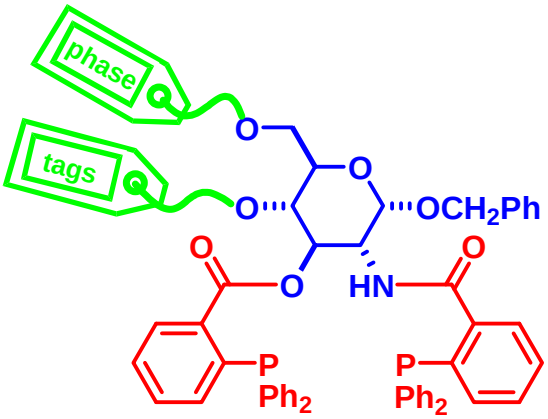
UNIVERSITA' DEGLI STUDI DI NAPOLI FEDERICO II

FACOLTA' DI SCIENZE MATEMATICHE FISICHE E NATURALI

Doctoral Thesis (XXI cycle)

2005-2008

Ligands derived from natural substances for asymmetric catalysis



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Abstract

The interaction between biological systems and synthetic chiral molecules has a huge impact on contemporary everyday life and applications range from flavors, fragrances, and food additives to agrochemicals and life-saving drugs. The development of efficient methodologies for the synthesis of the individual enantiomers of a chiral target compound is therefore of continuous interest to scientists in both industry and academia.

Among various methods for the preparation of enantiopure molecules, the application of asymmetric catalysis is an attractive option. In the last decades considerable progress has been made in the development of metal-catalyzed asymmetric transformations based on enantiopure ligands complexed to a (transition) metal centre. However, the identification of suitable asymmetric catalysts still poses one of the most challenging endeavours of contemporary chemistry.

The research described in this thesis aimed to develop a new class of *privileged* chiral ligands for asymmetric catalysis, by functionalization of natural molecules such as carbohydrates.

Sugars were chosen as building blocks since an appropriate derivatization of the hydroxyls present in their skeleton is suited for the achievement of finely tailored ligands.

In particular, the first part of the work was addressed towards the synthesis of new ligands derived from glucose, mannose or galactose with the structure reported in Figure 1.

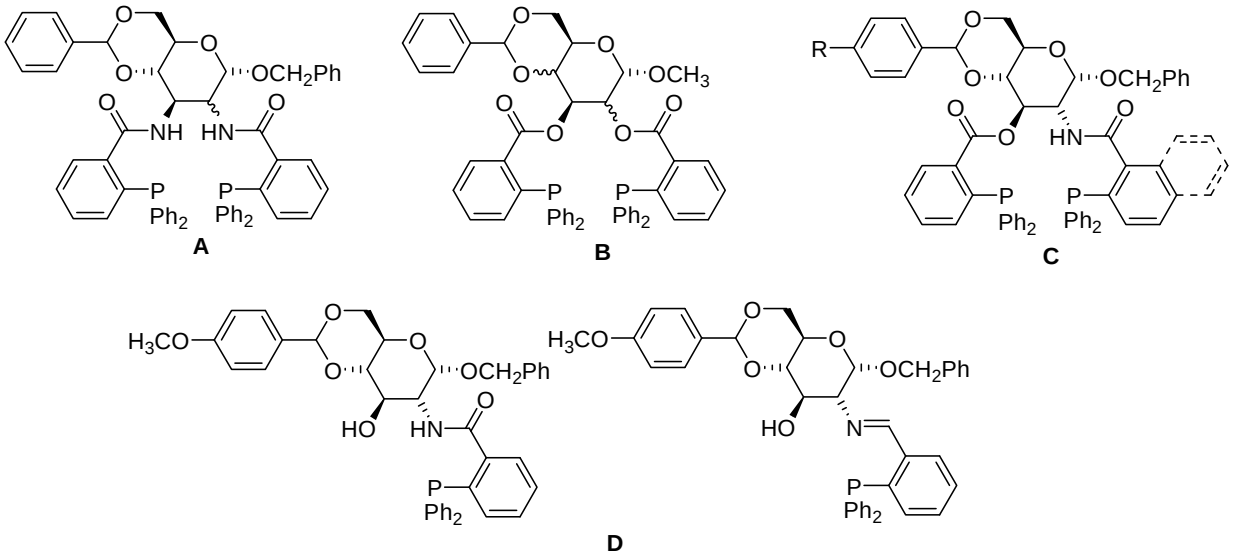
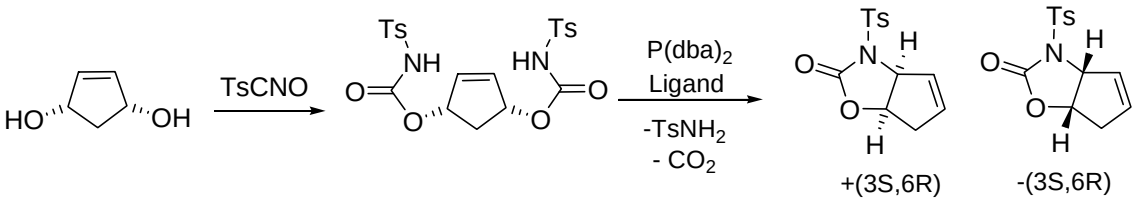


Figure 1

Ligands A-C, which are structurally analogous to the *privileged* Trost ligands, were examined in the Pd-catalysed asymmetric desymmetrization of *meso*-2-cyclopenten-1,4-diol biscarbamate in traditional conditions (Scheme 1).

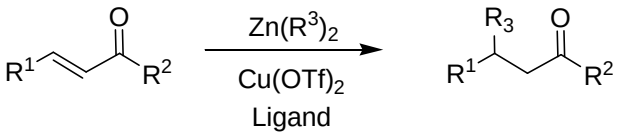


Scheme 1

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. Bis(phosphinoamide) (**A**) yielded the product with high ee's (up to 97%), though the multi-step synthesis does not encourage its use. On the other hand, the bis(phosphinoester) (**B**) is immediately available from commercial sources. Unfortunately, its activity is less satisfying, because the ee of the product did not exceed 82%.

On these grounds and with the intent of combining both synthetic convenience and high catalytic performance, attention was conveyed towards the synthesis of mixed (phosphinoester-phosphinoamide) ligands (**C**). They plainly fulfil the expectations because the synthesis is very convenient, and requires only four simple steps from inexpensive N-acetylglucosamine, and in traditional catalytic conditions, the corresponding Pd complexes were as active as the analogous bis(phosphinoamide) (**A**).

In order to demonstrate the applicability of the ligands in other catalytic processes, their use was investigated also in the asymmetric Cu-catalyzed 1,4-conjugate addition of organozinc reagents to acyclic enones.



Scheme 2

High reactivities and good enantioselectivities (ee values up to 95%) were achieved also in this process. Activity and selectivity depended strongly on the type of functional group attached to the carbohydrate backbone and on its electronic and steric properties.

The second part of the actitity aimed at combining the high chemical performance of these catalysts with the increasing need of sustainability demanded by the modern industrial chemistry.

For this reason "tagged" versions of the ligands were prepared in order to extend their use in the innovative *multiphasic homogeneous conditions* (Figure 2).

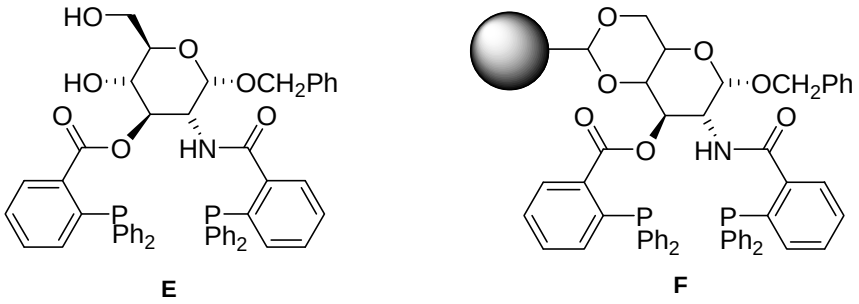


Figure 2

It should be remember that the methodology requires heterogenization of the catalyst, through either its anchorage to a solid support or its selective immobilization in a liquid phase immiscible with the products phase. In these conditions, the catalyst is easily recycled at the end of the reaction by simple phase separation.

Thus, the desymmetrization of *meso*-cyclopenten-2-ene-1,4-diol biscarbamate was performed in the ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate [BIMIM]BF_4 by using the polar form of the ligand (**E**). In addiction, the anchored version (**F**) was employed in the same reaction as supported catalyst.

The promising results achieved in both cases (up to 4 recycles) give more emphasis to the quality of the new sugar-based ligands, and further stimulates investigation on their use in asymmetric catalysis.

1.Introduction

1. 1 *Enantioselective catalysis from a sustainable industrial point of view*

The role of chemistry is essential to improve wellness and quality of life. Its unique contribution is referred to the synthesis of new pharmaceuticals, agrochemicals, flavours and fragrances, to the production of new polymeric materials, to the depollution technologies and to the production and conversion of energy. Of course, the improvement of the quality of life must also encompass the contemporaneous protection of the environmental and human health. This responsibility, combined with the need to satisfy the growing manufacture demand, has increased the attention towards innovative solutions able to reduce the environmental impact of chemical production.

The expression *Green Chemistry* indicates the modern guidelines aiming to satisfy this urgent requisite and consists in a group of principles proposed in 1990 from the US Environmental Protection Agency in order to reduce or remove the use and the formation of hazardous substances in the synthetic processes.[1]

These principles encourage the adoption of safe solvents and reagents, the use of renewable raw materials, the energy saving, the minimization of auxiliary substances and the reduction of by-products.

These strict conditions are generally satisfied by reactions that occur catalytically. The catalysts, in fact, promote very effective processes by allowing milder reaction conditions compared with those performed without catalysts.

The use of a catalyst allows to control the chemoselectivity of a reaction (e.g. a double C=N bond can be hydrogenated leaving unchanged a double bound C=C), the regioselectivity (e.g. a reagent X-Y can add to an alkene $RCH=CH_2$ leading $RCHX-CH_2Y$ as the only product), the stereoselectivity (the formation of one enantiomer is privileged compared to the other one). This produces environmental benefits, because high selectivity reduces the unwanted by-products, the number of separation processes and the use of related auxiliary substances.

For this reason, metal promoted homogeneous catalysis[2] has a central role in the modern chemical industry and, in particular, asymmetric catalysis[3] is acknowledged as an excellent methodology for the stereoselective synthesis of chiral molecules.[4]

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[1] Anastas P.T.; Warner J.C.; *Green Chemistry: Theory and Practice*, 1st ed.; Oxford University Press Inc.: New York, USA, **1998**.

[2] *Multiphase Homogeneous Catalysis,* 1st ed.; Cornils, B.; Herrmann, W.A., Horvarth, I.T.; Leitner, W.; Mecking, S.; Olivier-Borbigou, H.; Vogt, D.; Eds.; Wiley-VCH: Weinheim, Germany, **2005**.

[3] *Asymmetric Catalysis on Industrial Scale,* 1st ed.; Blaser, H.U., Schmidt, E., Eds.; Wiley-VCH: Weinheim, Germany, **2004**.

Within this respect, it should be remembered that living systems preferentially produce and use enantiomerically pure compounds, and not racemic mixtures. In particular, only one enantiomer has the desired biological property, while its mirror image has no effect, or, worst, undesired activity.

For this reason, current regulations demand the separation of both enantiomers of a biologically active compound, such as a medicine, before its approval. This trend has given a great motivation to the development of enantioselective synthesis for the production of enantiorich or, better, enantiopure compounds.

In these scenarios, asymmetric catalysis is certainly the preferred methodology, because it allows to directly convert a prochiral reagent, often easily available, in an enantiopure chiral product, settling the premises to the achievement of efficient, convenient and clean processes.

Nowadays, there is a large number of industrial applications[3] of asymmetric catalysis for the production of pharmacological, agrochemical, cosmetic substances, and in general in the field of fine chemisty.[4]

A central example is the synthesis of a key intermediate of L-DOPA, drug used today for the Parkinson's disease therapy, and industrially produced on large scale (about a ton per year) from Monsanto. This synthesis makes use of a rhodium complex with a chiral diphosphine (DIPAMP) able to promote the asymmetric hydrogenation of olefin precursors (Figure 1.1).

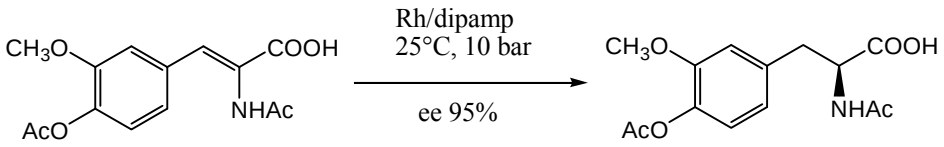


Figure. 1.1

Another remarkable example is represented by the synthesis of an intermediate of aspartame, a sweetener produced in about 15 tons per year by Enichem.

In this case a rhodium complex of a tetradentate ligand with phosphorous and nitrogen atoms as donors (ENIPHOS) is used, which is able to hydrogenate selectively C=C double bonds (Figure 1.2).

[4] The large importance of asymmetric catalysis is demonstrated by the Nobel prize-giving assignation to Noyori, Sharpless and Knowles in 2001, to Schrock and Grubs in 2005 for their crucial contribution to this sector.

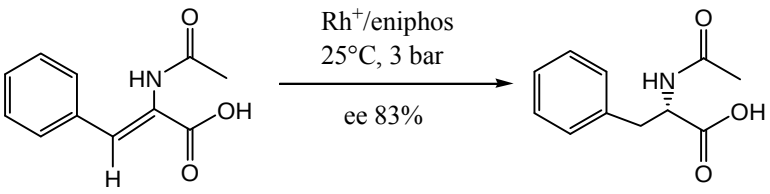


Figure 1.2

It is interesting to observe that one form of aspartame is a synthetic sweetener while the other one has bitter flavour.

1.2 *Privileged ligands*

In asymmetric catalysis the enantioselectivity is induced by metal transition complexes containing chiral ligands, whose appropriate design is a fundamental requirement to the achievement of high selectivity. Thousands of chiral ligands have been prepared and tested so far, but only a few of them have demonstrated large applicability in a variety of asymmetric reactions. These ligands are therefore called *privileged* (Figure 1.3), a term coined by Jacobsen for indicating ligand structures useful for the production of chiral molecules and the discovery of new enantioselective processes.[5]

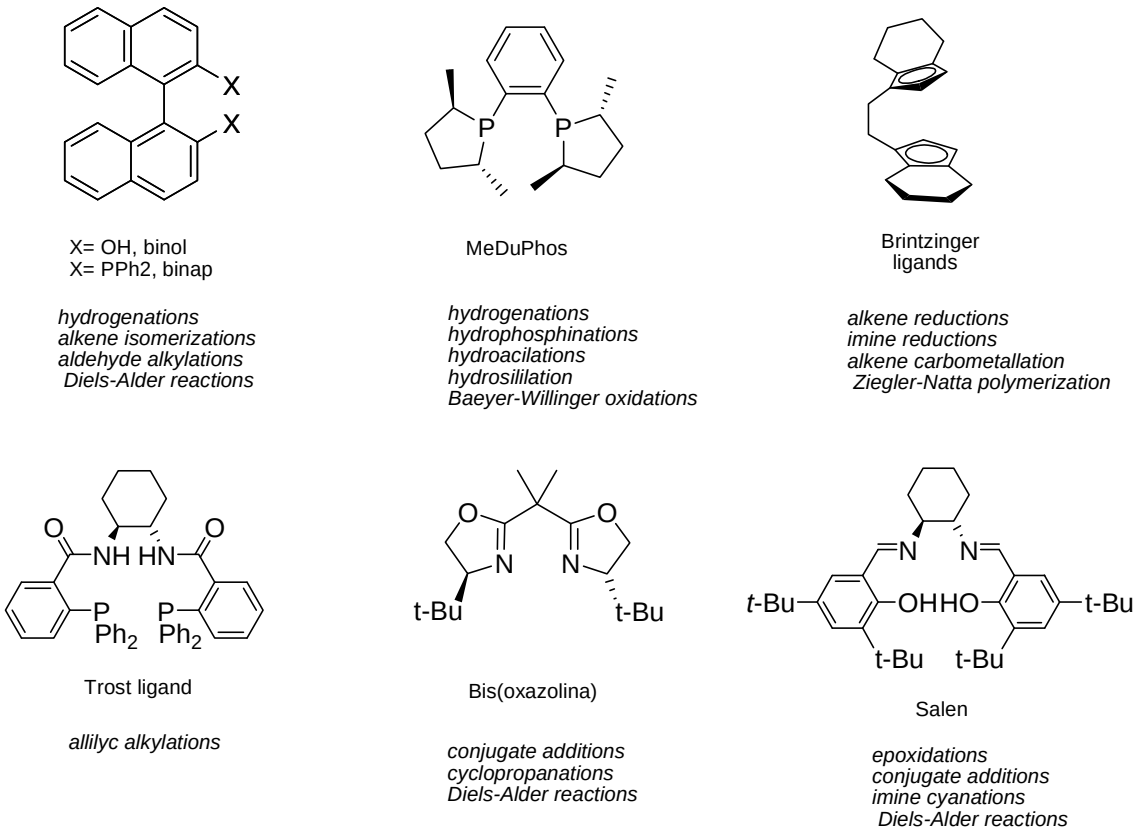
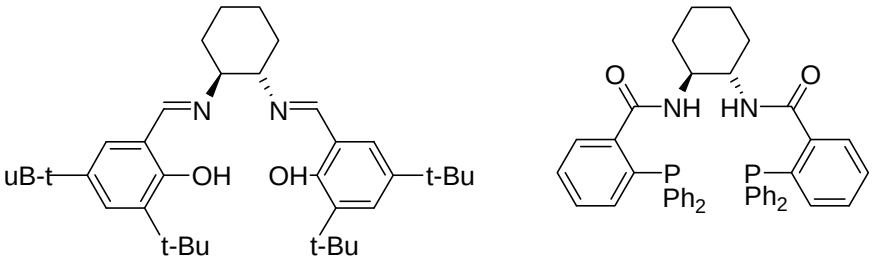


Figure 1.3 *Selected privileged ligands*

[5] Yoon, T.P.; Jacobsen, E.N. *Science* **2003**, *299*, 1691.

Among privileged ligands, remarkable examples are those obtained from *trans*-cyclohexanediamine, such as the "salen" (Figure 1.4a), acronym of bis(salicylaldehyde)ethylendiamine, and the Trost ligand, developed at the beginning of '90 by the american chemist Barry M. Trost (Figure 1.4b).[6]



Salen (a) Trost ligand (b)

Figure. 1.4

Both ligands are largely used for the production of pharmaceutical intermediates of prominent utility from ChiRex and Dow ChiroTech respectively.[7]

1.3 *Carbohydrates as building blocks of privileged ligands: aim of the thesis*

One key requirement in the efficient design of new catalytic asymmetric processes is the ready access to a library of diverse chiral ligands showing enough molecular diversity to allow the achievement of synthetically useful stereoselectivities (>90% ee) in initial screening.

In the last 10 years significant attention has been turned towards the use of chiral ligands based on natural carbohydrates. Large numbers of 'sugar-cores' have been developed that deliver diverse coordination architectures for different kind of reactions.[8]

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[6] (a)Trost, B.M.; Van Vranken, D.L. *Angew.Chem. Int. Ed. Engl.* **1992**, *31*, 228. (b) Trost, B.M.; Van Vranken, D.L.; Bingel, C. *J. Am. Chem. Soc.* **1992**, *114*, 9327. (c) Trost, B.M.; Van Vranken, D.L. *J. Am. Chem. Soc.* **1993**, *115*, 444. (d) Trost, B.M.; Breit, B. *Tetrahedron Lett.* **1994**, *35*, 5817. (e) Trost, B.M.; Breit, B.; Peukert, S.; Zambrano, J.; Ziller, J.W. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2386. (f) Trost, B.M.; Patterson, D.E. *J. Org. Chem.* **1998**, *63*, 1339. (g) Lee, S.; Lim, C.W.; Song, C.E.; Kim, K.M.; Jun, C.H. *J. Org. Chem.* **1999**, *64*, 4445. (h) Lim, C.W.; Lee, S. *Tetrahedron* **2000**, *56*, 5135. (i) Trost, B.M.; Zambrano, J. L.; Ritcher, W. *Synlett* **2001**, 907. (j) Buschmann, N.; Rueckert, A.; Blechert, S. *J. Org. Chem*. **2002** *67*, 4325. (k) 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. (l) Trost, B.M.; Pan, Z.; Zambrano, J.; Kujat, G. *Angew.Chem. Int. Ed. Engl* **2002**, *41*, 4691. (m) Agarkov, A.; Uffman, E.W.; Gibeltson, S.R. *Org. Lett.* **2003**, *5*, 2091. (n) Zhao, D.; Wang, Z.; Ding, K. *Synlett* **2005**, 2067.

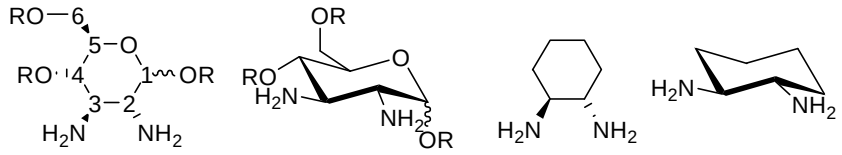
[7] Blaser, H.U.; Spindler, F.; Studer, M. *Applied Catalysis A: General* **2001**, *221*, 119.

[8] Reviews: (a) Diéguez M., Claver C., Pàmies O., *Eur. J. Org. Chem.* **2007**, 4621; (b) Diéguez M., Pàmies O., Claver C., *Chem. Rev.* **2004**, 3189; (c) Diéguez M., Pàmies O., Ruiz A., Diaz Y., Castillon S., Claver C., *Coord. Chem. Rev.* **2004**, 248, 2165.

Use of amino-sugar ligands in other areas has been reported. (a) Allylic substitution: Glegola K., Framery E., Goux-Henry C., Pietrusiewicz K. M., Sinou D., *Tetradedron* **2007**, 63, 7133. (b) Johannesen S. A., Glegola K.,

Within this challenging frame, the group where this Ph.D thesis has been carried out, has developed a strategy aimed at improving the performance of *privileged* ligands derived from *trans*-cyclohexanediamine (Figure 1.4), by incorporating their essential functions in a sugar ring. [9]

This approach grounds on the assumption that (1S,2S)-cyclohexanediamine has a structural analogy with the 2,3-glucodiamine frame, because in both cases the adjacent nitrogen atoms lie in *trans*-diequatorial position of a six-member ring (Fig. 1.5).



2,3-glucodiamine *trans*-cyclohexanediamine

Figure 1.5

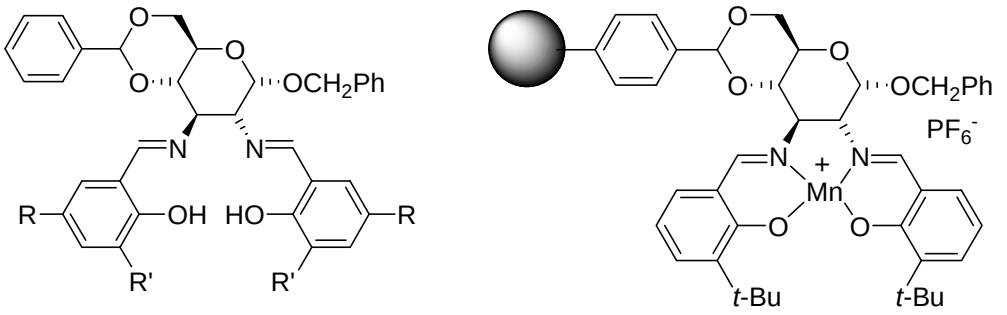
Thus, it is expected that the catalytic activity of the corresponding ligands is the same, provided a similar coordination environment. In addition, a benefit is gained by using the sugar backbone, because the other ring positions can be used for further functionalisations, helpful to modify the physical properties of the catalyst or for its anchorage to a solid matrix.

This may offer the brilliant possibility to extend the extraordinary performance of the privileged structure to innovative *multi-phase conditions*, the most efficient methodology for an effective recycling of the precious metal catalyst (see chapter 4).[2]

This strategy has already proven to be feasible. In fact, homogeneous and heterogeneous Mn(III) catalysts, which mimic the salen structure, were previously prepared with a glucose-based ligand (Fig. 1.6).[9]

Sinou D., Framery E., Skrydstrup T., *Tetrahedron Lett.* **2007**, 48, 3569 and references therein. (c) Suzuki reactions: Kolodziuk R., Penciu A., Tollabi M., Framery E., Goux-Henry C., Iourtchenko A., Sinou D., *J. Organomet. Chem.* **2003**, *687*, 384. (d) Hydrovinylation reaction: Park H., RajanBabu T. V., *J. Am. Chem. Soc.* **2002**, *124*, 737. (e) Oxidation: Del Litto R., Roviello G., Ruffo F., *Catalysts for Fine Chemical Synthesis*, **2007**, *5*, 293 and references therein; (f) Cucciolito M. E., Del Litto R., Roviello G., Ruffo F., *J. Mol. Catal. A* **2005**, *236*, 176.

[9] Borriello C., Del Litto R., Panunzi A., Ruffo F., *Tetrahedron: Asymm.*, **2004**, *15*, 681.



1Ga-H_2 a: R=R'= *t*-Bu
1Gb-H_2 b: R= H, R' = *t*-Bu

Figure 1.6 *Previous works*

This work has contributed to the development of the strategy by addressing the attention towards the achievement of sugar-based privileged ligands proposed by Trost (Figure 1.4 b). In particular, a ligand library (Figure 1.7) derived from glucose, mannose and galactose has been prepared.

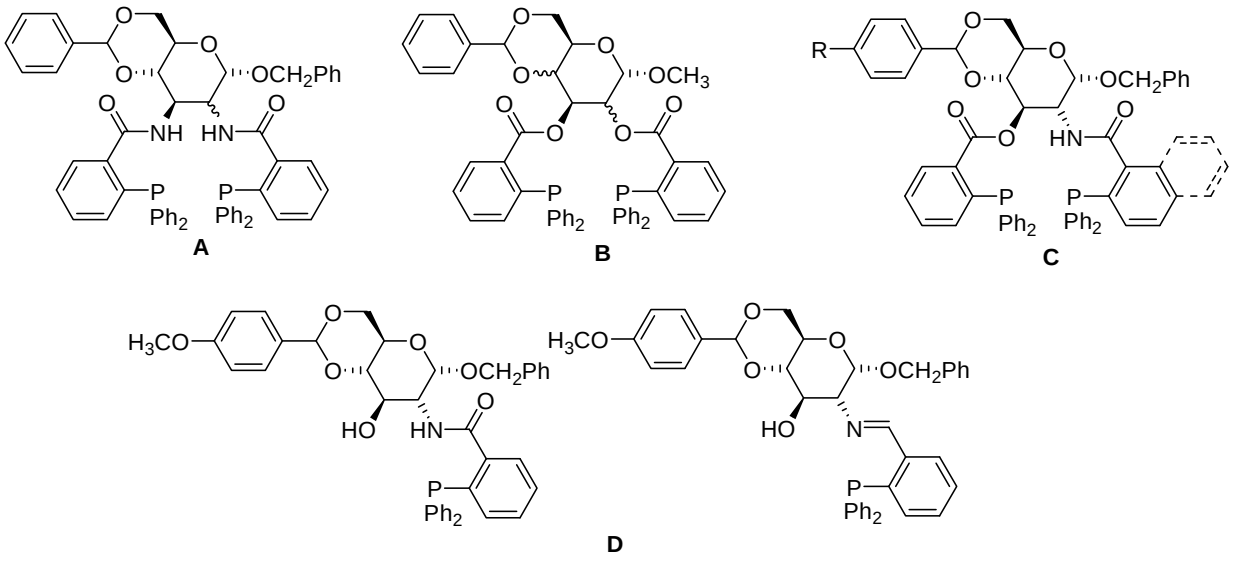


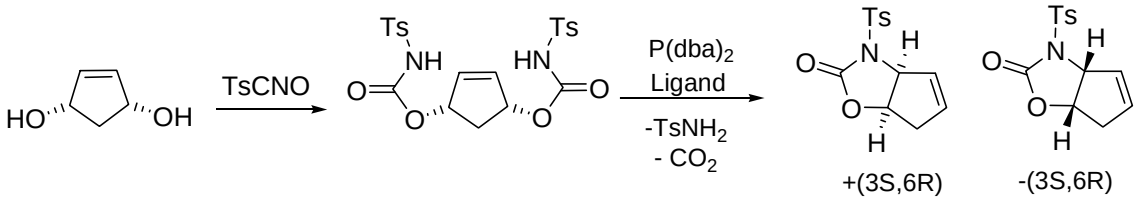
Figure 1.7

According to their tipology, it is possible to distinguish the following sub-classes:

- bis(phosphinoamido) ligands, type A
- bis(phosphinoester) ligands, type B
- 2-phosphinoamido,3-phosphinoester ligands, type C
- monophosphinic ligands, type D

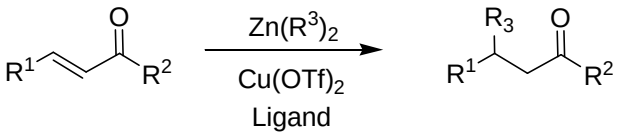
These ligands have been successfully used in two synthetically important reactions for the carbon–carbon bonds formation such as the asymmetric allylic alkylation (A.A.A.) of *meso*-2-

cyclopenten-1,4-diol biscarbamate promoted by palladium to afford an important pharmaceutical key precursor of mannostatine A (Scheme 1.1)



Scheme 1.1

and the copper catalyzed Me_2Zn and Et_2Zn conjugate additions (A.C.A.) to linear enones (Scheme 1.2).



Scheme 1.2

In line with the preliminary assumptions, this work has also involved the direct functionalisation of the hydroxyls on C4 and C6 of sugar backbone for extending the use of these ligands, and so the corresponding catalysts in *multi-phase* condition. In particular, catalytic tests in liquid-liquid biphase systems have been performed, such as in fluorinated solvents or ionic liquids, and in homogeneous supported catalysis.

In next chapters the synthesis of the ligands and their catalytic applications will be described.

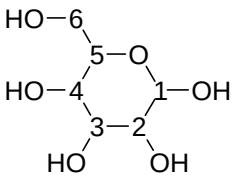
2. Ligands for homogeneous catalysis

2.1 *Classifications of ligands*

The ligands prepared in this work, shown in figure 2.1, are all identified with a number. In particular, **1** and **2** are bis(phosphinoamido) ligands derived from glucose and mannose; **3**, **4** and **5** are bis(phosphinoester) ligands derived from glucose, mannose and galactose respectively; **6**, **7**, **8** and **9** are 2-phosphinoamido-3-phosphinoester ligands derived from glucose. Ligand **6** differs from ligand **7** only for the protection on C4 and C6 (*p*-CH_3O-C_6H_4 instead of Ph), whereas ligand **9** is deprotected in these positions.[10] Ligand **8** shows a 2-diphenylphosphinonaphtoic group in C2 of sugar backbone, instead of the commonly used 2-diphenylphosphinobenzoic.

Ligands **10** and **11** are both characterized by the presence of the phosphinic unit only on C2, and its bond with the sugar ring is iminic for ligand **10** and amidic for ligand **11**.

[10] Carbon atoms in the sugar ring are numbered using the conventional IUPAC nomenclature, as shown in the following figure:



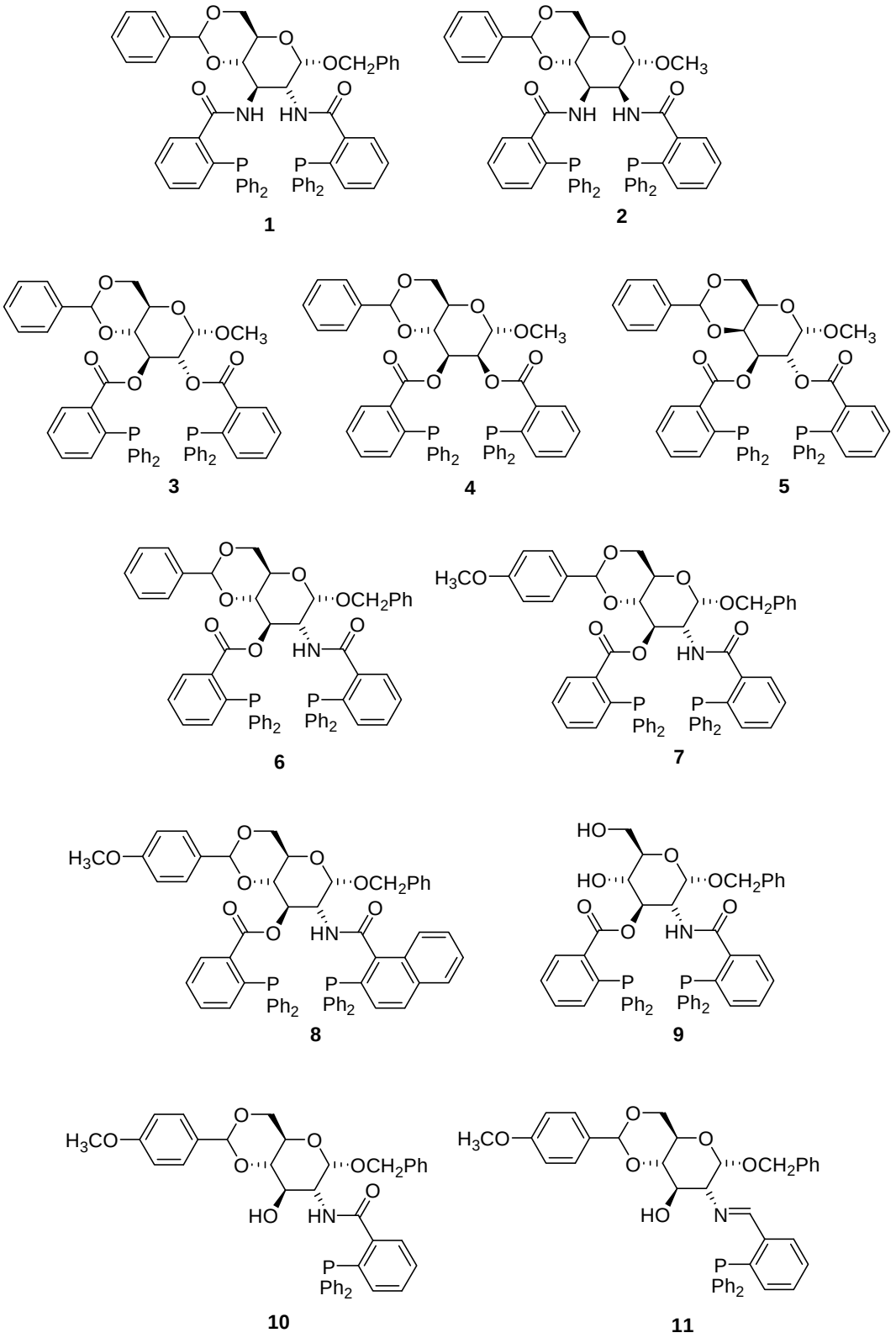


Figure 2.1 *Ligand library*

2.2 *Bis(phosphinoamido) ligands* **1** *and* **2**

2.2.1 *Synthesis of sugar precursors* **1G** and **1M**

Convenient commercial precursors for in the synthesis of **1** and **2** are N-acetyl-D-glucosamine (~0.5 Euro/gram) (**1g**) and methyl-α-D-mannoside (~0.2 Euro/gram)(**1m**) (Figure 2.2).

