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Preparation of copper(II)-BOX supported complexes and their application in stereoselective organic syntheses

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INTRODUCTION

1. Heterogeneous Catalysis

In recent years the need to reduce production costs and the increasing regulations in pollution prevention prompted industries and academia to revise old processes in order to obtain safer and cleaner procedures for fine chemicals and pharmaceuticals synthesis[1]. Novel processes should encounter several requirements such as high chemo-, regio- and stereoselectivity, one pot reactions or multi-component reactions[2] instead of multi-step procedures, use of no-toxic solvents or solvent-free reactions[3], elimination of toxic and/or harmful reagents, improvement of atom economy[4] etc.

Often the way to achieve these targets resides in the replacement of stoichiometric processes with catalytic ones. Catalysis is a powerful tool for organic synthesis as it generally allows the production of valuable chemicals with the aid of small amounts of a promoter. Moreover heterogeneous catalysis allows a few more improvements over the homogeneous one that can contribute to develop cleaner, safer and more economically feasible processes.

However, heterogeneous catalysts, in order to be practical, has to meet numerous requisites as:

- The catalyst preparation should be simple, efficient and of general applicability
- The performance of the immobilized catalyst should be comparable to (or better than) its homogeneous counterpart.
- Separation of the heterogeneous catalyst from the reaction mixture after reaction should be possible via a simple filtration in which more than the 95% of the catalyst should be recovered.
- Leaching of the active species from the heterogenized catalyst should be minimal.
- Recycling for several cycles should be possible without loss of activity.
- The supports carrying the catalyst should be mechanically, thermally and chemically stable. They should be compatible with the solvent and commercially available in a good quality.
- From an environmental (increasing disposal costs) and economical (cost of raw materials and of downstream separation) viewpoint, selectivity of the catalyst might sometimes become more important than its activity or lifetime.

In the class of solid catalysts, particularly interesting are the supported homogeneous catalysts as they combine the potential versatility and selectivity of homogeneous catalysts with the practical advantages of solid materials, such as easy separation of the catalyst from the reaction medium, recovery, recyclability, higher stability of the supported species and possibility of using a large variety of solvents and reaction conditions.

1.1 Chiral Heterogeneous Catalysts

Molecular chirality plays a key role in science and technology and in fact life itself depends on molecular chirality, as the most part of biological activities are basically dissymmetric[5]. Molecular recognition of chiral host molecules toward two enantiomeric guests is at the basis of most physiological phenomena. There are several examples where effects of enantiomers are completely different (as an example different smell and taste). Moreover the different structure of enantiomers can have peculiar activity with respect to synthetic drugs as receptor sites in the human body interact only with drug molecules having the proper chirality. A striking example of the correlation between pharmacological activity and molecular structure was offered by the tragic case of thalidomide, a sedative which was given to pregnant women in the 1960s. (*R*)-Thalidomide has desirable effect, while its (*S*)-enantiomer is teratogenic and causes fetal malformations[6].

Even so, up to early 1990s, about 90% of synthetic chiral drugs were still racemic mixtures. Finally, in recent years, the Food and Drug Administration (FDA) introduced market regulations in order to encourage the commercialization of single enantiomeric drugs[7]. Such policies for synthetic drugs and recent progress in stereoselective organic synthesis, determined a considerable boost in the production of single-enantiomer drugs.

The development of truly efficient methods to achieve enantiopure compounds has been a substantial challenge for chemists in both academia and industry. Available methodologies to obtain enantiomerically pure compounds are based on four main approaches:

- Racemate resolution
- Transformation of readily accessible, naturally occurring chiral compounds (amino acids, tartaric and lactic acids, carbohydrates, terpenes, or alkaloids)
- Use of chiral auxiliaries
- Stereoselective conversion of a prochiral compound to a chiral product (asymmetric catalysis or biocatalysis)

Among these, asymmetric catalysis is the most attractive approach as it allows the flexible synthesis of a wide array of enantiopure organic substances from achiral precursors. Traditional asymmetric synthesis (chiral auxiliaries) and racemate resolution which use a stoichiometric amount of a chiral compound is practical only if the expensive chiral auxiliary is readily recyclable being, otherwise, a wasteful procedure from an economical and ecological point of view. Transformation of natural occurring chiral starting materials is not of general applicability

due to the limited availability of enantiomerically pure building blocks. Also the use of enzymes, cell cultures, or whole microorganisms is limited because of the inherent single-handed, lock-and-key specificity of biocatalysts.

The requirements for practical asymmetric synthesis include high stereoselectivity, high rate and productivity, atom economy, cost efficiency, operational simplicity, environmental friendliness, and low-energy consumption. Of various potentialities, the use of chiral organometallic molecular catalysts would be the most powerful strategy for this purpose. However chiral complexes found limited application so far due to intrinsic drawbacks related to their use: high cost of the metal and/or the chiral ligand, difficult removal of the catalyst from the crude after the reaction, metal contamination. An elegant way to overcome these negative aspects is the heterogenization of chiral catalysts. In fact enantioselective solid catalysts are easily removed from reaction mixtures by simply filtration and this determines lower metal contamination. Moreover the possibility to recover the precious catalyst allows its recycling with evident economical returns.

An heterogeneous asymmetric catalyst can be obtained following mainly two different approaches:

- Modification of heterogeneous catalysts: solid catalyst modified with a chiral auxiliary[8] (e.g. Pt and Pd hydrogenation catalysts modified with cinchona alkaloids) or metals supported onto chiral polymers[9] (e.g. Pd/silk fibroin)
- Heterogenization of homogeneous catalysts

The focus of this dissertation regards the immobilization of (enantio)selective catalysts onto solid supports (inorganic silica and/organic polymers)

1.1.1. Supported homogeneous catalysts

In the last years many efforts have been devoted to the catalysts heterogenization and different strategies were developed for the preparation of supported homogeneous catalysts[10]. The particular interest in these modified materials comes from their special features: in fact they combine the potential adaptability and selectivity of homogeneous catalysts with the practical advantages of solid materials, such as easy separation of the catalyst from the reaction medium, recovery, recyclability, higher thermal and chemical stability of the supported species and possibility of using a large variety of solvents and reaction conditions. The ideal supported catalyst should thus satisfy many requirements in order to combine both advantages of homogeneous and heterogeneous catalysis (Figure 1).

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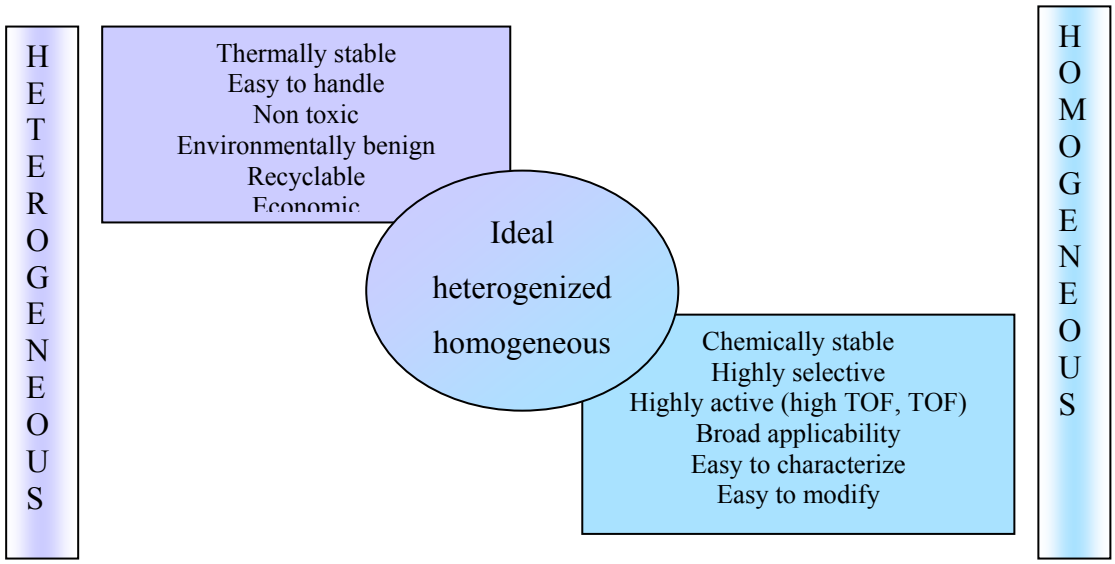

Figure 1. Ideal supported homogeneous catalyst

However the creation of the ideal supported catalyst is far to be accomplished and indeed many problems related to this technology have to be overcome. First of all the heterogenization procedure usually causes a decreasing in both stereoselectivity and activity of the homogeneous catalyst. The solid support, in fact, determines limited diffusion of reactants to the active sites of the catalyst and this results in lower reaction rates. Also the lower stereoselectivity, which is often reached with heterogeneous systems, has to be ascribed to the matrix effect. With its chemical and physical properties the support surface in close proximity of the anchored catalytic site can influence the extent of the reaction and determine a lower selectivity. As an example, when using silica as support the polar surface can easily form hydrogen bonds with many

organic polar functional groups or interact with metal atoms and this effect can change the spatial orientation of reactants towards catalysts thus affecting the induction of chirality. On the other hand organic polymeric supports have usually little porosity therefore there is a spatial constriction of catalysts which are not completely free to assume the best orientation towards prochiral reactants.

Moreover, recyclability of solid catalysts has not yet reached a good level of efficiency to be of practical interest. In this respect there are many problems related both to the catalyst and the support. The catalyst can be damaged during the reaction or if it is a metal complex there can be a partial leaching of the metal in the reaction medium that determines a partial deactivation of the catalyst itself. In some cases however the supporting procedure can improve the catalyst's stability by eliminating dimerization and/or aggregation effects which are the main causes of deactivation under homogeneous conditions. In fact "site isolation", i.e. attaching the catalyst to a support in such a way that the active sites can no longer interact with each other, is a key concept that might lead to better performing heterogeneous catalysts[11].

With a careful design of the catalyst and an appropriate choice of the support based on reaction conditions (e.g. solvent, temperature, reactant etc.) it is possible to overcome these drawbacks.

1.2. The Supporting Methodologies

The most common procedures to immobilize a homogeneous catalyst onto a polymeric material are depicted in Figure 2.

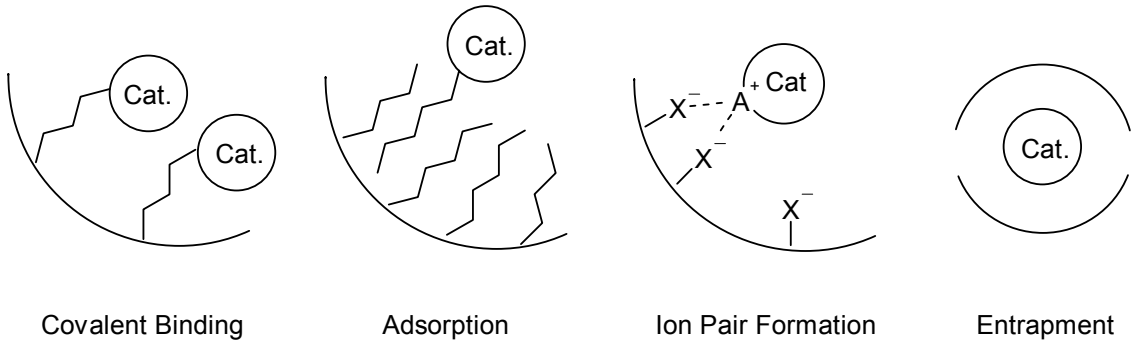

Figure 2. Techniques for catalyst's immobilization

Covalent Bond

The formation of covalent bonds to support a catalyst onto a solid material is the far most used technique as it usually gives more stable materials. The anchoring can be performed basically in two ways:

a) Copolymerization of the homogeneous catalysts (opportunely modified with a functional group reactive towards polymerization) with comonomers
b) Supporting of the catalysts onto a preformed polymer.

In both cases the support of choice can be organic (polystyrene, polyacrylate, PEG etc.) or inorganic (alumina, silica, zeolites etc)[12].

Moreover when supporting a homogeneous catalyst onto a preformed polymer two strategies can be followed: grafting and tethering. Through the grafting methodology[13] the active site is directly bound to the polymer surface while with the tethering strategy[14] an appropriate linker is used to space the catalyst from the support surface. This latter methodology allows reduced interactions between the catalyst and the support thus rendering the heterogeneous catalyst more similar to its homogeneous counterpart. However some problem might occur when using a tether to covalently support a catalyst. It is sometimes difficult to understand the exact influence of this additional group on the intrinsic activity of the derivatized species, especially if the tether is attached close to the active site. Moreover some times the solid matrix could create some steric restriction, inhibiting the activity of the catalyst, A clear example of this drawback is Jacobsen's Salen catalyst. Sherrington at all showed that there is a matrix effect in this catalyst immobilizes on polymer resins[15]. If the Mn sopported complex is obtained by copolymerization of distyryl derivatives of chiral Salen ligand, the alkene epoxidation occurs with low levels of enantiocontrol. However, if the catalyst is attached by a single flexible linkage to the polymer support in order to minimize local steric restrictions (Figure 3), the reaction achieves more than 90% e.e., as in homogeneous phase.[16]

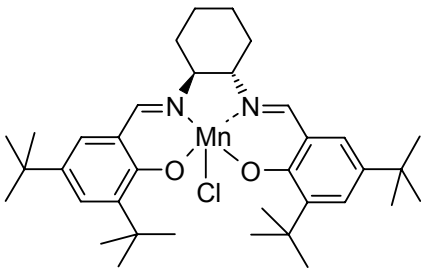

Figure 3. Jacobsen's catalyst for olefins epoxidation

The practice of covalently supporting homogeneous catalysts allowed achieving significant results in the field of heterogeneous catalysis in particular with hydrogenation catalysts. Bayston et al.[16] reported a polystyrene-supported BINAP which was used in the catalytic hydrogenation of α-ketoesters and dehydroamino acids with conversions and enantioselectivities comparable to those obtained under homogeneous catalysis (heterogeneous: yield 99%; ee 97%; homogeneous:

yield 100%; ee 99%). Even more successful was the system developed by de Rege et al.[17]: MCM-41 heterogenized [(*R*,*R*)-Me-DuPHOS)Rh(COD)]$^+$ catalyst for the asymmetric hydrogenation of amidoacrylic acids. The heterogeneous catalyst gave the same excellent performances of the homogeneous one (99% conv., 99% ee) and with some solvents it proved to be even better. Moreover the reuse of the catalysts showed no loss of activity or enantioselectivity.

1.2.1. Adsorption

In this methodology the catalyst is bound to the polymeric materials via absorptive interactions such as hydrophobic interactions between aliphatic chains[18]. However this technique did not find a broad applicability due to the leaching of the active species that often occurs. This drawback limits the recycling of the catalyst and determines a contamination of the crude thus rendering difficult the purification of the product.

1.2.2. Ion exchange

Ion pair formation between a negatively (positively) charged support surface and a positively (negatively) charged catalyst determines the immobilization of the latter via an electrostatic interaction.

The main disadvantage of this immobilization strategy is due to high mobility of ionic catalyst in the pores of the support which can lead to the leaching of the active species into the reaction mixture or the aggregation of catalyst's molecules (in particular with metal complexes) that can result in a deactivation of the catalyst itself.

However in the literature there are some successful examples of the potentiality of this methodology. Selke and coworkers[19,20] developed cationic rhodium-diphosphine complexes supported onto ionic resins. The final catalyst was tested in hydrogenation reactions and proved to be highly efficient and recyclable up to 20 times without an appreciable loss of activity and with little leaching.

Langham and co-workers[21] reported a copper-exchanged zeolite Y modified with chiral bis(oxazolines) that afforded remarkable yields and enantioselectivities in olefins aziridation even with very low level of chiral modifiers. However some activity was lost with repeated use.

1.2.3. Entrapment

The entrapment or "Ship in the bottle" technique exploits well-defined cages of porous materials (e.g. zeolites) where the active catalyst is assembled and cannot get out because of its greater dimension in respect to the one of the pores of the support[22]. One of the first examples of heterogenization via entrapment was the encapsulation of chiral Salen in zeolitic materials[23,24]. Depending on the size of zeolite supercages (FAU or EMT) different kinds of complexes could be fitted; in all cases activities of supported catalysts were lower in respect to homogeneous counterparts. Lower reaction rates observed for the epoxidation of alkenes were attributed to the restrictions imposed on the diffusion of substrate and products through the micropores of the solid. Moreover if the complex is too bulky reagents cannot reach the active sites due to limited diffusion and the reaction does not take place.

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1.3. The Solid Supports

The development of supported catalysts for heterogeneous reactions prompted research groups all over the world to investigate many different solid supports as these have an important role in the outcome of the process. Solid supports can be roughly divided in two classes: organic polymers and inorganic materials.

1.3.1. Organic Polymers

Organic polymers as solid phases for heterogeneous catalysis are mainly of three types: soluble polymers (linear non cross-linked), cross-linked insoluble polymers and macroreticulated resins.

Linear polymers

Polystyrene-based materials are by far the most widely employed and they can give a good insight on the effect of the nature of heterogeneous support. The conclusions, however, can be extended to other polymer supports.
Linear polystyrene is easily prepared from styrene in a radical polymerization reaction (Figure 4).

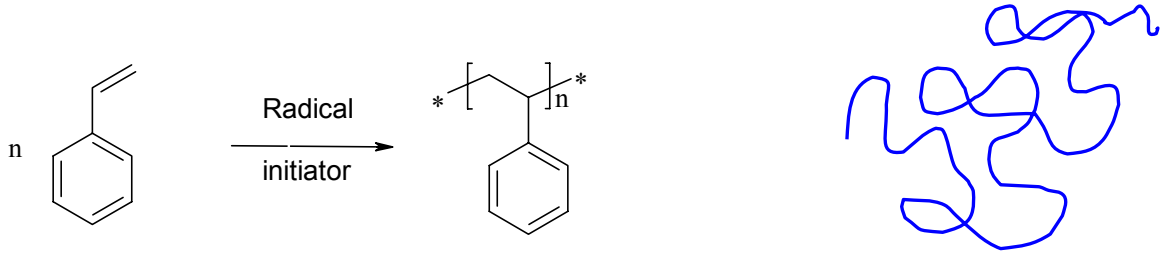


Figure 4. Schematic representation of linear polystyrene synthesis.

Synthetic polymers are generally devoid of any significant secondary and tertiary structure, such as commonly occurs with natural polymers (proteins, DNA), and individual isolated polymer molecules exist like a random coil typically ~ 10-20 nm in size, depending upon the molecular weight[25]. A collection of chemically similar polymer molecules exists as a mass of interpenetrating random coils. In the case of polystyrene in the solid state, at room temperature, individual polymer chains cannot migrate relative to each other and even bond rotations in the polymer backbone is very inhibited. Only the rotation of phenyl side chains occurs freely at room temperature and the polystyrene structure is essentially frozen (the material is below its *glass transition temperature* T_g).

Changes in the polymer structure can be induced by increasing the temperature or by the addition of small solvent molecules which can interact with the polymer framework. An interacting molecule can penetrate in the polystyrene and allow backbone rotation to occur; this is termed *plastification* and the polymer changes from a glass–like solid into a soft plastic material. An adsorbed solvent may interact even more favourably with the polymer chains, heavily solvate them, and allow them to move apart. Such solvents are called *thermodynamic-good* solvents or *swelling* solvents. In this dissolution process if enough solvent is added the individual polymer coils can separate each other completely to form an isotropic (uniform) solution in the solvent (solubilization of the polymer).

If the solvent is not able to interact properly and solvate the coils is termed '*bad*' solvent, *i e.*, non-solvents, or precipitants. On the other hand if a polymer is dissolved in a good solvent, and an excess of a bad solvent is added, then the polymer can precipitate as a solid material. In the case of polystyrenic materials examples of good and bad solvents are given in Table 1.

GOOD SOLVENTS	***δ (MPa)$^{0.5}$***	***BAD SOLVENTS***	***δ (MPa)***
Aromatic		Water	47.9
hydrocarbon	18.8		
Benzene	18.2	*Aliphatic alcohols*	
Toluene	18.0	Methanol	29.7
Xylenes		Ethanol	26.0
		2-ethylhexanol	19.4
Chlorocarbons			
1,2-dichloroetane	20.1	*Aliphatic*	
Chloroform	19.0	*hydrocarbons*	
		Hexane	14.9
Cyclic ethers		Dodecane	16.2
THF	18.6		
Dioxane	20.5	*Others*	
		Diethyl ether	15.1
		Acetic acid	20.7

Table 1. Classification of solvents for polystyrene.

The term δ of Table 1 is a useful thermodynamic parameter that refers to the solubility. This is a measure of the attractive strength between molecules in a material. The best compatibility between a polymer and a solvent is obtained when the two have very similar solubility parameters (the solubility parameter for polystyrene and for copolymer styrene-divinylbenzene is ~ 17-18 $(MPa)^{0.5}$). If the solubility parameters differ, the solvent is likely to be a bad solvent or precipitant for the polymer.

Soluble linear polymers have been broadly used as catalyst supports as once they are solubilized in the reaction mixture they allow rapid access of reactants to the active sites, and the recovery and separation of the polymer might be achieved by adding of a suitable precipitant and then by micro- or ultra-filtration.

However many drawbacks seems to limit their extensive utilization. First of all linear polymers as supports are useful only in solvent in which they can dissolve. In many cases the impossibility to find the appropriate solvent prevents the development of the supported catalysts for a given reaction. Moreover, micro- and ultra-filtration processes are relatively costly and part of the catalyst can be lost during the process. Another disadvantage is that in the precipitation of a

linear polymer with a suitable non-solvent, the material can trap the good solvent giving a sticky material impossible to filter. It is also important to realize that linear polymer coils in solution remain isolated from each other at concentration below ~ 1-2% wt. Above this threshold, polymeric coils interact and start to interpenetrate, and at concentration > 5% wt, solutions can became impractically viscous.

On the contrary lightly cross-linked polymer networks can swell more than five times their own mass and yet remain in a physical form useful for manipulation and this feature renders these materials more attractive than linear polymer as support.

Nevertheless there are situation where linear soluble polymers can be extremely useful, for example they permit the reaction monitoring by high-resolution solution phase ^{1}H- and ^{13}C-NMR[26].

Crosslinked polymers

When styrene is copolymerized in a mixture with *p*-divinylbenzene (DVB), the latter become the constituent of two polymers chains, effectively linking (*crosslinking*) the chains together. When all the chains are mutually connected an infinite network is formed (Figure 5).

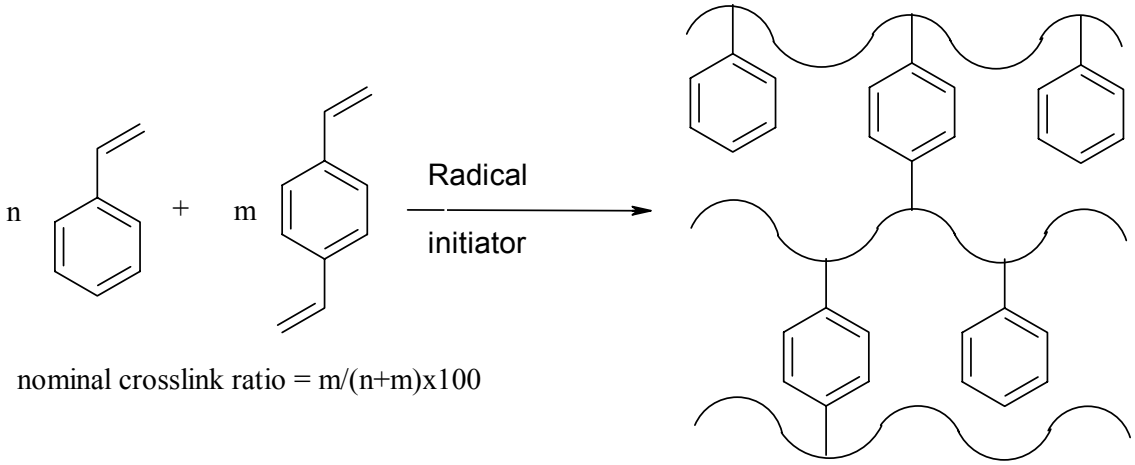


Figure 5. Schematic representation of crosslinked polystyrene synthesis.

There are several crosslinking monomers which can be used to tailor the properties of the final polymer; among these:

- Ethylene glycol dimethacrylate (EGDMA)
- Trimethyloylpropane trimethacrilate (TRIM)
- [1,1,1-Tris(methacryloyloxymethyl)-propane]
- N,N-Methylenbisacrylamide (MBA)

Although a defined level of crosslinker is used to synthesize a polymer matrix, there is no guarantee that both vinyl groups of all the crosslinker molecules will react. Indeed it is well known that, particularly when high DVB are used, significant number or vinyl groups remain unreacted. As an example a resin prepared with 100% DVB has ~45% of vinyl group unreacted, *i.e.* an effective crosslink ratio of 55%.

During the formation of crosslinked network it is also possible to produce additional mobile crosslinks by virtue of spurious entanglements which cannot disassemble (Figure 6). Generally 'entanglement crosslinks' increase when the rate of polymerization is increased and in non-agitated polymerization systems.

Figure 6. Representation of an entanglement crosslink.

Moreover when the polymer is subjected to further functionalization, post preparation additional reticulation can occur in the polymer network. Some reactions like chloromethylation or sulfonation of styrene are well known to be accompanied by intramolecular side-reactions that introduce additional crosslinks (CH_2 and SO_2 bridges between aromatics rings).

The process of crosslinking initially is a local phenomenon with the formation of small volumes of microgels (*microgelation*)[27] (Figure 7).

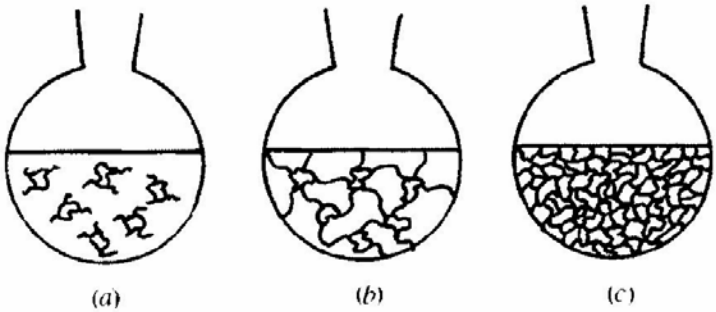


Figure 7. Polymerization of a monomer and crosslinker: *(a)* microgelation, *(b)* macrogelation, and *(c)* forming a solid monolith.

Eventually, however, the mass of growing polymer molecules dissolved in solution becomes crosslinked into one infinite network; the system reaches its '*gel point*'. At the point of macrogelation the polymer mass becomes a monolith soft gel filling the container vessel and diffusion of molecular compounds starts to become impaired, with the problem growing more acute as crosslinking increases. If polymerization is allowed to continue, the liquid co-monomers are gradually consumed, the polymer mass becomes increasingly desolvated and finally an amorphous crosslinked glassy monolith is formed in the shape of the containing vessel. The monolith can be recovered, crushed, solvent extracted and dried to form crosslinked polymer particles or powder of irregular size and shapes.

In these materials the polymeric chains are in molecular contact with each other and the surface areas at the dry state are typically very low (less than 10 m^2/g) so the diffusion of even small molecule through the crosslinked network is very slow. These materials will however swell in 'good solvent', *e.g.* toluene, with the percentage swelling being inversely related to the degree of crosslinking. Swelling creates space or *'solvent porosity'* within the resin and allows ready access by small molecules to the polymer network.

Macroporous resins

The term 'macroporous' resin is used to indicate a class of polymers which have a permanent well-developed porous structure even at the solid state.

If a polymerization of styrene-DVB mixture is carried out with the co-monomer mixture also containing an appropriate organic solvent (*diluent* or *porogen*) at some appropriate level then the internal structure (morphology) of the product resin can be very different to that of a gel-type resin. Removal of the porogen at the end of the polymerization can leave a heterogeneous and non-uniform matrix: some areas consist of impenetrable crosslinked and entangled polymer chains, other areas are devoid of polymer. Most importantly these materials can have much higher surface areas in the dry state than gel type polymers, typically ranging from ~50 to ~1000 m^2/g. Unlike gel-type polymers, the macroporous resins do not need to swell in a solvent to allow access to the interior because they posses a permanent network of pores whose dimension can be manipulated by the precise conditions used in the polymerization. When a good solvent is contacted with a macroporous resin it can swell the polymer matrix in some extent as well as filling the pore volume. The swelling often occurs rapidly because the permanent pore structure gives fast access to the solvent throughout the whole resin.

Figure 8[22] shows the process involved in the pore network development. Pores are formed when the polymerization induces a phase separation between the growing polymeric matrix and the liquid porogen. At full conversion the material is composed by a crosslinked polymer phase and a discrete porogen phase, the latter acting as template for the permanent porous structure of the resin.

