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FACOLTA' DI SCIENZE MATEMATICHE, FISICHE E NATURALI

XXIII CICLO DOTTORATO IN SCIENZE CHIMICHE

TESI SPERIMENTALE

CARBOHYDRATES AS LIGANDS FOR ASYMMETRIC CATALYSIS

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INDEX

CHAPTER 1
INTRODUCTION

1.1 BACKGROUND:[1] HOMOGENEOUS ENANTIOSELECTIVE CATALYSIS

Chirality is all over around you: it's with you when you go to work, when you pay your taxes, when you write on a computer, like I'm doing, with a chiral object: your hand!!!. The fascinating chemistry of life is based upon asymmetric interactions, which occur through chiral recognition. Hence, a wide number of biologically active molecules, such as aminoacids, carbohydrates and vitamins, exists as a single enantiomer. The same concept holds true for important manufactured products, such as pharmaceuticals, agrochemicals, flavours and fragrances. Since only one enantiomer has the desired biological property, recent regulations demand the production of the only active enantiomer, strongly disfavouring commercialisation of racemates. Four general approaches (Fig. 1) are commonly pursued for producing enantiopure compounds, and all of them are based upon the consideration that chiral compounds can be artificially produced only in the presence of another chiral agent[1] (see

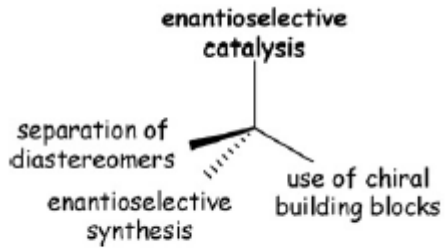

Fig. 1. Strategies for the synthesis of chiral molecules.

[1] Blaser, H. U.; Pugin B.; Splinder F. *Journal of Molecular Catalysis A: Chemical 231* **2005** *1–20 Progress in enantioselective catalysis assessed from an industrial point of view.*

Table 1.1 for a comparison of the different methodologies and an assessment concerning their suitability for industrial applications).[2]

Scope and limitations of major production methods for enriched chiral molecules

	Chemocatalysis	Biocatalysis	Chiral pool	Crystallisation	HPLC
Enantioselectivity	1–2	1	1	1–2	1–2
Activity and productivity	1–2	2–3	–	–	–
Availability and diversity	1–2	2–3	2	1	1
Substrate specificity	2	2–3	1	1	2
Work-up and ecology	1–2	2–3	2	2	2
Development time and effort	2	3	1	1–2	1
Application in the lab	2	3	1	1–2	1
Application in development	1–2	2	1	2	2
Small-scale production	1–2	1–2	1	1–2	2
Large-scale production	1	2	2–3	1–2	3

Rating: 1: broad scope, 2: medium scope and/or some problems, 3: narrow scope and/or often problematic.

Table 1.1

While *crystallisation* of diastereomeric adducts can be applied on any scale, separation via *HPLC* is probably most important in the early phase of product development and is restricted to small-scale (100 kg to tonnes), high-value products. In both cases, large amounts of solvents have to be handled and of course at least 50% of the material with the wrong absolute configuration has to be either recycled or discarded.

The *chiral pool approach* uses chiral building blocks originating from natural products for the construction of the final molecule. This approach is very often chosen in the early phases of drug development but, depending on the commercial availability of the starting material, it can also be used for large-scale products. Because natural products very often have high enantiomeric purity, no further enrichment is usually necessary.

Enantioselective syntheses are performed with the help of covalently bound chiral auxiliaries, often from the chiral pool. These are not incorporated in the target molecule but are removed after the stereogenic centres have been established, and must be either recycled or discarded.

[2] J. Crosby, in: A.N. Collins, G.N. Sheldrake, J. Crosby (Eds.), *Chirality in Industry I*, John Wiley, Chichester, **1992**, *p. 1*.

In many respects the most elegant approach is *enantioselective catalysis* where prochiral starting materials are transformed to enantioenriched products with the help of chiral catalysts. Effective catalysts are either synthetic (chemocatalysis) or can be of natural origin (biocatalysis). An important issue is often the time needed to find and to develop an efficient biocatalyst, especially when the starting material is not a very close analogue to the natural substrate. In addition, product isolation can be a serious problem since reactions are often carried out in a rather dilute aqueous solution. But as several recent publications convincingly show,[3] these hurdle can be overcome.

