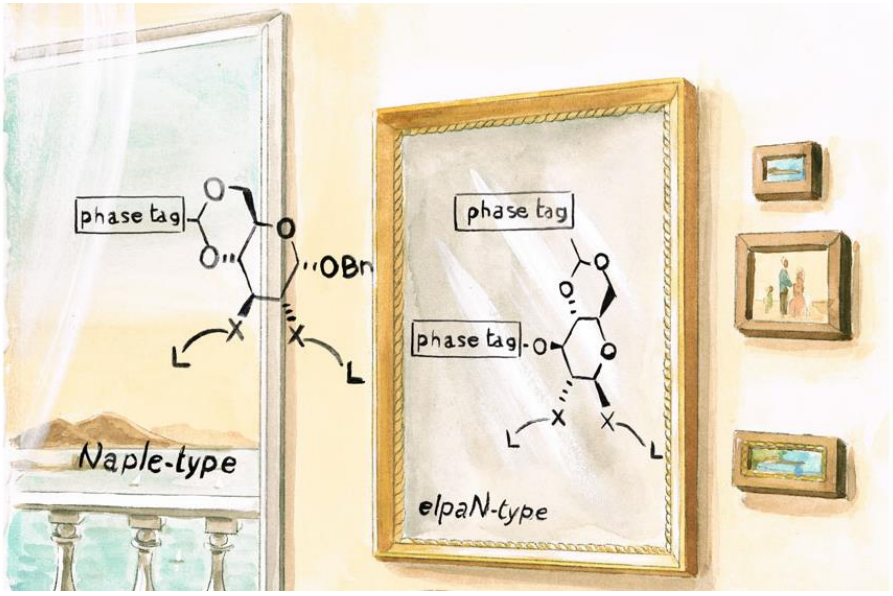
UNIVERSITÀ DEGLI STUDI DI NAPOLI "FEDERICO II"

SCUOLA POLITECNICA E DELLE SCIENZE DI BASE

DOCTORAL THESIS IN CHEMICAL SCIENCES (XXVI cycle)
2011-2014



DEVELOPMENT OF CHIRAL LIGANDS FROM NATURAL MOLECULES FOR METAL-PROMOTED ASYMMETRIC CATALYSIS

Tutor: Prof. Francesco Ruffo
Supervisor: Prof. Daniela Montesarchio
Coordinator: Prof. Luigi Paduano

PhD student:
Matteo Lega

Contents

1. Introduction

1.1 Homogeneous metal-promoted asymmetric catalysis

The very first synthesis of chiral molecules by means of homogeneous metallic catalysts were reported in 1966 and 1968, by the groups of Nozaki et al. [1], Horner et al. [2] and Knowles and Sabacky [3]. The ee's were lower than 15%, but those experiments were the proof of principles: *a metal complex with a chiral ligand is able to promote a catalytic reaction where non chiral or racemic substrates are converted into chiral products with preference for one enantiomer*. Due to the increasing interest in this field, dramatic improvements were made in the next decades; the prime examples are the works of Noyori [4], Sharpless [5] and Knowles [6], who were awarded of the Nobel prize in 2001 *"for their work on chirally catalysed hydrogenation reactions and on chirally catalysed oxidation reactions"*.
Nowdays, enantiopure chiral molecules are required in several productions, such as pharmaceuticals and vitamins [7], agrochemicals [8] and flavors and fragrances [9]. Other applications are functional materials such as chiral polymers, materials with non-linear optical properties or ferroelectric liquid crystals [10]. For many applications of such chiral compounds, the racemic forms will no longer be accepted [7, 8]. On this basis, different general approaches have been developed for the production of enantiopure or enantioenriched chiral molecules:

1) *classical separation of enantiomers*. This methodology is based on the resolution of diastereoisomeric adduct by crystallization or, on smaller scale, on the separation of enantiomers by chiral HPLC. In both cases, large amounts of solvents have to be handled and at least 50% of the material with the wrong absolute configuration has to be either recycled or discarded.
2) the use of *building blocks from the chiral pool*, is very often chosen in the early phases of drug development but, depending on the commercial availability of the starting material, it can also be used

for large-scale products. Because natural products very often have high enantiomeric purity, no further enrichment is usually necessary.

3) *enantioselective synthesis with chiral auxiliaries*, which are not incorporated in the target molecule but are removed after the stereogenic centres have been established, is an alternative, but it should be considered that additional steps are required, and the chiral auxiliarie must be either recycled or discarded.
4) *enantioselective catalysis*, where prochiral starting materials are transformed to enantioenriched products with the help of chiral catalysts. Effective catalysts are either synthetic (chemocatalysis, i.e. metal complexes or organocatalysts) or can be of natural origin (biocatalysis).

Depending on the specific case study, one of those methods may be the best one but, as a general consideration, the enantioselective catalysis should be considered the more efficient in terms of atom economy [11] and the more responding the the principles of green chemistry [12] ("*Green chemistry efficiently utilizes (preferably renewable) raw materials, eliminates waste and avoids the use of toxic and/or hazardous reagents and solvents in the manufacture and application of chemical products*" [12b]). In particular, homogeneus metal-promoted asymmetric catalysis, compared with asymmetric biocatalysis, asymmetric heterogeneous catalysis or asymmetric organocatalysis, is attractive due to its versatility in terms of reaction conditions, reactivity and fine tuning of the catalyst [13]. Nevertheless, it is not a paradox that relatively few enantioselective catalysts are used on an industrial scale; asymmetric catalysis is a young discipline, and its application presents some special challenges and problems, such as: the small scale, the cost of the metal, the substrate specificity, the development time and the cost and availability of the chiral ligand.

In order to generalize the principles of homogeneus metal-promoted asymmetric catalysis, the role of three main components should be considered: *the metal, the substrate* and *the ligand.*

Usually t*he metal* activates the substrates in order to make them more reactive. The activation takes places in different ways depending on the selected system, and examples range from simple interaction as Lewis acid (Dies-Alder) to more complex interactions with delocalized orbitals of the substrate (π-allyl complexes in the Asymmetric Allylic Alkylation).

Alternatively, the metal can play the role of group-transfer (Mn promoted asymmetric epoxidations) or cross-coupler (Suzuki-Miyaura reaction). On this basis, it is evident that the proper chose of the metal is fundamental to obtain the right balance of the catalyst proprieties.

The substrates involved in the homogeneus metal-promoted asymmetric catalysis are usually prochiral or racemic. In the first case, interaction of the two enantiofaces of the substrates with the chiral complex lead to diastereoisomeric reaction pathways, which implies kinetic preference for one enantiomer of the product. Similar considerations can be done for the interaction of the two enantiomers of racemic substrates, taking also into account that the two enantiomer may be in equilibrium (dynamic kinetic resolution) or not (kinetic resolution).

The chiral ligand has a double function, tuning the electronic proprieties of the metal and directing the stereochemistry of reaction by sterical interaction with the substrate.

As a matter of fact, the topic of this introductive paragraph is a "*mare magnum*". Several asymmetric processes and a huge variety of chiral ligands exist, and this diversity reflects the scope of the modes of asymmetric induction. Among those, in 2002 a few selected ligands were indicated as 'privileged' by Jacobsen [14] (in brackets in **Figure 1.1**), in order to define structures of wide and proven applicability both in the development of new asymmetric processes, both in the improvement of existing ones. Over the years, this original class of privileged ligands was gradually extended to include other effective structures, and in 2008, the Aldrich Chemical Company reviewed an entire class comprising more than 30 structures (in **Figure 1.1**).

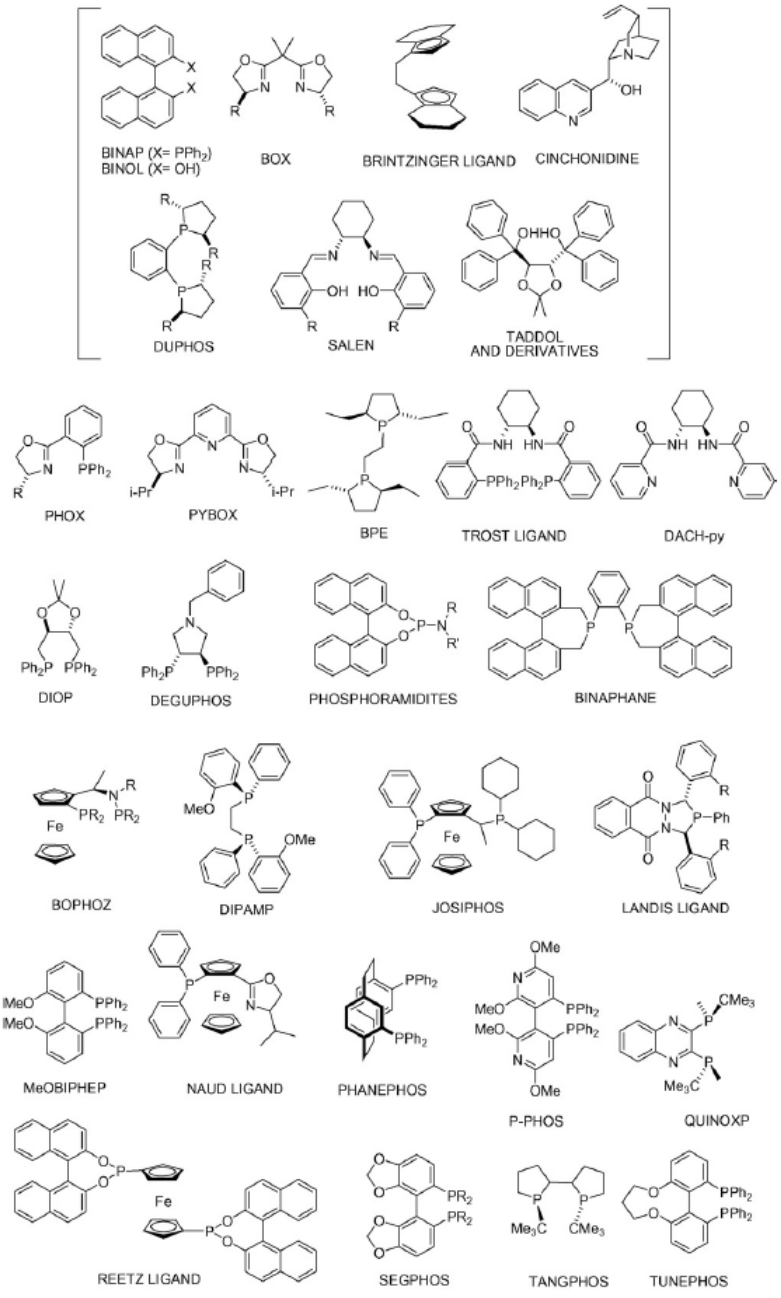

BINAP (X= PPh2)
BINOL (X= OH)
BOX
BRINTZINGER LIGAND
CINCHONIDINE
DUPHOS
SALEN
TADDOL
AND DERIVATIVES
PHOX
PYBOX
BPE
TROST LIGAND
DACH-py
DIOP
DEGUPHOS
PHOSPHORAMIDITES
BINAPHANE
BOPHOZ
DIPAMP
JOSIPHOS
LANDIS LIGAND
MeOBIPHEP
NAUD LIGAND
PHANEPHOS
P-PHOS
QUINOXP
REETZ LIGAND
SEGPHOS
TANGPHOS
TUNEPHOS

Figure 1.1

1.2 Carbohydrates as building blocks of "privileged" ligands.

The accurate design of the chiral ligand is crucial for its effective application. The ligand must possess a well-defined three-dimensional structure, capable of directing the stereochemistry of the reaction. Several research groups demonstrated that highly performing ligands can be obtained by simple modification of molecules from the *natural chiral pool*, such as carbohydrates [16]. This strategy is based upon the following assumptions:

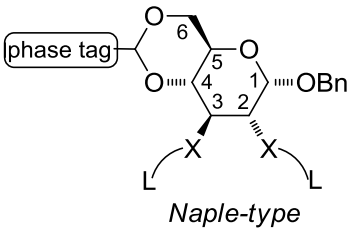
- Sugar are abundant building blocks, therefore easily available. This feature is important since, as mentioned before, the cost of the ligand may limit its application in asymmetric processes.
- Carbohydrates are intrinsically chiral, available in nature as enantiopure molecules and they present more centres of chirality. This allows to synthesize chiral ligands starting from natural sugars without any complicated resolution of racemates.
- Several functional groups are present on the sugar backbone, usually hydroxy and amino groups. Those may easily and selectively be functionalized, using easy and assessed synthetic procedures. This allows a simple tuning of the chemical-physical proprieties of the ligand, such as selective solubility into a green solvent suitable for multiphase catalysis. Moreover, the high ability of being functionalized is particularly attractive because modular ligands with similar structural motifs can be created, thus making possible the generation of libraries.

The use of sugar as building blocks for chiral ligands is expected to be especially productive when carbohydrates are used as backbone of "privileged" ligands, aiming to amplify the scope of their application. The introduction of privileged moieties into a sugar backbone promises to afford unique ligand structures, which combine efficiency with convenience and flexibility. The sugar versions of these well-known ligands are more versatile compared to the classic version, because activity and selectivity are supposed to be the similar, due to the similar coordinating environment, but the sugar backbone allows an easier tuning of the chemical-physical

proprieties. This was demonstrated on several occasions, and today many "privileged" ligands of **Figure 1.1** do possess a corresponding sugar version [16g].

An additional benefit is that the generous presence of functional groups in sugars can be employed for "tagging" the "privileged" ligands in view of their application in *multiphase homogeneous catalysis*. This methodology allows easy catalyst re-cycling via simple phase separation, and relies on using two immiscible solvents and a phase-tagged catalyst, which is selectively soluble in one of the two solvents (catalyst phase), while being insoluble in the other solvent (reactant/product phase)[17].

Given this premise, the research group, where this PhD thesis was carried on, focalized the last years activity in the development of sugar-derived chiral ligands, which are analogues of the privileged ligands derived from *trans*-1,2-cyclohexanediamine (namely, Trost's ligand, DACH-Py ligand, and Salen ligand of **Figure 1.1**). This aim was accomplished by simple and immediate derivatisation of common carbohydrates, such as D-glucose [18]. Interest towards this class of molecules is due to the analogy between *trans*-1,2-cyclohexanediamine and the 2,3 diaminoglucose, because in both cases the coordinating function are in the trans-diequatorial adjacent position of a six members ring. The general structure of these ligands was named *Naple-type,* and is illustrated in **Figure 1.2**



Naple-type

-X-L	*Asymmetric Catalytic applications*
-NHCH$_2$Ar	*Cu promoted cyclopropanation*
-NH(CO)C$_6$H$_4$-2-PPh$_2$	*Pd promoted Allylic Alkylation* *Cu promoted conjugate addition*
-N=CH-2-py	*Mo promoted Allylic Alkylation*
-N=CHC$_6$H$_4$-2-OH	*Mn promoted epoxidation*

Figure 1.2

D-glucose is the sugar "building block", and its dress was optimized to ensure synthetic convenience and high performance in catalysis. More precisely, C-1 is glycosylated with a benzyl group, which can be selectively introduced in α-position. Positions 2 and 3 are decorated with the coordinating functions that typically characterize the privileged ligands based on chiral *trans*-1,2-diaminocyclohexane (*DACH-salen*, *DACH-py* and *Trost ligands*). Finally, the "auxiliary" positions 4 and 6 are generally protected with a benzylidene ring, which stabilizes the chair conformation of the sugar ring. This option can be advantageous for the result of the catalysis. At the same time, the protection can be easily removed and replaced by more specific tags [18c, 19]. Over the years, the *Naple-type* library was successfully examined in several asymmetric reactions involving unsaturated substrates, in both traditional and unconventional conditions [18, 19, 20].

However, in each of these enantioselective processes, only one enantiomer of the chiral product can actually be favored. In fact, for privileging the production of the other one, use of the enantiomeric ligands based on L-glucose would be necessary. This alternative is unlikely due to the high cost of this non-natural sugar. At the same time, it should be considered that in some notable cases, both enantiomers of a molecule do present wanted properties, and, hence, it is necessary to find convenient methods for their synthesis. For instance, (+*S*,*R*,*R*,*R*)-nebivolol and (-*R*,*S*,*S*,*S*)-nebivolol synergistically act to produce a highly beneficial cardiovascular profile [21]. Within this thesis, it was explored the possibility to develop ligands pseudo-enantiomeric to *Naple-type* and based on the same D-glucose scaffold. Aim of this strategy is the production of the same chiral products with opposite stereochemistry.

1.3 *Pseudo-enantiomeric* ligands based on pyranose. Primary aim of the thesis: the *elpaN-type* library.

From now on, we shall define as *pseudo-enantiomeric* those *pyranoses derived ligands that possess the same connectivity within the cyclometallated ring, and, on the basis of a rational design, provide enantiomorphous*

coordination environment. This definition is based on the assumption that the enantioselectivity of a reaction depends only on the local chirality in close proximity to the active metal center [22a]. On this basis, it is possible to direct the enantioselectivity of a system by a proper design of the active, chiral, catalytic center.

This goal may be achieved in different ways on the case of sugar-derived ligands, taking in account some simple considerations. As mentioned before, most of the ligands based on *trans*-1,2-disubstitued-cyclohexane do present the coordinating functions L in adjacent *trans*-diequatorial position of the six-member ring. **Figure 1.3** shows the two corresponding enantiomers (**a** e **b**).

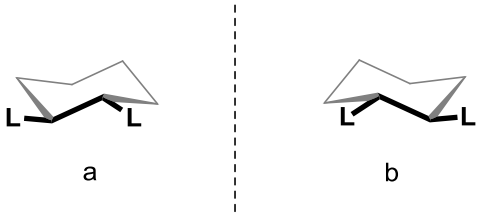


Figure 1.3

These relative configurations can be easily obtained in several ways within the stable chair of the most convenient pyranoses.

For instance, positioning the donor atoms in positions 2 and 3 of glucose (as in *Naple-type)* (**Figure 1.4a**) replies the relative configuration of **Figure 1.3a**. Then, a simple shift of the coordination sites to positions 1β and 2 clearly produces a *pseudo*-enantiomeric environment (**Figure 1.4b**). The same effect (**Figure 1.4c**) occurs involving positions 3 and 4 of mannose (or even of the same glucose).

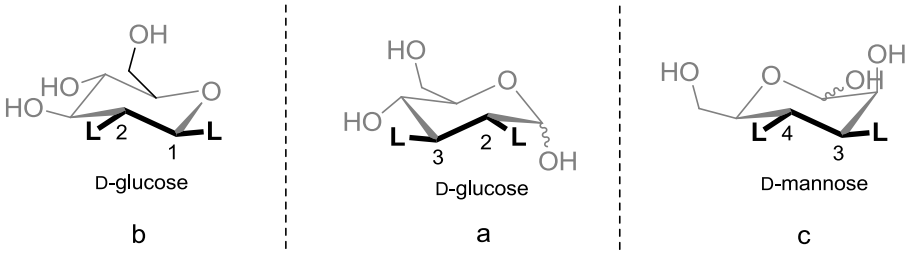


Figure 1.4

In other notable cases, the coordinating functions L are *not* directly bound to the six-member ring of cyclohexane, but are spaced with a linker X.
Seen along the oriented C(XL)—C(XL) axis, in both enantiomers the C—X(L) vectors give rise to a dihedral angle, the sign of which can be defined as positive, if the overlap of the upper L over the lower L requires a clockwise rotation (**Figure 1.5a**), negative in the other case (**Figure 1.5b**).

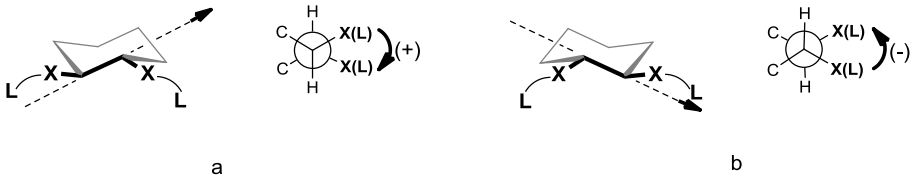


Figure 1.5

In most of the catalytic processes, the sign of the dihedral angle regulates the stereochemical outcome of catalysis. In other words, in any given reaction, ligands with the same sign of dihedral angle will favor the obtaining of the same enantiomer. These relative spatial arrangements can be obtained in several ways in the stable chair of the most convenient pyranoses, For instance, the positive sign ensues from an appropriate di-equatorial substitution (*e.g.* 2,3 in the glucose ring, **Figure 1.6a**), but also from an axial,equatorial arrangement (*e.g.* 3,4 in galactose, **Figure 1.6a'**).
In analogous way, use of other suitable couples and/or sites affords the opposite dihedral angle, as the illustrated by the examples of **Figure 1.6b** and **1.6b'**.

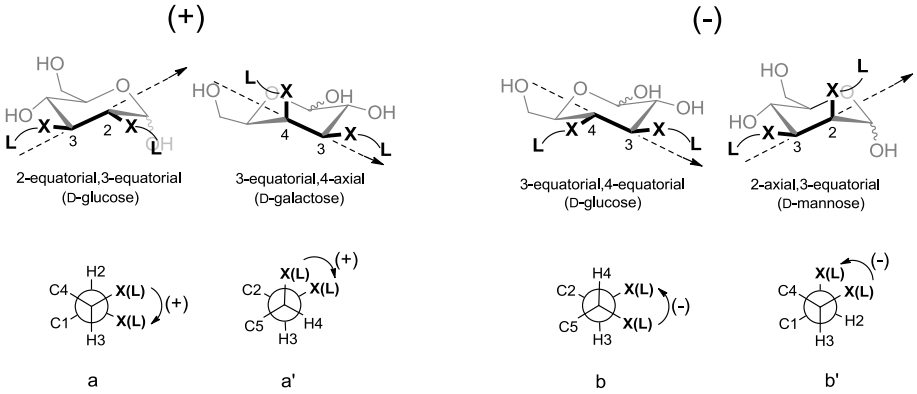


Figure 1.6

Given this premise, it is clear how, depending on the circumstances, it is possible to find the most convenient synthetic strategy for designing modular libraries of *pseudo*-enantiomeric ligands, with a well-defined stereochemical activity; some exemples are reported in literature [22].

The main aim of this PhD thesis was concentrated on the development of a library of ligands, derived from D-glucose, pseudo-enantiomeric to the previously cited *Naple-type* library. This innovative library of ligands was called *elpaN-type* (**Figure 1.7**, the name *elpaN* come from the world *Naple* spelled on the contrary), and was successfully employed in the same relevant asymmetric processes promoted by the *Naple-type* library, but with opposite enantioselectivity.

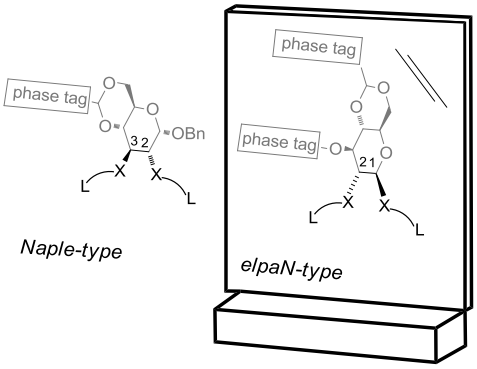
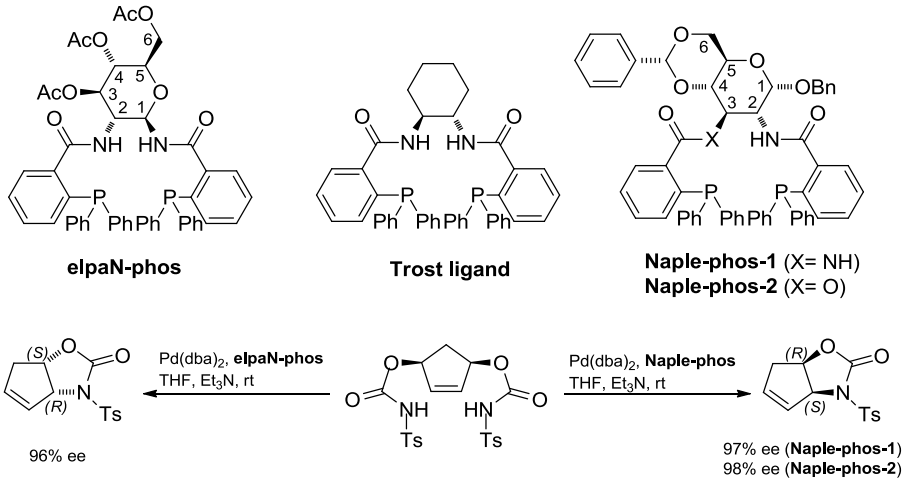


Figure 1.7

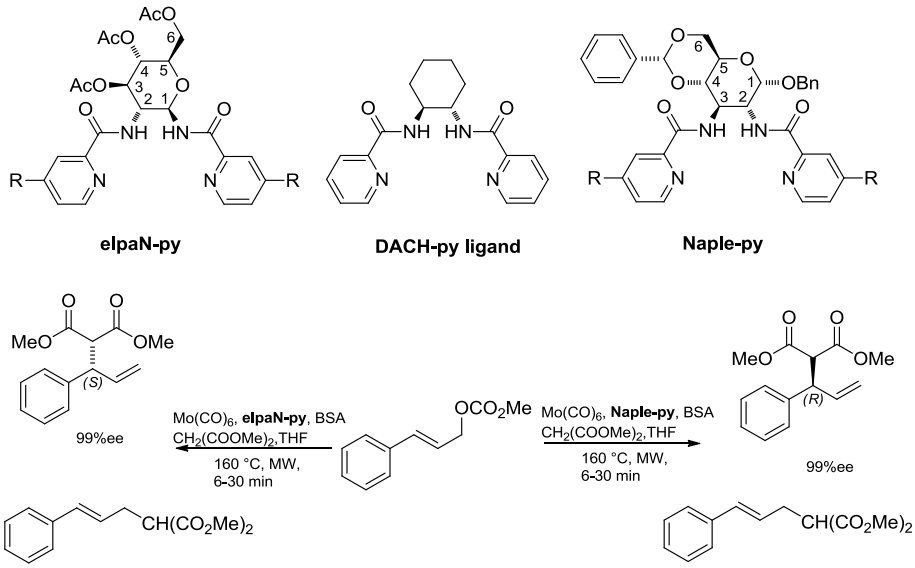
According to the strategy mentioned before, this aim was pursued by shifting the same coordinating motifs *X-L*, respectively from positions 2,3 (*Naple-type*) to position 1,2 (*elpaN-type*). The multifunctional nature of the carbohydrate scaffold was also employed for a precise tailoring of the ligands, through the introduction of appropriate phase-tags in the other available ring positions. Depending on the type of functionalization *X-L*, three subsets of ligands were prepared.

When X-L was a 2-diphenylphosphinoamido arms, typical motif of the privileged Trost's ligand, the library was named **elpaN-phos** and was employed in the Pd promoted asymmetric allylic substitution (**Scheme 1.1)**.



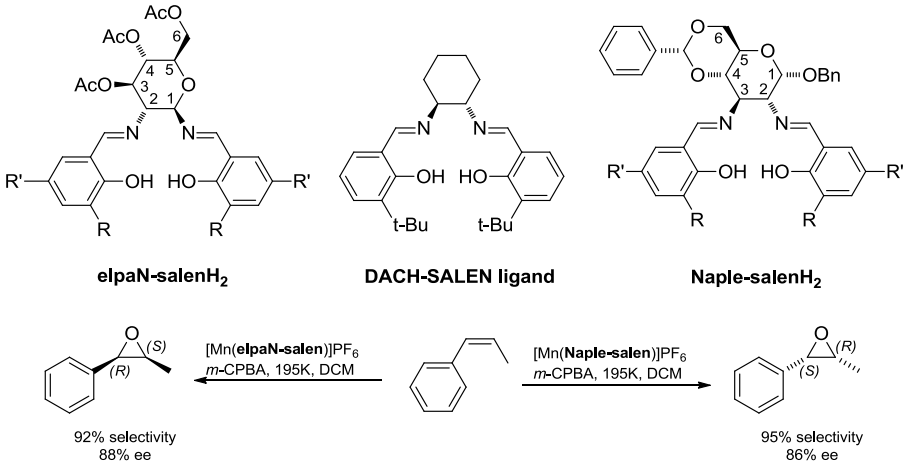
Scheme 1.1

When X-L was a amido-pyridin arm (DACH-Py like ligand), the ligands, named *elpan-Py* family, were used in the Asymmetric Allylic Alkylation (AAA) of allylic carbonate promoted by Mo and assisted by microwaves irradiation (MW) (**Scheme 1.2)**.



Scheme 1.2

At last, when the ligands were funtionalized by an iminohydroxyphenyl arm, like the *DACH-Salen,* they promoted the manganese-catalysed asymmetric epoxydation of styrene (**Scheme 1.3)**.



Scheme 1.3

1.4 Secondary aim of the thesis: Pd (0) complexes with sugar-derived ligands for aqueous Suzuki-Miyaura cross-coupling.

As mentioned before, organometallic catalysis is a powerful tool for the reduction of pollution by the use of the green chemistry principles. In fact, metal catalysts are able to produce clean and high selective reactions, thus saving time and reducing separation steps and waste of auxiliaries. Furthermore, the high tunability of metal complexes allows accurate tailoring of their properties, for performing catalysis in non-toxic alternative solvents. This latter features is particularly attractive because the choice of the solvent strongly affects the impact of a reaction.

An ideal solvent should be capable to dissolve reagents or products, chemically inert (it must not react both with reagents and products), liquid at temperature and pressure demanded by the reaction, available in large

quantity, economically affordable, not toxic (towards humans, animals and environment) and not flammable [23]. These considerations allow to select four possible alternative solvents [24]: water, ionic liquids, perfluorinated solvents, supercritical solvents.
Among them, water is the only one solvent that instead of being toxic, is indispensable to life. Aqueous media were not generally used in synthetic processes for their poor ability to dissolve organic compounds and for the reactivity that many compounds show towards water. Nevertheless, this solvent displays several benefits:

1) is not flammable;
2) is polar and easily separates from apolar organic solvents;
3) is amphoteric;
4) is available in large quantities and economically affordable;
5) is odorless and colorless, that makes easy to detect contaminations;
6) dissolves many gases;
7) its density is different from that of most organic solvents;
8) can affect advantageously the kinetic of reactions.

Organic processes promoted by metals in aqueous media are, therefore, currently of great interest, due to the green nature of water[25].

On the ground of the previous considerations, secondary aim of the thesis has been the synthesis of hydrophilic complexes of Pd(0) containing diphenylphosphino,imino (**PN**) and pyridino,imino (**NN**) bidentate ligands derived from sugars (**Figure 1.8**), taking advantage of their solubility in water:

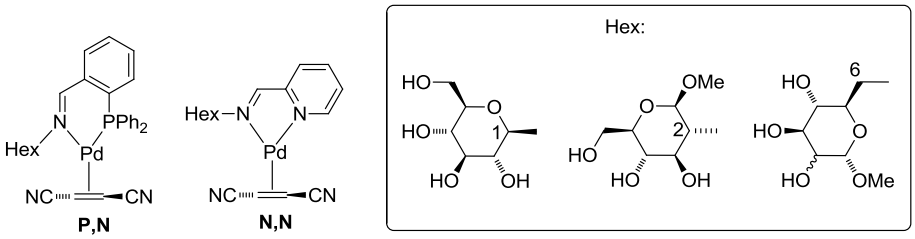
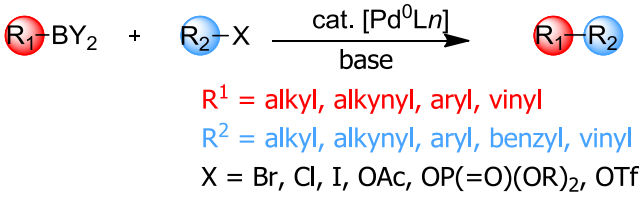


Figure 1.8

The design of the ligands was aimed at ensuring their easy, high-yield synthesis. Four imino sugar residues were employed: three derive from glucose functionalized in positions C1, C2 and C6, respectively. The fourth is instead a mannoside derivatized at C6.

As expected, all the complexes were found to be highly soluble in aqueous media, and could be fruitfully employed in the Suzuki-Miyaura coupling (**Scheme 1.4**).



Scheme 1.4

1.5 References

[1] Nozaki, H.; Moriuti, S.; Takaya, H.; Noyori, R.; *Tetrahedron Lett.* **1966**, *43*, 5239.

[2]Horner, L.; Siegel, H.; Büthe, H.; *Angew. Chem., Int. Ed. Engl.* **196 8**, *7*, 942.

[3] Knowles, W. S.; Sabacky, M. J.; *Chem. Commun.* **1968,** 6429.

[4] Noyori, R.; *Nobel Lecture: Asymmetric Catalysis: Science and Technology* **2001.**

[5] Sharpless, K. B.; *Nobel Lecture: Facts* **2001.**

[6] Knowles, W. S.; *Nobel Lecture: Asymmetric Hydrogenations* **2001.**

[7] Rouhi, A. M.; *C&EN* **2004**, 47.

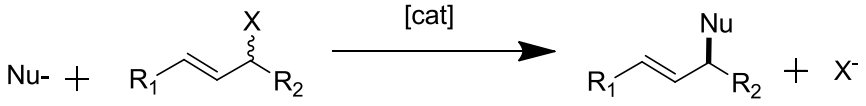
[8] Ramos Tombo, G.M.; Blaser, H. U.; in: Brooks, G. T.; Roberts T. R.; (Eds.) *Pesticide Chemistry and Bioscience*, Royal Society of Chemistry, Cambridge, **1999**, 33, and references cited therein.
[9] Noyori, R.; *Chemtech* **1992,** *22,* 366.
[10] (a) Pauluth, D.; Wachter, A. E. F.; in: Collins, A. N.; Sheldrake, G. N.; Crosby, J.; (Eds.) *Chirality in Industry II,* John Wiley, Chichester, **1997**, 263; (b) Polastro, E.; in: Jannes, G. V.; Dubois (Eds.), *Chiral Reaction in Heterogeneous Catalysis,* Plenum Press, New York, **1995**, 5.
[11] Trost, B. M.; *Angew. Chem. Int. Ed. Engl.* **1995**, *34,* 259
[12] (a) Anastas, P. T.; Warner, J. C.; *Green Chemistry: Theory and Practice*, Oxford Univ. Press, Oxford **1998**. (b) Sheldon, R. A.; Acad, C. R; Sci. Paris, *IIc,Chimie/Chemistry*, **2000**, *3*, 54.
[13] Blaser, H. U.; Pugin, B.; Splinder, F.; *Journal of Molecular Catalysis A: Chemical* **2005**, *231*, 1
[14] Yoon, T. P.; Jacobsen, E. N. *Science* **2003**, *299,* 1691.
[15] *ChemFiles, Asymmetric Catalysis, Privileged Ligands and Complexes, Vol. 8, Aldrich Chemical*, **2008**
[16] (a) Steinborn, D.; Junicke, H.*; Chem. Rev*. **2000**, *100,* 4283. (b) Dièguez, M.; Pàmies, O.; Ruiz, A.; Diaz, Y.; Castillòn, S.; Claver, C.; *Coord. Chem. Rev.;* **2004**, *248,* 2165. (c) Dièguez, M.; Pàmies, O.; Claver, C.; *Chem. Rev.* **2004**, *104,* 3189. (d) Diaz, Y.; Castillòn, S.; Claver, C.; *Chem. Soc. Rev*. **2005,** *34,* 702. (e) Dièguez, M.; Claver, C.; Pàmies, O.; *Eur. J. Org. Chem*. **2007,** 4621. (f) Boysen, M. M. K.; *Chem. Eur. J*. **2007**, *13,* 8648. (g) Dièguez, M.; Pàmies, O.; *Chem. Eur. J.* **2008,** *14,* 944. (g) Benessere, V.; De Roma, A.; Del Litto, R.; Ruffo, F.; *Coord. Chem. Rev.* **2010**, *254,* 390. (h) Diéguez, M.; Pàmies, O.;Woodward, S.; *Coord. Chem. Rev.* ***2010****, 254,* 2007.
[17] B. Cornils,W. A.; Herrmann, I. T.; Horvarth,W.; Leitner, S.; Mecking, H.; Olivier-Borbigou, D.; Vogt (Eds.), *multiphase Homogeneous Catalysis,* 1st ed., Wiley-VCH,Weinheim, Germany, ***2005***
[18] (a) Benessere, V.; Del Litto, R.; Ruffo, F.; Moberg, *C.*; *Eur. J. Org. Chem*. **2009**, 1352; (b) De Roma, A.; Ruffo, F.; Woodward, S.;

Chem. Commun. **2008**, *5*, 384; (c) Benessere, V.; De Roma, A.; Ruffo, F.; *ChemSusChem* **2008**, *1*, 425. (d) Benessere, V.; Ruffo, F.; *Tetrahedron: Asymmetry* **2010** *21*, 171. (e) Borriello, C.; Del Litto, R.; Panunzi, A.; Ruffo, F.; *Tetrahedron: Asymmetry* **2004,** *15*, 681.
[19] Benessere, V.; Lega, M.; Ruffo, F.; Silipo, A.; *Tetrahedron* **2011,** *67*, 4826.
[20] Benessere, V. ; De Roma, A.; Del Litto, R.; Lega, M.; Ruffo, F.; *Eur. J. Org. Chem.* **2011**, 5779.
[21] Ignarro, L. J.; *Cardiovasc. Ther.* **2008,** *26*, 115.
[22] (a) RajanBabu, T. V.; Ayers, T. A.; Halliday, G. A.; You, K. K.; Calabrese, J. C.; *J. Org. Chem.* **1997**, *62*, 6012. (b) RajanBabu, T. V.; Ayers, T. A.; Casalnuovo, A. L. ; *J. Am. Chem. Soc.* **1994**, *116*, 4101. (c) RajanBabu, T. V.; Radetich, B.; You, K. Y.; Ayers, T. A.; Casalnuovo, A. L.; Calabrese, J. C.; *J. Org. Chem.* **1999**, *64*, 3429. (d) Wang, L.; Li, Y. M.; Yip, C. W.; Qiu, L.; Zhou, Z.; Chan, A. S. C.; *Adv. Synth. Catal.* **2004**, *346*, 947. (e) Khiar, N.; Suárez, B.; Valdivia, V.; Fernández, I.; *Synlett* **2005**, 2963. (f) Khiar, N.; Serrano Araúgio, C.; Suárez, B.; Fernández, I.; *Eur. J. Org. Chem.* **2006**, 1685. (g) Huang, H.; Zheng, Z.; Chen, H.; Bai, C.; Wang, J.; *Tetrahedron: Asymm.* **2003**, *14*, 1285.
[23] Ruffo, F.; *Metodi innovativi per catalisi omogenea*, CUES .
[24] (a) Adams, D.; Dyson, P.; Tavener, S.; *Chemistry in Alternative Reaction Media*, John Wiley & Sons, **2004**. (b) Wasserscheid, P.; Welton, T. *Ionic Liquids in Synthesis*, Wiley-VCH, **2005**. (c) Gladysz, J. A.; Curran, D. P.; Horvàth, I. T.; *Handbook of Fluorous Chemistry*, Wiley-VCH, **2006**. (d) Inperato, G.; König, B.; Chiappe, C.; *Eur. J. Org. Chem.*, **2007**, 1049.
[25] (a) Li, Ch.-J.; *Chem. Rev.* **2005**, *105*, 3095. (b) Polshettiwar, V.; Decottignies, A.; Len, C.; Fihri, A.; *ChemSusChem* **2010**, *3*, 502.

2. The *elpaNphos* ligands: Pd promoted Asymmetric Allylic Substitution.

2.1 Background of the Pd promoted Asymmetric Allylic Substitution: scope of the reaction, mechanisms, state of the art.

The first stoichiometric, palladium-mediated, allylic substitution was reported by Tsuji in 1965 [1]. In this seminal work it was shown that soft carbon nucleophiles, such as ethyl malonate and acetoacetate, react with dimeric π-allyl palladium chloride to afford allylated products. In 1970, Atkin et al. and Hata et al. published papers about a catalytic version of the reaction [2, 3], and in 1977 Trost reported the first palladium-catalyzed asymmetric allylic alkylation [4].
In the next decades, the Tsuji–Trost reaction has known a remarkable development and numerous transition metals such as molybdenum [5], tungsten [6], iridium [7], rhodium [8], ruthenium [9], platinum [10], nickel [11], copper [12], iron, and cobalt [13] have been recognized as efficient catalysts for this reaction. Nowadays, metal-promoted allylic substitution is a powerful tool for organic synthesis. Moreover, asymmetric allylic alkylation (AAA) has become a benchmark reaction to test the efficiency of new chiral ligands [14] and has been widely used as a key step for the preparation of bioactive compounds [15].
The generic Pd-promoted asymmetric allylic substitution is reported below (**Scheme 2.1**).



Scheme 2.1

The neat reaction is a substitution of a leaving group X, in allylic position, by a nucleophile. This occurs in milder condition than the tipical ordinary

S_N2 or S_N2' reactions and with different chemo-, regio- and stereoselectivities. The scope of the reaction is really wide in terms of nucleophile, substrate, and leaving group:

- **Nucleophiles:** The most common nucleophiles, which lead to a formation of a new C-C bond, are soft (pK_a below 20 [16]) carbanions stabilized by π-acceptors. In particular, dimethyl malonate has become the standard nucleophile for testing new catalysts, but carbanions bearing carbonyl, sulfone, nitrile, or nitro groups have been used [17]. Only few exemples of hard C-nucleophiles are reported [17]. By the way, heteroatomic (H, O, N, S, P) anions have been widely employed [15, 17]; specifically, due to the important role of chiral amine as pharmaceutical, N-nucleophile are of great interest. Also, the use of chiral nucleophile is reported [18].
- **Substrates:** One of the reason for the success of the Pd-promoted asymmetric allylic substitution is that it is quite tolerant towards several functional group [15], allowing the wide use of this methodology in total synthesis of natural products. Hence, several substrate have been used. In terms of general structure, achiral, meso or racemic substrate can be converted to an optically active product by allylic substitution [15d]. The 1 and 3 positions of the allylic moiety may be symmetrically or unsimmetrically substituted, and also cyclic substrates are used; these structural feature will strongly influence the regio- and stereo- chemical outcome of the reaction (see mechanism, section 2.1.1) . Substrates with the proper requisites in terms of structure and functional groups undergo intramulecolar reaction.
- **Leaving groups:** In the metal-catalyzed allylic substitutions rather unreactive leaving groups can be used which are usually inert toward nucleophiles in the absence of a catalyst [19]. The most typical substrates are allylic acetates and carbonates. Carbonates generates alkoxide in the ionization step, and it can serve as a base for generating the nucleophile Nu^- from the precursor Nu-H, avoiding the use of an external base [20]; the resulting steady low concentration of base allow the use of base-sensitive compounds. Allylic halides are not common substrate because imply the

drawback of the background uncatalyzed reaction, but some example are reported [21]. In cases where more reactive leaving groups are needed, phosphates may be a good choice [22].