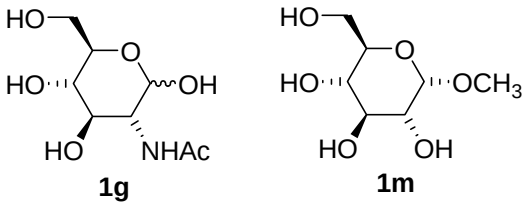
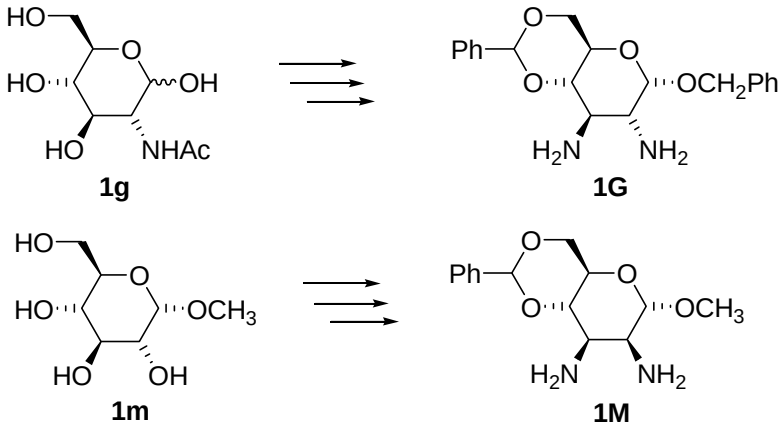


Figure 2.2

The synthetic strategy involves the introduction of the nitrogen functions at C2 and C3, affording the key intermediate **1G** and **1M** (Scheme 2.1) [11].



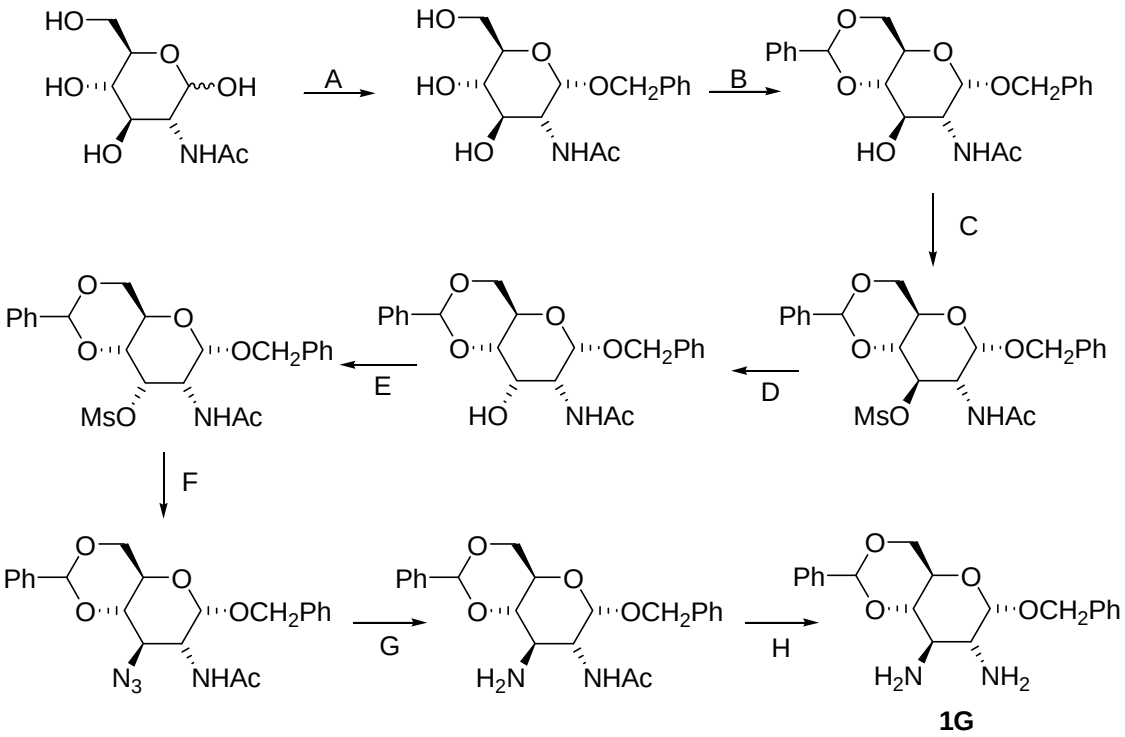
Scheme 2.1

More precisely, synthesis of **1G** (Scheme 2.2) starts with the initial introduction of a benzyl group on C1 by reaction with benzyl alcohol (step A). Next, the free hydroxyl groups on C4 and C6 of the sugar ring are protected by reaction with benzaldehyde (step B) and then C3 is esterified using methanesulfonyl chloride (step C).

Next step is the reaction with sodium acetate to restore the hydroxyl group on C3 with inverted axial configuration (step D). This group is subsequently again esterified (step E) and treated with sodium azide (step F), which allows to introduce the nitrogen function on C3

[11] (a) Meyer zu Reckendorf, W., Weber, R., Hehenberger, H. *Chem. Ber.* **1981**, *14*, 1306; (b) Gurthrie, R. D., Murphy, D. J. *Chem. Soc.* **1965**, 6956;

with the glucose configuration. The azide is hydrogenated to amine with Pd on activated carbon (step G) and finally hydrolysis of the amido function on C2, with KOH in ethyl alcohol (step H), affords the expected 2,3-glucodiamine (**1G**).



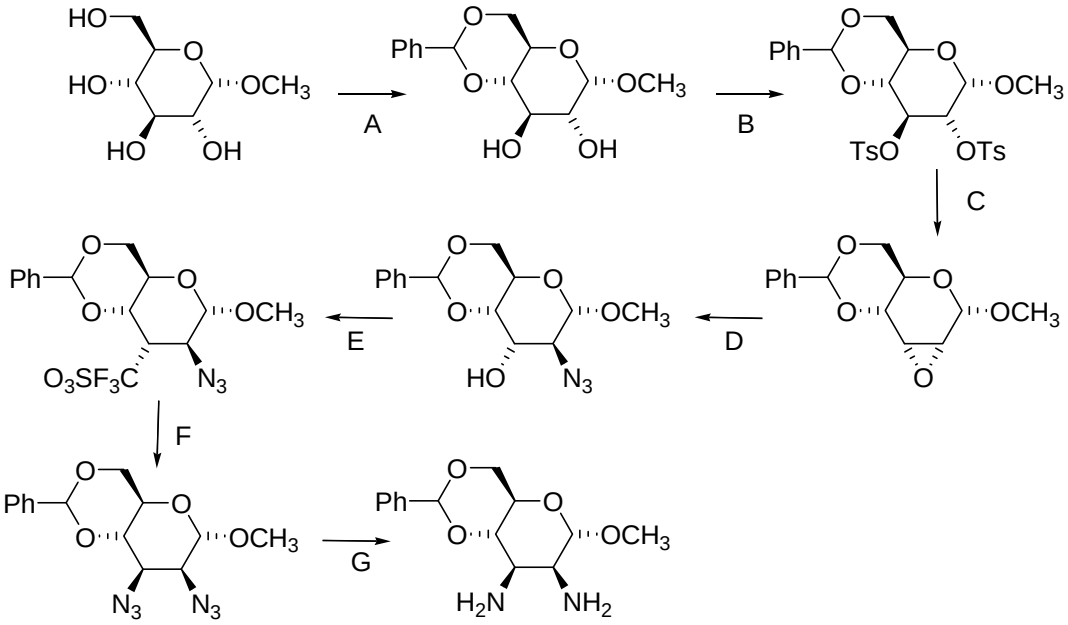
(A) benzyl alcohol
(B) benzaldehyde
(C) metansulfonyl chloride
(D) sodium acetate
(E) metansulfonyl chloride
(F) NaN_3
(G) H_2 and Pd/C
(H) KOH, diethyl alcohol

Scheme 2.2

Synthesis of **1M** (Scheme 2.3) involves the initial protection of the free hydroxyl groups on C4 and C6 with benzaldehyde (step A) and the functionalization of those on C2 and C3 by treatment with *p*-toluensulfonylchloride (step B). The tosyl group can be removed with alkali, inducing the inversion of configuration on C3 and the following epoxide formation on C2 and C3 (step C). Reaction with sodium azide (step D) gives 3-azido-4,6-O-benzylidene-3-deoxy-alloside as the only product.

Triflate on C3 is formed by reaction with trifluoromethanesulfonic anhydride (step E).

In step F reaction with sodium azide affords the 2,3-diazide with the desired mannose configuration. Finally, hydrogenation with Pd on activated carbon (step G) gives the 2,3-mannodiamine **1M**.

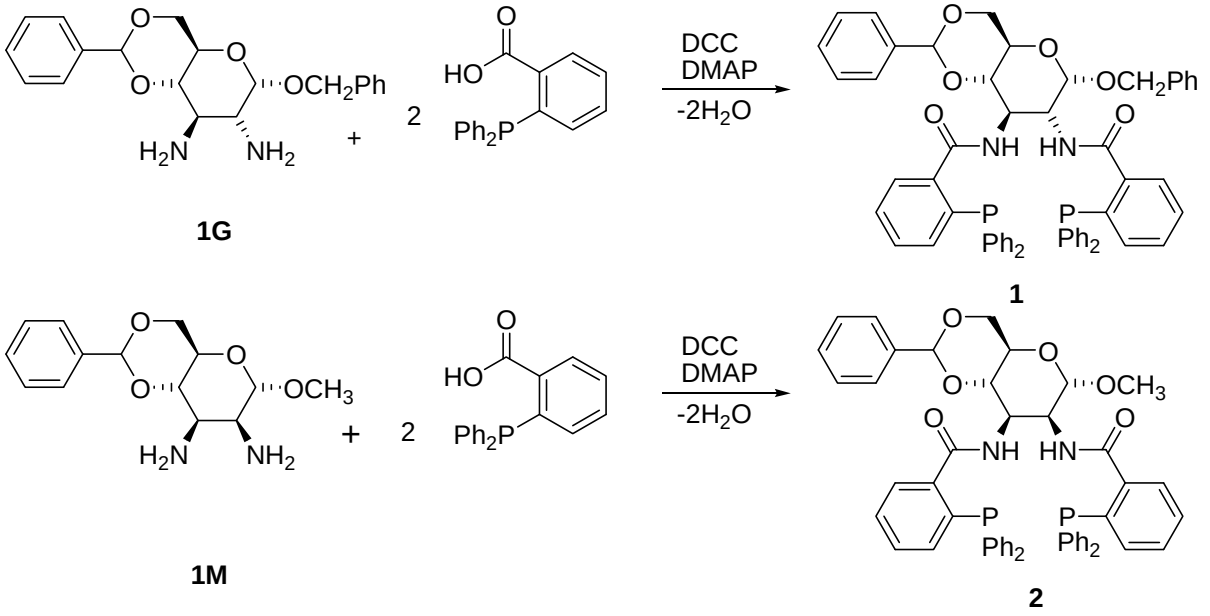


(A) benzaldehyde
(B) p-toluensulfonyl chloride
(C) $NaOCH_3$
(D) NaN_3
(E) triflic anhydride
(F) NaN_3
(G) H_2 and Pd/C

Scheme 2.3

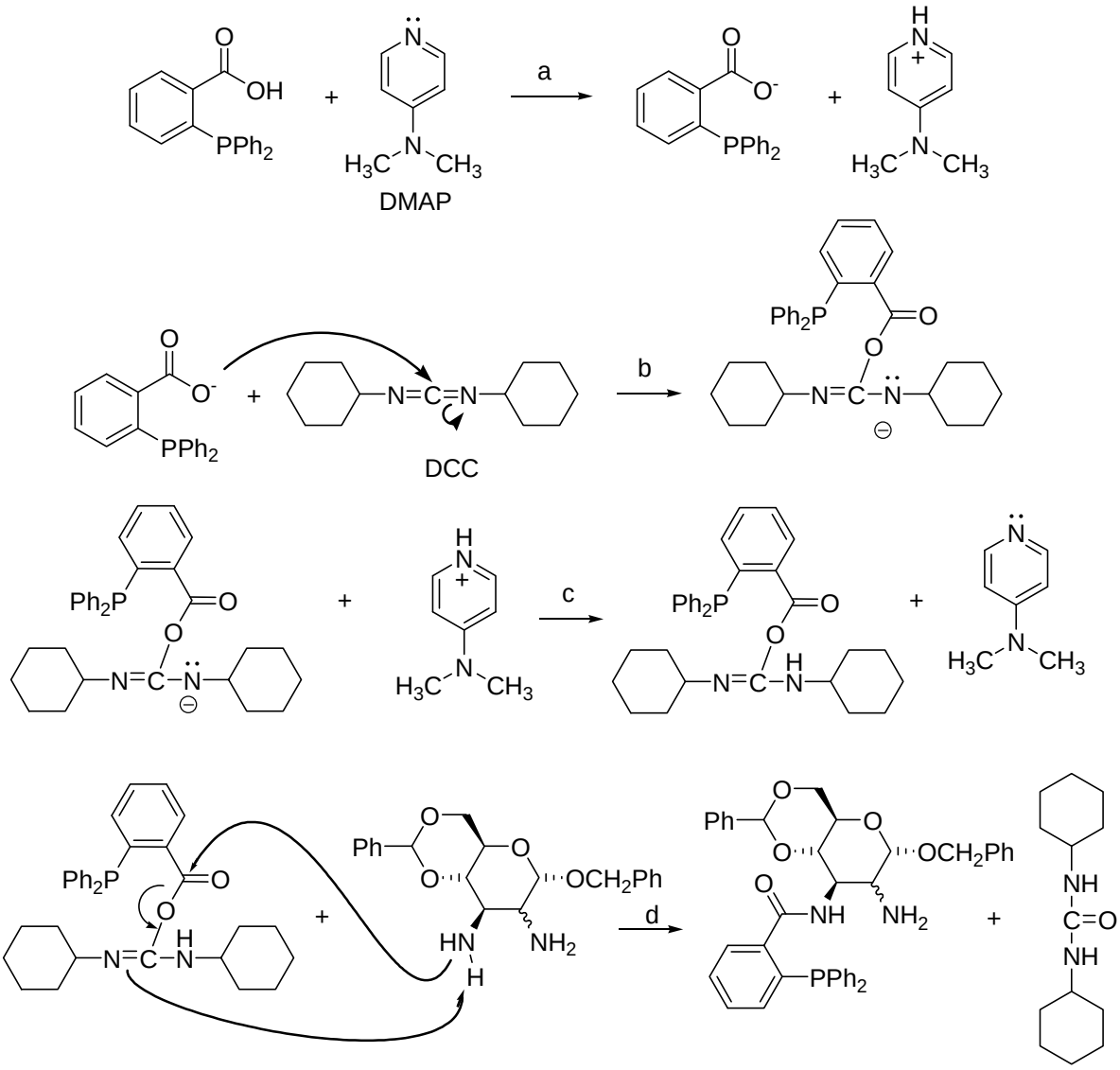
2.2.2 *Synthesis of ligands* **1** *and* **2**

Preparation of bis(phosphinoamido) ligands **1** and **2** from 2,3-glucodiamine (**1G**) and 2,3-mannodiamine (**1M**) involves reaction with 2-diphenylphosphinobenzoic acid in dry dichloromethane, using dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) (Scheme. 2.4).



Scheme 2.4

Dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) promote the amidic bond formation by activation of the carboxylic group of 2-diphenylphosphinobenzoic acid towards the nucleophilic substitution (the mechanism is described in scheme 2.5).



Scheme 2.5 *Ligand's synthesis mechanism*

Initially, DMAP deprotonates 2-diphenilphosphinobenzoic acid (step a), thus activating the carboxylic group towards the nucleophilic attack to the DCC central carbon (step b). The formed intermediate species is, first, protonated (step c) and then attacked by the nucleophilic sugar aminic nitrogen (e.g. on C3, step d), with formation of the desired mono-amide and 1,3-dicyclohexylurea.

In the same way the amino group on C2 is acylated.

Synthesis of ligand **1,** derived from glucose, gives a yellow solid that is purified by column chromatography. Ligand **2,** derived from mannose, is crystallized by adding hexane to the reaction mixture.

2.3 *Bis(phosphinoester) ligands* **3**, **4** *and* **5**

Commercial precursors useful to the synthesis of bis(phosphinoester) ligands are inexpensive methyl-α-D-glucoside (**2g**), methyl-α-D-mannoside (**2m**) and methyl-α-D-galactoside (**2gt**) (Figure 2.4).

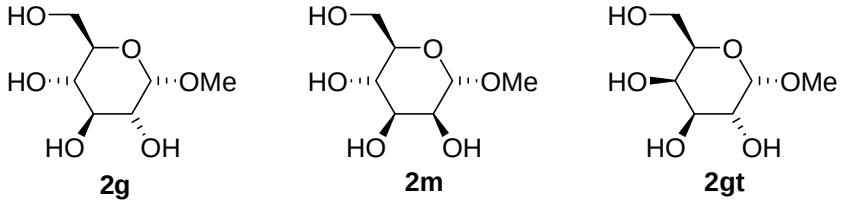
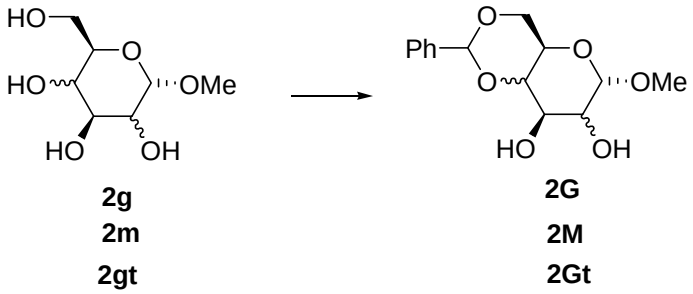


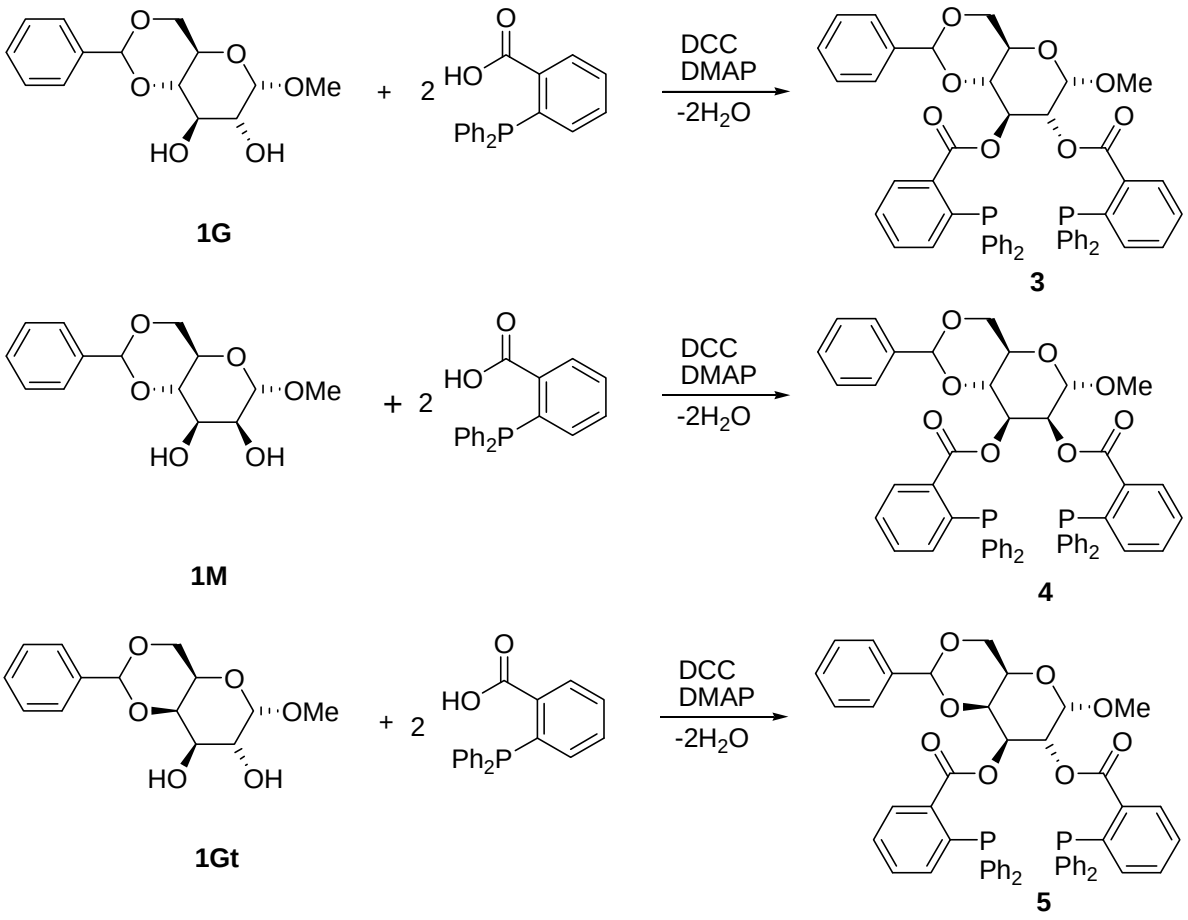
Figure 2.4

Monosaccharides hydroxyls on C4 and C6 are initially protected with a benzylidene function affording the intermediate products methyl-4,6-*O*-benzylidene-α-D-glucopyranoside (**2G**), methyl-4,6-*O*-benzylidene-α-D-mannopiranoside (**2M**) and methyl-4,6-*O*-benzylidene-α-D-galactopiranoside (**2Gt**), using standard procedures (Schema 2.6) [9].



Scheme 2.6

Next, precursors **2G**, **2M** and **2Gt** react with 2-diphenylphosphinobenzoic acid in dry dichloromethane, using dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) (Scheme 2.7).



Scheme 2.7

Under these conditions, the two hydroxyl functions on C2 and C3 are readily acylated (The mechanism is the same described in scheme 2.5 for bis(phosphinoamido) ligands). The three bis(phosphinoester) ligands are crystallized from hot ethyl alcohol affording white solids

2.4 *Phosphinoester-phosphinoamide ligands* **6**, **7** *and* **8**

The commercial precursor useful to the synthesis of these ligands is again the low cost N-acetyl-D-glucosamine (Figure 2.5).

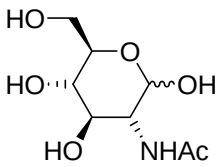
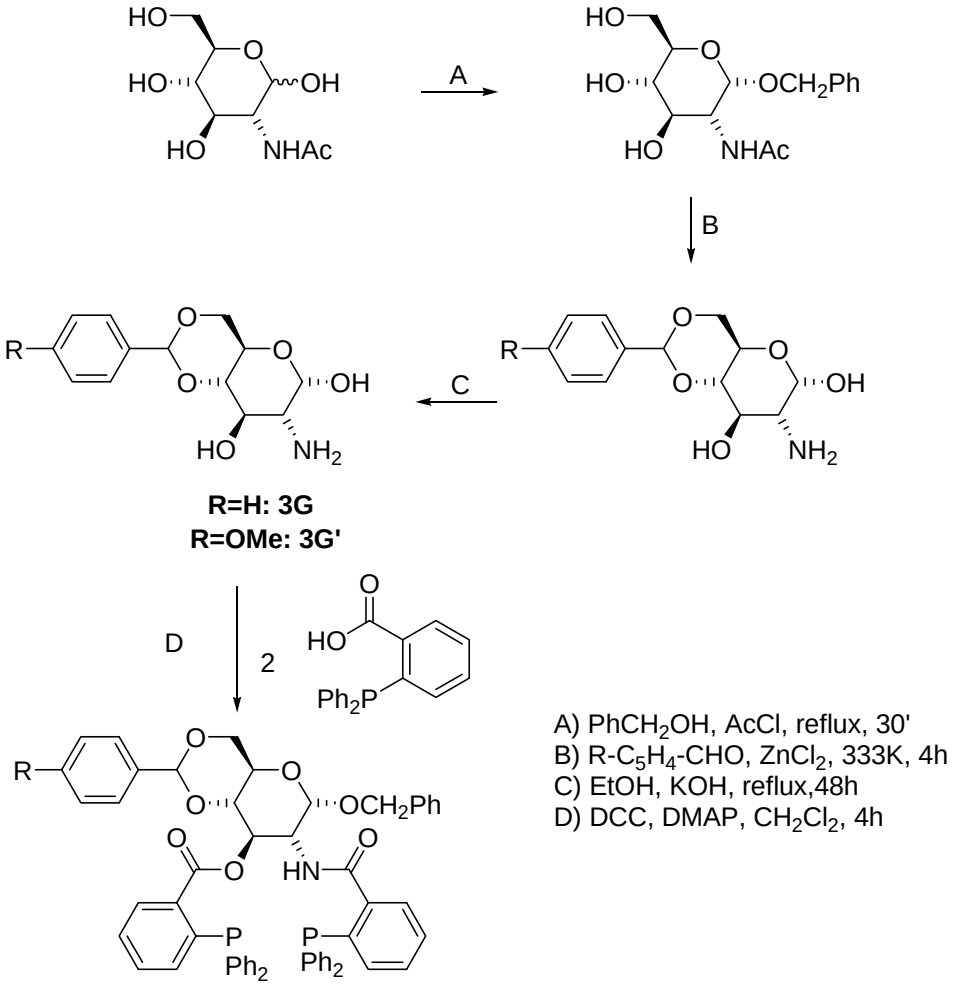


Figure 2.5

The synthetic strategy involves the preliminary protection the hydroxyl groups on C1 with benzyl alcohol (Scheme 2.8, step A), and on C4-C6 with the appropriate aldehyde (benzaldehyde for ligand **6** and *p*-methoxy benzaldehyde for ligand **7** and **8**) (Step B). Hydrolysis of the acetamide on C2 affords precursors **3G** and **3G'** (step C).[10]

Preparation of 2-phosphinoamido-3-phosphinoester ligands is completed by their reaction with 2-diphenylphosphinobenzoic acid in dry dichloromethane, in presence of dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) (step D).

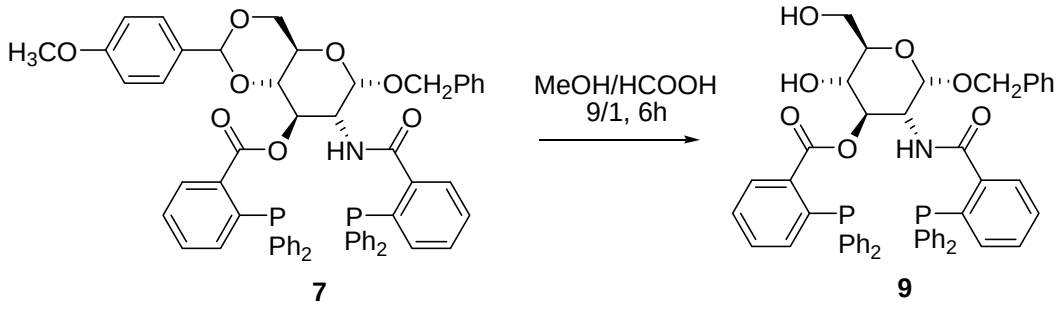


Scheme 2.8

These three ligands are purified by column chromatography affording yellow solids.

2.5 *Synthesis of ligand* **9**

This ligand is prepared by selective deprotection of hydroxyls on C4 and C6 of sugar ring of ligand **7**, using a mixture of 9:1 methanol/formic acid. This treatment allows to preserve the coordinating functions on C2 and C3 and, at the same time, it is able to make 4,6 positions available for next functionalizations (Scheme 2.9).

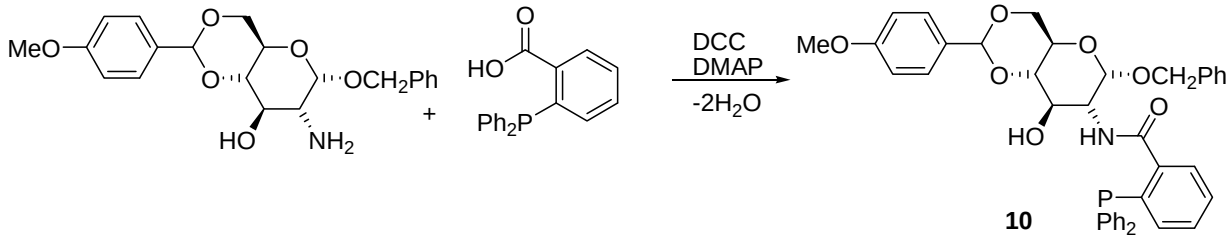


Scheme 2.9

2.6 *Monophosphinic ligands*

2.6.1 *Synthesis of ligand* **10**

Preparation of ligand **10** is performed by reaction of the amino sugar precursors (**3G'**) with only one equivalent of 2-diphenylphosphinobenzoic acid in dry dichloromethane using dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) (Scheme 2.10).

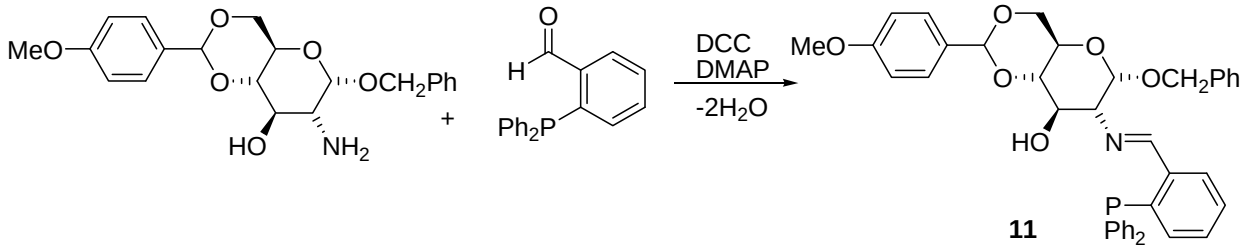


Scheme 2.10

The acid reacts selectively with the amino function because of its major nucleophilicity.

2.6.2 *Synthesis of ligand* **11**

Preparation of ligand **11** is performed by condensation of the amino group on C2 of the sugar precursor **3G'** with 2-diphenylphosphinobenzaldehyde in toluene using dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) (Scheme 2.11).



Scheme 2.11

After 6 hours refluxing the product is purified by crystallization with hexane.

2.7 *Characterization of ligands*

All the ligands have been characterized by elemental analysis and ^{1}H e ^{13}C NMR spectroscopy in $CDCl_3$. NMR spectra of ligand **11** have been performed in C_6D_6 because of the hydrolysis susceptibility of the N=C double bond when acid solvents, such as the chloroform, are used.

Spectra analysis allows to confirm the ligands structures and to check their purity.

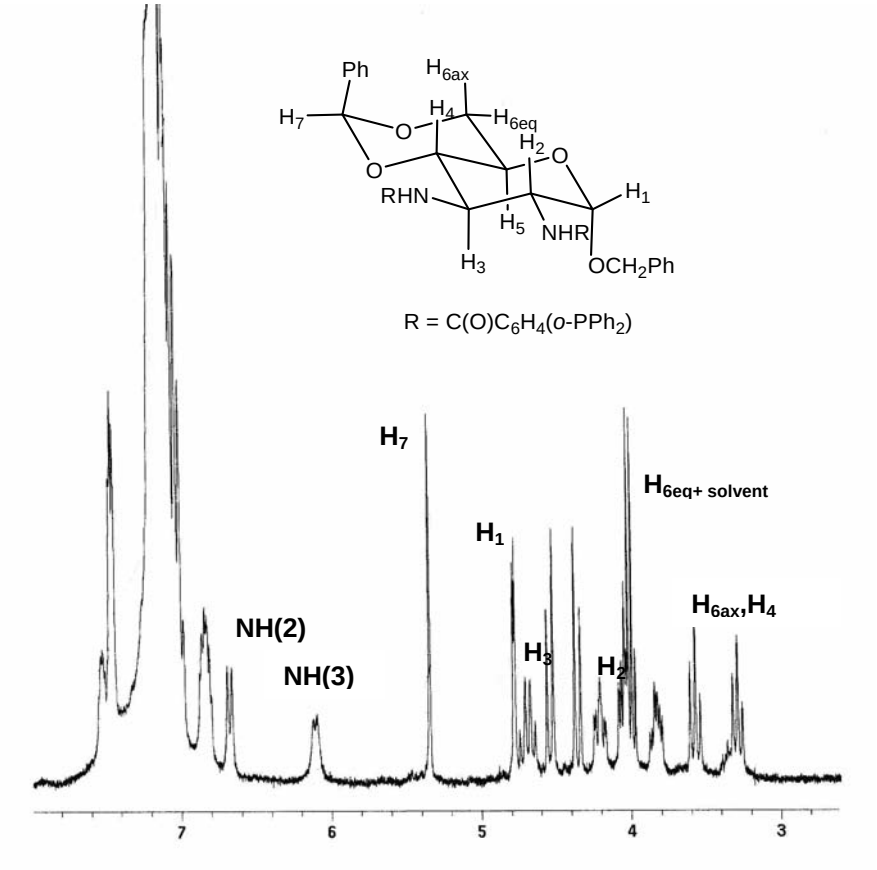
It is possible to do some relevant observations:

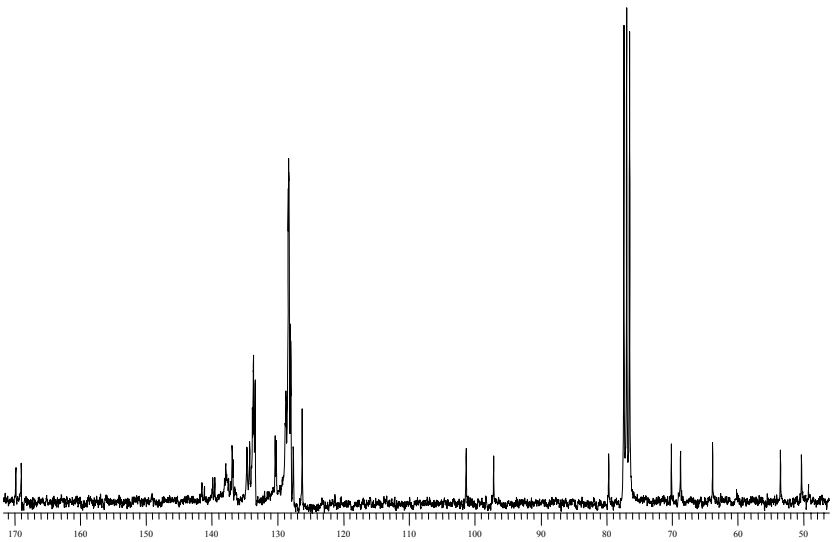
- The sugar identity is confirmed by the typical pattern of glucose, mannose and galactose.
- The formation of the amidic bond in ligand **1** is demonstrated by presence of two typical signals at δ 6.10 and at δ 6.63, that appear as doublets due to coupling with the sugar protons; in the ligand **2** spectrum, there is only one doublet at δ 6.18 because the other is hidden by the aromatic signals.
- In the bis(phosphinoester) spectra, acylation is demonstrated by the typical high-frequency shift of H2 and H3 signals compared to those of the sugar precursors. In particular, for ligand **3**, the H2 signal shifts from δ 3.60 to δ 4.83 and appears as a double doublet due to coupling with H1 and H3. In the same way the triplet of H_3 is shifted from δ 3.90 to δ 5.92.

