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Dipartimento di Chimica "G.Ciamician"

DOTTORATO IN SCIENZE CHIMICHE

XXV CICLO

SYNTHESIS AND APPLICATION OF LINEAR AND MACROCYCLIC NITROGEN LIGANDS

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SUMMARY

ABSTRACT

Linear and macrocyclic nitrogen ligands have been found wide application during the years. Nitrogen has a much stronger association with transition-metal ions than has oxygen, because it is less electronegative and the electron pair is more available for complexing purposes. For this reason, we decided to investigate the synthesis of new macrocyclic and linear ligands and study their application as complexing agent.

We started our investigation with the synthesis of new chiral perazamacrocycles containing four pyrrole rings. This ligand has been synthesized by the [2+2] condensation of (*R*,*R*)-diaminocyclohexane and dipirranedialdehydes and was tested, after a complexation with 2 equiv $Cu(OAc)_2$, in Henry reactions. The best yields (up to 90%) and higher ee's (up to 96%) were obtained when the *meso*-substituent on the dipyrrandialdehyde was a methyl group. The positive influence of the pyrrole-containing macrocyclic structure on the efficiency/enantioselectivity of the catalytic system was demonstrated by comparison with the Henry reactions performed using analogous macrocyclic ligands. Where the dialdehyde unit was replaced by a triheteroaromatic dialdehyde (furan-pyrrol-furan), the new macrocyclic ligand allowed to obtain the Henry product with a good yield but only 73% of ee in standard reaction condition.

Another well known macrocyclic ligand is calix[4]pyrrole (phorphyrins analogue). We decided to investigate, in collaboration with Neier's group, the metal-coordinating properties of calix[2]pyrrole[2]pyrrolidine compounds obtained by the reduction of calix[4]pyrrole in very harsh conditions. Before studying the complexation properties, we focused our attention on the reduction conditions, and tested different Pd supported (charcoal, grafite) catalysts at different pressures and temperatures. We observed that, using catalytic amounts of Pd/C in AcOH as solvent at 100 bar of H_2 pressure and 100 °C, the calix[4]pyrrole was converted to the two half-reduced compounds; otherwise, using 10 equiv of Pd on charcoal in the same other reaction conditions only fully reduced products were observed.

Concerning the synthesis of linear polyamine ligands, we focused our attention to the synthesis of 2-heteroaryl- and 2,5-diheteroarylpyrrolidines. The chiral, substituted pyrrolidine ring has found application in organocatalysis as well as in catalytic organometallic reactions. The reductive amination reaction of diaryl ketones and aryl-substituted keto-aldehydes with different chiral primary amines was exploited to prepare a small library of diastereo-enriched 2-aryl- and 2,5-diaryl-substituted pyrrolidines.

We have also described a new synthetic route to 1,2-disubstituted 1,2,3,4-tetrahydropyrrole[1,2-*a*]pyrazines, which involves the diastereoselective addition of Grignard reagents to chiral oxazolidines. The diastereoselectivity was dependent on the nature of both the chiral auxiliary, (*S*)-1-phenylglycinol or (*S*)-valinol, and the nature of the organometallic reagent. The best stereochemical outcome (98:2) was obtained by the use of MeMgBr on the oxazolidine derived from (*S*)-phenylglycinol. The NH free target was finally obtained by reductive cleavage of the chiral auxiliary.

Chapter 1: Perazamacrocyclic ligands

1.1 Introduction

Macrocyclic ligands with a ring size of at least nine members and containing three or more identical or different heteroatoms are important complexing agents for cations, anions, and also neutral molecules. Particularly, azacrown ethers play an important role in this field. Nitrogen is less electronegative and a stronger basic site with respect to oxygen, so that the nitrogen electron pair is more available for complexing purposes and especially allows a much stronger association with transition-metal ions. The aza-crown ethers have metal ion complexing properties that are intermediate between those of the crown ethers, which strongly coordinate alkali and alkaline-earth metal ions, and those of the perazamacrocycles, which form strong complexes with heavy-metal ions. These complexing properties make the nitrogen-containing macrocycles interesting to researchers in many areas.[1a]

The chemistry of nitrogen-containing macrocyclic compounds started over 100 years ago when Bayer prepared tetraazaquaterene, that is calix[4]pyrrole, (**1**) in 1886.[1b] Hinsberg and Kessler in 1905 prepared similar nitrogen-containing macrocycles.[2] Cyclic tetraamines **2** and the dibenzo-hexaazacrowns **3** were prepared by Krassig and Greber.[3] The important complexing properties of the perazamacrocycles were known before the milestone discovery of all oxygen-containing crown ligands **4** by Pedersen.[4]

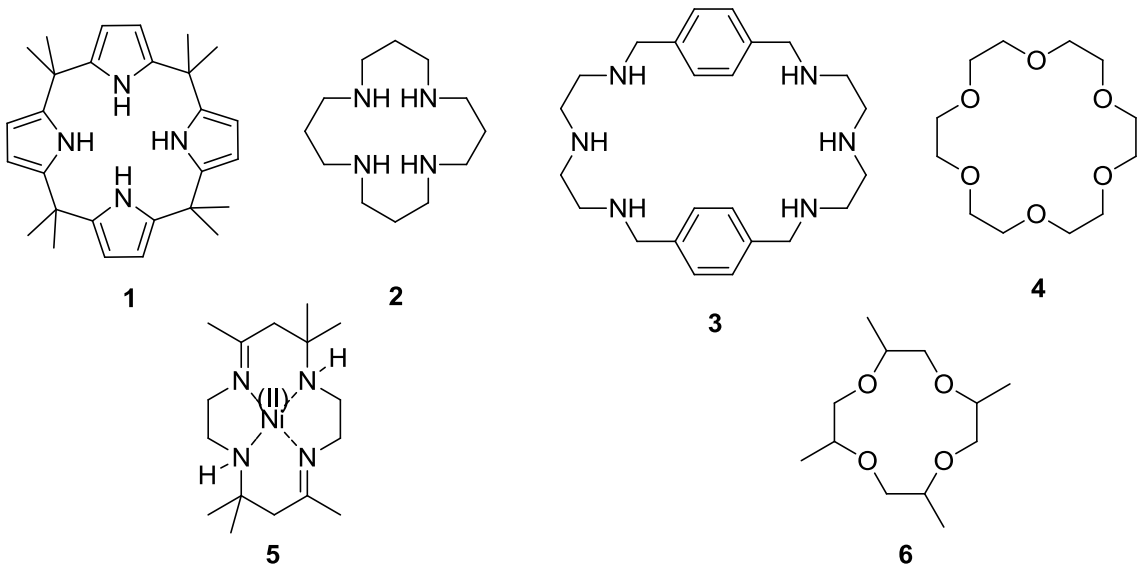

Fig 1. Typical macrocyclic ligands.

The metal ion-templated synthesis of a bis(aminoimino) macrocycle was reported more than 30 years ago by Curtis. The macrocycle resulted from the reaction of tris(1,2-diaminoethane)nickel(II) perchlorate with acetone to form the 14-membered macrocyclic ligand-Ni(II)complex (**5**). Numerous examples of this and other metal ion-templated reactions have been investigated in the intervening years.[5] Macrocycle **6** founded interesting application as a ligand of alkali metal anion favoring their solubilization in organic solvents.[6]

The most important characteristic of the macrocyclic polyamines is their ability to form complexes with cations, anions and neutral organic molecules. There are many reviews on the complexing abilities of the crowns and azacrowns.[7] The azacrown macrocycles generally form 1:1 complex with metal ions. However, di-and trinuclear complexes are known where two or three metal ions are coordinated by a single perazamacrocyclic ligand, especially when the ring is large and the cation is small, and the number of basic sites is adequate. Substitution of oxygen by nitrogen in ligand such as 18-crown-6 and dibenzo-18-crown-6 result in macrocycles that have less affinity for the alkali metal ions such as K^+, than did the parent peroxa-crown. The log *K* values in these cases decrease in the order: O > NR > NH. However, replacing the oxygen donor atom by nitrogen resulted in increased affinities for the heavy metal ions such as Ag^+ and Pb^{2+}. Increasing interaction for $Ca^{2+,}$ Sr^{2+}, and Ba^{2+} was observed for [15]aneN_2O_3 where the two ring nitrogen atoms bear ω-hydroxyalkyl substituents. These examples of modified ligand-metal ion interactions by changing the macrocycle cavity size, the nature of donor atoms, and the *N*-substituent justify the great interest in these macrocyclic compounds. The design and synthesis of macrocycles having selectivity for a desired cation or group of cations are now possible.

1.1.1 The macrocyclic effect

The peraza macrocycles form more stable complexes with a variety of metal ions than do those formed by the corresponding open-chain polyamines. This feature is called the *macrocyclic effect.* Triazacrown macrocycles, in nearly every case, form 1:1 complexes with metal ions that are thermodynamically more stable than those derived from diethylenetriamine. Only complexes of the open chain triamine with Cu^{2+} and Hg^{2+} ions are more stable than those obtained from the cyclic triamine.[7a] Triazacyclononane **7** forms stronger complexes with most cations than does the triazacyclodecane **8**, -cycloundecane **9**, and -cyclododecane **10**. The tetraazacycloalkanes, particularly the 14-membered cyclic tetraamine (called *cyclam*) **11**, exhibit the macrocyclic effect due to a more favorable enthalpy contribution to complex stability.[8] Complexes of the pentaaza- macrocycles have been studied extensively from a thermodynamic point of view.

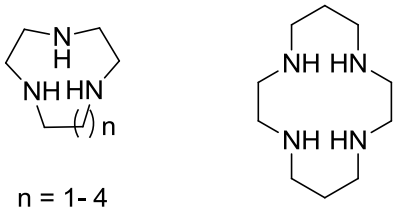

Fig 2. Triaza- and tetraazamacrocycles

Perazamacrocycles that have large cavities do not exhibit the macrocycle effect. They have several features: 1) they are polybases producing highly charged protonates species in solution in the pH range in which they could serve as model reagents for the study of nucleotide complexation; 2) they are suitable for anion-coordination studies; and 3) because of the great number of donor atoms, they can form polynuclear metal ion complexes that could prove useful in the search for more effective catalysts.

The possibility for these ligands to bind more than one metal ion in the macrocyclic framework has aroused the interest of several research groups. Since second and third-row metal ions complexes are active as calalysts and several of these cations have large affinities for nitrogen. In general, large polyazacycloalkanes can form mono-, di- and trinuclear (e.g. with copper) species, as well polyprotonated complexes. The dinucleating and trinucleating abilities of these ligands increase as the ring size increases.

1.1.2 Azacyclophanes

Azacyclophanes, macrocycles with cyclophane subunits incorporated into the ring, have internal cavities and are able to interact with neutral molecules, cations, and anions through hydrophobic host-guest interactions that are scarcely affected by external factors such as pH, temperature, and ionic strength. The azacyclophane **12** consisting of diphenylamine and piperazine fragments was synthesized and found to be an effective ligand for alkali metal and ammonium cations. Thus, the log $K(CHCl_3)$ value for Li^+ interaction is 8.06, and the ligand is effective in the selective extraction of Li^+ from H_2O to $CHCl_3$. Corey-Pauling-Koltun molecular model shows that the cavity of this ligand is too large to include the bare Li^+, but $Li(H_2O)_6^+$ can fit into the cavity by formation of hydrogen bonds between the piperazine moieties and two metal-coordinated water molecules.

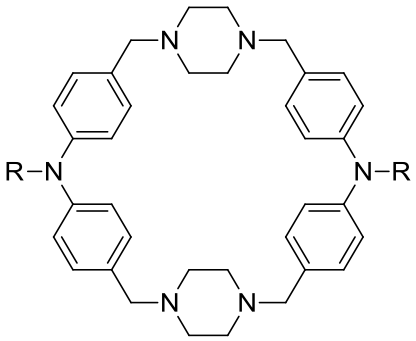

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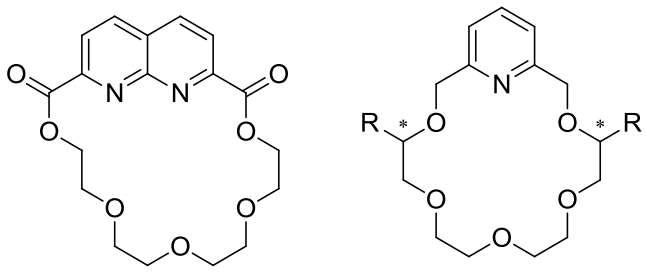
Fig 3. Azacyclophane macrocycle.

1.1.3 Selective complexation of cations

The main target in macrocyclic ligand design is the capability to discriminate among different cations. The many factors influencing the selectivity of macrocyclic ligands for cations have been determined. They may be divided roughly into several groups, including macrocycle cavity dimension, shape and topology, substituent effects, conformational flexibility/rigidity, donor atom type and number.[4b,7a-c-f-l,9]

Macrocycles of the "rigid" type (e.g. small cryptands) and other rigid discriminate the cation that exactly fits into the cavity among other smaller and larger cations. Macrocycles of the "flexible" type, e.g. larger polyether crowns and cryptands, discriminate principally among smaller cations ("plateau selectivity").[9c] Incorporating benzene, cyclohexane or pyridine rings, and/or other cyclic fragments into a macrocyclic skeleton leads to a more rigid macroring and possibly alters the strength and selectivity of the ligand-cation interaction. As an example, the 20-membered crown ether **13** with an incorporated 1,8-naphthyridine ring shows excellent selectivity for Ba^{2+} over Ca^{2+} in $CDCl_3$[10]. Moreover, chiral substituents incorporated in a polyether macrocyclic framework, see **14**, allow separation of enantiomeric organic ions.[9c,7d,11]



13 **14**

Fig 4. Example of typical achiral and chiral chelating structures.

1.1.4 Selective complexation of anions and organic molecules

Macrocyclic polyamines that can be fully or nearly fully protonated in pH range close to neutrality appear to be the best ligands for biologically important carboxylates and adenosine phosphate anion because the formation of these anions occurs in these pH regions. Lehn and Dietrich and their coworkers have synthesized macrocyclic polyamines [24]N_6 and [32]N_8, based on propylene units, and macrocycles [27]N_6O_3 with mixed nitrogen-oxygen donor atoms connected by ethylene units.

Both types of protonated macrocycles were found to form stable and selective complexes with both organic and inorganic polyanions in aqueous solution at almost neutral pH. Since selectivity in these systems depend on electrostatic and geometric effects, modification of macrocyclic cavity shape and size should allow one to control the selectivity sequence. The most stable complex is formed when the macrocycle is fully protonated and the dicarboxylate anion complements the ammonium sites separation in the macrocycle. In the case of the (2-aminoethyl)-substituted [14]N_4 ligand **15**, protonation occurs first at the primary amines in the side arms and the flexibility of this tetra-protonated receptor leads to a better matching in its interaction with anions.[12]

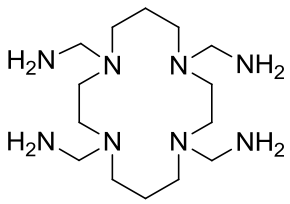


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Fig 5. pH-Sensible polyamine macrocycle.

Azacyclophane-type macrocycles possess large cavities of different sizes that have pronounced hydrophobic character. They form host-guest inclusion complexes with charged or uncharged organic compounds in aqueous solution by electrostatic or hydrophobic interactions, respectively. In these complexes, the shape of the hydrophobic anion is important for optimum complex stability. In addition, increasing the hydrophobic volume of the cavity improves formation of the complex. Azacyclophan-type macrocycles are able to select guest by recognition of steric structure and charge of the guests. For example, they form strong complexes with anions having naphthalene rings, weaker although relatively strong complexes with anions having benzene rings, and only weak complexes with non aromatic anions.[13]

1.1.5 Medical uses of the azamacrocycles

There are important medical application of azamacrocycles. The perturbation of metabolic processes based on biological metal ion-ligand coordination can produce a disease or even death. Conversely, undesirable biological processes can be prevented by using certain metal ion-ligand interaction; for example, the weak Pt-Cl bond in *cis*-platin (**16**) allow this complex to display antitumor activity. In fact, when applied in biological systems, chlorine dissociates, and the platinum ion can interact with the DNA molecules of the cancer tissue. Other drugs such as metallocene dichloride and diorganotin dihalide use this mechanism for their antitumor action. Up to the mid 1980s, only metal ion complexes of linear ligands had been tested, and only in the first part of 1990s complexes of tetrabenzyl[14]N_4 **17** with copper, gold and silver have been tested for antitumor activity.[14]

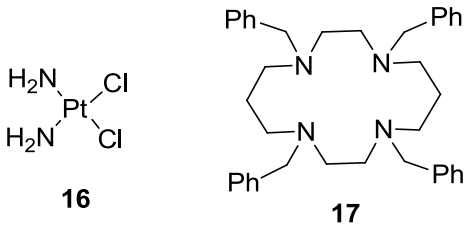


Fig 6. a) cis-Platinum, b) tetrabenzyltetraazamacrocyclic ligand: Cu, Au and Ag complexes show antitumoral activities

Other antitumor active compounds such as the bleomycin, antracycline, and stempomycin antibiotics have different mode of action. Antitumor activity is manifested by DNA binding to the antibiotics followed by DNA strand cleavage. Cleavage requires oxygen and a metal ion to form a complex. A different method to localize and treat tumors by means of a ligand-radioisotope complex attached to an antibody is now being tested. Cyclic polyamines are ideal ligands for this purpose as they coordinate the appropriate radioactive metal ions forming complexes that are kinetically inert with respect to dissociation either at the pH of body fluids, or by reaction with the common metal ions in body fluids.[15]

Early experiments in tumor localization and treatment using C-functionalized EDTA and DTPA chelates were not promising because the complexes with Cu^{2+} and In^{3+} were labile in body fluids and mixed complexes with Ca^{2+}, Mg^{2+} and Zn^{2+} were formed. Since the radioactive metal ions can damage liver and bone marrow, it is very important to use ligands that form very strong complexes with those cations. Complexes of Bi^{3+} and DTPA incorporating rigid cyclohexane rings between the nitrogen atoms exhibit good in vivo stability. Azamacrocycles of 9-14-ring members and with acetic or phosphoric acid group attached to each nitrogen atoms appear to be good candidates to replace DTPA or EDTA for this application. A number of these macrocycles were tested and the inefficient labeling was only found for the complex of [12]N_4-tetraacetate and ^{90}Y, where cations such as Ca^{2+} and Zn^{2+} effectively competed for the ligand.

1.1.6 Synthesis of perazamacrocycles

Perazamacrocycle are preferably prepared starting from difunctional reagents and using three different methods to achieve ring closure involving formation of a C-N bond:

1) S_N2 reaction of a bistosylamide and a dihalide
2) Nucleophilic acyl substitution between an activated derivative of an arenedicarboxylic acid and a diamine (formation of amide)
3) Condensation of an aromatic dialdehyde and a diamine (formation of imine) with or without metal ion template

These simple approaches have been used to prepare many perazacyclophanes containing more than two benzene ring and more than two nitrogen atoms, and can produce one or more of different macromolecules incorporating [1+1, [2+2], [3+3],… molecules of the starting reaction partners, depending on their shape and size. For example, the perazacyclophane **18** containing four nitrogen atoms was prepared in 40% yield by Stetter and Roos[16] by [1+1] cyclocondensation of the disodium salt of *N*,*N*′-ditosyl-*p*-phenylenediamine with a suitable dibromide under high-dilution condition. On the other hand, reaction of the bistosylamide of *m*-phenylenediamine with a *m*-phenylene dibromide gave the [2+2] cycloadduct **19**.[17]

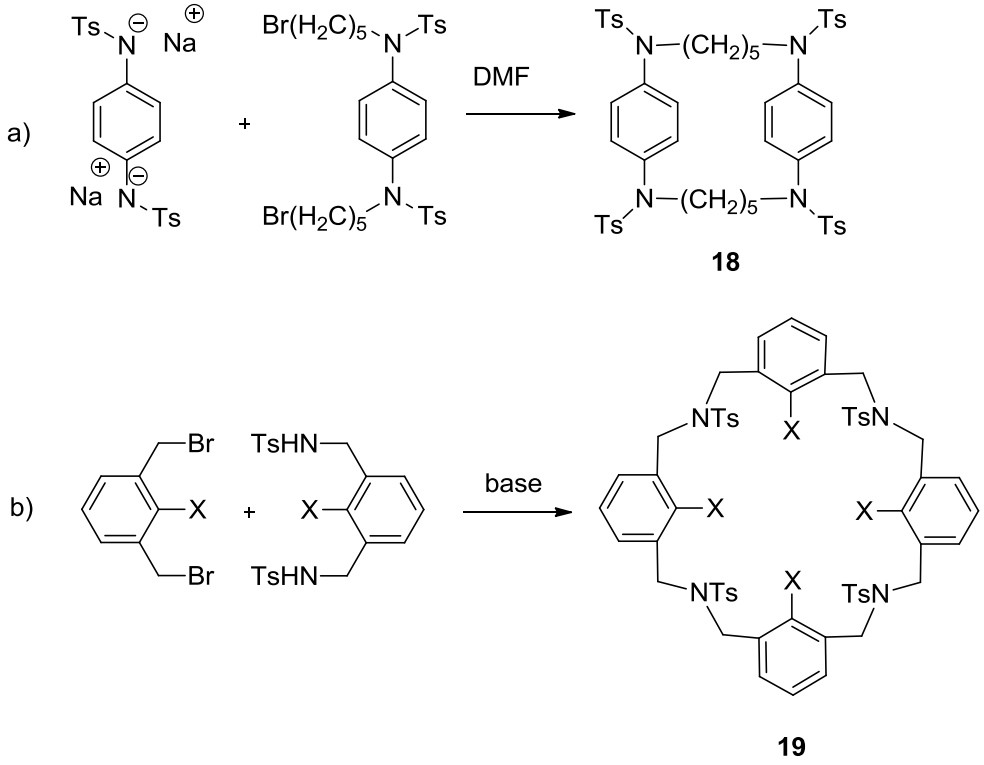


Fig 7. a) Synthesis of [1+1] macrocycle; b) Synthesis of [2+2] macrocycle

The reaction of an aromatic diacyl chloride with a diamine is also a common method for preparing cyclocondensation products containing amide functions, which can be successively reduced to amines.[18] The formation of [1+1] cyclocondensation products **20**[19a] was favored in

the reaction of two extended aromatic systems, otherwise, using more compact diacid dichlorides and diamines the [2+2] product **21**[19] was prevalent (Fig 8).

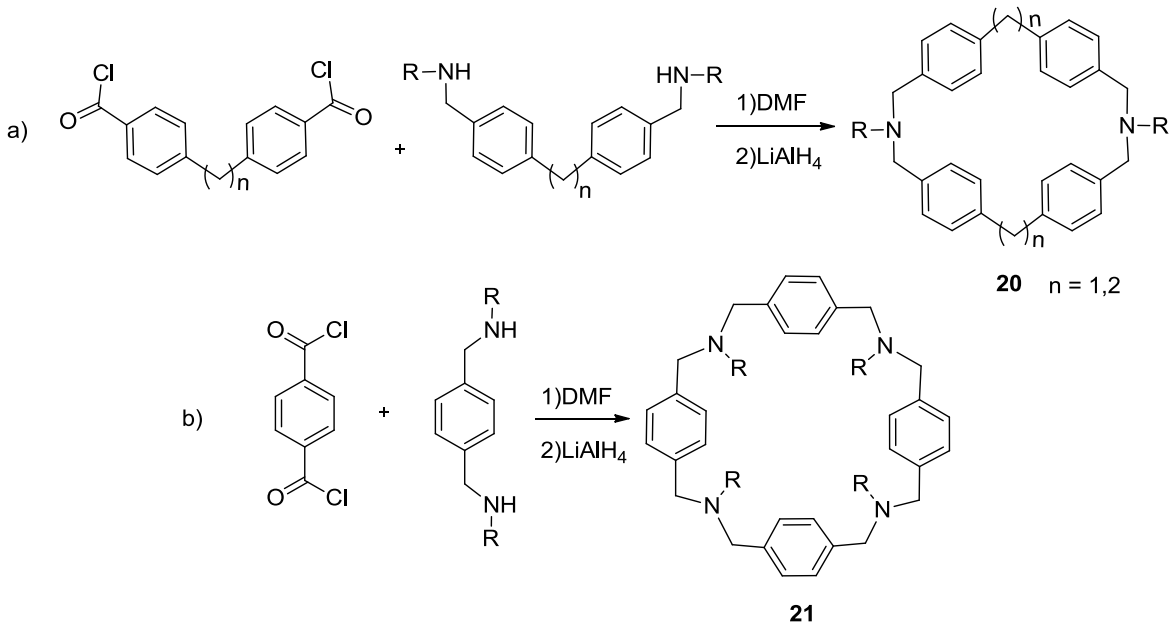


Fig 8. a) [1+1] Cyclocondensation reaction; b) [2+2] cyclocondensation reaction

Rodger[20] and coworker thoroughly studied the reaction of terephthaloyl dichloride with various linear aliphatic diamines. Owing to the lack of rigidity of the diamine, mixtures of products were always obtained, the composition being dependent on the length of the aliphatic fragment (Fig 9).

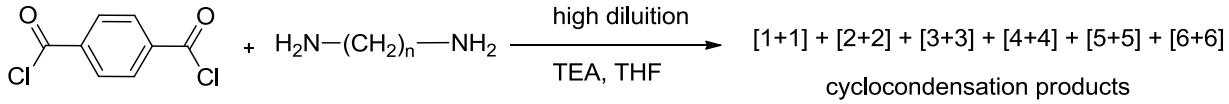


Fig 9. Range of products in macrocyclization using an aliphatic diamine

Finally the reaction between dialdehydes and diamines is a useful method to form cyclic oligo-imines. A metal ion can be used as a template agent to favor ring closure, e.g. preparation of macrocyclic complexes **22** and **23** (Fig. 10).

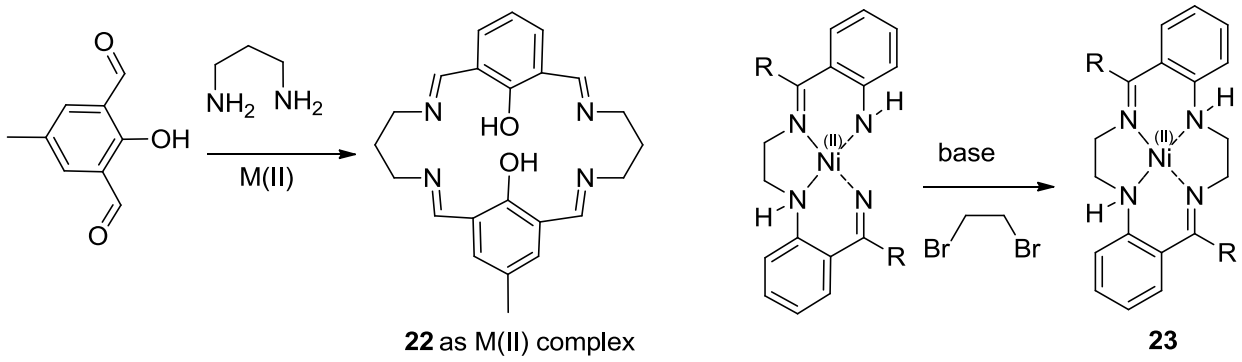


Fig 10. Use of a metal ion as a template agent

Starting from 5-methylisophthaldialdehyde and 1,3-propanediamine was necessary to use a metal ion template (Cu(II), Ni(II), or Co(II)) to observe the desired [2+2] cyclization product **22**. Select the perfect ion template is very difficult, because changing the type of metal ion is possible to obtain macrocycle with different sizes. The self condensation of *o*-aminobenzaldehyde has been studied extensively: it undergoes cyclo-condensation reactions to give metal complexes with differently sized macrocyclic ligands. The trimer **24** was obtained using VO^{2+} as a template, the tetramer **25** with Cu(II) or Zn(II), and mixtures of trimers and tetramers with Co(II) and Ni(II).[21]

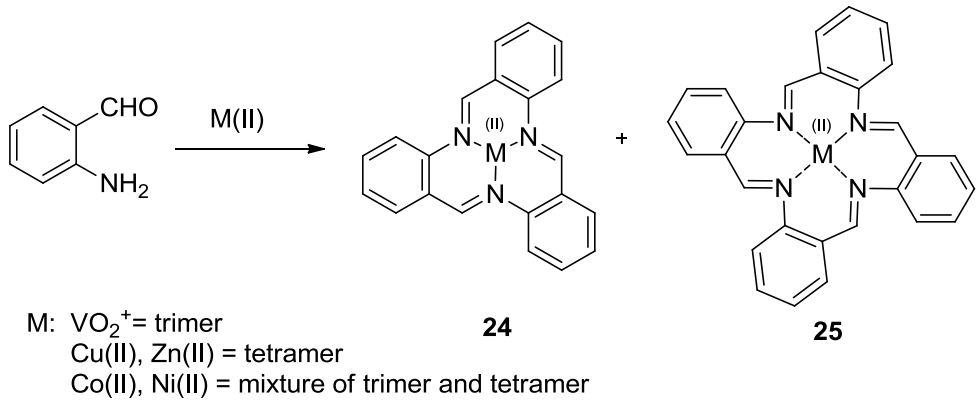


Fig 11. Use of metal ions as template agents to obtain differently sized macrocycles

Non-template-assisted formation of macrocyclic Schiff base has also been used to prepare perazamacrocycles. This required rigid starting materials, mostly due to the presence of aromatic ring.[22] The first example was reported by Lyndoy and coworkers in 1977 and Owston in 1980. It is likely that internal hydrogen bonding in the starting tetraamine **26** helped the ring closure process.

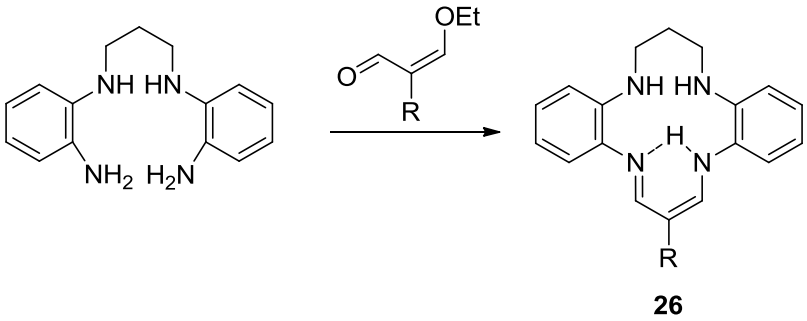


Fig 12. Internal hydrogen bonding act as template effect

1.2 Chiral perazamacrocycles

1.2.1 Synthesis

In the last two decade perazamacrocycle have found increased interest in the scientific world. The possibility to use cheaper and natural building blocks as starting material to obtain a final well organized product has gained attention. Chiral building blocks (aminoacids or their derivatives) are used as starting material to insert one or more carbon stereocenters in the final macrocyclic ring, e.g. **27**-**30**[23] shown in Fig 13.

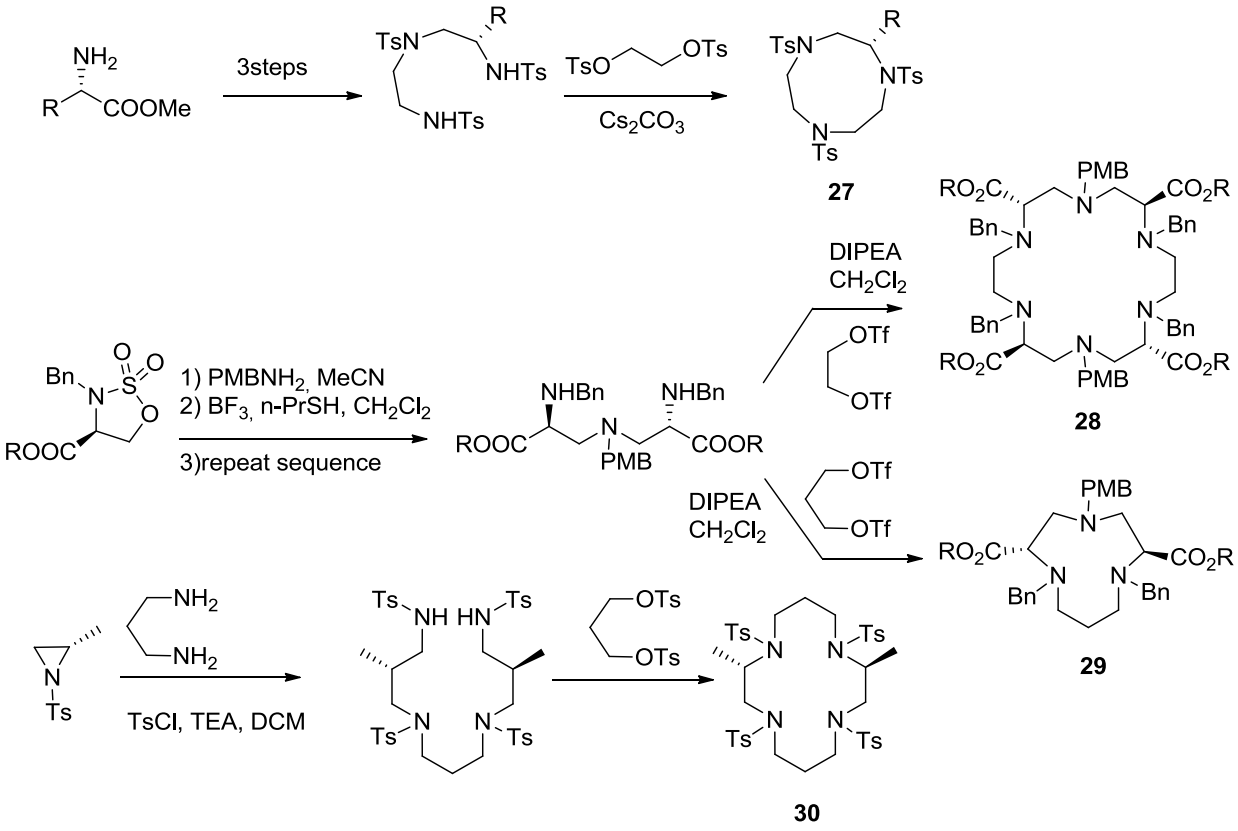


Fig 13. Chiral building blocks as starting material

The formation of chiral macrocycle can be achieved by different methodologies which usually exploit the sequential formation of C-N bonds by reaction of several nucleophilic nitrogen functions with electrophilic compounds. Chiral non-racemic macrocycles containing at least three nitrogen atoms in the ring have found applications in supramolecolar and material chemistry as well as in pharmaceutical and biological fields, preparation of new material, gel formation, chiral recognition and separation of organic anions and biologically important molecules, catalysis and ion transport across the membranes. Another class of interesting ligands have been prepared starting from optically pure or racemic *trans*-1,2-

diaminocyclohexane. DOTA-gadolinium(III) complex **31** has found us as contrast agent for magnetic resonance imaging (MRI).[24] The synthesis of a DOTA analogue from racemic *trans*-1,2-diaminocyclohexane results in the formation of two diasteroisomers: *trans-syn-trans* **33** and *trans-anti-trans* **32**.[25] DOTA analogues with increased hydrophobicity were then prepared, e.g. **34**.

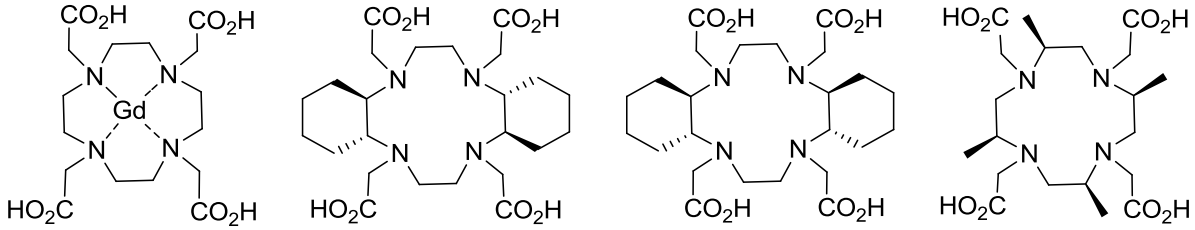


Fig 14. DOTA-Gd complex and chiral analogues

Other procedures can be applied to achieve the synthesis of DOTA analogues. The tetra-substituited macrocycle **35** was prepared in low overall yield by a sequence of steps involving photoelectron transfer-induced tetramerization of (*R*)-1-benzyl-2-benzyloxymethylaziridine, which led to a mixture of compounds. Alternatively, the poly(amido-amino) macrocycle **36** was prepared by reaction between a chiral diamine and the bis(*N*-chloroacetyl) derivative of another diamine, followed by reduction with $LiAlH_4$ or borane.[26]

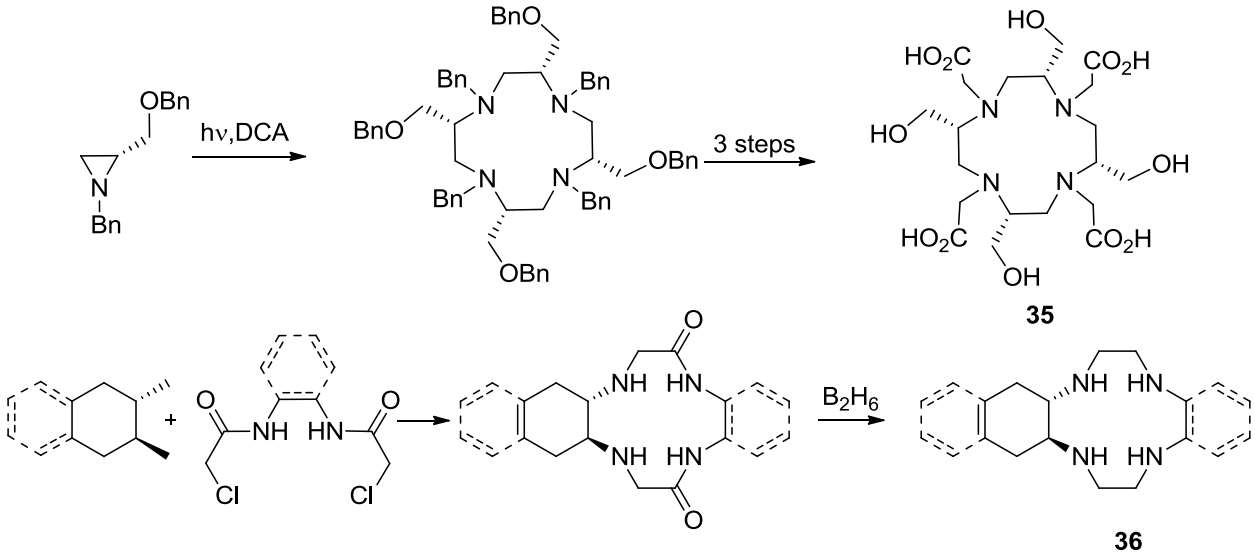


Fig 15. Alternative routes to DOTA analogues

Incorporating aromatic rings in the carbons skeleton of chiral macrocycles serves to increase the structure rigidity of the macrocycle, which assumes a well defined conformation. For this reason, the rigid compounds have found applications as chiral shift reagents (to resolve the NMR spectra of enantiomerically enriched compounds) or ligands of metal catalysts in

enantioselective reactions. Gautam and co workers[27] presented a new synthesis of a DOTA analogues **37** and **38** using Mitsunobu reactions in the cyclization step (Fig 16).

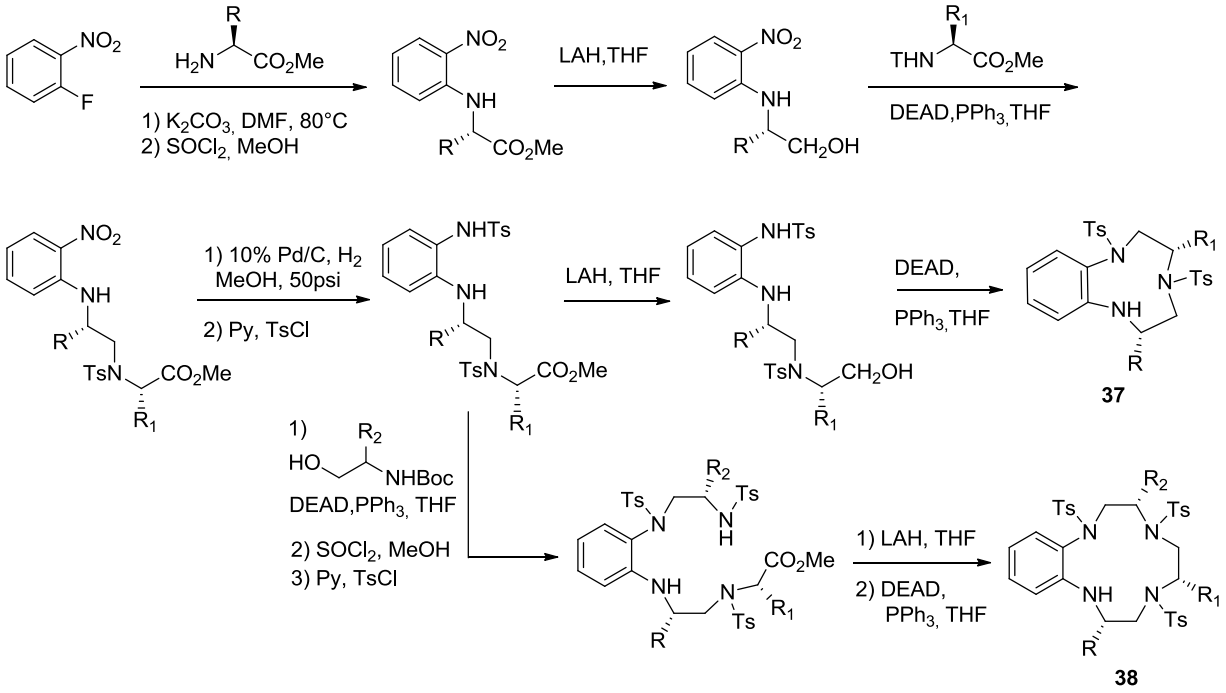


Fig 16. Mitsunobu reaction in the synthesis of DOTA analogues

This strategy offers the advantages of mild reaction conditions, short reaction times and good product yields. Natural amino acids were used as starting materials, so that changing the aminoacid a library of chiral macrocycle with different substituents could be prepared.

Chiral hexaazamacrocycles **39** were prepared by condensation of 2,6-pyridinedialdehyde with substituted ethylenediamines in the presence of $BaCl_2$ or lanthanide salts, followed by reduction with $NaBH_4$.[28] This family of ligands forms strong complexes with lanthanide metal ions; this particular affinity became attracting for future applications, considering the maintaining of luminescence and paramagnetism, typical properties of lanthanide ions.

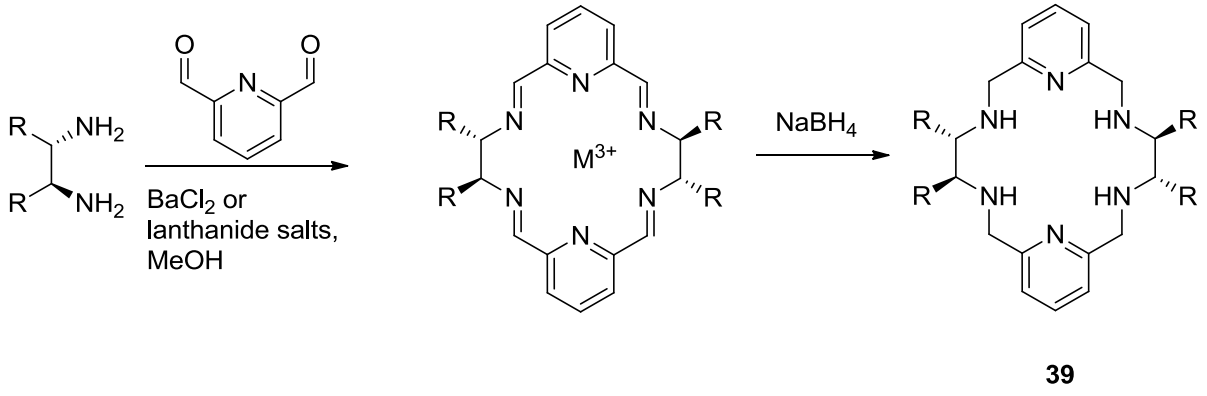


Fig 17. Synthesis of a chiral hexaazamacrocycle

Simply changing the procedure/solvent for the condensation of the same organic precursor that previously produced [2+2] macrocycles (MeOH-$BaCl_2$), an easy access to the [3+3] cycloadducts was achieved.[29] Another procedure to synthesize the [3+3] macrocycle ("trianglimine") involves the use of tartrate salt of 1,2-diaminocyclohexane as chiral starting material.[30] Routine reduction of the hexaimine macrocycles gave the corresponding hexaamino macrocycle **40**.

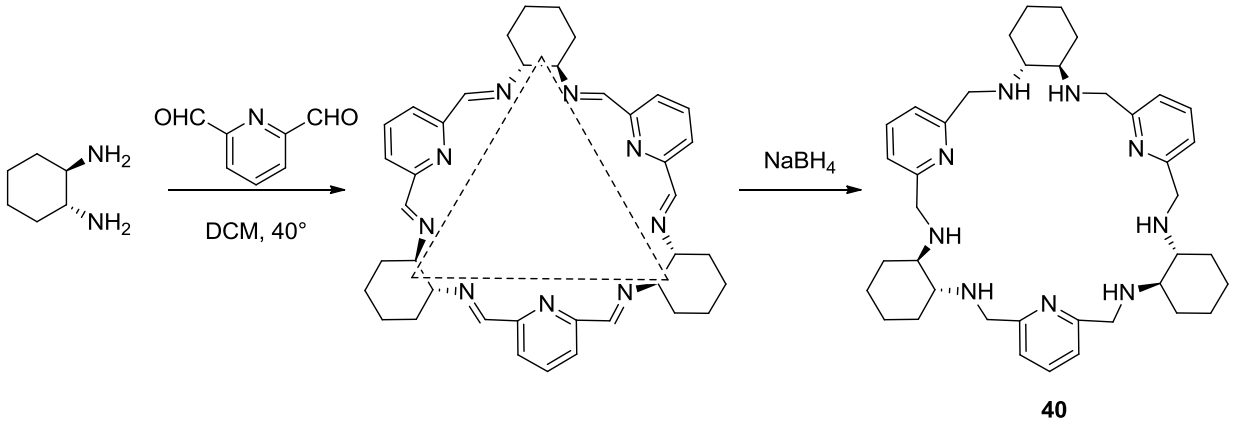


Fig 18. Synthesis of a [3+3] macrocycle

Procedure allowing the construction of polyiminomacrocycles in the absence of metal salts have been recently reviewed.[31] A large variety of [3+3] polyimino-macrocycles and the corresponding reduced products have been prepared using different aromatic dialdehydes.[32] The formation of [3+3] macrocycle is favored by the favorable geometrical features of the substrates and thermodynamically if the aldehyde has a rigid structures. The study of cyclocondensation of (*R*,*R*)-1,2-diaminocyclohexane with biaryl- and terphenyldialdehydes showed that the ratio [2+2]/[3+3] macrocycles was dependent on the geometry of the dialdehyde. All compounds with a liner arrangement of carbonyl carbons and the biaryl axis, produce trianglimines by [3+3] cyclocondensations. Conversely, in the case of non-linear arrangement of the carbonyl carbons, mixtures of [2+2], and [3+3] macrocycle were formed, but increasing the reaction time the more stable smaller products **41** and **42** were prevalently formed.[33k] Sometimes, it is possible to convert the [3+3] hexaimino-products **43** to the [2+2]tetraimino-products **44** by warming in dichloromethane.[33f]

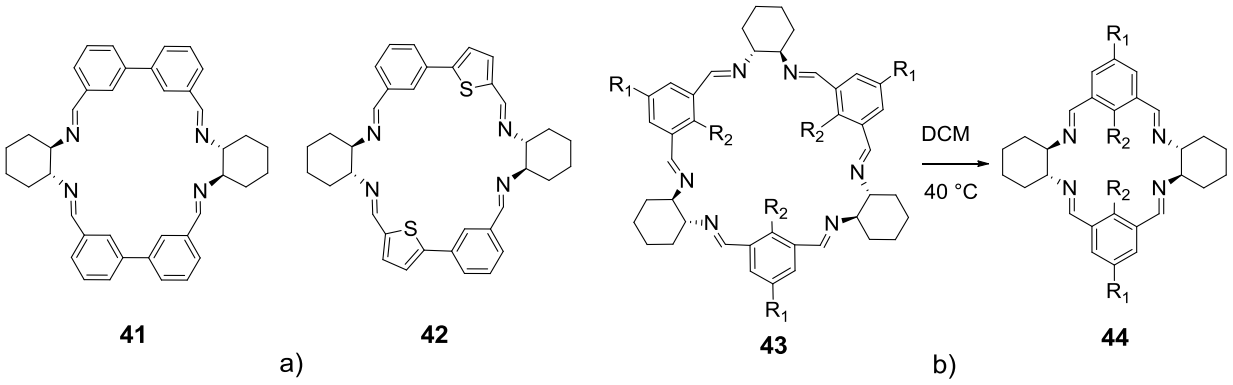


Fig 19. a) Favored [2+2] condensation reaction, b) conversion of [3+3] to [2+2] macrocycles

Using linear aliphatic aldehyde or dialdehyde with a preferred *anti*-conformation, led to preferential formation of linear products; the [3+3] macrocyclic product **45** was isolated with only 14% yield starting from 1,1′-ferrocenedialdeyde.[33j]

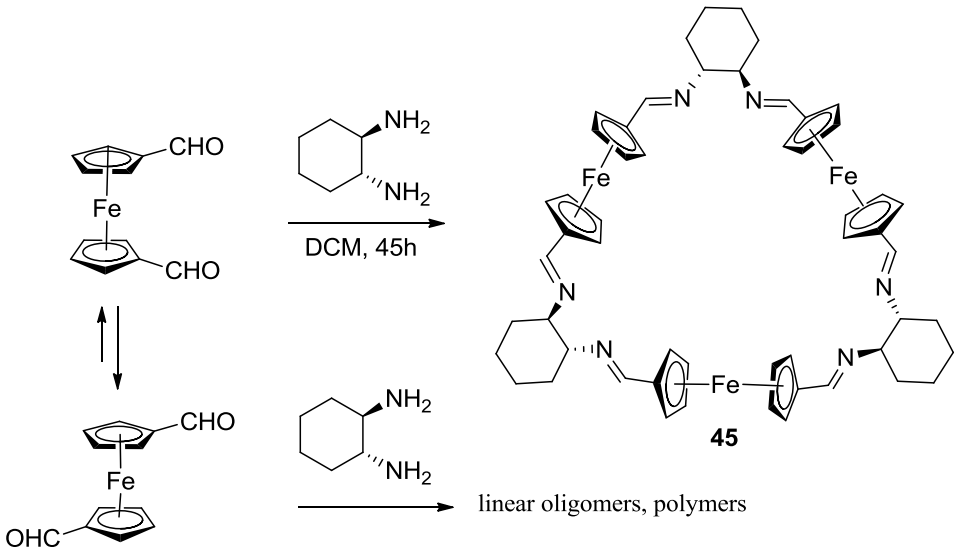


Fig 20. Effect of lack of rigidity of the dialdehyde

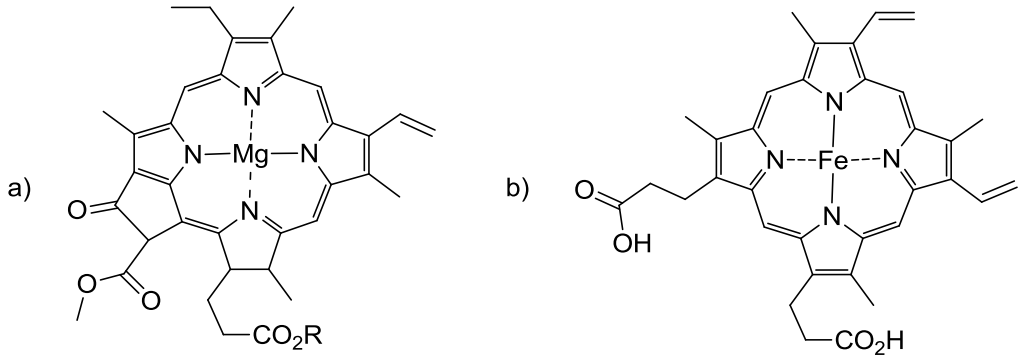
The synthesis of macrocycles with definite size is important in traditional host-guest chemistry and particulary in the emerging field of molecular devices and machines. In the restricted domain of chiral perazamacrocycles derived from dialdehyde/diamine cyclocondensation, the proper choice of the starting material and the reaction procedure permits the preparation of a lot of [2+2] and [3+3] macrocycles with a wide range of cavity size and different number of nitrogen atoms. Moreover oxygen and sulfur can be introduced in the macrocycle to modulate the basicity and coordination properties of the final ligand.

1.2.2 Applications

Perazamacrocycle ligands finds application in different fields, as catalyst, as chiral solvating agent and as ions or molecules recognition. Depending on the foreseen use, the desired macrocycle displaying the required steric, geometrical and chemical (basic) properties, can be synthesized by choosing the appropriate reagents. In the case of diamine-dialdehyde condensation, there is a wide choice of both partners, especially the dialdehyde (aromatic, heteroaromatic, *meta*- or *para*-substituted,…), whereas the chirality of the macrocycle is usually derived from the starting diamine, principally 1,2-diaminocyclohexane.

Ion recognition

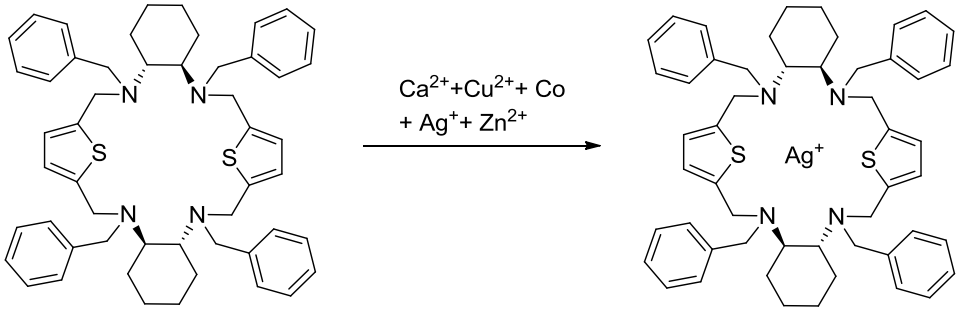
The most important macrocycles capable of cation recognition are porphyrin and its analogue pyrrole macrocycles. In chlorophyll **46** and HEME **47** (Fig 21), which are metallo-porphyrins, the four pyrrole nitrogens are strongly bound to a divalent metal ion (Mg^{2+} or Fe^{2+}). We will discuss in detail this class of macrocycle in subchapter 1.4.



