-yl)ethylamino)-3-methylbutan-1-ol (23e): Red oil; $[\alpha]_D^{20}$ +24.3 (*c* 1.4, $CHCl_3$). IR (neat): *v* = 3357, 3061,3028, 2959, 2925, 1589, 1453, 1434, 1261, 1072, 1027, 698. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.60 (ddd, *J* = 0.8, *J* = 1.7, *J* = 4.9, 1 H), 7.71 (td, *J* = 1.9, *J* = 7.6, 1 H), 7.36 (m, 9H), 7.23 (m, 3H), 3.96 (dd, *J* = 6.7, *J* = 6.9, 1 H), 3.84 (d, *J* = 13.8 2H), 3.64 (dd, *J* = 4.1, *J* = 10.8, 1 H), 3.42 (d, *J* = 13.8 2 H), 3.37 (m, 2 H), 3.20 (dd, *J* = 7.4, *J* = 11.6, 1 H), 2.38 (dd, *J* = 4.1, *J* = 6.9, 1 H), 1.76 (sept, *J* = 6.8, 1 H), 0.95 (d, *J* = 6.8, 3 H), 0.89 (d, *J* = 6.8, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ= 159.4, 148.8, 139.8, 136.1, 128.7, 128.3, 127.0, 124.5, 122.2, 64.5, 62.2, 60.9, 54.3, 45.5, 29.5, 19.6, 18.9. MS (ES) *m/z* 404.5 $(M+H)^+$. Anal. Calcd for $C_{26}H_{33}N_3O$: C, 77.38; H, 8.24; N, 10.41. Found C, 77.10; H, 8.27; N, 10.37.



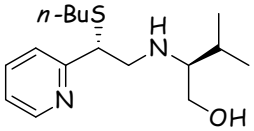
(*S*)-2-[(*R*)-2-(2-Naphthylthio)-2-(2-pyridyl)ethylamino]-3-methyl-1-butanol (23f): Yellowish oil; $[\alpha]_D^{20}$ +51.8 (*c* 1.7, $CHCl_3$). IR (neat): *v* = 3412, 3330, 3055, 3009, 2954, 1584, 1565, 1474, 1432, 1105, 1044, 748, 692. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.56 (ddd, *J* = 0.9, *J* = 1.9, *J* = 4.8, 1 H), 7.71 (m, 2 H), 7.69 (m, 2 H), 7.59 (dt, *J* = 1.8, *J* = 7.7, 1 H), 7.46 (m, 2 H), 7.39 (dd, *J* = 1.8, *J* = 8.5, 1 H), 7.28 (dt, *J* = 0.9, *J* = 7.8, 1 H), 7.16 (ddd, *J* = 1.1, *J* = 4.9, *J* = 7.8, 1 H), 4.61 (dd, *J* = 6.4, *J* = 6.6, 1 H), 3.60 (dd, *J* = 4.1, *J* = 10.8, 1 H), 3.40 (dd, *J* = 6.4, *J* = 12.3, 1 H), 3.33 (dd, *J* = 7.4, *J* = 10.8, 1 H), 3.29 (dd, *J* = 6.4, *J* = 12.2, 1 H), 2.65 (bs, 2 H), 2.42 (ddd, *J* = 4.1, *J* = 6.4, *J* = 7.4, 1 H), 1.78 (sept, *J* = 6.8, 1 H), 0.93 (d, *J* = 6.8, 3 H), 0.88 (d, *J* = 6.8, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.8, 149.4, 136.6, 133.5, 132.3, 131.4, 130.9, 129.4, 128.4, 127.6, 127.4, 126.5, 126.2, 123.1, 122.4, 64.7, 60.8, 54.8, 50.5, 29.2, 19.6, 18.6. MS (ES) *m/z* 367.3 $(M + H)^+$, 389.1 $(M + Na)^+$. Anal. Calcd for $C_{22}H_{26}N_2OS$: C, 72.09; H, 7.15; N, 7.64. Found C, 71.83; H, 7.16; N, 7.62.



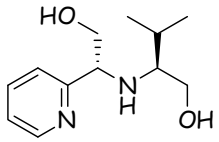
(*S*)-2-[(*R*)-2-(Phenylthio)-2-(2-pyridyl)ethylamino]-3-methyl-1-butanol (23g): Yellow oil; $[\alpha]_D^{20}$ +87.7 (*c* 1.2, $CHCl_3$). IR (neat): *v* = 3419, 3332, 3056, 3006, 2957, 2925, 2871, 1589, 1569, 1471, 1434, 1385, 1109, 1049, 1025, 747, 691. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.57 (ddd, *J* = 0.9, *J* = 1.8, *J* = 4.8, 1 H), 7.74 (dt, *J* = 1.8, *J* = 7.7, 1 H), 7.33 (m, 3 H), 7.25 (m, 3 H), 7.17 (ddd, *J* = 0.9, *J* = 4.8, *J* = 7.4, 1 H), 4.47 (dd, *J* = 6.7, *J* = 6.9, 1 H), 3.60 (dd, *J* = 4.1, *J* = 10.7, 1 H), 3.35 (dd, *J* = 6.7, *J* = 12.3, 1 H), 3.31 (dd, *J* = 7.6, *J* = 10.7, 1 H), 3.26 (dd, *J* = 6.9, *J* = 12.3, 1 H), 2.48 (bs, 2 H), 2.31 (ddd, *J* = 4.1, *J* = 7.1, *J* = 7.6, 1 H), 1.77 (sept, *J* = 6.9, 1 H), 0.93 (d, *J* = 6.8, 3 H), 0.89 (d, *J* = 6.8, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.9, 149.3, 136.5, 134.1, 132.2, 128.8, 127.3, 123.0, 122.2, 64.5, 60.8, 55.2, 50.6, 29.2, 19.5, 18.6. MS (ES) *m/z* 317.1 $(M + H)^+$. Anal. Calcd for $C_{17}H_{23}N_2OS$: C, 67.29; H, 7.64; N, 9.23. Found C, 67.01; H, 7.65; N, 9.21.



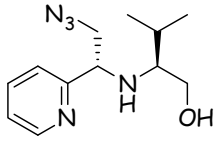
(*S*)-2-[(*R*)-2-(Benzylthio)-2-(2-pyridyl)ethylamino]-3-methyl-1-butanol (23h): Yellow oil; $[\alpha]_D^{20}$ +143.0 (*c* 1.2, $CHCl_3$). IR (neat): *v* = 3383, 3061, 3028, 2956, 2925, 1590, 1494, 1471, 1453, 1434, 1049, 749, 702. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.56 (ddd, *J* = 0.8, *J* = 1.6, *J* = 4.8, 1 H), 7.74 (dt, *J* = 1.8, *J* = 7.8, 1 H), 7.29 (m, 5 H), 7.18 (m, 2 H), 3.97 (dd, *J* = 6.8, *J* = 6.8, 1 H), 3.79 (d, *J* = 13.3, 1 H), 3.60 (d, *J* = 13.3, 1 H), 3.54 (dd, *J* = 4.1, *J* = 10.7, 1 H), 3.24 (dd, *J* = 7.6, *J* = 10.7, 1 H), 3.21 (dd, *J* = 6.7, *J* = 12.1, 1 H), 3.11 (dd, *J* = 7.0, *J* = 12.1, 1 H), 2.40 (bs, 2 H), 2.31 (dd, *J* = 4.1, *J* = 7.6, 1 H), 1.71 (sept, *J* = 6.9, 1 H), 0.89 (d, *J* = 6.8 , 3 H), 0.84 (d, *J* = 6.8, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.6, 149.3, 137.9, 136.7, 128.9, 128.5, 127.0, 122.9, 122.2, 64.5, 60.8, 51.2, 50.6, 35.4, 29.2, 19.5, 18.6. *GC-MS m/z* 105 (100), 91 (93), 93 (70), 104 (40), 78 (31), 65 (30), 226 (26), 124 (26), 194 (25), 226 (18), 207 (16), 51 (16), 136 (12). Anal. Calcd for $C_{19}H_{26}N_2OS$: C, 69.05; H, 7.93; N, 8.48. Found C, 69.16; H, 7.95; N, 8.46.



(*S*)-2-[(*R*)-2-(Butylthio)-2-(2-pyridyl)ethylamino]-3-methyl-1-butanol (23i): Yellow oil; $[\alpha]_D^{20}$ +36.8 (*c* 1.0, $CHCl_3$). IR (neat): *v* = 3346, 2957, 2926, 2872, 1590, 1569, 1468, 1434, 1049, 788, 748. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.54 (ddd, *J* = 0.8, *J* = 1.8, *J* = 4.7, 1 H), 7.67 (dt, *J* = 1.8, *J* = 7.7, 1 H), 7.39 (dt, *J* = 0.8, *J* = 7.7, 1 H), 7.17 (ddd, *J* = 1.0, *J* = 4.7, *J* = 7.7, 1 H), 4.06 (dd, *J* = 7.1, *J* = 7.1, 1 H), 3.59 (dd, *J* = 4.2, *J* = 10.7, 1 H), 3.30 (dd, *J* = 7.5, *J* = 10.7, 1 H), 3.24 (dd, *J* = 7.1, *J* = 12.1, 1 H), 3.16 (dd, *J* = 7.1, *J* = 12.1, 1 H), 2.60 (bs, 2 H), 2.43 (dd, *J* = 6.8, *J* = 7.2, 2 H), 2.39 (dd, *J* = 4.2, *J* = 7.5, 1 H), 1.78 (sept, *J* = 6.9, 1 H), 1.47 (m, 2 H), 1.31 (m, 2 H), 0.92 (d, *J* = 6.9, 3 H), 0.88 (d, *J* = 6.9, 3 H), 0.84 (t, *J* = 7.3, 3 H). ^{13}*C* NMR (75 MHz, $CDCl_3$): δ = 160.9, 149.1, 136.7, 122.8, 122.1, 64.6, 60.8, 51.6, 50.6, 31.6, 30.4, 29.2, 21.9, 19.5, 18.6, 13.6. MS (ES) *m/z* 297.2 $(M + H)^+$. Anal. Calcd for $C_{16}H_{28}N_2OS$: C, 64.82; H, 9.52; N, 9.45. Found C, 64.73; H, 9.52; N, 9.43.

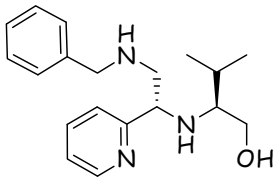


(*S*)-2-[(*R*)-2-Hydroxy-1-(2-pyridyl)ethylamino]-3-methyl-1-butanol (24a): Yellow oil; $[\alpha]_D^{20}$ +38.6 (*c* 1.2, $CHCl_3$). IR (neat) *v* = 3330, 2957, 2921, 2873, 1670, 1595, 1571, 1468, 1436, 1049, 774, 751. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.60 (ddd, *J* = 0.8, *J* = 1.6, *J* = 4.9, 1 H), 7.75 (dt, *J* = 1.8, *J* = 7.7, 1 H), 7.34 (dt, *J* = 0.9, *J* = 7.7, 1 H), 7.28 (m, 1 H), 4.12 (dd, *J* = 4.2, *J* = 6.6, 1 H), 3.96 (dd, *J* = 4.2, *J* = 11.3, 1 H), 3.84 (dd, *J* = 6.6, *J* = 11.3, 1 H), 3.81 (dd, *J* = 3.7, *J* = 11.6, 1 H), 3.65 (dd, *J* = 6.1, *J* = 11.6, 1 H), 2.47 (dd, *J* = 3.7, *J* = 6.1, 1 H), 1.81 (sept, *J* = 6.8, 1 H), 0.95 (d, *J* = 6.8, 3 H), 0.90 (d, *J* = 6.8, 6 H). ^{13}*C* NMR (75 MHz, $CDCl_3$) δ= 159.7, 149.1, 137.1, 123.1, 122.7, 65.6, 64.1, 62.8, 61.1, 29.3, 19.3, 18.9. MS (ES) *m/z* 225.4 $(M + H)^+$. Anal. Calcd for $C_{12}H_{20}N_2O_2$: C, 64.26; H, 8.99; N, 12.49. Found C, 64.10; H, 9.02; N, 12.45.

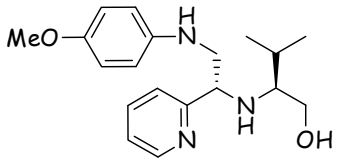


(*S*)-2-[(*S*)-2-Azido-1-(2-pyridyl)ethylamino]-3-methyl-1-butanol (24b): Yellow oil; $[\alpha]_D^{20}$ +52.8 (*c* 1.1, $CHCl_3$). IR (neat): *v* = 3378, 2950, 2923, 2106, 1594, 1470, 1438, 1153, 1112. ^{1}H

NMR (300 MHz, $CDCl_3$): δ = 8.64 (ddd, *J* = 0.9, *J* = 1.7, *J* = 4.8, 1 H), 7.72 (dt, *J* = 1.8, *J* = 7.7, 1 H), 7.30 (dt, *J* = 0.9, *J* = 7.7, 1 H), 7.26 (ddd, *J* = 0.9, *J* = 4.8, *J* = 7.7, 1 H), 3.98 (dd, *J* = 6.5, *J* = 6.5, 1 H), 3.69 (dd, *J* = 3.9, *J* = 11.1, 1 H), 3.63 (dd, *J* = 6.5, *J* = 12.1, 1 H), 3.55 (dd, *J* = 6.57.1, *J* = 12.1, 1 H), 3.50 (dd, *J* = 5.4, *J* = 11.1, 1 H), 2.54 (bs, 2 H), 2.31 (dd, *J* = 3.9, *J* = 5.4,1 H), 1.69 (sept, *J* = 6.8, 1 H), 0.86 (d, *J* = 6.8, 3 H), 0.82 (d, *J* = 6.8, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.7, 149.7, 136.6, 122.9, 122.7, 63.2, 31.6, 30.9, 29.5, 19.4, 18.7. MS (ES) *m/z* 250.2 $(M + H)^+$. Anal. Calcd for $C_{12}H_{19}N_5O$: C, 57.81; H, 7.68; N, 28.09; O, 6.42. Found C, 57.58; H, 7.71; 28.00.

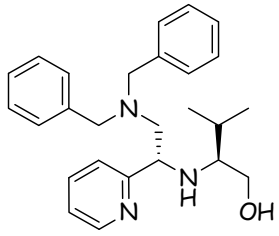


(*S*)-2-[(*S*)-2-Benzylamino-1-(2-pyridyl)ethylamino]-3-methyl-1-butanol (24c): Yellow oil. $[\alpha]_D^{20}$ +22.3 (*c* 1.7, $CHCl_3$). IR (neat): *v* = 3308, 3062, 2955, 2915, 2866, 2850, 1590, 1454, 1434, 1366, 1120, 749, 698. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.60 (ddd, *J* = 0.8, *J* = 1.6, *J* = 4.8, 1 H), 7.68 (dt, *J* = 1.8, *J* = 7.6, 1 H), 7.32 (m, 5 H), 7.15 (m, 1 H), 7.18 (ddd, *J* = 0.8, *J* = 4.8, *J* = 7.6, 1 H), 3.91 (dd, *J* = 4.6, *J* = 8.5, 1 H), 3.69 (d, *J* = 12.7, 1 H), 3.64 (dd, *J* = 4.6, *J* = 11.1, 1 H), 3.63 (d, *J* = 12.7, 1 H), 3.42 (dd, *J* = 7.7, *J* = 11.1, 1 H), 3.03 (dd, *J* = 4.4, *J* = 12.0, 1 H), 2.90 (dd, *J* = 8.6, *J* = 12.0, 1 H), 2.67 (bs, 3 H), 2.43 (dd, *J* = 4.6, *J* = 7.7, 1 H), 1.82 (sept, *J* = 6.9, 1 H), 0.97 (d, *J* = 6.9, 3 H), 0.91 (d, *J* = 6.9, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.9, 149.2, 140.1, 136.4, 128.3, 128.2, 127.1, 127.1, 126.7, 122.7, 122.3, 64.7, 62.5, 61.7, 60.3, 54.5, 53.6, 30.2, 19.3, 18.7. MS (ES) *m/z* 314.3 $(M + H)^+$. Anal. Calcd for $C_{19}H_{27}N_3O$: C, 72.81; H, 8.68; N, 13.41. Found C, 73,15; H, 8.71; N, 13.38.

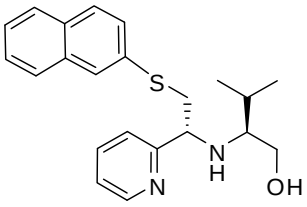


(*S*)-2-[(*S*)-2-(4-Methoxyphenylamino)-1-(2-pyridiyl)ethylamino]-3-methyl-1-butanol (24d): Yellow oil; $[\alpha]_D^{20}$ −38.8 (*c* 1.0, $CHCl_3$). IR (neat): *v* = 3372, 2956, 2922, 2104, 1598, 1464, 1116. ^1H NMR (300 MHz, $CDCl_3$) δ= 8.61 (ddd, *J* = 0.9, *J* = 1.8, *J* = 4.8, 1 H), 7.66 (dt, *J* = 1.8, *J* = 7.7, 1 H), 7.22 (m, 2 H), 6.78 (d, *J* = 9.0, 2 H), 6.62 (d, *J* = 9.0, 2 H), 4.02 (dd, *J* = 5.6, *J* = 7.3, 1 H), 3.75 (s, 3 H), 3.61 (dd, *J* = 3.9, *J* = 11.0, 1 H), 3.43 (dd, *J* = 5.4, *J* = 11.0, 1 H),

3.40 (dd, *J* = 5.6, *J* = 12.5, 1 H), 3.29 (dd, *J* = 7.3, *J* = 12.5, 1 H), 2.69 (bs, 3 H), 2.26 (dd, *J* = 3.9, *J* = 5.4,1H), 1.66 (sept, *J* = 6.8, 1 H), 0.84 (d, *J* = 6.9, 3 H), 0.80 (d, *J* = 6.9, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ= 161.4, 152.3, 149.6, 142.1, 136.5, 122.8, 122.5, 114.9, 114.7, 63.1, 61.1, 60.4, 55.7, 50.9, 29.5, 19.4, 18.9. MS (ES) *m/z* = 330.2 $(M + H)^+$. Anal. Calcd for $C_{19}H_{27}N_3O_2$: C, 69.27; H, 8.26; N, 12.76. Found C, 69.49; H, 8.29; N, 12.73.

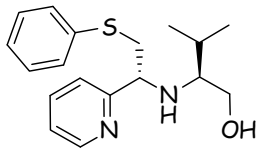


(*S*)-2-((*S*)-2-(dibenzylamino)-1-(pyridin-2-yl)ethylamino)-3-methylbutan-1-ol (24e): Yellow oil. $[\alpha]_D^{20}$ –24.7 (*c* 1.7, $CHCl_3$). IR (neat): *v* = 3320, 3085, 3062, 3027, 2959, 1593, 1453, 1364, 1261, 1118, 1027, 780, 746, 698. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.52 (ddd, *J* = 1.0, *J* = 1.8, *J* = 5.0, 1 H), 7.63 (dt, *J* = 1.9, *J* = 7.7, 1 H), 7.23 (td, *J* = 1.0, *J* = 7.7, 1 H), 7.18 (ddd, *J* = 1.0, *J* = 4.9, *J* = 7.5, 1 H), 3.93 (dd, *J* = 7.2, *J* = 7.2, 1 H), 3.73 (d, *J* = 13.5, 2 H), 3.66 (dd, *J* = 4.0, *J* = 10.9, 1 H), 3.58 (d, *J* = 13.5, 2 H), 3.45 (dd, *J* = 4.9, *J* = 11.0, 1 H), 2.73 (d, *J* = 7.0, 2 H), 2.18 (dd, *J* = 4.0, *J* = 4.9, 1 H), 2.09 (bs, 2H), 1.61 (sept, *J* = 6.8, 1 H), 0.80 (d, *J* = 6.8, 3 H), 0.77 (d, *J* = 6.8, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.9, 149.1, 138.9, 136.0, 128.0, 128.9, 128.2, 127.0, 126.9, 122.0, 62.6, 60.8, 60.7, 60.1, 59.2, 29.7, 19.2, 19.0. MS (ES) *m/z* = 404.3 $(M + H)^+$. Anal. Calcd for $C_{26}H_{33}N_3O$: C, 77.38; H, 8.24; N, 10.41. Found C, 77.10; H, 8.27; N, 10.37.

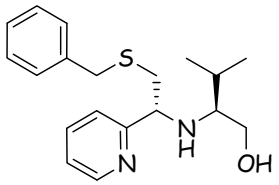


(*S*)-2-[(*R*)-2-(2-Naphthylthio)-1-(2-pyridyl)ethylamino]-3-methyl-1-butanol (24f): Yellowish oil; $[\alpha]_D^{20}$ +30.7 (*c* 1.2, $CHCl_3$). IR (neat): *v* = 3421, 3342, 3052, 2951, 1581, 1463, 1434, 1043, 1014, 742, 692. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.56 (ddd, *J* = 1.2, *J* = 1.7, *J* = 4.7, 1 H), 7.78 (m, 2 H), 7.74 (m, 2 H), 7.62 (dt, *J* = 1.8, *J* = 7.7, 1 H), 7.47 (m, 2 H), 7.39 (dd, *J* = 1.8, *J* = 8.7, 1 H), 7.17 (m, 2 H), 3.96 (dd, *J* = 6.2, *J* = 6.4, 1 H), 3.61 (dd, *J* = 3.8, *J* = 11.1, 1 H), 3.45 (dd, *J* = 5.0, *J* = 11.1, 1 H), 3.43 (dd, *J* = 6.4, *J* = 13.2, 1 H), 3.37 (dd, *J* = 6.2, *J* = 13.2, 1 H), 2.81 (bs, 2 H), 2.42 (ddd, *J* = 3.8, *J* = 4.8, *J* = 5.0, 1 H), 1.62 (sept, *J* = 6.9, 1 H), 0.76 (d, *J*

= 6.9, 3 H), 0.79 (d, *J* = 6.9, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.1, 149.7, 136.4, 133.7, 133.4, 131.7, 128.5, 127.7, 127.4, 127.1, 127.0, 126.5, 125.7, 122.9, 122.8, 63.3, 61.1, 60.4, 40.4, 29.3, 19.4, 18.7. *GC*-MS (EI) *m/z* 262 (100), 230 (55), 263 (51), 115 (46), 78 (27), 104 (15), 264 (12). MS (ES) *m/z* 367.3 $(M + H)^+$, 389.0 $(M + Na)^+$. *Anal. Calcd* for $C_{22}H_{26}N_2OS$: *C*, 72.09; H, 7.15; N, 7.64. Found *C*, 72.15; H, 7.17; N, 7.61.



(*S*)-2-[(*R*)-2-Phenylthio-1-(2-pyridyl)ethylamino]-3-methyl-1-butanol (24g): Yellow oil; $[\alpha]_D^{20}$ +11.4 (*c* 0.9, $CHCl_3$). IR (neat): *v* = 3424, 3345, 3057, 2959, 2925, 2972, 1643, 1589, 1467, 1436, 1258, 1042, 1013, 743, 690. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.61 (dt, *J* = 1.6, *J* = 4.4, 1 H), 7.66 (dt, *J* = 1.8, *J* = 7.8, 1 H), 7.38 (m, 1 H), 7.31 (m, 2 H), 7.21 (m, 2 H), 3.92 (dd, *J* = 6.3, *J* = 7.2, 1 H), 3.62 (dd, *J* = 3.8, *J* = 11.1, 1 H), 3.46 (dd, *J* = 5.0, *J* = 11.1, 1 H), 3.35 (dd, *J* = 7.2, *J* = 13.2, 1 H), 3.29 (dd, *J* = 6.3, *J* = 13.2, 1 H), 2.55 (bs, 2 H), 2.21 (ddd, *J* = 3.8, *J* = 5.0, *J* = 6.4, 1 H), 1.63 (sept, *J* = 6.9, 1 H), 0.82 (d, *J* = 6.9, 3 H), 0.78 (d, *J* = 6.9, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.3, 149.7, 136.3, 129.4, 128.9, 126.1, 122.7, 122.6, 63.0, 61.1, 60.6, 41.1, 29.4, 19.4, 18.8. *GC*-MS *m/z* 193 (100), 107 (39), 214 (35), 106 (17), 175 (12), 92 (12), 119 (11), 78 (10), 136 (9), 285 (3). *Anal. Calcd* for $C_{17}H_{23}N_2OS$: *C*, 67.29; H, 7.64; N, 9.23. Found *C*, 67.58; H, 7.67; N, 9.22.

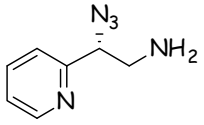


(*S*)-2-[(*R*)-2-Benzylthio-1-(2-pyridyl)ethylamino]-3-methyl-1-butanol (24h): Yellow oil; $[\alpha]_D^{20}$ −23.4 (*c* 1.2, $CHCl_3$). IR (neat): *v* = 3382, 3060, 3030, 2951, 2922, 1590, 1491, 1472, 1044, 741, 702. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.57 (ddd, *J* = 0.9, *J* = 1.7, *J* = 4.9, 1 H), 7.63 (dt, *J* = 1.7, *J* = 7.6, 1 H), 7.32 (m, 5 H), 7.26 (ddd, *J* = 0.9, *J* = 4.9, *J* = 7.6, 1 H), 7.13 d, *J* = 7.6, 1 H), 3.77 (dd, *J* = 6.3, *J* = 6.3, 1 H), 3.68 (s, 2 H), 3.61 (dd, *J* = 3.7, *J* = 11.1, 1 H), 3.46 (dd, *J* = 5.1, *J* = 11.1, 1 H), 2.86 (dd, *J* = 6.3, *J* = 13.3, 1 H), 2.77 (dd, *J* = 6.3, *J* = 13.3, 1 H), 2.36 (bs, 2 H), 2.39 (dd, *J* = 3.7, *J* = 5.1, 1 H), 1.62 (sept, *J* = 7.0, 1 H), 0.80 (d, *J* = 7.0, 3 H), 0.77 (d, *J* = 7.0, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.7, 149.6, 138.3, 136.3, 128.9, 128.5,

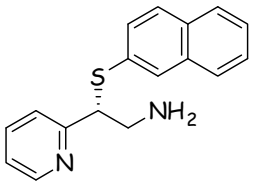
127.0, 122.4, 122.5, 63.0, 61.4, 60.6, 38.8, 37.1, 29.4, 19.4, 18.8. *GC-MS m/z* 91 (100), 193 (92), 107 (31), 106 (31), 228 (16), 124 (14), 65 (14), 281 (12), 136 (12), 78 (12), 175 (11), 51 (10), 299 (4), 207 (3). Anal. Calcd for $C_{19}H_{26}N_2OS$: C, 69.05; H, 7.93; N, 8.48. Found C, 69.26; H, 7.96; N, 8.45.

3.3.2 - Oxidative cleavage of the N-auxiliary. Preparation of the β-substituted primary amines and benzamides ***25b,e,f,h,i*** *and* ***26b,e,f,h.***

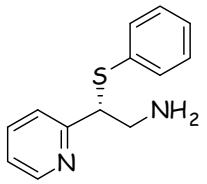
Typical procedure: To the valinol derivative **23b** (0,240 g, 0.96 mmol) dissolved in MeOH (5 mL) were added 40% $MeNH_2$ in water (1.2 mL), then a solution of H_5IO_6 (0.768 g) in H_2O (5 mL) was added dropwise. After stirring for 2 h at room temperature, the reaction was complete, as determined by T.L.C. analysis. Most of the solvent was evaporated at reduced pressure, then the organic materials were extracted with Et_2O (3 × 20 mL). The collected ethereal layers were dried over Na_2SO_4 and concentrated to leave the primary amine as a yellow oil. This was dissolved in acetone (5 mL), then Na_2CO_3 (0.200g), H_2O (5 mL) and benzoyl chloride (167 μl, 1.44 mmol) were added while magnetically stirring. After stirring for 12 h, the organic materials were extracted with Et_2O (3 x 20 mL). The collected ethereal layers were dried over Na_2SO_4 and concentrated to leave the benzamide **25b** as a yellow oil. The product was subjected to column chromatography (SiO_2) eluting with a 1:1 mixture cyclohexane-EtOAc to give pure **25b** as a yellow oil: 0.205 g (81%).



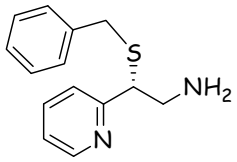
(*R*)-2-azido-2-(2-pyridyl)ethanamine: Red oil; IR (neat): *ν* = 3365, 2962, 2923, 2102, 1590, 1571, 1472, 1436, 1260, 1094, 1020, 798. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.60 (d, *J* = 4.7, 1 H), 7.72 (dt, *J* = 1.6, *J* = 7.9, 1 H), 7.35 (d, *J* = 7.9, 1 H), 7.24 (ddd, *J* = 1.6, *J* = 4.7, *J* = 7.9, 1 H), 4.55 (dd, *J* = 5.5, *J* = 13.3, 1 H), 3.18 (dd, *J* = 5.5, *J* = 13.3, 1 H), 3.06 (dd, *J* = 7.1, *J* = 13.3, 1 H), 1.76 (bs, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.4, 149.6, 136.9, 123.0, 121.7, 69.0, 46.3. MS (ES) *m/z* 164.3 $(M + H)^+$.