Over the years, three types of enantioselective chemocatalysts have proven to be synthetically useful. The most versatile ones are *homogeneous metal complexes* containing ligands with a chiral backbone carrying one or more coordinating heteroatoms. For noble metals, especially Rh, Pd, Ru, Ir and Os these are tertiary P or N atoms, for metals such as Ti, B, Zn, Co, Mn or Cu ligands with coordinating O or N atoms are usually preferred. This methodology has just received its due recognition in the 2001 Nobel Prize to W.S. Knowles and R. Noyori for enantioselective hydrogenation and to K.B. Sharpless for enantioselective oxidation catalysis.[4] Also useful for synthetic application are *heterogeneous metallic catalysts*, modified with chiral auxiliaries[5] and finally organocatalysis, i.e. the use of chiral *soluble organic bases and acids* is at the moment a very hot research topic with quite a lot promise for future industrial applications.[6] While most applications are in the field of *asymmetric synthesis* starting from a prochiral substrate, *kinetic*

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[3] (a) H.U. Blaser, E. Schmidt (Eds.), *Large Scale Asymmetric Catalysis*, Wiley-VCH, Weinheim, **2003**, *p.1*; (b) W.S. Knowles, in: H.U. Blaser, E. Schmidt (Eds.), *Large Scale Asymmetric Catalysis*, Wiley-VCH, Weinheim, **2003**, *p. 23*; (c) A.J.J. Straathof, S. Panke, A. Schmid, *Curr. Opinion Biotechnol*. 13; **2002**; *548*.

[4] For details see Nobel Lectures, *Angew. Chem. Int. Ed. 41;* **2002**; *1998–2022*.

[5] M. Studer, H.U. Blaser, C. Exner, Adv. Synth. Catal. *345;* **2003**; *45*.

[6] see K.N. Houk, B. List, *Acc. Chem. Res. 37;* **2004**; 487

resolution, i.e., the preferential transformation of one enantiomer of a racemic substrate, is of growing synthetic importance.[7]

Up to now, relatively few enantioselective catalysts are used on an industrial scale. One reason is that enantioselective catalysis is a relatively young discipline, but at the same time it is a rapidly expanding field. Up to 1985, only few catalysts affording enantioselectivities of more than 90% were known.[8] This has changed dramatically in recent years and there are now a large number of chiral catalysts able to catalyze a variety of transformation with ees >98%.[9] Some example of industrial application of enantioselective catalyst are the Monsanto *L*-DOPA process[7] and Jacobsen's hydrolytic kinetic resolution (HKR) of epichlorohydrin.[10]

Anyway, the application of homogeneous enantioselective catalysts on a technical scale presents some other special challenges and problems. Some of these problems are due to the special manufacturing situation of the products involved (small scale-high added values product, development time, etc.). Others Problems are due to the nature of the enantioselective catalytic processes. A major challenge which still remains is the transfer of the results obtained for a particular substrate to even a close analog due to the low tolerance for structure variation even within a class of substrates (substrate specificity). The industrial application of enantioselective catalysts is also hampered by a lack of information on their synthetic scope and limitations. In addition, catalyst activities or productivities are often not given for new catalysts (in the

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[7] (a) J.M. Keith, J.F. Larrow, E.N. Jacobsen, *Adv. Synth. Catal*. 343; **2001**; 5; (b) D.E.J.E. Robinson, S.D. Bull, *Tetrahedron: Asymmetry;* **2003;** *14 1407*.

[8] J.D. Morrison (Ed.), *Asymmetric Synthesis, vol. 5, Academic Press, New York*, **1985**.

[9] (a) For an exhaustive review on this topic, see: E. N. Jacobsen, A. Pfaltz and H. Yamamoto (Eds.), *Comprehensive Asymmetric Catalysis, Springer, Berlin*, **1999**, and references cited in the reviews. (b) For an exhaustive review on this topic, see: T. Ohkuma, M. Kitamura, R. Noyori, in: I. Ojima (Ed.), *Catalytic Asymmetric Synthesis, second ed., Wiley-VCH, Weinheim*, **2000** and references cited in these reviews.