For ligand **4** the H_2 e H_3 signals, which are both double doublets, shift from δ 3.90 respectively to a δ 5.43 and δ 5.70. Finally the multiplet accounting for H_2 e H_3 in **5**, moves from δ 3.90 to δ 5.61.

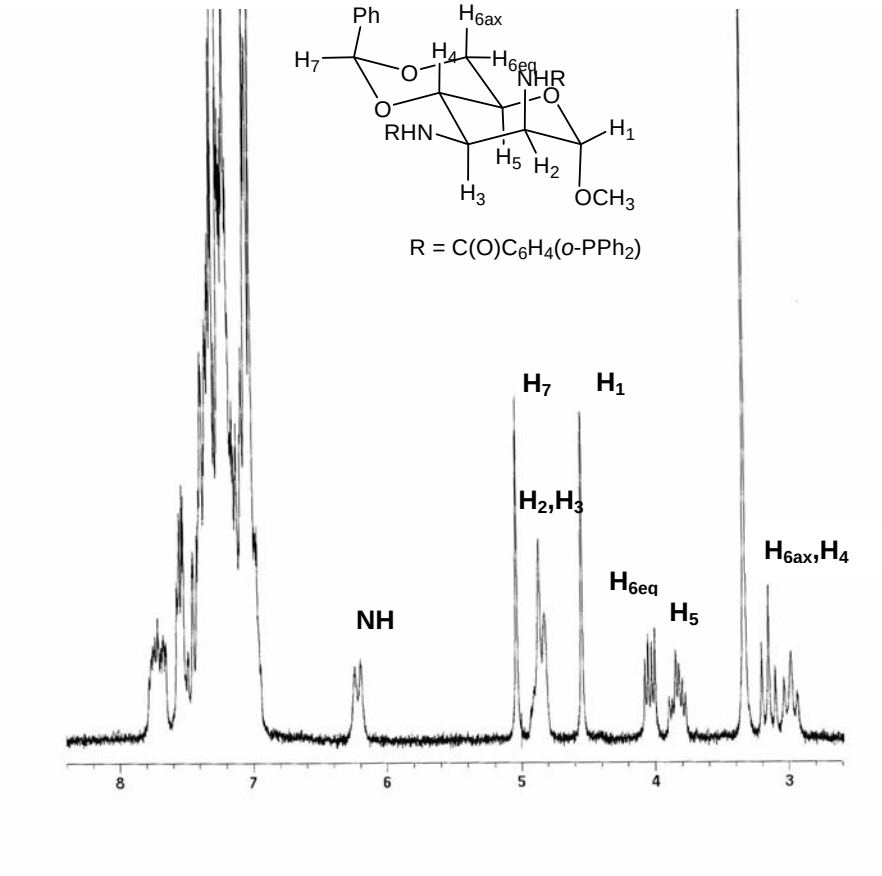
- For 2-phosphinoamido,3-phosphinoester ligands **6**, **7**, **8**, **9**, acylation on C2 is clearly demonstrated by the high-frequency shift of H2 and H3 and by the presence of the typical doublet at 6 ppm which corresponds to NH. In the case of ligand **9**, hydrolysis of the acetal group in the positions 4,6 of the sugar ring is demonstrated by the absence of the signal at δ 5.37 corresponding to the acetal proton of **7.**
- In the proton spectrum of monophosphinic ligand **10**, the absence of a high-frequency shift of the triplet H3 and the contemporaneous presence of the NH proton doublet confirm the ligand structure.
- The formation of the imino bond of ligand **11** is pointed out by the presence of the typical signal at δ 9.06, that appears as a doublet due to the coupling with H2.

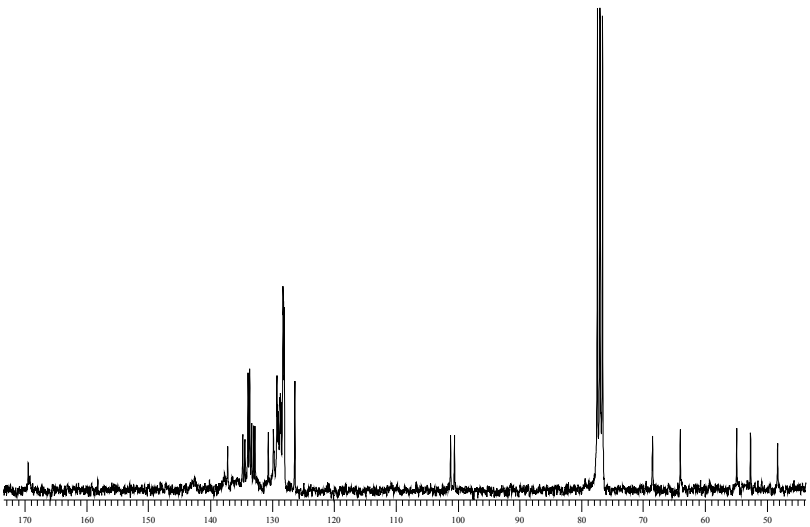
^{1}H NMR and ^{13}C spectra of ligand 1





^{1}H NMR and ^{13}C spectra of ligand 2





Suitable crystals for X-ray analysis have been obtained for ligand **2**, derived from mannose. The structure is illustrated in Figure 2.6.

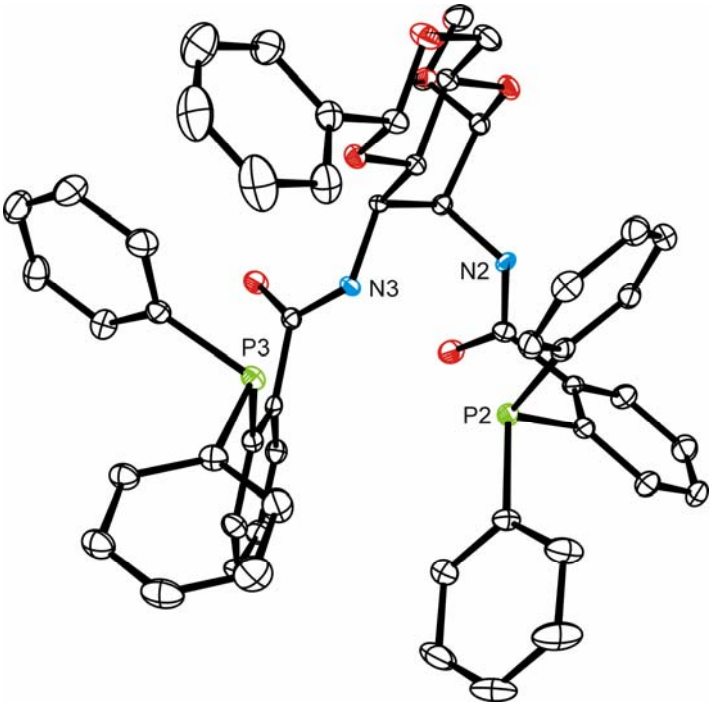
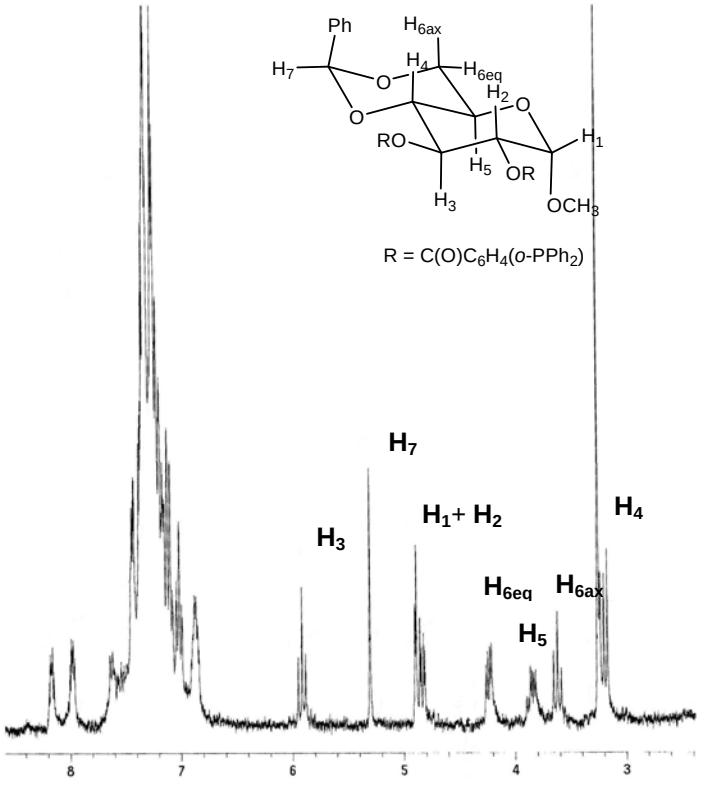
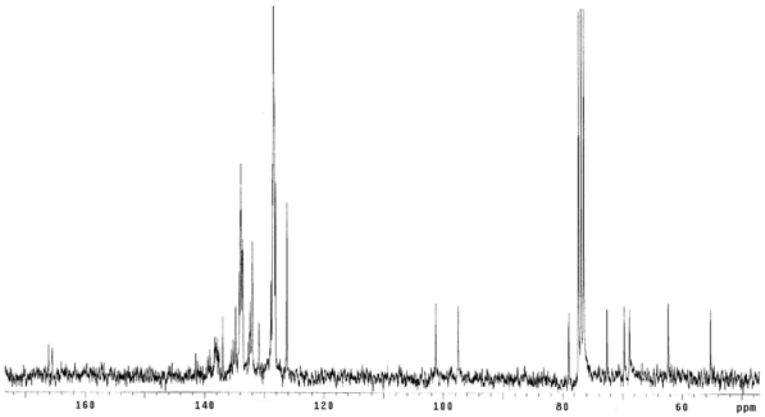


Figure 2.6

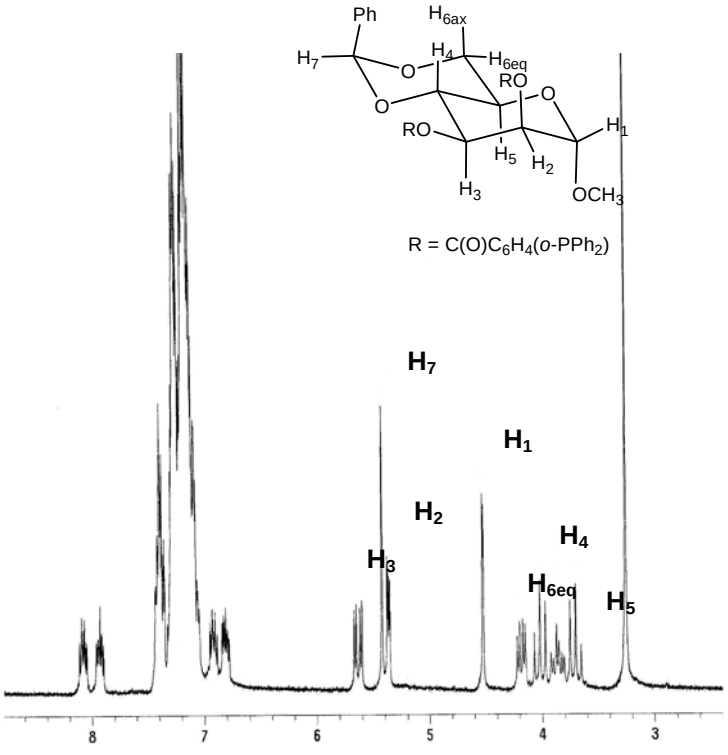
ORTEP representation of bis(phosphinoamido) ligands derived from mannose (the thermal ellipsoids are reported at 30% probability level). The hydrogen atoms and two molecules of CH_2Cl_2 are omitted. The structure was resolved by Dr. Giuseppina Roviello, using instruments of C.I.M.C.F. of University of Napoli "Federico II".

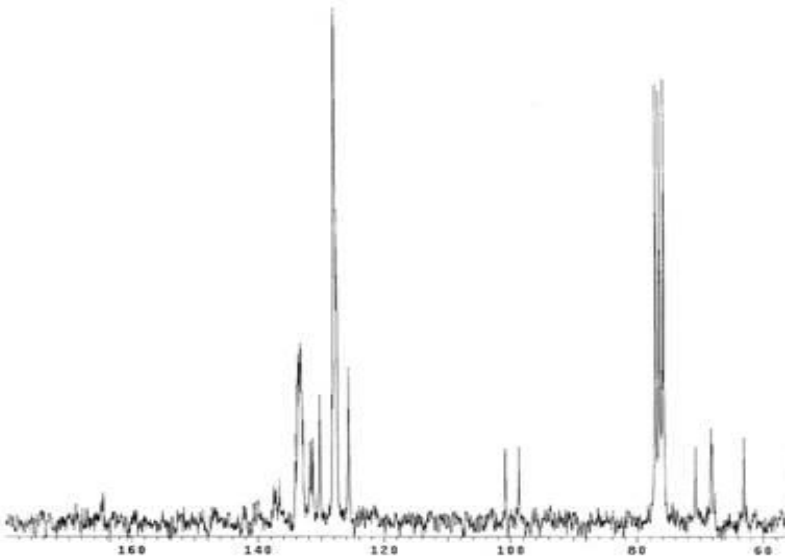
^{1}H NMR and ^{13}C spectra of ligand 3



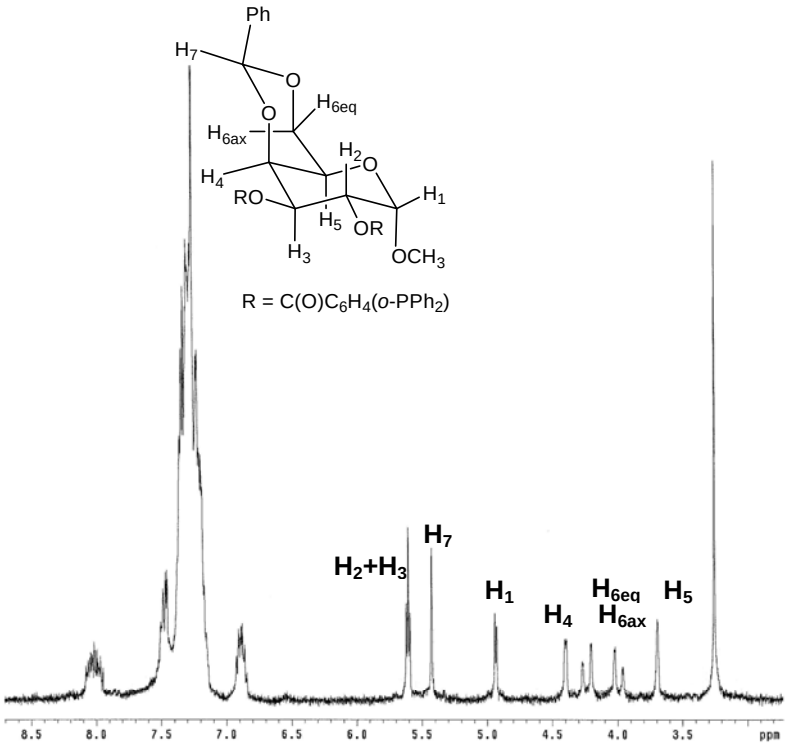


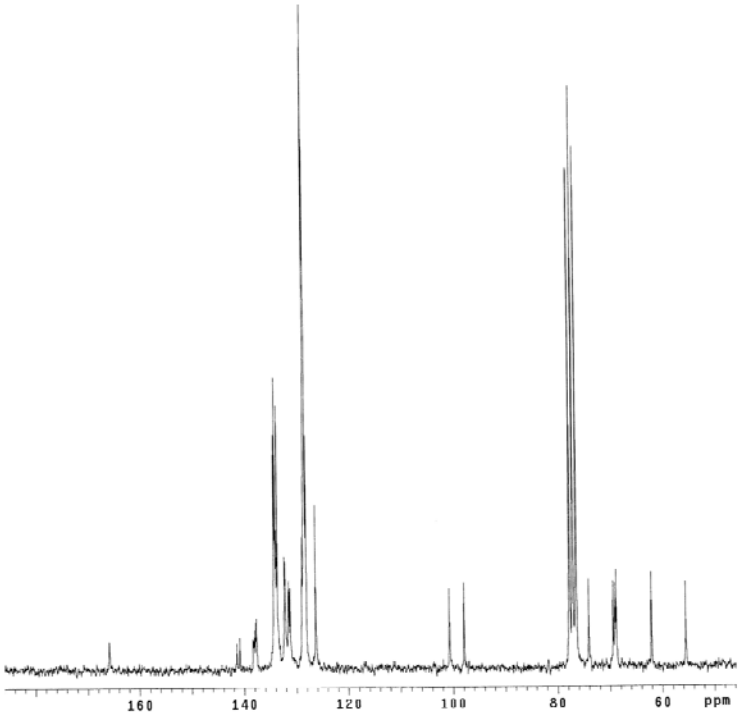
^{1}H NMR and ^{13}C spectra of ligand 4



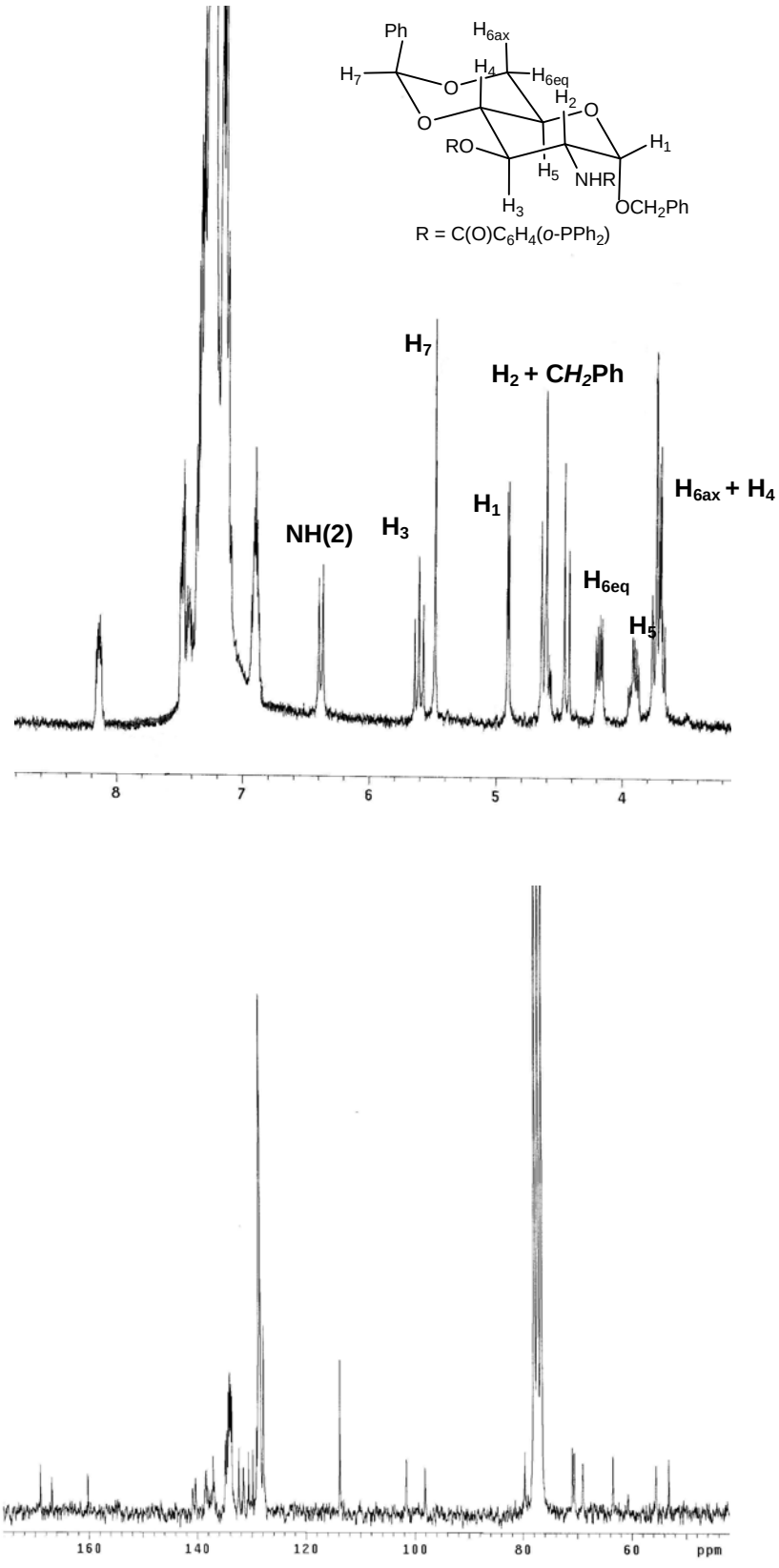


^{1}H NMR and ^{13}C spectra of ligand 5

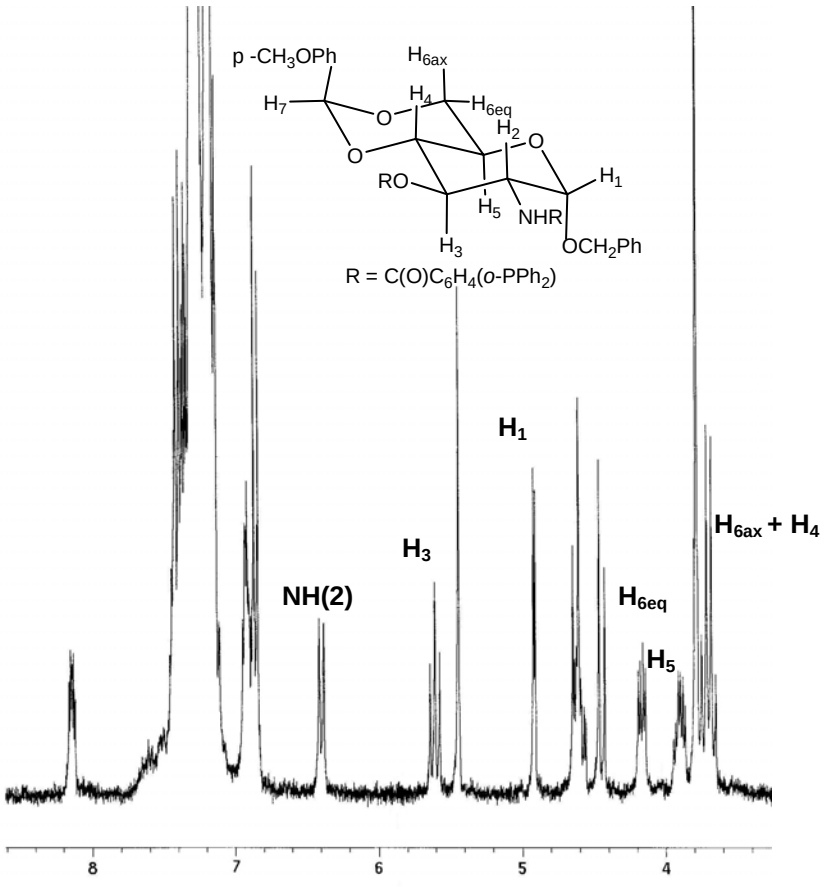


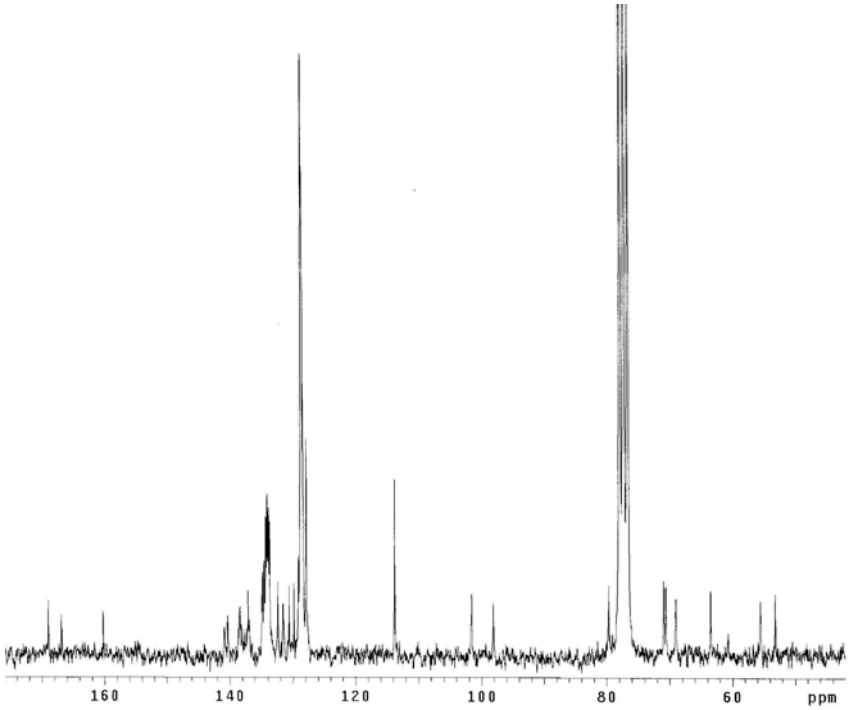


^{1}H NMR and ^{13}C NMR spectra of ligand 6

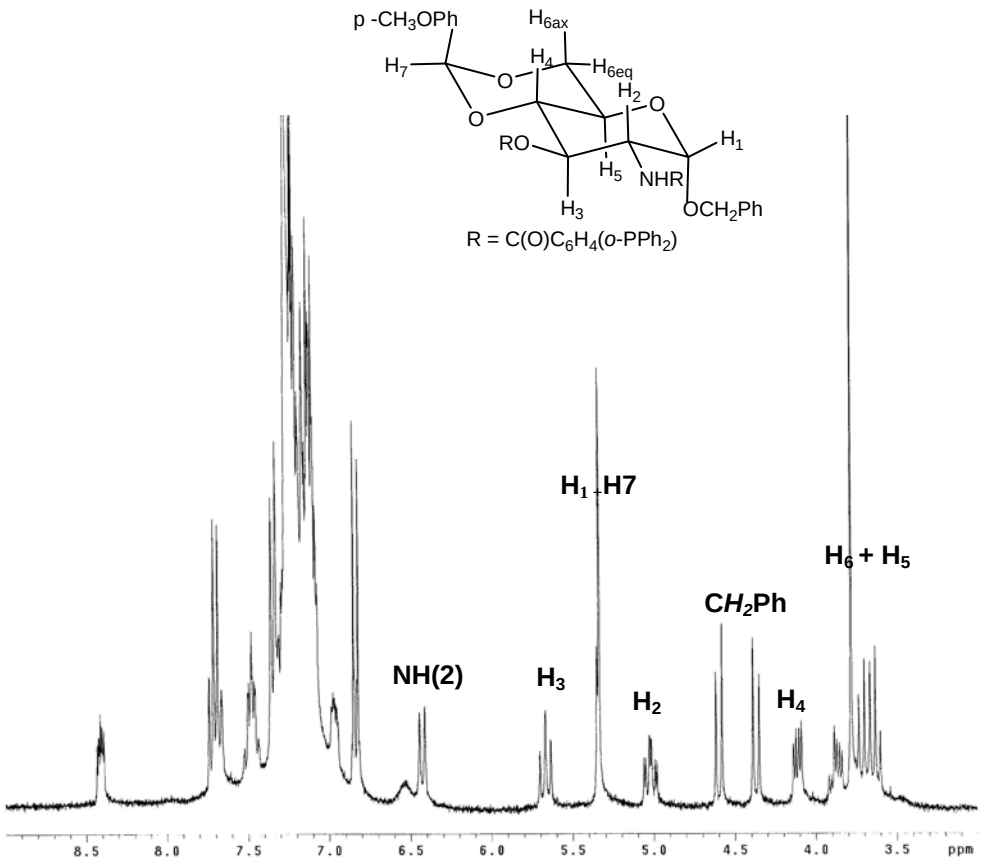


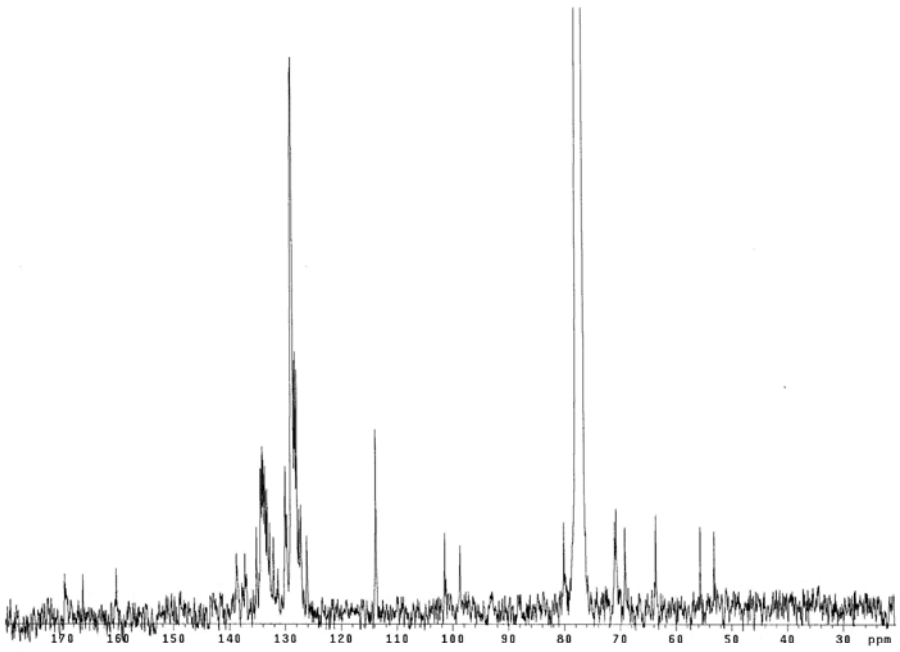
^{1}H NMR and ^{13}C NMR spectra of ligand 7



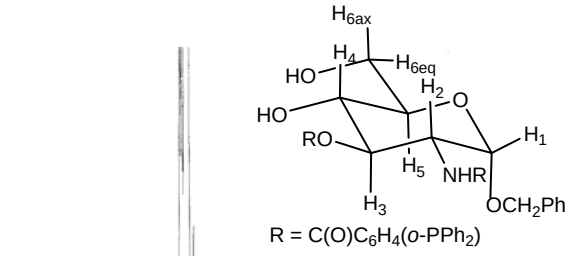


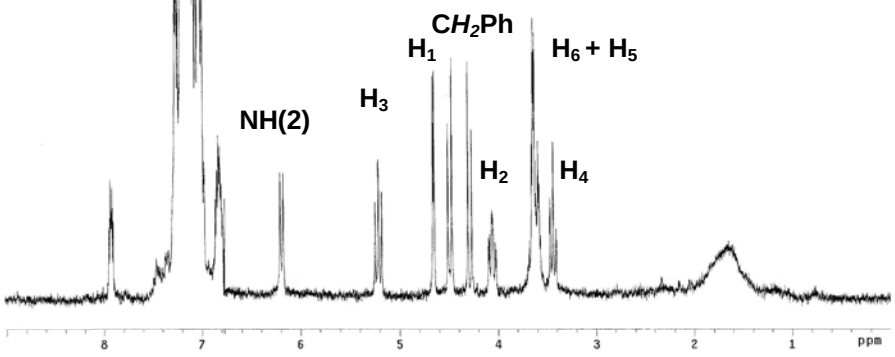
^{1}H-NMR and ^{13}C-NMR spectra of ligand 8

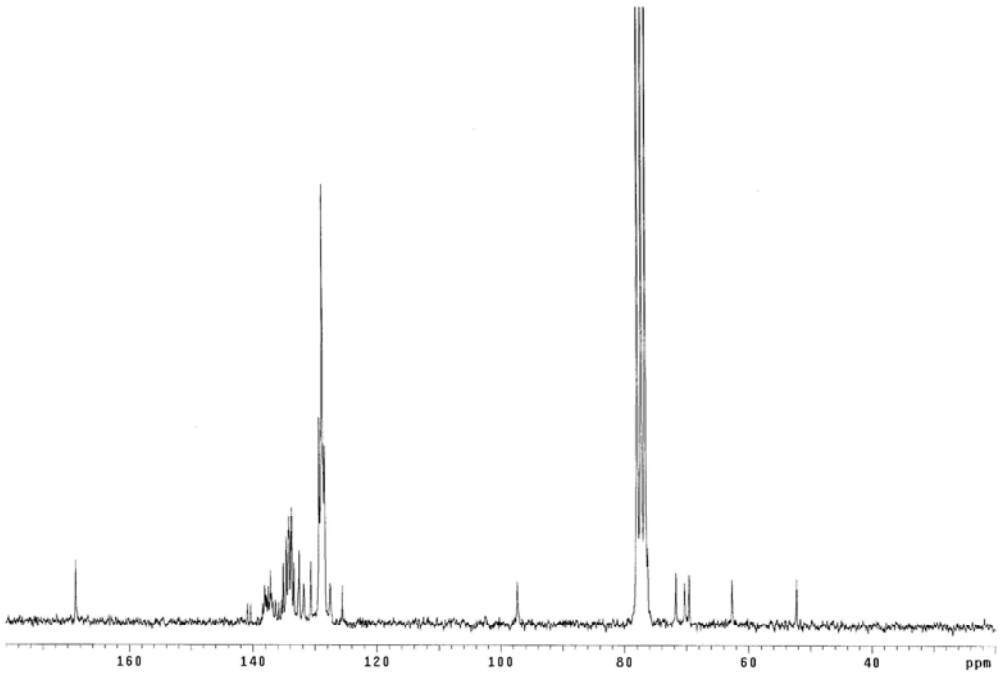




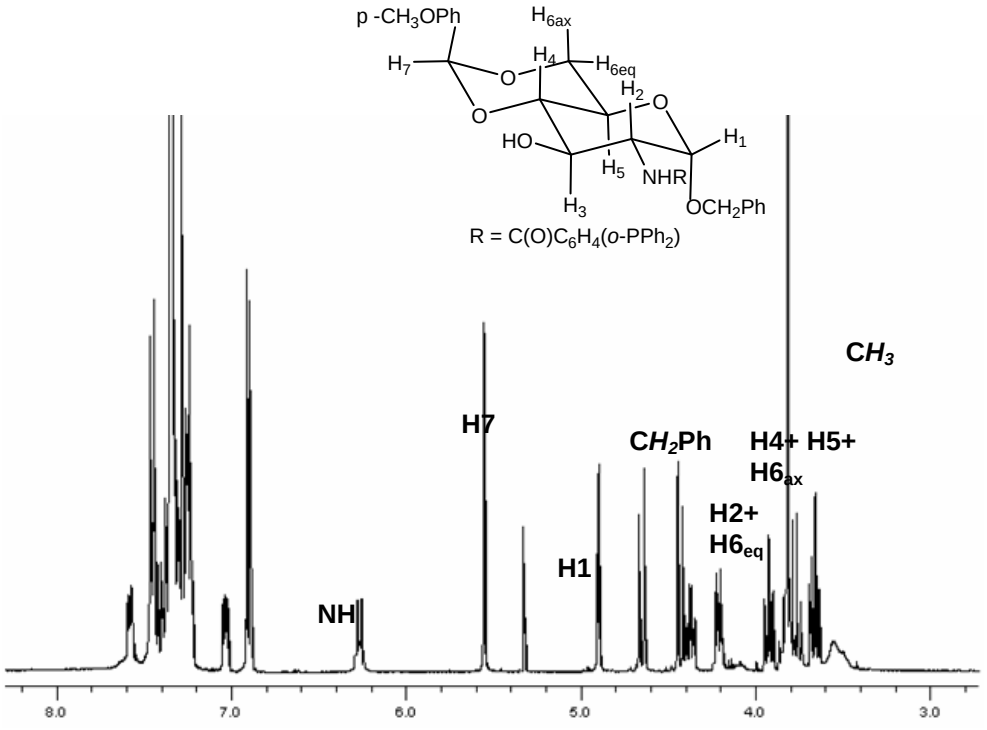
^{1}H NMR and ^{13}C NMR spectra of ligand 9