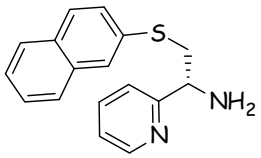
(*R*)-2-(2-Naphthylthio)-2-(2-pyridyl)ethanamine: Yellowish oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.56 (ddd, J = 0.9, J = 1.8, J = 4.9, 1 H), 7.79 (m, 2 H), 7.71 (m, 2 H), 7.61 (td, J = 1.9, J = 7.8, 1 H), 7.44 (m, 4 H), 7.32 (dt, J = 0.9, J = 7.7, 1 H), 7.14 (ddd, J = 1.1, J = 4.8, J = 7.8, 1 H), 4.49 (dd, J = 6.1, J = 7.2, 1 H), 3.39 (dd, J = 7.2, J = 13.5, 1 H), 3.27 (dd, J = 6.1, J = 13.5, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.5, 149.4, 136.5, 134.1, 130.5, 128.8, 127.5, 127.3, 126.9, 126.6, 126.3, 126.0, 125.5, 122.9, 122.2, 57.7, 46.0. *GC*-MS (EI) *m/z* 262 (100), 230 (49), 263 (44), 115 (42), 78 (31), 51 (14), 217 (11), 160 (8).



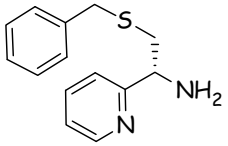
(*R*)-2-(2-Phenylthio)-2-(2-pyridyl)ethanamine: Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.56 (ddd, J = 1.0, J = 1.8, J = 4.8, 1 H), 7.61 (dt, J = 1.8, J = 7.7, 1 H), 7.33 (m, 2 H), 7.29 (m, 2 H), 7.19 (m, 2 H), 7.16 (m, 1 H), 4.33 (dd, J = 6.1, J = 7.2, 1 H), 3.31 (dd, J = 7.2, J = 13.4, 1 H), 3.19 (dd, J = 6.1, J = 13.4, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.8, 159.6, 149.4, 136.5, 134.1, 131.9, 128.8, 128.6, 124.6, 122.9, 122.2, 57.8, 46.0. *GC*-MS (EI) *m/z* 168 (100), 201 (99), 124 (20), 65 (17), 78 (16), 94 (15), 212 (9), 109 (9), 186 (4).



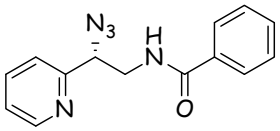
(*R*)-2-(Benzylthio)-2-(2-pyridyl)ethanamine: Yellow oil; ^{13}H NMR (300 MHz, $CDCl_3$): δ = 8.60 (d, J = 4.4, 1 H), 7.68 (dt, J = 1.8, J = 7.6, 1 H), 7.30 (m, 7 H), 3.90 (dd, J = 6.3, J = 7.0, 1 H), 3.72 (d, J = 13.2, 1 H), 3.64 (d, J = 13.2, 1 H), 3.25 (dd, J = 7.0, J = 13.4, 1 H), 3.16 (dd, J = 6.3, J = 13.4, 1 H), 1.94 (bs, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.4, 149.3, 136.7, 130.3, 128.9, 128.5, 127.0, 122.9, 122.1, 54.0, 45.8, 35.3. *GC*-MS *m/z* 124 (100), 91 (28), 215 (16), 122 (14), 105 (11), 106 (10), 65 (10), 79 (9), 227 (2).



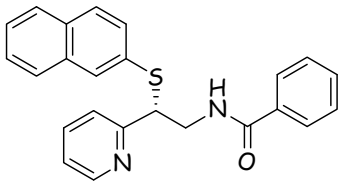
(*R*)-2-(2-Naphthylthio)-1-(2-pyridyl)ethanamine: Yellowish oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.59 (m, 1 H), 7.80 (m, 2 H), 7.76 (dt, J = 1.8, J = 7.7, 1 H), 7.49 (m, 3 H), 7.33 (m, 2 H), 7.18 (ddd, J = 0.7, J = 4.8, J = 7.7, 1 H), 4.23 (dd, J = 5.4, J = 8.2, 1 H), 3.57 (dd, J = 5.4, J = 13.4, 1 H), 3.32 (dd, J = 8.2, J = 13.3, 1 H), 2.44 (bs, 2 H). ^{13}*C* NMR (75 MHz, $CDCl_3$): δ = 162.5, 149.7, 136.9, 133.9, 129.2, 128.8, 127.9, 127.8, 127.7, 127.4, 126.8, 126.7, 126.1, 122.8, 121.9, 56.2, 42.7.



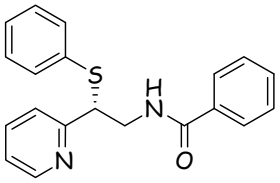
(*R*)-2-Benzylthio-1-(2-pyridyl)ethanamine: Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.57 (m, 1 H), 7.67 (m, 1 H), 7.31 (m, 6 H), 7.21 (m, 1 H), 4.56 (dd, J = 6.8, J = 7.8, 1 H), 3.67 (s, 2 H), 3.12 (dd, J = 6.8, J = 12.9, 1 H), 2.75 (dd, J = 6.8, J = 12.9, 1 H), 2.14 (bs, 2 H). ^{13}*C* NMR (75 MHz, $CDCl_3$): δ = 162.4, 149.4, 136.5, 135.7, 129.7, 129.4, 129.0, 126.2, 122.4, 121.6, 55.9, 42.7. *GC*-MS (EI) *m/z* 107 (100), 80 (20), 213 (4), 136 (4), 230 (2), 183 (2).



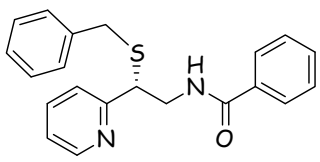
(*R*)-*N*-[2-Azido-2-(2-pyridyl)ethyl]benzamide (25b): Red oil; $[\alpha]_D^{20}$ +55.5 (*c* 1.1, $CHCl_3$). IR (neat): ν = 3288, 3068, 2937, 2104, 1638, 1540, 1321, 772, 707. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.64 (dt, J = 0.7, J = 4.8, 1 H), 8.11 (d, J = 6.9, 1 H), 7.77 (m, 2 H), 7.48 (m, 1 H), 7.42 (m, 3 H), 7.31 (ddt, J = 0.8, J = 4.9, J = 7.6, 1 H), 7.16 (m, 1 H), 4.90 (t, J = 6.1, 1 H), 4.07 (ddd, J = 6.1, J = 6.9, J = 12.4, 1 H), 3.87 (ddd, J = 6.1, J = 6.9, J = 12.4, 1 H). ^{13}*C* NMR (75 MHz, $CDCl_3$): δ = 167.7, 149.4, 137.5, 134.1, 133.2, 131.6, 129.9, 128.5, 128.3, 126.9, 123.6, 122.6, 64.1, 43.3. *GC*-MS (280 °C) *m/z* 105 (100), 218 (67), 77 (61), 262 (56), 263 (29), 115 (26), 219 (24), 230 (23), 384 (13), 160 (12). MS (ES) *m/z* 268.2 $(M + H)^+$, 290.1 $(M + Na)^+$, 557.2 $(2\ M + Na)^+$. Anal. Calcd for $C_{14}H_{13}N_5O$: *C*, 62.91; H, 4.90; N, 26.20. Found *C*, 63.10; H, 4.92; N, 26.12.



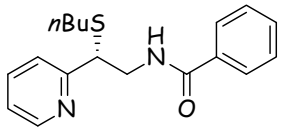
(*R*)-*N*-[2-(2-Naphthylthio)-2-(2-pyridyl)ethyl]benzamide (25f): White crystals. (from Et_2O); m.p. = 122.0-122.5 °C; $[\alpha]_D^{20}$ +58.7 (*c* 1.9, $CHCl_3$). IR (KBr): *v* = 3326, 3046, 3003, 2926, 1843, 1710, 1638, 1578, 1523, 1436, 1271, 822, 745, 701. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.56 (ddd, *J* = 0.7, *J* = 1.6, *J* = 4.9, 1 H), 7.93 (s, 1 H), 7.73 (m, 5 H), 7.58 (dt, *J* = 1.9, *J* = 7.8, 1 H), 7.45 (m, 5 H), 7.32 (m, 3 H), 7.16 (ddd, *J* = 0.7, *J* = 4.9, *J* = 7.8, 1 H), 4.85 (t, *J* = 6.6, 1 H), 4.21 (ddd, *J* = 6.1, *J* = 6.6, *J* = 13.5, 1 H), 4.15 (ddd, *J* = 6.1, *J* = 6.6, *J* = 13.5, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.4, 158.9, 149.0, 136.9, 133.5, 132.2, 131.2, 131.0, 129.2, 128.5, 128.3, 127.5, 127.4, 126.8, 126.4, 126.2, 123.6, 122.5, 52.3, 43.2. GC-MS (EI) (280 °C) *m/z* 384 (4), 263 (30), 230 (29), 211 (18), 160 (8), 136 (16), 115 (13), 105 (100), 77 (38). MS (ES) *m/z* = 385.1 $(M + H)^+$, 791.0 $(2 M + Na)^+$. Anal. Calcd for $C_{24}H_{20}N_2OS$: C, 74.97; H, 5.24; N, 7.29. Found C, 75.05; H, 5.26; N, 7.28.



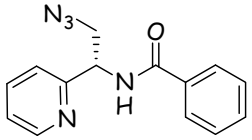
(*R*)-*N*-[2-Phenylthio-2-(2-pyridyl)ethyl]benzamide (25g): Red oil; $[\alpha]_D^{20}$ +51.8 (*c* 2.0, $CHCl_3$). IR (neat): *v* = 3323, 3058, 2925, 2853, 1644, 1579, 1537, 1484, 1436, 1292, 1075, 749, 692. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.61 (d, *J* = 4.6, 1 H), 7.74 (m, 2 H), 7.68 (td, *J* = 1.7, *J* = 7.7, 1 H), 7.49 (m, 2 H), 7.44 (m, 3 H), 7.32 (m, 2 H), 7.24 (m, 2 H), 4.72 (dd, *J* = 6.1, *J* = 6.9, 1 H), 4.16 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.4, 159.0, 149.1, 137.0, 134.4, 133.5, 132.5, 131.4, 129.0, 128.5, 127.7, 126.9, 123.8, 122.4, 52.5, 43.0. GC-MS (EI) *m/z* 105 (100), 77 (73), 168 (61), 213 (38), 201 (49), 334 (20), 180 (16), 225 (14), 119 (8). Anal. Calcd for $C_{20}H_{18}N_2OS$: C, 71.83; H, 5.42; N, 8.38. Found C, 71.58; H, 5.43; N, 8.35.



(*R*)-*N*-[2-Benzylthio-2-(2-pyridyl)ethyl]benzamide (25h): Colourless oil; $[\alpha]_D^{20}$ +26.1 (*c* 1.0, $CHCl_3$). IR (neat): ν = 3320, 3060, 2923, 1644, 1537, 1471, 1434, 1290, 697. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.59 (ddd, J = 1.0, J = 1.9, J = 4.9, 1 H), 7.76 (m, 2 H), 7.69 (dt, J = 1.9, J = 7.8, 1 H), 7.47 (m, 5 H), 7.32 (m, 4 H), 7.25 (m, 1 H), 4.23 (dd, J = 6.7, J = 9.7, 1 H), 4.17 (ddd, J = 4.6, J = 6.7, J = 13.1, 1 H), 3.97 (ddd, J = 4.6, J = 9.7, J = 13.1, 1 H), 3.89 (d, J = 13.5, 1 H), 3.75 (d, J = 13.5, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.4, 159.7, 148.6, 137.9, 137.3, 134.5, 131.4, 129.0, 128.6, 128.5, 127.1, 127.0, 123.8, 122.5, 48.7, 42.4, 35.7. GC-MS (EI) *m/z* 105 (100), 124 (76), 226 (74), 77 (49), 91 (45), 257 (41). Anal. Calcd for $C_{21}H_{20}N_2OS$: C, 72.38; H, 5.79; N, 8.04. Found C, 72.40; H, 5.80; N, 8.02.

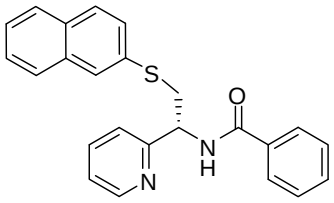


(*R*)-*N*-[(2-Butylthio-2-(2-pyridyl)ethyl]benzamide (25i): Yellow oil; $[\alpha]_D^{20}$ +27.4 (*c* 1.0, $CHCl_3$); 3314, 3057, 2913, 1647, 1534, 1477, 1297, 694. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.58 (ddd, J = 0.9, J = 1.7, J = 4.9, 1 H), 7.74 (m, 2 H), 7.71 (dt, J = 1.7, J = 7.4, 1 H), 7.47 (m, 1 H), 7.42 (m, 2 H), 7.23 (ddd, J = 0.9, J = 4.7, J = 7.5, 1 H), 4.29 (dd, J = 5.8, J = 7.4, 1 H), 4.11 (ddd, J = 6.2, J = 7.4, J = 13.6, 1 H), 4.01 (ddd, J = 5.8, J = 11.2, J = 13.6, 1 H), 2.57 (m, 2 H), 1,54 (m, 2 H), 1,38 (m, 2 H), 0.87 (t, J = 7.3, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.4, 160.0, 148.7, 137.4, 134.4, 133.3, 131.4, 130.1, 128.5, 128.4, 126.9, 123.7, 122.5, 49.2, 42.8, 31.6, 30.9, 21.9, 13.6. MS (EI) *m/z* 314 (4), 257 (16), 181 (11), 160 (18), 124 (57), 105 (100), 93 (14), 77 (55). MS (ES) *m/z* = 315.2 $(M + H)^+$, 651.3 $(2 M + Na)^+$. Anal. Calcd for $C_{18}H_{22}N_2OS$: C, 68.75; H, 7.05; N, 8.91. Found C, 68.38; H, 7.08; N, 8.89.

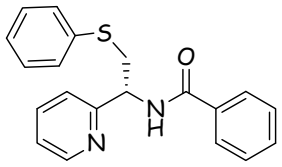


***N*-((*S*)-2-azido-1-(pyridin-2-yl)ethyl)benzamide (26b)**: Yellow oil; $[\alpha]_D^{20}$ +13.4 (*c* 1.2, $CHCl_3$); IR (neat): ν = 3282, 3071, 2932, 2108, 1631, 1547, 1315, 778. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.63 (ddd, J = 0.8, J = 1.6, J = 4.8, 1 H), 7.88 (m, 2 H), 7.75 (dd, J = 1.9, J = 7.7, 1 H), 7.45 (m, 3 H), 7.38 (dt, J = 0.8, J = 1.6, 1 H), 7.30 (ddd, J = 1.9, J = 4.8, J = 7.4, 1 H), 5.46 (ddd, J = 4.9, J = 5.7, J = 7.3, 1 H), 3.85 (dd, J = 4.9, J = 12.2, 1 H), 3.80 (dd, J = 5.7, J = 12.2, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.0, 156.4, 149.3, 13.1, 134.0, 131.8, 128.6, 127.1,

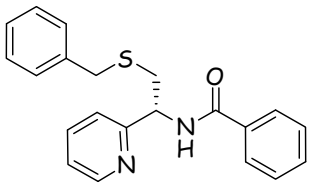
127.0, 123.2, 122.6, 55.0, 53.5. MS (ES) *m/z* = 268.2 $(M + H)^+$. Anal. Calcd for $C_{14}H_{13}N_5O$: C, 62.91; H, 4.90; N, 26.20. Found C, 63.21; H, 4.92; N, 26.18.



(*R*)-*N*-[2-Naphthylthio)-1-(2-pyridyl)ethyl]benzamide (26f): White crystals (from Et_2O); m.p. = 119.5-120 °C. $[\alpha]_D^{20}$ –22.7 (*c* 1.3, $CHCl_3$). IR (Nujol): *v* = 3310, 1638, 1518, 1468, 1370, 810, 729. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.58 (ddd, *J* = 0.8, *J* = 1.6, *J* = 4.8, 1 H), 8.12 (d, *J* = 7.0, 1 H); 7.81 (m, 2 H), 7.75 (m, 3 H), 7.63 (m, 2 H), 7.47 (m, 3 H), 7.38 (m, 2 H), 7.20 (m, 2 H), 5.56 (dd, *J* = 5.2, *J* = 6.8, 1 H), 3.82 (dd, *J* = 5.2, *J* = 13.6, 1 H), 3.51 (dd, *J* = 7.8, *J* = 13.6, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.8, 157.6, 149.0, 136.9, 133.7, 133.5, 131.5, 130.1, 128.5, 128.4, 127.6, 127.2, 127.1, 126.5, 125.7, 123.4, 123.6, 123.1, 53.9, 38.5. MS (ES) *m/z* 385.1 $(M + H)^+$, 791.0 $(2 M + Na)^+$. Anal. Calcd for $C_{24}H_{20}N_2OS$: C, 74.97; H, 5.24; N, 7.29. Found C, 75.10; H, 5.26; N, 7.27.



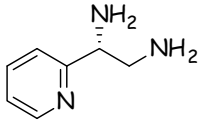
(*R*)-*N*-[2-Phenylthio-1-(pyridyl)ethyl]benzamide (26g): Red oil; $[\alpha]_D^{20}$ –19.2 (*c* 0.4, $CHCl_3$). IR (neat): *v* = 3321, 3054, 2927, 2852, 1642, 1572, 1533, 1482, 1431, 1290, 1078, 747, 691. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.58 (ddd, *J* = 0.9, *J* = 1.7, *J* = 4.9, 1 H), 7.82 (m, 2 H), 7.68 (dt, *J* = 1.8, *J* = 7.8, 1 H), 7.49 (m, 3 H), 7.42 (m, 3 H), 7.33 (dt, *J* = 0.9, *J* = 7.8, 1 H), 7.27 (m, 2 H), 7.15 (dt, *J* = 1.2, *J* = 6.5, 1 H), 5.48 (dd, *J* = 5.1, *J* = 7.2, *J* = 8.0, 1 H), 3.72 (dd, *J* = 5.1, *J* = 13.6, 1 H), 3.44 (dd, *J* = 8.0, *J* = 13.6, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.7, 157.5, 137.1, 134.1, 131.6, 129.2, 129.0, 128.5, 127.1, 126.1, 123.6, 123.1, 53.6, 38.7. GC-MS (EI) *m/z* 105 (100), 77 (69), 213 (68), 136 (47), 211 (31), 212 (26), 180 (11), 281 (5), 334 (4). Anal. Calcd for $C_{20}18_3N_2OS$: C, 71.83; H, 5.42; N, 8.38. Found C, 71.98; H, 5.41; N, 8.36.



(*R*)-*N*-[2-(Benzylthio)-1-(2-pyridyl)ethyl]benzamide (26h): Colourless oil; $[\alpha]_D^{20}$ –17.1 (*c* 0.5, $CHCl_3$). IR (neat): ν = 3320, 3060, 2923, 1645, 1589, 1536, 1434, 1290, 696. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.60 (ddd, *J* = 0.8, *J* = 1.7, *J* = 4.9, 1 H), 7.89 (m, 2 H), 7.48 (m, 2H), 7.39 (m, 2 H), 7.29 (m, 7 H), 5.46 (dd, *J* = 5.9, *J* = 7.5, 1 H), 3.65 (s, 2 H), 3.14 (dd, *J* = 5.7, *J* = 13.5, 1 H) 3.04 (ddd, *J* = 7.5, *J* = 13.6, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.5, 158.9, 147.8, 137.7, 137.2, 134.7, 131.7, 129.0, 128.6, 127.3, 127.2, 123.6, 122.4, 53.1, 36.7, 29.7. GC-MS (EI) *m/z* 105 (100), 257 (52), 77 (36), 91 (20), 136 (18), 211 (10), 258 (8). Anal. Calcd for $C_{21}H_{20}N_2OS$: C, 72.38; H, 5.79; N, 8.04. Found C, 72.11; H, 5.80; N, 8.03.

*3.3.3 - Preparation of the diamine **27***

To the valinol derivative **25b** (0,202 g, 0.81 mmol) dissolved in MeOH (5 mL) were added 40% $MeNH_2$ in water (1.0 mL), then a solution of H_5IO_6 (0.648 g) in H_2O (5 mL) was added dropwise. After stirring for 2 h at room temperature, the reaction was complete, as determined by T.L.C. analysis. Most of the solvent was evaporated at reduced pressure, then the organic materials were extracted with Et_2O (3 × 20 mL). The collected ethereal layers were dried over Na_2SO_4 and concentrated to leave the primary amine as a yellow oil. This was dissolved in THF (5 mL) and was cooled to 0 °C and PPh_3 (0.177 mg, 0.67 mmol) was added. Then 2h the solution was warm at room temperature ad water (2 mL) was added. After 16h $NaHCO_2$ (sat. solution, 5mL) was added and the organic materials were extracted with CH_2Cl_2 (3 x 20 mL) the collected organic layers were dried over Na_2SO_4 and concentrated to leave a red solid. Pure **27** (0.074 g, 67%) was obtained by column chromatography on a short neutral Al_2O_3 column eluting with EtOAc/MeOH (9/1) mixture.



(*R*)-1-(2-Pyridyl)ethane-1,2-diamine (27): Yellow oil; $[\alpha]_D^{20}$ –45.6 (*c* 0.7, $CHCl_3$). IR (neat): ν = 3361, 2968, 2922, 2101, 1476, 1435, 1092, 1016, 794. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.54

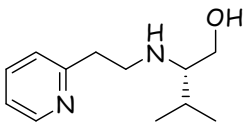
(ddd, *J* = 0.7, *J* = 1.7, *J* = 7.9, 1 H), 7.69 (dt, *J* = 1.7, *J* = 7.8, 1 H), 7.32 (d, *J* = 7.9, 1 H), 7.21 (ddd, *J* = 0.9, *J* = 4.7, *J* = 7.9, 1 H), 3.99 (dd, *J* = 5.2, *J* = 7.0, 1 H), 3.08 (dd, *J* = 5.2, *J* = 12.7, 1 H), 2.93 (dd, *J* = 7.0, *J* = 12.7, 1 H), 1.83 (bs, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.7, 149.2, 137.0, 122.8, 121.7, 59.6, 54.8. MS (ES) *m/z* 138.2 $(M + H)^+$. Anal. Calcd for $C_7H_{11}N_3$: C, 61.29; H, 8.08; N, 30.63. Found C, 60.99; H, 8.11; N, 30.50.

3.3.4 - Reaction with H_2-$Pd(OH)_2/C$

The mixture of the aziridine **22** (50 mg, 0.24 mmol) and 20% $Pd(OH)_2/C$ (5 mg) in MeOH-AcOH (85:15, 3 mL) was magnetically stirred under a H_2 atmosphere for 3 h. The mixture was filtered through a pad of celite. 1 N NaOH was added until pH 11 was reached, then most of the MeOH was evaporated at reduced pressure and the organic phase was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers was dried (Na_2SO_4) and concentrated to leave pure 33 as an oil: 0.45 g (91%).

3.3.5 - Reaction with HI

The aziridine **6** (0.100 g, 0.48 mmol) was dissolved in 47% HI (5 mL) and the solution was stirred for 12 h, then NaOH pellets were cautiously added until pH 11 was reached. The organic phase was extracted with Et_2O (3 x 5 mL) and the combined ethereal layers were washed with aq $Na_2S_2O_3$, then dried (Na_2SO_4) and concentrated to leave a residue consisting of a white solid and a yellow oil. Chromatography on a small SiO_2 column eluting with cyclohexane-EtOAc (1:9), then with EtOAc-MeOH-Et_3N (8:1:1) gave the compound **33**: 62 mg (62%).

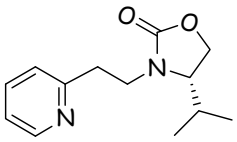


N-[2-(2-Pyridyl)]ethyl-(*S*)-valinol (28). This was obtained from the aziridine **22** by hydrogenation over $Pd(OH)_2/C$ (91% yield) and by reduction with HI (62% yield): $[\alpha]_D^{20}$ +16.8 (*c* 2.0, $CHCl_3$); IR (neat): *v* = 3334, 2962, 2925, 2872, 1651, 1589, 1467, 1427, 1384, 1274, 1070, 813, 716; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.49 (ddd, *J* = 1.0 Hz, *J* = 1.8 Hz, *J* = 4.9 Hz, 1 H), 7.59 (ddt, *J* = 1.3 Hz, *J* = 1.8 Hz, *J* = 7.7 Hz, 1 H), 7.59 (dd, *J* = 0.9 Hz, *J* = 7.8 Hz, 1 H), 7.11 (ddd, *J* = 1.3 Hz, *J* = 4.9 Hz, *J* = 7.7 Hz, 1 H), 3.63 (dd, *J* = 4.1 Hz, *J* = 10.9 Hz, 1 H), 3.34 (dd, *J* = 7.5 Hz, *J* = 10.9 Hz, 1 H), 2.90 (bs, 2 H, OH + NH), 3.15-2.92 (m, 4 H), 2.40 (dd, *J* =

4.1 Hz, *J* = 10.9 Hz, 1 H), 1.76 (sept, *J* = 6.7 Hz, 1 H), 0.90 (d, *J* = 6.7 Hz, 3 H), 0.85 (d, *J* = 6.7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.1 (Py), 149.0, 136.5, 123.4, 121.3, 64.6, 60.8, 46.5, 38.0, 29.1, 19.4, 18.5; MS (EI): *m/z* = 204 (6), 191 (8), 177 (46), 165 (21), 135 (11), 121 (10), 106 (55), 94 (100), 84 (20), 78 (15). Anal. Calcd for $C_{12}H_{20}N_2O$: C, 69.19; H, 9.68; N, 13.45. Found C, 69.41; H, 9.83; N, 13.42.

*3.3.6 – Preparation of compound **30***

To a solution of **28** (50 mg, 0.24 mmol) in dry CH_2Cl_2 (10 mL) was added CDI (40 mg, 0.24 mmol) in one portion. After stirring overnight, H_2O (5 mL) was added. The organic phase was extracted with CH_2Cl_2 (3 x 10 mL), and the combined organic phases was dried (Na_2SO_4) and concentrated at reduced pressure. The red oily residue was subjected to chromatography on a SiO_2 column, eluting with EtOAc then with a 90:10 EtOAc/MeOH mixture to give **30** as a red oil: 0.047 g (84%).

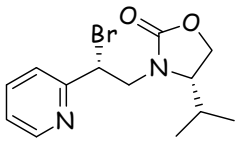


(*S*)-3-[2-(2-Pyridyl)ethyl]-1,3-oxazolidin-2-one (30): $[\alpha]_D^{20}$ +29.0 (*c* 1.9, $CHCl_3$); IR (neat): *v* = 2961, 2929, 2869, 1733, 1593, 1566, 1427, 1259, 1009, 759; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.52 (d, *J* = 4.9 Hz, 1 H, PyH), 7.62 (td, *J* = 1.8 Hz, *J* = 7.7 Hz, 1 H), 7.23 (d, *J* = 7.8 Hz, 1 H), 7.15 (dd, *J* = 4.9 Hz, *J* = 7.8 Hz, 1 H), 4.11 (dd, *J* = 8.8 Hz, *J* = 8.9 Hz, 1 H), 4.01 (dd, *J* = 5.4 Hz, *J* = 8.9 Hz, 1 H), 3.87 (ddd, *J* = 6.9 Hz, *J* = 7.1 Hz, *J* = 14.4 Hz, 1 H), 3.61 (ddd, *J* = 3.6 Hz, *J* = 5.4 Hz, *J* = 8.8 Hz, 1 H), 3.42 (ddd, *J* = 6.2 Hz, *J* = 7.9 Hz, *J* = 14.4 Hz, 1 H), 3.07 (m, 2 H), 2.87 (dsept, *J* = 3.5 Hz, *J* = 6.8 Hz, 1 H), 0.83 (d, *J* = 7.0 Hz, 3 H), 0.84 (d, *J* = 7.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.5, 157.5, 149.3, 136.6, 136.6, 123.5, 121.7, 62.7, 59.3, 41.5, 35.9, 27.4, 17.6, 14.1; MS (ES): *m/z* = 235.2 $(M + H)^+$, 491.1 $(2 M + Na)^+$. Anal. Calcd for $C_{13}H_{18}N_2O_2$: C, 66.64; H, 7.74; N, 11.96. Found C, 66.72; H, 7.77; N, 11.92.

*3.3.7 – Preparation of compound **32***

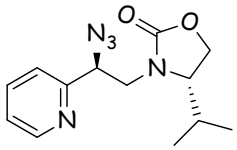
To the aziridine **22** (0.100 g, 0.48 mmol) dissolved in anhydrous MeCN (10 mL) were added, in order, CDI (0.080 g, 0.48 mmol) and allyl bromide (0.21 mL, 2.4 mmol). The mixture was stirred at room temperature for 2 h, then quenched with H_2O (10 mL). The organic phase

was extracted with Et_2O (2 x 10 mL) and CH_2Cl_2 (2 x 10 mL). The combined organic phases was washed with saturated aq $NaHCO_3$, then combined, dried (Na_2SO_4) and concentrated at reduced pressure. The oily residue was subjected to chromatography on a SiO_2 column eluting with cyclohexane-EtOAc (1:1) to give **32** as a whitish solid: 0.108 g (72%).