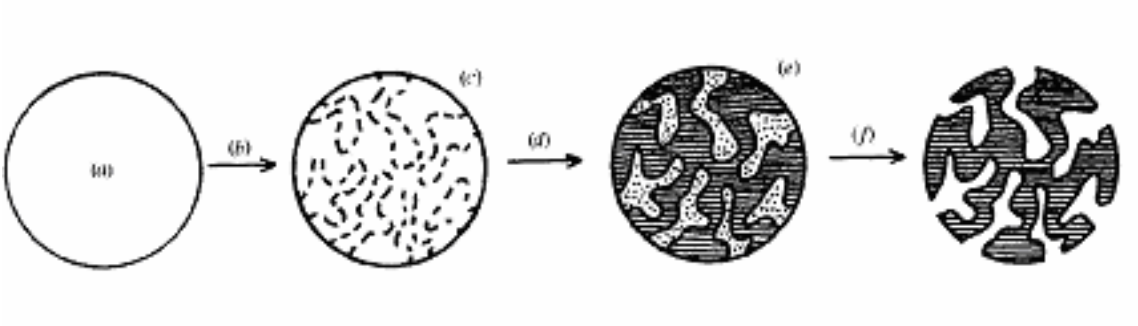
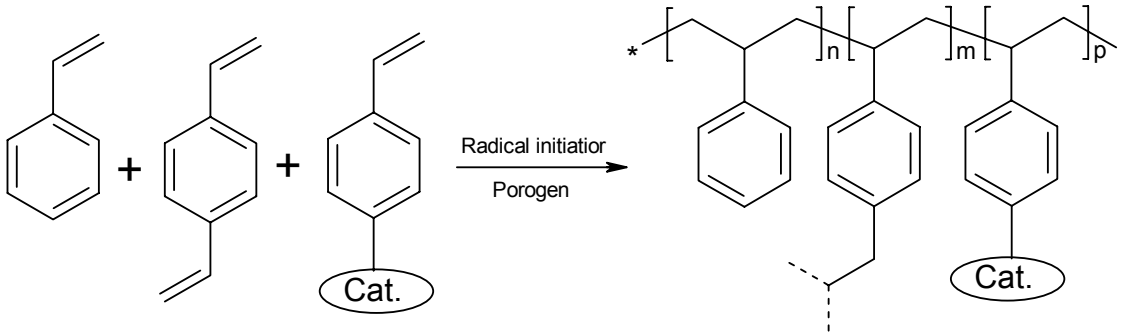


Figure 8. Action of porogen in forming porous morphology: *(a)* monomer, crosslinker a porogen isotopic phase; *(b)* polymerization; *(c)* polymer network forming; *(d)* porogen and network start to phase separate; *(e)* porogen phase acts as pore template; *(f)* elimination of porogen phase to yield pores.

The point at which phase separation occurs depends upon the nature of the porogen, its compatibility with the incipient polymer matrix and the level at which it is used. These are the key factors that control the fine detail of the polymer porous morphology.

In the present thesis work catalysts have been supported onto macroporous resins following the *copolymerization strategy*. In this approach the catalyst (or some precursor) is modified with an appropriate functional group which allows its incorporation in the final polymer during free radical polymerization (Scheme 1).



Scheme 1. Schematic synthesis of a Styrene-DVB supported catalyst via copolymerization technique

This approach can be useful in producing a structurally well-defined polymer, for controlling the proportion of functional groups introduced and for providing some information on the distributions of the group in the polymer chain.

1.3.2. Inorganic materials

Many different types of inorganic supports are known for the preparation of heterogenized catalysts. The most used can be divided mainly in three categories: a) amorphous materials (e.g. amorphous silica and alumina), b) mesoporous materials (e.g. MCM-41, MCM-48 and MSU silicas) and c) crystalline materials (e.g. zeolites).
Inorganic materials described in this dissertation are mainly of two types: amorphous silica and mesoporous silica (MCM-41).

Amorphous silica

Amorphous silica has a non-ordered structure with irregular channels and pore diameter that can broadly vary. The amorphous silica used in the following chapters is commercially available (Merck) with an average pore diameter of 60 Å. This material has the advantage to be readily available and economically advantageous. However, due to the irregular pore sizes, part of the catalyst can penetrate into small pores during the supporting procedure with the consequence that this part of the catalyst is not easily accessible from reactants.

Mesoporous synthetic silicas (MCM-41)

Ordered mesoporous (alumino)silicates offer interesting catalytic properties. These materials are synthesized with the help of surfactant micelle templates[28]. Exemplified by the Mobil M41S materials[29], of which MCM-41[30] is the most familiar, they posses uniform channels with tunable diameters in the range 1.5-10 nm .
M41S family is composed by three types of materials which have a very high surface area (often more than 700 m^2/g) and which differ for the mesoporous spatial organization (Figure 9):

- MCM-41 with a mono-dimensional array of hexagonal channels
- MCM-48 with a three-dimensional network of cubic channels
- MCM-50 with a lamellar, but not very stable, organization of channels.

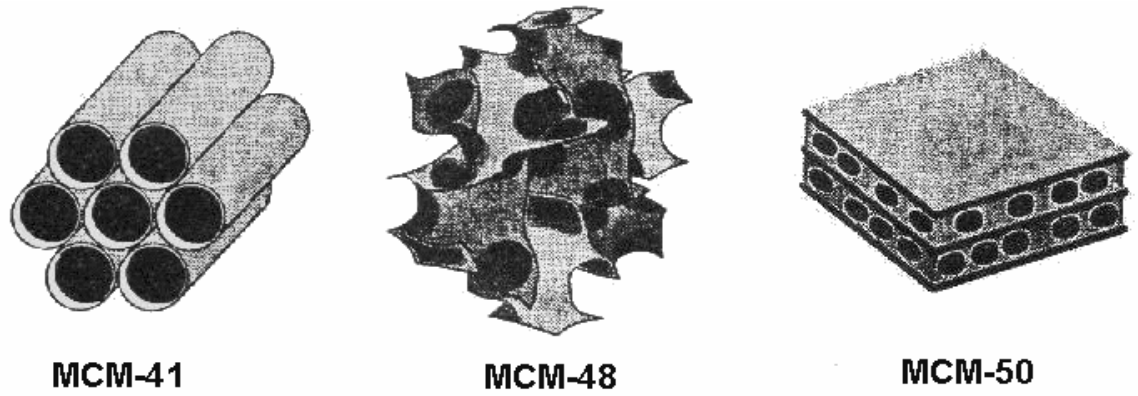


Figure 9. M41S mesoporous materials**.**

MCM-41 is the most studied and utilized material of the M41S family. The practical advantage in using MCM-41 as support for catalyst immobilization, lies in its high surface area and pore volume. Thus reactant and product molecules can easily diffuse and reach the catalytic sites, bulk catalysts can be accommodated in the mesopores (usually falling in the range 3-6 nm depending upon the synthesis conditions) and well-isolated and non-interacting catalytic site can be obtained (as an example see Figure 10).

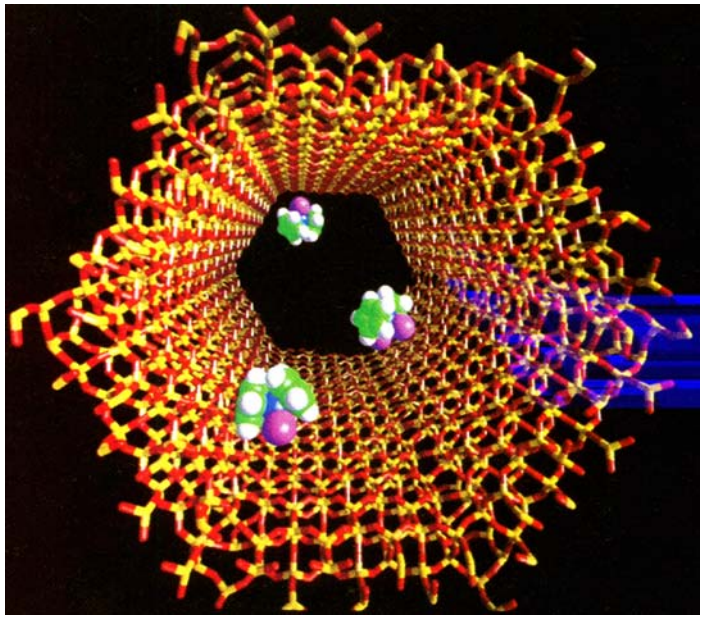


Figure 10. Representation of the accommodation of molecules of titanocene dichloride inside a pore of siliceous MCM-41. For simplicity, none of the pendant ≡Si–OH groups, that make it possible to graft organometallic moieties inside the mesoporous host, are shown. (Yellow: silicon, red: oxygen, green: carbon, white: hydrogen, purple: chlorine, blue: titanium).

The typical XRD pattern of MCM-41 shows an intense peak at low diffraction angles ([100] reflection line) and three less intense peaks at higher diffraction angles ([110], [200] and [210]

reflection lines)[24] (Figure 11). This type of diffraction pattern is typical of a hexagonal symmetry distribution of regular sized cylindrical mesopores. MCM-41 is usually defined as a long-range ordered structure because the material at the atomic level is amorphous and does not present a short-range organisation (as for example zeolite aluminosilicates)

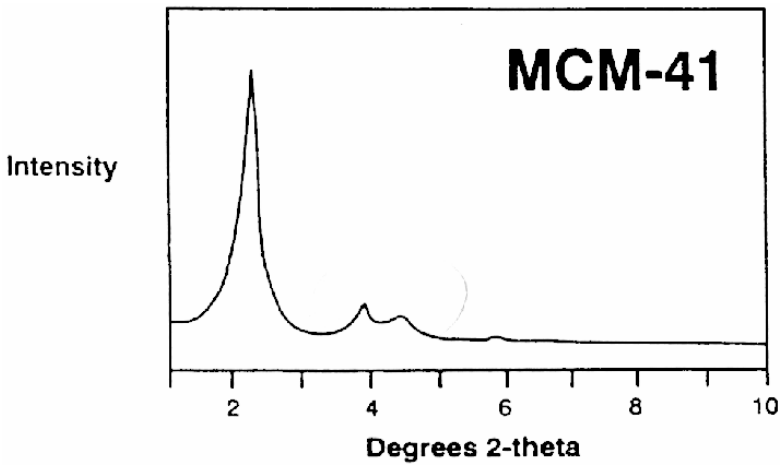


Figure 11. Typical XRD pattern of MCM-41.

The synthetic methodology to produce these materials is based on the liquid crystal templating mechanism that, in particular for MCM-41, is schematized in Figure 12.

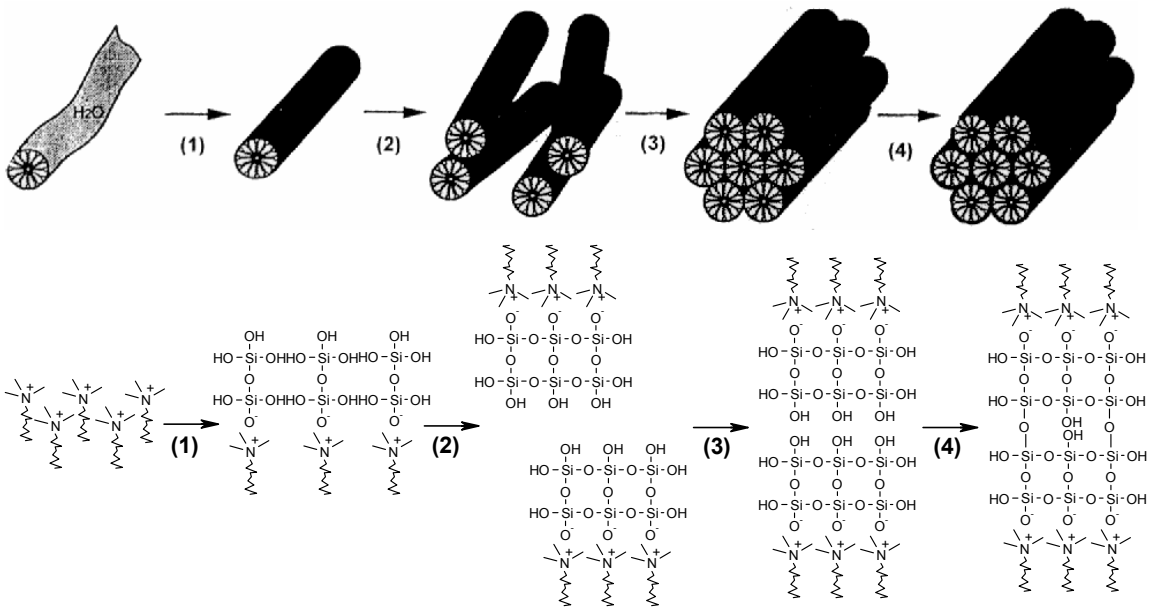


Figure 12. MCM-41 synthesis.

First the molecules of a template compound interact with themselves in the formation of cylindrical micellar aggregates which are then covered by monolayers of silica (1). At this point the cylindrical micelles assemble in parallel arrays according to the hexagonal geometry

characterizing the final material [(2) and (3)]. Long reaction times and high temperatures allow the condensation of silanols on the surface of adjacent cylinders with formation of Si–O–Si bonds that lend mechanical stability at the ending material (4). At this point the template compound is removed from the pores by calcination or washing with convenient solvents, affording the mesoporous MCM-41 silica.

In this dissertation organometallic homogeneous catalyst have been supported on cross-linked polymers and amorphous silica

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2. *Chiral bis(oxazoline) ligands in asymmetric catalysis*

2.1 Introduction

Asymmetric catalysis with chiral metal complexes has received considerable attention in recent years, and its contribution to the art of organic synthesis has become of leading importance. In the field of chiral Lewis acid catalysis, the catalyst, in general, consists of a cation coordinated/bound to an optically active ligand to give a chiral complex with at least one vacant Lewis acid site suitable for coordination and activation of the reagent. To induce a good level of enantioselection, the coordinated reagent should be suitably oriented to favor a selective attack to one specific face. One approach to an easier and less costly route to reduce the variables required for good face selectivity is the use of a *C*2-symmetric chiral ligand.[1]

Because of their ready accessibility, modular nature, and applicability in a wide range of metal-catalyzed transformation, *C*2-symmetric bis(oxazolines) (BOX's) are one of the most popular classes of chiral ligands , wich have received a great deal of attention in coordination chemistry and in asymmetric catalysis[2]. These ligands have two oxazoline rings separated by a spacer, and *C*2-symmetric bis(oxazolines) having a single carbon atom with two identical substituents[1]. (Figure 1)

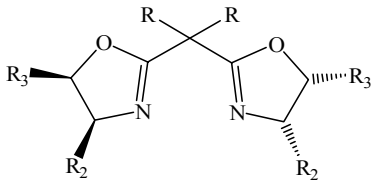
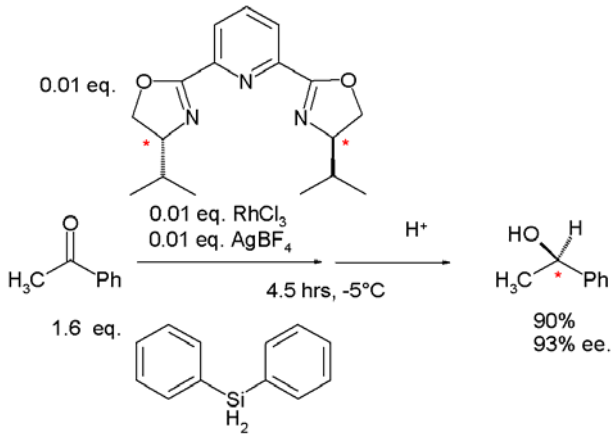


Figure 1: general bis(oxazoline) ligand

The large majority of these ligands are derived from readily available chiral amino alcohols in a few high-yielding synthetic steps. As a consequence, the enantiocontrolling stereocenter resides on the carbon atom neighboring the coordinating nitrogen of the oxazoline ring and, therefore, in close proximity to the metal active site, thus having a direct influence on the stereochemical outcome of the reaction[2].

BOX ligands are structurally related to C_2-symmetric semicorrins pionereed by Pfaltz and co-workers[3]. The inception of bis(oxazoline) ligands, however, added a new dimension in terms of flexibility in ligand design, convenient synthesis and availability of ligands in both enantiomeric

forms[4]. Chiral bis(oxazoline) ligands with a great deal of structural diversity have been introduced since 1989, year in wich the first reaction using a py-BOX ligand was published by Nishiyama[5] (Scheme 1).



Scheme 1: Nishiyama enantioselective hydrosilylation, 1989 (from ref 5)

In general BOX ligands with a one carbon spacer between the oxazoline rings (figure 1) are most frequently utilized, but a lot of different structures containing two oxazoline rings are known (figure 2)

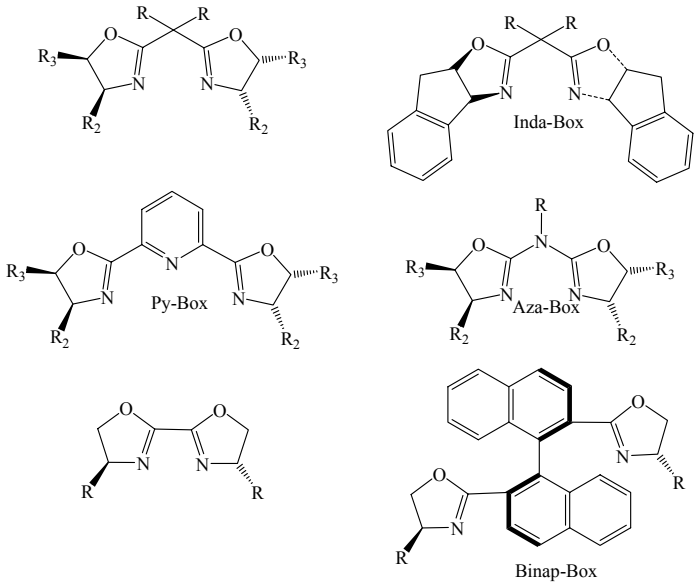
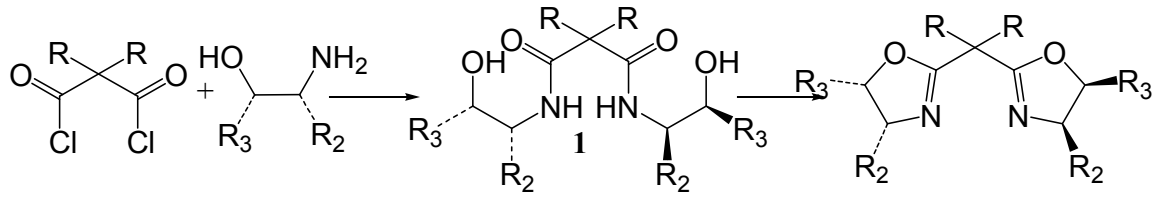


Figure 2: C_2-symmetric bis(oxazoline) ligands**.**

2.2 BOX synthesis

Since the late 1980s, numerous bis(oxazoline) ligands have been synthesized to use in metal-catalyzed asymmetric synthesis. There are different strategies: some of them allow to construct the oxazoline ring, others are modifications of preformed BOX[1,4]:

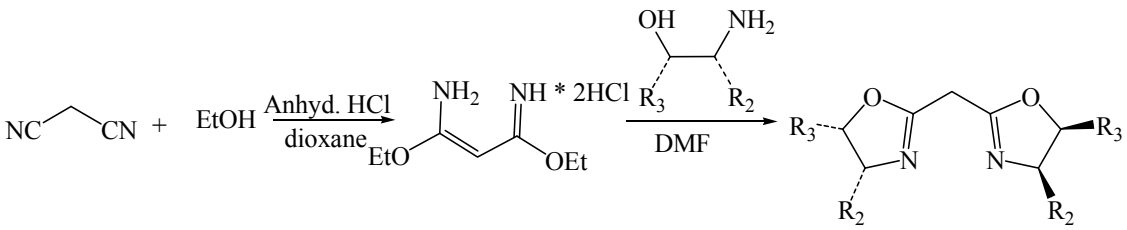
a. The construction of the oxazolidine rings starting from disubstituted malonyl dichloride, condensed with the corrisponding optically active 1,2-aminoalcohol to form the bis(hydroxyamide) derivatives. The hydroxyl groups were then activated and the resulting intermediate was cyclized to provide the bis(oxazoline) ligands (Scheme 2).



Scheme 2: sinthesys a of bis(oxazolines) by route a.

Activating agents such as $SOCl_2$ (Corey, Pfaltz), methanesulfonic acid, $MeSnCl_2$, $ZnCl_2$ were employed and sometimes by changing the conditions of cyclization it is possible to effect either retention or inversion of configuration at the C-5 position.

b. The construction of the bis(oxazoline) structure can occur even starting from malononitrile: it's reaction with anhydrous HCl in ethanol afforded the corrisponding imidate salt (Scheme 3) and the condensation of this salt with an optically active aminoalcohol furnished the bis(oxazoline) with the free methylene bridge.[1]



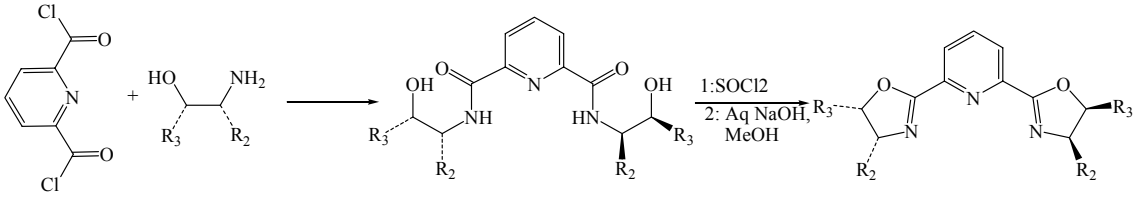
Scheme 3: sinthesys of bis(oxazoline) by route b

c. This method allows to introduce subtituent on the methylene bridge and is based on the acidity of the methylene protons, it consist of the formation of a dianion with 2 equiv of

NaH or BuLi (rarely with Et_3N) and of the nucleophilic substitution either with 2 equiv of alkyl halide or with 1 equiv of alkyl dihalide in order to construct a ring on the spacer.[1]

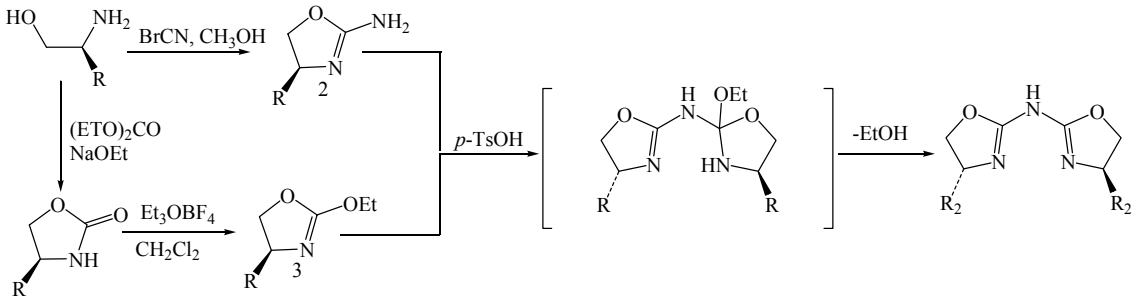
d. PyBOX synthesis[4]: Nishiyama and co-workers published in 1991[6] the synthesis of various PyBOX ligands. As shown in the Scheme 4 pyridine-2,6-dicarBOXylic acid chloride was first converted into the corresponding bis(hydroxy)amide by reaction with 2 equiv of chiral aminoalcohol. Treatment of bis(hydroxy)amide with $SOCl_2$ afforded the corrisponding chloramide, which was cyclized with aqueos NaOH.

e.



Scheme 4: Synthesis of Py-BOX ligands by Nishiyama's route.

f. Aza-BOX synthesis[7]: in recent years Reiser and co-workers introduced aza-bis(oxazolines), wich can be viewed as structural hybrids of bis(oxazolines) and aza-semicorrins. They combine the advantages of being accessible from the chiral pool like BOX's and the structural variability of aza-semicorrins due to the possibility of functionalizing the central nitrogen atom. Their synthesis is based on the conversion of commercially available aminoalcohols into two different oxazoline rings (2 and 3 in Scheme 5) as building blocks, wich are condensed using p-toluensulphonic acid. This strategy gives higher yields than the previous one, in which 2 equiv. of 2 were condensed using benzaldehyde and p-toluensulfonic acid in order to obtain an imine intemediate and the aza-BOX with formation of ammonia[7a].



Scheme 5: Synthesis of aza-bis(oxazolines) by Reiser's route

2.3 BOX- Metal Complexes

When a chiral BOX ligand is mixed with an inorganic salt in an organic solvent, a chiral BOX-metal complex is usually formed, wich can spontaneously precipitate or can be isolated by dilution with a less polar solvent. These chiral complexes are the precursors of the reacting intermediate involved in the catalytic cycle, and therefore each information concerning their structure is important to try to understand the configuration of how the molecules involved in the reaction are arranged at the metal center, since this is the source of the chiral discrimination producing the stereoselectivity in the reaction.

The preventive isolation of these precursors is not determinant for their success as enantioselective catalysts; they can be efficiently prepared "in situ" if is not necessary to analize them. Sometimes their structure can be investigated by spetroscopic methods, and depending on the metal involved in the complex, NMR spetroscopy might be the best tool for this purpose.[1]

When the solid BOX-metal complex is a crystalline compound suitable for X-ray nalysis, key information can be obtained about the coordination number, the nature of the ligand(s) other than BOX at the cation, wich allows one to propose reasonable models of the reacting intermediate participating in the catalytic process.

BOX with one carbon atom as the spacer generally behaves as a bidentate ligand though its nitrogen atoms, with few exceptions. The complexes with a single BOX as a bidentate ligand are the most popular and Cu(II) is the leading cation involved in their formation. For 4-Phenyl and 4-*tert*-buthyl-BOX the ordinarily found coordination number is four, derived from a distorted square-planar coordination. An example of this kind of complex is the [4-Phenyl-BOX · $CuBr_2$] shown in the Figure 3.

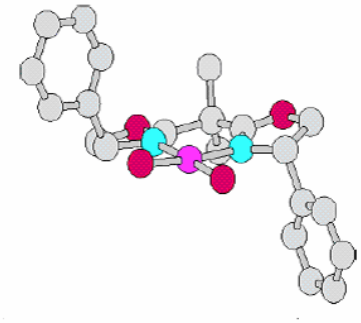


Figure 3: Molecular structure of [4-Phenyl-BOX·$CuBr_2$] (from ref 1) (**4**)

The importance of the structure of the complexes in their activity as catalysts can be understood through the comparrison of [(S)-4-Ph-BOX·Cu(SbF_6)·$2H_2O$] (Figure 4) and [(S)-4-*tert*-buthyl-BOX·Cu(SbF_6)·$2H_2O$] (Figure 5)[1]

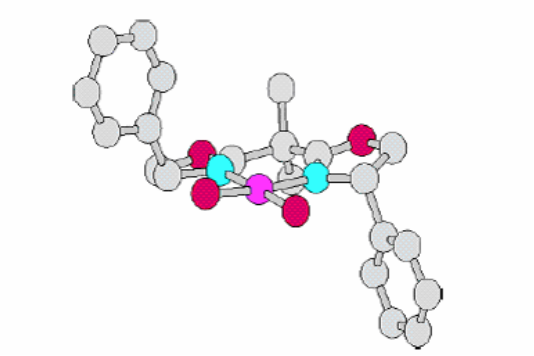


Figure 4: Molecular structure of [(S)-4-Ph-BOX·Cu(SbF_6)·2H_2O] (**5**) (from ref 1)

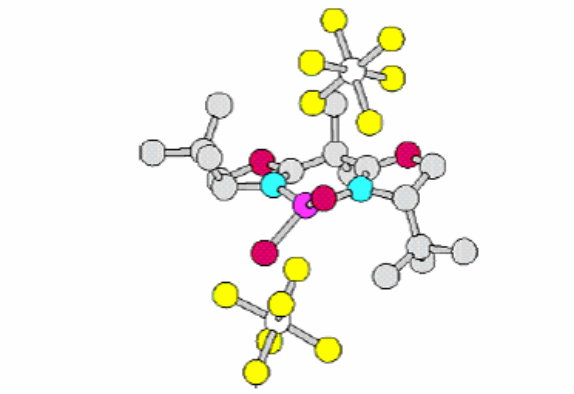


Figure 5: Molecular structure of [(S)-4-*tert*-buthyl·Cu(SbF_6)·2H_2O] (**6**) (from ref 1)

Both the structures present the two molecules of water in the coordination sphere with a distorted square planar structure, since SbF_6 does not enter in the coordination sphere. However the most important point is the sense of the distortion from the ideal BOX/cation plane. The complex **5** is more planar than **4** and the H_2O molecules reverses, infact de dihedral angles O-Cu-N-C are –11.3° and –7.2°, with the ligands oriented towards the oxazoline phenyl substituents. But in the complex 6 the distortion of the water molecules is large, with the ligands oriented far away from the *tert*-butyl groups and the dihedral angles O-Cu-N-C are +30.2° and +35.9°. It is clear that if complexes **5** and **6** are catalytic intermediates in a reaction and the reagent involved in ligation substitutes the H_2O molecules occupying their sites of coordination, then the opposite distortions of the complexes may have a leading role in the development of the sense of enantioselection. The reason for the inversion of the distortion from square planarity when moving from complex **5** to **6**, is still an open question, but the strong effect observed in the latter structure can be presumed to be due to steric interactions.

Several other [BOX/Cu(II)] crystal structures have been solved and one of them is the [indaBOX· Cu(II)· OAc] (figure 6), that will be analized in this dissertation.

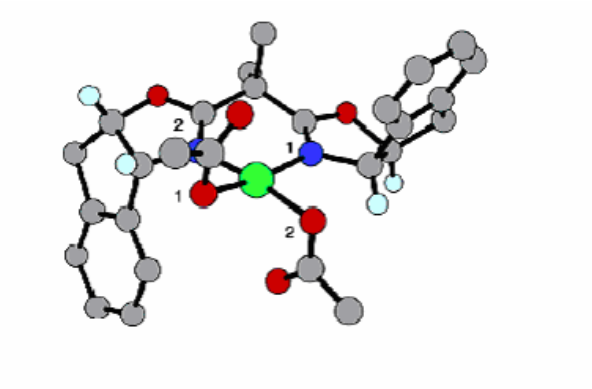


Figure 6: structure of the complex [indaBOX· Cu(II)· OAc] (**7**) (from ref 1).

The strucure shows square planar geometry with the acetate carbonyl moieties oriented toward the vacant apical position[8]. This aspect will be described in more detail in the following chapter in order to explain the mechanism of the aldol reaction.

2.4 BOX complexes in catalytic reactions

In the last 15 years the number of papers dealing with C_2-simmetric chiral BOX ligands appearing in the literature increased in an exponential way, from 6 in 1991 to 129 of 2004. BOX ligands can be used with many different metals and their complexes can catalyze a large number of different reactions. The purpose of this introduction is to show the versatility and utility of BOX metal complexes in order to explain the choose of these complexes as subject of this work, and not writing a review paper about BOX, so only some examples of the most important application of BOX metal complexes in asymmetric organic synthesis will be given.