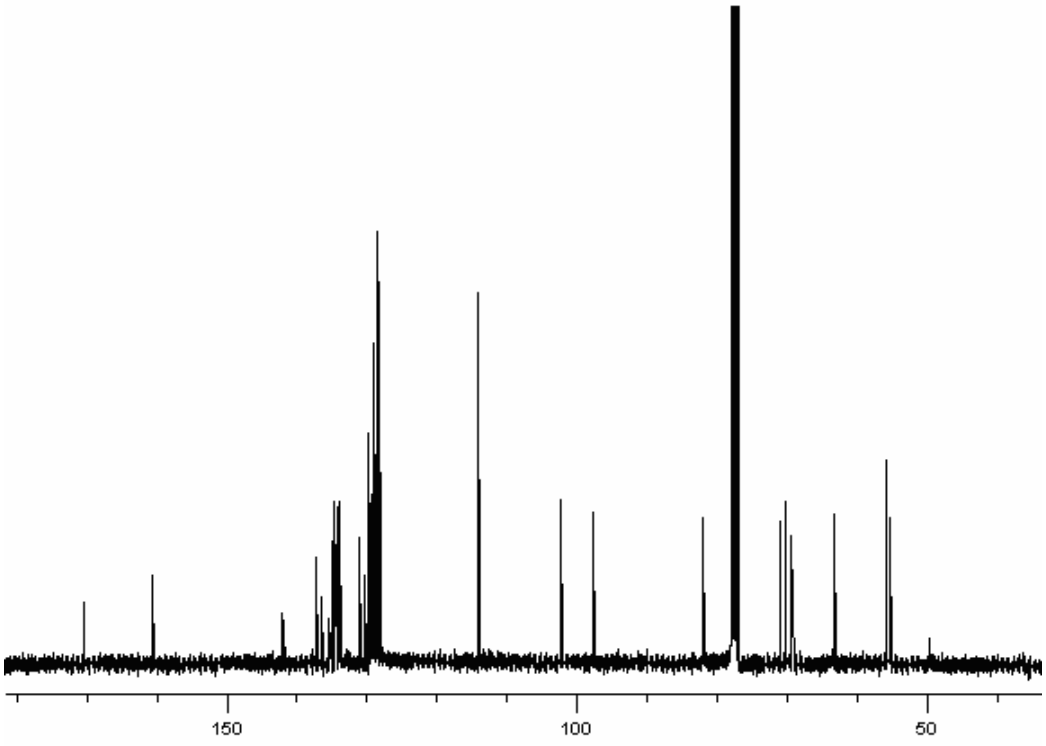




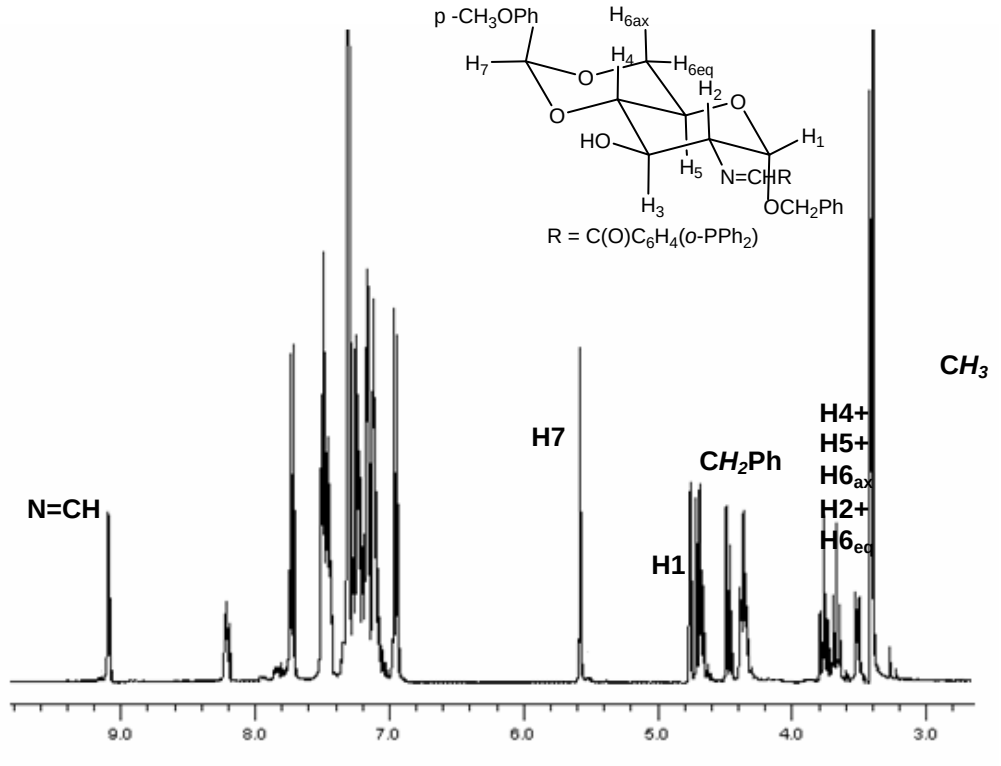


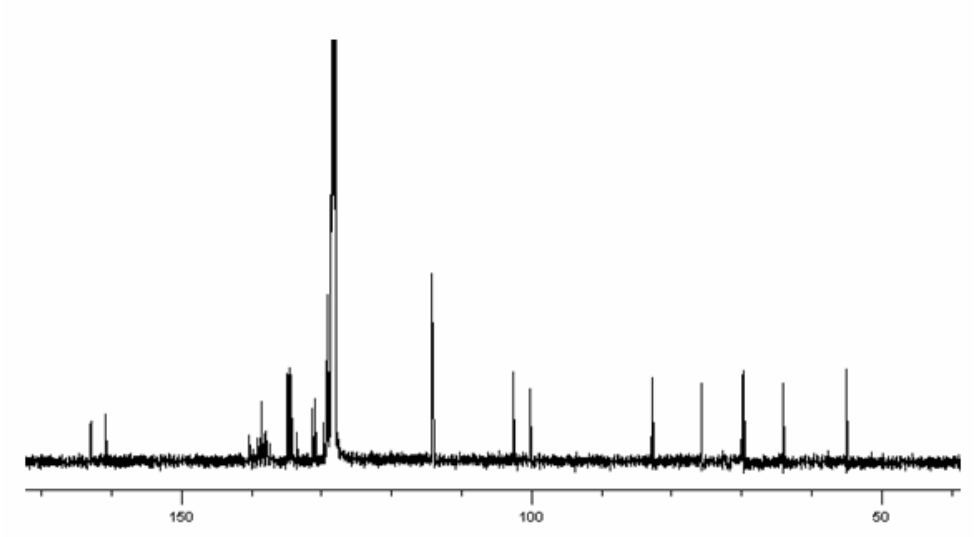
^{1}H NMR and ^{13}C NMR spectra of ligand 10





^{1}H NMR and ^{13}C NMR spectra of ligand 11





2.8 *Experimental section*

*General methods***.**

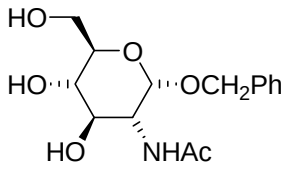
All experiments were carried out under argon atmosphere using standard Schlenk techniques. THF was distilled on Na/benzophenone, dichloromethane from CaH_2.

^1H and ^{13}C NMR spectra were recorded on Varian-Gemini 300 and Varian-Gemini 200 spectrometers. For all samples δ values were referenced to residual $CDCl_3$, only for ligand 11 they were referred to residual C_6D_6. All *J* values are in Hz. Specific optical rotatory powers [α] were measured with a Perkin-Elmer Polarimeter (model 141) at 298 K and 589 nm in dichloromethane (c= 1.0 g/100 mL). Yields were determined by isolation. Thin layer chromatography (TLC) was performed on Merck silica gel 60 F_{254} pre-coated plates (0.25 mm) silica. The plates were visualized by the use of a combination of ultraviolet light (254 and 366 nm). Liquid chromatography was carried out by forced flow (flash chromatography) with the solvent systems indicated, using silica gel 60 Å (200-400 mesh) supplied by Aldrich. Benzyl-4,6-O-benzylidene-2,3-deoxy-2,3-diamino-a-D-glucoside[10a] **(1G)** and methyl-4,6-O-benzylidene-2,3-deoxy-2,3-diamino-a-D-mannoside[10b] **(1M)** were prepared according to the literature methods.

2.8.1 *Synthesis of* **1G**

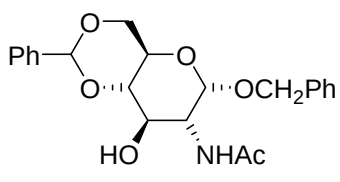
As already described, the synthesis is composed of several steps:

Benzyl-2-acetamido-2-deoxy-α -D-glucopyranoside (1):



A solution of N-acetyl-α-D-glucosamine (60 g, 0.27 mol) in benzyl alcohol (240 mL) and acetyl chloride (1.1 mL) was refluxed for 60 minutes. After the mixture was cooled to room temperature, diethyl ether was slowly added under magnetic stirring until the formation of a dark solid, which was washed several times with the same solvent and dried under vacuum. (71 g, 0.23 mol, yield: 85%).

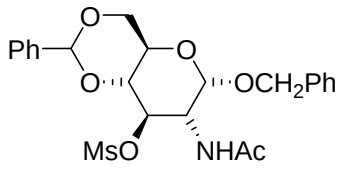
Benzyl-2-acetamido-4,6-O-benzylidene-2-deoxy-α-D-glucopyranoside (2):



Compound (1) (71 g, 0.23 mol) and anhydrous zinc chloride (71 g, 0.52 mol) were dissolved in benzaldehyde (300 mL) at 333K. After 60 minutes stirring at the same temperature, the mixture was cooled at room temperature and water (900 ml) was added

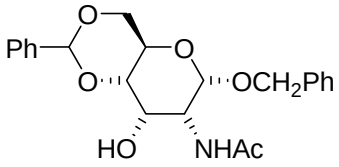
under magnetic stirring. The resulting solid was filtered, washed with water and diethyl ether (200 mL), and dried under vacuum (68 g, 0.17 mol, yield: 74 %).

Benzyl-2-acetamido-4,6-O-benzylidene-2-deoxy-3-O-methyl sulfonyl-α-D-glucopyranoside (3):



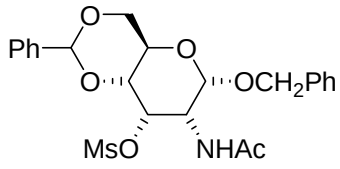
Compound (2) (68 g, 0.17 mol) was dissolved in pyridine (425 mL) and metansulfonyl chloride was added (68 mL) dropwise to the solution cooled at 273K. The mixture was kept at the same temperature for 16 hour and then added to water/ice affording the precipitation of the crude product, which was filtered and dried under vacuum (52 g, 0.11 mol, yield: 65%).

Benzyl-2-acetamido-4,6-O-benzylidene-2-deoxy-α-D-allopyranoside (4):



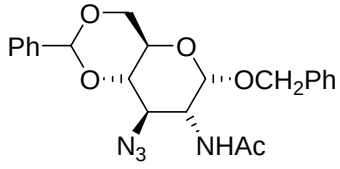
Compound (3) (52 g, 0.11 mol) was added to a solution of anhydrous sodium acetate (52 g, 0.63 mol) in a mixture of 2-methoxyethanol/water-95/5 V/V (640 mL). The mixture was refluxed for 48 hours. After cooling at room temperature, the crude reaction mixture was added to water affording the product as a white solid, that was washed and dried under vacuum (32 g, 0.080 mol, yield: 72%).

Benzyl-2-acetamido-3-azido-4,6-O-benyilidene-2,3-deoxy-3-O-metansulfonyl-α-D-allopyranoside (5):



To a solution of compound (4) (32 g, 0.080 mol) in pyridine (270 mL), metansulfinyl chloride (20 mL) was added at 273K. After overnight stirring at this temperature brine was added. Product was extracted with chloroform, washed with a diluted acetic acid solution, water, a diluted aqueous solution of sodium bicarbonate and again water. The solvent was removed under vacuum to yield the product as a dark syrup (28 g, 0.060 mol, yield: 75%).

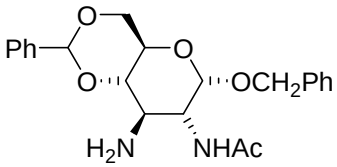
Benzyl-2-acetamido-3-azido-4,6-O-benzylidene-2,3-deoxy-α-D-glucopyranoside (6):



The syrup (5) (28 g, 0.060 mol) was dissolved in dimethylsulfoxide (200 mL) and sodium azide (18 g, 0.28 mol) was added. After stirring for 1 hour at 443K, the mixture was added to brine and the solid product was yielded by filtration and

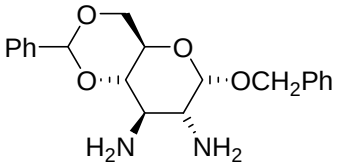
recrystallization from ethyl alcohol. (23 g, 0.054 mol, yield: 90%).

Benzyl-2-acetamido-3-amino-4,6-O-benzylidene-2,3-deoxy-α-D-glucopyranoside (7):



Compound (6) (3.0 g, 7.0 mmol) in methyl alcohol (340 mL) was hydrogenated using 10% Pd on activated carbon (1.0 g) and H_2 gas for 4 hours. Product was isolated by filtration (2.4 g, 6.0 mmol, yield: 86%).

Benzyl-2-acetammido-2,3-ammino-4,6-O-benzilidene-2,3-deoxy-α-D-glucopiranoside (8):

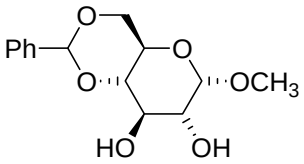


Compound (7) (2.4 g, 6.0 mmol) was added to a hot solution of KOH (11 g 0.95 mol) in ethyl alcohol (37 mL) and the mixture was heated under reflux. After 48 hours hot water (200 mL) was slowly added with consequent precipitation of the solid product, which was filtered and dried under vacuum (1.8 g, 5.1 mmol, yield: 85%).

2.8.2 *Synthesis of* **1M**

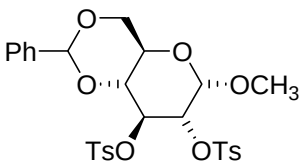
As already described, the synthesis is composed of several steps:

Methyl-4,6-O-benzylidene-α-D-glucopyranoside (1):



Methyl-α-D-glicoside (25 g, 0.13 mol) was added to a mixture of anhydrous zinc chloride (19 g, 0.14 mol) and benzaldehyde (67 mL). The resulting gel was stirred for 3 hours. Water (25 mL) was added to afford the product as a white solid which was filtered, washed with water and petroleum ether and recrystallized from benzene and petroleum ether (25 g, 0.088 mol, yield: 68%).

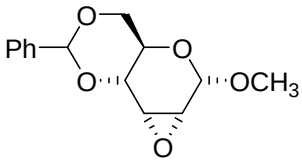
Methyl-4,6-O-benzylidene-2,3-di-O-p-toluensulfonyl-α-D-glucopyranoside (2):



To a solution of (1) (25 g, 0.088 mol) in pyridine (180 mL) and *p*-toluensulfonyl chloride was added (51 g, 0,27 mol) dropwise to the solution. After 10 days stirring at room temperature, the mixture was added to water/ice affording to the precipitation of the crude product. The suspension was extracted with dichloromethane (3 x 30 mL) and the organic phase was washed with HCl 6N at 273K (3 x 40 mL), with an aqueous solution of sodium

bicarbonate and water. The solvent was removed under vacuum and the product was dried over $CaCl_2$ (32 g, 0.055 mol, yield: 61%).

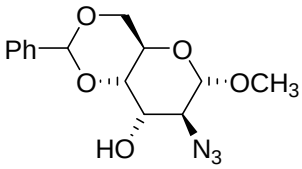
Methyl-2,3-epoxi-4,6-O-benzylidene-α-D-allopyranoside (3):



A solution of compound (2) (32 g, 0.055 mol) in dichloromethane (300 mL) was cooled at 273K. A solution of Na (7.0 g, 0.30 mol) in MeOH (90 mL) was added and the resulting mixture was preserved in the refrigerator for 3-4 days with occasional stirring, and then at 298K for 2 days. The solution was diluted with water, the organic phase was separated and the aqueous phase was extracted several times with small amount of dichlorometane.

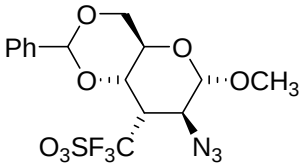
The combined organic phases were washed with water, dried over $CaCl_2$ and filtered. The product was yielded by recrystallization from chloroform/ diethylether (9.8 g, 0.037 mol, yield: 67%).

Methyl-2-azido-4,6-O-benzylidene-2-deoxy-α-D-altropyranoside (4):



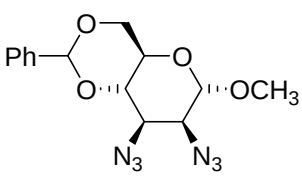
Compound (3) (6.2 g, 0.024 mol) and sodium azide (6.2 g, 0.095 mol) in 2-methoxyethanol (80 mL), water (10 mL) and ammonium chloride (2.0 g, 0.037 mol) were refluxed for 4 hours. The mixture was cooled at room temperature, added to brine (400 mL) and extracted with chloroform. The combined organic phases were dried over Na_2SO_4. Solvent was removed under vacuum to afford the product (7.0 g, 0.022 mol, yield 90%).

Methyl-2-azido-4,6-O-benzylidene-2-deoxy-α-D-altropyranoside-3-triflateo (5):



The crude monoazide (4) (7.0 g, 0.022 mol) was dissolved at 273K in pyridine(18 mL). Tryflic anhydride (6.0 mL) was slowly added at the same temperature and the mixture was stirred for 2 hours. Brine was added (500 mL) to afford the product which was filtered and washed several times with water (3 x 20 mL) and cold ethyl alcohol (7.2 g, 0.016 mol, yield: 73%).

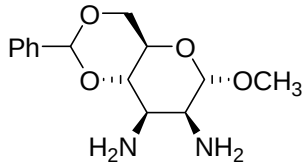
Methyl-2,3-diazide-4,6-O-benzylidene-2,3-didexy-α-D-mannopyranoside (6):



Compound (5) (7.2 g, 0.016 mol) was suspended in DMF (80 mL). Sodium azide (7.2 g, 0.11 mol) was added and the mixture was stirred over night at 348K. The resulting suspension was added to

water (400 mL) and stirred for 30 minutes. The white product was separated by filtration, washed with water and recrystallized from ethyl alcohol. (3.9 g, 0.012 mol, yield: 75%).

Methyl-2,3-diamino-4,6-O-benzylidene-2,3-dideoxy-α-D-mannopyranoside (7):

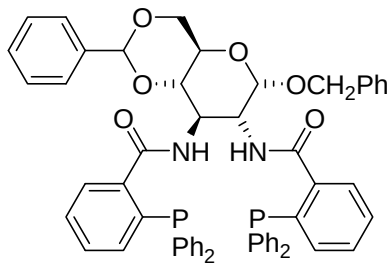


Compound (6) (3.9 g, 0.012 mol) in methyl alcohol (140 mL) was hydrogenated using 10% Pd on activated carbon (1.0 g) and H_2 gas for 4 hours. The product was yielded by filtration (2.4 g, 8.5 mmol, yield: 71%).

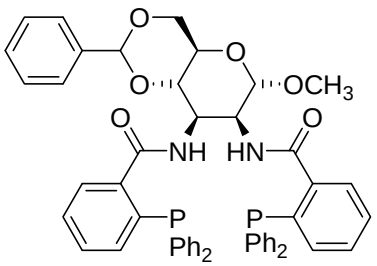
2.8.3 *Synthesis of* **1** *and* **2**

A solution of 2-(diphenylphosphino)benzoic acid (1.29 g, 4.2 mmol), 4-dimethylaminopyridine (0.048 g, 0.43 mmol) and 1,3-dicyclohexylcarbodiimide (0.89 g, 4.3 mmol) in dry dichloromethane (7 mL) was added to a solution of the diaminosugar (2.0 mmol) in the same solvent (7 mL). The resulting mixture was stirred for 12 h at room temperature under an inert atmosphere to afford a yellow suspension. The residue was removed by filtration. For ligand **2**, hexane (10 mL) was carefully added to the resulting yellow solution. After 24 h white microcrystals of products were separated, washed with hexane and dried under vacuum (yield: 70–75%).

In the case of ligand **1**, the resulting yellow solution was evaporated under vacuum, and the residue was chromatographed on silica gel (1:5 ethyl acetate–hexane) to afford the pure product as a white solid (yield: 60–65%).



Ligand **1**: ^{1}H NMR data (200 MHz, $CDCl_3$): δ 6.63 (d, 1H, NH–C2, $^{3}J_{NH–H2}$ = 9.9 Hz), 6.10 (d, 1H, NH–C3, $^{3}J_{NH–H3}$ = 9.9 Hz), 5.18 (s, 1H, $PhCHO_2$), 4.78 (d, 1H, H1, $^{3}J_{H1–H2}$ = 3.6 Hz), 4.70 (q, 1H, H3, $^{3}J_{H3–H4}$ = $^{3}J_{H3–H2}$ = 9.9 Hz), 4.54 (d, 1H, CHHPh, $^{2}J_{gem}$ = 11.4 Hz), 4.36 (d, 1H, CHHPh), 4.20 (dt, 1H, H2), 4.05 (dd, 1H, $H6_{eq}$, $^{3}J_{H6eq–H5}$ = 4.2, $^{2}J_{H6eq–H6ax}$=10.5Hz), 3.83 (dt, 1H, H5, $^{3}J_{H5–H6ax}$ = $^{3}J_{H5–H4}$ = 9.3 Hz), 3.58 (t, 1H, $H6_{ax}$), 3.28 (t, 1H, H4); ^{13}C NMR data (50.2 MHz, $CDCl_3$): δ 169.5, 169.1, 101.4, 97.2, 79.7, 70.2, 68.8, 63.9, 53.6, 50.2; $[\alpha]_D$ = +23 (c=1.0, CH_2Cl_2); Anal. Calcd for $C_{58}H_{50}N_2O_6P_2$: C, 74.67; H, 5.40; N, 3.00. Found: C, 74.88; H, 5.29; N, 2.97.



Ligand **2**: ^{1}H NMR data (200 MHz, $CDCl_3$): δ 6.18 (d, 1H, NH–C2, $^{3}J_{NH-H2}$ = 9.3 Hz), 5.03 5.18 (s, 1H, $PhCHO_2$), 4.82 (m, 2H, H2 and H3), 4.54 (s, 1H, H1), 4.09 (dd, 1H, $H6_{eq}$, $^{3}J_{H6eq-H5}$ = 5.0, $^{2}J_{H6eq-H6ax}$ = 9.9 Hz), 3.83 (dt, 1H, H5, $^{3}J_{H5-H6ax}$ = $^{3}J_{H5-H4}$ = 10.1 Hz), 3.32 (s, 3H, OMe) 3.25 (t, 1H, $H6_{ax}$), 2.98 (t, 1H, H4); ^{13}C NMR data (50.2 MHz, $CDCl_3$): δ 169.5, 169.2, 101.1, 100.5, 76.8, 68.5, 64.0, 54.9, 52.6, 48.3; $[\alpha]_D$ = -29 (c=1.0, CH_2Cl_2); Anal. Calcd for $C_{52}H_{46}N_2O_6P_2$: C, 72.89; H, 5.41; N, 3.27. Found: C, 72.56; H, 5.50; N, 3.33.

X-ray structure of ligand **2**

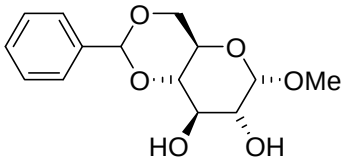
Single crystals suitable for X-ray analysis were obtained as small yellow prisms, by slow evaporation at room temperature, from a solution of ligand **2** in dichloromethane.

Data collection was performed in flowing N_2 at 173K, on a Bruker-Nonius kappaCCD diffractometer, using the Molibdenum Kα radiaction (0.71069 Å). Crystallographic data collection are reported in table.

Chemical formula	$C_{54}H_{50}Cl_4N_2O_6P_2$
Formula weight	1026.70
Temperature (K)	173
Λ	0.71069Å
Crystal system	Monocline
Space group	P_{21}
Cell size	A = 12.976(3) Å
	B = 13.855(4) Å
	C = 14.323(4) Å
	β = 90.95(1)°
Volume	2574.7 $Å^3$
Z, Calcolate density	2, 1.324 g/cm^3
Absorption coefficient	0.343 mm^{-1}
Crystal size (mm)	0.20 x 0.15 x 0.10
Range of θ (°)	3.14 a 27.50
Reflection collected/ reflection unique	23222/10665[R(int) =0.0292]
Data/ parameters	10665 / 614
R [I>2σ(I)]	R1 = 0.0403, wR2 = 0.0886
Largest difference in peak and hole	0.502 e $Å^{-3}$

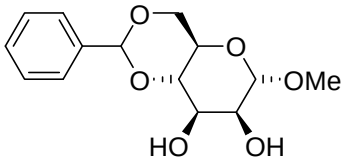
Structure was solved by direct methods (SIR 97 package),[12] and refined by the full matrix least-squares methods (SHELXTL program).[13] Semiempirical absorbtion correction multi-scan SADABS was applied. H atoms were placed in calculated positions. Final refinement was performed by anisotropic thermal parameter for each atoms different from hydrogen ones.

Methyl-4,6-O-benzylidene-α-D-glucopyranoside (**2G**):



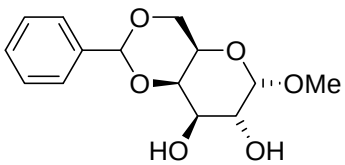
Methyl-α-D-glycoside (10 g, 0.05 mol) and anhydrous zinc chloride (7.6 g, 0.05 mol) were dissolved in benzaldehyde (27 mL, 0.26 mol) at room temperature. After 3 hours stirring water (25 mL) was added. The resulting solid was filtered, washed with water and petroleum ether. The crude product was crystallized from benzene and petroleum ether (9.90 g, 0.035 mol, yield: 69%).

Methyl-4,6-O-benzylidene-α-D-mannopyranoside (**2M**):



To a solution of methyl-α-D-mannoside (10 g, 0.05 mol) in benzaldehyde (27 mL, 0.26 mol) 40 ml formic acid 96% was added. After 3 hours stirring, water (25 ml) was added. The resulting solid was filtered, washed with water and petroleum ether. The crude product was crystallized from benzene and petroleum ether (10.5 g, 0.037 mol, yield: 74%).

Methyl-4,6-O-benzylidene-α-D-galattopyranoside (**2Gt**):

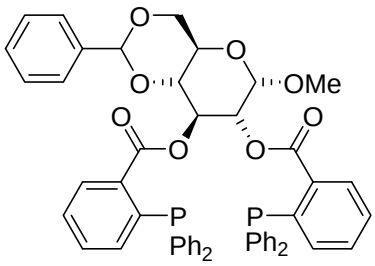


A solution of methyl-α-D-galattoside (10 g, 0.05 mol), anhydrous zinc chloride (7.6 g, 0.05 mol) and benzaldehyde (27 ml, 0.26 mol) was stirred for 6 hours at room temperature. A solution 1:1 water: methyl alcohol (8 ml) was added. The resulting mixture was extracted with petroleum ether (3 x 4 ml). Aqueous phase was extracted with dichloromethane (2 x 4 ml) and the combined organic phases were dried over Na_2SO_4. Petroleum ether was added to afford white microcrystals, which were washed with the same solvent and dried under vacuum (11.7 g, 0.041 mmol, resa 83 %).

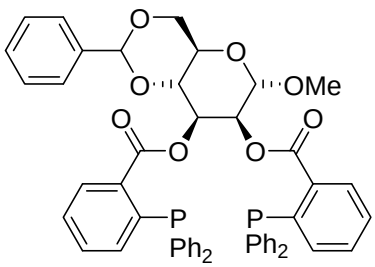
[12] Altomare, A.; Burla, M. C.; Camalli, G. L.; Cascarano, C.; Giacovazzo, C.; Guagliardi, A.; Moliterni, A. G. G.; Polidori, G.; Spagna, R. *J. Appl. Cryst* **1999**, *115*.
[13] Sheldrick, G.M.; *SHELX-97*, University of Göttingen, Germany, **1997**.

2.8.4 *Synthesis of* **3**, **4** *and* **5**.

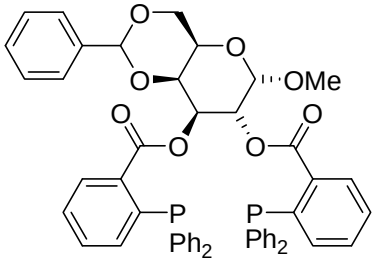
A solution of 2-(diphenylphosphino) benzoic acid (1.29 g, 4.2 mmol), 4-dimethylaminopyridine (0.048 g, 0.43 mmol) and 1,3-dicyclohexylcarbodiimide (0.89 g, 4.3 mmol) in dry dichloromethane (7 mL) was added to a solution of the appropriate precursor (2.0 mmol) in the same solvent (7 mL). The resulting mixture was stirred overnight at room temperature under inert atmosphere affording a suspension. After filtration, the solvent was removed under vacuum, and the residue was crystallized in hot ethanol affording the product as a white solid (yields: 3, 85%; 4, 85%; 5, 80%).



Ligand **3**: ^{1}H NMR data (200 MHz, $CDCl_3$): δ 5.92 (t, 1H, H3, $^{3}J_{H3–H2}$ = 3JH3–H4 = 9.9 Hz), 5.30 (s, 1H, $PhCHO_2$), 4.89 (d, 1H, H1, $^{3}J_{H1–H2}$ = 3.6 Hz), 4.83 (dd, 1H, H2), 4.25 (dd, 1H, $H6_{eq}$, $^{3}J_{H6eq–H5}$ = 4.8, $^{2}J_{H6eq-H6ax}$ = 10.5 Hz), 3.86 (dt, 1H, H5, $^{3}J_{H5–H6ax}$ = $^{3}J_{H5–H4}$ = 9.9 Hz), 3.62 (t, 1H, $H6_{ax}$), 3.26 (s, 3H, OMe), 3.23 (t, 1H, H4); ^{13}C NMR data (50.2 MHz, $CDCl_3$): δ 166.1, 165.5, 101.2, 97.5, 79.0, 72.6, 69.7, 68.8, 62.3, 55.3; $[\alpha]_D$ = -41.5 (c 1.0, CH_2Cl_2); Anal. Calcd for $C_{52}H_{44}O_8P_2$: C, 72.72; H, 5.16. Found: C, 72.78; H, 5.09.



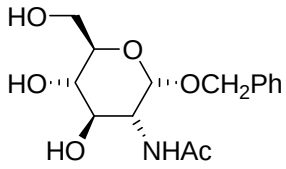
Ligand **4**: ^{1}H NMR data (200 MHz, $CDCl_3$): δ 5.70 (dd, 1H, H3, $^{3}J_{H3–H2}$ = 3.4, $^{3}J_{H3–H4}$ = 10.0 Hz), 5.49 (s, 1H, $PhCHO_2$), 5.43 (dd, 1H, H2, $^{3}J_{H2–H1}$ = 1.6 Hz), 4.58 (d, 1H, H1), 4.25 (dd, 1H, $H6_{eq}$, $^{3}J_{H6eq–H5}$ = 4.2, $^{2}J_{H6eq–H6ax}$ = 9.8 Hz), 4.09 (t, 1H, H4, $^{3}J_{H4–H5}$ = 10.0 Hz), 3.92 (dt, 1H, H5, $^{3}J_{H5–H6ax}$ = 10.0 Hz), 3.77 (t, 1H, H_{6ax}), 3.22 (s, 3H, OMe); ^{13}C NMR data (50.2 MHz, CDCl3): δ 162.4, 162.3, 100.8, 98.6, 76.8, 70.7, 68.2, 68.0, 63.0, 54.4; $[\alpha]_D$ = -26.9 (c 1.0, CH_2Cl_2); Anal. Calcd for $C_{52}H_{44}O_8P_2$: C, 72.72; H, 5.16. Found: C, 72.55; H, 5.24.