[10] (a) Schaus S.E., Brandes B. D.,. Larrow J. F., Tokunaga M., Hansen K. B., Gould A. E., Furrow M. E., Jacobsen E. N., *J. Am. Chem. Soc*. **2002**, *124, 1307*.
(b) for a list of chiral building blocks available via the HKR chemistry, see: www.rhodia.com

literature enantioselectivity is still the dominant criterion) and applications to the synthesis of "real" substrates are rather scarce (usually simple model reaction are studied). Finally, many chiral ligands and metal precursors are expensive and/or not easily available in technical quantities.. Over the years, *homogeneous chemo-catalysts* based on metal centres tailored with suitable chiral ligands have attracted increasing academic and industrial interest because relevant reactionparameters, such as activity, selectivity and catalyst life can often be rationally optimised Therefore, *homogeneous enantioselective catalysis* is today a fundamental technology for the production of fine chemicals. [11]

Enantiomerically enriched compounds produced in this way are typically used as pharmaceuticals and vitamins,[12] agrochemicals[4] and flavors and fragrances. Other applications are functional materials such as chiral polymers, materials with non-linear optical properties or ferroelectric liquid crystals. For many applications of such chiral compounds, the racemic forms will no longer be accepted.[13] As a consequence, the importance of enantioselective synthesis in general, and of enantioselective catalysis in particular, has increased.

As a consequence of the peculiarities of enantioselective catalysis described above, the following critical factors often determine the viability of an enantioselective process:

- The *enantioselectivity*, expressed as enantiomeric excess (% ee), i.e., % desired−% undesired enantiomer. The ee of a catalyst should be >99% for pharmaceuticals if no purification is possible (via recrystallization or at a later stage via separation of diastereomeric intermediates). This case is

[11] Blaser, H. U.; Schmidt, E. *Asymmetric Catalysis on Industrial Scale*, 1st ed.; Wiley-VCH: Weinheim, Germany, **2004**.
[12] For a recent update on chiral pharmaceuticals see A.M. Rouhi, *C&EN*, **June 14, 2004**, *p. 47*.

quite rare and ees >90% are often acceptable; for agrochemicals ees >80% can be sufficient.

- The *chemoselectivity and/or functional group tolerance* will be very important when multifunctional substrates are involved.
- The *catalyst productivity*, given as turnover number (TON), determines catalyst costs. TONs ought to be >1000 for small scale, high value products and >50,000 for large scale or less expensive products (catalyst re-use increases the productivity).
- The *catalyst activity*, given as turnover frequency for >95% conversion (TOF, h^{-1}), determines the production capacity. For hydrogenations, TOFs ought to be >500 h^{-1} for small scale and >10,000 h−1 for large scale products.
- *Availability and cost of ligands*. In the majority of cases these are chiral diphosphines that need special synthetic know how and can be rather expensive. Typical prices are 100–500 $/g for laboratory quantities and 5000 to >20,000 $/kg on a larger scale. Chiral ligands such as diamines or amino alcohols used for early transition metals are usually cheaper.
- *Intellectual property*. Many chiral ligands and/or catalysts are patent protected. It is essential to obtain the right to use proprietary catalysts on a commercial basis at reasonable costs and conditions.
- *Availability and cost of starting materials*. Starting materials are often expensive and difficult to manufacture on a large scale with the high purity required for catalytic reactions.
- *Development time*. Can be crucial if an optimal ligand has to be developed for a particular substrate (substrate specificity) and when not

[13] G.M. Ramos Tombo; H.U. Blaser, in: G.T. Brooks, T.R. Roberts (Eds.), *Pesticide Chemistry and Bioscience,* Royal Society of Chemistry, Cambridge, **1999**, *p. 33*, and references cited therein.

much know-how is available on the catalytic process (technological maturity).

For most other aspects such as catalyst stability and sensitivity, handling problems, catalyst separation, space time yield, poisoning, process sensitivity, toxicity, safety, special equipment, etc., enantioselective catalysts have similar problems and requirements as nonchiral homogeneous catalysts.

Which of these criteria will be critical for the development of a specific process depends on the specific catalyst and transformation (see **Table 1.2** for a comparison of the different industrial applications of enantioselective catalytic reaction).