46 **47**

Fig 21. a) Chlorophyll; b) HEME

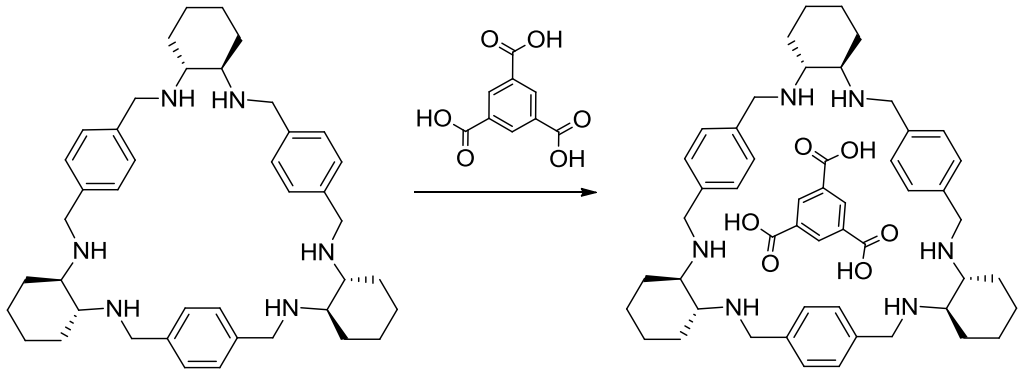
The capability to extract selectively a particular metal ion from a mixture of cations can be achieved exploiting the multiple cooperative coordination of heteroatoms other than nitrogens. As reported by Gao[33] (Fig 22) the [2+2] macrocycle **48** derived from 2,5-thiophenedialdehyde is able to extract silver ions from a mixture of different cations.



48

Fig 22. Ag+ recognition by a chiral N_4S_2 macrocyclic ligand

Concerning the recognition of organic molecules, the trianglamine **49** resulted very useful in the recognition of 1,3,5-benzenetricarboxylic acid,[34] thanks to the hydrogen bond interactions with the amine groups as shown in **49a** (Fig 23).



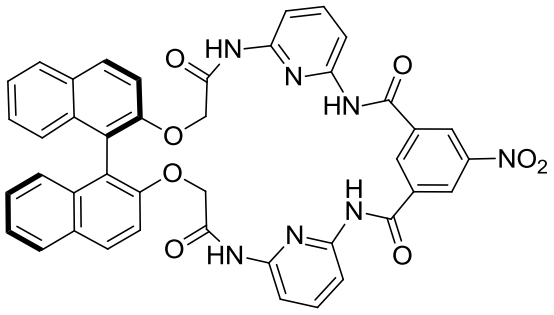
49 **49a**

Fig 23. Molecular recognition

Chiral Solvating Agents (CSA)

The interaction of a chiral host (mixture of enantiomers in any ratios) and a homochiral guest forms formal diastereomeric complexes, mainly due to hydrogen bonding interactions between the partners, and different chemical shifts are observed in NMR experiments. In this case, the guest is called Chiral Solvating Agent (CSA). The enantiomeric purity of the host can be determined just by adding a small amount of the CSA reagent to the chiral compound in a deuterated solvent.[35] In the ideal but rare case, a catalytic amount of CSA is enough for the chiral discrimination. Chiral solvating agents have an advantage over chiral derivatizing agents,[36] which are used in excess for derivatization before analysis, and over chiral HPLC, which consumes much more solvent. Various types of chiral solvating agents or shift reagents have been reported, such as lanthanide complexes,[37] cyclodextrins,[38] crown ethers,[39] calixarenes,[40] porphyrins,[41] BINOL derivatives,[42] and others.[43,44,45] Although a few of them are commercially available, the lanthanide complexes often cause signal broadening particularly at a high magnetic field because of the paramagnetic metal, and sometimes form precipitates via ligand exchange. On the other hand, crown ethers are effective only for amines. In many cases, a large amount of CSA is needed to give rise to signal splitting.

It has been envisioned that bifunctional guests bearing both hydrogen-bond donor and acceptor sites could bind a wide range of compounds. Sakai and co worker[46] presented a very attracting and particular CSA **50** (Fig 24) which can discriminate a wide range of chiral compounds, such as carboxylic acids, oxazolidinones, carbonates, lactones and epoxides using hydrogen bonding as the driving force of binding interaction (Table 1).



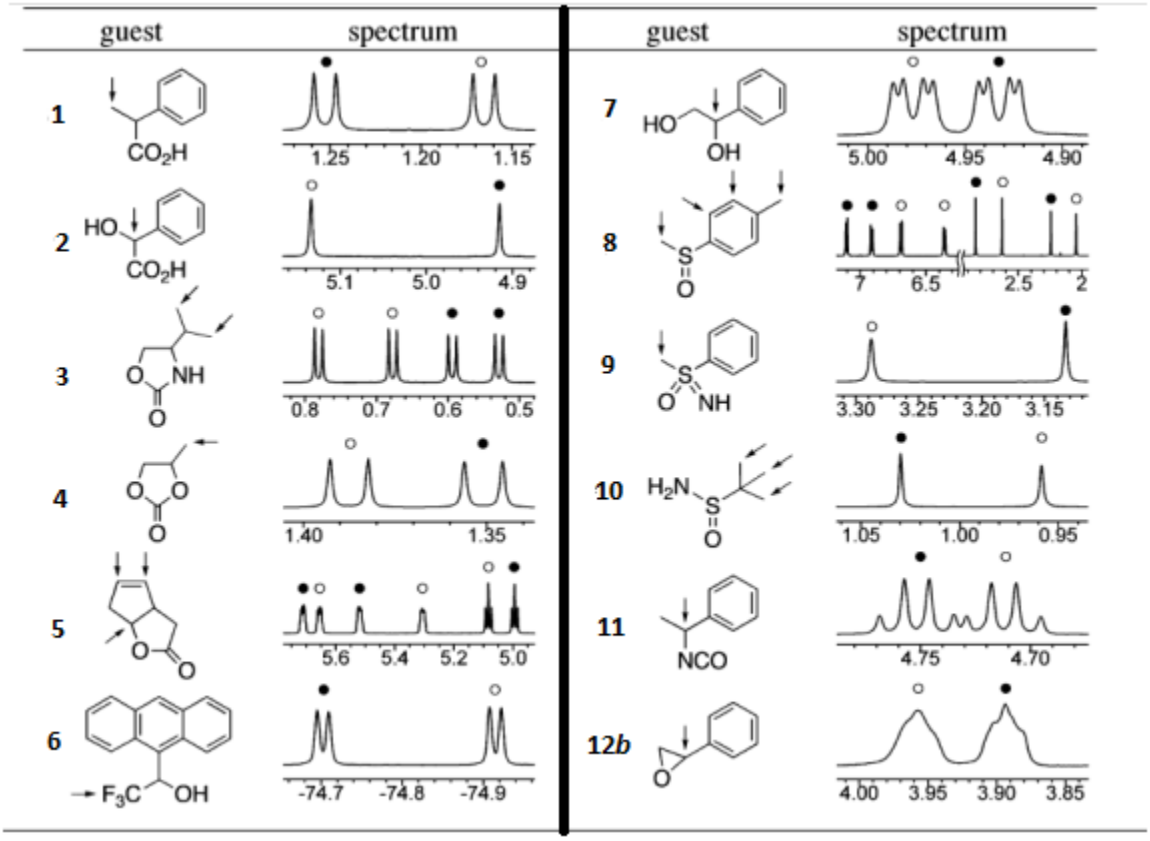
50

Fig 24. Highly effective CSA

Other chiral solvating agents are trianglamines. Several examples of differently funzionalized trianglamines used as CSA have been reported in the literature. They were prepared from a number of aromatic dialdehydes and presented different substituents on the amine nitrogens.

The research group of Prof. Savoia, where I carried out my research program, focused the attention on the diasteroselective synthesis of trianglamines by addition of organolithium reagents to the trianglimine **51** (Fig 25).[47] Particularly, the addition of phenyllithium occurred with complete stereocontrol giving the adduct **52** with the *R* configuration of the six newly formed stereocenters. Previous work of Periasamy[48] described the successful use of diamines and macrocyclic polyamines derived from (*R*,*R*)-1,2-diaminocyclohexane in the enantiodiscrimination of carboxylic acids, in contrast to the failure reported by Tanaka.[49]

Table 1. Selected Regions of NMR Spectra of Racemic Guests 1-12 in the Presence of (R)-50



[a] 600 MHz ^{1}H NMR of **6**-**10** and **12**-**16**; 300 MHz ^{1}H NMR of **17**; and 565 MHz ^{19}F NMR of **11** in the presence of (*R*)-**1** (15 mM, 1 equiv except for **12** and **17** (2 equiv) in $CDCl_3$ at 22 °C. The resonances for the protons or fluorines indicated by the arrows are shown in the right column. The signals for the enantiomers were assigned by adding some amount of one enantiomer to the above solution. Filled and open circles represent (*R*)/(1*R*,5*S*)- and (*S*)/(1*S*,5*R*)-enantiomers, respectively, which are shown only when the signals for the enantiomers are separated well. [b] At -50 °C.

Inspired by the results of Periasamy the possible use of trianglamine **52** as CSA with chiral carboxylic acids was investigated by my group (Table 2).

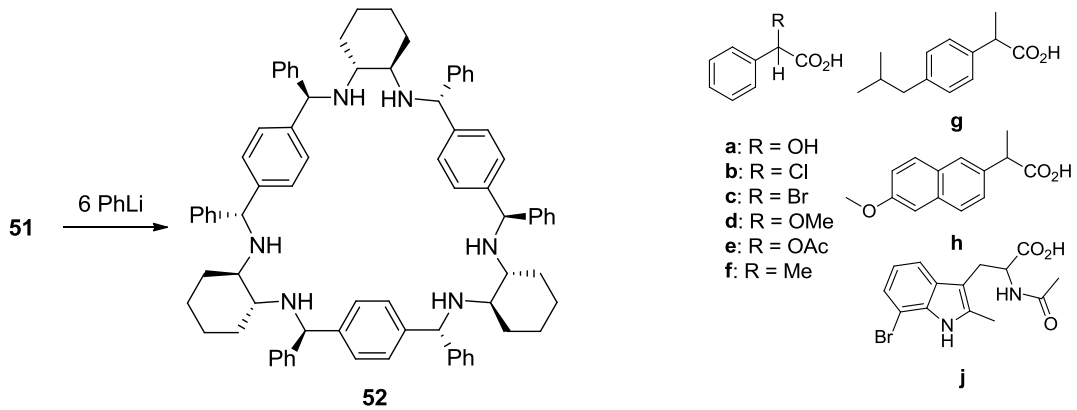


Fig 25. Synthesis of the trianglamine 52, useful as CSA

The experiment was performed by successively adding aliquots of racemic carboxylic acids to a 10 mM solution of **52** in $CDCl_3$ in the NMR tube, after each addition the ^1H NMR was acquired at 400 MHz and 25 °C. Table 2 shows the values of the induced chemical shift (Δδ) on selected signals of *rac*-carboxylic acids and the difference (ΔΔδ) between the shifts of two different enantiomers after the addition of the macrocyclic ligand.

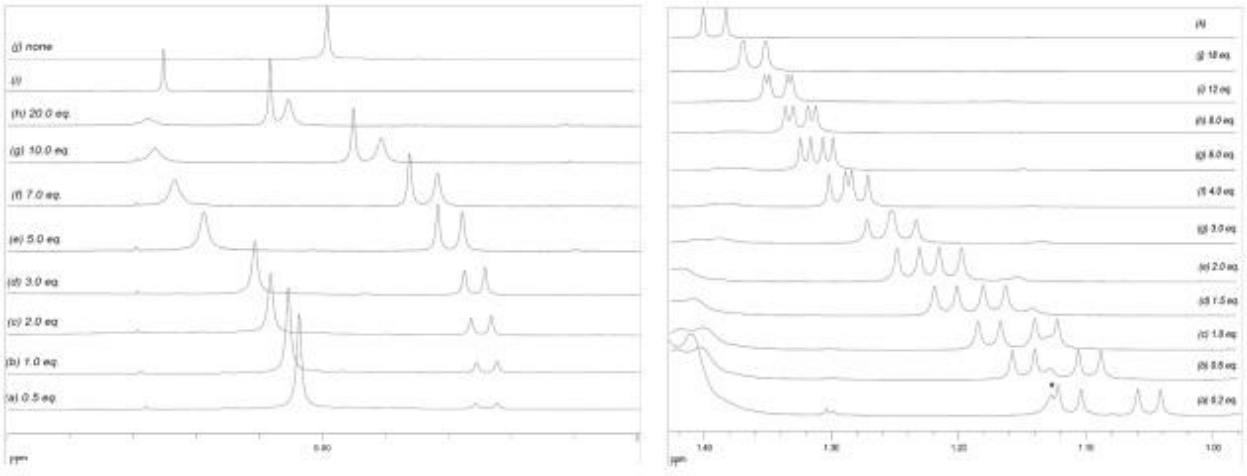
Table 2. Induced chemical shifts (Δδ) and chemical shift non-equivalences (ΔΔδ) of selected be signals for a mixture of 52 and different guests

Guest	52:Acid ratio	Probe signal	Δδ[a] (ppm)	ΔΔδ (ppm)
a	1:10	$C^{\alpha}H$	-0.319	0.044
b	1:14	$C^{\alpha}H$	-0.227	0.061
c	1:10	$C^{\alpha}H$	-0.165	0.066
d	2:1	$C^{\alpha}H$	-0.360	0.066
		OCH_3	-0.323	0.023
d	1:4	$C^{\alpha}H$	-0.224	0.033
		OCH_3	-0.323	0.037
e	4:1	$C^{\alpha}H$	-0.166	0.006
		CH_3	-0.168	0.119
f	5:1	$C^{\alpha}H$	-0.316	0.006
		CH_3	-0.297	0.062
g	4:1	$C^{\alpha}H$	-0.178	0.002
		CH_2CH	-0.019	0.010
		$CHCH_3$	-0.184	0.058
		$CH(CH_3)_2$	-0.003	0.008
h	4:1	$C^{\alpha}H$	-0.220	0.002
		OCH_3	-0.004	0.010
		CH_3	-0.204	0.051
j	1:4	$COCH_3$	-0.319	0.057
		CH_3	-0.143	0.027

Spectroscopic information: ^1H NMR, 400 MHz, 10 mM in $CDCl_3$, 25 °C.

As a general trend, observed in Fig 26a, the average signal of the two enantiomers of mandelic acid moved upfield (Δδ<0), suggesting that the deprotonation of the carboxylic acid function had occurred. At the same time, the absorption of the benzylic proton of the macrocycle **52**

moved downfield ($\Delta\delta > 0$), also indicating that an acid–base reaction occurred between the two species. Increasing the amount of mandelic acid, the ^{1}H NMR benzylic signal of **52** kept moving downfield, while the signal of the acid kept moving upfield, approaching the position of the signals observed for a solution of the pure acid. The same behavior was observed in the titration of racemic acids (**b**,**c**), instead, for the racemic acid (**d**,**e**) where the signal of the alfa group of the two enantiomers were splitted 0.119 ppm when 4 eq. of **52** were added, whereas for the C$^{\alpha}$H signal a small $\Delta\Delta\delta$ value (0.006 ppm) was determined. Fig 26b shows the split of the methyl group when the CSA **52** was used with racemic mixture of 2-phenylpropanoic acid (*rac*-**f**), the signal relative to the C$^{\alpha}$H on the stereogenic centre was not considered because the $\Delta\Delta\delta$ value was smaller than width of the quartet and the signal of the two enatiomers resulted overlapped. Baseline separation of the methyl signals of the two enantiomers was observed until 2 eq. of *rac*-**f** were added, after which the two signals became overlapped and unsuitable for the enantiomeric excess determination. Plotting the $\Delta\delta$ corresponding to a particular NMR signal versus the increasing ratio of host in solution, a Job-plot graphics[50] was elaborated that gave information on stoichiometric ratio between host and guest spaces.



[a] [b]

Fig 26. [a] Partial ^{1}HNMRspectra (400 MHz, $CDCl_3$, 25 ◦C) showing: (*a*–*h*) the CαH signal of **a** and the PhCH signal of 52 after the addition of different aliquots of **a** to a 10 mM solution of **52**; (*i*) CαH signal of **a**; (*j*) PhCH signal of **52.**

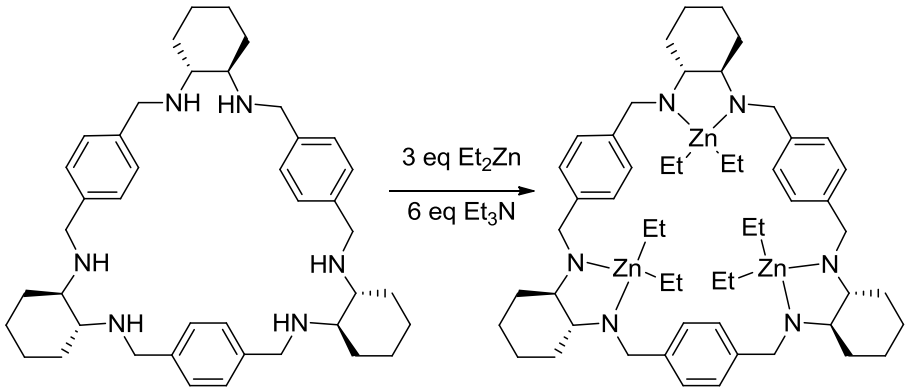
[b] (*a*–*j*) Partial ^{1}H NMR spectra (400 MHz, $CDCl_3$, 25 °C) of **f** showing signals of the CH_3 group after the addition of aliquots of **f** to a 10 mM solution of 52. (*k*) A partial ^{1}H NMR spectrum (400 MHz,10 mM, $CDCl_3$, 25 °C) of **f** showing the CH_3 signal.

Catalytically active metal complexes

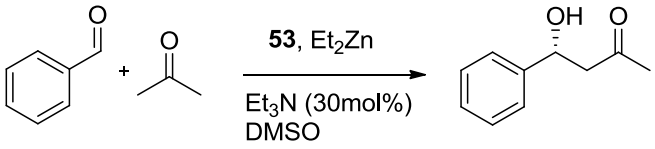
The potential of the chiral macrocyclic structures as ligands of metal species in enantioselective catalytic reactions was then evaluated.

An enantioselective aldol reaction between 4-nitrobenzaldehyde and acetone was successfully performed in the presence of a catalytic amount of the complex **53** formed *in situ* by the reaction of the trianglamine **48** with diethylzinc in the presence of triethylamine (Fig 24). It

was observed that the enantiomeric excess increased by increasing the amount of diethylzinc with respect to the ligand **48**, which indicated a cooperative effect within the macrocyclic framework of the 3:1 complex (Fig 27).[51]



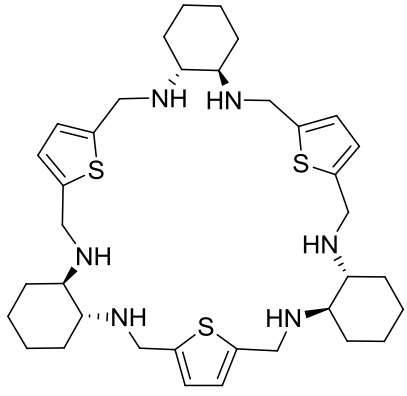
48 **53**



Catalyst (5mol%)	**Yield(%)**	**E.e(%)**
L	92	36
L-$ZnEt_2$	93	42
L-$2ZnEt_2$	93	48
L-$3ZnEt_2$	94	56

Fig 27. Legand 48 tested in condensation reaction

Similarly, the trianglamine obtained by [3+3] cyclocondensation of 1,2-diaminocycloexane and 2,5-thiophenedialdehyde **54** was used to prepare the zinc complex by treating it with different equivalent of diethylzinc, and this complex could catalyze a typical Henry reaction. It was observed that a better enantioselectivity was obtained with the trinuclear zinc complex (Fig 28).[33]



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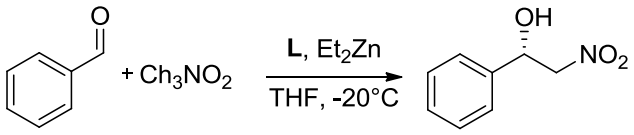


Catalyst (5mol%)	**Yield(%)**	**E.e(%)**
L-$ZnEt_2$	54	51
L-$2ZnEt_2$	63	57
L-$3ZnEt_2$	68	75

Fig 28. Tio-trianglamine ligand used in the Henry reaction

Macrocyclic chiral salen complexes were synthetized by [2+2] condensation of 2,6-diformyldiphenol ad optical active 1,2-diphenylethylenediamine, then heating the formed tetraimine with an excess of Mn(II) and Co(II) acetate in ethanolic solution. Further heating of Mn(II)complex with LiCl afforded the Mn(III) complex,[52] which was tested in enantioselctive

epoxidation reactions. Starting from the same reagents, it was possible to prepare the corresponding [3+3] macrocyclic hexaimine,[53] called calixsalen by analogy with calixarenes. Reduction of the macrocycle with $NaBH_4$ gave the saturated macrocycle **55**, whose crystalline Zn_3, Zn_2Cu, and lanthanide ions complexes were studied by X-ray diffraction. When the $ZnEt_2$ complexes of calixsalen **55** were used in aldol condensation the highest enantiomeric excess was obtained when the ration between the ligand and the metal was 1:3.[54]

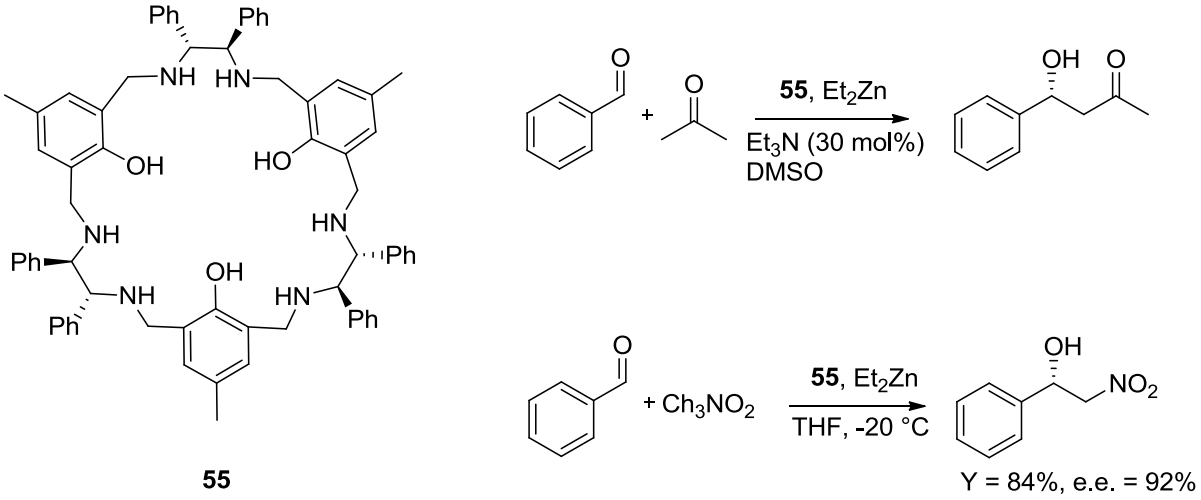
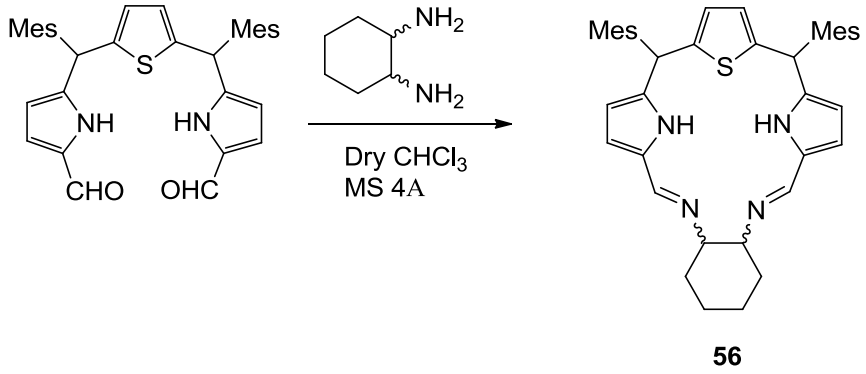


Fig 29. Calixsalen ligand tested in condensation and Henry reaction

1.3 Synthesis of new chiral macrocyclic ligand and application

1.3.1 Introduction

We were surprised to observe that although a large number of aromatic and heteroaromatic dialdehydes including pyridine, furan- and thiophenedialdehydes had been used for the construction of chiral macrocycles by condensation with optically pure *trans*-1,2-diaminocyclohexane, the synthesis of analogous chiral macrocycles from pyrroledialdehydes had been neglected. This contrasts with the ubiquitous presence of pyrrole rings in biologically active macrocycles as well as unnatural macrocyclic compounds, including porphyrins, expanded porphyrins, cryptophyrins, calyxpyrroles, calyxphyrins, and sapphyrins, which are mostly useful as ligands of metal ions and as receptors, carriers and sensors of inorganic and organic anions.[55] For example, the anion-binding capabilities of calixpyrroles,[56,57] and the partially reduced calixpyrrole[58] have been documented.
The first example of chiral macrocycle incorporating a pyrrole ring was the hybrid compound **56**, reported by Lee,[59] it is composed in part by a fragment of phorfyrin and in part by racemic *trans*-1,2-diaminocyclohexane (Fig 30).

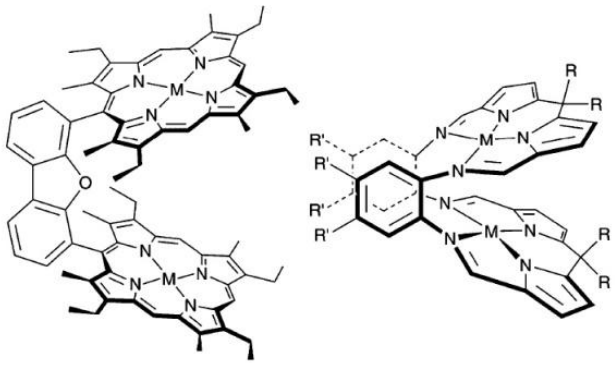


56

Fig 30. First example of chiral macrocycle containing pyrrole

The condensation of diformyldipyrromethanes with o-phenylenediamine has been exploiyed to synthesize achiral macrocyclic tetraimines,[60] which display binding properties toward transition-metal and uranyl salts,[61a-c] anions,[61d] and metallo-macrocycles.[61] Love and coworkers[61a] focussed their attention on the study of new compounds that can promote efficient chemical transformation of small molecules (such as O_2, H_2O, alkanes, CO_2, N_2) and the development of technologies for the synthesis of carbonius compound with low energy generation. Strategies directed towards the development of suitable catalysts for multielectron redox processes have often taken inspiration from nature, which takes advantage of metalloenzymes that contain bi- or multimetallic reaction sites that are organized precisely.[62] For this reason, the design of ligands that can promote the construction of bi- and multimetallic complexes that imitate enzymes activities as catalysts in multielectron redox processes has both a long held fascination and strategic significance.[63] This approach is

exemplified by the synthesis and chemistry of cofacial or Pacman diporphyrin complexes, e.g. **57**, in which the well-known coordinative properties of the porphyrin are combined with exceptional control of the intrametallic separation by a rigid and well-defined spacer between the two porphyrinic units (Fig. 31). [64,65,66]



57 **58**

Fig 31. Pacman phorphyrin complex 57 vs macrocyclic Schiff-base complex 58

Schiff-base polypyrrolic macrocycles that combine the coordinative and physicochemical properties of the pyrrole moiety with the particular geometric feature of macrocyclic Schiff-bases can be easily obtained by the [2+2] cyclocondensation procedure (Fig 32).

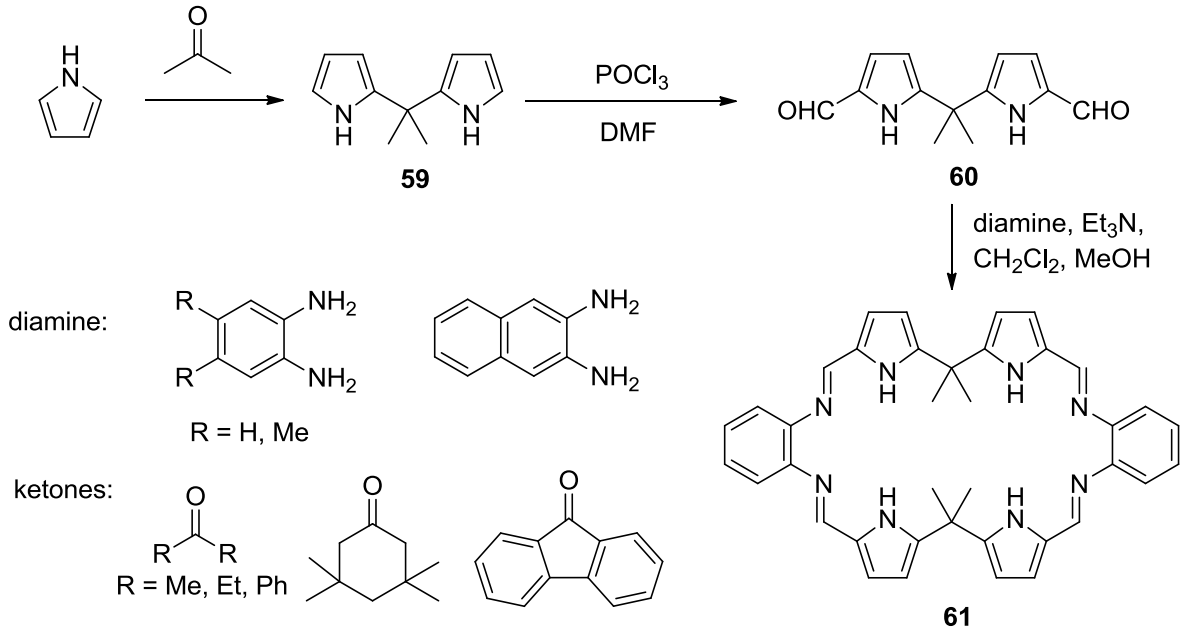
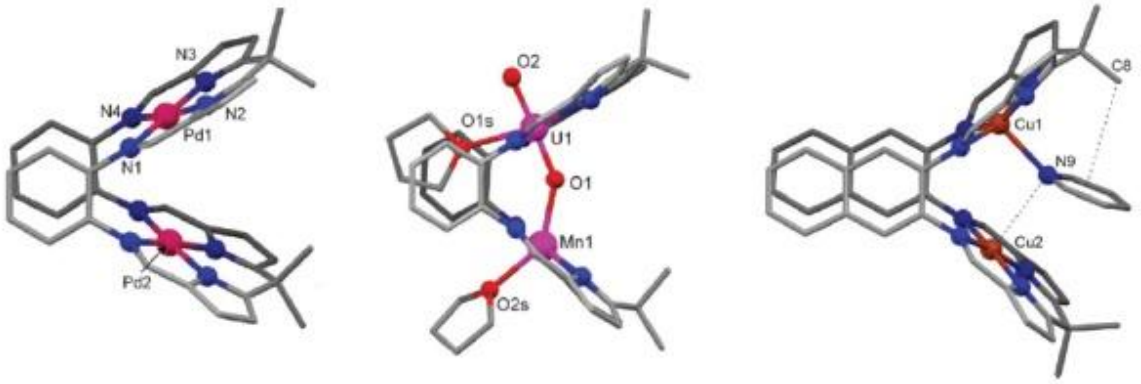


Fig 32. Synthesis of pyrrole containing Schiff-base macrocycle

Furthermore, polypyrrolic macrocycles exhibit a rich and diverse chemistry. Their flexible frameworks can accommodate a variety of transition metals, forming complexes with Cu, Co, Fe, Pd, Cd, Ni, Ti, V (Fig 33a,c) and f-block elements in a range of oxidation states, from which elegant transformations of the macrocycle itself or activation of small molecules can

ensue.[67] Schiff-base polypyrrolic lanthanide complexes such as motexafin lutetium, where one pyrrole unit of the phorphyrin system is replaced by an aromatic Schiff-base unit, are receiving considerable attention as photodynamic therapy agents.[68] Similarly, iminopolypyrroles can complex actinide cations such as uranyl (Fig 33b) and late first-row transition metals.



a) b) c)

Fig 33. a) Pd-Pacman complex. b) U-Pacman complex. c) Cu-Pacman complex.

1.3.2 Synthesis of new chiral pyrrole macrocyclic ligands useful for Cu-catalyzed asymmetric Henry reaction

As a continuation of our ongoing research on the synthesis of (chiral) peraza macrocycles and on the use of chiral 2-pyrroleimines for the synthesis of stereochemically defined molecules,[69] we now report the first preparation of C_2-symmetric, optically pure macrocycles containing pyrrole rings and their application as ligands in enantioselective Henry reactions. We choose to begin our research by preparing a few macrocycles (Fig 34) from (*R*,*R*)-1,2-diaminocyclohexane and *meso*-disubstituted diformyldipyrromethanes.

Among the many synthetic tools of organic chemists, the Henry reaction is prominent because of the versatile chemistry of the nitro group. In particular, the asymmetric version of the reaction affords enantiomerically enriched β-hydroxy nitroalkanes which are precursors of valuable bifunctional compounds, such as β-amino alcohols and α-hydroxy carboxylic acids.[70] Metal complexes with chiral ligands are widely used as catalysts for Henry reactions. Among the enantioselective protocols, those exploiting copper complexes with a variety of ligands have provided remarkably high levels of enantioselectivity.[71] A very important class of catalyst previously used as cupper catalyst are the bis-oxazoline, called BOX. The first application as organo-metallic catalyst (as copper-complex) was reported by Jorgensen,[72] in condensation reaction between nitromethane and an α-ketoester. The same catalyst was tested also in Henry reaction with very good enantiomeric excess (around 90%), using aromatic or aliphatic aldehydes. Evans[73] synthesized a new BOX ligand with bigger chiral group, and tested it in Henry reaction using very low catalyst loading with high e.e. Recently, diammine-Cu complexes as catalysts have provided interesting results. Good values of enantiomeric ratio were observed when (-)-sparteine[74] or oligothiophene-substituted (*R*,*R*)1,2-diaminocyclohexane[75] were used in combination with copper salts ($CuCl_2$ or $Cu(OAc)_2$).

The choice of the dialdehydes **60** was dictated first of all by their easy preparation. Moreover, they allow the study of the effect of different substituents R in the macrocyclic ligand on the activity and enantioselectivity of the derived catalysts. The dialdehydes **60** were prepared by formylation of the pyrrole nuclei of the dipyrrole derivatives **59**, in turn obtained by reaction of pyrrole with different ketones. Then, condensation of **60** with (*R,R*)-1,2-diaminocyclohexane, formed *in situ* by treatment of the corresponding L-tartrate salt with triethylamine, gave the expected macrocyclic tetraimines **62** with good yields. The subsequent reduction of the crude imines with sodium borohydride occurred without event to give the octadentate macrocyclic ligands **63** with good overall yields.

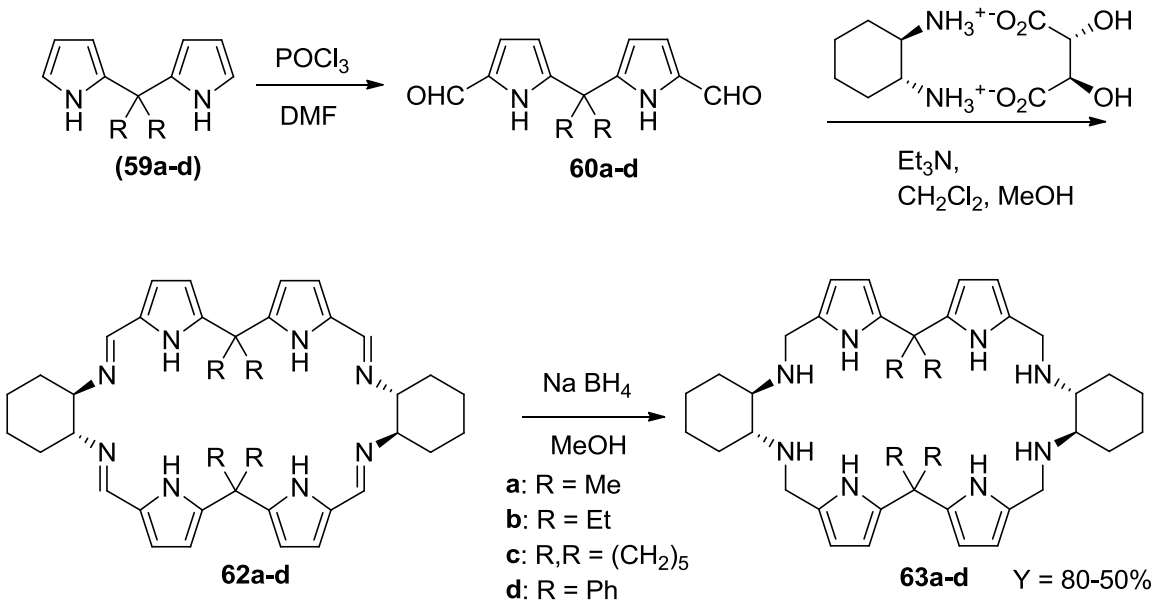


Fig 34. Synthesis of ligands useful for Cu-catalyzed Henry reactions

In order to evaluate the importance of the macrocyclic structure of the ligands **63** on the enantioselectivity of the catalytic system, we also synthesized the acyclic, tetraaza ligands **64**, **65**,[76] and **66**, which feature different fragments present in the macrocyclic ligands (Fig 35).

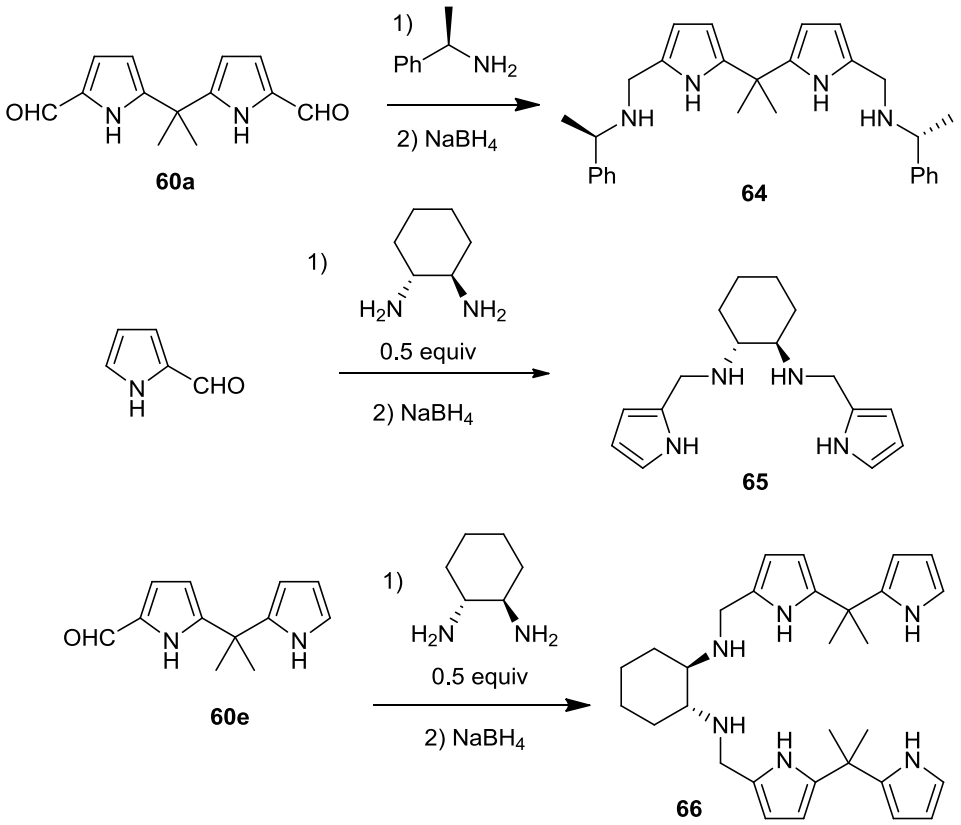


Fig 35. Synthesis of acyclic pyrrole ligands from 1,2-diaminocyclohexane

The former was prepared from dipyrroledialdehyde **60a**, and the chirality was derived from (*S*)-1-phenylethylamine. On the other hand, the ligands **65** and **66** were prepared from (*R*,*R*)-1,2 diaminocyclohexane by condensation with 2 equivalents of 2-pyrrolecarboxaldehyde and mono-formylated dipyrrole **60e** , respectively, followed by routine reduction in both cases.

With all these ligands in hand, the prototypical Henry reaction between benzaldehyde and nitromethane was explored, first looking for the optimal metal salt/ligand combination. The reactions were carried out in ethanol as the solvent at room temperature using 10 molar equiv of nitromethane and were analyzed after 14 h (Fig 36 and Table 3).

Table 3. Copper-catalyzed enantioselective Henry reactions of benzaldehyde with nitromethane[a]

Entry	L(mol %)	Metal salt (mol %)	Base(mol %)	67a(Yield%)[a]	e.e.(%)[b]
1	**63a** (5)	-	-	90	0
2	″ (5)	$CuCl_2$ (10)	-	0	0
3	″ (5)	$Cu(OTf)_2$ (10)	-	0	0
4	″ (5)	$Cu(OTf)_2$ (10)	Et_3N (10)	98	8
5	″ (5)	$Zn(OAc)_2 \cdot 2H_2O$(10)	-	99	5[c]
6	″ (5)	$Cu(OAc)_2 \cdot H_2O$ (10)	-	95	90
7	″ (5)	$Cu(OAc)_2 \cdot H_2O$ (10)	Et_3N (10)	99	64
8	**63b** (5)	$Cu(OAc)_2 \cdot H_2O$ (10)	-	92	61
9	**63c** (5)	$Cu(OAc)_2 \cdot H_2O$ (10)	-	99	75
10	**63d** (5)	$Cu(OAc)_2 \cdot H_2O$ (10)	-	85	61
11	-	$Cu(OAc)_2 \cdot H_2O$ (20)	-	10	0
12	**64** (10)	$Cu(OAc)_2 \cdot H_2O$ (10)	-	59	3
13	**65** (10)	$Cu(OAc)_2 \cdot H_2O$ (10)	-	99	59
14	**66** (10)	$Cu(OAc)_2 \cdot H_2O$ (10)	-	30	52

[a]Conditions: 0.25 mmol of benzaldehyde, 2.5 mmol of nitromethane, 1.5 mL of EtOH, rt, 14 h. [b] Yield determined by ^{1}HNMR. [c] Determined by HPLC on chiral column. [d] A slight prevalence of the (*S*)-enantiomer was observed.

We observed that the methyl-substituted ligand **63a** (5 mol%) in the absence of a metal salt was an effective organocatalyst, as the nitro alcohol **67a** was produced with 90% yield by stirring overnight (14 h) but, unfortunately, as a racemic compound (entry 1). On the other hand, when the reaction was carried out with the same ligand in the presence of either $CuCl_2$ or $Cu(OTf)_2$ (10 mol %), no reaction took place (entries 2 and 3). However, the presence of a small amount of triethylamine had a dramatic effect on the copper-catalyzed reaction, as an almost complete formation of the product was observed (entries 4). Therefore, since a weakly basic medium was required, we directed our attention to the use of zinc(II) and copper(II) acetates because the acetate anion is more basic than chloride and triflate anions, so that the presence of triethylamine should have been avoided. As a matter of fact, the use of these salts enabled us to obtain excellent conversions to the nitro alcohol **67a** without the need to use added base (entries 5 and 6). A strikingly different degree of stereoocontrol was observed with the two salts, as only with copper acetate a remarkable degree of enantioselectivity was obtained (90% ee, entry 6). Moreover, when the reaction was performed in the presence of

triethylamine the ee decreased to 64% (entry 7).[77] On the basis of these results, the following experiments were carried out using the other ligands in the presence of $Cu(OAc)_2$. In this way, we assessed that increasing the size of the substituents R on the carbon tether linking the pyrrole nuclei had a detrimental effect on the enantioselectivity, which decreased down to 75% ee for ligand **63b** and 61% ee for ligand **63c** (entries 8 and 9). Successively, in order to verify the importance of the macrocyclic structure of the ligand on the enantioselectivity, we checked the acyclic ligands **64**, **65** and **66**, each of them featuring a different fragment of the macrocyclic ligands **63a**. Ligand **64**, which lacks rigidity of the peripheral chiral moieties, gave an unsatisfactory performance, particularly in terms of enantioselectivity (3% ee, entry 12). On the other hand, ligand **65** with the rigid 1,2-diaminocyclohexane structure afforded **67a** with excellent yield and moderate stereocontrol (59% ee, entry 13). Using the ligand **66** was observed a good yield and good enantioselectivity (entry 14). Finally, we demonstrated that copper acetate in the absence of the ligand was unable to catalyze the reaction to a significant extent, as *rac*-**67a** was formed in 10% yield (entry 11). Overall, it was demonstrated that the combined use of copper acetate and the macrocyclic polydentate ligand **63a** was necessary for the efficient enantioselective catalysis.

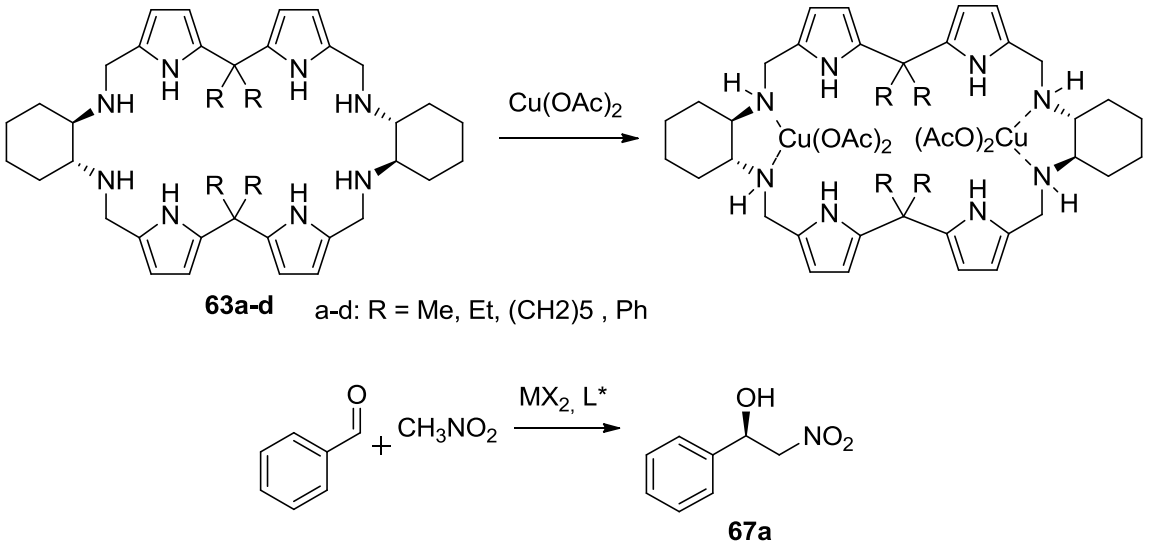


Fig 36. Enantioselective Cu-catalyzed Henry reaction with macrocyclic pyrrole ligands

The role of the solvent was investigated by performing the reaction in other protic, polar aprotic and apolar solvents using the $Cu(OAc)_2 \cdot 3H_2O$/**63a** (2:1 ratio) system (Table 4). It was demonstrated that the nature of the solvent affected to a limited extent the yield and the enantioselectivity. When the protic solvents MeOH, *i*-PrOH, and H_2O were used, comparable levels of ee were achieved, but a lower yield of **67a** was obtained in water. Among the polar aprotic solvents, CH_2Cl_2 gave an unsatisfactory performance in terms of both yield (81%) and ee (60%, entry 5), whereas in MeCN an almost complete conversion (99%) but a moderate ee (74%) were obtained (entry 6). On the other hand, either in THF and in $MeNO_2$ (entries 7 and 8, respectively) the levels of enantioselectivity were comparable to or slightly higher than those obtained in alcoholic solvents, but the yields were slightly lower. Finally, 92% ee was obtained in toluene, but the yield was very low (entry 9). In conclusion, it appeared that the use of EtOH as the solvent gave a convenient balance of yield and enantioselectivity.

Table 4. Effect of solvent in the 63a-Cu-catalyzed reaction of benzaldehyde and nitromethane[a]

Entry	Solvent	67a (Yield %)	e.e. (%)[b]
1	EtOH	95	90
2	MeOH	84	91
3	*i*-PrOH	92	89
4	H_2O	94	71
5	CH_2Cl_2	81	60
6	CH_3CN	99	74
7	THF	84	92
8	CH_3NO_2	79	91
9	Toluene	35	92

[a] Conditions: 0.25 mmol of benzaldehyde, 2.5 mmol of nitromethane, $Cu(OAc)_2 \cdot 3H_2O$ (0.025 mol), **63a** (0.012 mmol), 1.5 mL of solvent, rt, 14 h. [b] Yield determined by ^1H NMR. [c] Determined by HPLC on chiral column.

The effect of the ligand/metal ratio and catalyst loading on reaction rate and enantioselectivity was investigated next working in the previously established optimal conditions (Table 5). Working with a fixed amount of the ligand (5% molar equivalents), the loading of copper acetate was varied with respect to the 2-fold amount previously employed. Thus, it was observed that reducing to half the metal loading resulted in the decrease of the enantioselectivity to 80% ee (entry 2), although a comparable conversion was achieved. On the other hand, an increase of the metal loading to 15 mol% had no influence on ee (entry 3). Having so established the optimal ligand/metal ratio 1:2, we performed a set of reactions by varying the loading of the catalytic system. Using a 2-fold amount of the catalytic system **63a**/$Cu(OAc)_2 \cdot 3H_2O$ (10/20 mol%) did not change the outcome of the reaction (entry 4), although it is likely that a complete conversion should have been accomplished in a reduced time. In particular, reducing the L/Cu loading to 3/6 and then 1/2 mol % had no significant effect on the yield and enantioselectivity (entries 5 and 6), whereas a further reduction of the L/Cu loading to 0.2/ 0.4 mol % slowed the reaction and a moderate yield of **67a** was obtained after the canonical 12 h, although the same level of enantioselectivity was maintained (entry 7). At this point, we hoped that higher ee could have been obtained at a lower temperature, so we performed two tests at 0°C using different catalyst loading. This allowed us to establish that the same high levels of reactivity and enantioselectivity were maintained using a L/Cu ratio of 4:8 mol % (entry 8), but a further decrease of the loading to L/Cu 1:2 reduced both the yield (82% after 48 h) and the ee (86%) (entry 9). This negative trend was confirmed when the reaction was carried out

at 25 °C using a L/Cu loading of 5:10 mol %, when 45% yield (after 48 h) and 83% ee were obtained.

Table 5. Effect of Cu/63a ratio, catalyst loading, and temperature in the Henry reaction[a]

Entry	63a(mol%)	$Cu(OAc)_2 \cdot 3H_2O$(mol%)	T (°C)	67a(Yield%)[b]	E.e.(%)[c]
1	5	10	22	95	90
2	5	5	22	92	80
3	5	15	22	92	90
4	10	20	22	94	90
5	3	6	22	99 (92)[d]	92
6	1	2	22	93	90
7	0.2	0.4	22	56 (42)[d]	92
8	4	8	0	97	92
9	1	2	0	82[e]	86
10	5	10	-25	45 [e]	83

[a] The reactions were performed using 0.25 mmol of benzaldehyde, 2.5 mmol of nitromethane, and copper acetate as the catalyst in 1.5 mL of EtOH at 22 °C for 14 h. [b] Determined by ^{1}H NMR. [c] Determined by HPLC on chiral column. [d] Isolated yield. [e] Reaction performed at 0 °C. [f] Reaction time: 48 h. [g] Reaction performed at 25 °C.

The study was then extended to other aldehydes (Table 6) to verify the full scope of the catalytic system. A number of aromatic and aliphatic aldehydes were screened in the reaction with nitromethane in the optimized experimental conditions: $Cu(OAc)_2$ $3H_2O$ (6 mol %), **63a** (3 mol %), EtOH, 22 °C, 14 h (Scheme 5). The results obtained showed that the protocol can be successfully applied to most aldehydes, although structural and electronic features of the substrate can affect significantly the reaction outcome (Table 4). The results obtained with aromatic aldehydes did not allow a rationalization of steric and electronic effects of the substituents. Methyl, methoxy, and fluoro orthosubstituents (entries 1-3) on the phenyl ring allowed to maintain or even increase the enantioselectivity observed with benzaldehyde, and the highest ee was observed with 2-methoxybenzaldehyde (95% ee). On the other hand, lower yield and enantioselectivity were obtained with 2-nitrobenzaldehyde (entry 4), and the 2-hydroxybenzaldehyde reacted efficiently but produced a racemic compound (entry 5).

Table 6. Synthesis of β-nitro alcohols in the optimized conditions [a]

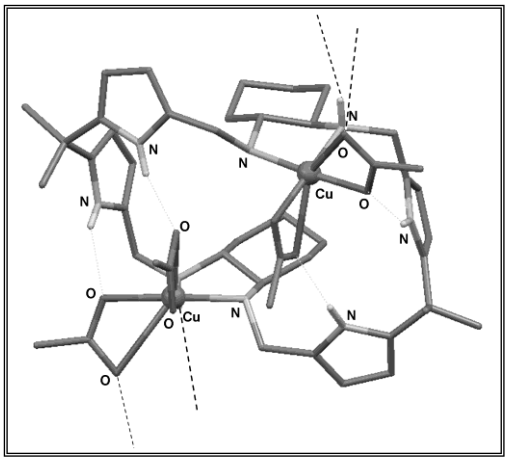
Entry	R	Product, Yield (%)[b]	e.e.(%)[c]
1	2-MePh	**67b**, 91	91
2	2-MeOPh	**67c**, 90	95
3	2-FPh	**67d**, 80	90
4	2-NO_2Ph	**67e**, 66	84
5	2-HO-Ph	**67f**, 87	0
6	4-HOPh	**67g**, 40	77
7	4-NO_2Ph	**67h**, 96	71
8	4-ClPh	**67i**, 78	86
9	4-MeOPh	**67j**, 61[d]	83
10	4-BocOPh	**67k**, 81	87
11	3-MeOPh	**67l**, 75	86
12	4-MePh	**67m**, 93	91
13	2-Naphthyl	**67n**, 67	86
14	PhCH=CH	**67o**, 45	91
15	Ferrocenyl	**67p**, 20	43
16	*N*-Boc-3-Indolyl	**67q**, 60	73
17	3-Py	**67r**, 92	74
18	*i*-Bu	**67s**, 98[e]	85[f]
19	*t*-Bu	**67t**, 98[e]	89[f]
20	Cyclohexyl	**67u**, 79	91

[a] Conditions: aldehyde (0.25 mmol), nitroalkane (2.5 mmol), 63a (3 mol %), $Cu(OAc)_2$ $2H_2O$(6 mol %), EtOH (1.5 mL), 22 °C, 14 h. [b] Determined by 1H NMR. [c] Determined by HPLC on chiral column. [d] Reaction time: 48 h. [e] Yield of crude product, which decomposed during purification.[f] Determined on the crude mixtures. [g]Syn/anti 61:39. [h] Reaction performed at 0 _C. i Syn/anti 67:33.