Ligand **5**: ^{1}H NMR data (200 MHz, $CDCl_3$): δ 5.61 (m, 2H, H2 and H3, $^{3}J_{H2–H1}$ = 3.0 Hz, $^{3}J_{H3–H4}$ = 2.4 Hz,), 5.43 (s, 1H, $PhCHO_2$), 4.93 (d, 1H, H1), 4.39 (s, 1H, H4), 4.11 (ABq, 2H, $H6_{ax}$ and $H6_{eq}$, $^{2}J_{gem}$ = 14 Hz), 3.69 (s, 1H, H5), 3.26 (s, 3H, OMe); ^{13}C NMR data (50.2 MHz, CDCl3): δ 165.9 (2C), 100.6, 97.8, 74.0, 69.3, 69.0, 68.8, 62.0, 55.4; $[\alpha]_D$ = +27.7 (c 1.0, CH_2Cl_2); Anal. Calcd for $C_{52}H_{44}O_8P_2$: C, 72.72; H, 5.16. Found: C, 72.68; H, 5.30.

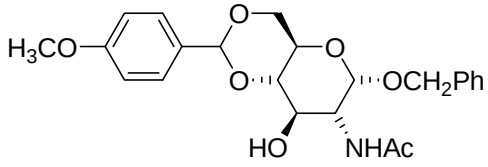
2.8.5 *Synthesis of* **3G** *and* **3G'**

Benzyl-2-acetamido-2-deoxy-α -D-glucopyranoside (1):



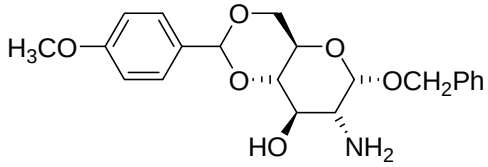
A solution of N-acetyl-α-D-glucosamine (60 g, 0.27 mol) in benzyl alcohol (240 mL) and acetyl chloride (1.1 mL) was refluxed for 60 minutes. After the mixture was cooled to room temperature, diethyl ether was slowly added under magnetic stirring until the formation of a dark solid, which was washed several times with the same solvent and dried under vacuum. (71 g, 0.23 mol, yield: 85%).

Benzyl-2-acetamido-4,6-O-benzylidene-2-deoxy-α-D-glucopyranoside (2):



Compound (1) (71 g, 0.23 mol) and anhydrous zinc chloride (71 g, 0.52 mol) were dissolved in the appropriate benzaldehyde (300 mL) at 333K (benzaldehyde for **3G** and *p*-methoxy benzaldehyde for **3G'**). After 60 minutes stirring at the same temperature, the mixture was cooled at room temperature and water (900 ml) was added under magnetic stirring. The resulting solid was filtered, washed with water and diethyl ether (200 mL), and dried under vacuum (68 g, 0.17 mol, yield: 74 %).

Benzyl-2-amino-4,6-O-(4-methoxy)benzylidene-2,3-deoxy-α-D-glucopyranoside (3):

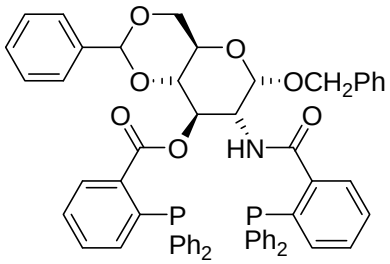


Compound (2) (2.4 g, 6.0 mmol) was added to a hot solution of KOH (11 g, 20 mmol) in ethanol (35 mL) and the mixture was refluxed. After 48 hours, hot water (200 mL) was slowly added with consequent precipitation of the solid product, which was filtered and dried under vacuum (1.8 g, 5.1 mmol, yield: 85%).

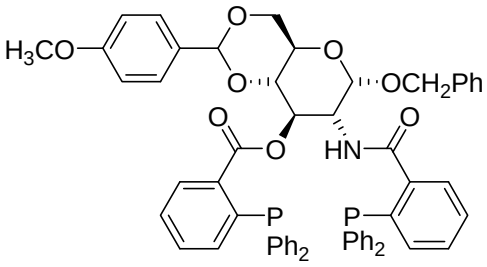
2.8.6 *Synthesis of* **6** *and* **7**

A solution of 2-(diphenylphosphino)benzoic acid (1.3 g, 4.2 mmol), 4-dimethylaminopyridine (0.048 g, 0.43 mmol) and 1,3-dicyclohexylcarbodiimide (0.89 g, 4.3 mmol) in dry dichloromethane (7 mL) was added to a solution of the appropriate aminosugar **3G** and **3G'** (2.0 mmol) in the same solvent (7 mL). The resulting mixture was stirred for 12 hours at room temperature under inert atmosphere affording a yellow suspension. The residue was removed by filtration. The resulting yellow solution was evaporated under vacuum, and the residue was

chromatographed on silica gel (1:5 ethyl acetate:hexane) affording the pure product as a white solid (yield: 60-65%).



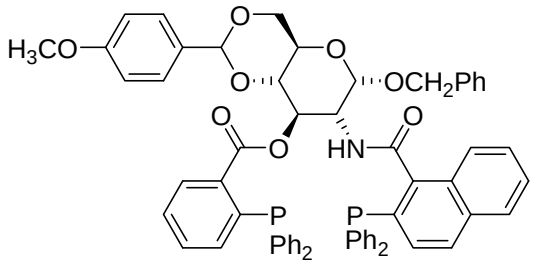
Ligand **6**: ^{1}H NMR (300 MHz, $CDCl_3$): δ= 6.26 (d, $^{3}J_{NH-H2}$ =9.6 Hz, 1H; NH), 5.50 (t, $^{3}J_{H3-H4}$ = $^{3}J_{H3-H2}$ = 10.2 Hz, 1H; H3), 5.37 (s, 1H; $PhCHO_2$), 4.79 (d, $^{3}J_{H1-H2}$=3.6 Hz, 1H; H1), 4.49 (m, 2H; C*H*HPh, H2), 4.32 (d, ^{2}J=12 Hz, 1H; CH*H*Ph), 4.08 (dd, $^{2}J_{H6eq-H6ax}$=10.5 Hz, $^{3}J_{H6eq-H5}$=4.8 Hz, 1H; H_{6eq}), 3.79 (dt, $^{3}J_{H5-H6ax}$= $^{3}J_{H5-H4}$= 9.6 Hz, 1H; H5), 3.59 (m, 2H; H_4, H_{6ax});^{13}C NMR (300 MHz, $CDCl_3$): δ= 168.7, 140.1-126.3, 101.3, 97.8, 79.5, 70.7, 68.8, 63.2, 52.9; IR(Nujol): ν=1699 cm^{-1} (C[dbond]O); $[\alpha]_D$ = +7 mL g^{-1} dm^{-1};Anal. Calcd (%) for $C_{58}H_{49}NO_7P_2$ (933,3): C 74.59, H 5.29, N 1.50; found: C 74.87, H 5.33, N 1.62.



Ligand **7**: ^{1}H NMR (200 MHz, $CDCl_3$): δ= 6.40 (d, $^{3}J_{NH-H2}$=9.8 Hz, 1H; NH), 5.61 (t, $^{3}J_{H3-H4}$=$^{3}J_{H3-H2}$=10.2 Hz, 1H; H3), 5.44 (s, 1H; $PhCHO_2$), 4.92 (d, $^{3}J_{H1-H2}$=3.4 Hz, 1H; H1), 4.66-4.55 (m, 2H; C*H*HPh, H_2), 4.44 (d, ^{2}J=12 Hz, 1H; CH*H*Ph), 4.17 (dd, $^{3}J_{H6eq-H5}$=4.4 Hz, $^{2}J_{H6eq-H6ax}$=9.8 Hz, 1H; H_{6eq}), 3.90 (dt, $^{3}J_{H5-H6ax}$=$^{3}J_{H5-H4}$=9.3 Hz, 1H; H5), 3.78 (s, 3H, OMe), 3.68 (m, 2H; H_4, H_{6ax}); ^{13}C NMR (300 MHz, $CDCl_3$): δ= 169.0, 166.9, 160.2, 140.3-127.8, 113.7, 101.5, 98.1, 79.6, 70.9, 70.6, 69.0, 63.5, 55.5, 53.1; IR(Nujol): ν=1699 cm^{-1} (C[dbond]O); $[\alpha]_D$ = +2 mL g^{-1} dm^{-1}; Anal. Calcd (%) for $C_{59}H_{51}NO_8P_2$ (963.31): C 73.51, H 5.33, N 1.45; found: C 73.40, H 5.47, N. 1.44.

2.8.7 *Synthesis of* **8**

A solution of 2-(diphenylphosphino)naphtoic acid (2.6 mmol), 4-dimethylaminopyridine (0.60 mmol) and 1,3-dicyclohexylcarbodiimide (6.1 mmol) in dry dichloromethane (7 mL) was added to a solution of the amino sugar **3G'** (2.6 mmol) in the same solvent (7 mL). The resulting mixture was stirred at room temperature under inert atmosphere affording a yellow suspension. After 12 hours 2-(diphenylphosphino)benzoic acid (2.6 mmol) was added and the suspension was stirred for other 12 hours. The residue was removed by filtration. The resulting yellow solution was evaporated under vacuum and the residue was chromatographed on silica gel (4:9 ethyl acetate:hexane) affording the pure product as a white solid (yield: 60-65%).

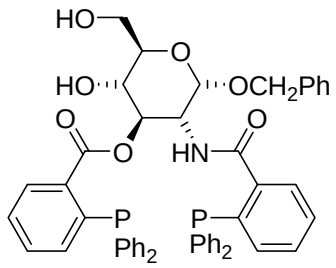


^{1}H NMR (200MHz, $CDCl_3$): δ 6.42 (d, 1H, NH-C2, $^3J_{NH-H2}$ = 9.3Hz), 5.66 (t, 1H, H3, $^3J_{H3-H4}$ = 20.4Hz, $^3J_{H3-H2}$ = 10.0Hz), 5.35 (m, 2H, H1 e H7, $^3J_{H1-H2}$ = 3.9Hz), 5.01 (dt, 1H, H2, $^3J_{H2-H3}$ = 11.1Hz), 4.60 (d, 1H, C*H*HPh, $^2J_{gem}$ = 12Hz), 4.37 (d, 1H, CH*H*Ph), 4.17 (dd, 1H, $H6_{eq}$, $^3J_{H6eq-H5}$ = 4.4, $^3J_{H6eq-H6ax}$ = 9.8 Hz), 3.90 (dt, 1H, H5, $^3J_{H5-H6ax}$ = $^3J_{H5-H4}$ = 9.3Hz), 3.78 (s, 3H, OCH_3) 3.68 (m, 2H, H4, $H6_{ax}$).

^{13}C NMR (200MHz, $CDCl_3$): δ 169.6,166.8,160.3,138.7-126.2,113.8,101.4,98.7,80.0, 70.7,69.1,63.6,55.7,53.2. ^{31}P NMR (400MHz, $CDCl_3$): δ -4.95, -13.38; $[\alpha]_D$ = + 54.20 (c= 0.60, CH_2Cl_2). HRMS (ESI) M+Na calcd: 1014.3265 m/z, found: 1014.3319 m/z.

2.8.8 *Synthesis of* **9**

Ligand **7** (0.49 g, 0.56 mmol) was dissolved in 50 mL of a mixture of methanol/formic acid 9/1. The suspension was stirred 5 hours at room temperature to afford a limpid yellow solution. The solvent was removed by evaporation and the crude product was purified by a column chromatography on silica gel (2:1 ethyl acetate:hexane with drops of triethylamine) affording the pure product as a white solid (yield: 60-65%).

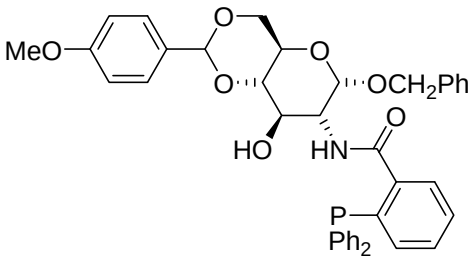


^{1}H NMR (300 MHz, $CDCl_3$,): δ= 6.19 (d, $^3J_{NH-H2}$=9.3 Hz, 1H; NH-C2), 5.21 (t, $^3J_{H3-H4}$= $^3J_{H3-H2}$=9.3 Hz, 1H; H3), 4.65 (d, $^3J_{H1-H2}$=3.6 Hz, 1H; H1), 4.49 (d, ^{2}J=12 Hz, 1H; C*H*HPh), 4.29 (d, 1H; CH*H*Ph), 4.06 (dt, $^3J_{H2-H3}$=10.5Hz, 1H; H2), 3.68-3.58 (m, 2H; H5, H6), 3.44 (t, $^3J_{H4-H5}$=9.3Hz, 1H; H4); ^{13}C NMR (300 MHz, $CDCl_3$): δ= 168.6, 140.8-125.5, 97.29, 71.7, 70.3, 69.5, 62.6, 52.3; IR(Nujol): ν=1699 cm^{-1} (C[dbond]O); Anal.Calcd (%) for $C_{51}H_{45}NO_7P_2$ (845.27): C 72.42, H 5.36, N 1.66; found: C, 72.28, H 5.32, N 1.55; $[\alpha]_D$ = +66 (c 1.0, CH_2Cl_2).

2.8.9 *Synthesis of* **10**

A solution of 2-(diphenylphosphino)benzoic acid (2.6 mmol), 4-dimethylaminopyridine (0.60 mmol) and 1,3-dicyclohexylcarbodiimide (6.1 mmol) in dry dichloromethane (7 mL) was added to a solution of the appropriate amino sugar (2.6 mmol) in the same solvent (7 mL). The resulting mixture was stirred for 12 hours at room temperature under inert atmosphere affording a yellow suspension. The residue was removed by filtration. The resulting yellow

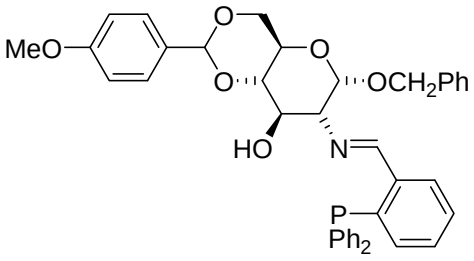
solution was evaporated under vacuum, and the residue was chromatographed on silica gel (4:9 ethyl acetate:hexane) affording the pure product as a white solid (yield: 60-65%).



^{1}H NMR (400MHz, $CDCl_3$): δ 6.27 (d, 1H, NH-C2, $^{3}J_{NH-H2}$ = 8.0Hz), 5.56 (s, 1H, H7), 4.95 (d, 1H, H1,$^{3}J_{H1-H2}$ = 4.0Hz), 4.66 (d, 1H, C*H*HPh, $^{2}J_{gem}$ = 12Hz), 4.45 (d, 1H, CH*H*Ph), 4.39(dt, 1H, H2, $^{3}J_{H2-H3}$ = 12Hz), 4.22 (dd, 1H, $H6_{eq}$, $^{3}J_{H6eq-H5}$ = 4.0, $^{2}J_{H6eq-H6ax}$ = 12Hz), 3.93 (t, 1H, H3, $^{3}J_{H3-H4}$ = 20.4Hz, $^{3}J_{H3-H2}$ = 12Hz), 3.83 (s, 3H, OCH_3), 3.85-3.75(m, 2H, H5 and $H6_{ax}$), 3.67 (t, 1H, H4, $^{3}J_{H4-H5}$ =7.9Hz). ^{13}C NMR (400MHz, $CDCl_3$): δ 169.8, 160.2, 136.8-127.7, 113.6, 101.9, 97.2, 81.6, 70.5, 69.8, 68.8, 63.0, 55.3, 54.9. ^{31}P NMR (400MHz, $CDCl_3$): δ -11.37; $[\alpha]_D$ = + 46.85 (c= 0.815, CH_2Cl_2). HRMS (ESI) M+H calcd: 676.2459 m/z, found: 676.2449 m/z.

2.8.10 *Synthesis of* **11**

A solution of 2-(diphenylphosphino)benzaldehyde (2.6 mmol) in toluene (5 mL) was added to a solution of the amino sugar (2.6 mmol) in the same solvent (5 mL). The resulting mixture was stirred for 2 hours at 353K affording a yellow solution. The volume of the solvent was reduced under vacuum at ca. 1 mL and hexane (5-6 mL) was slowly added to afford the product as a yellow microcrystalline powder, which was washed with hexane and dried under vacuum (yield: 60%).

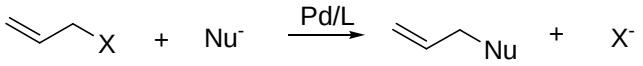


^{1}H NMR (200MHz, C_6D_6): δ 9.06 (d, 1H, N=CH), 5.55 (s, 1H, H7), 4.73 (d, 1H, H1, $^{3}J_{H1-H2}$ = 4.0Hz), 4.66 (m, 2H, C*H*HPh, H3), 4.44 (d, 1H, CH*H*Ph, $^{2}J_{gem}$ = 12Hz), 4.35-4.30 (m, 2H, H5 and $H6_{eq}$), 3.74 (t, 1H, $H6_{ax}$, $^{3}J_{H6ax-H5}$ = 8.0Hz), 3.64 (t, 1H, H4, $^{3}J_{H4-H5}$= 12Hz, $^{3}J_{H4-H3}$= 12Hz), 3.47 (dd, 1H, H2, $^{3}J_{H2-H3}$= 12Hz), 3.38 (s, 3H, OCH_3). ^{13}C NMR (200MHz, C_6D_6): δ 162.5, 138.5-127.5, 113.5, 102.1, 99.7, 82.3, 75.3, 72.9, 69.4, 69.2, 64.3, 62.7, 54.6. ^{31}P NMR (400MHz, $CDCl_3$): δ -11.62; $[\alpha]_D$ = + 37.97 (c= 0.52, CH_2Cl_2). HRMS (ESI) M+H calcd: 660.2510 m/z, found: 660.2495 m/z.

3. Catalysis

3.1 *Enantioselective allylic substitution*

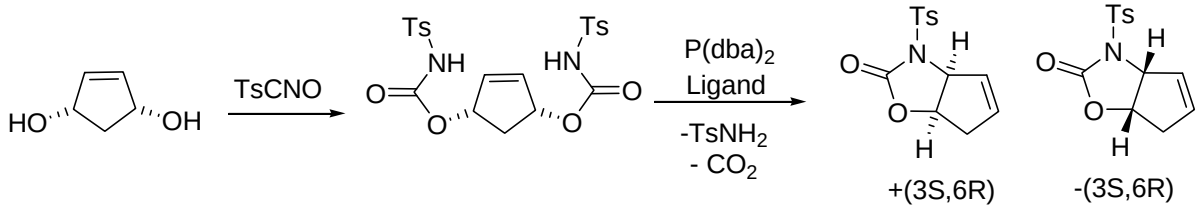
Allylic alkylation reaction has demonstrated to be an exceptionally powerful method for the efficient formation of multiple types of bonds (C-C, C-O, C-S, C-N) in sharp contrast to many others catalytic methods (Scheme 3.1)[14].



Scheme 3.1

In particular, metal-catalyzed Asymmetric Allylic Alkylations (AAA) is one of the best methods for preparation of a wide variety of chiral compounds useful in pharmaceutical and biological fields. These reactions has been extensively studied with a wide spectrum of metals, such as Pd, W, Mo, Ir, Ni, Rh and Ru.[15] The most common one, palladium, has been used with considerable success using soft stabilized nucleophiles for the eponym Trost reactions.

One of these is the desymmetrization of the *meso*-2-cyclopenten-1,4-diol biscarbamate (Scheme 3.2) to afford an important pharmaceutical key precursor of mannostatine A.[6]



Scheme 3.2

Mannostatine A is a non toxic and specific inhibitor of α-D-mannosidase, which is an enzyme class of the glycosidases, able to resolve mannose α-glycosides. Its synthesis is reported in scheme 3.3.

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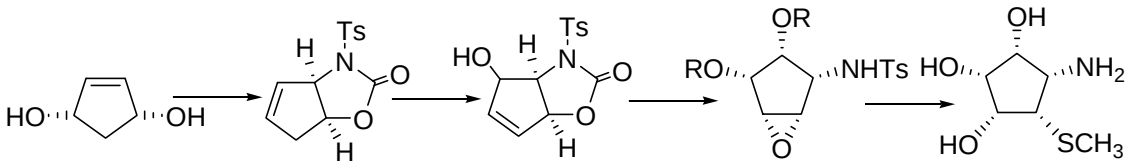
[14] Godleski S. A., Comprehensive Organic Synthesis, ed. By Trost B.M., Fleming I., Semmelhack M. F., Pergamon Press, Oxford, **1990**, Vol. 4, Chapter 3

[15] a) Trost B. M., Lee C., *Catalytic Asymmetric Synthesis* (Ed.:I. Ojima), 2nd ed., Wiley, NewYork, **2000**, 593–649; b) Pfaltz A., Lautens M., *Comprehensive Asymmetric Catalysis I–III* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**, 833–884.

For reviews of asymmetric allylic alkylation with various metals, see: a) Miyabe H., Takemoto Y., *Synlett* **2005**, 1641–1655; b) Trost B. M., *J. Org. Chem.* **2004**, *69*, 5813–5837; c) Trost B. M., Crawley M. L., *Chem. Rev.* **2003**, *103*, 2921–2943; d) Takeuchi R., *Synlett* **2002**, 1954–1965.



MANNOSTATINE A

Scheme 3.3

Mannosidase inhibitors are strong antiviral agents, anti-HIV potential agents and antitumorals. They are largely used in immunology, in virology, diabetes and cancer therapy and for these reasons chemistry community is interested to the stereoselective synthesis of these molecules.

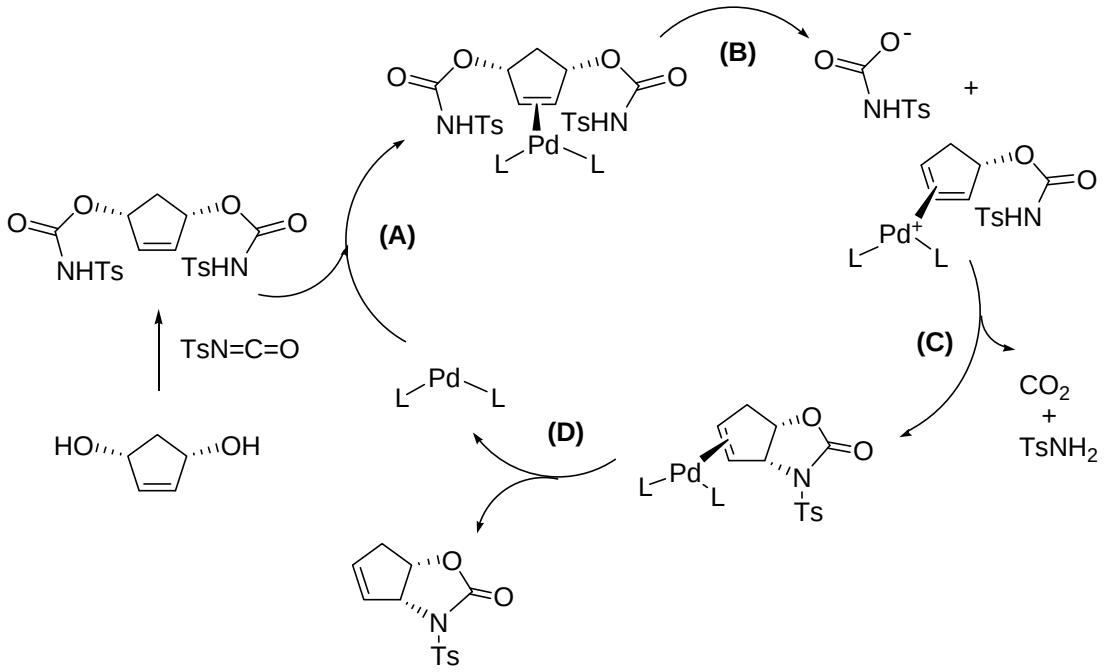
Pioneering works on the reaction in scheme 3.3 have been reported by Trost[6(b,f)] which, using the new chiral ligands (Fiugure 1.4b) derived from *trans*-cyclohexanediamine, obtained excellent results with very high yield and enantioselectivity.

Afterwards studies regarding the discovery of new chiral ligands to improve the performances of Trost ligand were carried out.[6(l,m,n)]

A reasonable mechanism for this reaction is reported in Scheme 3.4 and is referred to the synthesis of one of the two enantiomers.[16]

The initial coordination of the *meso*-carbammate to Pd(0) (step A) is followed by the intramolecular oxidative addition with formation of a π-allyl palladium(II) intermediate and a carbamate ion (that decomposes into carbonic anhydride and tosylamine) (step B). In the third step (C) an intramolecular nucleophilic attack gives rise to the product, which upon the decomplexation restores the Pd(0) specie that can re-enter the catalytic cycle (step D).

[16] Trost, B.M.; Van Kranken, D.L.; Bingel, C. *J. Am. Chem. Soc.* **1992**, *114*, 9327.



Scheme 3.4 *Asymmetric induction in Pd-catalyzed oxadolidin-2-one synthesis*

An analysis of the mechanism suggests that the enantiodiscriminating step occurs early in the catalytic cycle (step B) because the enantiomorphology of the substrate doesn't change by subsequent steps.

Later, Trost also demonstrated the positive influence of a base, such as the triethylamine, in the reaction sistem.[17] Its presence favours the formation of a zwitterionic specie, shown in Figure 3.1, through the deprotonation of the nitrogen atom on the allylic palladium intermediate.

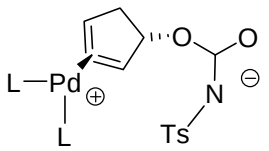


Figure 3.1

This step should accelerate the ring closing reaction (step C) with positive consequence on enantioselectivity.

[17] Trost, B.M.; Patterson, D.E., *J. Org. Chem.* **1998**, *63*, 1339.

3.1.1 *Catalytic tests: results and discussion*

The oxazolidinone-forming scheme is easily carried out by preparing the bis-carbamate substrate in situ. Cis-cyclopenten-2-ene-1,4-diol in THF is treated with two equivalents of *p*-toluensulfonyl isocyanate to give the bis-carbamate in an exothermic reaction.

The bis-carbamate solution is then added to a solution of the catalyst, prepared by stirring a mixture of the ligand and $Pd(dba)_2$ in dry THF. The substrate/catalyst ratio used is of 20/1.

In order to examine the influence of temperature on the process, catalytic tests are performed at 298K, 273K and 258K. The influence of an added base is investigated by performing the catalysis in presence of triethylamine.

In all cases the conversion of the substrate is complete in 30 minutes, as inferred from ^{1}H-NMR spectra of the crude product.

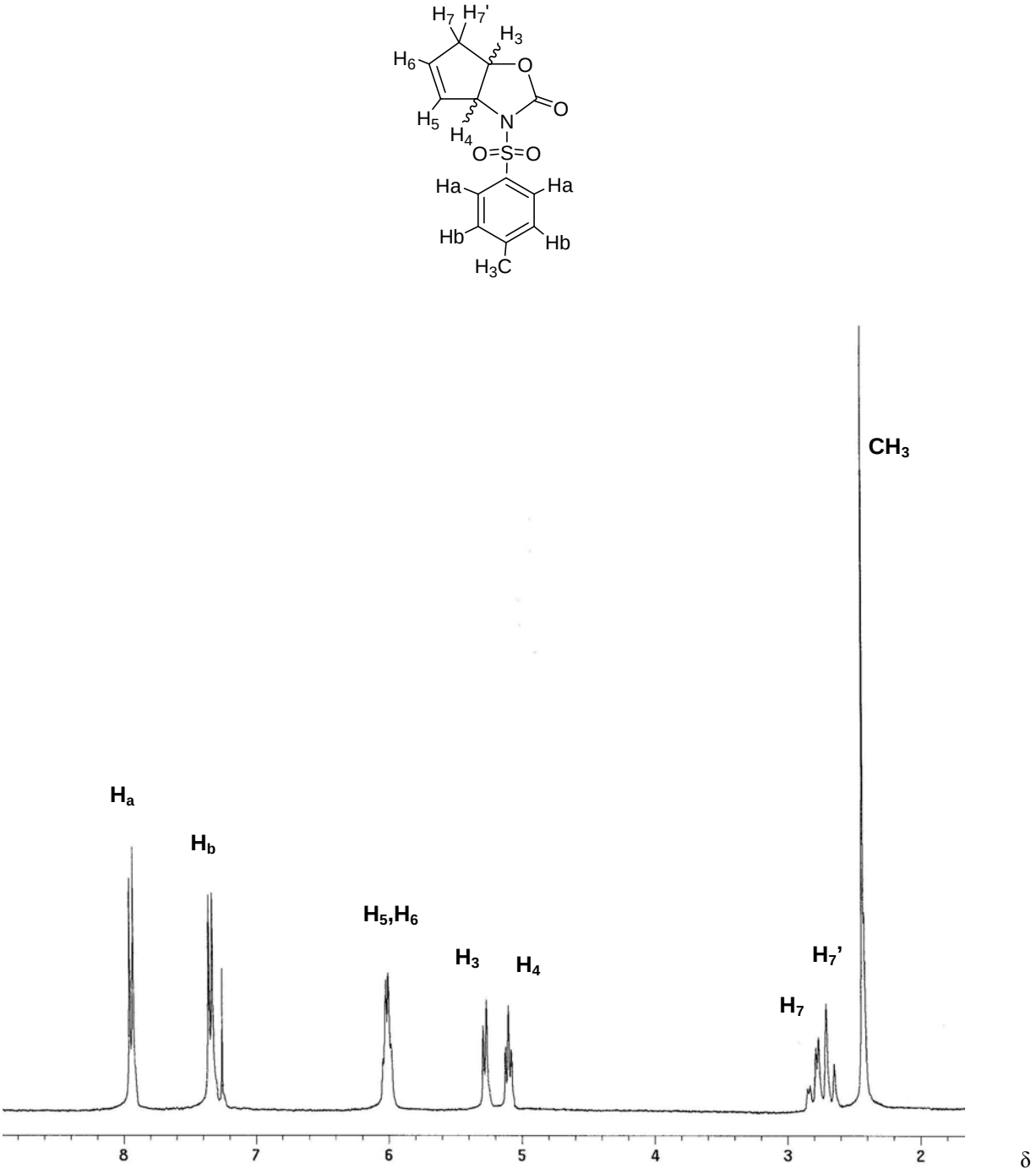
This is purified (yield=59%) by column chromatography and the separation of the two enantiomers occurs because they have different interactions with the chiral column and therefore display different retention times (22-24 min for [-(3R,6S)] and 30-32 min for [+(3S,6R)]).

Enantioselectivity is determined by High Performance Liquid Chromatography (HPLC), with a chiral column (Chiracel OD-H) using an UV detector with λ = 254 nm and a mixture 1:10 isopropanol:hexane as solvent.

The absolute configuration of the stereoisomers has been assigned by comparing the retention times with those of the product of known configuration.[6(b,e)] Integration of each peak allows to calculate the enantiomeric excess.[18]

[18] Ee is the percentage ratio between the difference of concentration of the two enantiomers and their addition: ee%= ([R]-[S])*100/([R]+[S])

^{1}H NMR spectrum of the catalytic reaction product



3.1.2 *Catalysis with bis(phosphinoamide) ligands*

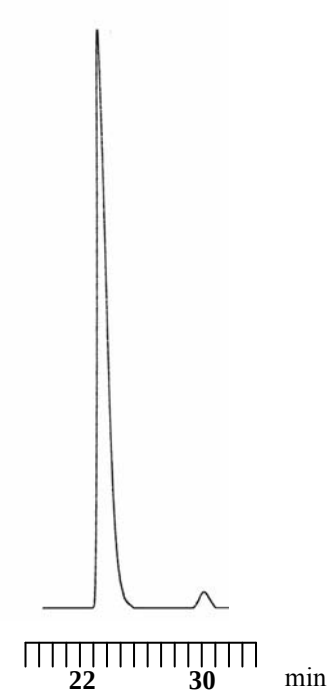
The results of the allylic substitution reactions of *meso*-cyclopenten-2-ene-1,4-diolbiscarbamate using ligands **1** and **2**, are reported in table 3.1.

entry	*ligand*	*T(K)*	*NEt_3(eqv.)*	*t(min)*	*conversion(%)*	*ee(%)*
a	**1**	273	-	30’	99%	80 [-(3R,6S)]
b	**1**	258	-	30’	99%	68 [-(3R,6S)]
c	**1**	273	1	30’	99%	93 [-(3R,6S)]
d	**1**	258	1	30’	99%	97 [-(3R,6S)]
e	**2**	273	-	30’	99%	91 [+(3S,6R)]
f	**2**	258	-	30’	99%	70 [+(3S,6R)]
g	**2**	273	1	30’	99%	95 [+(3S,6R)]
h	**2**	258	1	30’	99%	97 [+(3S,6R)]

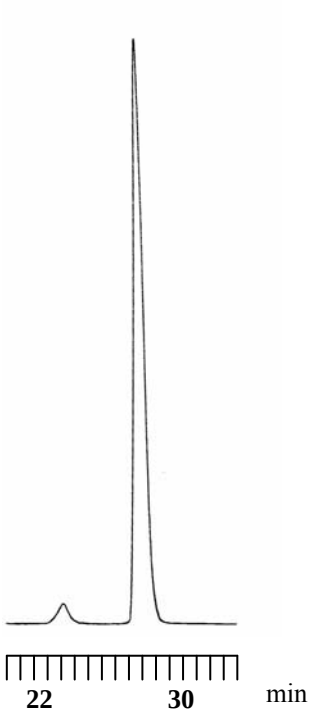
Table 3.1

It should be noted that:

- glucose and mannose promote preferential formation of the opposite enantiomers;
- the marked beneficial influence of an added base is demonstrated: in all cases, the ee of the reaction increases in presence of triethylamine
- lowering the temperature from 273 to 258 K influences the enantioselectivity, with a favorable effect only if the additive is present. Thus, the optimal reaction conditions have been found at 258 K in presence of triethylamine, which allow the attainment of the two enantiomers in 97% ee (entries d and h), as the chromatograms show.



Chromatogram using ligand **1**
in favour of[-(3S,6R)] with 97%ee



Chromatogram using ligand **2**
in favour of[+(3S,6R)] with 97%ee.

These data are also in accordance with optical activity measurements: [+(3S,6R)] = +141°, [-(3R,6S)] = -141°.