3-[2(*R*)-Bromo-2-(2-pyridyl)ethyl]-4(*S*)-isopropyl-1,3-oxazolidin-2-one (32): m.p. = 107-108 °C; $[\alpha]_D^{20}$ +41.5 (*c* 1.2, $CHCl_3$); IR (KBr): ν = 3050, 3013, 2953, 2874, 1728, 1588, 1487, 1436, 1258, 1159, 1050, 932, 788, 751, 706, 597; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.57 (ddd, *J* = 0.9 Hz, *J* = 1.7 Hz, *J* = 4.8 Hz, 1 H), 7.59 (dt, *J* = 1.8 Hz, *J* = 7.7 Hz, 1 H), 7.38 (td, *J* = 0.9 Hz, *J* = 7.8 Hz, 1 H), 7.22 (ddd, *J* = 1.0 Hz, *J* = 4.8 Hz, *J* = 7.7 Hz, 1 H), 5.21 (dd, *J* = 6.3 Hz, *J* = 9.0 Hz, 1 H), 4.12 (dd, *J* = 6.3 Hz, *J* = 14.2 Hz, 1 H), 3.89 (m, 3 H), 3.08 (ddd, *J* = 1.0 Hz, *J* = 6.1 Hz, *J* = 7.6 Hz, 1 H), 2.09 (dsept, *J* = 3.6 Hz, *J* = 6.9 Hz, 1 H), 0.76 (d, *J* = 6.9 Hz, 3 H), 0.72 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.1, 157.2, 149.5, 137.1, 123.6, 123.5, 62.8, 59.1, 48.0, 46.4, 27.1, 17.3, 14.0; MS (ES); *m/z* = 313.2 $(M + H)^+$, 336.9 $(M + H + Na)^+$. Anal. Calcd for $C_{13}H_{17}BrN_2O_2$: C, 49.85; H, 5.47; Br, 25.51; N, 8.94. Found C, 49.98; H, 5.41; Br, 25.43; N, 8.90.

*3.3.8 – Preparation of compound **33***



The bromide **32** (40 mg, 0.13 mmol) was dissolved in dry DMF (5 mL) and sodium azide (48 mg, 0.73 mmol) was added. The mixture was heated at the reflux temperature for 8 h, then brine (5 mL) and EtOAc (10 mL) were added. The organic phase was extracted with EtOAc (3 x 10 mL), and the combined organic phases was concentrated at reduce pressure. The yellowish residue was subjected to chromatography on a SiO_2 column eluting with cyclohexane, then with a 80:20 cyclohexane/EtOAc mixture to give the azide **38** as a yellowish oil: 28 mg (78%).

3-[2(*S*)-Azido-2-(2-pyridyl)ethyl]-4(*S*)-isopropyl-1,3-oxazolidin-2-one (33): $[\alpha]_D^{20}$ +12.8 (*c* 1.1, $CHCl_3$); IR (neat) ν = 2964, 2935, 2874, 2102, 1738, 1597, 1560, 1425, 1268, 1001, 757;

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.62 (ddd, J = 0.8 Hz, J = 1.6 Hz, J = 4.6 Hz, 1 H), 7.74 (dt, J = 1.8 Hz, J = 7.7 Hz, 1 H), 7.39 (d, J = 7.8 Hz, 1 H), 7.28 (ddd, J = 0.8 Hz, J = 4.9 Hz, J = 7.7 Hz, 1 H), 4.95 (dd, J = 4.6 Hz, J = 9.1 Hz, 1 H), 4.27 (dd, J = 8.8 Hz, J = 8.9 Hz, 1 H), 4.09 (dd, J = 4.8 Hz, J = 8.8 Hz, 1 H), 3.97 (ddd, J = 3.5 Hz, J = 4.8 Hz, J = 8.8 Hz, 1 H), 3.85 (dd, J = 4.6 Hz, J = 14.6 Hz, 1 H), 3.45 (dd, J = 9.1 Hz, J = 14.5 Hz, 1 H), 2.16 (dsept, J = 3.5 Hz, J = 6.9 Hz, 1 H), 0.89 (d, J = 6.9 Hz, 3 H), 0.82 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.3, 155.7, 149.8 (PyH), 137.2, 123.6, 122.3, 64.4, 63.1, 60.4, 45.4, 27.4, 17.6, 14.1; MS (ES): m/z = 276.1 $(M + H)^+$, 298.2 $(M + Na)^+$. Anal. Calcd for $C_{14}H_{21}N_5O_2$: C, 57.71; H, 7.27; N, 24.04. Found C, 57.56 ; H, 7.29; N, 23.94.

3.5 - References

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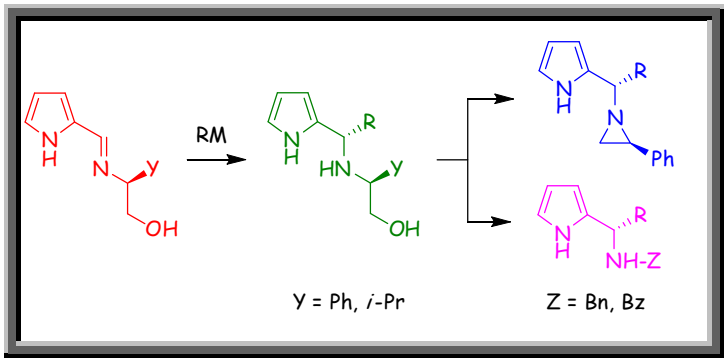
Chapter Index

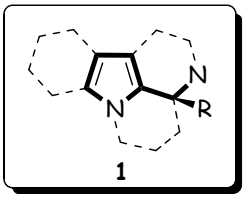
Chap. 4 – Asymmetric Synthesis of 1-(2-Pyrrolyl)alkylamines by Addition of Organometallic Reagents to Chiral 2-Pyrroleimines



4.1 – Introduction

4.1.1 – 1-(2-Pyrrolyl)alkylamino moiety

The chiral 1-(2-pyrrolyl)alkylamino moiety highlighted in structure **1** (Scheme 1), bearing a stereocenter at the benzylic carbon (one configuration is shown), is a common structural motif in non-cinchona indole alkaloids,[1] and terpene-indole alkaloids,[2] which display potent biological and physiological properties. Mytosene aziridines are also important compounds containing this skeleton fragment.[3] In Scheme 1 we report some examples of these molecules. The hydrochloride of Yohimbine (**1**) is a selective and competitive α_2-adrenergic receptor antagonist and it has been used to treat erectile dysfunction, Ajmaline (**2**) and Raumacline (**3**) are antiarhythmic agents. Eudistomine L (**4**) have strong antiviral and antitumour activity, Fumitremorgin C (**5**) is a potent and specific inhibitor of the breast cancer resistance protein (BCRP/ABCG2), Geissoschizine (**6**) is a vasorelaxant. The pyrrolo[1,2-b][1,2,5]benzothiadiazepine 5,5-dioxides (PBTDs) (**7**) as potent non-nucleoside inhibitors of the HIV-1 reverse transcriptase.[4] 7-aminoleucoaziridinomitosene **8**) and 1,4-aziridomitosene (**9**) have shown activity against various tumor model systems.[5]



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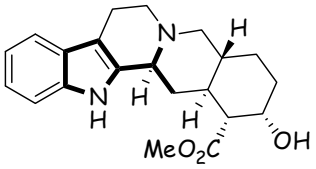
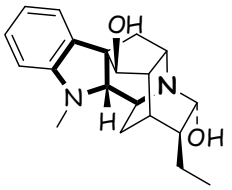
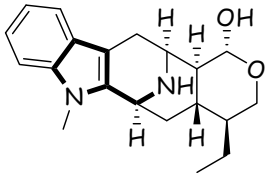


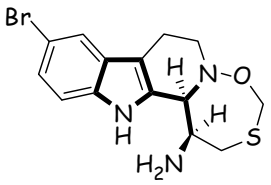
1,
Yohimbine



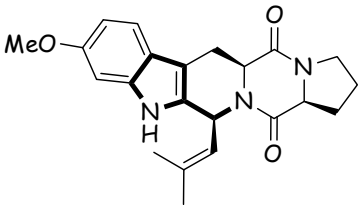
2,
Ajmaline



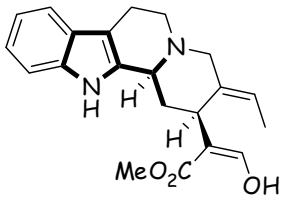
3,
Raumacline



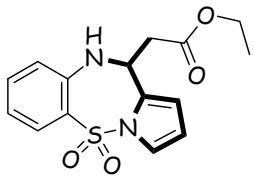
4,
Eudistomine L



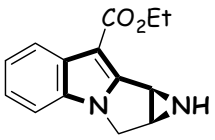
5,
Fumitremorgine C



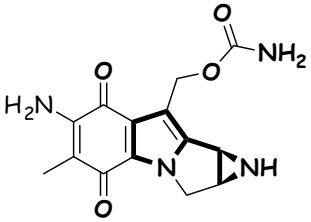
6,
Geissoschizine



7,
PBDTS



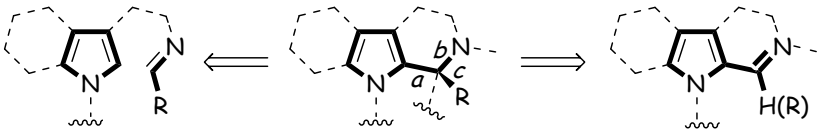
8,
7-aminoleucoaziridinomitosene



9,
1,4-aziridinomitosene

Scheme 1

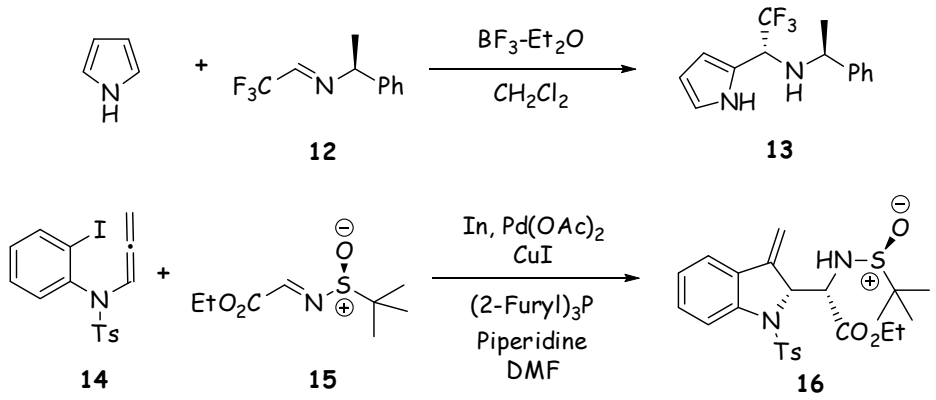
Given their enormous importance, synthetic methods have been developed for these compounds, but efficient asymmetric procedures for the construction of the heterobenzylic stereocenter are still lacking. In principle, this goal can be accomplished during the formation of any of the four bonds involved. Three of these possibilities, concerning the formation of bonds *a*, *b* and *c* are described in Scheme 2.



10 **1** **11**

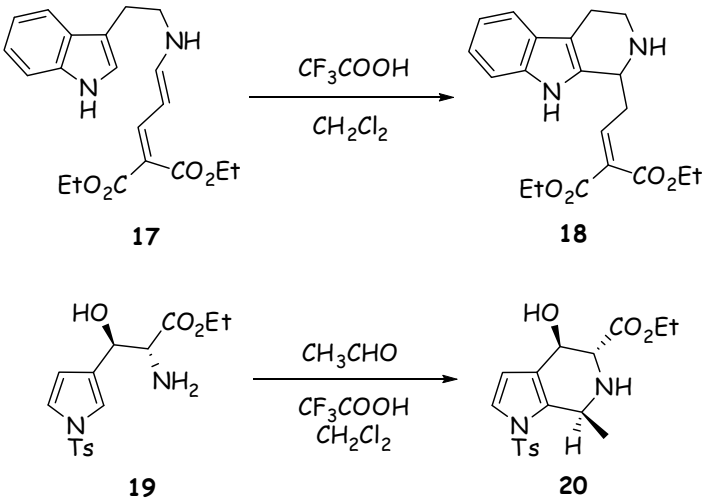
Scheme 2

For example, the *a* bond in compounds **1** can be formed by the inter- or intramolecular attack of the nucleophilic pyrrole C2 carbon at the electrophilic carbon of an azomethine compound, generally activated by a Lewis acid and an electron-withdrawing *N*-substituent, or an iminium ion, possibily formed in situ (three-component Mannich reaction).[6] For example, the BF_3-mediated addition of pyrrole to (*S*)-*N*-trifluoromethylidene-1-phenylethylamine **12** (Scheme 3) occurred with good yield but only moderate diastereoselectivity (d.r. 78:22) to give amine **13**, whereas indole reacted (at C3) with complete stereocontrol.[6d] On the other hand, an allylic 3-methylene-2,3-dihydro-2-indolylindium **16** species generated by a Pd-In bimetallic cascade process from 2-iodo-*N*-allenylaniline **14** added to enantiopure *N*-[(*R*)-*t*-butylsulfinyl] glyoxylate imine **15** with complete stereocontrol.[6f]



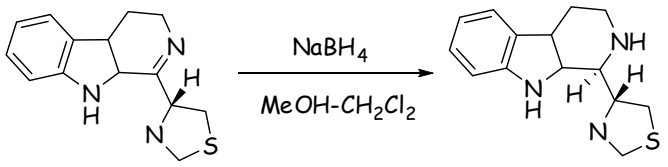
Scheme 3

The 1-2-(indolyl)alkylamino moiety has been commonly prepared by the intramolecular version of this approach, i.e. the Pictet-Spengler reaction, which has been a key step in the synthesis of a large number of alkaloids.[1s,t,7,8] In this reaction, an imine or iminium ion function, that is formed in situ by *N*-functionalization of tryptamine and its substituted derivatives by reaction with an aldehyde (e.g. **17**), undergoes intramolecular attack by the indole-C2 carbon (Scheme 4) to give tricyclic compound (**18**). Although the reaction often gives mixtures of diastereomers, a number of highly stereoselective reactions have been reported, relying on the asymmetric induction of the stereocenter(s) present in the tryptamine aliphatic chain, or in the aldehyde, or in the amine substituent (chiral auxiliary). To our knowledge, the Pictet-Spengler reaction has rarely been applied to a pyrrole derivative. One example is the reaction developed by Dodd[7s] between the chiral amine **19** and acetaldehyde to give the product **20**.



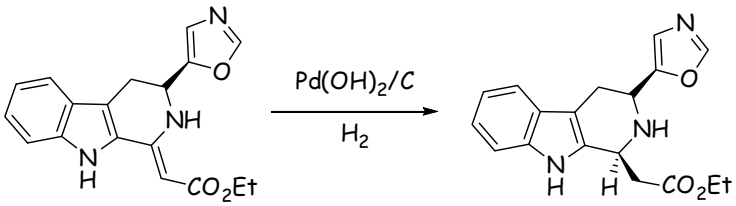
Scheme 4

Alternatively, the stereocenter in structure **1** can be constructed via formation of bond *b* (Scheme 2) from the azomethine compounds **11**.[7t,9] For example, quinolizidine alkaloids have often been prepared by a sequence of steps where a tetracyclic quaternary 2-indolyliminium ion (R-substituted *N*-charged cyclic structure **11**) was formed by the Bischler-Napieralski reaction between indole and lactam rings, then submitted to catalytic hydrogenation or hydride reduction (Scheme 5).



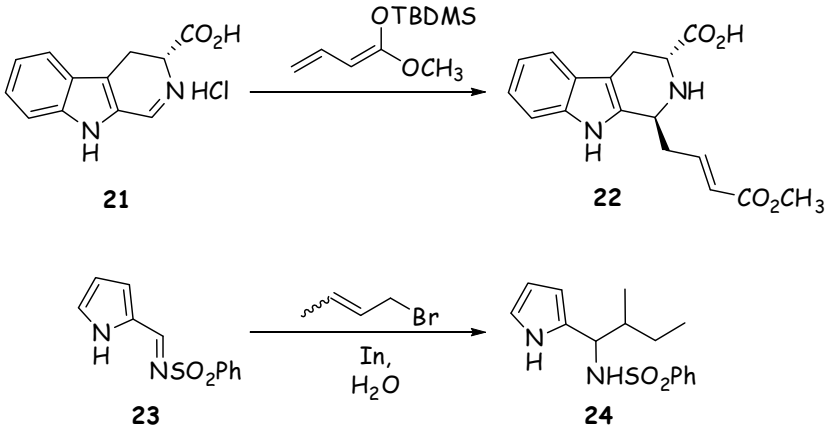
Scheme 5

More recently, novel polycyclic indolyldiamines have been prepared by completely diastereoselective reductions of chiral, optically pure 2-indolylenamines (Scheme 6).[9f]



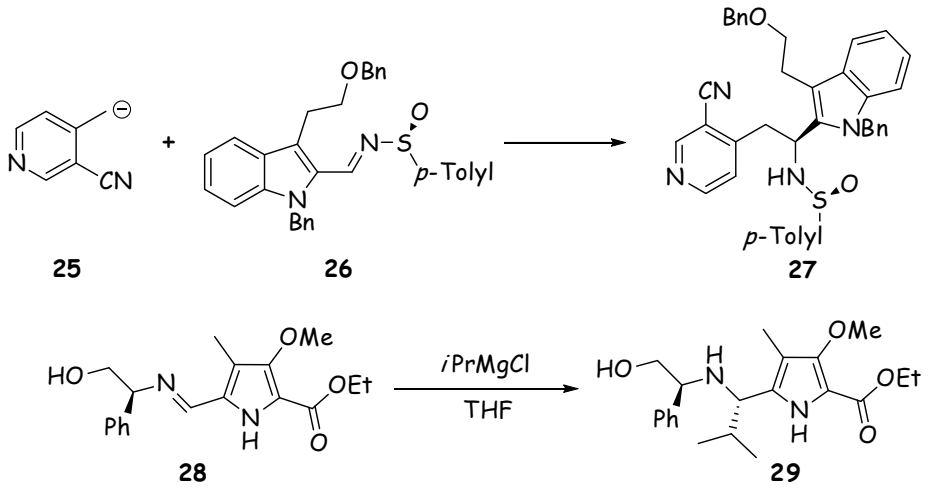
Scheme 6

The construction of bond *c* (Scheme 2) involves the addition of a carbon nucleophile or an organometallic reagent to a 2-pyrrolealdimine **11**. However, 2-pyrrole- and 2-indoleimines are less electrophilic than other aromatic imines, owing to the electron-donating effect of the pyrrole/indole ring. For example, 9-benzyl-3,4-dihydro-β-carboline was unreactive towards a laterally metalated pyridine, although a successful reaction was observed when the imine was preliminarily activated by addition of trimethylsilyl trifluoromethanesulfonate.[1d] Similarly, the Lewis acid promoted addition of a ketene silyl acetal to a β-carboline hydrochloride derived from L-tryptophan[1r] (**21**) and the addition of allyltrimethylsilane to iminium ions derived from D-tryptophan have been described (Scheme 7).[10] Benzylic and allylic organometallic reagents reacted smoothly with analogous imines bearing *N*-aryl or *N*-benzenesulfonyl substituents.[11]



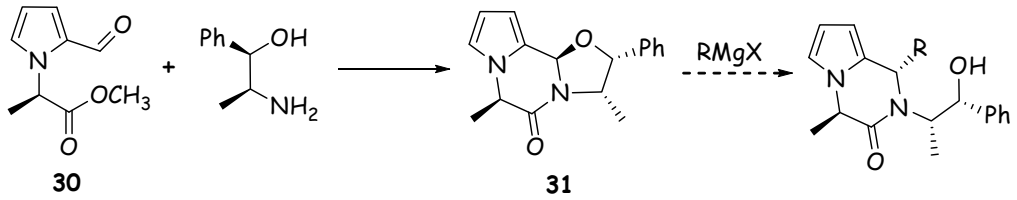
Scheme 7

Recently, the chiral auxiliary approach has been exploited for the asymmetric synthesis of 2-(1-aminoalkyl)indoles. The addition of laterally metallated 3-cyano-4-methylpyridine (**25**) to a 1,3-disubstituted-2-indoleimine derived from optically pure sulfinamides (**26**), gave the product **27** with a d.e. of 82% (Scheme 8).[12] Recently, a ring-substituted 2-pyrroleimine prepared from (*R*)-phenylglycinol (**28**) underwent highly diastereoselective addition of isopropylmagnesium chloride (4-5 equivalents) to give product **29**, whereas the addition of allylzinc bromide to an analogous imine prepared from (*R*)-phenyl glycineamide was unsatisfactory.[13]



Scheme 8

In the addition of an optically pure allylsilane to an acylhydrazone derived from 2-pyrrolealdehyde the yield and e.e. were found to be dependent on the pyrrole *N*-substitution: a lower yield (49%) but higher e.e. (92%) was obtained with the *N*-Boc-pyrrole imine, with respect to the unprotected imine (e.e. 48%).[14] Interestingly, tricyclic pyrrole-pyrazine-oxazole structures (**31**) were prepared from 2-formylpyrroles derived from (*S*)-α-amino esters and (+)- or (–)-norephedrine[15] (**30**). However, the potential of such compounds as precursors of chiral iminium ions, suitable substrates for the addition of Grignard reagents, eventually leading to 2-(1-aminoalkyl)pyrroles, has not been considered yet.



Scheme 9

Another widely exploited method for the asymmetric synthesis of polycyclic indole alkaloids by construction of the bond *c* (Scheme 2) is the Diels-Alder cycloaddition of β-carbolines and 2-indoleimine with 1,4-dienes.[16,17] Notably, a chiral 2-pyrroleimine failed to react with 1,3-butadiene.[18] For the sake of completeness, the C-N bond can also be formed by nucleophilic substitution of oxygen-substituted compounds. For example, dihydropyrrolizine esters gave the corresponding amines by reaction with ammonia and alkyl

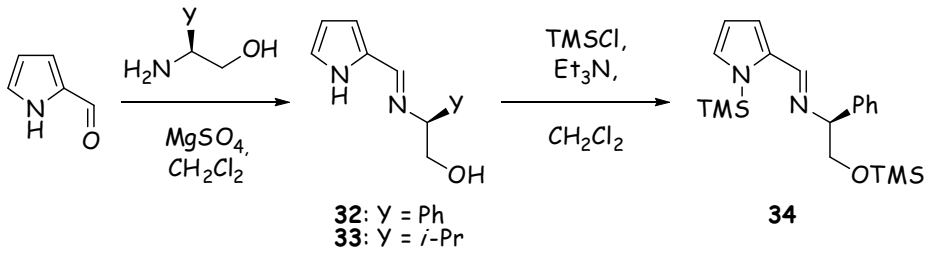
amines, but loss of the stereochemical integrity of the stereocenter was observed, pointing to an S_N1 mechanism for these reactions.[19]

Following this extensive literature search, we observed that the asymmetric synthesis of 1-(2-pyrrolyl)alkylamines was scarcely explored, as compared to the analogous indole derivatives. So, we were prompted to study the auxiliary-induced diastereoselective addition of organometallic reagents to 2-pyrroleimines, so filling a gap in our long term investigation on the asymmetric synthesis of benzylic and heterobenzylic amines from chiral imines.[20] It should also be observed that optimization of this route would open an avenue to optically pure compounds with the pyrrolidine, pyrrolizidine and indolizidine skeletons,[21] including alkaloids and pharmacologically interesting molecules, taking advantage of the possible hydrogenation of the pyrrole nucleus[22] and the nucleophilicity of the pyrrole/pyrrolidine nitrogen atom.

4.2 - Results and discussion

4.2.1 - Addition of organometallic reagents to chiral pyrrole imines derived from (S)-valinol and (S)-phenylglycinol

Optically pure phenylglycinol and valinol are among the most used chiral auxiliaries for the diastereoselective addition of organometallic reagents to imines.[23] In particular, we described that the addition of organolithium reagents to 2-pyridineimines derived from (*S*)-valinol and (*S*)-phenylglycinol occured effectively and with very highly diastereoselectivity following protection of the OH function as its trimethylsilyl ether.[20] Hence, we began our investigation on the *N,O*-disilylated imine **34**, which was prepared in two steps and almost quantitative yield from 2-pyrrolealdehyde and (*S*)-phenylglycinol through the intermediate unprotected imine **32**. (Scheme 10).

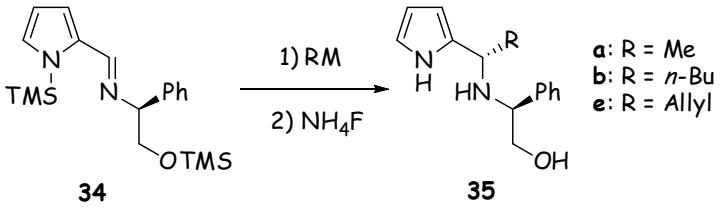


32: Y = Ph
33: Y = *i*-Pr

34

Scheme 10

The addition of organolithium reagents to the imine **32** was carried out in diethyl ether at −15 or 0 °C, as no reaction was observed at lower temperatures. By using 2-3 equivalents of organometallic reagents, good yields of the β-hydroxyamines **35** (Scheme 11) were obtained after protonolysis and desilylation of organometallic adducts with ammonium fluoride in the biphasic system THF/H_2O (Table 1). The (*S*,*S*)-configuration of the prevalent diastereomer in products **35** was assumed on the basis of the sense of asymmetric induction previously determined in organometallic reactions of analogous aromatic and heteroaromatic imines.[20]



34 **35**

Scheme 11

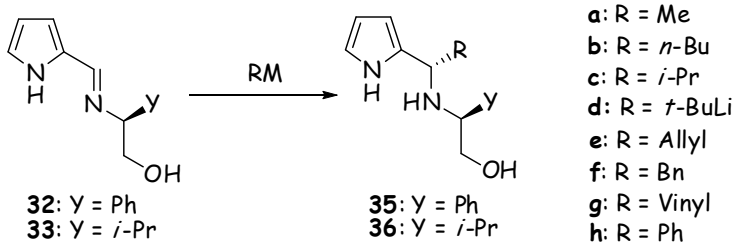
Very high diastereoselectivity (d.r. >95%) was observed in the formation of amines **35a** and **35b** with MeLi and *n*BuLi, respectively, and the main diastereomer (*S*,*S*)-**35a,b** were isolated with good yields after column chromatography. The homoallylic amine **35e** was then prepared using either allylzinc bromide or allylmagnesium chloride in tetrahydrofuran, but a better diastereoselectivity was obtained with the magnesium reagent (d.r. 90:10 versus >96:4). Instead, no reaction was observed with vinylmagnesium bromide.

Table 1

RM (equivalents)	**Solvent**	**D.r.[a]**	**(*S*,*S*)-35 Yield %[b]**
MeLi (3)	Et_2O	>95:5	**35a**, 87
*n*BuLi (3)	Et_2O	>95:5	**35b**, 82
AllylZnBr (2)	THF	>90:10	**35e**, 81
AllylMgCl (2)	THF	>96:4	**35e**, 83
VinylMgCl (3)	Et_2O	-	no reaction

[a] Determined by ^1H NMR analysis. [b] The crude product was treated with NH_4F (3 equiv.) and a catalytic amount of TBAF in THF-H_2O (1:1), then submitted to column chromatography (SiO_2).

Subsequently, taking into account a recent report,[13] we wished to check the reactivity of the unprotected imines **32** and **33** derived from (*S*)-phenylglycinol and (*S*)-valinol, respectively (Scheme 12). This choice required the use of an excess of the orgamometallic reagent, the first two equivalents being quenched by the acidic OH and NH functions. Moreover, it was expected that the negatively charged pyrrole substituent would decrease the reactivity of the imine function. As a matter of fact, the addition of MeLi (4 equivalents) to the imine **32** in THF occurred smoothly at −15 to 0 °C to give the amine **35a** with 96% yield and d.r. >95 (Table 2). Similarly, the reaction with *n*BuLi in the same conditions gave the amine **35b** in high yield and with (almost) complete diastereoselectivity, only one diastereomer being observed by ^{1}H NMR analysis of the crude reaction product. Similarly, the addition of *i*PrMgCl proceeded smoothly to give **35c** in 92% yield and with complete diastereoselectivity.



Scheme 12

On the other hand, the addition of *t*-BuLi occurred with quite poor diastereoselectivity, although the two diastereomers of **35d** could be seperated by column chromatography. A low conversion of the imine **32** was observed by TLC and GC analyses after addition of allylzinc bromide, however, the use of allylmagnesium chloride allowed the homoallylic amine **35e** to be obtained with good yield and high diastereoselectivity (dr >95:5); higher yield and complete stereocontrol were then obtained using 4 equivalents of the allyldiethylzincate prepared by the addition of allylmagnesium chloride to diethylzinc.[23] Aiming to reduce the overall excess of organometallic reagents, we subsequently developed a more economic protocol that involved the preliminary addition of diethylzinc (2 equivalents) to the imine **32**, followed by the addition of allylmagnesium chloride (2 equivalents); in this way, the homoallylic amine **35e** was obtained with almost identical yield and complete stereocontrol. Good results were also obtained using benzylmagnesium chloride, providing access to the amines **35f** in high yield and with d.r. >95:5. No reaction was observed with

vinylmagnesium bromide and phenylmagnesium bromide, however, phenyllithium proved to be more reactive and gave the desired amine **35h**. Unfortunately, the crude amine **35h**, decomposed upon attempted purification by column chromatography, perhaps owing to the acidity of the methine proton linked to the carbon stereocenter.

Table 2

Imine	Y	RM (equivalents)	D.r.[a]	(*S,S*)-35, (*S,S*)-36, Yield %[b]
32	Ph	MeLi (4)	>95:5	**35a**, 96
32	Ph	*n*BuLi (4)	>99:1	**35b**, 91
32	Ph	*i*PrMgCl (4)	>95:5	**35c**, 92
32	Ph	*t*BuLi (4)[c]	55:45	(*S,S*)-**35d**, 31; (*R,S*)-**35d**, 28
32	Ph	AllylZnBr (4)	-	**35e**, 10[a],[d]
32	Ph	AllylMgCl (4)	>95:5	**35e**, 87
32	Ph	AllylEt_2ZnMgCl (4)	>99:1	**35e**, 89
32	Ph	1) Et_2Zn (2), 2) AllylMgCl (2)	>99:1	**5e**, 86
32	Ph	BnMgCl (4)	>95:5	**35f**, 91
32	Ph	VinylMgBr (4)	-	**35g**, 0
32	Ph	PhMgBr (4)	-	**35h**, 0
32	Ph	PhLi (4)	>95:5	**35h**, 95[e]
33	*i*Pr	MeLi (4)	>99:1	**36a**, 91
33	*i*Pr	*n*BuLi (4)	>99:1	**36b**, 87
33	*i*Pr	1) Et_2Zn (2), 2) AllylMgCl (2)	>99:1	**36e**, 89
33	*i*Pr	AllylMgCl (4)	>99:1	**36e**, 78
33	*i*Pr	BnMgCl (4)	>99:1	**36f**, 90
33	*i*Pr	1) MeLi (2), 2) VinylLi (2)	>99:1	**36g**, 92[e]
33	*i*Pr	PhLi (4)	>95:5	**36h**, 91[e]

[a] Determined by ^1H NMR analysis. [b] Yield of the pure (*S,S*)-diastereomer which was isolated by column chromatography (SiO_2). [c] The reaction was performed in Et_2O. [d] The product was not isolated. [e] The product decomposed during chromatography on a SiO_2 column.