The variable effect of steric and electronic factors was confirmed when para- and meta-substituted benzaldehydes, bearing either electron-withdrawing and -donating substituents, such as 4-OH, 4-NO_2, 4-Cl, 4-OMe, 4-OBoc, and 3-OMe (entries 6-11), were converted to the corresponding products with variable yields and lower ee's (in the range 74-86%), with the exception of *p*-tolualdehyde (93% yield and 91% ee, entry 12). In particular, the behavior of 4-hydroxybenzaldehyde (40% yield, 77% ee, entry 6) was opposite to that of 2-hydroxybenzaldehyde. Moderate to good yields and high ee's were obtained from 2-naphthylcarbaldehyde and cinnamaldehyde (entries 13 and 14), whereas ferrocenylcarbaldehyde proved to give a bad substrate yield and an especially poor enantioselectivity (entry 15). Among the heterocyclic aldehydes, N-Boc-3-indolylcarbaldehyde and 3-pyridinecarbaldehyde, which display opposite electronic effects, provided the same level of enantioselectivity (73-74% ee, entries 16 and 17). Aliphatic aldehydes with primary, secondary, and tertiary alkyl substituents were efficiently converted to the expected products with high levels of enantioselectivity (85-91% ee, entries 18-20), but problems were often encountered during the isolation of the products, as previously observed. As a matter of fact, extensive decomposition of the products **67s** (R = *i*-Bu) and **67t** (R = *t*-Bu) occurred during purification by chromatography on a silica gel column, and only the cyclohexyl derivative **67u** could be isolated. The reaction of nitromethane with racemic 2-phenylpropanal under the standard conditions gave the nitro alcohol **67v** as a mixture of diastereoisomers, with a moderate prevalence of the syn diastereoisomer, as the result of similar reactivities of the two enantiomers of the aldehyde (entry 21). The enantioselectivity for anti-**67v** (90% ee) was higher than for *syn*-**67v** (78% ee). For both diastereomers, we assume that the asymmetric induction is only slightly affected by the configuration of the starting aldehyde and the OH-substituted stereocenter is prevalently formed with the R configuration, by analogy with the reactions of achiral aldehydes. An almost complete conversion and a similar outcome was observed by performing the same reaction at 0 °C for 48 h, although increased yield and ee of syn-**67v** but slightly lower ee of anti-**67v** were obtained (entry 22).

Crystals of the complex **63a**-2[$Cu(OAc)_2$] were then obtained by slow evaporation of a solution of the amine and copper acetate (1:2 molar ratio) in methanol. The X-ray structure of the complex (Fig 37a) shows that both copper atoms assume the square planar geometry, where the N,N bidentate diaminocyclohexane moiety and one oxygen of each carboxylate groups occupy cis equatorial positions in the plane. The other two oxygens are toward the vacant apical positions. Both cyclohexane rings have the chair conformation and the amino groups are equatorially disposed, and the dinuclear complex can be ideally split in two identical halves. In both halves, the two acetate ligands are involved in intramolecular hydrogen bonding: one equatorial oxygen atom is linked to the adjacent pyrrole N-H group, and the axial oxygen of the other acetoxy ligand is oriented toward the non-adjacent pyrrole N-H group. Moreover, intermolecular hydrogen bonding interactions were observed between the oxygens of the apical carboxylate groups and the amino groups of adjacent macrocycles, thus determining the formation of a chain with a helicity feature (Fig 37b).

a)



b)

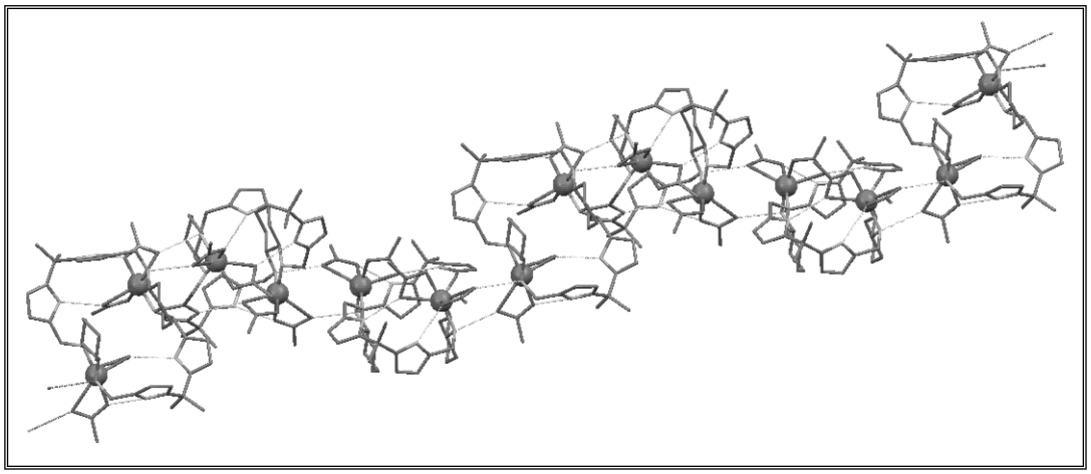


Fig 37. a: X-ray structure of the compound 63a-2[Cu(OAc)2]. b: Helicity feature

The nitro-aldol derivative **14k** was then used to synthesize (*R*)-isopropylnorsynephrine, alias *N*-isopropyloctopamine[78] (Scheme 38), a member of the class of biologically active and pharmacologically active 1-aryl-2-amino alcohols[79] that have been prepared by a variety of asymmetric methods.[80] For that purpose, the nitro group of **68** was reduced by heterogeneous hydrogenation to give the β-hydroxy amine,[81] and then reductive amination with acetone and sodium borohydride followed by removal of the Boc protection with HCl/MeOH afforded the hydrochloride salt of (*R*)-isopropylnorsynephrine with an overall yield of 47%.

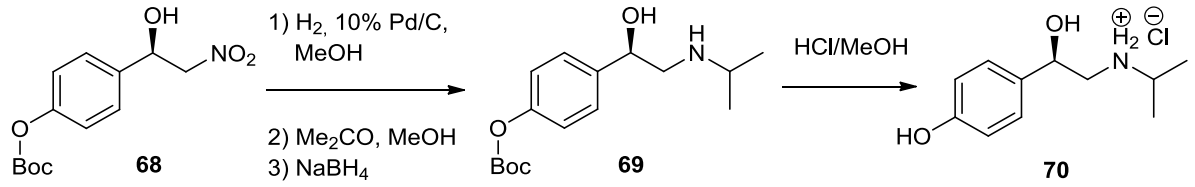


Fig 38. Synthesis of (*R*)-isopropylnorsynephrine

We can assume in the end that the best ligand is the **63a**, the different group in alfa position are extremely important in the enantiomeric ratio because can modify the 3D disposition of the ligand in the final complex. Finally to evaluate the importance of methyl group we decided to synthesized a new macrocycle without any substituent. The synthetic way to obtain

the macrocycle **74** is the same previously described (Fig 39). The dipyrran intermediate **71** was synthesized as reported in literature,[82] by reaction of pyrrole and formaldehyde and TFA as catalyst. The crude product was purified by Kugelrohr distillation to obtain the final product as a white solid in 40%yield. The dialdehydes **72** were prepared by formylation of the pyrrole nuclei of the dipyrrole derivative **71.**

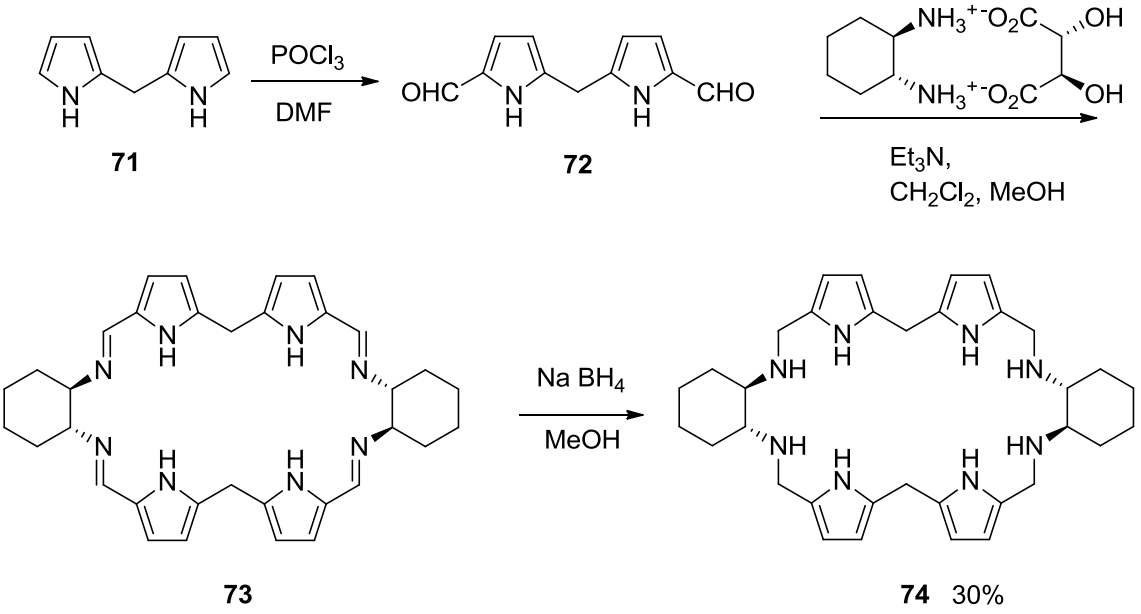


Fig 39. Synthesis of macrocycle 74 lacking *meso* substituents

In this case the condensation of the dialdehyde **71** with 1,2-cyclohexan diamine is more difficult than in the macrocycle **63a**. Probably, the "non rigid" structure of the dialdehyde decrease the reactivity in the final macrocycle synthesis. Finally the tetraimmine macrocycle **73** was reduced by $NaBH_4$ to obtain the tetraamino macrocycle **74** that was tested in standard condition with 2 equiv of $Cu(OAc)_2$ in the Henry reaction (benzaldehyde, nitromethane, EtOH). The corresponding nitroalchool was obtaind with good yield (60%) but low enantiomeric excess (37%).

1.3.3 Synthesis of new [2+2] macrocycles from diformyl-tris(heteroarenes)

Observing the X-ray structure of macrocycle **64** it can be observed that the copper center was not coordinated by the pyrrolic rings, which, however, formed hydrogen bonds with the acetate substituents on copper. For this reason we focussed our attention to the synthesis of new macrocyclic ligands differing from the previous ones for the ring size and the number and nature of the incorporated heteroaromatic rings. By this way, the heteroaromatic units might directly coordinate the metal ion. The simultaneous presence of polyaromatic structure or aromatic unit and Schiff base, are the optimal conditions to obtain a square planary coordination by the heteroatoms. Expanded porphyrins (sapphyrins, rubyrin, hexapyrrin)[83] Fig 40, are capable of strong ion complexation.

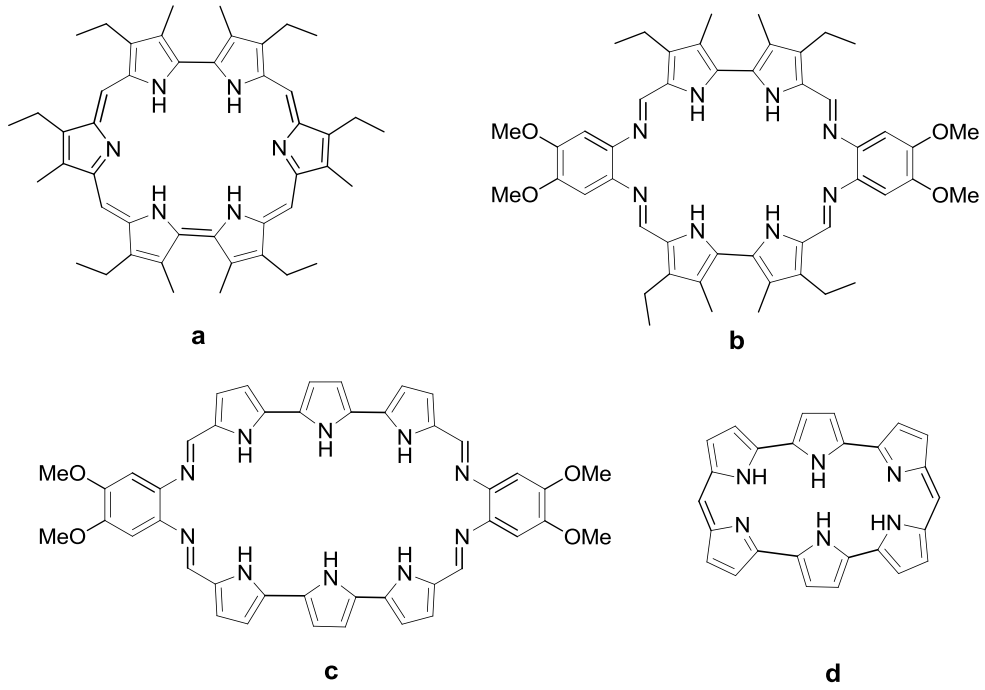


Fig 40. Rubyrin (a), Schiff base porphyrins (b,c), hexapyrrin (d),

Sessler prepared a huge amount of expanded porphyrins and analogues macrocycles containing Schiff base units. One example of this latter type of ligands is the Schiff base porphyrin shown in Fig 41; in this case, the ligand **c** can coordinate two Cu(I) ions through the imine nitrogens. X-ray structure showed that no interaction was present between the metal ion and the aromatic rings.

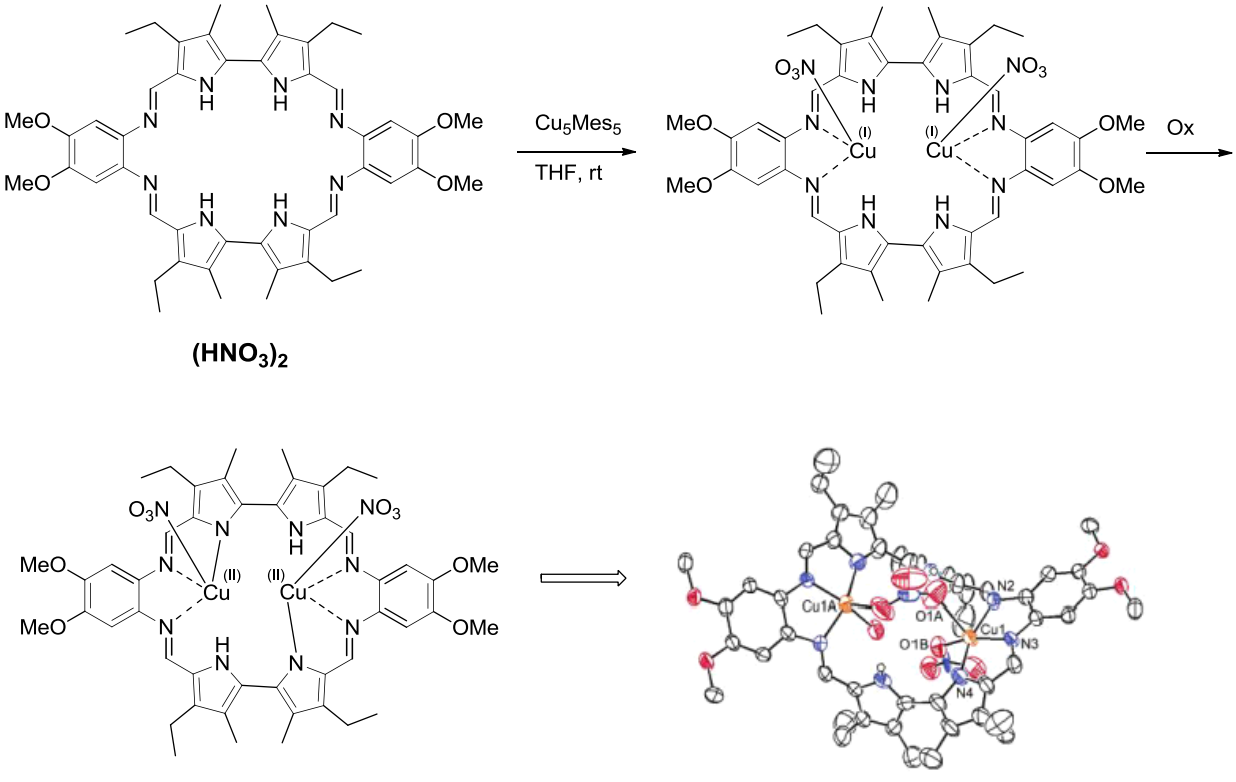


Fig 41. Effect of the oxidation state of copper on the coordination pattern of the polypyrrole ring

When the complex was exposed to the O_2 flow, each metal ions underwent oxidation and could coordinate one pyrrole ring to balance its new charge. As a consequence, the metal ions lie in a distorted square-pyramidal ligand environment that includes a bridging nitrate ion (Fig 41). [84]

Considering the particular coordination behavior of complex **c**, where the pyrrole rings are directly linked together through the position 2,2′, we decided to synthesize a new macrocycle containing three linearly linked heteroaromatic units and 1,2-diaminocyclohexane moiety. Schiff base porphyrins with different aromatic units have been studied during the years, but the presence of furan in such structures was neglected. Considering the easy preparation of the starting material and the excellent results obtained in catalysis with furan-containing chiral ligands, we decided to focus our attention on the furan-pyrrole-furan triaromatic unit as building block in the construction of chiral macrocyclic ligands.

As reported in the literature by Skarzewski,[85] chiral complex of the diamine **75** and copper acetate was tested as catalyst in nitroaldol reaction and showed good enantioselectivityes (Fig 42).

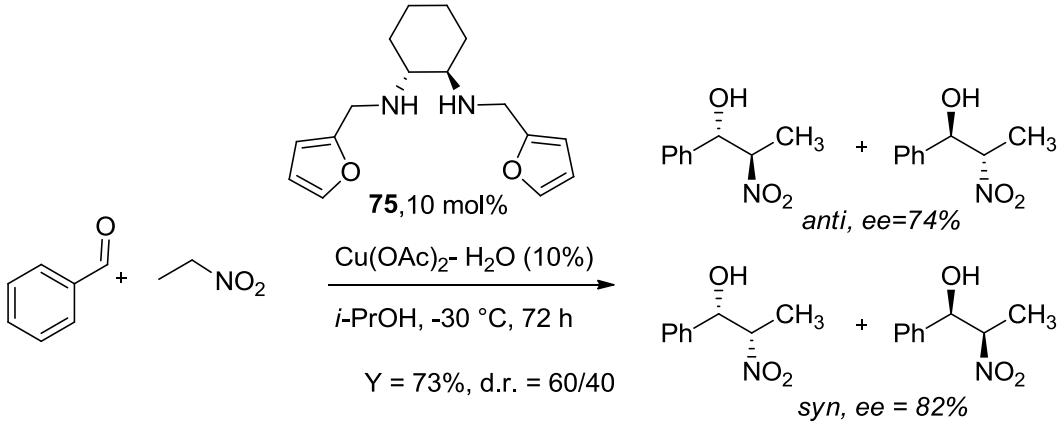
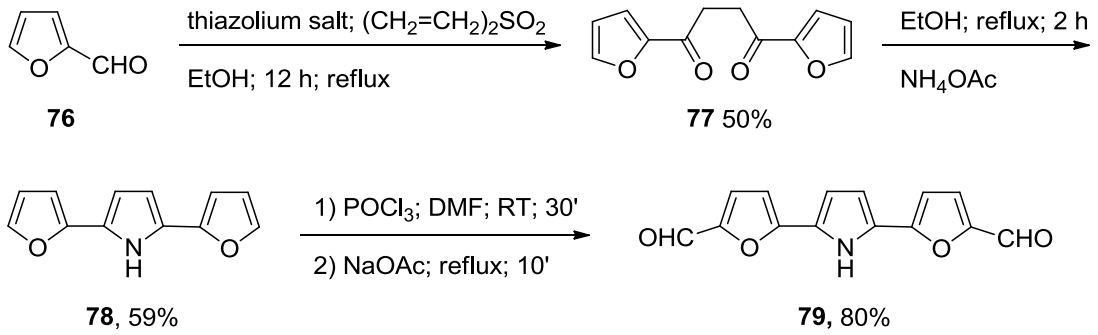


Fig 42. Henry reaction catalyzed by chiral furan-containing ligand

In the synthesis of a new macrocycle the [2+2] condensation reaction take place between the (*R*,*R*)-1,2-diaminocyclohexane and the dialdehyde of furan-pyrrole-furan system. The diformylation of 2-2'bridged systems was reported by Sessler in the synthesis of the analogue macrocycle **c**[86] shown in Fig. 39.

Starting from the furfural **76**, applying a Stetter reaction[87] with divinylsulphone and a catalytic amount of a thiazolium salt, the 1,4-di(2-furan)-1,4-butanedione **77** was obtained. The triaromatic system **78** was obtained by Paal-Knorr[88] reaction of the dicarbonyl compound **77** with NH_4OAc in EtOH at reflux for 2 h, then Vilsmeier formylation gave the diformylated triaromatic structure **79**, which was isolated as a red-brown solid and characterized by ^1H NMR spectroscopy in d^8-DMSO.



76 **77** 50% **78**, 59% **79,** 80%

Fig 43. Synthesis of the tris(heteroarene) dialdehyde

The key step in the full sequence is the Stetter reaction which led to the 1,4-di(2-furyl)-1,4-diketone **77**. Observing the mechanism, it is noteworthy that the thiazolium salt allows the umpolung of the the reactivity of the aldehyde group as the intermediate **b** acts as a nucleophile attacking divinyl sulfone to form the α,β-unsaturated compound **d** through **c**. Further reaction between compounds **b** and **d** leads to the diketone **77** through the intermediate **e** (Fig 44).

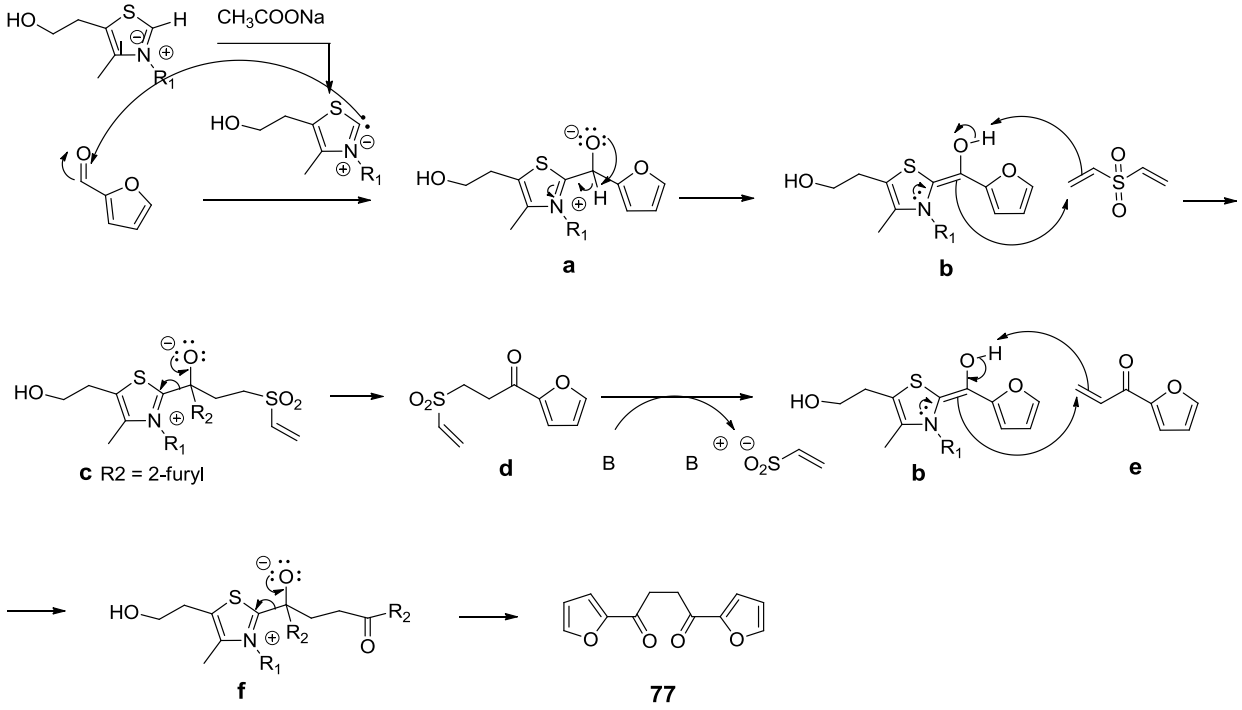


Fig 44. Mechanism of the Stetter reaction

The condensation of the dialdehyde **79** with (*R,R*)-1,2-diaminocyclohexane, formed *in situ* by treatment of the corresponding L-tartrate salt with triethylamine, gave the expected macrocyclic tetraimines **80**. The subsequent reduction of the crude imine with sodium borohydride occurred without event to give the macrocyclic ligands **81** with good yield (Fig 45).

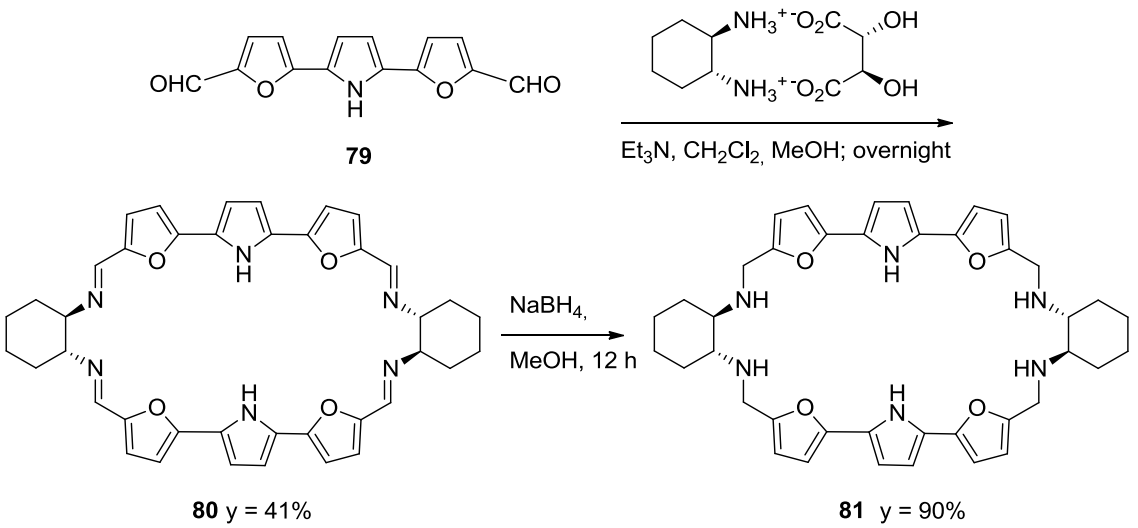


Fig 45. Synthesis of the macrocycle 81

The poor rigidity of the dialdehyde **79** can explain the relatively low yield of the cyclocondensation product and can increase the formation of linear product during the **80** synthesis. To evaluate the structure of a new macrocycle we decide to tested it in Henry reaction. The catalyst was prepared from the ligand **81** and 2 equivalent of $Cu(OAc)_2$ under nitrogen atmosphere in ether, to obtain a green-gray powder after the solvent stripping. The complex was tested in standard Henry condition and the corresponding nitroalchool was obtained in 90% yield and good enantiomeric excess (73%).

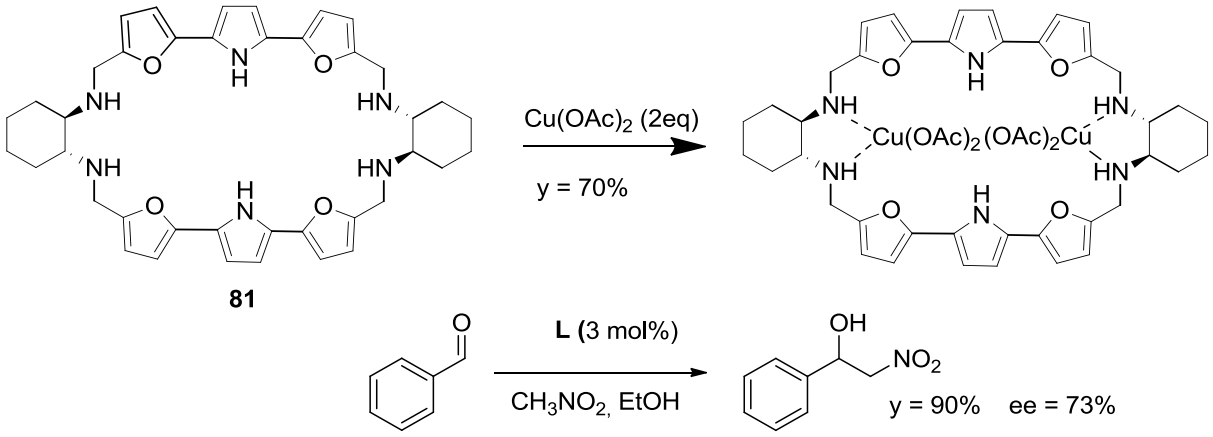


Fig 46. Henry reaction using 81 as a ligand

Unfortunatly, the enantiomeric excess was lower than the previously described catalyst **63a**. To justify the lower e.e. ratio we tried to obtain crystals of the Cu-complex to determine its 3D structure and evaluate which coordination capability of the ligand to the metallic center, but we got no success. Then we carried out NMR NOE (Nuclear Overhauser Effect) experiments to determine the conformation of the triarene moieties. The experiment showed

the proximity of the furan C-H protons and the pyrrole NH proton in the same furan-pyrrole-furan segment, due the *trans-trans* orientation of the three rings. Moreover, irradiating the pyrrole NH proton a response was observed for the pyrrole CH protons of the opposite triarene fragment. Therefore, we could assume that the ligand structure was particularly narrow and elongated.

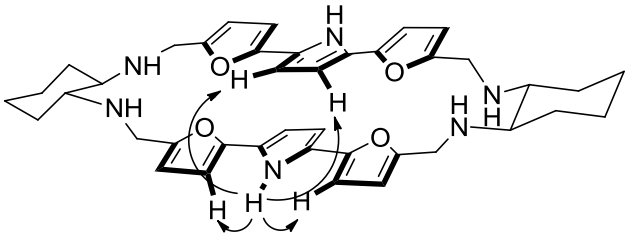
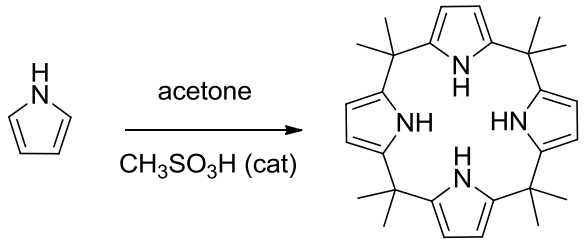


Fig 47. NOE effect.

1.4 Hydrogenation of calix[4]pyrrole

1.4.1 Introduction

Many organic ligands used by nature in important biological processes[89] are formed by the condensation of simple starting materials.[90] Uroporphyrinogen III, the biosynthetic precursor of the "pigments of life", forms metal complexes only under specific reaction conditions.[91] The first *meso*-octaalkylporphyrinogen **82** was synthesized more than 120 years ago by Baeyer.[92]



82

Fig 48. Baeyer synthesis of calix[4]pyrrole

The correct structure was proven by Rothemund in 1955.[93] Forty years later the X-ray structure analysis of this class of compounds showed alternating conformations of the pyrrole rings in the solid state.[94a] The X-ray structures of these macrocycles acting as ion-pair receptors revealed a conelike conformation and resembled the structures observed for calixarenes.[90] Hydrogen bonding, the dominating mode of interaction of neutral calixpyrroles, allows these compounds to be used as anion sensors.[95] Many interesting modifications of calixpyrroles have been reported: calixphyrins,[96] hybrids between calixpyrroles and porphyrins, expanded calixpyrroles like the calix[6]pyrroles,[97] and calixpyridines, hybrids containing pyrroles and pyridines.[98] Many of these studies were carried out with the aim to improve the anion-binding properties.[90b,99] As they have numerous applications, macrocyclic nitrogen-containing ligands and their metal complexes have been thoroughly studied.[100]

Inspired by naturally occurring metalloenzymes, chemists have invested their efforts in designing biomimetic metalbased catalysts, with the goals of understanding the mechanistic details of biochemical dioxygen activation and oxygen transfer reactions and of developing novel oxidation technologies.[101] The first and some of the most studied catalysts in the field were the iron and manganese-porphyrin derivatives, which were investigated as chemical models of heme enzymes and were shown to perform alkane and alkene oxidations in the presence of a variety of oxidants.[102] The planar and electron-rich structure of metalloporphyrins is well-suited for the stabilization of high-valent metaloxo intermediates, which are believed to be the active oxygen transfer species during these reactions.[103] Nonporphyrin iron and manganese complexes, as mimics of non-heme enzymes, were also intensively studied.[104] They present the advantage of being more accessible and readily

tunable compared to porphyrins.[105] A wide variety of ligands with N-donor and O-donor functionalities, from bidentate to pentadentate and forming mono- or dinuclear metal centres have been designed for modelling the active site of non-heme enzymes and for developing catalytic alkane hydroxylations, alkene epoxidations and alkene dihydroxylations.
Similarly, the products of hydrogenation of calix[4]pyrrole are very interesting, new macrocyclic nitrogen-containing ligands. The reduction of pyrroles usually require relatively harsh conditions.[106] Most efficient reductions of alkylpyrroles require an acid as the solvent or as a component of the solvent mixture.

1.4.2 Optimized synthesis of calix[2]pyrrole[2]pyrrolidine and calix[4]pyrrolidine

As reported by preliminary studies by the Neier group,[107,108] the hydrogenation reactions were performed during 24 hours using Pd/C as the catalyst in acetic acid as the solvent at 100 °C and 100 bar of H_2 pressure to give two half-reduced diastereoisomeric products **83a,b**, and only one fully reduced product, the all-*cis* calix[4]pyrrolidine **84b**.

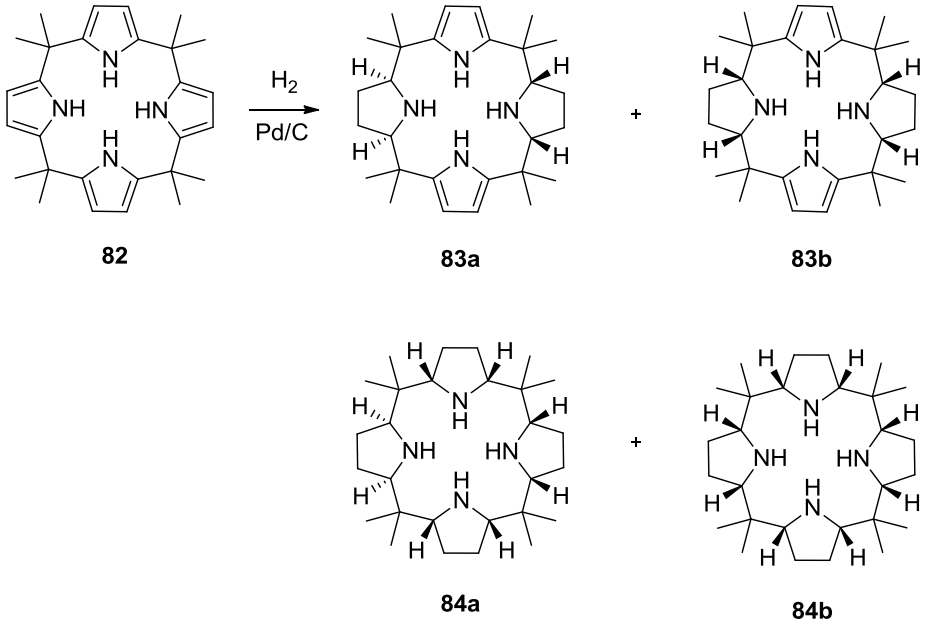
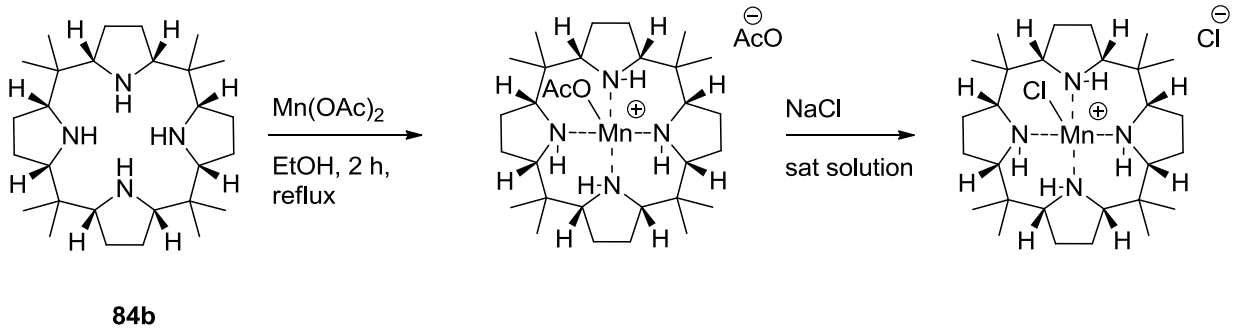


Fig 49. Hydrogenation reaction in standard condition

The totally-reduced product **84b** displayed very interesting application as new ligand. As reported by the same group,[14] using salts of Cu, Ni, and Pd, it was possible to prepare stable complexes. The Mn complex found application as catalyst in the epoxidation of alkenes.[109]

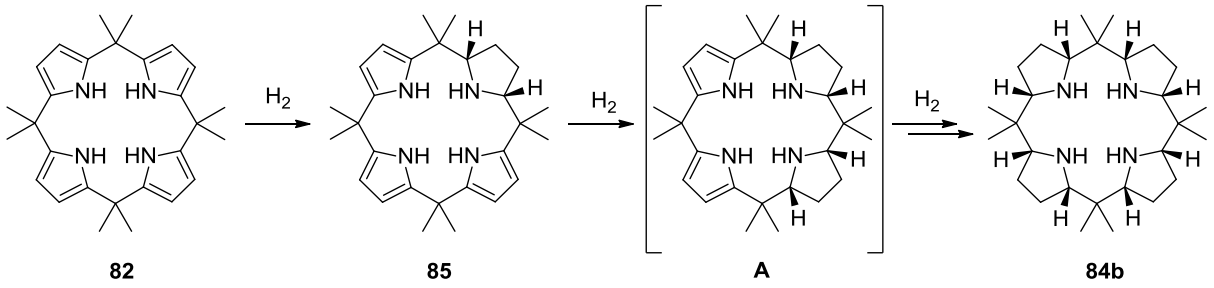


84b

Fig 50. Calix[4]pyrrolidine-Mn(II) complex

Starting from this exciting results, Neier group proposal was to thoroughly investigate the reaction conditions to optimize the preparation of the semi-hydrogenated compounds **83a,b** and the two fully reduced product **84a,b**. The attention was focused on reaction time, temperature, and solvent and then on the amount and type matrix of the Pd/C catalyst.

Based on the experimental results, Neier proposed a plausible mechanism of the hydrogenation of calix[4]pyrrole **82** to the fully reduced product **84** involves the consecutive hydrogenation of two adjacent pyrrole rings to form the intermediates **85** (Fig 51).



82 **85** **A** **84b**

Fig 51. Mechanism of the formation of the totally reduced macrocycle 84b

Compound **A** has never been observed, presumably because it is a very reactive species toward hydrogenation. On the other hand, compound **85**, coming from hydrogenation of the first pyrrole ring, could be isolated by stopping the reaction before conversion of the starting material was completed. It should be observed that hydrogenation occurs only in acidic medium, hence the pyrrole ring must undergo protonation to become enough reactive, and after reduction the formed pyrrolidine ring is obviously protonated. It is likely that if a double protonation of the starting calix[4]pyrrole is required, this should preferentially occur on two opposite pyrrole rings. As an alternative, after a first pyrrole ring has been reduced to a protonated pyrrolidine, the opposite pyrrole ring should preferentially undergo a second protonation step. Probably, two neighbour protonated pyrrole rings would suffer a more important charge repulsion. Consequently, a complete mechanistic sequence of the hydrogenation process is depicted in Fig 52.

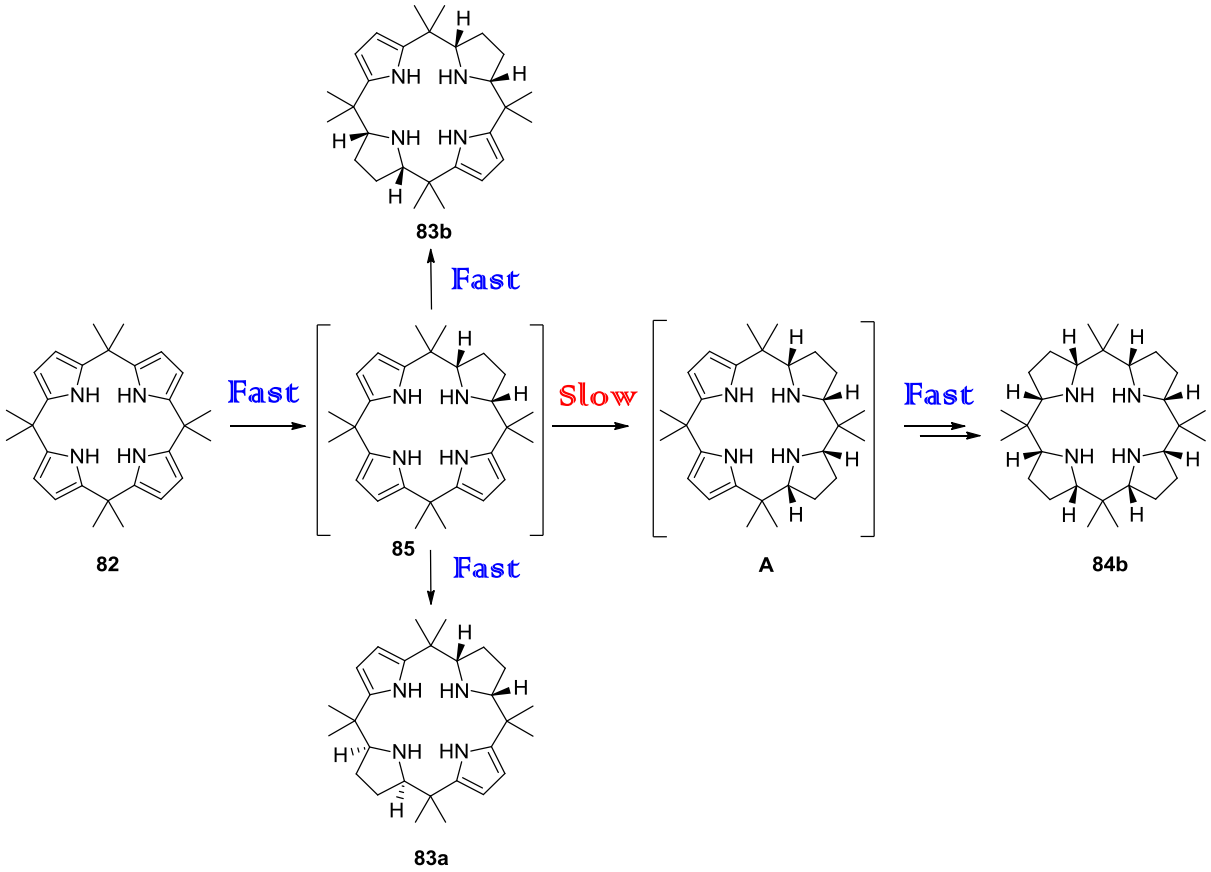


Fig 52. Sequence of steps in the hydrogenation of calix[4]pyrrole

The two diastereoisomeric semi-hydrogenated products **83a** and **83b** are formed from intermediate **85** in a relatively fast steps, but their subsequent hydrogenation is too slow. On the other hand, hydrogenation of **85** to give **A** is quite slow. This explain the fact that the fully hydrogenated product **84b** was obtained in a low yield, despite the fast hydrogenation steps ensuing on the intermediate **A**. Starting from these preliminary results we tried to optimize the conversion of **82** to compounds **83a,b** and **84a,b**. For this purpose, we first examined the effects of the reaction time and the catalyst loading (Table 7). We observed that decreasing the reaction time to 1 h and the amount of Pd to 4 mol%, **83** and **84** were obtained only in 75% yield and side products were observed (Table 7, entry 2,3) together with a new intermediate product **85** (25% yield) (Table 7, entry 4).

Table 7. Final optimization of the catalytic hydrogenation of calix[4]pyrrole 82[a]

Entry	10% Pd/C (mol%)	Time (h)	Conversion of 82	83a/83b[b]	84[b]
1	16	2	100	34/48	10
2	16	1	100	31/43[c]	1
3	8	1	100	23/33[c]	1
4	4	1	90	23/26[c] [d]	0.5

[a] The reactions were performed in an autoclave using AcOH as solvent at 100 bars of H_2 and 100 °C. [b] Yields (%) were calculated by GC analysis using the internal standard methodology. [c] Side products were observed coming from the degradation of **82**. [d] A new product **85** has been identified with 25% yield.

We attempted to achieve the total reduction of the isolated semi-hydrogenated compound **83b** (Fig 53). Submitting **83b** to optimal hydrogenation conditions applied to calix[4]pyrrole **82,** it was impossible to obtain the complete hydrogenation to **84**. Using a specific sample of Pd/C (Fluka), small but reproducible quantities of **84** were obtained, however, with a new batch of Pd/C from the same provider the hydrogenation did not work anymore.

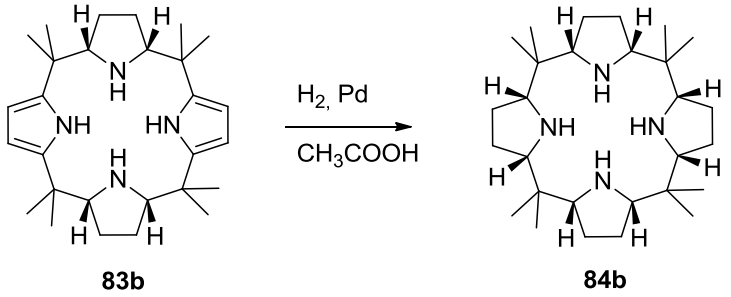


Fig 53. Hydrogenation of the half-reduced compound 83b

Faced to the irreproducibility, it became important to analyze the influence of different Pd catalysts on the hydrogenation of **83b**. For such purpose, we varied Pd/C catalyst achieved from different providers, the catalyst loading and even the solid matrix of the Pd catalyst. The results of hydrogenation runs carried out on compound **83b** in the different conditions are summarized in Table 8. In all cases, no conversion of the starting material was observed over any catalyst (36 mol%), even under harsh conditions.

Table 8. Catalytic hydrogenation of calix[2]pyrrole[2]pyrrolidine 83b.[a]

Entry	Catalyst	Provider, type	84
1	10% Pd/C	Aldrich, basis	-
2	10% Pd/C	Fluka, basis	-
3	5% Pd/C	Aldrich, basis	-
4	10% Pd/C	Stream, reduced, dry powder	-
5	5% Pd/C	Stream, reduced, dry powder	-
6	5% Pd/C	Stream, eggshell, reduced (50% wet), evonik E5	-
7	20% Pd/C	Stream/(Pearlman cat.), unreduced (50% wet)	-
8	30% Pd/C	Aldrich/basis	-
9	0.6% Pd/C	Stream, 50% wet	-
10	0.5% Pd/Al_2O_3	Stream, reduced, dry	-
11	1% Pd/SiO_2	Stream, supported on polyethylenimine	-
12	5% Rh/Al_2O_3	Aldrich/powder	-

[a] The reactions were performed in an autoclave using 36 mol% of catalyst, 100 bars of H_2, at 100 °C for 12 h.

The mechanism we have proposed attributes a considerable importance to the protonation degree of the starting material and intermediate compounds. Therefore, the influence of the acidic medium at different temperatures was investigated (Table 9).

Table 9. Catalytic hydrogenation of calix[2]pyrrole[2]pyrrolidine 83b.[a]

Entry	Pd (mol%)	Solvent/Acid	T (°C)	84
1	34	AcOH	100	-
2	34	AcOH / TFA (8/2)	100	-
3	34	AcOH / H_2SO_4 (8/2)	100	-
4	34	AcOH / BF_3OEt_2	100	-
5	34	*i*-PrOH / BF_3OEt_2	65	-
6	34	AcOH/aqHCl[c] (1/1)	100	-
7	34	TFA	65	-
8	34	aq HCl[c]	50	-

[a] The reactions were performed in an autoclave using 10% Pd/C (0.34 mol%, Aldrich), 100 bar of H_2 for 12 h. [b] Degradation of the starting material was observed. [c] Commercially available 37% aq HCl.

Even increasing the temperature to 150 °C, we only observed a degradation of the starting material. Moreover, in the presence of different strong acids (Table 9, entry 2-8) including 37% HCl as the solvent, no traces of the totally reduced product **84** were detected and starting material was completely recovered. The semi hydrogenated compound **83b** proved to be stable and very resistant under extremely strong acidic conditions.
Lastly, it appeared that the nature of the catalyst is the key parameter on which work to increase the yield of compound **84**. Having observed that a specific batch of Pd/C-Fluka gave a better result than other Pd/C catalysts of other brands, three reasons were considered as possible cause(s) of the diverse reactivities: 1) The efficiency of the catalyst was due to the dispersion of palladium on the matrix. 2) The matrix had a special surveying/morphology. 3) An impurity on the catalyst was the key of this success. At the moment, we cannot choose among the three hypothesis.

Having tested so many different types of catalyst with no success, further hydrogenation runs were performed increasing the catalyst loading. The first trial in the hydrogenation of **84b** by increasing the amount of catalyst of 34 mol% to 70 mol% failed, for these reason was decided to carry out the reaction with stoechiometric amounts of catalyst until 10 eq of Pd (Table 10). As shown in Table 10, increasing the amount of Pd/C up to 9.5 equivalents, the yield of compound **84** increased to 80%.

Table 10. Stoechiometric hydrogenation of calix[2]pyrrole[2]pyrrolidine 83b.[a]

Entry	Pd (equiv.)	Conversion of 83b[b]
1	1	32
2	2.5	41
3	3.5	53
4	4.5	51
5	5.5	60
6	7.5	72
7	9.5	**100/80[c]**

[a] The reactions were performed in an autoclave using 10% Pd/C (Aldrich) in AcOH at 100°C and 100 bars of H_2. [b] Conversions (%) were calculated by GC. [c] Isolated yield (%).

Considering the deep knowledge of Prof. Savoia group on the particularly reactive transition metals supported on graphite,[110] we started an investigation of the matrix-effect on the hydrogenation process. As reported in the literature, switching from activated carbon to graphite has several advantages, including lower costs, easier manipulation, greater thermal conductivity, and an ordered planar structure. Graphite can accommodate alkali metals between the carbon sheets. Intercalation compounds of graphite and alkali metals of known stoichiometry, e.g. C_8K and $C_{24}K$, can be prepared by melting potassium metal on graphite with the proper molar ratios at 150 °C by stirring under an inert atmosphere. By this way, the 4s electrons of the potassium are transferred to the π-system of graphite, and a compound with negatively charged graphite layers intercalated by layers of potassium cations is formed. Potassium graphite C_8K has a very high reducing power that can be exploited to reduce C=N, C=O, or activated C=C double bonds or to cleave C–S or C–CN bonds.[111] Most importantly, treatment of C_8K with metal salts, including Ti(III), Ti(IV), Mn(II), Cu(II), Fe(III), Co(II), Sn(II), Pd(II) and Zn(II) salts in refluxing tetrahydrofuran or 1,2-dimethoxyethane gives the corresponding highly dispersed zero-valent metal in a highly active form on the graphite surface (Fig 54).

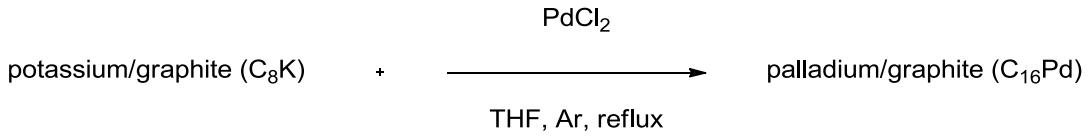


Fig 54. Synthesis of Pd/grafite catalysts

We hoped that using a different carbon morphology to support palladium could be useful to improve the hydrogenation reaction. We synthesized three different Pd/graphites with different metal loading using the procedure shown in Fig 54. Each of the catalysts prepared was structurally characterized by TEM and powder X-ray diffraction. In Fig 55 is reported the TEM image of 15% Pd/graphite ($C_{48}Pd$), where Pd nanoparticles are deposited on the grafite surface.

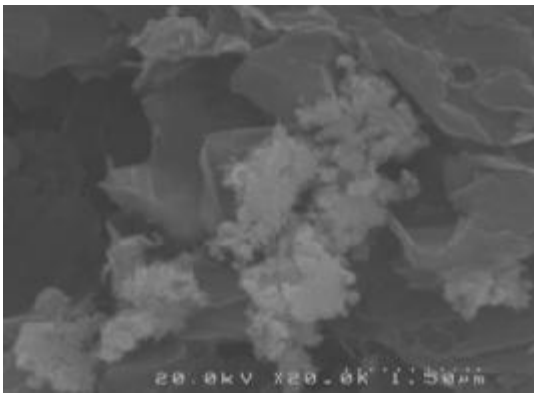


Fig 55. TEM image of 15% Pd/graphite (C48Pd) (20.0 kVx 20.0 K, 1.50 μm)

We carried out hydrogenation reactions using Pd/C and Pd/graphite with different metal loadings and compared the activities of these catalysts with those obtained using the catalyst 10% Pd/C (2.5 equiv) as a reference (Table 11, column **a**, entry 1). Moreover, the effect of increased molar equivalents of Pd on each reaction was investigated. We first observed that increasing the pressure to 120 bar afforded in the decomposition product of **82**, whereas at 70 bar no product was formed. This was confirmed in the two runs performed using different loadings of Pd/C (Table 11,column a, entries 2 and 3). When 5% Pd/C was used, an increases of the yield to 65% was observed (Table 11, column a, entry 2). On the contrary, using a highly loaded catalyst decrease the amount of matrix and therefore decrease the yield of the reaction to 15% (Table 11, column a, entry 3). By comparing the reactivity of Pd/C to Pd/graphite, we observed that only $C_{96}Pd$ showed a small activity in the same reaction conditions(Table 11, column a, entry 7). This result supported our hypothesis that the nature and morphology of the matrix, besides the dispersion of the metal, is determinant for the success of the hydrogenation. Increasing the amount of Pd to 10 euiv, 20% yields was observed (Table11, column b, entry6).