Statistics for the industrial application of enantioselective catalytic reactions [15]

Transformation	Production		Pilot		Bench scale
	>5 t/year	<5 t/year	>50 kg	<50 kg	
Hydrogenation of enamides	1	1	2	6	4
Hydrogenation of C=C–COOR and C=C–CH–OH	1	0	3	4	6
Hydrogenation of other C=C	1	0	1	2	2
Hydrogenation of α and β functionalized C=O	2	2	3	6	4
Hydrogenation/reduction of other C=O	0	0	0	1	4
Hydrogenation of C=N	1	0	1	0	0
Dihydroxylation of C=C	0	1	0	0	4
Epoxidation of C=C, oxidation of sulfides	2	1	2	0	2
Isomerization, epoxide opening, addition	2	0	3	0	1
Total	10	5	15	19	27

Definitions: production processes are operated on a regular basis; pilot processes are technically on a similar level but are not (yet) applied on a regular basis; bench scale processes have an optimized catalyst system and have been carried out on a kg scale.

Table 1.2

1.2 CARBOHYDRATES AS BUILDING BLOCKS OF PRIVILEGED LIGANDS[14]

Beside the choice of the active metal, the accurate design of the chiral ligand is crucial for its effective application. The ligand must possess a well-defined three-dimensional structure, capable of directing the stereochemistry of the reaction. Accordingly, in 2002 a few selected ligands of wide and proven applicability were indicated as 'privileged' by Jacobsen[15] (in brackets in **Figure 2**). Over the years, this original class of privileged ligands was gradually extended to include other effective structures, and in 2008, the Aldrich Chemical Company reviewed[16] an entire class comprising more than 30 structures (in **Figure 2**). At the same time, several research groups demonstrated that highly performing ligands can be attained by simple modification of molecules from the *natural chiral pool*, such as carbohydrates.[17] This strategy is based upon the assumption that sugars are both abundant (therefore easily available) and "naturally chiral", which avoids the complicated resolution of racemates. Furthermore, carbohydrates are highly functionalised and their chemistry is extremely well developed. This latter feature is particularly attractive because modular ligands with similar structural motifs can be created, thus making possible the generation of libraries.

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[14] For an exhaustive review on this topic, see: V. Benessere, A. De Roma, R Del Litto, F. Ruffo*; Coordination Chemistry Reviews 254;* **2010**; *390–401*

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

[16] *ChemFiles, Asymmetric Catalysis, Privileged Ligands and Complexes, Vol. 8, Aldrich Chemical*, **2008**

[17] (a) D. Steinborn, H. Junicke*, Chem. Rev. 100;* **2000;** *4283*; (b) M. Dièguez, O. Pàmies, A. Ruiz, Y. Diaz, S. Castillòn, C. Claver*, Coord. Chem. Rev. 248;* **2004** *2165*; (c) M. Dièguez, O. Pàmies, C. Claver*, Chem. Rev. 104;* **2004**; *3189*; (d) Y. Diaz, S. Castillòn, C. Claver, *Chem. Soc. Rev. 34;* **2005**; *702*; (e) M. Dièguez, C. Claver, O. Pàmies, *Eur. J. Org. Chem*.; **2007**; *4621*; (f) M.M.K. Boysen, *Chem. Eur. J. 13;* **2007**; *8648*; (g) M. Dièguez, O. Pàmies, *Chem. Eur. J. 14;* **2008**; *944.*