Hundreds of chiral ligands have proven to efficiently promote this reaction, with a variety of backbones, coordinating motives and donating systems (P, P–P, P–N, P–O, P–S, N–N, N–S, S–S, and NHC) [23], but Trost's ligands are undoubtedly the most successful in asymmetric allylic substitutions (**Figure 2.1**) and, in a wide range of case-studies, they represent the state of the art in terms of catalytic performances and applicability.

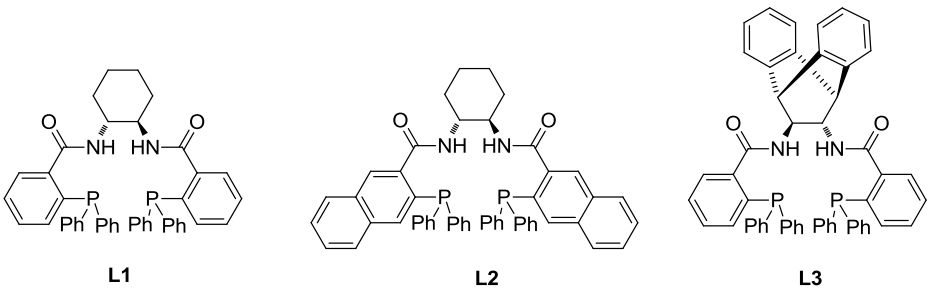
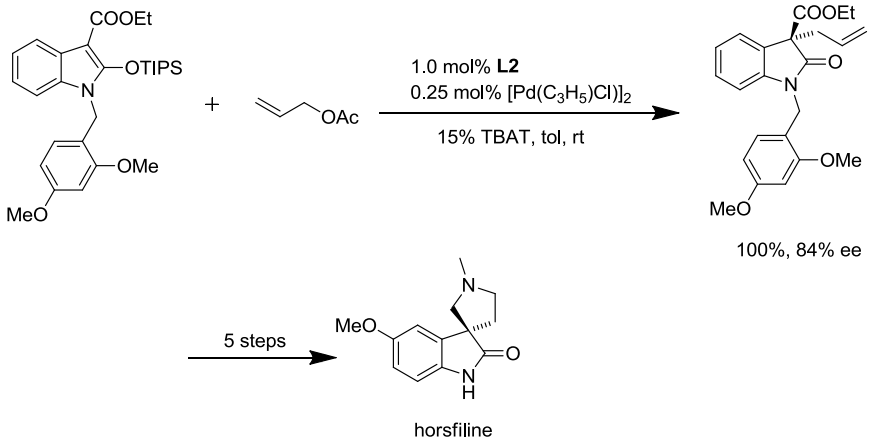
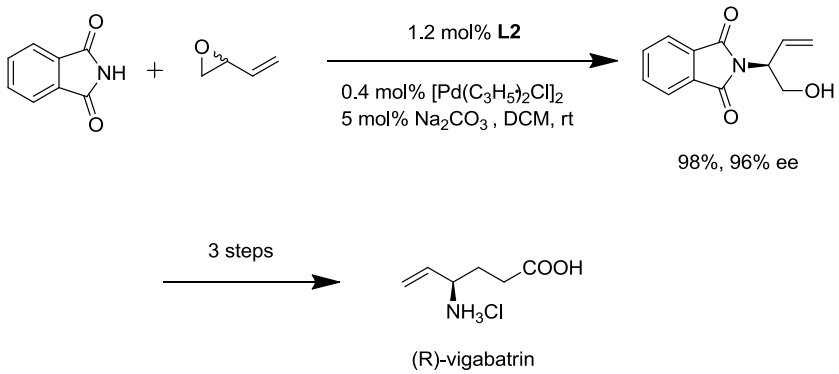
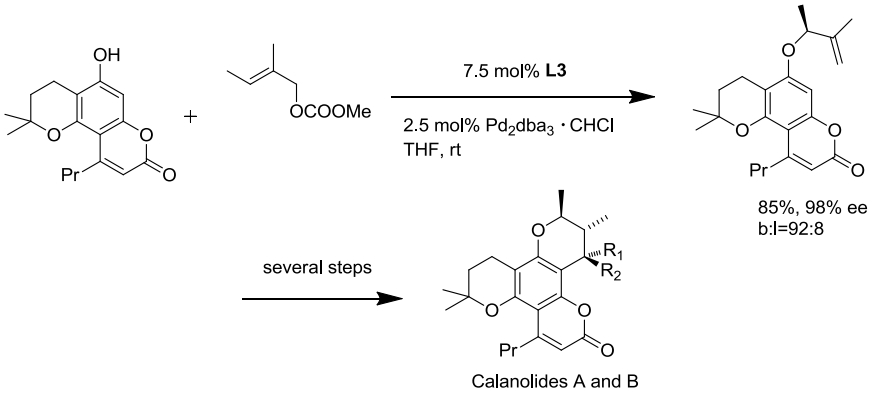


Figure 2.1

Notable examples are the total synthesis of horsfiline, a natural product leaf extract with structural similarities to the active indole alkaloid natural products, the current synthesis of the (R)-vigabatrin, an important marketed drug for the treatment of epilepsy, and the syntheses of calanolide (-)-calanolide A (R_1 = H; R_2 = OH) and (-)-calanolide B (R_1 = OH; R_2 = H), both natural products that demonstrate HIV-1 specific reverse transcriptase inhibition (**Scheme 2.2**).[24]


COOEt
OTIPS
N
OMe
MeO
OAc
1.0 mol% L2
0.25 mol% [Pd(C3H5)Cl)]2
15% TBAT, tol, rt
COOEt
O
N
OMe
MeO
100%, 84% ee
5 steps
MeO
N
O
N
H
horsfiline

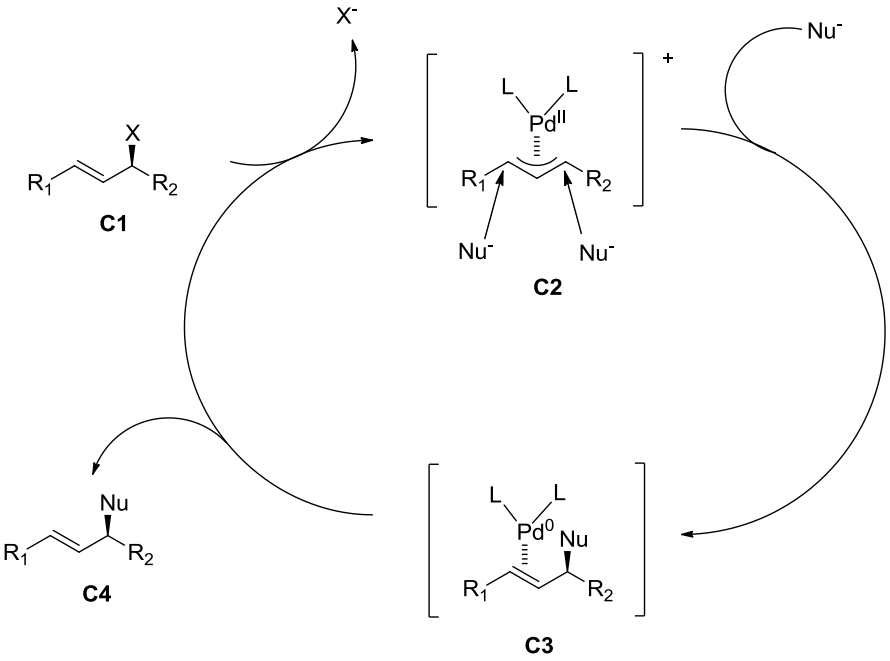

O
NH
O
O
1.2 mol% L2
0.4 mol% [Pd(C3H5)2Cl]2
5 mol% Na2CO3 , DCM, rt
O
N
OH
O
98%, 96% ee
3 steps
COOH
NH3Cl
(R)-vigabatrin


OH
O
O
Pr
O
OCOOMe
7.5 mol% L3
2.5 mol% Pd2dba3 · CHCl
THF, rt
O
O
O
Pr
O
85%, 98% ee
b:l=92:8
several steps
O
R1
R2
O
O
Pr
O
Calanolides A and B

Scheme 2.2

2.1.1 Mechanism and enantiodiscrimination

The mechanism of these reactions has been firmly established and a detailed picture of the catalytic cycle can be described [17, 19, 25]. The generally accepted mechanism of palladium-catalyzed allylic substitutions is shown in **Scheme 2.3**.



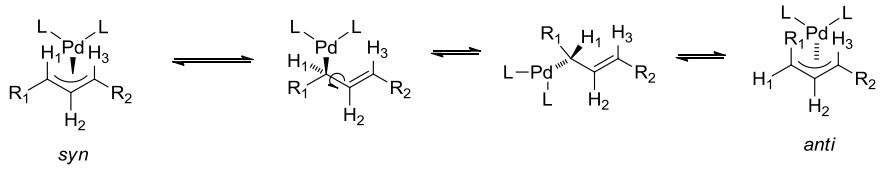
Scheme 2.3

An allylic substrate **C1** reacts with the catalyst, which enters the catalytic cycle as Pd(0). Both Pd(0) and Pd(II) complexes can be used as precatalysts (typically $[Pd(dba)_2]$, $[Pd(C_3H_5)Cl]_2$, $PdCl_2$ and $Pd(OAc)_2$), because Pd(II) is easily reduced in situ to the active Pd(0) form. Presumably, the reaction is initiated by formation of a π-complex which eliminates X^- to produce an (η^3-allyl)palladium(II) complex. This process occurs with inversion of configuration. Depending on the ligand, the solvent and X^-, the product of

the oxidative addition can be a cationic complex **C2** or a neutral complex if the resulting anion X^- coordinates with palladium; classically, the more reactive cationic complex predominates when bidentate ligands are involved. The allyl complexes **C2** can isomerize in various ways and this strongly influences the outcome of the reaction. It is worth to underline that the intermediate allyl complexes are stable and can be isolated in the absence of nucleophiles. This uncommon feature allowed valuable insights into the mechanism of allylic substitutions and the origin of enantioselection in reactions with chiral catalysts. The electrophilic Pd(II) center activates the allyl system for nucleophilic attack at the allyl termini, which usually is the rate limiting step. Addition of the nucleophile at C1 or C3 generates an unstable Pd(0)-olefin complex **C3**, which readily releases the final product **C4** and enters again into the catalytic cycle. For soft nucleophiles, also the nucleophilic attack take place with inversion of configuration, because the nucleophile reacts with the allyl from the side opposite to palladium; as a consequence, the overall process proceeds with neat retention of configuration. On the contrary, hard nucleophiles such as organozinc reagents first coordinate to the metal center and then are transferred intramolecularly to the allyl; therefore, in this case the reaction occur with neat inversion of configuration.

As mentioned before, allyl complexes show dynamic behaviour trough different processes, namely the *π-σ-π isomerisation*, the *apparent allyl rotation* and the *Pd^0-catalyzed alkyl exchange*. These equilibriums should be taken in account in order to predict the stereo and regiochemical outcome of reaction.

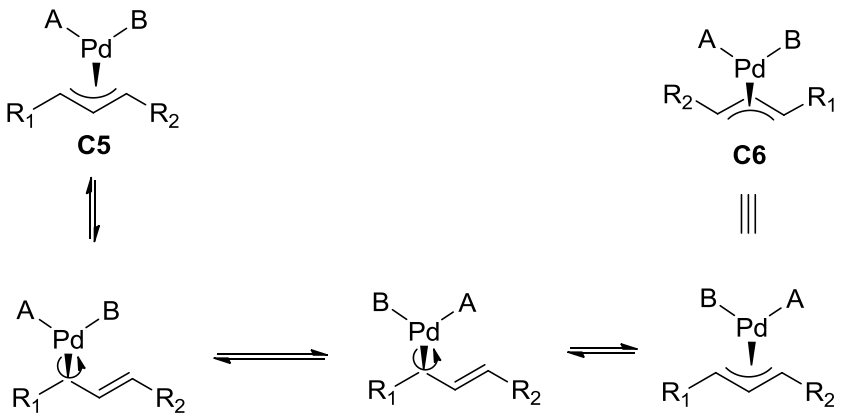
The *π-σ-π isomerisation* (**Scheme 2.4**) is a syn-anti interconversion by rotation around the σ-(C-C) bond in the η^1 -intermediate[1].



Scheme 2.4

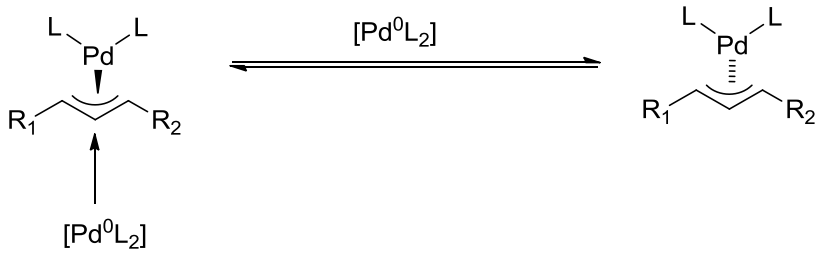
[1] *syn* and *anti* refer to the positions syn and anti to the substituent at C2.

Usually the syn position is sterically favored and, consequently, more stable.
An other isomerization processes that can occur by a π-σ-π mechanism is *apparent allyl rotation*, where the two termini of the allyl system switch position with respect to the other two coordination sites and at the same time, the central allyl C atom moves from one side of the coordination plane to the other. (**Scheme 2.5**).



Scheme 2.5

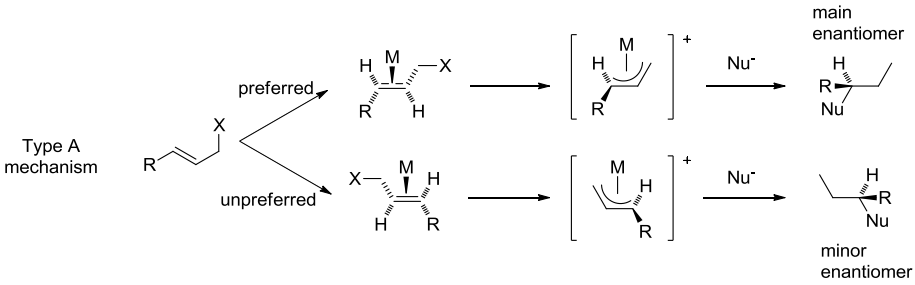
When A and B are different and chiral, as in chiral bidentate ligands, the two isomer **C5** and **C6** are diastereoisomers, then they can undergo nucleophilic addition with different rates and different regioselectivities and, consequently, the relative rate of apparent allyl rotation can strongly influence the product distribution of allylic substitutions, including the ee%. Catalytic amounts of anions such as chloride or fluoride [26] or polar solvents like DMSO and acetonitrile [27] that can coordinate to palladium have been shown to accelerate this process. Stabilization of the η^1-intermediates by coordination of an external ligand could explain these observations.
In the *Pd^0-catalyzed alkyl exchange* a Pd(0) complex adds to the free π- face of the allyl ligand and displaces the Pd(II), resulting in an inversion of configuration at all three allyl carbons (**Scheme 2.6**). Due to the low concentration of palladium (0), isomerization by allyl exchange is usually slow compared to product formation.



Scheme 2.6

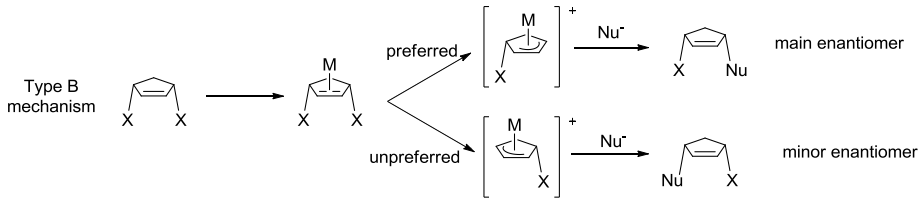
The origin of enantioselectivity is strongly dependent on the relative rate of these processes and the nucleophilic substitution, but also the symmetry of the ligand and the substrate play a foundamental role. Five different mechanisms of enantiodiscrimination may be observed [18 and reference cited therein].

The *type A* mechanism is quite common in asymmetric catalysis, and consist of the differentiation of the enantiotopic faces of a π-unsatured system (**Scheme 2.7**). The steric motif of the chiral ligand may induce preference toward the coordination of one enantioface of the substrate; for this reason, one of the two diastereoisomeric π-allyl complexes will be prevalent, and it will lead to the main enantiomer. On the basis of this mechanism, it is clear that the enantiodiscriminating step is the oxidative addition of the substrate to the metal; evidences are that 1) in intramolecular reaction racemic substrates leads to racemic products, and 2) enhancing the rate for the equilibration of the π-allyl intermediate lowers the ee%.



Scheme 2.7

The *type B* mechanism differentiate between enantiotopic leaving group; also in this case the enantiodiscriminating step is the metal induced ionization of the leaving group. (**Scheme 2.8**)



Scheme 2.8

The stereochemical outcome of the reaction can clearly be explained on the basis of the cartoon model proposed by Trost for this reaction [28]. For Trost's-like ligands, the phenyl groups arrange as depicted in **figure 2.2**, altering "flap" and "wall" groups; the resulting system may be easily described by the quadrants formalism. The rate-limiting step is the activation of one leaving group in **a** to give a π-allyl intermediate (**b** or **c**). Activation of the "left" leaving group function leads to the attainment of **b**, while activation of the "right" function preludes the achievement of **c**. Both reactions occur with simultaneous rotation of the five-membered ring, which is clearly inhibited by steric contacts only in the case of the clockwise rotation (i) that accompanies formation of **c**.

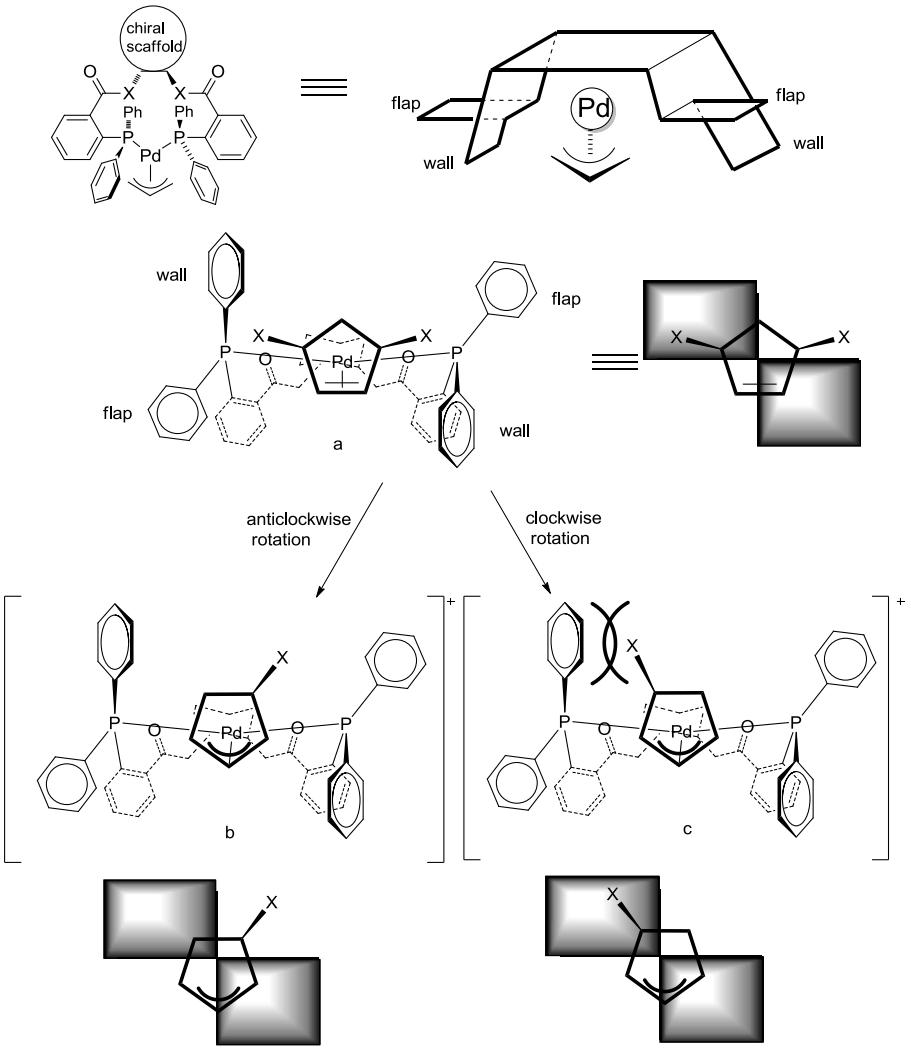
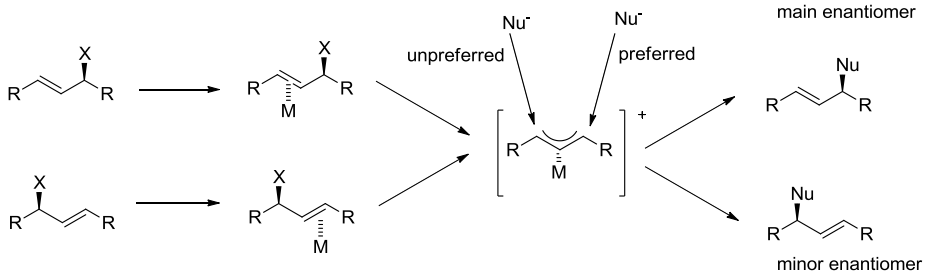


Figure 2.2

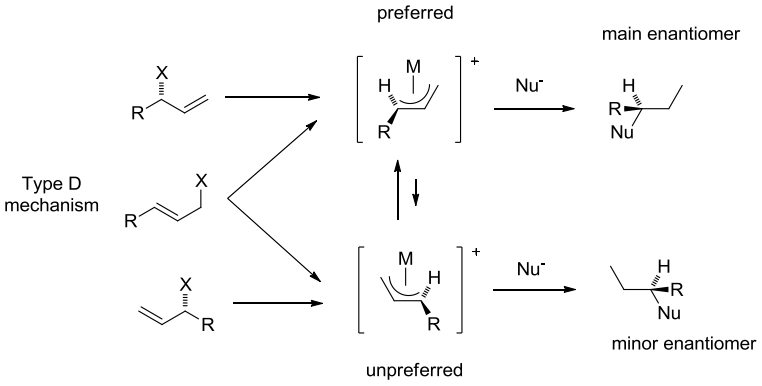
The *type C mechanism* involves a chiral racemic substrate which lose chirality when it is ionized into the π - allylmetal intermediate. The two allylic termini are enantiotopic, and by differentiating between them it is possible to induce enantioselectivity; hence, the nucleophilic attack is the enantiodiscriminating step for this mechanism (**Scheme 2.9**). One possible way to differentiate between the two allylic termini is the use of bidentate heteroleptic ligands, such as P-S or P-N; due to the *trans* effect, the

electrophilic position trans to the P atom will be more reactive, and then preferred. Since this intermediate derives from a precursor in which the chirality of the substrate is lost, this deracemization constitutes a dynamic kinetic asymmetric transformation (DYKAT).



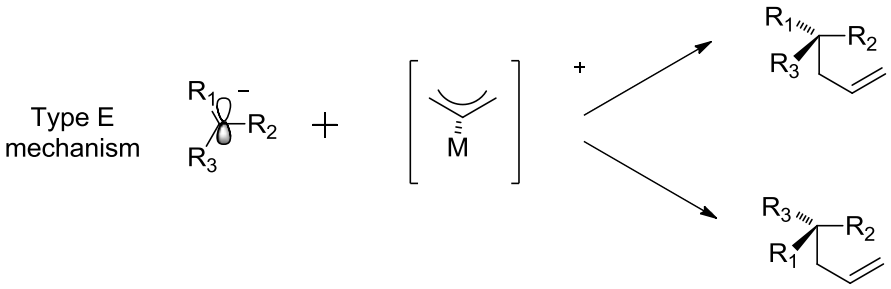
Scheme 2.9

An other exemple of DYKAT (when chiral substrates are used) where the nucleophilic attack is the enantiodiscriminating step is the *type D mechanism*; this is similar to *type A*, but in this case the π–allyl-metal intermediates interconvert faster than they are attacked by a nucleophile and asymmetric induction derives from differential rates of reaction of the two diastereomeric intermediates (**Scheme 2.10**).



Scheme 2.10

Type E Mechanism involves discriminating between the enantiotopic faces of the nucleophile . (**Scheme 2.11**)



Scheme 2.11

2.1.2 State of the art: the Naplephos ligands.

Within previous studies, the research group where this PhD thesis has been developed, contributed to the field of Pd-promoted asymmetric allylic substitution introducing the library of ligands *Naple-phos,* [29] based on D-glucose (**Figure 2.3**). The multifunctional nature of the carbohydrate scaffold is fully employed for a precise tailoring of the ligands: position 2 and 3 display a diphenylphosphinoamide or diphenylphosphinoester arm, essential coordination motif of Trost's privileged ligands based on *trans*-cyclohexanediamine. Positions 4 and 6 are instead useful for phase-tagging the ligands. Accordingly, the ligands were tested in traditional conditions in the Pd-catalysed desymmetrization of *meso*-cyclopent-2-ene-1,4-diol **S1** reported in **Figure 2.3**, a benchmarck reaction for these systems, affording the chiral products in high ees.

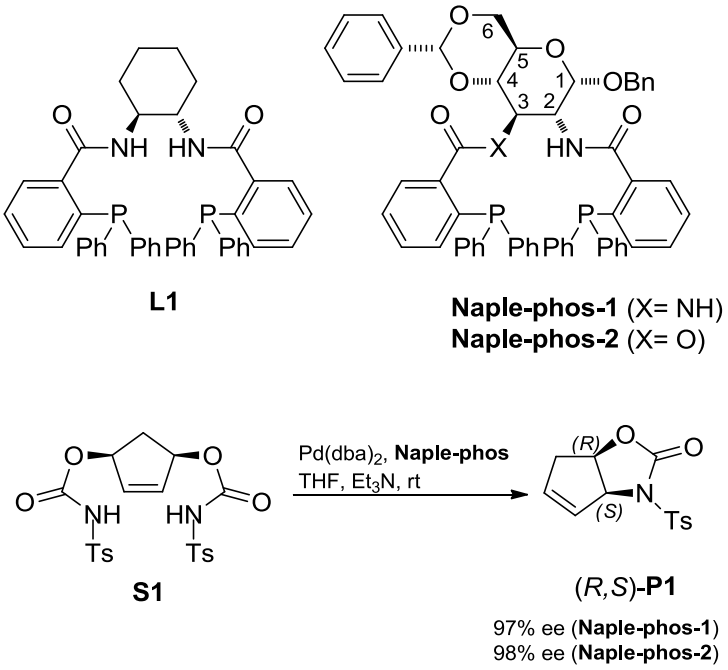


Figure 2.3

This family of ligand was also "tagged" for performing the reaction under alternative conditions [29 b,c,e]. Thus, the polar versions depicted in **Figure 2.4** were prepared and used for the same reaction in the ionic liquid $BMIMBF_4$, aiming to facilitate both separation and re-cycle of the catalyst.

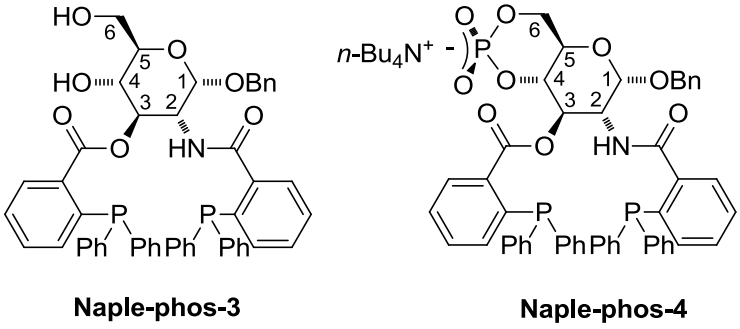
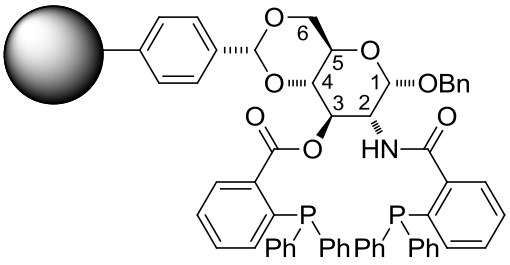


Figure 2.4

Naple-phos-3 and **Naple-phos-4** essentially differ for the conformational rigidity imposed by the functionalization in positions 4 and 6, but both ligands were only moderately selective, and the (*R*,*S*)-product was obtained in 57% ee irrespective of their rigidity. Another result [29c] within the field of multi-phase catalysis was achieved by anchoring **Naple-phos-3** to a commercial Stratosphere-CHO resin through ring positions not involved in coordination, *i.e.* C4 and C6 (**Figure 2.5**).



sup-Naple-phos-3

Figure 2.5

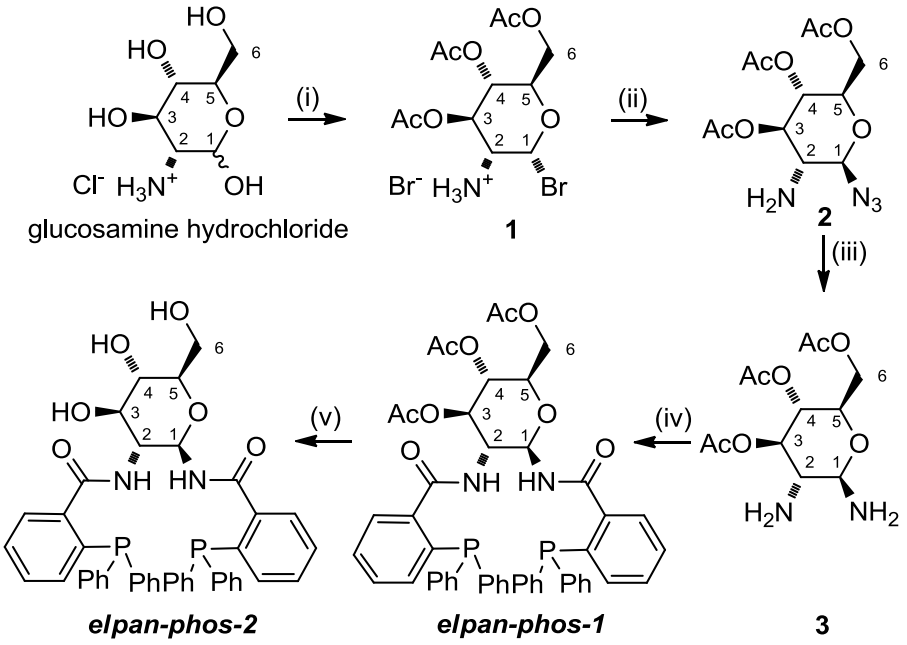
The supported ligand was reacted with a Pd precursor, and the resulting catalyst was examined in the desymmetrization of **S1** according to the scheme of **Figure 2.3**. After each run, the solid was filtered and re-used. Gradual decrease in both activity and selectivity was recorded upon re-cycling.

2.2 The *elpaN-phos* ligands: synthesis and characterization.

In order to validate the strategy of pseudo-enantiomeric ligands (see chapter 1), the *elpaN-phos* library was rationally designed, presenting a specular stereochemistry of coordination related to the *Naple-phos.* According to the strategy mentioned before, within this study pseudo-enantiomeric ligands have been designed and prepared, aiming to produce the same Pd-promoted asymmetric allylic substitution with opposite stereochemistry.

Based on the relative orientations of positions 2 and 3 in *naplephos* ligands, this approach has been pursued by introducing the same essential coordinating motifs in positions 1 and 2, which clearly provide a *pseudo*-enantiomeric coordination environment. It should be noted that **Naple-phos-1** and **elpaN-phos-1** are "truly" pseudo-enantiomeric according to the given definition, whereas in **Naple-phos-2** the original amido linkage in 3 is replaced by an ester. This substitution is important because it greatly simplifies the synthesis of the ligand, without affecting its stereochemical properties.

The very simple synthesis of the ligands **elpaN-phos-1** and **elpaN-phos-2** is reported in **Scheme 2.12**. This involved a new procedure for the ready attainment of the known key-intermediate 3,4,6-tri-*O*-acetyl-1,2-β-glucodiamine **3.** The precursor was the cheap glucosmine hydrochloride, which was treated with acetyl bromide to acetylate the hydroxyl groups, and to functionalize the C1 with a bromide selectively in α position, obtaining **1**. In the second step, an azide group was substituted to the bromide by an Sn2 mechanism, thus obtaining selectively the β anomer **2**. In this way the nitrogen group was in the equatorial position. The reaction was performed using the azidotrimethylsilane as a source of azide and potassium *tert*-butoxide as base and nucleophile that makes the azide available. In the next step, the azide was reduced to amine **3** by a typical Pd promoted hydrogenation. All the steps were almost quantitative and the products were purified by precipitation. Condensation of **3** with two equivalents of diphenylphosphinobenzoic acid (DPPBA) afforded **elpaN-phos-1**, which was highly soluble in common organic solvents, such as dichloromethane, THF and methanol. Treatment of the ligand with methanolic ammonia completely deprotected the acetyl groups, and the corresponding polar form of the ligand (**elpaN-phos-2**) could be obtained. This latter molecule is soluble in alcohols and in the most common ionic liquids, a feature particularly attractive as it allows performing biphasic asymmetric catalysis (see below).

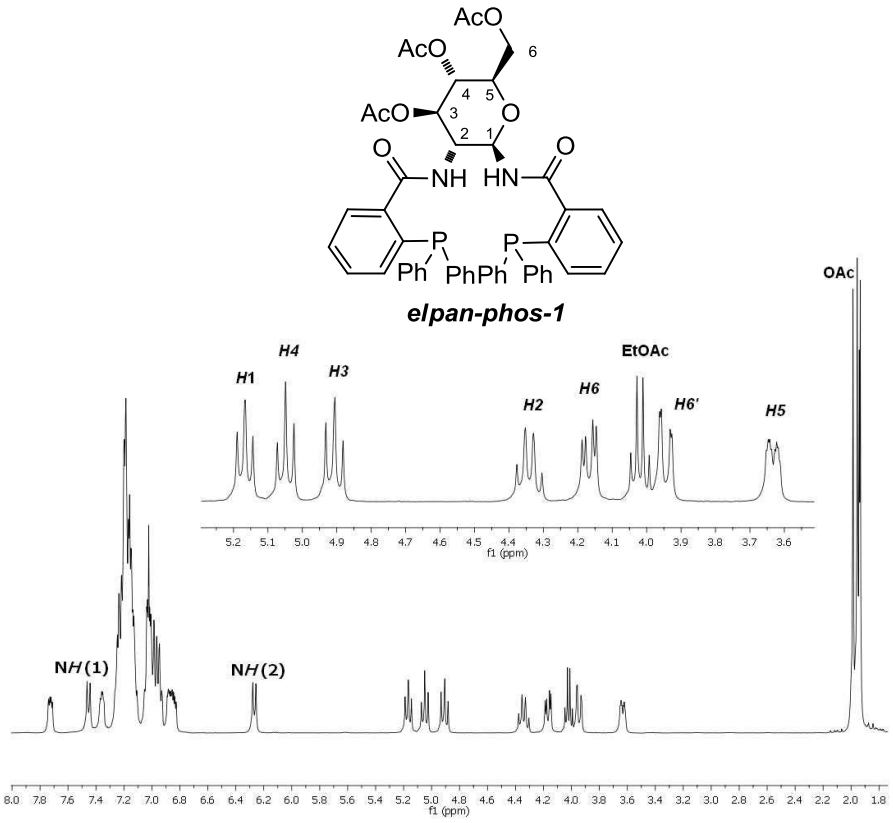


(i) AcOBr; (ii) $TMSN_3$, *t*BuOK, THF (iii) H_2, Pd/C, AcOEt;
(iv) DPPBA, DCC, DMAP, THF; (v) NH_3, MeOH

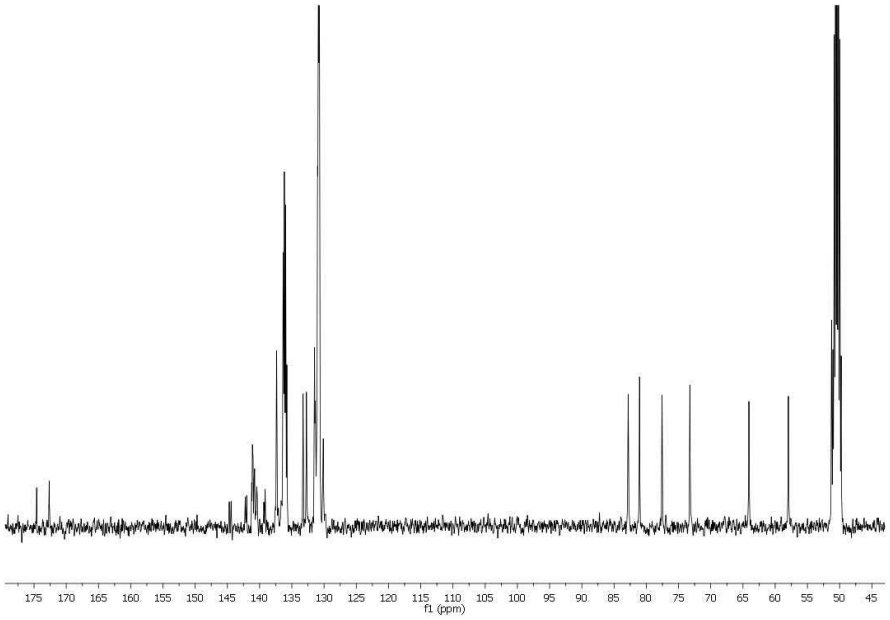
Scheme 2.12

The two ligands were fully characterized by ^{1}H, ^{13}C and ^{31}P NMR spectroscopy, in order to confirm their structure and purity. The spectra are shown below.

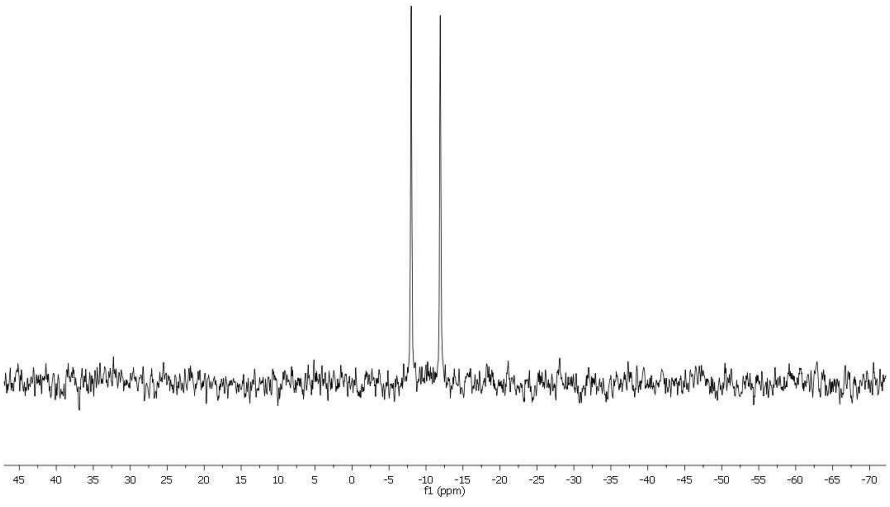
^{1}H NMR spectrum of elpan-phos-1, 400 MHz, $CDCl_3$



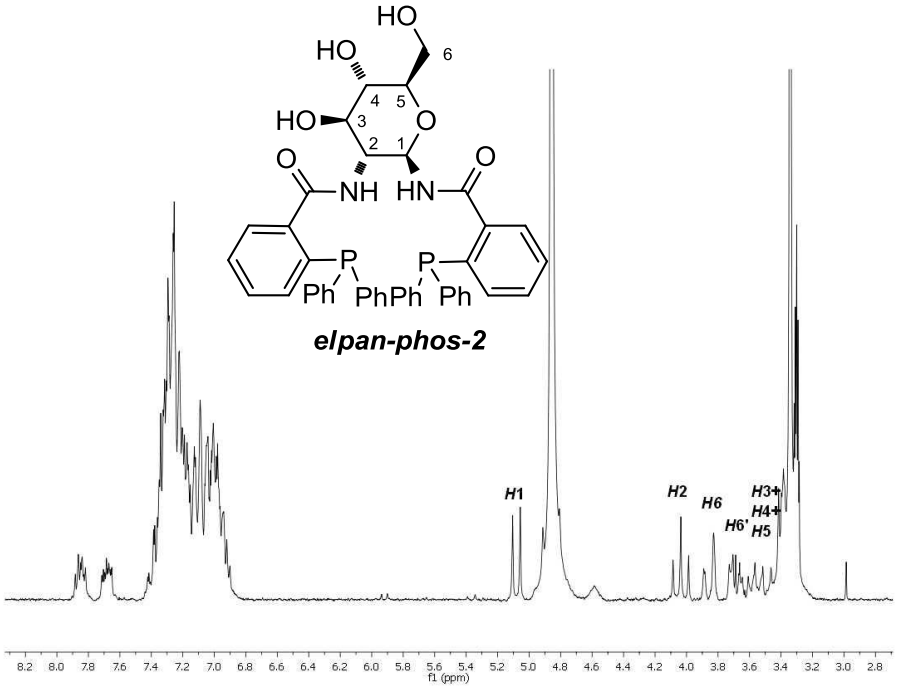
^{13}C NMR spectrum of elpan-phos-1, 100 MHz, $CDCl_3$



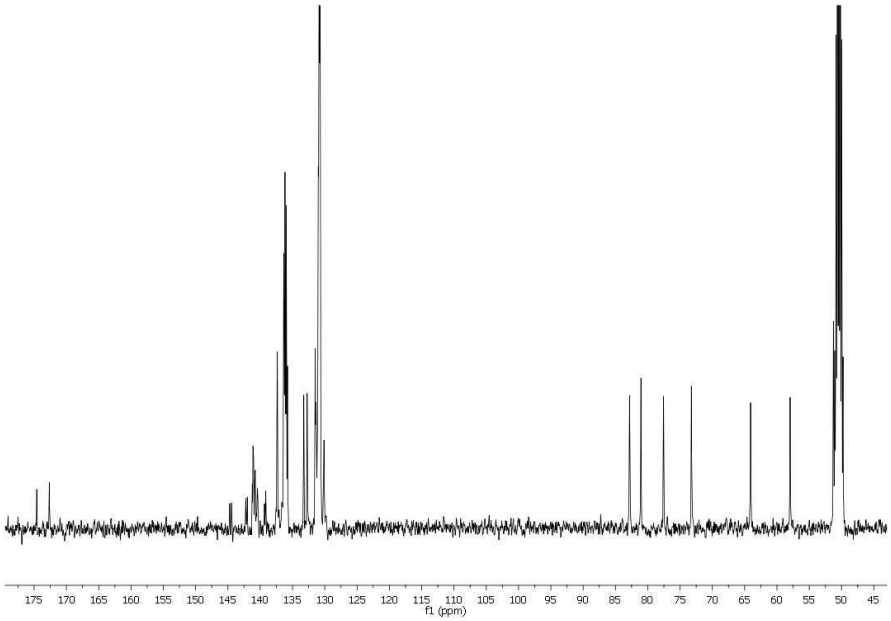
^{31}P NMR spectrum of elpan-phos-1, 162 MHz, $CDCl_3$



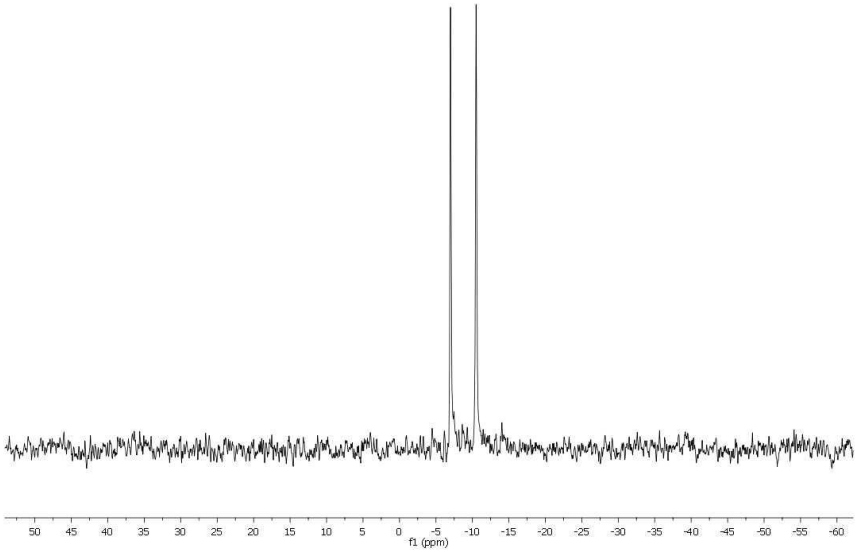
^{1}H NMR spectrum of elpan-phos-1, 400 MHz, $CDCl_3$



^{13}C NMR spectrum of elpan-phos-1, 100 MHz, $CDCl_3$



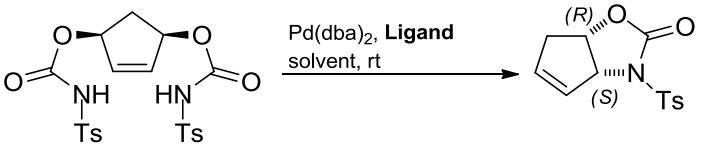
^{31}P NMR spectrum of elpan-phos-1, 162 MHz, $CDCl_3$



2.3 Catalytic performances of the *elpaN-phos* ligands in the Pd promoted Asymmetric Allylic Substitution.

2.3.1 Intramolecular reaction

Both *elpaN-phos* ligands represent the specular counterpart of *naplephos* family and, therefore, they were examined in the previously mentioned asymmetric desymmetrization of **S1** for useful comparison. This intramolecular allylic substitution affords the key precursors of mannostatines, and is also a standard test for the assessment of the stereo-orienting properties of new ligands [31]. Within this preliminary investigation, influence of temperature and additives on the catalysts performance was assessed (**Table 2.1**).