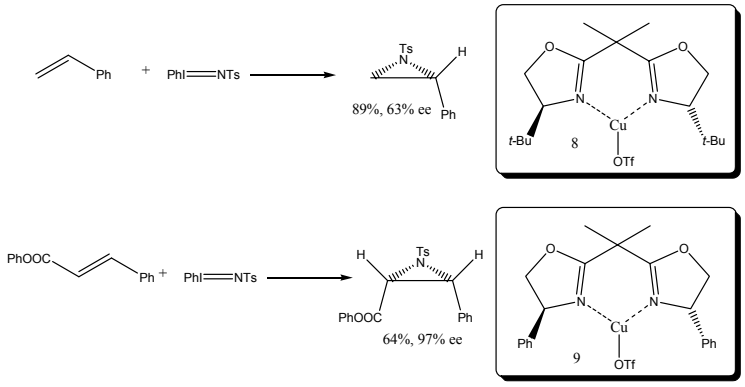
BOX complexes have been used in:

- intermolecular and intramulecular cyclopropanation reactions
- aziridination reactions
- aldol and aldol-like reactions
- Michael an Mukaiyama-Michael reactions
- Allylic substitution reactions
- radical reactions
- Diels-alder reactions
- 1,3-dipolar cycloaddition reactions

- other pericyclic reactions
- ene and hetero ene reactions.

2.4.1 Aziridination reactions

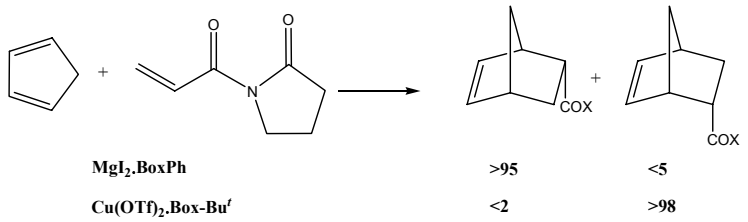
In 1993 Evans pubblished a report dealing with the reaction of several alkenes with N-(p-toluensulfonylimino)phenyliodinane as the nitrene source, catalyzed by both [(S)-4-phenyl-BOX/Cu(OTf)] and [(S)-4-*tert*-butyl-BOX/Cu(OTf)], to give aziridines[1,9]. (Scheme 6). The best results were obtained with unsaturated esters with enantioselectivities up to 96%, without any influence of both aryl and ester substituents. The best complex was **9** (Scheme 6) and an influence of the solvent was observed, better enantioselectivities were obtained using less polar solvents.



Scheme 6: aziridination reaction with Cu(I)BOX

2.4.2 Diels-Alder reactions

Since 1991 BOX's were used as ligands for the preparation of optically active catalysts used to perform the enantioselective Diels-Alder reaction of 3-acryloyl-2-oxazolidinone with cyclopentadiene (scheme 7): the reaction is usually endo-selective and gives good enantioselevtivities[1].



Scheme 7: Diels-Alder model reaction catalyzed by BOX complexes

From the investigations by Evans[9] and by Corey[10] it appears that the sense of asymmetric induction can be rationalized through a square-planar rather than tetrahedral reaction intermediate[1]. Infact the Mg complex has a tetrahedral geometry (Figure 7), while Cu complex shows a square planar coordination and the two reactions give reverse enantioselectivity (Scheme 7).

It is possible to change the selectivity by using a different metal salt, infact, as Figure 8 shows, tetrahedral Mg-complex, as [$Mg(ClO_4)_2$·BOX-Ph] gives one product, whyle octaedral complexes as [$Mg(ClO_4)_2$·2 H_2O· BOX-Ph] or [$Mg(OTf)_2$· BOX-Ph] (Figure 8), give the other product with good enantiomeric eccess[1].

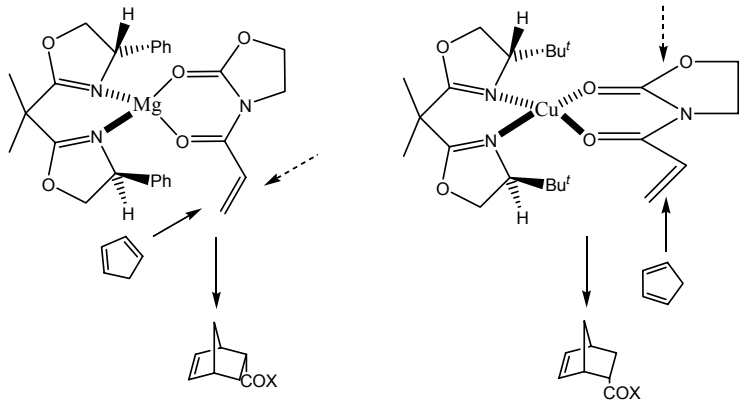


Figure 7: Cu(II) or Mg(II)-catalyzed Diels-Alder reactions: square planar vs tetrahedral coordination .

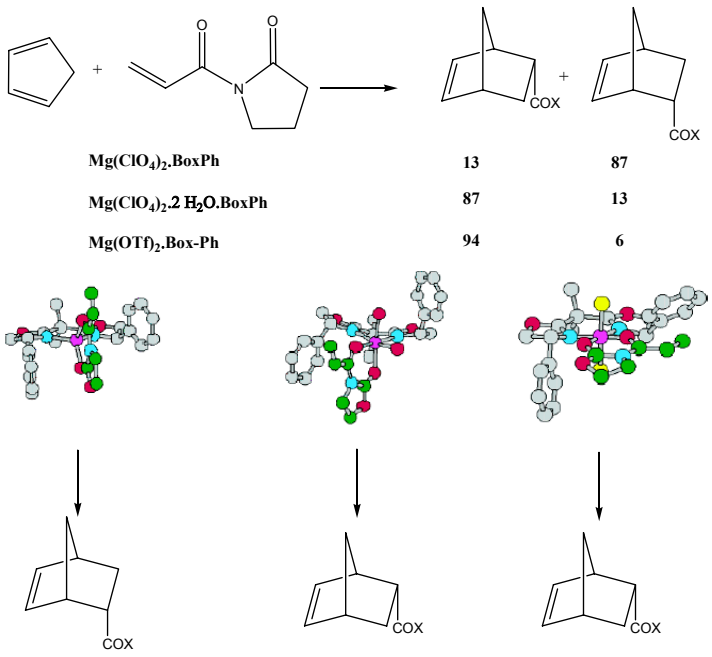


Figure 8: Mg(II)-catalyzed Diels-Alder reactions: tetrahedral vs. octaedral coordination

2.5 Heterogeneous bis(oxazoline) ligands

As shown in the previous part chiral bis(oxazoline) ligands were successfully used in the asymmetric catalysis of a variety of reactions. However, these versatile catalytic sytems suffer from one major drawback: a high catalyst-to-substrate ratio is required (generally 1-10 mol%). Their separation and recycling is therefore a prerequisite for their development as useful catalysts. Indeed, since 1997 many attempts to recycle BOX ligands in heterogeneous systems were reported.[11]

Three general methodologies for heterogenization of BOX ligands have been extensively studied:

- immobilization using non-covalent interactions
- covalent grafting onto organic or inorganic materials
- binding onto soluble polymers.

2.5.1 Immobilization using non-covalent interactions

Heterogenizations using non-covalent interactions, such as ionic or polar ones, are usually easy to perform, since they not require prior functionalization of the ligand. However, it is not always easy to avoid unwelcomed interactions of the support with catalytic site, as well as some leaching of the ligand and of the metal. Non-covalent heterogenizations of chiral BOX ligands

were reported before covalent ones. It is possible to use inorganic or organic solids. In the case of inorganic solid clays are used. Mayoral and his group reported the use of three inorganic cation-exchanged clays: *laponite* (a synthetic smectite clay silicate, manufactured from salts of Na, Mg and Li; with an ordered house of cards structure, made of very thin "cards". It is iron free and has a high swelling ability); *montmorillonite K10 (*a smectite clay, characterized by a three-layer crystalline structure, one alumina and two silica layers; disordered house of cards structure); and *bentonite* (a natural smectite, the sodium form of montmorillonite with a lamellar structure). For the ion exchange to be succesfull, it should be performed in a solvent with a high dielectric constant, in wichi the complex is soluble, as MeOH or $EtNO_2$.

In most cases, the use of non-covalent ionic interactions is proved to be of little practical interest. For the cyclopropanation reaction, for example, the enantioselectivities obtained using this method were much lower than those obtained by the homogeneous ligands. The reason for this could be the replacement of the counteranions of the metal by the support. Counteranions are known to influence the activity and enantioselectivity of catalytic complexes in many homogeneous reactions. Recycling of such catalytic materials was also problematic, due to leaching of both the metal and the ligand. Therefore, for such catalytic materials to be successful, it is important to control the design of both the ligand and the material. From this point of view, good enantioselectivities and an original effect of the inorganic matrix was described with a copper exchanged zeolite for the aziridination reaction. Hutchings and his group used a zeolite Y as solid support: they first exchanged zeolite Y with $Cu(OAc)_2$ to obtain CuHY and then they modified the CuHY with chiral BOX ligands. This catalyst rise to enantioselectivities wich were even better than those obtained in solution in the case of asymmetric aziridination.[11]

2.5.2 Covalent grafting onto organic or inorganic materials.

This method is more classical in asymmetric heterogeneous catalysis, and was proposed in the early stage of the discovery of practical asymmetric catalysis. Binding of BOX ligands onto organic or inorganic supports was successfully performed in several manners, and allowed the preparation of catalysts which were almost as selective and afficient as their homogeneous counterparts. In general these materials could also be recycled several times without loss of activity or enantioselectivity.

Several criteria seem to be required to keep the high enantioselectivity: in most cases it is important to keep a pseudo C_2 symmetry of the catalyst, i.e., the bridge of the BOX should be functionalized with two similar groups. The catalyst loading should not be too high, to avoid

interactions between the catalytic sites. And finally, the matrix should preferably no contain groups wich are likely to form complexes with the metal (such as ether oxigens, thioethers, silanol groups) since such complexes can either disturb the geometry of the bis(oxazoline) complex and the coordination around it, or form achiral catalytic species which can catalyze the reaction in a racemic manner. If such groups exist in the matrix itself, attempts to protect them should be made.[11]

This strategy was used succesfully in different reactions: Mayoral et al used BOX ligands with p-vynylbenzyl groups on the methylene bridge to obtain homopolymer: these ligands were used in the cyclopropanation reaction of styrene with EDA with good results (trans/cis 70/30; ee trans 94 %; ee cis 91%). Rechavi and Lamaire[11] reported as a suitable support for inda(BOX) ligand the polyurethane chain polymer. They tested the catalyst (with $Cu(OTf)_2$ as metal precursor) in the Diels Alder reaction for 3 times obtaining very good results (99% conversion, 90-87% endo with 51-56% ee). Also the grafting onto silica gave good results in the Diels Alder reaction after a protection of silanol groups and using $Cu(ClO_4)$ as metal precursor: the good activity (100% conv, 88% endo, 75% ee) was maintained for four cycles.

2.5.3 Binding onto soluble polymers

The approach of tethering the BOX ligands to soluble polymers as PEG is easier to perform and combines some of the advantages of homogeneous reaction (high reaction rate, no problems of accesibility to the catalytic sites and realtive ease of characterization of the catalyst), with the easy recovering of the catalyst by precipitation with another solvent at the end of the reaction. For example the reaction could be performed in CH_2Cl_2 and at the end the PEG-supported ligand could be precipitated by the addition of ether. However the separation is based on the difference in the solubilities of the product and the catalysts, that could be high, and the separation could therefore be quite good; but the catalyst can not be completely recovered. Another disadvantage is the large quantities of solvent required to precipitate the catalyst. This strategy is apllied in cyclopropanation reaction with good results (yield 82%, trans/cis 73/27; ee trans 92%; ee cis 84%), but a complete recovering and reusing of the catalyst is not possible.[11]

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HETEROGENEOUS CHIRAL BOX LIGANDS IN ASYMMETRIC CATALYSIS

3 Asymmetric synthesis of d-(+)-chrysanthemic acid promoted by chiral Cu(II)-bisoxazoline complexes on solid supports

3.1 Introduction

(+)-*trans*-Chrysanthemic acid (figure 1), synthesized and utilized by certain pyrethrum flowers as a defense against insect attack, was isolated and characterized by Standinger and Ruzicka since 1924[1].

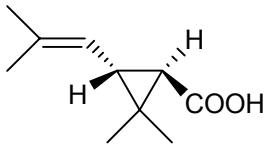

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Figure 1: (+)-*trans*-Chrysanthemic acid.

In 1997 the market value of this class of insecticides amounted to a staggering 1.5 billion US dollar.[2] Infact it is used as precursor of the pyrethroid group of insecticides, (figure 2) that are esters of Chrysanthemic acid. Pyrethroids, so named because of their structure similar to the natural pirethrin, have been considered to be ideal insecticides because of their rapid knock-down effect against insects in a minimal dose and low mammalian toxicity.

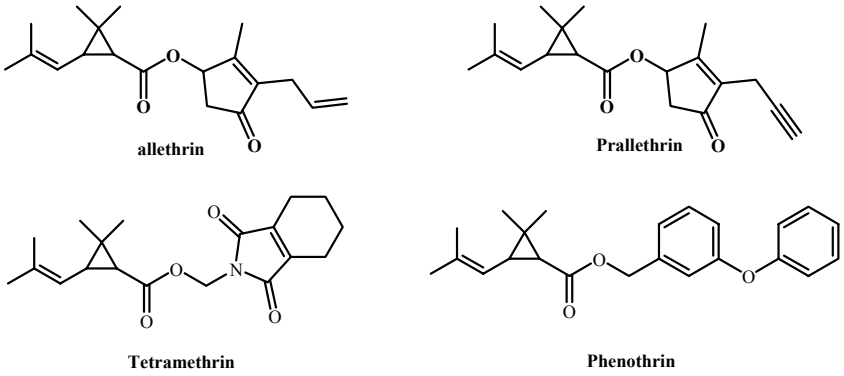


Figure 2: Pyretrhoids family.

The *trans* form of pyrethroids is usually more active than the *cis* one, and the esters of (+)-*trans*-chrysanthemic acid (or those of the chrysanthemic acid enriched in the (+)-*trans* form) show an excellent insecticide activity.

At the present time there are well known methods to convert the racemic form of chrysanthemic acid into the correct *cis/trans* ratio (usually 20/80) by reaction with resolving agents, as chiral amines, in order to obtain an enantiomerically enriched (+)-crhysanthemic acid. For example

Pavan and Bulidon are authors of a patent that uses D-methyl-ephedrine as resolving agent to obtain (+)-*trans*-chrysanthemic acid.

The patent US 3,879,451 describes a methods of separation of *trans/cis* racemic chrysanthemic acid using (+)-α-phenyl-β-p-tolyl-ethylamine as chiral resolving amine to obtain a (+)-*trans*/(+)-*cis* chrysanthemic acid mixture.

These methods need to use solvents in order to crystallize the diasteromeric salts and to recover the resolving amine, and this means an expensive process, with several steps.

One usefull method to synthesize (+)-*trans*-chrysanthemic acid is the stereoselective cyclopropanation reaction. The interest in this reaction has advanced tremendously in the past twenty years since the cyclopropane subunit represents the key structural feature of a broad range of compounds showing interest by the theoretic and synthetic point of view as well as in the natural product and medicinal chemistry.[3] However cyclopropanation is one of the first intermolecular reactions to be catalyzed in an enantioselective manner[4].

A general scheme of cyclopropanation is reported in Figure 3, showing the use of chiral metal complexes for the stereocontrolled carboalkoxy cyclopropanation reaction..

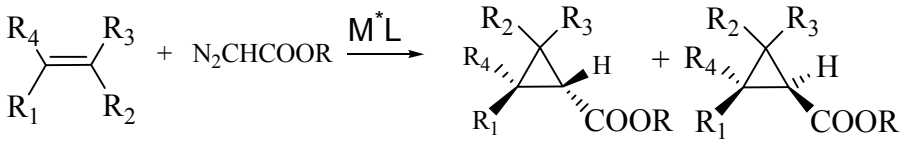


Figure 3: cyclopropanation reaction

In this kind of reaction the diazoacetate plays a key role as carbenic source .

Carbenes are useful reactants in organic synthesis, that allow to form two C-C bonds in a single step reaction like cyclopropanation.

The mechanism for decomposition of diazo compounds with transition metals was, originally, suggested by Yates in 1952[5] (Figure 4). The nitrogen loss from a diazo compound **2** is the consequence of its nucleophilic attack onto the metal complex. The metal-stablized carbene **3** then reacts with an olefin (electron-rich substrate) and regenerates the catalytic species.[5] Recent calculation and isotope effect and Hammett studies support the addition of the very reactive metallacarbene intermediate in an early transition state to the substrate alkene in a concerted pathway with substantial cationic character represented by the transition structure **4**, and not by a metallacyclobutane structure.[6]

Different metal complexes were tested for this purpose and the most suitable metals were found to be Cu, Rh, Co and Ru. Among these, copper complexes represent the most efficient catalysts for cyclopropanation of olefins with diazo compounds.

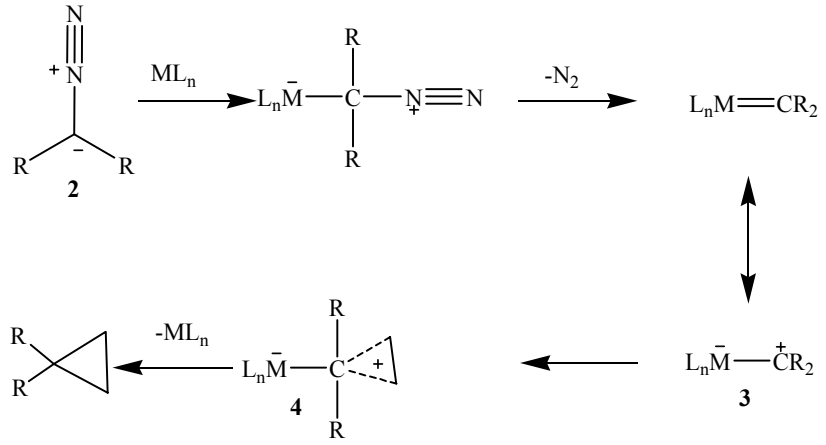
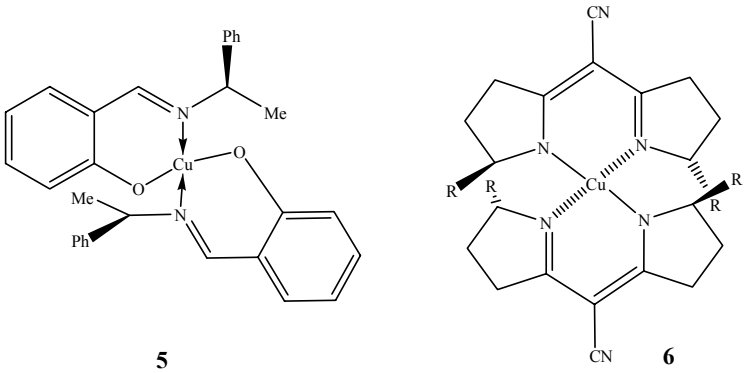


Figure 4: cyclopropanation mechanism

In 1973, Salomon and Kochi provided the basic understanding of copper catalysts in carbenoid transformations. They discovered that CuOTf is very effective for cyclopropanation reactions. Trifluoromethanesulfonate (OTf= Triflate), like perchlorate, is an extremely weak coordinating anion and metal salts such as Cu(I) and Cu(II) ones are extremely ionized even in nonaqueous solution. Thus, the electrophilic metal ion is capable of multiple coordination which makes the cyclopropanation a process extremely easy. They demonstrated that Cu(OTf) is higly efficient in promoting the decomposition of diazo compounds, and that Cu(II) complexes were reduced to Cu(I) deriatives by the diazocompounds[7]. Cu (II) complexes were also activated by reduction with sustitutes hydrazines or diisobutylaluminium hydride. (Figure 5)

Several Cu(I) and Cu(II) complexes were studied in the cyclopropanation reaction of styrene. The first asymmetric cyclopropanation was reported in 1966 bt Nozaky et al. They used a chiral Schiff base-Cu(II) complex to obtain trans and cis-2-phenylcyclopropanecarboxylate, although the enantioselectivity vas very poor (below 10%ee)[5]. A Schiff base-Cu(II) complex (**5**) gives also (+)-*trans*-chrysanthemic acid in 94% ee by reaction of 2,5-dimethylhexa-2,4-diene and (-)-menthyldiazoacetate.

Good results in cyclopropanation of styrene were obtained using chiral semicorrin-Cu(II) complexes: the Pfalts catalyst **6** (Figure 5) gives the trans product of cyclopropanation between styrene and (+)-menthyldiazoacetate with 97% ee.



5 **6**

Figure 5: Schiff base-Cu(II) and semicorrins Cu(II)complexes

However, since 1990 bisoxazoline-Cu(I) or Cu(II) complexes were used as catalysts in cyclopropanation reactions. Many different BOX ligands were synthesized and tested and they showed good risults even since their first report. Moreover, BOX-Cu complexes gave good results also with trisubstituted olefins, whyle semicorrins Cu catalysts did not afford similar good results.

The bis(oxazoline)-copper complex [4-tert-buthyl-BOX-Cu(I)] firstly reported by Evans,[8] still represent the most studied and applied metal catalyst for the diastero- and enantioselective cyclopropanation of alkenes with diazoalkanes and, for example, in the reaction of styrene and ethyldiazoacetate, provides 97% ee of the trans- product.

By a general point of view, the ideal catalyst must be easily and completely recovered from the reaction mixture and efficiently reused. This prerequisite is particularly needed for large scale production utilizing highly expensive catalysts such as BOX-Cu(I). Moreover, some metal can contaminate the final product giving rise to a major, often underestimated drawback for products destined for human consumption, for material chemistry or for agrochemicals. These drawbacks can be overcome by supporting the catalyst on the surface of a convenient heterogeneous material.[9]

Mayoral et al. developed the non-covalent immobilization of BOX-Cu(I) onto different solid supports and studied the scope and limitations of these solid catalysts[10]. The same catalysts have also been immobilized on both organic and inorganic supports via covalent bonds and utilized in cyclopropanation as well as other C-C forming reactions[11]. The good results achieved in the cyclopropanation reaction clearly demonstrate the viability to carry out asymmetric catalysis with immobilized BOX-Cu(I) complexes. However, despite the large number of studies in this area, none of these catalysts have been utilized in the preparation of chrysanthemic acid **1**, being the model olefinic substrates mainly represented by styrene and derivatives.

3.2 Purpose of the work

The aim of this work is to set up a competitive process to synthesize chrysanthemic acid in the usefull (+)-trans form to be utilized as precursor of commercial pyrethroids.

To achieve this target the first goal was to synthesize chiral Cu-BOX complexes and to study them as homogeneous catalysts in the asymmetric cyclopropanation reaction between 2,5-dimethyl-2,4-hexadiene with diazoacetates as carbene sources (Scheme 1) in order to obtain chrysanthemic acid enriched as much as possible in the (+)-*trans* form.

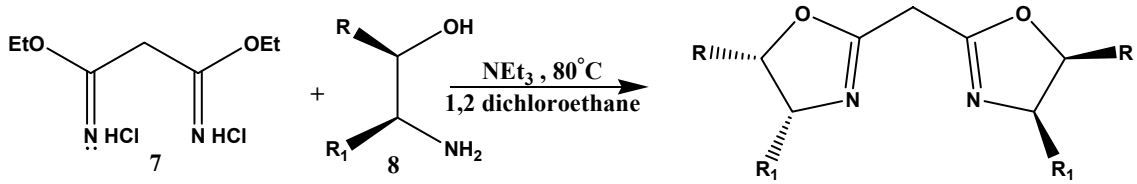
By a general point of view, the ideal catalyst must be easily and completely recovered from the reaction mixture and efficiently reused. This prerequisite is particularly needed for large scale production utilizing highly expensive catalysts such as BOX-Cu(I). Supporting the homogeneous catalyst can avoid the drawback of metal contamination of final products. For this reason the second phase of this work counts to heterogenize the homogeneous selected BOX ligand using organic and inorganic supports, to choose the best support and to optimize the reaction in heterogeneus bach systems.

However working in batch can produce some drawback, for example the catalyst can soffer a mechanic stress with the stirring, moreover filtering and washing of the catalyst at the end of each batch is needed, and this means to create a plant with a filtration system, using solvents to wash the catalyst. So the final aim of this work is to set up a continue flow system in wich the best heterogeneous catalyst fills a reaction column and the reactant mixture passes through the column continuously.

3.3 Homogeneous conditions set up

3.3.1 Synthesis of BOX

BOX ligands can be prepared starting from malonoimidate dichloride (**7)** and chiral amino alocohols (**8**)[1], in a chlorinated or aprotic dipolar solvent, using as catalyst a tertiary aliphatic amine or pyridine and warming up the solution from 20°C till the reflux temperature of the solvent (Scheme 1)



Scheme 1: BOX ligands synthesis

In this case, 1,2-dichloroethane has been selected as solvent, triethylamine as catalyst, that was added dropwise. The mixture, has reacted at 80°C for 3.5 hours (the reaction time is important because using longer reaction times BOX can decompose, and with shorter times the monoattack product can be produced in large amount).

In this way the first part of the bis(oxazolines) library, BOX **9-12** (Figure 6), was prepared. These compounds are characterized by the presence of 1 or 2 chiral centers, on the ring, free methylene bridge and different steric hindrance.They were synthesized as clear crystalline solids with yields between 50 and 80% after crystallization.

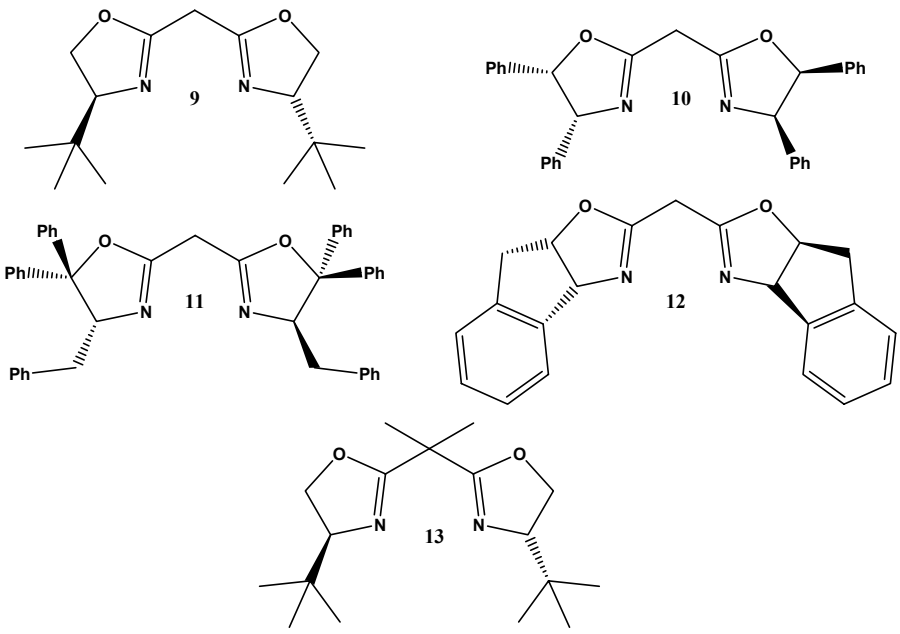
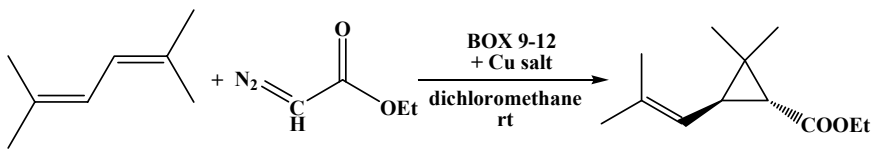


Figure 6: BOX ligands.

In order to evaluate the effect of the methylene bridge functionalization the library was then enriched with the commercial BOX **13,** that usually is very active.

3.3.2 Ligand screening

The ligands **9-13** were then tested in the cyclopropanation reaction between 2,5-dimethyl-2,4-hexadiene and ethyl diazoacetate (Scheme 2): the active complex was formed in situ by treatment of the ligand with the copper salt in dichlorometane for one hour in 1:1 ratio. The reactants were successively added (tetramethylbutadiene 10: ethyl diazoacetate 1), using 1 mol% of catalyst with respect to the diazoacetate. The reaction was followed by GLC (chyral column) to determine conversions, seletivities and e.e values.



Scheme 2: crysanthemic acid synthesis: model reaction for catalyst screening.

The risults of this first screening are reported in table 1

Entry	*Ligand*	*Cu salt*	*yield*	*cis/trans*	*ee d-cis*	*ee d-trans*
1	13	Cu(OTf)	25	32 : 68	-	14 (*l-trans*)
2	12	Cu(OTf)	57	38 : 62	27	31
3	10	Cu(OTf)	62	33 : 67	44	65
4	10	$Cu(OTf)_2$		30 : 70	44	
5	11	$Cu(OTf)_2$	53	27:73		73

Table 1: ligand screening results.

Best results have been obtained using the ligand **10**, with four phenyl groups on the oxazolinic rings and the free methylene bridge, complexed with $Cu(OTf)_2$ (entry **4**). Being the cyclopropanation achieved in 85% yield, 30/70 cis-trans ratio and 73% ee of d-trans chrysantemic acid. The same ligand complexed with the Cu(OTf) gave lower yield and ee value; similar results were achieved with ligands **12** and **13**.

3.3.3 Diazoacetate screening

The second parameter that was considered in order to set up the reaction conditions is the diazoacetate: four different diazoacetates have been tested in the model reaction (Table 2).

Entry	**diazoacetate R=**	**yield**	**cis/trans**	**ee cis**	**ee trans**
1	methyl	78	32/68	35	67
2	ethyl	85	30/70	44	63
3	menthyl	50	9/91	43	88
4	dicyclohexyl-methyl	33	10/90	51	88

Table 2: diazoacetate screening results

Ethyl diazoacetate gave the best yield (85%) but modest cis/trans and ee values. Optimum cis/trans and ee values were achieved with menthyl diazoacetate (9/91 cis/trans and 88% ee trans). The products were obtained in modest yield (50%), however, it must be underlined that the unreacted menthyl diazoacetate can be easily recoverd by distillation and reused.