Table 11. Hydrogenation of calix[2]pyrrole[2]pyrrolidine 83b with different Pd loading and matrix.[a]

a) Using 2.5 equiv of Pd

Entry	**Catalyst**	**84b[b]**
1	10%Pd/C	41
2	5%Pd/C	65
3	30%Pd/C	15
4	10%Présat.Pd/C	55
5	35%Pd/graphite ($C_{16}Pd$)	-
6	15%Pd/graphite ($C_{48}Pd$)	-
7	8%Pd/graphite ($C_{96}Pd$)	2

b) Using 10 equiv of Pd

Entry	**Catalyst**	**84b[b]**
1	10% Pd/C	90
2	5% Pd/C	90
3	30% Pd/C	70
4	35%Pd/graphite ($C_{16}Pd$)	6
5	15% Pd/graphite ($C_{48}Pd$)	9
6	8% Pd/graphite ($C_{96}Pd$)	20

b) [a] The reactions were performed in 0.1 mmol scale (0.01 M) in autoclave using AcOH as solvent at 100 °C and 100 bar H_2. [b] Conversions (%) were calculated by GC.

In view of these results, it is possible to suppose that the catalyst became "poisoned" during the reaction. The active sites of the catalyst are blocks, so the catalyst does not have a catalytic activity. The hypothesis that an impurity could be responsible to the reduced activity of the catalyst could be discarded on the basis of the performance of a presaturated by hydrogen catalyst (Table 11, column a, entry 4) that show a small increasing in activity compare to the normal reaction condition.

At this point we had now a good knowledge of the hydrogenation reaction allowing us to broaden our investigation to the preparation of other isomers **84a** starting from **83a** (Fig 56).

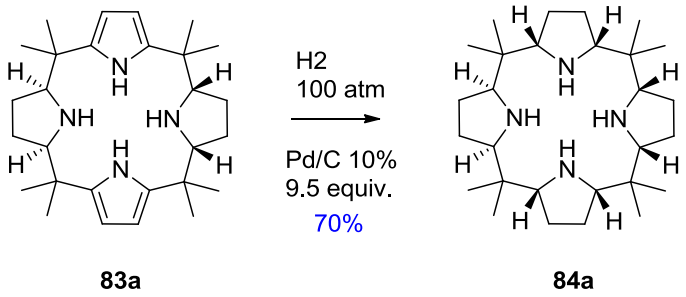


Fig 56. Hydrogenation of compound 84a

The hydrogenation of compound **83a** afforded infact the new diastereisomer of the calix[4]pyrrolidine, **84a**. The reaction was highly stereoselective, as only one diastereoisomer was formed. The stereochemistry of **84a** could be assigned by NMR analysis. The two possible isomers with their symmetry are represented Fig 57.

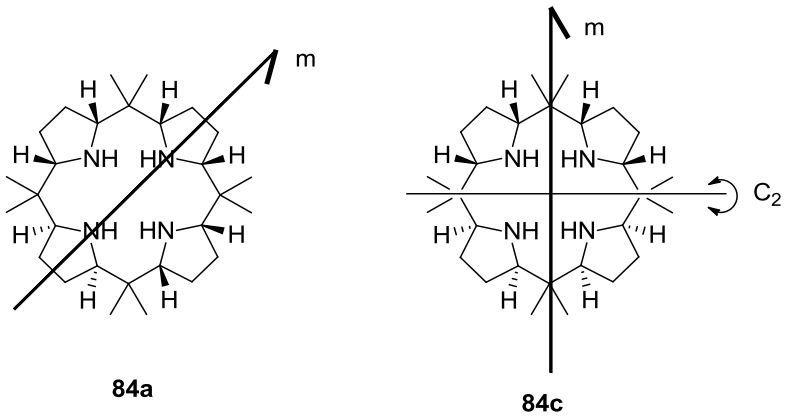


Fig 57. The two possible isomers 84a and 84c.

It can be seen that compound **84c** is more symmetrical than **84a**. As a matter of fact **84c** has a plane of symmetry m and a C_2 axis, where in compound **84a** a plane *m* is present. As a consequence, the ^{1}H-NMR spectra should shows only two different peaks for the methyl

groups of **84c**. The NMR spectra of **84a** was unexpected. In $CDCl_3$ two broad peaks corresponding to α-CH proton of pyrrolidines were observed. Surprisingly, after an unusual double protonation/deuteration presumably attributed to the solvent in the NMR tube, the spectrum appeared highly resolved and showed, as expected, four different signals for the α-CH proton. COSY analyses of the same sample showed two different NH signals (9.5 ppm, 6 ppm) corresponding to a highly selective protonation of opposite pyrrolidine rings. The protonation/deuteration of the porrolidines is a long process, is necessary leave the compound in NMR solution for a few days before obtain the totally conversion. Crystals of compound **84a** (Fig 58) were obtained, and confirmed the proposed structure.

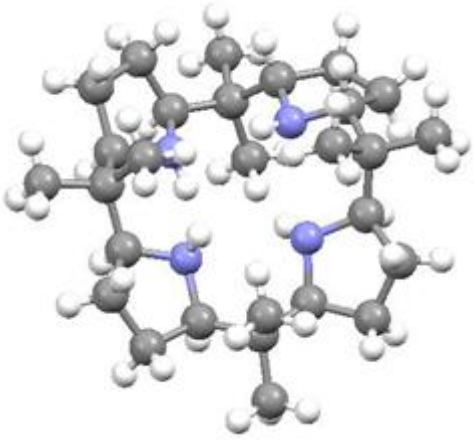


Fig 58. X-Ray structure of 84a

Finally, we applied the new reaction conditions (10 equivalents of 10% Pd/C, 0.01 M in AcOH, 100 bar,100°C) for the hydrogenation of the calix[4]pyrrole **82** to obtain directly the two diastereoisomeric calix[4]pyrrolidines **84a** and **84b** which were obtained in 60/40 radio and overall 82% yield (Fig. 59).

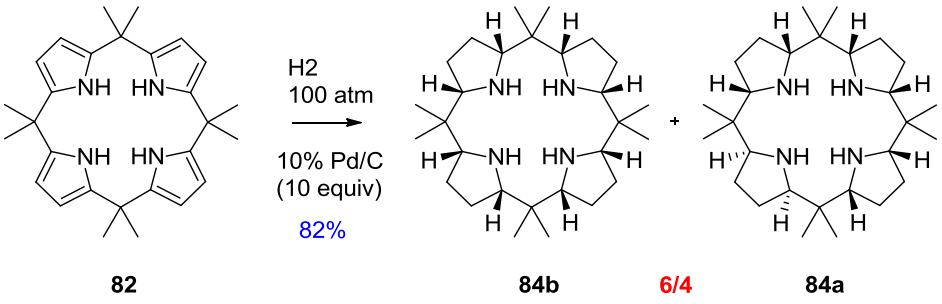


Fig 59. Full hydrogenation of calix[4]pyrrole

1.5 Synthesis of a new calix[2]pyrrole[2]pyrrolidine Pd(II) complex

The calix[2]pyrrole[2]pyrrolidine **83b** displays suitable coordination abilities towards metal species. We have previously described different metal complexes from the fully reduced macrocycle **84** where metals ions were surrounded by four nitrogen atoms. In the case of ligand **83b**, two pyrrolidine rings are present together with two pyrroles nuclei, which can undergo deprotonation and consequently bind metal ions by covalent bonds. Interestingly, metal complexes of **83b** would be closely related to metal complexes of porphyrins, as both ligands have the same size and the same way to chelate metals, i.e. by two dative and two covalent bonds (Fig 60). The only difference is the hybridization sp^3 or sp^2 of the nitrogen atoms acting as Lewis bases.

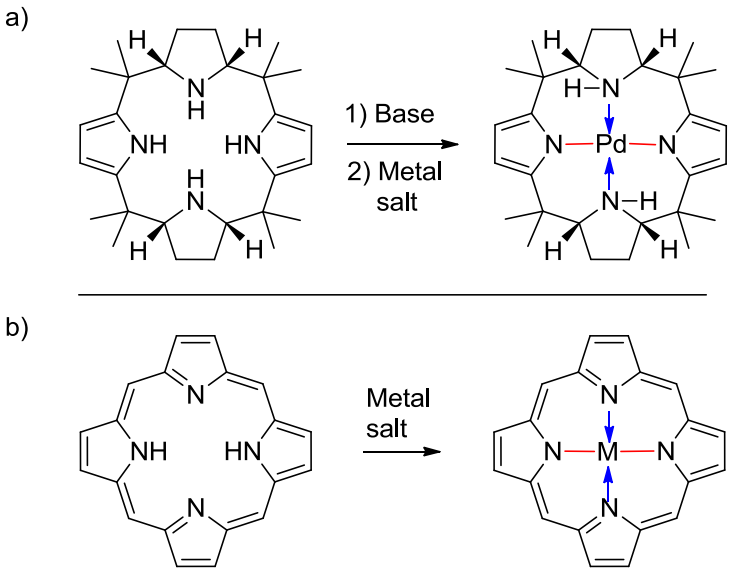


Fig 60. A) Calix[2]pyrrole[2]pyrrolidine-metal complexes. b) Porphyrine-metal complex

Curious to know more about the coordination behavior of ligand **83b**, we appled to it the successful conditions already developed for the synthesis of metal complexes from the fully recuced compound **84**. All the experiments were done under Ar atmosphere and using different metal salts, the formation of complex was indicated by a colour change of the solution

Moreover, the course of the reaction was monitored by ^{1}H NMR analysis. We prepared a 0.02 M solution of **83b** in $CDCl_3$ (0.5 mL) and added 1 equivalent of palladium acetate dissolved in $CDCl_3$ (0.2 mL) in an "open tube" (under air). Then, we followed the complexation of compound **83b** at 50 °C (Fig 61). A different orange color, was soon observed, that indicated the formation of different complexes. This was confirmed by the complete disappearance of the pyrrole signals typical of the free ligand at 5.80 ppm and the simultaneous appearance of a singlet signal at 6.06 ppm, presumably due to formation of a Pd complex. At increased times, the latter signal disappeared, meanwhile other small peaks growed correspondingly in the

region between the free ligand signal and the complex signal.This trend continued until the complete consumption of the complex.

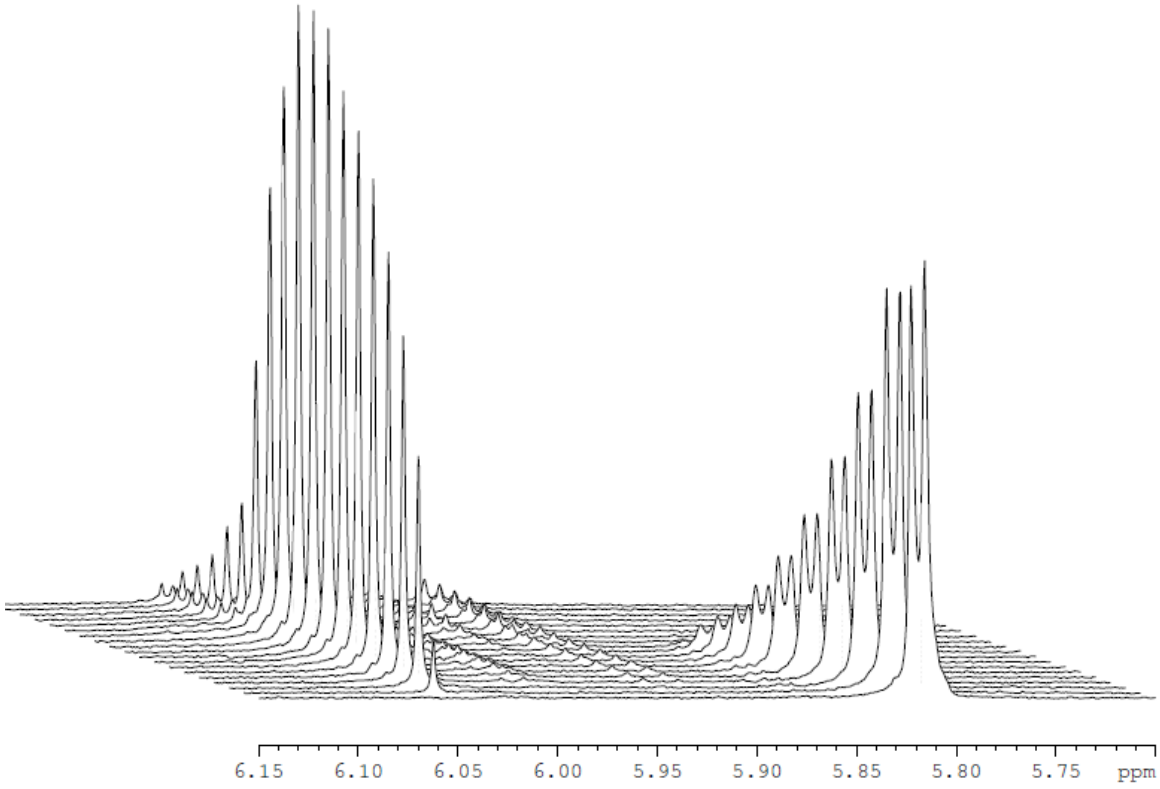


Fig 61. Variation of the 1H-NMR spectrum by increasing time at 50 °C in CDCl3. Only the spectral region of pyrrole absorptions is shown.

Meanwhile the NMR monitoring was developing, we took out samples of the solution at different time and analyze them by mass spectroscopy. The first sample was taken out after about 50% consumption of the starting material, and another one at the end. The MS analysis of both samples shown the same results. The mass spectrum displayed a very small peak at 437 corresponding to the starting material (M+1) and three other peaks at 541, 557 and 573, which possess the Pd isotope mass (zoom, Fig 62).

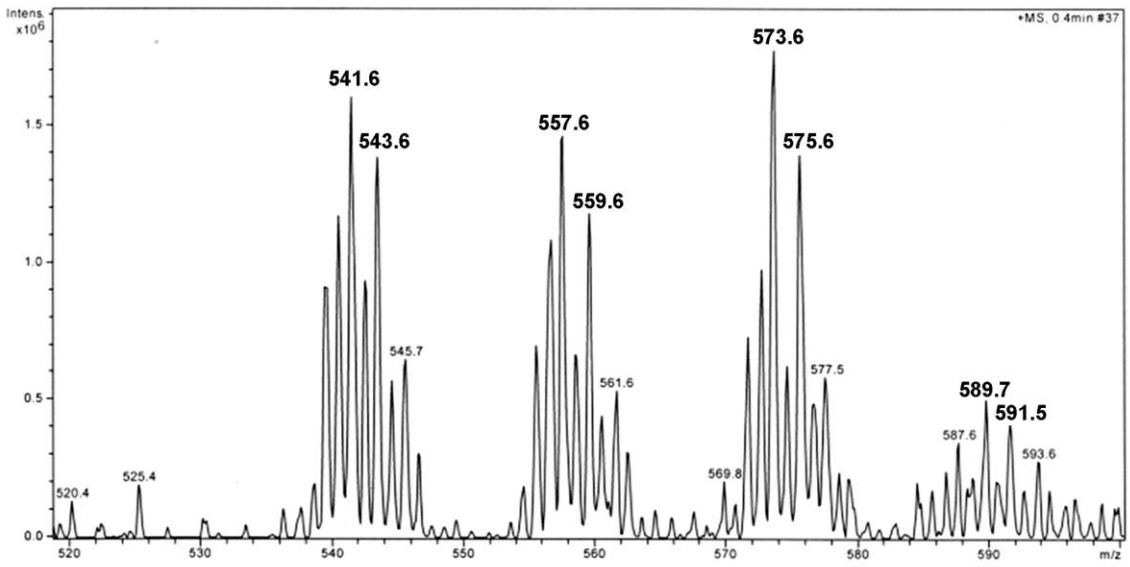


Fig 62. Zoom of the MS spectrum

We assigned the mass 541 to a Pd-legand symmetrical complex and 557 to a first oxidated product. The molecular weight 541 corresponds to a neutral Pd complex **86** where the metal is bound to ligand by two covalent and two dative bonds (Fig 63). This complex should be formed by deprotonation of the two pyrrole N-H bonds by the acetate counterions of Pd cation, it is confermed by NMR analysis that show the presence of Pd-complex in the reaction mixture. On the other hand, the molecular weight 557 corresponds to weight of complex **86** plus 16 (one oxygen), hence, apparently, an oxidation occurred. Analogously, the molecular weight 573 corresponds to the addition of two oxygen atoms to complex **86** and the last small peaks, 589 molecular weight, to the addiction of three oxygen atoms. Unfortunately for the moment considering the NMR and MS results we are not able to discuss if during the oxidation reaction we obtained different products with different molecular weight, or only one chiral product with the insertion of 3 oxygen atoms that produce different diasteroisomers easily observed during the NMR experiment.

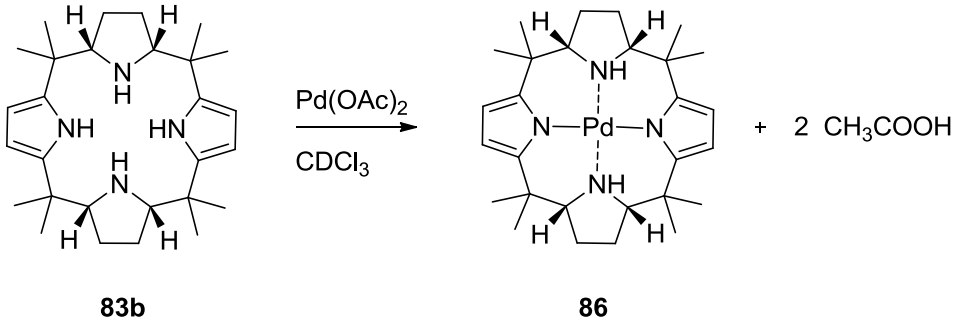


Fig 63. Preparation of the complex 86

Then, we repeated the same reaction under N_2 atmosphere to avoid such oxidation. Compound **83b** was mixed with palladium acetate in $CDCl_3$ under argon in the NMR tube which was sealed, and the formation of the metal complex **86** was followed by ^1H NMR at 50

°C (Fig. 64). A symmetrical structure of the so formed palladium complex **86** was hypothesized on the basis of the disappearance of the pyrrolic N-H signal of the starting material, the concomitant shift of the C-H pyrrole signal from 5.86 ppm (doublet) to 6.08 ppm and the appearance of a singlet to 2.1 ppm that corresponded to the two CH_3COOH molecules. To be sure that the "oxidized complexes" were formed from the initially formed Pd complex **86** and not from the free ligand **83b**, the NMR tube was opened to air atmosphere and the formation of the unsymmetrical oxidated complex was again observed.

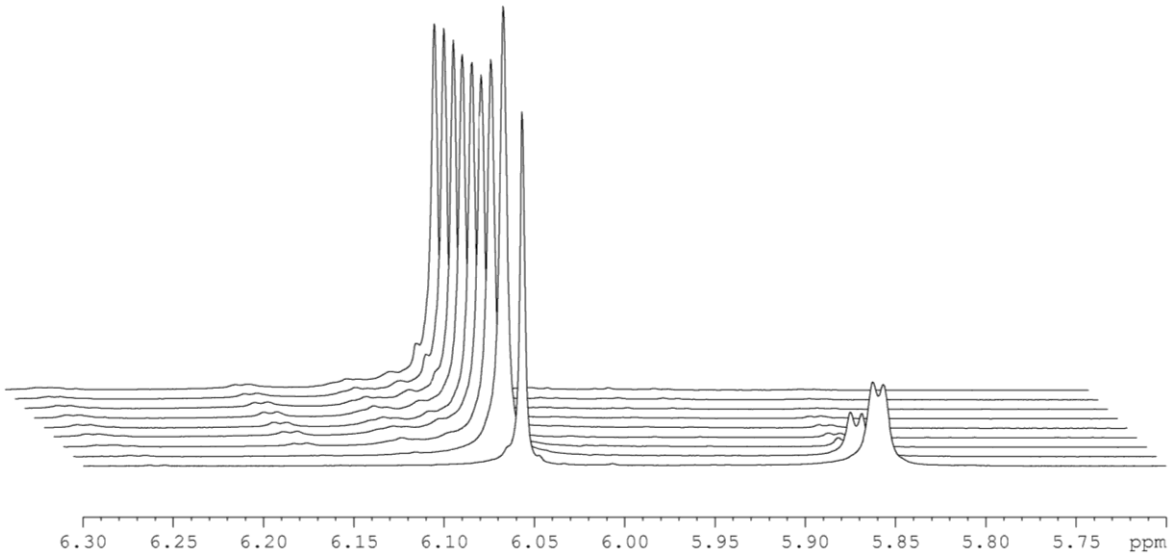


Fig 64. Superposition of 1H-NMR spectrum of complex 86 according to the time recorded at 50 °C in CDCl3 under inert atmosphere. Only the spectral region of pyrrole is shown

It appears that the complex **86** is highly sensitive toward oxygen; however, no simple explanation for such sensitivity can be advanced. It is likely that oxo- palladium complexes are intermediate in the oxidation process, or can be one of the products observed. Considering these results, we performed the complexation reactions in different solvents and at various temperatures (Table 12). When dichloromethane was used, even performing the reaction under air at 40 °C an amazing stability of the complex **86** was observed: it was accompanied by the ligand salt **83b-2AcOH**, but no oxidation had occurred during the reaction time (Fig. 65 and Table 12, entries 3 and 9).

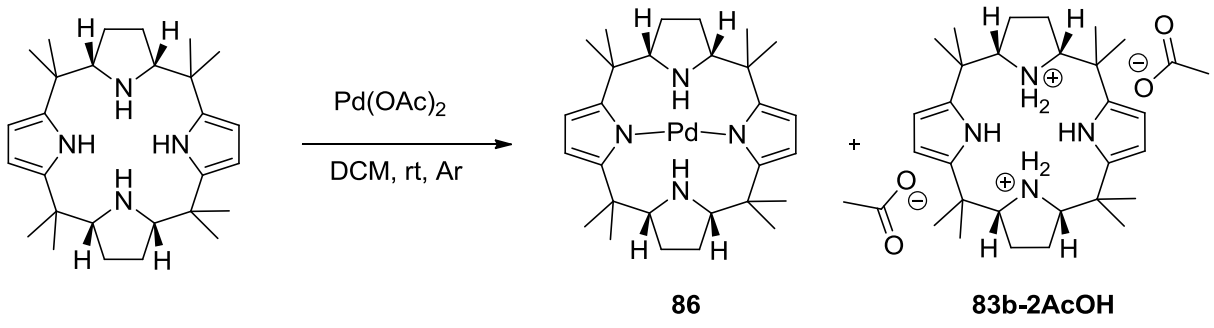


Fig 65. Pd-complex and protonated half reduced form

Performing the reaction in $CHCl_3$, MeOH, EtOH, CH_3CN at 50 °C for 3 h the oxidized product was formed together with small amounts of complex **86** and the ligand salt **83b-2AcOH** (Table 12, entry 2, 4, 5, 7), and similar results were obtained at room temperature (entries 10-13). In acetic acid at 50 °C or at r.t. only the salt was observed, without any traces of Pd complexes (Table 12, entries 6 and 14). Only performing the reaction in DCM at 40°C is possible to observe only the Pd complex and the salt were present in 80/20 ratio. Apart the case of dichloromethane, in all the other solvents the oxidation was favored working under O_2 atmosphere and at room temperature, probably because more gas is dissolved at the low temperature.

Table 12. reaction of ligand 83b with palladium acetate in diverse conditions

Entry	Solvent	Atmosphere	86/83b-2AcOH[a]	Other products	T (°C),time
1	$CHCl_3$	O_2	15/55	Ox-P	50, 3 h
2	CH_2Cl_2	O_2	80/20		40, 3 h
3	CH_2Cl_2	Ar	75/25		40, 3 h
4	MeOH	O_2	38/12	Ox-P	50, 3 h
5	EtOH	O_2	25/25	Ox-P	50, 3 h
6	AcOH	O_2	0/100	$Pd^{(0)}$	50, 3 h
7	CH_3CN	O_2	-/-	Ox-P	50, 3 h
8	CH_2Cl_2	Ar	50/50		r.t., 4 h
9	CH_2Cl_2	O_2	65/35		r.t., 4 h
10	$CHCl_3$	O_2	25/42	Ox-P	r.t., 4 h
11	MeOH	O_2	0/30	Ox-P	r.t., 4 h
12	EtOH	O_2	10/10	Ox-P	r.t., 4 h
13	CH_3CN	O_2	0/30	Ox-P	r.t., 4 h
14	AcOH	O_2	0/100		r.t., 4 h

[a] The ratio was determined by ^1H NMR

To avoid formation of the protonated ligand and increase the yield of complex **86b** we added an heterogeneous base (resins and inorganic base) to the reaction mixture (Table 13). If the reaction was performed in the presence of the base, the Pd complex was not formed and the ligand **86** was recovered. Unfortunately all the conversion was determined by NMR integration, considering that we can't identify the different oxidation product is very difficult attribute an exactly ration between all the different product.

Table 13. Complex formation in basic conditions

Entry	Base or basic resin	Reaction time / T(°C)	86/83b-2AcOH[b]
1	Dowex 1	2,5/rt	50/50
2	Lewatit VP OC 1065	2,5/rt	10/90
3	Amberlite IRA 67	3,5/rt	70/30
4	Amberlite IRA 400	3,5/rt	70/30
5	Na_2CO_3	3,5/rt	80/20
6	K_2CO_3	2,5/rt	20/80
7	Amberlist A21[a]	3,5/rt	-
8	DCM purified over basic Al_2O_3	3,5/rt	70/30
9	Al_2O_3[a]	3,5/rt	-
10	$CHCl_3$ degassed	3,5/rt	50/50

[a] Added after 2 h. [b]the ratio was determined by ^1H NMR

All the experiment was performed in DCM at room temperature. Amberlite IRA 67 and Amberlite IRA 400 (Table 13, Entry 3,4) have been show increasing of complex amount. Best result was observed using Na_2CO_3 as base, final complex was obtain in 80% yield (Table13, Entry 5). Particularly behavior was observed when DCM was pre purify over basic Al_2O_3 and the complex was obtain 70% yield (Table 13, Entry 8).The complex **86** is extremely stable, it can be purified by flash chromatography over basic alumina by a cyclohexane/ethylacetate solvent mixture obtaining a yellow-green solid that was crystallized in THF under Ar atmosphere. The crystal structure can confirm the NMR prediction, the Pd is square planary coordinate by the four heteroatoms, and in particular is covalently bound to the two pyrrole unit without the presence of acetate conter ions but with a molecule of THF in apical position.

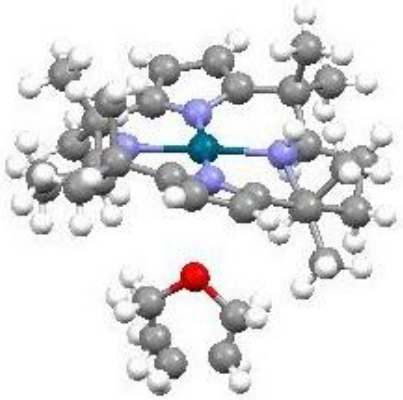


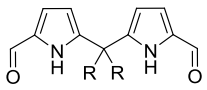
Fig 66. X-ray structure of the Pd-complex 86

To determinate how much is fast the oxidation process in acetonitrile, we performed an NMR experiment. Ar was bubbled inside through the CD_3CN solution of the Pd complex **86** deuterated, The complex was found stable for a long time in the absence of oxygen, then the NMR tube was opened to air and spectra were recorded at first every 5 minutes, and successively every 15 min, and again every 1 h. By this way we could observe that no oxidation producy was formed after 1 day. Probably, the surface area in the NMR tube is too small to permit a good exchange between Ar and air and Ar.

SUPPORTING INFO

General Methods. Chemical shifts are reported in ppm from TMS with the solvent resonance as the internal standard (deuterochloroform: δ 7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = duplet, t = triplet, q = quartet, bs = broad singlet, m = multiplet), coupling constants (Hz). Chemical shifts are reported in ppm from TMS with the solvent as the internal standard (deuterochloroform: δ 77.0 ppm). GC-MS spectra were taken by EI ionization at 70 eV. They are reported as m/z (relative intensity). Chromatographic purification was done with 240-400 mesh silica gel. Determination of enantiomeric excess was performed on HPLC instrument equipped with a variable-wavelength UV detector, using a DAICEL Chiralpak columns (0.46 cm i.d., 25 cm) and HPLC-grade 2-propanol and n-hexane were used as the eluting solvents. Optical rotations were determined in a 1 mL cell with a path length of 10 mm (NaD line). Melting points are not corrected. Materials: All reactions were carried out under inert gas and under anhydrous conditions. Commercially available anhydrous solvents were used avoiding purification.

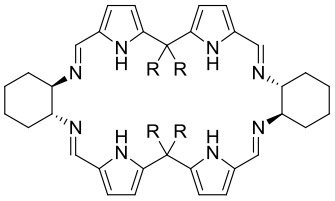
Chiral Pyrrole macrocyclic ligands for Cu-catalyzed asymmetric Henry reaction



62a-d

a-d: R = Me, Et, $(CH_2)_5$, Ph

Synthesis of Dialdehyde 60a-d. $POCl_3$ (0.13 mL, 1.4 mmol) was added dropwise to a stirred solution of 2,20-(cyclohexane-1,1-diyl) bis(1H-pyrrole) (150 mg, 0.7 mmol) in DMF (1 mL), which was cooled at 0 °C. The mixture was stirred at room temperature for 1 h and then cooled to 0 °C, and 10 N NaOH (10 mL) was added portionwise. The resultant precipitate was filtered and washed with water until pH = 7 was reached to obtain the crude product **60** as a white amorphous solid: 162 mg, (86%). Mp = 208.4-209.7 °C (dec). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.34 (m, 2 H), 1.61 (m, 4 H), 2.32 (t, J = 5.2 Hz, 4 H), 6.22 (d, J = 2.4 Hz, 2 H), 6.93 (d, J = 2.0 Hz, 2 H), 9.47 (s, 2 H), 10.45 (bs, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 22.5, 25.6, 34.9, 39.9, 108.7, 123.3, 132.6, 146.8, 179.5. IR (KBr): ν = 3281, 3198, 3131, 3109, 3093, 2925, 2856, 1679, 1472, 1269, 1193, 1052, 812, 776 cm^{-1}. ESI-MS m/z: 271.1 $[M+ H]^+$, 293.1 $[M +Na]^+$, 541.3 $[2 M + H]^+$. Anal. Calcd for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.29; H, 6.74; N, 10.40.



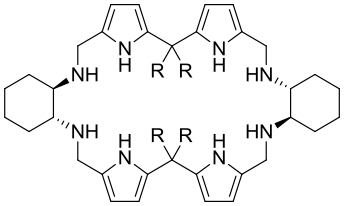
62a-d

a-d: R = Me, Et, $(CH_2)_5$, Ph

Synthesis of Imines 62a-c. **General Procedure**. To the suspension of (*R,R*)-1,2-diaminocyclohexane L-tartrate (0.580 g, 2.2 mmol) in MeOH (25 mL) were added aldehyde **60a** (0.51 g, 2.2 mmol) and triethylamine (0.67 mL, 4.8 mmol). The reaction mixture was stirred for 48 h, and the solvent was evaporated at reduce pressure. A saturated aqueous solution of $NaHCO_3$ (20 mL) was added, and the organic material was extracted with dichloromethane (3 × 30 mL). The collected organic layers were washed with brine (20 mL), dried over Na_2SO_4, and concentrated to leave a white solid, which was crystallized from MeOH to give pure **62a** (0.63 g, 1.0 mmol, 90%) as colorless crystals. Mp = 160-162 °C (dec). $[\alpha]^{20}_D$ = +689.2 (c 0.8, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.34 (m, 4 H), 1.53 (m, 4 H), 1.64 (m, 4 H), 1.67 (s, 12 H), 1.78 (m, 4 H), 3.16 (m, 4 H), 6.11 (d, J = 3.6Hz, 4 H), 6.29 (d, J = 3.6 Hz, 4 H), 7.90 (s, 4 H). 13C NMR (CDCl3, 100 MHz): δ = 24.7, 27.9, 34.1, 35.2, 73.5, 105.1, 115.1, 129.6, 142.8, 151.4. IR (KBr): ν = 3296, 2971, 2925, 2855, 1633, 1561, 1486, 1270, 1216, 1042, 776 cm^{-1}. ESI-MS m/z: 617.3 $[M + H]^+$. Anal. Calcd for $C_{38}H_{48}N_8$: C, 73.99; H, 7.84; N, 18.17. Found: C, 74.28; H, 7.87; N, 18.09.

62b. Colorless crystals, 80%. Mp = 197-199 °C (MeCN). [α]20 D = +379.5 (c 1.1, CHCl3). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.36-1.49 (m, 12 H), 1.52-1.52 (m, 4 H), 1.61-1.71 (m, 8 H), 1.78 (m, 4 H), 2.04 (m, 4 H), 2.25 (m, 4 H), 3.14 (m, 4 H), 6.08 (d, J = 3.6 Hz, 4 H), 6.26 (d, J = 3.6 Hz, 4 H), 7.85 (s, 4 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 22.5, 24.6, 26.0, 33.3 35.3, 39.5, 73.5, 105.7, 115.6, 129.6, 142.1, 151.4. IR (KBr): ν = 3447, 2929, 1633, 1560,1476, 1044, 775 cm^{-1}. ESI-MS m/z: 697.4 $[M+H]^+$. Anal. Calcd for $C_{44}H_{56}N_8$: C, 75.82; H, 8.10; N, 16.08. Found: C, 76.10; H, 8.12; N, 16.03.

62c. Red amorphous solid, 40%. Mp = 158-160 °C. [α]20 D = -498 (c 0.9, $CHCl_3$). ^{1}H NMR ($CDCl^3$, 400 MHz): δ = 1.36 (m, 4 H), 1.57 (m, 4 H), 1.78-1.82 (m, 8 H), 3.05 (m, 4 H), 5.80 (d, J = 3.6 Hz, 4 H),6.17 (d, J = 3.6 Hz, 4 H), 6.95-6.97 (m, 4 H), 7.21-7.23 (m, 16 H), 7.71 (s, 4 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 24.5, 32.7, 56.4, 72.9, 112.2, 114.6, 127.1, 127.8, 129.4, 129.6, 140.2, 144.3, 152.5. IR (KBr): ν = 3439, 2924, 2853, 1632, 1445, 1182, 1044,734, 700 cm^{-1}. ESI-MSm/z: 865.4 $[M+H]^+$. Anal. Calcd for $C_{58}H_{56}N_8$: C, 80.52; H, 6.52; N, 12.95. Found: C, 80.22; H, 6.55; N 12.97.



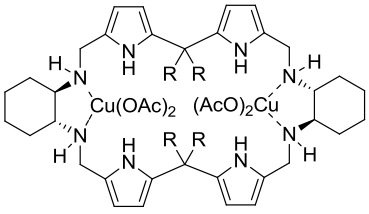
63a-d

a-d: R = Me, Et, $(CH_2)_5$, Ph

Synthesis of amines 63a-c. General procedure. NaBH4 (0.15 g, 4.1 mmol) was added to the solution of **62a** (0.50 g, 0.8 mmol) in MeOH (20 mL) and the reaction mixture was stirred during 20 h, then a 1 M NaOH solution (5 mL) was added and the solvent was evaporated at reduced pressure. The organic material was extracted with EtOAc (3 x30 mL). The collected organic layers were washed with brine (20 mL), dried over Na_2SO_4 and concentrated to leave **63a** (0.47 g, 0.76 mmol, 95%) as a white solid: mp =166-167 °C; [α]D 20 = -23.7 (c 0.8, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.72-0.82 (m, 6 H), 1.03-1.11 (m, 4 H), 1.46 (s, 12 H), 1.61 (m, 6 H), 1.99-2.09 (m, 4 H),3.37 (d, J = 14.7 Hz, 4 H), 3.62 (d, J = 14.7 Hz, 4 H), 5.72 (d, J = 2.4 Hz, 4 H), 5.89 (t, J = 2.4 Hz, 4 H), 10.82 (bs, 4 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 25.2, 31.4, 33.0, 35.8, 42.9, 60.3, 103.4, 103.9, 130.1, 137.6. IR (KBr): ν = 3442, 2928, 2856, 1646, 1456, 1075 cm^{-1}. ESI-MS m/z:
625.4 [MþH]þ. Anal. Calcd for C38H56N8:C, 73.04; H, 9.03; N, 17.93. Found: C, 73.26; H, 9.06;N, 17.88.

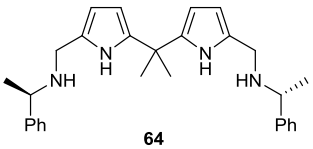
63b. White solid; 90%. Mp = 147.9-148.9 °C (MeCN).[α]20 D = -52.0 (c 1.0, CH2Cl2). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.89-0.96 (m, 4 H), 1.15 (m, 8 H), 1.39-1.42 (m, 2 H), 1.45-1.53 (m, 8 H), 1.54-1.72 (m, 10 H), 1.86-1.93 (m, 8 H), 2.06-2.14 (m, 4 H), 3.60 (d, J = 13.7 Hz, 4 H), 3.81 (d, J = 13.7 Hz, 4 H), 5.82 (t, J = 2.8Hz, 4 H), 5.90 (t, J = 2.8 Hz, 4 H), 8.78 (bs, 4 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 22.8, 25.0, 26.2, 31.5, 36.2, 39.1, 43.7, 60.6, 103.1, 106.1, 129.2. IR (KBr): ν = 3439, 2929, 2854, 2361, 2342, 1636, 1448, 1105, 1036, 770 cm^{-1}. ESI-MS m/z: 705.5 [M + H]$^+$. Anal. Calcd for C44H64N8: C, 74.96; H, 9.15; N, 15.89. Found: C, 75.11; H, 9.16; N, 15.87.

63c. Red amorphous solid; 80%. Mp = 230-231 °C dec. [α]20 D = -44.8 (c 0.8, CH2Cl2). 1H NMR (CDCl3, 400 MHz): δ = 0.77-0.82 (m, 6 H), 1.15-1.21 (m, 4 H), 1.27-1.49 (m, 6 H), 74-1.86 (m, 4 H), 1.99_2.16 (m, 4 H), 3.16 (m, 8 H), 5.79 (d, J = 2.4 Hz, 4 H), 6.13 (d, J = 2.4Hz, 4 H), 7.14-7.20 (m, 4H), 7.21-7.30 (m, 4 H), 7.40-7.62 (m, 12 H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 24.7, 25.9, 46.3, 47.6, 60.7, 102.3, 104.6, 127.3, 127.8, 129.2, 138.3, 140.2, 151.4. IR (KBr): ν = 3442, 2923, 2853, 2363, 1635, 1445, 1384, 1109, 1039, 700 cm^{-1}. ESI-MS m/z: 873.3 [M+ H]$^+$. Anal.Calcd for $C_{58}H_{64}N_8$: C, 79.78; H, 7.39; N, 12.83. Found: C, 79.99; H, 7.41; N, 12.80.



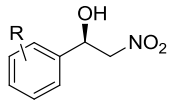
Synthesis of the Copper Complex (63a-2[Cu(OAc)$_2$]). To a solution of **63a** (0.075 g, 0.12 mmol) in DCM (5 mL) was added $Cu(OAc)_2$ $3H_2O$(0.048 g, 0.024 mmol), and the solution was stirred for 1 h. The solvent was removed in vacuo, and the residue was washed with pentane/Et2O9/1 (2x10 mL) and dried under vacuum to obtain 0.113 g (95%, 0.11 mmol) of copper complex 10a 3 2[Cu(OAc)2] as a slightly green solid. [R]20 D =-47.1 (c 1.1, $CHCl_3$).

Mp = 180 °C dec. IR (KBr): ν = 3405, 3239, 3160, 2966, 2932, 2859, 1559, 1404, 1211, 1050, 1003, 778, 680 cm^{-1}. ESI-MS m/z: 747 $[M-4\ CH3COOH + H]^+$, 749 $[M-4\ CH3COOH + H]^+$. CCDC numbers 803953 (9a(MeOH)4) and 803954 (63a 2[Cu-$(OAc)_2$]) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Synthesis of Amine 11.



64

Synthesis of compound 64: The dialdehyde **60a** (200 mg, 0.87 mmol) and (S)-phenylethylamine (0.22 mL, 1.74 mmol) were dissolved in DCM (10 mL), and then $MgSO_4$ (0.500 g) was added. The mixture was stirred at room temperature for 48 h and then filtered through a short pad of Celite, which was washed with DCM. The solvent was evaporated at reduced pressure. The crude product was dissolved in MeOH (10 mL), $NaBH_4$ (66 mg, 179 mmol) was added, and the mixture was stirred at room temperature overnight. Water (5 mL) was added, and the mixture was stirred 20 min and then concentrated at reduced pressure to remove MeOH. The organic phase was extracted with EtOAc (2 x20 mL), and the collected organic layers were concentrated at reduced pressure to leave a yellowish oil. Column chromatography (SiO_2, DCM/MeOH, 9:1) gave **64** as a colorless oil, 340 mg (90%). [α]20 D = -22.1 (c 1.0, CHCl3). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.36 (d, J = 6.6 Hz, 6H), 1.67 (s, 6 H), 1.88 (bs, 2 H), 3.48 (d, J = 13.6 Hz, 2 H), 3.57 (d, J = 13.6 Hz, 2 H), 3.73 (q, J = 6.6 Hz, 2 H), 5.94 (t, J = 2.7 Hz, 2 H), 6.00 (t, J = 2.9 Hz, 2 H), 7.25-7.41 (m, 10 H), 8.24 (bs, 2 H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 23.9, 29.2, 35.3, 44.3, 57.4, 103.3, 105.5, 125.6, 126.5, 126.9, 128.4, 129.8, 138.6. ESI-MS m/z: 439.3 $[M+H]^+$. Anal. Calcd for C29H36N4:C, 79.05; H, 8.24; N, 12.72. Found: C, 79.22; H, 8.26; N, 12.69.

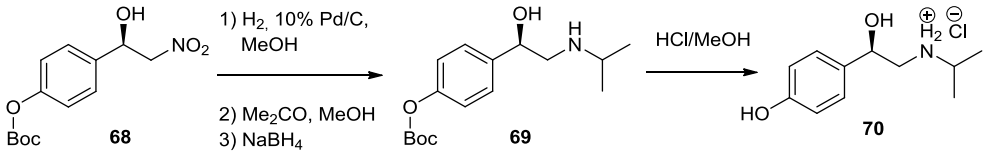


67

Enantioselective Henry Reaction. Typical Procedure. To a solution of Cu(AcO)2 3H2O (0.003 g, 0.015 mmol) in EtOH (1.5 mL) was added **63a** (0.004 g, 0.007 mmol), and the reaction mixture was stirred at room temperature for 30 min. Benzaldehyde (30 μL, 0.25 mmol) and nitromethane (134 μL, 2.5 mmol) were added. After 20 h, the reaction mixture was filtered through a small pad of silica, which was washed with EtOAc. Column chromatography (SiO_2, cyclohexane/EtOAc, 9:1) gave (R)-**67a**: 0.181 g (92%). 92% ee was determined by chiral HPLC (Chiralpak OD; 2-propanol/hexane 1:9, 0.8 mL/min.; 214 nm; 40 °C): retention times 14.5 min (S, minor enantiomer) and 17.4 min (R, major enantiomer).
67b. The ee was determined by chiral HPLC (Chiralpak OD; 2-propanol/hexane 25:75, 0.5 mL/min; 214 nm; 40 °C): retention times 11.6 min (S, minor enantiomer) and 15.1 min (R, major enantiomer).

67c. The ee was determined by chiral HPLC (Chiralpak OD; 2-propanol/hexane 1:9, 0.8 mL/min; 214 nm; 40 °C): retention times 14.2 min (S, minor enantiomer) and 18.1 min (R, major enantiomer).
67d. The ee was determined by chiral HPLC (Chiralpak OJ; 2-propanol/hexane 2:98, 0.8 mL/min.; 214 nm; 40 °C): retention times 19.5 min (S, minor enantiomer) and 21.1 min (R, major enantiomer).
67e. The ee was determined by chiral HPLC (Chiralpak OD; 2-propanol/hexane 1:9, 0.5 mL/min.; 214 nm; 40 °C): retention times 22.1 min (S, minor enantiomer) and 23.2 min (R, major enantiomer).
67f. The ee was determined by chiral HPLC (Chiralpak OD; 2-propanol/hexane 1:9, 0.6 mL/min.; 214 nm; 40 °C): retention times 19.3 min (S, minor enantiomer) and 21.0 min (R, major enantiomer).
67g. The ee was determined by chiral HPLC (Chiralpak OJ; 2-propanol/hexane 3:7, 0.8 mL/min.; 214 nm; 40 °C): retention times 16.4 min (S, minor enantiomer) and 19.5 min (R, major enantiomer).
67h. The ee was determined by chiral HPLC (Chiralpak OD; 2-propanol/hexane 2:8, 0.5 mL/min.; 214 nm; 40 °C): retention times 17.0 min (S, minor enantiomer) and 21.1 min (R, major enantiomer).
67i. The ee was determined by chiral HPLC (Chiralpak OD; 2-propanol/hexane 2:8, 0.5 mL/min.; 214 nm; 40 °C): retention times14.0 min (S, minor enantiomer) and 16.1 min (R, major enantiomer).
67j. The ee was determined by chiral HPLC (Chiralpak OD;2-propanol/hexane 2:8, 0.8 mL/min.; 214 nm; 40 °C): retention times 18.8 min (S, minor enantiomer) and 22.3 min (R, major enantiomer).
67k. White solid. [α]20 D = þ25.3 (c 0.8, CHCl3). Mp = 85.4-86.0 °C dec. ^{1}HNMR($CDCl_3$, 400 MHz): δ = 1.53 (s, 9 H), 3.29 (bs, 1 H), 4.48 (dd, J = 3.3 Hz, J = 13.2 Hz, 1 H), 4.51 (dd, J = 9.5 Hz, J = 13.1 Hz, 1 H), 5.36 (dd, J = 3.3 Hz, J = 9.3 Hz, 1 H), 7.13-7.17 (m, 2 H), 7.34-7.38 (m, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 27.6, 70.3, 81.1, 84.0, 121.8, 127.1, 135.9, 151.1, 151.8. IR (neat): ν = 3489, 2990, 2935, 1732, 1556, 1286, 1221, 1149 cm^{-1}. ESI-MS m/z: 301.1 $[M + H_2O]^+$, 306.0 $[M + Na]^+$, 322 $[M + K]^+$. Anal. Calcd for C13H17NO6: C, 55.12; H, 6.05; N, 4.94. Found: C, 55.00; H, 6.10; N, 4.99. The ee was determinedby chiral HPLC (Chiralpak OD; 2-propanol/hexane 1:9, 1.0 mL/min; 214 nm; 40 °C): retention times 11.9 min (S, minor enantiomer) and 13.71 min (R, major enantiomer).
67l. The ee was determined by chiral HPLC (Chiralpak OD; 2-propanol/hexane 3:7, 0.6 mL/min.; 214 nm; 40 °C): retention times 12.0 min (S, minor enantiomer) and 14.1 min (R, major enantiomer).
67m. The ee was determined by chiral HPLC (Chiralpak OD; 2-propanol/hexane 2:8, 0.8 mL/min.; 214 nm; 40 °C): retention times 11.9 min (S, minor enantiomer) and 13.8 min (R, major enantiomer).
67n. The ee was determined by chiral HPLC (Chiralpak OD; 2-propanol/hexane 1:1, 0.6 mL/min.; 214 nm; 40 °C): retention times 12.5 min (S,minor enantiomer) and 15.5 min (R, major enantiomer).

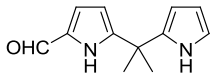
67o. The ee was determined by chiral HPLC (Chiralpak IC; 2-propanol/hexane 25:75, 0.5 mL/min.; 214 nm; 40 °C): retention times 22.6 min (S, minor enantiomer) and 24.8 min (R, major enantiomer).
67p. The ee was determined by chiral HPLC (Chiralpak IC; 2-propanol/hexane 5:95, 0.7 mL/min.; 214 nm; 40 °C): retention times 59.9 min (S, minor enantiomer) and 62.7 min (R, major enantiomer).
14q. Yellow oil. [α]20 D = +15.5 (c 0.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.65 (s, 9 H), 3.00 (bs, 1 H), 4.65 (dd, J = 3.1 Hz, J = 13.3 Hz, 1 H), 4.77 (dd, J = 9.4 Hz, J = 13.3 Hz, 1 H), 5.81 (dt, J = 3.0 Hz, J = 9.4 Hz, 1 H), 7.26 (ddd, J = 1.1 Hz, J = 7.3 Hz, J = 8.2 Hz, 1 H), 7.34 (ddd, J = 1.2 Hz, J = 7.3 Hz, J = 8.4 Hz, 1 H), 7.61 (dt, J = 0.9 Hz, J = 7.7 Hz, 1 H), 7.63 (s, 1 H), 8.15 (d, J = 8.6 Hz, 1 H). ^{13}CNMR ($CDCl_3$, 100 MHz): δ = 28.1, 65.2, 80.0, 84.4, 115.6, 117.9, 119.0, 123.1, 125.1, 127.4,135.7, 149.3. IR (neat): ν = 3468, 3054, 2979, 2928, 1735, 1555, 1373, 1155, 1097 cm^{-1}. ESI-MS m/z: 324.2 $[M+H_2O]^+$, 329.1 $[M+Na]^+$. Anal. Calcd for $C_{15}H_{18}N_2O_5$: C, 58.82; H, 5.92; N, 9.15. Found: C, 58.78; H, 5.97; N, 9.11. The ee was determined by chiral HPLC (Chiralpak OD; 2-propanol/hexane 1:9, 0.8 mL/min.; 214 nm; 40 °C): retention times 11.4 min (S, minor enantiomer) and 12.8 min(R, major enantiomer).
67r. The eewas determined by chiralHPLC (Chiralpak IC; 2-propanol/ hexane 4:6, 0.5 mL/min.; 214 nm; 40 °C): retention times 14.3 min (S, minor enantiomer) and 17.5 min (R, major enantiomer).
67s. The ee was determined by chiralHPLC (ChiralpakOJ; 2-propanol/ hexane 2:98, 0.5 mL/min.; 214 nm; 40 °C): retention times 35.1 min (S, minor enantiomer) and 39.2 min (R, major enantiomer).
67t. The ee was determined by chiral HPLC (Chiralpak OD; 2-propanol/ hexane 2:98, 0.7 mL/min.; 214 nm; 40 °C): retention times 16.9 min(S, minor enantiomer) and 18.9 min (R, major enantiomer).
67u. The ee was determined by chiral HPLC (Chiralpak IC; 2-propanol/hexane 5:95, 0.7 mL/min.; 214 nm; 40 °C): retention times 24.7 min (S, minor enantiomer) and 25.9 min (R, major enantiomer).
67v. The ee was determined by chiral HPLC (Chiralpak OD;2-propanol/hexane 1:9, 0.6 mL/min.; 214 nm; 40 °C): retention times 16.7 min (anti, S,S), 18.3 min (anti, R,R), 20.9 min (syn, R,S) and 22.9(syn, S,R).



Preparation of Compound 70. To a solution of compound **68** (123 mg, 0.43 mmol) in EtOH (2 mL) was added 10% Pd/C (17 mg). The mixture was stirred under a hydrogen atmosphere (balloon) for 22 h. The mixture was filtered through a short pad of Celite to remove the catalyst. Removal of the solvent under reduced pressure afforded 73 mg (70%) of primary amine. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.52 (s, 9 H), 2.74 (dd, J = 8 Hz, J = 13.2 Hz, 1 H),

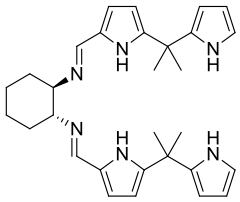
2.91 (dd, J = 3.6 Hz, J = 12.8 Hz, 1 H), 4.57 (dd, J = 4 Hz, J = 8 Hz, 1 H), 7.08 (d, J = 8.4 Hz, 2 H), 7.31 (d, J = 8 Hz, 2 H). A solution of amine **68** (73 mg, 0.29 mmol), acetone (34 μL, 0.46 mmol), and $MgSO_4$ (40 mg) in EtOH (2 mL) was stirred at rt overnight. Then the reaction mixture was cooled to 0 °C (ice bath), and $NaBH_4$ (16 mg, 0.43 mmol) was added. After being stirred for 1 h, the reaction mixture was filtered through a small pad of Celite, which was washed with EtOAc and MeOH to give 80 mg (94%) of compound **69**. ^{1}HNMR($CDCl_3$, 400 MHz): δ = 1.05 (d, J = 6.4 Hz, 6 H), 1.58 (s, 9 H), 2.62 (dd, J = 10 Hz, J = 13.2 Hz, 1 H), 2.78-2.85 (m, 1 H), 2.91 (dd, J = 3.6 Hz, J = 12.4 Hz, 1 H), 4.63 (dd, J = 4 Hz, J = 9.2 Hz, 1 H), 7.12 (d, J = 8.8 Hz, 2 H), 7.35 (d, J = 8 Hz, 2 H).

A solution of HCl in MeOH, prepared by addition of acetyl chloride (0.100 mL, 1.35 mmol) to MeOH (2 mL), was added dropwise to a solution of **69** (80 mg, 0.27 mmol) in MeOH (7 mL) at room temperature. After 6 h, the mixture was concentrated at reduced pressure. The solid was washed with Et_2O (3 x 3 mL) to give the crude salt **70** as a white solid, 0.04 g (0.22 mmol, 80%). Mp = 149-150 °C (lit. racemic compound, mp 151.5-152.5 °C). [R]20 D = -32.1 (c 1.2, MeOH). ^{1}H NMR ($CDCl_3$ with 10% DMSO, 400 MHz): δ = 1.41 (d, J = 6.4 Hz, 3 H), 1.44 (d, J = 6.4 Hz, 3 H), 2.89-2.98 (m, 1 H), 3.00-3.10 (m, 1 H), 3.35-3.42 (m, 1 H), 4.81 (dd, J = 2.4 Hz, J = 10 Hz, 1 H), 6.84 (d, J = 8.4 Hz, 2 H), 7.14 (d, J = 8.4 Hz, 2 H). ^{13}C NMR (DMSO, 100 MHz): δ = 18.5, 19.2, 49.8, 50.3, 56.1, 78.7, 115.9, 128.0, 128.5, 158.2. IR (KBr): ν = 3220, 2979, 1613, 1614, 1555, 1448, 1267, 1224, 1100, 838 cm^{-1}. ESI-MSm/z: 196.1 $[M+H]^+$.