In keeping with the initial assumption, **1** promote the formation of product with the same configuration of the Trost ligand based on (1S,2S)-cyclohexanediamine.[6(b)] This can be reasonably explained by assuming that the Trost ligand (Figure 3.3a) and **1** (Figure 3.3b) introduce similar steric motifs around Pd, as shown by using the model proposed by Trost for explaining the ligand effect on enantioselectivity.[6]

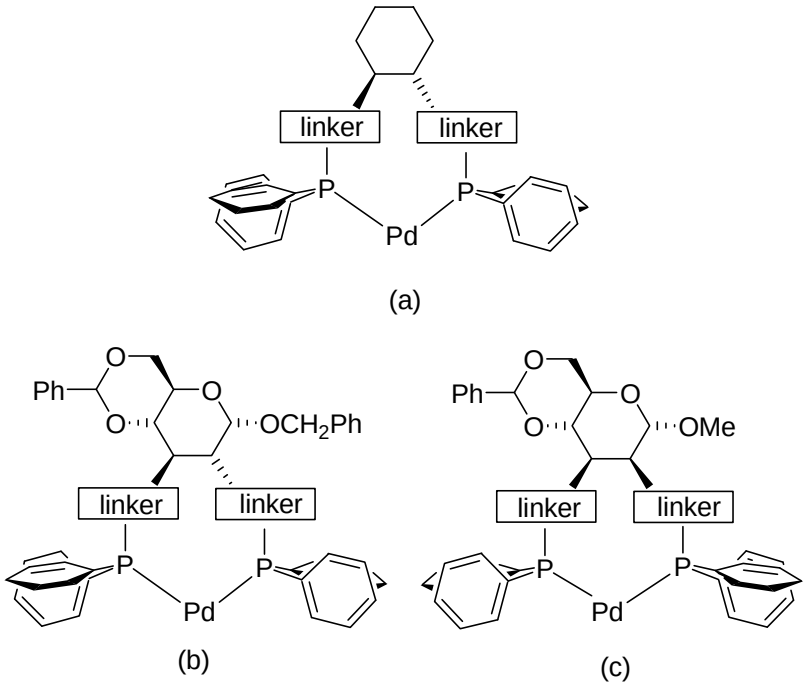


Figure 3.3

Mannose induces high selectivity in the opposite direction. A reasonable rationalization of this finding is that the chiral environment created by **2** is enantiomeric to that of **1** (Figure 3.3b and 3.3c).

This can occur because the torsional angles N(2)–C(2)–C(3)–N(3) of the chiral backbone are of opposite signs in the two sugars, due to the different orientations of the nitrogen functions, that is, N(2)eq–N(3)eq for glucose and N(2)ax–N(3)eq for mannose. As proposed by Trost, this geometrical feature directly correlates[16] with the stereochemistry of the chiral coordination environment (Figure 3.4).

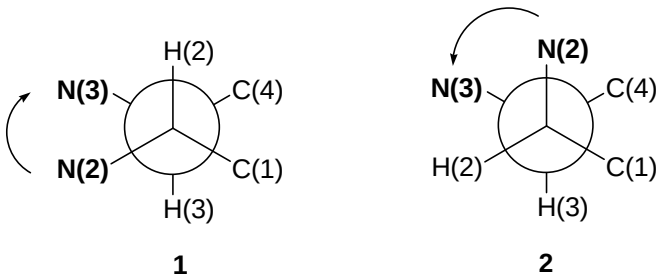


Figure 3.4

3.1.3 *Catalysis with bis(phosphinoester) ligands*

The results of the allilyc substitution reaction of *meso*-cyclopenten-2-ene-1,4-diolbiscarbamate using ligands **3, 4** and **5**, are reported in table 3.2.

entry	*ligand*	*T(K)*	*NEt3(eqv)*	*t(min)*	*conversion(%)*	*ee(%)*
a	3	273	-	30’	99%	80 [-(3R,6S)]
b	3	258	-	30’	99%	82 [-(3R,6S)]
c	3	273	1	30’	99%	74 [-(3R,6S)]
d	3	258	1	30’	99%	75 [-(3R,6S)]
e	3	273	10	30’	99%	70 [-(3S,6R)]
f	4	273	-	30’	99%	0
g	4	273	1	30’	99%	0
h	5	273	-	30’	99%	70 [-(3S,6R)]
i	5	273	1	30’	99%	48 [-(3S,6R)]

Table 3.2

An inspection of Table 3.2 suggests that:

- D-glucose ligand **3** largely favours formation of the – (R,S) enantiomer, in analogy with the corresponding diamide **1** (entries a–d). This is reasonable because changing the organic linker is expected to affect the sole flexibility of the ligand, with a minor influence on its stereochemistry of coordination. Of course this latter feature plays also a role, identifiable in the fact that ligands **3** and **1** display different enantioselectivities in the same conditions (see table).

– D-mannose derivative **4** affords product as a racemic mixture (entries f and g). This result is not completely unexpected, because previous work demonstrated that ligands based on 2,3-disubstitued D-mannose are generally poorly effective, due to the relative arrangement of the coordinating functions (axial–equatorial).[9] Nevertheless, this unsatisfactory result is in great contrast with the high ee’s (up to 97% of +(S,R)) obtained by using the corresponding diamide **2**. A combination of factors may determine this finding, i.e. the steric hindrance afforded by the D-mannose chair (Figure 3.5) may force the flexible ester linkers in a conformation unfavourable to enantiodiscrimination.

– galactose ligand **5** has the ester groups in the equatorial positions at C2 and C3 of the sugar chair, similarly to **1**. Accordingly, ligand **5** significantly promotes formation of -(R,S), though less effectively than **1** (entries h–i). The decrease of values switching from D-glucose to D-

galactose (e.g., from 80% to 70% ee, entries b and h) reveals that even the stereochemistry of substituents quite distant from the metal, coordination sphere is decisive for the selectivity.

– the influence of triethylamine has revealed to be small for ligands **3** and **4**, if compared to that observed with **1** and **2**. Instead, the performance of ligand **5** is more affected by the presence of a base. In all cases, a negative variation of ee's has been observed by adding one equivalent of triethylamine to the reaction mixture (entries a *vs* c, b *vs* d, h *vs* i). Accordingly, a large excess of triethylamine reduces even more considerably the selectivity, which decreases for **3** at 70% when 10 equivalents of base is present (entry e).

– the temperature plays an even minor effect, and no significant variation of ee's has been recorded by performing the reactions at 273 or 258 K (entries a *vs* b, or c *vs* d).

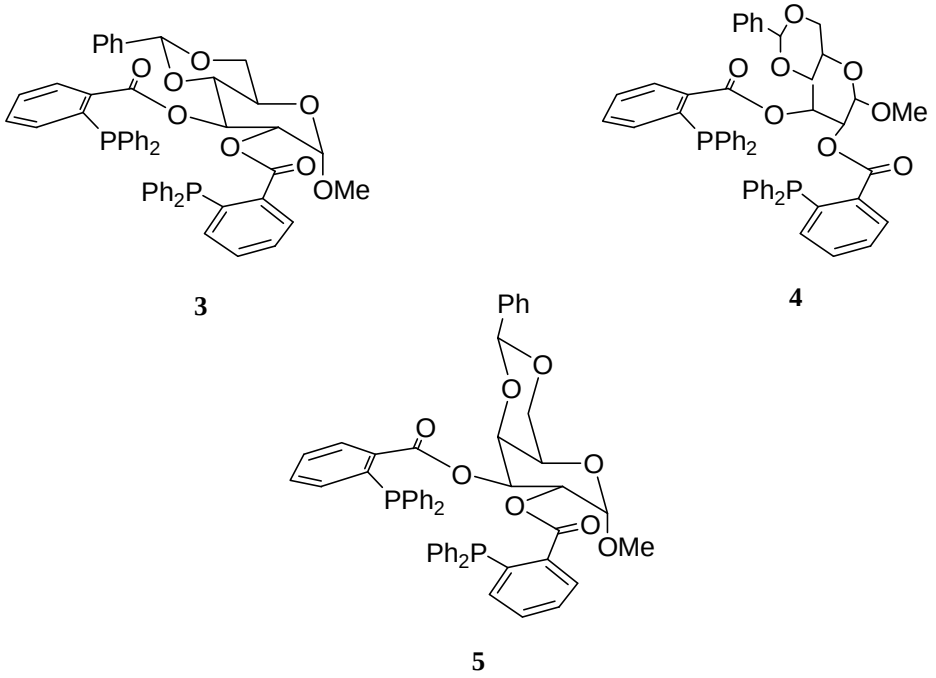
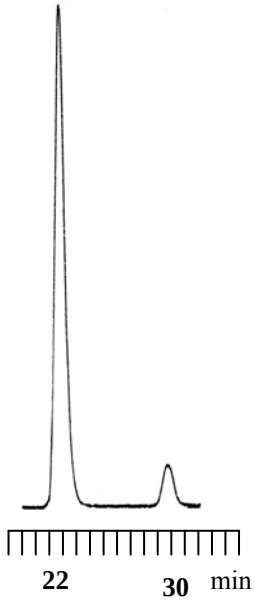


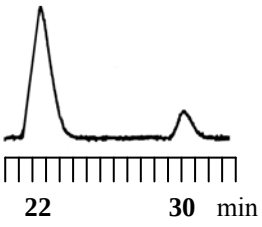
Figure 3.5

Thus, the most convenient conditions have been found by using **3** at 258 or 273 K in absence of an added base, which affords -(R,S) enantiomer in quantitative yield and 80–82% ee within 30 min.

Chromatograms of the best catalytic tests with ligands **3** e **5** (Fig. 4.5) at 258K and 273K without triethylamine are reported below. These dates are in accordance with optical rotation: [+(3S,6R)] = +141°, [-(3R,6S)] = -141°.



Chromatogram using ligand **3**
in favour of[-(3S,6R)] with 82%ee



Chromatogram using ligand **5**
in favour of[+(3S,6R)] with 70%ee

It should be noted that diester **3** does not reach the high performance of the corresponding diamide **1**, according to a general trend previously described by Trost et al, and ascribed to the higher conformational rigidity of the amido function. Notably, **3** is more effective than Trost's bis(phosphinoesters) (Figure 3.6), which promote ee's up to 75.1% in the same conditions.[15] This favourable comparison gives more emphasis to the quality of the new sugar-based ligands, and stimulates further investigation on their use in asymmetric catalysis.

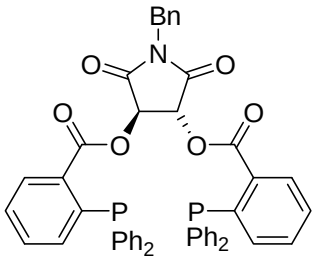


Figure 3.6

3.1.4 *Catalysis with phosphinoamide-phosphinoester ligands*

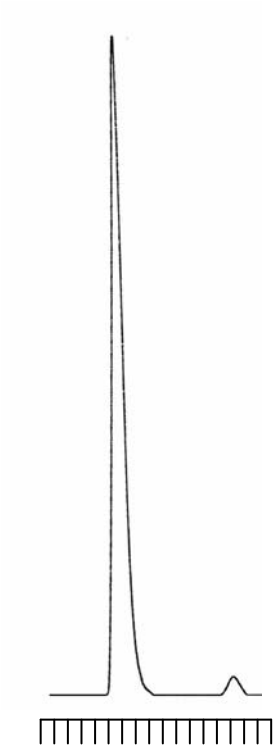
The results of allilyc substitution reactions of *meso*-cyclopenten-2-ene-1,4-diolbiscarbamate using ligands **6**, **7**, **8** and **9** are reported in table 3.3.

entry	*ligand*	*T(K)*	*NEt_3(eqv)*	*t(min)*	*conversion(%)*	*ee(%)*
a	**6**	258	-	30’	99%	94 [-(3R,6S)]
b	**6**	273	-	30’	99%	96 [-(3R,6S)]
c	**6**	298	-	30’	99%	94 [-(3R,6S)]
d	**6**	258	1	30’	99%	97 [-(3R,6S)]
e	**6**	273	1	30’	99%	90 [-(3R,6S)]
f	**6**	298	1	30’	99%	91 [-(3R,6S)]
g	**7**	258	-	30’	99%	98 [-(3R,6S)]
h	**7**	298	-	30’	99%	95 [-(3R,6S)]
i	**7**	298	1	30’	99%	91 [-(3R,6S)]
j	**8**	258	-	30’	99%	92 [-(3R,6S)]
k	**8**	298	-	30’	99%	98 [-(3R,6S)]
l	**9**	298	-	30’	99%	85 [-(3R,6S)]
m	**9**	298	1	30’	99%	80 [-(3R,6S)]

Table 3.3

Ligands **6**, **7** and **8** afford the substrates in excellent yields and high ee’s, which spanned from 90 to 98%.

A slight negative influence of the added base is also observed, as already disclosed for the corresponding diester. The highest ee (98%) is achieved by using **7** and **8** without base, as the chromatogram shows.



Chromatogram using ligand **7** and **8**
in favour of [-(3S,6R)] with 98%ee

This is particularly interesting because it demonstrates that low temperatures are not necessary for achieving excellent ee's. This is beneficial for both energetic and kinetic implications.[19]

More significant is the deprotection of the hydroxyls in 4 and 6. Ligand **9** is the least effective, and the ee reached 85% at 298 K. This outcome can be plausibly ascribed to a reduced rigidity of the ligand, whose structure is more flexible than that of the corresponding versions **6** and **7**.

The results obtained with the mixed phosphinoamide-phophinoester ligands shows that they are the right compromise that optimises both availability and high catalytic performance. In particular, their synthesis is very convenient because requires only four simple steps, and the corresponding Pd complexes are as active as those containing the analogous bis(phosphinoamide).

[19] Van Aken K., Strekowski L., Patiny L., "Eco-Scale, a semi quantitative tool to select an organic preparation based on economical and ecological parameters", *Beilstein Journal of Organic Chemistry*, **2006**, 2:3.

3.1.5 *Experimental section*

General methods

All experiments were carried out under an argon atmosphere using standard Schlenk techniques. THF was distilled on Na/benzophenone. ^{1}H and ^{13}C NMR spectra were recorded on Varian-Gemini 300 and Varian-Gemini 200 spectrometers. For all other samples δ values were referenced to residual $CDCl_3$. All *J* values are in Hz. Specific optical rotatory powers [α] were measured with a Perkin-Elmer Polarimeter (model 141) at 298 K and 589 nm in dichloromethane (c= 1.0 g/100 mL). Enantioselectivities were determined by High resolution liquid chromatografy (HPLC), using a chiral column (Chiracel OD-H). Eluent mixture used is 1:10 isopropanol:hexane and an UV detector with λ = 254 nm. Yields were determined by isolation. Thin layer chromatography (TLC) was performed on Merck silica gel 60 F_{254} pre-coated plates (0.25 mm) silica. The plates were visualised by the use of a combination of ultraviolet light (254 and 366 nm). Liquid chromatography was carried out by forced flow (flash chromatography) with the solvent systems indicated using silica gel 60 Å (200-400 mesh) supplied by Aldrich.

General procedures for catalytic reactions in traditional conditions.

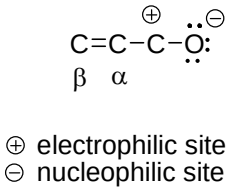
Without NEt_3: to a solution of *cis*-2,4-cyclopentenediol (0.112 g, 1.00 mmol) in dry THF (1.75 mL) was added tosyl isocyanate (0.404 g, 2.05 mmol). The colourless solution was stirred at room temperature for 15 min and at 333K for 30 min. The reaction mixture was allowed to reach the desired catalysis temperature, and then dropwise added to an orange solution of $[Pd(dba)_2]$ (0.028 g, 0.050 mmol) and the ligand (0.075 mmol) in dry THF (1.75 mL) kept at the same temperature. The orange reaction mixture was stirred for 30 min. The solvent was removed under vacuum and column chromatography on silica gel (1:10 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, 1:10 isopropanol:hexane, UV 254 nm, retention times: -(3R,6S): 22-24 min; +(3S,6R): 30-32 min. The absolute configuration was obtained by comparison with a sample of known chirality.

With NEt_3: to a solution of *cis*-2,4-cyclopentenediol (0.112 g, 1.00 mmol) in dry THF (1.75 mL) was added tosyl isocyanate (0.463 g, 2.35 mmol). The colourless solution was stirred at room temperature for 15 min and at 333K for 30 min. The reaction mixture was allowed to cool at room temperature, and triethylamine (0.101 g, 1.00 mmol) was added. The resulting white slurry was allowed to reach the desired catalysis temperature, and then dropwise added

to an orange solution of [Pd(dba)$_2$] (0.028 g, 0.050 mmol) and the ligand (0.075 mmol) in dry THF (75 mL) kept at the same temperature. The orange reaction mixture was stirred for 30 min. The solvent was removed under vacuum and column chromatography on silica gel (1:10 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, 1:10 isopropanol:hexane, UV 254 nm, retention times: -(3R,6S): 22-24 min; +(3S,6R): 30-32 min. The absolute configuration was obtained by comparison with a sample of known chirality.

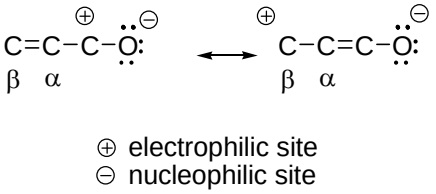
3.2 *Asymmetric conjugate addition*[20]

Addition of nucleophilic reagents to α,β-unsaturated compounds is one of the most powerful methods for the formation of carbon–carbon bonds in organic synthesis. This reaction involves covalent bonding of a nucleophile to the electrophilic carbon atom of a carbonyl group.



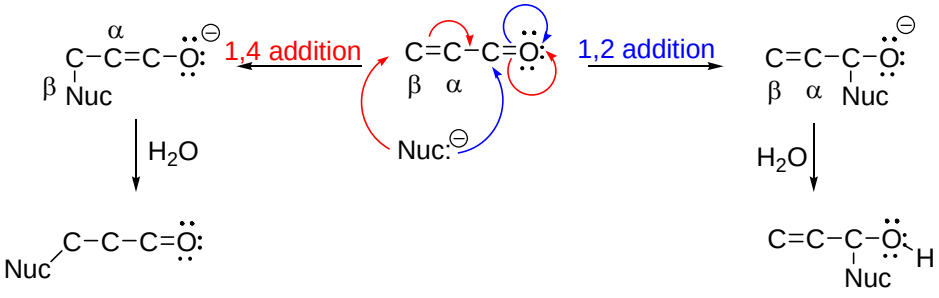
Scheme 3.5

Conjugation of a double bond to a carbonyl group can transmit the electrophilic character of the carbonyl carbon to the β-carbon of the double bond. A resonance description of this transmission is shown below.



Scheme 3.6

From this formula it should be clear that nucleophiles can attach the carbonyl carbon (1,2 addition) as for any aldehyde, ketone or carboxylic acid derivative, or the β-carbon. This alternative mode of reaction is referred as 1,4-addition.



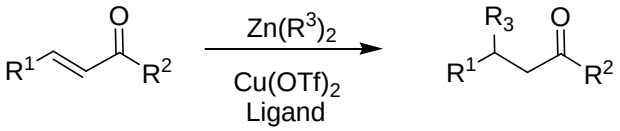
Scheme 3.7

[20] This work has been performed in the laboratory of Professor Simon Woodward, University of Nottingham, UK.

The nucleophile in this scheme is shown with a negative charge, which is neutralized in the addition products by treatment with water. Neutral nucleophiles such as 1º and 2º-amines may also add in the same manner, and do not require a neutralization step. The term "1,4-addition" is applied to the product of conjugate addition (initial nucleophile bonding at the β-carbon) because the product initially formed is presumably the unstable enol tautomer.

Most efforts have been addressed to the development of copper(II)[21] and rhodium(III)[22] asymmetric conjugate addition of various alkylmetal (organozinc reagents[23], organoaluminium reagents[24] and Grignard reagents[25]) and arylboronic acids[26] to cyclic and acyclic unsaturated carbonyls.

A prominent position in the rapid development of this process is occupied by the copper-catalyzed, ligand accelerated, 1,4-addition of organozinc reagents to a range of enones (Scheme 3.8).



Scheme 3.8

Acyclic α,β-unsaturated systems constitute a considerable challenge as it has proven to be much more difficult to obtain high enantioselectivity with these types of substrates.

Despite the synthetic importance of this promising catalytic process, as yet relatively few mechanistic studies have been reported on enantioselective copper-catalyzed addition reactions of dialkylzinc reagents.[27] No detailed mechanistic or structural study concerning the combination of ligands with copper salts and dialkylzinc reagents has been published to date,

---

[21] a) Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem.* **2002**, 3221; (b) Krause, N.; Hoffman-Ro¨ der, A. *Synthesis* **2001**,171; (c) Ferringa, B. L. *Acc. Chem. Res.* **2000**, *33*, 346.

[22] Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829.

[23] For recent examples, see: (a) Mizutani, H.; Degrado, S. J.; Hoveyda, A. H. *J. Am. Chem. Soc*. **2002**, *124*, 779; (b)Krauss, I. J.; Leighton, J. L. *Org. Lett*. **2003**, *5*, 3201; (c) Clavier, H.; Coutable, L.; Guillemin, J. C.; Mauduit, M. *Tetrahedron: Asymm.* **2005**, *16*, 921.

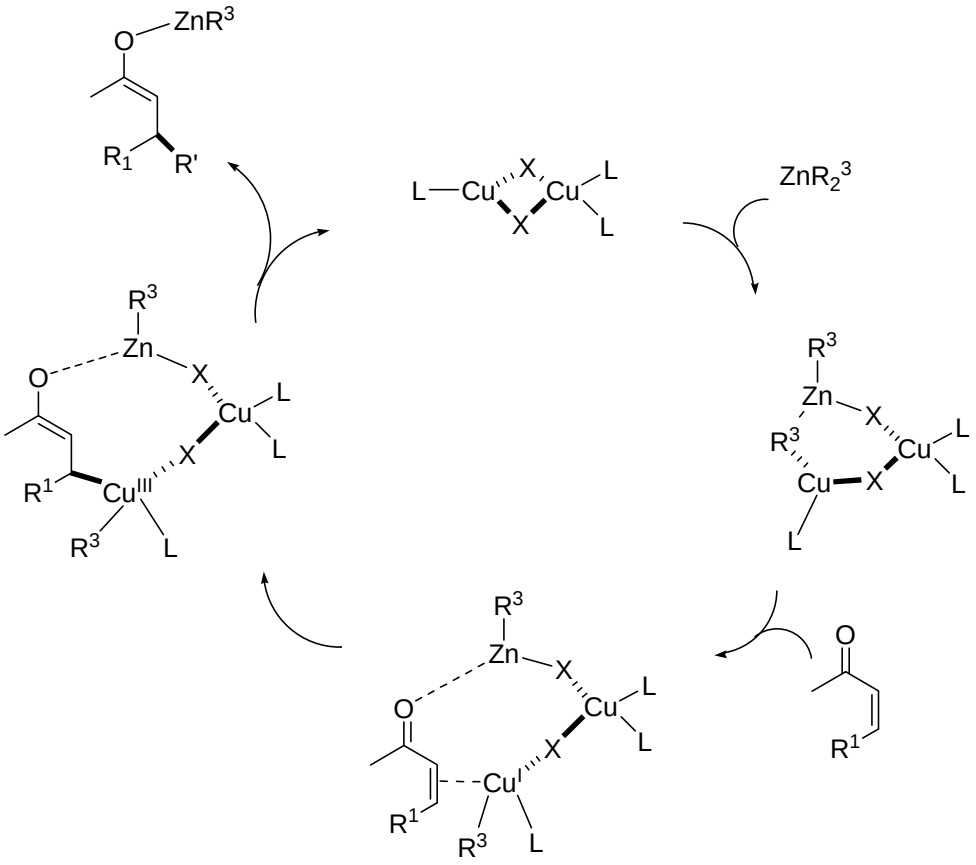
[24] For examples, see: (a) Die´gez, S. M.; Deeremberg, O.; Claver, C.; Van Leeuwen, P. W. N. M.; Kramer, P. *Tetrahedron: Asymm.* **2000**, *11*, 3161; (b) Fraser, P. K.; Woodward, S. *Chem. Eur. J*. **2003**, *9*, 776; (c) D'Augustin, M.; Palais, L.; Alexakis, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1376.

[25] For examples, see: (a) Lopez, F.; Harutyunyan, S. R.; Meetsma, A.; Minaard, A. J.; Feringa, B. L. *Angew. Chem.*,
Int. Ed. **2005**, *44*, 2752; (b) Lee, K.-S.; Brown, M. K.; Hird, A. W.; Hoveyda, A. H. *J. Am. Chem. Soc*. **2006**, *128*, 7182; (c) Martin, D.; Kehrli, S.; D'Augustin, M.; Clavier, H.; Mauduit, M.; Alexakis, A. *J. Am. Chem. Soc.*,**2006**, *128*, 8416.

[26] Takaya, Y.; Ogasawara, M.; Hayashi, T. *J. Am. Chem. Soc*.**1998**, *120*, 5579

[27] (a) M. Kitamura, T. Miki, K. Nakano, R. Noyori, Bull. Chem. Soc. Jpn., **2000**, *73*, 999; (b) K. Nakano, Y. Bessho, M. Kitamura, Chem. Lett. **2003**, *32*, 224; (c) T. Pfretzschner, L. Kleemann, B. Janza, K. Harms, T. Schrader, Chem. Eur. J. **2004**, *10*, 6048.

but some mechanisms has been postulated.[28] The current mechanistic view is that as a first step, a transmetalation between the organometallic compound and the copper species takes place (Scheme 3.9).



Scheme 3.9 *Proposed catalytic cycle for the copper-catalyzed 1,4-addition of dialkyl zinc to enone*

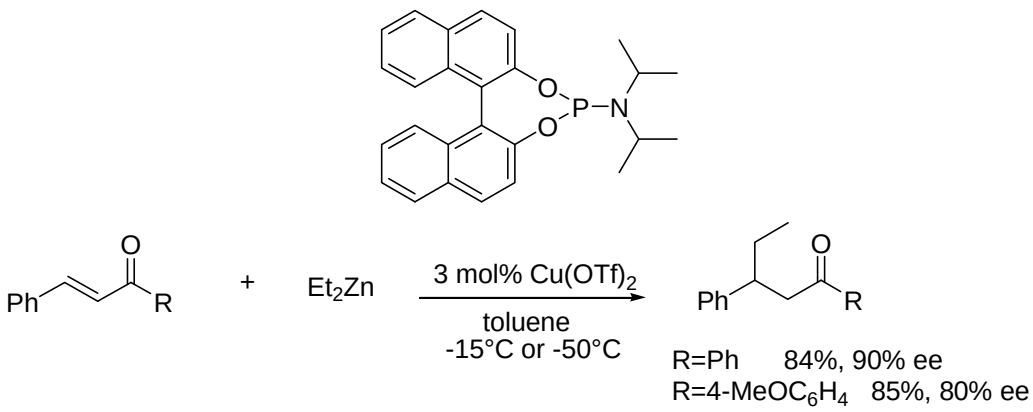
The cycloaddition itself is postulated to proceed through reversible formation of a copper(I)–alkene complex, followed by an oxidative addition to give a copper(III) species and finally a reductive elimination to form the enolate.

The widely accepted opinion that two ligands at one copper center are present in the active catalyst is based on the facts that at an optimum ligand-to-copper ratio of 2:1, nearly identical selectivities with mono- and bidentate ligands are obtained (except with cyclopentenones)[29] and nonlinear effects are observed. In contrast, Alexakis proposed a catalytic cycle with only

[28] (a) A. Alexakis, C. Benhaim, S. Rosset, M. Humam, J. Am. Chem. Soc., **2002**, *124*, 5262, L. A. Arnold, R. Imbos, A. Mandoli, A. H. M. de Vries, R. Naasz, B. L. Feringa, Tetrahedron **2000**, *56*, 2865.
[29] A. H. M. de Vries, A. Meetsma, B. L. Feringa, Angew. Chem. **1996**, *108*, 2526;

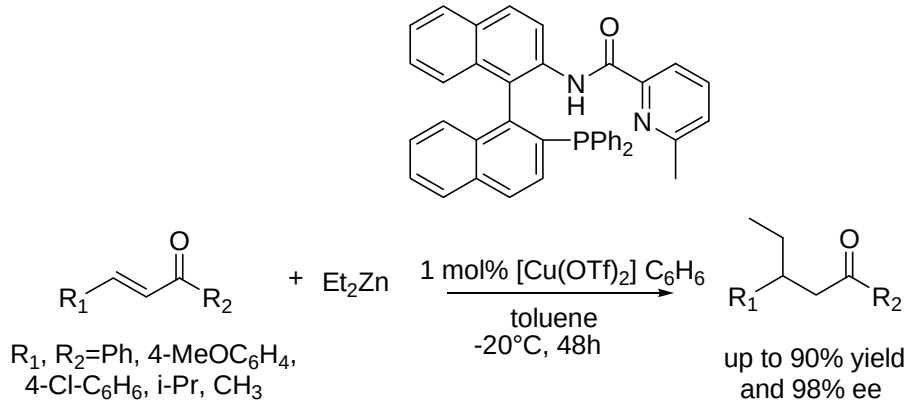
one ligand attached to copper, and synthetic optimization procedures showed that only ligand-to-copper ratios below 1.5:1, and not below 2:1, were detrimental to the catalysis.[30]

As for the best ligands used in this reaction, BINOL-based phosphoramidites were the first class of chiral ligands reported to achieve high enantioselectivities in the copper catalyzed conjugate addition of organozinc reagents to acyclic substrates (Scheme 3.10).[31]



Scheme 3.10

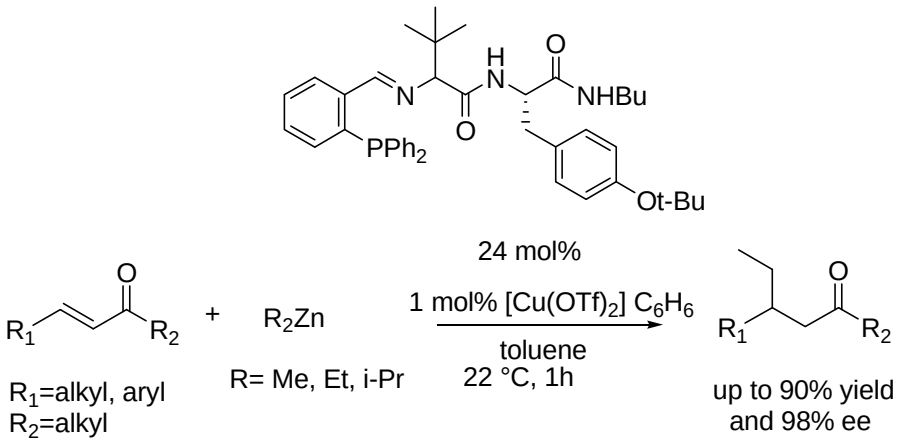
The addition of Et_2Zn to chalcone in the presence of $Cu(OTf)_2$ and a chiral ligand in a ratio of 1:2 afforded the desired product in 84% yield and with 90% ee (Scheme 3.10). A further improvement in the enantioselective addition of Et_2Zn to chalcone and its derivatives was achieved using the P,N chiral ligand depicted in Scheme 3.11, in combination with $[Cu(OTf)]_2 \cdot C_6H_6$.[32] However, long reaction times (48 h) are required.



Scheme 3.11

[30] A. Alexakis, C. Benhaim, Eur. J. Org. Chem. **2002**, 3221.
[31] de Vries, A. H. M.; Meetsma, A.; Feringa, B. L. *Angew. Chem. Int. Ed. Engl*. **1996**, *35*, 2374;
[32] Hu, X.; Chen, H.; Zhang, X. *Angew.Chem. Int. Ed*. **1999**, *38*, 3518;

Employing a new class of chiral diphenyl phosphine ligands, Hoveyda and coworkers[33] extended in 2002 the scope of the copper-catalyzed conjugate addition to linear α,β-unsaturated ketones to a wide range of dialkylzinc reagents. The copper complex of the chiral dipeptide phosphine ligand afforded the 1,4-products in moderate to high yields (42%-93%) and high enantioselectivities (up to 95%) (Scheme 3.12).



Scheme 3.12

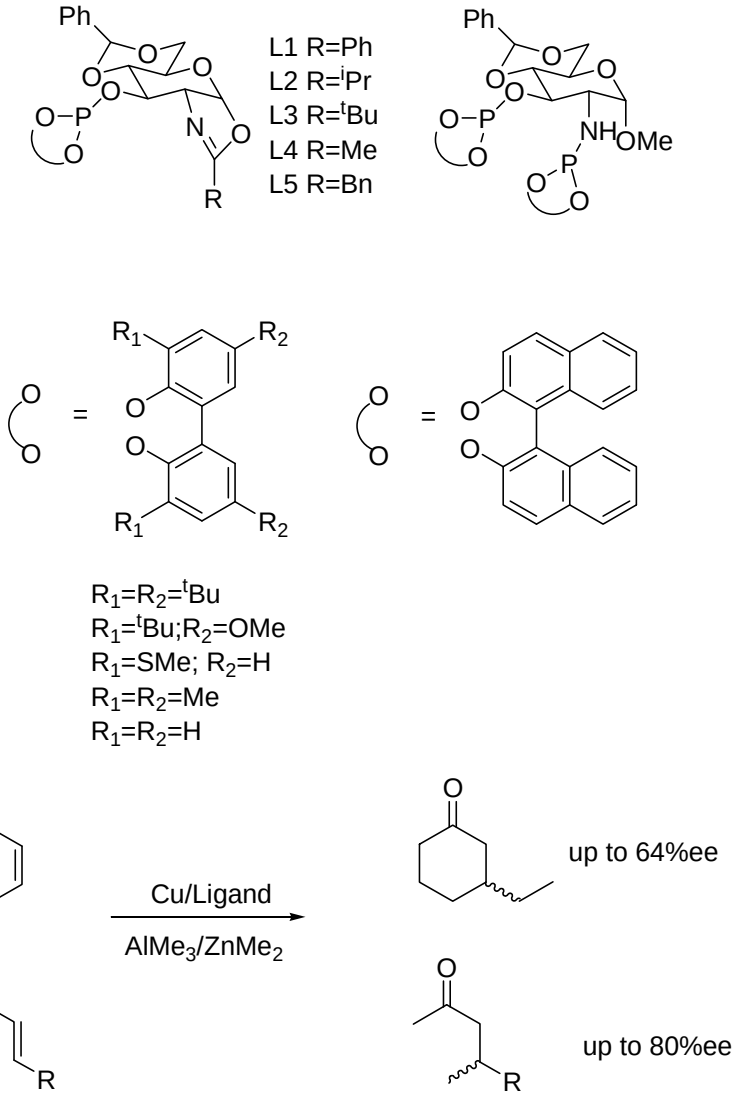
Since this report, several other chiral ligands for the copper catalyzed conjugate addition of dialkylzinc reagents to α,β-unsaturated ketones have been described.[34]

It should be noted that recent attempts to apply some ligands derived from carbohydrates to asymmetric conjugate addition (ACA) reactions were not as successful (Scheme 3.13).[35]

[33] Mizutani, H.; Degrado, S. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 779.

[34] a) Alexakis, A.; Benhaim, C.; Rosset, S.; Humam, M. *J. Am. Chem. Soc.* **2002**, *124*, 5262; b) Shintani R.; Fu, G. C. *Org. Lett.* **2002**, *4*, 3699; c) Hu, Y.; Liang, X.; Wang, J.; Zheng, Z.; Hu, X. *Tetrahedron: Asymm.* **2003**, *14*, 3907; d) Duncan A. P.; Leighton, J. L. *Org. Lett.* **2004**, *6*, 4117; e) Ito, K.; Eno, S.; Saitob, B. Katsuki, T. *Tetrahedron Lett.* **2005**, *46*, 3981; f) Takahashi, Y.; Yamamoto, Y.; Katagiri, K.; Danjo,H.; Yamaguchi, K.; Imamoto, T. *J. Org. Chem.* **2005**, *70*, 9009.