The improved results obtained with menthyl diazoacetate depend probably on steric effects and not on the presence of the chiral centre, infact the same enantioselectivity was obtained using dicyclohexylmethyl diazoacetate, even with a lower yield.

3.4 Heterogeneous conditions set up

3.4.1 Ligands heterogenization

Up to now the best conditions achieved in homogeneous phase were: 5% mol of BOX **10**: $Cu(OTf)_2$ 1:1 complex with respect to menthyl diazoacetate, 10 mol% of 2,5-dimethyl-2,4-hexadiene, at room temperature, in CH_2Cl_2. These results were considered a good homogeneous starting point for heterogenization.

In this work the heterogenization was performed through both the tethering and the copolymerization approaches and to this end BOX **10** was functionalized at the methylene bridge[12] (Figure 7) with both alkyl and aromatic spacers, in order to evaluate the effect of the spacer lenght and mobility. The synthetic strategy for the preparation of the supported catalyst was slightly modified with respect to the Mayoral approach[10] in order to bind the BOX ligand to the silica surface through both arms since the conservation of the C_2 symmetry in the immobilized bis(oxazolidine) ligand minimizes the number of the possible transition states and likely results in a more stereoselective reaction.

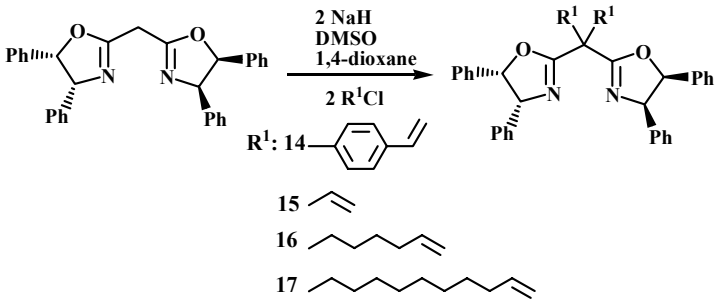


Figure 7: BOX **10** methylenic bridge functionalization

The spacers were attached to the methylene bridge via NaH promoted double alkylation with the correct alkyl halogenide to obtain the intermediates **14-17** which were successively reacted with 3-mercaptopropyltrimethoxysilane, in the presence of AIBN, affording compounds **14a-17a** which could be grafted on silica very likely through both arms. (Figure 8)

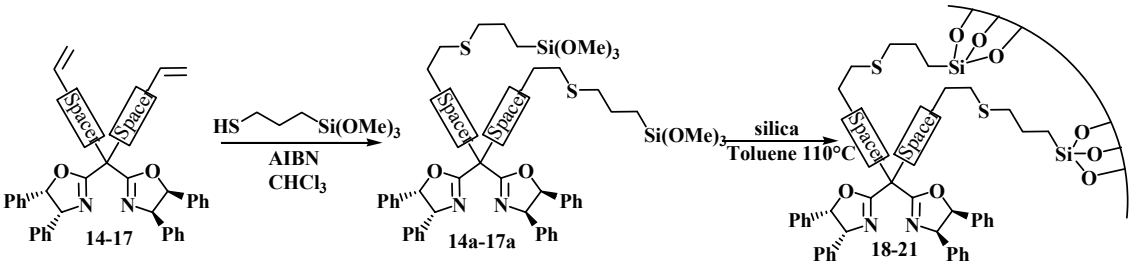


Figure 8: ligands tethering onto silica with our modified approach.

The four functionalized silicas **18-21** were characterized by elemental analysis in order to evaluate the BOX loading showing loading values between 0.15 and 0.17 mmol/g. All the silicas were also characterized by IR spettroscopy searching the diagnostic C=N stretching at 1646 nm.

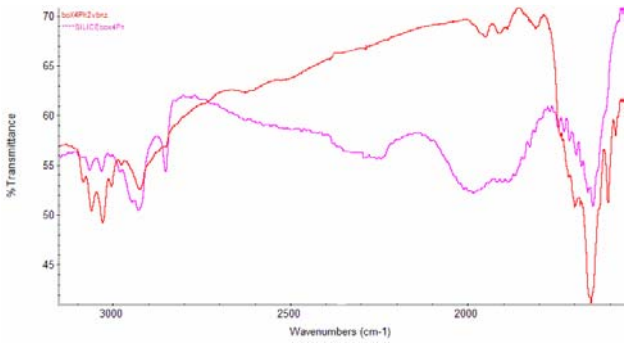


Figure 9: Example of IR characterization of silica, IR spectra of BOX **14** (red spectrum) and silica **18** (violet)

Similarly ligand **14** was supported on polystyrene *via* copolymerization with styrene and divinylbenzene as cross-linking agent in the presence of AIBN as radical initiator and 1-dodecanol/toluene as porogenic mixture[13].(Figure 10) . The polymer had a loading of 0.13 mmol/g and the IR spectrum showed the diagnostic band at 1652 nm due to C=N stretching.

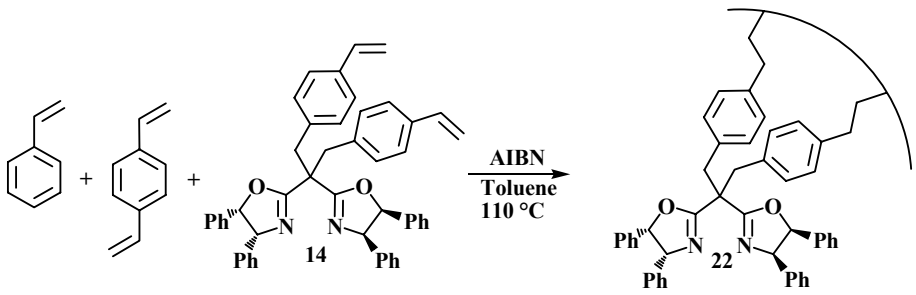


Figure 10: copolymerization of **14** to obtain polystyrene supported ligand **22**.

In order to evaluate the effect of the support matrix some polysiloxane materials were prepared: ligands **15** and **17** were supported on polysiloxane *via* copolymerization with two different siloxanes in a reaction promoted by a Pt catalyst in toluene (Figure 11), giving polysiloxanes **23** and 24 with 0.19 and 0.20 mmo/g loading.

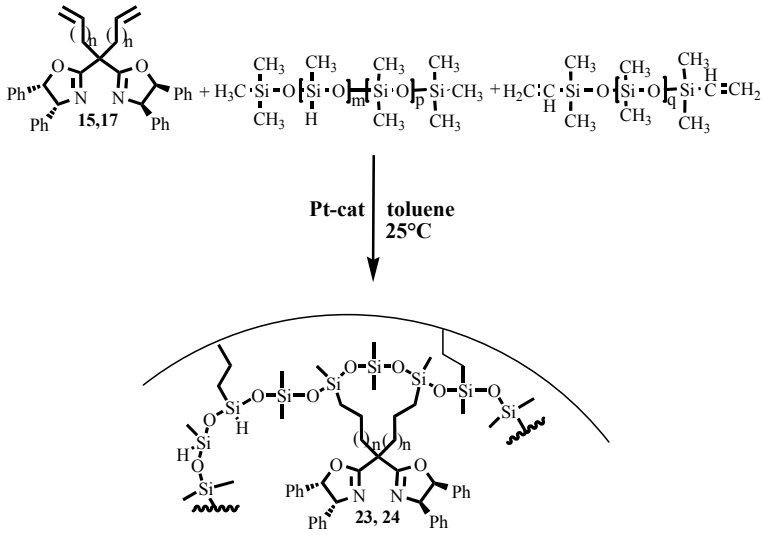


Figure 11: copolymerization of ligands **15** and **17** to obtain polysiloxanes **23** and **24**.

3.4.2 Heterogeneous batch system reaction

In a preliminary series of experiments the catalytic cyclopropanation of 2,5-dimethyl-2,4-hexadiene with (-)-menthyl diazoacetate has been carried out in a standard fashion in batch conditions using the catalysts prepared from $Cu(OTf)_2$ and the supported ligands **18-24**.

To this end to a suspension of immobilized bis(oxazoline) in CH_2Cl_2 was added $Cu(OTf)_2$ in a stoichiometric amount with respect to the supported BOX ligand. After stirring for 1 hour at rt, the solid was separated by filtration, washed with CH_2Cl_2 and dried under vacuum. The copper content was determined by plasma emission spectroscopy. Table 3 shows that in all supported catalysts the BOX/Cu ratio was always ~1. These values have been used for calculating the catalyst/substrate ratio in the reaction tests.

Entry	Ligand	Ligand loading (mmol/g)	Cu loading (mmol/g)	BOX/Cu
1	18	0.165	0.154	1.07
2	19	0.150	0.140	1.07
3	20	0.140	0.140	1
4	21	0.135	0.120	1.13
5	22	0.125	0.120	1.04
6	23	0.190	0.180	1.05
7	24	0.200	0.195	1.02

Table 3: BOX/Cu ratio in supported complexes between ligands 18-24 and $Cu(OTf)_2$.

The solid catalysts were tested in the batch cyclopropanation reaction of 2,5-dimethyl-2,4-hexadiene with (-)-menthyl diazoacetate using 5 mol% of catalyst with respect to menthyl diazoacetate and a menthyl diazoacetate/hexadiene ratio 1/10 (Figure 12). The reactions were routinely performed by adding a solution of (+)-menthyl diazoacetate in CH_2Cl_2 through a syringe pump to a suspension of the solid catalyst in the same solvent and 2,5-dimethyl-2,4-hexadiene under stirring at rt for 5 hours.

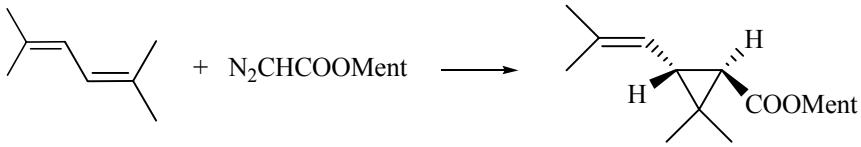


Figure 12: cyclopropanation reaction or 2,5-dimethyl-2,4-hexadiene with L-menthyl diazoacetate.

The activity of every catalyst was evaluated in three consecutive runs by comparing the product yield and the ee value of the trans isomer. (Table 4). The catalyst was simply recovered by filtration at the end of the reaction, washed with CH_2Cl_2 and reused in a successive run without further activation.

Entry	Lygand (cycle)	Yield (%)[a]	cis/trans[b]	ee cis[b] (%)	ee trans (%)
1	18 (1)	50	20 : 80	35	71
2	18 (2)	39	20 : 80	35	70
3	18 (3)	39	21 : 79	35	66
4	19 (1)	52	18 : 82	40	64
5	19 (2)	45	18 : 82	31	62
6	19 (3)	0	/	/	/
7	20 (1)	72	18 : 82		69
8	20 (2)	48	22 : 78		59
9	20 (3)	31	30 : 70		21
10	21 (1)	82	18 : 82	38	68
11	21 (2)	59	19 : 81	37	65
12	21 (3)	38	22 : 78		44
13	22 (1)	37	19 : 81		63
14	22 (2)	41	17 : 83	34	74
15	22 (3)	34	18 : 82	35	74
16	23 (1)	71	15 : 85	40	73
17	23 (2)	72	14 : 86	31	78
18	24 (1)	38	13 : 87	38	62
19	24 (2)	52	13 : 87	37	75

table 4: Heterogeneous catalysts test in batch conditions. [a] combined yield of the isolates diasteroisomer

[b] diastereoselectivities and optical yields were determined by GC analyses (chiral capillary Superchrom column) on the chrysanthemic acids upon basic hydrolisis.

All catalysts showedsatisfactory yields of the desidered product which, with silica and polystyrene supported catalysts (table 4, entry 1-15), decrease on recycling. However, the catalyst covalently bound to the silica support through the relatively rigid 4-phenylmethylene linker (entry 1-3) showed a slower deactivation and constant ee value of the trans-isomer, whereas a dramatic ee value lowering was observed on recycling the catalysts linked through floppy aliphatic chains. Even if these results are difficult to be fully rationalized, we can infer from them that the relatively rigid arm should project the catalytic Cu-BOX moiety more

effectively away from the support bulk thus mimicking the homogeneous conditions more effectively.[16]

The comparison of silica and polystyrene supported catalyst with the rigid spacer shows that the silica-supported catalyst was less recyclable than the polystyrene-supported counterpart even if a small, but constant, activity lowering accompanied by a practically constant ee value was observed on recycling (Table 1, entries 1-3 and 13-15).

The greater activity lowering of the silica-supported catalysts would be tentatively connected with the possible migration of complexed copper ions from the BOX ligand to the free silanol groups giving adventitious non-enantioselective catalytic sites and favoring the copper leaching. Moreover, when the catalyst is repeatedly utilized in batch systems, the vigorous stirring causes destruction of the support beads resulting in the formation of fine powder which dramatically hinders their handling in filtration giving rise to loss of catalytically active species and definitively reducing their ability to be efficiently recycled.

A different behaviour was observed with polysiloxane supported catalysts (Table 4 entry 16-19), they were tested only for two reactive cycles but they didn't show any activity lowering in the second cycle, however the diastero and enantioselctivities were high both in the first and in the second catalityc cycle, and in this case the floppy arm didn't affect the catalyst activity. The use of a polysiloxane (as polystyrene) matrix, as observed with the polystyrene supported catalyst, avoids the Cu migration towards the free silanol groups of silica, with the consequent hinibition of the non-selective reactions, achieving better selectivities. A possible rationale for this behaviour is based on the trapping of a long alkylic arm into the polysiloxane framework that minimizes the drawbacks observed for floppy spacers.

3.4.3 Heterogeneous continuous flow system reaction

With the aim of minimizing the destruction of the catalyst for continuous stirring, and enhancing its lifetime, a continuous flow system was set up.

A simple apparatus for the continuous flow cyclopropanation of 2,5-dimethyl-2,4-hexadiene was constructed by using a standard laboratory low pressure HPLC pump as CH_2Cl_2/tetramethylbutadiene/L-menthyl diazoacetate delivery device, an HPLC injector valve equipped with an injection loop for loading the reagent's solution into a stainless steel HPLC column packed with-supported BOX-Cu catalyst and a receiver flask for the collection of product

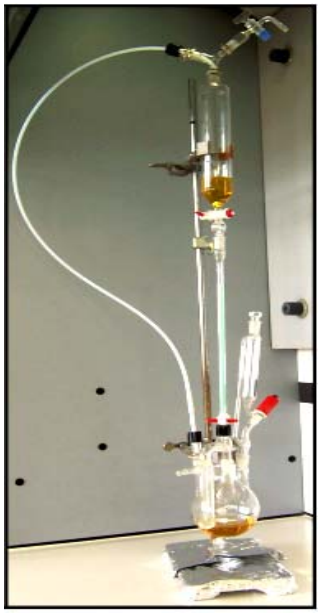
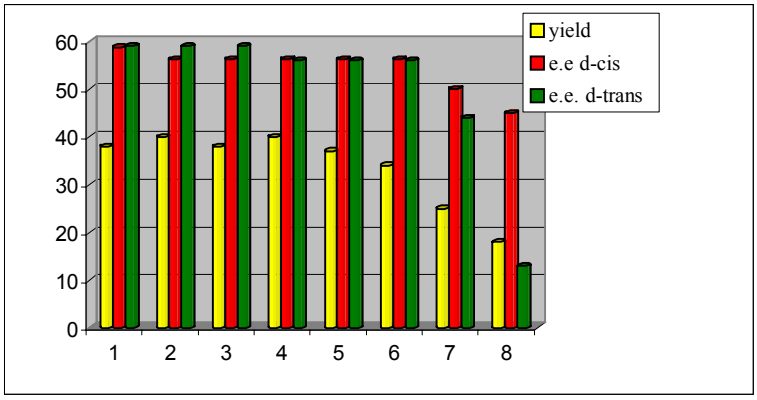


Figure 13: continuous flow apparatus

To keep as low as possible the production of dimeric by-products from diazoacetate (1% maleate and 4% fumarate), a starting solution of CH_2Cl_2/tetramethylbutadiene/L-menthyl diazoacetate (24/10/1 molar ratio) was re-circulated. After six hours, the mixture was subjected to distillation of the tetramethylbutadiene allowing 90% recovering of the excess reagent.

The first catalysts tested for this purpose were the polysiloxane and polystyrene $Cu(OTf)_2$ complexes, which in batch system gave the best risults. However in these conditions both supported complexes showed some problems: in CH_2Cl_2 solvent the polymeric catalysts swelled and the system needed very high pressure to work in a good way. To circumvent this drawback it was necessary to fill the column with the polymeric catalyst "diluted" into unfunctionalized silica. However applying high pressure, a separation of polymer and silica could be observed after some time.

For these reasons the $Cu(OTf)_2$**.18** silica supported complex, with the rigid benzylic arm, was tested in the model continuous fow reaction. A mixture of reagents in CH_2Cl_2 was flowed trhough the catalytic column for six hours and distilled to recover the reagent, hydrolized and analyzed by chiral GC. Chrysantemic acid was obtained in 38% yield, 37/63 cis/trans ratio, 43% cis ee value and 59% ee value for trans isomer. The catalyst was washed with CH_2Cl_2, dried with nitrogen flow and reused for 7 successive runs..



Graph 1: recycling on continuous flow system results.

Figure 14 shows that during the first 6 cycles the catalyst worked without any loss of activity and that only from the 7th cycle yield and enantiomeric eccess begun to decrease. These results can be considered good, infact industrial studies showed that if the process will be carried out for 8 cycles without any loss of activity, it will become a competitive process with the current industrial one.

3.5 Conclusions

In conclusion in this study the asymmetric cyclopropanation reaction of 2,5-dimethyl-2,4-hexadiene with L-menthyl diazoacetate promoted by $Cu(OTf)_2$**•**supported BOX **10** complexes was set up. Several supports and spacers were tested and the best results in batch system were obtained with polysiloxane supported catalyst with an alkyl short spacer, even if using silica and polystyrene supported catalysts the more rigid benzylic spacer achieved good results.

The polymeric support gave several problems when the reaction was transferred in a continuous flow system, because of the polymer swelling and the need to "dilute" with silica the catalyst into the column. The silica supported $Cu(OTf)_2$**•**BOX **18** complex was selected as the best one for the continuou flow reaction giving very good yield and selectivities for 6 different reactive cycles, without any loss of activity, and with decreasing activity during the 7^{th} and 8^{th} cycle.

To the aim of obtain the same activity for 8 or more different cycles and minimize the drawbacks of this operating methodologies (slow diffusional mass transfer of high molecular weight solutes into the stagnant liquid present in the pores of the beads, or the large void volume between the packed particles) the possibility to use monolithic systems is under investigation.

3.6 Experimental section

3.6.1 General.

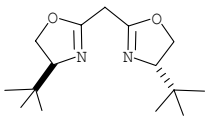
All chemicals were purchased from commercial suppliers and used as received.. All reactions were carried out under an anhydrous nitrogen atmosphere. Thin-layer chromatography was performed on aluminum sheets coated with silica gel 60F (Merck 5554). Column Chromatography was carried out by using silica gel (ICN 4663, 63-200 mesh). Melting points were measured on an Electrothermal apparatus and are uncorrected. All ^{1}H NMR were recorded at 300 MHz. Mass spectra were recorded in the CI (CH_4), ESI.

3.6.2 Synthesis of BOX ligands

A mixture of diethyl malonoimidate hydrochloride (1.155g, 5 mmol), 1,2-dichloroethane (20ml) abd (1R,2S)-(+)-cis-1-amino-2-alcohol was stirred at reflux temperature for 1h A solution of triethylamine (1.4 ml, 10 mmol) in 1,2-dichloroethane (5 ml) was then dropped in 30 min and the obtained mixture was stirred at reflux temperature for 3.5 h. The reaction was cooled at room temperature. filtered and the solution was evaporated under vacuum.

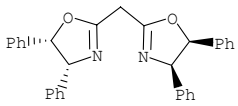
Crystals of the product were obtained from an 1:1 methanol: dichloromethane mixture.

2,2'-methylenebis[(4S)-4-tert-buthyl-2-oxazoline) ***(9)***



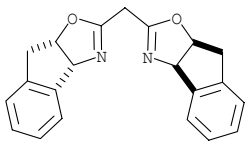
whyte solid, MW ($C_{15}H_{26}N_2O_2$): 266.01; mp 51-53°C: ; $[\alpha]_D$= - 118° (c=0.5, $CHCl_3$); H^1 NMR (300 MHz, $CDCl_3$): δ= 0.91 (s, 18H, 2*t*Bu), δ= 3.36 (t, 2H, CH_2, J=1.1), δ= 3.8-3.9 (m, 2H OCH_2C**H**tBuN), δ= 4.10 (dd, 2H, OC**H_2**CHtBuN J=7.7, 8.6), δ= 4.27 (dd, 2H, OC**H_2**CHtBuN J=8.7, 10.2); IR (KBr): 1666 cm^{-1}, 2859 cm^{-1}, 2903 cm^{-1}, 2949 cm^{-1}; MS (CI, m/z, int. rel %): 226 (M^+), 251 (5), 209 (39), 141 (100), 109 (32), 84 (21), 57 (14).

2,2'-methylenebis[4,5-dihydro-(4R,5S)-diphenyl]oxazole ***(10)***



White solid, yield 87%, MW ($C_{31}H_{26}N_2O_2$): 458.11; mp 205-208°C; $[\alpha]_D$= + 159.5° (c=0.5, $CHCl_3$); H^1 NMR (300 MHz, $CDCl_3$):δ= 3.91 (s, 2H, CH_2), δ= 5.63 (d, 2H, CHN, J=10.2), δ= 6.01 (d, 2H,CHO, J=10.2), δ= 6.9-7.2 (m, 20H, Ph); IR (KBr): 1629 cm^{-1}, 2924 cm^{-1}; MS (CI, m/z, int. rel %): 459 (MH^+, 100), 381 (18), 352 (12), 196 (10),180 (44).

*2,2'-methylenebis[3α, 8α-dihydro-(3aR,3'aR, 8aS,8'aS)]-8H-indeno[1,2-d]oxazole (***12***, INDA-BOX)*



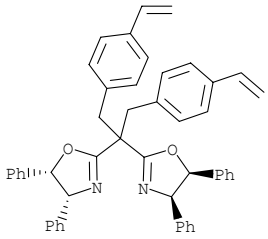
light yellow solid, MW ($C_{21}H_{18}N_2O_2$): 330.32; mp: 204-206°C; $[\alpha]_D$= + 350° (c=1, CH_2Cl_2); H^1 NMR (300 MHz, $CDCl_3$): δ= 3.09 (dd, 2H, OCHC**H_2**Ph, J=5.18), δ= 3.21 (s, 2H, CH_2), δ=3.43 (dd, 2H OCHC**H_2**Ph, J=6.9, 18.1), δ=5.37 (td, 2H, OCH, J=1.7, 7.0), δ=5.67 (d, 2H, CHN, J=7.9), δ= 7.2-7.3 (m, 6H, Ar), δ= 7.4-7.5 (m, 2H, Ar); IR (KBr): 1655 cm^{-1}, 2938 cm^{-1},

2985 cm^{-1}, 3023 cm^{-1}, 3040 cm^{-1}; MS (CI, m/z, int. rel %): 330 (M^+, 32), 207 (20), 173 (100), 157 (15),130 (69), 115 (43), 77 (26).

3.6.3 BOX funtionalization

To a solution of NaH (0.1 g, 2.5 mmol) in DMSO (30 mL) and 1,4-dioxane (5 mL), 2,2'-methylenebis[4,5-dihydro-(4R,5S)-diphenyl]oxazole (1.2 mmol) was added and the resulting reaction mixture stirred at room temperature until complete solution. An. alkylic or benzylic chloride (2.6 mmol) was then added and the reaction stirred at 40°C for 3 h. After cooling to room temperature, to the reaction mixture was added CH_2Cl_2 (20 mL). The mixture was washed with a HCl solution 1M (3x30 mL). The organic phase was dried over sodium sulfate and the solvent evaporated to dryness under reduced pressure. Purification of the residue by column chromatography (EtOAc/n-hexane) afforded a crude product which was recrystallised from CH_2Cl_2/MeOH (1:1 v/v).

2,2'-[2-(4-vinylphenyl)-1-(4-vinylbenzyl)ethylene]bis[4,5-dihydro-(4R,5S)-diphenyl]oxazole (**14**)

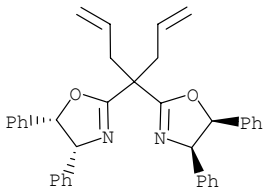


Column chromatography (EtOAc/n-hexane 7:3)Yield: 85% white solid compound: m.p: polymerizes before melting; $[\alpha]_D$ = +347,21°(*c*=1.004, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$): δ = 3.54 (d, *J* = 14.05 Hz, 2 H; CH_2), δ = 3.8 (d, *J* = 14.03 Hz, 2H; CH_2), δ = 5.27 (d, *J* = 10.74 Hz, 2H; CHN), δ = 5.44 (d, *J* = 10.28 Hz, 2H; CHO), δ = 5.79 (dd, J_1 = 17.6 Hz, J_2 = 10.2 Hz, J_3 = 0.7 Hz, 4H; CH=C<u>H</u>$_2$), δ = 6.76 (dd, J_1 = 17.6 Hz, J_2 = 10.9 Hz, 2H; C<u>H</u>=CH_2), δ = 6.88-6.99 (m, 20H; Ph), δ = 7.42-7.50 (m, 8H; Bz);

MS (CI, CH_4): *m/z* (%) 691 (100) [MH^+].

IR(NaBr): 3020 cm^{-1}, 2910 cm^{-1}, 1651 cm^{-1}, 1180 cm^{-1}, 990 cm^{-1}.

*2,2'-(1-allylbutyl-3-enylidene)bis[4,5-dihydro-(4R,5S) diphenyl] oxazole (**15**):*

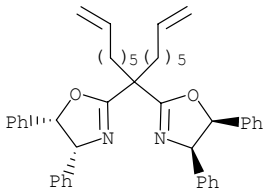


column chromatography (EtOAc/n-hexane=6:4); Yield: 82%; white solid compound: m.p. 113.8-117.9°C (24 mbar); $[\alpha]_D$ = +365,07°(*c*=1.002, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 25°C, TMS): δ = 3.0 (dd, J_1 = 14.31 Hz, J_2 = 7.5 Hz, 2H; C<u>H</u>$_2$CH=CH_2), δ =3.20 (dd, J_1 = 14.61 Hz, J_2 = 6.98 Hz, 2H; C<u>H</u>$_2$CH=CH_2), δ = 5.25-5.35 (m, 4H; CH_2CH=C<u>H</u>$_2$), δ = 5.57 (d, *J* = 10.05 Hz, 2H; CHN), δ = 5.93 (d, *J* = 10.08 Hz, 2H; CHO), δ = 6.01-6.08 (m, 2H; CH_2C<u>H</u>=CH_2), δ = 6.92-7.04 (m, 20H; Ph);

MS (CI, CH_4): *m/z* (%) 539 (100) [MH^+].

IR(NaBr): 3061 cm^{-1}, 2921 cm^{-1}, 1655 cm^{-1}, 1451 cm^{-1}, 1204 cm^{-1}, 993 cm^{-1} 920 cm^{-1}, 733 cm^{-1}, 699 cm^{-1}.

*2,2'-[1-(6-epten-1-il)octen-7-enylidene]bis[4,5-dihydro-(4R,5S)-diphenyl]oxazole (**16**):*



Column chromatography (EtOAc/n-hexane=8:2); yield: 70%; white solid compound; m.p. 84.6-85.6°C (24 mbar); $[\alpha]_D$ = +275,7°(*c*=1.002, CH_2Cl_2);

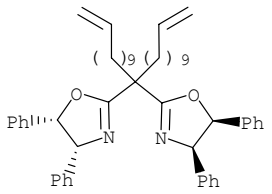
^{1}H NMR ($CDCl_3$, 25°C, TMS):

δ = 1.4-1.6 (m, 12 H; CH_2(C<u>H</u>$_2$)$_3$$CH_2$CH=$CH_2$), δ=2.0-2.11,(m, 4H; C<u>H</u>$_2$(CH_2)$_3$$CH_2$CH=$CH_2$), δ=2.20-2.5 (m, 4H; CH_2(CH_2)$_3$C<u>H</u>$_2$ CH=CH_2), δ =4.9-5.1 (m, 4H; CH_2(CH_2)$_3$$CH_2$CH=C<u>H</u>$_2$), δ = 5.59 (d, *J* = 10.059 Hz, 2H; CHN), δ = 5.8-5.9 (m, 2H; CH_2(CH_2)$_3$$CH_2$C<u>H</u>=$CH_2$), δ = 5.95 (d, *J* = 10.074 Hz, 2H; CHO), δ = 6.9-7.0 (m, 20H, Ph);

MS (ESI): *m/z* (%) 673.6 (100) [M^+].

IR(NaBr): 3063 cm^{-1}, 2924 cm^{-1}, 2855 cm^{-1}, 1651 cm^{-1}, 1651 cm^{-1}, 1452 cm^{1}, 1494 cm^{-1}, 1322 cm^{-1}, 1203 cm^{-1}, 986 cm^{-1}, 913 cm^{-1}, 698 cm^{-1}.