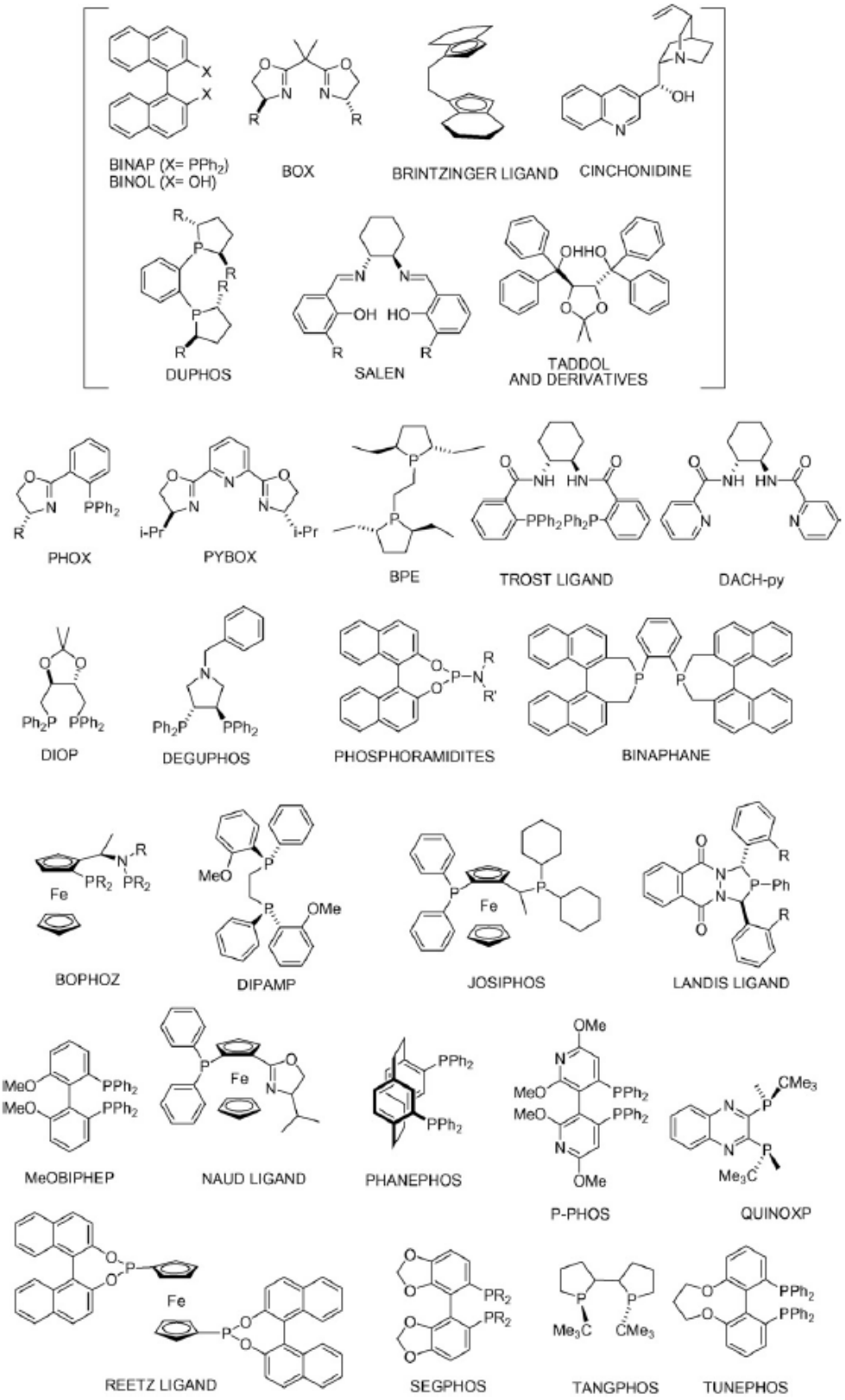

Figure 2: the privileged ligands

This strategy is expected to be especially productive when carbohydrates are used as building blocks of "privileged" ligands, aiming to amplify the scope of their application. The introduction of privileged moieties into a sugar backbone promises to afford unique ligand structures, which combine efficiency with convenience and flexibility. This was demonstrated on several occasions, and today many "privileged" ligands of **Figure 2** do possess a corresponding sugar version.[14] An additional benefit is that the generous presence of functional groups in sugars can be employed for "tagging" the "privileged" ligands in view of their application in *multiphase homogeneous catalysis*. This methodology allows easy catalyst re-cycling via simple phase separation, and relies on using two immiscible solvents and a phase-tagged catalysts, which are soluble in only one of the two solvents (catalyst phase), while being insoluble in the other solvent (reactant/product phase).[18]

Given this premise, the research group where this thesis was carried out on focalized the last years activity in optimising the attainment of effective chiral ligands by simple derivatisation of common carbohydrates,[19] for example, D-glucose. This successful approach,[20] developed in this thesis, produced the modular ligands' library **naplephos**, whose general structure is shown in **Figure 3.**