60c

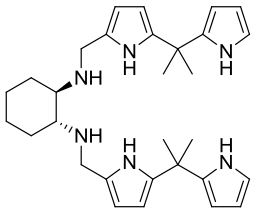
Synthesis of Dialdehyde 60c. POCl3 (0.13 mL, 1.4 mmol) was added dropwise to a stirred solution of **cc** (150 mg, 0.7 mmol) in DMF (1 mL), which was cooled at 0 °C. The mixture was stirred at room temperature for 1 h and then cooled to 0 °C, and 10 N NaOH (10 mL) was added portionwise. The resultant precipitate was filtered and washed with water until pH = 7 was reached to obtain the crude product **60c** as a red crystal : 162 mg, (86%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.68 (s, 3 H), 2.16 (s, 3 H), 6.09 (s, 1 H), 6.13 (s, 1 H), 6.18 (s, 1 H), 6.67 (s, 1 H), 6.87 (s, 1 H) 9.37 (s, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 178.5, 131.9, 122.0, 117.8, 108.2, 107.5, 104.7, 30.9, 28.7 ppm. ESI-MS m/z = 203.1 $[M+ H]^+$.



66a

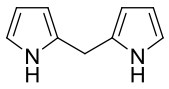
Synthesis of Imines 66a. To the suspension of (R,R)-1,2-diaminocyclohexane L-tartrate (0.580 g, 2.2mmol) in MeOH (25 mL) were added aldehyde 8a (0.51 g, 2.2 mmol) and triethylamine (0.67 mL, 4.8 mmol). The reaction mixture was stirred for 12h, and the solvent

was evaporated at reduce pressure. A saturated aqueous solution of $NaHCO_3$ (20 mL) was added, and the organic material was extracted with dichloromethane (3 x 30 mL). The collected organic layers were washed with brine (20 mL), dried over Na_2SO_4, and concentrated to leave a white solid, which was crystallized from MeOH to give pure 9a (0.63 g, 1.0 mmol, 90%) as orange solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.32-1.42 (m, 2 H), 1.53-1.60 (m, 2 H), 1.62 (s, 12 H), 1.70-185 (m, 4 H), 3.07-3-14 (m, 2 H), 6.00 (d, J = 3.56 Hz, 2 H), 6.04-6.07 (m, 2 H), 6.12 (t, J = 2.96 Hz, 2 H), 6.26 (d, J = 3.56 Hz, 2 H), 6.60 (s, 2 H) 7.80 (s, 2 H). 7.95 (bs, H, NH). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 151.1, 138.4, 129.4, 116.9, 114.6, 114.5, 107.8, 105.8, 103.8, 73.2, 35.6, 33.4, 29.1, 24.5 ppm. ESI-MS m/z: 483.1 $[M+ H]^+$.



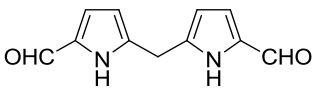
66

Synthesis of amines 66. $NaBH_4$ (0.15 g, 4.1 mmol) was added to the solution of 9a (0.50 g, 0.8 mmol) in MeOH (20 mL) and the reaction mixture was stirred during 20 h, then a 1 M NaOH solution (5 mL) was added and the solvent was evaporated at reduced pressure. The organic material was extracted with EtOAc (3 x30 mL). The collected organic layers were washed with brine (20 mL), dried over Na_2SO_4 and concentrated to leave 10a (0.47 g, 0.76 mmol, 95%) as a white solid: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.90-1.00 (m, 2 H), 1.03-1.20 (m, 2 H), 1.62 (s, 12 H), 1.80-2.00 (m, 4 H), 3.68 (d, J = 14.2 Hz, 2 H), 3.93 (d, J = 14.2 Hz, 2 H), 5.85 (s, 2 H), 5.92 (s, 2 H), 5.98 (s, 2 H), 6.04 (s, 2 H), 6.47 (s, 2 H), 8.32 (bs,2 H, NH). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 140.1, 116.4, 107.7, 107.5, 103.4, 102.9, 58.6, 42.8, 35.3, 30.6, 29.2, 28.8, 24.7 ppm. ESI-MS m/z: 487.1 $[M+ H]^+$.



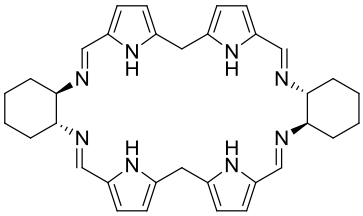
71

Synthesis of dipyrrole 71. This compound was synthesized following the reported procedure.



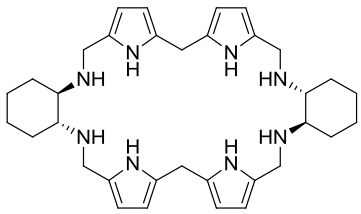
72

Synthesis of Dialdehyde 72. POCl3 (0.13 mL, 1.4 mmol) was added dropwise to a stirred solution of **71** (150 mg, 0.7 mmol) in DMF (1 mL), which was cooled at 0 °C. The mixture was stirred at room temperature for 1 h and then cooled to 0 °C, and 10 N NaOH (10 mL) was added portionwise. The resultant precipitate was filtered and washed with water until pH = 7 was reached to obtain the crude product **72** as a white amorphous solid: 162 mg, (86%).



73

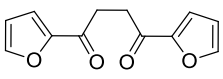
Synthesis of Imines 73. To the suspension of (R,R)-1,2-diaminocyclohexane L-tartrate (0.580 g, 2.2mmol) in MeOH (25 mL) were added aldehyde **72** (0.51 g, 2.2 mmol) and triethylamine (0.67 mL, 4.8 mmol). The reaction mixture was stirred for 12 h, and the solvent was evaporated at reduce pressure. A saturated aqueous solution of $NaHCO_3$ (20 mL) was added, and the organic material was extracted with dichloromethane (3 x 30 mL). The collected organic layers were washed with brine (20 mL), dried over Na_2SO_4, and concentrated to leave a white solid, **73** (0.63 g, 1.0 mmol, 90%) as. ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.34 (m, 4 H), 1.53 (m, 4 H), 1.64 (m, 4 H), 1.67 (s, 12 H), 1.78 (m, 4 H), 3.16 (m, 4 H), 6.11 (d, J = 3.6Hz, 4 H), 6.29 (d, J = 3.6 Hz, 4 H), 7.90 (s, 4 H).



74

Synthesis of amines 74. $NaBH_4$ (0.15 g, 4.1 mmol) was added to the solution of **73** (0.50 g, 0.8 mmol) in MeOH (20 mL) and the reaction mixture was stirred during 20 h, then a 1 M NaOH solution (5 mL) was added and the solvent was evaporated at reduced pressure. The organic material was extracted with EtOAc (3 x 30 mL). The collected organic layers were washed with brine (20 mL), dried over Na_2SO_4 and concentrated to leave **74** (0.47 g, 0.76 mmol, 95%) as a white solid.

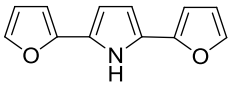
Chiral Pyrrole macrocyclic ligands for Cu-catalyzed asymmetric Henry reaction



77

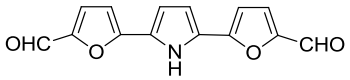
Synthesis of 1,4-bis(2-furyl)-1,4-butandione 77: To a solution of furfurale (1.6ml, 20mmol) in EtOH were added 3-benzyl-5-(2-hydrossiethyl)-4-methyl-1,3-tiazolio chloride (816mg, 3mmol) e NaOAc (418 mg, 5.1mmol). the mixture was refluxed for any minut and after that divynilsulphone (1 ml, 10 mmol) was added drop by drop and the reaction was refluxed for

12h. A with precipitate was observed in the mixtureand was removed by filtraction and washed by cool water and etere. The crude mixture was recrystalized by EtOH. With solid , 2.2 g (50%) ; ^{1}H NMR (200 MHz, $CDCl_3$): 3.33 (s, 4H); 6.58 (m, 2H); 7.29 (m, 2H); 7.62 (m, 2H). GC-MS (m/z): 218 (22), 123 (30), 95 (100). IR (CH_2Cl_2): 1700 (CO).



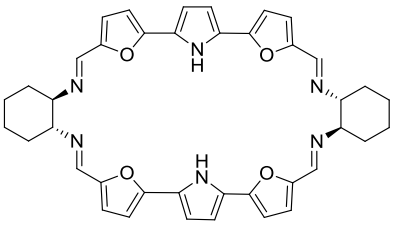
78

Synthesis of 2,5-bis(2-furyl)pyrrole 78: 77 (2.2g, 10mmol) and NH_4OAc (7.7 g, 100 mmol) were dissolved in EtOH and the solution was refluxed for 2 h. H_2O was added to the coolled solution and the reaction was extracted by DCM, all the collected organic fases were dried over Na_2SO_4. The crude mixture obtained after the solvent remotion was purified by flash chromatography (cyclohesan:EtOAc 8:2). The pure product was obtain as a Green amorfus solid (1.2 g) Resa: 59%. ^{1}H NMR (200 MHz, $CDCl_3$): 6.41 (t, *J* = 4 Hz, 2H), 6.46-6.48 (m, 2H), 7.39 (t, *J* = 8 Hz, 2H), 8.8 (bs). GC-MS (m/z): 199 (100), 170 (31), 142 (47), 115 (25).



79

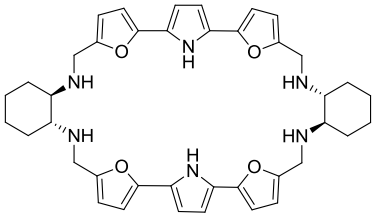
Synthesis of 5,5'-(1H-pyrrol-2,5-diil)difuryl-2-carbaldehyde 79. POCl3 (1.3 ml, 14 mmol) was added dropwise to a stirred solution of **78** (1.2 g, 5.9 mmol) in DMF (5 mL), which was cooled at 0 °C for 20 min ander Ar athmospher. The mixture was stirred at room temperature for 1 h and then cooled to 0 °C, and saturated spolution of NaOAc (10 mL) was added portionwise and the mixture was refluxed for 10min after that the soluzion was leave at rt for 30 min. The resultant precipitate was filtered and washed with water until pH = 7 was reached to obtain the crude product **79** as a red-brown amorphous solid: 1 g, yields: 80%. Mp= decomposition. ^{1}H NMR (400 MHz, DMSO-d_6): 6.78 (s, 2H), 6.97 (d, *J* = 3 Hz, 2H), 7.58 (d, *J* = 3 Hz, 2H), 9.93 (s, 2H). ^{13}C NMR (100MHz, DMSO-d_6): 107.38, 112.0, 126.3, 150.8, 153.7, 177.4. GC-MS (m/z): 255 (100), 188 (58), 141(22).



80

Synthesis of Imines 80: To the suspension of (R,R)-1,2-diaminocyclohexane L-tartrate (1 g, 3.9 mmol), in MeOH (10 mL) were added aldehyde **79** (1g, 3.9 mmol), triethylamine (0.8 ml,5.8mmol) and DCM (3ml) to increase the akdehyde solubility. The reaction mixture was stirred for 12 h, and the solvent was evaporated at reduce pressure. A saturated aqueous

solution of $NaHCO_3$ (20 mL) was added, and the organic material was extracted with dichloromethane (3 x30 mL). The collected organic layers were washed with brine (20 mL), dried over Na_2SO_4, and concentrated to leave **80** (1.23 g, 1.8 mmol, 41%) as brown powder. ^{1}H NMR (400MHz, DMSO-d_6): 1.40-1.53 (m, 8H), 1.58-1.90 (m, 8H), 3.23-3.34 (m, 4H), 6.48 (s, 1H), 6.66 (dd, *J* = 4Hz, 4H), 6.88 (dd, *J* = 4Hz, 4H). HPLC-MS (m/z): 667$[M+H]^+$, 334 $[M+H]^{2+}$, 255

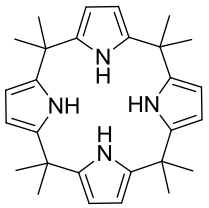


81

Synthesis of amines 81: $NaBH_4$ (49 mg, 1.32 mmol) was added to the solution of) **80** (879 mg, 1.32 mmol), in MeOH (20 mL) and the reaction mixture was stirred during 20 h, then a 1 M NaOH solution (5 mL) was added and the solvent was evaporated at reduced pressure. The organic material was extracted with EtOAc (3 x 30 mL). The collected organic layers were washed with brine (20 mL), dried over Na_2SO_4 and concentrated to leave **81** (40 mg, 1.0 mmol, 70%) as brown solid :^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.46 (s, 12 H), 1.61 (m, 6 H), 1.99-2.09 (m, 4 H), 3.37 (d, *J* = 14.7 Hz, 4 H), 3.62 (d, *J* = 14.7 Hz, 4 H), 5.72 (d, *J* = 2.4 Hz, 4 H), 5.89 (t, *J* = 2.4 Hz, 4 H), 10.82 (bs, 4 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 25.2, 31.4, 33.0, 35.8, 42.9, 60.3, 103.4, 103.9, 130.1, 137.6. ESI-MS *m/z*: 675 $[M + H]^+$.

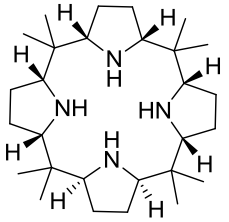
Calix[4]pyrrole hydrogenation and calix[2]pyrrole[2]pyrrolidine-Pd(II) complex

Palladium/Graphite (C_{96}Pd): Graphite powder (5,91 g, 496mmol) was poured into a three-necked flask equipped with a condenser, a dropping funnel, an argon inlet, and amagnetic stirrer bar, and the contents of the flask were heated under argon at 150 °C for 10 min. Freshly cut potassium (0.39 g, 10 mmol) was slowly added to the graphite at 150 °C with stirring. After all the potassium pieces had melted and bronze-colored $C_{48}K$ powder was formed, the flask was allowed to cool to r.t. and the $C_{48}K$ was covered with anhyd THF (15 mL) without stirring. A suspension of anhydrous $PdCl_2$ (0.88 g, 5 mmol) in THF (50 mL) was slowly added with stirring. The mixture was then refluxed for 3 h, cooled to 0 °C, and H_2O (10 mL) was slowly added. The mixture was stirred for 30 min and then filtered. r.t. under vacuum and the solid was washed successively with H_2O, MeOH, and Et_2O (30 mL each). The drark-gray powed was heated at 70°C for 6 h under pressure to give C_{16}Pd as a dark grey powder; yield: 6.031 g (96%).



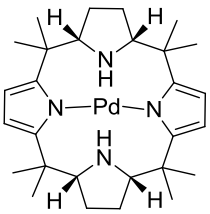
82

Calix[4]pyrrole: ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.01 (4H, br s, NH), 5.89 (8H, d, *J*=2.5 Hz, β-pyrrole), 1.50 (24 H, s). HRMS (ESI-MS) : $C_{28}H_{36}N_4$ [M-H]- : calcd : 427.2862, found : 427.2860



84a

Unprotonated *trans*-calix[4]pyrrolidine : ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.73 (s, 6H), 0.76 (s, 6H), 0.84 (s, 12H), 1.22-1.34 (m, 6H), 1.39-1.55(m, 10H), 2.73 (s, 2H), 2.78 (s, 2H), 2.88 (m, 3H), 2.99 (s, 1H). ^{13}C-NMR (400 MHz, $CDCl_3$): δ 12.07, 23.02, 23.17, 25.25, 25.61, 26.63, 25.80, 27.41, 37.44, 38.49, 65.51, 68.12, 70.22. HRMS (ESI-MS): m/z 445.42619[MH^+]. IR(): 3376.45, 3325,79, 2963.12, 2870.62, 1467.07, 1383.70, 1287.03, 1258.04 cm^{-1}



86

Synthesis procedure Pd-complex: 100 mg (0.23 mmol) of Calix[2]pyrrole[2]pyrrolidine was stirred with 51.4mg (0.23mmol) of $Pd(OAc)_2$ in 25 ml of DCM at room temperature under Ar atmosphere. After 2 hours the solvent was removed and the crude was directly purified by chromatographic column over basic Al_2O_3 (cyclohexane/Ethylacetate, 9/1); 70% yield. The pure product was obtain as yellow-green solid. It was crystallized in THF under Ar atmosphere: ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.30 (s, 12H), 1.38 (s, 12H), 1.64-1.67(m, 4H), 1.93-1.96 (m, 4H),3.01 (t, *J*=12, 2H), 3.55-3.61 (m, 4H), 6.06 (s, 4H). ^{13}C-NMR (400 MHz, $CDCl_3$): δ 23.73, 25.97, 28.40, 36.08, 67.33, 102.25,143.56. HRMS (MALDI-MS): m/z 540.24485[$M+H^+$] and 542.24359[$M+H^+$] isotope of Pd.

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Chapter 2: Synthesis of enantio-enriched 2-aryl- and 2,5-diaryl-substituted pyrrolidines

2.1 Introduction

N-Heterocyclic compounds have attracted considerable attention owing to their many applications in pharmaceutical chemistry, material chemistry, and synthetic organic chemistry.[112] In particular, pyrrolidine, piperidine, and morpholine derivatives are present in a large class of biologically active natural products.[113] A huge amount of natural derivatives containing such heterocyclic rings are involved in many biological regulation processes, so it is extremely important to study the behavior of novel synthetic analogues. Alkaloids, for examples, are produced by a large variety of organisms, including bacteria, fungi, plants, and animals, and are part of the group of natural products that are called secondary metabolites. They often have pharmacological effects and are used as therapeutics, as recreational drugs, or in entheogenic rituals.

Examples are the local anesthetic and stimulant cocaine, the psychedelic psilocin, the stimulant caffeine and nicotine, the analgesic morphine, the antibacterial berberine, the anticancer compound vincristine, the antihypertension agent reserpine, the cholinomimetic galantamine, the spasmolysis agent atropine, the vasodilator vincamine, the antiarhythmia quinidine, the antiasthma therapeutic ephedrine, and the antimalarial drug quinine.

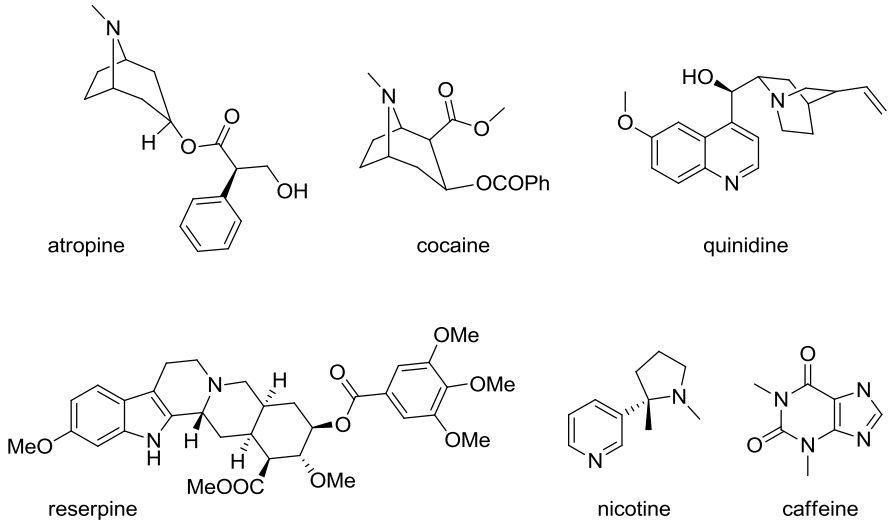


Fig 67. Some important alkaloids.

The need of new chiral, optically pure drugs has become more and more pressing in pharmaceutical industry, and consequently the development of synthetic procedures for an ever increasing number of such compounds represents the most important goal in organic

synthesis. The asymmetric synthesis of chiral products can be achieved starting from chiral materials ("ex-chiral pool" synthesis), using chiral auxiliaries (either derived from natural compounds or cheap intermediates from chemical industry) which can be removed in a subsequent step, or using chiral catalysts. Natural products are the first chiral catalysts used in enantioselective catalytic processes.

A nitrogen-containing functional group can act as a strong base, as in guanidines, or as a strong nucleophile, as in hydrazines. The absence of an available *d*-orbital in such functionalities could, at first glance, be considered as a limitation for an effective interaction with transition metal complexes. This weakness could, nevertheless, be counterbalanced by numerous other types of interactions. Indeed, natural metal transition complexes (i.e., porphyrines) in which nitrogen acts as a ligand have already proven their efficiency not only for precious metal complexes (such as Rh, Pd, Ru,...) but also for early transition metal complexes (such as Mn, Cu, Ni, Co,...).

Quinine, cinchonine, sparteine, strychnine, and emetine are only few examples of chiral natural products used as catalysts in homogeneous and heterogeneous systems.

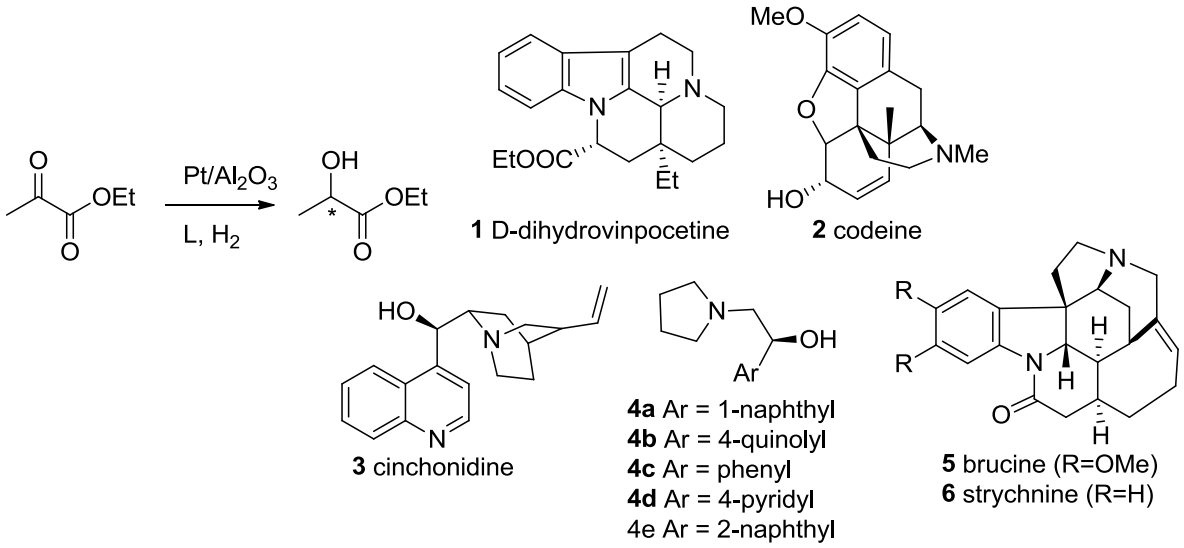


Figure 2. Natural compounds used as chiral catalysts in heterogeneous hydrogenation reaction.

Although nitrogen-containing ligands were only rarely used in the 70's and the 80's, some of the first historic asymmetric catalysts were heterogeneous nitrogen-containing chiral systems. One of the first application of the "chiral pool" derived chiral catalyst was presented by Orito[114] in 1978: Pt/Al_2O_3 modified by cinchona alkaloids **3** allowed the reduction of ketoesters to *R*-α-hydroxy acids. Since its discovery, no new chiral catalyst with similar efficiency has been reported. During the years other alkaloids catalysts were proposed in the same reaction as an example finely dispersed poly-(vinylpyrrolidone) stabilized platinum clusters[115]. Up to 97% ee in favor of the (*R*)-(+)-methyl lactate was measured in the presence of cinchonodine. Contrary to most observations of the Pt/cinchonidine system, the smallest Pt clusters gave the best results despite having no flat surface large enough for the adsorption of cinchonidine. Studies on the structural requirements for the modifiers to reach good to excellent ee led Pfaltz and Baiker[116] to the conclusion that it was the interaction of the

substrate and the quinuclidine part of the ligand which determined the ee. They, therefore, proposed ligands with simpler structures (Figure 2). Using ligand **4a** with the *N*-substituted pyrrolidine structure, only 75% ee was reached at 100% conversion as compared to the 95% ee obtained using the classic dihydrocinchonidine.[117] Wells[118] then proposed codeine **2** and strychnos alkaloids **5** and **6** for the same reduction. To summarize, the best ligands proved the cinchona alkaloid at high-pressure and 1-(1-naphthyl)ethylamine at low-pressure conditions.

In the same years it was discovered that proline **7** was an efficient ligand for transition metal complexes used in asymmetric catalysis, e.g. heterogeneous hydrogenation. Most importantly, proline itself is an effective organocatalyst of several powerful asymmetric transformation, such as the aldol, Mannich, and Michael reactions, Robinson annulation, Diels Alder reaction, and so on. (*S*)-Proline is an abundant chiral molecule that is inexpensive and also the unnatural enantiomer is commercially available. Particularly, both acid or base fuctionalities present in proline act in concert to facilitate chemical transformations, similarly to enzymatic catalysis.
During the years a big family of similar compounds were synthesized, Corey-Bakshi-Shibata[119,120] catalyst (**10**), MacMillan[121] catalyst (**8**), and the Hayashi-Jørgensen [122]catalyst (**9**) were tested in the same reaction obtaining enthusiastic results.

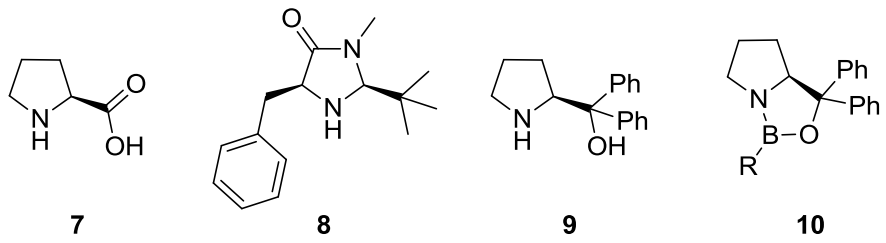


Figure 68: Proline (7) and similar compounds commonly used in organocatalysis: MacMillan catalyst (8), Hayashi-Jørgensen catalyst (9), Corey-Bakshi-Shibata catalyst (10).

In the last decade the search for new catalysts and biological active molecules with pyrrolidine core has grown exponentially. Pyrrolidines play important roles in the drug discovery process.[123] Several polysubstituted pyrrolidines have shown very potent activities as enzyme inhibitors, agonists, or antagonists of receptors.[124] Furthermore, the advanced progress achieved in genomic research increases the demand for identification of small molecules that are active and selective against a broader range of therapeutical targets. In the perspective of more biologically interesting targets becoming available, the efficient synthesis and optimization of new drug-like chemical entities actually constitutes the bottleneck in medicinal chemistry.[125] The functional assay technology R-SATTM[126] enables exploration of an enormous range of possible drug targets in a nonbiased manner.
Considering the high value of chiral pyrrolidine as a catalyst[127,128] (chiral ligand or organocatalyst) or as component in chiral biological molecules,[129] different asymmetric routes have been proposed in the last decade. Recent examples include 1,3-dipolar cycloadditions of azomethine ylides to electron-deficient alkenes,[130] reduction of pyrroles,[131] intramolecular hydroamination,[132] annulation reactions of allyl-,[133] vinyl-,[134] and allenylsilanes,[135] and ring-closing metathesis.[136]

2.1.1 Organocatalysis or Organometallic catalysis ?

Pyrrolidine-based compounds can be used as ligands of organometallic catalysts, or can act themseves as organocatalysts. Here, I will report some examples that perfectly illustrate both the catalytic applications.

2.1.1.1 Organocatalysis

Organocatalysis has become a favourite theme of research thanks to activity displayed by proline.[137] Since then, new similar compounds have been prepared and studied aiming to achieve a higher activity than proline. In all cases. the new molecules were made of a five-membered nitrogen ring with a hindered substituent in the α position. The catalytic pathway ("iminium" or "enammine" catalysis) was dependent on the nature of the substrate[138] as well as of catalyst. Over the last 10 years, imidazolidinones have been established as LUMO-lowering iminium catalysts that can be employed in a wide variety of enantioselective transformations including conjugate additions, Friedel– Crafts alkylations, hydrido reductions, and cycloadditions. While imidazolidinones can also serve as enamine catalysts, they do not contain the necessary structural features to participate in bifunctional enamine catalysis (wherein activation of the electrophilic reaction partner is also performed by the amine catalyst). In contrast, proline has been shown to be an enamine catalyst for which bifunctional activation is a standard mode of operation across a variety of transformation types; yet, remarkably, this amino acid is generally ineffective as an iminium catalyst with enals or enones. Given these mutually orthogonal reactivity profiles, MacMillan has been hypothesized that the combination of imidazolidinone and proline should provide a dual-catalyst system that fully satisfies the chemoselectivity requirements for cycle-specific catalysis as show in Fig 4.

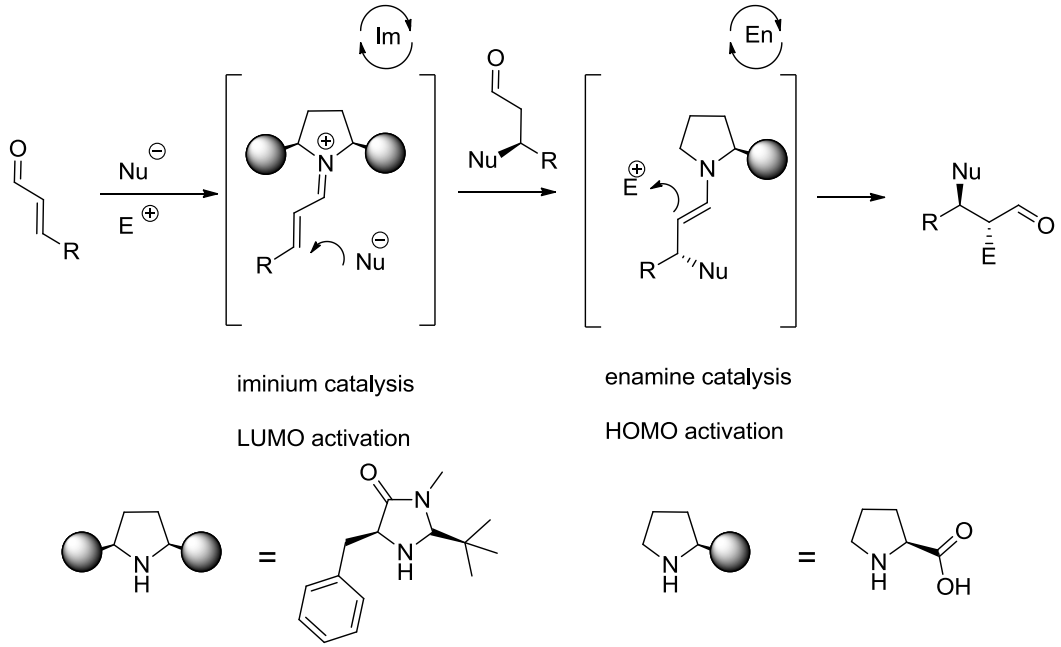


Fig 69. Different affinities of MacMillan catalyst and proline; imminum-enamine catalysis.

It was possible to take advantages of the different abilities of the two catalysts and design cascade reactions with the two catalysts acting in different steps of the one-pot process. As show in Fig 5 starting from simple and cheaper starting material as α,β-insaturated aldehyde **11** and substituted furan is possible to obtain a complex final product **15** using at the same time imminium (**12**) and enamine catalysis (**14**). This is only one example of the hundreds publications in the last years, that clearly demonstrates why the application of this kind of catalysis has found a so rapid development.

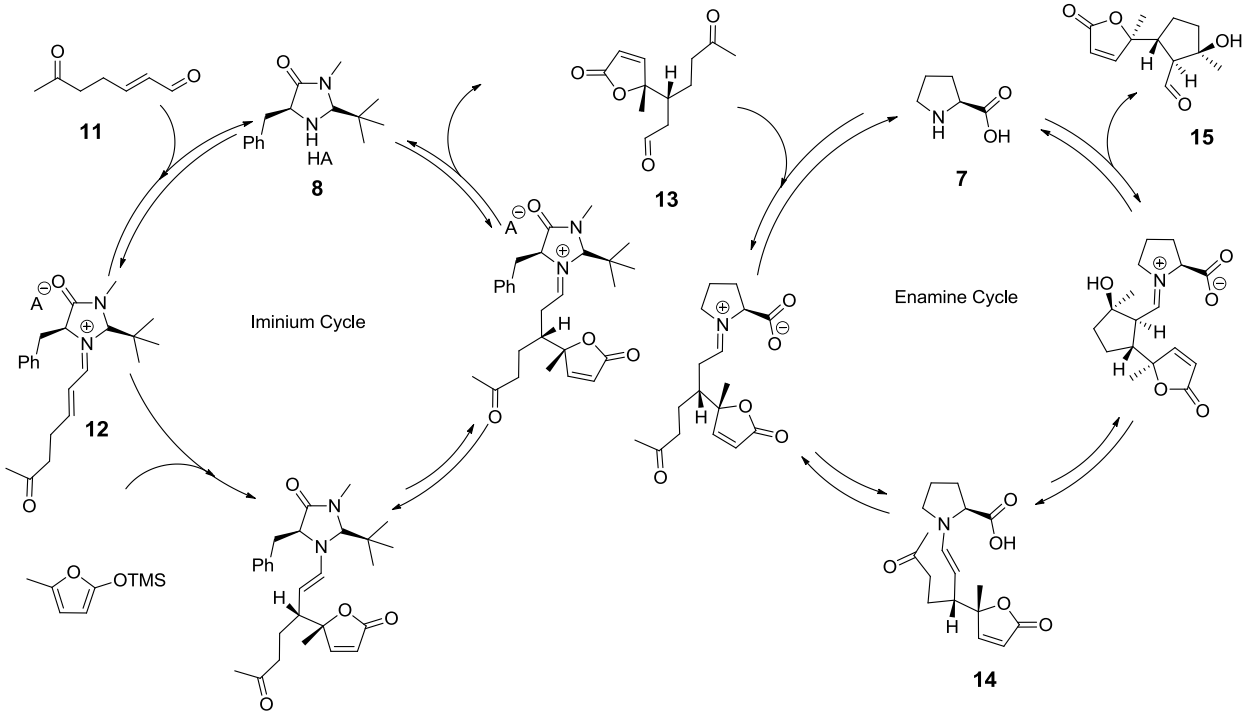


Fig 70. Catalityc cycle of the combined MacMillan-proline catalysis.

2.1.1.2 Organometallic catalysis

On the other hand the applications of pyrrolidine-based ligands in organometallic catalysis are not as much diffused as in organocatalysis. The Overman complex **16** is one of the first example of pyrrolidine-organometallic catalyst.[139] The bidentate ligand creates a chiral environment around $PdCl^+$, and both the monomeric and dimeric complexes were observed. It was used in the enantioselective rearrangement of allylic imidates to allylic amide with good yields and ee (Figure 6).

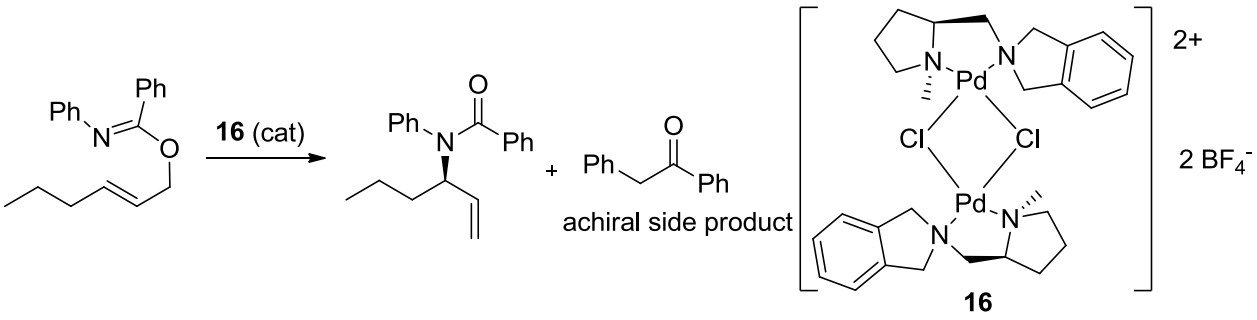


Fig 71. Pyrrolidine-Pd complex 16 in the allylic imidates rearrangement.

Another chiral Pd-pyrrolidine complex was presented by McGrath.[140] The ligand **17** contains the *trans-2,5-disubstituted* pyrrolidine moiety linked to a pyridine ring. Pyridine is a strong electron donor ligand, but, because of the delocalized π-framework, also has the capacity to be a strong electron acceptor depending on ring substituents.[141] Electronic character can play an extremely important role in ligands for transition metal-catalyzed processes, affecting both rate and stereoselectivity,[142,143] and the presence of the pyridine moiety should allow to alter the electronic character of these ligands. The ^{1}H NMR spectrum of the allyl-Pd complex prepared from the ligand **17** showed that diastereomeric allyl complexes (π-allyl rotamers **a** and **b**) an approximately 1:1 ratio, which underwent slow exchange at room temperature (400 MHz ^{1}H NMR).

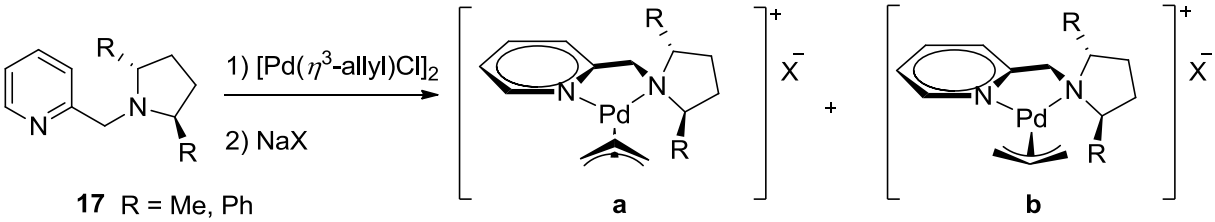


Fig 72. Pyridine-pyrrolidine ligands in allyl Pd-complexes.

At the same time Furukawa presented a different application of proline as ligand in the Ru complex **18** used in the homogeneous hydrogenation of aromatic ketones,[144] where good yields and ee were obtained.

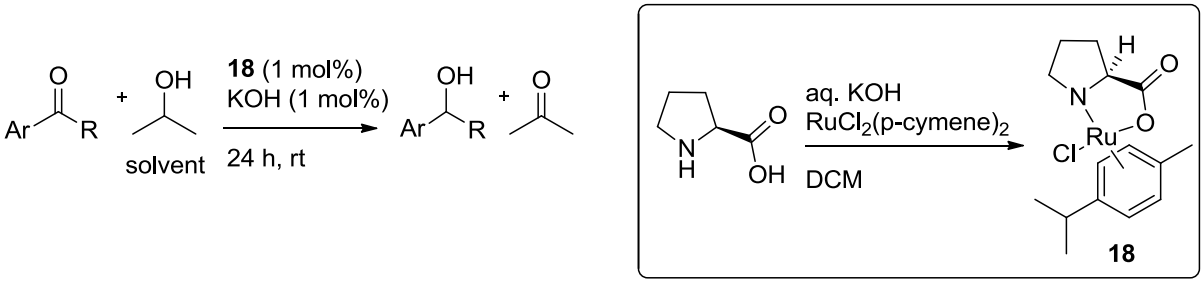


Figure 73. Proline-Ru complex 18 in homogeneous ketone hydrogenation reaction.

(*R*,*R*)-2,2′-Bispyrrolidine **19** was firstly prepared by Hirama by resolution of the racemic compound with tartaric acid.[145] An asymmetric synthesis was reported by Kotsuki starting from mannitol or tartaric acid.[146] On the other hand, Alexakis has developed a shorter route,[147] which is feasible on a large scale: the first steps are based on the chiral diamine synthesis reported by Neumann[148] and later improved by Savoia, which starts from a chiral glyoxal diimine.[149] The two pyrrolidine complexes with $ZnCl_2$ **20** and **21** were prepared, and the X-ray structures were determined.

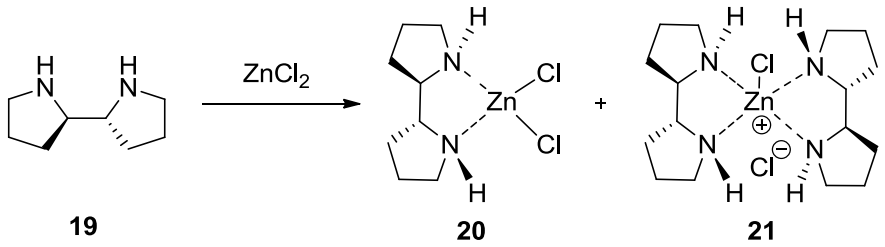


Fig 74. Alexakis' 2′,5′-bispyrrolidine-$ZnCl_2$ complexes.

The same scaffold **19** was used by White to prepare a new organometallic Fe complex useful in sp^3 carbon oxidation reactions.[150] It was hypothesized that site-selective oxidations of unactivated sp^3 C–H bonds could be predictably controlled provided that a reactive metal catalyst could be capable of discriminating C–H bonds in complex molecules on the basis of subtle electronic and steric differences. The electrophilic iron catalyst **22** shown in Figure 10, featuring a tetradentatate ligand framework, uses H_2O_2 as an inexpensive, environmentally friendly oxidant to effect highly selective oxidations of unactivated sp^3 C–H bonds over a broad range of substrates. The corresponding reactions catalyzed by the achiral complex **23** were less selective.

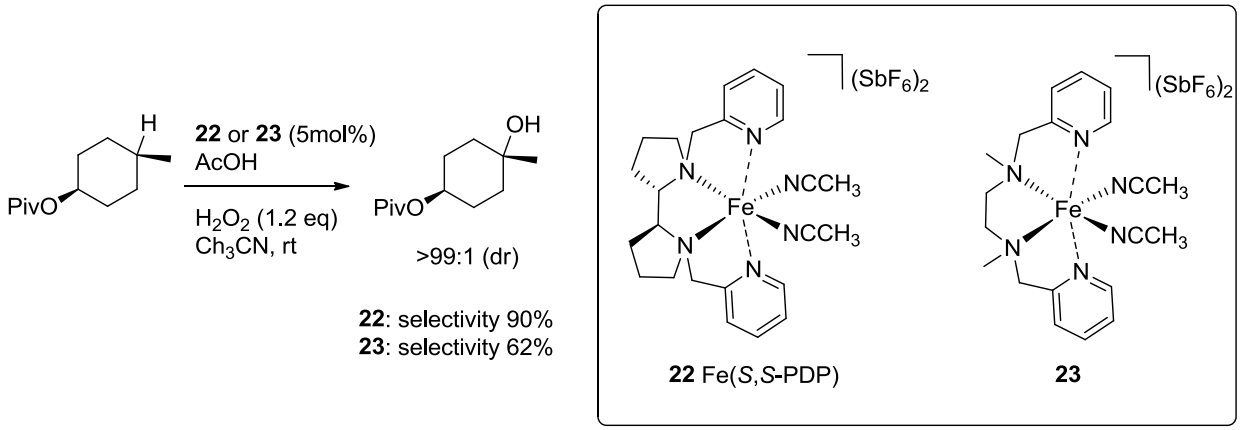


Fig 75. sp^3-Carbon oxidation reaction using White's catalyst.

The site of oxidation in complex organic substrates using **22** can be predicted on the basis of the electronic and steric environment of the C–H bonds (Figure 11).

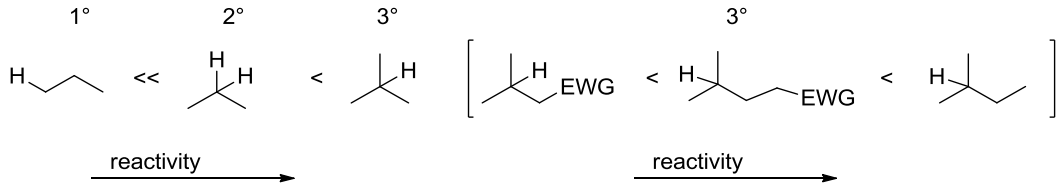
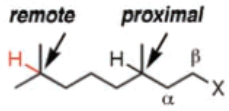
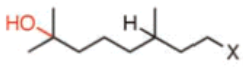
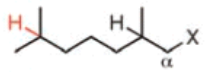
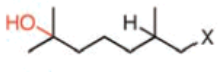
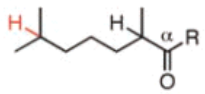
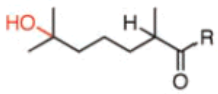


Fig 76. Reactivity scale of *sp*^{3} carbons in oxidation reaction catalyzed by 22.

Table 1 shows that the highly selective oxidation process preferentially occurred at the remote tertiary hydrogen, remote from the electron-withdrawing substituent. This report is one of recent examples where pyrrolidine core ligands have been used in organometallic catalysis with amazing results.

Table 14. Exploring substrates

Entry	Substrate	Major Product		Isolated %Yield* (rsm)†	[Remote: Proximal]‡
1			**15**, X = H	48§(29)	1:1
2			**16**, X = OAc	43 (35)	5:1
3			**17**, X = Br	39 (32)	9:1
4			**18**, X = F	43 (20)	6:1
5			**19**, X = OAc	49 (21)	29:1
6			**20**, X = Br	48 (17)	20:1
7			**21**, R = CH_3	52 (18)	>99:1
8			**22**, R = OCH_3	56 (32)	>99:1

2.2 Synthetic routes to pyrrolidines

During the years different synthetic routes have been proposed leading to new enantiomerically pure pyrrolidine derivatives. We divide such reactions in four classes:

1) Annulation
2) Cyclopropane expansion
3) Hydroamination

1) Annulation reaction

Somfai reported the annulation reaction where a Lewis acid promoted the reaction of γ-silyl-substituted allylsilanes to α-amino aldehydes, leading to the stereoselective formation of pyrrolidine rings **24** (Figure 12).[151]

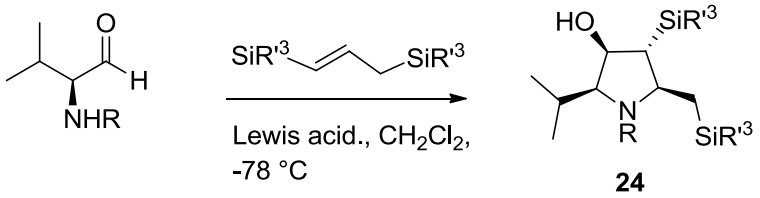


Fig 77. [3 + 2] Annulation reaction

Allylsilanes can also function as synthetic equivalents of 1,2-[152] or 1,3-dipoles[153] in annulations reactions to activated C=X π-bonds, due to the efficient σ–>p hyperconjugative stabilization of β-silyl carbocations by adjacent C-Si bonds. Li[154] and Kobayashi[155] have presented reactions in which modified amino acids were used as starting material. Kobayashi observed that Brønsted base catalysts such as alkaline earth metal alkoxides ($Ca(O^iPr)_2$) bound to chiral ligands, e.g. PhBOX **26a-c,** were highly active complexes in the Michael reaction of imine derivatives and methyl acrylates. Using this complexes the desired Michael adduct was obtained in 88% yield and 94% ee when the reaction was conducted in THF at -30 °C for 12 h in the presence of 4A MS 4A. During the examination of the substrate scope, it was discovered that when other unsaturated carbonyl compounds was allowed to react with enamine under the standard reaction conditions, the reaction also proceeded smoothly; however, the product was the corresponding pyrrolidine **25**, obtained in excellent yield and enantioselectivity via a formal [3+2] cycloaddition pathway (Figure 13).[156]

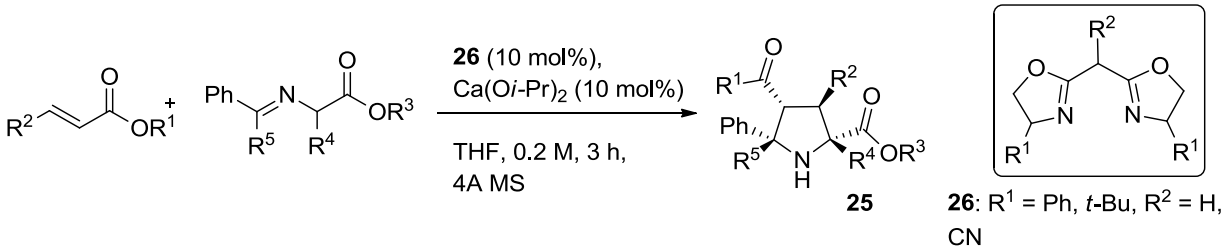


Fig 78. [3 + 2] Annulation reactions catalyzed by Ca(O*i*-Pr)$_2$ and PhBOX.

2) Cyclopropane expansion

Ring opening of cyclopropyl ketones with metal iodides affords attractive synthetic intermediates incorporating either a nucleophile (i.e. metal enolate) and an electrophile (i.e. alkyl iodide) within the same molecule. Oshima and co-workers reported the formation of acyltetrahydrofurans by trapping metal enolates derived from cyclopropyl ketones with aldehydes.[157] Encouraged by those results, Olson envisioned that replacing the aldehydes with imines formed *in situ* would be an efficient way to synthesize pyrrolidines **27** (Figure 14).[158]

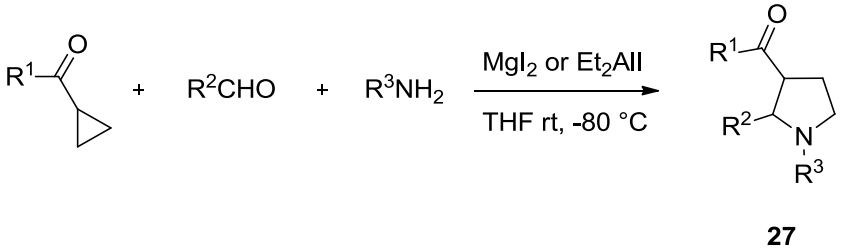


Fig 79. Cyclopropane expansion as a tool to synthesize pyrrolidines.

Recently, Carreira has reported the ring expansion of a cyclopropanecarboxamide with aldimines using the same LA of Olson.[159] Sun proposed a new cyclopropane expansion starting from 2-substituted 1,1-cyclopropane carboxylates and phenyl-immin in catalityc amount of different LA. Highly functionalized pyrrolidines **28** were obteined in good yield and very good enantioselectivity (Figure 15).[160] The same procedure but with different sobstituted cyclopropen were performed by Carreira and Lautens.[161]

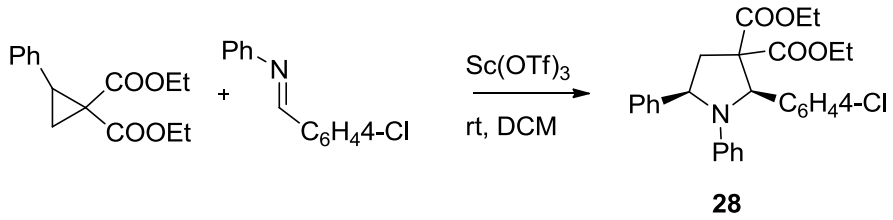


Fig 80. Cyclopropane expansion.

3) Hydroamination

The first reaction of this type was disclosed by Widenhoefer,[162] who used $[PtCl_2(H_2C{=}CH_2)]_2/PPh_3$ and later $PtCl_2$/biarylphosphine (5-10 mol% Pt) for the cyclization of secondary alkylamines. More recently, the same author reported a mild and effective Au-catalyzed protocol for the intramolecular hydroamination of alkenyl carbamates to form protected nitrogen heterocycles.[163] More recently, Hollis[164] reported the use of pincer-type *N*-heterocyclic carbene complexes (5 mol%) of Rh and Ir for the intramolecular hydroamination of terminal alkenes by tethered secondary alkyl- and phenylamine functions. Liu and Hartwig[165] disclosed the use of $[Rh(COD)_2]BF_4$/Cy-DavePhos for the cyclization of substrates that contain primary or secondary alkylamines and terminal or internal alkenes. In this vein, Stradiotto reported herein that $[Ir(COD)Cl]_2$ was an effective catalyst for the hydroamination of unactivated alkenes with pendant secondary alkyl- and arylamines at relatively low loadings of the catalyst (0.25-5 mol%) without the need for added ligands or cocatalysts (Figure 16).[166]

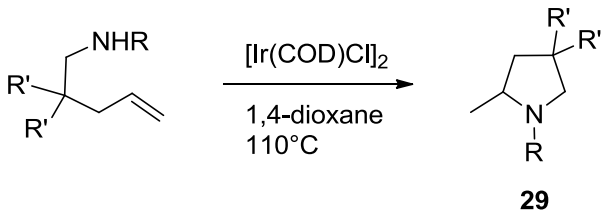


Fig 81. Ir-catalyzed intramolecular hydroamination reaction.

2.3 2-Arylpyrrolidines and 2,5-diarylpyrrolidines

Considerable attention has been devoted in recent years to the synthesis of enantiopure 2-substituted pyrrolidines, such as 2-arylpyrrolidines,[167] which are useful as chiral bases, chiral auxiliaries, and chiral ligands.[168] A general method for the enantioselective arylation of *N*-Boc-pyrrolidine to give 2-aryl-*N*-Boc-pyrrolidines **30** is lacking.[169] As an alternative, Beak[170] reported the enantioselective lithiation/intramolecular substitution of *N*-(γ-chloropropyl) benzylic amines, which afforded (*S*)-2-aryl-*N*-Boc-pyrrolidines with high enantiomeric excesses (Figure 17).

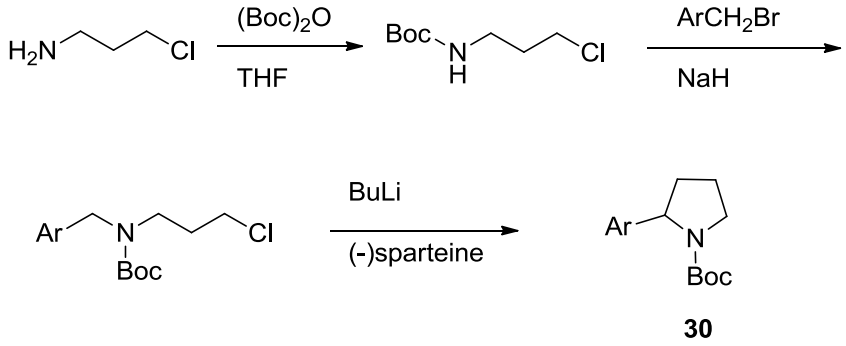


Fig 82. Metalation/cyclization of *N*-(γ-chloropropyl) benzylic amines.