S1 (*S*,*R*)-**P1**

N°	ligand	T (K)	solvent	time	conversion[b]	ee(%)[c] +(*S*,*R*)-**P1**
1	**elpaN-phos-1**	298	THF[d]	5’	>99%	95
2	**elpaN-phos-1**	273	THF[d]	15’	>99%	95
3	**elpaN-phos-1**	258	THF[d]	30’	92%	96
4	**elpaN-phos-1**	298	THF	30’	>99%	84
5	**elpaN-phos-1**	273	THF	30’	>99%	86
6	**elpaN-phos-1**	258	THF	30’	>99%	86
7	**elpaN-phos-2**	298	THF[d]	5’	>99%	96
8	**elpaN-phos-2**	298	$bmpyBF_4$[e]	30’	>99%	94
9	**elpaN-phos-2**	298	$bmpyBF_4$[e] I recycle	30’	>99%	89
10	**elpaN-phos-2**	298	$bmpyBF_4$[e] II recycle	30’	>99%	79
11	**elpaN-phos-2**	298	$bmimBF_4$[e]	30’	>99%	90
12	**elpaN-phos-2**	298	$bmimBF_4$[e] I recycle	30’	>99%	81
13	**elpaN-phos-2**	298	$bmimBF_4$[e] II recycle	30’	>99%	77

[a]Catalyst:substrate 1:20. [b]Determined by NMR spectra of the crude reaction mixtures. [c]Determined by HPLC on Chiracel OD-H, using 2-propanol/hexane 1:10, 1.0 mL/min, UV (254 nm), (–)-(*R*,*S*)-**P1**: 22–24 min; (+)-(*S*,*R*)-**P1**: 30–32 min. [d] Triethylamine as additive. [e]Catalyst:substrate 1:10. Triethylamine as additive.

Table 2.1

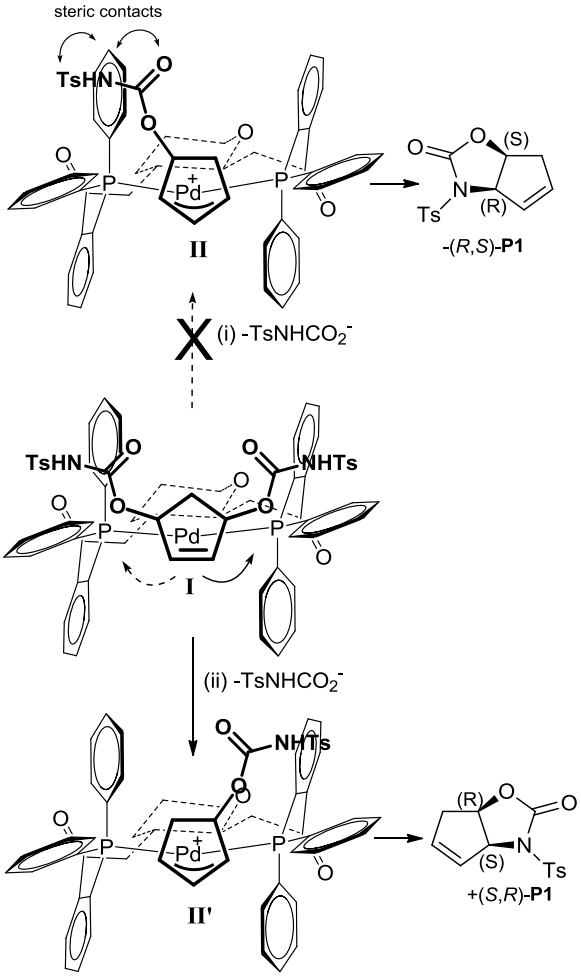
The following should be observed:

(i) as desired, *elpaN-phos* ligands produced preferential formation of the opposite enantiomer with respect to N*aple-phos* ligands, +(*S*,*R*)-**P1** *vs* -(*R*,*S*)-**P1**.

(ii) in THF (entries 1-7), the reaction proceeded in high yield within short reaction times.

(iii) the marked beneficial influence of an added base was demonstrated [31e]: the ee of the reaction increased in the presence of triethylamine (entry 1 *vs* 4 or 2 *vs* 5 or 3 *vs* 6).

(iv) lowering the temperature from 298 to 258 K poorly influenced the enantioselectivity, with a little favorable effect. Thus, the optimal reaction conditions were found at 298 K in the presence of triethylamine, which allowed the attainment of the product *within only 5'* in 95-96% ee with both ligands (entries 1 and 7). This also demonstrates that the presence of diverse phase-tags has no effects on the stereochemistry of the reaction.
The stereochemical outcome of the reaction can be clearly explained on the basis of the mechanism proposed by Trost for this reaction.[31a] In our case, his cartoon models can be translated as in **Scheme 2.13**, where, of the sugar moiety, only the chair has been reported for sake of clarity. The rate limiting step is the activation of one carbammate in **I** to give a π-allyl intermediate (**II** or **II'**). Activation of the "left" carbammate function (step i) leads to the attainment of **II**, which then results in -(*R*,*S*)-**P1**, while activation of the "right" function (step ii) preludes to the achievement of +(*S*,*R*)-**P1**. Both reactions occur with simultaneous rotation of the five-member ring, which is clearly inhibited by steric contacts only in the case of the clockwise rotation (i) which accompanies formation of **II**.



Scheme 2.13

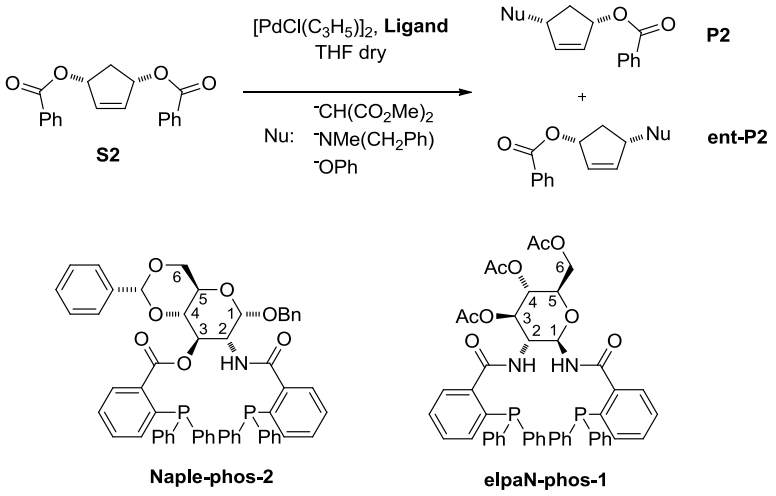
(v) finally, according to our assumption, the presence of free hydroxyls in *enpalphos-a'* allowed the catalytic study in ionic liquids,[2] where the original Trost ligand based on *trans*-cyclohexanediamine does not show appreciable solubility.

[2] Two convenient ionic liquids were used: 1-butyl-3-methylimidazolium tetrafluoroborate (bmimBF_4) and 1-butyl-4-methylpyridinium tetrafluoroborate (bmpyBF_4).

The reactions were performed by adding the substrate and triethylamine to a solution of the catalyst at 298 K. After 30 minutes the organic product was extracted with diethyl ether and analyzed. The catalyst phase was re-cycled for further runs. In $bmpyBF_4$, the first run quantitatively afforded the chiral product in high ee (94%, entry 8), which is the highest value reported so far [29a,c] for this reaction under unconventional conditions. In the subsequent recycles the conversion was still high (entries 9 and 10), and, as rarely observed in ionic solvents for AAA,[32] the enantioselectivity only slightly decreased. After the second re-cycle, the catalytic solution was left aside, and *24 hours later*, fresh substrate was added to the resting catalyst. Notably, the product was again obtained in quantitative yield and with significant ee (55%).
Similar general behavior was observed in $bmimBF_4$, where the ee were comprised within 90 and 77% ee.

2.3.2 Intermolecular reaction

The pseudoenantiomeric ligands **elpaN-phos-1** and **Naple-phos-2** were also tested in the desymmetrization of *cis*-4-ciclopenten-1,3-dibenzoate **S2**, using different nucleophile in order to explore the scope of these ligands in the C-C, C-N and C-O bond formation (**Scheme 2.14**).



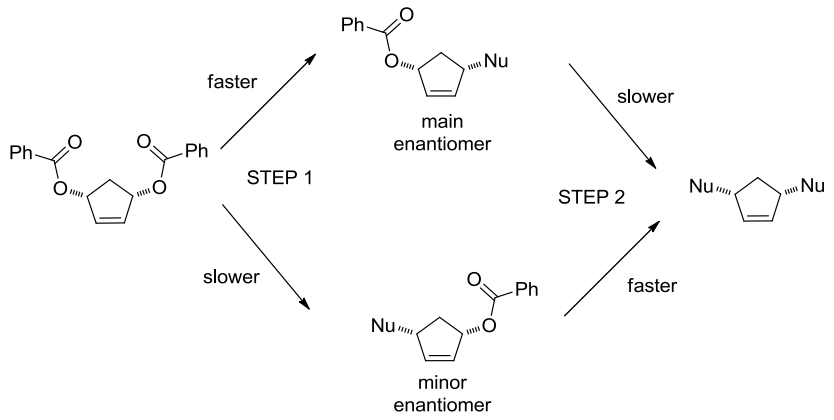
Scheme 2.14

A preliminary screening was performed, in order to set up the reaction conditions, using **Naple-phos-2** as ligand and dimethylmalonate as nucleophile. (**Table 2.2**). Both decreasing the temperature to 0°C and the nucleophile/substrate ratio strongly increased ee and influenced selectivity. Moreover, the only difference of energy between diastereoisomeric pathways of reaction cannot explain such a difference of enantioselectivity for the two different temperatures [33]; this behaviour was clarified by Trost [17], assuming that the minor enantiomer obtained in the first nucleophilic attack react faster in a second attack, because the favoured leaving group is available for ionization (**Scheme 2.15**). This enhances the ee for the main enantiomer but decreases the yield for increasing reaction times. Moreover, this phenomenon explains the better selectivity and the lower ee for a higher substrate/nucleophile ratio (entry 2 vs 3).

N°	Substrate/ Nucleofile	T (K)	Time (min)	Conversion[a] (%)	Selectivity[b] (%)	Yield (%)	ee (1*R*,4*S*) (%)[c]
1	1/2.8	298	10	>99	11	11	87
2	1/2.8	273	10	>99	40	40	>99
3	1/1	273	40	67	>99	67	90

Reaction conditions: THF dry, 0.27 mmol of substrate, 0.27 or 0.75 mmol of dimethylmalonate, 0.75 mmol of NaH, 0.0054 mmol of $[Pd(Cl)(\eta^3\text{-}C_3H_5)]_2$, 0.016 mmol of **Naple-phos-2**. [a] Determined by ^{1}HNMR spectroscopy on the crude of reaction [b] Expressed as percent of monosubstituted product over the total mono- and disubstituted product; determined by ^{1}HNMR spectroscopy on the crude of reaction [c] Determined by HPLC on Chiracel OD-H, using 2-propanol/hexane 1:99, 1.0 mL/min, UV (254 nm), rt: (1*R*,*4S*) 15.6 min, (1*S*,*4R*) 17.2 min.

Table 2.2



Scheme 2.14

The rection conditions which maximized the yield, in particular the ratio substrate/nucleophile = 1/1, were used for the screening of nucleophiles with the two pseudoenantiomeric ligands (**Table 2.3**). As expected, **Naple-phos-2** and **elpaN-phos-1** induced opposite enantioselectivity, but in all cases the latter one resulted in better selectivity for all the nucleophiles.

(i) Satisfactory results were achieved with dimethylmalonate (entry 1 and 2), but a drop of yield was observed for the *Naple* ligand.

(ii) The two ligands shown similar performances with N-benzylmethylamine, as expected on the basis of the literature (entry 3 and 4). [35]

(iii) The performances of the ligands were unsatisfactory for the phenol (entry 5 and 6), probably because the the *Pd^0-catalyzed alkyl exchange* is competitive with the slow nucleophilic attack, and this allow epimerization of the allyl complex.

N°	Ligand	Nucleophile	T (K)	t (h)	Conv.[a] (%)	Seletivity[b] (%)	ee% [c]
1[d]	**Naple-phos-2**	$CH_2(CO_2Me)_2$	273	0.67	67	>99	90 (1*R*,4*S*)[e]
2[d]	**elpaN-phos-1**	$CH_2(CO_2Me)_2$	273	0.67	25	>99	71 (1*S*,4*R*)[e]
3[f]	**Naple-phos-2**	$NH(Me)CH_2Ph$	273	2.5	80	>99	74(-)[g]
4[f]	**elpaN-phos-1**	$NH(Me)CH_2Ph$	273	2.5	84	>99	72(+)[g]
5[h]	**Naple-phos-2**	PhOH	303	16	56	>99	36(-)-(1*S*,4*R*)[i]
6[h]	**elpaN-phos-1**	PhOH	303	16	50	>99	0

[a] Determined by ^{1}HNMR spectroscopy on the crude of reaction [b] Expressed as percent of monosubstituted product over the total mono- and disubstituted product; determined by ^{1}HNMR spectroscopy on the crude of reaction. [c] Determined by HPLC on Chiracel OD-H, using 2-propanol/hexane 1:99, 1.0 mL/min, UV 254 nm. [d] Reaction conditions: THF dry, 0.27 mmol of substrate, 0.27 of nucleophile, 0.27 mmol of NaH, 0.0054 mmol of $[Pd(Cl)(\eta^3\text{-}C_3H_5)]_2$, 0.016 mmol of **Ligand.** [e] rt: (1*R*,4*S*) 15.6 min, (1*S*,4*R*) 17.2 min. [f] Reaction conditions: THF dry, 0.27 mmol of substrate, 0.27 of nucleophile, 0.27 mmol of NEt_3, 0.0054 mmol of $[Pd(Cl)(\eta^3\text{-}C_3H_5)]_2$, 0.016 mmol of **Ligand.** [g] rt: (-) 9.73 min, (+) 13.2 min- [h] Reaction conditions: THF dry, 0.27 mmol of substrate, 0.27 of nucleophile, 0.27 mmol of NaH, 0.0054 mmol of $[Pd_2(dba)_3CHCl_3]$, 0.016 mmol of **Ligand.** [i] rt: (+)-(1*R*,4*S*) 10.7 min, (-)-(1*S*,4*R*) 18.4 min. absolute configuration assigned on the basis of the literature [34].

Table 2.3

2.4 Conclusion.

In conclusion, this work substantiates the strategy aimed at preparing effective ligands in a simple way from the chiral pool. Thus, the *elpanphos* library was designed by starting from convenient glucosamine hydrochloride, proving to be much more viable compared to species otherwise accessible only from the expensive L series.

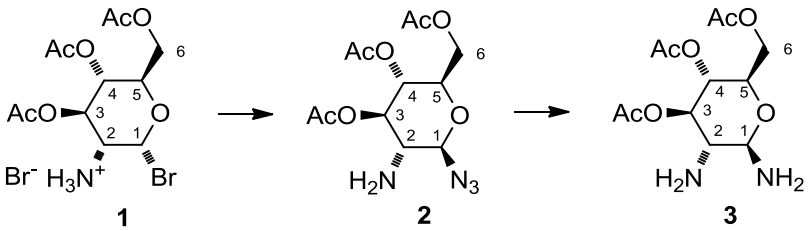
Furthermore, the natural presence of polar phase-tags in the multifunctional [36] sugar structure allowed to perform the same asymmetric process in ionic liquids and with unprecedented enantioselectivity.

2.5 Experimentals.

2.5.1 General Considerations:

NMR spectra were recorded in $CDCl_3$ ($CHCl_3$, δ = 7.26 ppm, and $^{13}CDCl_3$ δ = 77 ppm, as internal standards) with a 200 MHz (Varian Model Gemini) and a 400 MHz (Bruker DRX-400). ^{31}P NMR experiments were carried out by using aqueous 85% phosphoric acid as external reference (δ = 0 ppm). Specific optical rotatory powers [α] were measured with a Perkin–Elmer Polarimeter (model 141) at 298 K and 589 nm in chloroform or in methanol (c = 1.0 g/100 mL). THF was distilled from $LiAlH_4$, dichloromethane from CaH_2, diethyl ether from Na.

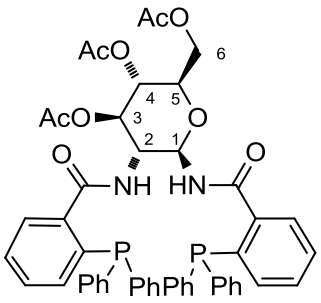
2.5.2 Preparation of 3,4,6-Tri-O-acetyl-β-1,2-D-diamineglucose (**3**):



a solution of 1-bromo-3,4,6-tri-*O*-acetyl-α- d-glucosamine hydrobromide (**1**) (2.0 g, 4.5 mmol) in THF (50 mL) was treated with $TMSN_3$ (0.59 mL, 4.5 mmol) and *t*BuOK (2.1 eq, 1.1 g, 9.5 mmol). After stirring for 18 h, KBr was filtrated and the solvent was removed under vacuum. The residue was dissolved in DCM (2.0 mL) and filtrated over celite. Hexane was added to precipitate 1-azido-3,4,6- tri-*O*-acetyl-β-d-glucosamine (**2**) as a yellow solid in quantitative yield. The compound was dissolved in ethyl acetate (10 mL)

in the presence of 10% Pd/C (0.18 g) and treated with H2 (1 atm) for 1.5 h. After filtration, the solvent was removed under vacuum to afford pure 3,4,6-tri-*O*acetyl-β-1,2-D-diamineglucose (**3**) in quantitative yield.

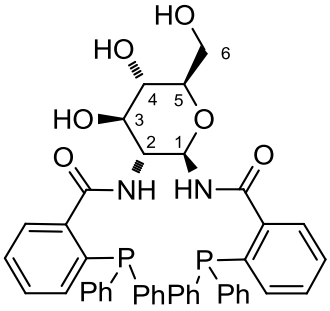
*2.5.3 Preparation of e**lpan-phos-1**:*



elpan-phos-1

A solution of 3,4,6-tri-*O*-acetyl-β-1,2-D-diamineglucose (**3**) (0.61 g, 2.0 mmol), diphenylphosphanylbenzoic acid (1.2 g, 2.0 mmol), 4-dimethylaminopyridine (0.49 g, 4.0 mmol) and 1,3-dicyclohexylcarbodiimide (0.82 g, 4.0 mmol) in dry dichloromethane (10 mL) was stirred for 18 h at room temperature under inert atmosphere to afford a suspension. The residue was removed by filtration. The resulting solution was evaporated under vacuum, and the residue was chromatographed on silica gel (2:1 ethyl acetate: hexane) to afford the pure product as a white solid (1.2 g, 72%). $C_{50}H_{46}N_2O_9P_2$ (880.87): calcd. C 68.18, H 5.26, N 3.18; found C68.72, H 5.34, N 3.35. [α] = 3.5 (*c* 1.0, $CHCl_3$). ^{1}H NMR: δ_H = 7.85 (m, 1 H), 7.58 (d, $^3J_{NH\text{-}H1}$=9.0Hz, 1 H, N*H*), 7.47 (m, 1 H), 7.36-6.97(m, 26 H), 6.37 (d, $^3J_{NH\text{-}H2}$=8.5Hz, 1H, N*H*), 5.29 (t, $^3J_{H1\text{-}NH}$=$^3J_{H1\text{-}H2}$, 1H, 1-H), 5.18(t, $^3J_{H4\text{-}H3}$=$^3J_{H4\text{-}H5}$=9.5 Hz; 1 H, 4-H), 5.02 (t, $^3J_{H2\text{-}H3}$=$^3J_{H3\text{-}H4}$, 1H, 3-H), 4.47 (q, 1H, 2-H), 4.17 (dd, $^3J_{H6\text{-}H5}$=4.11 Hz, $^2J_{H6\text{-}H6'}$=12.4 Hz, 1H, 6-H), 3.94 (dd, $^3J_{H6'\text{-}H5}$=1.86, 1H, 6'-H), 3.63 (m, 1H, 5-H), 1.99 (s, 3H, AcO), 1.96 (s, 3H, AcO), 1.93 (s, 3H, AcO)ppm. ^{13}C NMR: δ_c =172.3, 171.2, 170.8, 169.7, 168.8, 141-127 (aromatici), 80.8, 73.8, 73.3, 68.14, 62.2, 53.9, 21.4, 21.2, 21.0 ppm. ^{31}P NMR: δ_P= -8.0, -12.0 ppm.

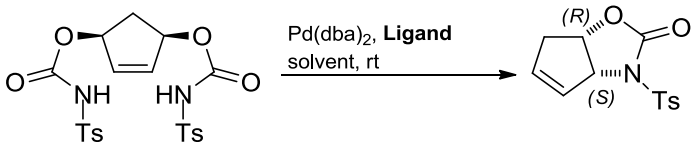
*2.5.4 Preparation of e**lpan-phos-2**:*



elpan-phos-2

Preparation of Elpanphos-a_: A solution of elpanphos-a (0.44 g, 0.50 mmol) in methanol (5 mL) was saturated with gaseous ammonia. After a few hours, addition of diethyl ether (50 mL) caused
precipitation of the product as a white solid, which was filtered, washed with diethyl ether and dried under vacuum (0.30 g, 80%). C44H40N2O6P2 (754.76): calcd. C 70.02, H 5.34, N 3.71; found C
69.77, H 5.41, N 3.59. [α] = 10.5 (*c* 1.0, MeOH). ^{1}H NMR: δ_H = 7.85 (m, 1 H), 7.70 (m, 1 H), 7.5-6.9(m, 26 H), 5.09 (d, $^{3}J_{H1-H2}$=9.7Hz, 1H, 1-H), 4.05 (t, $^{3}J_{H3-H2}$=9.9Hz, 1H, 2-H), 3.87(d, $^{2}J_{gem}$=12.5 Hz, 1 H, 6-H), 3.71 (dd, $^{3}J_{H6'-H5}$=4.9Hz, 1H, 6'-H), 3.65-3.30 (m, 3H, 3-H, 4-H, 5-H)ppm. ^{13}C NMR: δ_c = 174.6, 172.6, 145-130 (aromatici), 82.8, 81.0, 77.6, 73.2, 64.1, 58.0 ppm. ^{31}P NMR: δ_P = -7.0, -10.5 ppm.

*2.5.5 Desymmetrization of meso-2-Cyclopenten-1,4-diol-isocyanate (**S1**) in THF:*



S1 (*S,R*)-**P1**

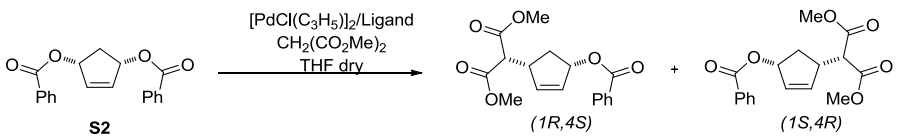
Without NEt_3: meso-2-cyclopenten-1,4-diol-isocyanate (**S1**) (0.10 g, 0.20 mmol), $[Pd_2(dba)_3]\cdot CHCl_3$ (0.005 g, 0.005 mmol) and the ligand (0.015 mmol) were dissolved in dry THF (1 mL). The mixture was stirred at the desired temperature, and, after the required reaction time, the solvent was removed under vacuum. Column chromatography on silica gel (1:2 ethyl acetate/hexane) gave the desired product as a white solid in 80–85% yield.

With NEt3: meso-2-cyclopenten-1,4-diol-isocyanate (**S1**) (0.10 g, 0.20 mmol), $[Pd_2(dba)_3]\cdot CHCl_3$ (0.005 g, 0.005 mmol) and the ligand (0.015 mmol) were dissolved in dry THF (1 mL) containing triethylamine (0.030 g, 0.30 mmol). The mixture was stirred at the desired temperature, and, after the required reaction time, the solvent was removed under vacuum. Column chromatography on silica gel (1:2 ethyl acetate/hexane) gave the desired product as a white solid in 80–85% yield.

In RTIL: *meso*-2-cyclopenten-1,4-diol-isocyanate (**S1**) (0.050 g, 0.10 mmol), $[Pd_2(dba)_3]\cdot CHCl_3$ (0.005 g, 0.005 mmol) and **elpan-phos- 2** (0.012 g, 0.015 mmol) were vigorously stirred in RTIL (1 mL) under an inert atmosphere. After 30 min, the product was extracted with dry diethyl ether (3X15 mL) in 70–80% yield and analyzed. Recycling was carried out by adding fresh substrate and triethylamine to the active catalytic solution.

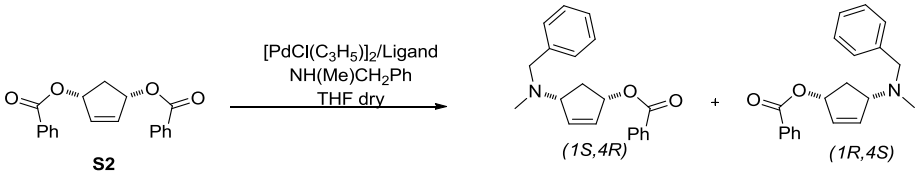
The enantiomeric excesses were determined by chiral HPLC, Chiracel OD-H, 1:10 2-propanol/hexane, UV 254 nm, retention times: (–)-(*R*,*S*)-2: 22–24 min; (+)-(*S*,*R*)-2: 30–32 min. The absolute configuration was obtained by comparison with a sample of known chirality.

*2.5.6 General procedure for the asymmetric allylic substitution of cis-4-ciclopenten-1,3-dibenzoate (**S2**) with dimethylmalonate:*



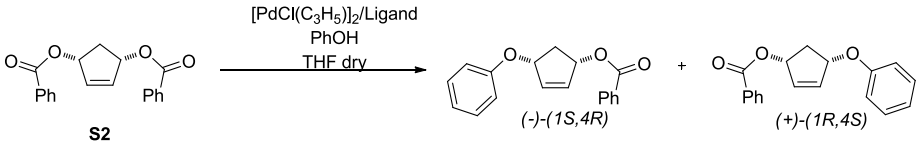
A solution of $[Pd(\mu\text{-}Cl)(\eta^3\text{-}C_3H_5)]_2$ (0.0020 g, 0.0054 mmol), the ligand (0.016 mmol) and *cis*-4-ciclopenten-1,3-dibenzoate (0.083 g, 0.27 mmol) in 1.0 mL of dry THF were stirred at 0°C for 0.2h under inert atmosphere. A solution of dimethylmalonate (31 μL, 0.27 mmol) and NaH (0.011 g) in 2.0 mL of the same solvent at 0°C was added. After the desired time, the reaction was quenched by addition of methanol. Column chromatography on silica gel (1/2 ethyl acetate/hexane) gave the desired product as a white solid in 80–85% yield. The enantiomeric excesses were determined by chiral HPLC, Chiracel OD-H, 1:99 2-propanol/hexane, UV 254 nm, 1.0 mL/min, retention times: (1*R*,*4S*) 15.6 min, (1*S*,*4R*) 17.2 min. The absolute configuration was obtained by comparison with a sample of known chirality.

*2.5.7 General procedure for the asymmetric allylic substitution of cis-4-ciclopenten-1,3-dibenzoate (**S2**) with N-benzylmethylamine:*



A solution of $[Pd(\mu\text{-}Cl)(\eta^3\text{-}C_3H_5)]_2$ (0.0020 g, 0.0054 mmol), the ligand (0.016 mmol) and *cis*-4-ciclopenten-1,3-dibenzoate (**S2**) (0.083 g, 0.27 mmol) in 1.0 mL of dry THF were stirred at 0°C for 0.2h under inert atmosphere. A solution of N-benzylmethylamine (35 μL, 0.27 mmol) and triethylamine (85 μL) in 2.0 mL of the same solvent at 0°C was added. After the desired time, the reaction was quenched by addition of 6.0mL of diethyl ether and 5mL of a solution of NaOH 2.0M. The organic phase was separated and extracted with a solution of $NaHCO_3$ (sat, 1x5 mL), water (1X5mL) and brine (1X5mL), then anhydrified with sodium sulphate. Column chromatography on silica gel (1/4 ethyl acetate/hexane) gave the desired product as a white solid in 80–85% yield. The enantiomeric excesses were determined by chiral HPLC, Chiracel OD-H, 1:99 2-propanol/hexane, UV 254 nm, 1.0 mL/min, retention times: (-) 9.73 min, (+) 13.2 min.

*2.5.8 General procedure for the asymmetric allylic substitution of cis-4-ciclopenten-1,3-dibenzoate (**S2**) with phenol:*



A solution of $[Pd(\mu\text{-}Cl)(\eta^3\text{-}C_3H_5)]_2$ (0.0020 g, 0.0054 mmol), the ligand (0.016 mmol) and *cis*-4-ciclopenten-1,3-dibenzoate (**S2**) (0.083 g, 0.27 mmol) in 1.0 mL of dry THF were stirred at 30°C for 0.2h under inert atmosphere. A solution of N-benzylmethylamine (35 μL, 0.27 mmol) and NaH (0.011 g) in 2.0 mL of the same solvent at 30°C was added. After the desired time, solvent was evaporated. Column chromatography on silica gel (1/20 ethyl acetate/hexane) gave the desired product as a white solid in 80–85% yield. The enantiomeric excesses were determined by chiral HPLC, Chiracel OD-H, 1:99 2-propanol/hexane, UV 254 nm, 1.0 mL/min, retention times: (+)-(1*R*,*4S*) 10.7 min, (-)-(1*S*,*4R*) 18.4 min. The absolute configuration was obtained on the basis of the optical rotatory power.

2.6 References.

[1] Tsuji, J.; et al; *Tetrahedron Lett.* **1965**, *6*, 4387.
[2] Atkins, K. E.; et al; *Tetrahedron Lett.* **1970**, *11*, 3821.
[3] Hata, G.; et al; *J Chem Soc D, Chem. Commun.* **1970**,1392.
[4] Trost, B. M.;, Strege, P. E.; *J. Am. Chem. Soc.* **1977**, *99*, 1649.
[5] Trost, B. M.; Lautens, M.; *J. Am. Chem. Soc.* **1982**, *104*, 5543.
[6] Trost, B. M.; Hung, M. H.; *J. Am. Chem. Soc.* **1983,** *105*, 7757.
[7] Takeuchi, R.; Kashio, M. *Angew. Chem. Int. Ed*. **1997**, *36*, 263.
[8] Tsuji, J.; et al; *Tetrahedron Lett.* **1984**, *25*, 5157.
[9] Zhang, S.; et al; *J. Organomet. Chem.* **1993**, *450*, 197.
[10] Kurosawa, H.; *J. Chem. Soc., Dalton Trans*. **1979**, 939.
[11] (a) Cuvigny, T.; Julia, M.; *J. Organomet. Chem.* **1983**, *250*, C21. (b) Consiglio, G.; et al;

J. Chem. Soc., Chem. Commun. **1983**, 112.
[12] Fouquet, G.; Schlosser, M.; *Angew. Chem. Int. Ed.* **1974**, *13*, 82.
[13] Roustan, J. L.; et al; *Tetrahedron Lett.* **1979**, *20*, 3721.
[14] Auburn, P. R.; et al; *J. Am. Chem. Soc.* **1985**, *107*, 2033.
[15] (a) Trost, B. M.; Crawley, M. L.; *Chem. Rev.* **2003**, *103*, 2921. (b) Trost, B. M.; *J. Org. Chem.* **2004**, *69*, 5813. (c) Trost, B. M.; *Acc. Chem. Res.* **1996**, *29*, 355. (d) Pfaltz, A.; Lautens, M. (1999) *Allylic substitution reactions*. In: Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H.; (eds) *Comprehensive asymmetric catalysis.* Springer, Heidelberg **1999**.
[16] (a) Rieck, H.; Helmchen, G.; *Angew. Chem.* **1995**, *107*, 2881. (b) Rieck, H.; Helmchen, G.; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2687. (c) Genêt, J-P.;, Grisoni, S.; *Tetrahedron Lett*. **1988**, *29*, 4543.
[17] Trost, B. M.; Van Vranken, D. L.; *Chem. Rev.* **1996**, *96*, 395.
[18] Trost, B. M.; *Chem. Pharm. Bull.* **2002**, *1*, 14.
[19] Godleski, S. A.; In: Trost, B. M.; Fleming, I.; Semmelhack, M. F.; (eds) *Comprehensive organic synthesis.* **1991**, Pergamon, Oxford, vol 4, chap 3.3.
[20] (a) Tsuji, J.; *Pure Appl. Chem.* **1986**, *58*, 869. (b) Tsuji, J.; *Tetrahedron* **1986**, *42*, 4361. (c) Tsuji, J.; *J. Organomet. Chem.* **1986**, *300*, 281.
[21] Sennhenn, P.; Gabler, B.; Helmchen, G.; *Tetrahedron Lett.* **1994**, *35*, 8595.
[22] (a) Lloyd-Jones, G. C.; Pfaltz, A.; *Angew. Chem.* **1995**, *107*, 534. (b) Lloyd-Jones, G. C.; Pfaltz, A.; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 462. (c) Lloyd-Jones, G. C.; Pfaltz, A.; *Z Naturforsch B* **1995**, *50*, 361.
[23] (a) Ma, S.; Lu, Z.; *Angew. Chem. Int. Ed. Engl.* **2008**, *47*, 258. (b) Milhau, L.; Guiry, P. J.; *Palladium-Catalyzed Enantioselective Allylic Substitution* in Kazmaier, U.; (ed) *Transition Metal Catalyzed Enantioselective Allylic Substitution in Organic Synthesis* **2012** Top Organomet Chem *38*, 95. Springer-Verlag Berlin Heidelberg.
[24] (a)Trost, B. M.; Brennan, M. K.; *Org. Lett*. **2006**, *8*, 2027. (b) Trost, B. M.; Lemoine, R. C.; *Tetrahedron Lett*. **1996**, *37*, 9161. (c) Trost, B. M.; Toste, F. D.; *J. Am. Chem. Soc.* **1998**, *120*, 9074.
[25] (a) Tsuji, J.; *Organic synthesis with palladium compounds.* **1980**, Springer, Berlin Heidelberg
New York. (b) Trost, B. M.; Verhoeven, T. R.; In: Wilkinson, G.; Stone, F. G.; Abel, E. W.; (eds) *Comprehensive organometallic chemistry*. **1982**, Pergamon, Oxford, chap 8. (c) Frost, C. G.; Howarth, J.; Williams, J. M. J.; *Tetrahedron Asymmetry* **1992** *3*, 1089. (d) Tsuji, J.; *Palladium Reagents and*

Catalysts, Innovations in Organic Synthesis. **1995** Wiley, Chichester. (e) Heumann, A.; In: Beller, M.; Bolm, C.; (eds) *Transition metals for organic synthesis.* **1998** Wiley-VCH, Weinheim, vol 1, chap 2.15. (f) Consiglio, G.; Waymouth, R. M.; *Chem. Rev.* **1989** *89*, 257. (g) Hayashi, T.; In: Ojima, I.; (ed) *Catalytic asymmetric synthesis*. **1993** VCH, New York, chap 7.1.

[26] (a) Hansson, S.; Norrby, P.-O.; Sjögren, M. P. T.; Åkermark, B; Cucciolito, M. E.; Giordano, F.; Vitagliano, A.; *Organometallics* **1993** *12*, 4940. (b) Burckhardt, U.; Baumann, M.; Trabesinger, G.; Gramlich, V.; Togni, A.; *Organometallics* **1997** *16*, 5252. (c) Burckhardt, U.; Baumann, M.; Togni, A.; *Tetrahedron Asymmetry* **1997** *8*, 155.

[27] Brown, J. M.; Hulmes, D. I.; Guiry, P. J.; *Tetrahedron* **1994** *50*, 4493.

[28] Trost, B. M.; Machacek, M.; Aponick, A.; *Acc. Chem. Res.* **2006**, *39*, 747.

[29] (a) Benessere, V.; Ruffo, F.; *Tetrahedron. Asymm.* **2010**, *21*, 171. (b) Benessere, V.; Lega, M.; Ruffo, F.; Silipo, A.; *Tetrahedron* **2011**, *67*, 4826. (c) Benessere, V.; De Roma, A.; Ruffo, F. *ChemSusChem* **2008**, *1*, 425. (d) De Roma, A.; Ruffo, F.; Woodward, S. *Chem. Commun* **2008**, 5384. (e) Benessere, V.; De Roma, A.; Del Litto, R.; Lega, M.; Ruffo, F.; *Eur. J. Org. Chem.* **2011,** 5779.

[30] Bertho, A.; Révész, A. *Justus Liebigs Ann. Chemie* **1953**, *581*, 11.

[31] (a) Trost, B.M.; Van Vranken, D.L. *Angew.Chem. Int. Ed. Engl.* **1992**, *31*, 228; (b) Trost, B.M., Van Vranken, D.L. *J. Am. Chem. Soc.* **1993**, *115*, 444; (c) Trost, B.M., Breit, B. *Tetrahedron Lett.* **1994**, *35*, 5817; (d) Trost, B.M.; Breit, B.; Peukert, S.; Zambrano, J.; Ziller, J.W. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2386; (e) Trost, B.M.; Patterson, D.E. *J. Org. Chem.* **1998**, *63*, 1339; (f) Lee, S.; Lim, C.W.; Song, C.E.; Kim, K.M.; Jun, C.H. *J. Org. Chem.* **1999**, *64*, 4445; (g) Lim, C.W.; Lee, S. *Tetrahedron* **2000**, *56*, 5135; (h) Trost, B.M.; Zambrano, J.; Ritcher, W. *Synlett* **2001**, 907; (i) Buschmann, N.; Rueckert, A.; Blechert, S. *J. Org. Chem.* **2002**, *67*, 4325; (j) Song, C.E.; Yang, J.W.; Roh, E.J.; Lee, S.G.; Ahn, J.H.; Han, H. *Angew. Chem. Int. Ed. Engl.* **2002**, *41*, 3852; (k) Trost, B.M.; Pan, Z.; Zambrano, J.; Kujat, G. *Angew. Chem. Int. Ed. Engl.* **2002**, *41*, 4691; (l) Agarkov, A.; Uffman, E.W.; Gibeltson, S.R. *Org. Lett.* **2003**, *5*, 2091; (m) Zhao, D.; Wang, Z.; Ding, K. *Synlett* **2005**, 2067.

[32] See, for example: Rosa Castillo, M.; Castillón, S.; Claver, C.; Fraile, J.M.; Gual, A.; Martín, M.; Mayoral, J.A.; Sola, E. *Tetrahedron* **2011**, *67*, 5402.