*2,2'-[1-(10-undecen-1-il)dodec-11-enylidene]bis[4,5-dihydro-(4R,5S-diphenyl]oxazole (**17**):*



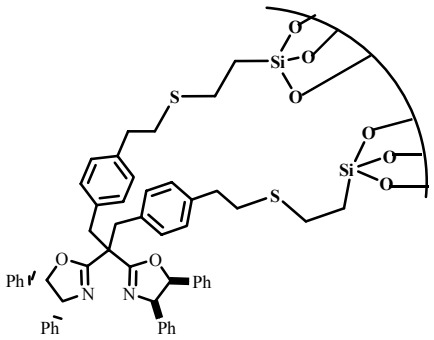
Column chromatography (EtOAc/n-hexane = 8:2) yield: 72%; colourless oil: b.p 35–38°C (0.3 mbar); $[\alpha]_D$ = +123,3°(*c*=0.504, CH_2Cl_2);

^{1}H NMR ($CDCl_3$, 25°C, TMS): δ = 1.26-1.49 (m, 28 H; $CH_2(C\underline{H}_2)_7CH_2CH=CH_2$), δ =2.01-2.08 (m, 4H; $C\underline{H}_2(CH_2)_7CH_2$ $CH=CH_2$), δ = 2.20-2.43 (m, 4H; $CH_2(CH_2)_7C\underline{H}_2CH=CH_2$), δ = 4.91-5.02 (m, 2H; $CH_2(CH_2)_7CH_2CH=C\underline{H}_2$), δ = 5.58 (d, *J* = 10.08 Hz, 2H; CHN), δ = 5.75-5.88 (m, 2H; $CH_2(CH_2)_7CH_2C\underline{H}=CH_2$), δ = 8.02 (d, *J* = 10.13 Hz, 2H; CHO), δ = 6.89-7.04 (m, 20H, Ph);
MS (CI, CH_4): *m/z* (%) 763 (100) [M^+].
IR(NaCl): 3065 cm^{-1}, 2924 cm^{-1}, 1651 cm^{-1}, 1456 cm^{-1}, 1206 cm^{-1}, 992 cm^{-1}, 912 cm^{-1}, 698 cm^{-1}.

*3.6.4 Synthesis of silica supported ligands **18-21***

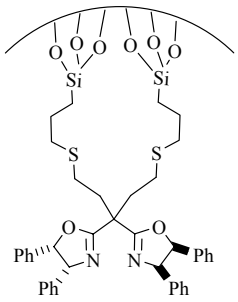
To a solution of bis(oxazoline) (**14-17**) (0.6 mmol) in anhydrous and degasaded $CHCl_3$ (26 mL), was added 3-mercaptopropyltrimethoxysilane (0.238 mL, 1.2 mmol) and azoisobutyronitrile (0.174 g, 1.06 mmol). This solution mixture was heated under reflux for 15 h. After cooling to room temperature the solvent was evaporated to dryness under reduced pressure. To the yellow oil residue was added anhydrous toluene (26 mL) and 4 g of silica gel (Grace GmbH & Co, 6 nm, dried at 400°C for 5 h). The suspension was heated under reflux for 24 h. The solution, after cooling, was filtered and washed with toluene (1x50 mL). The solid was subjected to Soxhlet extraction with CH_2Cl_2/Et_2O (1:1 v/v) for 16 h and subsequently dried under vacuum at room temperature. The content of chiral ligant was determinated by elemental analysis .

*ligand **18***



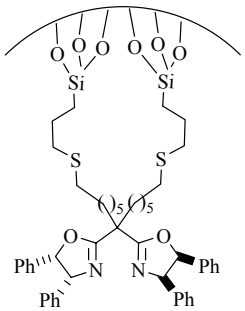
Light yellow solid; loading 0165 mmo/g

*ligand **19***



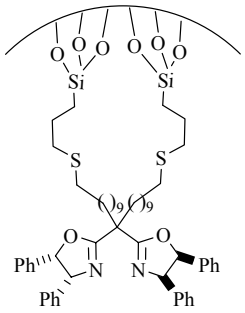
White solid; loading 0.150 mmol/g

*ligand **20***



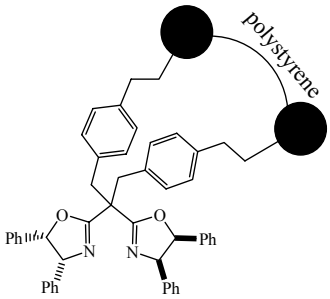
White solid; loading: 0.140 mmol/g

*ligand **21***



White solid; loading: 0.135 mmol/g

*3.6.5 Praparation of polystyrene supported ligand **22***

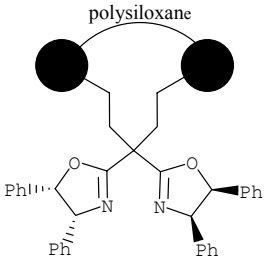


To a solution of functionalized BOX **14** (0.037 g 0.054 mmol) in toluene (5ml), styrene (0.27 ml, 2.38 mmol) and technical grade divinylbenzene (80%, meta:para=2:1, 0.26ml) and AIBN (0.008 g) were added. The mixture was v stirred at reflux temperature for 20h. The solid product was precipitate with methanol (10 ml), separated by filtration, washed with CH_2Cl_2 and MeOH (2x500 ml) and milled to obtain a powder. The content of chiral ligand was determined by elemental analysis and was 0.125 mmol/g.

*3.6.6 Preparation of polysiloxane supported ligands **23** and **24***

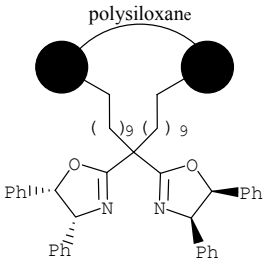
Polydimethlsiloxane vinyldimethylsiloxy terminated (DMS-V05) (0.2 g, 0.5 mmol of vinyl group), methylhydrosiloxan-dimethylsiloxan copolymer (HMS-301) (0.32 g, 1.25 mmol of Si-H group) and ligand 15 or 17(0.2 mmol) were suspended in 1.5 mL of toluene. Platin-divinyltetramethyl-disiloxan complex (100 mg) was added, and the reaction was stirred at rt under nitrogen for 20 h. The yellow polysiloxanic material was isolated by filtration on buchner. The rubber obtained was then minced and washed with CH_2Cl_2 (100 mL) and MeOH (100 mL), until the washing solution became colorless. The new hybrid material was dried under vacuum and at last characterized by elemental analysis.

*ligand **23***



yellow rubber, loading 0.19 mmol7g

*ligand **24***



yellow rubber, 0.2 mmol/g.

3.6.7 Preparation of Immobilized Copper Complexes:

To a suspension of one of the immobilized bis(oxazoline) **18-24** (0.19 mmol) in CH_2Cl_2 (30 mL) was added $Cu(OTf)_2$ (stoichiometric amount). The mixture was stirred at room temperature for 1 h. The solid was separated by filtration, washed with CH_2Cl_2, and dried under vacuum at room temperature. The copper content was determined by plasma emission spectroscopy.

Ligand	**Cu loading (mmol/g)**
18	0.154
19	0.140
20	0.140
21	0.120
22	0.120
23	0.180
24	0.195

3.6.8 General procedure for homogeneous cyclopropanation reaction

To a suspension of the corrisponding catalyst (0.015 mmol) in a solution of dichlorometane (3 mL) and 2,5-dimethyl-2,4-hexadiene (4.2 mL, 30 mmol) at room temperature, was added with stirring (-)-menthyl diazoacetate (0.672 g, 3 mmol) in the same solvent (4.5 mL) over 2 h using a syring pump. After addition, stirring was continued for 3 h until N_2 evolution ceased. The results were determined by gascromatografy

3.6.9 General procedure for cyclopropanation reactions in batch

To a suspension of the corrisponding catalyst (0.015 mmol) in a solution of dichlorometane (3 mL) and 2,5-dimethyl-2,4-hexadiene (4.2 mL, 30 mmol) at room temperature, was added with stirring (-)-menthyl diazoacetate (0.672 g, 3 mmol) in the same solvent (4.5 mL) over 2 h using a syring pump. After addition, stirring was continued for 3 h until N_2 evolution ceased. The catalyst was separated by filtration, washed with dichlorometane and dried. The catalyst was reused under the same conditions. The results were determined by gascromatografy .

Ligand (cycle)	yield (%)[a]	cis/trans[b]	ee cis[b] (%)	ee trans[b] (%)
18 (1)	50	20 : 80	35	71
18 (2)	39	20 : 80	35	70
18 (3)	39	21 : 79	35	66
19 (1)	52	18 : 82	40	64
19 (2)	45	18 : 82	31	62
19 (3)	0	/	/	/
20 (1)	72	18 : 82		69
20 (2)	48	22 : 78		59
20 (3)	31	30 : 70		21
21 (1)	82	18 : 82	38	68
21 (2)	59	19 : 81	37	65
21 (3)	38	22 : 78		44
22 (1)	37	19 : 81		63
22 (2)	41	17 : 83	34	74
22 (3)	34	18 : 82	35	74
23 (1)	71	15 : 85	40	73
23 (2)	72	14 : 86	31	78
24 (1)	38	13 : 87	38	62
24 (2)	52	13 : 87	37	75

3.6.10 Cyclopropanation Reactions in continuous flow

2,5-dimethyl-2,4-hexadiene (54 mL, 380 mmol) and ethyl diazoacetate (4 mL, 38 mmol) were dissolved in dichlorometane (75 mL) and this solution was pumped countinously into one end of a fine column packed with supported catalyst (1,1 g, 0.19 mmol) and silica (2.2 g) over 6 h. From the other end the product solution emerged countinously.

After the reaction was finished, the support was consecutively washed with dichlorometane. The catalyst was reused under the same conditions. The yield and e.e. were determined by gascromatografy

cycle	**yield (%)**	***cis:trans***	***cis* ee (%)**	***trans* ee (%)**
1	38	37:63	43	59
2	40	36:64	40	59
3	38	36:64	42	59
4	40	36:64	40	56
5	37	36:46	40	56
6	34	36:64	40	56
7	25	36:64	30	44
8	18	35:65	9	13

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4. Asymmetric Henry reaction promoted by Cu(II)-BOX complexes

4.1 Introduction

Among the various C-C bond forming reactions, Henry raction is one of the classical named reactions in organic synthesis. Essentially the coupling of the nucleophile generated from a nitroalkane with a carbonyl electrophile is a widely used transformation, since its discovery in 1895.[1]

Since this first preliminary studies the reaction was known as a classical route to obtain the extension of carbon chains in organic synthesis.

The vigourous development of oganic chemistry in the last twenty years reveals an increasing interest in the use of nitroalkanes in synthesis and the Henry reaction has found different applications in the assembly of carbon structures and functional groups with high chemo- and regio- selectivity.

The Henry reaction is an aldol reaction (Figure 1) and usually the activation of primary or secondary nitroalkanes is promoted by an organic or inorganic base, to generate the nitronate anion (**2**). The nitro group is able to stabilize the negative charge on the contiguous carbon. Nitroalkanes have pK_a values roughly included among 9 and 10, and for this reason they show a particular activity.

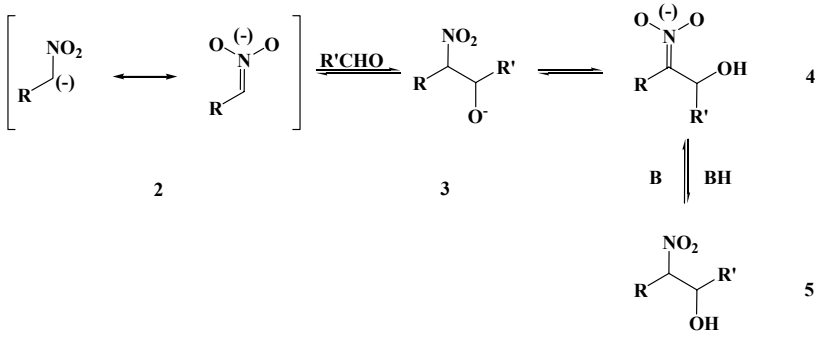


Figure 1: Henry reaction

The corrisponding nitronic acids or aci-nitro compounds seems to be carBOXilic acids for their acidity (pK_a 2-6), so they are easily deprotoned to obtain nitronate anions. For this reason the forms nitro and aci-nitro, related by the nitro-aci-nitro tautomery, present a common anion 2 (Figure 2), that is an ambidental nucleophilic group.

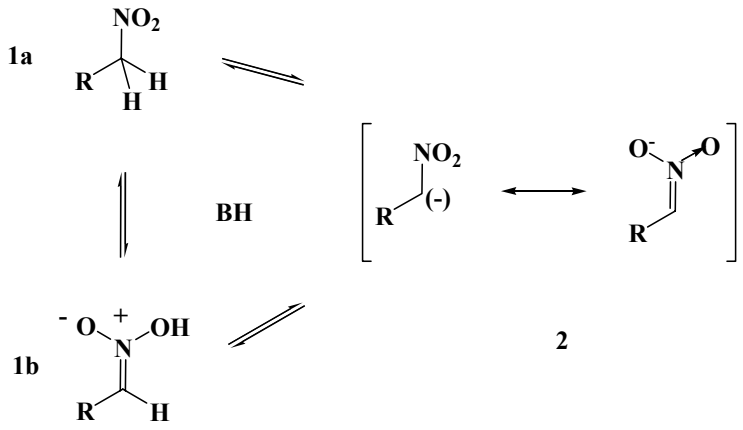


Figure 2: **nitro-aci-nitro tautomery**

Since the oxygen is more electronegative than the others atoms, that centre should be considered the most reactive, giving the O-alkylation product rather than the exclusive C-alkylation. But this kind of reagents are weak O-nucleophiles and usually give the C-alkylation with electrophiles.

Figure 1 shows the typical steps of a nitroaldol reaction: deprotonation of a nitroalkane to obtain the anion **2**; nucleophilic attack to the carbonyl group to give the oxydrilated anion (**3**↔**4**) and final protonation to give the nitroalcohol **5**.

However, when primary nitroalkanes or nitromethane are used, the product of this first sequence of reactions has a second acid proton and the process can repeat itself giving dihydroxy and trihydroxy products **6** and **7** (Figure 3)

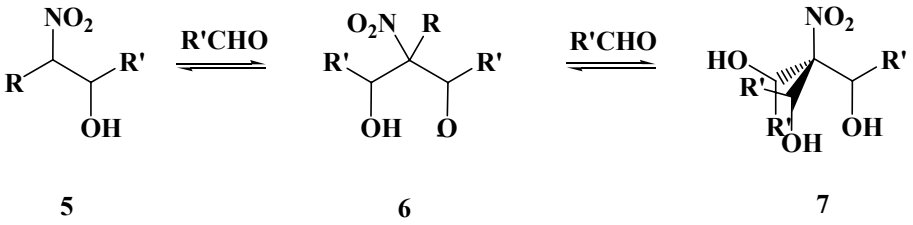


Figure 3: consecutive condensation reactions**.**

But the further hydroxyalkylation is more difficult than the first one because the first hydroxyalkyl group introduced reduces the acidity of the contiguous proton, moreover, the carbon is more sterically hindered.

When nitroalkanes undergo a reaction catalysed by a base with α,β–unsaturated aldehydes or ketons, Michael reaction competes with the nitroaldol one (Figure 4)

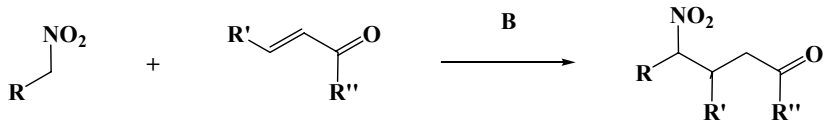


Figure 4: Micheal reaction between nitroakenes and a,b-unsaturated aldehydes or ketones.

Michael reaction is an other important C-C bond forming reactions and it is usually catalyzed by homogeneous organic bases, as tetramethylguanidine (TMG), diisopropylamine, tri-n-buthylphosphine and triphenylphosphine, or inorganic bases, like KF/18-crawn-6 and recently chromatographyc alumina in solvent free conditions.[2]

Different applications of conjugated addictions of nitroalkanes to α,β-insaturated compounds were used, for example, in the prostaglandins synthesis, preparation of α,β-insaturated aldehydes, as well as 1,4- and 1,5-dicarbonylic compounds.[3]

Between the two competitive 1,2 and 1,4 addictions the second one appears the favourite one if the substrate is an α,β–unsaturated, β-substituted ketone. When an α,β-unsaturated aldehyde is used Michael reaction seems to proceed better but the conditions of selectivity for this two reactive pathways were not well stabilized.

The classical Henry reaction is normally realized in the presence of catalytic amount of base. The most used are carbonate, bicarbonate, alkoxides, calcium, barium magnesium and aluminium hydroxides. However also anionic exchange resins and primary and tertiary amines were used with good results. In this case the mechanism is the normal aldolic one when a tertiary amine is used (Figure 5), but it passes through an imine intermediate (9, Figure 5) when the catalyst is a primary amine.

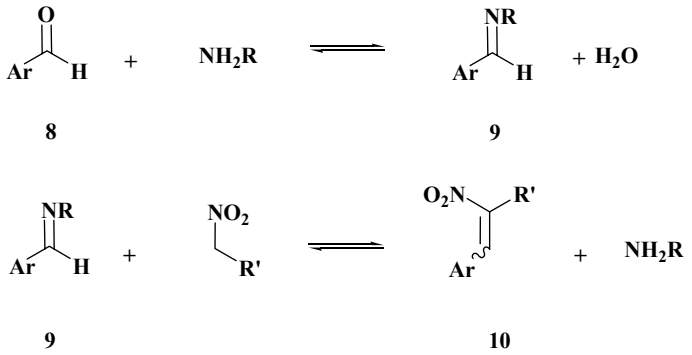


Figure 5: Henry reation promoted by primary amine.

The main interest of the nitroaldol products stems from the potential offered by nitro compounds for transformation into other compound families. For many application nitro acohol adducts are

subjected either to subsequent dehydration reactions to afford conjugate nitroalkenes, which are important building blocks in synthesis, or to oxidation of the hydroxy group to provide the corresponding ketone, so stereogenicity at either C^{α} and/or C^{β} positions is lost. In these instances the stereochemical outcome of nitroaldol reaction becames irrilevant. For many other applications, however, in which the newly formed C^{β} and/or C^{α} stereocentres are retained in the target molecules, control of the configuration at those stereocentres is crucial during the nitroaldol reaction. In particular the nitro group affords versatile routes to other functionalities. The $CH\text{-}NO_2$ moiety in a nitroaldols product can thus be converted (Figure 6) into the corresponding ketone, aldehyde or carBOXylic acid trhough Nef oxidation (path a nad b), into an amino compound trhough reduction (path c) or into other derivatives through substitution of the nitro group by various carbon and heteroatom-centred nucleophiles.[4]

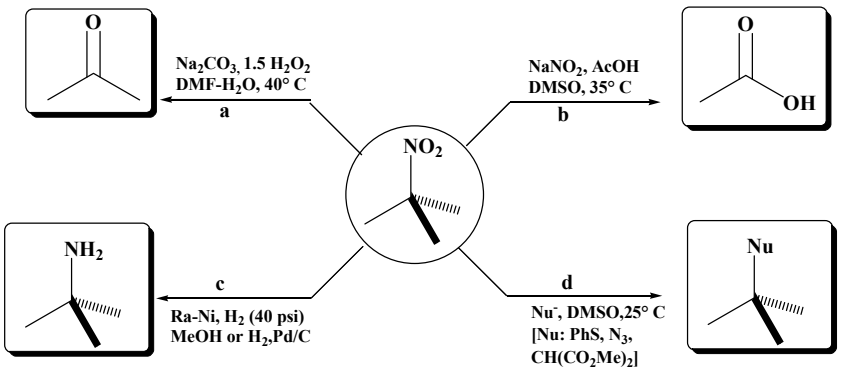


Figure 6: The nitro group as a versatile source of other compound families.

The β–aminoalcohols product[5] through the path c present several applications in synthetic chemistry and their biological importance can be observed for example in the epinephrin structure. However they are important intermediates in pharmaceutical chemistry: for example 3-amino-2-hydroxy-4-phenylbuthanoic acid **10a** (Figure 7),is a component of some HIV protease inhibitors, while (S)-(-)-Pindolol **10b** is a β-adrenergic antagonist with sympathomimetic activity[6].

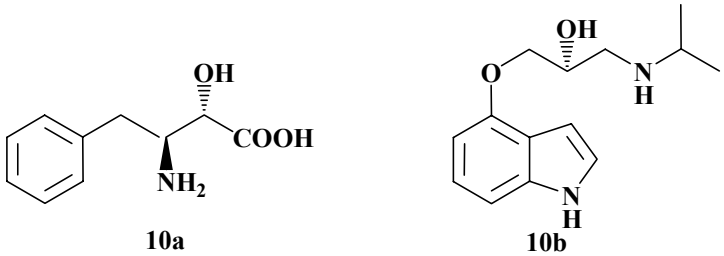


Figure 7: examples of pharmaceutical product derived from β-aminoalcohols.

From a formal point of view, the nitroaldol reaction very closely resembles the aldol reaction, and the two are comparable in several aspects. Nevertheless, they have important distinguishable features that justify their unequal degrees of development. In particular, the field of stereoselective nitroaldol reactions has remained less studied in comparison with the wealth of methods for stereocontrolled aldol reactions.[7] An inherent limitation of the nitroaldol reaction in this respect is the lack of trivial points for covalent attachmemnt of chiral auxiliares in either the nitroalkane (nucleophile) or the carbonyl (electrophile) component.[4] Additional issues that often erode stereocontrol are the reversible natures of many nitroaldol reactions and the relatively ease with which racemisation of the carbon stereocentre located α to the nitro group can occur. Not surprisingly, catalyst-controlled asymmetric versions of the nitroaldol reaction were essentially undocumented until 1992, while three main reviews on catalytic asymmetric aldol reactions covering the literature up to the 2003 have been published.[8]

From 1992 till now a considerable effort was directed toward the development of asymmetric catalysts for the Henry reaction. When coupled with an efficient, high yield reduction of the products, the overall sequence offers an excellent expedient for the preparation of optically-enriched aminoalcohols.

For example the product **10b** was preparated by the Shibasaki method shown in Figure 8. The β-nitroalcohol derives from the condensation of the indoloyloxyaldehyde with nitromethane in the presence of a lanthanum-lithium (R)-(+)-Binol catalyst (10 mol%).

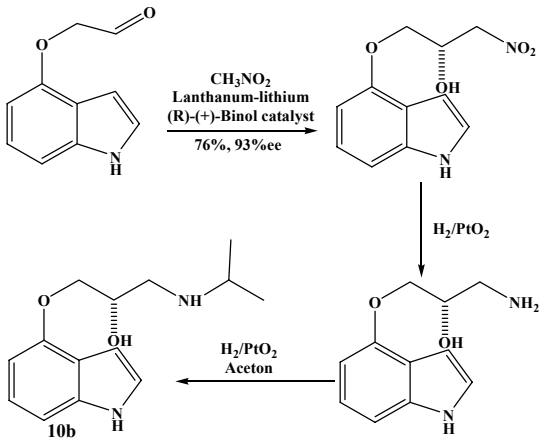


Figure 8: (S)-(-)-Pindolol synthesis trhough Shibasaki method.

The product **10a** was prepared using the scheme of Figure 9. The sequence involves the nitroaldol reaction of the (S)-N-phthalimidoaldehyde and nitromethane with dilithium-(R)-binaphthoxide, La(O-*i*-Pr)$_3$, H_2O in THF

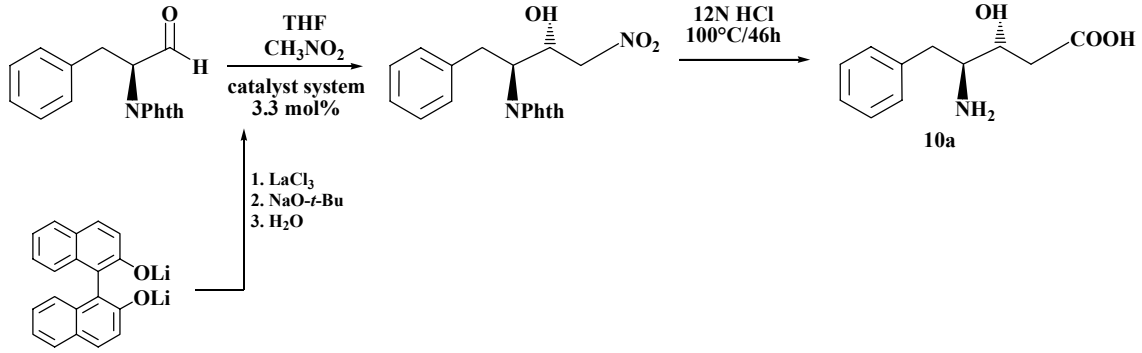


Figure 9: Synthesis of 3-amino-2-hydroxy-4-phenylbutanoic acid.

The last examples show the use of rare earth-Binol complexes, which are a kind of asymmetric catalyst for Henry reaction, but in literature are reported different systems:

Trost et al. have revealed a new class of dinuclear zinc complexes **11**, that convert α-branched aldehydes to the corresponding β-nitroacohol (up to 93% ee).[1]

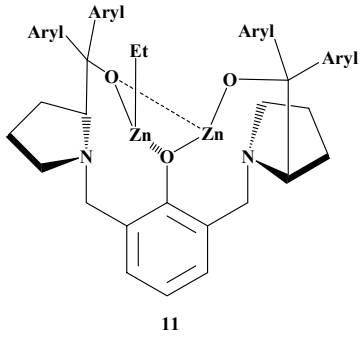


Figure 10: dinuclear zinc complexes

Others examples are the Co Salen complexes or the combination of Zn(II) salt, an amine base and a chiral amino alcohol ligand discovered by Palomo's group, and also exist some examples of organocatalysis throught chiral guanidine[1].

Among the Cu-BOX complexes Evans studied the application of the complex **12** in the asymmetic catalytic Henry reaction of aromatic aledhydes and nitromethane, that will be the model reaction of this study.

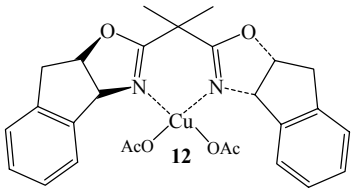


Figure 11: $Cu(OAc)_2$-IndaBOX complex

The catalyst is a weakly acidic metal complex bearing moderately basic charged ligand, that would facilitate deprotonation of nitroalkanes.[9]

The mechanism proposed by Evans[10] for this reaction is shown in Figure 12:

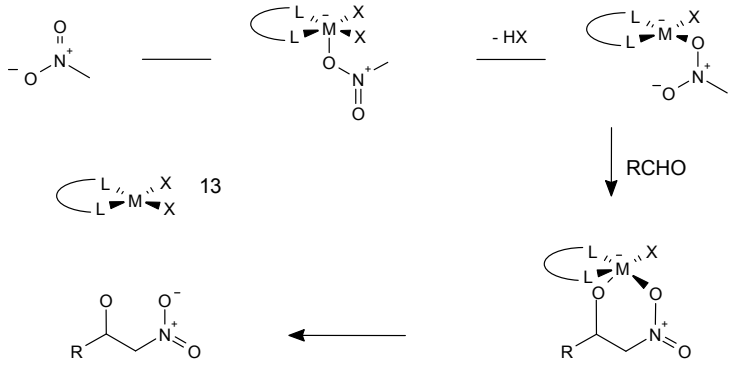


Figure 12: model reaction mechanism.

An attempt to rationalize how asymmetric induction is imparted from complex **12** begins with a statement of the impact of the Jahn-Teller (JT) effect on Cu(II) coordination. As illustrated in Figure 13, JT distortion of an octahedral Cu(II) complex creates four strongly coordinating and two weakly coordinating sites labeled red and blue, respectively. Addition of a bidentate ligand L2 affords a complex positioning the two cis-oriented strongly coordinating sites in the ligand plane and two trans-oriented weakly coordinating sites perpendicular to the ligand plane. For those complexes that simultaneously bind both electrophile and nucleophile, the most reactive transition states should position the nucleophile perpendicular to the ligand plane, while the electrophile, for maximal activation, should be positioned in one of the more Lewis acidic equatorial sites in the ligand plane as illustrated for complex **B**. By the same argument, complex **D** should exhibit the lowest reactivity (greatest stability). While transition states **14** (boat), **15** (chair), and **16** (chair) all predict the observed sense of asymmetric induction, our predisposition is to favor **14** on the basis of both steric and electronic considerations.

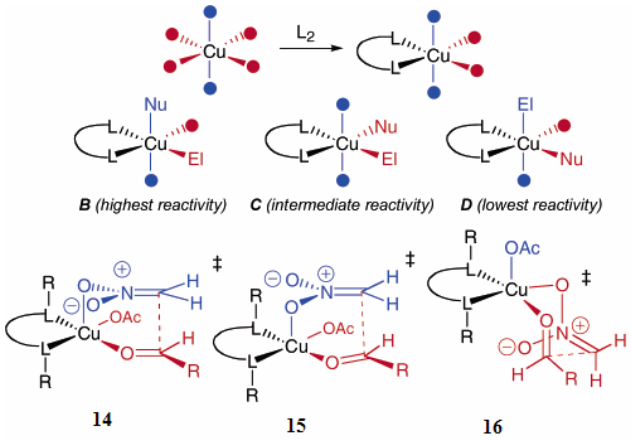


Figure 13: Plausible transition state for Henry reaction

4.2 Purpose of the work

This work intends to set up an asymmetric, catalytic Henry reaction to synthetize chiral β–nitroalchohols with high yields and enantiomeric excesses.

In order to earn this results the following program would be developed:

- Prepare a new set of chiral BOX, with different substituents on the ring in position 4 and 5, or at the methilene bridge, symmetric or asymmetric.
- Complex this ligands with different Cu salt and test the new complexes in the model reaction of *p*-chlorobenzaldehyde with nitromethane.
- Select the more active complex and set up the conditions in order to find the best homogeneous system.
- Test the optimized reaction with different aromatic aldehydes in order to evaluate the efficiency of the catalyst.
- Heterogenize the best catalyst trhough the tethering approach onto different solid materials and test the heterogeneous complexes in the model reaction in order to find the best heterogeneous catalyst.
- Optimize the heterogeneous system evaluating leaching of metal and recovering and reusing of the catalyst.

4.3 Homogeneous studies

4.3.1 Synthesis and BOX ligand screening

Starting from literature information we chose to test Cu(II)-BOX complexes as catalysts in the Henry model reaction of *p*-chlorobenzaldehyde with nitromethane (Figure 15), in order to obtain an axample of chiral β-nitroalcohol, useful intermediate for fine and pharmaceutical products.