Chiral auxiliary-mediated approaches have been reported. [171,172] Savoia and coworkers have used (*S*)-valine as the chiral auxiliary for the stereoselective synthesis of 2-phenylpyrrolidine by reductive ammination.[173] Catalytic methods have also been developed for the syntheses of enantioenriched 2-arylpyrrolines and -pyrrolidines. Ozawa and Hayashi have used palladium acetate-2(*R*)-BINAP complex for the catalytic asymmetric C-2 arylation of 1-alkoxycarbonyl 2-pyrrolidines with aryltriflate compound to obtain optically active (*R*-1-(alkoxycarbonyl-5-aryl-2-pyrrolines of up to 83% ee, together with the regioisomers 1-(alkoxycarbonyl)-5-aryl-3-pyrrolines.[174] An especially efficient approach has been reported by Willoughby and Buchwald who used an enantioselective chiral titanocene-based catalyst to reduce 2-aryl and 2-alkyl-1-pyrrolines to 2-aryl- and 2-alkylpyrrolidines with very high enantioselectivities.[175]

2,5-Diaryl-substituted pyrrolidines can find same application as the mono-substituted analogues, but they are often synthesized by different methods. Since the first preparation of optically pure C_2- symmetrical amines,[176] such as *trans*-2,5-disubstituted pyrrolidines, by Whitesell in 1977,[177] these compounds have been extensively applied in various types of stereoselective syntheses, and a number of procedures for their preparation have been proposed.[178] Among them, one of the most accessible methods involves the enantioselective reduction of 1,4-diketones, which was realized by using chiral diisopinocamphenylchloroborane as reducing agent,[179] or by oxazaborolidine catalyzed reduction with borane.[180] For example, the 1,4-diphenyl-1,4-butanediol was obtained with high optical purity and the transformed into the optically pure 2,5-diphenylpyrrolidine **32** in good yield thanks to Salen-type Co complex **31** (Figure 18). A few reports have been

published dealing with the preparation of optically pure 2,6-diphenylpiperidine,[181] and 2,4-diphenylazetidine.[182] Yamada[183] presented an analogous synthetic way, which was limited to the preparation of pyrrolidines.

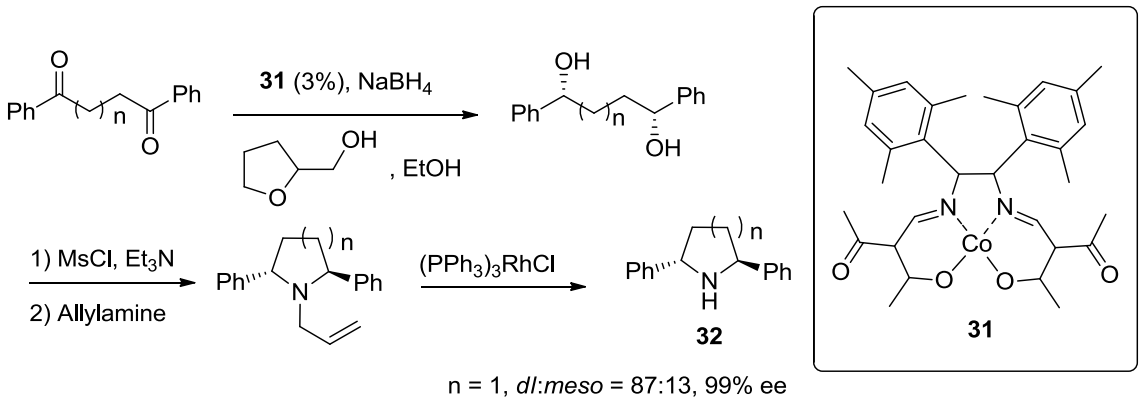


Fig 83. Synthesis of 2,5-diaryl pyrrolidines from optically pure 1,4-diols.

The application of the pyrrolidine **32** as chiral auxiliary in asymmetric Diels-Alder reactions was presented by Rawal.[184] Working on differently substituted acrylates, he observed excellent facial selectivity in the formation of functionalized cyclohexenones **33**.

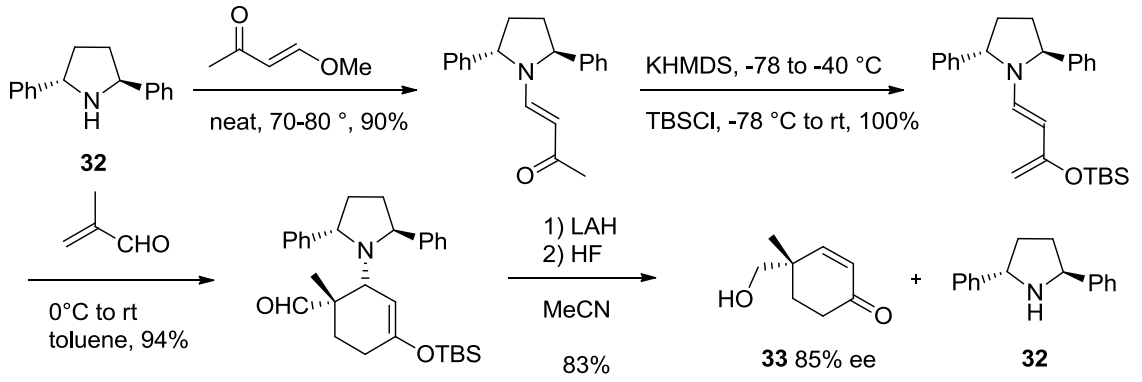


Fig 84. Diarylpyrrolidine used as chiral auxiliary in Diels-Alder reactions.

Rawal also used diphenylpyrrolidine as chiral auxiliary in asymmetric Thio-Claisen Rearrangements,[185] which proceeded with good to exceptionally high diastereoselectivities. The use of a C_2-symmetric amine prevents the rotomer issue as a consequence of free rotation around the C-N bond in the *N*,*S*-ketene acetal intermediate so reducing the number of different transition states, and produce only one isomer, and generally allow a higher stereoselectivity to be obtained.

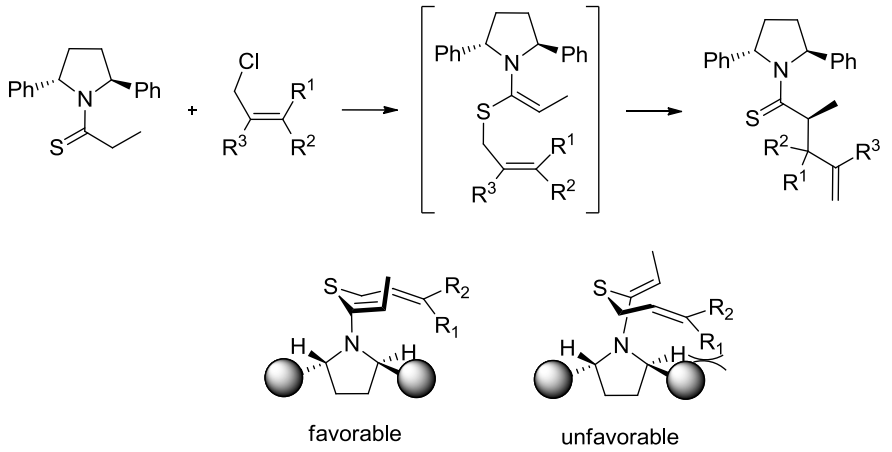


Figure 85. Auxiliary-induced stereoselective Thio-Claisen Rearrangement.

The diaryl pyrrolidine has found application also as ligand of organometallic species. An example was reported by Kim who used a BINOL-diarylpyrrolidine ligand in the asymmetric conjugate addition of organometallic compounds to enones.[186]

2.3.1 Synthesis of 1-substituted 2,5-di(2-furyl)pyrrolidines

Having observed the large number of aryl- and diarylpyrrolidines reported in literature, we could recognize that only the phenyl and similar aromatics groups have been widely used as substituents of the pyrrolidine ring, whereas only a few heteroaryl (pyridine or imidazolium) substituted pyrrolidines were reported. For this reason, we decided to investigate the asymmetric synthesis of heteroaryl and diheteroaryl substituted pyrrolidines, and began with 2,5-di(2-furyl)pyrrolidine.

Taking in account the knowledge of Savoia's group on the preparation of chiral pyrrolidines[187] by reductive amination of 1,4-diketones and 1,4-ketoaldehydes using optically pure primary amines as chiral auxiliaries, and the different strategic ways to obtain 1,4-diaryl-1,4-diketones thanks to Stetter procedures, we thought to combine these background informations to synthesized new di-heteroaryl pyrrolidine. In this way we decide to start our investigation applying the reductive amination route to the known 1,4-difuryl-1,4-butanedione (product **77**, subchapter 1.3.3) previously described in the synthesis of corresponding triaromatic scaffolds. Using several optically pure primary amines and sodium cyanoborohydride as reductive agent in ethanol at controlled pH, the reductive ammination reaction took place and afforded 2,5-di(2-furyl)pyrrolidines **34b-g** in good yields and moderate to high diasteromeric ratio.

The reaction proceeds through two consecutive reductive amination processes¸in both cases, the reactive intermediate which undergoes attack by hydride ion is an iminium ion (Figure 21).

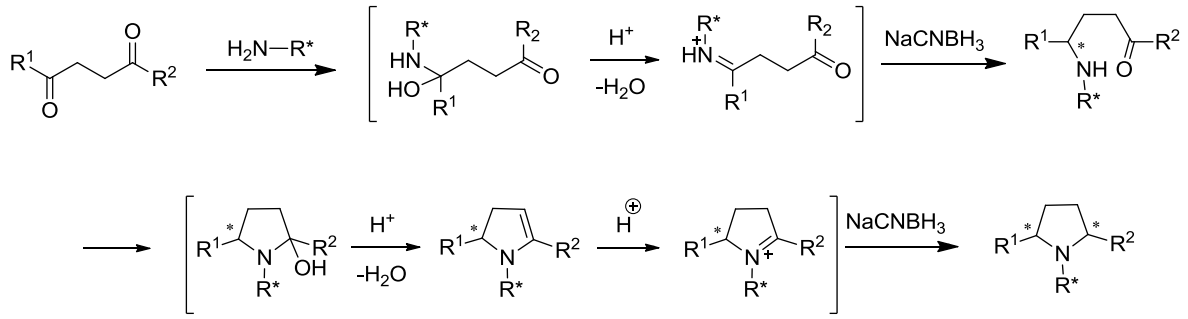


Figure 86. Reductive amination mechanism.

Owing to the presence of a fixed stereocenter in the nitrogen substituents (chiral auxiliary, R*), the reaction can give three different diastereoisomers of the expected product, i.e. one *cis* and two, C_2-symmetric, *trans* diastereoisomers.

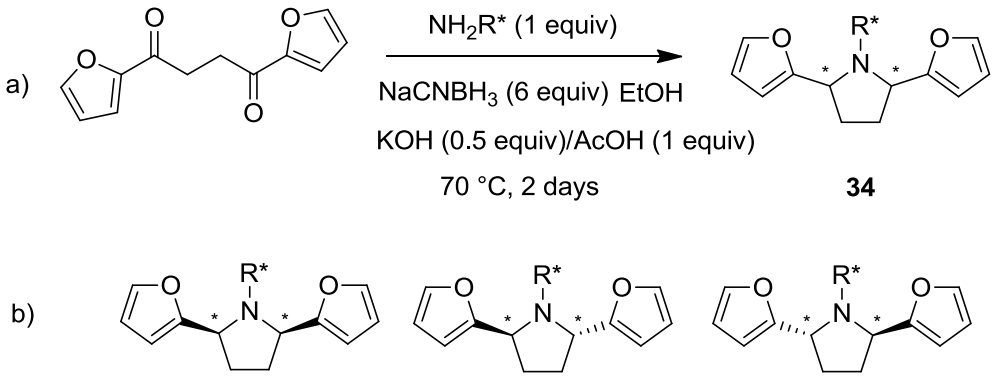
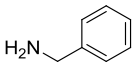
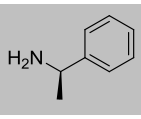
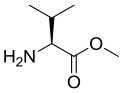
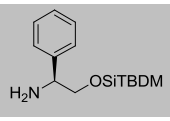
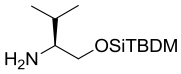
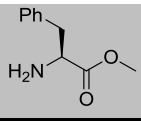


Fig 87. a) Reductive amination reaction, b) *cis* and *trans* products.

Different chiral primary amines were tested in the reductive ammination reaction, so that we could observe the effect of the nature of R* on the degree of asymmetric induction. The reactions occurred only by heating at 70 °C in EtOH as the solvent, the reaction rate being too low at lower temperature. The yields and the diasteroisomeric ratios observed for all the products prepared **34a-g** are reported in Table 2.

Table 15. Synthesis of 2,5-di(2-furyl)pirrolidines 34a-g from 1,4-di(2-furyl)-1,4-butandione and chiral primary amines.[a]

Entry	Amine	Product, Yield (%)	d.r.[b] (*cis*/*trans*)
1	NH_4OAc	**34a**, 80	50/50
2		**34b**, 85	70/30
3		**34c**, 85	90/10
4		**34d**, 70	80/20
5		**34e**, 60	93/7
6		**34f**, 55	90/10
7		**34g**, 70	70/30

[a] Reaction conditions: 1 equiv diketone, 1.1 equiv amine, 6 equiv $NaCNBH_3$, 0.5 equiv KOH, 1 equiv AcOH, EtOH, 70 °C, 3 d. [b] Determined by GC-MS. The distero results was reported in the same order to the GC time eluition. **[c**] Determined by GC-MS after reaction with TBDMSCl

All the diasteroisomeric ratios were determined by GC-MS of the crude mixtures. Using NH_4OAc as ammonia source, the NH-free 2,5-di(2-furyl)pyrrolidine was obtained, obviously as a racemic compound (Table 2, entry 1).

It can be observed that increasing the size of the *N*-substituent, the relative amount of the cis diastereoisomer increases at the expense of the *trans*-diastereoisomer (presumably, only one of the two possible *trans* diastereoisomers was formed, as an effect of the auxiliary-induced asymmetric induction). If we compare the results of the reactions performed with *O*-*t*-butyldimethylsilyl (*S*)-valinol and (*S*)-valine methylester, we can observe different diasteroselectivity (Table 2, entries 4 and 6). The prevalence of the 2,5-*cis*- over the 2,5-*trans*-disubstituted products can be explained considering that the former is definitely more stable than the latter, because in the 2,5-*cis*-disubstituted pyrrolidine each aryl substituent is in a *trans* relationship with the *N*-substituent. Consequently, even the transition state for the hydride attack to the intermediate iminium ion leading to the 2,5-*cis*-diastereoisomer has a lower energy compared to the alternative transition state leading to the 2,5-*trans* diastereoisomer, so we can conclude that the cis- product is major thanks to kinetic and termonidamic contribute .

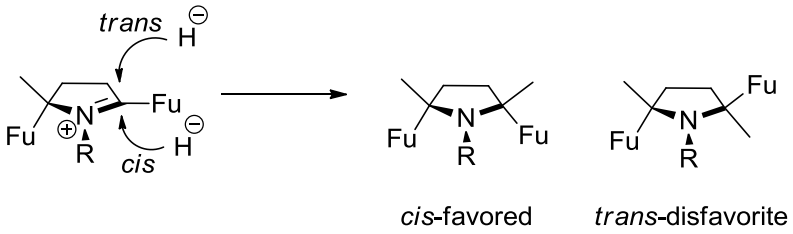


Figure 88. Iminium reduction

The compounds **34 a-g** could be separated by column chromatography, so that their *cis* and *trans* configuration could be determined by ^{1}H NMR analysis. It was so confirmed that the *cis* isomers were the prevalent products in the reductive amination reaction.

2.3.2 Asymmetric synthesis of 1-substituted-2-(2-furyl)pyrrolidines

To synthesize the 2-(2-furyl)pyrrolidine moiety we performed the same, previously described. reductive amination procedure, but used different route to prepare the required γ-ketoaldehyde **36**. Furan was lithiated at C-2 by *n*-BuLi at -78 °C in THF,[188] then the 2-furyllithium was added to γ-butyrrolacton to obtain the corresponding γ-hydroxyketone **35**. Using PCC, the alcohol was converted in the corresponding aldehyde **36** in good yields. The reductive amination reactions were carried out with the same optically pure primary amines we had previously used and following the previous protocol. The yields and diasteroisomeric ratios of the corresponding pyrrolidines **37a-h** are reported in Table 3.

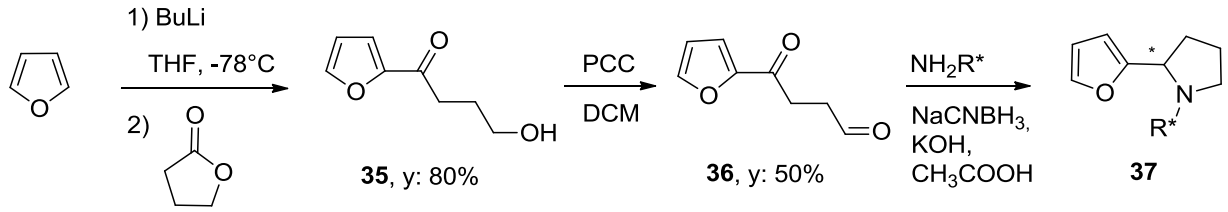
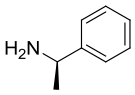
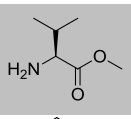
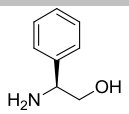
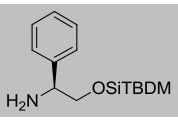
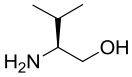
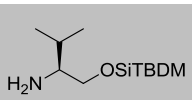
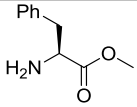


Fig 89. Synthesis of *N*-substituted 2-furylpyrrolidines

Table 16. Synthesis of 2-(2-furyl)pyrrolidine 37a-h by reductive amination of γ-ketoaldehyde 36.[a]

Entry	Amine	Product, Yield (%)	d.r.[b]
1	NH_4OAc	**37a**, 40	50/50
2		**37b**, 60	33/67
3		**37c**, 70	88/12
4		**37d**, 50	50/50[c]
5		**37e**, 75	57/43
6		**37f**, 37	61/39[c]
7		**37g**, 60	8/92
8		**37h**, 60	75/25

[a] Reaction conditions: 1 equiv **36**, 1.1 equiv amine, 6 equiv $NaCNBH_3$, 0.5 equiv KOH, 1 equiv AcOH, EtOH, 70 °C, 1 d. [b] Determined by GC-MS. The distero results was reported in the same order to the GC time eluition. [c] Determined by GC-MS after reaction with TBDMSCl.

Very good results was observed when (*S*)-valine methyl ester was used as chiral amine (Table 3, entry 3) and especially using *O*-*t*-butyldimethylsilyl (*S*)-valinol (Table 3, entry 7). On the other hand, worse results were observed using (*S*)-phenylglicinol and its *O*-*t*-butyldimethylsilyl derivative (Table 3, entries 4 and 5). The silyl protection of the OH group was necessary to determine by GC-MS analysis the diastereoisomeric ratio (dr) of the products obtained using (*S*)-valinol and (*S*)-phenylglycinol (Table 4, entry 6). An expected phenomena was observed comparing the dr of entry 6 and 7. Firstly we observed that there is an increase in yield and in dr an at last we can assume that using as starting material the OH protected valinol the diasteroselectivity is inverted. In the first case the diastero selectivity was evaluate only after the OH protection, so finally we will observe during the GC analysis the same product. We can conclude with an unexpected result that the sililation of the free OH in (S)valinol permit to obtain the opposite diastroisomers.

2.3.3 Synthesis of 1-substituted-2-(2-pyrrolyl)pyrrolidines

In the synthesis of 2-(2-pyrrolyl)pyrrolidines, the intermediate product **38** was obtained according to the Nicolau procedure.[189] The subsequent oxidation reaction, performed using PCC, afforded the desired ketoaldehyde **39**, which was submitted to the reductive amination step (Figure 25).

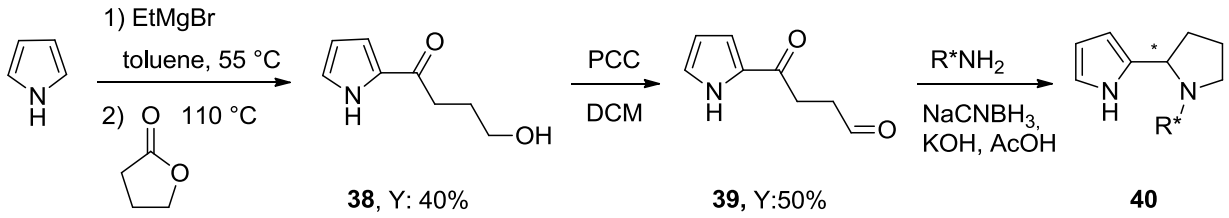
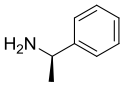
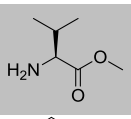
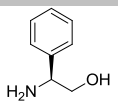
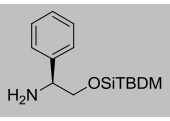
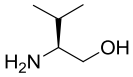
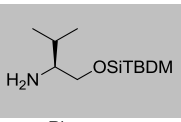
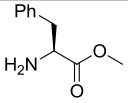


Fig 90. Synthesis of 2-(2-pyrrolyl)pyrrolidine 40a-h derivatives.

Table 17. Synthesis of 2-pyrrolyl pyrrolidine 40a-h using chiral amines.[a]

Entry	Amine	Product, Yield (%)	d.r.[b]
1	NH_4OAc	**40a**, 30	50/50
2		**40b**,70	66/34[d]
3		**40c**,75	70/30
4		**40d**,55	80/20[c]
5		**40e**,70	29/71
6		**40f**,35	60/40[d]
7		**40g**,55	83/17
8		**40h**,60	77/23

[a] Reaction condition: 1 equiv **39**, 1.1 equiv amine, 6 equiv $NaCNBH_3$, 0.5eq KOH, 1 equiv AcOH, EtOH, 70 °C, 2 d. [b] Determined by GC-MS. The distero results was reported in the same order to the GC time eluition. [c] Determined by GC-MS after reaction with TBDMSCl. [d] Determined by ^{1}H NMR.

Table 4 shows that the diasteroselectivity was moderate to good in most cases, and the best d.r. was observed for the product **40d** coming from (*S*)-phenylglycinol, whereas preliminary protection of the OH group led to a decreased d.r. and for the product **40g** (OH-protected (S)-valinol with d.r. of 83/17). As observed before after a OH protection of phenylglycinol (Table 4, entry 5) there is an disteroselectivity inversion compare to the OH free product (Table 4, entry 4) that was sililated only after the reductive ammination reduction. In this case unfortunately we observe (Table 4, entry 5) an increase in yields but a small decrease in dr. This is in sharp contrast with the stereochemical outcomes of the analogous reactions performed with the furyl ketoaldehyde. Since the reactions were performed in a very small scale, we did not attempt to separate the diastereoisomers for a more safe identification.

2.3.4 Asymmetric synthesis of 1-substituted 5-(2-furyl)-2-methylpyrrolidines and 2-methyl-5-(2pyrrolyl)pyrrolidines

Using the same synthetic procedure we have synthesized other two unsymmetrically 2,5-disubstituted pyrrolidines **41a-d** and **42a-d**. This has been achieved simply using γ-valerolactone in the reactions with 2-furyllithium and pyrrolylmagnesium bromide, respectively, in the first step of a previously exploited sequence.

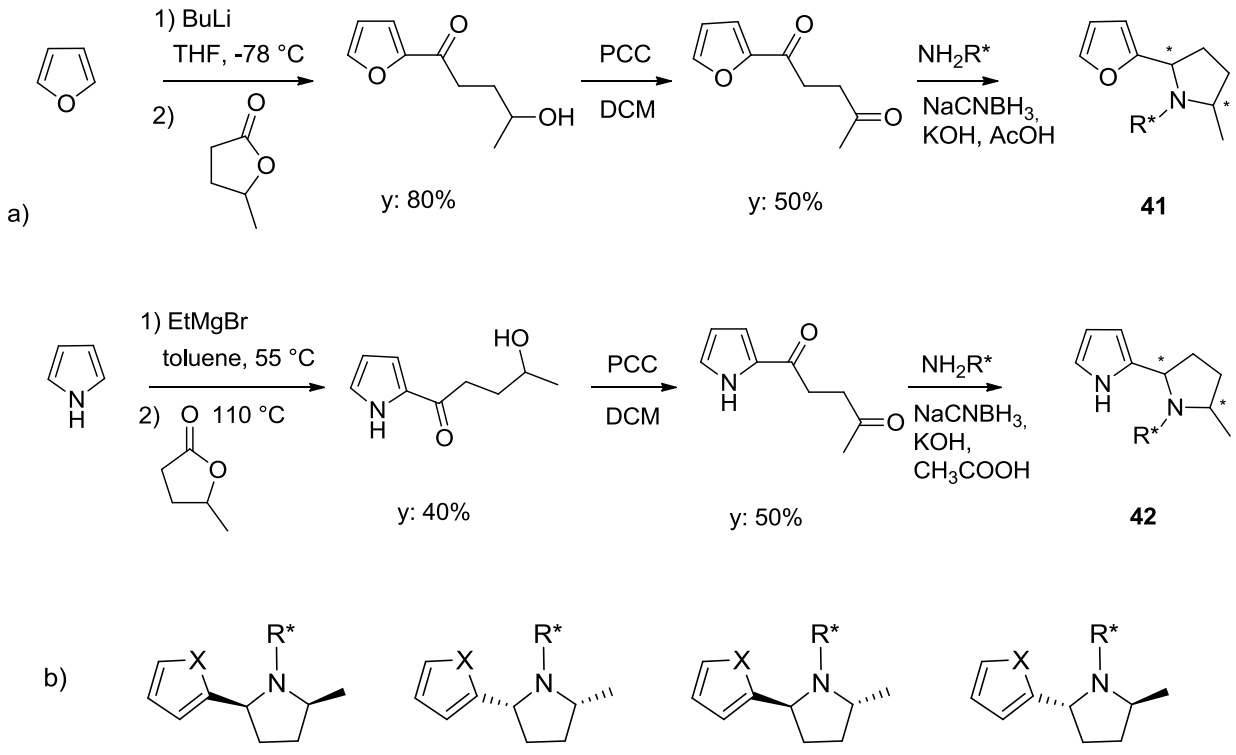
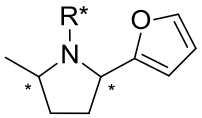


Figure 91. a) Synthesis of new disubstituted pyrrolidines 42. b) The four diastereoisomers of compounds 41 and 42.

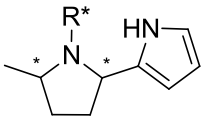
After the lactone ring opening step, the γ-hydroxy ketones were oxidized to obtain the required 1,4-diketones; then, the reductive amination step was carried on by the previously applied protocol. In this case, the 1,2,5-trisubstituted pyrrolidine could be generated as up to four diasteroisomers (Figure 26b). However, GC-MS analysis of the crude reaction mixtures showed in some cases the presence of only two or three peaks. We can not exclude, however, that minor amounts of other diastereoisomer(s) could be present but were eluted together with the prevalent ones.

The four diastereoeisomers can be distinguished as *cis* and *trans*, considering the relative orientation of the two substituents at the C-2 and C-5 positions. Our hypothesis, analogous to that advanced for the symmetrically 2,5-disubstituted pyrrolidines, is that two of the major components the mixture are *cis* isomers. Since the reactions were performed in a very small scale, we did not attempt to separate the diastereoisomers for a more safe identification.

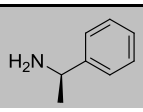
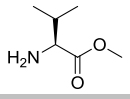
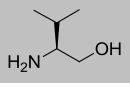
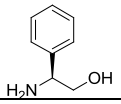
Table 18. Synthesis of 1-substituted 2-furyl-5-methylpyrrolidine and 5-methyl-2-pyrrolylpyrrolidine by reductive amination with chiral amines.



41a-d



42a-d

Entry	Product, Yield (%)	d.r.[b]	Amine	Entry	Product, Yield (%)	d.r.[b]
1	**41a**, 85	31/51/18		**5**	**42a**, 75	45/45/5/5
2	**41b**, 80	29/41/39		**6**	**42b**, 80	27/34/39
3	**41c**, 55	31/43/26[c]		**7**	**42c**, 40	25/30/45[c]
4	**41d**, 60	50/35/7/8[c]		**8**	**42d**, 50	45/55[c]

[a] Reaction condition: 1 equiv diketone, 1.1 equiv amine, 6 equiv $NaCNBH_3$, 0.5 equiv KOH, 1 equiv AcOH, EtOH, 70 °C, 2 d. [b] Determined by GC-MS. [c] Determined by GC-MS after reaction with TBDMSCl

2.4 Removal of the chiral auxiliary

The diasteroisomers of compounds **37a-h** and **40a-h** could be separated by flash cromatografy. On the other hand, separation of diastereoisomers of **41a-d** and **42a-d** was very difficult and only one compound could be isolated in a pure state. Removal of the chiral auxiliary from a pure diastereoisomer would give an enantiomerically pure pyrrolidine, whose absolute configuration should be determined by comparison of the optical rotation with that of the authentic compound, or by analogy with similarly substituted pyrrolidines.[190]

For this reason we focused our attention on the removal of the chiral auxiliary of isolated N-substituted pyrrolidines. Concerning the removal of valinol group, Savoia used an oxidative protocol with periodic acid and methylamine.[191] The mechanism of such oxidative cleavage was described by Coates[192] and involves formation of an imminium ion, whose hydrolysis forms the free amine and isobutyrraldehyde, which is captured by methylamine (Figure 27).

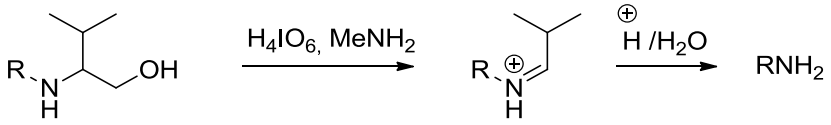


Fig 92. Remotion auxiliary mechanism

For this reason we reduced the methyl ester group of **37c** using $LiAlH_4$ to obtain the corresponding alcohol (Fig 28). Unfortunately, the oxidative cleavage failed on our substrate.

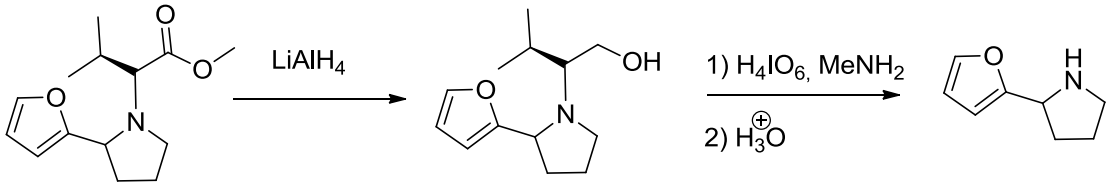


Fig 93. Envisioned removal of valine methylester or valinol.

At the same time we tested an alternative procedure:[193] we firstly hydrolyzed the ester group to the corresponding acid **37c**, which was then reacted with $POCl_3$ for the decarboxylation step proceeding through the formation of the enamine/iminium intermediates followed by hydrolysis to give the NH-free pyrrolidine (Fig 29).

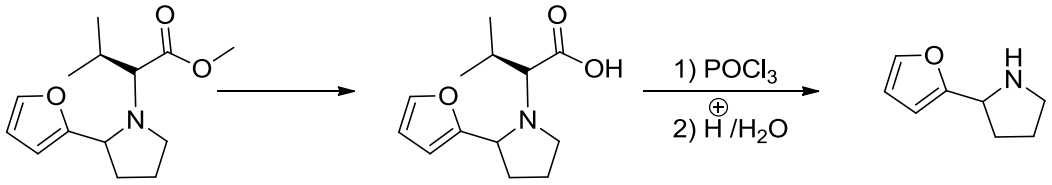


Fig 94. Hydrolysis of ester and removal of the chiral auxiliary.

However, the ester hydrolysis was problematic and gave poor results in different basic conditions. Considering our experience[194] on the reductive hydrogenolysis of benzylic amines, we applied the known protocols to the phenyl glycinol **37e** and phenylethylamine derivatives **37e** and **37b**, respectively. Normally these particular auxiliaries are removed by Pd/C catalyzed hydrogenolysis under hydrogen pressure in neutral or acidic medium.

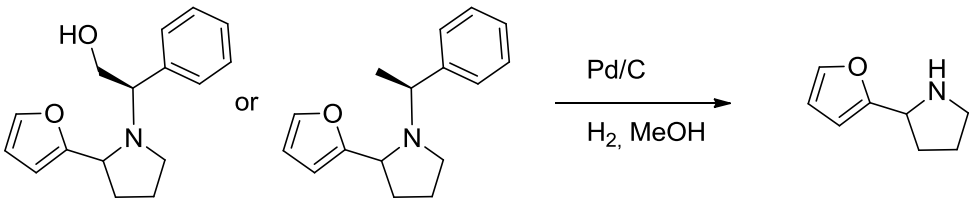


Fig 95. Envisioned hydrogenolysis of benzylic amines.

Surprising results were observed during the hydrogenation of compound **37b** in standard conditions. The ^{1}H NMR analysis of the product showed a complete conversion of the starting material into a new product where the furan signals were absent, wheres the molecular weight determined by HPLC-MS analysis was consistent simply with an uptake of six hydrogen atoms, rather than with the removal of the *N*-substituent. The novel product **43** was formed by full hydrogenation of the heterocyclic ring and reductive cleavage of the substituted C-O bond (Fig 31).

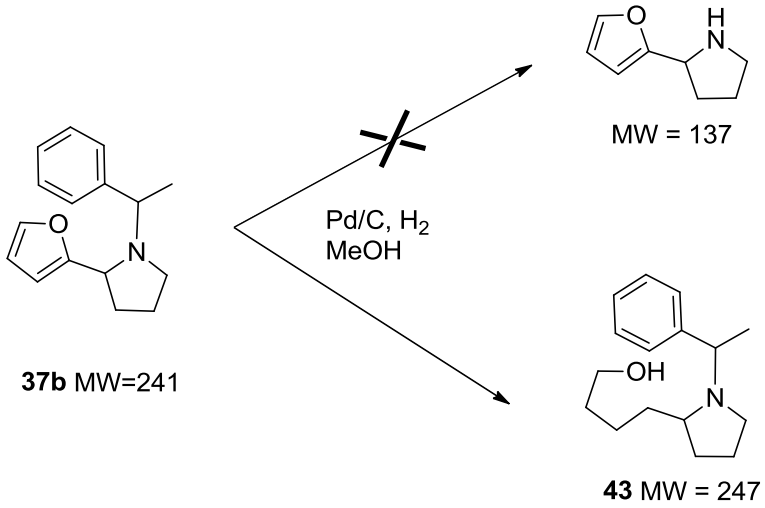
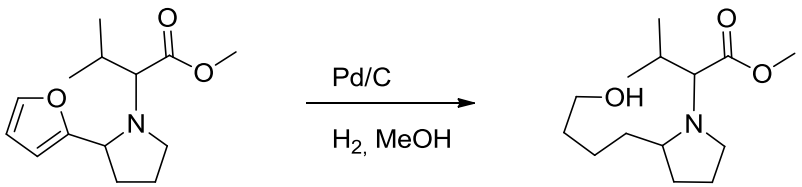


Fig 96. Hydrogenaion-hydrogenolysis of a substituted furan ring.

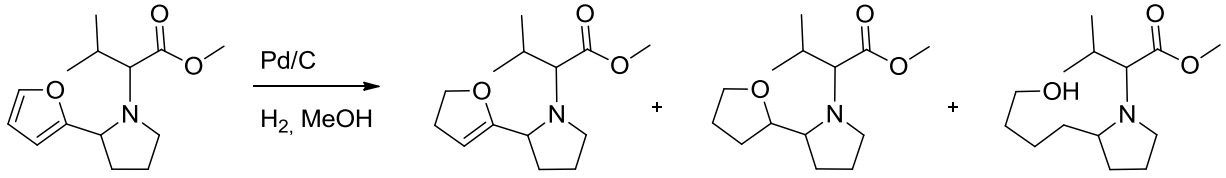
Moreover, we successively observed that the same unexpected reaction occurred when the hydrogenolysis conditions were applied to substrate **37c** which underwent conversion to substituted pyrrolidine **44**. (Figure 32).



37c MW = 251 **44** MW = 257

Fig 97. Hydrogenaion-hydrogenolysis of a substituted furan ring.

We observed that using a low amount of 10%Pd/C (5% mol), the rate of the reaction decreased, so that we could monitor its progress by ^{1}H NMR and GC-MS analysis of samples, and observed the formation of the intermediate hydrogenated product (Fig 33).



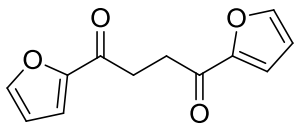
MW=251 MW=253 MW=255 MW=257

Fig 33. Intermediate hydrogenation product

SUPPORTIN INFO

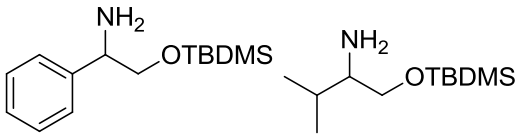
General Methods. Chemical shifts are reported in ppm from TMS with the solvent resonance as the internal standard (deuterochloroform: δ 7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = duplet, t = triplet, q = quartet, bs = broad singlet, m = multiplet), coupling constants (Hz). Chemical shifts are reported in ppm from TMS with the solvent as the internal standard (deuterochloroform: δ 77.0 ppm). GC_MS spectra were taken by EI ionization at 70 eV. They are reported as m/z (relative intensity). Chromatographic purification was done with 240_400 mesh silica gel. Determination of enantiomeric excess was performed on HPLC instrument equipped with a variable-wavelength UV detector, using a DAICEL Chiralpak columns (0.46 cm i.d. _25 cm) and HPLC-grade 2-propanol and n-hexane were used as the eluting solvents. Optical rotations were determined in a 1 mL cell with a path length of 10 mm (NaD line). Melting points are not corrected. Materials: All reactions were carried out under inert gas and under anhydrous conditions. Commercially available anhydrous solvents were used avoiding purification.

General Procedure for the synthesis of 2,5difuryl pyrrolidine



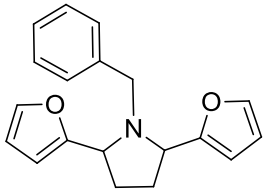
77

Procedure to synthesize of starting material 1,4-difuryl-1,4- butanedione(77): The compound **77** is the same previously describe in the synthesis of the triaromatic unit starting material in the diformylation reaction for the synthesis of triaromatic macrocycle **81** in subchapter 1.3.3



General Sililation procedure of phenyl glycinol and valynol: An aminoalcohol (1eq) was dissolved in DCM and TEA (1eq), DMAP (0.1eq) and terbutyldimethylsilil chloride (1 eq) were added. After 12h the reaction mixture was quenched by a saturated solution of $NaHCO_3$ end extract in DCM. All the organic fases were collected and concentrate to obtain the desired product in very good yields (90%).

General Procedure for the synthesis of 2,5difuryl pyrrolidine: In a vials the difuryldiketon (1 eq) was dissolved in EtOH and KOH (0.5 eq) and Aceticacid (1eq) was added to the mixture. $NaCNBH_3$ (6eq) and finally the amine were added and the reaction mixture was heated to 70°C. The progress of the reaction was monitored by TLC and after 3 days the reaction mixture was quenched by a saturated solution of $NaCO_3$ and water and extract with EtOAc (3 times). The crude product was purified by flash column chromatography (cyclohexane/EtOAc, 98/2 to 90/10).

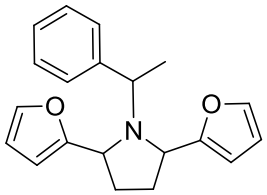


34b

34b:Compound **34c** was prepared according to the general procedure. Amount of reagents included 30 mg (0.14 mmol) of difuryldiketon , 4 mg (0.07 mmol) of KOH, 10 µl (0.14 mmol) of Acetic acid, 53 mg (0.84 mmol) $NaCNBH_3$ and 17 µl (0.14 mmol) of benzylamine in 3ml of EtOH. Compound **34b** (24 mg, 0.08 mmol, 60%) was obtained as yellow oil. Dr =60/40 was determined by GC-MS.

Major diasteroisomer: ^{1}H NMR ($CDCl_3$, 400 MHz): δ= 2.00-2.15 (m, 4H), 3,76 (s, 2H), 3.85 (t, *J* = 5.4 Hz, 2H), 6.24 (d, *J* = 3.0 Hz, 2H), 6.27 (t, *J* = 2.0 Hz, 2H), 7.10-7.22 (m, 5H), 7.35 (s, 2H). GC-MS m/z = 307 (10), 292 (60), 230 (10), 202 (30), 187 (50), 105 (100), 77 (70).

Minor diasteroisomer: ^{1}H NMR ($CDCl_3$, 400 MHz): δ= 2.00-2.10 (m, 2H), 2.39-2.47 (m, 2H), 3.09 (d, *J* = 13.8 Hz, 2 H), 3.68 (d, *J* = 13.8 Hz, 2 H), 4.18-4.40 (m, 2 H), 6.12 (d, *J* = 3 Hz, 2 H), 6.32 (t, *J* = 2 Hz, 2 H), 7.13 (s, 2H), 7.15 (s, 1H), 7.24(s, 2H), 7.41 (s, 2 H) ppm.

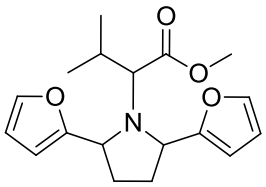


34c

34c:Compound **34c** was prepared according to the general procedure. Amount of reagents included 30mg (0.14 mmol) of **77** , 4 mg (0.07 mmol) of KOH, 10 µl (0.14 mmol) of Acetic acid, 53 mg (0.84 mmol) $NaCNBH_3$ and 17 µl (0.14 mmol) of S-methylbenzylamine in 3ml of EtOH. Compound **34c** (33 mg, 0.11 mmol, 80%) was obtained as yellow oil. Dr = 90/10 (determined by GC-MS).

Major diasteroisomer: ^{1}H NMR ($CDCl_3$, 400 MHz): δ= 1.29 (d, *J* = 7 Hz, 3 H), 1.77-1.83 (m, 1 H), 1.91-1.97 (m, 3H), 3.99-4.05 (m, 2H), 4.19 (dd, *J* = 4.5 Hz, *J* = 8 Hz, 1 H), 6.25 (d, *J* = 3.12 Hz, 1 H), 6.29-6.30 (m, 3H), 7.25-7.28 (m, 5 H), 7.33-7.34 (m, 2 H). ^{13}C NMR ($CDCl_3$,

100 MHz): δ=159.4, 157.9, 141.6, 141.2, 140.9, 128.1, 127.9, 126.7, 58.7, 58.1, 56.8, 31.3, 31.0, 18.6.

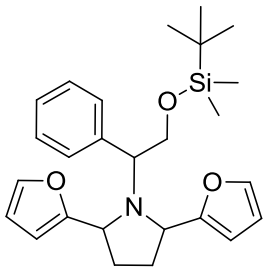


34d

34d:Compound **34d** was prepared according to the general procedure. Amount of reagents included 30mg (0.14 mmol) of difuryldiketon, , 4 mg (0.07 mmol) of KOH, 10 µl (0.14 mmol) of Aceticacid, 53 mg (0.84 mmol) $NaCNBH_3$, 23 mg (0.14 mmol) of valine methylester hydrochloride and 20 µl (0.14 mmol) of TEA in 3ml of EtOH. Compound **34d** (34 mg, 0.11 mmol, 80%) was obtained as yellow oil. Dr = 83/17(determined by GC-MS).

Major diasteroisomer: ^{1}H NMR ($CDCl_3$, 400 MHz): δ= 0.68 (d, *J* = 6.5 Hz , 3H), 0.75 (d, *J* = 6.5 Hz , 3H), 1.80-1.90 (m, 1H), 1.91-1.98 (m, 1H), 2.01-2.12 (m, 2H),2.13-2.23(m, 1H), 3.05 (d, *J* = 10.4 Hz, 1H), 3.75 (s, 3H), 4.04 (dd, *J* = 6 Hz, *J* = 3.5 Hz, 1H), 4.73 (dd, *J* = 2.8 Hz, *J* = 5 Hz, 1H), 6.25 (d, *J* = 3 Hz, 1H), 6.29 (dd, *J* = 1.8 Hz, *J* = 1.3 Hz, 1H), 6.31 (d, *J* = 3 Hz, 1H), 6.34 (dd, *J* = 1.8 Hz, *J* = 1.3 Hz, 1H), 7.33 (dd, *J* = 1 Hz, 1H), 7.39 (dd, *J* = 1 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ=198.1, 173.7, 159.6, 157.0, 141.7, 140.9, 110.1, 110.0, 106.2, 105.8, 69.6, 61.8, 55.3, 50.9, 32.0, 30.9, 29.4, 20.0 ppm.

Minor diasteroisomer: ^{1}H NMR ($CDCl_3$, 400 MHz): δ= 0.76 (d, *J* = 6.5 Hz, 3H), 0.83 (d, *J* = 6.5 Hz, 3H), 1.90-2.00 (m, 3H), 2.42-2.50 (m, 2H), 3.40 (s, 3H), 4.53-4.58 (m, 2H), 6.15 (d, *J* = 3.2 Hz, 2H), 6.31 (dd, *J* = 1.8 Hz, *J* = 1.3 Hz, 2H), 7.34 (s, 2H) ppm.^{13}C NMR ($CDCl_3$, 100 MHz): δ=157.4, 141.2 (2C), 109.8 (2C), 106.9 (2C), 64.8, 55.7 (2C), 50.9, 30.4 (2C), 29.7, 20.1 ppm.

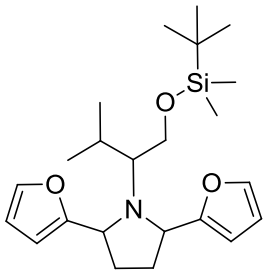


34e

34e:Compound **34e** was prepared according to the general procedure. Amount of reagents included 30mg (0.14 mmol) of **77**, , 4 mg (0.07 mmol) of KOH, 10 µl (0.14 mmol) of Acetic acid, 53 mg (0.84 mmol) $NaCNBH_3$ and 34 mg (0.14 mmol) of *O*-*t*-butyldimethylsilyl (*S*)-phenylglycinol in 3ml of EtOH. Compound **34e** (33 mg, 0.11 mmol, 80%) was obtained as yellow oil. Dr = 93/7(determined by GC-MS)

Major diasteroisomer: ^{1}H NMR ($CDCl_3$, 400 MHz): δ= -0.14 (d, *J* = 10.04 Hz, 6 H), 0.72 (s, 9 H), 1.78-1.82(m, 1H), 1.90-1.99 (m, 4H), 3.69 (dd, *J* = 8 Hz, *J* = 10.32 Hz, 1 H), 3.83 (dd, *J* = 6 Hz, *J* = 10.4 Hz, 1 H), 3.98 (dd, *J* = 6.06 Hz, *J* = 7.88 Hz, 1 H), 4.19 (t, *J* = 7 Hz, 1 H), 4.23 (dd, *J* = 5.16 Hz, *J* = 8 Hz, 1 H), 6.26 (d, *J* = 3 Hz, 1 H), 6.29 (d, *J* = 1.8 Hz, 1 H), 6.31 (bs, 2H), 7.20-7.26 (m, 4H), 7.34 (s, 2H), 7.36 (bs, 1H).

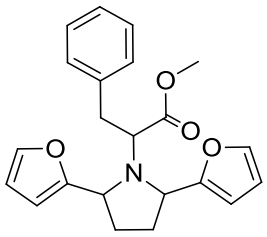
Minor diasteroisomer: ^{1}H NMR ($CDCl_3$, 400 MHz): δ= 0.01 (d, *J* = 6 Hz, 6 H), 0.88 (s, 9 H), 1.25 (s, 2H), 1.55-1.75 (m, 2H), 3.50-3.68 (m, 3H),3.72-3.82 (m, 2H), 6.09 (d, *J* = 3.04 Hz, 2H), 6.29 (dd, *J* = 1.08 Hz, *J* = 3.04 Hz, 2H), 7.25-7.40 (m, 7H).



34f

34f:Compound **34f** was prepared according to the general procedure. Amount of reagents included 30mg (0.14 mmol) of **77** , 4 mg (0.07 mmol) of KOH, 10 µl (0.14 mmol) of Acetic acid, 53 mg (0.84 mmol) $NaCNBH_3$ and µl (0.14 mmol) of *O*-*t*-butyldimethylsilyl (*S*)-valinol in 3ml of EtOH. Compound **34f** (16 mg, 0.04 mmol, 300%) was obtained as yellow oil. Dr = 90/10 was determined by GC-MS.

Mix of diasteroisomer: ESI-MS *m/z*: 404.1 $[M+ H]^+$.

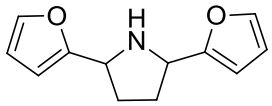


34g

34g:Compound **34g** was prepared according to the general procedure. Amount of reagents included 30mg (0.14 mmol) of **77** , 4 mg (0.07 mmol)of KOH, 10 µl (0.14 mmol) of Aceticacid, 53 mg (0.84 mmol) $NaCNBH_3$ and 30 mg (0.14 mmol) of phenylalanine methylester hydrochloride and 20 µl (0.14 mmol) of TEA in 3ml of EtOH. Compound **34g** (40 mg, 0.11 mmol, 80%) was obtained as yellow oil. Dr = 70/30 (determined by GC-MS)

Major diasteroisomer: ^{1}H NMR ($CDCl_3$, 400 MHz): δ= 1.95-2.01 (m, 1 H), 2.04-2.20 (m, *J*3H), 2.78 (dd, *J* = 6.88 Hz, *J* = 14 Hz, 1 H), 2.90-3.00 (m, 1 H), 3.62 (s, 1H), 3.81 (t, *J* =

7.32 Hz, 1H), 4.09 (dq, *J* = 2.64 Hz, *J* = 7.08 Hz, *J* = 14.2 Hz, 1 H), 4.19 (t, *J* = 7.96 Hz, 1H), 4.63 (dd, *J* = 2.56 Hz, *J* = 7.52 Hz, 1 H), 6.05 (s, 1H), 6.19 (s, 1H), 6.26 (s, 2H), 6.89 (d, *J* = 85.92 Hz, 2 H), 7.09-7.18 (m, 3 H), 7.34 (s, 2H).



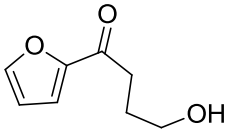
34a

34a:Compound **34a** was prepared according to the general procedure. Amount of reagents included 30mg (0.14 mmol) of difuryldiketon , 4 mg (0.07 mmol) of KOH, 10 μl (0.14 mmol) of Acetic acid, 53 mg (0.84 mmol) $NaCNBH_3$ and 11 mg (0.14 mmol) of NH_4OAc in 3ml of EtOH. Compound **34a** (14 mg, 0.07 mmol, 50%) was obtained as yellow oil. Dr = 50/50 was determined by GC-MS.

Cis: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.02-2.10 (m, 2 H), 2.12-2.20 (m, 1 H), 2.2.22-2.32 (m, 1H), 2.70 (s, 1H, NH), 4.31 (t, *J* = 5.6 Hz, 1H), 4.45 (t, *J* = 5.76 Hz, 1 H), 6.17 (d, *J* = 3.16 Hz, 1 H), 6.18 (d, *J* = 3,12 Hz, 1 H), 6.28 (s, 2H), 7.33 (s, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ=157.2, 156.6, 141.5, 141.4, 109.9, 109.9, 105.2, 104.9, 56.0, 54.8, 30.6, 30.4 ppm. GC-MS (EI): m/z = 91 (100), 174 (95), 202 (35), 65 (30), 77 (15).

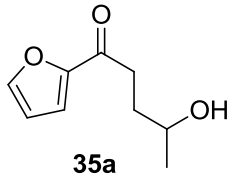
Trans: ^{1}H NMR ($CDCl_3$, 400 MHz): δ= 1.90-2.10 (m, 4 H), 3.10 (bs, 1H, NH), 4.74 (s, 2 H), 6.22 (d, *J* = 3.16 Hz, 2 H), 46.30 (s, 2 H), 7.34 (*s*, 2 H).

General Procedure for the starting material synthesis: At a solution of furan (1eq) in THF at -78°C under Ar atmosphere was added under magnetical stirring a 2M n-BuLi in n-hexane (1eq). After 1h all the solution was added dropwise to a lactone solution (1.1eq) in THF at -78°C. After 5h the reaction was quenched by NH_4Cl and exatracted by Ethylacetate (3x20ml), all the organic fases were collected, dried over Na_2SO_4, and concentrated to obtain the crude product. The mixture was purify by flash chromatography to obtain the final product.



35

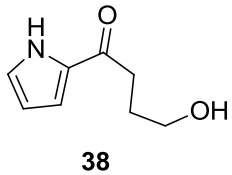
35: After flash cromatography (cyclohexane/ethylacetate, 80/20 to 50/50), the product was obtain at orange oli in 70% yield.[195]



35a

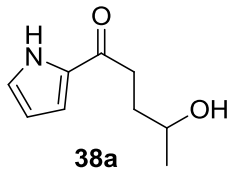
XX: After flash cromatography (cyclohexane/ethylacetate, 80/20), the product was obtain at orange oli in 70% yield : ^{1}H NMR ($CDCl_3$, 400 MHz): δ= 1.20 (d, *J* = 13.2 Hz, 6.2 H), 1.75-1.95 (m, 2H), 2.40 (s, 1H, OH), 2.95 (dt, *J* = 2.36 Hz, *J* = 7.36 Hz, 2 H), 3.80-3.90 (m, 1H), 6.50 (dd, *J* = 1.68 Hz, *J* = 3.52 Hz, 1 H), 7.19 (d, *J* = 3.52 Hz, 1 H), 7.56 (s, 1H).