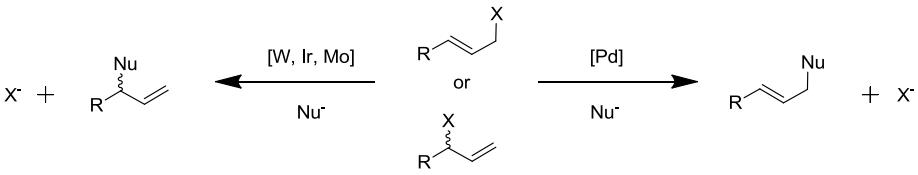
[33] Walsh, P. J.; Kozlowski, M. C.; *Fundamental of asymmetric catalysis* University Science Books **2009**
[34] Patent JP, 11-255695,A **1999**.
[35] Trost, B. M.; Van Vranken, D. L.; Bingel, C.; *J. Am. Chem. Soc*., **1992**, *114*, 9327.
[36] Crabtree, R.H. *New J. Chem.* **2011**, *35*, 18.

3. The *elpaNpy* ligands: Mo promoted Asymmetric Allylic Substitution promoted by microwaves.

3.1 Background of the Mo promoted Asymmetric Allylic Substitution: scope of the reaction, mechanisms, state of the art.

As mentioned in chapter 2, asymmetric allylic substitutions have been widely studied in recent years due to their high synthetic versatility. This feature arises from the variety of systems able to promote this reaction, because the stereo- and regiochemistry of the product are a function of the metal, the ligand, the nucleophile, and the substrate. This makes possible to access alternative reactivity by switching between different catalytic systems.

Among them, those based on Pd have been most widely explored, but since Mo, W and Ir [1] catalysts exhibit complementary regiochemistry when unsymmetrically substituted allyl derivatives are used, catalysts containing these metals are valuable. Typically, Pd complexes afford the achiral linear products from monosubstituted allylic substrates, while Ir, W or Mo catalysts preferentially lead to the branched chiral products (**Scheme 3.1**).



Scheme 3.1

This section will focus on molybdenum as active metal center. The first Mo-promoted allylic alkylation was reported in 1982 by by Trost and Lautens [2], but it took more than a decade to find suitable chiral catalysts. Up today,

this system have been used as key steps in enantioselective syntheses of several biologically active compounds.
Molybdenum catalysts are generally less reactive than palladium ones in this reaction and rather high catalyst loadings are usually necessary, but efficient chiral ligands are available. At the same time, Ir complexes have a wider scope [3], but the cheap Mo catalyst precursors (typically $Mo(CO)_6$, plus its derivates $Mo(CO)_3(EtCN)_3$ and $Mo(CO)_3(\eta^6\text{-}C_7H_8)$) are attractive due to theirs low cost and high stability [4]. Moreover, when AAA catalysed by Mo are performed under microwave irradiation (MW), $Mo(CO)_6$ can be used directly without any pretreatment and the product is usually obtained in less than ten minutes with high regio- and stereoselectivity [5].
The scope of the reaction is fairly wide in terms of nucleophile, substrate, and leaving group [1b]:

- **Nucleophiles:** The nucleophiles compatible with this system are stabilized carbon nucleophiles. Malonate esters are good nucleophiles in molybdenum-catalyzed allylations, and dimethyl malonate is the benchmark nucleophile for this reaction. Diketones and β-ketoesters react poorly, while a range of stabilized enolates exhibit high reactivity.
- **Substrates:** The benchmark substrates *rac*-1-Aryl-2-propenyl methyl carbonate and cinnamyl methyl carbonate are readly available and the most commonly used. Allylic substrates with aryl and alkenyl substituents were reported, but resulted to be less reactive. Mo-catalyzed allylic alkylations are compatible with the presence of ketone, enone, ester, sulfone, acetal, olefin, alkyl halide, silyl, allyl ether, silyl ether, and enol ether functional groups.
- **Leaving groups:** In Mo-catalyzed allylic alkylations allylic phosphates are more reactive than allylic carbonates, which are more reactive than allylic carboxylates. Usually branched allylic substrates are more reactive than their linear analogs.

Among the several ligands used, the more efficients belong to bis-pyridylamides family (**L1** and **L2** in **Figure 3.1**), readily obtained in one step by condensation of the desired carboxylic acid with the desired chiral

diamine. Alternative systems contains dihydrooxazole rings in place of pyridyl rings (**L3** in **Figure 3.1**).

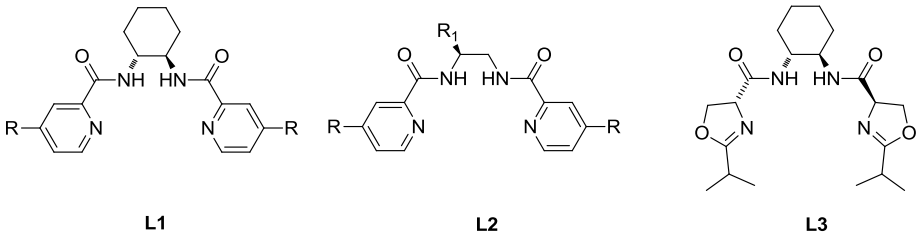
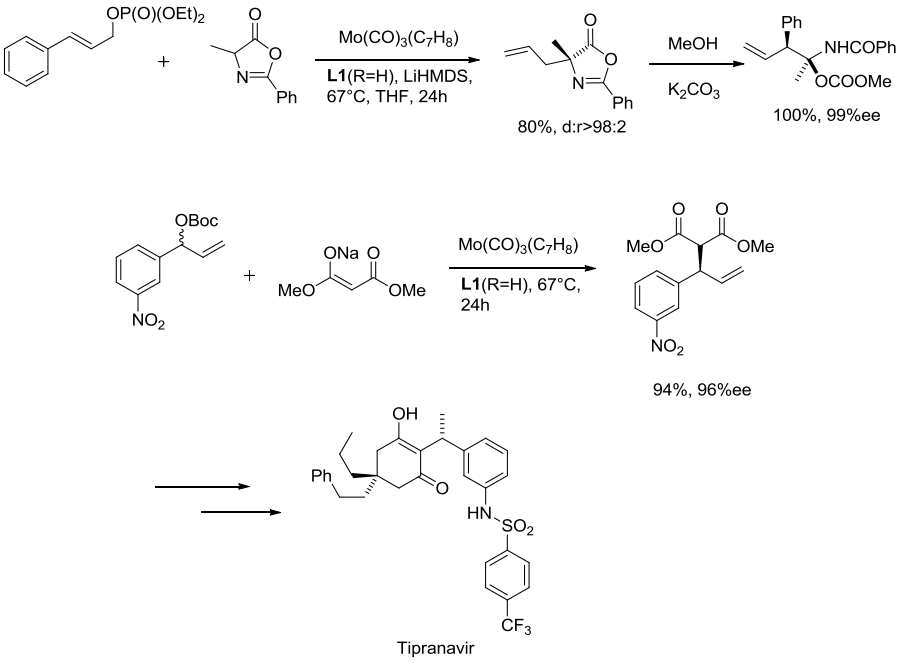


Figure 3.1

These ligands have been used in a wide range of case-studies, and they represent the state of the art in terms of catalytic performances and applicability. Notable examples are the synthesis of α-amino acids using azlactones as nucleophiles [6] and the synthesis of *Tipranavir*, a nonpeptide HIV protease inhibitor [7]. (**Scheme 3.2**)



Scheme 3.2

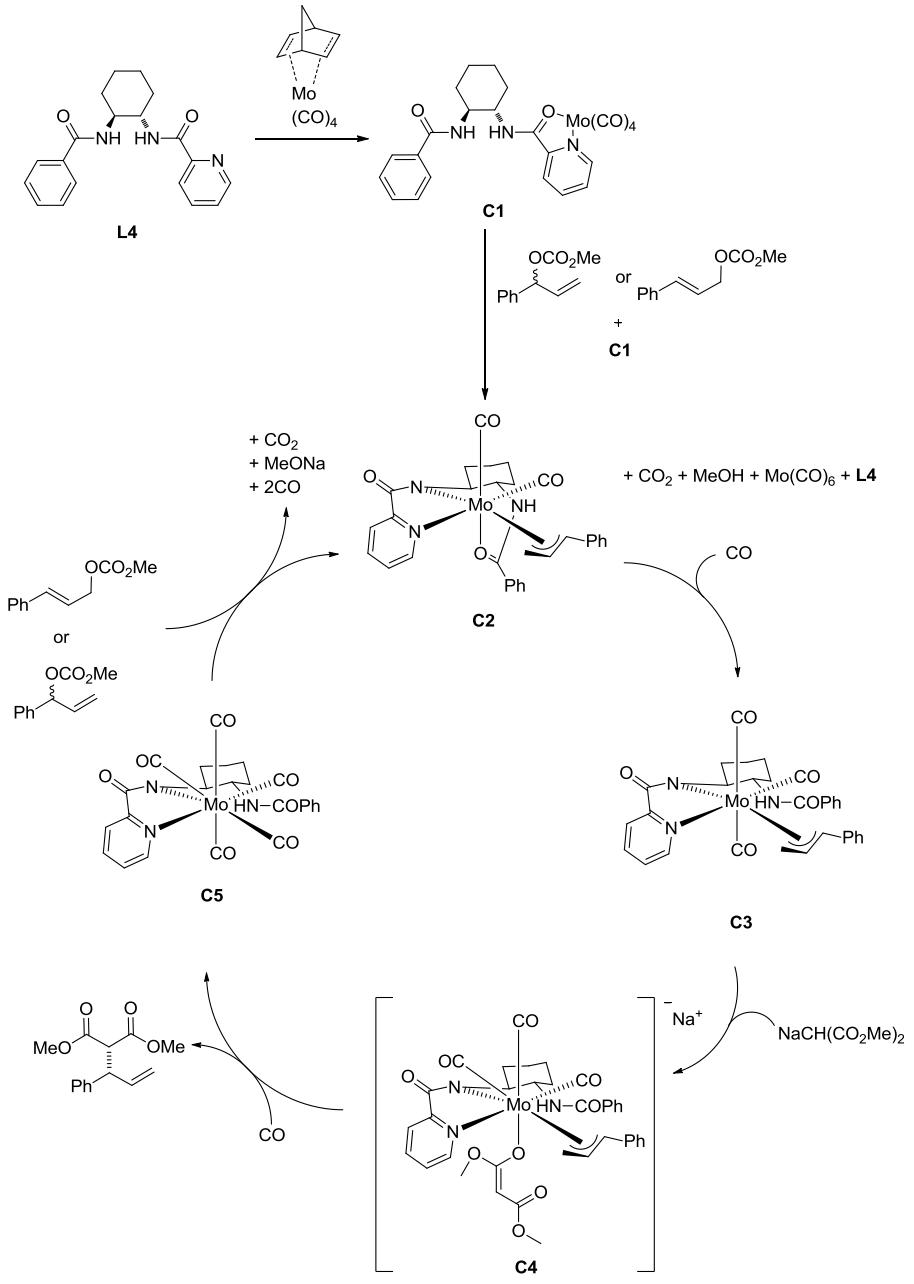
3.1.1 Mechanism and enantiodiscrimination

Detailed mechanistic studies have been performed using the monopyridine ligand **L4** of **Scheme 3.3**, where the catalytic cycle is reported [8]**.** The ligand combines with the Mo source to yield the neutral Mo(0) complex **C1**, which then reacts with the substrate (linear or branched) to generate complex **C2**, an 18-electron η^3-allyl Mo(II) complex with close to octahedral geometry. The stoichiometry for this reaction is:

$$2\ \mathbf{C1}\ + \text{substrate} \rightarrow \mathrm{C}\mathbf{2} + CO_2 + MeOH + Mo(CO)_6 + \mathbf{L4}$$

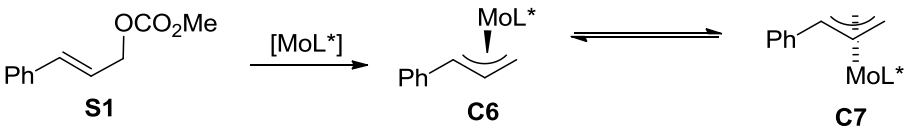
The addition of the substrate occurs with retention of configuration, and the ligand coordinates to the metal in a tridentate, *fac*-binding mode through the pyridine nitrogen, a deprotonated amide nitrogen and the benzamide oxygen. In the next step, the weakly bound amide carbonyl oxygen in 4 is replaced by a CO with formation of **C3**, followed by coordination of malonate, leading to **C4**. Final reductive elimination yields the product and complex **C5**. In this step the coordinated nucleophile attacks the substrate with retention of configuration; the overall process occurs then with double retention**.**

The η^3-allyl complexes that are intermediates are rapidly equilibrating by the mechanisms reported in section 2.1.1 (*π-σ-π isomerisation*, *apparent allyl rotation*, M^0*-catalyzed alkyl exchange*), which leads to the formation of a single major complex and thereby to high site- and stereoselectivity in the catalytic reactions. Equilibration of intermediate η^3-allyl complexes is usually rapid in comparison to nucleophilc attack, and therefore almost the same mixtures of enantiomers and constitutional isomers are obtained from enantioenriched or racemic branched substrates as well as from linear substrates.


L4
Mo
(CO)4
C1
OCO2Me
Ph
or
C1
+ CO2
+ MeONa
+ 2CO
+ CO2 + MeOH + Mo(CO)6 + L4
C2
CO
C3
C5
C4
Na+
NaCH(CO2Me)2
MeO
OMe

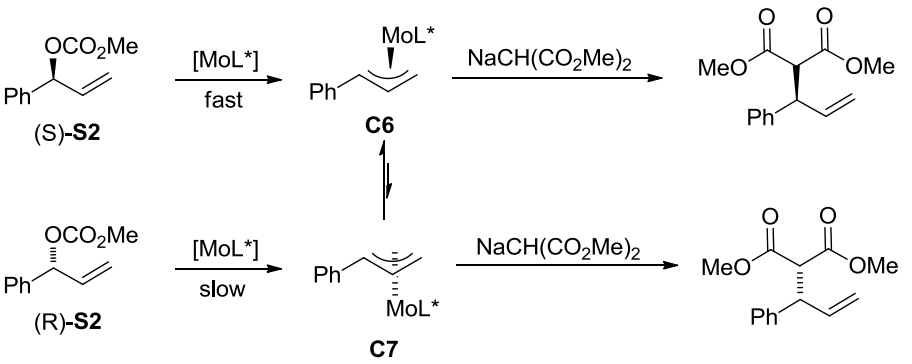
Scheme 3.3

In reactions with linear, achiral substrates, the catalyst may recognize one of the enantiotopic faces leading to selective formation of one of the diastereomeric η^3-allyl complexes **C6** or **C7** (**Scheme 3.4**). Alternatively, the two complexes may be in dynamic equilibrium, with one of them being preferentially attacked by the nucleophile. Both situations may lead to efficient enantiodiscrimination. The equilibrium between **C6** and **C7** proceeds mainly via η^1-allyl Mo intermediates.



Scheme 3.4

Oxidative addition of the branched substrates (S)-**S2** and (R)-**S2** to the [MoL*] catalyst leads to complexes **C6** and **C7**, respectively (**Scheme 3.5**). The absolute configuration of the product is determined by which one of these two complexes reacts with the nucleophile. Then, reaction of the branched racemic substrates would, in the absence of isomerization of intermediate allyl complexes, inevitably lead to the formation of racemates. If, in contrast, equilibration of the diastereomeric η^3-allyl complexes is fast compared to nucleophilic attack, a dynamic kinetic asymmetric transformation (DYKAT)[9] results, which may lead to formation of a single enantiomer.



Scheme 3.5

Branched substrates frequently react with somewhat lower enantioselectivity than the corresponding linear substrates, demonstrating that equilibration of the allyl complexes under certain conditions is not sufficiently rapid, resulting in a so called *memory effect*: the two diastereoisomers **C6** and **C7** equilibrate via η^3-η^1-η^3 isomerization, and if this process is slow compared to the nucleophilic attack, which also occurs by a *syn* mechanism, a memory effect may be observed, leading to lower enantioselectivity.

3.1.2 State of the art: the Naplepy ligands.

Within previous studies, the research group where this PhD thesis has been developed, contributed to the field of Mo-promoted asymmetric allylic substitution introducing the library of ligands *naple-py* [10], based on D-glucose (**Figure 3.1**). This second subset of ligands can be considered as the sugar counterpart of the privileged DACH-py ligand.

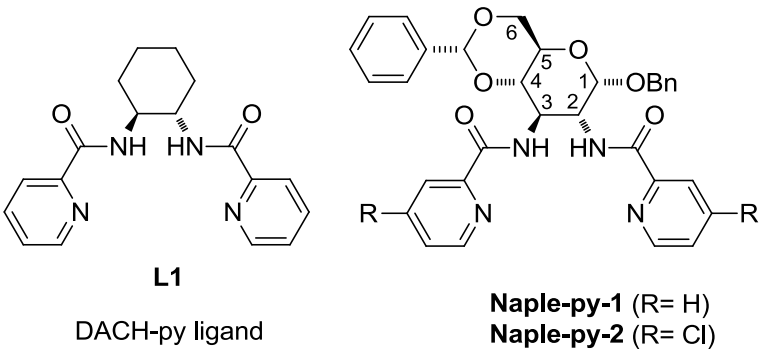
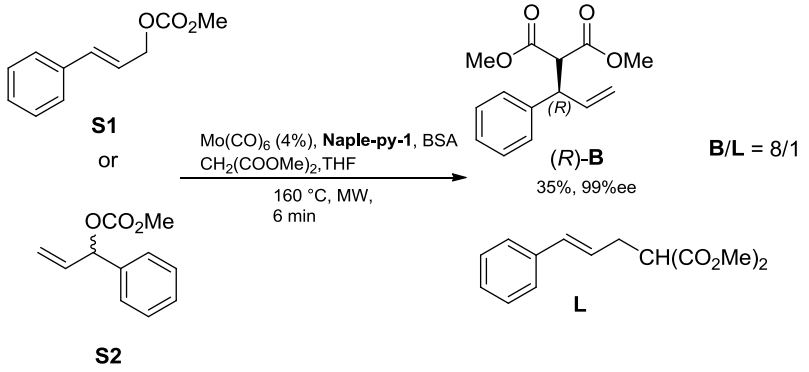


Figure 3.1

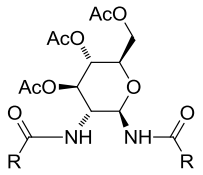
This family of ligands finds its most effective application in the asymmetric allylic alkylation promoted by Mo and assisted by microwaves, where the product for the benchmark reactions was obtained with good yield and selectivity (**Scheme 3.6**), comparable with the results for the correspondent DACH-Py ligand.



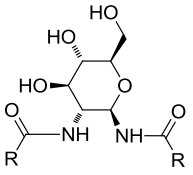
Scheme 3.6

3.2 the *elpaNpy* ligands: synthesis and characterization.

In order to corroborate the strategy of pseudo-enantiomeric ligands (see chapter 1), the *elpaN-py* library was rationally designed, presenting a specular stereochemistry of coordination related to the *Naple-py*. According to the strategy mentioned before, within this study pseudo-enantiomeric ligands have been designed and prepared, aiming to produce the same Mo-promoted asymmetric allylic substitution with opposite stereochemistry.
In this section, the synthesis of the new subset of the **elpaN-type** bouquet (**elpaN-Py** series of **Figure 3.2**) is described; these ligands were applied in the Mo-catalysed AAA promoted by MW.



R = R1 **elpaN-py**
R = R2 **elpaN-py-p-OMe**
R = R2 **elpaN-qui**



R = R1 **elpaN-py'**

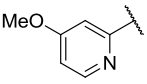
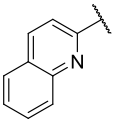
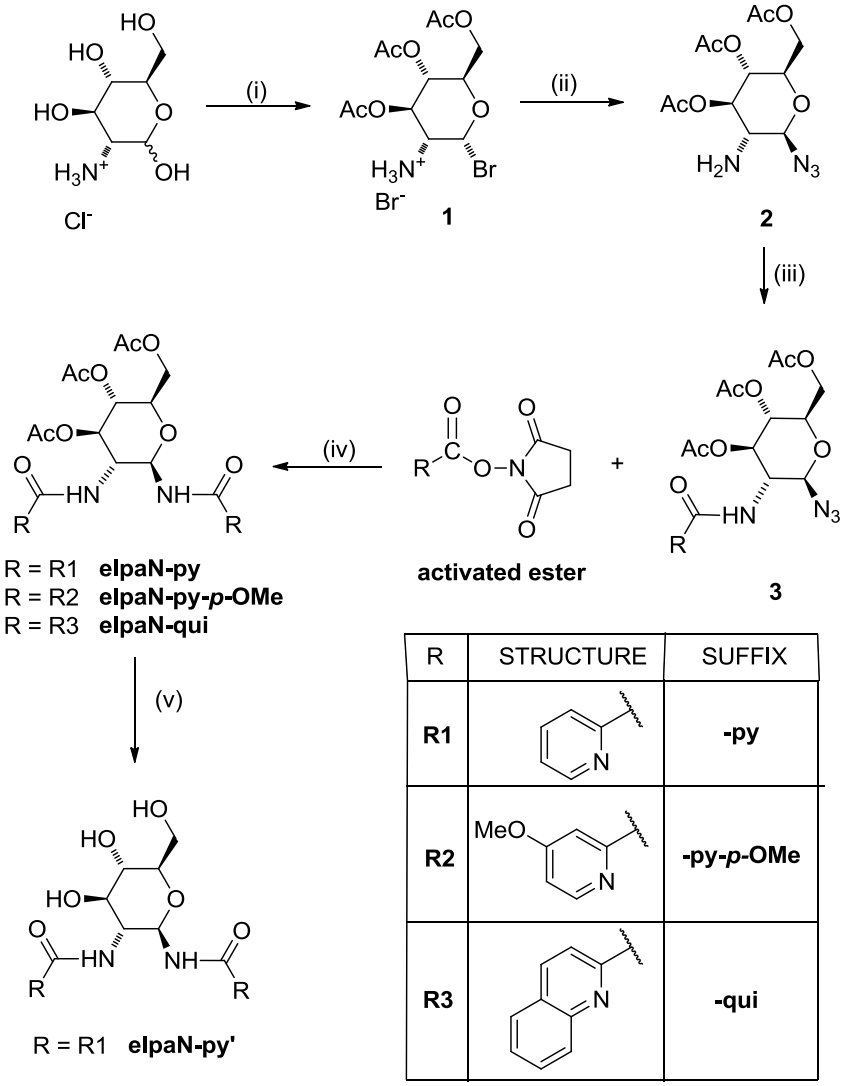
R	STRUCTURE	SUFFIX
R1		**-py**
R2		**-py-*p*-OMe**
R3		**-qui**

Figure 3.2

The synthesis of the ligands is is reported in S**cheme 3.7**. The key intermediate in the synthesis of the ligands is the known 1-azido-2-aminoglucose derivative **2** described in section 2, prepared from the bromide **1** (step ii).

The amino group of compound **2** was condensed with the desired acid (step iii), employing *N*,*N'*-dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP). Compound **3** was converted into the ligand by a Staudinger reaction, using PMe_3 and the appropriate activated ester (step iv). This procedure is necessary because anomerization at C1 was usually observed when the azide was reduced to amine by H_2 over Pd/C.

Finally, the acetate groups of the **elpaN-py** ligand were conveniently deprotected by stirring a methanolic solution of the ligand in presence of ammonia to yield a ligand with free hydroxyl groups (step v). The deprotected ligand **elpaN-py'** is soluble in water and ionic liquids (RTIL), but almost insoluble in DCM and toluene and was synthesized in order to explore the feasibility of a Mo promoted AAA under unconventional conditions.



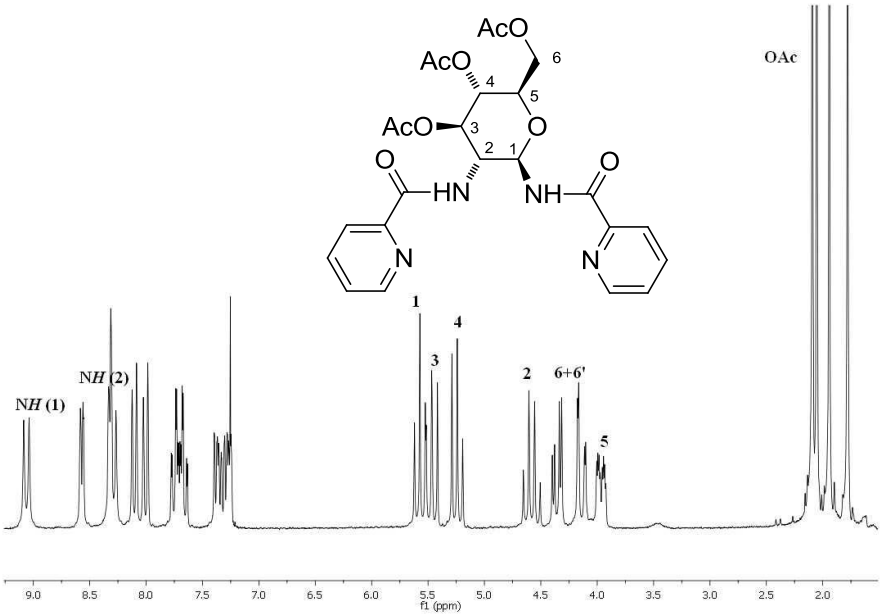
R	STRUCTURE	SUFFIX
R1		**-py**
R2		**-py-*p*-OMe**
R3		**-qui**

(i) AcBr, 3d; (ii) Me_3SiN_3, *t*-BuOK, THF, 18h; (iii) DMAP, R-CO_2H, DCC, DCM; (iv) PMe_3, DCM; (v) NH_3, MeOH.

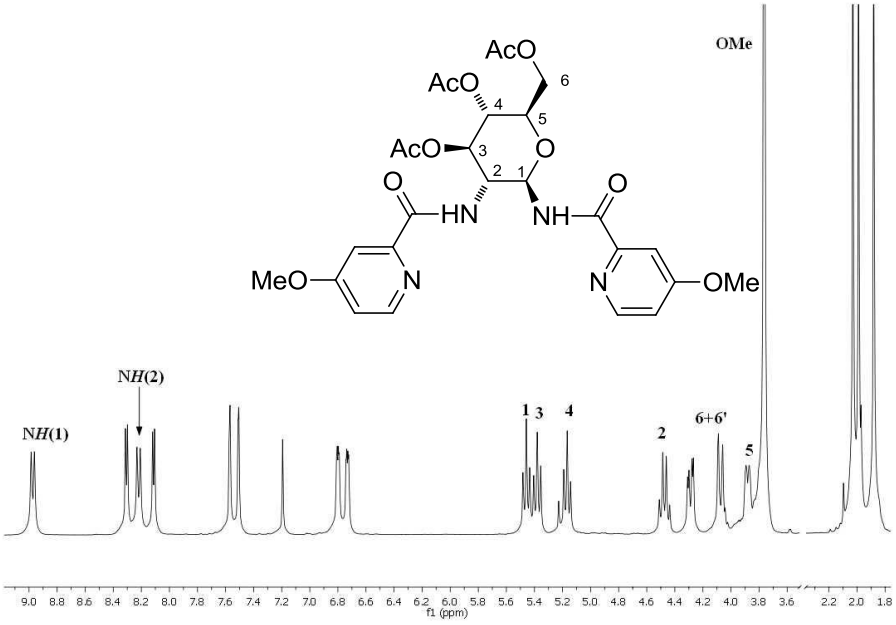
Scheme 3.7

The four ligands were fully characterized by ^{1}H and ^{13}C NMR spectroscopy, in order to confirm their structure and purity. The spectra are shown below.

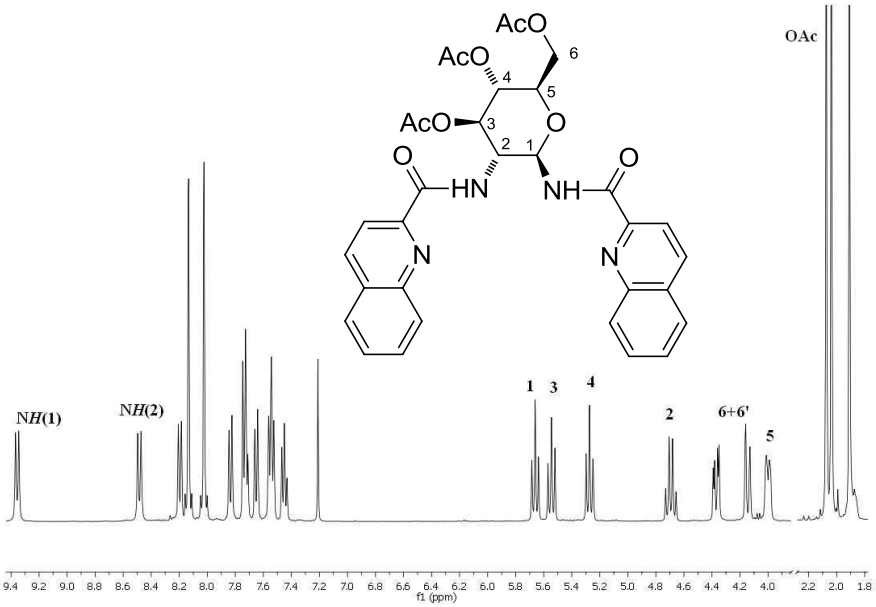
^{1}H NMR spectrum of elpaN-py, 200 MHz, $CDCl_3$



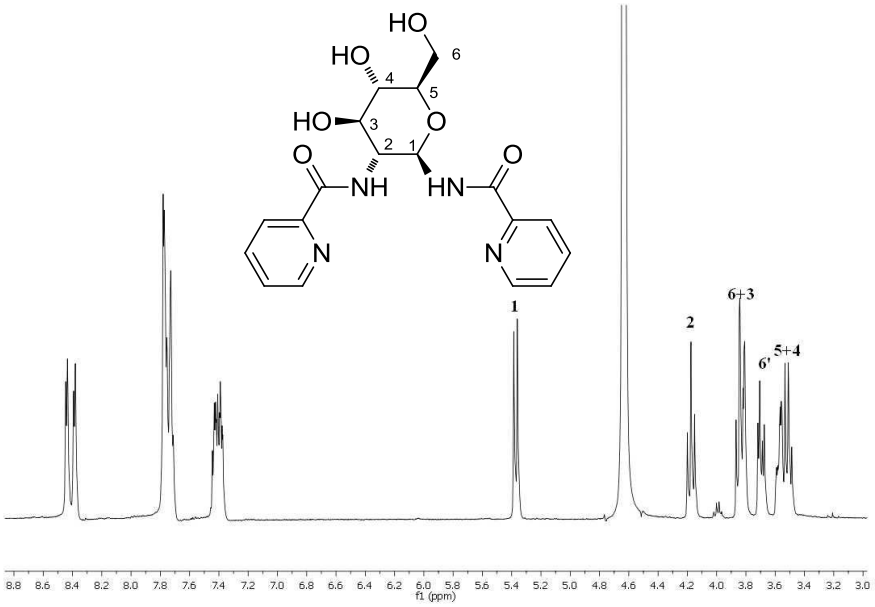
^{1}H NMR spectrum of elpaN-py-*p*-OMe, 400 MHz, $CDCl_3$



^{1}H NMR spectrum of elpaN-qui, 400 MHz, $CDCl_3$

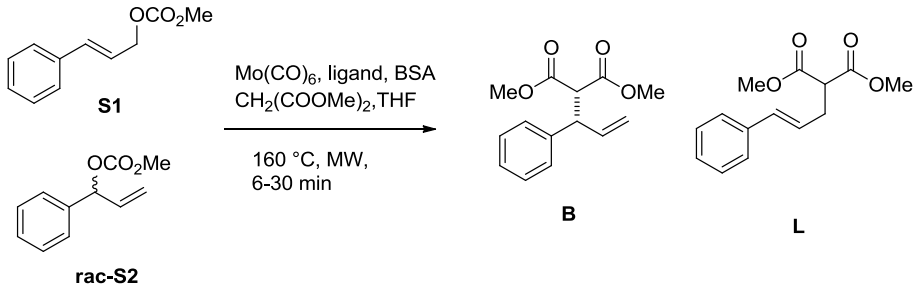


^{1}H NMR spectrum of elpaN-py', 400 MHz, D_2O



3.3 Catalytic performances of the *elpaNpy* ligands in the Mo promoted Asymmetric Allylic Substitution assistem by microwaves.

The catalytic reactions (**Scheme 3.8**) were performed by using both a linear (**S1**) and a branched allylic carbonate (**rac-S2**) which, as mentioned before, are crucial substrates because the knowledge of their reactivity provides the necessary information for assessing the qualities of the ligands [8,11].



Scheme 3.8

According to experimental conditions previously developed [10], $Mo(CO)_6$, ligand, allylic carbonate **S1**, dimethyl malonate, and *N*,*O*-bis-(trimethylsilyl)acetamide (BSA) were mixed in THF and heated at 160°C in the microwave cavity under air. After the desired reaction time, conversions and branched/linear ratios were determined by ^{1}H NMR spectroscopy, and enantioselectivities by chiral HPLC.

The different performances of the ligands were assessed by using 4 mol% of Mo catalyst, a ligand/metal ratio of 1.3:1 and a nucleophile/substrate ratio of 1.1:1. The results of reactions of the linear substrate **S1** are shown in **Table 3.1**. As expected, **Naple-type** and **elpaN-type** ligands afforded products with opposite absolute configurations, the latter leading preferentially to the (*S*)-**B** product. Except for the ligand containing a quinoline group (entry 4), which was expected to be the less active and selective,[16] good conversions, yields, regioselectivity, and stereoselectivity were observed.

N°	**elpaN-Py** ligand	Time [min]	Cat. [mol%]	Conv. [%][a]	Isolated yield [%][a]	B/L[b]	*ee* [%][c]
1	**-py**	6	4	94	65	14/1	98 (*S*)
2	**-py-*p*-OMe**	6	4	92	70	25/1	99 (*S*)
3	**-py'**	6	4	100	72	6/1	97 (*S*)
4	**-qui**	6	4	51	45	15/1	90 (*S*)
5	**-py-*p*-OMe**	30	1	23	16	14/1	97 (*S*)

Reaction conditions: dimethyl malonate (0.77 mmol), allylic carbonate *rac*-5 (0.71 mmol),$Mo(CO)_6$ (0.026 mmol, 4 mol%), ligand (0.034 mmol), BSA (208 μL), THF (2mL), 160 °C, 6 min. [a]Determined by NMR spectroscopy of the crude reaction mixture. [b]Yield of product isolated by column chromatography (EtOAc/petroleum ether=1/5). [c]Determined by chiral HPLC Daicel OD-H (0.46 cm i.d. 25 cm) column.

Table 3.1

In analogy with the results obtained for the ligands derived from 1,2-diaminocyclohexane,[11b] the presence of π-donating substituents in the 4-position of the pyridyl rings increased the enantio- and site selectivity.[12] Thus, ligand **elpaN-py-*p*-OMe** was more selective than **elpaN-py** (entry 1 *vs* entry 2).

A catalyst containing the deprotected ligand **elpaN-py'** resulted in a similar activity, but lower regio- and stereoselectivity compared to the acetylated ligand (entry 1 *vs* entry 3). As expected, lower amounts of catalyst resulted in lower conversion and lower regioselectivity (entry 1 *vs* entry 5), although the enantioselectivity was still good (97% *ee*).

Branched substrates, such as *rac*-**S2**, often react with lower enantioselectivity than their linear isomers as a result of the previously mentioned *memory effect*. The results for reactions of substrate *rac*-**S2** are reported in **Table 3.2**.

As expected, the branched substrate **S2** resulted in lower enantio- and regioselectivity than the linear substrate, but still acceptable levels of enantioselectivity (88–96% *ee* (*S*)). Conversions observed for this substrate were lower but still good in all cases. The trend was analogous to that experienced for substrate **S1**, except that ligand **elpaN-qui** gave the highest branched/linear ratio (entry 4).

N°	Ligand	Conversion [%][a]	Isolated yield [%][b]	B/L[a]	*ee* [%][c]
1	**elpaN-py**	94	72	17/1	96 (*S*)
2	**elpaN-py-*p*-OMe**	78	66	21/1	95 (*S*)
3	**elpaN-py'**	73	55	6/1	86 (*S*)
4	**elpaN-qui**	67	41	24/1	90 (*S*)

Reaction conditions: dimethyl malonate (0.77 mmol), allylic carbonate **4** (0.71 mmol)**,** BSA (208 μL), THF (2 mL), 160 °C. [a]Determined by NMR spectroscopy of the crude reaction mixture. [b]Yield of product isolated by column chromatography (EtOAc/petroleum ether=1/5). [c]Determined by chiral HPLC Daicel OD-H (0.46 cm i.d. 25 cm) column.

Table 3.2

The performance of ligand **elpaN-py'** was also tested in water and in hydrophilic RTIL, taking advantage of its solubility in these solvents. Disappointingly, when water was used as solvent, the main product obtained from the allylic carbonate **S1**, as well as from the corresponding acetate, consisted of a mixture of the branched and linear alcohols. The hydrolysis was, at least in part, catalyzed by the metal complex as shown by the formation of only the linear product from the Mo-free background reaction, thus suggesting a π-allylic intermediate in the hydrolysis. In the ionic liquid bmimBF_4, the allylic carbonate afforded the allylic ether in racemic form, mainly as product of a background decarboxylation, while the allylic acetate did not react.

3.4 Conclusion.

This work demonstrates the validity of a strategy, namely that it is possible to prepare libraries of pseudo-enantiomeric ligands from easily accessible natural compounds, with both synthetic and economic benefits.[13]
In particular, the library elpaN-type, based on 1,2-disubstituted D-glucose, was expanded through the preparation of the bis(pyridine-2-carboxamide) derivatives elpaN-Py. The ligands were obtained in both protected and deprotected versions, and this has allowed to verify their ability in the AAA promoted by Mo under traditional and non-conventional conditions. High enantioselectivities were accomplished in the former case, starting from both

a linear and a branched allylic substrates. In water, although the enantioselective process was almost ineffective, a peculiar reactivity was disclosed, that could be the subject of further future research.

3.5 Experimentals.

3.5.1 General considerations:

THF and toluene were dried by using a Glass-contour solvent dispensing system. Dichloromethane was distilled from CaH_2. Microwave heating was performed by using a Smith Creator™ single-mode cavity from Biotage. ^{1}H and ^{13}C NMR spectra were recorded respectively at 400 or 200 MHz, and 100.6 and 50.3 MHz. The ^{1}H and ^{13}C chemical shifts are reported using $CHCl_3$ (for spectra recorded in $CDCl_3$), HDO (for proton spectra recorded in water) or dioxane (for carbon spectra recorded in water) as internal standards.

*2.5.2 Synthesis of the activated esters, R = **-Py** and **–Qui***

2-Pyridine carboxylic acid or 2-quinoline carboxylic acid (5.0 mmol), DCC (1.025 equiv), and *N*-hydroxysuccinimide (1.0 equiv) were suspended in 50 mL of THF and the solution was stirred overnight. The suspension was filtered, and the solvent was evaporated under reduced pressure. The crude product was dissolved in DCM and precipitated by the addition petroleum ether. The resulting product was used without any further purification (yield: 41 and 65% respectively, 0.46 g and 0.90 g). **Activated Ester-Py:** ^{1}H NMR (400 MHz, $CDCl_3$): □ = 8.83 (d, ^{3}J = 4.6 Hz, 1 H, aromatic), 8.21 (d, ^{3}J = 7.8 Hz, 1 H, aromatic), 7.91 (td, ^{3}J = 1.4 Hz, ^{3}J = 7.8 Hz, 1 H, aromatic), 7.59 (m, 1 H, aromatic), 2.92 (s, 4 H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 169.24, 160.84, 150.91, 144.50, 137.72, 128.87, 127.05, 26.10. **Activated Ester-Qui:** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.36 (d, ^{3}J= 8.5 Hz, 1 H, aromatic), 8.31 (d, ^{3}J = 8.6Hz, 1H, aromatic), 8.21 (d, ^{3}J = 8.5 Hz, 1 H, aromatic), 7.92 (d, ^{3}J = 8.2 Hz, 1 H, aromatic), 7.83 (t, ^{3}J = 7.6 Hz, 1 H, aromatic), 7.71 (t, ^{3}J = 7.5 Hz, 1 H, aromatic), 2.95 (s, 4H,); ^{13}C NMR

(100.6 MHz, $CDCl_3$) δ = 169.00, 160.85, 147.87, 143.93, 137.74, 131.09, 130.98, 129.94, 129.97, 127.80, 121.69, 25.86. **R = -Py-*p*-OMe:** The acid (5.0 mmol), DCC (2.5 equiv), and *N*-hydroxysuccinimide (1.1 equiv) were suspended in 130 mL of THF and the solution stirred overnight. The suspension was filtered, and the solvent was evaporated under reduced pressure. The crude product was extracted twice with boiling *n*-hexane in order to remove excess DCC. The solid was dissolved in EtOAc (50 mL), the solution was filtered, and then washed with EtOAc (2x25 mL). The solvent was removed under reduced pressure, leading to the crude product that was used with no further purification (yield: 580 mg, 45%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.65 (d, ^3J = 5.7 Hz, 1 H, aromatic), 7.72 (d, 1 H, ^3J = 2.4 Hz aromatic), 7.09 (dd, ^3J = 2.5 Hz, ^3J = 5.7 Hz, 1 H, aromatic), 3.94 (s, 3 H, OMe), 2.91 (s, 4H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ = 171.86, 186.99, 166.88, 160.57, 151.67, 141.43, 113.27, 55.99, 25.86.

*3.5.3 Synthesis of **3***

Compound **2** (1.32 g, 4.00 mmol) was dissolved in 25 mL of DCM (for the synthesis of **3-Py** and **3-Qui**) or 50 mL of THF (for the synthesis of **3-Py-*p*-OMe**). DMAP (0.0489 g, 0.40 mmol), the desired acid (4.20 mmol) and DCC (1.24 g, 6.00 mmol) were added in this order, and the solution was stirred for the desired time. DCU was removed by filtration, and the solution was concentrated under reduced pressure. The crude product was precipitated by slow addition of petroleum ether, and washed twice with the same solvent. The solid was extracted twice with boiling *n*-hexane and further purified by flash chromatography (silica/crude = 50/1 w/w).