A new library of BOX ligands (Figure 14) containing some of the BOX used for cyclopropanation, and some new ones, was prepared using the method set up in the previous chapter.

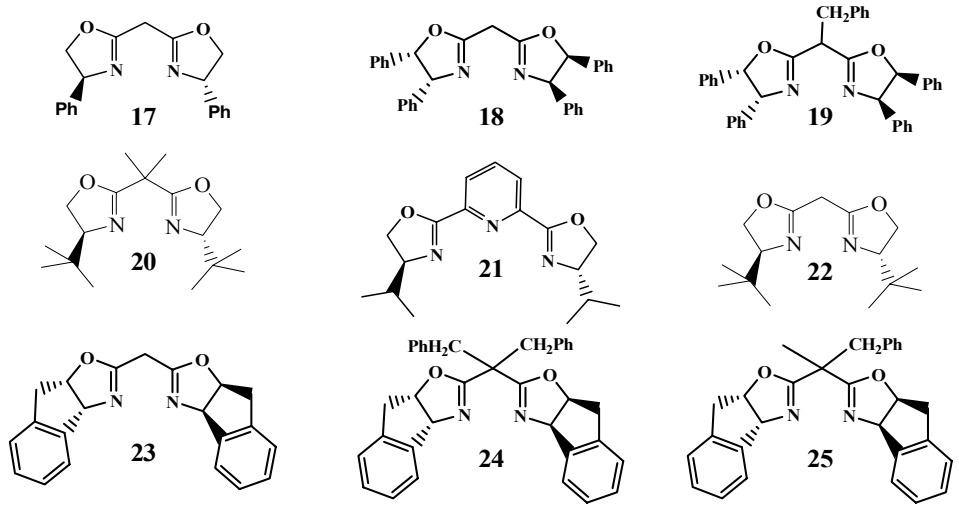


Figure 14: BOX ligands 17-25

Ligands **17-25** were obtained with different yields and their optical rotation was evaluated by polarimetric measurement. Thay were complexed in situ using $Cu(OAc)_2 \cdot H_2O$ and tested in the model reaction shown in figure 15.

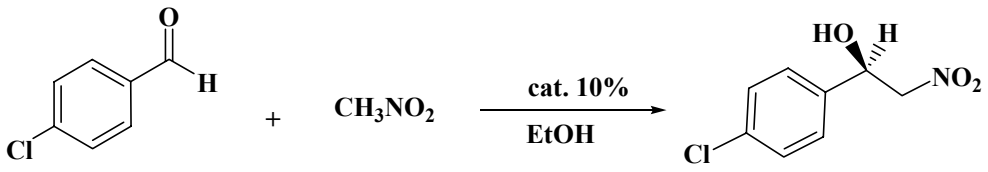


Figure 15: model notroaldol reaction of *p*-chlorobenzaldehyde with nitrometane.

The final reaction mixtures of this screening were avaluated by HPLC using a chiral column and are shown in Table 1

entry	ligand	Yield (%)	e.e (%)
1	17	30	34
2	18	65	30
3	19	76	39
4	20	95	83
5	21	89	2
6	22	66	49
7	23	57	47
8	24	88	81
9	25	95	84

Table 1: ligands efficiency in model reaction.

Ligands **20** and **25** showed similar and best activity, this is important because while ligand **20** is a C_2 symmetric bis(oxazoline), ligand **25** carries two different substituents at the methylene bridge. The role of this substituent seems to play a key role in the enantioselection, infact ligand **17, 18, 19, 22** and **23**, that have the free methylenic bridge, present a lower selectivity with respect the corresponding substituted ligands. This probably depends on the formation of the dimeric complex of Figure 16, that doesn't permit the formation of the catalytic active complex because there aren't enough free coordination sites.

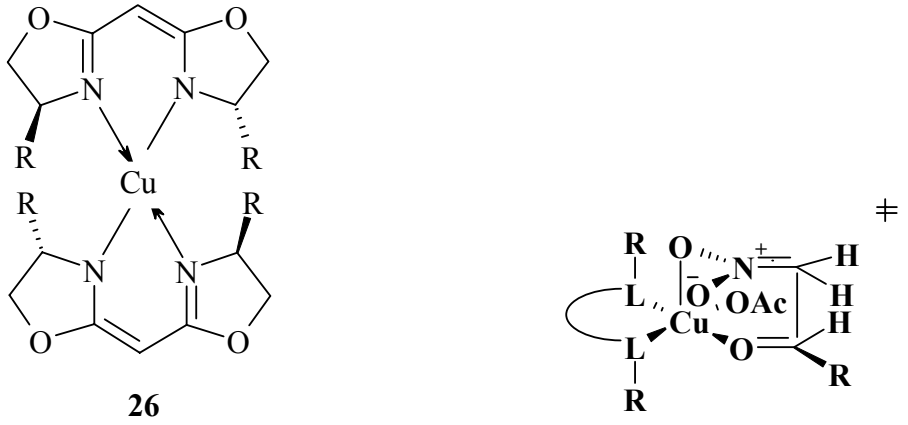
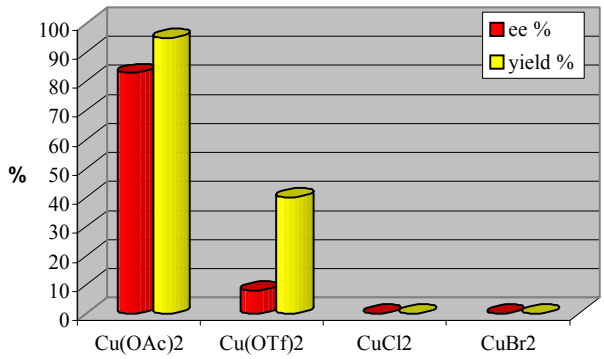


Figure 16: dimeric complex and supposed catalitic active transition state.

The hypotesis could be confirmed by the violet color of the solution, observed when ligand **23** was used in the model reaction: infact usually the Cu(II)/BOX complexes present a blue/green colour while a violet colour is proper of complexes **26**.

4.3.2 Copper source screening

In order to optimize the homogeneous conditions it was decided to test different copper (II) salts namely: $Cu(OAc)_2$, $Cu(OTf)_2$, $CuCl_2$ and $CuBr_2$. These salts were used to form the complex in situ with ligand **20** and tested in the model reaction, giving the results shown in Graph. 1.

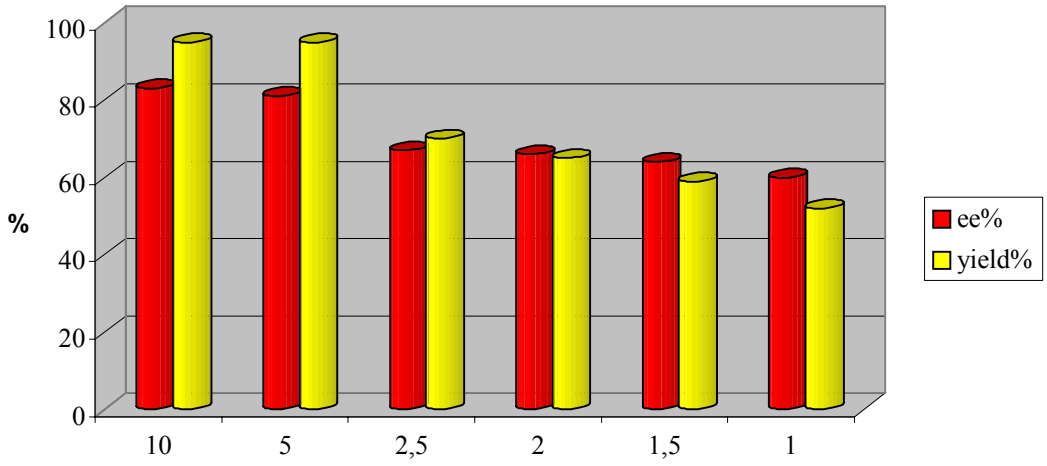


Graph 1: copper source screening

Copper acetate gave the best yield and ee values, this is not a surprising result because acetate anion is basic enough to facilitate the nitromethane activation, in the same way it is not surprising that $CuCl_2$ and $CuBr_2$ are not active catalysts for this reaction, infact the machanism requires the leak of one ligand, so that the aldehyde could enter in the Cu coordination sphere; probably Cl and Br are too hard ligands for copper and they don't leave the complex, hampering the catalytic active complex formation.

4.3.3 Catalyst amount screening

Up to now large amounts of catalysts (10% mol) were used in the present reaction. Thus the experiments were carried out with lower amounts of BOX **20**/ $Cu(OAc)_2$ complexes, and quite good risults can be achieved with 5% mol catalyst with respect to the aldehyde, without any loss of activity, but when the catalyst amount decreases below the 5% both yield and enantioselectivity decrease (Graph 2).



Graph 2: influence of substrate/catalyst ratio on model reaction.

4.3.4 Substituent effect evaluation

The effect of the aromatic aldehyde substituent was successively evaluated. Five differently substituted benzaldehydes were tested in the model reaction at room temperature, for 24 h, in EtOH, with 5% mol of BOX **20** /$Cu(OAc)_2.H_2O$ with respect to benzaldehyde and with aldehyde/nitromethane ratio of 10.

R	***Yield (%)***	***ee (%)***
p-Cl	95	83
m-Cl	57	77
o-Cl	75	87
H	93	85
p-Br	80	86
p-NO2	98	44
p-OMe	92	84

Table 2: substituent effect.

The *o,m,p*-chloro benzaldehyde series didn't afford surprising data, infact when the substituent is in meta position, and the aldehyde less activated, both yield and selectivity decrease ; in the same way when chloro is in orto position, the steric hindrance of the group, lowers the reaction rate and a lower yield but an higher enantiomeric excess are observed. Both electron-withdrawing and electron-releasing groups gave similar results, only *p*-NO_2-benzaldehyde afforded a very high yield with low enantiomeric excess (44% ee). Probably the NO_2 group makes benzalehyde too much active and the reaction rate increases, with detriment of enantiomeric excess.

4.4 Heterogeneous studies

4.4.1 Ligand functionalization

In order to evaluate the activity of heterogeneous Cu/BOX complexes in the Henry reaction, it was decided to support BOX **22** and **23**, as precursors of the best homogeneous catalysts. Infact the best point to functionalize a BOX ligand is the methylene bridge and it was not possible to use BOX **20** or **25**. Unlike cyclopropanation, for Henry reaction a mono-functionalization was chosen as the best approach, infact the ligand screening showed that C_2 symmetry is not important in order to have a selective raction, and a single spacer gives a grater mobility of the ligand, and therefore an easier availability of the catalytic site.

Using the same method reported in chapter 3 for cyclopropanation, BOX **22** and **23** were funtionalized with 4-vinylbenzylchloride, but using the correct amounts of NaH and 4-vinylbenzylchloride to obtain the attack of only one spacer.

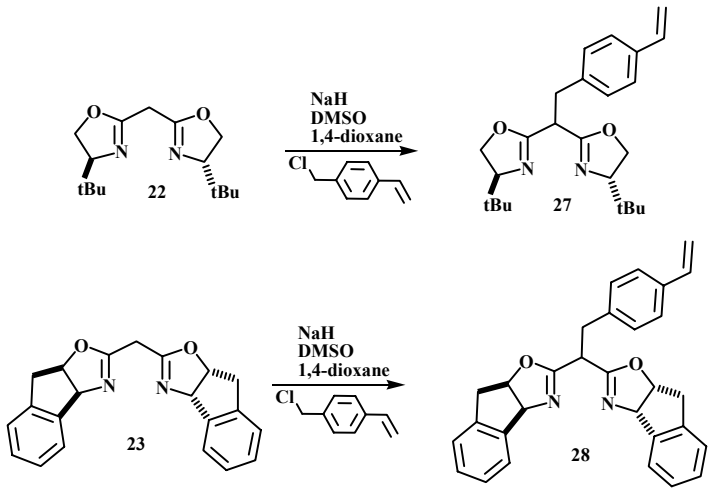


Figure 17: BOX **22** and 2**3** functionalization with a single vinylbenzyl spacer.

4.4.2 Synthesis and evaluation of polymer supported complexes activity

Ligands **27** and **28** were co-polymerized with styrene and divinylbenzene using the method described in chapter 3, but in this case different ratios of reagents were used in order to obtain polymers with different ligand loading. A constant value of styrene/divinylbenzene ratio was utilized in order to obtain polymers with the same cross linking.

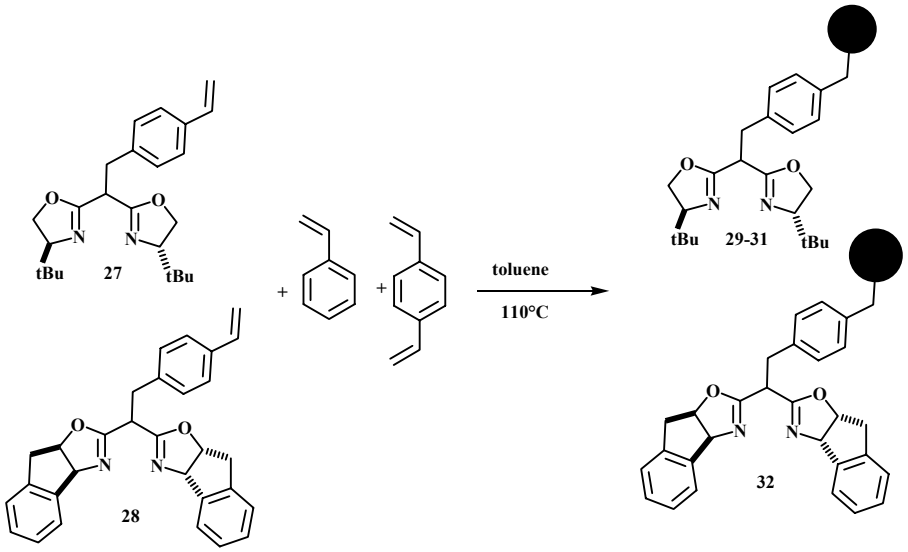


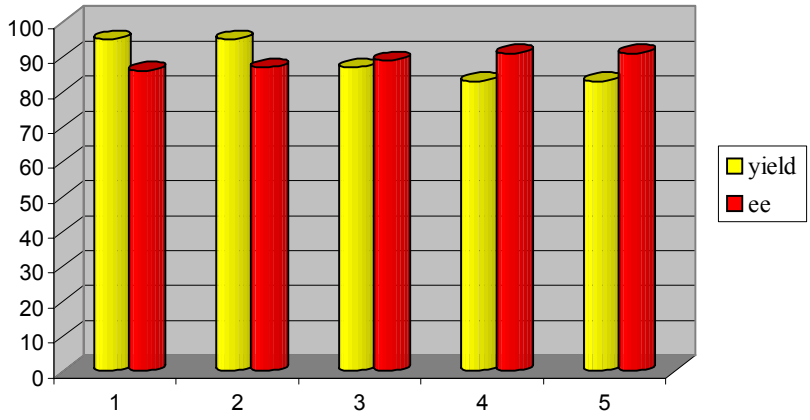
Figure 17: synthesis of polymers **29-32**.

Four polymers **29-32** were prepared and ligand loading was determined through elemental analysis (Table 3), then they were complexed with $Cu(OAc)_2.H_2O$ and tested as heterogenaous catalysts in the model reaction. The results (Table 3) showed that the inda-BOX polymer **32** is not so active in heterogeneous phase, whyle polymers 29-31 resulted very active, and a better activity was observed for polymer 31, with the higher loading.

polymer	**Loading (mmol/g)**	**Yield (%)**	**ee (%)**
29	0.46	95	75
30	0.6	95	75
31	0.8	95	86
32	0.78	75	11

Table 3: activity of polymers **29-32** in model reaction.

Polymer **31** was selected to evaluate the catalyst recycling, after the first reaction it was filtered out from the reaction mixture, washed with EtOH, dried under vacuum and reused in the same conditions. Graph 3 shows that the catalyst worked in the first five reactive cycles without any activity loss.



Graph 3: polymer 32/$Cu(OAc)_2.H_2O$ complex recycle.

4.5 Conclusions

The aim of this work was the development of a new heterogeneous recyclable catalyst for the asymmetric Henry reaction of substituted benzaldehyde with nitromethane, with the final goal to obtain an environmentally benign process. The synthesis of a small library of BOX ligands was investigated and these compounds were then used in the copper catalyzed asymmetric Henry reaction to afford chiral β-nitroalcohols. Yields and enantioselectivities were very good in homogeneous catalysis, so a strategy to heterogenize the best homogeneous ligand was developed. The ligand was heterogenized on organic polymers with different loading values and the activity of these catalysts were similar to the homogeneous ones in both yield end enantioselectivity.

The possiblity to recycle the catalyst was also investigated and the best heterogeneous catalyst resulted recyclable for five cycles without any loss of activity.

4.6 Experimental section

4.6.1 General

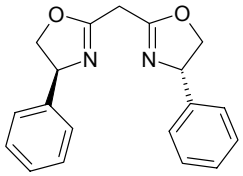
All *^1H NMR* were recordered with a BRUKER AC300 instrument at 300 MHz, the chemical shifts are expressed in ppm (δ).

Elemental analysis were obtained with a CARLO ERBA CHNS-0 EA1108 ELEMENTHAL ANALYZER. instrument. The *tin layer chromatographies (TLC)* were performed on Kieselgel 60 F_{254} of 0.25mm and the products were detected with an UV lamp at 254 nm. All the *flash chromatographies* were performed with con Kieselgel 60 (0.040-0.063nm) silica, while the silica used to prepare heterogeneous catalysts is GRACE DADISON. The *mass spectra* were obtained with HP 5971 A Mass Selective Detector (column SE 52). *The optical rotation* of ligands was estimated with a polarimeter PERKIN ELMER 341, with a Na lamp at 589 nm, at 20 °C, in a microcell containing 10 ml of solution. *enantiomeric excesses* were calculated by HPLC (*Chiracel OD-H* column).

4.6.2 Synthesis of BOX ligands

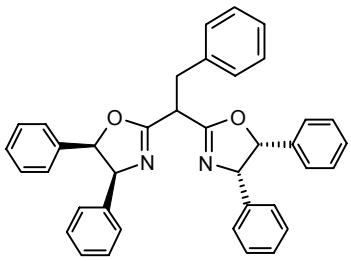
Several BOX ligands were prepared according with the method reported in chapter 3 of this thesis. Here were reported only the phisical data of bis(oxazolines) that are not present in the last section.

*2,2'-methylenebis[4,5-dihyidro-(4R)-phenyl]oxazole **17** :*



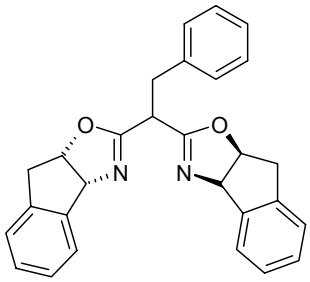
White solid compound; yield:55%; $C_{19}H_{18}N_2O_2$; mw: 306.65; $[\alpha]_D$ = +21.6 (c = 0.96 in EtOH); ^{1}H NMR (300MHz,$CDCl_3$): δ= 3.6 (t ,2H, CH_2, *J = 1.1);* δ= 4.2 (dd, 2H, OC**H**$_2$CHt-BuN, *J* = 8,8.3); δ= 4.7 (dd, 2H, OC**H**$_2$CHt-BuN, *J =8.3,10.2)*; δ= 5.2 (t, 2H, OCH_2C**H**t-BuN, *J =9)*; δ= 7.2-7.4 (m, 10H 2ph).

*(4S,5R)-4,5-dihydro-2-(1-((4S,5R)-4,5-dihydro-4,5-diphenyloxazol-2-yl)-2-phenylethyl)-4,5-diphenyloxazole **19***



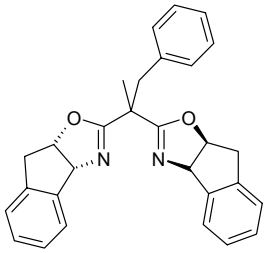
Whyte solid compound;yield: 68%; $C_{38}H_{32}N_2O_2$; MW: 548.67**;** $[\alpha]_D$= + 132° (c=0.5, CH_2Cl_2);^{1}H NMR (300MHz,$CDCl_3$) δ=: 3.7 (d, 2H, C**H$_2$**Ph, *J =8.2);* δ= 4.4 (t, 1H, C**H**CH_2Ph, *J =8);* δ= 5.6 (dd, 2H, C**H**O, *J =10.4, 12.9);* δ= 5.9 (dd, 2H, C**H**N, *J =10.3, 13.7);* δ= 6.8-7.5 (m, 30H 5ph)

2,2'-(1-phenyl)methylenebis[3α,8α-dihydro-(3aR,3'aR, 8aS,8'aS)]-8H-indeno[1,2 d]oxazole



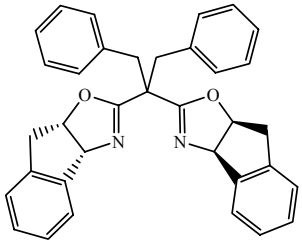
White solid; $C_{28}H_{24}N_2O_2$; MW: 420.5; $[\alpha]_D$= -40° (c=0.3, CH_2Cl_2); H^1 NMR (300 MHz, $CDCl_3$): δ= 3.02 (t, 2H, OCHC**H₂**, J=10.3), δ= 3.11 (d, 2H, C**H₂**Ph, J=3.2), δ=3.35 (dd, 2H OCHC**H₂**Ph, J=7.9, 7.7), δ= 4.46 (t, 1H, C**H**CH_2Ph); δ=5.34 (m, 2H, C**H**O); δ= 5.54 (dd, 2H, C**H**N, J=2.5, 7.9), δ= 6.7-7.4 (m, 13H, Ar); MS (CI , m/z , int. rel. %) : 420(M+100) , 303(20) , 260(16)

2,2'-(1-phenyl)-isopropylidenebis[3α, 8α-dihydro-(3aR,3'aR, 8aS,8'aS)]-8H-indeno[1,2-d]oxazole ***25***



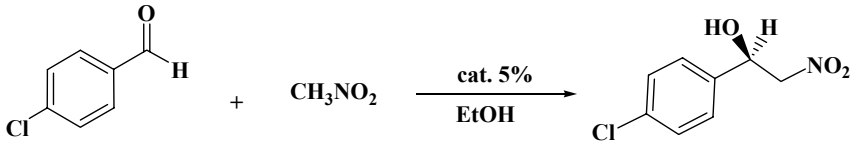
White solid; Yield 39% (efter purification by flash chromatography in exane/ethyl-acetate 75%) $C_{29}H_{26}N_2O_2$; MW: 434.11; $[\alpha]_D$= +324° (c=0.5, CH_2Cl_2); H^1 NMR (300 MHz, $CDCl_3$): δ= 1.19 (s, 3H, CH_3); δ= 3.02 (t, 2H, OCHC**H₂**, J=10.3), δ= 3.09 (d, 2H, C**H₂**Ph, J=3.2), δ=3.31 (dd, 2H OCHC**H₂**Ph, J=7.9, 7.7), δ=5.34 (m, 2H, C**H**O); δ= 5.49 (dd, 2H, C**H**N, J=2.5, 7.9), δ= 6.7-7.4 (m, 13H, Ar); MS (CI , m/z , int. rel. %) : 434(M+100); 419 (8) 318(20) , 274(45)

2,2'-(1,1'-diphenyl)-isopropylidenebis[3α,8α-dihydro-(3aR,3'aR, 8aS,8'aS)]-8H-indeno[1,2-d]oxazole ***24***

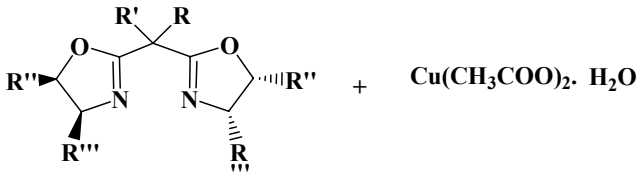


White solid; Yield 83% (efter purification by crystallization in CH_2Cl_2/MeOH 1/1) $C_{35}H_{30}N_2O_2$; MW: 510.55; $[\alpha]_D$= +230° (c=1, CH_2Cl_2); H^1 NMR (300 MHz, $CDCl_3$): δ= 3.02 (dd, 2H, OCHC**H₂**, J=6.6, 13.9), δ= 3.21 (d, 4H, C**H₂**Ph, J=14), δ=3.29 (dd, 2H OCHC**H₂**Ph, J=7.9, 7.7), δ=5.33 (t, 2H, C**H**O, J= 6.7); δ= 5.59 (d, 2H, C**H**N, J=7.6,), δ= 6.7-7.4 (m, 18H, Ar).

4.6.3 Model Henry reaction: synthesis of (R)-1-(4-Chlorophenyl)-2-nitroethanol



Catalyst:



In a 25 ml round bottomed flask are solved Cu $(CH_3COO)_2$ •H_2O (0.05mmol in 0.5 ml of ETOH),obtaining a homogeneous blue solution; and BOX (0.055 mmol in 0.5 ml di ETOH. After 1h p-Chloro-benzaldehyde (1 mmol) and nitromethane (10 mmol) are added and the mixture is stirred at room temperature for 24 h. During the time the solution becames slowly dark green. At the end of the 24h the solvent is evaporated under vacuum. The crude is purified by flash chromatography with CH_2Cl_2 as eluent; The colorless oil obtained is analyzed by HPLC in order to calculated the enantiomeric excess. (CHIRALCEL OD-H column, hexane/iPrOH 85/15)

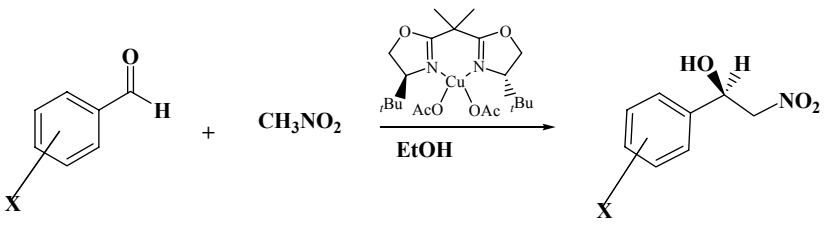
phisical data:

colorless oil, $C_8H_8NO_3Cl$; MW: 201.61; ^{1}H-NMR (300MHz, $CDCl_3$): δ= 3.01 (bs, 1H, OH), δ=4.49 (dd, 1H PhCHOHC**H$_2$**NO_2, J=3.3, 13.4), δ=4.634 (dd, 1H, PhCHOHC**H$_2$**NO_2, J=9.2, 13.4); δ= 5.41 (dd, 1H, PhC**H**$OHCH_2NO_2$, J=3.3, 9.1), δ= 7.3-7.4 (m, 4H, Ar); MS (CI , m/z , int. rel. %) : 185(86); 136 (100); 101(94) , 75(54)

BOX screening results

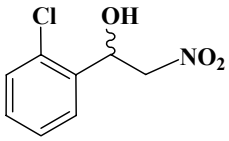
entry	**ligand**	**Yield (%)**	**e.e (%)**
1	17	30	34
2	18	65	30
3	19	76	39
4	20	95	83
5	21	89	2
6	22	66	49
7	23	57	47
8	24	88	81
9	25	95	84

4.6.4 Synthesis of aromatic β–nitroalcohols



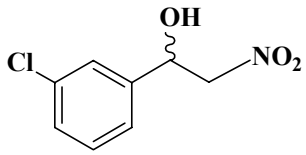
By the same method used to prepare 1-(4-Chlorophenyl)-2-nitroethane, different 2-ntroalcohols were prepared. Yields and ee values were obtained trhough NMR spetroscopy and HPLC with Chiralcel OD-H column and different eluents.

1-(2-Chlorophenil)-2-nitroethanol :



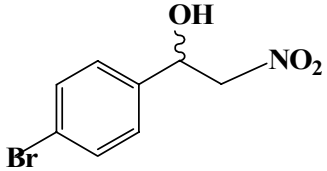
Light yellow oil; $C_8H_8NO_3Cl$; MW: 201.06; ^{1}H NMR (300 MHz, $CDCl_3$): δ= 3.41 (d, 1H, OH, *J=4.3),* δ= 4.39 (dd, 1H, PhCHOHC**H**$_2$NO$_2$, *J=9.5,13.3);* δ= 4.62, (dd, 1H, PhCHOHC**H**$_2$NO$_2$, *J=2.5, 13.4);* δ= 5.83 (m, 1H, PhC**H**OHCH$_2$NO$_2$); δ= 7.29, (m, 3H, Ar); δ= 7.64, (d, 1H, Ar, J=8.9); MS (EI, m/z, int. rel. %): 201 (6),154 (100), 141 (96), 125 (6), 113 (21), 101(13), 91 (47), 77 (56), 65 (14). HPLC (Chiralcel OD-H column): Eluent= hexane:$_i$PrOH 97:3, t_{r1}= 31.8 min, t_{r2}= 33.5 min. Absolute configuration of major enantiomer= R; yield= 75%; ee= 87%.

1-(3-Chlorophenyl)-2-nitroethanol



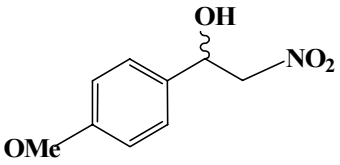
colorless oil; $C_8H_8NO_3Cl$; MW= 201.01; ^{1}H NMR (300 MHz, $CDCl_3$): δ= 3.39 (s, 1H, OH*),* δ= 4.5-4.6 (m, 2H, PhCHOHC**H**$_2$NO$_2$*);* δ= 5.43 (dd, 1H, PhC**H**OHCH$_2$NO$_2$, J=3.5, 8.9); δ= 7.2-7.4, (m, 4H, Ar); MS (EI, m/z, int. rel. %): 183 (100), 149 (35), 120 (9), 101 (71), 89 (19), 75 (47), 63 (89). HPLC (Chiralcel OD-H column): Eluent= hexane:$_i$PrOH 85:15, t_{r1}= 12.5 min, t_{r2}= 13.1 min. Absolute configuration of major enantiomer.= R; yield= 57%; ee= 77%.