General Procedure for the starting material synthesis: At a solution of pyrrole (1eq) in THF/toluene at 50°C under Ar atmosphere was added under magnetical stirring a 2M solution of EtMgBr in THF (1eq). After 1h a lactone solution (1.1eq) in THF was added drop by drop to the mixture at 50°C. The reaction was warmed to100°C for 24h, finally the reaction was quenched by saturated solution of $NaHCO_3$ and extracted by Ethylacetate (3x20ml), all the organic fases were collected, dried over Na_2SO_4, and concentrated to obtain the crude product. The mixture was purify by flash chromatography to obtain the final product.



38

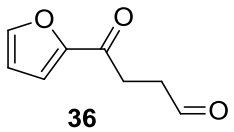
XX: After flash cromatography (cyclohexane/ethylacetate, 80/20, to 50/50), the product was obtain at pink oil in 45% yield : ^{1}H NMR ($CDCl_3$, 200 MHz): δ= 2.00 (t, *J* = 8 Hz, 2H), 2.60 (bs, 1H, OH), 3.00 (t, *J* = 8 Hz, 2H), 3.75 (t, *J* = 8 Hz, 2H), 6.30 (s, 1H), 7.00 (s, 1H), 7.08 (s, 1H), 10.05 (bs, 1H, NH).



38a

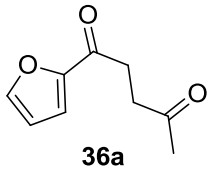
XX: After flash cromatography (cyclohexane/ethylacetate, 70/30 to 40/60), the product was obtain at yellow oil in 60% yield : ^{1}H NMR ($CDCl_3$, 200 MHz): δ= 2.20 (s, 3 H), 2.86 (t, *J* = 13.2 Hz, 2 H), 3.10 (t, *J* = 12.8 Hz, 2 H), 6.30 (s, 1 H), 6.98 (s, 1 H), 7.02 (s, 1 H), 9.41 (bs, 1H, NH).^{13}C NMR ($CDCl_3$, 100 MHz): δ=195.2, 131.7, 124.9, 116.6, 110.6, 67.5, 34.3, 33.8, 23.6 ppm.

General Procedure for the oxidation process: The ketoalcohol (1 eq) compound was dissolved in DCM and an excess of PCC (1,5 eq) was added and the reaction mixture was stirred at rt. After 12h SiO_2 was added to the mixture and the solvent was removed by evaporation to obtain the solid mixture that was directly purify by flash chromatography to achieve the desired product.



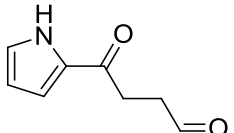
36

36: After flash cromatography (cyclohexane/ethylacetate, 90/10), the product was obtain at orange oli in 60% yield : ^{1}H NMR ($CDCl_3$, 400 MHz): δ= 2.87 (t, *J* = 6.04 Hz, 3 H), 3.15 (t, *J* = 6.24 Hz, 1 H), 6.51 (dd, *J* = 1.72 Hz, *J* = 3.6 Hz, 1 H), 7.19 (d, *J* = 3.56 Hz, 1 H), 7.56 (s, 1 H), 9.83 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ= 200.2, 187.0, 152.2, 146.4, 117.1, 112.3, 37.2, 30.6 ppm.



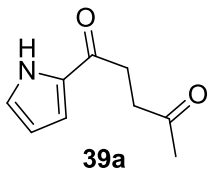
36a

36a: After flash cromatography (cyclohexane/ethylacetate, 90/10), the product was obtain at yellow solid in 60% yield ^{1}H NMR ($CDCl_3$, 200 MHz): δ=2.19(s, 3H), 2.87 (t, *J* = 6.04 Hz, 3 H), 3.14 (t, *J* = 6.24 Hz, 1 H), 6.51 (dd, *J* = 1.72 Hz, *J* = 3.6 Hz, 1 H), 7.19 (d, *J* = 3.56 Hz, 1 H), 7.56 (s, 1 H), 9.83 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ= 206.9, 187.6, 152,4, 146.3, 116.9, 112.2, 36.6, 32.0, 29.9 ppm. GC-MS (EI) m/z: 95 (100), 124 (20), 166 (10).



39

39: After flash cromatography (cyclohexane/ethylacetate, 80/20, to 50/50), the product was obtain at pink solid in 50% yield : ^{1}H NMR ($CDCl_3$, 200 MHz): δ= 2.85 (t, *J* = 6.04 Hz, 2 H), 3.19 (t, *J* = 6.24 Hz, 2 H), 6.28 (s, 1 H), 6.98 (s, 1 H), 7.05 (s, 1 H), 9.85 (s, 1H), 9.93 (bs, 1H, NH).

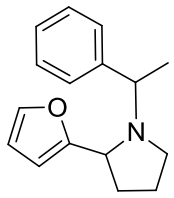


39a

39a: After flash cromatography (cyclohexane/ethylacetate, 80/20), the product was obtain at orange oli in 50% yield : ^{1}H NMR ($CDCl_3$, 200 MHz): δ= 2.20 (s, 3 H), 2.86 (t, *J* = 6.04 Hz,

2 H), 3.10 (t, *J* = 6.24 Hz, 2 H), 6.30 (s, 1 H), 6.98 (s, 1 H), 7.02 (s, 1 H), 9.41 (bs, 1H, NH), 9.90 (s, 1H).

General Procedure for the synthesis of 2-furyl pyrrolidine: In vials the **36** (1 eq) was dissolved in EtOH and KOH (0.5 eq) and Acetic acid (1eq) was added to the mixture. $NaCNBH_3$ (6eq) and finally the amine were added and the reaction mixture was heated to 70°C. The progress of the reaction was monitored by TLC and after 1 days the reaction mixture was quenched by a saturated solution of $NaCO_3$ and water and extract with EtOAc (3 times). The crude product was purified by flash column chromatography (cyclohexane/EtOAc, 98/2 to 90/10).

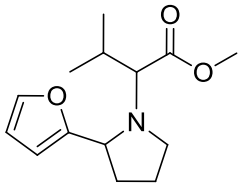


37b

37b:Compound **37b** was prepared according to the general procedure. Amount of reagents included 20 mg (0.13 mmol) of **36**, 4 mg (0.07 mmol) of KOH, 8 µl (0.13 mmol) of Acetic acid, 49 mg (0.78 mmol) $NaCNBH_3$ and 16 µl (0.13 mmol) of S-methylbenzylamine in 3ml of EtOH. Compound **37b** (26 mg, 0.11 mmol, 80%) was obtained as yellow oil. Dr = 33/67 (determined by GC-MS)

Major diasteroisomer: ^{1}H NMR ($CDCl_3$, 400 MHz): δ= 1.38 (d, *J* = 6.64 Hz , 3 H),1.75-1.185 (m, 1H), 1.90-2.00 (m, 2H), 2.07-2.17 (m, 1H), 2.58 (q, *J* = 8 Hz, *J* = 14.9 Hz, 1 H), 2.80-2.87 (m, 1H), 3.57 (q, *J* = 6.56 Hz, *J* = 13.12 Hz, 1 H), 4.08 (dd, *J* = 4.12 Hz, *J* = 8.52 Hz, 1 H), 6.00 (d, *J* = 8.4 Hz, 2 H), 6.23-6.25 (m, 1H), 7.15-7.31 (m, 5H), 7.32 (s, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ=144.6, 141.1, 128.1, 127.9 (2C), 127.5 (2C), 109.8, 106.3, 60.1, 58.1, 49.3, 31.1, 22.8, 18.3ppm. GC-MS (EI): m/z= 241 (10), 226(100), 105 (50), 77 (50), 91(40.)

Minor diasteroisomer: ^{1}H NMR ($CDCl_3$, 400 MHz): δ= 1.36 (d, *J* = 6.8 Hz, 3 H), 1.50-1.70 (m, 2H), 1.85-2.00 (m, 2H), 2.45-2.55 (m, 1H), 2.90-3.10 (m, 1H), 3.60-3.75 (m, 2H), 6.14 (s, 1H), 6.33 (s, 1H), 7.25 (s, 2H), 7.31(s, 1H), 7.33 (s, 2H), 7.39 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ=151.0, 141.3, 128.1(3C), 127.9 (2C), 109.8, 106.2, 59.6, 59.0, 48.5, 43.3, 22.5, 21.9 ppm.

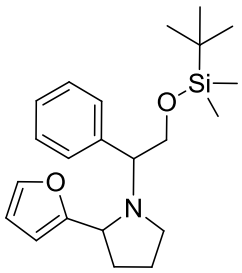


37c

37c:Compound **37c** was prepared according to the general procedure. Amount of reagents included 20mg (0.13 mmol) of **36** , 4 mg (0.07mmol) of KOH, 8 µl (0.13 mmol) of Acetic acid, 49 mg (0.78 mmol) $NaCNBH_3$ and 22 mg (mmol) of valinemethylester.hydrochloride, 18 µl (0.13 mmol) of TEA in 3ml of EtOH. Compound **37c** (27 mg, 0.11 mmol, 80%) was obtained as OIL. Dr=90/10(determined by GC-MS).

Major diasteroisomer: ^{1}H NMR ($CDCl_3$, 400 MHz): δ= 0.82 (d, *J* = 6.6 Hz, 3H), 0.94 (d, *J* = 6.64 Hz, 3 H), 1.72-2.05 (m, 5H), 2.82-2.92 (m, 2H), 3.00-3.07 (m, 1H), 3.72 (s, 3H), 2.81 (t, *J* = 7.56 Hz, 1 H), 6.18 (d, *J* = 3.12 Hz, 1 H), 6.30 (dd, *J* = 1.84 Hz, *J* = 3.12 Hz, 1 H), 7.35 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ=172.8, 156.7, 141.5, 109.8, 106.4, 67.7, 58.9, 50.5, 45.8, 31.2, 28.6, 23.2, 19.8, 19.5 ppm. GC-MS (EI): m/z= 192(100), 121 (30), 208 (20).

Minor diasteroisomerδ= 0.80 (dd, *J* = 10.8 Hz, *J* = 6.68 Hz, 6 H), 1.73-1.82 (m, 1 H), 1.85-2.10 (m, 5H), 2.74 (q, *J* = 7.76 Hz, *J* = 15.4 Hz, 1 H), 3.00 (d, *J* = 18.64 Hz, 2 H), 3.10-3.17 (m, 1H), 3.59 (s, 3H) 4.16 (dd, *J* = 3.56 Hz, *J* = 7.92 Hz, 1 H), 6.07 (d, *J* = 3.12 Hz, 1 H), 6.24 (dd, *J* = 1.88 Hz, *J* = 3.12 Hz, 1 H), 7.30 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ=173.5, 158.2, 141.2, 109.8, 106.1, 70.6, 56.6, 50.9, 50.8, 31.7, 29.1, 31.7, 29.1, 23.6, 20.0, 19.2 ppm.



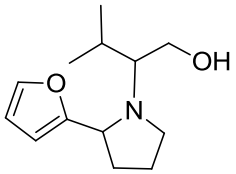
37e

37e:Compound **37e** was prepared according to the general procedure. Amount of reagents included 20mg (0.13 mmol) of **36**, 4 mg (0.07 mmol) of KOH, 8µl (0.13 mmol) of Acetic acid, 49 mg (0.78 mmol) $NaCNBH_3$ and 7 mg (0.13mmol) of *O*-*t*-butyldimethylsilyl (*S*)-phenylglycinol in 3ml of EtOH. Compound **37e** (33 mg, 0.09 mmol, 70%) was obtained as OIL. Dr = 57/43 (determined by GC-MS)

Major diasteroisomer: ^{1}H NMR ($CDCl_3$, 400 MHz): δ= -0.18 (d, *J* = 7.88 Hz, 6 H), 0.72 (s, 9H), 1.68-1.75 (m, 1H), 1.80-2.00 (m, 3H), 2.56 (q, *J* = 7.32 Hz, *J* = 16 Hz, 1 H), 2.94 (dt, *J* = 4 Hz, *J* = 8.64 Hz, 1 H), 3.56 (dd, *J* = 5.64 Hz, *J* = 7.36 Hz, 1 H), 3.73 (dd, *J* = 7.48 Hz, *J* = 10.04 Hz, 1 H), 3.82 (dd, *J* = 4.52 Hz, *J* = 8.12 Hz, 1 H), 3.86 (dd, *J* = 5.56 Hz, *J* = 10.08 Hz, 1 H), 6.95 (d, *J* = 2.96 Hz, 1 H), 6.28 (dd, *J* = 1.84 Hz, *J* = 3.12 Hz, 1 H),7.20-7.30(m, 5H),

7.34 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ=157.6, 141.3, 139.6, 129.1(2C), 127.6 (2C), 126.9, 109.8, 106.6, 66.7, 66.3, 58.1, 49.4, 30.5, 25.7(3C), 22.8, 18.1, -5.7(2C) ppm. ESI-MS *m/z*: 169.1 $[M^{\square}+H]^+$, 191.1 $[M+Na]^+$.

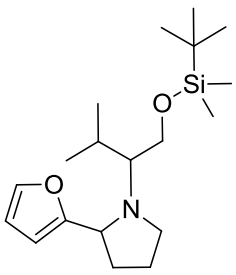
Minor diasteroisomer: ^{1}H NMR ($CDCl_3$, 400 MHz): δ= -0.09 (d, *J* = 7.88 Hz, 6 H), 0.78 (s, 9H), 1.75-1.82 (m, 1H), 1.85-1.95 (m, 2H), 1.97-2-07 (m, 1H), 2.74 (dd, *J* = 7.32 Hz, *J* = 14.88 Hz, 1 H), 2.90-3.00 (m, 1H), 3.65 (t, *J* = 6.08 Hz, 1 H), 3.77 (dd, *J* = 6.08 Hz, *J* = 10.04 Hz, 1 H), 4.05 (dd, *J* = 5.92 Hz, *J* = 10.04 Hz, 1 H), 4.12 (dd, *J* = 4.4 Hz, *J* = 8.4 Hz, 1 H), 5.91 (d, *J* = 2.84 Hz, 2 H), 6.18 (dd, *J* = 1.84 Hz, *J* = 3.12 Hz, 1 H), 7.13-7.22 (m, 5H), 7.31 (s, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ=157.5, 141.1, 141.0, 128.4 (2C), 127.6 (2C), 126.6, 109.8, 106.1, 66.7, 66.1, 58.8, 49.9, 31.1, 25.8 (3C), 23.0, 18.1, -5.6 (2C) ppm.



37f

37f:Compound **37f** was prepared according to the general procedure. Amount of reagents included 20mg (0.13 mmol) of **36** , 4 mg (0.07 mmol) of KOH, 8 μl (0.13 mmol) of Acetic acid, 49 mg (0.13 mmol) $NaCNBH_3$ and 28 mg (0.13 mmol) of (S)-valinol in 3ml of EtOH. Compound **37f** (30 mg, 0.09 mmol, 70 %) was obtained as OIL. Dr= 50/50 (determined by GC-MS).

Major diasteroisomer: ^{1}H NMR ($CDCl_3$, 400 MHz): δ= 7.40 (m, 2H), 6.30 (s, 1H), 3.73-3.66 (m, 1H), 3.35-3.23 (m, 1H), 2.26-1.86 (m, 6H), 0.92 (d, J=12.0Hz, 3H), 0.86(d, J=12.0Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ=157.7, 141.3, 110.0, 105.8, 65.6, 60.8, 55.0, 52.0, 32.2, 28.2, 23.6, 21.6, 19.7 ppm.

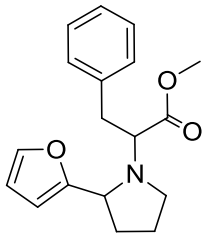


37g

37g:Compound **37g** was prepared according to the general procedure. Amount of reagents included 20mg (0.13 mmol) of **36**, 4 mg (0.07 mmol) of KOH, 8 μl (0.13 mmol) of Acetic acid, 49 mg (0.13 mmol) $NaCNBH_3$ and 28 mg (0.13 mmol) of *O*-*t*-butyldimethylsilyl (*S*)-valinol in 3ml of EtOH. Compound **37g** (30 mg, 0.09 mmol, 70 %) was obtained as OIL. Dr= 92/8 (determined by GC-MS)

Major diasteroisomer: ^{1}H NMR ($CDCl_3$, 400 MHz): δ= 0.03 (d, *J* = 2.12 Hz, 6), 0.77(d, *J* = 6.64 Hz, 1 H), 0.84 (d, *J* = 6.64 Hz, 1 H), 0.88 (s, 9 H), 1.65-1.80 (m, 2H), 1.81-1.90 (m, 2H), 1.93-2.05 (m, 1H), 2.27-2.33 (m, 1H), 2.81 (q, *J* = 7.76 Hz, *J* = 15.4 Hz, 1 H), 2.90-2.97 (m, 1H), 3.76 (dq, *J* = 3.76 Hz, *J* = 10.64 Hz, *J* = 18.64 Hz, 2 H), 4.16 (dd, *J* = 5.84 Hz, *J* = 8.08 Hz, 1 H), 6.11 (d, *J* = 3.12 Hz, 1 H), 6.25 (dd, *J* = 1.88 Hz, *J* = 3.12 Hz, 1 H), 7.30 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ=158.7, 141.1, 109.8, 105.9, 63.6, 61.0, 59.5, 57.0, 45.9, 31.3, 29.0, 25.9, 24.0, 20.3, -5.4 ppm.

Minor diasteroisomer^{1}H NMR ($CDCl_3$, 400 MHz): δ= 0.02 (d, *J* = 2.88 Hz, 6), 0.85-0.92 (m, *15* H), 1.75-195 (m, 3H), 1.97-2.09 (m, 1H), 2.35-2.40 (m, 1H), 2.89 (q, *J* = 7 Hz, *J* = 15.72 Hz, 1 H), 3.05-3.15 (m, 1H), 3.65 (d, *J* = 5.04 Hz, 2H), 4.26 (dd, *J* = 3.8 Hz, *J* = 8.48 Hz, 1 H), 6.12 (d, *J* = 3.2 Hz, 1 H), 6.27 (dd, *J* = 1.84 Hz, *J* = 3.12 Hz, 1 H), 7.31 (s, 1H).

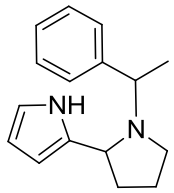


37h

37h:Compound **37h** was prepared according to the general procedure. Amount of reagents included 20mg (0.13 mmol) of **36** , 4 mg (0.07 mmol) of KOH, 8 μl(0.13 mmol) of Acetic acid, 49 mg (0.78 mmol) $NaCNBH_3$ and 28 mg (0.13 mmol) of phenylalanine methylester-hydrochloride, 18 μl (0.13 mmol) of TEA in 3ml of EtOH. Compound **37h** (26 mg, 0.09 mmol, 70%) was obtained as OIL. Dr= 75/25(determined by GC-MS).

Major diasteroisomer: ^{1}H NMR ($CDCl_3$, 400 MHz): δ= 1.40-160 (m, 3H), 1.61-1.75 (m, 1H), 2.47-255 (m, 2H), 2.72 (dd, *J* = 8.04 Hz, *J* = 13.68 Hz, 1 H), 2.79-2.85 (m, 1H), 3.24 (s, 3H), 3.56 (t, *J* = 7 Hz, 1 H), 5.47(d, *J* = 2.96 Hz, 1 H), 5.83 (bs, 1 H), 6.70-6.95 (m, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ= 172.7, 156.3, 141.7, 138.6, 129.1 (2C), 128.2 (2C), 126.3, 109.9, 106.6, 63.0, 59.1, 51.0, 46.8, 37.4, 31.3, 23.3 ppm.

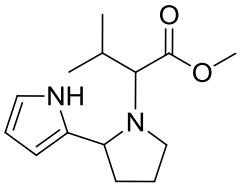
General Procedure for the synthesis of 2pyrrolyl pyrrolidine: In vials the starting material **39** (1 eq) was dissolved in EtOH and KOH (0.5 eq) and Acetic acid (1eq) was added to the mixture. $NaCNBH_3$ (6eq) and finally the amine were added and the reaction mixture was heated to 70°C. The progress of the reaction was monitored by TLC and after 2 days the reaction mixture was quenched by a saturated solution of $NaCO_3$ and water and extract with EtOAc (3 times). The crude product was purified by flash column chromatography (cyclohexane/EtOAc, 95/5 to 80/20).



40b

40b:Compound **40b** was prepared according to the general procedure. Amount of reagents included 20 mg (0.13 mmol) of **39** , 4 mg (0.07 mmol) of KOH, 8 µl (0.13 mmol) of Acetic acid, 49 mg (0.78 mmol) $NaCNBH_3$ and 16 µl (0.13 mmol) of S-methylbenzylamine in 3ml of EtOH. Compound **40b** (21 mg, 0.09 mmol, 70%) was obtained as yellow oil. Dr = 66/34(determined by NMR).

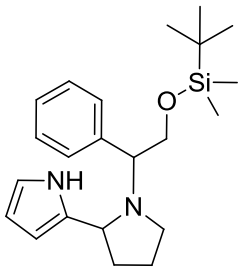
Identification signal of Mix of diasteroisomers: ^{1}H NMR ($CDCl_3$, 400 MHz): δ= 1.30 (d, *J* = 6.84 Hz,3H, Maj), 1.32 (d, *J* = 6.69 Hz, 3 H, Min), 3.61-370 (m, 5H, Maj) 3.81 (q, *J* = 6.76 Hz, *J* = 13.52 Hz, 1 H, Min), 3.91 (dd, *J* = 5.84 Hz, *J* = 7.96 Hz, 1 H, min), 5.97 (bs, 1H, Min), 6.01 (bs, 1H, Maj)6.09 (q, *J* = 2.72 Hz, *J* = 5.84 Hz, 1 H), 6.17 (q, *J* = 2.72 Hz, *J* = 5.84 Hz, 1 H), 6.68 (q, *J* = 2.56 Hz, *J* = 4.08 Hz, 1H, Min), 6.73 (q, *J* = 2.56 Hz, *J* = 4.04 Hz, 1H, Maj), 715-7.35 (m, 5H maj+5Hmin, mix), 8.45 (bs, 1H, NH, Min), 8.55 (bs, 1H, NH, Maj). ^{13}C NMR ($CDCl_3$, 100 MHz): δ=128.2, 128.0, 127.9, 127.4, 126.9, 126.3, 116.3, 115.9, 108.1, 107.9, 105.2, 104.8, 59,7, 58.45, 58.43, 58.3, 57.2, 48.5, 46.7, 33.6, 22.9, 21.44, 21.41, 13.3 ppm.



40c

40c:Compound **40c** was prepared according to the general procedure. Amount of reagents included 20mg (0.13 mmol) of **39**, 4 mg (0.07mmol) of KOH, 8 µl (0.13 mmol) of Acetic acid, 49 mg (0.78 mmol) $NaCNBH_3$ and 22 mg (mmol) of valinemethylester hydrochloride, 18 µl (0.13 mmol) of TEA in 3ml of EtOH. Compound **40c** (27 mg, 0.11 mmol, 80%) was obtained as OIL. Dr=90/10 (determined by GC-MS).

Mix of diasteroisomers: ^{1}H NMR ($CDCl_3$, 400 MHz): δ= 0.83 (d, *J* = 6.6 Hz, 3H, Maj), 0.92 (d, *J* = 6.76 Hz ,3H, Min), 0.95 (d, *J* = 6.6 Hz, 3 H, Maj), 0.98 (d, *J* = 6.76 Hz ,1H, Min), 3.72 (s, 3H, Maj), 3.74 (s, 3H, Min), 4.13 (q, *J* = 7.08 Hz, *J* = 14.26 Hz, 1H, Maj), 4.75-4.80 (m, 1H, Min), 7.22 (d, *J* =3.52 Hz, 1 H, min), 7.35 (m, 1H, Maj), 7.60 (m, 1H, Min).

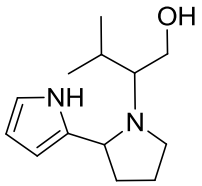


40e

40e:Compound **40e** was prepared according to the general procedure. Amount of reagents included 20mg (0.13 mmol) of **39** , 4 mg (0.07 mmol) of KOH, 8 μl (0.13 mmol) of Acetic acid, 49 mg (0.78 mmol) $NaCNBH_3$ and 7 mg (0.13mmol) of *O*-*t*-butyldimethylsilyl (*S*)-phenylglycinol in 3ml of EtOH. Compound **40e** (28 mg, 0.08 mmol, 60%) was obtained as OIL. Dr = 71/29 (determined by GC-MS)

Mix of diasteroisomers: : ^{1}H NMR ($CDCl_3$, 400 MHz): δ= -0.02 (d, *J* = 1.68 Hz,6H, Maj), 0.87 (s, 9H, Maj), 0.98 (d, *J* = 6.4 Hz,3H, Maj), 1.03 (d, *J* = 6.4 Hz, 3 H, Min), 3.52 (q, *J* = 8.28 Hz, *J* = 9.8 Hz, 2 H, Maj), 3.65 (q, *J* = 4.24 Hz, *J* = 9.84 Hz, 2 H, Maj), 4.02 (q, *J* = 7.72 Hz, *J* = 9.56 Hz, 1 H, Maj), 4.26 (dd, *J* = 3.84 Hz, *J* = 7.98 Hz, 1 H, min), 5.90 (bs, 1H, Min), 5.98 (bs, 1H, Maj), 6.11 (q, *J* = 2.76 Hz, *J* = 5.76 Hz, 1 H, Min), 6.18 (q, *J* = 2.76 Hz, *J* = 5.76 Hz, 1 H, Maj), 6.62 (m, 1H, Min), 6.68 (m, 1H, Maj), 7.10-7.38 (m, 5H maj+5Hmin, mix) 8.95 (bs, 1H, NH,Min), 9.30 (bs, 1H, NH ,Maj).

Major compound : ^{13}C NMR ($CDCl_3$, 100 MHz): δ= 157.6, 141.8, 129.0, 128.1, 127.8, 127.6, 127.0, 115.6, 108.2, 104.1, 68.3, 62.4, 46.1, 25.9, 24.4, 23.1, 22.2, 18.2, -5.5 ppm.



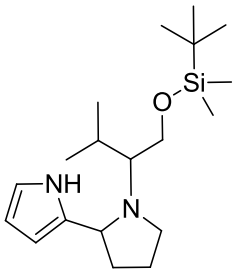
40f

40f:Compound **40f** was prepared according to the general procedure. Amount of reagents included 20mg (0.13 mmol) of **39** , 4 mg (0.07 mmol) of KOH, 8 μl(0.13 mmol) of Acetic acid, 49 mg (0.13 mmol) $NaCNBH_3$ and 13 mg (0.13 mmol) of valinole in 3ml of EtOH. Compound **40f** (10 mg, 0.04 mmol, 30 %) was obtained as OIL. Dr= (determined by GC-MS after sililation).

Major diasteroisomer : ^{1}H NMR ($CDCl_3$, 400 MHz): δ= 0.89 (d, *J* = 6.76 Hz, 3H), 0.97 (d, *J* = 6.76 Hz ,3H), 2.55-2.62 (m, 1H), 3.55- 3.65 (m, 2H), 4.62 (s, 1H), 4.67 (dd, *J* = 3.68 Hz, *J* = 4.92 Hz, 1 H), 5.97 (bs, 1H), 6.15 (t, *J* = 3.08 Hz, 1 H), 6.92 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ=127.0, 117.5, 107.9, 102.7, 55.6, 45.8, 36.4, 32.1, 29.7, 23.4, 17.0, 15.4 ppm.

Minor diasteroisomer: ^{1}H NMR ($CDCl_3$, 400 MHz): δ= 1.13 (d, *J* = 7.04 Hz, 3H), 1.21 (d, *J* = 7.04 Hz ,3H), 1.87-1.92 (m, 3H), 2.25-2.32 (m, 1H), 2.35-2.45 (m, 2H), 2.98-3.05 (m, 1H),

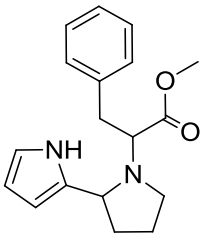
3.15 (d, *J* = 3.92 Hz, 1H), 3.55 (t, *J* = 6.36 Hz, 1 H), 5.92 (bs, 1H), 6.21 (t, *J* = 3.2 Hz, 1 H), 7.29 (m, 1H).



40g

40g:Compound **40g** was prepared according to the general procedure. Amount of reagents included 20mg (0.13 mmol) of **39** , 4 mg (0.07 mmol) of KOH, 8 μl(0.13 mmol) of Acetic acid, 49 mg(0.13 mmol) $NaCNBH_3$ and 28 mg (0.13 mmol) of *O*-*t*-butyldimethylsilyl (*S*)-valinol in 3ml of EtOH. Compound **40g** (30 mg, 0.09 mmol, 70 %) was obtained as OIL. Dr= 83/17 (determined by NMR).

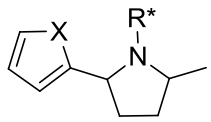
Mix of diasteroisomers: ^{1}H NMR ($CDCl_3$, 400 MHz): δ= 0.06 (d, *J* = 4.48 Hz, 6H, Maj), 0.14 (d, *J* = 2.4 Hz ,6H, Min), 0.84 (d, *J* = 6.68 Hz, 3H, Maj), 0.87 (d, *J* = 6.72 Hz, 3H, Min), 0.91 (s, 9H, Maj), 0.96 (s, 9H, Min), 0.97 (d, *J* = 6.68 Hz, 3H, Maj), 3.71 (q, *J* = 5.56 Hz, *J* = 10.76 Hz, 2 H, Maj), 3.83 (q, *J* = 2.88 Hz, *J* = 10.76 Hz, 2 H, Maj), 4.18 (q, *J* = 7 Hz, 1 H, Maj), 4.37 (dd, *J* = 3.68 Hz, *J* = 4.92 Hz, 1 H, min), 5.86 (bs, 1H, Min), 5.96 (bs, 1H, Maj), 6.12 (q, *J* = 2.76 Hz, *J* = 5.76 Hz, 1 H, Maj), 6.15 (q, *J* = 2.76 Hz, *J* = 5.76 Hz, 1 H, Min), 6.60 (m, 1H, Min), 6.69 (m, 1H, Maj), 8.50 (bs, 1H, NH ,Maj), 10.01 (bs, 1H, NH, Min).



40h

40h:Compound **40h** was prepared according to the general procedure. Amount of reagents included 20mg (0.13 mmol) of **39**, 4 mg(0.07 mmol) of KOH, 8 μl (0.13 mmol) of Acetic acid, 49 mg (0.78 mmol) $NaCNBH_3$ and 28 mg (0.13 mmol) of phenylalanine methylester-hydrochloride, 18 μl (0.13 mmol) of TEA in 3ml of EtOH. Compound **40h** (26 mg, 0.09 mmol, 70%) was obtained as OIL. Dr= 75/25(determined by GC-MS).

Mix of diasteroisomers: ESI-MS *m/z*: 299.1 $[M + H]^+$.



X=O, NH
NH_2R^*= glicinol, valinol, valinemethylester
, phenylethylamine

General Procedure for the synthesis of 2-aryl-5-methyl N-substituted pyrrolidine: In vials the starting material **36a** or**39a** (1 eq) was dissolved in EtOH and KOH (0.5 eq) and Acetic acid (1eq) was added to the mixture. $NaCNBH_3$ (6eq) and finally the chiral amine were added and the reaction mixture was heated to 70°C. The progress of the reaction was monitored by TLC and after 2 days the reaction mixture was quenched by a saturated solution of $NaCO_3$ and water and extract with EtOAc (3 times).

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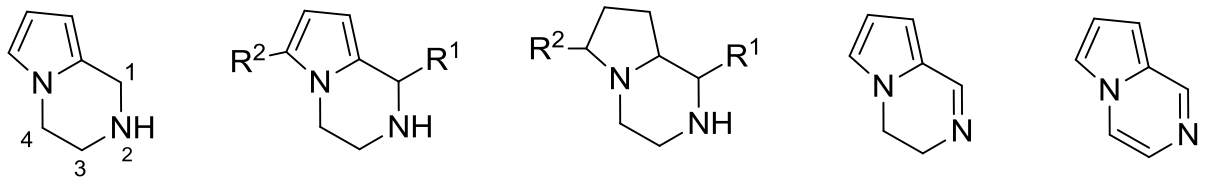
Chapter 3: New synthesis of 1,2,3,4-tetrahydropyrrole[1,2-a]pyrazines

3.1 Introduction

Substituted 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazines, e.g. **1**, are compounds of considerable utility because of their antiamnesic, antihypoxic,[196] psychotropic,[197] and antihypersensitive[198] activities.[199] Moreover, a stereochemically defined 3,5,5-trisubstituted-2,4-dioxo derivative displayed significantly potent aldose reductase inhibitory property.[200]



I **II** **III** **IV** **V**

Figure 98. Pyrrole/pyrrolidine [1,2-α]pyrazine derivatives.

1-Substituted- and 1,2-disubstituted-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazines **1** were previously synthesized by hydrogenation or reduction of 2-substituted-3,4-dihydropyrrolo[1,2-*a*]pyrazines **2**.[,201,202,203] The compounds **2** were in turn prepared by reaction of 2-furylcarboxaldehyde or 2-furyl ketones with ethylenediamine,[204,205,206] or by addition of Grignard reagents to the unsubstituted **2** (R = H).[207] Furthermore, hydrogenation of the pyrrole ring in more forcing conditions were exploited for the preparation of octahydro derivatives which were useful intermediates for the synthesis of coronary-dilators and neuroleptics. Compounds **2** were also prepared by $POCl_3$-mediated condensation of *N*-[2-(pyrrol-1-yl)]ethyl carboxylic acid amides **3**, which were in turn obtained in moderate yields from 2,5-dimethoxytetrahydrofuran.[208,209] N2-Substituted derivatives **1** can be easily obtained from the NH-free precursors by routine alkylation/acylation reactions.[210] An alternative route to **1** (R^1 = H, R^2 = CH_2R) involves reaction of 1-(2-aminoethyl)pyrrole with 2 equivalents of formaldehyde and benzotriazole, followed by reactions with Grignard reagents, which provide the R substituent. Moreover, 5,6,9,10,11,11a-hexahydro-8*H*-pyrido[1,2-*a*]pyrrolo[2,1-*c*]pyrazines (**1**, R^1-R^2 = $CH_2CH_2CH_2CHR$) were prepared by the same benzotriazole methodology using glutaric dialdehyde.[211]

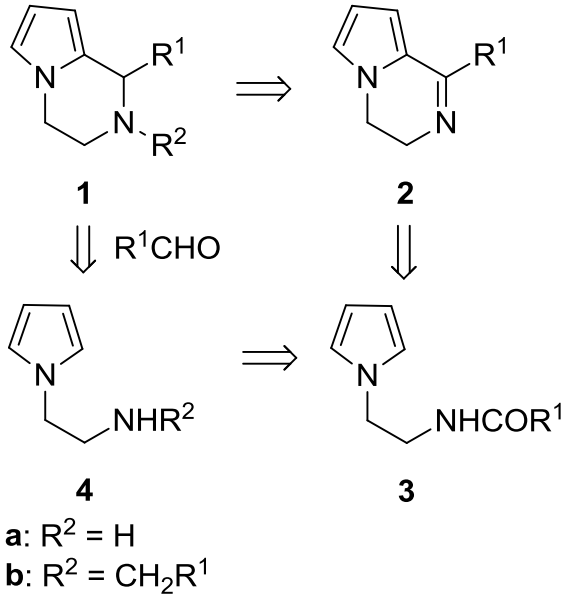


Figure 99. Retrosynthetic pathways of substituted 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazines 1.

Interesting substances with the same skeleton but containing a substituent on the pyrrole ring are the compounds **5** and **6** (Scheme 2). The former is a modulator for mGluR5, useful for control and prevention of cronical neurological disorders.[212] For 7-(1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazin-7-yl)quinolones **6** with methyl-substituted 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine side chains, the position of the methyl group with the *S* configuration at C3 on the tetrahydropyrazine ring was important for the *in vivo* efficacy in a murine lethal systemic infection model. On the other hand the configuration of the methyl substituted C1 was not determinant. It is noteworthy that the 1,2,3,4-tetrahydropyrazine fragment was stereoselectively constructed starting from (4*R*)-hydroxy-L-proline and the pyrrole nucleus was obtained by dehydrogenation of an intermediate pyrroline.[213]

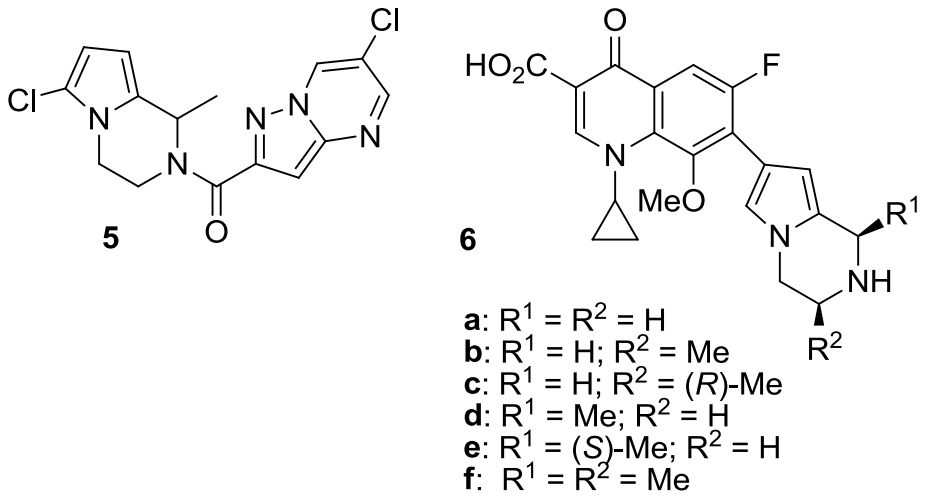


Figure 100. Drugs containing substituted 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazines fragments.

Other syntheses of configurationally pure 1-substituted 1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazines were lacking in the literature. Hence, as a part of our ongoing research on the stereoselective synthesis of 1-(pyrrol-2-yl)alkylamines[214] and considering the potential of stereochemically defined, substituted 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazines we aimed at developing an efficient asymmetric route to this class of compounds. Among various possible routes to the target compound **1**, we privileged those exploiting 2-pyrrolecarboxaldehyde **10** as the convenient, easily available starting material. Thus three alternative retrosynthetic pathways were envisaged, as described in Figure 4, which rely on the different order of formation of three C-N bonds (*a*-*c*) and one C-C bond (*d*) and involve 1-(2-pyrrolyl)alkylamines **8** and cyclic iminium ions **9** as intermediates.[215] In both cases, the chiral auxiliary, i.e. the nitrogen substituent R*, would induce asymmetry in the formation of the C1-R bond. Final removal of the chiral auxiliary from **1** would led to the desired enantiomerically pure or enantiomerically enriched NH-free 1-substituted 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazines.

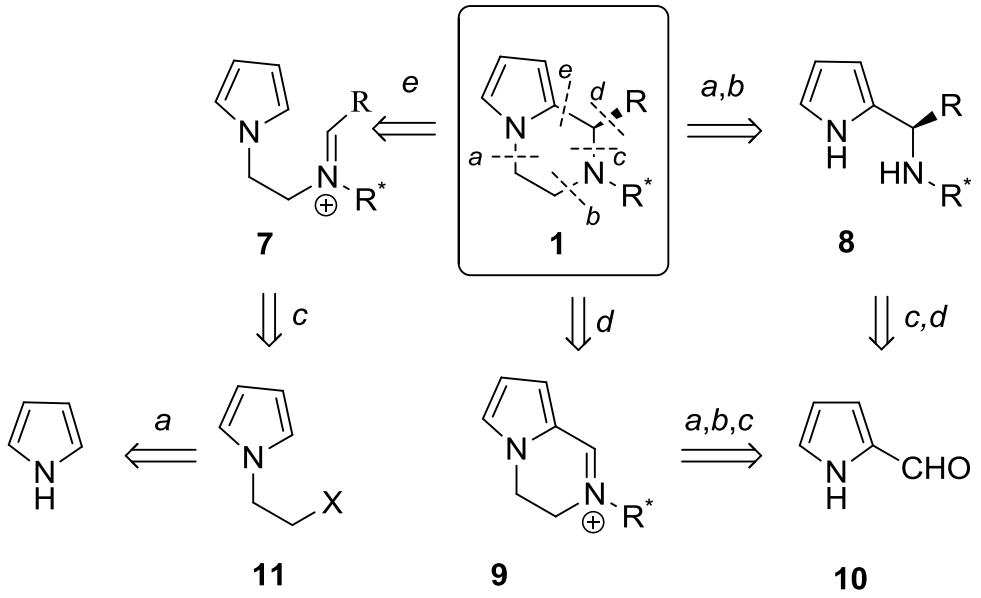


Figure 101. Retrosynthetic pathways of chiral 1-substituted 1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazines 7.

We have previously reported that the secondary amines **8** with *R* configuration of the shown stereocenter can be prepared in high yields and with excellent diastereoselectivities from the aldehyde **10** through formation of the imine with (*S*)-phenylglycinol and subsequent addition of organolithium reagents (paths *c*, *d*).

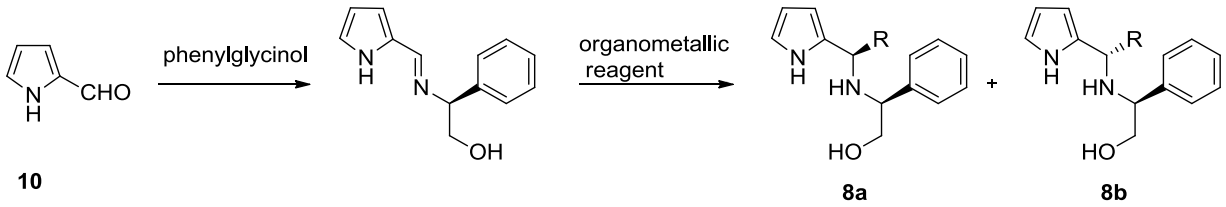


Figure 102. Alternative synthesis of pyrazine ring.

After separation of the minor diastereoisomer (traces) and removal of the chiral auxiliary by oxidative cleavage of the β-aminoalcohol moiety, the optically pure primary amines were finally obtained. Then, in order to obtain the desired compounds **1** from **8**, the formation of two C-N bonds would be required (paths *a*, *b*). In a preliminary experiment, insertion of the two carbons tether between the two nitrogen atoms of 1-(pyrrole-2-yl)-3-butenamine **8** (R = allyl, R* = H) was attempted by reaction with 1,2-dibromoethane (NaH, THF, Δ) but the outcomes were disappointing, as no reaction occurred. Perhaps, the goal would be accomplished by the proper choice of the two-carbon 1,2-dielectrophilic reactant, e.g. chloroacetyl chloride in a three step sequence.[216]

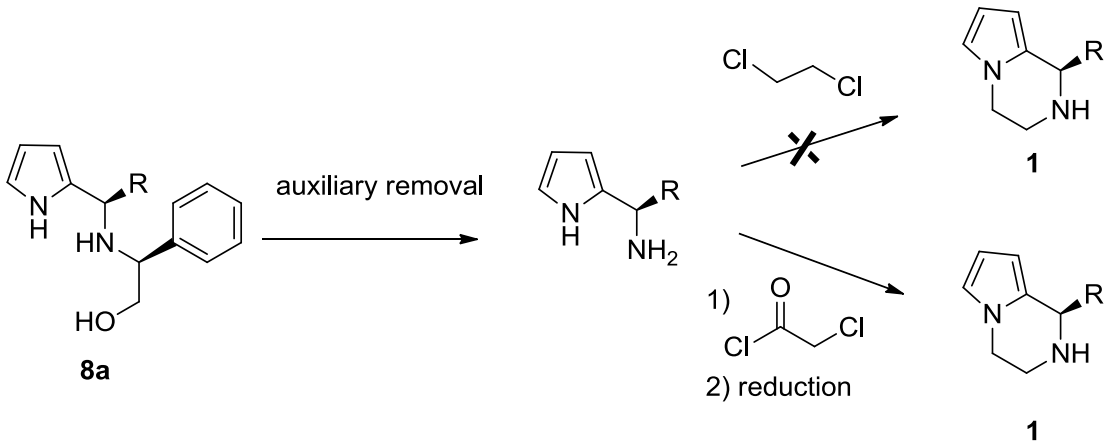


Figure 103. Alternative synthesis of pyrazine ring.

A different retrosynthetic pathway (sequence: *e, c, a*) can describe a potentially route starting from 2-(1-pyrrolyl)ethaneamine **11** that after a reaction with an aldheyde produce a pyrazine ring that can be functionalize in different way. The first way propose by Katritzky[211] show belong (Figure 7, way a) show as Grignard reagent can be useful in the insertion of different R groups obtaining very good yields.

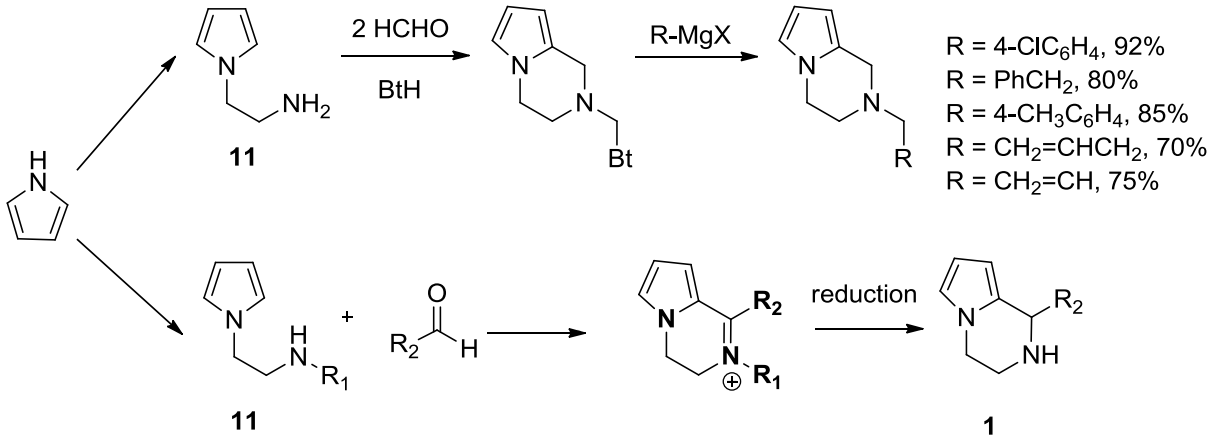


Figure 104. Previous syntheses of 2-substituted and 1-substituted 1,2,3,4-tetrahydropyrrol[1,2-*a*]pyrazines.

Using the same procedure it was possible to introduce different R groups in position 1 of the pyrazine ring starting from different aldehydes.[209] The reduction of the iminium intermediate produced the desired product as a mixture of enantiomers.

However, we reasoned that the alternative route described in Figure 8 (sequence: *a*, *b*, *c*, *d*) would offer several advantages:

1) the higher acidity of the pyrrole N-H bond in **10**, due to the electron-withdrawing effect of the formyl function, would facilitate the pyrrole metalation and formation of the first C-N bond by reaction with a 1,2-dihaloethane (step *a*);

2) ring-closure to the iminium ion **9** by subsequent reaction with an optically pure primary amine would occur in a single step by consecutive formation of two C-N linkages (*b*, *c* or *vice versa*);

3) the higher reactivity of the iminium ion with respect to the imine would allow the general use of more convenient Grignard reagents.

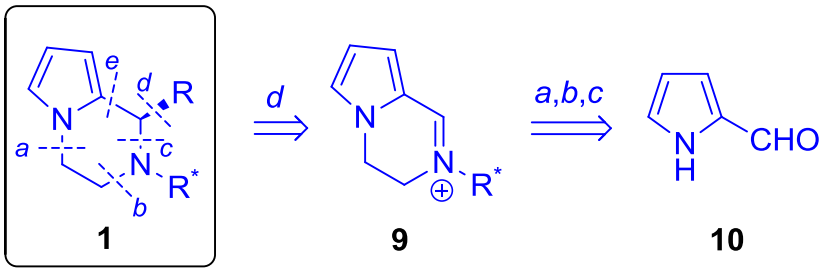


Figure 105. Alternatively retrosynthetic route: *d, a, b, c.*

3.2 New synthetic route to1,2,3,4-tetrahydropyrrole[1,2*a*] pyrazines

Hence, we began our investigation looking for optimal reaction conditions for the conversion of 2-pyrrolecarboxaldehyde **10** to *N*-(2-haloethyl) derivatives **11a,b** (Figure 9). Treatment with KOH in DMSO (0 °C, 1 h) followed by slow addition of 1,2-dibromoethane (20 equiv)[217] and stirring for 24 h gave a good conversion to **11a**, which was accompanied by little amounts of the *N*-vinyl derivative. After purification by column chromatography, the desired **11a** was isolated in 69% yield, however, slow decomposition was observed by storing it at room temperature. To prevent this, the product was stored at 4 °C. On the other hand, stirring overnight the aldehyde **10** in the two-phase system 50% aqueous NaOH-CH_2Cl_2 in the presence of the phase-transfer catalyst tetrabutylammonium iodide (TBAI), afforded cleanly the air-stable *N*-(2-chloroethyl) derivative **11b** in 92% yield.[218]

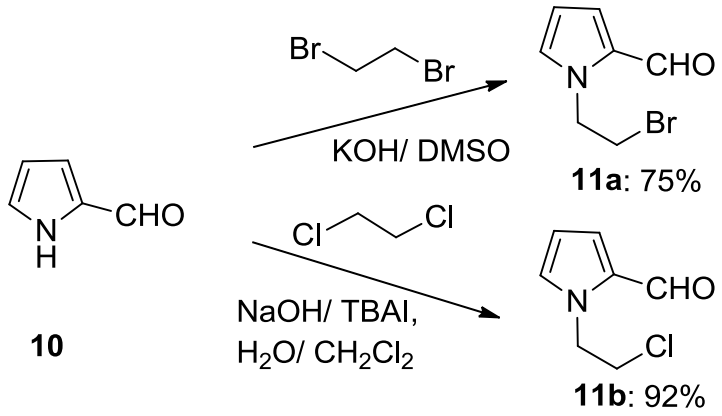


Figure 106: Synthesis of *N*-(2-haloethyl)pyrrole-2-carboxaldehyde.

Both halo-aldehydes were submitted to reaction with a slight excess of either (*S*)-phenylglycinol and (*S*)-valinol in anhydrous CH_2Cl_2 in the presence of $MgSO_4$ as dehydrating agent for 2 days. In all cases the corresponding bicyclic iminium ions **12** were observed in the crude products isolated by filtration of the solid and evaporation of the solvent. Variable, although minor amounts of starting materials, a different aldehyde (presumably 1-vinyl-2-pyrrolecarboxaldehyde) and the tricyclic compound **14** were also present in the crude mixtures.

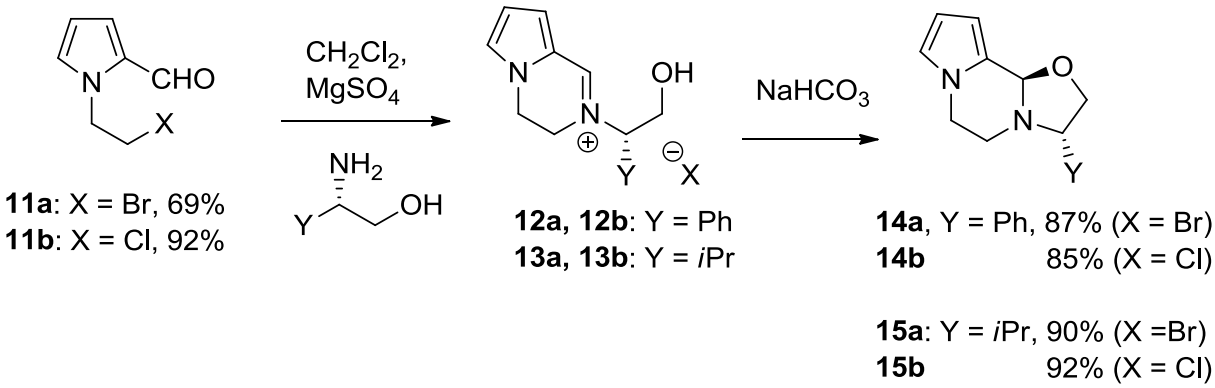


Figure 107. Diastereoselective synthesis of tricyclic oxazolidines 14 and 15 from 2-pyrrolecarboxaldehyde.

Testing different solvent we observed that the crude iminium bromide **12** precipitated from its CH_2Cl_2 solution upon addition of Et_2O, and it was obtained in a 70% yield. This particular low affinity to Et_2O could be useful during the workup. The ^1H NMR spectrum of compound **12** in $CDCl_3$ showed an adsorption of the H-C=N^+ proton at δ 9.33 ppm, distinctly higher than the proton of the formyl group in **11a** (δ 9.49 ppm). It was also observed that in the $CDCl_3$ solution an equilibrium was slowly attained betweeb the open species and the oxazolidine derivative **14**, the chemical shift of the O-CH-N proton being observed at δ 5.24 ppm. However, this result could not be always reproduced by repeating the same procedure several times. On the other hand, treatment directly the CH_2Cl_2 solution of compound **12** or **13** with sat aq $NaHCO_3$ and extraction of the organic phase afforded the tricyclic compound **14** and **15** in 87% yield and 90% respectively in a pure state. The ^1H NMR spectra of the tricyclic structures **14** and **15** gave singlet peaks at δ 5.58 and 5.24, respectively, for the O-CH-N protons of the oxazolidine groups. Minor amounts (about 5%) of another diastereoisomer could be observed with some difficulty in the spectrum at room temperature, but the relative signals were narrower and more evident at lower temperature. Other reaction conditions were also tested by varying the solvent (DMF), the dehydrating agent (molecular sieves), the temperature, but with less satisfactory results. Moreover, mixtures of products **12a** and **13a** were obtained by carrying out the reactions in the presence of a base (K_2CO_3 or Et_3N).

Successively, crystals suitable for a single X-ray diffraction study, grown by slow evaporation of a THF solution of **14**, allowed the structure determination (Figure 11) of **14** in the solid state that corresponds to the most stable of the possible diastereomers (the N atom is a stereocenter, too), as previously hypothesized by NMR-nOe experiment and calculated at the MM2 level.

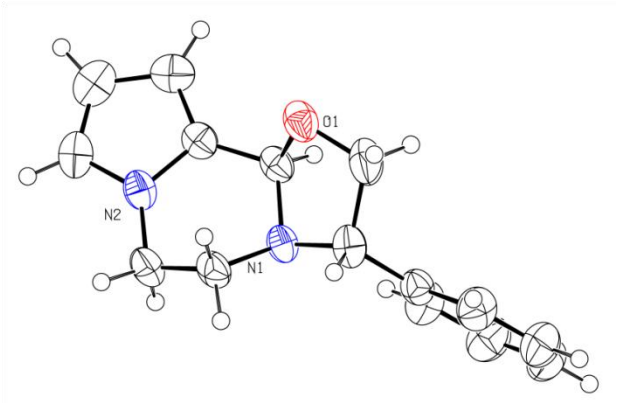


Figure 108. ORTEP drawing of compound 14. Thermal ellipsoids are at 30% probability.