Then we moved to evaluate the degree of asymmetric induction offered by the (*S*)-valinol-derived 2-pyrroleimine **33** in the same organometallic reactions carried out on the imine **32**. We were delighted to observe that even better results were obtained, as complete stereocontrol was achieved in the preparation of the amines **36a,b,e-h** (Table 2). These results are in line with the previously observed evidence that a better stereocontrol was provided by valinol as the chiral auxiliary for imines with respect to phenylglycinol.[20] The reaction with *t*-butyllithium was not carried out, as we had no chance to improve significantly the diastereoselectivity previously obtained with the imine **32**. The β-aminoalcohols **36g,h** were obtained using vinyllithium and phenyllithium, respectively. Vinyllithium was prepared by reaction of tri(*n*-butyl)vinyltin and n-BuLi, however, we found more convenient to initially add two equivalents of MeLi to the imine **33**, since the first two equivalents of organometallic reagent are consumed by the acidic NH and OH groups, and then add two equivalents of vinyllithium. As previously observed with the amine **35h**, the novel amines **36g,h** underwent decomposition during attempted chromatographic purification. Nevertheless, it is likely that the crude amines **35h** and **36g,h**, being obtained with satisfactory purity, could be used as such in subsequent steps involving transformation of the alkene function.

4.2.2 - Addition of organometallic reagents to chiral pyrrole imines derived from valine methyl ester

We also prepared the imine **38** (Scheme 13) derived from 2-pyrrolecarboxaldehyde and (*S*)-valine methyl ester following protection of the NH function as its trimethylsilyl derivatives.

The addition of allylzinc bromide to the imine **38** gave a mixture of two products: the desire product **39** with only the 51% of yield and the product **40** derivate from a double addition of the organometallic reagent to the ester function (Table 3). Increasing the temperature and using allylmagnesium chloride gave only the product **40** with good yields.

Scheme 13

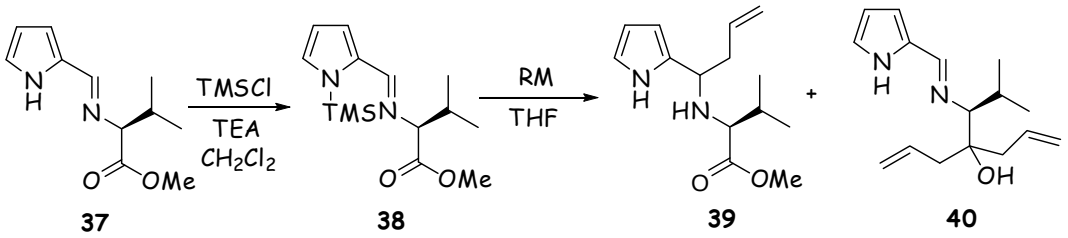


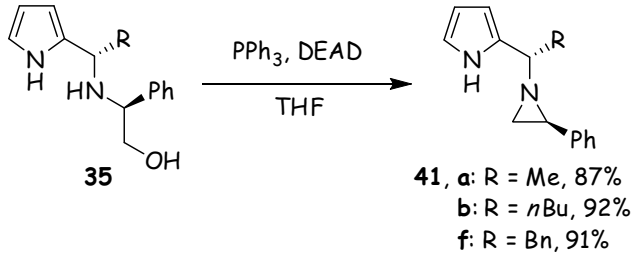
Table 3

RM (equivalents)	T (°C)	D. r. of 38[a]	39 Yield(%)	40 Yield(%)
AllylZnBr (3)	-78 → -10	92:8	51[b]	15[a]
AllylZnBr (3)	0 → 25	-	-	84[b]
AllylMgCl (3)	0 → 25	-	-	90[b]

[a] Determined by ^{1}H NMR analysis. [b] After cromatographic purification (SiO_2).

*4.2.3 – Elaboration of amines **35** and **36***

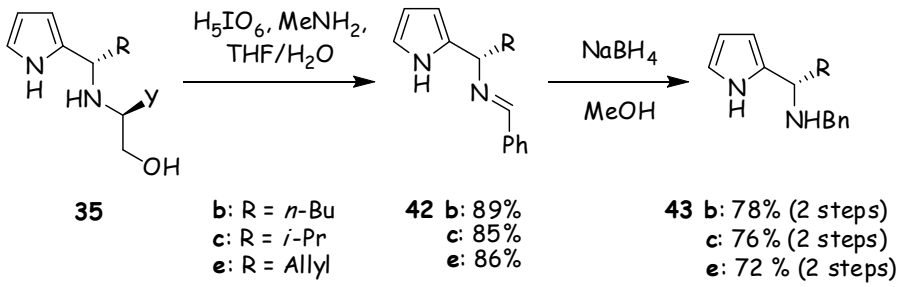
At this point we assessed the possibility of using the β-aminoalcohol **35** and **36** for the construction of new optically active, pyrrole-containing molecules, such as aziridines by intramolecular cyclization and secondary amines through oxidative cleavage of the chiral auxiliary (Scheme 14). For the first goal we followed the same protocol previously applied for the synthesis of analogous 1-(2-pyridyl)alkylaziridines.[20b,c] As a matter of fact, the pyrrole-aziridines **41a,b,f** were successfully obtained in high yields by treatment of the β-hydroxyamines **35a,b,f** with triphenylphosphine and diethylazodicarboxylate (DEAD) in THF at room temperature.



Scheme 14

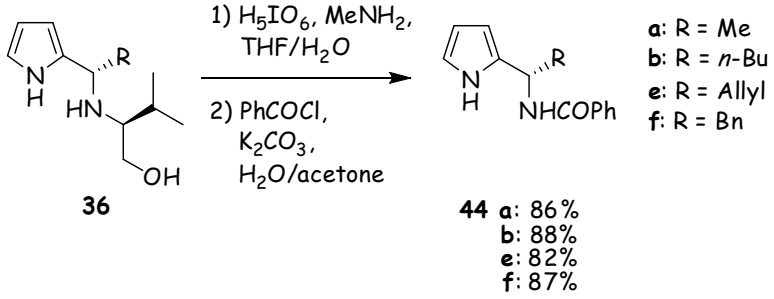
On the other hand, hydrogenolysis of **35a** with ammonium formate and Pd/C in ethanol at the reflux temperature gave disappointing results, as a complex mixture of products was

obtained. Instead, the oxidative procedure making use of periodic acid and methylamine in THF-H_2O was successful; however, starting from the β-aminoalcohols **35b,c,e** the benzaldimines **42b,c,e** were isolated, apparently being stable towards hydrolysis in the reaction conditions. In particular the imine **42c** was isolated as a solid and could be purified simply by washing with pentane. Both the crude imines **42b,c,e** were readily reduced to the corresponding benzylamines **43b,c,e** by sodium borohydride in methanol (Scheme 15). It is worthy of note that this procedure is more convenient than the usual stepwise removal of the chiral auxiliary followed by *N*-benzylation.



Scheme 15

On the other hand, the primary amines were formed by carrying out the oxidative procedure on the valinol derivatives **36** (Scheme 16); in this case the crude compounds were preferably treated with benzoyl chloride and potassium carbonate in acetone-H_2O mixture, so easily obtaining the corresponding pure *N*-benzoyl derivatives **44a,b,e,f** in good yields.



Scheme 16

In conclusion, we have developed a convenient asymmetric route to 1-[2-(pyrrolyl)]alkylamines exploiting the highly diastereoselective addition of organometallic reagents to chiral 2-pyrroleimines derived from (*S*)-phenylglycinol and (*S*)-valinol. Although a larger excess of organometallic reagents was needed, better diastereoselectivities were

obtained working on the imines with unprotected N-H and O-H functions. Complete or excellent stereocontrol was achieved, especially with the (*S*)-valinol-derived imine. Removal of the chiral auxiliaries was achieved by an oxidative procedure to give the corresponding imines or primary amines, from which the *N*-benzyl and *N*-benzoylamines could be easily prepared. Pyrrole-aziridines were also prepared by cyclization of the (*S*)-phenylglycinol derived secondary amines. Future efforts in our laboratory will be devoted to converting the unsaturated amines **35h** and **36g,h** into bicyclic compounds by linking the pyrrole-NH and alkene functions.

4.2.4 – Use of the synthesized compounds as chiral ligands

Finally we tested the imine **32** and the aziridines **41a,f** in the enanatioselctive addition of diethylzinc to benzaldehyde **45** (Scheme 17). The reaction proceeded slowly, moderate to good yield was obtained only after 24 hours at room temperature (Scheme 17), to gave the addition product **46** with low e.e..

Scheme 17

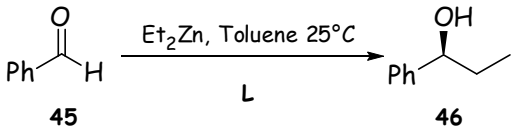


Table 4

L	Conversion 46 (%)	e.e. 46 (%)
32	75	9
41a	96	21
41f	88	15

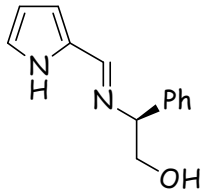
4.3 – Experimental section

Melting points are uncorrected. Optical rotations were measured on a digital polarimeter in a 1-dm cell and $[\alpha]_D$-values are given in 10^{-1} deg cm^3 g^{-1}. ^1H NMR spectra were recorded on Varian Inova and Gemini instruments for samples in $CDCl_3$ which was stored over

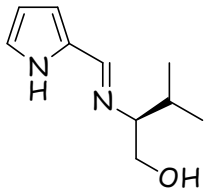
Mg: ^1H chemical shifts are reported in ppm relative to $CHCl_3$ (δ_H 7.27), J-values are given in Hz. and in the assignments s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, m = multiplet, bs = broad singlet, dd = doublet of doublets and dt = doublet of triplets. Infrared spectra were recorded on a Nicolet FT-380 spectrometer and IR assignments are reported in wavenumbers (cm^{-1}). MS spectra were taken at an ionising voltage of 70 eV on a Hewlett-Packard 5975 spectrometer with GLC injection. Molecular weight was determined on an Agilent Technologies MS 1100 instrument. Chromatographic separations were performed on columns of SiO_2 (Merck, 230-400 mesh) at medium pressure. All the organic, inorganic and organometallic reagents and reactants and anhydrous solvents were purchased from Aldrich.

*4.3.1 – General protocol for the preparation of Imines **32**, **33***

To a solution of (*S*)-phenylglycinol (0.823 g, 6 mmol) or (*S*)-valinol (0.618 g, 6 mmol) in anhydrous CH_2Cl_2 (30 mL) was added anhydrous $MgSO_4$ (5 g) and 2-pyrrolecarboxaldehyde (0.571 g, 6 mmol) and the mixture was stirred overnight. The solid was filtered off through a pad of Celite and the organic phase was concentrated at reduced pressure. The residue was crystallized from pentane:CH_2Cl_2 mixture (5:1) to give the imine, which was used in the following step avoiding purification.

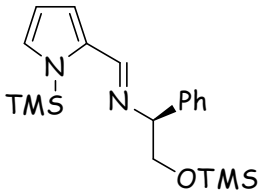


(*S*)-*N*-(2-Pyrrolmethylidene)phenylglycinol (32): 1.262 g (98%); white solid, mp 109-109.6 °C. $[\alpha]_D^{20}$ +24.3 (c 1.1, $CHCl_3$). IR (KBr): ν_{max} = 3331, 3113, 3061, 2921, 2854, 1640, 1425, 1366, 1313, 1073, 1061, 1043, 813, 737, 701. ^1H NMR (300 MHz, $CDCl_3$): δ = 4.03 (dd, J = 3.6, J^2 = 12.2, 1 H), 4.20 (dd, J = 9.9, J = 12.2, 1 H), 4.46 (dd, J = 3.6, J = 9.9, 1 H), 6.20 (m, 2 H), 6.99 (m, 1 H), 7.38 (m, 5 H), 7.75 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 67.9, 76.6, 109.6, 117.7, 122.9, 126.9, 127.4, 128.6, 128.9, 140.7, 154.6. GC-MS m/z: 183 (100), 156 (12), 214 (7), 80 (7). Anal. Calcd for $C_{13}H_{14}N_2O$ (214.11): C, 72.87; H, 6.59; N, 13.07. Found: C, 72.57; H, 6.62; N, 13.10.



(*S*)-*N*-(2-Pyrrolmethylidene)valinol (33): 1.051 g (97%); white solid, mp 122.4-123 °C. $[\alpha]_D^{20}$ +121.5 (c 0.5, $CHCl_3$). IR (KBr): ν_{max} = 3239, 3114, 3085, 2966, 2924, 2868, 2843, 1633, 1473, 1419, 1373, 1359, 1317, 1217, 1131, 1075, 1053, 1035, 934, 824, 761, 735. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.86 (d, *J* = 6.9, 3 H), 0.92 (d, *J* = 6.9, 3 H), 1.81 (sept, *J* = 6.9, 1 H), 2.92 (dd, *J* = 3.5, *J* = 8.8, 1 H), 3.83 (dd, *J* = 3.5, *J* = 11.8, 1 H), 3.96 (dd, *J* = 8.8, *J* = 11.8, 1 H), 6.16 (dd, *J* = 2.6, *J* = 3.6, 1 H), 6.26 (m, 1 H), 6.89 (m, 1 H), 7.66 (s, 1 H). ^{13}*C* NMR (75 MHz, $CDCl_3$): δ = 19.0, 19.6, 30.7, 64.5, 78.3, 109.3, 116.7, 122.3, 129.0, 153.7. *GC*-MS m/z: 149 (100), 80 (47), 137 (38), 68 (26), 106 (24), 180 (23). Anal. Calcd for $C_{10}H_{16}N_2O$ (180.13): *C*, 66.63; H, 8.95; N, 15.54. Found: *C*, 66.31; H, 8.98; N, 15.51.

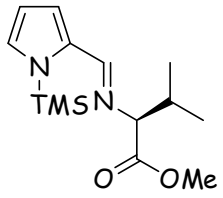
*4.3.2 – Preparation of Imine **34***



(*S*)-*N*-[(1-Trimethylsilylpyrrol-2-yl)methylidene]phenylglycinol trimethylsilyl ether 34: The crude imine **32** (1.26 gr, 5.9 mmol) was dissolved in CH_2Cl_2 (20 mL) and triethylamine (1.23 g, 12 mmol) and chlorotrimethylsilane (1.30 g, 12 mmol) were added to the solution cooled at 0 °C. After 3 h the solvent was removed at reduced pressure. A solution of cyclohexane/diethyl ether (1:1, 50 mL) was added and the solid precipitate was filtered off through a pad of Celite. The organic solvent was evaporated under reduced pressure to leave the imine **34** which was used in the following step avoiding purification: 2.074 gr (98%); white solid, m.p. 94.2-94.9 °C (from pentane:Et_2O 5:1). $[\alpha]_D^{20}$ –48.1 (c 0.5, $CHCl_3$). IR (KBr): ν_{max} = 3105, 3062, 2962, 2908, 2857, 1640, 1451, 1425, 1247, 1122, 1084, 1051, 916, 902, 842, 739, 700. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.11 (s, 9 H), 0.58 (s, 9 H), 3.93 (d, *J* = 6.7, 2 H), 4.37 (t, *J* = 6.7, 1 H), 6.36 (dd, *J* = 2.6, *J* = 3.3, 1 H), 6.78 (dd, *J* = 1.5, *J* = 3.3, 1 H), 7.05 (m, 1 H), 7.37 (m, 2 H), 7.51 (m, 3 H), 8.26 (s, 1 H). ^{13}*C* NMR (75 MHz, $CDCl_3$): δ = -0.5, 1.6, 67.6, 77.3, 100.4, 120.5, 127.1, 127.8, 128.2, 129.5, 141.4, 153.0. *GC*-MS m/z: 255 (100), 73 (34), 183

(22), 150 (19), 343 (15), 358 (12). Anal. Calcd for $C_{19}H_{30}N_2OSi_2$ (358.19): C, 63.63; H, 8.43; N, 7.81. Found: C, 63.48; H, 8.45; N, 7.79.

4.3.3 - Preparation of Imine ***38***



To a solution of (*S*)-valine methyl ester hydrochloride (1.68 g, 10 mmol) in anhydrous CH_2Cl_2 (30 mL) was added anhydrous $MgSO_4$ (5 g) and 2-pyrrolecarboxaldehyde (0.951 g, 10 mmol). Triethylamine (1.23 g, 12 mmol) was added and the mixture was stirred overnight. The solid was filtered off through a pad of Celite and the organic phase was concentrated at reduced pressure.

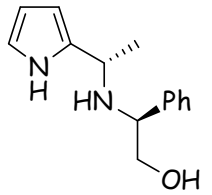
The crude imine was dissolved in CH_2Cl_2 (20 mL) and triethylamine (1.23 g, 12 mmol) and chlorotrimethylsilane (1.30 g, 12 mmol) were added to the solution cooled at 0 °C. After 3 h the solvent was removed at reduced pressure. A solution of cyclohexane/diethyl ether (1:1, 50 mL) was added and the solid precipitate was filtered off through a pad of Celite. The organic solvent was evaporated under reduced pressure to leave the imine **38** which was used in the following step avoiding purification.

(*S*)-*N*-(2-Pyrrolmethylidene)valine methylester (38): 2.74 g (98%); yellow oil. $[\alpha]_D^{20}$ +101.4 (c 0.5, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0,53 (s, 9 H), 0.95 (d, J = 6.9, 3 H), 1.02 (d, J = 6.9, 3 H), 2.38 (dsept, J = 8.0, J = 6.9, 1 H), 3.53 (d, J = 8.0, 1 H), 3.76 (s, 3 H), 6.33 (m, 1 H), 6.76 (dd, J = 1.5, J = 3.4, 1 H), 7.05 (m, 1 H), 8.07 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 1.3, 18.9, 19.5, 28.8, 31.2, 52.4, 81.1, 110.5, 121.5, 130.3, 135.4, 154.2, 172.6, 179.1. GC-MS m/z: 150 (100), 73 (89), 165 (85), 178 (69), 237 (65), 221 (61), 205 (52), 265 (34), 280 (26).

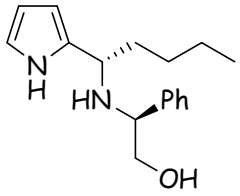
4.3.4 – General protocol for the preparation of β-Aminoalcohols ***35, 36***

Methyllithium (1.6 M in diethyl ther, 2.4 mL, 3.8 mmol) was added to a magnetically stirred solution of the imine **32** (0.203 g, 0.95 mmol) in THF (15 mL) cooled at –15 °C. After 30 min the reaction mixture was slowly warmed up until room temperature was reached, and stirring was continued for 24 h. The mixture was quenched by adding a saturated aqueous solution of $NaHCO_3$ (10 mL) at 0 °C, then the organic material was extracted with diethyl

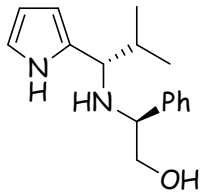
ether (3 ×10 mL). The collected ethereal layers were dried over Na_2SO_4 and concentrated to leave the crude product. The diastereomeric ratio was determined by ^1H NMR analysis. Flash column chromatography (SiO_2) eluting with cyclohexane/ethyl acetate 1:1 mixtures gave the product **35a**. This compound, as well as all the β-aminoalcohols **35** and **36** prepared, decomposed on attempted GC-MS and HPLC-MS analyses.



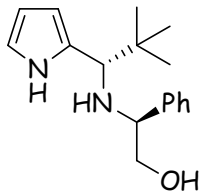
(*S*)-*N*-[(*S*)-1-(2-Pyrrolyl)ethyl]phenylglycinol (35a): 0.210 g, (96%); white solid, mp 86.9-87.4 °C (Et_2O). $[\alpha]_D^{20}$ +34.5 (c 0.8, $CHCl_3$). IR (Nujol): ν_{max} = 3295, 2090, 2955, 2928, 2854, 1540, 1459, 1261, 1090, 735. ^1H NMR (300 MHz, $CDCl_3$): δ 1.39 (d, *J* = 6.7, 3 H), 2.66 (bs, 2 H), 3.57 (dd, *J* = 8.1, *J* = 10.8, 1 H), 3.74 (dd, *J* = 4.3, *J* = 10.8, 1 H), 3.80 (q, *J* = 6.7, 1 H), 3.96 (dd, *J* = 4.3, *J* = 8.1, 1 H), 5.97 (m, 1 H), 6.13 (m, 1 H), 6.97 (m, 1 H), 7.34 (m, 5H), 8.68 (bs, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.0, 47.7, 61.1, 66.8, 104.4, 107.9, 116.7, 127.3, 127.7, 128.7, 135.6, 140.4. Anal. Calcd for $C_{14}H_{18}N_2O$ (230.14): C, 73.01; H, 7.88; N, 12.16. Found: C, 72.82; H, 7.91; N, 12.15.



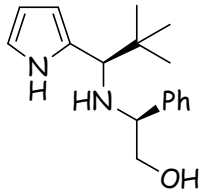
(*S*)-*N*-[(*S*)-1-(2-Pyrrolyl)pentyl]phenylglycinol (35b): 0.235 g, (91%); yellow oil. $[\alpha]_D^{20}$ +48.6 (c 0.7, $CHCl_3$). IR (neat): ν_{max} = 3424, 3023, 2856, 2863, 1495, 1391, 1264, 1093, 1021. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 7.3, 3 H), 1.24 (m, 4 H), 1.74 (m, 2 H), 2.51 (bs, 2 H), 3.59 (dd, *J* = 7.5, *J* = 10.8, 1 H), 3.72 (dd, *J* = 4.3, *J* = 8.0, 1 H), 3.77 (dd, *J* = 4.5, *J* = 10.8, 1 H), 3.91 (dd, *J* = 4.4, *J* = 7.5, 1 H), 5.97 (m, 1 H), 6.13 (q, *J* = 2.8, 1 H), 6.69 (m, 1 H), 7.23-7.43 (m, 5 H), 8.54 (bs, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 22.7, 25.6, 27.9, 53.3, 61.2, 66.1, 105.4, 107.8, 116.7, 127.1, 127.5, 128.6, 134.0, 140.9. Anal. Calcd for $C_{17}H_{24}N_2O$ (272.19): C, 74.96; H, 8.88; N, 10.28. Found: C, 74.85; H. 8.89; N, 10.26.



(*S*)-*N*-[(*S*)-2-Methyl-1-(2-pyrrolyl)propyl]phenylglycinol (7c): 0.243 *g*, (92%); yellowish oil. $[\alpha]_D^{20}$ +32.4 (c 1.0, $CHCl_3$). IR (neat): ν_{max} = 3422, 3024, 2853, 2865, 1492, 1261, 1099, 1021, 742. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (d, *J* = 6.7, 3 H), 0.97 (d, *J* = 6.7, 3 H), 2.02 (dsept, *J* = 5.7, *J* = 6.7, 1 H), 2.50 (bs, 2 H), 3.61 (dd, *J* = 5.8, *J* = 10.2, 1 H), 3.67 (d, *J* = 5.7, 1 H), 3.78 (dd, *J* = 4.5, *J* = 5.7, 1 H), 3.84 (dd, *J* = 4.5, *J* = 10.2, 1 H), 5.98 (m, 1 H), 6.15 (q, *J* = 2.8, 1 H), 6.65 (m, 1 H), 7.25-7.39 (m, 5 H), 8.39 (bs, 1 H). ^{13}*C* NMR (75 MHz, $CDCl_3$): δ = 18.0, 19.7, 32.2, 59.5, 61.2, 63.4, 106.3, 107.6, 114.2, 127.1, 127.2, 127.3, 128.5, 132.2, 141.2. Anal. Calcd for $C_{16}H_{22}N_2O$ (258.17): *C*, 74.38; H, 8.58; N, 10.84. Found: *C*, 74.15; H. 8.60; N, 10.83.

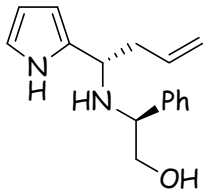


(*S*)-*N*-[(*S*)-2,2-Dimethyl-1-(2-pyrrolyl)propyl]phenylglycinol ((*S,S*)-35d): 0.081 *g*, (31%); yellowish oil. $[\alpha]_D^{20}$ +40.7 (c 1.0, $CHCl_3$). IR (neat): ν_{max} = 3425, 2953, 2868, 2867, 1478, 1391, 1362, 1260, 1095. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.98 (s, 9 H), 2.15 (bs, 2 H), 3.51 (s, 1 H), 3.59 (dd, *J* = 5.9, *J* = 8.1, 1 H), 3.63 (dd, *J* = 8.1, *J* = 12.2, 1 H), 3.83 (dd, *J* = 5.9, *J* = 12.2, 1 H), 5.92 (m, 1 H), 6.08 (q, *J* = 2.7, 1 H), 6.55 (m, 1 H), 7-21-7.32 (m, 5 H), 8.07 (bs, 1 H). ^{13}*C* NMR (75 MHz, $CDCl_3$): δ = 27.1, 35.4, 61.5, 64.2, 64.3, 107.0, 107.6, 115.8, 127.1, 127.3, 128.4, 132.0, 142.1. Anal. Calcd for $C_{17}H_{24}N_2O$ (272.19): *C*, 74.96; H, 8.88; N, 10.28. Found: *C*, 74.98; H, 8.91; N, 10.26.

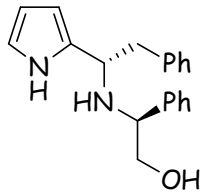


(*S*)-*N*-[(*R*)-2,2-Dimethyl-1-(2-pyrrolyl)propyl]phenylglycinol ((*S,R*)-35d): 0.072 *g*, (28%); yellowish oil. $[\alpha]_D^{20}$ +109.6 (c 1.9, $CHCl_3$). IR (neat): ν_{max} = 3425, 3029, 2853, 2868, 1492,

1392, 1363, 1260, 1096, 1028. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.39 (s, 9 H), 2.33 (bs, 2 H), 3.26 (s, 1 H), 3.55 (dd, J = 4.6, J = 8.1, 1 H), 3.61 (dd, J = 8.1, J = 10.0, 1 H), 3.68 (dd, J = 4.6, J = 10.0, 1 H), 5.97 (m, 1 H), 6.19 (m, 1 H), 6.77 (m, 1 H), 7.22 (2 H), 7.31-7.40 (m, 3 H), 8.44 (bs, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.0, 34.8, 61.7, 63.1, 66.7, 107.6, 108.3, 116.5, 127.4, 127.7, 128.6, 130.4, 140.1. Anal. Calcd for $C_{17}H_{24}N_2O$ (272.19): C, 74.96; H, 8.88; N, 10.28. Found: C, 74.82; H. 8.89; N, 10.26.

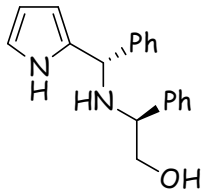


(*S*)-*N*-[(*S*)-1-(2-Pyrrolyl)-3-buten-1-yl]phenylglycinol (35e): 0.217 g, (89%); yellow oil. $[\alpha]_D^{20}$ +16.5 (c 0.4, $CHCl_3$). IR (neat): ν_{max} = 3364, 3102, 3076, 2958, 2930, 2873, 1466, 1437, 1093, 1044, 2026, 914, 796, 717. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.40 (bs, 2 H), 2.79 (m, 2 H), 3.84 (dd, J = 7.6, J = 10.8, 1 H), 4.01 (dd, J = 4.5, J = 10.8, 1 H), 4.09 (t, J = 5.9, 1 H), 4.19 (dd, J = 4.5, J = 7.6, 1 H), 5.36 (dd, J = 10.8, J = 17.2, 2 H), 6.01 (m, 1 H), 6.23 (m, 1 H), 6.38 (d, J = 2.7, 1 H), 6.91 (dd, J = 1.5, J = 2.7, 1 H), 7.52-7.61 (m, 5H), 8.73 (bs, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 38.9, 52.5, 61.3, 66.4, 105.3, 108.0, 116.7, 117.9, 127.3, 127.7, 128.7, 133.6, 134.7, 140.3. Anal. Calcd for $C_{16}H_{20}N_2O$ (256.16): C, 74.97; H, 7.86; N, 10.93. Found: C, 75.02; H, 7.87; N. 10.89.