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

[19] Also other groups are active within this field of research. For reviews, see reference 14 and: (a) Steinborn, D.; Junicke, H. *Chem. Rev*. **2000**, *100, 4283*; (b) Dièuez, M.; Pàmies, O.; Ruiz, A.; Diàz, Y.; Castillòn, S.; Claver, C. *Coord. Chem. Rev*. **2004**, *248, 2165*; (c) Dièguez, M.; Pàmies, O.; Claver, C. *Chem. Rev*. **2004**, *104, 3189*; (d) Diàz, Y.; Castillòn, S.; Claver, C. *Chem. Soc. Rev*. **2005**, *34, 702*; (e) Dièguez, M.; Claver, C.; Pàmies, O. *Eur. J. Org. Chem*. **2007**, *4621*; (f) Dièguez, M.; Pàmies, O. C*hem. Eur. J*. **2008**, *944*; (g) Boysen, M. M. K. *Chem. Eur. J*. **2007**, *13, 8648*;

[20] (a) Benessere, V.; Del Litto, R.; Ruffo, F.; Moberg, *C. Eur. J. Org. Chem*. **2009**, *1352*; (b) De Roma, A.; Ruffo, F.; Woodward, S. *Chem. Commun*. **2008**, *5, 384*; (c) Benessere, V.; De Roma, A.; Ruffo, F. *ChemSusChem* **2008***, 1, 425*.

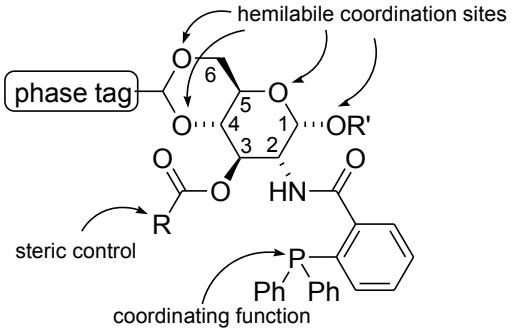


Figure 3

This general structure combines the essential structural motifs of the Trost 'privileged' ligands based on 1,2-trans-cyclohexanediamine[16] with increased flexibility and accessibility ***(Figure 4)***.

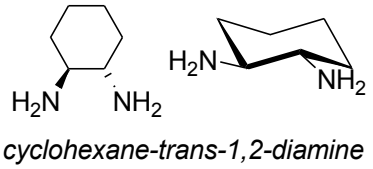


Figure 4

Position 1 shows a α-benzyl (R'= CH_2Ph), of immediate and selective introduction. Positions 4 and 6, so far protected with a benzylidene ring, are potentially useful for phase-tagging the ligands and, hence, for defining the physical properties of the catalyst. Position 3 is instead useful for introducing tailored hindrance next to the metal centre.

In fact, by proper choice of the R residue (**Figure 5**), the basic structure **naplephos** was already previously effectively adapted[20(b)(c)] to two different enantioselective processes, affording in all cases the chiral product in high ee's (reactions a and b in **Scheme 1.1**).

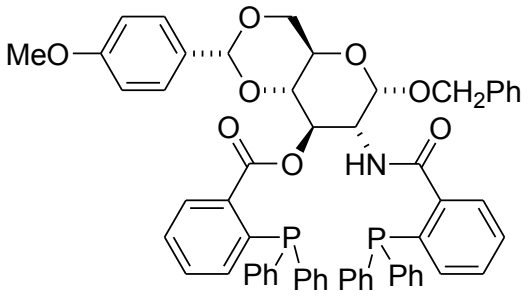
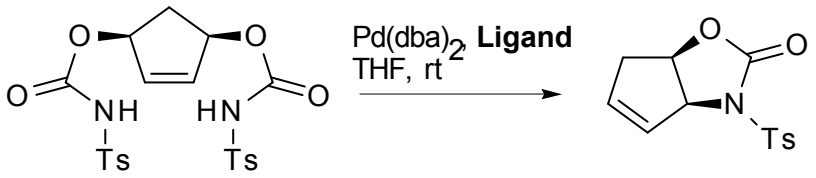