Oxazolidines are useful substrates for conducting organometallic reactions, particularly with Grignard reagents. The tricyclic oxazolidines **14** and **15** were used as substrates in organometallic reactions.[219] Reactions of phenylglycinol-derived *N*-substituted oxazolidines with organometallic reagents have been previously exploited for the diastereoselective synthesis of secondary amines.[220,221]

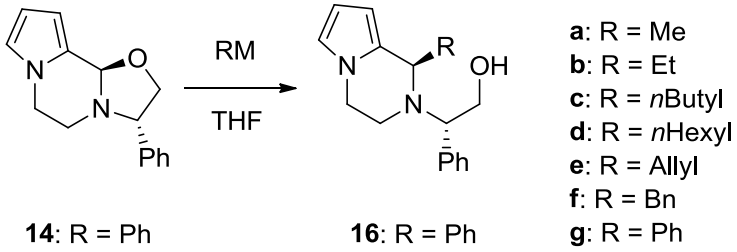


Figure 109. Addition of organometallic reagents to the tricyclic oxazolidines 14.

In our hands, Grignard reagents proved to be the reagents of choice for **14**, as in many cases high yields and diastereoselectivities were obtained for the resulting 1,2-disubstituted-1,2,3,4-tetrahydropyrrolo-[1,2-*a*]pyrazines **16** (Figure 12 and Table 1).

The addition of methylmagnesium bromide in THF was particularly effective in terms of both the yield and diastereoselectivity at −78 °C, as the prevalent diastereomer **16a** (d.r. 98:2) was obtained pure in 95% yield after column chromatography (entry 1). The stereocontrol progressively decreased with increasing the length of the alkyl group of the Grignard reagents, *e.g.* ethyl and *n*-hexyl (entries 2 and 3). Allylmagnesium chloride was totally devoid of stereoselectivity (entry 4) and gave no reaction in presence of titanium tetrachloride (entry 5). Hence we moved to allylzinc bromide, but the diastereoselectivity increased only slightly (entry 6) and a better stereocontrol (d.r. 76:24) was finally obtained using preformed mixed zincate, $AllylEt_2ZnMgCl$ (entry 7). Benzylmagnesium chloride gave only a moderate diastereoselectivity (d.r. 65:35, entry 8). Finally, phenylmagnesium bromide reacted with almost complete stereocontrol, affording the crude secondary amine with high yield and more than 99:1 diastereomeric ratio (entry 9), whereas phenyllithium reacted sluggishly even by raising the temperature to 20 °C (entry 10).

Table 19. Addition of organometallic reagents to the tricyclic oxazolidine 14.[a]

Entry	RM	°C, h	D. r. [b]	Products (Yield %) [c]
1	MeMgBr	–78, 2	98:2	**16a** (95)
2	EtMgBr	–78, 1	92:8	**16b** (78), *epi*-**16b** (3)
3	*n*HexylMgBr	–78, 1	93:7	**16d** (77), *epi*-**16d** (6)
4	AllylMgCl	–78, 1	50:50	**16e** (41), *epi*-**16e** (35)
5	AllylMgCl-$TiCl_4$	–78, 2 [d]	-	-
6	AllylZnBr	–78 to 20, 4	62:38	**16e** (47), *epi*-**16e** (24)
7	AllylEt_2ZnMgCl [e]	–78, 1	76:24	**16e** (38), *epi*-**16e** (14)
8	BnMgCl	–78, 1	65:35	**16f** (53), *epi*-**16f** (29)
9	PhMgBr	–78, 1	>98:2	**16g** + *epi*-**16g** (72) [f]
10	PhLi	–78 to 20, 12	78:22	**16g** + *epi*-**16g** (45) [f]

[a] The reactions were performed by adding the organometallic reagents (4 equiv.) to the solution of the imine in anhydrous THF under an atmosphere of N_2. [b] The diastereomeric ratios were determined by ^{1}H NMR analyses of the crude reaction product. [c] Yields refer to pure diastereoisomers isolated by column chromatography (SiO_2). [d] No reaction occurred. [e] The zincate was prepared by adding allylmagnesium chloride to Et_2Zn in THF and stirring for 1 h at 0 °C. [f] Pure diastereoisomers could not be obtained because epimerization occurred during chromatography on SiO_2 column.

Unfortunately, attempted purification of the crude phenyl-substituted product **16g** obtained in entry 9 by chromatography an a silica gel column produced epimerized product in all eluted fractions. This can be explained by the acidity present in silica which induces heterolytic cleavage of the benzydrylic C-N bond, to form a carbenium ion which is stabilized by both adjacent aromatic rings (Figure 13). To confirm the role of SiO_2 in the epimerization process, we leave for a week a mixture of **16g** and silica in DCM. The silica was removed by filtration and the solvent was evapourate to obtain the crude product as a 1:1 mixture of the two disteroisomers. We can assume that because of this unfortunately behaviour is impossible to purify the **16g** product by flash cromatografy.

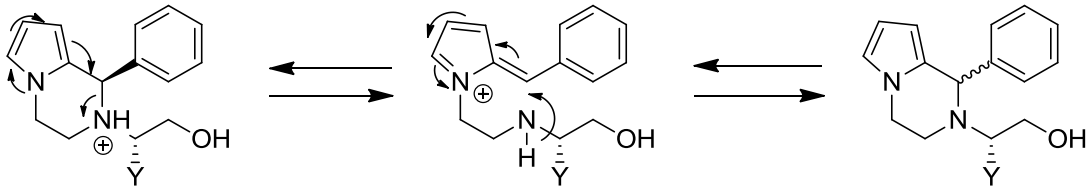


Figure 110. Epimerization mechanism in product 16g.

Then, we examined the effectiveness of (*S*)-valinol as chiral auxiliary by performing the same organometallic reactions on the oxazolidine **15** (Figure 14 and Table 2) and obtained in all cases unsatisfactory stereochemical outcomes, as the diastereomeric ratios ranged between 70:30 and 50:50 using Grignard reagents and *n*-butyllithium.

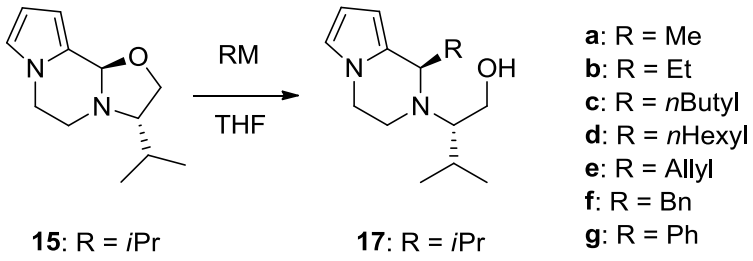


Figure111. Addition of organometallic reagents to the tricyclic oxazolidines 15.

Also in this case on of the best results in diasteroselectivities was obtained using MeMgBr (Table 2, entry 1) that show 70/30 diastero ratio. The same result was obtained using *n*-BuLi as organometallic reagent (Table 2, entry 3). Allyl(tri-*n*-butyl)tin-$SnCl_4$ and $–BF_3$ systems were totally unreactive (Table 2, entries 7 and 8), whereas allyltitanium reagent formed *in situ* from the Grignard reagent and titanium tetraethoxide afforded **17e** (Table 2, entries 4 and 5) with lower yield with respect to the Grignard reagent alone, and the d.r. remained unsatisfactory. Moreover, column chromatography was not adequate to separate the diastereoisomers of the products **17b,e-g** (Table 2, entried 2,5,6,7). Particularly, the phenyl-substituted product **17i** (Table 2, entry 9), initially obtained with a d.r. of 65:35, was eluted with an inverted 40:60 ratio.

Table 20. Addition of organometallic reagents to the tricyclic oxazolidine 15.[a]

Entry	RM	°C, h	D. r. [b]	Products (Yield %) [c]
1	MeMgBr	–78, 2	70:30	**17a** (49), *epi*-**17a** (17)
2	EtMgBr	–78, 1	65:35	**17b** + *epi*-**17b** (68) [d]
3	*n*BuLi	–78, 1	70:30 [e]	**17c** [f]
4	AllylMgCl	–78, 1	50:50	**17e** + *epi*-**17e** (64) [d]
5	AllylMgCl-Ti(OEt)$_4$	–78, 1	54:46	**17e** + *epi*-**17e** (50) [d]
6	Allyl(*n*Bu)$_3$Sn-SnCl$_4$	–78 to 20, 4	-[f]	-
7	Allyl(*n*Bu)$_3$Sn-BF$_3$	–78 to 20, 4	-[f]	-
8	BnMgCl	–78, 1	50:50	**17f** + *epi*-**17f** (76) [d]
9	PhMgBr	–78, 1	65:35	**17g** + *epi*-**17g** (78) [d]

[a] The reactions were performed by adding the organometallic reagent (4 equiv) to the solution of the imine in anhydrous THF under an atmosphere of Ar. [b] The diastereomeric ratios (d.r.) were determined by ^{1}H NMR analysis of the crude reaction product. [c] Yields refer to pure diastereoisomers isolated by column chromatography (SiO_2). [d] The diastereomers could not be separated by column chromatography. [e] The reaction mixture contained mainly unreacted **15** and minor amount of the addition product **17c** (ca 10%). [f] No reaction occurred.

The absolute stereochemistry of the main diastereoisomers could not be unambiguously demonstrated, however, the *R*-configuration can reasonably be postulated by analogy with all the previously reported outcomes of Grignard reactions performed on various *N*-substituted oxazolidines derived from (*S*)-phenylglycinol.[25] We assume that the same mechanism considered for those reactions is also operating with our substrate **14**, as described in Figure 15. The Lewis acidity of the Grignard reagent is determinant for the successful reaction, which therefore proceeds by the preliminary O-Mg coordination. This leads to the incipient formation of the carbenium ion **18** which undergoes attack of the R nucleophile from the same face of the C-O bond being broken, obtaining finally a product with the same absolute *R* configuration.

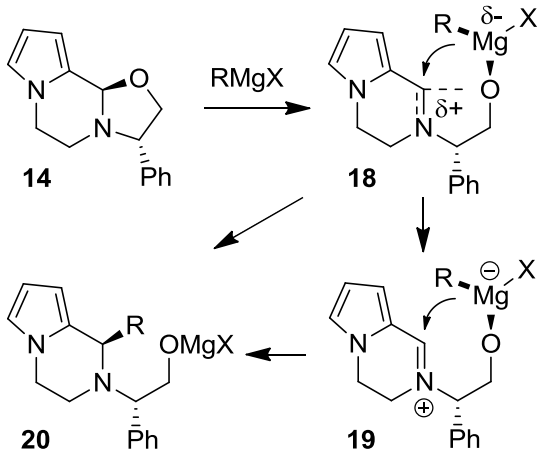


Figure 112. Mechanism and stereochemical model for the organometallic addition to oxazolidine 14.

The formation of a true carbenium ion **19** cannot be excluded, and in this case a reduced diastereoselectivity might be expected owing to the possible rotation of the nitrogen substituent around the C*-N bond. Moreover, the lower diastereoselectivity of allylic reagents can be explained by the unfavourable transition state that should be attained for the γ-attack in allylic rearrangement (Figure 16).

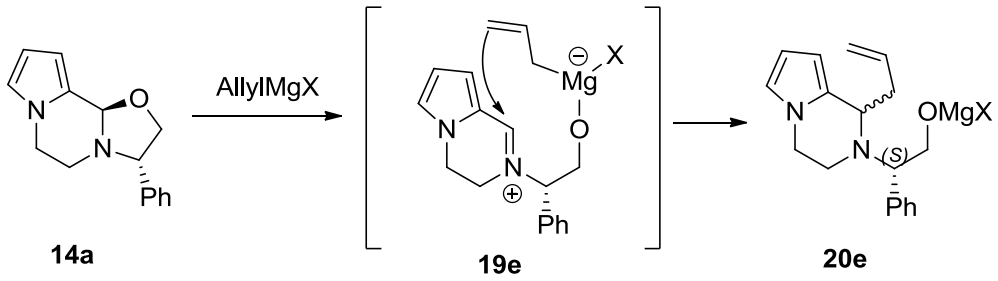


Figure 113. Formation of product 20e.

Finally, we directed our efforts to the removal of the chiral auxiliary. Unfortunately, all efforts to achieve this goal from both amines **16a** and **17a** by oxidative procedures including the use of periodic acid/methylamine (Figure 17) and lead tetraacetate were unsuccessful.

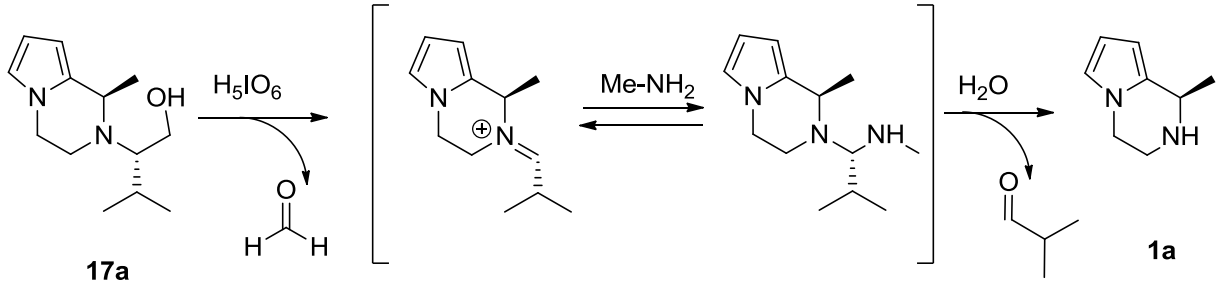


Figure 114. Envisioned removal of the chiral auxiliary of 17a by H_5IO_6 and $MeNH_2$.

For compounds **16**, however, another efficient way is possible for the removal of phenylglycinol fragment, that is the hydrogenolysis catalyzed by Pd/C. The first test took place on compound **16b**, it has been react with ammonium formate and Pd/C afforded a complex mixture of products. Being this way particularly problematic we decided to change the hydrogen source. Compounds **16a,b** were submitted to 7 bar of hydrogen pressure in the presence of 10% Pd/C in methanol for 2 days gave mainly the desired secondary amines **21a,b** in about 80% yield, which were accompanied by 2-phenylethanol and trace amounts of the fully hydrogenated compounds **22** (Figure 18) identify by HPLC-MS.

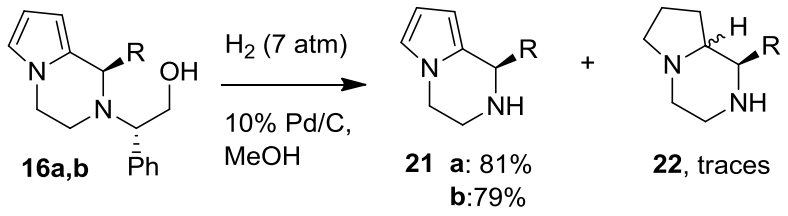


Figure 115. Removal of the chiral auxiliary from 1,2-disubstituted-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazines 16a,b.

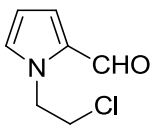
In conclusion, we have developed the first asymmetric synthesis of 1-substituted-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazines by a four step route starting from 2-pyrrolecarboxaldehyde. The key intermediate was a tricyclic pyrrole-tetrahydropyrazine-oxazolidine that was formed with very high diastereoselectivity by condensation of 1-(2-haloethyl)-2-pyrrolecarboxaldehyde with (*S*)-phenylglycinol. This compound reacted with Grignard reagents to give 1,2-disubstituted-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazines with variable level of diastereoselectivity, which decreased with increasing the length of the alkyl group of the Grignard reagent. The highest d.r. was obtained with methylmagnesium bromide (98:2) and phenylmagnesium bromide (>98:2). In the latter case, the product could not be purified by chromatography on silica gel, as epimerization occurred at considerable extents. The chiral auxiliary was removed from 1-methyl- and 1-ethyl-substituted products by hydrogenolysis.

SUPPORTING INFO

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 MR400 and Gemini 200 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. Infrared spectra were recorded on a Nicolet FT-380 spectrometer and IR assignments are reported in wave numbers (cm^{-1}). MS spectra were taken at an ionising voltage of 70 eV on a Hewlett-Packard 5975 spectrometer with GLC injection (using HP-5 column, 30 m, ID 0.25 mm). Molecular weights were 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 anhydrous solvents were purchased from Aldrich.

11a

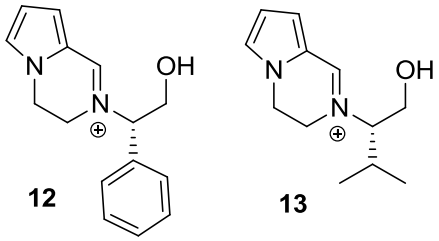
Preparation of 1-(2-bromoethyl)-2-pyrrolecarboxaldehyde (11a): To a stirred solution of pyrrole-2-carboxaldehyde **10** (1.00 g, 10 mmol) in dry DMSO (6 mL), KOH (5.88 g, 100 mmol) was added in one portion at room temperature. After 1 h, 1,2-dibromoethane (18.1 mL, 0.2 mol) was slowly added at 0 °C. The resulting solution was stirred overnight at room temperature. The reaction was quenched by addition of water (10 mL) and the organic layer was extracted with EtOAc (3 x 20 mL). The collected organic layers were washed with brine (20 mL), dried over Na_2SO_4 and concentrated to leave the crude product. Purification was achieved by flash column chromatography (SiO_2, cyclohexane/EtOAc, 9:1) and gave the product **11a** as a yellow oil: 1.59 g (75%). IR (neat): *v* = 3111, 2947, 2807, 2722, 1660, 1530, 1479, 1321, 1208, 1075, 822, 623, 607. ^1H NMR (200 MHz, $CDCl_3$): δ = 9.49 (s, 1 H), 7.04-6.99 (m, 2 H), 6.29-6.25 (m, 1 H), 4.8 (t, *J* = 5.8 Hz, *J* = 6.2 Hz, 2 H), 3.7 (t, *J* = 5.8 Hz, *J* = 6.2 Hz, 2 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 179.4, 150.9, 132.5, 125.6, 109.6, 50.6, 31.7. MS (EI): *m/z* = 122 (100), 94 (36), 201 (14), 203 (12), 202 (3). Anal. Calcd for C_7H_8BrNO (202,05): C, 41.61; H, 3.99; N, 6.93. Found: C, 41.50; H, 4.01; N, 6.91.



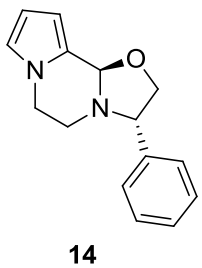
11b

Preparation of 1-(2-chloroethyl)-2-pyrrolecarboxaldehyde (11b):218 To a solution of pyrrol-2-carboxaldehyde (0.500 g, 5.3 mmol) in CH_2Cl_2 (2 mL), 1,2-dichloroethane (9.7 mL,

0.12 mol), TBAI (1.94 g, 5.3 mmol) and a 50% solution of NaOH (5 mL) were added. The reaction was vigorously stirred overnight and water (2 mL) was added. The organic layers were extracted with CH_2Cl_2 (2 x 30 mL) washed with HCl (2 x 20 mL, 1 M), $NaHCO_3$ (2 x 20 mL, sat. sol.) and brine (2 x 20 mL). After drying over Na_2SO_4 and the organic layers were concentrated *in vacuo* producing orange slurry. Purification was achieved by column chromatography (SiO_2, cyclohexane/EtOAc, 9:1) gave the product **11b** as a yellow oil: 0.76 g , (92% yield). IR (neat) ν = 3111, 2959, 2809, 1663, 1655, 1479, 882, 766, 705, 678, 656, 608; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 9.51 (s, 1 H), 7.03-6.97 (m, 2 H) , 6.23 (t, *J* = 2.6 Hz, 1 H), 4.57 (t, *J*= 5.8 Hz, *J* = 5.4 Hz, 2 H), 3.79 (t, *J* = 5.8 Hz, *J* = 5.4 Hz, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 179.2, 132.7, 130.7, 125.4, 109.5, 50.5, 43.7; MS (EI): *m/z* = 122 (100), 94 (50), 157 (34), 53 (19), 108 (18), 80 (14). Anal. Calcd for C_7H_8ClNO (157.6): C, 53.35; H, 5.12; N, 8.89. Found: C, 53.19; H, 5.14; N, 8.86.

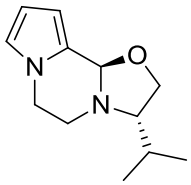


Preparation of the iminium salt 12 and 13. Typical procedure : The mixture of 1-(2-bromoethyl)pyrrole-2-carboxaldehyde (0.203 g, 1.0 mmol), (*S*)-phenylglycinol (0.138 g, 1.2 mmol) and $MgSO_4$ (0.5 g) in dry CH_2Cl_2 (4 mL) was protected from light and magnetically stirred for 2 d under inert atmosphere. Then, the mixture was filtered through a small pud of celite and washed with CH_2Cl_2. The filtered solution was concentrated under reduced pressure to a final volume of 1 mL and Et_2O (3 mL) was slowly added, so producing a brown precipitate of compond **12**: 0.228 g (71%). IR (neat): *ν* = 3381, 2962, 2924, 2848, 1646, 1629,1491,1377, 1103,1067. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.33 (s, 1 H), 7.39-7.26 (m, 7 H), 6.44-6.36 (m, 1 H), 5.56-5.49 (m, 1 H), 5.39 (bs, OH), 4.60-4.20 (m, 3 H), 4.10-3.93 (m, 2 H), 3.80-3.60 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.8, 134.5, 132.7, 129.5, 127.9, 127.3, 122.6, 115.4, 72.5, 60.1, 45.9, 43.4. MS (ES): *m/z* = 241.1 $[M - HBr + H]^+$ (100).



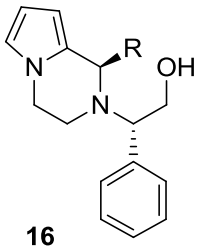
Preparation of the tricyclic oxazolidine 14: The mixture of 1-(2-bromoethyl)pyrrole-2-carboxaldehyde (1.515 g, 7.5 mmol), (*S*)-phenylglycinol (1.233 g, 9.0 mmol) and $MgSO_4$ (5

g) in dry CH_2Cl_2 (15 mL) was protected from light and stirred for 2 d under inert atmosphere. Then, the mixture was filtered through a small pad of celite and washed with CH_2Cl_2. The collected organic layers were washed with sat. aq. $NaHCO_3$ (20 mL) and brine (20 mL). The organic phase was concentrated under reduced pressure to give **14** as a white solid: 1.531 g (85%). mp = 85.1-85.5 ^oC; $[\alpha]_D^{20}$ = +8.5 (*c* = 1.0, $CHCl_3$). IR (KBr): *v* = 3101, 3027, 2847, 1600, 1449, 1212, 1190, 873, 798, 757, 698. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.49-7.34 (m, 5 H), 6.63 (dd, *J* = 1.6 Hz, *J* = 2.8 Hz, 1 H), 6.28 (d, *J* = 2.2 Hz, 1 H), 6.20 (t, *J* = 3.0 Hz, 1 H), 5.53 (s, 1 H), 4.50 (t, *J* = 7.9 Hz, 1 H), 4.30 (t, *J* = 6.8 Hz, 1 H), 4.14-4.03 (m, 2 H), 3.76 (dd, *J* = 6.6 Hz, *J* = 8.5 Hz, 1 H), 3.37-3.27 (m, 1 H), 3.16-3.07 (m, 1 H) ppm. ^{13}C NMR(100 MHz, $CDCl_3$): δ = 141.4, 134.9, 128.7, 127.3, 126.5, 119.5, 108.7, 107.6, 86.6, 71.2, 67.8, 47.4, 44.1 ppm. MS (EI): *m/z* = 239 (100), 210 (20), 106(15). Anal. Calcd for $C_{15}H_{16}N_2O$ (240.30): C, 74.97; H, 6.71; N 11.66. Found: C, 74.78; H, 6.74; N, 11.62.

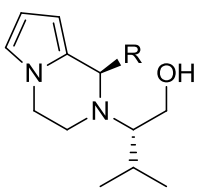


15

Preparation of the tricyclic oxazolidine 15: This was prepared by the same procedure followed for **14** starting from **11a** (1.515 g, 7.5 mmol): yellow oil, 1.443 g (92%). $[\alpha]_D^{20}$ = –13.0 (*c* = 1.2, $CHCl_3$). IR (neat): *v* = 3101, 2957, 2868, 1663, 1494, 1469, 1299, 1195, 1037, 861, 769, 609. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.59 (s, 1 H), 6.28-6.24 (m, 1 H), 6.19 (t, *J* = 2.9 Hz, 1 H), 5.24 (s, 1 H), 4.14 (t, *J* = 8.0 Hz, 1 H), 4.06 (ddd, *J* = 3.5 Hz, *J* = 12.0 Hz, 1 H),3.98-3.88 (m, 1 H), 3.50 (dd, *J* = 6.0 Hz, *J* = 8.1 Hz, 1 H), 3.21 (dt, *J* = 3.4 Hz, *J* = 11.5 Hz, 1 H), 2.86-2.78 (m, 1 H), 2.74-2.64 (m, 1 H), 1.74-1.64 (m, 1 H) 1.07 (d, *J* = 6.4 Hz, 3 H), 0.88 (d, *J* = 6.4 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 124.7, 119.2, 108.6, 107.5, 85.7, 72.7, 67.6, 48.7, 44.9, 31.9, 20.3, 18.9 ppm. MS (EI): *m/z* = 205 (100), 161 (90), 176 (13). Anal. Calcd for $C_{12}H_{18}N_2O$ (206.28): C, 69.87; H, 8.80; N 13.58. Found: C, 69.60; H, 8. 83; N, 13.54.



16



17

Preparation of 1,2-disubstituted-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazines 16 and 17. Typical procedure: Methylmagnesium bromide (3.0 M in Et_2O, 1.3 mL, 4.0 mmol) was added to a magnetically stirred solution of **14** (0.240 g, 1.0 mmol) in anhydrous THF (15 mL)

cooled at –78 °C. The reaction was stirred until TLC showed the disappearance of starting material, then was quenched by adding a sat aq $NaHCO_3$ (10 mL). The organic material was extracted with Et_2O (3 × 10 mL). The collected ethereal layers were dried over Na_2SO_4 and concentrated to leave an oil. The diastereomeric ratio was determined by ^1H NMR analysis of a sample solution in $CDCl_3$. Flash column chromatography (SiO_2) eluting with cyclohexane/EtOAc (9:1) gave the product **16a** as a yellow oil: 0.253 g (99%): $[\alpha]_D^{20}$ = –21.4 (*c* = 1.3, $CHCl_3$). IR (neat): *v* = 3415, 3101, 3050, 2970, 2928, 1601, 1492, 1453, 1266, 1186, 1056, 735, 609; ^1H NMR(400 MHz, $CDCl_3$): δ = 7.45-7.29 (m, 5 H), 6.50 (t, *J* = 1.7 Hz, 1 H), 6.15 (t, *J* = 3.0 Hz, 1 H), 5.85-5.80 (m ,1 H), 4.30 (q, *J* = 6.8 Hz, *J* = 13.0, 1H), 4.02-3.90 (m, 3 H), 3.82-3.75 (m, 1 H), 3.43 (t, *J* =6.7 Hz, 1 H), 3.38-3.21 (m, 1 H), 3.10-3.02 (m, 1 H), 1.39 (d, *J*= 6.6 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.4, 132.1, 128.6, 128.4, 128,3, 117.9, 107.8, 102.9, 65.4, 63.2, 50.8, 43.38, 41.3, 19.2 ppm. MS (ES): *m/z* = 271.2 $[M + H]^+$ (100). Anal. Calcd for $C_{16}H_{20}N_2O$ (256.34): C, 74.97; H, 7.86; N 10.93. Found: C, 74.75; H, 7.88; N, 10.90.

16b: yellowish oil, 0.210 g (78%). $[\alpha]_D^{20}$ = –10.5 (*c* = 0.5, $CHCl_3$). IR (neat): *v* = 3411, 3109, 3046, 2974, 2921, 1605, 1457, 1174, 1050, 736; ^1H NMR (400 MHz, $CDCl_3$): δ= 7.40-7.29 (m, 5 H), 6.52 (t, *J* = 1.8 Hz, 1 H), 6.12 (t, *J* = 3.2 Hz, 1 H), 5.79-6.75 (m, 1 H), 4.04 (dt, *J* = 4.6 Hz, *J* = 11.8 Hz, 1 H), 3.96-3.88 (m, 3 H), 3.82-3.73 (m, 2 H), 3.46-3.36 (m, 1 H), 3.22-3.14 (m, 1 H), 1.86-1.74 (m, 1 H), 1.71-1.58 (m, 1 H), 0.92 (t, *J* = 7.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.5, 130.0, 128.5, 127.7, 118.3, 107.4, 104.0, 65.2, 63.6, 56.4, 41.6, 40.9, 26.8, 11.0 ppm. MS (ES): *m/z* = 271.2 $[M + H]^+$ (100). Anal. Calcd for $C_{17}H_{22}N_2O$ (270.37): C, 75.52; H, 8.20; N 10.36. Found: C, 75.68; H, 8.21; N, 10.32.

epi-**16b**: yellowish oil, 0.008 g (3%). $[\alpha]_D^{20}$ = +6.8 (*c* = 1.2, $CHCl_3$). IR (neat): *v* = 3414, 3107, 3054, 2978, 2923, 1611, 1497, 1451, 1263, 1051, 736; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.38-7.24 (m, 5 H), 6.47 (t, *J* = 1.8 Hz, 1 H), 6.12 (t, *J* = 2.9 Hz, 1 H), 5.85-5.81 (m, 1 H), 4.20 (dd, *J* = 5.2 Hz, *J* = 9.6 Hz), 4.07 (dd, *J* = 10.4 Hz, 1 H), 3.98 (t, *J* = 4.2 Hz, 1 H), 3.96-3.84 (m, 2 H), 3.76 (dd, *J* = 4.9 Hz, *J* = 10.8 Hz, 1 H), 3.28-3.20(m,1 H), 3.02 (bs, 1 H), 2.54-2.45 (m, 1 H), 2.21-2.14 (m, 1 H), 1.98-1.88 (m, 1 H), 0.92 (t, *J* = 7.3 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.3, 129.9, 129.0, 128.4, 118.1, 107.9, 103.5, 62.4, 60.7, 55.9, 44.3, 41.7, 25.6, 8.3 ppm. MS (ES): *m/z* = 271.2 $[M + H]^+$ (100).

16d: light brown oil, 0.251 g (77%). $[\alpha]_D^{20}$ = – 5.9 (*c* = 0.6, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.39-7.28 (m, 5 H), 6.52 (t, *J* = 2.2 Hz, 1 H), 6.11 (t, *J* = 3.2 Hz, 1 H), 5.78-5.76 (m, 1 H), 4.05 (dt, *J* = 4.7 Hz, *J* = 11.7 Hz, 1 H), 3.97-3.91 (m, 3 H), 3.80-3.74 (m, 1 H), 3.50-3.38 (m, 1 H), 3.21-3.16 (m, 1 H), 1.85-1.71 (m, 1 H), 1.70-1.55 (m, 1 H), 1.41-1.18 (m, 10 H), 0.90 (t, *J* = 6.7 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.5, 128.6, 128.4, 127.8, 118.3, 107.5, 104.0, 65.3, 63.8, 54.9, 41.4, 40.9, 34.1, 31.8, 29.2, 26.4, 22.6, 14.0 ppm. MS (ES): *m/z* = 327.1 $[M + H]^+$ (100). Anal. Calcd for $C_{21}H_{30}N_2O$ (326.48): C, 77.26; H, 9.26; N, 8.58. Found: C, 77.56; H, 9.29; N, 8.55.

epi-**16d**: yellow oil, 0.020 g (6%). $[\alpha]_D^{20}$ = +5.4 (*c* = 0.9, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.41-7.28 (m, 5 H), 6.60 (t, *J* = 2.2 Hz, 1 H), 6.20 (t, *J* = 2.5 Hz, 1 H), 5.80-5.75 (m, 1 H), 4.36-4.26 (m, 1 H), 4.25-4.16 (m, 2 H), 3.72-3.66 (m, 1 H), 3.37-3.27 (m, 1 H), 3.15-3.08 (m, 1 H), 2.04-1.98 (m,2 H), 1.40-1.18 (m, 10 H), 0.90 (t, *J*= 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.4, 131.3, 128.6, 127.8, 127.5, 118.6, 107.9, 104.9, 72.7 63.0, 42.2, 31.8, 30.1, 29.6, 29.4, 26.8, 23.6, 22.6, 14.1 ppm. MS(ES): *m/z* = 327.1 $[M + H]^+$ (100).

16e: light brown oil, 0.107 g (38%). $[\alpha]_D^{20}$ = +18.3 (*c* = 0.9, $CHCl_3$). IR (neat): ν = 3416, 3068, 2924, 2852, 1639, 1569, 1492, 1333, 1290, 1069, 1029, 914, 702; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39-7.26 (m, 5 H), 6.52 (t, *J* = 1.7 Hz, 1 H), 6.11 (t, *J* = 2.9 Hz, 1 H), 5.88-5.80 (m, 1 H), 5.79-5.76 (m, 1 H), 5.09-4.99 (m, 2 H), 4.06 (t, *J* = 6.7 Hz, 1 H), 4.03-3.93 (m, 2 H), 3.92-3.87 (m, 2 H), 3.79-3.72 (m, 1 H), 3.46-3.38 (m, 1 H), 3.20-3.13 (m, 1 H), 2.63-2.52 (m, 1 H), 2.47-2.38 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.2, 136.1, 129.5, 128.5, 128.4, 127.8, 118.4, 116.8, 107.5, 103.9, 65.7, 63.4, 54.6, 41.7, 41.6, 38.8 ppm. MS (ES): *m/z* = 283.2 $[M + H]^+$ (100), 305.2 $[M + Na]^+$ (15). Anal. Calcd for $C_{18}H_{22}N_2O$ (282.38): C, 76.56; H, 7.85; N, 9.92. Found: C, 76.58; H, 7.87; N, 9.90.

epi-**16e**: yellowish oil, 0.039 g (14%). $[\alpha]_D^{20}$ = –13.4 (*c* = 0.8, $CHCl_3$). IR (neat): ν = 3415, 3078, 2975, 2926, 2849, 2793, 1639, 1496, 1485, 1339, 1219, 1119, 1002, 849, 704; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38-7.23 (m, 5 H), 6.47 (t, *J* = 1.6 Hz, 1 H), 6.12 (t, *J* = 3.3 Hz, 1 H), 5.89-5.86 (m, 1 H), 5.80-5.67 (m, 1 H), 5.23-5.17 (m, 1 H), 5.22 (s, 1 H), 5.14 (t, *J* = 11.6 Hz, 1 H), 4.22 (dd, *J* = 4.8 Hz, *J* = 9.7 Hz, 1 H), 4.13 (t, *J* = 4.1 Hz, 1 H), 4.05 (t, *J* = 10.6 Hz, 1 H), 3.94-3.87 (m, 2 H), 3.73 (dd, *J* = 4.8 Hz, *J* = 10.9 Hz, 1 H), 3.26-3.18 (m, 1 H), 2.94-2.85 (m, 1 H), 2.76-2.68 (m, 1 H), 2.55-2.47 (m, 1 H), 1.57 (bs, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ =136.0, 134.6, 128.9, 128.4, 128.2, 118.2, 117.7, 108.0, 103.8, 62.7, 60.6, 54.7, 44.2, 41.5, 38.3 ppm. MS (ES): *m/z* = 283.2 $[M + H]^+$ (100), 305.1 $[M + Na]^+$ (23).

16f: yellowish oil, 0.176 g (53%). $[\alpha]_D^{20}$ = –86.2 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34-7.03 (m, 10 H), 6.48 (dd, *J* = 1.7 Hz, *J* = 2.6 Hz, 1 H), 6.06 (t, *J* = 3.1 Hz, 1 H), 5.48 (dd, *J* = 1.4 Hz, *J* = 3.4 Hz, 1 H), 4.14 (t, *J* = 7.4 Hz, 1 H), 4.10-3.98 (m, 1 H), 3.90 (t, *J* = 5.1 Hz, 1 H), 3.79-3.70 (m, 1 H), 3.67-3.58 (m, 1 H), 3.36-3.24 (m, 1 H), 3.13 (dd, *J* = 7.9 Hz, *J* = 13.2 Hz, 1 H), 2.83 (dd, *J* = 6.3 Hz, *J* = 13.2 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.0, 139.2, 131.2, 129.6, 129.1, 128.5, 128.4, 128.2, 128.1, 127.7, 127.6, 127.5, 126.2, 118.3, 107.4, 104.2, 66.1, 63.8, 56.3, 41.5, 41.3, 40.9 ppm. MS (ES): *m/z* = 333.2 $[M + H]^+$ (100). Anal. Calcd for $C_{22}H_{24}N_2O$ (332.44): C, 79.48; H, 7.28; N, 8.43. Found: C, 79.28; H, 7.31; N, 8.41.

epi-**16f**: yellowish oil, 0.096 g (29%). $[\alpha]_D^{20}$ = +14.3 (*c* = 1.6, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32-7.12 (m, 10 H), 6.46 (m, 1 H), 6.12 (t, *J* = 3.1 Hz, 1 H), 5.77 (m, 1 H), 4.04 (dd, *J* = 4.9 Hz, *J* = 7.1 Hz, 1 H), 3.75 (dd, *J* = 7.7 Hz, *J* = 11.0 Hz, 1 H), 3.71-3.54 (m, 4 H), 3.10 (dd, *J* = 5.8 Hz, *J* = 13.2 Hz, 1 H), 2.75

(ddd, *J* = 4.2 Hz, *J* = 5.8 Hz, *J* = 13.2 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.8, 137.2, 129.5, 128.7, 128.4, 128.3, 128.2, 128.0, 126.5, 118.2, 104.2, 64.4, 61.7, 56.7, 42.5, 41.9, 40.4 ppm. MS (ES): *m/z* = 333.1 $[M + H]^+$ (100).

16g + ***epi*****-16g**: this was obtained as an oil**,** 0.141 g (45%, d.r. 60:40). Representative signals of **16g** in the ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of the mixture were observed at δ = 6.61 (dd, *J* = 2.0 Hz, *J* = 2.8 Hz, 1 H), 6.15 (dd, *J* = 2.8 Hz, *J* = 3.6 Hz, 1 H), 5.59 (m, 1 H), 5.06 (s, 1 H), 3.29 (m, 1 H), 3.21 (m, 1 H) ppm. MS (ES): *m/z* = 319.1 $[M + H]^+$ (100). Representative signals of *epi*-**16g**: δ = 6.51 (t, *J* = 1.6 Hz, 1 H), 6.03 (t, *J* = 3.2 Hz, 1 H), 5.27 (m, 1 H), 4.79 (s, 1 H), 4.22 (dd, *J* = 4.6 Hz, *J* = 10.6 Hz, 1 H), 4.22 (ddd, *J* = 1.9 Hz, *J* = 3.0 Hz, *J* = 12.1 Hz, 1 H), 2.59 (ddd, *J* = 3.7 Hz, *J* = 12.1 Hz, *J* = 12.2 Hz, 1 H) ppm. MS (ES): *m/z* = 319.1 $[M + H]^+$ (100). Anal. Calcd for $C_{21}H_{22}N_2O$ (318.41): C, 79.21; H, 6.96; N, 8.80. Found: C, 79.02; H, 6.97; N, 8.78.

17a: yellowish oil, 0.033 g (15%). $[\alpha]_D^{20}$ = +23.4 (*c* = 1.0, $CHCl_3$). IR (neat): *v* = 3361, 2968, 2934, 2853, 1466, 1449, 1367, 1315, 1114, 1080, 1069, 1019, 886, 733, 715. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.56-6.53 (m, 1H), 6.18 (t, *J* = 3.3 Hz, 1 H), 5.91-5.89 (m, 1 H), 4.34 (q, *J* = 6.2 Hz, *J* = 12.2 Hz, 1 H), 4.00-3.92 (m, 2 H), 3.62 (dd, *J* = 5 Hz, *J* = 10.2 Hz, 1 H), 3.31 (t, *J* = 10.6 Hz, 1 H), 3.19-3.12 (m, 1 H), 3.10-3.00 (m, 1 H), 2.99-2.90 (m, 1 H), 2.00-1.90 (m, 1 H), 1.47 (d, *J* = 6.4 Hz, 3 H), 1.08 (d, *J* = 6.4 Hz, 3 H), 0.90 (d, *J* = 6.9 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 132.5, 118.4, 108.0, 103.2, 63.1, 58.8, 53.0, 45.7, 41.4, 27.9, 22.6, 20.9, 19.9; MS (EI): *m/z* = 207 (100), 121 (53), 191 (35), 222 (1); MS (ES): *m/z* = 223.1 $[M + H]^+$ (100). Anal. Calcd for $C_{13}H_{22}N_2O$ (222.33): C, 70.23; H, 9.97; N, 12.60. Found: C, 70.19; H, 10.00; N, 12.58.

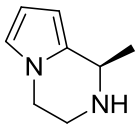
epi-**(17a)**: yellow oil, 0.011 g (5%). $[\alpha]_D^{20}$ = −15.2 (*c* = 1.0, $CHCl_3$). IR (neat) *v* = 3407, 2954, 2921, 1581, 1450, 1348, 1066, 1029, 731, 702. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.53-6.50 (m, 1 H), 6.15 (t, *J* = 3.0 Hz, 1 H), 5.88-5.84 (m, 1 H), 4.21 (q, *J* = 6.4 Hz, *J* = 12.7 Hz, 1 H), 4.00-3.86 (m, 2 H), 3.81 (dd, *J* = 3.7 Hz, *J* = 11.2 Hz, 1 H), 3.69 (dd, *J* = 7.1 Hz, *J* = 11.1 Hz, 1 H), 3.24-314 (m, 1 H), 2.68-2.60 (m, 1 H), 2.03-190 (m, 1H), 2.00-1.90 (m, 1 H), 1.41 (d, *J* = 6.2 Hz, 3 H), 1.02 (d, *J* = 6.8 Hz, 3 H), 0.98 (d, *J* = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ =133.2 118.0, 107.8, 102.8, 66.2, 60.2, 52.2, 45.7, 44.9, 27.6, 21.7, 20.9, 20.1 ppm. MS (EI): *m/z* = 207 (100), 121 (51), 191 (19), 222 (1); MS (ES): *m/z* = 223.1 $[M + H]^+$ (100).

17b + ***epi*****-17b**: yellow oil, 0.160 g (68%, d.r. 65:35). Representative signals of **17b** in the ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of the mixture were present at δ = 4.23 (t, *J* = 4.6 Hz, 1 H), 3.64 (dd, *J* = 5.2 Hz, *J* = 10.4 Hz, 1 H), 3.35 (t, *J* = 10.4 Hz, 1 H), 3.04 (dt, *J* = 3.2 Hz, *J* = 11.7 Hz, 1 H), 2.77 (m, 1 H). Representative signals of *epi*-**17b**: δ = 4.08 (t, *J* = 4.7 Hz, 1 H), 3.82 (dd, *J* = 3.5 Hz, *J* = 11.4 Hz, 1 H), 3.69 (dd, *J* = 6.1 Hz, *J* = 6.8 Hz, 1 H), 3.20 (dt, *J* = 4.0 Hz, *J* = 12.3 Hz, 1 H), 2.50 (m, 1 H). Anal. Calcd for $C_{14}H_{24}N_2$ (236.25): C, 71.14; H, 10.23; N, 11.85. Found: C, 71.11; H, 10.25; N, 11.84.

17e + *epi*-17e: yellowish oil, 0.158 g (64%, d.r. 50:50). Representative signals of **17e** in the ^{1}H NMR spectrum (400 MHz, $CDCl_3$) were observed at δ = 6.57-6.55 (m, 1 H), 5.95-5.88 (m, 1 H), 5.62-5.49 (m, 1 H), 4.39 (t, *J* = 4.2 Hz, 1 H), 4.23 (t, *J* = 5.1 Hz, 1 H), 3.36 (t, *J* = 10.4 Hz, 1 H), 3.09-2.93 (m, 2 H), 1.05 (d, *J* = 6.8 Hz, 3 H), 0.90 (d, *J* = 6.8 Hz, 3 H) ppm. Representative signals of *epi*-**17e**: δ =6.54-6.50 (m, 1 H), 5.87-5.84 (m, 1 H), 5.83-5.71 (m, 1 H), 3.28 (dt, *J* = 4.6 Hz, *J* = 12.8 Hz, 1 H), 2.85-2.77 (m, 1 H), 0.87 (t, *J* = 7.2 Hz, 3 H) ppm. Anal. Calcd for $C_{15}H_{24}N_2$ (248.36): C, 72.54; H, 9.74; N, 11.28. Found: C, 72.28; H, 9.76; N, 11.24.

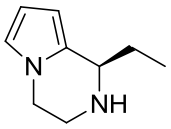
17f + *epi*-17f: light red oil, 0.226 g (76%, d.r. 50:50). Representative signals of **17f** in the ^{1}H NMR spectrum (400 MHz, $CDCl_3$) were observed at δ = 7.33-7.21 (m, 4 H), 6.95 (m, 1 H), 6.54 (m, 1 H), 6.11 (dd, *J* = 2.8 Hz, *J* = 3.6 Hz, 1 H), 5.64 (ddd, *J* = 0.7 Hz, *J* = 1.6 Hz, *J* = 3.5 Hz, 1 H), 4.54 (dd, *J* = 4.8 Hz, *J* = 6.1 Hz, 1 H), 3.86 (dt, *J* = 3.9 Hz, *J* = 12.1 Hz, 1 H), 3.64 (dd, *J* = 5.1 Hz, *J* = 10.7 Hz, 1 H), 3.54 (m, 1 H), 3.33 (t, *J* = 10.7 Hz, 1 H), 3.17 (dd, *J* = 4.6 Hz, *J* = 13.1 Hz, 1 H), 3.00-2.87 (m, 3 H), 2.82 (ddd, *J* = 5.1 Hz, *J* = 7.9 Hz, *J* = 13.1 Hz, 1 H), 1.87 (m, 1 H), 0.97 (d, *J* = 6.7 Hz, 3 H), 0.87 (d, *J* = 6.7 Hz, 3 H) ppm. Representative signals of **17f** in the ^{13}C NMR (100 MHz, $CDCl_3$) sèectrum were present at δ = 138.3, 129.7, 128.5, 128.1, 126.3, 118.3, 107.4, 104.5, 66.8, 50.1, 44.9, 43.8, 43.0, 40.6, 28.4, 22.0, 19.7 ppm. MS (ES): *m/z* = 299.2 $[M + H]^+$ (100). Representative signals of *epi*-**17f** in the ^{1}H NMR spectrum (400 MHz, $CDCl_3$) were observed at δ = 4.34 (t, *J* = 6.7 Hz, 1 H), 3.93 (ddd, *J* = 4.3 Hz, *J* = 8.3 Hz, *J* = 12.3 Hz, 1 H), 3.78 (ddd, *J* = 4.3 Hz, *J* = 5.3 Hz, *J* = 12.3 Hz, 1 H), 3.44 (dd, *J* = 4.3 Hz, *J* = 8.3 Hz, *J* = 13.1 Hz, 1 H), 2.65 (t, *J* = 7.7 Hz, 1 H), 2.58 (ddd, *J* = 3.8 Hz, *J* = 6.3 Hz, *J* = 10.2 Hz, 1 H), 1.80 (m, 1 H), 0.89 (d, *J* = 6.8 Hz, 3 H), 0.85 (d, *J* = 6.8 Hz, 3 H) ppm. MS (ES): *m/z* = 299.2 $[M + H]^+$ (100). Anal. Calcd for $C_{19}H_{26}N_2$ (298.42): C, 76.47; H, 8.78; N, 9.39. Found: C, 76.45; H, 8.78; N, 9.37.

17g + *epi*-17g: light red oil, 0.221 g (78%, d.r. 40:60). Representative signals of **17g** in the ^{1}H NMR spectrum (400 MHz, $CDCl_3$) were observed at δ = 7.36-7.28 (m, 5 H), 6.58 (m, 1 H), 6.08 (dd, *J* = 2.8 Hz, *J* = 3.5 Hz, 1 H), 5.32 (m, 1 H), 5.19 (s, 1 H), 4.15 (ddd, *J* = 4.0 Hz, *J* = 11.3 Hz, *J* = 11.4 Hz, 1 H), 4.08 (ddd, *J* = 2.1 Hz, *J* = 3.9 Hz, *J* = 11.4 Hz, 1 H), 3.42 (dd, *J* = 5.2 Hz, *J* = 10.7 Hz, 1 H), 3.35 (t, *J* = 10.7 Hz, 1 H), 3.29 (ddd, *J* = 1.9 Hz, *J* = 4.0 Hz, *J* = 12.1 Hz, 1 H), 3.16 (m, 1 H), 2.61 (ddd, *J* = 5.4 Hz, *J* = 6.4 Hz, *J* = 11.6 Hz, 1 H), 2.04 (m, 1 H), 1.05 (d, *J* = 6.4 Hz, 3 H), 0.83 (d, *J* = 6.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.8, 131.8, 129.4, 128.6, 128.0, 118.2, 108.3, 105.7, 63.7, 62.5, 58.5, 45.7, 42.0, 26.9, 22.9, 19.6 ppm. Representative signals of *epi*-**17g**: δ = 6.55 (m, 1 H), 6.05 (dd, *J* = 2.8 Hz, *J* = 3.6 Hz, 1 H), 5.30 (m, 1 H), 5.10 (s, 1 H), 3.94 (dd, *J* = 2.9 Hz, *J* = 11.7 Hz, 1 H), 3.72 (dd, *J* = 5.7 Hz, *J* = 11.7 Hz, 1 H), 2.26 (m, 1 H), 0.93 (d, *J* = 6.6 Hz, 3 H), 0.80 (d, *J* = 6.6 Hz, 3 H) ppm. Anal. Calcd for $C_{18}H_{24}N_2O$ (284.40): C, 76.02; H, 8.51; N, 9.85. Found: C, 76.16; H, 8.50; N, 9.83.



21a

Removal of the chiral auxiliary. Typical procedure: 10% Pd/C (0.048 g) was added to a solution of **16a** (0.476 g, 1.9 mmol) in MeOH (10 mL) inside an autoclave. The reaction mixture was kept under 7 bar of H_2 for 2 d, then the catalyst was filtered through a small pad of Celite and the organic solution was concentrated under vacuum. The oily residue was subjected to column chromatography (SiO_2, CH_2Cl_2/MeOH mixture 95:5) to give (*R*)-1-methyl-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine **21a** (0.205 g, 81%) as an orange oil. $[\alpha]_D^{20}$ = +8.3 (*c* = 0.7, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.54 (t, *J* = 2.4 Hz, 1 H), 6.15 (dd, *J* = 2.8 Hz, *J* = 3.6 Hz, 1 H), 5.90-5.80 (m, 1 H), 4.06 (q, *J* = 6.8 Hz, 1 H), 3.95-3.90 (m, 2 H), 3.38-3.31 (m, 1 H), 3.24-3.15 (m, 1 H), 1.06 (d, *J* = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ =132.9, 119.0, 107.7, 102.3, 49.5, 45.4, 43.4, 31.0 ppm. MS (ES): *m/z* = 136.1 $[M + H]^+$. Anal. Calcd for $C_8H_{12}N_2$ (136.19): C, 70.55; H, 8.88; N, 20.57. Found: C, 70.28; H, 8.91; N, 20.50.



21b

(*R*)-1-Ethyl-(1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine (21b): this was prepared starting from **16a** (0.156 g, 0.6 mmol) as an orange oil: 0.156 g (79%). $[\alpha]_D^{20}$ = +11.8 (*c* = 0.7, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.55 (t, *J* = 2.1 Hz, 1 H), 6.15 (t, *J* = 3.4 Hz, 1 H), 5.90-5.88 (m, 1 H), 3.95-3.87 (m, 2 H), 3.38-3.35 (m, 1 H), 3.20-3.12 (m, 1 H), 2.03-1.94 (m, 2 H), 1.06 (t, *J* = 7.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 131.5, 118.8, 107.5, 102.3, 55.0, 45.3, 42.9, 28.2, 10.2 ppm. MS (ES): *m/z* = 151.1 $[M + H]^+$ (100). Anal. Calcd for $C_9H_{14}N_2$ (150.22): C, 71.96; H, 9.39; N, 18.65. Found: C, 71.63; H, 9.43; N, 18.58.

X-ray crystallographic study of 14: The X-ray intensity data for **14** were measured on a Bruker SMART Apex II diffractometer equipped with a CCD area detector and a graphite monochromated Mo-K_α radiation source (λ = 0.71073 Å). Cell dimensions and the orientation matrix were initially determined from a least-squares refinement on reflections measured in three sets of 20 exposures, collected in three different ω regions, and eventually refined against all data. For all crystals, a full sphere of reciprocal space was scanned by 0.3° ω steps. The software SMART[222] was used for collecting frames of data, indexing reflections and determination of lattice parameters. The collected frames were then processed for integration by software SAINT[222] and an empirical absorption correction was applied with SADABS.[223] The structure was solved by direct methods (SIR 97)[224] and subsequent Fourier syntheses and refined by full-matrix least-squares calculations on F^2 (SHELXTL)[225] attributing anisotropic thermal parameters to the non-hydrogen atoms. All hydrogen atoms

were located in the Fourier map. The aromatic and methylene hydrogen atoms were placed in calculated positions and refined with isotropic thermal parameters *U(H)* = 1.2 *Ueq*(C), and allowed to ride on their carrier carbons whereas the methine H atoms were located in the Fourier map and refined isotropically [*U*(H) = 1.2 U_{eq}(C)]. CCDC-792774 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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ABBREVIATIONS

EDTA = Ethylenediaminetetraacetic acid

DTPA = Diethylenetriaminepentaacetic acid

DMAP = Dimethylaminopyridine

TEA = Triethylamine

DOTA = 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid

DMF = N,N-Dimethyl formamide

CSA = Chiral solvating agent

BOX= Bisoxazoline

TFA= Trifluoroacetic acid

TEM = Transmission electron microscopy

TBAI = tetrabutylammonium iodide

MCR = multicomponent reactions

COD = cyclooctadiene

BINAP = (1,1′-Binaphthalene-2,2′-diyl)bis(diphenylphosphine)

SALEN = N,N′-Disalicylidene-ethylenediamine

PCC = Pyridinium chlorochromate