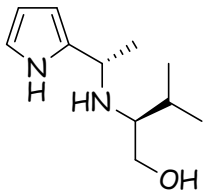


(*S*)-*N*-[(*S*)-2-Phenyl-1-(2-pyrrolyl)ethyl]phenylglycinol (35f): 0.265 g, (91%); white solid, mp 115.2-116.2 °C (pentane:Et_2O 1:1). $[\alpha]_D^{20}$ +82.5 (c 1.1, $CHCl_3$). IR (Nujol): ν_{max} = 3353, 3028, 2926, 2856, 1539, 1453, 1261, 1094, 1027, 749. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.94 (bs, 2 H), 3.08 (d, J = 6.6, 2 H), 3.55 (dd, J = 7.4, J = 10.8, 1 H), 3.71 (dd, J = 4.3, J = 10.8, 1 H), 3.86 (dd, J = 4.3, J = 7.4, 1 H), 3.08 (t, J = 6.6, 1 H), 5.98 (m, 1 H), 6.12 (q, J = 6.7, 1 H), 6.63 (m, 1 H), 7.09 (m, 2 H), 7.24-7.38 (m, 8H), 8.19 (bs, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 42.3, 54.9, 61.6, 66.1, 105.3, 108.0, 116.6, 126.4, 127.2, 127.6, 128.2, 128.6, 129.3, 133.7,

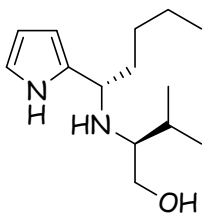
138.5, 140.8. Anal. Calcd for $C_{20}H_{22}N_2O$ (306.17): C, 78.40; H, 7.24; N, 9.14. Found: C, 78.50; H, 7.27; N. 9.11.



(*S*)-*N*-[(*S*)-1-Phenyl-1-(2-pyrrolyl)methyl]phenylglycinol (35h): this compound was not purified; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.22 (bs, 2 H), 3.62-6.70 (m, 3 H), 4.73 (s, 1 H), 5.84 (m, 1 H), 6.13 (q, J = 3.1, 1 H), 6.71 (m, 1 H), 7.26-7.49 (m, 10 H), 8.54 (bs, 1 H).

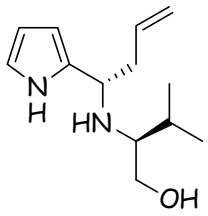


(*S*)-*N*-[(*S*)-1-(2-Pyrrolyl)ethyl]valinol (36a): Starting from 1 mmol of **33** 0.179 g, (91%); yellow oil. $[\alpha]_D^{20}$ –7.7 (c 0.9, $CHCl_3$). IR (neat): ν_{max} = 3394, 2961, 2927, 2874, 1465, 1373, 1262, 1104, 1029, 793, 747, 720. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.89 (d, J = 6.8, 3 H), 0.95 (d, J = 6.8, 3 H), 1.39 (d, J = 6.5, 3 H), 1.77 (sept, J = 6.8, 1 H), 2.2 (bs, 2 H), 2.45 (dd, J = 4.1, J = 6.2, 1 H), 3.64 (dd, J = 6.2, J = 10.8, 1 H), 3.39 (dd, J = 4.1, J = 10.8, 1 H), 4.01 (q, J = 6.5, 1 H), 6.02 (m, 1 H), 6.15 (m, 1 H), 6.72 (m, 1 H), 8.55 (bs, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.4, 19.3, 22.3, 29.2, 48.9, 60.0, 61.1, 104.4, 107.8, 116.7, 135.7. MS (EI) m/z: 197 [M + H]$^+$, 94 [M – valinol]$^+$. Anal. Calcd for $C_{11}H_{20}N_2O$ (196.16): C, 67.31; H, 10.27; N, 14.27. Found: C, 67.02; H, 10.30; N, 14.23.

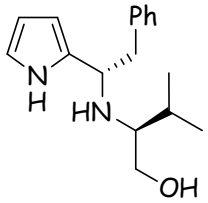


((*S*)-*N*-[(*S*)-1-(2-Pyrrolyl)pentyl]valinol (36b): 0.207 g, 0.173 g, (87%); yellow oil. $[\alpha]_D^{20}$ –4.6 (c 0.5, $CHCl_3$). IR (neat): ν_{max} = 3362, 3301, 3101, 2957, 2929, 2860, 1567, 1464, 1026, 925, 792, 717. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.85 (t, J = 5.2, 3 H), 0.89 (d, J = 6.7, 3 H), 0.92 (d, J = 6.7, 3 H), 1.25 (m, 4 H), 1.62 (m, 2 H), 1.74 (m, 1H), 1.98 (bs, 2 H), 2.36 (ddd, J =

4.3, *J* = 5.3, *J* = 8.0, 1 H), 3.41 (dd, *J* = 5.6, *J* = 10.8, 1 H), 3.64 (dd, *J* = 4.1, *J* = 10.8, 1 H), 3.77 (dd, *J* = 5.9, *J* = 8.0, 1 H), 5.99 (m, 1 H), 6.13 (q, *J* = 2.9, 1 H), 6.72 (m, 1 H), 8.42 (bs, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8, 18.5, 19.2, 22.5, 26.4, 29.2, 36.3, 54.2, 60.3, 61.1, 105.5, 107.4, 116.6, 134.0. MS(EI) m/z: 136.1 $[M - n\text{-}Bu]^+$. Anal. Calcd for $C_{14}H_{26}N_2O$ (238.20): C, 70.54; H, 10.99; N, 11.75. Found: 78.59; H, 10.97; N, 11.71.

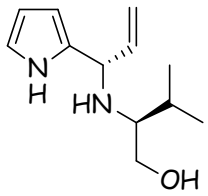


(*S*)-*N*-[(*S*)-1-(2-Pyrrolyl)-3-buten-1-yl]valinol (36e): 0.173 g, (78%), yellow oil. $[\alpha]_D^{20}$ –12.4 (c 1.1, $CHCl_3$). IR (Neat): ν_{max} = 3296, 3090, 3062, 2956, 2928, 2858, 1582, 1454, 1379, 1264, 1093, 1027, 934. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.87 (d, *J* = 6.8, 3 H), 0.93 (d, *J* = 6.8, 3 H), 1.74 (sept, *J* = 6.8, 1 H), 1.96 (bs, 2 H), 2.37 (dd, *J* = 4.1, *J* = 5.3, 1 H), 2.46 (dd, *J* = 6.7, *J* = 6.9, 2 H), 3.43 (dd, *J* = 5.3, *J* = 10.8, 1 H), 3.68 (dd, *J* = 4.1, *J* = 10.8, 1 H), 3.90 (t, *J* = 6.7, 1 H), 5.08-5.17 (m, 2 H), 5.76 (m, 1 H), 6.01 (m, 1 H), 6.14 (q, *J* = 2.7, 1 H), 6.72 (m, 1 H), 8.52 (bs, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.7, 19.3, 29.2, 41.3, 53.3, 60.4, 61.2, 105.3, 107.8, 116.6, 117.4, 133.9, 135.1. MS(EI) m/z: 120 [M - valinol]$^+$. Anal. Calcd for $C_{13}H_{22}N_2O$ (222.17): C, 70.23; H, 9.97; N, 12.60. Found: C, 69.96; H, 9.99; N, 12.58.

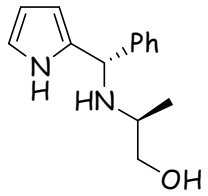


(*S*)-*N*-[(*S*)-2-Phenyl-1-(2-pyrrolyl)ethyl]valinol (36f): 0.245 g, (90%); white solid, mp 109.5-110.8 °C (pentane:Et_2O 1:1). $[\alpha]_D^{20}$ –9.8 (c 0.8, $CHCl_3$). IR (KBr): ν_{max} = 3295, 3021, 2948, 2818, 1711, 1492, 1457, 1361, 1334, 1095, 1040, 989, 798, 753, 729, 728, 714, 700. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.84 (d, *J* = 6.8, 3 H), 0.90 (d, *J* = 6.8, 3 H), 1.58 (bs, 2 H), 1.69 (sept, *J* = 6.8, 1 H), 2.29 (dd, *J* = 4.1, *J* = 4.9, 1 H), 2.91 (dd, *J* = 7.6, *J* = 13.6, 1 H), 3.00 (dd, *J* = 6.0, *J* = 13.6, 1 H), 3.34 (dd, *J* = 4.9, *J* = 11.2, 1 H), 3.53 (dd, *J* = 4.1, *J* = 11.2, 1 H), 2.29 (dd, *J* = 6.0, *J* = 7.6, 1 H), 5.59 (m, 1 H), 6.14 (q, *J* = 2.7, 1 H), 6.69 (m, 1 H), 7.10-7.16 (m, 2 H), 7.20-7.32 (m, 3 H), 8.33 (bs, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.0, 19.5, 29.4, 44.4,

55.4, 60.4, 61.5, 105.3, 108.1, 116.4, 126.5, 128.4, 129.2, 134.1, 138.8. MS(EI) m/z: 170 [M - valinol]$^+$. Anal. Calcd for $C_{17}H_{24}N_2O$ (272.19): C, 74.96; H, 8.88; N, 10.28. Found: C, 74.62; H, 8.91; N, 10.25.



(*S*)-*N*-[(*S*)-1-(2-Pyrrolyl)-2-propen-1-yl]valinol (36g): the crude compound could not be purified, owing to decomposition by column chromatography; its structure was confirmed by ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.91 (d, *J* = 6.9, 3 H), 0.97 (d, *J* = 6.9, 3 H), 1.87 (m, 1 H), 2.58 (dd, *J* = 4.1, *J* = 7.2, 1 H), 3.39 (dd, *J* = 7.2, *J* = 10.7, 1 H), 3.66 (dd, *J* = 4.1, *J* = 10.7, 1 H), 4.43 (d, *J* = 7.6, 1 H), 5.18 (dd, *J* = 1.4, *J* = 10.0, 1 H), 5.25 (dd, *J* = 1.4, *J* = 17.4, 1 H), 5.90 (ddd, *J* = 7.6, *J* = 10.0, J^3 = 17.4, 1 H), 6.07 (m, 1 H), 6.17 (t, *J* = 3.1, 1 H), 6.75 (dd, *J* = 1.4, *J* = 2.7, 1 H), 8.78 (bs, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.9, 19.3, 28.8, 57.3, 60.6, 61.1, 105.3, 108.1, 116.0, 117.1, 132.8, 139.5. The compound was not eluted by GC-MS analysis.

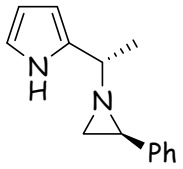


(*S*)-*N*-[(*S*)-1-Phenyl-1-(2-pyrrolyl)methyl]valinol (36h): the crude compound could not be purified, owing to decomposition by column chromatography; its structure was confirmed by ^{1}H NMR analysis ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.95 (d, *J* = 6.9, 3 H), 0.98 (d, *J* = 6.9, 3 H), 1.95 (m, 1 H), 2.07 (bs, 2 H), 2.45 (dd, *J* = 4.1, *J* = 6.8, 1 H), 3.40 (dd, *J* = 6.8, *J* = 10.8, 1 H), 3.58 (dd, *J* = 4.1, *J* = 10.8, 1 H), 5.05 (s, 1 H), 6.01 (m, 1 H), 6.14 (q, *J* = 3.1, 1 H), 6.71 (m, 1 H), 7.29-7.45 (m, 5 H), 8.32 (bs, 1 H). The compound was not eluted by GC-MS analysis.

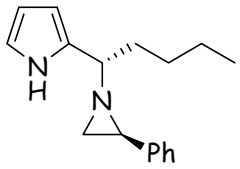
*4.3.5 – General protocol for the preparation of aziridines **35**, **36***

To a solution of the β-aminoalcohol **35a** (0.299 g, 1.3 mmol) in THF (20 mL) was added PPh_3 (0.511 g, 1.95 mmol), then DEAD (0.340 g, 1.95 mmol) was added dropwise. After stirring for 4 h the mixture was concentrated at reduce pressure and the residue was subJected to

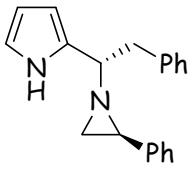
flash-chromatography on a SiO_2 column eluting with cyclohexane/ethyl acetate 9:1 mixtures to give the compound **41a** as yellow oil.



(*S*)-2-Phenyl-1-[(*S*)-1-(2-Pyrrolyl)ethyl]aziridine (41a): 0.240 g, (87%); yellow oil. $[\alpha]_D^{20}$ +85.4 (c 0.8, $CHCl_3$). IR (neat): ν_{max} = 3214, 3103, 2922, 2856, 1460, 1383, 805, 748, 712. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.54 (d, J = 6.6, 3 H), 1.89 (d, J = 3.5, 1 H), 2.10 (d, J = 6.7, 1 H), 2.55 (dd, J = 3.5, J = 6.6, 1 H), 2.93 (q, J = 6.6, 1 H), 6.02 (m, 1 H), 6.16 (q, J = 2.8, 1 H), 6.66 (m, 1 H), 7.21-7.35 (m, 5 H), 8.44 (bs, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.0, 36.8, 41.1, 63.2, 104.4, 107.9, 116.6, 126.3, 127.0, 128.4, 134.4, 139.8. *GC*-MS m/z : 118 (100), 93 (91), 94 (54) 92 (50), 156 (12), 197 (9), 212 (5). Anal. Calcd for $C_{14}H_{16}N_2$ (212.13): *C*, 79.21; H, 7.60; N, 13.20. Found: *C*, 79.02; 7.63; N, 13.18.



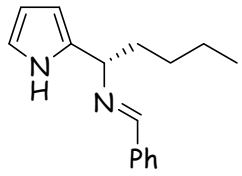
(*S*)-2-Phenyl-1-[(*S*)-1-(2-pyrrolyl)pentyl]aziridine (41b): 0.304 g, (92%); white solid, mp 78.3-79.6 °C; $[\alpha]_D^{20}$ +74.8 (c 0.7, $CHCl_3$). IR (KBr): ν_{max} = 3218, 3100, 3055, 2924, 2852, 1461, 1388, 1135, 1096, 1029, 807, 744, 718, 699. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.94 (t, J = 6.7, 3 H), 1.36-1.38 (m, 6 H), 1.92 (d, J = 3.4, 1 H), 2.14 (d, J = 6.6, 1 H), 2.55 (dd, J = 3.4, J = 6.6, 1 H), 2.76 (dd, J = 5.2, J = 7.8, 1 H), 6.01 (m, 1 H), 6.15 (q, J = 2.7, 1 H), 6.67 (dd, J = 1.7, J = 2.7, 1 H), 7.16-7.22 (m, 2 H), 7.24-7.34 (m, 3 H), 8.44 (bs, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 22.8, 28.2, 36.4, 37.9, 40,1, 68.3, 105.4, 107.5, 116.6, 126.3, 126.8, 128.3, 133.1, 140.0. *GC*-MS m/z: 106 (100), 118 (74), 1636 (62), 80 (51), 91 (34), 197 (16), 254 (10). Anal. Calcd for $C_{17}H_{22}N_2$ (254.18): *C*, 80.27; H, 8.72; N, 11.01. Found: *C*, 80.35; H. 8.75; N, 11.00.



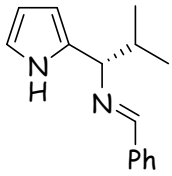
(*S*)-2-Phenyl-1-[(*S*)-2-phenyl-1-(2-pyrrolyl)ethyl]aziridine (41f): 0.341 g, (91%); white solid, mp 80.9-81.3 °C (pentane). $[\alpha]_D^{20}$ +94.4 (c 0.3, $CHCl_3$). IR (KBr): ν_{max} = 3426, 3175, 3107, 3059, 3026, 2976, 2917, 2832, 1494, 1454, 1396, 1125, 1100, 1030, 1014, 744, 725 699. ^1H NMR (300 MHz, $CDCl_3$): δ 1.72 (d, J = 6.6, 1 H), 2.05 (d, J = 3.5, 1 H), 2.48 (dd, J = 3.5, J = 6.6, 1 H), 3.80 (t, J = 6.5, 1 H), 3.14 (dd, J = 6.5, J = 13.1, 1 H), 3.22 (dd, J = 6.5, J = 13.1, 1 H), 5.89 (m, 1 H), 6.11 (q, J = 2.7, 1 H), 6.62 (dd, J = 1.6, J = 2.7, 1 H), 7.15-7.22 (m, 5 H), 7.26-7.35 (m, 5 H), 8.28 (bs, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.9, 38.5, 40.1, 43.9, 69.9, 105.5, 107.6, 126.2, 126.9, 128.1, 128.3, 129.7, 132.4, 138.6, 139.9. GC-MS m/z: 168 (100), 169 (94), 197 (66), 118 (60). Anal. Calcd for $C_{20}H_{20}N_2$ (288.16): C, 83.30; H, 6.99; N, 9.71. Found: C, 83.42; H. 7.01; N, 9.68.

*4.3.6 - Preparation of the amines **43b,c,e** through the imines **42b,c,e**.*

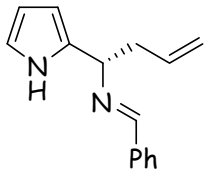
The phenylglycinol derivative **35b** (0.136 g, 0.5 mmol) and a 40% solution of $MeNH_2$ in H_2O (0.6 mL) were dissolved in THF (5 mL). Then a solution of H_5IO_6 (0.400 g) in H_2O (5 mL) was added dropwise. After stirring for 1 h at room temperature, most of the solvent was evaporated at reduced pressure and the organic materials were extracted with Et_2O (3 $\times$ 20 mL). The collected ethereal layers were dried over Na_2SO_4 and concentrated to leave the intermediate imine **42b**. This was dissolved in MeOH and $NaBH_4$ (0.75 mmol, 0.028 g) was added at 0 °C After 1 h the mixture was quenched with H_2O (5 mL), and the mixture was concentrated to remove most of the MeOH, then the organic materials were extracted with Et_2O (3 $\times$ 20 mL). The collected ethereal layers were dried over Na_2SO_4 and concentrated to leave a yellow oil which was subjected to flash-chromatography on a SiO_2 column eluting with a 8:2 cyclohexane/ethyl acetate mixture to give the compound **43b** (0.39 mmol,) as yellow oil.



(*S*)-*N*-[1-(2-Pyrrolyl)butyl]benzaldimine (42b): 0.117 g, (93%), >90% pure; brown oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.98 (t, *J* = 6.4, 3 H), 1.32 (m, 4 H), 1.94 (m, 2 H), 4.44 (t, *J* = 6.6, 1 H), 6.09 (m, 1 H), 6.18 (q, *J* = 2.9, 1 H), 6.74 (m, 1 H), 7.45 (m, 3 H), 7.79 (m, 2 H), 8.32 (s, 1 H), 8.57 (bs, 1 H). ^{13}*C* NMR (75 MHz, $CDCl_3$): δ = 160.6, 136.0, 134.0, 130.7, 128.5, 128.2, 116.6, 108.0, 104.3, 68.7, 32.3, 28.5, 22.5, 14.0. *GC*-MS m/z: 106 (100), 80 (60), 136 (56), 183 (56), 93 (16), 240 (7).

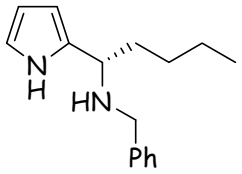


(*S*)-*N*-[2-Methyl-1-(2-pyrrolyl)propyl]benzaldimine (42c): 0.096 g, (85%); white solid; mp = 135.2-135.8 °*C* (pentane). $[\alpha]_D^{20}$ –31.2 (c 0.7, $CHCl_3$). IR (neat): ν_{max} = 3457, 3249, 2964, 2868, 2825, 1634, 1447, 1383, 1096, 1012, 725, 696. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (d, *J* = 6.7, 3 H), 0.96 (d, *J* = 6.7, 3 H), 2.12 (dsept, *J* = 6.6, *J* = 6.7, 1 H), 4.14 (d, *J* = 6.6, 1 H), 6.06 (m, 1 H), 6.19 (q, *J* = 2.9, 1 H), 6.74 (q, *J* = 2.6, 1 H), 7.44 (m, 3 H), 7.79 (m, 2 H), 8.31 (s, 1 H), 8.60 (bs, 1 H). ^{13}*C* NMR (75 MHz, $CDCl_3$): δ = 160.6, 136.2, 133.1, 130.6, 128.5, 128.2, 116.3, 107.8, 104.8, 75.2, 35.2, 19.4, 19.2. *GC*-MS m/z: 183 (100), 104 (51), 121 (36), 80 (32), 156 (6), 226 (3). *Anal. Calcd* for $C_{15}H_{18}N_2$ (226.15): *C*, 79.61; H, 8.02; N, 12.38. Found: *C*, 79.31; H, 8.05; N, 12.35.

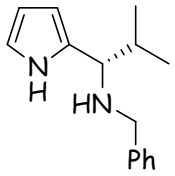


(*S*)-*N*-[1-(2-Pyrrolyl)-3-buten-1-yl]benzaldimine (42e): isolated impure as a brown oil in 86% yield (0.096). Relevant absorptions for structural identification of the main compound were drawn from the ^{1}H NMR spectrum (300 MHz, $CDCl_3$): δ = 2.68 (m, 2 H), 4.51 (dd, *J* =

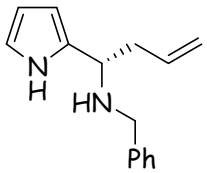
6.3, *J* = 7.6, 1 H), 5.11 (m, 2 H), 5.80 (m, 1 H), 6.06 (m, 1 H), 6.17 (q, *J* = 3.2, 1 H), 6.75 (m, 1 H), 7.42 (m, 3 H), 7.77 (m, 2 H), 8.30 (s, 1 H), 8.61 (bs, 1 H).



(*S*)-Benzyl-1-(2-pyrrolyl)pentylamine (43b): 0.094 g (78%); yellow oil. $[\alpha]_D^{20}$ –26.5 (c 0.6, $CHCl_3$). IR (neat): ν_{max} = 3432, 3376, 3297, 3062, 3027, 2955, 2928, 2857, 1494, 1453, 1092, 1026, 792, 717. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.91 (t, *J* = 6.8, 3 H), 1.32 (m, 4 H), 1.73 (m, 2 H), 2.11 (bs, 1 H), 3.65 (d, *J* = 13.4, 1 H), 3.74 (d, *J* = 13.4, 1 H), 3.80 (t, *J* = 7.0, 1 H), 6.09 (m, 1 H), 6.20 (q, *J* = 2.7, 1 H), 6.79 (m, 1 H), 7.31-7.39 (m, 5 H), 8.69 (bs, 1 H). ^{13}*C* NMR (75 MHz, $CDCl_3$): δ 14.0, 22.6, 28.3, 36.4, 51.4, 55.9, 106.1, 107.7, 116.6, 126.9, 128.1, 128.4, 133.7, 140.4. Anal. Calcd for $C_{16}H_{22}N_2$ (242.18): *C*, 79.29; H, 9.15; N, 11.56. Found: *C*, 79.06; H, 9.16; N, 11.53.



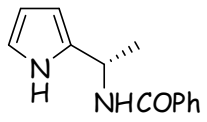
(*S*)-Benzyl-[2-methyl-1-(2-pyrrolyl)propyl]amine (43c): 0.087 g, (76%), yellow oil; $[\alpha]_D^{20}$ –37.6 (c 0.8, $CHCl_3$). IR (Nu*J*ol): ν_{max} = 3430, 3371, 3062, 3024, 2953, 2922, 2853, 1491, 1022, 794. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.83 (d, *J* = 6.7, 3 H), 0.95 (d, *J* = 6.7, 3 H), 1.87 (sept, *J* = 6.7, 1 H), 3.52 (d, *J* = 5.8, 1 H), 3.58 (d, *J* = 13.1, 1 H), 3.71 (d, *J* = 13.1, 1 H), 6.04 (m, 1 H), 6.15 (m, 1 H), 6.76 (m, 1 H), 7.25-7.38 (m, 5 H), 8.58 (bs, 1 H). ^{13}*C* NMR (75 MHz, $CDCl_3$): δ = 18.8, 19.7, 33.9, 52.0, 62.1, 106.9, 107.7, 116.2, 126.9, 128.1, 128.4, 131.1, 140.6, 150.9. Anal. Calcd for $C_{15}H_{20}N_2$ (228.16): *C*, 78.90; H, 8.83; N, 12.27. Found: *C*, 79.10; H, 8.85: N, 12.26.



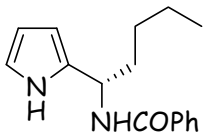
(*S*)-Benzyl-[1-(2-pyrrolyl)-3-buten-1-yl]amine (43e): yellowish oil, 0.081 g, (72%). $[\alpha]_D^{20}$ -13.9 (c 1.2, $CHCl_3$). IR (Nu*J*ol): ν_{max} 3430, 3373, 3292, 3065, 2957, 2922, 2853, 1499, 1454, 797. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.04 (bs, 1 H), 2.53 (m, 2 H), 3.66 (d, *J* = 13.2, 1 H), 3.77 (d, *J* = 13.2, 1 H), 3.90 (t, *J* = 5.5, 1 H), 5.16 (m, 2 H), 5.82 (m, 1 H), 6.12 (m, 1 H), 6.22 (dq, *J* = 2.7, *J* = 5.5, 1 H), 6.79 (m, 1 H), 7.30-7.41 (m, 5 H), 8.72 (bs, 1 H). ^{13}*C* NMR (75 MHz, $CDCl_3$): δ = 41.2, 51.1, 54.7, 105.6, 107.9, 116.6, 117.8, 126.9, 128.0, 128.4, 133.5, 135.1, 140.3. Anal. Calcd for $C_{15}H_{18}N_2$ (226.15): *C*, 79.61; H, 8.02; N, 12.38. Found: *C*, 79.91; H, 8.05: N, 12.36.

*4.3.7 - Preparation of the α-substituted benzamides **44a,b,e,f**.*

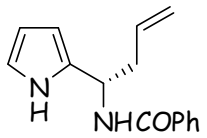
The valinol derivative **36b** (0.238 g, 1.1 mmol) and a 40% solution of $MeNH_2$ in H_2O (1.3 mL, 17 mmol) were dissolved in THF (5 mL), then a solution of H_5IO_6 (0.907 g, 4.0 mmol) in H_2O (5 mL) was added dropwise and the mixture was stirred for 2 h at room temperature. The organic materials were extracted with Et_2O (3 $\times$ 20 mL), then the collected ethereal layers were washed with brine, dried over Na_2SO_4 and concentrated to leave the primary amine as a yellow oil. This was dissolved in acetone (5 mL), then H_2O (5 mL), K_2CO_3 (0.304 g, 2.2 mmol) and benzoyl chloride (191 μl, 1.7 mmol) were added while magnetically stirring. After 12 h most of the solvent was evaporated at reduced pressure, and the organic materials were extracted with Et_2O (3 $\times$ 20 mL). The collected ethereal layers were dried over Na_2SO_4 and concentrated to leave a white solid, which was crystallized from acetone to give pure **44b**.



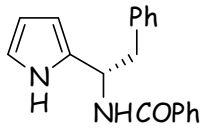
(*S*)-*N*-[1-(2-Pyrrolyl)ethyl)]benzamide (44a): 0.203 g, (86%); white solid, mp 167.9-168.5 °C. $[\alpha]_D^{20}$ −74.1 (c 0.8, $CHCl_3$). IR (KBr): ν_{max} = 3396, 3312, 2925, 1853, 1625, 1578, 1524, 1331, 1083, 1031, 736, 717, 655. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.69 (d, *J* = 7.0, 3 H), 5.34 (qd, *J* = 7.0, 1 H), 6.12 (m, 2 H), 6.33 (d, *J* = 7.0, 1 H), 6.75 (m, 1 H), 7.72-7.78 (m, 5 H), 9.36 (bs, 1 H). ^{13}*C* NMR (75 MHz, Cl_3): δ 18.3, 43.0, 104.1, 107.3, 117.9, 126.9, 128.6, 131.7, 134.0, 134.3, 168.0. *GC*-MS m/z: 105 (100), 77 (74), 93 (55), 214 (46), 121 (24), 199 (18). Anal. Calcd for $C_{13}H_{14}N_2O$ (214.11): *C*, 72.87; H, 6.59; N, 13.07. Found: *C*, 73.03; H, 6.58; N, 13.05.



(*S*)-*N*-[1-(2-Pyrrolyl)pentyl)]benzamide (42b): 0.247 *g* (88%); white solid, mp 137.5-138.2 °*C*. $[\alpha]_D^{20}$ –90.7 (c 0.8, $CHCl_3$). IR (KBr): ν_{max} = 3336, 2957, 2927, 2856, 1625, 1533, 1337, 12643, 1091, 1029, 801, 722. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.95 (t, *J* = 5.2, 3 H), 1.47 (m, 4 H), 1.96 (m, 1 H), 2.15 (m, 1 H), 5.17 (dt, *J* = 6.1, *J* = 8.3, 1 H), 6.08 (m, 1 H), 6.12 (q, *J* = 2.9, 1 H), 6.26 (d, *J* = 8.3, 1 H), 6.73 (m, 1 H), 7.39-7.55 (m, 5 H), 9.18 (bs, 1 H). ^{13}*C* NMR (75 MHz, $CDCl_3$): δ = 13.9, 22.4, 28.7, 32.4, 47.5, 104.1, 107.4, 117.6, 126.9, 128.5, 131.6, 133.6, 134.1, 168.1. *GC*-MS m/z : 105 (100), 106 (97), 77 (61), 199 (42), 135 (36), 121 (27), 256 (11). *Anal. Calcd* for $C_{16}H_{20}N_2O$ (256.16): *C*, 74.97; H, 7.86; N, 10.93. Found: 74.76; H, 7.89; N, 10.89.