Product	Reaction time (h)	Eluent ratio (EtOAc/PE + 3% TEA)	Yield (%)
3-Py	2	1/1	68
3-Py-*p*-OMe	18	3/1	57
3-Qui	18	3/2	60

3-Py: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.49 (d, ^{3}J = 4.2 Hz, 1 H, aromatic), 8.12 (d, $^{3}J_{NH,2\text{-}H}$ = 7.9 Hz, 1 H, NH), 7.79 (td, ^{3}J = 1.4 Hz, ^{3}J = 7.7 Hz, 1 H, aromatic), 7.39 (m, aromatic), 5.41 (t, $^{3}J_{3\text{-}H,2\text{-}H}$ = $^{3}J_{3\text{-}H,4\text{-}H}$ = 9.9 Hz, 1 H, 3-H), 5.10 (t, $^{3}J_{4\text{-}H,3\text{-}H}$ = $^{3}J_{4\text{-}H,5\text{-}H}$, 1 H, 4-H), 4.93 (d, $^{3}J_{1\text{-}H,2\text{-}H}$ = 9.2 Hz, 1 H,1-H), 4.26 (dd, $^{3}J_{6\text{-}H,5\text{-}H}$= 4.8 Hz, $^{3}J_{6\text{-}H,6'\text{-}H}$= 12.4 Hz, 1 H, 6-H), 4.15 (dd, $^{3}J_{6'\text{-}H,5\text{-}H}$= 1.9 Hz, 1 H, 6'-H), 4.03 (q, 1 H, 2-H), 3.81 (m, 1H, 5-H), 2.06 (s, 3 H, AcO), 1.98 (s, 3 H, AcO), 1.87 (s, 3 H, AcO); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 170.83, 170.60, 169.54, 164.84, 148.90, 148.34, 137.61, 126.82, 122.65, 88.69, 74.20, 72.03, 68.43, 62.03, 54.27, 34.09, 20.89, 20.75, 20.68. **3-Py-p-OMe**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.31 (d, ^{3}J = 5.6Hz, 1 H, aromatic), 8.21 (d, $^{3}J_{NH,2\text{-}H}$= 8.2 Hz, 1 H, NH), 7.69 (dd, ^{3}J = 2.4 Hz, ^{3}J = 12.7 Hz, 1 H, aromatic), 6.92 (m, 1 H, aromatic), 5.46 (t, $^{3}J_{3\text{-}H,2\text{-}H}$= $^{3}J_{3\text{-}H,4\text{-}H}$ = 9.5 Hz, 1 H, 3-H), 5.14 (t, $^{3}J_{4\text{-}H,3\text{-}H}$ = $^{3}J_{4\text{-}H,5\text{-}H}$, 1H, 4-H), 4.97 (d, $^{3}J_{1\text{-}H,2\text{-}H}$= 9.2 Hz, 1H, 1-H), 4.31 (dd, $^{3}J_{6\text{-}H,5\text{-}H}$ = 4.8Hz, $^{3}J_{6\text{-}H,6'\text{-}H}$ = 12.4 Hz, 1 H, 6-H), 4.20 (dd, $^{3}J_{6'\text{-}H,5\text{-}H}$= 2.1 Hz, 1 H, 6'-H), 4.07 (q, 1 H, 2-H), 3.90 (s, 3H, OMe), 3.86 (m, 1H, 5-H), 2.11 (s, 3H, AcO), 2.03 (s, 3 H, AcO), 1.93 (s, 3 H, AcO); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ = 171.07, 170.82, 169.79, 167.42, 165.12, 151.20, 149.70, 113.86, 108.07, 88.95, 74.47, 72.28, 68.75, 62.30, 56.14, 55.95, 54.57, 35.31, 25.85, 25.07, 21.11, 20.98, 20.91. **3-Qui**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.35 (d, $^{3}J_{NH,2\text{-}H}$= 9.0 Hz, 1 H, NH), 8.25 (q, ^{3}J = 8.5Hz, 2H, aromatic), 8.07 (d, ^{3}J = 8.5 Hz, 1 H, aromatic), 7.83 (d, ^{3}J = 8.1 Hz, 1 H, aromatic), 7.73 (t, ^{3}J = 7.7 Hz, 1 H, aromatic), 7.58 (t, ^{3}J = 7.5 Hz, 1 H, aromatic), 5.51 (t, $^{3}J_{3\text{-}H,2\text{-}H}$= $^{3}J_{3\text{-}H,4\text{-}H}$= 9.9 Hz, 1 H, 3-H), 5.14 (t, $^{3}J_{4\text{-}H,3\text{-}H}$ = $^{3}J_{4\text{-}H,5\text{-}H}$, 1 H, 4-H), 5.02 (d, $^{3}J_{1\text{-}H,2\text{-}H}$= 9.2 Hz, 1 H, 1-H), 4.30 (dd, $^{3}J_{6\text{-}H,5\text{-}H}$ = 4.7Hz, $^{3}J_{6\text{-}H,6'\text{-}H}$ = 12.4 Hz, 1 H, H-6), 4.17 (dd, $^{3}J_{6'\text{-}H,5\text{-}H}$= 1.8 Hz, 1 H, 6'-H), 4.09 (q, 1 H, 2-H), 3.86 (m, 1 H, 5-H), 2.09 (s, 3 H, AcO), 2.00 (s, 3H, AcO), 1.88 (s, 3H, AcO); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ = 171.11, 170.87, 169.83, 165.37, 148.97, 146.81, 138.06, 130.65, 130.24, 129.95, 128.64, 128.14, 119.20, 89.00, 74.50, 72.27, 68.78, 62.31, 54.71, 34.36.

*3.5.4 Synthesis of the **elpaN** ligands*

The desired intermediate **3** (1.35 mmol) and the desired activated ester (1.25 equiv) were dissolved in dry DCM (15 mL) under inert atmosphere. The

solution was cooled to -78 °C and a solution of 0.89 M PMe_3 in dry toluene (1.25 equiv) was slowly added. The system was warmed to RT, and when evolution of N_2(g) ceased, the reaction was quenched by the addition of 15 mL of a saturated solution of Na_2CO_3 (aq). The organic phase was separated, and the water was extracted with DCM (2x20 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was precipitated by slow addition of petroleum ether, and washed twice with the same solvent. The solid was purified by flash chromatography (silica/crude = 50/1 w/w).

Product	Eluent ratio (EtOAc/PE + 3% TEA)	Yield (%)
elpaN-Py	1/0	58
elpaN-Py-p-OMe	1/0	41
elpaN-Qui	2/1	67

elpaN-Py: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.06 (d, $^3J_{NH,1-H}$ = 9.6 Hz, 1 H, NH), 8.57 (d, ^3J = 4.71 Hz, 1 H, aromatic), 8.31 (d, $^3J_{NH,2-H}$ = 9.6 Hz, 1H, NH), 8.03 (m, 2 H, aromatic), 7.70 (m, 2 H, aromatic), 7.33 (m, 2 H, aromatic), 5.57 (t, $^3J_{1-H,NH}$ = $^3J_{1-H-2-H}$, 1 H, 1-H), 5.47 (t, $^3J_{3-H,2-H}$ =$^3J_{3-H,4-H}$ = 10 Hz, 1 H, 3-H), 5.24 (t, $^3J_{4-H,3-H}$= $^3J_{4-H,5-H}$, 1 H, 4-H), 4.58 (q, 1 H, 2-H), 4.36 (dd,$^3J_{6-H,5-H}$ = 4.21 Hz, $^3J_{6-H,6'-H}$ = 12.4 Hz, 1 H, 6-H), 4.14 (dd, $^3J_{H6',5-H}$= 2.0 Hz, 1 H, 6'-H), 3.96 (m, 1 H, 5-H), 2.09 (s, 3 H, AcO), 2.05 (s, 3H, AcO), 1.94 (s, 3 H, AcO); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ = 170.79, 169.51, 165.26, 148.36, 148.19, 137.04, 126.56, 126.36, 122.63, 122.20, 79.89, 73.72, 73.11, 68.29, 61.95, 52.92, 20.67. HRMS (ESI) calcd. for $C_{24}H_{26}N_4NaO_9$ [*M* + Na]$^+$: 537.1597, found 537.1581. **elpaN-Py-p-OMe**: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.97 (d, $^3J_{NH,1-H}$= 9.3 Hz, 1 H, NH), 8.58 (d, ^3J = 5.6 Hz, 1 H, aromatic), 8.22 (d, $^3J_{NH,2-H}$ = 9.4 Hz, 1 H, NH), 8.11(d, ^3J = 5.6 Hz, 1 H, aromatic), 7.57 (s, 1 H, aromatic), 7.51 (s, 1 H, aromatic), 6.80 (m, 1 H, aromatic), 6.73 (m, 1 H, aromatic), 5.46 (t, $^3J_{1-H,NH}$ = $^3J_{1-H,2-H}$, 1 H, 1-H), 5.38 (t, $^3J_{3-H,2-H}$ = $^3J_{3-H,4-H}$ = 9.9 Hz, 1 H, 3-H), 5.17 (t, $^3J_{4-H,3-H}$= $^3J_{4-H,5-H}$, 1 H, 4-H), 4.47 (q, 1 H, 2-H), 4.29 (dd, $^3J_{6-H,5-H}$ = 4.1Hz, $^3J_{6-H,6'-H}$= 12.4

Hz, 1 H, 6-H), 4.07 (dd, $^{3}J_{6'\text{-H},5\text{-H}}$= 1.8 Hz, 1 H, 6'-H), 3.90 (m, 1 H, 5-H), 3.76 (s, 6 H, 2xOMe) 2.06 (s, 3H, AcO), 1.98 (s, 3 H, AcO), 1.88 (s, 3 H, AcO); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ = 171.20, 171.12, 169.93, 167.09, 165.68, 165.61, 151.13, 151.01, 149.92, 149.74, 113.62, 113.38, 108.32, 108.02, 80.29, 74.12, 73.44, 68.74, 62.37, 55.89, 53.38, 34.36. HRMS (MALDI) calcd. for $C_{26}H_{30}N_4O_{11}$ $[M]^+$: 574.1911, found 574.5331. **elpaN-Qui**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.36 (d, $^{3}J_{\text{NH},1\text{-H}}$ = 9.2 Hz, 1 H, NH), 8.48(d, $^{3}J_{\text{NH},2\text{-H}}$ = 9.5 Hz, 1 H, NH), 8.22 (d, ^{3}J = 8.8Hz, 1 H, aromatic), 8.13 (m, 2 H, aromatic), 8.02 (m, 2 H, aromatic), 7.83 (d, ^{3}J= 8.5Hz, 1 H, aromatic), 7.73 (m, 2 H, aromatic), 7.65 (d, ^{3}J = 8.8 Hz, 1 H, aromatic), 7.54 (m, 2 H, aromatic), 7.45 (t, ^{3}J= 7.5Hz, 1 H, aromatic), 5.66 (t, $^{3}J_{\text{1-H,NH}}$ = $^{3}J_{\text{1-H,2-H}}$, 1 H, 1-H), 5.54 (t, $^{3}J_{\text{3-H,2-H}}$ = $^{3}J_{\text{3-H,4-H}}$= 9.9 Hz, 1 H, 3-H), 5.27 (t, $^{3}J_{\text{4-H,3-H}}$= $^{3}J_{\text{4-H,5-H}}$, 1 H, 4-H), 4.69 (q, 1 H, 2-H), 4.37 (dd, $^{3}J_{\text{6-H,5-H}}$= 4.2 Hz, $^{3}J_{\text{6-H,6'-H}}$ = 12.4 Hz, 1 H, 6-H), 4.07 (dd, $^{3}J_{6'\text{-H},5\text{-H}}$ = 1.8 Hz, 1 H, 6'-H), 3.90 (m, 1 H, 5-H), 2.07 (s, 3 H, AcO), 2.04 (s, 3 H, AcO), 1.91 (s, 3 H, AcO); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ = 171.24, 169.95, 166.02, 148.79, 148.73, 146.91, 146.64, 137.67, 137.55, 130.68, 130.46, 130.40, 130.35, 129.83, 129.61, 128.59, 128.43, 127.89, 127.76, 119.27, 119.00, 80.64, 74.29, 73.55, 68.81, 62.43, 53.58. HRMS (ESI) calcd. for $C_{32}H_{31}N_4O_9$ $[M + H]^+$: 615.2091, found 615.2041.

*3.5.5 Synthesis of **elpaN-py'***

The **elpaN-py** ligand (0.50 mmol) was dissolved in MeOH (10 mL) under a NH_3 atmosphere. After 20 h the solvent was removed under vacuum, affording the pure product as a solid in quantitative yield. Relevant NMR data: **elpaN-Py'**: ^{1}H NMR (400 MHz, D_2O): δ = 8.42 (m, 2 H, aromatic), 7.75 (m, 2 H, aromatic), 7.41 (m, 2 H, aromatic), 5.37 (d, $^{3}J_{\text{1-H,NH}}$ = $^{3}J_{\text{1-H-2-H}}$= 9.65 Hz, 1 H, 1-H), 4.18 (t, $^{3}J_{\text{2-H,NH}}$ = 9.93 Hz, 1 H, 2-H), 3.81 (m, 2H, 6-H and 3-H), 3.70 (dd, $^{3}J_{6'\text{-H},5\text{-H}}$= 4.9 Hz, 1H, 6'-H), 3.58 (m, 2 H, 5-H and 4-H); ^{13}C NMR (100.6 MHz, D_2O) □ = 171.01, 170.51, 151.82, 151.64, 151.34, 150.67, 141.20, 130.58, 130.22, 125.68, 125.46, 81.95, 80.77, 76.82, 72.54, 63.49, 57.76. HRMS (ESI) calcd. for $C_{18}H_{20}N_4NaO_6$ $[M + Na]^+$: 411.1281, found 411.1279.

3.5.6 Microwave-assisted allylic alkylations.

General procedure: two different stock solutions were prepared: solution N, containing the nucleophile, was prepared by adding dimethyl malonate (880 μL, 7.7 mmol) to a suspension of 60% NaH in mineral oil in tetrahydrofuran (10 mL), and solution S, containing the substrate, was prepared by dissolving the allylic carbonate (**S1** or **S2**) (7.1 mmol) in THF (10 mL). Then the appropriate ligand (0.034 mmol) and $Mo(CO)_6$ (6.9 mg, 0.026 mmol) were transferred to a flame-dried SmithProcess VialTM. Solution N (1 mL), solution S, and BSA (208 μL) were added in this order, and the suspension was heated in the microwave cavity at 160 °C for the desired time. The brown solution obtained was diluted with Et_2O to a total volume of 10 mL, resulting in a dark precipitate. A sample of the solution was filtered through silica gel and analysed by ^1H NMR spectroscopy to determine the conversion and the regioselectivity. The crude product was then purified by chromatography on silia gel (eluent: petroleum ether/EtOAc, 5/1). The ee was determined by HPLC using a Daicel OD-H (0.46 cm i.d. 25 cm) column. The structures of the products were confirmed by comparison with published spectroscopic data.

3.6 References.

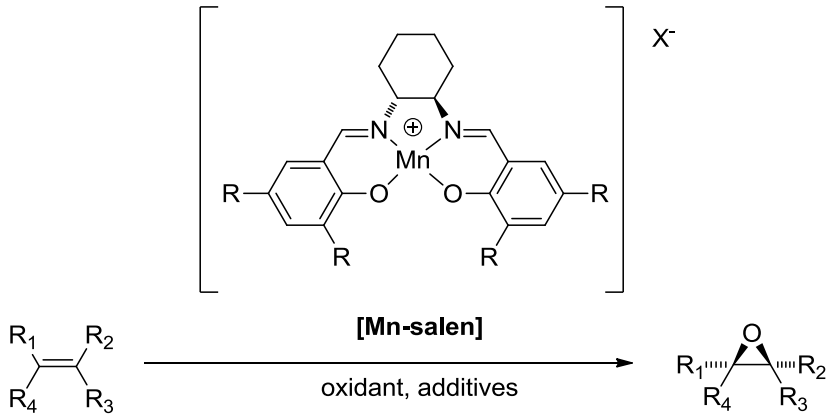
[1] (a) Belda, O.; Moberg, C. *Acc. Chem. Res.* **2004**, *37*, 159. (b) Moberg, C. *Top.Organometal. Chem*. **2012**, *38*, 209. 8c) Helmchen, G.; Dahnz, A.; Dübon, P.; Schelwies, M.; Weihofen, R. *Chem. Commun.* **2007**, 675. (d) Liu, W.-B.; Xia, J.-B.; You, S.-L. *Top. Organometal. Chem.* **2012**, *38*, 155.
[2] Trost, B. M.; Lautens, M.; *J. Am. Chem. Soc.* **1982**, *104*, 5543.
[3] (a) Bartels, B.; Garcia-Yebra, C.; Rominger, F.; Helmchen, G. *Eur. J. Inorg. Chem.* **2002**, 2569. (b) Helmchen, G.; Dahnz, A.; Dübon, P.; Schelwies, M.; Weihofen, R. *Chem. Commun.* **2007**, 675.
[4] Belda, O.; Moberg, C. *Acc. Chem. Res.* **2004**, *37*, 159.
[5] Kaiser, N.F.K.; Bremberg, U.; Larhed, M.; Moberg, C.; Hallberg, A. *Angew. Chem. Int. Ed.* **2000**, *39*, 3595.
[6] Trost, B. M.; Dogra, K. *J. Am. Chem. Soc*. **2002**, *124*, 7256.
[7] Trost, B. M.; Andersen, N. G.; *J. Am. Chem. Soc.* **2002**, *124*,14320.
[8] Hughes, D. L.; Lloyd-Jones, G. C.; Krska, S. W.; Gouriou, L.; Bonnet, V. D.; Jack, K.; Sun, Y.; Mathre, D. J.; Reamer, R. A. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5379.

[9] Trost, B. M. *Chem. Pharm. Bull*. **2002**, *50*, 1.
[10] Benessere, V.; Del Litto, R.; Moberg, C.; Ruffo, F.; *Eur. J. Org. Chem.* **2009**, 1352.
[11] (a) Trost, B.M.; Dogra, K.; Hachiya, I.; Emura, T.; Hughes, D.L.; Krska, S.; Reamer, R.A.; Palucki, M.; Yasuda, N.; Reider, P.J. *Angew. Chem. Int. Ed*. **2002**, *41*, 1929. (b) Hughes, D.L.; Palucki, M.; Yasuda, N.; Reamer, R.A.; Reider, P.J. *J. Org. Chem.* **2002**, *67*, 2762. (d) Krska, S.W.; Hughes, D.L.; Reamer, R.A.; Mathre, D.J.; Palucki, M.; Yasuda, N.; Sun, Y.; Trost, B.M. *Pure Appl. Chem.* **2004**, *76*, 625. (e) Lloyd-Jones, G.C.; Krska, S.W.; Hughes, D.L.; Gouriou, L.; Bonnet, V.D.; Jack, K.; Sun, Y.; Reamer, R.A. *J. Am. Chem. Soc.* **2004**, *126*, 702.
[12] (a) Belda, O.; Kaiser, N.-F. ; Bremberg, U.; Larhed, M.; Hallberg, A.; Moberg, C. *J. Org. Chem.* **2000**, *65*, 5868. (b) Belda, O.; Moberg, C. *Synthesis* **2002**, 1601.
[13] (a) Rajanbabu, T.V.; Ayers, T.A.; Casalnuovo, A.L. *J. Am. Chem. Soc*. **1994**, *116*, 4101. (b) Khiar, N.; Suárez, B.; Valdivia, V.; Fernández, I. *Synlett* **2005**, 2963. (c) Grugel, H.; Albrecht, F.; Minuth, T.; Boysen, M.M.K. *Org. Lett.* **2012**, *14*, 3780.

4. The *elpaN-salen* ligands: [Mn-salen] promoted Asymmetric Epoxidation.

4.1 Background of the Mn-salen promoted Asymmetric Epoxidation: scope of the reaction, mechanisms, state of the art.

The asymmetric epoxidation of olefins is of great interest because the resulting optically active epoxides are valuable intermediates for a wide variety of pharmaceutically relevant compounds; [1] various nucleophiles react with epoxides stereospecifically to give 1,2-difunctionalized products, establishing the stereochemistry of two vicinal carbons.
The pioneering studies on Asymmetric Epoxidation (AE) were performed on allylic alcohols and have been reported by Yamada [2] and Sharpless [3], independently. In 1980, a highly enantioselective epoxidation of allylic alcohols promoted by Titanium tartrate was first reported by Katsuki and Sharpless [4].
The enormous success of the Sharpless epoxidation reaction, which was awarded of the Nobel Prize in 2001, helped inspire widespread efforts to identify more general catalytic systems which might be effective for AE of unfunctionalized olefins, but efficient catalysts were designed only relatively recently [5]. The rational design of these catalyst was performed on the basis of the analogy with several stereoselective biological oxidation systems [6], and is based on highly enantioselective oxo-transfer [7]. Among them, Mn-salen complexes play a key role, but also Fe- and Mn-porphyrine are widely used [1b]. More recently, chiral dioxiranes have been developed as effective epoxidation catalysts, widening the substrate scope [8]. The following section will focus mainly on the Mn-salen complexes.
The generic AE promoted by Mn-salen is reported below in **Scheme 4.1.** The neat reaction is the simple formation of an epoxide starting from a double bond; a stochiometric oxidant is necessary, and usually additives increase the selectivity of the reaction.



Scheme 4.1

The scope of the reaction is wide in terms of substrate, oxidant and additives:

- **Substrates:** Cyclic and acyclic *cis*-disubstituted olefins have traditionally been the best substrates for the [Mn(salen)]-catalyzed epoxidation reaction; also *trans*-disubstituted olefins can be used, although progress in this area has been limited. Alternative methods exist to promote the epoxidation of *cis*-olefins to *trans*-epoxide as the major, and in some cases nearly exclusive, product [9]. A wide range of trisubstituted olefins are outstanding substrates for asymmetric epoxidation [10]. For monosusbstituted olefins, such as styrene, diminished catalyst enantioselectivity is reported, for then less using low-temperature protocol; improved enantioselectivities were attainable for most substrates under low-temperature conditions, but the effect was especially pronounced in the case of terminal olefins.[11]
- **Oxidants:** A extensive variety of stoichiometric oxidants have been recognized to be effective oxygen atom donors in oxo-transfer reactions with the catalysts. NaOCl [12] is problaly the most used, but alternatives are alkyl hydroperoxides [13], peroxy acids [14], amine N-oxides [15], ozone [16], potassium hydrogen persulfate (Oxone) [17], hydrogen peroxide [18], and periodate [19].
- **Additives:** In many cases, the addition of Lewis bases has been found to have a beneficial effect on catalyst activity and selectivity, probably due to coordination of the metal centre. Commonly used

additives include pyridine, imidazole, and pyridine N-oxide derivatives.

The generic structure of the salen ligands, reported in **Figure 4.1a**, incorporate a dissymmetric diimine bridge, derived from a C2-symmetric 1,2-diamine, and bulky substituents on the 3- and 3'-positions of the salicylide ligand. Several variants of this system exist.

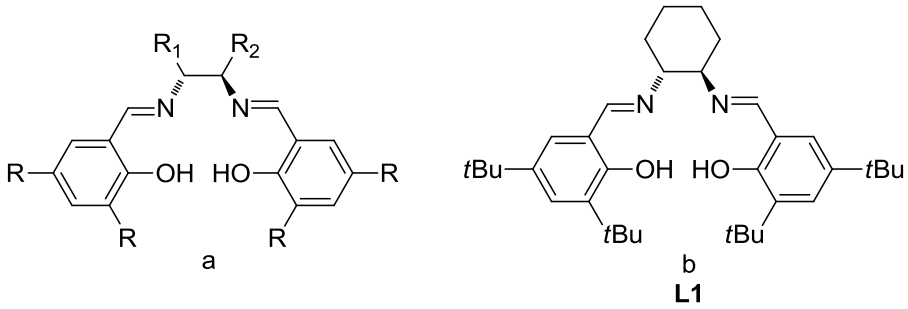
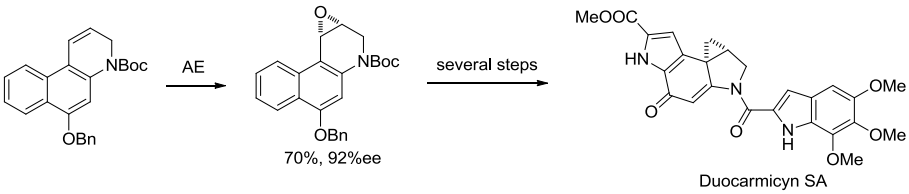


Figure 4.1

The most used ligands is based on 1,2-*trans*-cyclohexandiamine and the 3,5-di-*tert*-butyl salycilaldehyde (**Figure 4.1b**), due to a good compromise between selectivity and synthetic accessibility, although it is not the most selective.

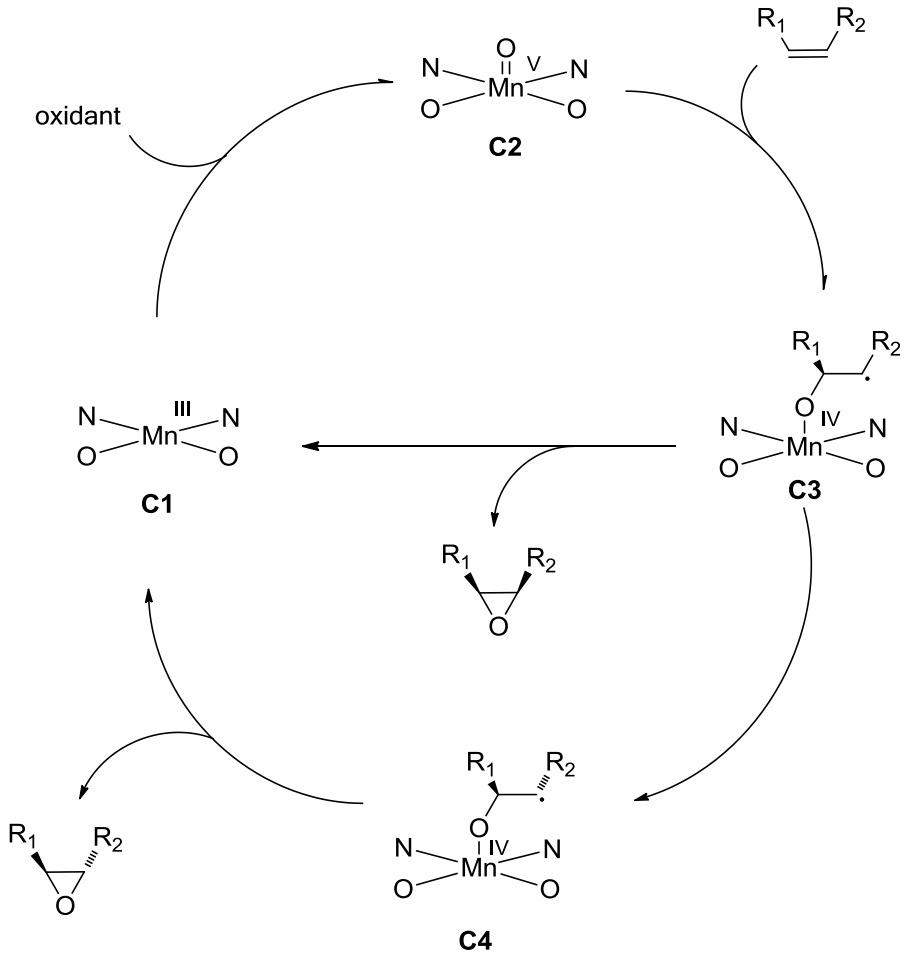
L1 has been employed widely on both laboratory and industrial scales for the epoxidation of cis-disubstituted and trisubstituted olefins, and its synthesis has been commercialized on the multi-hundred kg scale [20]. A notable example of its use in synthesis of Duocarmicyn SA, an antitumour antibiotics (**Scheme 4.2**).[21]



Scheme 4.2

4.1.1 Mechanism and enantiodiscrimination

As mentioned before, the mechanism of AE promoted by [Mn(salen] goes thought oxo-transfer from metal complexes to olefins, resulting in a net two-electron reduction at the metal center. For this reason, only metals capable of shuttling between oxidation states can be effective oxo-transfer catalysts, such as iron, manganese, ruthenium, and chromium [22]. The more widely accepted mechanism, typical for AE with tetradentate porphyrin and salen ligand frameworks, is reported in **Scheme 4.3**.



Scheme 4.3

The square planar Mn^{III} complex **C1** is oxidized to the correspondent oxo-specie **C2**, which is attacked directly by the substrate with sequential C-O bond formation. The olefin approachs to the Mn-O bond by a side-on, perpendicular trajectory. The radical **C3** can lead to the *cis* epoxide, or can isomerize to **C4** by rotation on the σ bond; this specie is responsible for the formation of the *trans*-epoxide. The extent of *trans*-epoxide formation depends strongly on the nature of the substrate: it is negligible for alkyl-substituted *cis*-olefins, it is more evident for aryl-substituted *cis*-olefins, while is prevalent for conjugated dienes. Additives such as pyridine N-oxide positively influence the rate, yield, cis/trans ratio, and enantioselectivity of the [Mn(salen)]-catalyzed epoxidation because the binding of N-oxide to the manganese center is thought to facilitate the rate-limiting oxidation to the metal-oxo, as well as stabilize the high-valent Mn(V) species.
The origin of enantioselectivity is explained on the basis of the active oxo-specie conformation. [23] The *stepped* conformation of F**igure 4.2** is reported to be the more stable.

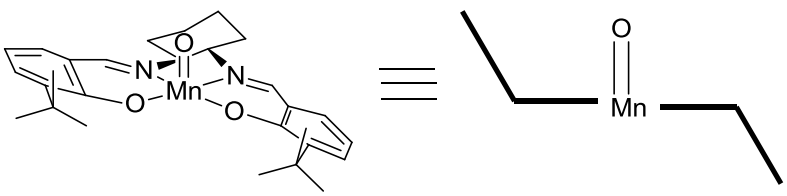


Figure 4.2

As mentioned before, the olefin will approach side-on to this "lenticular" molecule; several trajectories are possible (*i-v* in **Figure 4.3**, where the system is reported from above) but all of them, except *iv*, are reported to be unfeasible due to steric interaction between the olefin and the ligand; in particular, *i* is inhibited for the stepped conformation, *ii* and *iii* for the interaction with the cyclohexyl moiety, *v* for the interaction with the *t*Bu groups. Enantioselectivity originates from the substrate approaching trough *iv* preferentially from only one enantioface, namely the one which minimize the steric interaction between the bulkier group R_L on the alkene and the hindered group in position 3 of the salylicaldehyde.

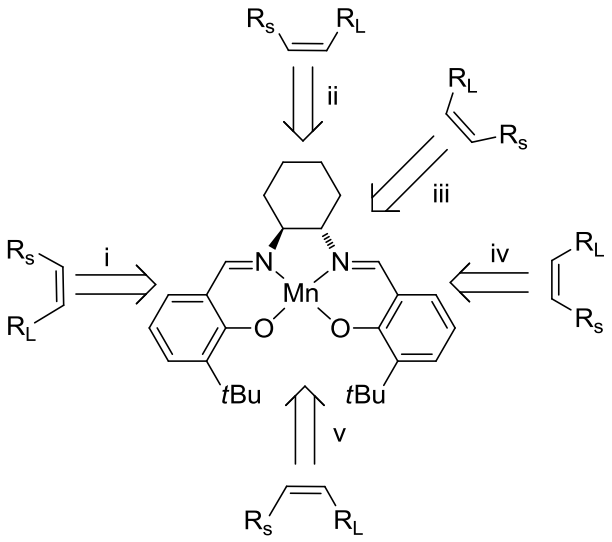
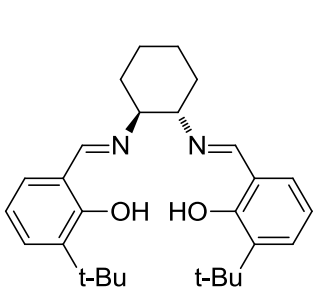


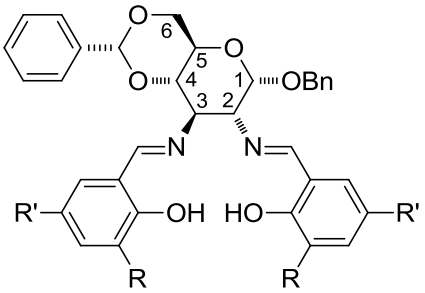
Figure 4.3

4.1.2 State of the art: the Naple-salen ligands.

This further "bouquet" of ligands, prepared in the research group where this PhD thesis has been performed [24], expanded the scope of the previously mentioned *Naple-type* ligands and contains the coordinating functions of the privileged salen ligands, namely two iminohydroxyphenyl arms in adjacent positions (**Figure 4.4**).



a chiral SALEN ligand



Naple-salenH_2-1 (R= *t*-Bu, R'= H)
Naple-salenH_2-2 (R=R'= *t*-Bu)

Figure 4.4

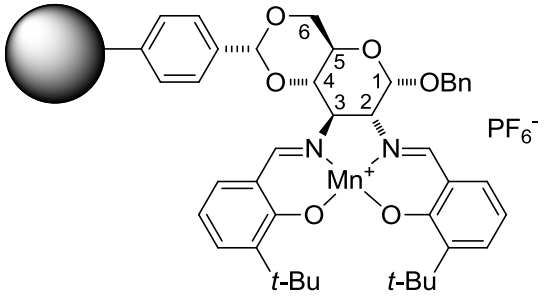
The cationic *N,N',O,O'*-Mn(III) complexes of the doubly deprotonated ligands were prepared and investigated in this important asymmetric reaction affording chiral epoxides.

A preliminary screening under four different conditions (with *m*-chloroperbenzoic acid, H_2O_2, NaClO and oxone) allowed to select the best oxidizing conditions, which were found in the use of *m*-chloroperbenzoic acid in the presence of *N*-methylmorpholine oxide at 195K in DCM. As shown in **Scheme 4.4**, (1S,2R)-**P1** was obtained in excellent yield, high selectivity and good ees. These values are close to that obtained by using the original Jacobsen catalyst under the same experimental conditions.

Scheme 4.4

Analogously, styrene was reacted with acceptable selectivities.

The possibility to extend use of the catalysts to multi-phasic catalysis was explored, by preparing a homogenous supported version of Mn(**Naple-salen-1**)]PF_6 [24b] (**Figure 4.5**).



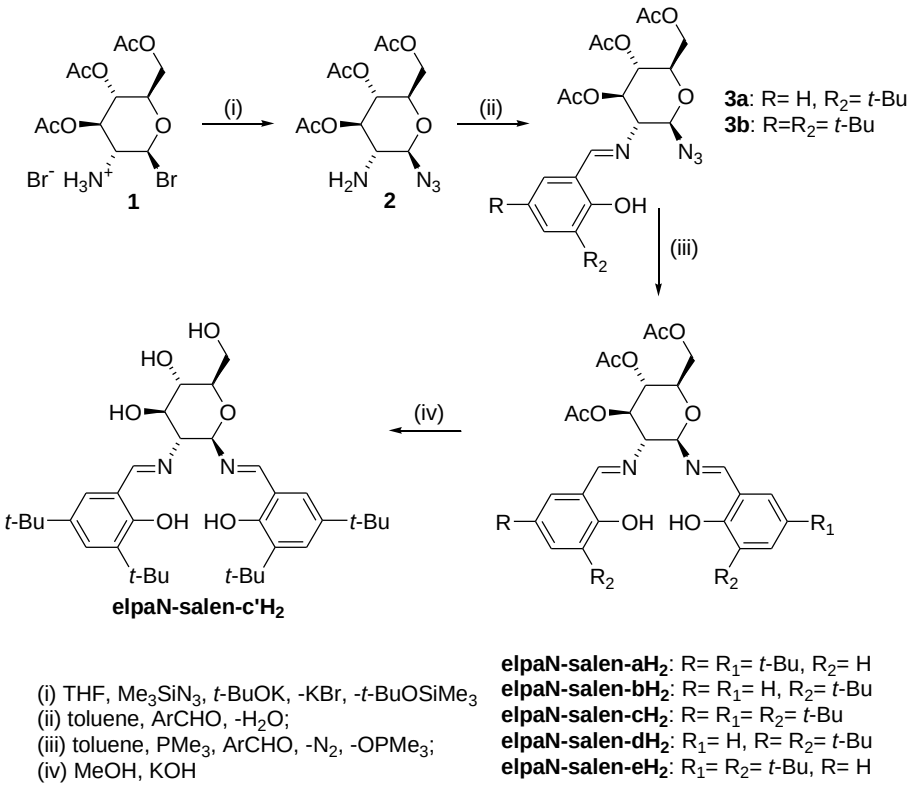
sup-[Mn(**Naple-salen-1**)]PF_6

Figure 4.5

The supported catalyst was prepared again by anchorage to the Stratosphere-CHO resin through the ring positions C4 and C6. It was found to contain 0.16–0.18 mmol of Mn per gram, and was examined in the epoxidation of *cis*-β-methylstyrene under the above mentioned conditions. Significant leak of metal from the matrix occurred during its use, which prevented efficient re-cycling of the catalyst.

4.2 the *elpaN-salen* ligands and the corresponding Mn complexes: synthesis and characterization.

In order to fully employ the versatility of the approach of pseudo-enantiomeric ligands (see chapter 1), the library of ligands *elpaN-salen* was rationally designed. This shows a specular stereochemistry of coordination related to the *Naple-salen*, aiming to produce the same Mn-promoted asymmetric epoxidation with opposite stereochemistry.
Scheme 4.5 reports the simple synthesis of the **elpaN-salen-H_2** ligands along with their labels.



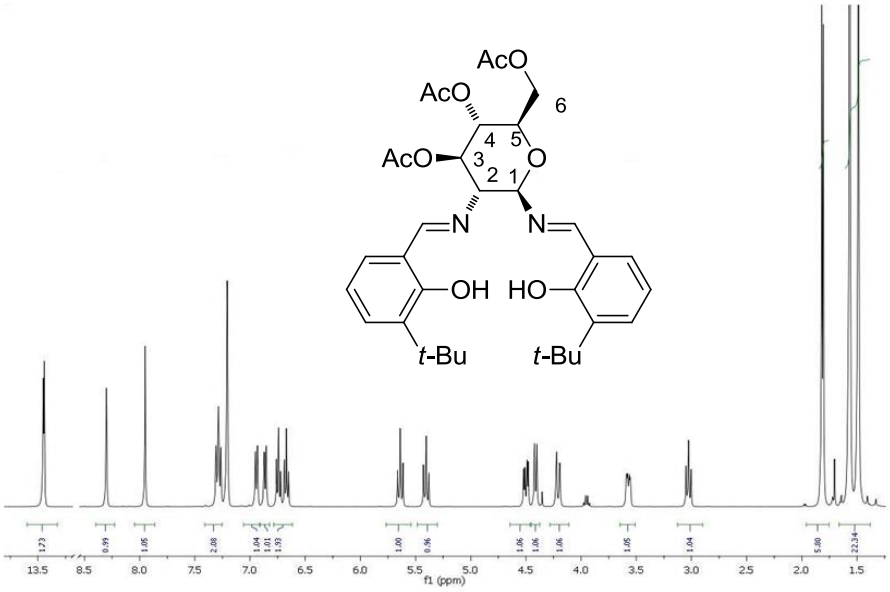
Scheme 4.5

The key-intermediate was the previously mentioned 1-azido-2-aminoglucose derivative **2**, which **2** could be reacted with the appropriate salicylaldehyde ArCHO (step ii), affording the 2-iminoderivatives **3a-b**. Condensation with a second equivalent of aldehyde (via Staudinger reaction, step iii) provided the target ligands. Steps ii and iii could be conveniently performed in one pot, although the syntheses of **elpaN-salen-dH$_2$** and **–eH$_2$** required isolation in the solid state of the intermediates **3b** and **3a**.

The five ligands differ for the position and the number of *t*-butyls in positions 3' and 5' of the aromatic portions. All of them, with the exception of **elpaN-salen-aH$_2$**, show tactical *t*-Bu groups in 3', *i.e.* ortho to the alcoholic oxygen. This steric motif is acknowledged as essential requirement for promoting high ees in the asymmetric epoxidation of styrenes promoted by the corresponding Mn(III) complexes.

ElpaN-salen-bH$_2$ and **–cH$_2$** are symmetrically substituted: the former shows only the just mentioned *t*-butyls in 3', the latter displays subsidiary *t*-butyls in the 5'-positions of both imino arms.
Instead, **elpaN-salen-dH$_2$** and **–eH$_2$** do present only one additional t-butyl group in 5', respectively in the imino function at C2 (**elpaN-salen-dH$_2$**) and C1 (**elpaN-salen-eH$_2$**).
This set of ligands was selected and prepared for assessing primary and secondary effects of the steric hindrance around the metal center, as well for disclosing possible enhancement of enantioselectivity due to selective crowding at only one side of the ligand.
A deprotected ligand (**elpaN-salen-c'H$_2$**) was also prepared, by treatment of the parent compound with catalytic potassium hydroxide in methanol (step iv). This action returned the hydroxyl functions available for further functionalization, and such a possibility was exploited for assessing the effect of other coordinating functions on the outcome of the catalysis.
The characterisation of the ligands was carried out through elemental analysis, IR and NMR spectroscopy. Deuterobenzene was used as solvent for NMR measurements, in order to inhibit hydrolysis of the imino functionalities, which takes place more easily in the acidic chlorinated solvents. As expected, the CH=N protons resonated at high frequency, as well as the –OH nuclei which were detected in the range 12-14 ppm. As an exemple, the ^{1}HNMR spectrum of **elpaN-salen-bH$_2$** is reported.
The absorptions at ca. 1630 cm^{-1} in the IR spectra recorded in nujol mull were attributed to the C=N stretchings.

^{1}H NMR spectrum of elpaN-salen-bH_2, 400 MHz, C_6D_6



The X-ray structure of **elpaN-salen-bH_2** was also determined (**Figure 4.6**).

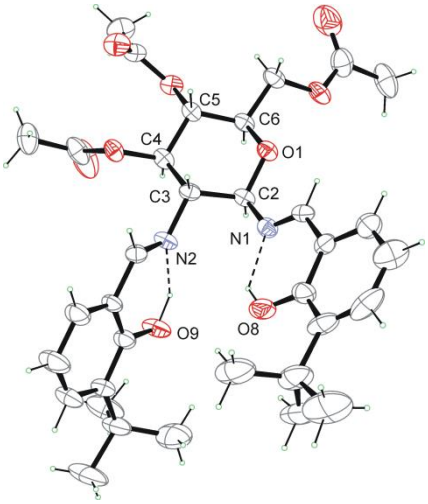


Figure 4.6

All bond distances fall in the normal range [25]. In the molecule the sugar ring adopts the expected chair conformation and the substituents at C2, C3, C4, C5, C6 occupy the equatorial positions. A planar conformation of both the phenoxyimine groups is stabilized by intramolecular OH···N hydrogen bonds (O8-H···N1 0.968(7), 1.821(6) Å, 130.8(4)°; O9-H···N2 1.023(6), 1.610(6) Å, 155.2(4)°). An angle of 71.4(2)° is observed between their mean planes. In the crystal packing weak C-H····O interactions favour the sugar rings to pile up along **b** axis, forming layers of molecules perpendicular to **c** axis. The layers of molecules face each to the other through hydrophobic *t*-butylic contacts.