[35] (a) Meta Y., Diéguez M., Pàmies O., Woodward S., *J. Organomet. Chem*. **2007**, *692*, 4315. (b) Mata Y., Diéguez M., Pàmies O., Woodward S., *Inorg. Chim. Acta* **2008**, *361*, 1381; c) Mata Y., Diéguez M., Pàmies O., Biswas K., Woodward S., *Tetrahedron Asymm.***2007**, *18*, 1613.



Scheme 3.13 *Phosphite–oxazoline and phosphite–phosphoroamidite ligand libraries.*

On these grounds we have decided to explore the unprecedented use of amino-sugar based ligands developed by us in such ACA transformations.

The sugar ligands used for this reaction are shown in Figure 3.7. The phosphinoamido-phosphinoester ligands have been prepared due to the already mentioned balance between synthetic approach and expected performance.

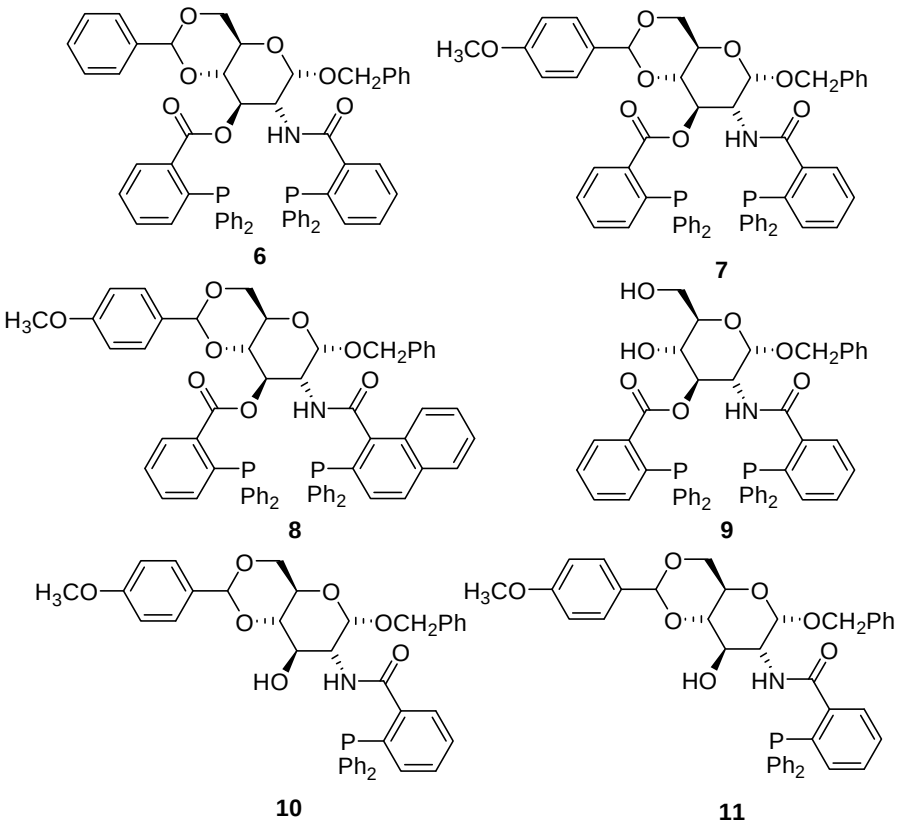


Figure 3.7

The amino-sugar family **6-11** have been also compared against the amino-sugar precursors **3G** and **3G'**

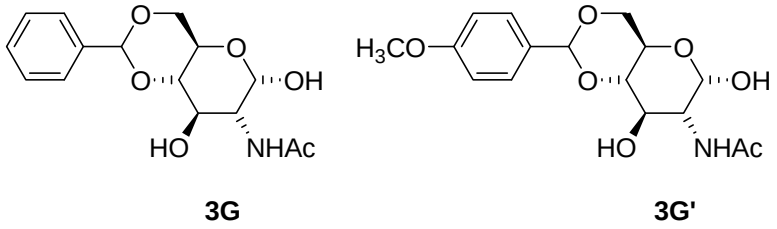


Figure 3.8

and the nearest commercial analogues of such architectures the 'Trost ligands' indicated with numbers **12** and **13** (Figure 3.9).

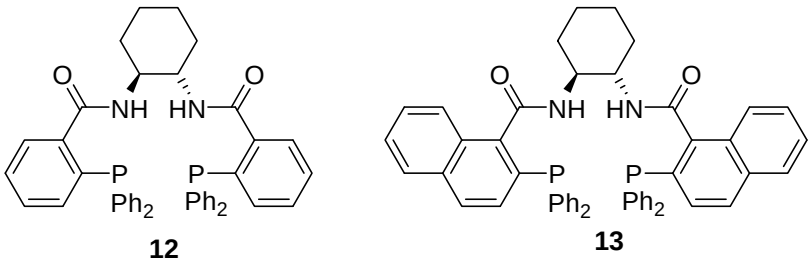
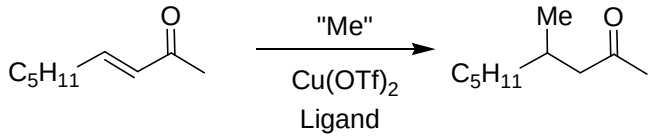


Figure 3.9

3.2.1 *Results and discussion*

Initially, the library of ligands shown in paragraph 3.2 is screened in demanding additions of methyl nucleophiles to (*E*)-nonen-2-one (Table 3.4).



entry	*ligand*	*MeSource*	*yield(%)*	*ee(%)*
a	**7**	$AlMe_3$	<5	-
b	**7**	$AlMe_3$	<5	-
c	**7**	$ZnMe_2$	70	95(R)
d	**8**	$ZnMe_2$	10	17(S)
e	**9**	$ZnMe_2$	25	53(S)
f	**3G**	$ZnMe_2$	<5	-
g	**3G'**	$ZnMe_2$	<5	-
h	**10**	$ZnMe_2$	78	61(S)
i	**11**	$ZnMe_2$	75	92(R)
j	**12**	$ZnMe_2$	<5	-
k	**13**	$ZnMe_2$	<5	-

Table 3.4

Reactions are performed at 298K for 12 hours in dry THF for the first two cases (entry a and b), in toluene for all others. The substrate/catalyst ratio used is of 40/1. After 2 h, the reaction is quenched with HCl (2M) and the appropriate internal standard is then added. The organic layer filtered twice through a plug of silica. Yields and enantiomeric excesses are measured by GC.

No activity for 1,4-additions of $AlMe_3$ has been found, the behavior of ligand **7** and **11** are representative of all the ligands tried.

The situation with $ZnMe_2$ is radically different:

- In toluene and the presence of the air-stable, non-hygroscopic Cu^{I} precursor $Cu(OTf)_2$ the amino-sugar library conforme as expected delivering >24:1 stereoselectivities with ligands **7** and **11**. The attainment of such selectivites in all alkyl substrates is rare.[36]

- The presence of the phosphorus donor (**7** and **11** *vs*. **3G** and **3G'**) is vital as is the inclusion of an *O,N*-linker set as opposed to *N,N* versions (**7** *vs.* the 'Trost' ligands **12** and **13**).

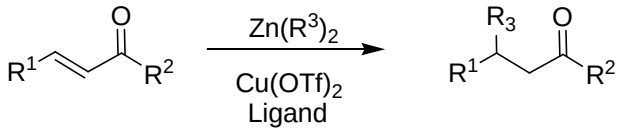
- Previously, Woodward proposed that the presence of appropriately placed free hydroxide functions in bimetallic cuprate complexes can be beneficial.[37] Removal of the diphenylphosphinobenzoic ester fragment lead to a highly significant reversal in the stereoselectivity: +95 to -61% ee (**7** *vs*. **10**). However, removal of the 4,6-acetal unit lead to a loss in selectivity (**7** *vs*. **9**).

- Trost ligands **12** and **13** don't show any activity in this catalytic reaction under the used experimental conditions. This result demonstrates that the sugar backbone is essential for the outcome of the reaction. In fact, it is plausible that, beside coordination of copper through P, there is also an interaction between the oxygen atoms of the sugar ring and Zn.

The generality of the best ligand archetectures has been further tested against a range of demanding substrates (Table 3.5).

[36] Reviews: Alexakis A., Bäckvall J. E., Krause N., Pàmies O., and Diéguez M., *Chem.Rev.*, **2008**, *108*, 2796. (b)Harutyunyan S. R., den Hartog T., Geurts K., Minnaard A. J., and Feringa B. L., *Chem. Rev.*, **2008**, *108*, 2824. Specific cases: (c) Mizutani H., Degrado S. J., Hoveyda A. H., *J. Am. Chem. Soc.*, **2002**, *124*, 779. (d) Hajra A., Yoshikai N.,. Nakamura E, *Org. Lett.*, **2006**, *8*, 4153. (e) Lòpez F., Harutyunyan S. R., Minnaard A. J., Feringa B. L., *J. Am. Chem. Soc.*, **2004**, *126*, 12784.

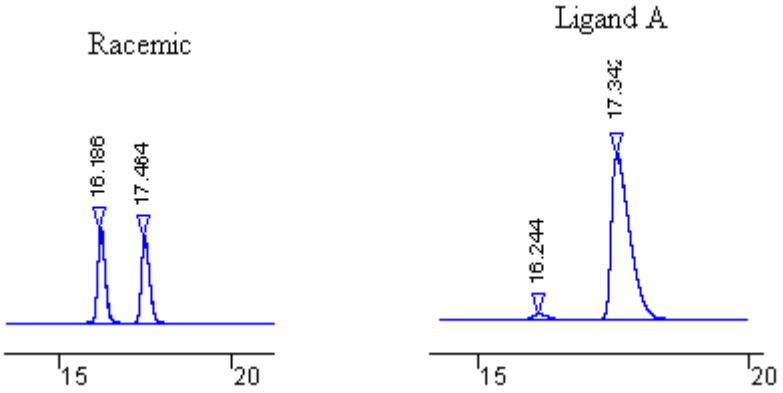
[37] Woodward S., *Synlett*, **2007**, 1490.



entry	*ligand*	R_1	R_2	R_3	*yield(%)*	*ee(%)*
a	**7**	C_5H_{11}	Me	Me	70	95(R)
b	**11**	C_5H_{11}	Me	Me	75	92(R)
c	**7**	C_5H_{11}	Me	Et	80	91(R)
d	**11**	C_5H_{11}	Me	Et	80	87(R)
e	**7**	C_6H_{13}	Me	Me	57	91(R)
f	**11**	C_6H_{13}	Me	Me	52	90(R)
g	**7**	C_6H_{13}	Me	Et	95	93(R)
h	**11**	C_6H_{13}	Me	Et	99	90(R)
i	**7**	Pr^i	Me	Me	47	89(R)
j	**11**	Pr^i	Me	Me	33	94(R)
k	**7**	Pr^i	Me	Et	79	93(R)
l	**11**	Pr^i	Me	Et	66	88(R)
m	**7**	Me	Et	Et	65	67(S)
n	**11**	Me	Et	Et	78	91(S)

Table 3.5

It is found that the most successful ligands **7** and **11** are effective for the addition of both $ZnMe_2$ and $ZnEt_2$ to a class of enones possessing only aliphatic substituents with minimal steric profiles. In general, for all substrates, ligand **7** gives better yields and enantioselectivities. The chromatogram of the best catalytic tests with ligands **7** (entry a) is reported below.



An exception is ligand **11,** which gives a superior result in $ZnMe_2$ addition to the branched enone $R^1 = Pr^i$ (run j). The selectivity is also affected by the presence of a bigger substituent R^2. Infact when both R^2 and R^3 both increas steric profile, only ligand **11** gives good results (run m and n).

3.2.2 *Experimental section*

All experiments were carried out under an argon atmosphere using standard Schlenk techniques. Toluene was distilled on Na/benzophenone. ^{1}H and ^{13}C NMR spectra were recorded on JEOL EX270, Bruker 400. For all other samples δ values were referenced to residual $CDCl_3$. All *J* values are in Hz. Specific optical rotatory powers [α] were measured with a ADP 440 Polarimeter in dichloromethane (c= 1.0 g/100 mL). Enantioselectivities were determined by chiral GC. GC analyses were performed on a Varian 3900 gas chromatograph using an octakis (6-*O*-methyl-2,3-di-*O*-pentyl)-γ-CD column under the conditions given. Yields were determined by calibration against authentic samples using undecane or dodecane as an internal standard. Thin layer chromatography (TLC) was performed on Merck silica gel 60 $F_{254+366}$ pre-coated plates (0.25 mm) silica. The plates were visualised by the use of a combination of ultraviolet light (254 and 366 nm) and/or aqueous potassium permanganate with heating. Liquid chromatography was carried out by forced flow (flash chromatography) with the solvent systems indicated using silica gel 60 (220-240 mesh) supplied by Fluka. The diorganozinc samples used were commercial products from the following sources: $ZnMe_2$ (2.0 M toluene solution; Aldrich) and $ZnEt_2$ (1.0 M hexane solution; Aldrich). All enones were commercially available (Aldrich). The compound 5-methylhex-3-en-2-one was available from Aldrich as a 75-80% mixture with isomeric 5-methylhex-4-en-2-one. This was removed from commercial product by selective MCPBA epoxidation followed by flash chromatography. All other compounds were used as supplied.

Preparation of racemic $ZnEt_2$ addition products

A solution of the copper-catalyst precursor CuTC (1mol%, 0.015 mmol) and the corresponding ligand (2 equiv., 0.03 mmol) in 5 mL of dry diethyl ether was stirred for 12 hours at room temperature. The alkylating organometallic reagent $ZnEt_2$ (1.2 equiv., 3.6 mmol) was added dropwise and then the substrate (3 mmol).

After 12 hours the reaction was quenched with 2M HCl (2 mL). The organic layer was filtered twice through a plug of silica and dried.

Preparation of racemic $ZnMe_2$ addition products

To a suspension of CuI (5 mmol) in diethyl ether 25 ml at 268K was added MeLi (2 eq., of a 1.6M solution in hexane, 10 mmol), dropwise. The cloudy yellow mixture was allowed to warm at 0°C over a 30 min period, affording a clear solution. The flask was cooled at 195K and a solution of enone (3.2 mmol) in diethyl ether was added dropwise. The mixture was

kept at 273K and became again yellow. The reaction was quenched with 2M HCl and the product was extract with diethyl ether.

Table 3.6 describes the columns and conditions used to determine the ee value from the catalytic reactions.

R1	***R2***	***R3***	***Column***	***Programme***	***Retention times/mins***
C_5H_{11}	CH_3	CH_3	6-Me-2,3-pe-γ-CD	60 °C isothermal	*S* 16.2
					R 17.5
C_5H_{11}	CH_3	CH_2CH_3	6-Me-2,3-pe-γ-CD	60 °C isoterma	*S* 30.0
					R 31.1
C_6H_{13}	CH_3	CH_3	6-Me-2,3-pe-γ-CD	60 °C isothermal	*S* 33.9
					R 35.9
C_6H_{13}	CH_3	CH_2CH_3	6-Me-2,3-pe-γ-CD	60 °C isothermal	*S* 64.0
					R 65.9
Pr^i	CH_3	CH_3	6-Me-2,3-pe-γ-CD	60 °C isothermal	*S* 8.75
					R 9.65
Pr^i	CH_3	CH_2CH_3	6-Me-2,3-pe-γ-CD	60 °C isothermal	*S* 12.4
					R 12.9
CH_3	CH_2CH_3	CH_2CH_3	6-Me-2,3-pe-γ-CD	60 °C isothermal	*S* 9.87
					R 11.0

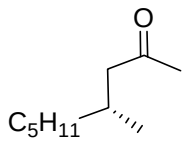
6-Me-2,3-pe-γ -CD is 25 m octakis(6-*O*-methyl-2,3-di-*O*-pentyl)-γ-cyclodextrin 0.25 μm internal diameter (60% in OV1701, w/w).

Catalytic Reaction: General procedure for additions to enones

A solution of the copper-catalyst precursor $Cu(OTf)_2$ (1mol%, 0.003 mmol) and the corresponding ligand (2.5 equiv., 0.0075 mmol) in 2 mL of dry toluene was stirred for 30 minutes at room temperature. The alkylating organometallic reagent ZnR_2 (2 equiv., 0.24 mmol) was added dropwise and then the substrate (0.12 mmol).

After 12 hours the reaction was quenched with 2M HCl (2 mL). Undecane or dodecane (10 μL) was then added as internal standard and the organic layer filtered twice through a plug of silica. Yields and enantiomeric excesses were measured by GC using a octakis (6-*O*-methyl-2,3-di-*O*-pentyl)-γ-CD column.

Chiral GC traces for individual compounds



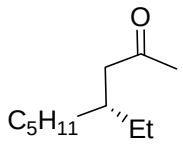
(R)-4-methylnonan-2-one

Literature compound,[38] authenticated by comparison against an existing sample and by ^{1}H NMR (270MHz, $CDCl_3$):δ 2.38 (dd, 1H, CH*H*=COMe,

[38] a) Mizutani H., Degrado S. J., Hoveyda A. H., *J. Am. Chem. Soc*. **2002,** 124, 779; b) Bennett S. M. W., M. Brown S., Cunningham A., Dennis M. R., Muxworthy J. P., Oakley M. A., Woodward S., *Tetrahedron* **2000**, 56, 2847.

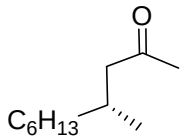
J=15.8, 5.7), 2.22 (dd, 1H, C*H*H=COMe), 2.11 (s, 3H, *Me*CO), 2.0-1.9 (m, 1H, nPentC*H*Me), 1.4-1.1 (m, 8H, (CH_2)$_4$), 0.9-0.88 (m,6H, (CH$_2$)$_4$*Me*, *Me*CH); ^{13}C NMR (400MHz, $CDCl_3$):δ 209.3 (C=O), 51.3, 36.9, 32.0, 30.4, 39.3, 26.6, 22.6, 19.8, 14.1.

(R)-4-ethylnonan-2-one



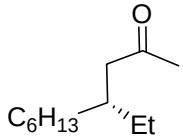
Literature compound,[39] authenticated by comparison against an existing sample and by ^{1}H NMR (270MHz, $CDCl_3$): δ 2.33 (m, 2H, CH_2=COMe, J=7.0Hz), 2.11 (s, 3H, *Me*CO), 1.83 (m, 1H, nPentC*H*Et), 1.31-1.16 (m, 10H, (CH_2)$_4$, CH_2 of Et), 0.88-0.80 (m, 6H, (CH$_2$)$_4$*Me*, CH_3 of Et); ^{13}C NMR (400MHz, $CDCl_3$):δ 209.3 (**C**=O), 48.4, 35.4, 33.5, 32.1, 30.3, 26.4, 26.4, 22.6, 14.0.

(R)-4-methyldecan-2-one



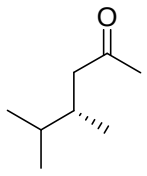
Literature compound,[38b,39]authenticated by comparison against an existing sample and by ^{1}H NMR (270MHz, $CDCl_3$): δ 2.40 (dd, 1H, CH*H*=COMe, J=16, 5.7), 2.22 (dd, 1H, C*H*H=COMe), 2.13 (s, 3H; *Me*CO), 1.89 (m, 1H; nHexC*H*Me), 1.1-1.35 (m, 10H, (CH_2)$_5$), overlapped by 0.89 (m, 6H, *Me*CH, (CH$_2$)$_5$*Me*); ^{13}C NMR (400MHz, $CDCl_3$): δ 209.6 (C=O), 51.7, 37.3, 32.3, 30.8, 29.8, 29.7, 27.3, 23.0, 20.2, 14.5.

(R)-4-ethyldecan-2-one



Literature compound,[40] authenticated by comparison against an existing sample and by ^{1}H NMR (270MHz, $CDCl_3$): δ 2.33 (m, 2H, CH_2=COMe, J=7.0Hz), 2.14 (s, 3H, *Me*CO), 1.83 (m, 1H, nHexC*H*Et), 1.31-1.16 (m, 12H, (CH_2)$_5$, CH_2 of Et), 0.88-0.80 (m, 6H, (CH$_2$)$_4$*Me*, C$H_3$of Et);^{13}C NMR (400MHz; $CDCl_3$): δ 209.7 (**C**=O), 48.4, 35.4, 33.5, 32.0, 30.4, 29.6, 26.6, 26.4, 22.7, 14.0, 10.83.

(R)-4-methyl-5-methylhexan-2-one

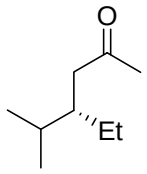


Literature compound,[41] authenticated by comparison against an existing sample and by ^{1}H NMR (270MHz, $CDCl_3$): δ 2.20 (dd, 1H, CH*H*=COMe, J=16, 5.4), 2.18 (dd, 1H, C*H*H=COMe), 2.15 (s, 3H; *Me*CO), 1.90 (m, 1H; C*H*(Me)$_2$),

[39] Fraser P. K.and Woodward S., *Chem. Eur. J.* **2003**, *9*, 776.
[40] Alexakis A., Benhaim C., Humam M., Rosset S.**,** *J. Am. Chem. Soc.* **2002,** *124*, 5262.
[41] Börner C., Dennis M. R., Sinn E., Woodward S., *Eur. J. Org. Chem.* **2001**, 2435.

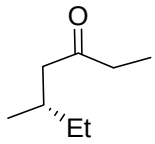
overlapped by 0.86 (m, 6H, *Me*$_2$CH, *Me*), ^{13}C NMR (400MHz, CDCl3) δ= 209.5 (C=O), 48.5, 34.75, 32.2, 30.4, 19.8, 18.4, 16.0.

(R)-4-ethyl-5-methylhexan-2-one



Literature compound,[42] authenticated by comparison against an existing sample and by ^{1}H NMR (270 MHz, $CDCl_3$)**:** δ 2.40 (dd, 1H, CH*H*=COMe, J= 16.0Hz, 5.6Hz), 2.25 (dd, 1H, C*H*H=COMe, J=16Hz, J=7.6Hz), 2.15 (s, 3H; *Me*CO), 1.80-1.65 (m, 2H, C*H*Me$_2$ and C*H*Et), 1.38-1.30 (m, 1H, CH*H* of Et), 1.16-124 (m, 1H, C*H*H of Et), 0.90 (t, 3H, C*H*$_3$ of Et, J= 7.4Hz), 0.86 (t, 3H, *Me*CHMe, J= 7.4Hz), 0.82 (t, 3H, MeCH*Me*, J= 7.0Hz); ^{13}C (270MHz; CDCl3) 209.6 (**C**O), 45.1, 41.1, 30.3, 29.3, 23.9, 19.5, 18.5, 11.7.

(S)-5-methyl-heptan-3-one



Literature compound,[43] authenticated by comparison against an existing sample and ^{1}H NMR (270MHz, $CDCl_3$)**:** δ 2.43-2.33(m, 1H, CH_3CH_2COCH*H*), 2.18 (dd, 1H, COC*H*HCH J=16Hz, J=7.6Hz), 1.80-1.65 (m, 1H, MeC*H*Et), 1.29-1.16 (m, 4H, CHC*H*$_2$CH$_3$, COC*H*$_2$Me), 1.02 (m, 3H, $COCH_2C$*H*$_3$), 0.88 (m, 6H, CH*Me*, $CHCH_2C$*H*$_3$); ^{13}C (400MHz; CDCl3) 211.9 (**C**O), 49.6, 36.5, 31.0, 29.7, 19.5, 11.3, 7.8. The reversal of the stereochemistry is due to the use of $ZnEt_2$ (vs $ZnMe_2$) and the found selectivity was confirmed by polarimetry vs. the literature.

[42] Alexakis A., Vastra J., Mangeney P., *Tetrahedron Lett.* **1997**, *38*, 7745; Hu X., Chen H., Zhang X., *Angew. Chem. Int. Ed.* **1999**, *38*, 3518; Bennett S. M. W., Brown S. M., Muxworthy J. P., Woodward S., *Tetrahedron Lett.* **1999**, *40*, 1767.
[43] Ahlbrecht H., Schmidt R., Beyer U., *Eur. J. Org. Chem*., **1998**, 1371.

4. Multiphase catalysis

4.1 *State of the Art*

The twelve principles of *Green Chemistry* have played a major role helping to explain what the definition means in practice, ever since they were first propounded by Paul Anastas and John Warner.[1] The chemists Poliakoff M., Tang S.L.I. and Smith R.L. tried to capture the spirit of each of them in the acronym, 'PRODUCTIVELY'[44], as shown below (Figure 4.1):

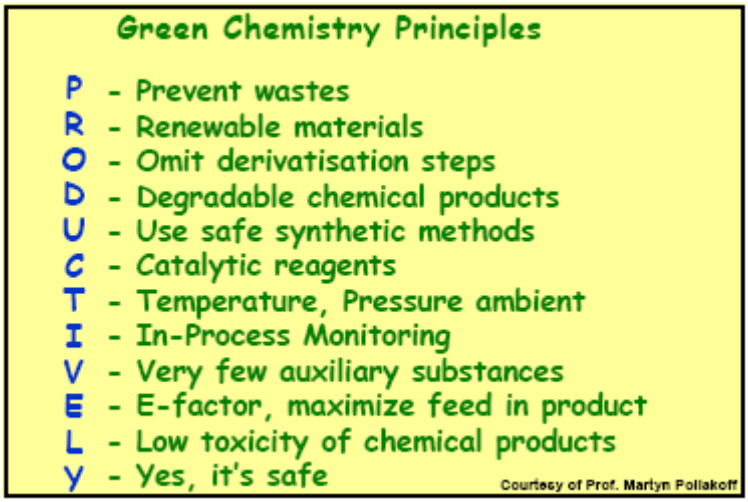


Figure 4.1

As required from the principle that answers to the letter **C**, catalytic processes must be preferred rather than those stecheometric.

For this reason both homogeneous and heterogeneous catalysis hold a fundamental role in the modern chemical industry. Nowaday, about 85% of industrial processes use the heterogeneous catalysis, but it is incontestable that the homogeneous counter-part is finding more and more applications. Certainly, both of them have precise advantages and disadvantages, which are summarized in the following table:

[44] Tang S.L.Y.,Smith R.L., Poliakoff M., *Green Chemistry*, **2005,** *7*, 761.

	Homogeneous	Heterogeneous
Form	Soluble metal complexes, usually mononuclear	Metals, usually supported, or metal oxides
Active site	well-defined, discrete molecules	poorly defined
Phase	Liquid	Gas/solid
Temperature	**Low** (<250°C)	High (250 – 500°C)
Activity	Moderate	**High**
Selectivity	**High**	Low
Diffusion	**Facile**	Can be very important
Heat transfer	**Facile**	Can be problematic
Product separation	Generally problematic	**Facile**
Catalyst recycle	Expensive	**Simple**
Catalyst modification	**Easy**	Difficult
Reaction mechanisms	**Reasonably well understood**	Poorly understood

Table 4.1

Looking at the table it is clear how homogeneous catalysis is more competitive, about yield and selectivity, than heterogeneous catalysis. Moreover, spectroscopic studies make often possible the understanding of the mechanism in homogeneous catalysis; this allows to improve the performance of a reaction with appropriate modifications of the catalyst.

Unfortunately, homogeneous catalysis has an Achilles' heel, frequently insuperable: the difficulty of the catalyst separation from the products and its recycling.

Separation techniques, such as distillation, require an extra energy expenditure and, sometimes, can lead to degradation of both products and catalyst used. As the catalyst requires extraction before a new reaction run can be performed, the 'turn around time' between runs becomes also a prime factor. Moreover, the rise in costs of catalyst recycling is often unsustainable for the production cycle and, above all, its nature is far to satisfy the *Green Chemistry* principles.

This set of factors, that causes the redoubt applicability of homogeneous catalysis to the industrial processes, induced the researchers to find alternative solutions in order to derive profits from the typical benefits of homogeneous catalysis, getting over the problems of catalyst recycling.

A very promising technology, which found industrial applications and keeps on with receiving attention from the researchers is the *Homogeneous Multiphase Catalysis*.

The homogeneous multiphase methodology adopted in the last years regards basically two approaches:

- liquid-liquid biphasic catalysis

- homogeneous supported catalysis

Both of these techniques allow the catalyst recycling and its efficient separation from products. In order to have industrial applicability, they must comprise some fundamental requirements:

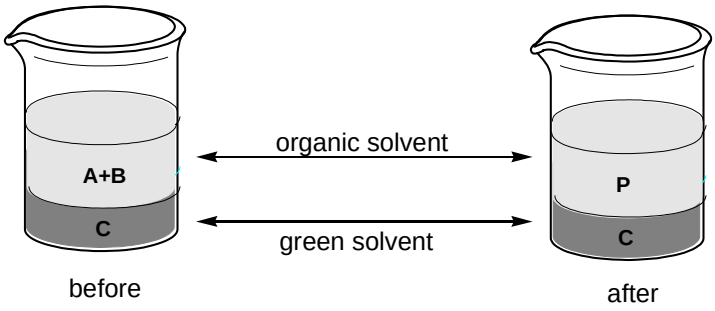
- Metal activity and its catalytic performances must not be forbidden in these new conditions or, at least, they have to be comparable to the metal activity in traditional condition.
- Coordinating centres have to belong to easily derivatizable ligands, in order to have a catalyst suitable for multiphase conditions with few synthetic steps.

4.2 *Liquid-Liquid biphasic catalysis*

In a generic reaction catalyzed by a metal complex C,

$$A + B \xrightarrow{C} P$$

liquid-liquid biphasic systems are built up of two solvents with limited mutual solubility, one that is able to dissolve selectively the catalyst C and other one the product. Reaction between A and B occurs at the biphasic system interface vigorously stirred and, at the end, the catalyst recycling can be achieved through the facile phase separation (Scheme 4.1).



Scheme 4.1

Certain biphasic systems show a sharp phase transition into a homogeneous phase when the temperature is raised. If the resulting homogeneous liquid phase dissolves both the substrates and the catalyst, than a genuine homogeneous catalytic reaction takes place (without limitation of mass transfer at the liquid-liquid phase boundary). After the reaction is completed, the temperature is lowered and the two immiscible liquid phases are obtained again, leading to the easy separation of the catalyst and the products.

In these conditions it is possible to combine the advantages of homogeneous and heterogeneous catalysis, pledging high activity and selectivity and, meanwhile the easy catalyst recycling.

Typically, the product's phase is formed by an organic solvent, while the catalytic phase can be of various kinds.

Vigorous efforts were aimed precisely at finding the most suitable liquids for this purpose, and higher value results have been obtained so far using water, ionic liquids or fluorinated and supercritical solvents which are considered as alternative environment-friendly solvents.

For each of these systems success depends largely on the possibility of giving to the metal complex properties so peculiar to make it selectively soluble only in the catalytic phase. So, the effort is to draw effective catalysts through a right choice of ligands. The golden rule to follow to achieve this goal is probably *similia similibus solvunture* or "like dissolves like ", which means to attach to the metal appropriate solubilizing groups.

4.3 *Biphasic catalysis with ionic liquid*

ILs (Ionic Liquids) are known as a new, unique and exciting class of solvents that could potentially replace volatile organic solvents currently used in large volumes. They have attracted lots of attention since their discovery as a reaction media for catalytic reactions. They are composed of a bulky and organic cation as well as organic or inorganic anions and are liquid at room temperature, mainly due to the large asymmetrical cations preventing close packing of the ions, which can cause their low melting points (Room Temperature Ionic Liquids, RTILs). The most commonly used cations in ionic liquids are based on alkylammonium (1 in Figure 4.2), alkylphosphonium (2), imidazolium (3), pyridinium (4), and many anions, which can be used in combination with cations, such as BF_4^-, PF_6^-, NO_3^- SO_3^-, $(CF_3SO_2)_2N^-$.

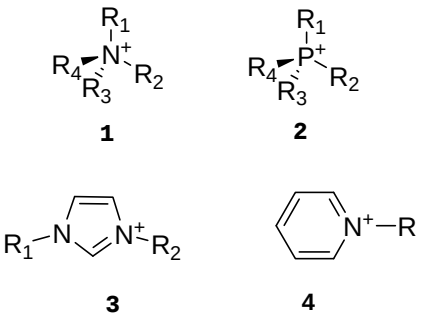


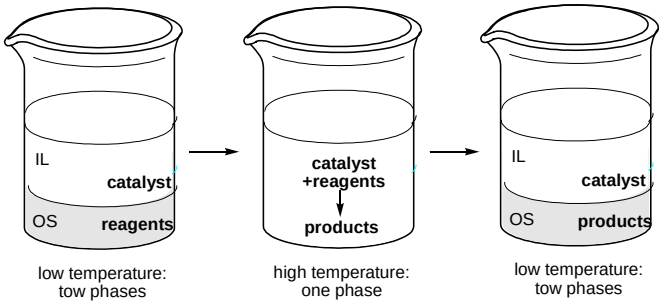
Figure 4.2

ILs are attracting increasing attention from industry because they promise significant environmental as well as product and process benefits. In fact, ILs are classified as "Green Solvents" and some of their physical properties, which make them attractive as potential solvents include:

- Highly polar, non coordinating solvents
- Negligible vapor pressure
- Wide liquid range
- High density
- Immiscibility with a wide range of common organic solvents
- High electrical conductivity
- Tunable physicochemical properties (Designer Solvents)
- High thermal stability
- Non flammability

Making changes to the cation or anion of ILs can result in significant changes in their properties, such as solubility, density, refractive index and viscosity to suit the needs for a specific application.

About their use in catalysis, as solvents, in an plausible scenary the organometallic catalyst maybe easily recovered in the ionic liquid phase, whereas products and unconverted reactants remain in the other one (generally an organic phase). In ideal systems the organic starting materials are miscible with the ionic liquid, but if this is not possible, good contact between the substrate and catalyst may be achieved simply by rapid stirring of the mixture. On completion of the reaction, separation of the organic product from the catalyst layer can be realized simply by allowing the two layers to settle. In this way, straightforward reuse of the transition metal catalyst may be achieved (Scheme 4.2).



Scheme 4.2

Clearly, the success of these separations depends on the possibility to dissolve selectively catalysts, reagents and products in the expected phases. The peculiarity to modulate the ionic liquid properties through the appropriate choice of anion and cation often allows using directly the traditional catalysts, without introducing any additional functional groups to help

the dissolution. However, it was also demonstated that the affinity of a catalyst for an ionic liquid considerably grows increasing the polarity of the ligands.