(*S*)-*N*-[1-(2-Pyrrolyl)-3-buten-1-yl)]benzamide (44e): 0.217 *g*, (82%); white solid, m.p. 122.3-122.8 °*C* (Et_2O). $[\alpha]_D^{20}$ –53.7 (c 2.1, $CHCl_3$). IR (Nu*J*ol): ν_{max} = 3320, 3081, 3001, 2922, 2853, 1626, 1577, 1529, 1489, 1292, 720, 691. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.83 (m 2 H), 5.22 (m, 2 H), 5.25 (m, 1H), 5.95 (m, 1 H), 6.10 (m, 1 H), 6.14 (q, *J* = 2.9, 1 H), 6.52 (d, *J* = 6.9, 1 H), 6.74 (m, 1 H), 7.37-7.46 (m, 3 H), 7.47-7.54 (m, 2 H), 9.39 (bs, 1 H). ^{13}*C* NMR (75 MHz, $CDCl_3$): δ = 36.9, 46.6, 104.5, 107.4, 117.8, 118.4, 126.9, 128.5, 131.6, 132.7, 134.0, 134.4, 168.1. *GC*-MS m/z : 105 (100), 77 (51), 199 (46), 118 (42), 240 (6). *Anal. Calcd* for $C_{15}H_{16}N_2O$ (240.13): *C*, 74.97; H, 6.71; N, 11.66. Found: *C*, 75.16; H, 6.70; N, 11.68.



(*S*)-*N*-[2-Phenyl-1-(2-pyrrolyl)ethyl)]benzamide (44f): 0.278 *g* (87%); white solid, mp 115.5-116.4 °*C* (cyclohexane:CH_2Cl_2 9:1). $[\alpha]_D^{20}$ –61.8 (c 0.8, $CHCl_3$). IR (KBr): ν_{max} = 3056, 2925, 2676, 1690, 1622, 1532, 1423, 1291, 1174, 1042, 1017, 935, 804, 778, 707. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.26 (dd, *J* = 9.8, *J* = 14.2, 1 H), 3.48 (dd, *J* = 5.7, *J* = 14.2, 1 H), 3.96

(ddd, J = 4.3, J = 8.3, J = 9.8, 1 H), 6.10 (q, J = 2.7, 1 H), 6.14 (m, 1 H), 6.27 (d, J = 8.3, 1 H), 6.72 (m, 1 H), 7.17-7.38 (m, 3 H), 7.69-7.50 (m 3 H), 7.51-7.64 (m, 4 H), 9.35 (bs, 1 H). ^{13}C NMR (75 MHz, Cl_3): δ = 38.8, 48.8, 104.6, 107.5, 118.0, 126.8, 128.5, 128.6, 128.7, 129.0, 130.2, 131.7, 133.7, 168.5. GC-MS m/z: 105 (100), 168 (56), 199 (55), 169 (52), 77 (48), 121 (15). Anal. Calcd for $C_{19}H_{18}N_2O$ (290.14): C, 78.59; H, 6.25; N, 9.65. Found: C, 78.14; H, 6.27; N, 9.62.

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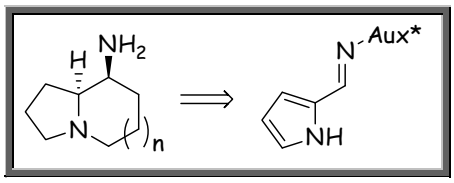
Chapter Index

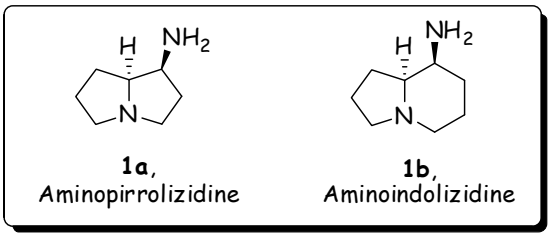
Chap. 5 – Asymmetric Synthesis of 8-Aminoindolizidine from Chiral 2-Pyrroleimines



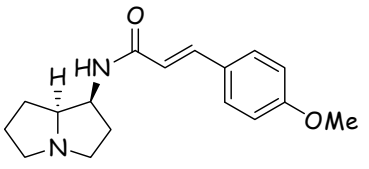
5.1 – Introduction

7-Aminopirrolizidine **1a**[1,2,] and 8-aminoindolizidine **1b** (Scheme 1)[1] and their ring-substituted derivatives are relatively unexplored classes of compounds, despite their presence in nature and their potential activity as glycosidase inhibitors and Anti-HIV drugs.

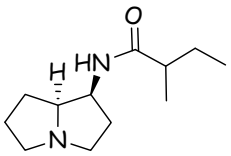
Some examples are the alkaloid (+)-absouline (**2**),[2,3] laburnamine (**3**),[2,4] and the compound **4**,[5] a selective serotonin agonists versus the subunit receptor 5-HT_4. Another example are the mitomycine antibiotics, among which mitomycine C (**5**) is clinically used as an antitumor agent.[6] A derivative of racemic 8-amino-8a-phenylindolizidine (**6**) was prepared as an analogue of the substance P antagonist CP 99,994, but it displayed low biological activity.[7] Finally, some oligonucleotides containing interchain cross-links of bifunctional pyrrole (**7**) were synthesized by Harris and co-workes.[8]



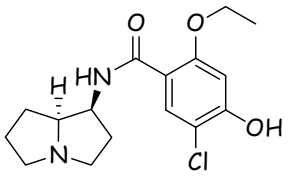
Scheme 1



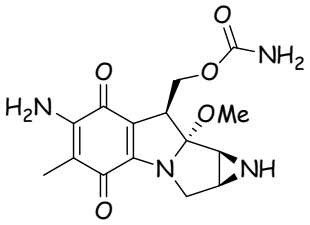
2, absouline



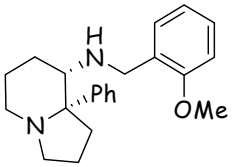
3, laburnamine



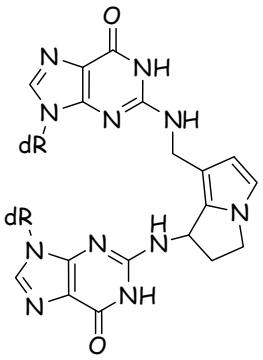
4



5, Mitomycine *C*



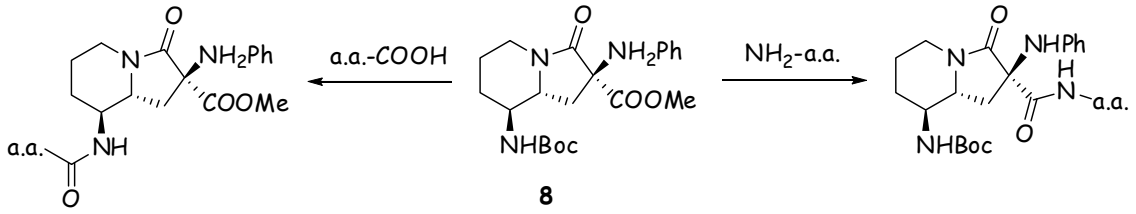
6



7

Scheme 2

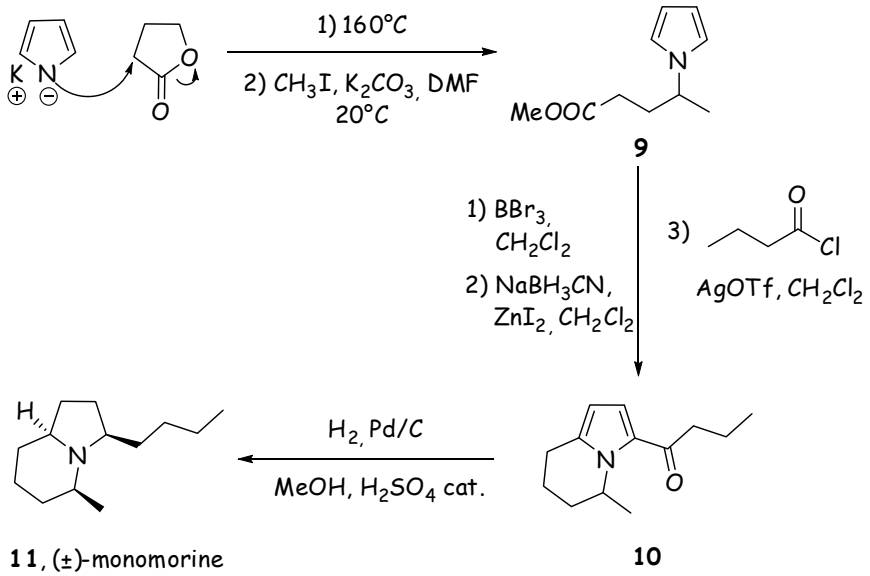
Also 3-oxo-8-aminoindolizidine (**8**) has been considered a constrained analogue of bioactive peptides and substitutes of β-turns (Scheme 3).[9]



8

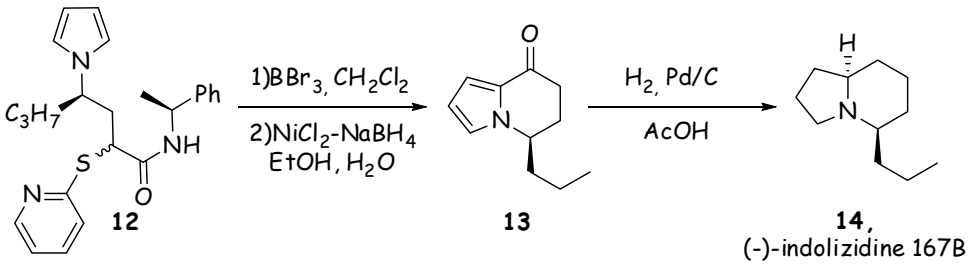
Scheme 3

Pyrroles have been used as building blocks for the stereoselective synthesis of indolizidines, as the heteroaromatic ring can be hydrogenated to pyrrolidine, and the six membered ring was constructed by diverse cyclization strategies.[10] For example, Smith and co-workers prepared racemic pheromone mormorine **11** by hydrogenantion of compound **10**.[11] The first step involved the ring opening of γ-valerolactone by the potassium salt of pyrrole, then *O*-alkylation with methyl iodide, gave the product **9**. The compound was converted by a three step sequence to the bicyclic pyrrole ketone **10**, was hydrogenation finally gave racemic mormorine **11**.



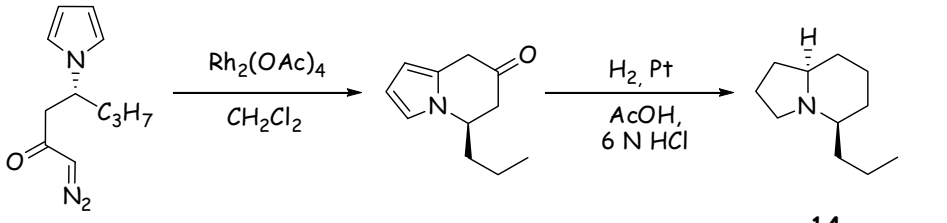
Scheme 4

Pereira[12] reported the synthesis of (-)-indolizidine 167B (**14**) by cyclization of the optically pure amide **12** with boron tribromide. The ketone **13** was then reducted to give the alkaloid with good yield (Scheme 5).



Scheme 5

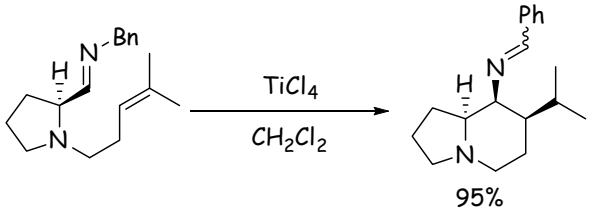
Another enantioselective synthesis of (-)-indolizidine 167B (**14**)[13] involved a Rh-catalyzed intramolecular cyclization of the diazocompound **15** to give the ketone **16**, which was hydrogenated to give **14**.



15 **16** **14**, (-)-indolizidine 167B

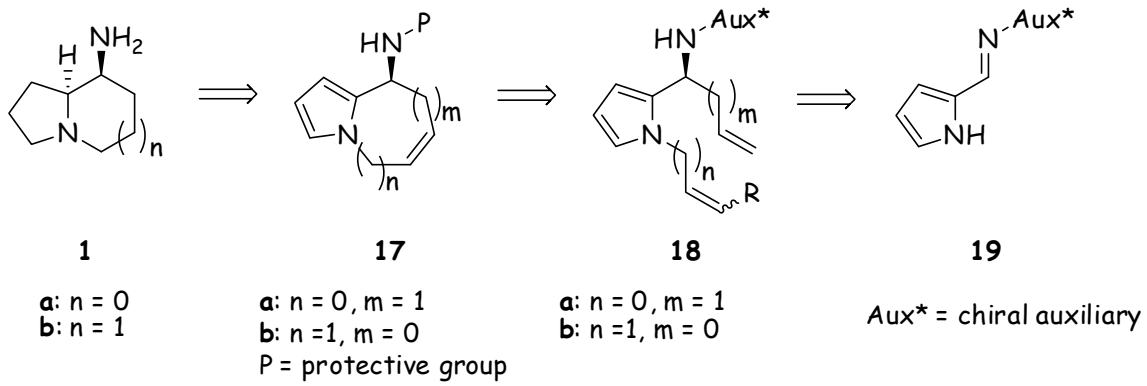
Scheme 6

7-Alkyl-8-aminoindolizidines have been synthesized by intramolecular imino-ene reactions of (L)-1-(3-alkene-1-yl)prolinal imines, so forming the fused six-membered ring (Scheme 7).[14] Certainly, this procedure is advantageous because two C-C bonds are formed in a single step and the reduction of the pyrrole ring is avoided. However, it should be noticed that it allows formation only of the diastereomers with the retained configuration of the stereocenter present in the "ex chiral pool" starting material, which is also not readily available.



Scheme 7

On the other hand, an approach which exploit the double reactivity of the chiral 2-pyrroleimine derived by an optically active amine, acting as a chiral auxiliary available in both the enatiomeric form as depicted in Scheme 8, would allow in principle to synthesize all the four possible diastereomers of 8-aminopirrolizidine **1a** and 7-aminopirrolizidine **1b**.



1

a: n = 0
b: n = 1

17

a: n = 0, m = 1
b: n =1, m = 0
P = protective group

18

a: n = 0, m = 1
b: n =1, m = 0

19

Aux* = chiral auxiliary

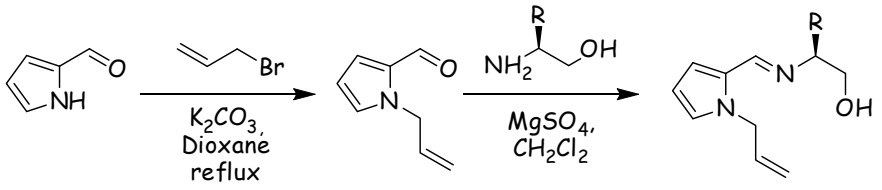
Scheme 8

The route we have envisioned takes advantage of the electrophilic reactivity of the imine function and nucleophilicity of the pyrrole nitrogen atom, allowing the easy preparation of the crucial intermediate **18**. Ring closing methatesis (RCM) to construct the bicyclic skeleton of fused pyrrole derivatives **17**, which can be subsequently hydrogenated to give the fully saturated compounds **1**.[15] The crucial intermediates **18** are in turn obtained by addition of an unsaturated organometallic reagent to the 2-pyrroleimine bearing a chiral auxiliary at the imine nitrogen and an alkenyl group at pyrrole nitrogen **19**. In principle, diversely sized rings can be constructed in the RCM step, depending on the nature of the either pyrrole *N*-substituent and the organometallic reagent, i.e. by varying "n" and "m" in the intermediate **18**. Particularly, a five membered ring is formed when n = m = 0, and a six-membered ring by choosing n = 1, m = 0, or vice versa. All the routes appeared viable at first glance, as we previously described the highly diastereoselective addition of various organometallic reagents to chiral 2-pyrrole imines derived from (*S*)-valinol and (*S*)-phenylglycinol, having unprotected or trimethylsilyl-protected OH and NH functions.[16]

5.2 - Results and discussion

5.2.1 - Addition of organometallic reagents to chiral pyrrole imines derived from 1(S)-valinol and (S)-phenylglycinol

We started our research by routinely preparing with high yields the 1-allyl-2-pyrroleimines **21a** and **21b** from 1-allyl-2-pyrrolealdehyde (**20**), [16] as desribed in Scheme 9.



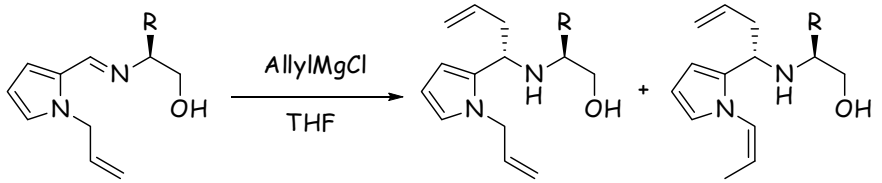
20, 89%

21a, R = *i*Pr 98%
21b, R = Ph 97%

Scheme 9

The OH-free imines **21a,b** were treated with variable amount of allylmagnesium chloride in THF at 0 °C (Scheme 10) and the results reported in Table 1

Scheme 10



21a
21b

a: R = *i*-Pr
b: R = Ph

22a,b

23a,b

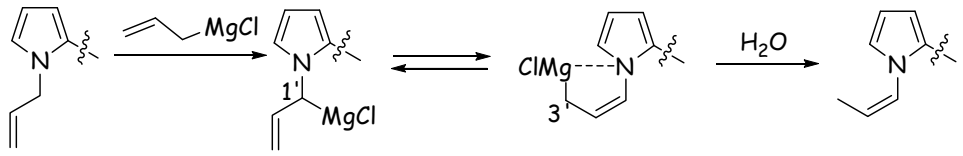
Table 1

Entry	Imine	AllylMgCl (equiv.)	Time (h)	Ratio 22/23[c]	22 + 23 (Yield %)[b]	23 (Yield %)[c]
1	**21a**	2.5	48	53:47	98	**23a** (-[d])
2	**21a**	3	24	24:76	97	**23a** (66)
3	**21a**	4	24	0:100	98	**23a** (92)
4	**22b**	4	24	0:100	98	**23b** (96)

[a] Determined by ^{1}H NMR analysis. [b] Yield of crude product. [c] Yield of isolated, pure product. [c] The product was not isolated.

Unexpectedly, in the first reaction run on the imine **21a**, using only a slight exess of Grignard reagent (2.2 equivalents), a 53:47 mixture of two isomeric amines were obtained, as evidenced by ^{1}H NMR analysis of the crude product. The major isomer was identified as the expected product (**22a**) on the basis of the ^{1}H NMR spectrum, whereas the minor one (**23a**) was supposed to have an isomerized propenyl substituent on the pyrrole nitrogen. The base-promoted isomerisation was attributed to the action of the Grignard reagent in excess amount (Scheme 11), hence the reaction was carried out with increased amounts of

allylmagnesium chloride in order to optimize the yield of compound **23a**, because this compound has the required 1,7-octadiene moiety for the construction of a six-membered ring by the RCM methodology. The results of this investigation are reported in Table 1.

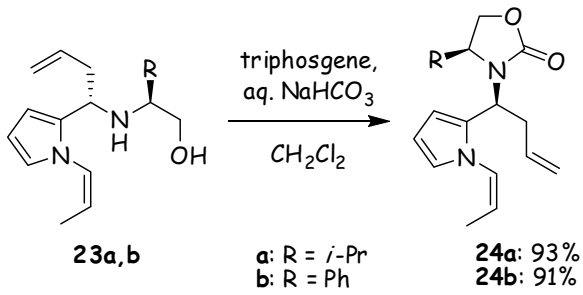


Scheme 11

Thus, it was observed that by increasing the amount of the Grignard reagent a corresponding increased conversion of **22a** to **23a** occurred (entries 2 and 3) and the complete conversion was achieved using 4 equivalents of allylmagnesium chloride (entry 4). The ^{1}H NMR spectrum of the crude product, obtained in 98% yield, showed the presence of only one diastereomer, concerning both the newly formed stereocenter and the alkene geometry, which was determined as *Z* on the basis of the coupling constant of the vinylic protons. On the other hand, GC-MS analysis could not be used to determine the purity and diastereomeric ratio of **23a,b**,[17] as the products were not eluted or underwent massive decomposition. The pure product **23a** was then obtained with 92% yield by chromatography an a SiO_2 column. However, we found that the crude compound could be used without purification in the successive step. Similarity in the same conditions, the imine **21b** was converted to the homoallylic amine **23b** with complete selectivity and excellent yield.

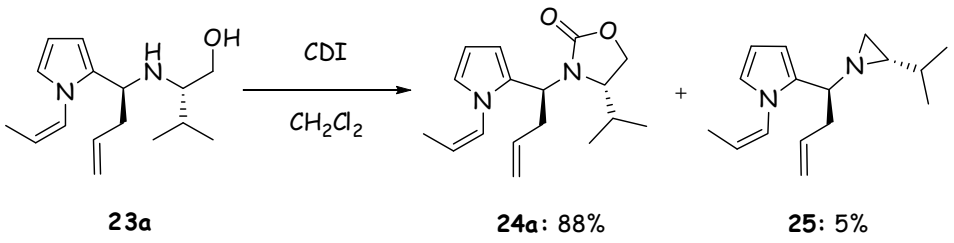
5.2.2 – Protection of amino function and RCM reaction

Before performing the RCM step, it was necessary to protect the amino function. As acidic conditions are not suitable in the presence of the pyrrole ring, we chose to convert the β-aminoalcohol moiety of **23a,b** into an oxazolidinone and prepared the compound **24a,b** by routine reactions with triphosgene (Scheme 12).



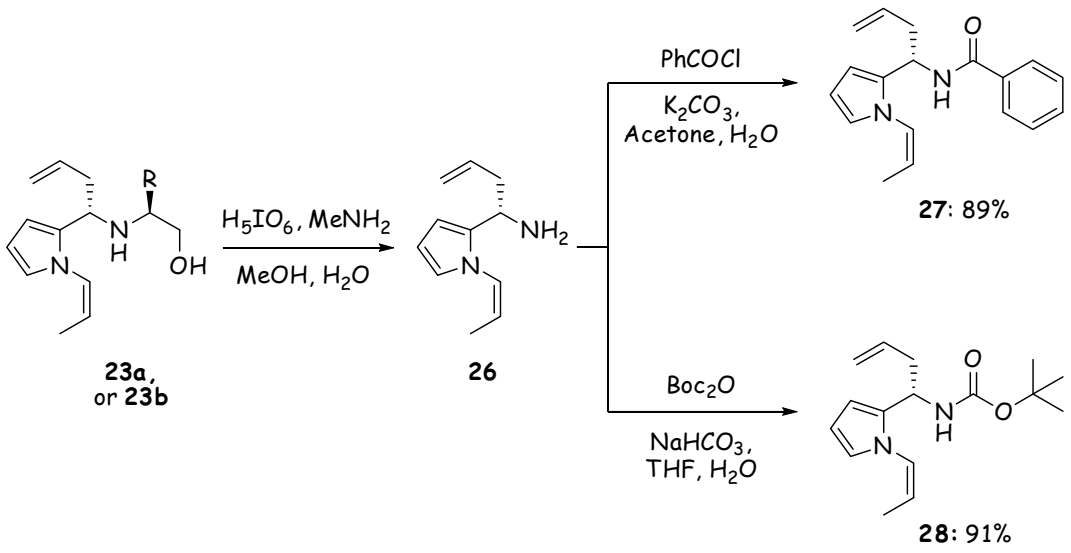
Scheme 12

The reaction performed on the amine **23a** using carbonyldiimidazole (CDI) as reagent (Scheme 13) gave a mixture of the desired product **24a** and the aziridine **25**, which were isolated with 88% and 5% yields, respectively, by column chromatography.



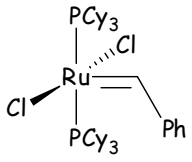
Scheme 13

Moreover, other derivatives of compounds **23a,b**, with protected amino function were prepared (Scheme 14). Particularly, we removed the auxiliary group by common oxidative procedures and transformed the primary amines **26** into the corresponding benzamide **27** or *N*-Boc derivate **28**.

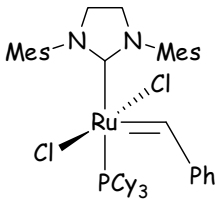


Scheme 14

On this compounds the RCM step was investigated, exploring the effectiveness of first generation and second generation Grubbs catalysts (ruthenium benzylidene complexes **I** and **II**, respectively Scheme 15).



I
Grubbs 1st generation

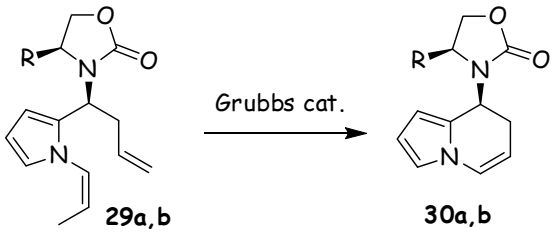


II
Grubbs 2nd generation

Scheme 15

The results obtained, reported in Table 2, showed that both catalysts can be used to that purpose, although **II** was more effective and allowed the reaction to reach completion in less time than **I**: 0.5 h vs 4 h in dichloromethane at the reflux temperature, using 5 mol% both catalyst (entries 1 and 2). Moreover, the same high yields of bicycling product **30a** could be obtained using catalyst **II** in toluene at 115 °C for 0.5 h with 5 mol% loading (entry 3) and in dichloromethane at 40 °C for 1.5 h with 2.5 mol% loading (entry 4). By further decreasing the catalyst loading to 1 mol%, the reaction time was increased to 4 h achive the same high yield (entry 5). The latter conditions were then applied to the diene **30b** to obtain the same efficient ring closing to give **30b** (entry 6).

Scheme 16



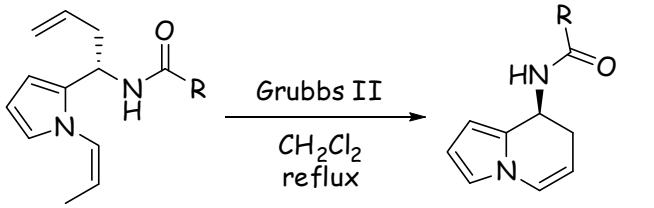
29a,b **30a,b**

Table 2

Entry	Compound	Grubbs cat. (mol%)	Solvent	Temp. (°C)	Time (h)	Product (Yield %)[a]
1	**29a**	**I** (5.0)	CH_2Cl_2	40	4	**30a** (93)
3	**29a**	**II** (5.0)	CH_2Cl_2	40	0.5	**30a** (94)
2	**29a**	**II** (5.0)	Toluene	115	0.5	**30a** (95)
4	**29a**	**II** (2.5)	CH_2Cl_2	40	1.5	**30a** (94)
5	**29a**	**II** (1.0)	CH_2Cl_2	40	4	**30a** (95)
6	**29b**	**II** (1.0)	CH_2Cl_2	40	4	**30b** (96)

[a] Yield of isolated, pure product.

The compounds **27** and **28** were also submitted to RCM using 1 mol% of Grubbs catalyst **II** in reflux dichloromethane and the corrisponding bicyclic products (**32** and **32**) were obtained with good yields (Scheme 17).



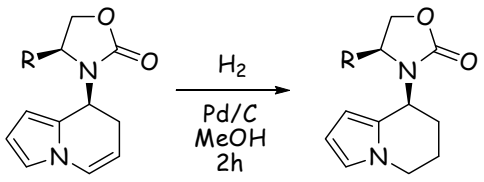
27: R = Ph
28: R = t-BuO

31: R = Ph 92%
32: R = t-BuO 94%

Scheme 17

5.2.3 – Hydrogenation of the pyrrole ring

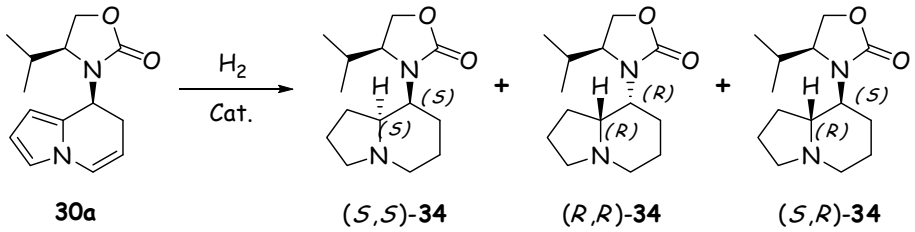
Finally, we directed our efforts to the hydrogenation of the unsaturated bicyclic compounds **30a,b**, **31** and **32**. Hydrogenation of only the alkene function of **30a,b** to give **33a,b** was easily achieved by stirring a solution of **30a,b** in methanol under 1 atm H_2 in the presence of 10% Pd/C for 2 hours. However we were interested to achieve the fully saturated, indolizidine derivatives.



30a,b **33a,b**

Scheme 18

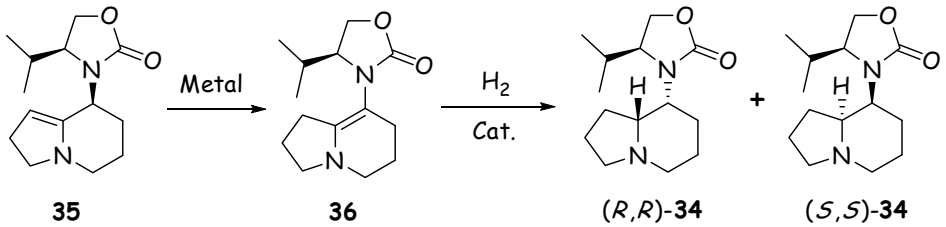
Literature survey showed that substituted pyrroles can be hydrogenated to give pyrrolidine derivatives in the presence of palladium, platinum and rhodium heterogeneous catalysts.[10,18] We have carried out reaction on **30a** using 10% Pd/C, 10% $Pd(OH)_2/C$, PtO_2, most frequently using methanol as the solvent, and the resulta are reported in Table 3. In all cases, mixtures of three diastereomers were formed with poor diastereoselectivity, as evinced by GC-MS analyses of the crude products (Scheme 19).