Cationic manganese(III) complexes (**Figure 4.7**) were prepared from $Mn(AcO)_2$ through a known established procedure and according to the following illustrative stoichiometry, where elpaN-salen-a indicates the doubly deprotonated form of **elpaN-salen-aH2**:

$$2\,[Mn(AcO)_2] + 1/2\,O_2 + 2\,\textbf{elpaN-salen-aH}_2 + 2\,NaPF_6 = 2\,[Mn(\textbf{elpaN-salen-a})]PF_6 + 2\,NaOAc + 2\,HOAc + H_2O$$

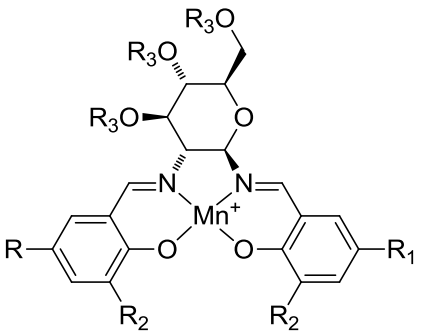


Figure 4.7

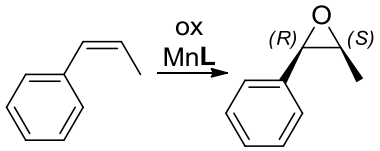
Only in the case of **elpaN-salen-c'H$_2$** was found more convenient the isolation of the neutral hydroxospecies [Mn(OH)(**elpan-salen-c'**)], which was expected to show a very similar catalytic behaviour.

The dark brown compounds were soluble in chlorinated solvents and aromatic hydrocarbons, and were characterised through elemental analysis, conductivity measurements, MS and IR spectroscopy. The molar conductivity of the cationic species in dichloromethane is within the range

20-25 S-1cm2mol-1, which confirms that they are 1:1 electrolytes.[26]
The IR CH=N stretchings are at lower frequencies with respect to those observed for the parent ligands. The PF_6^- anion gives rises to the expected broad band at ca. 850 cm-1.

4.3 Catalytic performances of the *elpaN-salen* ligands in the Mn promoted Asymmetric Epoxidation.

The ability of the new sugar based Mn complexes to promote the asymmetric epoxidation of styrenes was examined, also in comparison with the **Naple-type** counterpart.
First, epoxidation of *cis*-β-methylstyrene was carried out under diverse conditions by using [Mn(**elpaN-salen-b**)]PF_6 as catalyst. This screening was necessary in order to find out the best conditions for the catalysis, and the results are shown in **Table 4.1**.



S1 (1*R*,2*S*)-**P1**

N°	Oxidant	t (h)	Conversion(%)[a]	*cis*/*trans*	ee(%)[b]
1	*m*-CPBA[c]	0.5	>99	92/8	84(1*R*,2*S*)
2	NaClO[d]	4.5	>99	88/12	68(1*R*,2*S*)
3	*n*-Bu_4NHSO_5[e]	4.5	>99	71/29	50(1*R*,2*S*)
4	H_2O_2[f]	4.5	-	-	-

[a]The conversion was calculated by integration of suitable peaks in NMR spectrum; [b]The determination of ees was carried out by ^1H NMR analysis in $CDCl_3$ in the presence of Eu(hfc)$_3$ as shift reagent. The ees refer to the *cis*-epoxide. [c]At 196 K, in dichloromethane (4 mL). Ingredients (mmol): Mn/alkene/*m*-CPBA/NMO= 0.024/0.48/0.96/2.40. [d]At 273K in dichloromethane/water(pH 11.5) 1:2 (3 mL). Ingredients (mmol): Mn/alkene/NaClO(0.4 M)/py-*N*-oxide= 0.024/0.48/1.00/0.072. . [e]At 255 K in acetonitrile (3 mL). Ingredients (mmol): Mn/alkene/(*n*-$Bu_4N)HSO_5$/NMO= 0.024/0.48/0.75/0.48 [f]At 273 K in acetonitrile/acetic acid 16:1 (8 mL). Ingredients (mmol): Mn/alkene/H_2O_2(35%)= 0.024/0.48/1.00

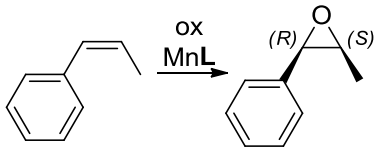
Table 4.1

Satisfactory results were obtained in dichloromethane at 196 K, by using *m*-chloroperbenzoic acid (*m*-CPBA) as the oxidant in the presence of *N*-methylmorpholine-*N*-oxide (NMO). In these conditions, the catalyst (entry 1) afforded the *cis* epoxide (*cis*/*trans* 92/8) as major product, with high conversions (>99% within 30 mins) and good ee (84%, *1R*,*2S*). An important outcome of this reaction is that the product was obtained with similar enantiomeric excess but opposite configuration with respect to what found by using the corresponding **Naple-type** derivative [24] (86%, *1S*,*2R*).

On the other hand, use of NaClO or oxone (entries 2 and 3) was accompanied by reduced *cis*/*trans* ratios (respectively 88/12 and 71/29) and moderate enantioselectivities (respectively 68% and 50%).

Hydrogen peroxide failed to promote the reaction.

Once found the optimal reaction conditions, *cis*-β-methylstyrene was oxidised with *m*-CPBA by using the entire set of ligands (**Table 4.2**).



S1 (1*R*,2*S*)-**P1**

N°	ligand	t (h)	conversion[b]	*cis*/*trans*	ee(%)[c]
1	**elpaN-salen-b**	0.5	99	92/8	84(1*R*,2*S*)
2	**elpaN-salen-c**	0.5	99	92/8	88(1*R*,2*S*)
3	**elpaN-salen-d**	0.5	99	90/10	82(1*R*,2*S*)
4	**elpaN-salen-e**	0.5	99	92/8	86(1*R*,2*S*)
5	**elpaN-salen-c'**[d]	0.5	>99	88/12	83(1R,2S)

[a]At 196 K, in dichloromethane (4 mL). Ingredients (mmol): Mn/alkene/*m*-CPBA/NMO= 0.024/0.48/0.96/2.40. [b]The conversion was calculated by integration of suitable peaks in NMR spectrum. [c]The determination of ees was carried out by ^{1}H NMR analysis in $CDCl_3$ in the presence of $Eu(hfc)_3$ as shift reagent. The ees refer to the *cis*-epoxide. [d]The catalyst was the neutral hydroxospecies [Mn(OH)(**elpaN-salen-c'**)]

Table 4.2

As expected, complex [Mn(**elpaN-salen-a**)]PF_6, which lacks of the strategic *t*-butyl groups in 3', failed to promote any enantioselectivity. All the other complexes afforded the *cis* product in reasonable selectivity and good ees (up to 88% ee), with little differences due to the diverse distributions of the subsidiary *t*-butyls in 5'. Good levels of enantioselectivity were observed also with the deprotected ligand **elpaN-salen-c'**, which demonstraates that decoration of the ligand does not affect its performance.

The discrepancies are very small, and therefore not sufficient to establish secondary effects on the stereochemical outcome of the reaction. However, this screening at least allowed to identify the most efficient catalyst, namely [Mn(**elpaN-salen-c**)]PF_6 (Table 3).

This compound was therefore also used for promoting epoxidation of other styrenes in the same conditions: styrene and β-methylstyrene were functionalised respectively in 45% and 50% ees. These findings are in agreement with literature data, because the oxidation of terminal olefins promoted by Mn salen complexes generally proceeds with lower

enantioselectivity. For instance, under the same experimental conditions the corresponding Jacobsen catalyst promotes the epoxidation of styrene in 56% ee [27].
Finally, the reaction on *cis*- and *trans*-stilbene provided the trans-oxide as a racemate. While these latter findings are not as satisfactory, the ensemble of results herein described significantly upgrade those obtained with the other rare examples of Mn(III)/ salen complexes derived from carbohydrates [28].

4.4 Conclusion.

This work substantiates the original idea on the possibility to prepare libraries of pseudo-enantiomeric ligands based on D-glucose by simply switching the positions of coordination from C2 and C3 (**Naple-type**) to C1 and C2 (**elpaN-type**). Thus, the series of **elpaN-salen-H_2** ligands was prepared through a straightforward synthesis starting from inexpensive sources. The Mn(III) complexes of the corresponding *O,O'*-deprotonated chelates were found to be active in the asymmetric epoxidation of styrenes. A comparison with the enantiomeric **Naple-type** counterpart, returns a gratifying view about the performance of the new complexes. The next application will concern the extension to multiphase catalysis [29], using appropriate phase-tags on the auxiliary sugar positions at C3, C4 and C6.

4.5 Experimentals.

4.5.1. General consideration:

NMR spectra were recorded in $CDCl_3$ ($CHCl_3$, δ = 7.26 ppm, and $^{13}CDCl_3$ δ = 77 ppm, as internal standards), or C_6D_6 (TMS, δ = 0 ppm, and $^{13}C_6D_6$ δ = 128.62 ppm, as internal standards) with a 400 MHz (Bruker DRX-400). *J* values are given in Hz. Dichloromethane was distilled from CaH_2, toluene from Na.

4.5.2. Preparation of elpaN-salen-aH$_2$, -bH$_2$, -cH$_2$:

Azide **2** (0.66 g, 2.0 mmol) was stirred in dry toluene (8.0 mL) under inert atmosphere at 273 K. The desired aldehyde was added (4.2 mmol), followed by P(Me)Ph$_2$ (0.40 g, 2.0 mmol). The system was stirred over night at RT. The solvent was removed under vacuum and the crude product was purified by flash cromatography on silica (eluent: EtOAc / PE =1/3, NEt$_3$ 1%) **elpaN-salen-aH$_2$**: MS(MALDI) calcd. for $C_{34}H_{45}N_2O_9$ $[LH]^+$: 625.31, found 625.40- ^{1}H NMR(C_6D_6): δH = 12.62 (1 H, s, OH), 12.53 (1 H, s, OH), 8.37 (1 H, s, N=CH) 8.03 (1 H, s, N=CH), 7.29-7-05 (5 H, m, aromatics), 6.94 (1 H, d, J = 6.9, aromatic) 5.67 (1 H, t, $J_{3,4} = J_{3,2} = 9.7$, 3-H), 5.42 (1 H, t, $J_{4\text{-}5} = 9.7$, 4-H), 4.50 (1 H, dd, $J_{6,6'} = 12.3$, $J_{5,6} = 4.7$, 6-H), 4.46 (1 H, d, $J_{1,2} = 8.6$, 1-H), 4.22 (1 H, dd, $J_{5,6'} = 1.2$, 6'-H), 3.57 (1 H, m, 5-H), 3.18 (1 H, t, 2-H), 1.80 (3 H, s, OAc), 1.77 (3 H, s, OAc), 1.55 (3 H, s, OAc), 1.17 (9 H, s, *t*-Bu), 1.12 (9 H, s, *t*-Bu). ^{13}C NMR(C_6D_6): δC = 170.2, 170.1, 169.6, 169.4, 165.9, 159.8, 159.7, 141.6, 141.5, 131.2, 131.1, 129.1, 128.7, 118.2, 118.1, 117.6, 117.5, 92.1, 74.8, 74.7, 74.4, 68.8, 62.4, 34.0, 33.9, 31.5 (6C), 20.5, 20.4, 20.1; IR: ν_{max}/cm^{-1} = 1751 (C=O), 1635 (C=N). **elpaN-salen-bH$_2$**: MS(MALDI) calcd. for $C_{34}H_{45}N_2O_9$ $[LH]^+$: 625.31, found 625.43. ^{1}H NMR(C_6D_6): δH = 13.45 (1 H, s, OH), 13.44 (1 H, s, OH), 8.30 (1 H, s, N=CH) 7.95 (1 H, s, N=CH), 7.29 (2 H, t, J = 8.6, aromatics), 6.94 (1 H, d, J = 6.9, aromatic), 6.86 (1 H, d, J = 6.9, aromatic), 6.74 (1 H, t, J = 6.7, aromatic), 6.67 (1 H, t, J = 6.7, aromatic), 5.64 (1 H, t, $J_{3,4} = J_{3,2} = 9.7$, 3-H), 5.40 (1 H, t, $J_{4\text{-}5} = 9.7$, 4-H), 4.50 (1 H, dd, $J_{6,6'} = 12.4$, $J_{5,6} = 4.6$, 6-H), 4.41 (1 H, d, $J_{1,2} = 8.6$, 1-H), 4.21 (1 H, dd, $J_{5,6'} = 1.5$, 6'-H), 3.57 (1 H, m, 5-H), 3.03 (1 H, t, 2-H), 1.82 (3 H, s, OAc), 1.81 (3 H, s, OAc), 1.57 (3 H, s, OAc), 1.56 (9 H, s, *t*-Bu), 1.49 (9 H, s, *t*-Bu). ^{13}C NMR(C_6D_6): δC = 170.6, 170.2, 169.6, 169.4, 166.2, 161.0(2C), 138.0(2C), 131.1, 131.0(2C), 130.9, 118.8, 118.7(3C), 92.0, 74.6, 74.2, 74.1, 68.8, 62.3, 35.2, 35.2, 29.7(3C), 29.6(3C), 20.4, 20.3, 20.1.; IR: ν_{max}/cm^{-1} = 1752 (C=O), 1629 (C=N). **elpaN-salen-cH$_2$**: MS(MALDI) calcd. for $C_{42}H_{61}N_2O_9$ $[LH]^+$: 737.44, found 737.50. ^{1}H NMR(C_6D_6): δH = 13.38 (1 H, s, OH), 13.30 (1 H, s, OH), 8.37 (1 H, s, N=CH) 8.03 (1 H, s, N=CH), 7.56 (1 H, s, aromatic), 7.54 (1 H, s, aromatic), 7.07 (1 H, s, aromatic), 7.00 (1 H, s, aromatic), 5.70 (1 H, t, $J_{3,4} = J_{3,2} = 9.7$, 3-H), 5.43 (1 H, t, $J_{4\text{-}5} = 9.7$, 4-H), 4.50 (1 H, dd, $J_{6,6'} = 12.3$, $J_{5,6} =$

4.6, 6-H), 4.46 (1 H, d, $J_{1,2}$ = 8.6, 1-H), 4.21 (1 H, dd, $J_{5,6'}$ = 1.5, 6'-H), 3.59 (1 H, m, 5-H), 3.17 (1 H, t, 2-H), 1.80 (3 H, s, OAc), 1.77 (3 H, s, OAc), 1.61 (9 H, s, *t*-Bu), 1.58 (3 H, s, OAc), 1.54 (9 H, s, *t*-Bu), 1.31 (9 H, s, *t*-Bu), 1.23 (9 H, s, *t*-Bu). ^{13}C NMR(C_6D_6): δC = 171.0, 170.2, 169.7, 169.5, 166.8, 159.0, 158.9, 140.8(2C), 137.5, 137.4, 127.5(2C), 127.0(2C), 118.3, 118.2, 92.1, 74.7, 74.5, 74.3, 68.9, 62.4, 35.5(2C), 34.4, 34.3, 31.7(3C), 31.6(3C), 29.8(6C), 20.5, 20.4, 20.2. IR: ν_{max}/cm^{-1} = 1752 (C=O), 1628 (C=N).

4.5.3 Preparation of 3a-b:

Azide **2** (0.66 g, 2.0 mmol) was stirred in dry toluene (8.0 mL) under inert atmosphere. The desired aldehyde was added (2.0 mmol), and the system was left to react over night. The solvent was removed under vacuum and the crude product was purified by flash cromatography on silica gel (eluent: EtOAc/PE =1/2, NEt_3 1%) **3a**: ^{1}H NMR(C_6D_6): δH = 13.22 (1 H, s, OH), 8.03 (1 H, s, N=CH), 7.62 (1 H, d, J = 2.3, aromatic), 7.06 (1 H, d, J = 2.2, aromatic), 5.44 (1 H, t, $J_{3,4}$ = $J_{3,2}$ = 9.7, 3-H), 5.31 (1 H, t, $J_{4\text{-}5}$ = 9.7, 4-H), 4.40 (1 H, dd, $J_{6,6'}$ = 12.4, $J_{5,6}$ = 4.4, 6-H), 4.13 (1 H, d, $J_{1,2}$ = 8.7, 1-H), 4.06 (1 H, dd, $J_{5,6'}$ = 1.9, 6'-H), 3.40 (1 H, m, 5-H), 3.07 (1 H, t, 2-H), 1.81 (3 H, s, OAc), 1.78 (3 H, s, OAc), 1.63 (9 H, s, *t*-Bu), 1.51 (3 H, s, OAc), 1.32 (9 H, s, *t*-Bu). ^{13}C NMR(C_6D_6): δC = 166.4(2C), 166.1, 165.6, 165.3, 157.2, 134.3, 127.2, 127.0, 114.9, 85.2, 70.5, 69.6, 68.8, 64.4, 57.9, 31.3, 25.8(3C), 16.4, 16.3, 16.0. **3b**: ^{1}H NMR(C_6D_6): δH = 13.28 (1 H, s, OH), 7.90 (1 H, s, N=CH), 7.30 (1 H, d, J = 7.7, aromatic), 6.85 (1 H, d, J = 7.7, aromatic), 6.72 (1 H, t, J = 7.7, aromatic), 5.34 (1 H, t, $J_{3,4}$ = $J_{3,2}$ = 9.7, 3-H), 5.24 (1 H, t, $J_{4\text{-}5}$ = 9.7, 4-H), 4.34 (1 H, dd, $J_{6,6'}$ = 12.4, $J_{5,6}$ = 4.5, 6-H), 4.06 (1 H, d, $J_{1,2}$ = 8.7, 1-H), 4.00 (1 H, dd, $J_{5,6'}$ = 2.0, 6'-H), 3.33 (1 H, m, 5-H), 2.91 (1 H, t, 2-H), 1.74 (3 H, s, OAc), 1.69 (3 H, s, OAc), 1.52 (9 H, s, *t*-Bu), 1.45(3 H, s, OAc). ^{13}C NMR(C_6D_6): δC = 166.9(2C), 166.1, 165.6, 165.3, 155.2, 133.8, 124.7, 123.2, 114.3, 85.3, 70.6, 69.7, 69.0, 64.5, 58.0, 31.6, 30.4, 27.8(3C), 25.8(3C), 16.3, 16.1(2C).

4.5.4 Preparation of elpaN-salen-dH$_2$ and elpaN-salen-eH$_2$:

A solution of **3a**/**3b** (1.0 mmol) in dry dichloromethane (5.0 mL) under inert atmosphere was added to a solution of P(Me)Ph$_2$ (0.20 g, 1.0 mmol) in dichloromethane (5.0 mL) at 0°C. The system was stirred 2 h at RT, and then the desired aldehyde was added (1.0 mmol). After 20 h, the solvent was removed under vacuum and the crude product was purified by flash cromatography on silica gel (eluent: EtOAc / PE =1/3, NEt$_3$ 1%) **elpaN-salen-dH$_2$**: MS(MALDI) calcd. for $C_{38}H_{53}N_2O_9$ $[LH]^+$: 681.38, found 681.65. ^{1}H NMR(C_6D_6): δH = 13.40 (1 H, s, OH), 13.32 (1 H, s, OH), 8.28 (1 H, s, N=CH) 7.97 (1 H, s, N=CH), 7.55 (1 H, d, J = 2.2, aromatic), 7.22 (1 H, d, J = 7.7, aromatic), 7.04 (1 H, d, J = 2.2, aromatic), 6.81 (1 H, d, , J = 7.7, aromatic), 6.62 (1 H, t, J = 7.7, aromatic), 5.66 (1 H, t, $J_{3,4} = J_{3,2} = 9.7$, 3-H), 5.38 (1 H, t, $J_{4\text{-}5} = 9.7$, 4-H), 4.45 (1 H, dd, $J_{6,6'} = 12.4$, $J_{5,6} = 4.6$, 6-H), 4.37 (1 H, d, $J_{1,2} = 7.9$, 1-H), 4.17 (1 H, dd, $J_{5,6'} = 1.8$, 6'-H), 3.52 (1 H, m, 5-H), 3.08 (1 H, t, 2-H), 1.76 (6 H, s, OAc x 2), 1.58 (9 H, s, *t*-Bu), 1.54 (3 H, s, OAc), 1.44 (9 H, s, *t*-Bu), 1.29 (9 H, s, *t*-Bu). ^{13}C NMR(C_6D_6): δC = 167.1(2C), 166.2, 165.7, 165.6, 162.2(2C), 157.0, 155.0, 136.8, 133.9, 133.6, 127.2, 127.0, 123.1, 114.8, 114.3, 87.8, 70.7, 70.5, 70.2, 64.9, 58.4, 31.6, 31.2, 30.4, 27.8(3C), 25.9(3C), 25.8(3C), 16.5, 16.4, 16.2. IR: ν_{max}/cm^{-1} = 1751 (C=O), 1617 (C=N); MS(ESI) *m/z* = 681.65 (LH^+) **elpaN-salen-eH$_2$**: MS(MALDI) calcd. for $C_{38}H_{53}N_2O_9$ $[MH]^+$: 681.38, found 681.53. ^{1}H NMR(C_6D_6): δH = 13.47 (1 H, s, OH), 13.29 (1 H, s, OH), 8.29 (1 H, s, N=CH) 7.90 (1 H, s, N=CH), 7.53 (1 H, d, J = 1.9, aromatic), 7.25 (1 H, d, J = 7.4, aromatic), 6.97 (1 H, d, J = 2.1, aromatic), 6.87 (1 H, d, , J = 6.7, aromatic), 6.68 (1 H, t, J = 7.7, aromatic), 5.62 (1 H, t, $J_{3,4} = J_{3,2} = 9.7$, 3-H), 5.39 (1 H, t, $J_{4\text{-}5} = 9.7$, 4-H), 4.48 (1 H, dd, $J_{6,6'} = 12.4$, $J_{5,6} = 4.5$, 6-H), 4.40 (1 H, d, $J_{1,2} = 8.5$, 1-H), 4.16 (1 H, dd, $J_{5,6'} = 1.5$, 6'-H), 3.53 (1 H, m, 5-H), 3.03 (1 H, t, 2-H), 1.76 (3 H, s, OAc), 1.75 (3 H, s, OAc), 1.52 (3 H, s, OAc), 1.51 (9 H, s, *t*-Bu), 1.44 (9 H, s, *t*-Bu), 1.21 (9 H, s, *t*-Bu). ^{13}C NMR(C_6D_6): δC = 170.6(2C), 170.2, 169.7, 169.5, 166.8, 161.0, 158.9, 140.8, 138.0, 137.5, 131.0(2C), 127.4, 118.8, 118.7, 118.1, 92.4, 74.7, 74.3, 74.1, 68.7, 62.3, 35.5, 35.2, 34.3, 31.6(3C), 29.7(3C), 29.7(3C), 20.5, 20.4, 20.1. IR: ν_{max}/cm^{-1} = 1751 (C=O), 1617 (C=N).

4.5.5. Preparation of elpaN-salen-c'H_2:

elpaN-salen-cH_2 (0.50 mmol) was dissolved in methanol (15 mL), and a catalytic amount (5% respect to the ligand) of KOH was added. The reaction was controlled by TLC, and after 2h was complete. The solvent was removed under vacum, and the residue was dissolved in THF and filtrated over a short pad of celite in order to remove the residual base. Evaporation of the solvent afforded the product in quantitative yield. ^{1}H NMR(C_6D_6): δH = 13.77 (1 H, s, OH), 13.51 (1 H, s, OH), 8.36 (1 H, s, N=CH) 8.18 (1 H, s, N=CH), 7.54 (1 H, s, aromatic), 7.50 (1 H, s, aromatic), 7.07 (1 H, s, aromatic), 7.02 (1 H, s, aromatic), 4.58 (1 H, d, $J_{1,2}$ = 8.5, 1-H), 3.99-3.90 (2 H, m, 6-H + 6'-H), 3.84 (1 H, t, $J_{3,4}$ = $J_{3,2}$ = 8.9, 3-H), 3.74 (1 H, t, $J_{4,5}$ = $J_{3,4}$, 4-H), 3.47 (1 H, m, 5-H), 3.17 (1 H, t, 2-H), 1.64 (9 H, s, *t*-Bu), 1.50 (9 H, s, *t*-Bu), 1.26 (9 H, s, *t*-Bu), 1.22 (9 H, s, *t*-Bu). ^{13}C NMR(C_6D_6): δC = 166.8, 158.9, 140.7(2C), 137.4, 137.1, 127.4, 127.3, 118.6, 118.2, 93.4, 78.1, 76.5, 75.9, 70.7, 62.7, 35.5(2C), 34.4(2C), 31.7(3C), 31.6(3C), 29.9(3C), 29.8(3C).

4.5.6. Preparation of [Mn(elpaN-salen)]PF_6 complexes:

The proper ligand (0.30 mmol) and $Mn(OAc)_2$•$4H_2O$ (0.30 mmol) were dissolved in absolute ethanol (7 mL). The mixture was stirred bubbling air through the solution. After 8 h, a solution of $NaPF_6$ (3.0 mmol) in 1.5 mL of water was added. After stirring further 18 h, water (50 mL) was added, obtaining a brown precipitate which was filtered and washed with water. The solid was dissolved in DCM, anhydrified with sodium sulphate, concentred and precipitated in hexane, obtaing the title products in 75-80% yield. [Mn(**elpaN-salen-a**)]PF_6: found: C, 49.05; H, 5.22; N, 3.27; Mn, 6.69%. Calc. for $C_{34}H_{42}F_6MnN_2O_9P$: C, 49.64; H, 5.15; N, 3.41; Mn, 6.68%; IR: ν_{max}/cm^{-1} = 1751 (C=O), 1617 (C=N), 845 (PF_6^-); MS(ESI): 676.77 $[M]^+$, 144.91 $[PF_6]^-$. [Mn(**elpaN-salen-b**)]PF_6: found: C, 50.79; H, 5.14; N, 3.56; Mn, 6.73%. Calc. for $C_{34}H_{42}F_6MnN_2O_9P$: C, 49.64; H, 5.15; N, 3.41; Mn, 6.68%; IR: ν_{max}/cm^{-1} = 1752 (C=O), 1617 (C=N), 845 (PF_6^-); MS(ESI): 677.14 $[M]^+$, 144.91 $[PF_6]^-$. [Mn(**elpaN-salen-c**)]PF_6: found: C, 53.39; H, 6.45; N, 2.94; Mn, 5.64%. Calc. for $C_{42}H_{58}F_6MnN_2O_9P$: C, 53.96; H, 6.25;

N, 3.00; Mn, 5.88%; IR: ν_{max}/cm^{-1} = 1752 (C=O), 1610 (C=N), 843 (PF_6^-); MS(ESI): 789.35 $[M]^+$, 144.91 $[PF_6]^-$. [Mn(**elpaN-salen-d**)]PF_6: Found: C, 52.12; H, 5.90; N, 3.27; Mn, 6.48%. Calc. for $C_{38}H_{50}F_6MnN_2O_9P$: C, 51.94; H, 5.74; N, 3.19; Mn, 6.25%; IR: ν_{max}/cm^{-1} = 1752 (C=O), 1613 (C=N), 843 (PF_6^-); MS(ESI): 732.90 $[M]^+$, 144.91 $[PF_6]^-$. [Mn(**elpaN-salen-e**)]PF_6: found: C, 51.46; H, 5.88; N, 3.07; Mn, 5.99%. Calc. for $C_{38}H_{50}F_6MnN_2O_9P$: C, 51.94; H, 5.74; N, 3.19; Mn, 6.25%; IR: ν_{max}/cm^{-1} = 1752 (C=O), 1613 (C=N), 843 (PF_6^-); MS(ESI): 732.90 $[M]^+$, 144.91 $[PF_6]^-$.

4.5.7. Preparation of complex [Mn(OH)(elpaN-salen-c')]:

Ligand **elpaN-salen-c'H_2** (0.30 mmol) and $Mn(OAc)_2 \cdot 4H_2O$ (0.30 mmol) were dissolved in absolute ethanol (7 mL), and the mixture was stirred for 8 h bubbling air through the solution. After 18h, 50 mL of water were added, and the solution was extracted three times with dichloromethane. The organic phase was anhydrified with sodium sulphate, concentred and precipitated in hexane, obtaing the title product in 74% yield. Found: C, 63.22; H, 7.70; N, 4.27; Mn, 8.28%. Calc. for $C_{36}H_{53}MnN_2O_7$: C, 63.52; H, 7.85; N, 4.12; Mn, 8.07%; IR: ν_{max}/cm^{-1} = 1618 (C=N); MS(MALDI): 663.20 $[M - OH]^+$.

4.5.8. Typical procedure for the asymmetric epoxidation using m-chloroperbenzoic acid as oxidant:

The olefin substrate (0.48 mmol) and *N*-methylmorpholine-*N*-oxide (2.4 mmol) were added to a solution of the appropriate Mn complex (0.024 mmol in 4 mL of dichloromethane. The mixture was cooled at 196 K, then *m*-chloroperbenzoic acid (0.96 mmol) was added as a solid over a 2 min period. After an established period of time, 5 mL of 1 M NaOH were added, and the organic phase separated, washed with brine (10 mL) and dried over sodium sulphate. The resulting solution was purified by filtration through a small pad of silica gel. The solvent was removed under vacuum, and the yield was determined by ^1H NMR using $Eu(hfc)_3$ for the valutation of the ee%.

4.5.9. Typical procedure for the asymmetric epoxidation using NaClO as oxidant:

cis-β-methylstyrene (0.48 mmol) and pyridine-*N*-oxide (0.072 mmol) were added to a solution of [Mn(**elpaN-salen-b**)]PF_6 (0.024 mmol) in dichloromethane (1 mL). After the addition of 2 mL of buffered NaClO solution (1.0 mmol, pH 11.3) as the oxidant at 273 K, the resulting mixture was stirred vigorously. After 4.5h, the mixture was diluted with DCM (2.5 mL). The organic layer was separated, washed with brine, and then dried with sodium sulphate. The resulting solution was purified by filtration through a small pad of silica gel. The solvent was removed and yield was determined by ^{1}H NMR using Eu(hfc)$_3$ for the valutation of the ee%.

4.5.10. Typical procedure for the asymmetric epoxidation using n-Bu_4HSO_5 as oxidant.

cis-β-methylstyrene (0.48 mmol) and *N*-methylmorpholine-*N*-oxide (0.48 mmol) were added to a solution of [Mn(**elpaN-salen-b**)]PF_6 (0.024 mmol) in 3 mL of acetonitrile. The mixture was cooled at -18°C, then the oxidant (0.75 mmol) was added as a solid over a 15 min period. After an established period of time, the reaction was quenched by adding dimethyl sulfide (ca. 1 mmol). Excess solid K_2CO_3 was added, the mixture was allowed to reach room temperature and then filtered. The filtrate was concentrated and the residue was purified through a small pad of silica gel (eluent *n*-hexane/ethylacetate = 9/1). The solvent was removed and yield was determined by ^{1}H NMR using Eu(hfc)$_3$ for the valutation of the ee%.

4.5.11. X-ray crystallography of elpaN-salen-bH$_2$ [3]:

Single crystal suitable for X-ray analysis were obtained by slow evaporation of a methanol solution at ambient temperature. The quality of the crystals was rather poor as witnessed by the fact that the diffraction pattern gave few high θ reflections. Data were collected on a Bruker-Nonius Kappa-CCD diffractometer using graphite monochromated MoKα radiation (λ = 0.71073 Å) at ambient temperature. Unit cell parameters were determined by least squares refinement of the θ angles of 70 strong reflections in the range 3.089°<θ<12.966°. Data reduction and semiempirical absorption correction were done using SADABS program [27]. The structure was solved by direct methods (SIR97 program [28]) and refined by the full matrix least-squares method on F2 using SHELXL-97 program [30] with the aid of the program WinGX [31]. Non-hydrogen atoms were refined anisotropically; H atoms of hydroxyl groups were found in difference Fourier maps, the positions of the other H atoms were determined stereochemically. H atoms were refined by the riding model with Uiso = 1.2·Ueq of the carrier atom (1.5·Ueq for H atoms of methyl groups).

4.6 References.

[1] (a) Katsuki, T.; *Epoxidation of Allylic Alcohols*. In: Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H.; (eds) *Comprehensive asymmetric catalysis.* Springer, Heidelberg **1999**. (b) Jacobsen, E. N.; Wu, H. M.; *Epoxidation of Alkenes Other than Allylic Alcohols* In: Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H.; (eds) *Comprehensive asymmetric catalysis.* Springer, Heidelberg **1999**.

[2] Yamada, S.; Mashiko, M.; Terashima, S.; *J. Am. Chem. Soc.* **1977**, *99*, 1988.

[3] Empirical formula: $C_{34}H_{44}N_2O_7$; Formula weight: 624.71; Crystal system: monoclinic; Space group: C2; a/Å: 21.835(4); b/Å: 9.207(2); c/Å: 18.641(3); β/°: 106.804(8); Volume/Å^3: 3513(1); Z: 4; Calculated density (g/cm^3): 1.181; μ/mm^{-1}: 0.085; θ range for data collection (°): 3.13-25.00; Reflections collected/unique: 9950/3244 [R_{int}=0.1138]; Data/restraints /parameters: 3244 /1/414; R indices: [I > 2σ(I)]; R_1: 0.0740; wR_2: 0.1234; R indices (all data) R_1: 0.2084; wR_2: 0.1573; Largest difference peak and hole (electron/Å^3) 0.251, -0.177.

[3] Michaelson, R. C.; Palermo R. E.; Sharpless, K. B.; *J. Am. Chem. Soc*. **1977** *99*, 1990.
[4] Katsuki, T.; Sharpless, K. B.; *J. Am. Chem. Soc*. **1980** *102*, 5974.
[5] (a) Jacobsen, E. N.; *Asymmetric Catalytic Epoxidation of Unfunctionalized Olefins*. In: Ojima, I.; (ed) *Catalytic Asymmetric Synthesis*. VCH, New York, chap 4.2 **1993**. (b) Jacobsen, E. N.; *Transition Metal-catalyzed Oxidations: Asymmetric Epoxidation*. In: Wilkinson, G.; Stone, F. G. A.; Abel, E. W.; Hegedus, L. S.; (eds) *Comprehensive Organometallic Chemistry II*. Pergamon, New York, chap 11.1 **1995**.
[6] (a) McMurry, T. J.; Groves, J. T.; In: Ortiz de Montellano, P. R.; (ed) *cytochrome P-450: Structure, Mechanism, and Biochemistry*. Plenum, New York, chap. 1, **1986**. (b) Holland, H. L.; *Organic Synthesis with Oxidative Enzymes*. VCH, New York **1992**. (c) Allain, E. J.; Hager, L. P.; Deng, L.; Jacobsen, E. N.; *J. Am. Chem. Soc*. **1993** *115*,4415.
[7] (a) Zhang, W.; Loebach, J. L.; Wilson, S. R.; Jacobsen, E. N.; *J. Am. Chem. Soc*. **1990**, *112*, 2801. (b) Jacobsen, E. N.; Zhang, W.; Muci, A. R.; Ecker, J. R.; Deng, L.; *J. Am. Chem. Soc*. **1991**, *113*, 7063.
[8] (a) Adam, W.; Smerz, A. K.; *Bull. Soc. Chim. B. elg*. **1996**, *105*, 581. (b) Curci, R.; Dinoi, A.; Rubino, M. F.; *Pure Appl. Chem*. **1995**, *67*, 811. (c) Murray, R. W.; *Chem. Rev*. **1989**, *89*, 1187.
[9] Chang, S.; Galvin, J. M.; Jacobsen, E. N.; *J. Am. Chem. Soc*. **1994**, *116*, 6937.
[10] (a) Fukuda, T.; Irie, R.; Katsuki, T.; *Synlett* **1995**, 197. (b) Brandes, B. D.; Jacobsen, E. N.; *J. Org. Chem*. **1994**, *59*,4378.
[11] Palucki, M.; Pospisil, P. J.; Zhang, W.; Jacobsen, E. N.; *J. Am. Chem. Soc*. **1994**, *116*, 9333.
[12] (a) Tabushi, I.; Koga, N.; *Tetrahedron Lett*. ***1979***, *20*, 3681. (b) Guilmet, E.; Meunier, B.; *Tetrahedron Lett*. **1980**, *21*, 4449. (c) Meunier, B.; *Chem. Rev*. **1992**, *92*, 1411. (d) Banfi, S.; Montanari, F.; Quici, S.; *J. Org. Chem*. **1989**, *54*, 1850. (e) O'Malley, S.; Kodadek, T.; *J. Am. Chem. Soc*. **1989**, *111*, 9116. (f) Zhang, W.; Jacobsen, E. N.; *J. Org. Chem*. **1991** *56*, 2296. (g) Halterman, R. L.; Jan, S.-T.; *J. Org. Chem*. **1991** *56*, 5253.
[13] (a) Mansuy, D.; Battioni, P.; Renaud, J.-P.; *J. Chem. Soc., Chem. Commun*. **1984**, 1255. (b) Bruice, T. C.; *Aldrichimica Acta* **1988** *21*, 87. (c) He, G.-X.; Bruice, T. C.; *J. Am. Chem. Soc*. **1991**, *113*, 2747.
[14] Yuan, L.-C.; Bruice, T. C.; *J. Am. Chem. Soc*. **1986**, *108*, 1643.

[15] (a) Nee, M. W.; Bruice, T. C.; *104*, 6123. (b) Higuchi, T.; Ohtake, H.; Hirobe, M.; *Tetrahedron Lett*. **1989**, *30*, 6545.
[16] Campestrini, S.; Robert, A.;, Meunier, B.; *J. Org. Chem.* **1991**, *56*, 3725.
[17] De Poorter, B.; Meunier, B.; *Nouv. J. Chim.* **1985**, *9*, 393.
[18] (a) Battioni, P.; Renaud, J. P.; Bartoli, J. F.; Reina-Artiles, M.; Fort, M.; Mansuy, D.; *J. Am. Chem. Soc*. **1988**, *110*, 8462. (b) Pietikänen, P.; *Tetrahedron Lett*. **1994**, *35*, 941.
[19] (a) Suslick, K. S.; Acholla, F. V.; Cook, B. R.; *J. Am. Chem. Soc.* **1987** *109*, 2818. (b) Pietikänen, P.; *Tetrahedron Lett*. **1995**, *36*, 319.
[20] (a) Larrow, J. F.; Jacobsen, E. N.; Gao, Y.; Hong, Y.; Nie, X.; Zepp, C. M.; *J. Org. Chem.* **1994** *59*, 1939. (b) Larrow, J. F.; Jacobsen, E. N.; *Org. Synth.* **1997** *75*, 1.
[21] Boger, D. L.; McKie, J. A.; Boyce, C. W.; *Synlett* **1997**, 515.
[22] (a) Sheldon, R. A.; Kochi, J. K.; *Metal-Catalyzed Oxidations of Organic Compounds*. Academic Press, New York, **1981**. (b) Jørgensen, K. A.; *Chem. Rev*. **1989**, *89*, 431.
[23] McGarrige, E. M.; Gilheany, D. G. *Chem. Rev*. **2005**, *105*, 1563.
[24] (a) Borriello, C.; Del Litto, R.; Panunzi, a.; Ruffo, F.; *Tetrahedron: Asymm.* **2004**, *15*, 681. (b) Borriello, C.; Del Litto, R.; Panunzi, a.; Ruffo, F.; *Inorg. Chem. Commun.* **2005**, 8, 717.
[25] Allen, F.H.; O Kennard,.; Watson, D.G.; Brammer, L.; Orpen, A.G;. Taylor, R .; *J. Chem. Soc. Perkin Trans. 2* **1987** 19.
[26] Geary, W. J.; *Coord. Chem. Rev*. **1971**, *7*, 81.
[27] Bruker-Nonius SADABS, Bruker-Nonius: Delft, The Netherlands, **2002**.
[28] Altomare, A.; Burla, M.C.; Camalli, M.; Cascarano, G.L.; Giacovazzo, C.; Guagliardi, A.; Moliterni, G.G.; Polidori, G.; Spagna, R. *J. Appl. Crystallography* **1999**, *32*, 115.
[29] Multiphase Homogeneous Catalysis, Cornils, B.; Herrmann, W.A.; Horvarth, I.T.; Leitner, W. ; Mecking, S.; Olivier-Borbigou, H.; Vogt, D. Eds. Wiley-VCH: Weinheim, **2005**.
For a recent example of epoxidation in water: Ballistreri, F.P. ; Brinchi, L.; Germani, R.; Savelli, G.; Tomaselli, G.A.; Toscano, R.M.; *Tetrahedron* **2008**, *64* 10239.
For recent examples of epoxidation with supported catalysts: (a) Kureshy, R.I.; Roy, T.; Khan, N.H.; Abdi, S.H.R.; Sadhukhan, A. ; Bajaj, H.C.;

Journal of Catalysis **2012,** *286*, 41; (b) Ji, R.; Yu, K.; Lou, L.-L.; Zhang, C.; Han, Y.; Pan, S.; Liu S.; *Inorg. Chem. Commun.* **2012**, *25*, 65; (c) Milo, A.; Neumann, R. ; *Chem. Commun.* **2011**, *47*, 2535; (d) Wei, S.; Tang, Y.; Xu, X.; Xu, G.; Yu, Y.; Sun, Y.; Zheng, Y.; *Appl. Organomet. Chem.* **2011**, *25*, 146.
[30] Sheldrick, G.M.; *Acta Cryst. A* **2008**, *64*, 112.
[31] Farrugia, L.J.; *J. Appl. Crystallography* **1999**, *32*, 837.

5. Pd (0) complexes with sugar-derived ligands for aqueous Suzuki-Miyaura cross-coupling.

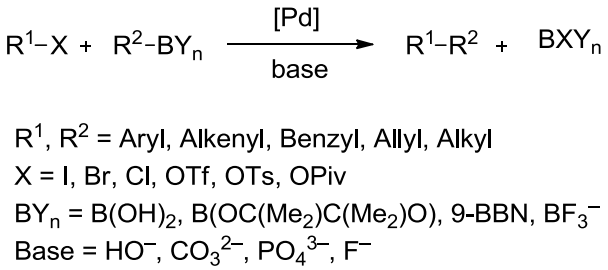
5.1 Background of the Pd-promoted Suzuki-Miyaura cross-coupling: scope of the reaction, mechanisms, state of the art.