1-(4-Bromophenyl)-2-nitroethanol:



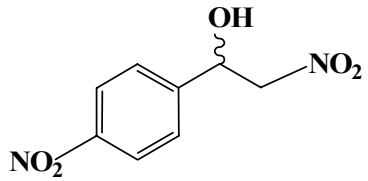
light green oil; $C_8H_8NO_3Br$; MW= 246.86; ^{1}H NMR (300 MHz, $CDCl_3$): δ= 3.39 (s, 1H, OH*)* δ= 4.5-4.6 (m, 2H, PhCHOHC**H**$_2$NO$_2$*);* δ= 5.33 (d, 1H, PhC**H**OHCH$_2$NO$_2$, J=9); δ= 7.19, (d, 2H, Ar, J=12), δ= 7.54, (d, 2H, Ar, J=12); MS (EI, m/z, int. rel. %): 229 (22), 182 (28), 148 (24), 102 (100), 75 (30), 65 (11). HPLC (Chiralcel OD-H column): Eluent= hexane:$_i$PrOH 85:15, t_{r1}= 13.9 min, t_{r2}= 17.6 min. Absolute configuration of major enantiomer= R; yield= 80%, ee= 86%.

1-(4-methoxyphenyl)-2-nitroethanol:



Yellow oil; $C_9H_{11}NO_4$; MW= 197.15; ^{1}H NMR (300 MHz, $CDCl_3$): δ= 2.89 (s, 1H, OH*)* ,,δ= 4.42 (dd, 1H, PhCHOHC**H**$_2$NO$_2$ J=3.3,13.3),. δ= 4.59 (dd, 1H, PhCHOHC**H**$_2$NO$_2$, 9.5, 13.3*);* δ= 5.32 (dd, 1H, PhC**H**OHCH$_2$NO$_2$, J=3, 9.5); δ= 6.91, (d, 2H, Ar, J=11), δ= 7.29, (d, 2H, Ar, J=11); MS (EI, m/z, int. rel. %): 135 (100), 107 (10), 92 (9), 77 (21). HPLC (Chiralcel OD-H column): Eluent= hexane:$_i$PrOH 90:10, t_{r1}= 16.9 min, t_{r2}= 20.9 min. Absolute configuration of major enantiomer= R; yield= 92%, ee= 84%.

1-(4-Nitrophenyl)-2-nitroethanol

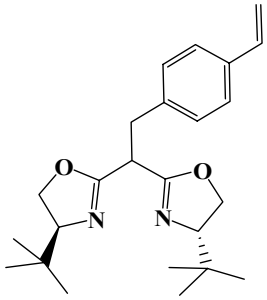


Yellow oil; $C_8H_8N_2O_5$; MW= 212.13; ^{1}H NMR (300 MHz, $CDCl_3$): δ= 3.42 (s, 1H, OH)*,* δ= 4.5-4.6 (m, 2H, PhCHOHC**H**$_2$NO$_2$)*;* δ= 5.63 (dd, 1H, PhC**H**OHCH$_2$NO$_2$, J=5); δ= 7.61, (d, 2H, Ar, J=8.6), δ= 8.32, (d, 2H, Ar, J=8.6); MS (EI, m/z, int. rel. %): 151 (100), 135 (4), 120 (8) 105 (21), 92 (9), 77 (44), 65 (12). HPLC (Chiralcel OD-H column): Eluent= hexane:$_i$PrOH 85:15, t_{r1}= 21.4 min, t_{r2}= 26.4 min. Absolute configuration of major enantiomer= R; yield= 98%, ee= 84%.

4.6.5 Preparation of functionalized BOX

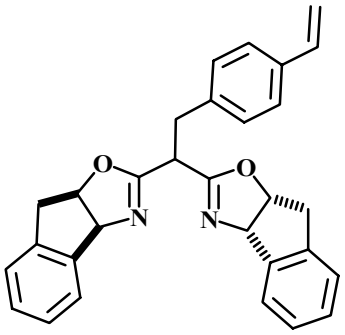
In a two neck round bottomed flask under N_2 flow 0,5 mmol di NaH al 60% are washed 3 times with 5 ml of hexane in order to remuve the oil of dispersion of the solid.
The BOX and 5 ml of DMSO are added and the mixture is stirred at room temperature for 1 h. With a droppel funnel is added a solution containing, 0.5 mmol of 4-vinylbenzyl chloride in 1,2 ml of DMSO and the mixture is wormed at 50°C for 3 h .
At the end the reaction is cooled at room temperature, diluted with 10 ml of CH_2Cl_2 , extracted with HCl 1M (3 x 20 ml), dried with $MgSO_4$ and evaporated . The product is purified by flash chromatography using as eluent CH_2Cl_2 /CH_3CN al 10%, an yellow oil is obtained with a yield of 85% .

(S)-4-tert-butyl-2-(1-((S)-4-tert-butyl-4,5-dihydrooxazol-2-yl)-2-(4-vinylphenyl)ethyl)-4,5-dihydrooxazole ***27***



Light yellow oil; $C_{24}H_{34}N_2O_2$; MW: 382.54; Purified by flash chromatography (eluent CH_2Cl_2 /CH_3CN 10%), Yield:85%; ^{1}H NMR (300 MHz, $CDCl_3$): δ= 0.81 (s, 9H, $C(CH_3)_3$), δ=0.82 (s, 9H, $C(CH_3)_3$); 3.21(t, 2H, C**H**CN, J=9), δ= 3.83 (dd, 2H, C**H$_2$**Ph, J=20, 10), δ= 3.99 (t, C**H**CH_2Ph 1H, J=9), δ=4.09 (dd, 4H, C**H$_2$**O J=29,21) δ= 5.15 (d, 1H, CH=C**H**$_2$, J=12), δ= 5.65 (d, 1H, CH=C**H**$_2$ J=18.5), δ= 6.62 (dd, 1H, C**H**=CH_2 J=18.5, 11.7), δ= 7.23 (d, 2H, Ar, J=8.9), δ= 7.32 (d, 2H, Ar, J=8.9); MS (CI , m/z , int. rel. %): 382 (M+32), 367 (4), 325 (17), 225 (27), 157 (14), 117 (100), 57 (13).

(3aS,8aR)-8,8a-dihydro-2-(1-((3aS,8aR)-8,8a-dihydro-3aH-indeno[1,2-d]oxazol-2-yl)-2-(4-vinylphenyl)ethyl)-3aH-indeno[1,2-d]oxazole ***28***



White solid; $C_{30}H_{26}N_2O_2$; MW: 446.54; Purified by cristallization from CH_2Cl_2, Yield: 50%; H^1 NMR (300 MHz, $CDCl_3$): δ= 3.2-3.5 (m, 6H) δ=5.17 (d, 1H, PhCH=C**H**$_2$, J=11) δ=5.42 (t, 2H, C**H**O, J= 6.3); δ= 5.6-5.7 (m, 3H, C**H**N + PhCH=C**H**$_2$), δ= 6.64 (dd, 1H, PhC**H**=CH_2, J=11,17) δ=6.97 (d, Ar, J=8), δ= 7.2-7.4 (m, 10H, Ar), δ=8.07 (d, 2H, J=7, Ar); MS (CI , m/z , int. rel. %): 446 (44), 329 (14), 314 (10), 225 (20), 155 (14), 130 (18), 115 (100), 77 (14).

4.6.6 Synthesis of polystyrene supported ligands ***29-32***

To a solution of functionalized BOX in toluene , styrene and technical grade divinylbenzene (80%, meta:para=2:1) and AIBN (0.008 g) were added. The mixture was stirred at reflux temperature for 20h. The solid product was precipitated with methanol (10 ml), separated by filtration, washed with CH_2Cl_2 and MeOH (2x50 ml) and milled to obtain a powder. The content of chiral ligand was determined by elemental analysis.

4.6.8 Henry reaction in heterogeneous catalysis:

In a Shlenk tube under N_2 atmosphere the polymer supported bis(oxazoline) (0.055mmol,) was dried for 1 h under vacuum. Copper(II) acetate (0.05mmol) was solved in 0.5ml of absolute EtOH and the solution was added to the polymer in the Shlenk tube, than EtOH up to 3ml was added. The mixture was stirred for 1h at room temperature and aldehyde (1 mmol) and nitromethane (10 mmol) were added. After 24h the polymer was filtered and washed with EtOH (15ml) and CH_2Cl_2 (15ml), dried under vacuum for 3h and reused in the same way.Yields and ee values were determined by HPLC.

*polymer **29-32** results*

polymer	Loading (mmol/g)	Yield (%)	ee (%)
29	0.46	95	75
30	0.6	95	75
31	0.8	95	86
32	0.78	75	11

*polymer **31** recycling*

cycle	yield (%)	ee (%)
1	95	86
2	95	87
3	87	89
4	83	91
5	83	91

4.7 References

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2. F. A. Luzzio; *Tetrahedron*; **2007**; 57; 915.
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5 *Synthesis and application of aza-BOX metal complexes*

(This study has been performed at the" Grupo de catálisis heterogénea en síntesis orgánica selectivas" of Zaragoza University, under the supervision of prof. José Antonio Mayoral).

5.1 Introduction

In the previous chapters Cu(II) bis(oxazoline) complexes were studied as optimum catalysts both in homogeneous and in heterogeneous phase. However in 2000 Reiser introduced[1] a new class of ligands, similar to bis(oxazoline), but with a nitrogen atom in place of the methylene bridge (Figure 1), that are called aza-bis(oxazolines) (aza-BOXs).

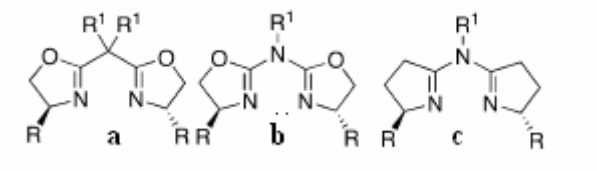


Figure 1: BOX, aza-BOX and aza-semicorrin ligands

Reiser started from a comparison between aza-semicorrins (**c** in Figure 1) and bis(oxazolines): Aza-semicorrins offer a greater structural flexibility than bis(oxazolines), because the central nitrogen atom can be functionalized by alkylating reagents. Moreover, they display a more rigid conformation due to the planar bridging nitrogen functionality. Otherwise bis(oxazolines) are easier to prepare using readily available amino alcohols as the source of chirality. Aza-BOX ligands combine the advantages of easy accessibility of BOX and the structural flexibility of aza-semicorrins. The sinthetic route to obtain aza-BOX will be discussed in the next section of this chapter, now the attention will be focused on application of aza-BOX complexes both in heterogeneous and homogeneous phase, and in comparrison between BOX and aza-BOX metal complexes.

Mayoral and cowarkers demonstred by theoretical and experimental data[2] that aza-BOX Cu(I) complexes immobilized by electrostatic interaction show higher binding constant than the BOX-Cu(I) ones. This depend on the presence of the electron donating amino group in the central bridge of aza-BOX ligands, that are more electron rich than BOX ones. A high binding constant seems to be more important in heterogeneous that in homogeneous phase, in fact a weak complex may lead to the presence of free metal precursor, and , consequently, non enantioselective centres. In homogeneous phase this limitation is frequently overcome by adding an excess of chiral ligand, but this is not possible when the complex is immobilized by electrostatic intractions. Moreover, in heterogeneous phase the situation is more difficult because of the site isolation. This hypotesis was corroborated by the efficient electrostatic immobilization

of the **1**-Cu (Figure 2) complex and by its successfull application in the asymmetric cyclopropanation of styrene, in comparison with the results obtained with the analogous BOX catalyst **2**-Cu.

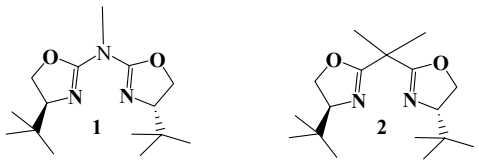


Figure 2: ligands used by Mayoral to test the role of binding constant in the activity of Cu complexes immobilized by electrostatic interactions.

Aza-BOX were used, both in homogeneous and heterogenous phase, in several reactions,and they were immobilized on different materials. Majoral and Reiser[3] set up a synthetic strategy to obtain phosphorous dendrimer immobilized aza-BOX ligands (Figure 3), and they tested these materials in the Cu(II)-catalyzed asymmetric benzoylation of diols, with good yields (40%) and excellent ee values (99%).

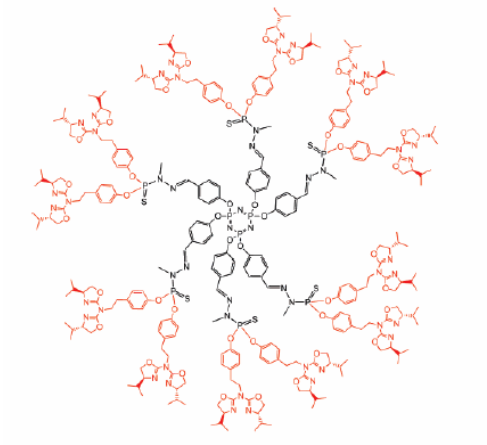


Figure 3: dendrimer immobilized aza-BOX ligand (from ref 3)

The asymmetric benzoylation was also used by Reiser[4] to achieve the kinetic resolution of 1,2-diols and α-hydroxy carbonyl compounds in the presence of Cu(II)-aza-BOX complex immobilized on MeOPEG (Figure 4), achieving, good yields (37-49%) and very high ee values (91-99%) for five reactive cycles.

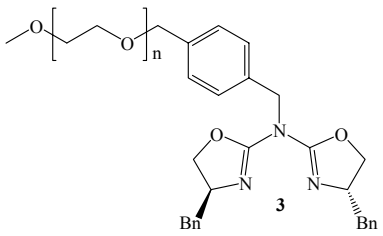


Figure 4: MeOPEG-aza-BOX ligand

Aza-bis(oxazoline) copper complexes were used as catalysts of cyclopropanation reaction, both in homogeneus and heterogeneous phase. For example polymeric ligand **4** (Figure 5) was tested in the cyclopropanation of styrene with methyl diazoacetate, achieving very good results (yield: 69%, trans/cis: 71/29, ee trans: 91%, ee cis: 87%) and similar to those obtained with the corresponding homogeneous complex[1].

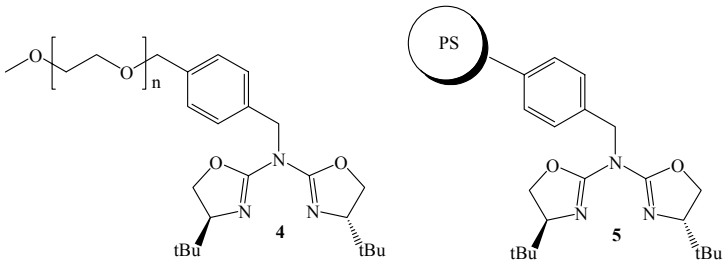


Figure 5: polymeric immobilized aza-BOX ligands

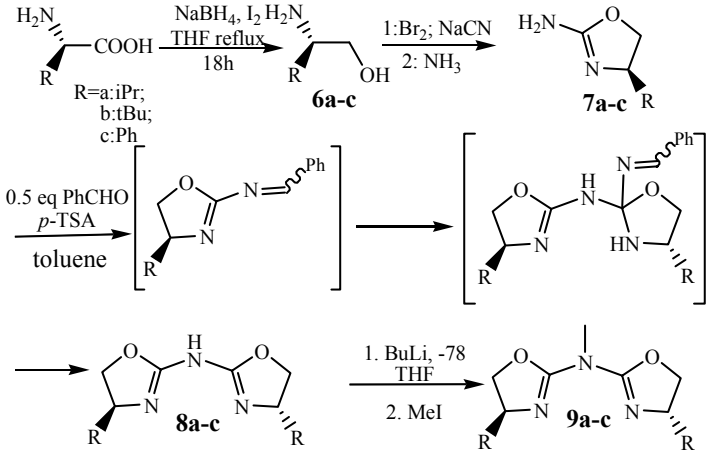
As previously seen also **Cu-1** complex immobilized on laponite by electrostatic interactions[2] (**LCu-1** in Table 1) is an active catalyst in cyclopropanation, similar to the covalently immobilized complex on Merrifield's resin analogous **5** (Figure 5). These complexes result very active in cyclopropanation even when they result deactivated for other reactions as, for example, Mukaiyama condensation (Table 1)[5]

Catalyst	reaction	run	yield (%)	trans/cis	ee (%)
LCu-1	Mukaiyama	1	53		76
	cyclopropanation	2	48	70/30	82,76
Cu-5	Mukaiyama	1	44		84
	Mukaiyama	2	25		85
	cyclopropanation	3	99	71/29	97,92

Table 1: results obtained in Mukaiyama and cyclopropanation reactions using the multiporpuse aza-BOX-Cu heterogeneous complexes **LCu-1** and **Cu-5** (from ref 5).

5.2 aza-BOX synthesis

4-*iso*-propyl (**9a** in Scheme 1) and 4-*tert*-butyl (**9b**) aza-BOX were synthesized by Rayser's approach[1,6] (Scheme 1). The strategy starts from an aminoacid reduction with $NaBH_4$ and I_2[7] in order to obtain the corresponding chiral aminoalcohol, with a quantitative yield.



Scheme 1: scheme of aza-BOX synthesis

The amino(oxazoline) rings **7a-c** were obtained by reaction of aminoalcohols **6a-c** with BrCN produced in situ, and rapresent the key building block for the assembly of aza-bis(oxazoline) ligands. The reaction involves an imine intermediate and the final condensation with formal loss of amonia, by heating in toluene in the presence of *p*-toluen suplphonic acid and benzaldehyde. Deprotonation of **8a-c** with *n*-butyllithium readily occurred, however, and the resulting anions could be cleanly trapped with alkyl halides giving rise to **9a-c**.

5.3 Ionic immobilization to laponite.

The three ligands 9a-c were complexed with several copper salts and immobilized by electrostatic interactions onto laponite clay obtaining solid catalysts **10-15** (Table 2).

Clays are good supports for cationic interchange because of the electrostatic interactions with the negative heads of sodium silicate[8]. Laponite is a synthetic clay and, as all clays, is a layned silicate. In each leyer there is an octahedric head of MgO_6 units between two tetrahedric heads of SiO_4 units. It is a magnesium silicate in which negative charges are created for substitution of Mg with a less charged metals, as for example Li, and the charge balence is obtained through the presence of Na^+ ions present in a solvated form in the interlayer space (Figure 7).

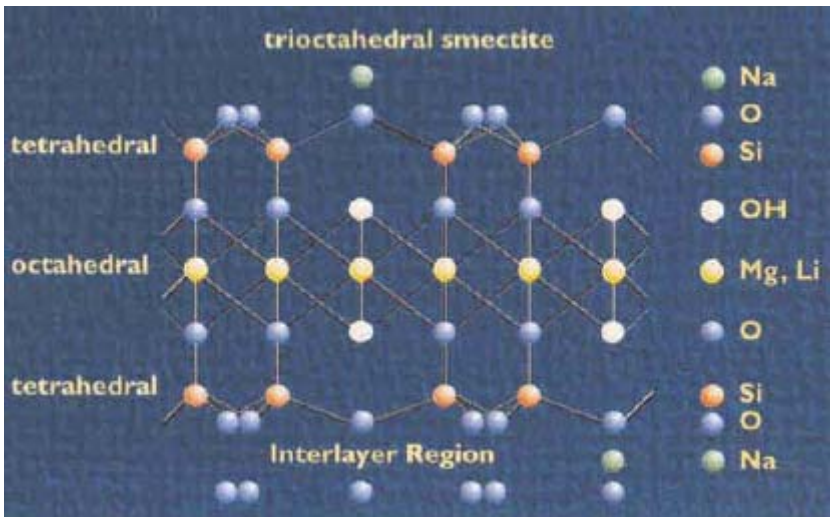


Figure 7: Laponite structure.

Mayoral demonstred that laponite is the best clay for Cu(II)-BOX and aza-BOX complexes immobilization. One advantage come from the particles dimension derived from the crystallization conditions. This means that laponite presents a large amount of external sites more accessible for large species as Cu(II)-aza-BOX complexes. Moreover a synthetic clay is more reproducible than a natural one.

The cationic interchange is a complex equilibrium process (Figure 8): one of the reation involved is the equilibrium process between the free and the complexed form of the cation, and this is important in order to evaluate the real chiral activity of the solid material. For this reason both the Cu and the ligand loadings were evaluated in the characterization of catalysts **10-15** .(Table 2)

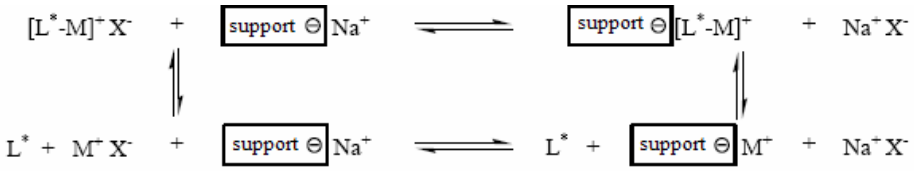


Figure 8: cationic interchange process.

Catalyst **10-15** (Table 2) were prepared solving $Cu(OAc)_2$ or $Cu(OTf)_2$ in CH_2Cl_2 with the BOX ligand. After the complex formation solvent was evaporated and the interchange was obtained in MeOH solution.

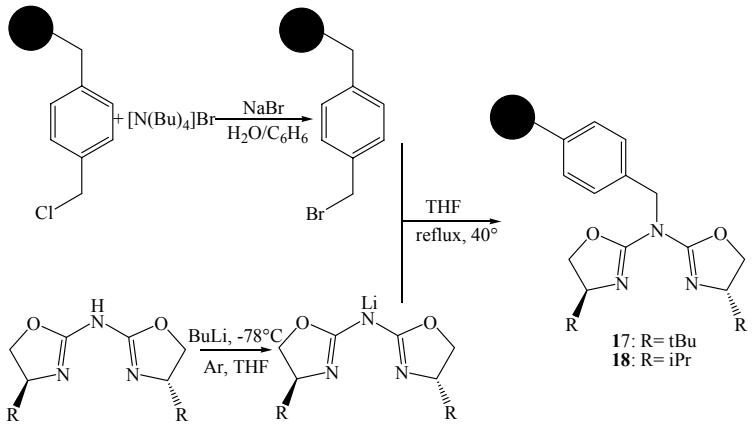
Catalyst	ligand	salt	Cu loading	ligand loading
10	9c	$Cu(OAc)_2$	0.221	0.082
11	9a	$Cu(OAc)_2$	0.23	0.18
12	9b	$Cu(OAc)_2$	0.245	0.19
13	9c	$Cu(OTf)_2$	0.264	0.16
14	9a	$Cu(OTf)_2$	0.36	0.198
15	9b	$Cu(OTf)_2$	0.217	0.18

Table 2: evaluation of Cu and ligand loadings of catalysts **10-15**

All the catalysts showed an higher Cu than ligand loading value. This means that in all the solid catalysts some copper could act as an achiral catalyst.

5.4 Covalent immobilization on Merrifield's resin

In order to evaluate the difference between the ionic and the covalent immobilization, aza-BOX ligands were tethered to a modified Merrifield's resin, in which the terminal chlorine was substituted with the more active bromine. (Scheme 2)

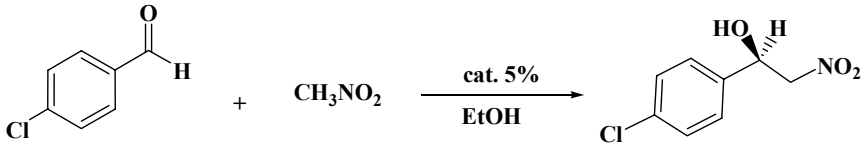


Scheme 2: aza-BOX immobilization to Merrifield's resin preparation of ligand **17** and **18**

The two ligands **17** and **18** were characterized by elemental analysis and they presented loading values of 0.803 (**17**) and 0.845 (**18**) mmol/g of ligand, that were higher than the loading of complexes **10-15**, immobilized by ionic interactions.

5.5 Test of aza-BOX complexes as heterogeneous catalysts for Henry reaction.

Heterogeneous complexes **11**, **12** (Table 2), as well **17**-$Cu(OAc)_2$ and **18**-$Cu(OAc)_2$, were tested in the model Henry reaction between p-Cl-benzaldehyde and nitromethane. The reaction was also tested in homogeneous phase with the two Cu (II) complexes, **9a**-$Cu(OAc)_2$ and **9b**-$Cu(OAc)_2$.



Catalyst	ligand	salt	Solid support	Yield (%)	ee(%)
11	9a	$Cu(OAc)_2$	Laponite	80	4
12	9b	$Cu(OAc)_2$	Laponite	90	2
19	17	$Cu(OAc)_2$	Merrifield's	96	77

			resin		
20	18	$Cu(OAc)_2$	Merrifield's resin	84	53
21	9a	$Cu(OAc)_2$	-	95	81
22	9b	$Cu(OAc)_2$	-	88	58

Table 3: results of Henry reaction catalized by Cu(II)-aza-BOX complexes.

Table 3 shows that Cu(II)-aza-BOX complexes are very active catalysts for Henry reaction in homogeneous phase, achieving not different results in comparrison with Cu(II)-BOX ones. However, catalyst **11** and **12** resulted not stereoselective. This probably depends on the presence of not complexed copper in the solid catalyst, that promote not-stereoselective reactions, but also on the protic solvent. Infact the reaction was performed in EtOH, which resulted the best solvent in previous studies. In EtOH it is possible to obtain a leaching of chiral complex from the laponite matrix, and the equilibrium between laponite-Cu(II) ion and laponite Cu(II)complex was probably affected, giving higher amount of free Cu(II). Unfortunately up to now it was not possible to evaluate the Cu(II) content of catalysts **11** and **12** after the reaction, but elemental analysis showed a ligand leaching (Table 4).

Catalys	ligand loading before reaction	ligand loading after reaction
11	0.18 mmol/g	0.102 mmol/g
12	0.193 mmol/g	0.124 mmol/g

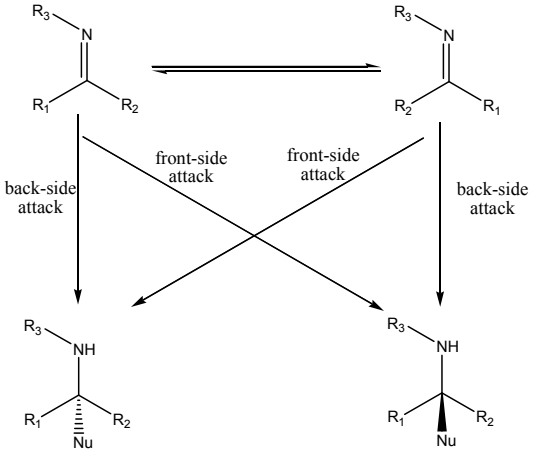
Table 4: ligand leaching evaluation.

Table 3 shows that catalysts **19** and **20**, immobilized through covalent bonds to Merrifield's resin, gave very good preliminary results, according to the data discussed in chapter 4 for polymer-supported Cu(II)-BOX complexes. Better results were obtained with 4-*i*Pr-aza-BOX than with 4-*t*Bu-aza-BOX both in homogeneous and heterogeneous phase.

5.6 Homogeneous aza-Henry reaction catalyzed by BOX and aza-BOX complexes.

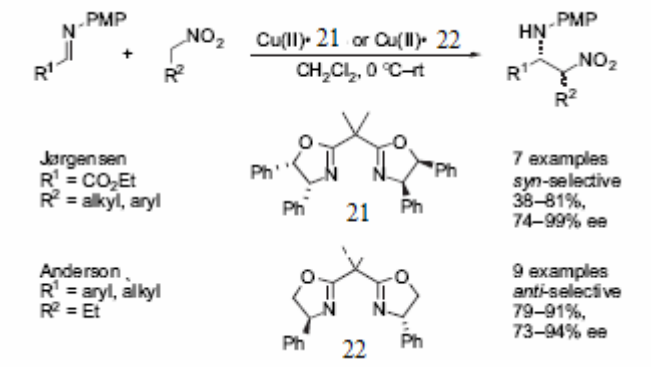
The aza-Henry reaction is a condensation between a nitroalkane and an imine, achieving, with a chiral catalist, chiral α–branched nitroamines, that are important building blocks in bioorganic and medicinal chemistry, as well as in natural product synthesis[9]. Infact chiral-α-branched amines are common substructures utilized in the preparation of biologically active materials. However there are some difficulties in performing catalytic enantioselective reactions of imines. For example, in the case of chiral Lewis acid promoted asymmetric reactions, aldehydes usually

coordinate the metal centres of the Lewis acids using one of the lone pairs of carbonyl oxygen. In addition, Corey et al. suggested that the second interactions between counteranions of Lewis acids and formyl hydrogens made a rigid complex. On the other hand, imines often exist as mixtures of geometrical isomers ascribed to the rapid equilibrium of C-N double bonds. Therefore, plural transition states exist when Lewis acids coordinate imines, which often decrease selectivities (Scheme 3)[10]. In addition, most Lewis acids are trapped by the basic nitrogen atoms of the starting materials (imines and/or products), and therefore, catalytic reactions using imines as electrophiles and metal catalysts are difficult to control.



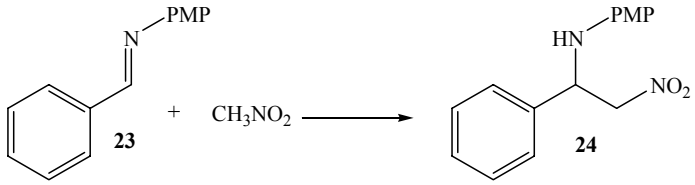
Scheme 3: relationship between selectivities and C=N isomerization.

The best results in asymmetric aza-Henry reaction were obtained by Shibasaki[11], and Jøergensen[12]. Anderson[13] has extended the versatility of the Jøergensen method, finding conditions which were suitable for aromatic and aliphatic aldimines with 10% mol catalyst loading, using preformed silyl nitronates.[9] Jøergensen obtained very interesting results working with Cu-BOX complexes in CH_2Cl_2 at 0°C. (Scheme 4), using PMP as protecting group for imines.