30a (*S*,*S*)-**34** (*R*,*R*)-**34** (*S*,*R*)-**34**

Scheme 19

By assuming that hydrogen addition took plan to both the pyrrole faces and the stereocenter present in the six-membered ring is uninfluenced in the reaction condition only two stereoisomers should be observed. A third stereoisomer should be formed by a mechanism involving stepwise reduction of the pyrrole ring to give pirrolines (**35**) which undergo isomerization by migration of the C=C bond to the six-membered ring. The intermediate **36** is the obtained, causing loss of the pre-existing stereocenter, than uptake of hydrogen can occur on both faces leading two either (*R*,*R*)-**34** and (*S*,*S*)-**34** (Scheme 20).



35 **36** (*R*,*R*)-**34** (*S*,*S*)-**34**

Scheme 20

Fortunately the three diasteroisomers could be separated, cromatographically at lest in part and suitable crystals were obtained for two isomers allowing structurely identification by X-Ray analysis. So, we could assigned the (*S*,*S*), (*S*,*R*) configurations of the stereocenters in bicylclic skeleton of two diateroisomers, the first and third eluted in GC analysis (Figure 1).

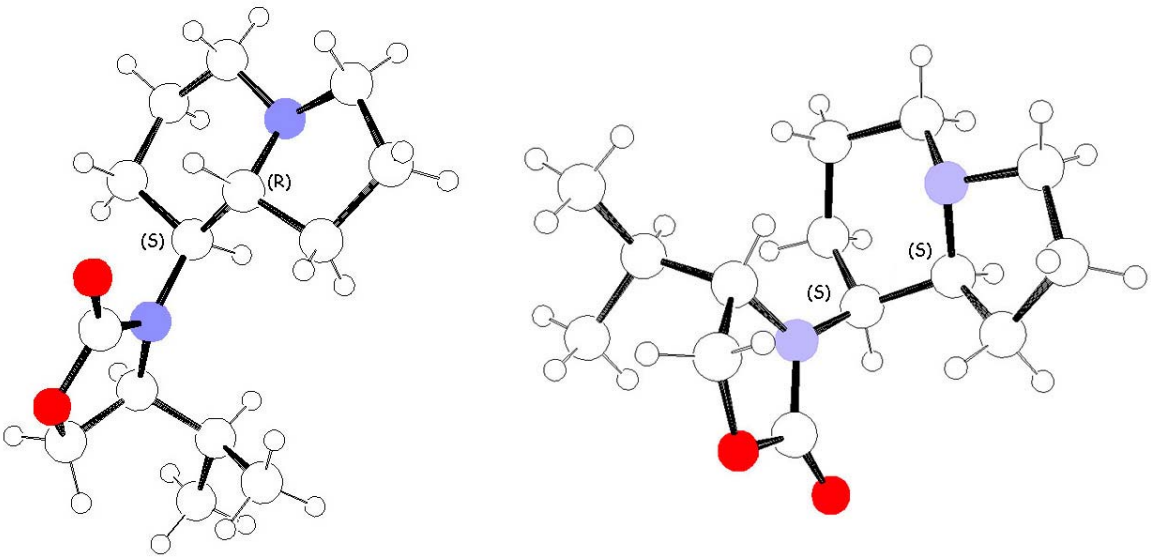


Figure 1 (*R*,*S*)-**34** and (*S*,*S*)-**34**

The results are several reports of analogous hydrogenation of, chiral pyrroles having stereocenters at the benzylic position. It is noteworthy that (*S*,*R*)-**34** was the minor one when the reaction was performed at 1 atm of H_2 in the presence of 10% Pd/C, even in the presence of acetic acid (entries 1 and 2). Instead, it was the major diastereomer when 10% $Pd(OH)_2/C$ was used, although at low conversion of **30a** (entry 3). Aiming to improve the yield of saturated products, hydrogenation was carried out at higher pressure (8 atm of H_2) and in the presence of acetic acid, and in these conditions a mixture of the three diastereomers was again obtained in quantitative yield (entry 4). The addition of 1M solution of hydrochloridric acid in diethyl ether to the MeOH improved the rate of the reaction and a complete conversion was observed at 1 atm H_2 after 24 hours (entry 5). The Adam catalyst (PtO_2, 10 mol%) proved to be ineffective, as only 10% conversion was observed after 48 h in MeOH (entry 6).

Table 3

Entry	Catalyst (%)	Solvent	t (h)	P H_2 (atm)	Conversion (%)[a]	(*S*,*S*)-34 (%)[a]	(*R*,*R*)-34 (%)[a]	(*S*,*R*)-34 (%)[a]
1	10% Pd/*C* (20%)	MeOH	48	1	100	43	42	15
2	10% Pd/*C* (20%)	MeOH-AcOH(20%)	24	1	100	38	47	15
3	20% $Pd(OH)_2$/*C* (20%)	MeOH	48	1	30	16	11	73
4	20% $Pd(OH)_2$/*C* (20%)	MeOH-AcOH(20%)	24	8	100	24	28	48
5	20% $Pd(OH)_2$/*C* (20%)	MeOH-1 M HCl in Et_2O (20%)	24	1	100	54	32	14
6	PtO_2 (10%)	MeOH	48	1	10	14	14	72

[a] Determined by GC-MS analysis.

Then we tested rhodium-based catalysts for the hydrogenation of pyrrole ring. 5%-Rh/Al_2O_3 gave more satisfactory results (Table 4), as mixture of only (*S*,*S*)-**34** and (*S*,*R*)-**34** was quantitatively formed with a moderate prevalence of the latter compound (entry 1, Table 4). An increase of their ratio (74:26) was obtained in MeOH at 8 atm hydrogen pressure (entry 2), whereas substitution of methanol by ethyl acetate gave a slightly less satisfactory conversion and diastereoselectivity (entry 3). The use of DMF as solvent increased markedly the diasteroselectivity (d.r. 93:7), but had a negative effect on the rate of the reaction (entry 4). When the reaction was carried out using a 1:1 MeOH:DMF mixture we observed an increase of rate of the reaction with almost the same disteroselectivity rate (entry 5). No reaction occurred when 0.5M of K_2CO_3 was added to MeOH (entry 6); instead the addition of triethyl amine (20 mol%) slightly increase the disteroselectivity but slowly the rate of reaction (entry 7).

We also prepared Rh-graphite from potassium graphite (C_8K) and $RhCl_3$. We were delighted to observe that this new catalyst was fairly more reactive that Rh/Al_2O_3 and gave the indolizidine **34** after only 11 hours with comparable diasteroselectivity.

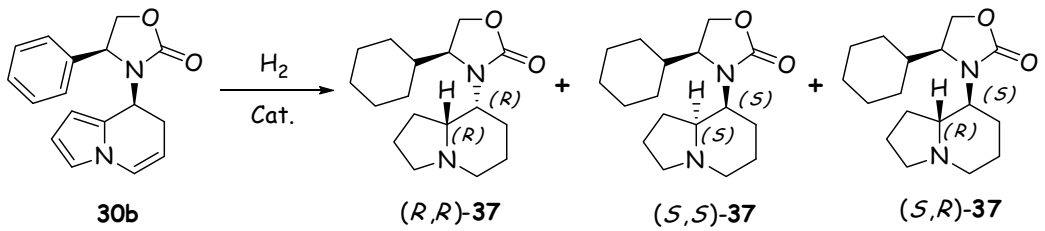
Table 4

Entry	Catalyst (%)	Solvent	t (h)	P H_2 (atm)	Conversion (%)	(*S*,*S*)-34 (%)	(*R*,*R*)-34 (%)	(*S*,*R*)-34 (%)
1	5% Rh/Al_2O_3 (10%)	MeOH	24	1	100	31	0	69
2	5% Rh/Al_2O_3 (10%)	MeOH	24	8	100	26	0	74
3	5% Rh/Al_2O_3 (10%)	AcOEt	24	8	96	40	0	60
4	5% Rh/Al_2O_3 (10%)	DMF	72	1	30	7	0	93
5	5% Rh/Al_2O_3 (20%)	DMF:MeOH 1:1	72	1	70	10	0	90
6	5% Rh/Al_2O_3 (10%)	MeOH-H_2O (10%)-K_2CO_3	72	1	0	-	-	-
7	5% Rh/Al_2O_3 (10%)	MeOH-TEA(20%)	72	1	100	22	0	78
9	26% Rh-Graphite (1,5%)	MeOH	11	1	100	39	0	61
10	26% Rh-Graphite (1,5%)	MeOH-TEA(20%)	72	1	100	24	0	76

[a] Determined by GC-MS analysis.

The same protocol was applied to the phenylglicinol derivate **30b**. Using Pd/C and Rh/Al_2O_3 in MeOH we observed a complex a mixture of compounds. Accurate GC-MS analyse, demonstrated that hydrogenation of the phenyl ring had partially occurred. Only when the reaction was carried out in the presence of acetic acid the fully hydrogenated products (**37**) where only observed being formed with moderate diasteroselectivity. Substitution of methanol by acetonitrile gave hydrogenation of the only alkene function. The configuration of products was confirmed by X-Ray analysis of (*S*,*R*)-**37** (Figure 2).

Scheme 21



30b (*R*,*R*)-**37** (*S*,*S*)-**37** (*S*,*R*)-**37**

Table 5

Entry	Catalyst (%)	Solvent	t (h)	P H_2 (atm)	Conversion (%)[a]	(*S*,*S*)-37 (%)[a]	(*R*,*R*)-37 (%)[a]	(*S*,*R*)-37 (%)[a]
1	10% Pd/C (20%)	MeOH	48	1	-[b]	-	-	-
2	5% Rh/Al_2O_3 (10%)	MeOH	48	1	-[b]	-	-	-
3	5% Rh/Al_2O_3 (10%)	MeOH-AcOH(20%)	48	1	100	5	31	64
4	5% Rh/Al_2O_3 (10%)	MeOH-AcOH(20%)	24	8	100	3	28	69
5	5% Rh/Al_2O_3 (10%)	MeCN	72	1	0[c]	-	-	-
6	26% Rh-Graphite (1,5%)	MeOH-AcOH(20%)	24	1	100	5	29	66

[a] Determined by GC-MS analysis. [b] Complex mixure of coumponds. [c] Only the product **33b** was recoved with 97% of yield.

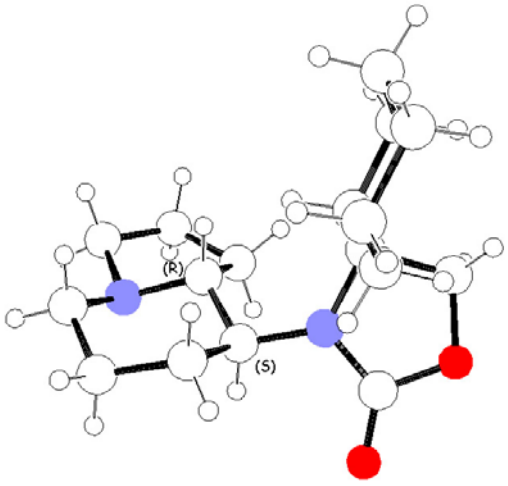
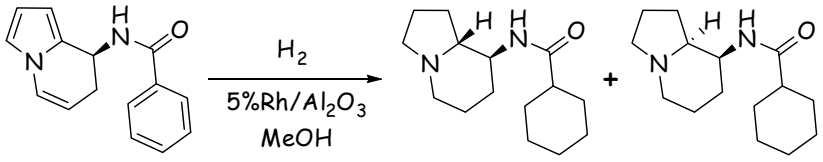


Figure 2 (*S*,*R*)-**37**

Hydrogenation of the amide **31** using 5%-Rh/Al_2O_3 afforted the products with saturation of all the aromatic rings (Scheme 22). We obtained two different separable diasteroisomers from the GC-MS analysis, but after chiral GC analysis, the compound (*S*,*S*)-**38** was present as mixture of enantiomers. The better results was obtained using MeOH as solvent under a 1 atm pressure of hydrogen (Table 6).

Scheme 22



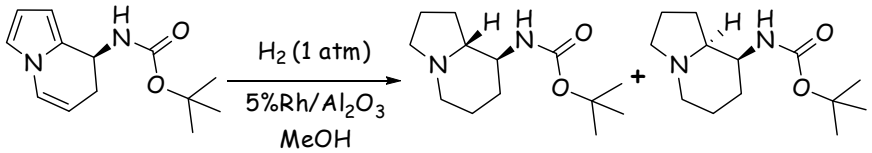
31 (*S*,*R*)-**38** (*S*,*S*)-**38**

Table 6

t (h)	P H_2 (atm)	Conversion (%)[a]	(*S*,*R*)-38 (%)[a]	(*S*,*S*)-38 (%)[a]	e.e.(*S*,*S*)-38 (%)[b]
96	1	100	32	68	84
24	8	100	38	62	88

[a] Determined by GC-Ms analysis. [b] Determined by chiral GC analysis.

With the same procedure *N*-Boc derivate **32** was hydrogenated to give two separable diasteroisomer, one of which was present as a mixture of enantiomers (*S*,*S*)-**39** and (*R*,*R*)-**39**.



32 (*S*,*R*)-**39** 35% (*S*,*S*)-**39** 67% (e.e. 91%)

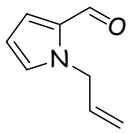
Scheme 23

5.3 – Experimental section

Melting points are uncorrected. Optical rotations were measured on a digital polarimeter in a 1-dm cell and $[\alpha]_D$-values are given in 10^{-1} deg cm^3 g^{-1}. ^1H NMR spectra were recorded on Varian Inova and Gemini instruments for samples in $CDCl_3$ which was stored over Mg: ^1H chemical shifts are reported in ppm relative to $CHCl_3$ (δ_H 7.27), J-values are given in Hz. and in the assignments s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, m = multiplet, bs = broad singlet, dd = doublet of doublets and dt = doublet of triplets. Infrared spectra were recorded on a Nicolet FT-380 spectrometer and IR assignments are reported in wavenumbers (cm^{-1}). MS spectra were taken at an ionising voltage of 70 eV on a Hewlett-Packard 5975 spectrometer with GLC injection. Analytical gas chromatography (GC) was performed on a Hewlett-Packard HP 6890 gas chromatograph with a flame ionization

detector and split mode capillary injection system, using a Megadex 5 chiral column (25 m, flow rate 15mL/min). Molecular weight was determined on an Agilent Technologies MS 1100 instrument. Chromatographic separations were performed on columns of SiO_2 (Merck, 230-400 mesh) at medium pressure. All the organic, inorganic and organometallic reagents and reactants and anhydrous solvents were purchased from Aldrich.

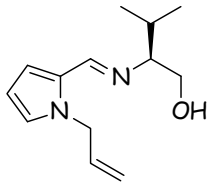
5.3.1 – Preparation of Aldehyde ***20***



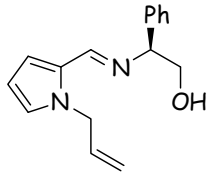
To a solution of 2-pyrrolecarbaldehyde (2.420 g, 25.4 mmol) in dioxane (40 mL) allylbromide was added (6.6 mL, 9.22 g, 76.2 mmol) and K_2CO_3 (12.30 g, 89.0 mmol) and the mixture was refluxed for 8 hours. Then the mixture was cooled at room temperature and cyclohexane (40 mL). The solid was filtered off through a pad of Celite and the organic phase was concentrated at reduced pressure. Flash column chromatography (SiO_2) eluting with cyclohexane/ethyl acetate 9:1 mixtures gave the product **20** (89 %, 3.05 g, 22.6 mmol).
1-allyl-2-pyrrolealdehyde (20): Red oil; IR (neat): ν = 3109, 3085, 2929, 2807, 2768, 2724, 1662, 1479, 1405, 1369, 1317, 1218, 1075, 1030, 993, 924, 749, 609; ^1H NMR (300 MHz, $CDCl_3$): δ = 9.55 (d, J = 0.9 Hz, 1 H), 6.95 (m, 2 H), 6.26 (dd, J = 2.6 Hz, J = 3.9 Hz, 1 H), 5.99 (m, 1 H), 5.18 (dd, J = 1.3 Hz, J = 2.7 Hz, 1 H), 5.15 (dd, J = 1.3 Hz, J = 2.7 Hz, 1 H), 5.08 (dd, J = 1.5 Hz, J = 3.2 Hz, 1 H), 4.98 (t, J = 1.7 Hz, 2 H), 4.96 (d, J = 1.5 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 50.7, 109.7, 116.9, 124.4, 130.9, 131.2, 133.9, 179.1; MS (EI): m/z = 118 (100), 134 (67), 106 (62), 135 (61), 79 (46).

5.3.2 – General protocol for the preparation of imines ***21a*** *and* ***21b***

To a solution of (*S*)-phenylglycinol (1.50 g, 11.1 mmol) or (*S*)-valinol (1.14 g, 11.1 mmol) in anhydrous CH_2Cl_2 (40 mL) was added anhydrous $MgSO_4$ (5 g) and **5** (1.5 g, 11.1 mmol) and the mixture was stirred overnight. The solid was filtered off through a pad of Celite and the organic phase was concentrated at reduced pressure to gave the desire imine.



(*S*)-*N*-(1-Allyl-2-pyrrolmethylidene)valinol (21a): Red oil; 2.39 g (98%); $[\alpha]_D^{20}$ -101.5 (*c* 1.3, $CHCl_3$); IR (neat): *ν* = 3060, 3023, 2831, 1642, 1530, 1367, 1025, 920, 733; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.11 (s, 1 H), 6.77 (t, *J* = 2.1 Hz, 1 H), 6.53 (ddd, *J* = 0.6 Hz, *J* = 1.7 Hz, *J* = 3.7 Hz, 1 H), 6.19 (dd, *J* = 2.7 Hz, *J* = 3.6 Hz, 1 H), 5.99 (ddd, *J* = 5.0 Hz, *J* = 5.2 Hz, *J* = 10.1 Hz, 1 H), 5.14 (t, *J* = 1.4 Hz, 1 H), 5.10 (t, *J* = 1.7 Hz, 1 H), 5.03 (m, 2 H), 3.73 (d, *J* = 6.0 Hz, 2 H), 2.80 (q, *J* = 6.0 Hz, 1 H), 2.08 (bs, 1 H), 1.87 (sept, *J* = 6.8 Hz, 1 H), 0.93 (d, *J* = 6.8 Hz, 3 H), 0.86 (d, *J* = 6.8 Hz, 3 H); ^{13}*C* NMR (75 MHz, $CDCl_3$): δ = 19.5, 20.2, 30.7, 51.3, 65.2, 79.6, 109.0, 116.2, 117.4, 128.5, 129.6, 135.9, 153.4; *GC*-MS (EI): *m/z* = 118 (100), 189 (34), 134 (26), 117 (18), 205 (7), 220 (4).

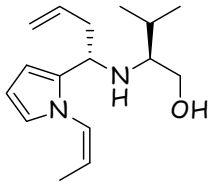


(*S*)-*N*-(1-Allyl-2-pyrrolmethylidene)phenylglycinol (21b): Red oil; 2.73 g (97%); $[\alpha]_D^{20}$ -126.3 (*c* 1.8, $CHCl_3$); IR (neat): *ν* = 3387, 3083, 3062, 3027, 2825, 2863, 1638, 1534, 1425, 1371, 1310, 1031, 921, 733; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.26 (s, 1 H), 7.29-7.44 (m, 5 H), 6.82 (t, *J* = 2.1 Hz, 1 H), 6.58 (dd, *J* = 1.8 Hz, *J* = 3.8 Hz, 1 H), 6.33 (dd, *J* = 2.7 Hz, *J* = 3.8 Hz, 1 H), 6.07 (ddd, *J* = 5.1 Hz, *J* = 10.3 Hz, *J* = 17.1 Hz, 1 H), 5.22 (ddt, *J* = 1.7 Hz, *J* = 5.2 Hz, *J* = 16.0 Hz, 1 H), 5.17 (dq, *J* = 1.7 Hz, *J* = 10.3 Hz, 1 H), 5.03 (ddt, *J* = 1.7 Hz, *J* = 4.7 Hz, *J* = 16.0 Hz, 1 H), 4.93 (dq, *J* = 1.7 Hz, *J* = 17.1 Hz, 1 H), 4.36 (t, *J* = 6.4 Hz, 3 H), 3.86 (d, *J* = 6.4 Hz, 2 H); ^{13}*C* NMR (75 MHz, $CDCl_3$): δ = 50.9, 68.0, 76.6, 108.5, 115.8, 117.7, 126.4, 127.1, 127.3, 128.3, 128.8, 135.3, 141.1, 153.6; *GC*-MS (EI): *m/z* = 118 (100), 223 (92), 106 (41), 91 (34), 79 (30), 239 (21), 254 (11).

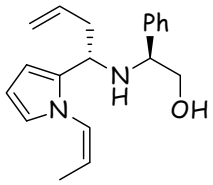
5.3.3 – General protocol for the preparation of β-Aminoalcohols ***23a,b***

Allylmagnesium chloride (1.0 M in THF, 23.6 mL, 23.6 mmol) was added to a magnetically stirred solution of the imine **23b** (1.50 g, 5.9 mmol) in THF (25 mL) cooled at 0 °C. After 30 min the reaction mixture was slowly warmed up until room temperature was reached, and stirring was continued for 24 h. The mixture was quenched by adding a saturated aqueous

solution of $NaHCO_3$ (30 mL) at 0 °C, then the organic material was extracted with diethyl ether (3 ×20 mL). The collected ethereal layers were dried over Na_2SO_4 and concentrated to leave the crude product. Flash column chromatography (SiO_2) eluting with cyclohexane/ethyl acetate 9:1 mixtures gave the product **24b**. This compound decomposed on attempted GC-MS and HPLC-MS analyses.



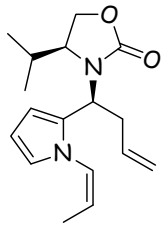
(23a): Yellow oil; $[\alpha]_D^{20}$ -27.3 (*c* 1.6, $CHCl_3$); IR (neat): *v* =3326, 3062, 2918, 2864, 1662, 1474, 1363, 1067, 915; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.66 (dq, *J* = 1.8 Hz, *J* = 8.3 Hz, 1 H), 6.62 (dd, *J* = 1.7 Hz, *J* = 2.8 Hz, 1 H), 6.16 (dd, *J* = 2.8 Hz, *J* = 3.6 Hz, 1 H), 6.16 (dd, *J* = 1.7 Hz, *J* = 3.6 Hz, 1 H), 5.73 (m, 1 H), 6.16 (ddd, *J* = 7.0 Hz, *J* = 8.3 Hz, *J* = 14.1 Hz, 1 H), 5.06 (m, 2 H), 3.85 (dd, *J* = 4.1 Hz, *J* = 4.7 Hz, 1 H), 3.56 (dd, *J* = 4.1 Hz, *J* = 10.7 Hz, 1 H), 3.37 (dd, *J* = 4.7 Hz, *J* = 10.7 Hz, 1 H), 2.45 (tt, *J* = 1.2 Hz, *J* = 7.0 Hz, 2 H), 2.37 (m, 1 H), 2.16 (bs, 2 H), 1.74 (dd, *J* = 1.8 Hz, *J* = 7.0 Hz, 3 H), 0.92 (d, *J* = 6.9 Hz, 3 H), 0.87 (d, *J* = 6.9 Hz, 3 H); ^{13}*C* NMR (75 MHz, $CDCl_3$): δ = 12.5, 18.7, 19.6, 29.5, 41.2, 52.2, 59.9, 61.2, 106.2, 107.5, 117.2, 121.2, 121.4, 126.1, 135.0, 135.3; MS (ES): *m/z* = 285.4 $[M + Na]^+$, 160.2 [M - valinol]$^+$.



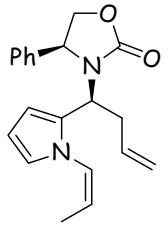
(23b): Yellow oil; $[\alpha]_D^{20}$ -31.9 (*c* 1.5, $CHCl_3$); IR (neat): *v* = 3407, 3077, 2957, 2872, 1662, 1640, 1470, 1311, 1068, 917, 713; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.22-7.44 (m, 5 H), 6.63 (dd, *J* = 1.7 Hz, *J* = 2.8 Hz, 1 H), 6.43 (dq, *J* = 1.6 Hz, *J* = 8.4 Hz, 1 H), 6.16 (t, *J* = 3.4 Hz, 1 H), 5.63-5.83 (m, 1 H), 5.37 (ddd, *J* = 7.0 Hz, *J* = 8.4 Hz, *J* = 14.2 Hz, 1 H), 4.98-5.06 (m, 2 H), 3.85 (dd, *J* = 4.5 Hz, *J* = 7.6 Hz, 1 H), 3.78 (t, *J* = 6.6 Hz, 1 H), 3.68 (dd, *J* = 4.5 Hz, *J* = 10.7 Hz, 1 H), 3.50 (dd, *J* = 7.6 Hz, *J* = 10.7 Hz, 1 H), 2.49 (dd, *J* = 6.4 Hz, *J* = 7.0 Hz, 2 H), 2.26 (bs, 2 H), 1.68 (dd, *J* = 1.8 Hz, *J* = 7.0 Hz, 3 H); ^{13}*C* NMR (75 MHz, $CDCl_3$): δ = 12.4, 39.1, 51.7, 60.9, 65.7, 106.6, 107.4, 117.2, 120.7, 121.3, 125.8, 127.2, 127.5, 128.5, 134.1, 135.0, 141.0; MS (ES): *m/z* = 319.4 $[M + Na]^+$, 160.1 [M - valinol]$^+$.

*5.3.4 – General protocol for the preparation of Oxazolidinones **24a,b***

To a solution of β-aminoalcohol **23b** (1.3 g, 4.4 mmol) in CH_2Cl_2 (20 mL) was added a saturated aqueous solution of $NaHCO_3$ (10 mL), triphosgene (0.652 g, 2.2 mmol) at 0 °C, and the mixture was stirred overnight. The mixture was extracted with dichlorometane (3 ×20 mL). The collected organic layers were dried over Na_2SO_4 and concentrated to leave the crude product. Flash column chromatography (SiO_2) eluting with cyclohexane/ethyl acetate 8:2 mixtures gave the product **24b** (91 %, 1.290 g, 4 mmol).



(24a): White solid; 93 % (0.785 g, 2.73 mmol) from 3.0 mmol (0.787 g) of **8a**; mp = (77.3-77.5)°C; $[\alpha]_D^{20}$ -76.8 (*c* 1.0, $CHCl_3$); IR (KBr): *ν* = 3129, 3104, 2932, 2873, 1732, 1665, 1482, 1412, 1230, 1070, 1049, 925, 745, 725, 626; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.77 (dd, *J* = 1.6 Hz, *J* = 2.8 Hz, 1 H), 6.48 (ddd, *J* = 1.7 Hz, *J* = 3.5 Hz, *J* = 8.2 Hz, 1 H), 6.2 (m, 2 H), 5.90 (m, 1 H), 5.55 (ddd, *J* = 6.1 Hz, *J* = 8.4 Hz, *J* = 13.9 Hz, 1 H), 5.04-5.21 (m, 2 H), 4.00 (dd, *J* = 4.8 Hz, *J* = 9.0 Hz, 1 H), 3.92 (dd, *J* = 8.2 Hz, *J* = 9.0 Hz, 1 H), 4.01 (ddd, *J* = 3.2 Hz, *J* = 4.9 Hz, *J* = 9.0 Hz, 1 H), 2.74-2.89 (m, 2 H), 1.98 (dsept, *J* = 3.3 Hz *J* = 6.9 Hz, 1 H), 1.76 (dd, *J* = 1.9 Hz, *J* = 7.2 Hz, 1 H), 0.92 (d, *J* = 6.9 Hz, 3 H), 0.70 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.2, 13.6, 29.7, 37.6, 50.6, 58.3, 62.2, 107.3, 108.9, 117.5, 120.7, 122.5, 124.9, 128.1, 134.5, 158.2; GC-MS (EI): *m/z* = 247 (100), 118 (67), 159 (38), 86 (25), 207 (16), 281 (5).

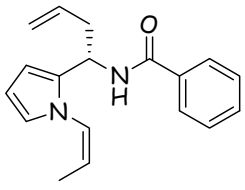


(24b): Yellow oil; $[\alpha]_D^{20}$ -83.9 (*c* 1.6, $CHCl_3$); IR (neat): *ν* = 3076, 3034, 2977, 2918, 2858, 1746, 1663, 1476, 1403, 1218, 1070, 1045, 918, 702; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38 (m, 3 H), 7.23 (m, 2 H), 6.84 (dd, *J* = 1.6 Hz, *J* = 2.8 Hz, 1 H), 6.58 (dq, *J* = 1.7 Hz, *J* = 8.4 Hz, 1 H),

6.20 (t, *J* = 3.3 Hz, 1 H), 5.96 (ddd, *J* = 0.8 Hz, *J* = 1.5 Hz, *J* = 3.6 Hz, 1 H), 5.74 (dddd, *J* = 6.1 Hz, *J* = 7.3 Hz, *J* = 10.2 Hz, *J* = 13.7 Hz, 1 H), 5.61 (ddd, *J* = 7.1 Hz, *J* = 8.4 Hz, *J* = 14.2 Hz, 1 H), 5.14 (dd, *J* = 6.9 Hz, *J* = 7.0 Hz, 1 H), 5.01 (dq, *J* = 1.3 Hz, *J* = 10.2 Hz, 1 H), 4.89 (dq, *J* = 1.5 Hz, *J* = 17.0 Hz, 1 H), 4.40 (t, *J* = 7.9 Hz, 1 H), 4.14 (dd, *J* = 7.9 Hz, *J* = 13.9 Hz, 1 H), 4.09 (dd, *J* = 7.9 Hz, *J* = 13.6 Hz, 1 H), 2.18-2.28 (m, 1 H), 2.03-2.13 (m, 1 H), 1.84 (dd, *J* = 1.8 Hz, *J* = 8.1 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.3, 36.5, 50.9, 57.7, 70.2, 107.2, 109.6, 117.4, 120.7, 122.6, 125.2, 127.6, 128.5, 128.8, 134.3, 139.8, 158.0; GC-MS (EI): *m/z* = 281 (100), 118 (66), 159 (25), 91 (24), 322 (2).