Cross-coupling, defined as a catalytic reaction where two hydrocarbon fragments are coupled by a transition metal, is one of the most straightforward and general methods for the formation of C-C bonds. Several reactions can be defined as cross-coupling (Sonogashira, Negishi, Stille, etc…), and all share the same steps in the catalytic cycle: oxidative addition, trans-metallation and reductive elimination. Nevertheless, their developments has been surprisingly sluggish until a few decades ago. Before 1960 the scope of cross-coupling was largely limited to those involving Mg and Li organoreagents. Focusing on the Suzuki-Miyaura (SM) cross-coupling, only in 1978 Negishi and coworkers discovered that 2-iodotoluene could be coupled with lithium 1-heptynyltributylborate, establishing for the first time that organoboranes were effective transmetalating agents in Pd-mediated cross-couplings [1]. Neutral alkenylboranes were next tested by Suzuki and Miyaura in 1979, [2] and in further works they found that the addition of a base was necessary to effect the cross-coupling of these organometallic species [3]. From then on, the methodology has evolved and has expanded its scope, and today the SM reaction is the most commonly applied cross-coupling reaction in both academia and industry [4]. Several features can address the success of this methodology [5], which allowed Suzuki to be awarded of the Nobel prize in 2010:

1. ready availability of reactants.
2. mild reaction conditions and high product yields.
3. water stability.
4. easy use of the reaction both in aqueous and heterogeneous conditions.
5. toleration of a broad range of functional groups.
6. high regio- and stereoselectivity of the reaction.

7. insignificant effect of steric hindrance.
8. use of a small amount of catalysts.
9. application in one-pot synthesis.
10. nontoxic reaction.
11. easy separation of inorganic boron compound.
12. environmentally friendly process.

The generic SM cross-coupling and the scope of reaction are reported below (**Scheme 5.1**):



Scheme 5.1

In this reaction a new C-C bond is formed from an organic halide or pseudo-halide and an organo-boron compound. Both sp^2 and sp^3 carbon may be involved in this process. A stoichiometric excess of base is necessary, whosechoice is dependent on the specific system.

Typical solvents are ethereal and aromatic hydrocarbons, but in recent years the interests towards aqueous solvents increased [6], due to greener protocols. Aqueous conditions are the main topic of this chapter, hence the following discussion will focus on this field.

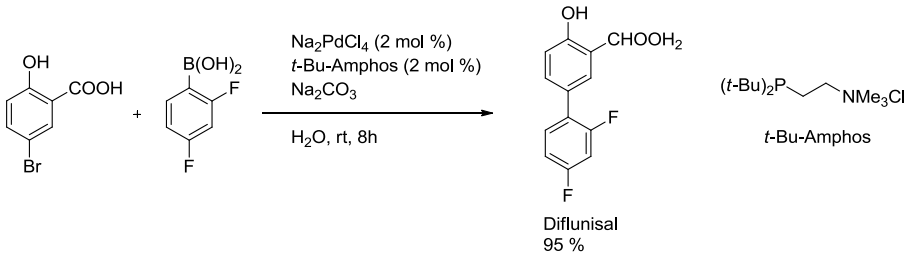
As mentioned in the introduction, a diverse set of approaches can be used to make a process green and sustainable but, in general, reaction solvents have a key influence on the environmental impact and also affect cost, safety, and health issues. Organic solvents are volatile and highly inflammable, and often are at the origin of pollution. Thus, their substitution with alternative solvents presenting superior ecological, health, and safety properties is one way to make a protocol green and sustainable [7]. Examples are supercritical fluids, biosolvents, and ionic liquids, but often their costs are still challenging. Another alternative are solvent-free protocols, which are

usually hardly applicable to industrial scales due to inadequate heat- and mass-transfer.

On this basis, naturally abundant water is one of the best choices as a reaction medium because it is nontoxic, noncorrosive, nonflammable and has a low vapour pressure. The main drawback usually is low the solubility of substrates and catalysts in this medium, and this represent the main challenge for the research of aqueous green protocols.

Several systems, both homogenous and heterogeneous, demonstrated to be effective in aqueous Pd-promoted SM cross-coupling [6]. Notable examples are water-soluble phosphines and bipyridines, carbenes, palladacycles, silica supported catalysts or alternative protocols involving the use of microwaves or surfactants.

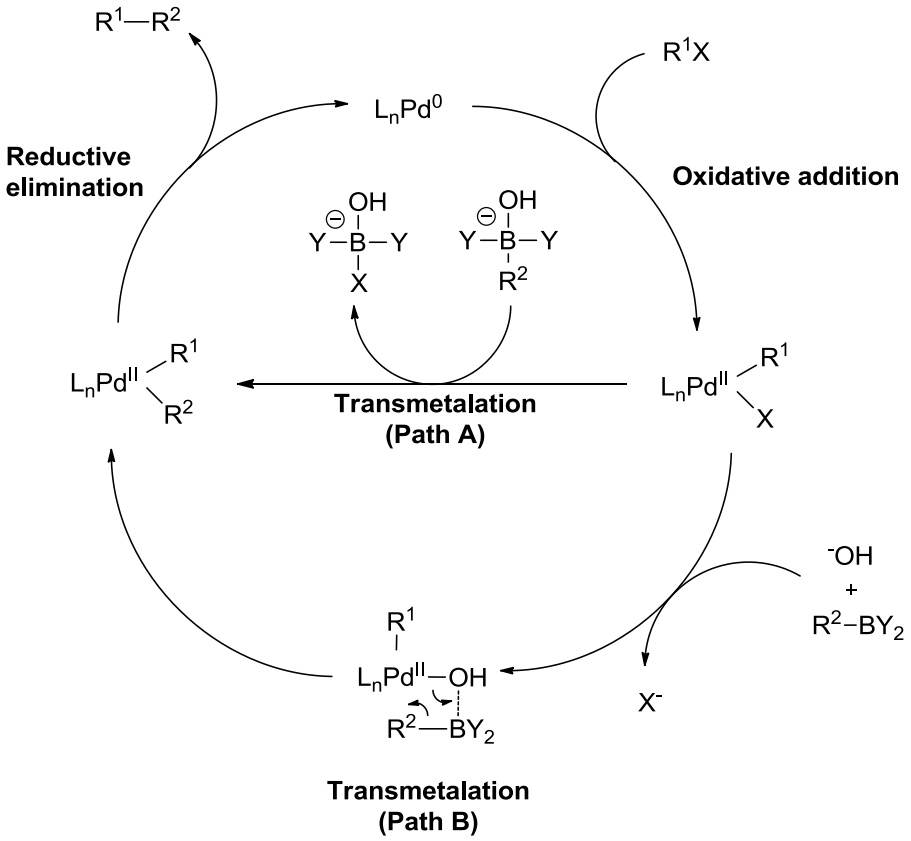
These systems have been used in a wide range of case-studies, and they represent the state of the art in terms of catalytic performances and applicability of the aqueous Pd-promoted SM cross-coupling. One excellent example is the synthesis of Diflunisal, a non-steroidal anti-inflammatory drug [7] (**Scheme 5.2**), which is obtained by aqueous-phase methodology in high yield in one step without use of organic solvents in the reaction or purification.



Scheme 5.2

5.1.1 Mechanism

As any other cross-coupling, the mechanism of the SM reaction has been extensively studied [8] and consists of three steps: oxidative addition, transmetalation and reductive elimination.



Scheme 5.3

The oxidative addition is the rate limiting step of the cycle, and its rate depends on the halide (X) of the substrate, increasing in the order X= Cl < Br < I.

The transmetalation is the reaction stage where the organic group R^2 bound to the electropositive boron is transferred to the catalyst. This is supposed to happen trough two different paths (A and B), but in both cases it is rationalized the observed enhancement in rate caused by the base. In Path A, the boronic acid react with the base to form a borate which is sufficiently electron-rich to transmetalate with the Pd(II) species. In Path B, a transient hydroxyl-palladium(II) adduct is formed prior to transmetalation with a neutral organoborane. In most SM cross-couplings, both Path A and B are

believed to be operational concurrently, and it is not immediately clear why one pathway predominates under a particular set of reaction conditions.
In order to close the catalytic cycle, the reductive elimination step after the transmetalation process is needed. This step consists of the coupling of the two organic groups, R^1 and R^2, in *cis* position; if these are in *trans* position, an isomerization occours.

5.1.2 State of the art: sugar derived ligands for aqueous SM cross-coupling

Although sugar-derived ligands have been applied in several catalytic C-C and C-X bond formation (X = O, N, S, P) [9], their scope has not been extended comprehensively to other powerful couplings, such as the Suzuki-Miyaura reaction, where only some sporadic examples are reported [6, 10]. Nevertheless, in this field sugars candidate are really attractive building blocks, due to their solubility in water, which allow green and sustainable synthesis of biaryls. Moreover, their intrinsic chirality may promote the enantioselective synthesis of binaphthyl rings.
Example of sugar-derived ligands for aqueous SM are reported in **figure 5.1**

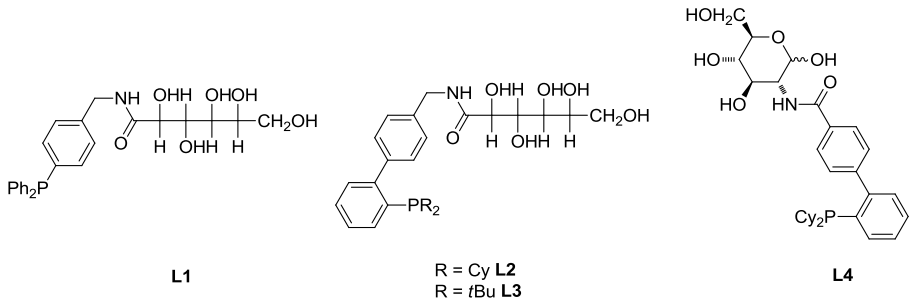


Figure 5.1

In all the protocols reported the Pd complexes were formed in situ. The best performance was obtained with ligand **L3**, which afforded the coupling product of 4-bromoanisole and *p*-tolyl boronic acid with 62% yield at 25°C and 0.1% mol catalyst loading.

5.2 PN and NN ligands and the corresponding Pd^0 complexes: synthesis and characterization.

In order to extend the use of sugar-derived ligands in aqueous SM, part of this PhD thesis focused on the development of new systems. The preparation of diphenylphosphino,imino (**PN**) and pyridino,imino (**NN**) sugar based ligands is reported, along with the synthesis of the corresponding hydrophilic Pd^0 complexes (**Figure 5.2**, fdn= fumarodinitrile). Some imino ligands, employed in Suzuki-Miyaura couplings, were reported in recent literature [11] but in all cases the activities ranged from low to moderate.

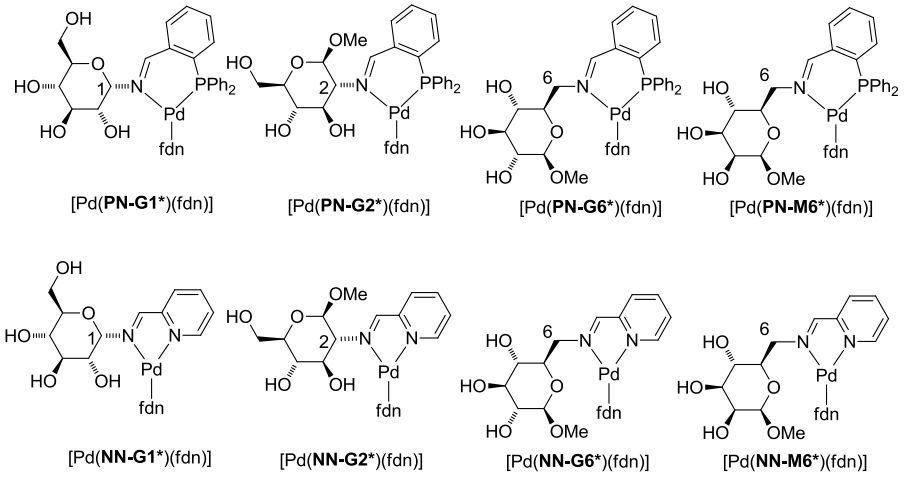


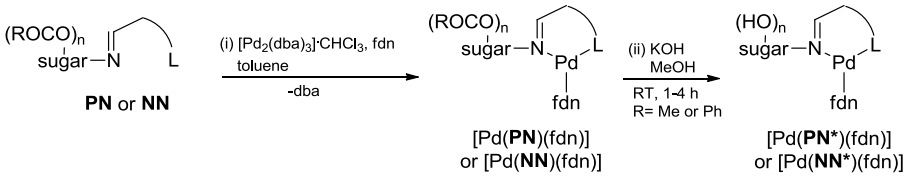
Figure 5.2

The design of both **PN** and **NN** ligands was aimed at achieving higher TONs and ensuring their easy, high-yield synthesis.

Four imino sugar residues were employed: three of them derive from glucose functionalized in positions 1, 2 and 6, respectively. The fourth is instead a mannoside derivatized in 6.

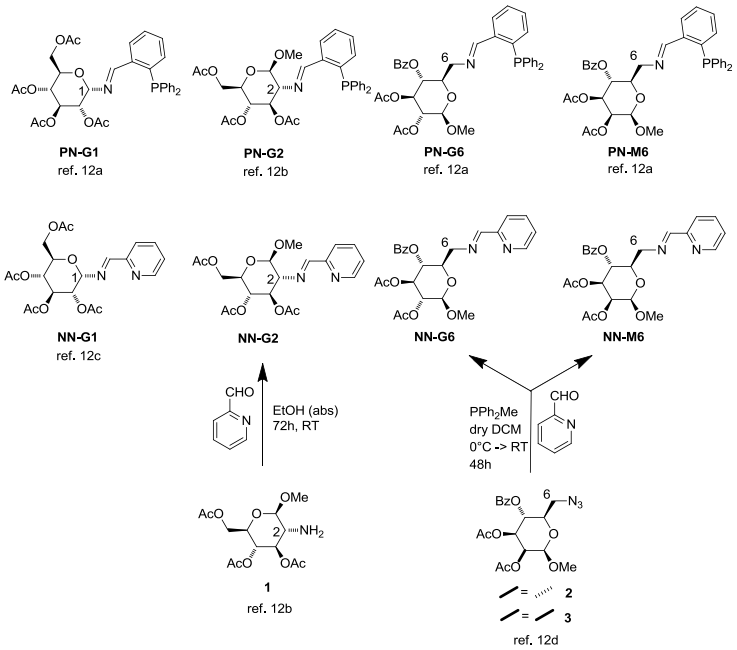
As expected, all the complexes were found to be soluble in aqueous media, and could be fruitfully employed in the aqueous SM coupling.

The strategy for the synthesis of the complexes involved three major steps. First, protected **PN** and **NN** ligands were synthesized from suitable precursors. In a second phase, the corresponding Pd(0) complexes [Pd(**PN**)(fdn)] or [Pd(**NN**)(fdn)] were prepared (step i in **Scheme 5.3**), which were in turn transformed into the deprotected hydrophilic species [Pd**(PN*)**(fdn)] or [Pd(**NN***)(fdn)] (step ii).



Scheme 5.3

Some of the ligands were already known (**Scheme 5.4**) [12] , while the others were synthesized for the first time. The molecules were prepared from the corresponding amino or azido precursors **1**, **2** and **3**, by condensation with the proper aldehyde in the former case, and by aza-Wittig reaction in the latter cases. The products were isolated in high yield by column chromatography or precipitation.



Scheme 5.4

The corresponding [Pd(**PN**)(fdn)] and [Pd(**NN**)(fdn)] complexes were prepared in good yield from fresh $[Pd_2(dba)_3 \cdot CHCl_3]$ (dba = dibenzylideneacetone) with an established procedure [12d], path i of **Scheme 5.3**.

Dba molecules were readily displaced in toluene by one alkene and one chelating molecule, as revealed by the rapid change of colour of the reacting mixture from brown to orange-yellow. After removal of the solvent under vacuum, the complexes were obtained as yellow to orange microcrystalline solids by column chromatography over silica. All the isolated complexes could be handled in air at room temperature and were stored for several weeks at 277 K without appreciable decomposition.

The compounds were characterized by proton, carbon and phosphorous NMR spectroscopy. Upon coordination to Pd, the signals of the olefin undergo a large shift at lower frequencies. This behaviour is reported in literature [12a, 12d, 13, 14], and is attributed to the substantial degree of π-backdonation in the Pd(0)-olefin bond, which stabilizes the low oxidation state of palladium. The consequent partial re-hybridisation $sp^2 \rightarrow sp^3$ of the

alkene carbons shift the corresponding signals towards the aliphatic regions in both ^{1}H and ^{13}C NMR spectra.

It is worth to note that Pd^{0} compounds soluble in water are quite rare [12c, 12d, 15]. The hydrophilic Pd^{0} complexes [Pd(**PN***)(fdn)] and [Pd(**NN***)(fdn)] were obtained by basic hydrolysis of the acetyl and benzoyl groups (path ii of **Scheme 5.3**). The yellow microcrystalline products, which are fairly soluble in water, methanol and ethanol, were isolated in high yield by precipitation with diethyl ether from the reaction mixture. Also in this case, all the isolated complexes could be handled in air at room temperature and were stored for several weeks at 277 K without appreciable decomposition. The only exception is complex [Pd(**PN-G1***)(fdn)], which in solution slowly underwent a transformation to another species; this phenomenon is currently under study.

In both the *O*-acylated and the deprotected species, the coordination of fdn affords two diastereoisomers, because the olefin is prochiral. The diastereoisomers are known to interconvert via an associative mechanism [14-16], where an external olefin coordinates to the metal with the enantioface opposite to that initially coordinated, which then dissociates.

The isomeric equilibrium is rapidly reached after dissolution of the complexes, and the presence of two resolved patterns for the two isomers indicates that this process is slow at RT compared with the NMR time-scale (**Figure 5.3** shows an example) [12a].

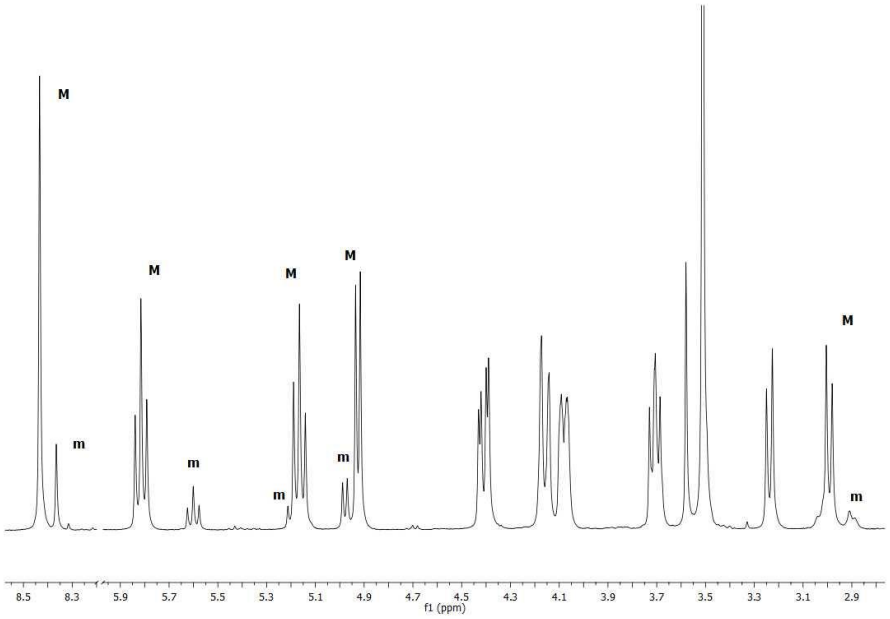


Figure 5.3

Integration of suitable separated peaks allowed to calculate the diastereomeric ratios, reported in **Table 5.1**.

In almost all cases, a significant discrimination has been found. As a general consideration, the O-acylated complexes have a similar selectivity, with small differences for the two coordinating system (**PN** and **NN**; entry 1 vs 5, 2 vs 6; exceptions are entry 3 vs 7 , 4 vs 8), their position on the sugar backbone (C1, C2 and C6; entry 1 vs 2 vs 3 and entry 5 vs 6 vs 7, entry 7 beeing the only exception) and the epimer used (glucose and mannose; entry 3 vs 4 and 7 vs 8).

The differences are larger among the deprotected complexes, where there is a general drop of selectivity, probably due to the lack of steric hindrance provided by the acyl groups. For these complexes, the presence of the bulky diphenylphosphino group provides a better selectivity compared with the pyridyl group (entry 12 vs 16).

Entry	Complex	Solvent	Diastereomeric ratio
1[a]	[Pd(**PN-G1**)(fdn)]	$CDCl_3$	70:30
2	[Pd(**PN-G2**)(fdn)]	$CDCl_3$	86:14
3[a]	[Pd(**PN-G6**)(fdn)]	$CDCl_3$	72:28
4[a]	[Pd(**PN-M6**)(fdn)]	$CDCl_3$	80:20
5[b]	[Pd(**NN-G1**)(fdn)]	$CDCl_3$	80:20
6	[Pd(**NN-G2**)(fdn)]	$CDCl_3$	84:16
7	[Pd(**NN-G6**)(fdn)]	$CDCl_3$	55:45
8	[Pd(**NN-M6**)(fdn)]	$CDCl_3$	60:40
9	[Pd(**PN-G1***)(fdn)]	CD_3OD	50:50
10	[Pd(**PN-G2***)(fdn)]	CD_3OD	60:40
11	[Pd(**PN-G6***)(fdn)]	CD_3OD	87:13
12	[Pd(**PN-M6***)(fdn)]	CD_3OD	73:27
13[b]	[Pd(**NN-G1***)(fdn)]	CD_3OD	55:45
14	[Pd(**NN-G2***)(fdn)]	CD_3OD	65:35
15	[Pd(**NN-G6***)(fdn)]	CD_3OD	50:50
16	[Pd(**NN-M6***)(fdn)]	CD_3OD	50:50

[a] From ref. 12a. [b] from ref. 12c.

Table 5.1

5.3 Catalytic performances of the [Pd(PN*)fdn] and [Pd(NN*)fdn] complexes in aqueous SM cross-coupling.

The Suzuki-Miyaura cross-coupling is an extremely useful tool for C-C bond formation, due to its versatility and efficiency [17].

This reaction is usually performed in organic solvents, neat or mixed with water. The drawbacks of aqueous solvents are the low solubility of several substrates and the general lower stability of the metal catalysts in water. On this basis, in recent years a large variety of water-compatible protocols has been developed, which include hydrophilic complexes,[12,13] surfactants,[14] and use of microwaves.[15] However, only few of them display significant activity.

A good compromise between organic and aqueous solvents is the use of ethanol/water mixtures, being small alcohols among the greenest solvents in terms of impact on health and environment, and in term of the energy needed for manufacture and disposal.[16] Ethanol increases the solubility of the substrate, does not interfere with the separation of the product (as surfactants

do) and is bio-available at a low cost. Hydro-alcoholic mixtures are the media of choice[17] for reducing the use of dangerous, environmental-unfriendly organic solvents, and aiming to an easy separation of the product from the reacting system.

For these reasons, the water soluble complexes [Pd(**PN***)(fdn)] and [Pd(**NN***)(fdn)] were tested in the Suzuki-Miyaura reaction in ethanol/water mixtures. It is worth to note that a protocol should be intended as "truly green" when toxic organic solvent are not involved in any step, including the workup [10]. Our workup procedure involved an extraction with DCM and a chromatography using Hex/EtOAc mixtures, but this choice was due to the small scale of our screening reactions and the necessity of reporting isolated yield also for partial conversion. In test experiments, we demonstrated that, with higher scales and complete conversion, it was possible to isolate the pure hydrophobic products in almost quantitative yields by simple addition of water followed by filtration of the solid products. Analogue protocols were already reported in literature[23].

In principle also the parent *O*-acylated [Pd(**PN)**(fdn)] and [Pd(**NN**)(fdn)] species may function as pre-catalysts, because in the basic coupling conditions the acyl groups are expected to hydrolyze easily. Nevertheless, the deprotected species were preliminarily isolated in order to demonstrate their actual existence, and, hence, for assessing the nature of the catalytic complexes.

Furthermore, their high solubility in ethanol allowed to prepare concentrated stock solutions for an accurate dosage of the catalyst.

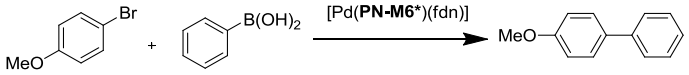
The first screenings were performed in order to optimize the reaction conditions (**Table 5.2**) in terms of ethanol/water ratio (entries 1-5), concentration (entries 3, 6, 7), and equivalents of base (entries 8-12).

Phenylboronic acid and 4-bromoanisole were used as benchmark substrates, while [Pd(**PN-M6***)(fdn)] was selected as catalyst.

The reaction in neat ethanol or water (respectively entries 1 and 5) resulted in poor yield. This was expected, because the former is not able to dissolve the base, while the latter does not dissolve the substrate properly. The best water/ethanol ratio resulted to be 1/1 (entry 3).

This ratio was used in order to adjust the concentration, using a total volume of 6, 4 and 3 mL (entries 3, 6 and 7). Unexpectedly, the highest concentration resulted in a drop of activity, probably because the resulting higher concentration of complex favours the formation of metallic Pd.

Similar behaviours are reported in literature for the formation of Pd_2Te_3 nanoparticles [24].



Entry	EtOH/H_2O (v/v)	Volume (mL)	K_2CO_3 (mmol)	Isolated yield[a](%)
1	6/0	6	1.5	5
2	2/1	6	1.5	32
3	1/1	6	1.5	47
4	1/2	6	1.5	42
5	0/6	6	1.5	12
6	1/1	4	1.5	69
7	1/1	3	1.5	57
8	1/1	4	without base	0
9	1/1	4	0.50	21
10	1/1	4	1.0	80
11	1/1	4	2.25	61
12	1/1	4	3.0	56

Conditions: 4-bromoanisole (0.50 mmol), phenylboronic acid (0.55 mmol), catalyst [Pd(**PN-M6***)(fdn)], $5*10^{-3}$mmol, 1mol%), 1h, 120°C. [a]Average of two runs.

Table 5.2

The volume resulting in the best yield (4 mL, entry 6) was used for the screening of the equivalents of base. As reported, its presence is fundamental for this reaction, as confirmed by entry 8. The highest yield was obtained with 2 equivalents of base with respect to the aryl bromide (entry 10).
The optimized conditions were used in the next screening, where lower amounts of catalyst were used (**Table 5.3**).

Entry	Catalyst loading (mol %)[a]	Isolated yield (%)[b]	TOF (h^{-1})
1	1.0	80	80
2	0.10	95	950
3	0.010	75	7500
4	0.0050	83	16600
5	0.0010	0	0

Conditions: 4-bromoanisole (0.5 mmol), phenylboronic acid (0.55 mmol), catalyst: [Pd(**PN-M6***)(fdn)], K_2CO_3 (1.0 mmol), water (2 mL), ethanol (2 mL), 1h, 120°C. [a]Catalyst loading with respect to 4-bromoanisole. [b]Average of two runs.

Table 5.3

Interestingly, catalyst loading less than 1.0 mol% resulted in higher yield, most likely due to the mentioned faster deactivation of the catalyst with formation metallic Pd at higher complex concentration. The catalyst resulted in no activity decreasing to 0.0010 mol% (entry 5).
On these bases, other complexes were tested with a loading of 0.010 mol% or lower, in order to find the most active catalyst (**Table 5.4**).
All the **PN** complexes and one **NN** complex were tested at a catalyst loading of 0.010% with good results (entries 1-4). The best performing **PN** species and the **NN** complex, namely [Pd(**PN-G1***)(fdn)] and [Pd(**NN-M6***)(fdn)] were then examined at the lower ratios, respectively 0.0050% and 0.0020% (entries 5-8). In the latter case, the **PN** catalysts showed lack of reproducibility, with isolated yields ranging from 0 to 15%.

Entry	Complex	Catalyst loading (mol %)[a]	Isolated yield[b](%)
1	[Pd(**PN-G1***)(fdn)]	0.010	87
2	[Pd(**PN-G2***)(fdn)]	0.010	56
3	[Pd(**PN-G6***)(fdn)]	0.010	72
4	[Pd(**NN-M6***)(fdn)]	0.010	68
5	[Pd(**PN-G1***)(fdn)]	0.0050	58
6	[Pd(**NN-M6***)(fdn)]	0.0050	97
7	[Pd(**PN-G1***)(fdn)]	0.0020	0-15
8	[Pd(**NN-M6***)(fdn)]	0.0020	65

Conditions: 4-bromoanisole (0.5 mmol), phenylboronic acid (0.55 mmol), K_2CO_3 (1.0 mmol), water (2 mL), ethanol (2 mL), 1h, 120°C. [a]Catalyst loading with respect to 4-bromoanisole. [b]Average of two runs.

Table 5.4

Given the satisfying result achieved with [Pd(**NN-M6***)(fdn)], the whole **NN** family was tested in the same condition with good yield, demonstrating that they are more active than the corresponding **PN** species (**Table 5.5**).
Only [Pd(**NN-G1***)(fdn)] revealed to be almost ineffective, probably due to the higher sensitivity of the sugar functionalized in position C1.
The complexes [Pd(**NN-G2***)(fdn)] and [Pd(**NN-G6***)(fdn)] were further employed at 0.0010% loading, where they presented still appreciable yield after 1h, while [Pd(**NN-M6***)(fdn)] was ineffective and hence not reported in table (entries 4-5).

Entry	Complex	Catalyst loading (mol %)[a]	Isolated yield[b](%)
1	[Pd(**NN-G6***)(fdn)]	0.0020	65
2	[Pd(**NN-G1***)(fdn)]	0.0020	4
3	[Pd(**NN-G2***)(fdn)]	0.0020	70
4	[Pd(**NN-G6***)(fdn)]	0.0010	12
5	[Pd(**NN-G2***)(fdn)]	0.0010	12
6[c]	[Pd(**NN-G6***)(fdn)]	0.0010	37
7[c]	[Pd(**NN-G2***)(fdn)]	0.0010	38

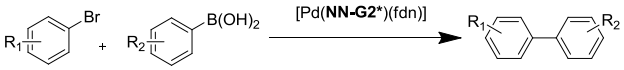
Conditions: 4-bromoanisole (0.5 mmol), phenylboronic acid (0.55 mmol), K_2CO_3 (1.0 mmol), water (2 mL), ethanol (2 mL), 1h, 120°C. [a]Catalyst loading with respect to 4-bromoanisole. [b]Average of two runs. [c]Reaction time: 4h.

Table 5.5

When the reaction was prolonged up to 4h, the yield increased to 38% (entry 6-7), demonstrating that the complexes are still active after the first hour of reaction. The activities of the two complexes were almost the same.

On the ground of the easier synthesis, the entire set of substrates was tested by selecting [Pd(**NN-G2***)(fdn)] as the catalyst of choice (**Table 5.6**).

The catalyst resulted effective also over sterical demanding substrates, (entry 2, 3, 8, 9) although with slightly lower activity, and towards substrates with electron releasing or electron withdrawing groups.



Entry	R_1	R_2	Isolated Yield[a](%)
1	4-OMe	4-Me	74
2	4-OMe	3-Me	63
3	4-OMe	2-Me	48
4	4-OMe	4-NO_2	<5
5	4-OMe	4-CHO	25
6	4-OMe	4-OH	<5
7	4-OMe	4-OMe	33
8	2-OMe	H	30
9	3-OMe	H	76
10	4-NO_2	H	85
11	4-OH	H	15
12	4-CHO	H	85
13	H	H	50

Conditions: aryl bromide (0.50 mmol), arylboronic acid (0.55 mmol), catalyst [Pd(**NN-G2***)(fdn)], $5*10^{-5}$mmol, 0.010 mol%), 1h, 120°C. [a]Average of two runs.

Table 5.6

5.4 Conclusion.

In this work, two classes of Pd^0 water-soluble complexes (**PN** and **NN**) were prepared and tested in the Suzuki-Miyaura cross-coupling, using aqueous environmental-friendly conditions. The best catalyst, namely [Pd(**NN-G2***)(fdn)], was active at really low loading (0.0010%) and resulted to be tolerant towards different substrates and very efficient by comparison with reported systems; the TOFs are up to $9.5 \cdot 10^3$ h^{-1}, which is close to the best results [25] for reactions in aqueous medim.

5.5 Experimentals.

5.5.1. General consideration:

NMR spectra were recorded in $CDCl_3$ ($CHCl_3$, δ = 7.26 and $^{13}CDCl_3$ δ 77, as internal standards), C_6D_6 (TMS, δ = 0 and $^{13}C_6D_6$ δ 128.6, as internal standards) and CD_3OD (CHD_2OD, δ = 3.34 and $^{13}CD_3OD$ δ 49.9 as internal standards) with a 200 MHz (Varian Model Gemini), and a 400 MHz (Bruker DRX-400) spectrometers. ^{31}P NMR experiments were carried out using aqueous 85% phosphoric acid as external reference (δ 0). The following abbreviations were used for describing NMR multiplicities: s, singlet; d, doublet; dd, double doublet; t, triplet; dt, double triplet; m, multiplet; app, apparent, br broad. **PN-G1**, **PN-G2**, **PN-G6**, **PN-M6, NN-G1,** [Pd(**PN-G1**)(fdn)], [Pd(**PN-G6**)(fdn)], [Pd(**PN-M6**)(fdn)], [Pd(**NN-G1**)(fdn)], [Pd(**NN-G1***)(fdn)] were prepared according to literature methods [12a,b,c]. THF was distilled from $LiAlH_4$, dichloromethane from CaH_2.

*5.5.2. Preparation of **NN-G2**:*

The amino intermediate **1** (640 mg, 2.0 mmol) was suspended in 25 mL of EtOH (abs), then 2-pyridincarboxyaldehyde (240 mg, 2.20 mmol) was added. After 72h, hexane (80 mL) was added, and the precipitated product

was filtrated and washed 3 times with hexane (yield: 560 mg, 69%) obtaining a white powder. Detailed presentation of physical data for **NN-G2**: [Found: C, 55.64; H, 5.85; N, 7.01. $C_{19}H_{24}N_2O_8$ requires C, 55.88; H, 5.92; N, 6.86]; δ_H (400 MHz; C_6D_6; TMS) 8.64 (1 H, d, ^3J = 4.6 Hz, aromatic), 8.31 (1 H, s, N=C*H*), 7.97 (1 H, d, ^3J = 7.8 Hz, aromatic), 7.73 (1 H, t, ^3J = 7.7 Hz, aromatic), 7.33 (1 H, dd, ^3J = 5.4 Hz, ^3J = 6.7 Hz, aromatic), 5.43 (1 H, t, $^3J_{3,4}$ = $^3J_{3,2}$ = 9.6 Hz, 3-H), 5.14 (1H, t, $^3J_{3,4}$ = $^3J_{4,5}$, 4-H), 4.69 (1 H, d, $^3J_{1,2}$ = 7.8 Hz, 1-H), 4.36 (1 H, dd, $^3J_{6,5}$ = 4.6 Hz, $^{gem}J_{6,6'}$ = 12.2 Hz, 6-H), 4.18 (1 H, dd, $^3J_{6',5}$ = 1.8 Hz, 6'-H), 3.84 (1 H, m, 5-H), 3.49 (3 H, s, OMe), 3.42 (1 H, t, 2-H), 2.10 (3 H, s, OAc), 2.03 (3 H, s, OAc), 1.88 (3 H, s, OAc). δ_C (100 MHz, C_6D_6, TMS) 171.2, 170.3, 170.2, 166.2, 154.3, 149.9, 137.1, 125.6, 122.2, 102.9, 74.4, 73.5, 72.3, 69.0, 62.6, 57.6, 21.2, 21.1, 21.0.

*4.5.3 Preparation of **NN-G6** and **NN-M6**:*

Adapting a known procedure [12d], the desired azide (810 mg, 2.0 mmol) was dissolved in 10 mL of dry dichloromethane under argon. Then, 2-pyridincarboxyaldehyde (235 mg, 2.2 mmol, 210 μL) and PPh_2Me (440 mg, 410 μL, 2.2 mmol) were added in this order at 0°C. the reaction was left to heat up to RT, and after 72h the solvent was removed under vacuum. The crude product was purified by column chromatography on florisil (eluent Hex/EtOAc=1/1), (yields: **NN-G6** 480 mg, 51%; **NN-M6** 510 mg, 54%). Detailed presentation of physical data for **NN-G6**: [Found: C, 61.49; H, 5.68; N, 5.83. $C_{24}H_{26}N_2O_8$ requires C, 61.27; H, 5.57; N, 5.95]; δ_H (400 MHz; C_6D_6; TMS) 8.48 (1 H, s, N=C*H*), 8.44 (1 H, d, ^3J = 4.8 Hz, aromatic), 8.13 (2 H, m, aromatic), 8.06 (1 H, d, ^3J = 7.9 Hz, aromatic), 7.16-6.97 (4 H, m, aromatic), 6.60 (1 H, m, aromatic), 6.19 (1 H, t, $^3J_{3,4}$ = $^3J_{3,2}$ = 9.9 Hz, 3-H), 5.73 (1 H, t, $^3J_{3,4}$ = $^3J_{4,5}$, 4-H), 5.14 (1 H, dd, $^3J_{1,2}$ = 3.7 Hz, 2-H), 4.91 (1 H, d, 1-H), 4.38 (1 H, m, 5-H), 3.78 (1 H, dd, $^3J_{6,5}$ = 3.1 Hz, $^{gem}J_{6,6'}$ = 13.0 Hz, 6-H), 3.58 (1 H, dd, $^3J_{6',5}$ = 6.7 Hz, 6'-H), 3.01 (3 H, s, OMe), 1.60 (3 H, s, OAc), 1.58 (3 H, s, OAc). δ_C (100 MHz, C_6D_6, TMS) 169.8, 165.7, 165.0, 155.6, 149.7, 136.1, 133.4, 130.4 (2X), 130.2, 128.8(2X), 124.6, 97.1, 72.0, 71.9, 70.8, 69.0, 61.5, 54.9, 32.1, 23.1, 20.3, 14.5. **NN-M6**: [Found: C, 61.10; H, 5.54; N, 6.03. $C_{24}H_{26}N_2O_8$ requires C, 61.27; H, 5.57; N, 5.95]; δ_H (400 MHz; C_6D_6; TMS) 8.46 (1 H, s, N=C*H*), 8.42 (1 H, d, ^3J = 4.2 Hz,

aromatic), 8.07 (3 H, m, aromatic), 7.16-6.97 (4 H, m, aromatic), 6.60 (1 H, m, aromatic), 6.09 (1 H, t, $^{3}J_{3,4} = {}^{3}J_{4,5} =$ 9.6 Hz, 4-H), 6.02 (1 H, dd, $^{3}J_{3,2} =$ 3.3 Hz, 3-H), 5.63 (1 H, dd, $^{3}J_{1,2} = 1.7$ Hz, 2-H), 4.54 (1 H, d, 1-H), 4.45 (1 H, m, 5-H), 3.90 (1 H, dd, $^{3}J_{6,5} = 1.4$ Hz, $^{gem}J_{6,6'} = 11.3$ Hz, 6-H), 3.70 (1 H, dd, $^{3}J_{6',5} = 7.3$ Hz, 6'-H), 2.98 (3 H, s, OMe), 1.67 (3 H, s, OAc), 1.56 (3 H, s, OAc). δ_C (100 MHz, C_6D_6, TMS) 169.8, 165.8, 164.8, 155.6, 149.6, 136.0, 133.4, 130.3 (2X), 130.2, 128.9, 128.8, 128.7, 124.6, 120.9, 98.9, 70.6, 70.4, 70.0, 69.4, 62.0, 54.8, 20.4, 20.3.