Scheme 4: from ref 9.

Scheme 5 describes the model reaction utilized in the present study, carried out under the same condition of Henry reaction set up in chapter 4 (room temperature, 10% of catalyst with respect to imine, 1/10 imine, nitromethane ratio, EtOH as solvent)



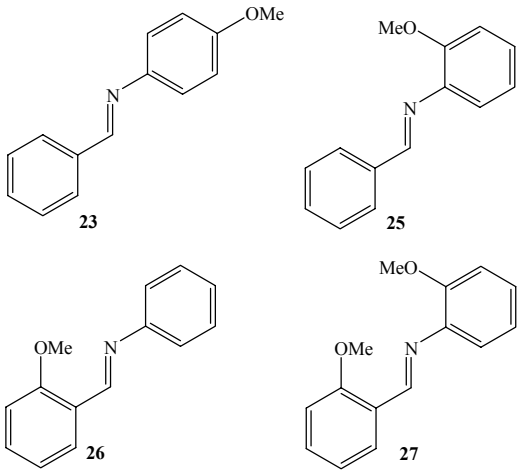
Scheme 5: aza-Henry model reaction.

When both homogeneous and heterogeneous catalysts **10-15** and **19-22** were tested in the model reaction good yields but very low selectivities were observed (Table 5). Moreover the solution colour, when reagent 23 was added, tourned from green to black.

Catalyst	yield (%)	conv (%)	ee (%)
10	62	78	4
11	56	77	2
12	70	85	0
13	65	76	0
14	52	75	0
15	68	80	2
19	65	80	2
20	55	80	2
21	67	81	2
22	54	79	2
23[a]	72	88	4

Table 5: catalysts test in model aza-Henry reaction. [a]4-Ph-BOX/$Cu(OAc)_2$ complex

Since in the aza-Henry reaction the in situ formation of a chelate involving the reagent and the Lewis acid plays a crucial role, it was decided to sinthesize imines **25-27**, changing the position of OMe group from *para* to *ortho* position on the ring.



Scheme 6: imine reagents synthesized.

The homogeneous catalysts **21-23** were tested in the aza-Henry reaction with imines **25-27** and nitromethane, but the results were not different from those obtained with imine 23. In all cases racemic products were obtained with 60 % yield. Also 4-*tBu*-BOX/$Cu(OAc)_2$ complex was tested but with the same results. It was observed that in all cases the solution changed the colour when imine was added, from blue to black. Probably these imines are too electron rich and Cu(II) could pass to Cu(0), that is not active. It was also observed that the reaction carried out in EtOH at room temperature gave some product without catalyst. For this reason it was decided to test metal catalysts with a different redox potential in different solvents.

5.6.1 THF tests

The model reaction was tested using THF as solvent and complex of **9a**, **9b** and **9c** with several metal salts. (Table 6)

Metal salt	ligand	yield (%)	ee (%)
---	---	0	-
$Cu(OAc)_2$	9a,9b, 28[a]	0	-
$Cu(OTf)_2$	9a,9b,28	5,6,16	7,5,7
$Mg(OTf)_2$	9a,9b,28	0	-
$Zn(OTf)_2$	9a,9b,28	0	-
$Mg(ClO_4)_2$	9a,9b,28	0	-
$Ni(ClO_4)_2 \cdot 6H_2O$	9a,9b,28	0	-

Table 6: metal salts screening in THF. all the reaction were performed using imine 26. [a]: ligand **28** is isopropylidenebis-4-ph-bis(oxazoline), were used in order to test also a bis(oxazoline) complex.

Results from Table 6 suggest that THF was a bad solvent for the present reaction, being all metal catalysts examined inactive or poorly active.The reaction was thus tested in a less basic solvent such as CH_2Cl_2 (Table 7)

5.6.2 CH_2Cl_2 tests

metal salt	**ligand**	**imine**	**yield (%)**	**ee (%)**
---	---	24-27	---	---
$Mg(OTf)_2$	9a,9b, 28	26	12,2,9	0,0,10
$Mg(OTf)_2$	28	25	38	41
$Zn(OTf)_2$	28	26,25	10,12	23, 34
$Mg(ClO_4)_2$	28	26	10	10
$Yb(OTf)_2$	28	26	5	4

Table 7: results of metal salts screening in CH_2Cl_2.

Table 7 shows that in CH_2Cl_2 the reaction was still inert without catalyst at room temperature, but with all catalysts tested the reaction gave some results. The best result was obtained using $Mg(OTf)_2$, bis(oxazoline) **28** and imine **25**. The reaction was performed at riflux temperature achieving 50% yield and 41% ee value.

5.7 Conclusions

In this chapter the preparation of aza-BOX ligands and their immobilization through ionic and covalent bounds was discussed. In particular aza-BOX ligands **9a-c** were supported on Laponite clay through ionic interactions and on Merrifield's resin by covalent bond. The catalysts obtained were tested in preliminary studies on Henry and aza-Hanry reaction.

The results obtained for the Henry reaction show that catalysts immobilized on Merrifield's resin are more efficient than those on laponite, probably because of the presence of free Cu(II) sites in the ionic catalysts.

More difficult resulted the study of aza-Henry reaction in the presence of these catalysts. Infact the reaction proceeds without any enantiomeric excess, probably because of a reduction of Cu(II) to the inactive Cu(0) form. Several homogeneous conditions were tested, changing metal, ligand, solvent and temperature, some promising results (yields and ee values around 50%) were obtained.

These preliminary studies open the way of interesting studies both in Henry and in aza-Henry reaction.

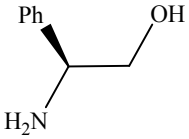
5.8 Experimental section

Aminoacids reduction

In a two neck round bottomed flask, under Ar atmosphere were introduced $NaBH_4$ (183 mmol) and 200 ml of THF dry. The solution was cooled to 0°C with an ice bath. A solution of I_2 (76 mmol in 50ml of THF dry) was added dropwise in 30 minutes. When all the I_2 is in the mixture, the aminoacid was added and the solution was warmed up to reflux temperature.

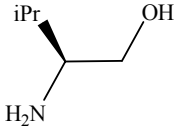
After 18 h the reaction was cooled to room temperature and methanol was added slowly till all the $NaBH_4$ excess was deactivated, there wasn't any solid in solution and any gas develops. The solution was concentrate under vacuum and the product was solved in KOH (150 ml of a 20% solution). The solution was stirred for 4 h at room temperature and then extracted with CH_2Cl_2 (3x 150 ml). The organic layers were dried with Na_2SO_4, filtered and concentrated under vacuum.

(S)-2-Phenylglycinol



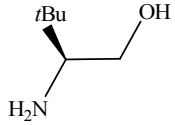
H^1-NMR (CDCl3, 300 MHz): δ= 2.13 (sa, 3H), δ= 3.55 (dd, 1H; J=8.3, 10.7 Hz) δ= 3.73 (dd, 1H; J=4.3, 10.7 Hz), δ= 4.04 (dd, 1H; J=4.3, 8.3Hz) δ= 7.31 (m, 5H); C^{13}-NMR (CDCl3, 75 MHz): 57.3,67.7, 126.5, 127.5, 128.6, 142.1; IR (KBr, ν cm-1): 3329, 3273.

(S)-valinol:



H^1-NMR (CDCl3, 300 MHz): δ= 0.82 (d, 3H; J=3 Hz), δ=0.84 (d, 3H; J=3Hz), δ=1.51 (m, 1H) , δ=2.51 (m, 4H) δ=3.23(dd, 1H; J=10,8, 9 Hz) δ=3.55 (dd, 1H; J=10.8, 3.6 Hz); C^{13}-NMR (CDCl3, 75 MHz): 18.3, 19.2, 31.1, 58.3, 64.4 ; IR (ν cm-1): 3343

(S)-tert-leucinol:

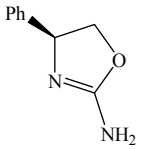


H^1-NMR (CDCl3, 300 MHz): δ= 0.83 (s, 9H), δ=2.36 (sa, 3H), δ=2.47 (dd, 1H, J=3.4, 10 Hz) δ=3.17 (t, 1H; J=10 Hz) δ=3.65 (dd, 1H; J=10, 3.4 Hz); C^{13}-NMR (CDCl3, 75 MHz): 26.3, 33.1, 61.7, 62.4 ; IR (ν cm-1): 3364

Preparation of amino oxazole ring

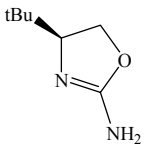
To an ice cooled solution of bromine (5.72 g, 33 mmol) in methanol (40 mL) sodium cyanide (1.62 g, 33 mmol) was added in portions over 1 h. After all was dissolved a solution of (*S*)-*aminoalcohol* (30 mmol) in methanol (70 mL) was added and stirring continued for 1 h. After treatment with a 25% ammonia solution (15 mL) most of the solvent was evaporated under vacuum. Under vigorous stirring a 20 % NaOH solution (30 mL) was added to the residue and a colorless solid precipitated. The mixture was extracted with ethyl acetate (4 x 40 mL) and the combined organic layers were dried over MgSO4. The solvent was evaporated and residual amino alcohol was removed by heating to 60°C under vacuum .

2-Amino-4,5-dihydro-(4S)-phenyl-1,3-oxazole



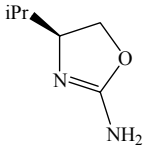
whyte solid, Yield: 90%; H^1 NMR (CDCl3, 300 MHz): δ= 7.29 (m, 5H), δ= 4.59 (dd, 1H, *J* = 7.8, 9.1 Hz), δ= 4.02 (dd, 1H, *J* = 7.4, 7.8 Hz) ; $C^{1\text{-}}$NMR (CDCl3, 62.5 MHz) δ 162.0,143.6, 128.5, 127.2, 126.3 75.1, 67.4; IR (KBr, cm^{-1}) 3424, 3326, 1704, 1481, 1453, 1407.

2-Amino-4,5-dihydro-(4S)-(1,1-dimethylethyl)-1,3-oxazole



colorless solid, Yield: 89%. C7H14N2O, Mp 196-198°C; $[\alpha]^{20}_D$ = -41° (c = 0.5, MeOH); H^1 NMR (CDCl3, 300 MHz):δ= 4.21 (dd, 1H, *J* = 9.3, 8.3 Hz), δ= 4.07 (dd, 1H, *J* = 8.3, 7.1 Hz), δ= 3.74 (dd, 1H, *J* = 9.3, 7.1 Hz), δ= 3.65 (bs, 2H), δ= 0.87 (s, 9H); $C^{1\text{-}}$NMR (CDCl3, 62.5 MHz) δ 161.0, 73.7, 69.5, 33.7, 25.6; IR (KBr, cm^{-1}) 3525, 2960, 2913, 1765, 1653, 1492, 1420, 1366, 1327,1292, 1103, 1026, 939.

2-Amino-4,5-dihydro-(4S)-4-isopropyl-oxazole

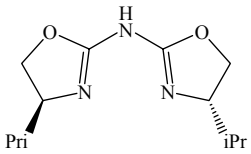


colorless solid, Yield: 89%,H^1 NMR (CDCl3, 300 MHz):δ= 4.21 (dd, 1H, *J* = 9.3, 8.3 Hz,C*H*2CH), δ= 4.24 (dd, 1H, *J* = 8.7, 7.9 Hz), δ= 4.07 (bs,2H); δ= 3.91 (dd, 1H, *J* = 7.9, 7.3 Hz), δ= 3.70 (ddd, 1H, J=8.9, 8.7, 7.2 Hz), δ= 1,58 (m, 1H); δ= 0.9 (d, 3H, J=6.9 Hz) δ= 0.82 (d, 3H, J=6.9 Hz); C^{1-}NMR (CDCl3, 62.5 MHz) δ 160.7, 71.1, 69.9, 33.3, 18.8, 18.3; IR (KBr, cm^{-1}) 3525, 1765, 1653, 1492.

General Procedure for the Synthesis of Aza-bis(oxazolines).

A mixture of aminooxazole (22 mmol), benzaldehyde (11 mmol, 1.11 mL) and *p*toluenesulfonic acid hydrate (104 mg, 0.55 mmol) in toluene was heated to reflux for 22 h using a Dean Stark trap. The solvent was evaporated and the residue chromatographed on silica gel

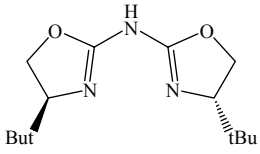
Bis[4,5-dihydro-(4S)-(1-methylethyl)-1,3-oxazol-2-yl]-amine .



Yellow solid, yield: 51%: (ethyl acetate/hexanes 9:1); mp 72-74 °C;

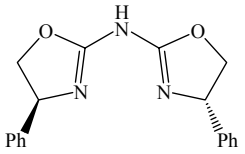
$[\alpha]^{20}_D$= +118.9 (*c* 1.0, CH3OH); 1H NMR (300 MHz, CDCl3) δ= 8.5 (br s, 1 H), δ=4.38 (dd, 2 H, *J* = 8.7, 8.7 Hz), δ= 4.05 (dd, 2 H, *J* = 7.1, 8.7 Hz), δ= 3.78-3.87 (m, 2 H), 1.65-1.79 (m, 2 H), 0.98 (d, 6 H, *J*= 6.8 Hz), 0.90 (d, 6 H, *J* = 6.8 Hz); 13C NMR (CDCl3) δ= 165.9, 65.6, 33.0, 18.6, 18.1; IR 3510, 3305, 3003, 1671, 1489, 1448, 1401, 1318.

Bis[4,5-dihydro-(4S)-(1,1-dimethylethyl)-1,3-oxazol-2-yl]-amine



Yellow solid; yield**:** 92% (ethylacetete/hexanes 9:1); mp 152- 154 °C; $[\alpha]^{20}_D$: +148.6 (c 1.0, CH3OH); 1H NMR (300 MHz, CDCl3) δ= 8.5 (br s, 1 H), δ= 4.30 (dd, 2 H, *J* = 9.1, 9.1 Hz), δ= 4.15 (dd, 2 H, *J* = 8.9, 6.7 Hz), δ= 3.81 (dd, 2 H, *J* = 9.4, 6.7 Hz), δ= 0.90 (s, 18 H); 13C NMR (CDCl3) δ= 166.1, 68.8, 67.4, 33.6, 20.0; IR 3528, 3193, 2989, 2879, 1762, 1674, 1599, 1481, 1450, 1406, 1370, 1257, 1061.

Bis[4,5-dihydro-(4S)-phenyl-1,3-oxazol-2-yl]amine **.**

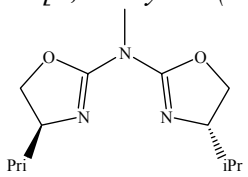


Yellow solid; yield; 35% (ethylacetete/hexanes 9:1); mp 198- 201 °C; $[\alpha]^{20}{}_{D}$= +475.8 (c 1.0, CHCl3); 1H NMR (300 MHz, $CDCl_3$) δ= 7.39-7.25 (m, 10 H), δ= 5.13 (dd, 2 H, *J* = 9.3, 7.3 Hz), δ= 4.72 (dd, 2 H, *J* = 9.3, 8.6 Hz), δ= 4.18 (dd, 2 H, *J* = 8.6, 7.3 Hz); 13C NMR (CDCl3) δ= 166.4, 141.3, 128.9, 128.2, 126.4, 73.6, 63.1; IR 3432, 3182, 3029, 2975, 2901, 1647, 1606, 1428, 1239, 1073, 390.

Metlhylation of aza-BOX

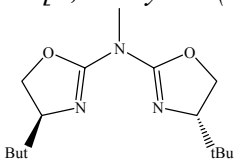
The bis(oxazoline) (1 mmol) was dissolved in THF (10 mL) and a 15% solution of *n*-butyllithium in hexane (1.5 N, 688 μL) was added at -78°C. After stirring for 20 min methyl iodide (710 mg, 5 mmol, 312 μL) was added. The cooling bath was removed and stirring at room temperature continued for 10 h. After evaporation of the solvent the residue was partitioned between CH_2Cl_2 (10 mL) and saturated $NaHCO_3$ (10 mL). The aqueous phase was extracted with CH_2Cl_2 (5 mL) and the combined organic phases dried over $MgSO_4$. Evaporation of the solvent yielded the product

Bis[4,5-dihydro-(4S)-(1-methylethyl)-1,3-oxazol-2-yl]-methylamine (9a) .



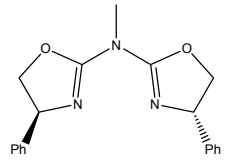
Yellow solid, yield: 95%; 1H NMR (300 MHz, CDCl3) δ=4.39 (dd, 2 H, *J* = 8.5, 9.0 Hz), δ= 4.12 (dd, 2 H, *J* = 7.1, 8.5 Hz), δ= 3.85 (ddd, 2 H, J=9.0, 7.1, 6.6 Hz) δ=3.37 (s, 3H), δ=1.65-1.79 (m, 2 H), δ=0.94 (d, 6 H, *J*= 6.6 Hz), δ= 0.85 (d, 6 H, *J* = 6.6 Hz); 13C NMR (CDCl3) δ= 157.7,71.6, 69.7,37.1, 32.8, 18.7, 17.7; IR 1755, 1640.

Bis[4,5-dihydro-(4S)-(1,1-dimethylethyl)-1,3-oxazole-2-yl] methylamine (9b)



Yellow solid; yield 98 %; Mp: 110-111°C; $[\alpha]^{20}_{D}$ = -22.6 (c = 1, MeOH). ^{1}H NMR ($CDCl_3$, 300 MHz): δ= 4.35 (dd, 2H, *J* = 9.0. 9.0 Hz), δ= 4.24 (dd, 2H, *J* = 8.6, 6.7 Hz), δ=3.79 (dd, 2H, *J* = 9.5, 6.7 Hz), δ= 3.41 (s, 3H,), δ= 0.88 (s, 18H,); ^{13}C NMR ($CDCl_3$,75 MHz) δ=157.8, 73.3, 70.2, 37.4, 33.9, 25.5; IR (KBr) 3532, 3004,2913, 1761, 1679, 1479, 1442, 1395, 1366, 1223, 1131, 992, 959 cm^{-1};

*Bis[4,5-dihydro-(4S)-phenyl-1,3-oxazol-2-yl]methylamine (9c)***.**



Yellow solid; yield 98%;$[\alpha]^{20}_{D}$ =-84,5º (c=1.01, CH_2Cl_2) 1H NMR (300 MHz, $CDCl_3$) δ= 7.39-7.25 (m, 10 H), δ= 5.20 (dd, 2 H, *J* = 9.3, 7.5 Hz), δ= 4.79 (dd, 2 H, *J* = 9.3, 8.4 Hz), δ= 4.25 (dd, 2 H, *J* = 8.4, 7.5 Hz); δ=3.52 (s, 3H) ; 13C NMR (CDCl3) δ= 158.9, 142.5, 128.6, 127.5, 126.5, 76.3 67.4, 37.3; IR 1638,1459.

Preparation of laponite immobilized Cu(II)aza-BOX complexes

To a solution of aza-BOX (1mmol) in methanol was added $Cu(OAc)_2$ or $Cu(OTf)_2$ (1mmol). To this solution laponite (1g) was slowly added, and the suspension was stirred at room temperature for 24 h. The solid was filtere, washed with methanol and then with dichloromethane, and dried at 50°Cunder vacuum.

Catalysts were characterized by plasma emission spettroscopy and elemental analisys in order to evaluate Cu and ligand loading.

Catalyst	**ligand**	**salt**	**Cu loading**	**ligand loading**
10	9c	$Cu(OAc)_2$	0.221	0.082
11	9a	$Cu(OAc)_2$	0.23	0.18
12	9b	$Cu(OAc)_2$	0.245	0.19
13	9c	$Cu(OTf)_2$	0.264	0.16
14	9a	$Cu(OTf)_2$	0.36	0.198
15	9b	$Cu(OTf)_2$	0.217	0.18

Immobilization of aza-BOX on Merifield's resin.

step A:

In a 2 neck round bottomed flask under Argon atmosphere, the Merrifield's resin (2g) was suspended in a H_2O/toluene mixture (120 ml), $[N(Bu)_4]Br$ (4.2 g, 18.6 mmol) and NaBr (16.16g, 158 mmol) were added. The mixture was stirred at 80°C for 5 days, then the solid was filtered and washed with H_2O, THF and CH_2Cl_2.

step B:

In a 2 neck round bottomed flask under Argon atmosphere the aza-BOX (2 mmol) was solved in THF dry (10 ml) and the solution was cooled at -78°C. Through a syringe *n*BuLi (2.2 mmol, 1.375 ml of 1.6M sol) was added and after some minute the cold bath was removed. When the mixture was at room temperature it was passed by syringe in a second 2 neck round bottomed flask containing a suspension of Merrifield's resin of step A (0.6 g) in THF dry (16ml). The mixture was stirred for 40h at reflux temperature. At the end the solid was filtered and washed with THF, methanol and CH_2Cl_2.

The solid was characterized by elemental analysis to evaluate aza-BOX loading.

polymer 17: 0.8 mmol/g

polymer 18: 0.845 mmol/g.

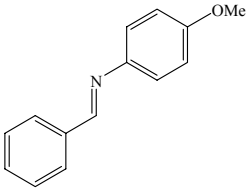
Henry reaction:

The reaction was carried out with the same procedure described in chapter 4 (pag 124).

General procedure for imine synthesis

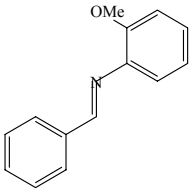
The amine (9 mmol) and the aldehyde (10 mmol) were solved in methanol and stirred for 30 minute. If the imine was solid, it was filtered and washed with cold methanol, then the solution was evaporated and the solid crystallized from methanol. If the imine is an oil the solution was evaporated and the oil distilled under vacuum.

N-benzylidene-4-methoxybenzenamine (23)



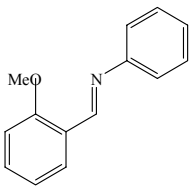
Whyte solid; yield 98% (crystalized from methanol), $C_{14}H_{13}NO$,MW: 211; H^1-NMR ($CDCl_3$, ppm, 300 MHz): δ= 3.83 (s, 3H), δ=6.93 (d, 2H, J=8.7 Hz), δ= 7.24 (d, 2H, J=8.6 Hz), δ=7.3-7-5 (m, 3H), δ=7.7-7.9 (m, 2H), δ=8.49 (s, 1H); MS (CI, m/z, int. rel %):211 (M^+), 196 (100), 167 (28), 141 (9), 115 (11), 92 (10), 77 (16).

N-benzylidene-2-methoxybenzenamine (25):



Yellow oil, yield 80% , $C_{14}H_{13}NO$, MW 211, H^1-NMR ($CDCl_3$, ppm, 300 MHz): δ= 3.88 (s, 3H), δ=6.9-7.0 (m, 3H,), δ= 7.20 (ddd, 1H, J=2.4, 7.0, 8.0 Hz), δ=7.1-7.3 (m, 3H), δ=7.4-7.5 (m, 2H), δ=8.47 (s, 1H)

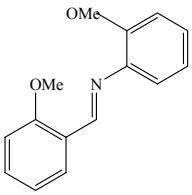
N-(2-methoxybenzylidene)benzenamine (26)



Whyte solid, yield 95%, $C_{14}H_{13}NO$, MW 211,

H^1-NMR ($CDCl_3$, ppm, 300 MHz): δ= 3.92 (s, 3H), δ= 6.96 (d, 1H, 8.4), δ=7.05 (t, 1H, J=7.4 Hz), δ= 7.2 (m, 3H), δ=7.3-7.4 (m, 2H), δ= 7.45 (ddd, 1H, J=1.6,7.2, 8.4 Hz) δ=8.15 (dd, 1H, J=1.6, 7.6 Hz), δ=8.92 (s, 1H) C^{13}-NMR ($CDCl_3$, ppm, 75 MHz): 55.9, 111.4, 121.2, 121.4, 126.0, 127.9, 129.3, 133.0,153.1, 156.9, 159.8

N-(2-methoxybenzylidene)-2-methoxybenzenamine (27)



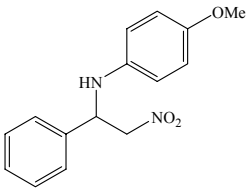
Brown solid, yield 95%, $C_{14}H_{13}NO$, MW 211,

H^1-NMR ($CDCl_3$, ppm, 300 MHz): δ= 3.88 (s, 3H), δ= 3.89 (s, 3H) δ= 6.9-7.1 (m, 5H,), δ=7.18 (ddd, 1H, J=2, 7.2, 8 Hz),, δ= 7.43 (ddd, 1H, J=1.6, 7.2, 8 Hz) δ=8.20 (dd, 1H, J= 2, 8 Hz), δ=8.91 (s, 1H) C^{13}-NMR ($CDCl_3$, ppm, 75 MHz): δ= 55.7, 55.9, 111.3, 111,7 121.1, 121.3, 121.4 125.6, 126.7, 128.1, 132.9, 152.7, 157.6, 159.8, 159.9.

General procedure for aza-Henry reaction.

In a Schlenk tube under nitrogen atmosphere $Cu(OAc)_2$ (0.05 mmol) and BOX or aza-BOX ligand (0.055 mmol) were solved in dry solvent (2 ml). After 1 h imine (1 mmol) and nitromethane (10 mmol) were added with the help of 1 ml of solvent. The reaction was stirred for 24h. At the and the solution was filtered on silica gel and washed with ethyl acetate. Yields and ee values were obtained by HPLC analysis using OD-H column and a mixture Hexane/iPrOH as eluent.

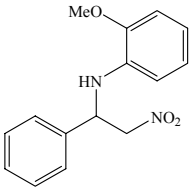
4-methoxy-N-(2-nitro-1-phenylethyl)benzenamine



orange oil, $C_{15}H_{16}N_2O_3$; MW: 272;

H^1-NMR ($CDCl_3$, ppm, 300 MHz): δ= 3.71 (s, 3H), δ=3.8 (bs, 1H), δ= 4.69 (d, 2H, J=6.7 Hz), δ= 5.09 (t, 1H, J= 6.7), δ= 6.58 (d, 2H, J=8.9 Hz), δ= 6.73 (d, 2H, J=8.8 Hz) δ=7.3-7.4 (m 5H). tr1:61.1 min, tr2: 65.0 min (hexane 85/iPrOH 15, 0.8 ml/min)

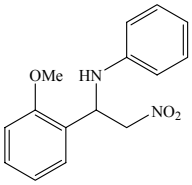
2-methoxy-N-(2-nitro-1-phenylethyl)benzenamine



yellow oil, $C_{15}H_{16}N_2O_3$; MW: 272;

H^1-NMR ($CDCl_3$, ppm, 300 MHz): δ= 3.89 (s, 3H), δ= 4.75 (dd, 1H, J=12, 21.6 Hz), δ= 4.73 (dd, 1H, J=12.4,19.2 Hz) δ=5.04 (bs, 1H), δ= 5.23 (dd, 1H, J=6, 6.2 Hz), δ= 6.56 (dd, 1H, J=1.6, 8 Hz), δ= 6.7-6.8 (m, 3H), δ=7.2-7.5 (m, 5H). tr1:32.1 min, tr2: 40.5 min (hexane 75/iPrOH 25, 0.8 ml/min)

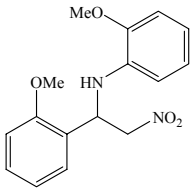
N-(1-(2-methoxyphenyl)-2-nitroethyl)benzenamine



Yellow oil, $C_{15}H_{16}N_2O_3$, MW 272,

H^1-NMR ($CDCl_3$, ppm, 300 MHz): δ= 3.96 (s, 3H), δ= 4.76 (dd, 1H, J=4.8, 8 Hz), δ= 4.9 (dd, 1H, 4.8, 8 Hz), δ= 5.41 (dd, 1H, J=5.2, 7.2), δ= 6.62 (d, 2H, J=8 Hz), δ=6.72 (t, 1H, J=7.4 Hz), δ= 6.8-6.9 (m, 2H), δ=7.1 (m, 2H), δ= 7.2-7.3 (m, 3H) tr1:20.7.1 min, tr2: 35.2 min (hexane 80/iPrOH 20, 0.8 ml/min)

2-methoxy-N-(1-(2-methoxyphenyl)-2-nitroethyl)benzenamine



Brown oil: $C_{15}H_{16}N_2O_3$, MW 272;

H^1-NMR ($CDCl_3$, ppm, 300 MHz): δ= 3.87 (s, 3H), δ= 3.91 (s, 3H), δ=4.73 (dd, 1H, J=8, 12 Hz), δ= 4.83 (dd, 1H, J=4.8, 12 Hz), δ= 5.2 (bs, 1H), δ= 5.47 (t, 1H, J= 6.8), δ= 6.51 (d, 1H, J=7.6), δ=6.7 (7, 1H, J= 7.6, Hz), δ= 6.76 (t, 2H, J= 7.6, Hz) δ=6.9 (dd, 2H, J= 7.6, 8.4 Hz), δ= 7.2 (m, 2H). tr1:15.1 min, tr2: 17.7 min (hexane 75/iPrOH 25, 0.8 ml/min)

5.9 References

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Curriculum Vitae

Chiara Oro was born in 1979 in Palermo..

She went to school in Parma where she received her high school degree from the *Istituto Magistrale A. Sanvitale* in 1998.

She graduated in Parma in July 2004 with a major in Organic Chemistry in the laboratory of Prof. G. Sartori studying asymmetric catalysis in general and in particular new Ru complexes for transfer hydrogenation of ketons..

In 2005 she began a Doctorate in the same group focusing her scientific interest in chemo- and enantio-selective heterogeneous catalysis with a key focus on the development of environmentally "green" processes for the chemical industry.

During her Ph.D., from September 2006 to March 2007, she spent six months of research as Guest Scientist in Spain, at the "Grupo de catálisis heterogénea en síntesis orgánica selectivas" of Zaragoza University, under the supervision of prof. José Antonio Mayoral.

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