4.4 *Catalysis in fluorinated solvents*

Fluorinated solvents are perfluoroalkanes $C_n(CH_{2n+2})$ perfluorodialkyl ethers $(C_nF_{2n+1})_2O$, perfluorotrialkylamines $(C_nF_{2n+1})_3N$. These solvents have unusual chemical-physic properties and most of them are the results of the strong stability of C-F bond: hydrophobicity, non-toxicity, high solubility in many gas, remarkable chemical inertness, thermal stability, non flammability, good heat conduction, non toxicity by oral ingestion or inhalation.

Moreover they are characterized by their non polar nature which, combined with poor miscibility with organic solvents at room temperature, makes possible the design of biphase catalytic systems. These are typically formed by a fluorous phase containg preferentially a fluorous soluble catalyst and a second product phase which may be any organic or inorganic solvent with limited solubility in the fluorous phase.

Conventional homogeneous catalysts can be made fluorous soluble by incorporating fluorocarbon moieties into their structure in appropriate size and number. The most effective fluorocarbon moieties are linear or branched perfluoroalkyl chains with high carbon number that may contain heteroatoms (the “fluorous ponytails”). It should be emphasized that perfluoroaryl groups offer dipole-dipole interactions, making the perfluoroaryl containing catalyst soluble in common organic solvents and therefore less compatible with fluorous biphase systems. Fluorous biphase system might become a one phase system by increasing the temperature. Thus, a fluorous catalyst could combine the advantages of one phase catalysis with biphasic product separation by running the reaction at higher temperatures and separating the products at lower temperature (Figure 4.3).

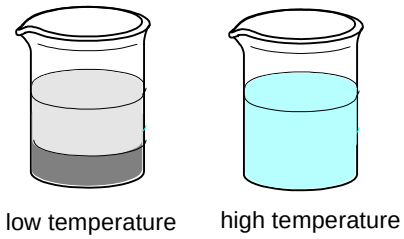


Figure 4.3

Because of the well-known electron-withdrawing properties of fluorine atom, the attachment of fluorous ponytails to conventional catalysts could change significantly their electronic properties and consequently their reactivity. Insertion of insulating groups (such as $–(CH_2)_n$)

before the fluorous ponytail may be necessary to decrease the strong electron withdrawing effects. This is an important consideration if catalyst reactivity is desired to approximate to that observed for unmodified species in hydrocarbon solvents.

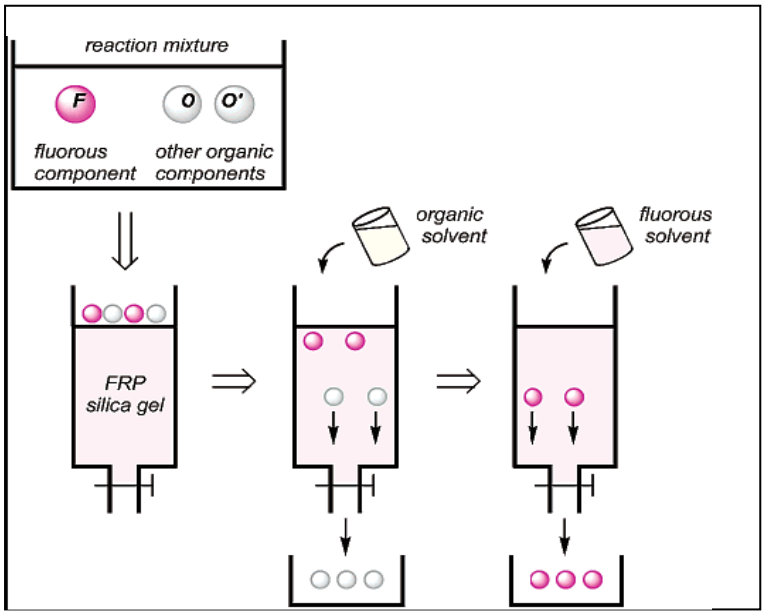
A large number of fluorinated solvents are commercially available but their disadvantage to be more expensive than the common organic solvents restrict their large scale use.

4.5 *Light fluorous catalysis*

It is known in literature that, in order to be totally soluble in a fluorous solvent, a ligand has to contain 60% w/w of fluorine atoms. Nevertheless, a so important fluoruration makes long and hard-working the synthetic strategy because many synthetic steps are required in order to introduce the necessary fluorine atoms. In term of synthetic economy, large importance assume the starting ligand molecular weight, because if it is too big, it is not possible to get the weight percent with few and easy synthetic steps, relating to the available precursor sites.

The light fluorous approach is useful to avoid a complex synthesis because it makes possible to recycling a catalyst which contains 20% w/w of fluorine atoms. In this way ligand synthesis become easy and immediate.

The approach consists in making the catalysis in traditional organic solvents and then, at the end of the reaction, eluting the reaction mixture on a chromatographic column (functionalized with fluorinated silica gel), with fluorophobic solvents (es. THF) in order to recover the product, and with fluorophilic solvents (such as MeOH) to recover and recycle the catalyst (Scheme 2.3).



Scheme 4.3

Fundamental in this case is the appropriate choice of solvents: both of them must not compromise the metal complex stability and have to assure a good phase separation between the product phase and the catalyst phase.

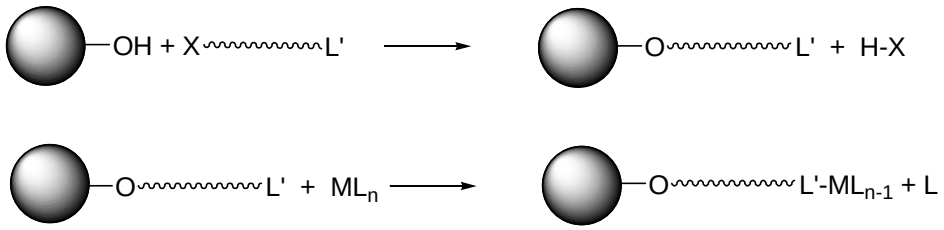
4.6 *Homogeneous supported catalysis*

Supported catalysis involves the immobilization of a homogeneous phase active catalyst to a solid support in order to allow its recycling through an easy phase separation. It is defined *Homogeneous Supported Catalysis* when the heterogeneization is made in such way that the presence of solid support doesn't noticeably influence the metal coordination environment from chemical and stoichiometric points of view.

Solids supports must have some basic requirements to be suitable for the purpose: inertia to many reagents, poor acidity (which may promote secondary reactions), good thermal stability, big superficial area and possession of groups useful for the heterogeneization.

Inorganic used solids are silica, alumina and zeolite. Organic matrices are functionalized polymers (polystyrene-divinylbenzene).

In all cases the presence of surface functional groups, like –OH, makes the use of bifunctional units X------L' possible, such that the group X immediately reacts with the resin's functions and the group L is coordinated to the metal centre. So, X is in general a Cl-, Cl_3Si-, $(OEt)_3Si$-, HO- or $R'_2(OR)Si$-, as shown in the scheme 4.4.



Schema 4.4

4.7 *Ligands for multiphase homogeneous catalysis*

Aiming at extending the use of the ligands in innovative multi-phasic conditions, useful for an effective recycling of the precious metal catalyst, suitable functionalization of C4 and C6 has been performed on ligand **9** as described below.

In particular, it has been prepared ligand **14,** with perfluoroalkyl tails as long to permit their application in light fluorous catalysis and the immobilized ligand **15** for use in "homogeneous supported catalysis".

4.7.1 *Synthesis and characterization of ligand* **14**

Ligand **14** is synthesized by reaction of ligand **9** with three equivalents of trydecafluorononanoic acid (ATDFN) (Figure 4.4).

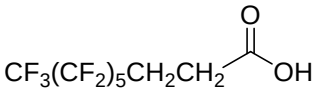
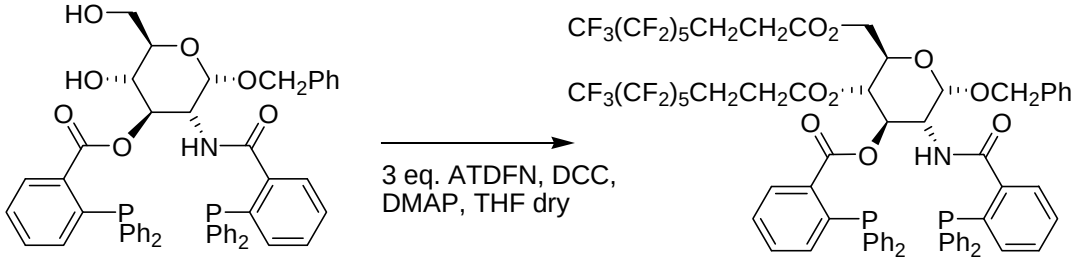


Figure 4.4

The reaction is performed using dry THF with DCC (dicyclohexylcarbodiimide) and DMAP (dimethyilaminopyridine) as activating reagents because they promote the acylation on C4 and C6.



9 **14**

Scheme 4.5

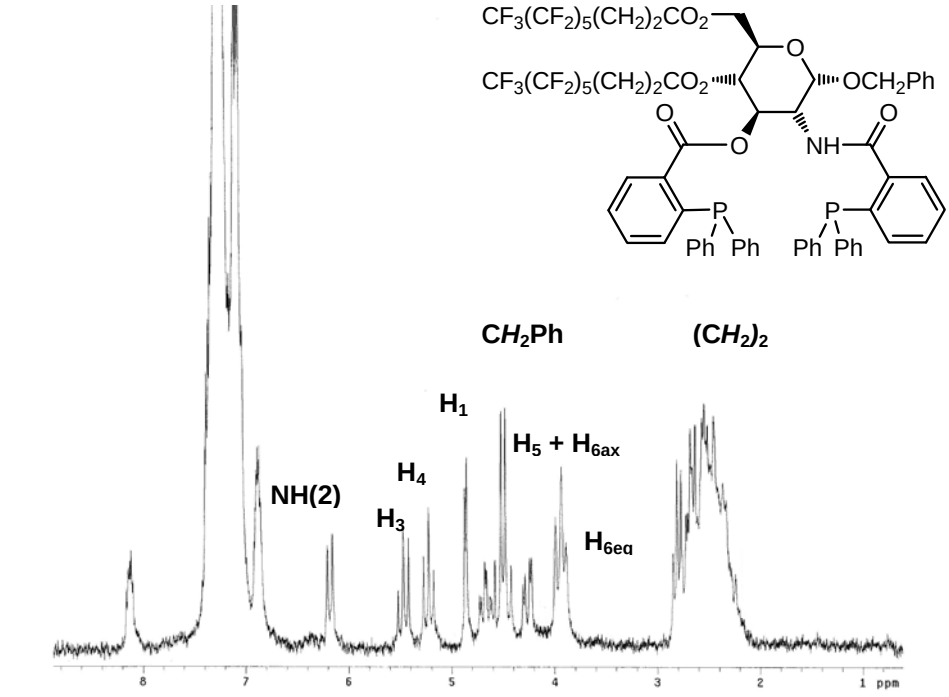
Through this functionalization, ligand **14** acquires 26 fluorine atoms, a fluorine percentage (31%) suitable to be used in multiphasic light fluorous catalysis.

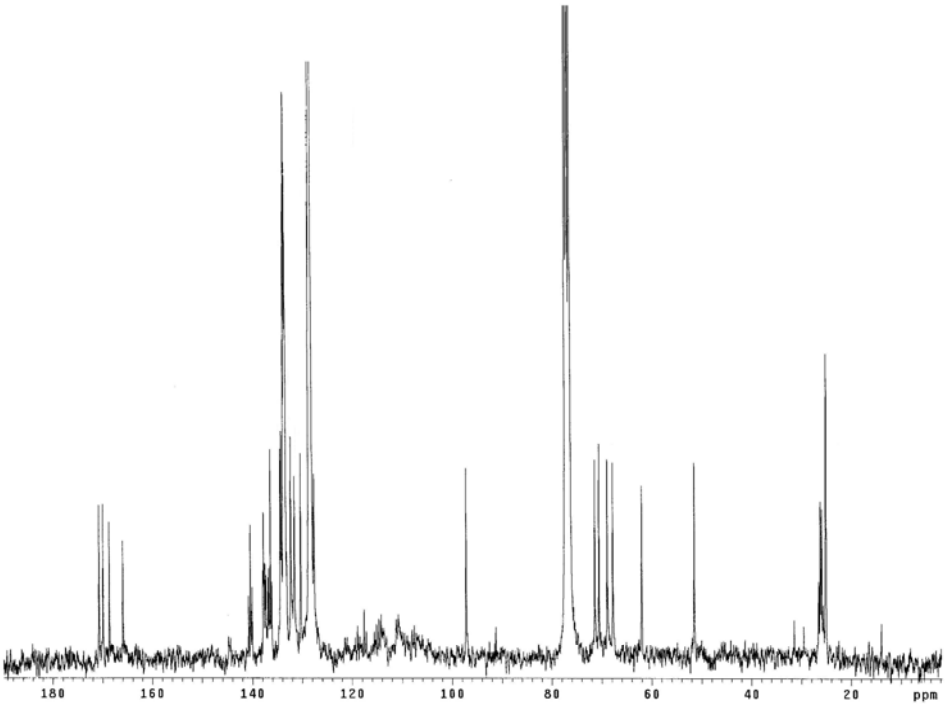
Ligand **14**, purified by column chromatography, is characterized by elemental analysis and NMR ^{1}H and ^{13}C spectroscopy in $CDCl_3$.

Spectra analysis allow to confirm the ligand structures and to check their purity.

Functionalization on 4,6 with perfluoroalkyl chains is pointed out by the high-frequency shift of H4 and $H6_{eq}$ signals at δ 5.23 and δ 4.26 because of the ester.

^{1}H NMR and ^{13}C NMR spectra of ligand 14





4.7.2 *Synthesis and characterization of ligand* **15**

Ligand **15** is synthesized by anchoring the free hydroxyl groups on C4 and C6 of ligand **9** to the solid polymeric matrix ARGOPORE.

This is a polyethylene resin, inserted with PEG and functionalized with 0,7 mmol typical aldehyde loading per gram (Figure 4.5).

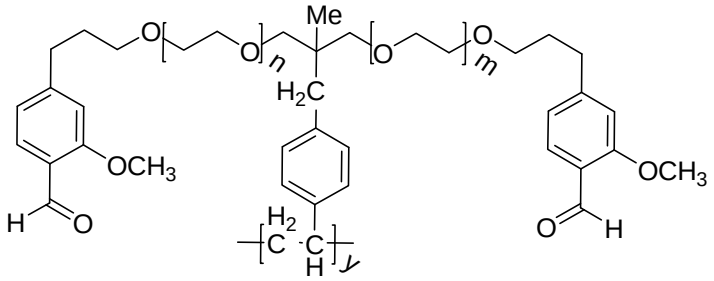
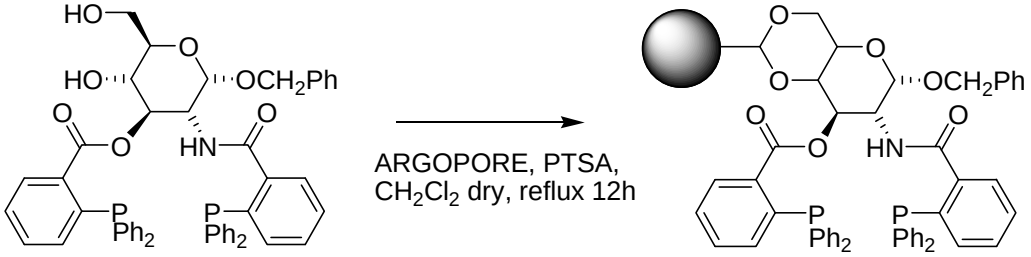


Figure 4.5

The anchorage takes place through formation of an acetal between the resin's aldehydic groups and the hydroxyls 4,6 precursor's positions by treatment with *p*-toluensulfonic acid in dry dichloromethane (Scheme 4.6).

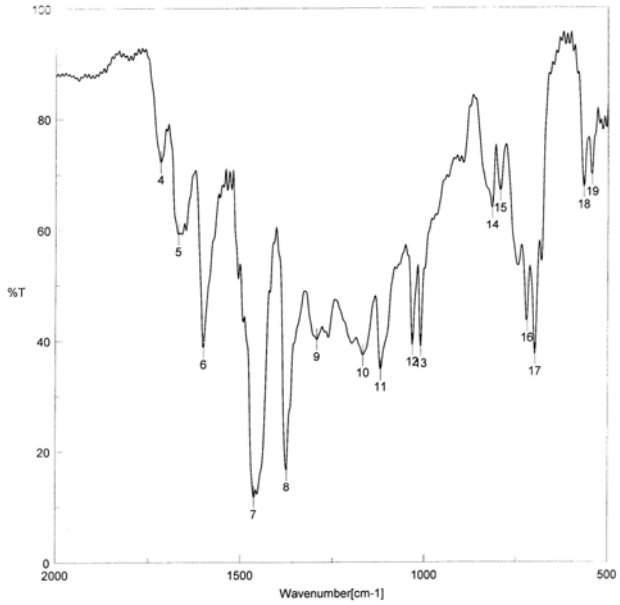


9 **15**

Scheme 4.6

Using this procedure, the coordinating sites are anchored to the solid matrix and combined to the metal sites affording the homogeneous supported catalyst. Confirmation of the successful functionalization of the resin is obtained through IR spectrum, which shows the presence of a peak at 1717 cm^{-1} (peak 4 in the spectrum), analogous to that observed for the free ligand **9**.

IR spectra of ligand **15**



4.8 *Catalytic tests under Multiphasic Homogeneous Conditions*

The reaction selected to test the ligands in *Multiphase Homogeneous Conditions* is the palladium catalysed desymmetrization of *meso*-2-cyclopenten-1,4-diol biscarbamate (Figure 4.6) where high enantioselectivities have been obtained in conventional conditions (Chapter 3).

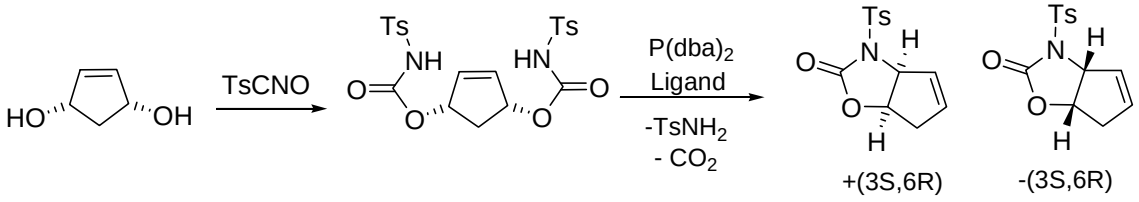


Figure 4.6

In particular, the ligands have been tested both in biphasic catalysis with ionic liquids and in homogeneous supported catalysis.

4.8.1 C*atalysis in ionic liquids*

Ionic liquids are among the most promising green solvents. Generally, their use does not require specific tagging of the catalyst. Nevertheless, on several occasions it has been demonstrated that its affinity for the ionic liquid dramatically improves by enhancing the polarity of the ligands. This also avoids leaching of the catalyst into the organic product phase

and increases the possibility of further recycling of the catalyst. This approach was exploited during this study. In fact, neither protected ligands **6** and **7** nor the original Trost ligand based on cyclohexanediamine show appreciable solubility in the ionic liquid used here, 1-butyl-3-methylimidazolium tetrafluoroborate [BIMIM]BF_4, selected on grounds of economic expediency.

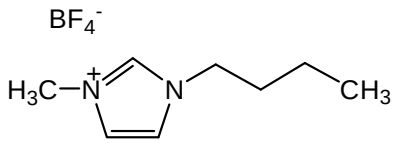


Figure 4.7

Instead, according to our assumptions, the presence of free hydroxyl groups in **9** results in prompt dissolution of the ligand (and of the corresponding Pd complex) in the ionic phase, which allowed the catalytic study to be performed under the desired conditions.

The reactions have been performed in [BIMIM]BF_4 by adding the substrate and triethylamine to a solution of the catalyst at 298 K. After 30 min, the organic product is extracted with diethyl ether and analysed. The catalyst phase is recycled for further runs (Table 4.2).

recycling	*T(K)*	*NEt_3(eqv)*	*t(min)*	*conversion(%)*	*ee(%)*
	298	1	30	99%	53 [-(3R,6S)]
1	298	1	30	99%	50 [-(3R,6S)]
2	298	1	30	99%	47 [-(3R,6S)]
3	258	1	30	99%	50 [-(3R,6S)]

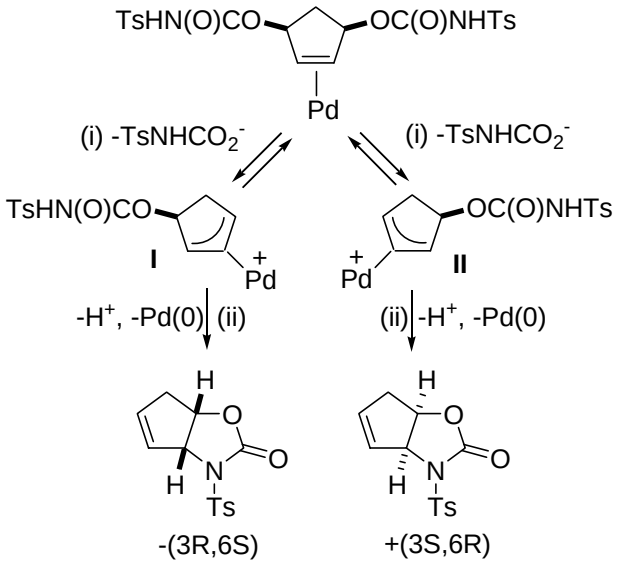
Table 4.2

The first four cycles are completely reproducible, all give high conversions (99%) and similar enantioselectivity. The latter is lower than that observed by using **9** in traditional homogeneous solution (Table 4.2). In successive recycles, the conversion progressively decrease. This trend is similar to that typically found for catalysis in ionic liquids, which is very often inhibited at this point.[45]

It should be noted that no reaction is observed when catalysis is carried out in the absence of triethylamine.

[45] See, for example: Ngo H.L., Hu A., Lin W., *Chem. Commun.* **2003**, 1912

A plausible explanation for the reduced enantioselectivity observed in the ionic liquid can be formulated by considering again the mechanism proposed by Trost for this catalyzed reaction (Scheme 6.1), with particular attention to the addition step:



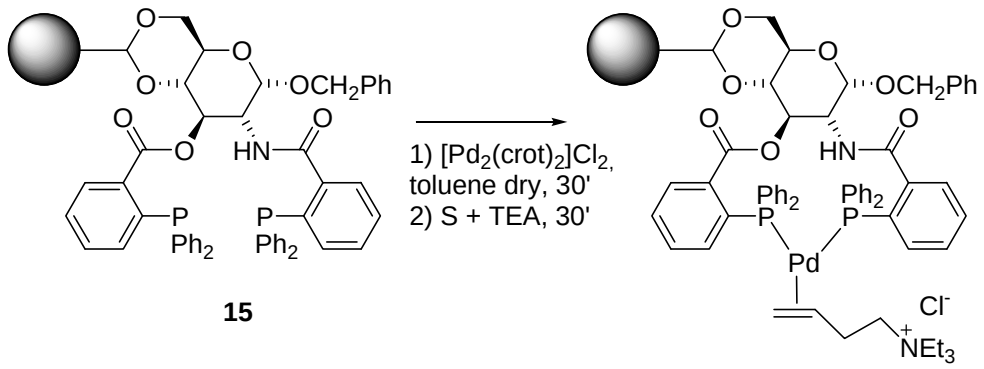
Scheme 4.7

Coordination of the double bond of the substrate is followed by the intramolecular oxidative addition (i) with attainment of the cationic π -allyl complex. This equilibrium reaction can afford two diastereomers I and II, according to the side from which the leaving groups is released. High enantioselectivity is achieved if the kinetically favoured π-allyl diastereomer rapidly undergoes the subsequent intramolecular nucleophilic attack (ii), affording the chiral compound. In THF, it is likely that the intermediate π-allyl compound is poorly stabilised, and its formation is indeed followed by fast attack. This would account for the excellent enantiomeric excess observed under traditional conditions.

On the other hand, the high polarity of the ionic liquid may stabilise the cationic π-allyl intermediate. In this case, the π-allyl diastereomers may equilibrate to their thermodynamic mixture prior to the nucleophilic addition step, with a consequent loss of enantioselectivity. This is also consistent with the lack of reactivity observed in the absence of any external base, which is necessary for promoting the ring closure.

4.8.2 *Homogeneous supported catalytic reactions*

This investigation considered immobilisation of the metal catalyst in a solid matrix as alternative stratagem for helping its separation and recycle.[46] The functionalised ligand **15** [47] is palladated by reaction with $[Pd_2(crot)_2]Cl_2$ and triethylamine (Scheme 4.8).



15

Scheme 4.8

The freshly prepared catalyst is immediately used for catalysis, which is carried out by adding the substrate and triethylamine to a THF suspension of the resin at 298 K. After each run, the resin is filtered, washed with THF, and reused.

recycling	*T(K)*	*NEt_3(eqv)*	*t(hours)*	*conversion(%)*	*ee(%)*
	298	1	2	99%	80 [-(3R,6S)]
1	298	1	2	99%	60 [-(3R,6S)]

Table 4.3

The results obtained can be summarised as follows:

- In the first two runs, the reactions are complete within 2 h, that is, slightly slower than those observed in the traditional solvent (Table 3.3).

- The enantioselectivity of the reaction decrease from 80% for the first run to 60% for the second run.

- The performance of the catalyst in successive cycles is more irregular in both yield and enantioselectivity. Complete conversion is generally achieved within 4 hours. In all cases, a significant lowering of performance is observed.

[46] For recent reviews, see: (a) Choplin A., Quignard F., *Coord. Chem. Rev.* **1998**, *178-180*, 1679; (b) Q.-H Fan, Y.-M. Li, A.S.C. Chan, *Chem. Rev*. **2002**, 102, 3385; (c) S. Kobayashi, R. Akiyama, *Chem. Commun.* **2003**, 449; (d) P. Mastrorilli, C.F. Nobile, *Coord. Chem. Rev.* **2004**, *248*, 377; (e) P. McMorn, G.J. Hutchings, *Chem. Soc. Rev.* **2004**, *33*, 108; (f) M. Heitbaum, F. Glorius, I. Escher *Angew. Chem. Int. Ed.* **2006**, *45*, 4732.

[47] Matta K.L.,. Johnson E.A.Z, Barlow J.J., *Carbohydr. Res.* **1974**, *32*, 396.

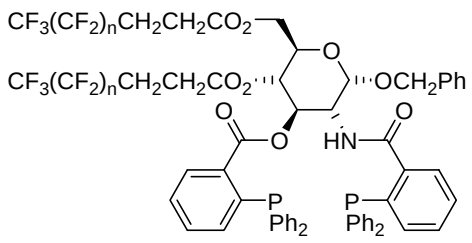
Though the results are less constant than under the other conditions described before, we wish to emphasize that these results demonstrate the possibility to recycle the catalyst also under supported conditions and thus validate the scope of the proposed strategy.

4.8.3 *Experimental section*

All experiments were carried out under an argon atmosphere using standard Schlenk techniques. THF was distilled on Na/benzophenone. ^{1}H and ^{13}C NMR spectra were recorded on Varian-Gemini 300 and Varian-Gemini 200 spectrometers. For all other samples δ values were referenced to residual $CDCl_3$. All *J* values are in Hz. Specific optical rotatory powers [α] were measured with a Perkin-Elmer Polarimeter (model 141) at 298K and 589 nm in dichloromethane (c= 1.0 g/100 mL). Enantioselectivities were determined by High resolution liquid chromatografy (HPLC), using a chiral column (Chiracel OD-H). Eluent mixture used is 1:10 isopropanol:hexane and an UV detector with λ = 254 nm. Yields were determined by isolation. Thin layer chromatography (TLC) was performed on Merck silica gel 60 F_{254} pre-coated plates (0.25 mm) silica. The plates were visualised by the use of a combination of ultraviolet light (254 and 366 nm). Liquid chromatography wascarried out by forced flow (flash chromatography) with the solvent systems indicated using silica gel 60 Å (200-400 mesh) supplied by Aldrich.

Synthesis of ligand **14**

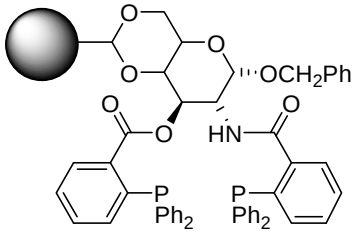
A solution of tridecafluorononananoic acid (0.36 mmol), 4-dimethylaminopyridine (3.9 mmol) and 1,3-dicyclohexylcarbodiimide (3.6 mmol) in dry THF (7 mL) was added to a solution of ligand **9** (0.12 mmol) in the same solvent (7 mL). The resulting mixture was stirred for 12 hours at room temperature under inert atmosphere affording an orange suspension. The residue was removed by filtration. The resulting solution was evaporated under vacuum, and the residue was chromatographed on silica gel (2:8 ethyl acetate:hexane and triethylamine(2 mL for each 250 mL) affording the pure product as a white solid (yield: 80-85%).



^{1}H NMR (300Mz): $CDCl_3$, δ 6.15 (d, 1H, NH-C2, $^{3}J_{NH-H2}$ = 9.3Hz), 5.47 (t, 1H, H3, $^{3}J_{H3-H4}$ = 9.6Hz, $^{3}J_{H3-H2}$ = 9.6Hz), 5.23 (t, 1H, H4, $^{3}J_{H4-H5}$ = 9.6Hz), 4.87 (d, 1H, H1, $^{3}J_{H1-H2}$ = 3.6Hz), 4.68 (dd, 1H, H2), 4.54 (d, 1H, CH*H*Ph, $^{2}J_{gem}$ = 12), 4.46 (d, 1H, CH*H*Ph, $^{2}J_{gem}$ = 12), 4.27 (dd, 1H, $H6_{eq}$, $^{3}J_{H6eq-H5}$ = 4.4Hz, $^{2}J_{H6eq-H6ax}$ = 9.8 Hz), 3.94 (m, 2H, H5, $H6_{ax}$,), 2-3 (m,

8H, (CH_2)$_2$).^{13}C NMR: δ, 70.0, 169.9, 168.2, 165.3, 140.8, 137.7, 136.5, 134.4, 133.82, 97.1, 69.6, 62.9, 51.6, 26.0, 25.5, 25.07.

Synthesis of ligand **15**



Ligand **9** (0.80 g, 0.95 mmol) and the commercial resin ARGOPORE-CHO (0.34 g, 0.24 mmol CHO sites) were suspended in dichloromethane (35 mL). To this mixture *p*-toluenesulphonic acid (0.044 g, 0.23 mmol) was added. After 12 hours refluxing, the solid was washed with dichloromethane (3x5 mL) and dried under vacuum. The functionalization of the resin was determined by weighting (0.44 g, 50% of sites). IR(Nujol): ν=1717 cm^{-1}.

General procedure for catalytic reaction in ionic liquids

To BMIM[BF_4] (1 mL) were added ligand **9** (0.012 g, 0.015 mmol), Pd(dba)$_2$ (0.0057 g, 0.010 mmol,), meso-2-cyclopenten-1,4-diol-isocianate[7k] (0.043 g, 0.10 mmol) and triethylamine (0.010 g, 0.10 mmol). After 30 minutes stirring, the product was extracted from the catalytic phase with diethyl ether (3x15 mL) in 70-80% yield, and analysed. The catalyst phase was re-cycled for further runs by adding another portion of substrate and triethylamine. The enantiomeric excesses were determined by chiral HPLC, Chiracel OD-H, 1:10 isopropanol:hexane, UV 254 nm, retention times: -(3R,6S): 22-24 min; +(3S,6R): 30-32 min.. The absolute configuration was obtained by comparison with a sample of known chirality.

General procedure for homogeneous supported catalysis

To a stirred suspension of ligand **15** (0.20 g, 0.054 mmol) in toluene (5 mL) was added [PdCl(allyl)]$_2$ (0.0062 g, 0.014 mmol). After 30 min triethylamine (0.030 g, 0.30 mmol) was added. After 1h the solid was yielded, washed with dry THF (2 mL) and dried under vacuum. The resin was then suspended in dry THF (1 mL) and a solution of *meso*-2-cyclopenten-1,4-diol (0.27 g, 0.58 mmol) and triethylamine (0.058 g, 0.58 mmol) in the same solvent (2 mL) was added. After 2 hours stirring the organic phase was separated and analysed. The catalyst was washed with dry THF and re-cycled for further runs. The enantiomeric excesses were determined by chiral HPLC, Chiracel OD-H, 1:10 isopropanol:hexane, UV 254 nm, retention times: -(3R,6S): 22-24 min; +(3S,6R): 30-32 min.. The absolute configuration was obtained by comparison with a sample of known chirality.

5. Concluding remarks

The aim of this work has been the development of high performing catalytic systems, able to afford the environmental compatibility and productivity demanded by the modern chemical industry. Core of the activity has been the design of new catalysts for the synthesis of fine chemical products through both traditional and *homogeneous multiphase catalysis*.

In this frame, the strategy has involved the synthesis of carbohydrate-based ligands, which exactly reproduce the structural and stereochemical motifs of *privileged* ligands. As an extra advantage, the available hydroxyls of the sugar ring have been also suitably functionalized, for extending the use of the corresponding metal catalysts in *homogeneous multiphase catalysis*.

The effectiveness of the approach has been examined in two powerful reactions for the asymmetric formation of new carbon-carbon bonds, such as the allylic substitution promoted by Pd, and the asymmetric Cu-catalyzed 1,4-conjugate addition of organozinc reagents to acyclic enones.

Excellent results (up to 98% ee) have been achieved in traditional conditions, while the encouraging data, obtained performing the firs reaction both in an ionic liquid and in supported catalysis, stimulate further investigations under the *multiphase* conditions.

List of publications

This thesis is based on the following papers:

1. "Bis(phosphinoamides) based on sugars for highly enantioselective allylic substitution: inversion of stereocontrol by switching from glucose to mannose"
   R. Del Litto, A. De Roma, A. D'Errico, S.Magnolia, F. Ruffo, *Tetrahedron Asymmetry*, 17, 2265, **2006**.

2. "A convenient route from simple sugars to new chiral bis(phosphinoesters) for asymmetric catalysis"
   R. Del Litto, A. De Roma, F.Ruffo, *Inorganic Chemistry Communications*, 10, 618-622, **2007.**

3. "Carbohydrate as building blocks of "privileged" ligands for multiphasic asymmetric catalysis"
   V. Benessere, A. De Roma, F.Ruffo, *ChemSusChem*, 5, vol 1, 425-430, **2008**.

4. "Amino Sugar Modular Ligands- Useful Cores for the Formation of Asymmetric Copper 1,4 Addition Catalysts"
   A. De Roma, F. Ruffo, S.Woodward, *Chem. Commun.*,5384 – 5386, **2008.**