5.3.5 – Preparation of benzamide ***27***

The valinol derivative **23a** (0.445 g, 1.7 mmol) and a 40% solution of $MeNH_2$ in H_2O (4.0 mL, 5.2 mmol) were dissolved in MeOH (5 mL), then a solution of H_5IO_6 (1.40 g, 6.0 mmol) in H_2O (5 mL) was added dropwise and the mixture was stirred for 2 h at room temperature. The organic materials were extracted with Et_2O (3 × 20 mL), then the collected ethereal layers were washed with brine, dried over Na_2SO_4 and concentrated to leave the primary amine **26** as a yellow oil. This was dissolved in acetone (5 mL), then H_2O (5 mL), K_2CO_3 (0.470 g, 3.4 mmol) and benzoyl chloride (296 μl, 2.6 mmol) were added while magnetically stirring. After 12 h most of the solvent was evaporated at reduced pressure, and the organic materials were extracted with Et_2O (3 × 20 mL). The collected ethereal layers were dried over Na_2SO_4 and concentrated to leave a white solid, which was crystallized from acetone to give pure **27** (88%, 420 mg, 1.7 mmol).

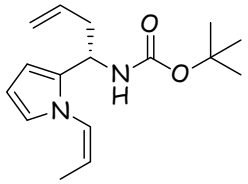


(27):White crystals (from pentane:Et_2O, 9:1); m.p. = (88.3-88.9) °C; $[\alpha]_D^{20}$ -23.2 (*c* 0.9, $CHCl_3$); IR (KBr): *ν* =3287, 3076, 3040, 2939, 1662, 1631, 1578, 1528, 1477, 1306, 1076, 719, 697; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.72-7.78 (m, 2 H), 7.41-7.54 (m, 3 H), 6.67 (dd, *J* = 1.7 Hz, *J* = 2.6 Hz, 1 H), 6.67 (dq, *J* = 1.8 Hz, *J* = 8.5 Hz, 1 H), 6.22 (ddd, *J* = 0.6 Hz, *J* = 1.7 Hz, *J* = 3.7 Hz, 1 H), 6.18 (dd, *J* = 2.7 Hz, *J* = 3.6 Hz, 1 H), 6.13 (d, *J* = 8.0 Hz, 1 H), 5.81-5.94 (m,

1 H), 5.52 (dd, *J* = 7.1 Hz, *J* = 8.5 Hz, *J* = 14.1 Hz, 1 H), 5.41 (q, *J* = 7.0 Hz, 1 H), 5.15 (dq, *J* = 1.5 Hz, *J* = 17.1 Hz, 1 H), 5.12 (ddd, *J* = 1.0 Hz, *J* = 2.0 Hz, *J* = 10.1 Hz, 1 H), 2.76 (m, 2 H), 1.74 (dd, *J* = 1.8 Hz, *J* = 7.1 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.3, 39.0, 45.3, 106.6, 107.5, 118.0, 121.1, 122.2, 125.5, 126.8, 128.5, 131.4, 132.3, 134.2, 134.4, 166.2; GC-MS (EI): *m/z* = 105 (100), 239 (77), 77 (44), 118 (14), 159 (12), 136 (9), 280 (2).

5.3.6 – Preparation of NBoc derivate ***28***

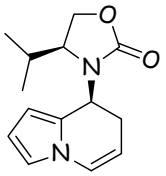
The phenylglycinol derivative **23b** (0.500 g, 1.7 mmol) and a 40% solution of $MeNH_2$ in H_2O (2.2 mL, 5.8 mmol) were dissolved in MeOH (5 mL), then a solution of H_5IO_6 (1.35 g, 5.7 mmol) in H_2O (5 mL) was added dropwise and the mixture was stirred for 2 h at room temperature. The organic materials were extracted with Et_2O (3 × 20 mL), then the collected ethereal layers were washed with brine, dried over Na_2SO_4 and concentrated to leave the primary amine **26** as a yellow oil. This was dissolved in THF (5 mL), then a saturated solution of $NaHCO_3$ (5 mL), and Boc_2O (744 mg, 3.4 mmol) were added while magnetically stirring. After 2 h Et_2O (10 mL) was added, and the organic materials were extracted with Et_2O (3 × 20 mL). The collected ethereal layers were dried over Na_2SO_4 and concentrated to leave a white solid, which was crystallized from acetone to give pure 414 mg of **28 (**1.5 mmol, 91%**)**.



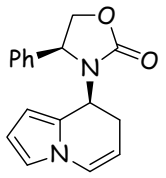
(28):White crystals (from pentane); m.p. = (46.8-47.5) °C; $[\alpha]_D^{20}$ -11.5 (*c* 0.7, $CHCl_3$); IR (KBr): *ν* = 3361, 2979, 2922, 2848, 1681, 1528, 1474, 1385, 1261, 1175, 1045, 1023, 712; ; ^1H NMR (300 MHz, $CDCl_3$): δ = 6.67 (s, 1 H), 6.61 (d, *J* = 8.1 Hz, 1 H), 6.12 (t, *J* = 3.0 Hz, 1 H), 6.09 (s, 1 H), 5.77 (m, 1 H), 5.53 (q, *J* = 7.1 Hz, 1 H), 5.12 (d, *J* = 16.9 Hz, 1 H), 5.06 (d, *J* = 10.7 Hz, 1 H), 4.78 (bs, 1 H), 4.63 (bs, 1 H), 2.57 (m, 2 H), 1.73 (d, *J* = 7.0 Hz, 3 H), 1.43 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.4, 28.3, 39.4, 46.4, 79.1, 106.0, 107.3, 117.5, 120.9, 121.7, 125.6, 132.9, 134.3, 154.8; GC-MS (EI): *m/z* = 179 (100), 235 (28), 135 (26), 118 (25), 57 (24), 158 (21), 276 (2).

5.3.7 - General protocol for the ring-closing metathesis reactions

The oxazolidinone **29b** (1.29 g, 4.4 mmol) was dissolved in anhydrous CH_2Cl_2 (20 mL). The solution was de-aerated by bubbling a stream of Ar through it, the Grubbs catalyst **II** (0.044 g, 0.01 mmol) was added, the solution was again de-aerated and heated to reflux. The progress of the reaction was monitored by TLC analysis and the disappearance of the starting material was observed within 4 h. The solvent was removed at reduced pressure to leave the crude product. Flash column chromatography (SiO_2) eluting with cyclohexane/ethyl acetate 9:1 mixtures gave the product **30b** (96 %, 1.182 g, 4.2 mmol).

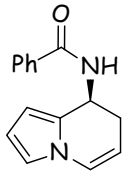


(30a): White solid (from pentane:Et_2O, 7:3); 95 % (0.795 g, 3.23 mmol) from 3.4 mmol (0.979 g) of **8a**; m.p. = (65.4-66.9) °C; $[\alpha]_D^{20}$ +68.3 (*c* 1.0, $CHCl_3$); IR (KBr): ν = 3448, 2966, 2874, 1732, 1658, 1482, 1298, 1229, 1079, 1047, 732; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.78 (m, 1 H), 6.66 (dd, J = 1.5 Hz, J = 2.8 Hz, 1 H), 6.18 (t, J = 3.4 Hz, 1 H), 6.14 (m, 1 H), 5.40 (dd, J = 4.7 Hz, J = 7.6 Hz, 1 H), 5.32 (ddd, J = 3.6 Hz, J = 5.0 Hz, J = 8.7 Hz, 1 H), 4.01 (d, J = 6.9 Hz, 2 H), 3.44 (dt, J = 3.3 Hz, J = 6.9 Hz, 1 H), 2.73 (dddd, J = 2.5 Hz, J = 6.0 Hz, J = 7.7 Hz, J = 18.0 Hz, 1 H), 2.58 (ddt, J = 1.4 Hz, J = 4.7 Hz, J = 18.0 Hz, 1 H), 1.87 (dsept, J = 3.3 Hz J = 6.8 Hz, 1 H), 0.88 (d, J = 6.9 Hz, 3 H), 0.72 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 18.1, 27.3, 29.3, 46.7, 58.1, 62.9, 108.0, 108.5, 108.9, 118.7, 123.8, 125.1, 158.7; GC-MS (EI): *m/z* = 117 (100), 86 (16), 132 (12), 158 (6), 245 (2).

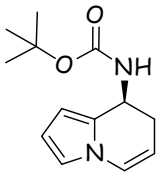


(30b):White crystals (from pentane:Et_2O, 9:1); m.p. = (97.9-98.5) °C; $[\alpha]_D^{20}$ +165.1 (*c* 1.3, $CHCl_3$); IR (KBr): ν = 3097, 2949, 2909, 1736, 1655, 1492, 1416, 1358, 1216, 1076, 1039, 888, 772, 722, 701; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.29-7.36 (m, 3 H), 8.07-7.11 (m, 2 H), 6.52 (t, J = 2.2 Hz, 1 H), 6.21 (m, 3 H), 5.41 (dd, J = 4.4 Hz, J = 7.3 Hz, 1 H), 4.72 (ddd, J = 3.3 Hz, J = 5.2 Hz, J = 8.1 Hz, 1 H), 4.52 (dd, J = 6.8 Hz, J = 9.1 Hz, 1 H), 4.50 (dd, J = 4.6 Hz, J = 9.1

Hz, 1 H), 4.08 (dd, *J* = 4.6 Hz, *J* = 6.8 Hz, 1 H), 2.44 (dddd, *J* = 2.7 Hz, *J* = 6.1 Hz, *J* = 7.1 Hz, *J* = 17.9 Hz, 1 H), 2.30 (dddd, *J* = 1.2 Hz, *J* = 4.5 Hz, *J* = 5.2 Hz, *J* = 17.9 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.0, 46.8, 58.2, 70.6, 107.6, 108.4, 108.5, 118.5, 123.3, 124.1, 127.1, 128.3, 128.4, 139.8, 158.5; *GC*-MS (EI): *m/z* = 117 (100), 118 (26), 104 (21), 132 (16), 176 (7), 280 (2).



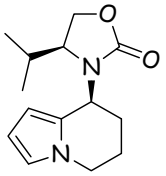
(31): White crystals (from pentane:Et_2O, 9:1); m.p. = (145.8-146.9) °*C*; $[\alpha]_D^{20}$ +53.4 (*c* 0.8, $CHCl_3$); IR (KBr): *v* = 3283, 3066, 2923, 1632, 1538, 1478, 1306, 1285, 1079, 728, 869; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.73-7.79 (m, 2 H), 7.40-7.53 (m, 3 H), 6.83 (dt, *J* = 1.7 Hz, *J* = 7.6 Hz, 1 H), 6.71 (dd, *J* = 1.8 Hz, *J* = 2.5 Hz, 1 H), 6.42 (d, *J* = 7.6 Hz, 1 H), 6.18 (m, 2 H), 5.51 (q, *J* = 6.2 Hz, 1 H), 5.35 (m, 1 H), 2.74 (dddd, *J* = 2.6 Hz, *J* = 4.0 Hz, *J* = 6.2 Hz, *J* = 17.1 Hz, 1 H), 2.50 (dddd, *J* = 1.4 Hz, *J* = 4.9 Hz, *J* = 6.2 Hz, *J* = 17.1 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.3, 42.9, 106.8, 107.9, 108.6, 118.8, 125.6, 126.9, 127.1, 128.5, 131.5, 134.3, 166.4; *GC*-MS (EI): *m/z* = 117 (100), 77 (32), 105 (29), 90 (13), 237 (4), 238 (2).



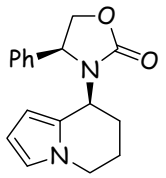
(32): White crystals (from pentane); m.p. = (91.7-92.3) °*C*; $[\alpha]_D^{20}$ -15.8 (*c* 0.6, $CHCl_3$); IR (KBr): *v* = 332, 2977, 2621, 1680, 1531, 1481, 1365, 1253, 1156, 1049, 716; ^1H NMR (300 MHz, $CDCl_3$): δ = 6.75 (dt, *J* = 1.6 Hz, *J* = 7.7 Hz, 1 H), 6.64 (t, *J* = 2.1 Hz, 1 H), 6.14 (m, 2 H), 5.29 (dd, *J* = 4.3 Hz, *J* = 7.7 Hz, 1 H), 4.98 (m, 1 H), 4.86 (bs, 1 H), 2.60 (dt, *J* = 4.2 Hz, *J* = 16.8 Hz, 1 H), 2.32 (dt, *J* = 4.9 Hz, *J* = 16.8 Hz, 1 H) 1.46 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.3, 28.6, 43.7, 79.4, 106.3, 107.7, 108.4, 118.5, 125.5, 127.9, 154.9; *GC*-MS (EI): *m/z* = 117 (100), 177 (16), 133 (15), 57 (12), 90 (10), 159 (69), 234 (4); MS (ES): *m/z* = 257.1 [M + Na]$^+$.

5.3.8 – General protocol for hydrogenation reactions

To a solution of **30a** (0.500 g, 2.0 mmol) in anhydrous (20 mL) was added 5% rhodium on alumina (10%, 0.050 g) and the mixture was strirres under hydrogen atmosphere. The progress of the reaction was monitored by GC-MS analysis and the disappearance of the starting material was observed within 24 h. The solid was filtered off through a pad of Celite and the organic phase was concentrated at reduced pressure. Flash column chromatography (SiO_2) eluting with ethyl acetate/methanol/30% NH_4OH 9:1:0.1 mixtures gave the product **33**.

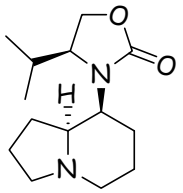


(33a):White Oil; 96 % (0.094 g, 0.38 mmol) from 0.40 mmol (0.100 g) of 30°; IR (Neat): ν = 2960, 2875, 1741, 1414, 1225, 1052, 716; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.57 (ddd, J = 0.6 Hz, J = 1.7 Hz, J = 2.4 Hz, 1 H), 6.13 (dd, J = 2.7 Hz, J = 3.6 Hz, 1 H), 5.89 (dt, J = 1.4 Hz, J = 3.5 Hz, 1 H), 5.13 (dd, J = 5.9 Hz, J = 10.6 Hz, 1 H), 4.15 (dd, J = 8.9 Hz, J = 17.5 Hz, 1 H), 4.12 (dd, J = 4.3 Hz, J = 8.9 Hz, 1 H), 3.81-3.99 (m, 3 H), 2.26 (m, 1 H), 2.07 (m, 1H), 1.76-1.98 (m, 4 H), 0.92 (d, J = 6.9 Hz, 3 H), 0.77 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8, 18.1, 22.6, 27.7, 29.4, 44.9, 50.1, 57.5, 62.7, 105.3, 107.8, 119.9, 126.1, 158.7; GC-MS (EI): m/z = 120 (100), 177 (98), 178 (79), 118 (68), 248 (54), 133 (22); MS (ES): m/z = 249.2 $[M + H]^+$, 519.2 $[M + Na]^+$.

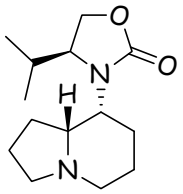


(33b): White solid (from Et_2O:Pentane, 1:1); 97 % (0.098 g, 0.35 mmol) from 0.36 mmol (0.100 g) of **30b**; $[\alpha]_D^{20}$ +34.1 (c 2.0, $CHCl_3$); IR (KBr): ν = 3093, 2965, 2921, 1746, 1407, 1364, 1229, 1069, 1048, 768, 715; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33-7.39 (m, 3 H), 7.07-7.11 (m, 2 H), 6.57 (dd, J = 1.7 Hz, J = 2.5 Hz, 1 H), 6.25 (dd, J = 2.8 Hz, J = 3.6 Hz, 1 H), 6.07 (dt, J = 1.5 Hz, J = 3.5 Hz, 1 H), 5.26 (dd, J = 6.1 Hz, J = 9.6 Hz, 1 H), 4.91 (dd, J = 5.6 Hz, J = 9.1 Hz, 1 H), 4.66 (t, J = 8.8 Hz, 1 H), 4.29 (dd, J = 5.6 Hz, J = 8.7 Hz, 1 H), 3.79 (dt,

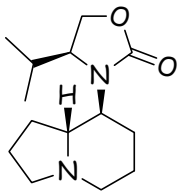
J = 4.5 Hz, J = 11.8 Hz, 1 H), 3.38 (ddd, J = 4.7 Hz, J = 9.9 Hz, J = 11.9 Hz, 1 H), 1.84-1.93 (m, 1 H), 1.53-1.76 (m, 2 H), 1.15-1.29 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.7, 27.1, 44.6, 49.7, 57.1, 70.1, 106.1, 108.0, 119.8, 125.6, 127.3, 128.7, 128.8, 140.2, 158.5; *GC*-MS (EI): *m/z* = 178 (100), 118 (35), 282 (34), 104 (33), 120 (33), 91 (18), 163 (11), 207 (10).



(*S,S*-34): White crystals (from Et_2O:CH_2Cl_2, 10:1); m.p. = (114.5-115.3) °C; IR (Neat): ν = 2928, 2782, 1741, 1415, 1220, 1100, 1040; ; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.32 (dt, J = 2.7 Hz, J = 7.5 Hz, 1 H), 4.21 (m, 1 H), 4.16 (dd, J = 2.7 Hz, 1 H), 4.12 (dd, J = 7.5 Hz, 1 H), 3.07 (dt, J = 3.7 Hz, J = 11.1 Hz, 1 H), 2.98 (ddd, J = 4.7 Hz, J = 5.7 Hz, J = 9.5 Hz, 1 H), 1.94-2.14 8m, 5 H), 1.63-1.82 (m, 6 H), 1.39 (m, 1 H), 0.92 (d, J = 6.9 Hz, 3 H), 0.89 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8, 18.4, 20.6, 22.5, 25.7, 26.9, 30.5, 49.9, 52.8, 5438, 59.8, 63.1, 67.6, 159.8; *GC*-MS (EI): *m/z* = 123 (100), 96 (20), 83 (16), 69 (10), 55 (8), 251 (1); MS (ES): *m/z* = 253.1 $[M + H]^+$.

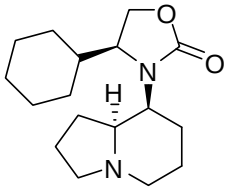


(*R,R*-34): White crystals (from Et_2O:CH_2Cl_2, 10:1); $[\alpha]_D^{20}$ +35.4 (*c* 1.1, $CHCl_3$); IR (KBr): ν = 2947, 2784, 1732, 1416, 1218, 1038, 973, 778; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8, 18.7, 20.7, 23.1, 24.8, 29.7, 28.4, 51.8, 51.9, 54.7, 59.1, 59.8, 63.1, 65.9, 159.5; *GC*-MS (EI): *m/z* = 123 (100), 96 (25), 122 (20), 97 (20), 83 (15), 69 (11), 55 (9); MS (ES): *m/z* = 253.1 $[M + H]^+$.

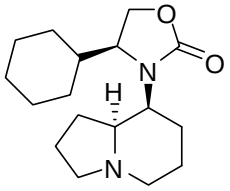


(*S,R*-34): White crystals (from Et_2O:CH_2Cl_2, 10:1); m.p. = (89.6-90.9) °C; $[\alpha]_D^{20}$ +9.4 (*c* 1.9, $CHCl_3$); IR (KBr): ν = 3440, 2936, 2785, 1728, 1428, 1253, 1117, 1064, 771, 714; ^{1}H NMR (300

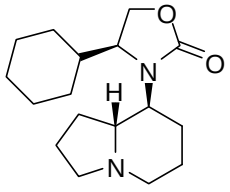
MHz, $CDCl_3$): δ = 4.15 (t, J = 9.0 Hz, 1 H), 4.08 (dd, J = 5.2 Hz, J = 8.9 Hz, 1 H), 3.71 (ddd, J = 3.2 Hz, J = 5.2 Hz, J = 9.0 Hz, 1 H), 3.02-3.19 (m, 3 H), 2.56 (q, J = 9.7 Hz, 1 H), 2.24 (q, J = 9.0 Hz, 1 H), 1.93-2.12 (m, 5 H), 1.48-1.83 (m, 5 H), 0.92 (d, J = 6.8 Hz, 3 H), 0.89 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8, 18.2, 20.4, 24.7, 27.9, 28.6, 28.7, 29.7, 51.8, 54.1, 59.9, 62.6, 64.8, 157.9; *GC*-MS (EI): *m/z* = 123 (100), 122 (70), 96 (44), 97 (35), 83 (26), 69 (24), 55 (18); MS (ES): *m/z* = 253.1 $[M + H]^+$.



(*R,R*-39): White solid (from Et_2O:CH_2Cl_2, 8:2); IR (KBr): ν = 3452, 2923, 2854, 2783, 1735, 1415, 1209, 1102, 1033, 803; *GC*-MS (EI): *m/z* = 123 (100), 96 (16), 124 (15), 55 (12), 83 (11), 209 (3), 291 (2).



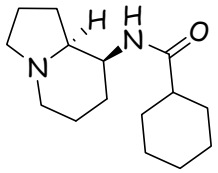
(*S,S*-37): White solid; IR (KBr): ν = 3449, 2932, 2853, 2785, 1732, 1420, 1248, 1035, 766, 710; *GC*-MS (EI): *m/z* = 123 (100), 96 (17), 97 (14), 55 (13), 83 (12), 209 (4),291 (2).



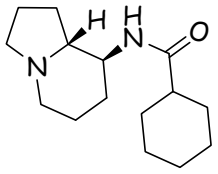
(*S,R*-37): White crystals (from Et_2O:CH_2Cl_2, 8:2); m.p. = (117.8-118.5) °C; $[\alpha]_D^{20}$ +77.6 (*c* 0.6, $CHCl_3$); IR (KBr): ν =2929, 2852, 2789, 1730, 1425, 1250, 1058, 768, 710; ^1H NMR (300 MHz, $CDCl_3$): δ = 4.14 (d, J = 3.5 Hz, 1 H), 4.12 (d, J = 1.2 Hz, 1 H), 3.65 (ddd, J = 2.9 Hz, J = 5.7 Hz, J = 8.6 Hz, 1 H), 3.00-3.18 (m, 3 H), 2.56 (dt, J = 6.1 Hz, J = 10.2 Hz, 1 H), 2.36 (q, J = 9.1 Hz, 1 H), 1.90-2.07 (m, 6 H), 1.57-1.86 (m, 7 H), 1.42-1.52 (m, 3 H), 1.09-1.32 (m, 2 H), 0.85-1.04 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.5, 24.3, 25.1, 25.5, 26.3, 28.2, 28.8,

28.9, 39.3, 51.9, 54.3, 57.5, 59.7, 63.4, 64.6, 157.9; *GC*-MS (EI): *m/z* = 123 (100), 96 (13), 55 (10), 83 (9)209 (2), 291 (2).

The e.e. of **38** was determined by chiral *GC* (Megadex Chiral column (25 m, flow rate: 15mL/min, isotherm 150 °C for 2 min. then 2°C/min. to 220°C, FID detection); retention times: ***S,R*-38** 21.2 min, *S,S*-**38** 28.2 min (major enantiomer), 28.6 min (minor enantiomer).

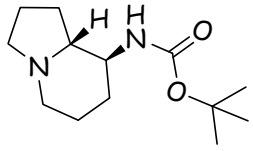


(*S,R*-38): White crystals (from Et_2O:CH_2Cl_2, 9:1); m.p. = (126.7-127.8) °C; $[\alpha]_D^{20}$ +20.9 (*c* 1.9, $CHCl_3$); IR (KBr): *ν* = 3464, 3297, 2927, 2852, 2785, 2745, 1638, 1528, 1449, 1340, 1262, 1123, 1099; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.09 (d, *J* = 6.9 Hz, 1 H), 4.16 (ddd, *J* = 2.7 Hz, *J* = 5.7 Hz, *J* = 8.7 Hz, 1 H), 3.02 (m, 1 H), 2.96 (m, 1 H), 1.92-2.12 (m, 4 H), 1.76-1.86 (m, 5 H), 1.61-1.70 (m, 5 H), 1.38-1.53 (m, 3 H), 1.17-1.31 (m, 5 H), 1.18-1.32 (m, 2 H); ^{13}*C* NMR (75 MHz, $CDCl_3$): δ = 20.6, 20.9, 25.6, 25.7, 29.5, 29.8, 29.9, 44.7, 45.7, 53.1, 24.5, 65.8, 175.8; *GC*-MS (EI): *m/z* = 123 (100), 55 (16), 70 (14), 83 (9), 108 (8), 249 (4).

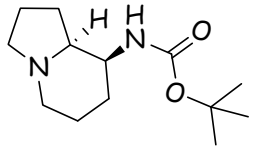


(*S,S*-38): White crystals (from Et_2O:CH_2Cl_2, 9:1); m.p. = (197.9-198.7) °C; $[\alpha]_D^{20}$ +22.1 (*c* 2.0, $CHCl_3$); IR (KBr): *ν* = 3460, 3077, 2828, 2853, 2790, 2722, 1638, 1550, 1445, 1331, 1260, 1113, 1095, 1022, 802, 702; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.30 (d, *J* = 8.6 Hz, 1 H), 3.76 (ddd, *J* = 4.2 Hz, *J* = 8.9 Hz, *J* = 11.6 Hz, 1 H), 3.07 (td, *J* = 1.6 Hz, *J* = 9.2 Hz, 1 H), 3.02 (dt, *J* = 2.7 Hz, *J* = 10.6 Hz, 1 H), 2.13 (q, *J* = 8.9 Hz, 1 H), 1.88-2.02 (m, 4 H), 1.75-1.83 (m, 5 H), 1.59-1.71 (m, 4 H), 1.37-1.48 (m, 2 H), 1.17-1.31 (m, 5 H), 0.97-1.10 (m, 1 H); ^{13}*C* NMR (75 MHz, $CDCl_3$): δ =20.3, 24.5, 25.6, 25.7, 25.8, 28.3, 29.5, 29.9, 31.8, 45.7, 50.9, 51.8, 54.3, 69.2, 175.4; *GC*-MS (EI): *m/z* =123 (100), 55 (11), 70 (10), 96 (9), 249 (2).

The e.e. of **39** was determined by chiral GC (Megadex Chiral column (25 m, flow rate: 15mL/min, isotherm 100 °C for 2 min. then 5°C/min. to 220°C, FID detection); retention times: ***S,R*-39** 15.8 min, ***S,S*-39** 17.6 min (major enantiomer), 18.3 min (minor enantiomer).



(*S,R*-39): White crystals (from Et_2O:CH_2Cl_2, 9:1); $[\alpha]_D^{20}$ -14.3 (*c* 0.4, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 5.19 (d, *J* = 8.6 Hz, 1 H), 3.86 (dq, *J* = 3.1 Hz, *J* = 9.6 Hz, 1 H), 2.95-3.01 (m, 2 H), 1.97-2.03 (m, 1 H), 1.86-1.95 (m, 2 H), 1.62-1.69 (m, 4 H), 1.50-1.57 (m, 2 H), 1.44 (s, 9 H), 1.33-1.39 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.6, 20.8, 25.6, 28.4, 29.9, 46.5, 53.2, 54.5, 66.1, 78.7, 155.9; GC-MS (EI): *m/z* =123 (100), 83 (31), 96 (21), 111 (17), 70 (14), 59 (12), 167 (11), 183 (6).



(*S,S*-39): White crystals (from Et_2O:CH_2Cl_2, 9:1); m.p. = (105.4-106.1) °C; $[\alpha]_D^{20}$ -5.4 (*c* 0.4, $CHCl_3$); IR (KBr): *v* = 3359, 2972, 2905, 2785, 2723, 1684, 1529, 1447, 1309, 1245, 1172, 1053, 994, 636; ^1H NMR (300 MHz, $CDCl_3$): δ = 4.35 (bs , 1 H), 3.38 (bs, 1 H), 3.08 (t, *J* = 7.8 Hz, 1 H), 3.02 (dt, *J* = 3.0 Hz, *J* = 10.7 Hz, 1 H), 2.14 (q, *J* = 8.9 Hz, 1 H), 2.01-2.07 (m, 1 H), 1.87-1.96 (m, 2 H), 1.76-1.82 (m, 1 H), 1.58-1.73 (m, 5 H), 1.44 (s, 9 H), 0.95-1.08 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.4, 24.7, 28.4, 28.5, 32.2, 51.9, 52.7, 54.3, 69.5, 79.0, 155.3; GC-MS (EI): *m/z* =123 (100), 83 (34), 97 (21), 96 (18), 70 (16), 69 (13), 57 (11), 167 (8), 183 (6).

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Chapter Index

Acknowledgements

First, I would like to dedicate this thesis to my wife *Silvia* for her love, her patience, and understanding during these many long days. Moreover I thank her for allowed me to spend most of the time on this thesis.

I am most grateful to my supervisor *Prof. Savoia.* I could not have imagined having a better advisor and mentor for my PhD, with his enthusiasm, his inspiration, and his great efforts to explain things clearly and simply, he helped me to make a 'good chemistry'. In particularly in these last months he subjected my text to rigorous scrutiny and much improved its quality.

I also thank GlaxoSmithKline Verona for the financial support in these years of PhD.

I would like to thank all my Wednesday's beer friends: *Alessandra, Claudio, Elisa, Filippo Massimo, Montse.*

Thanks are due also to all to my colleagues at Chemistry Department "G. Ciamician" for a huge variety of reasons, and in particularly *Claudio*, that in the first two years of the PhD helped me with stimulating discussion of chemistry and none.

Finally, I have to say 'thank-you' to my family, particularly my *Mum* and *Dad*.