*5.5.4 General procedure for the preparation of the [Pd(**ligand**)(fdn)] complex:*

Adapting a known procedure [12d], [$Pd_2(dba)_3$•$CHCl_3$] (215 mg, 0.21 mmol) was added to a solution of the desired ligand (0.50 mmol) and fdn (39 mg, 0.50 mmol) in toluene (5 mL). After 1h, the solution was filtered over celite and the solvent was evaporated; the crude product was purified by column chromatography over silica (eluent Hex/EtOAc = 1/1 for **PN** family, neat EtOAc for **NN** family), isolating the pure product as a yellow microcrystalline solid (yield 68-85%). Detailed presentation of physical data for: [Pd(**PN-G2**)(fdn)] [Found: C, 55.87; H, 4.56; N, 5.55. $C_{36}H_{36}N_3O_8PPd$ requires C, 55.71; H, 4.68; N, 5.41]; major diastereoisomer δ_H (400 MHz; $CDCl_3$; $CHCl_3$) 8.29 (1 H, d, $^{4}J_{H,P} = 1.5$ Hz, N=C*H*), 7.65-7.05 (14 H, m, aromatics), 6.08 (1 H, t, $^{3}J_{3,4} = {}^{3}J_{3,2} = 9.6$ Hz, 3-H), 5.12 (1 H, t, $^{3}J_{3,4} = {}^{3}J_{4,5}$, 4-H), 5.04 (1 H, d, $^{3}J_{1,2} = 7.8$ Hz, 1-H), 4.36 (1 H, dd, $^{3}J_{6,5} = 4.0$ Hz, $^{gem}J_{6,6} =$ 12.3 Hz, 6-H), 4.24 (1 H, m, 5-H), 4.14 (1 H, dd, $^{3}J_{6',5} = 1.8$ Hz, 6'-H), 3.44 (1 H, t, 2-H), 3.20 (3 H, s, OMe), 3.14 (1 H, dd, $^{3}J_{H,H} = 9.6$ Hz, $^{cis}J_{H,P} = 3.0$ Hz, fdn), 2.99 (1 H, t, $^{3}J_{H,H} = {}^{trans}J_{H,P}$, fdn), 2.07 (3 H, s, OAc), 2.04 (3 H, s, OAc), 1.67 (3 H, s, OAc). δ_C (100 MHz; $CDCl_3$; $^{13}CDCl_3$) 170.7, 170.2, 170.1, 169.1, 137.7, 137.6, 137.3, 137.1, 135.2, 134.1, 133.9, 133.8, 132.9, 132.7, 132.7, 132.6, 131.7, 131.4, 130.8, 130.6, 129.5, 129.4, 129.2, 129.1, 101.1, 80.9, 73.8, 72.2, 69.3, 62.0, 57.2, 27.1, 25.4 ($J_{C,P} = 44$ Hz), 20.5, 20.5, 20.0. δ_P (162 MHz; $CDCl_3$; H_3PO_4) 16.15. Relevant signal for the minor diastereoisomer: δ_H (400 MHz; $CDCl_3$; $CHCl_3$) 8.36 (1 H, d, $^{4}J_{H\text{-}P} = 1.5$ Hz N=C*H*), 5.78 (1 H, t, $^{3}J_{3,4} = {}^{3}J_{3,2} = 9.6$ Hz, 3-H), 5.19 (1 H, d, $^{3}J_{1,2} = 7.8$ Hz, 1-H), 3.39 (3 H, s, OMe), 2.61 (1 H, t, $^{3}J_{H,H} = {}^{trans}J_{H,P} = 9.6$ Hz, fdn). Detailed

presentation of physical data for: [Pd(**NN-G2**)(fdn)] [Found: C, 46.73; H, 4.52; N, 9.30. $C_{23}H_{26}N_4O_8Pd$ requires C, 46.59; H, 4.42; N, 9.45] major diastereoisomer δ_H (400 MHz; $CDCl_3$; $CHCl_3$) 8.92 (1 H, d, ^3J = 4.6 Hz, aromatic), 8.43 (1 H, s, N=C*H*), 8.05 (1 H, d, ^3J = 7.3 Hz, aromatic), 7.76 (1 H, t, ^3J = 7.6 Hz, aromatic), 7.67 (1 H, dd, ^3J = 5.5 Hz, ^3J = 6.8 Hz, aromatic), 5.82 (1 H, t, $^3J_{3,4} = {}^3J_{3,2}$ = 9.6 Hz, 3-H), 5.17 (1 H, t, $^3J_{3,4} = {}^3J_{4,5}$, 4-H), 4.93 (1 H, d, $^3J_{1,2}$ = 7.6 Hz, 1-H), 4.41 (1 H, dd, $^3J_{6,5}$ = 4.1 Hz, $^{gem}J_{6,6'}$ =12.4 Hz, 6-H), 4.16 (1 H, dd, $^3J_{6',5}$ = 1.2 Hz, 6'-H), 4.08 (1 H, m, 5-H), 3.71 (1 H, t, 2-H), 3.51 (3 H, s, OMe), 3.24 (1 H, d, $^3J_{H,H}$= 9.5 Hz, fdn), 2.99 (1 H, d, fdn), 2.09 (3 H, s, OAc), 2.06 (3 H, s, OAc), 1.93 (3 H, s, OAc). δ_C (100 MHz; $CDCl_3$; $^{13}CDCl_3$) 171.1, 170.6, 169.6, 166.9, 153.7, 152.4, 139.4, 129.7, 127.6, 124.3, 122.9, 101.4, 74.9, 74.8, 72.1, 68.8, 62.2, 58.1, 21.2, 21.1, 21.1, 20.1, 19.8. relevant signal for the minor diastereoisomer: δ_H (400 MHz; $CDCl_3$; $CHCl_3$) 8.37 (1 H, s, N=C*H*), 5.60 (1 H, t, $^3J_{3,4} = {}^3J_{3,2}$ = 9.6 Hz, 3-H), 5.19 (1 H, t, $^3J_{3,4} = {}^3J_{4,5}$, 4-H), 4.98 (1 H, d, $^3J_{1,2}$ = 7.6 Hz, 1-H), 3.58 (3 H, s, OMe), 3.00 (1 H, d, $^3J_{H,H}$ = 9.5 Hz, fdn), 2.91 (1 H, d, fdn). Detailed presentation of physical data for: [Pd(**NN-G6**)(fdn)]: [Found: C, 51.65; H, 4.44; N, 8.86. $C_{28}H_{28}N_4O_8Pd$ requires C, 51.35; H, 4.31; N, 8.55]; relevant signals for the major diastereoisomer δ_H (400 MHz; $CDCl_3$; $CHCl_3$) 8.84 (1 H, d, ^3J = 4.5 Hz, aromatic), 8.40 (1 H, s, N=C*H*), 8.08 (1 H, d, ^3J = 7.3 Hz, aromatic), 5.79 (1 H, t, $^3J_{3,4} = {}^3J_{3,2}$ = 9.6 Hz, 3-H), 5.27 (1 H, t, $^3J_{3,4} = {}^3J_{4,5}$, 4-H), 4.94 (2 H, m, 1-H + 2-H), 4.81 (1 H, m, 5-H), 3.55 (3 H, s, OMe), 2.97 (1 H, d, $^3J_{H,H}$ = 9.2 Hz, fdn), 2.91 (1 H, s, fdn), 2.09 (3 H, s, OAc), 1.92 (3 H, s, OAc). relevant signals for the minor diastereoisomer: δ_H (400 MHz; $CDCl_3$; $CHCl_3$) 8.58 (1 H, d, ^3J = 4.5 Hz, aromatic), 8.28 (1 H, s, N=C*H*), 3.53 (3 H, s, OMe). the other signals are in the following regions: δ_H (400 MHz; $CDCl_3$; $CHCl_3$) 8.06 – 7.02 (15 H, aromatics), 4.21 - 4.00 (m), 3.83 (m). δ_C (100 MHz; $CDCl_3$; $^{13}CDCl_3$) 170.9, 170.9, 170.1, 169.9, 166.4, 166.1, 165.2, 164.9, 153.7, 153.4, 152.6, 152.4, 143.8, 139.4, 139.0, 135.1, 134.3, 134.1, 131.0, 130.6, 130.4, 129.4, 129.2, 129.1, 128.8 (2X), 128.6, 128.4, 127.0, 126.8, 125.8, 123.2, 123.0, 122.7, 97.2, 97.0, 72.3, 71.5 (2X), 71.1, 70.2, 70.0, 69.1, 68.2, 65.3, 63.7, 57.1, 56.4, 21.2 (2X), 21.0 (2X), 19.3, 18.9, 18.8, 18.7. Detailed presentation of physical data for: **[Pd(NN-M6)(fdn)]:** [Found: C, 51.61; H, 4.14; N, 8.77. $C_{28}H_{28}N_4O_8Pd$ requires C, 51.35; H, 4.31; N, 8.55]; major diastereoisomer δ_H (400 MHz; C_6D_6; TMS) 8.46 (2 H, d, ^3J = 7.3 Hz, aromatic), 8.05 (1 H, d, ^3J = 4.7 Hz, N=C*H*), 7.26-6.86 (4 H, m, aromatics), 6.70 (1 H, t, ^3J = 7.6 Hz, aromatic), 6.30 (2 H, m,

aromatic), 6.06 (1 H, dd, $^3J_{3,4}$ = 10.1 Hz, $^3J_{3,2}$ = 3.3 Hz, 3-H), 5.94 (1 H, t, $^3J_{3,4}$ = $^3J_{4,5}$, 4-H), 5.68 (1 H, dd, $^3J_{1,2}$ = 1.6 Hz, $^3J_{3,2}$ = 3.3 Hz, 2-H), 4.97 (1 H, m, 5-H), 4.39 (1 H, m, 1-H), 3.95 (1 H, d, $^3J_{6,6'}$ = 12.4 Hz, 6-H), 3.40 (1 H, dd, $^3J_{5,6'}$ = 9.6 Hz, 6'-H), 3.33 (3 H, s, OMe), 2.82 (2 H, s, Hz, fdn), 1.73 (3 H, s, OAc), 1.59 (3 H, s, OAc). relevant signal for the minor diastereoisomer: δ_H (400 MHz; C_6D_6; TMS) 8.13 (2 H, d, ^3J = 7.3 Hz, aromatic), 7.92 (d, 1H, ^3J = 4.0 Hz, N=C*H*), 7.26 - 6.86 (4 H, m, aromatics), 6.64 (1 H, t, ^3J = 7.0 Hz, aromatic), 6.34 (2 H, m, aromatic), 6.10 (1 H, dd, $^3J_{3,4}$ = 10.0 Hz, $^3J_{3,2}$ = 3.3 Hz, 3-H), 5.88 (1 H, t, $^3J_{3,4}$ = $^3J_{4,5}$, 4-H), 5.72 (1 H, dd, $^3J_{1,2}$ = 1.5 Hz, $^3J_{3,2}$ = 3.0 Hz, 2-H), 4.94 (1 H, m, 5-H), 4.55 (1 H, m, 1-H), 3.90 (1 H, d, $^{gem}J_{6,6'}$ = 12.1 Hz, 6-H), 3.82 (1 H, dd, $^3J_{5,6'}$ = 9.6 Hz, 6'-H), 3.35 (3 H, s, OMe), 2.82 (2 H, s, fdn), 1.73 (3 H, s, OAc), 1.53 (3 H, s, OAc). δ_c (100 MHz; C_6D_6; TMS) for the two distereoisomer: 169.7, 169.6, 169.5, 169.4, 166.7, 166.3, 164.1 (2X), 163.9, 153.0 (2X), 152.6, 152.2, 152.1, 137.8 (2X), 137.5, 135.5, 134.2, 133.8, 130.9, 130.4, 129.4, 129.3, 129.2, 129.0, 128.7, 125.6, 122.9, 122.7 (2X), 122.6 (2X), 104.0, 99.3, 99.0, 70.8, 70.3, 70.2, 70.0, 69.9, 69.8, 69.6, 68.5, 65.6, 63.4, 56.5, 55.7, 20.5 (2X), 20.3 (2X), 20.2, 20.1, 19.3, 19.2.

*5.5.5. General procedure for the preparation of the [Pd(**ligand***)(fdn)] complexes:*

The desired [Pd(**ligand**)(fdn)] complex (0.50 mmol) was suspended in 5 mL of methanol, and KOH was added (2.8 mg, 0.050 mmol). The reaction was monitored by NMR, taking a small sample of the solution, evaporating the solvent and dissolving the residue in CD_3OD. After completion, the solution was concentrated to 0.5 mL and the product was precipitated adding 10 mL of diethyl ether. The yellow, microcrystalline product was washed 3 times with diethyl ether and dried under vacuum (yield: 80-95%). Detailed presentation of physical data for: [Pd(**PN-G1***)(fdn)]: [Found: C, 54.39; H, 4.28; N, 6.32. $C_{29}H_{28}N_3O_5PPd$ requires C, 54.77; H, 4.44; N, 6.61]; relevant signals for the major diastereoisomer δ_H (400 MHz; CD_3OD; CHD_2OD) 8.69 (1 H, d, $^4J_{H,P}$ = 2.5 Hz N=C*H*), 7.80-7.10 (28 H, m, aromatics), 4.55 (1 H, d, $^3J_{1,2}$ = 8.3 Hz, 1-H), 2.81 (1 H, t, 2-H), δ_P (162 MHz; CD_3OD; H_3PO_4) 22.9; relevant signals for the minor diastereoisomer: δ_H (400 MHz; CD_3OD;

CHD_2OD) 8.61 (1 H, d, $^4J_{H,P}$ = 2.8 Hz, N=C*H*), 4.43 (1 H, d, $^3J_{1,2}$ = 8.3 Hz, 1-H), δ_P (162 MHz; CD_3OD; H_3PO_4) 21.9; the other signals are in the following regions: δ_H (400 MHz; CD_3OD; CHD_2OD) 3.98-3.90 (3 H, m), 3.85-3.75 (2 H, m), 3.69-3.53 (4 H, m), 3.52-3.42 (4 H, m), 3.16-3.00 (2 H, m), δ_C (100 MHz; CD_3OD; $^{13}CD_3OD$) 172.79, 171.56, 164.0-130.0 (aromatics), 128.7, 128.5, 126.4 (2X), 105.6, 104.4, 83.5, 83.0, 81.9, 81.8, 76.8, 76.7, 74.8, 73.9, 66.4, 65.7, 27.3 (d, $J_{P,C}$ = 44 Hz), 26.9 (2X, d, $J_{P,C}$ = 59 Hz), 26.4 (d, $J_{P,C}$ = 46 Hz). Detailed presentation of physical data for [Pd(**PN-G2***)(fdn)]: [Found: C, 55.81; H, 4.50; N, 6.29. $C_{30}H_{30}N_3O_5PPd$ requires C, 55.44; H, 4.65; N, 6.46]; relevant signals for the major diastereoisomer δ_H (400 MHz; CD_3OD; CHD_2OD) 8.46 (1 H, d, $^4J_{H,P}$ = 2.9 Hz, N=C*H*), 5.12 (1 H, d, $^3J_{1,2}$ = 7.9 Hz, 1-H), 4.36 (1 H, t, $^3J_{3,4}$ = $^3J_{3,2}$ = 9.2 Hz, 3-H), 3.93 (1 H, dd, $^3J_{6,6'}$ = 11.4 Hz, $^3J_{5,6}$ = 1.4 Hz, 6-H), 3.21 (3 H, s, OMe), 3.16 (1 H, d, $J_{H,H}$ = 8.0 Hz, fdn), 2.86 (1 H, t, $J_{H,H}$ = $J_{H,P}$ fdn), δ_P (162 MHz; CD_3OD; H_3PO_4) 18.9; relevant signals for the minor diastereoisomer: δ_H (400 MHz; CD_3OD; CHD_2OD) 8.45 (1 H, d, $^4J_{H,P}$ = 2.7 Hz N=C*H*), 5.04 (1 H, d, $^3J_{1,2}$ = 7.9, 1-H), 4.22 (1 H, t, $^3J_{3,4}$ = $^3J_{3,2}$ = 9.2 Hz, 3-H), 3.89 (1 H, dd, $^{gem}J_{6,6'}$ = 11.4, $^3J_{5,6}$ = 1.4 Hz, 6-H), 3.10 (3 H, s, OMe), 3.09 (1 H, dd, $J_{H,H}$ = 8.0 $J_{H,P}$ = 3.5Hz, fdn), 2.84 (1 H, t, $J_{H,H}$ = $J_{H,P}$ = 8.0 Hz, fdn) δ_P (162 MHz; CD_3OD; H_3PO_4) 18.5; the other signals are in the following regions: δ_H (400 MHz; CD_3OD; CHD_2OD) 7.75 (2 H, m, aromatics), 7.66 (2 H, m, aromatics), 7.60-7.30 (22 H, m, aromatics), 7.08 (2 H, m), 3.78-3.66 (3 H, m), 3.55-3.45 (3 H, m), δ_C (100 MHz; CD_3OD; $^{13}CD_3OD$) 170.5, 170.0, 137.8 – 129.0 (aromatics), 122.2, 103.9, 101.4, 82.2, 81.0, 76.8, 76.4, 73.5, 72.9, 70.8, 70.5, 61.6, 61.4, 56.6, 56.2, 23.6, 22.5, 22.3 (d, $J_{P,C}$ = 46 Hz), 21.8 (d, $J_{P,C}$ = 46 Hz). Detailed presentation of physical data for [Pd(**PN-G6***)(fdn)]: [Found: C, 55.11; H, 4.88; N, 6.62. $C_{30}H_{30}N_3O_5PPd$ requires C, 55.44; H, 4.65; N, 6.46]; relevant signals for the major diastereoisomer δ_H (400 MHz; CD_3OD; CHD_2OD) 8.51 (1 H, d, $^4J_{H,P}$ = 2.0 Hz, N=C*H*), 8.01 (1 H, d, ^3J = 7.8 Hz, aromatics), 7.84 (1 H, m, aromatics), 7.72 (1 H, t, ^3J= 7.6 Hz, aromatics), 7.59 (1 H, t, ^3J= 7.4 Hz, aromatics), 7.50-7.15 (10 H, m, aromatics), 4.77 (1 H, d, $^{gem}J_{6,6'}$ = 11.4 Hz, 6-H), 4.35 (1 H, d, $^3J_{1,2}$ = 3.6, 1-H), 4.12 (1 H, t, $^3J_{5,6}$ = $^3J_{5,4}$ = 9.3Hz, 5-H), 3.90 (1 H, t, 6'-H), 3.62 (1 H, t, $^3J_{3,4}$ = $^3J_{3,2}$ = 9.1 Hz, 3-H), 3.30 (dd, covered by the signal of the solvent, 2-H), 3.16 (2 H, m, 4-H + fdn), 2.94 (1 H, t, $^3J_{H,H}$ = $^{trans}J_{H,P}$ = 9.7 Hz, fdn), 2.50 (3 H, s, OMe); δ_C (100 MHz; CD_3OD; $^{13}CD_3OD$) 171.4, 140.9, 140.5, 138.5, 136.2, 136.1, 135.6, 135.5, 135.3, 134.3, 133.3, 132.9, 131.8, 131.5,

131.4, 131.0, 125.0, 102.0, 89.4, 76.4, 75.0, 74.9, 73.5, 59.7, 56.2, 32.1, 26.5, 25.7, 25.3, 19.7; δ_P (162 MHz; CD_3OD; H_3PO_4) 20.2. relevant signals for the minor diastereoisomer: δ_H (400 MHz; CD_3OD; CHD_2OD) 8.42 (1 H, d, $^4J_{H,P}$ = 2.0 Hz, N=C*H*), 4.57 (1 H, d, $^{gem}J_{6,6'}$ = 10.6 Hz, 6-H), 4.47 (1 H, d, $^3J_{1,2}$ = 4.5 Hz, 1-H); δ_P (162 MHz; CD_3OD; H_3PO_4) 19.7. Detailed presentation of physical data for: [Pd(**PN-M6***)(fdn)]: [Found: C, 55.76; H, 4.87; N, 6.48. $C_{30}H_{30}N_3O_5PPd$ requires C, 55.44; H, 4.65; N, 6.46]; relevant signals for the major diastereoisomer δ_H (400 MHz; $CDCl_3$; $CHCl_3$) 8.37 (1 H, bs, N=C*H major*), 4.79 (1 H, d, $^3J_{6,6'}$ = 11.0 Hz, 6-H), 4.47 (1 H, s, 1-H), 3.68 (1 H, t, $^3J_{3,4}$ = $^3J_{5,4}$ = 9.5 Hz, 3-H), 3.20 (1 H, dd, $^3J_{H,H}$ = 9.6 Hz, $^{cis}J_{H,P}$ = 2.9 Hz, fdn), 2.89 (1 H, t, $^3J_{H,H}$ = $^{trans}J_{H,P}$, fdn), 2.61 (3 H, s, OMe); relevant signals for the minor diastereoisomer: δ_H (400 MHz; $CDCl_3$; $CHCl_3$) 8.37 (1 H, bs, N=C*H*), 4.71 (1 H, d, $^3J_{6,6'}$= 11.3 Hz, 6-H), 4.48 (1 H, s, 1-H), 3.65 (1 H, t, $^3J_{3,4}$ = $^3J_{5,4}$ = 9.5 Hz, 3-H), 3.11 (1 H, dd, $^3J_{H,H}$ = 9.6 Hz, $^{cis}J_{H,P}$=3.0 Hz, fdn), 2.74 (1 H, t, $^3J_{H,H}$ = $^{trans}J_{H,P,}$ fdn), 2.53 (3 H, s, OMe); the other signals are in the following regions: δ_H (400 MHz; $CDCl_3$; $CHCl_3$) 7.65-7.10 (m, aromatics), 4.20-3.55 (m) δ_C (100 MHz; $CDCl_3$; $CHCl_3$) 169.3, 168.5, 137.9 – 129.3 (aromatics), 125.1, 123.0, 100.8, 100.7, 73.2, 72.4, 72.2, 70.9 (2X), 70.4, 70.0, 69.7, 54.4, 54.2, 25.2, 24.7, 23.8 (J_{P-C} = 43 Hz), 22.6 (J_{P-C} = 44 Hz). δ_P (162 MHz; CD_3OD; H_3PO_4) 17.8. Detailed presentation of physical data for: [Pd(**NN-G2***)(fdn)]: [Found: C, 43.59; H, 4.35; N, 11.67. $C_{17}H_{20}N_4O_5Pd$ requires C, 43.74; H, 4.32; N, 12.00]; relevant signals for the major diastereoisomer δ_H (400 MHz; CD_3OD; CHD_2OD) 8.63 (1 H, s, N=C*H*), 4.92 (1 H, d, $^3J_{1,2}$ = 7.7 Hz, 1-H), 3.50 (3 H, s, OMe), 3.02 (2 H, ABq, fdn); relevant signals for the minor diastereoisomer: δ_H (400 MHz; CD_3OD; CHD_2OD) 8.60 (1 H, s, 1H, N=C*H*), 4.90 (1 H, d, $^3J_{1,2}$ = 7.7 Hz, 1-H), 3.57 (3 H, s, 3H, OMe), 2.97 (2 H, s, fdn); the other signals are in the following regions: δ_H (400 MHz; CD_3OD; CHD_2OD) 8.87 (m, aromatics), 8.16 (m, aromatics), 7.95 (m, aromatics), 7.64 (m, aromatics), 4.11 (t, J = 8.7 Hz), 3.97-3.85 (m), 3.60-3.32 (m), 3.07-2.94(m) δ_C (100 MHz; CD_3OD; $^{13}CD_3OD$) 171.32, 171.06, 157.2, 157.1 (2X), 157.0, 143.8 (2X), 133.1, 131.5, 127.7, 126.8, 108.2, 106.1, 81.1, 80.7, 80.1, 79.6, 77.7, 74.7, 74.1, 69.8, 65.6, 65.4, 60.5, 60.3, 21.2, 20.9, 18.4. Detailed presentation of physical data for [Pd(**NN-G6***)(fdn)]: [Found: C, 44.01; H, 4.36; N, 11.66. $C_{17}H_{20}N_4O_5Pd$ requires C, 43.74; H, 4.32; N, 12.00]; relevant signals for the major diastereoisomer δ_H (400 MHz; CD_3OD; CHD_2OD) 8.62 (1 H, s, N=C*H*), 4.59 (1 H, d, $^3J_{1,2}$ = 2.0 Hz, 1-H), 4.27 (1 H, t, $^3J_{3,4}$ = $^3J_{4,5}$ = 9.0 Hz,

4-H), 3.76 (1 H, t, $^{3}J_{6,5} = {}^{3}J_{6,6'}$ = 10.0 Hz, 6-H), 3.42 (3 H, s, OMe), 2.94 (2 H, ABq, fdn), relevant signals for the minor diastereoisomer: δ_H (400 MHz; CD_3OD; CHD_2OD) 8.59 (1 H, s, N=C*H*), 4.57 (1 H, d, $^{3}J_{1,2}$ = 2.0 Hz, 1-H), 4.24 (1 H, t, $^{3}J_{3,4} = {}^{3}J_{4,5}$ = 9.0 Hz, 4-H), 3.86 (1 H, t, $^{3}J_{6,5} = {}^{3}J_{6,6'}$ = 10.0 Hz, 6-H), 3.30 (3 H, s, OMe), 2.91 (2 H, s, fdn); the other signals are in the following regions: δ_H (400 MHz; CD_3OD; CHD_2OD) 8.85 (2 H, m, aromatics), 8.15 (2 H, m, aromatics), 7.92 (2 H, m, aromatics), 7.62 (2 H, m, aromatics), 4.48 (2 H, m), 3.70-3.65 (2 H, m), 3.50-3.25 (2 H, m); δ_C (100 MHz; CD_3OD; $^{13}CD_3OD$) 166.1, 165.7, 152.8 (2X), 152.5, 152.3, 139.0 (2X), 128.1 (2X), 126.3 (2X), 122.4 (2X), 122.0 (2X), 99.4, 99.03, 73.4 (2X), 72.0 (2X), 71.8 (2X), 70.3, 69.2, 64.0, 63.0, 54.5, 53.8, 16.5 (2X), 15.3 (2X). Detailed presentation of physical data for [Pd(**NN-M6***)(fdn)]: [Found: C, 43.39; H, 4.18; N, 12.36. $C_{17}H_{20}N_4O_5Pd$ requires C, 43.74; H, 4.32; N, 12.00]; relevant signals for the major diastereoisomer δ_H (400 MHz; CD_3OD; CHD_2OD) 8.63 (1 H, s, N=C*H*), 3.30 (3 H, s, OMe); relevant signals for the minor diastereoisomer: δ_H (400 MHz; CD_3OD; CHD_2OD) 8.61 (1 H, s, N=C*H*), 3.29 (3 H, s, OMe); the other signals are in the following regions: δ_H (400 MHz; CD_3OD; CHD_2OD) 8.85 (m, aromatics), 8.14 (m, aromatics), 7.92 (m, aromatics), 7.70 (m, aromatics), 4.50 (m), 4.20 (m), 3.78 (m), 3.63 (m), 2.91 (m, fdn); δ_C (100 MHz; CD_3OD; $^{13}CD_3OD$) 170.8, 170.4, 157.6 (2X) , 157.3 (2X), 143.8 (2X), 132.8 (2X), 131.0 (2X), 127.1, 126.8, 105.7, 105.4, 75.9, 75.4 (2X), 75.1, 74.9 (2X), 73.3, 73.1, 68.8, 67.7, 58.9, 58.2, 21.3 (2X) , 19.9 (2X).

5.5.7. Typical procedure for the Suzuki-Miyaura coupling:

To a solution of phenylboronic acid (0.55 mmol, 67 mg) and 4-bromanisole (0.50 mmol, 63 µL) in 1 mL of ethanol absolute were added a solution of potassium carbonate (1.00 mmol, 138 mg) in 2 mL of water and an opportune volume of a solution of the catalyst in ethanol absolute. The system was heated up to 120°C. After 1h the product was extract with dichloromethane (10 mL x 3 times), dried with anhydrous sodium sulfate, filtered and concentrated under vacuum. The solution was filtered through a short pad of silica and then chromatographed over Silica Gel (eluent: hexane→hexane / ethyl acetate 4:1). The structure of the pure product was

confirmed by MS and by comparison of the NMR spectra with data reported in literature.

5.6 References.

[1] Negishi, E.-i.; *Aspects ofMechanism and Organometallic Chemistry* (ed. J.H. Brewster), Plenum, New York, **1978**, 285.
[2] Miyaura, N.; Yamada, K.; Suzuki, A.; *Tetrahedron Lett.* **1979**, *20*, 3437.
[3] Miyaura, N.; Suzuki, A.; *Chem. Commun.* **1979**, 866.
[4] (a) Miyaura, N.; Suzuki, A.; *Chem. Rev.* **1995**, *95*, 2457. (b) Miyaura, N.; *Top. Curr. Chem.*, **2002**, *219*, 11. (c) Suzuki, A.; *J. Organomet. Chem.* **1999** *576*, 147.
[5] Suzuki, A.; *Cross-coupling reactions of organoboranes: an easy way for C-C bonding*. Nobel lecture, **2010**.
[6] Polshettiwar, V.; Decottignies, a.; Len, C.; Fihri, A.; *ChemSusChem* **2010**, *3*, 502.
[7] (a)Clark, J. H.; *Green Chem.* **2006**, *8*, 17. (b) Li, C. J.; Chen, L. ; *Chem. Soc. Rev.* **2006**, *35*, 68. (c) Poliakoff, M.; Licence, P.; *Nature* **2007**, 450, 810. (d) Polshettiwar, V.; Varma, R. S.; *J. Org. Chem.* **2007**, *72*, 7420.
[8] for an extensive review, see:García-Melchor, M.; Braga, A. A.; Lledós, A.; Ujaque, G.; Maseras, F.; *Acc Chem Res.* **2013,** *46*, 2626.
[9] (a) Beller, M.; Krauter, J. G. E.; Zapf, A. *Angew. Chem., Int. Ed.***1997**, 36, 772–774. (b) Kolodziuk, R.; Penciu, A.; Tollabi, M.; Framery, E.; Goux-Henry, C.; Iourtchenko, A.; Sinou, D. *J. Organomet. Chem.***2003**, 687, 384. (c) Konovets, A.; Penciu, A.; Framery, E.; Percina, N.; Goux-Henry, C.; Sinou, D. *Tetrahedron Lett.* **2005**, 46, 3205. (d) Ueda, M.; Nishimura, M.; Miyaura, N. *Synlett* **2000**, 856. (e) Nishimura, M.; Ueda, M.; Miyaura, N. *Tetrahedron* **2002**, 58, 5779. (f) Makhubela, B. C. E.; Jardine, A.; Smith G. S. *Applied Catalysis A: General* **2011** 393, 231
[10] Shaughnessy, K. H.; *Chem.Rev.* **2009**, *109* ,643.
[11] (a) Shahnaz, N. ; Banik, B. ; Das P.; *Tetrahedron Lett.*, **2013**, 54, 2886; (b) Wei, S. ; Ma, Z. ; Wang, P. ; Dong Z.; Ma, J.; *Journal of Molecular Catalysis A: Chemical*, **2013**, *370*, 175; (c) Sarmah, C. ; Sahu D. ; Das, P.; *Catalysis Today*, **2012**, *198*, 197; (d) Tang, X. ; Huang, Y.-T.; Liu, H. ; Liu, R.-Z.; Shen, D.-S.; Liu N. ; Liu, F.-S.; *J. Organomet. Chem.*, **2013**, 729, 95;

(e) Banik, B. ; Tairai, A. ; Shahnaz N. ; Das, P.; *Tetrahedron Lett*., **2012**, *53*, 5627.
[12] (a) Borriello, C.; Cucciolito, M. E.; Panunzi A.; Ruffo, F.; *Inorg. Chimica Acta*, **2003**, *353*, 238; (b) Glegola, K.; Johannesen, S. A.; Thim, L.; Goux-Henry, C.; Skrydstrup T.; Framery, E.; *Tetrahedron Lett.*, **2008**, *49*, 6635. (c) Borriello, C.; Ferrara, M. L.; Orabona, I.; Panunzi A.; Ruffo, F.; *Dalton*, **2000**, *15*, 2545; (d) Ferrara, M. L.; Giordano, F. ; Orabona, I.; Panunzi A.; Ruffo, F.; *Eur. J. Inorg. Chem.*, **1999**, *11*,1939.
[13] (a) Selvakumar, A.; Valentini, M.; Wörle M.; Pregosin, P. S.; *Organometallics*, **1999**, 18, 1207; (b) Klein, R. A.; Witte, P.; van Belzen, R.; Fraanje, J.; Goubitz, K.; Numan, M.; Schenk, H.; Ernsting J. M.; Elsevier, C. J.; *Eur. J. Inorg. Chem.*, **1998**, 319; (c) Canovese, L.; Visentin, F.; Uguagliati, P.; Crociani, B.; *J. Chem. Soc., Dalton Trans.*, **1996**, 1921; (d) van Asselt, R.; Smeets W. J. J.; Spek, A. L.; *Inorg. Chem.*, **1994**, *33*, 1521.
[14] (a) De Castro, C.; Giordano, F. ; Orabona, I.; Molinaro A.; Ruffo, F.; *Carbohyd. Res.*, **2002**, *337*, 651; (b) Borriello, C.; Cucciolito, M. E.; Panunzi, A.; Ruffo, F.; *Tetrahedron: Asymmetry*, **2001**, *12*, 2467; (c) Borriello, C.; De Renzi, A.; Fusto, M.; Molinaro, A.; Ruffo, F.; *Carbohyd. Res.*, **2001**, *331*, 209; (d) Ferrara, M. L.; Funicello, M.; Orabona, I.; Panunzi, A.; Ruffo, F.; *Organometallics*, **1998**, *17*, 3832; (e) Zehnder, M.; Neuburger, M.; Schaffner, S.; Jufer, M.; Plattner, D. A.; *Eur. J. Inorg. Chem.*, **2002**, 1511; (f) Bandoli, G.; Dolmella, A.; Crociani, L.; Antonaroli, S.; Crociani, B.; *Trans. Met. Chem.*, **2000**, *25*, 17.
[15] (a) Darensbourg, D. J.; Decuir, T. J.; Stafford, N. W.; Robertson, J. R.; Draper, J. D.; Reibenspies, J. H.; Kathó, A.; Joó, F.; *Inorg. Chem.*, **1997**, *36*, 4218; (b) Ellis, J. W.; Harrison, K. N.; Hoye, P. A. T.; Orpen, A. G.; Pringle, P. G.; Smith, M. P.; *Inorg. Chem.*, **1992**, *31*, 3026.
[16] (a) Canovese, L.; Visentin, F.; Uguagliati, P.; Crociani, B.; *J. Chem. Soc., Dalton Trans.*, **1996**, 1921; (b) van Asselt, R.; Elsevier, C. J.; Smeets, W. J. J.; Spek, A. L.; *Inorg. Chem.*, **1994**, *33*, 1521.
[17] (a) Suzuki, A.; in *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F.; Stang, P. J.; Eds.; Wiley-VCH: Weinheim, Germany, **1998**; pp 49-97; (b) Miyaura, N.; Suzuki, A.; *Chem. Rev.*, **1995**, *95*, 2457; (c) Suzuki, A.; *J. Organomet. Chem.*, **1999**, *576*, 147; (d) Kotha, S.; Lahiri K.; Kashinath, D.; *Tetrahedron*, **2002**, *58*, 9633; (e) Bo, S.-Z.; Schlüter, A. D.; *Chem. Eur. J.*, **2000**, *6*, 3235; (f) Miyaura, N.; Yanagi, T.; Suzuki, A.; *Synth. Commun.*, **1981**, *11*, 513.

[18] (a) Genet, J. P.; Savignac, M. J.; *J. Organomet. Chem.*, **1999**, *576*, 305; (b) Nájera, C.; Gil-Moltò, J.; Karlström, S.; Falvello, L. R.; *Org. Lett.*, **2003**, *5*, 1451; (c) Nájera, C.; Gil-Moltò, J.; Karlström, S.; *Adv. Synth. Catal.*, **2004**, *346*, 1798; (d) Nájera, C.; Gil-Moltò, J.; Karlström, S.; *Tetrahedron*, **2005**, *61*, 12168; (e) Botella, L.; Nájera, C.; *Angew. Chem., Int. Ed.*, **2002**, *41*, 179; (f) Botella L.; Nájera, C.; *J. Organomet. Chem.* **2002**, *663*, 46; (g) Bedford, R. B.; Blake, M. E.; Butts, C. P.; Holder, D.; *Chem. Commun.*, **2003**, 466; (g) Chen, C.-L.; Liu, Y.-H.; Peng, S.-M.; Liu, S.-T.; *Organometallics*, **2005**, *24*, 1075; (h) Ogo, S.; Takebe, Y.; Uehara, K.; Yamazaki, T.; Nakai, H.; Watanabe, Y.; Fukuzumi, S.; *Organometallics*, **2006**, **25**, 331.

[19] (a) Badone, D.; Baroni, M.; Cardamone, R.; Ielmini, A.; Guzzi, U. J.; *J. Org. Chem.*, **1997**, *62*, 7170; (b) Liu, L.; Zhang, Y.; Wang, Y.; *J. Org. Chem.*, **2005**, *70*, 6122; (c) Bhattacharya, S.; Srivastava A.; Sengupta, S.; *Tetrahedron Lett.*, **2005**, *46*, 3557; (d) Li, J.-H.; Hu, X.-C.; Xie, Y.-X.; *Tetrahedron*, **2006**, *62*, 31.

[20] (a) Leadbeater, N. E.; Marco, M.; *J. Org. Chem.*, **2003**, *68*, 888; (b) Leadbeater, N. E.; Marco, M.; *J. Org. Chem.*, **2003**, *68*, 5660; (c) Leadbeater, N. E.; Marco, M.; *Angew. Chem., Int. Ed.*, **2003**, *42*, 1407; (d) Arvela, R. K.; Leadbeater, N. E.; Sangi, M. S.; Williams, V. A.; Granados, P.; Singer, R. D.; *J. Org. Chem.*, **2005**, *70*, 161; (e) Arvela, R. K.; Leadbeater, N. E.; Mack, T. L.; Kormos, C. M.; *Tetrahedron Lett.*, **2006**, *47*, 217; (f) Chanthavong, F.; Leadbeater, N. E.; *Tetrahedron Lett.*, **2006**, *47*, 1909; (g) Yan, J.; Jin, H.; Shan, S.; *Tetrahedron*, **2006**, *62*, 5603.

[21] Jessop, P. G.; *Green Chem.*, **2011**, *13*, 1391.

[22] (a) Arvela, R. K.; Leadbeater, N. E.; Sangi, M. S.; Williams, V. A.; Granados, P.; Singer, R. D.; *J. Org. Chem.*, **2005**, *70*, 161; (b) Gil-Moltò, J.; Karlström, S.; Nájera, C.; *Tetrahedron*, **2005**, *61*, 12168; (c) Leadbeater, N. E.; Marco, M.; *J. Org. Chem.*, **2003**, *68*, 888; (d) Blettner, C. G.; Konig, W. A.; Stenzel, W.; Schotten, T.; *J. Org. Chem.*, **1999**, *64*, 3885; (e) Korolev, D. N.; Bumagin, N. A.; *Tetrahedron Lett.*, **2005**, *46*, 5751; (f) Shaughnessy, K. H.; Booth, R. S.; *Org. Lett.*, **2001**, *3*, 2757; (g) Genet, J. P.; Linquist, A.; Blart, E.; Mouriès, V.; Savignac, M.; Vaultier, M.; *Tetrahedron Lett.*, **1995**, *36*, 1443; (h) Molander, G. A.; Biolatto, B.; *J. Org. Chem.*, **2003**, *68*, 4302; (i) Amoroso, F.; Colussi, S.; Del Zotto, A.; Llorca, J.; Trovarelli, A.; *Catal. Commun.*, **2011**, *12*, 563. (j) Amoroso, F.; Colussi, S.; Del Zotto, A.; Llorca, J.; Trovarelli, A.; *J. Mol. Catal. A: Chemical*, **2010**, *315*, 197.

[23] Marziale, A. N.; Faul, S. H.; Reiner, T.; Schneider, S.; Eppinger, J.; *Green. Chem.*, **2010**, *12*, 35.
[24] Rao, G. K.; Kumar, A.; Singh, M. P.; Singh, A. K.; *J. Organomet. Chem.*, **2014**, *749*, 1.
[25] Kinzhalov, M. A.; Luzyanin, K. V.; Boyarskiy, V. P.; Haukka, M.; Yu. Kukushkin, V.; *Organometallics*, **2013**, *32*, 5212, and references cited therein.

6. Conclusions.

The main aim of this PhD thesis was the development of a new family of chiral ligands derived from D-glucose (*elpaN-type).* These ligands were designed in order to be *pseudo-enantiomeric* respect to the previously developed *Naple-type* family, and focusing on the obtainment of easy and straightforward synthesis.

On this basis, three libraries of *elapN-type* ligands were prepared and successfully employed in homogenous metal-promoted asymmetric catalysis: the *elpaN-phos*, for the Pd-promoted Asymmetric Allylic Substitution; the *elpaN-py*, for the Mo-promoted Asymmetric Allylic Alkylation enhanced by microwaves; the *elpaN-Salen*, for the Mn-promoted Asymmetric Epoxidation.

In all cases, performances were excellent and inversion of selectivity respect to the *Naple-type* family was achieved. In the particular case of the *elpaN-phos* subset, a phase-tagged version of the ligand was successfully employed in multiphase catalysis, achieving the recycle of the catalyst.

The secondary aim of this PhD thesis was the development of a library of sugar-derived, water soluble Pd^0 complexes for aqueous Suzuki-Miyaura cross-coupling. Also in this case, good performances were obtained (TOF up to 9500 h^{-1}), among the best in literature for this reaction in aqueous, sustainable condition.

7. List of publications.

This thesis is based on the following papers:

Chapter 1:
"Rational design of pseudo-enantiomeric libraries of ligands based on pyranoses for application in asymmetric catalysis"; Benessere, V.; Lega, M.; Ruffo, F.; *J. Organomet. Chem.* **2014**, accepted.

Chapter 2:
"Naplephos through the Looking-Glass: Chiral Bis(phosphanylamides) Based on β-1,2-D-Glucodiamine and their Application in Enantioselective Allylic Substitutions"; Benessere, V.; De Roma, A.; Del Litto, R.; Lega, M.;Ruffo, F.; *Eur. J. Org. Chem.* **2011**, *29*, 5779.

Chapter 3:
"Expanding the scope of the elpaN-type library: glucose-derived bis(pyridine-2-carboxamide) ligands (elpaN-Py) for molybdenum-catalyzed asymmetric allylic alkylations"; Lega, M.; Figliolia, R.; Moberg, C.; Ruffo, F.; *Tetrahedron* **2013**, *20*, 4061.

Chapter 4:
"The elpaN-salen series: multifunctional ligands based on D-glucose for the Mn(III)-catalyzed enantioselective epoxidation of styrenes"; Ruffo, F.; Bismuto, A.; Carpentieri, A.; Cucciolito, M. E.;Lega, M.; Tuzia, A.; *Inorg. Chim. Acta*, **2013**, *405*,288.

Chapter 5:
"Hydrophilic Pd(0) complexes based on sugars for the efficient Suzuki-Miyaura coupling in aqueous systems"; Tarantino, G.; Curcio, M.; Carpentieri, A.; Cucciolito, M. E.; Ruffo, F.; Vitagliano, A.; Lega, M.; *Green Chem.* **2014** (submitted)

Other papers published during the PhD:

"Application of pyranoside phosphite-pyridine ligands to enantioselective metal-catalyzed allylic substitution and conjugate 1,4-addition." Lega, M.; Margalef, J.; Ruffo, F.; Pàmies O.; Diéguez, M.;*Tetrahedron: Asymmetry* **2013**, *24*, 995.

"The application of pyranoside phosphitepyridine ligands to enantioselective Ir-catalyzed hydrogenations of highly unfunctionalized olefins." Margalef, J.; Lega, M.; Ruffo, F.; Pàmies O.; Diéguez, M.;*Tetrahedron: Asymmetry*. **2012**, *23*, 945.

"Shiff base complexes of zinc(II) as catalysts for biodiesel production" Di Serio, M.; Carotenuto, G.; Cucciolito, M. E.; Lega, M.; Ruffo, F.; Tesser, R.; Trifuoggi, M.; *J. Mol. Cat. A: Chemical* **2012**, *353*; 106

Ringraziamenti

A mia madre, che mi ha insegnato tante cose.
A mio padre, perchè per fortuna "tale padre tale figlio".
A Linda, che nel nostro rapporto ci mette anche quello che io, a volte, non riesco a mettere.
A Rita Q., che ha deciso di combattere al miofianco le battaglie della vita.
A Kikko, per avermi mostrato da subito affetto incondizionato.
A Franx e Becienzo, per essere stati dei punti di riferimento nella vita ancora prima che nel lavoro.
A Marco S., perché c'è nonostante la distanza.
Ad Andrea P., per avermi sopportato durante i miei discorsi noiosi.
Ai partecipanti della Champions Lega, per avermi insegnato che il calcio è metafora della vita.

SPECIAL THANKS

A marzo 2010 scrissi i ringraziamenti della mia tesi di laurea. Quattro anni dopo li rileggo, constatando che in questo lasso di tempo è cambiato molto. Persone sono entrate ed uscite dalla mia vita, ed ho affrontato le numerose prove di chi si affaccia ai 30. Non mi dilungherò, ma guardandomi indietro vorrei solo dire: *bravo il dottorando!*
Inoltre ringrazio in ordine sparso: i tre Giovanni che hanno avuto un ruolo molto importante nella mia vita (Giovanni Peroni, Giovanni il Lungo e Giovanni il Camminatore), Pino Mauro, Il Dio Nilo per avermi protetto, l'amico Izzo, tutti i tesisti con cui ho lavorato in questi anni, Grazia e Franco del campetto degli aranci.