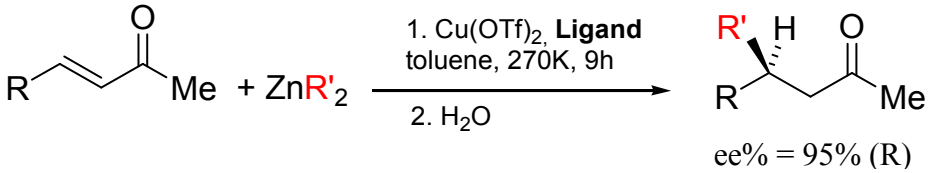
Figure 5

(a)



ee% = 98% -(R,S)

(b)



ee% = 95% (R)

Scheme 1.1

During this thesis, a library of **naplephos** ligands was prepared, aiming to study its application in another relevant reaction: the Pd-catalyzed asymmetric allylic alkylation[21] (AAA) depicted in **Scheme 1.2**.

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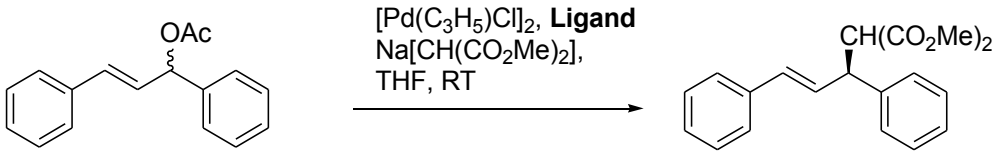
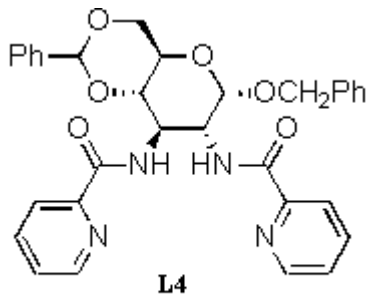
[21] For reviews, see: (a) Tsuji, J. *Palladium Reagents in Catalysis. In Innovation in Organic Synthesis*; Wiley: New York, **1995**; (b) Trost, B. M.; Van Vranken, D. L. *Chem. Rev*. **1996**, *96, 395*; (c) Johannsen, M.; Jorgensen, A. *Chem. Rev*. **1998**, *98, 1689*; (d) Pfaltz, A.; Lautens, M.. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, **1999**; *Vol. 2, Chapter 24*; (e) Trost, B. M.; Crawley, M. L. *Chem. Rev*. **2003**, *103, 2921*; (f) 450 Helmchen, G.; Pfaltz, A. *Acc. Chem. Res*. **2000**, *33, 336*; (g) Lu, Z.; Ma, S. *Angew. Chem*., Int. Ed**. 2008**, *120, 258*.



Scheme 1.2

This reaction is commonly used in different synthetic procedures, because it allows the enantioselective formation of carbon-carbon or carbon-heteroatom bonds on different allylic substrates using a wide variety of nucleophiles and different metal.

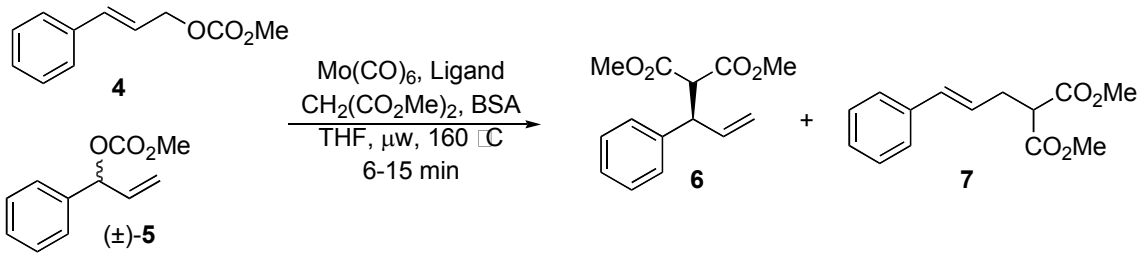


L4

Figure 6

Moreover, in order to verify the further versatility of the structure and its aptitude to afford chiral ligands of broad and established applicability, bispyridylamides ligands (**Figure. 6**) based on D-glucose were examined in Mo-catalyzed AAA (**Scheme 1.3**) reactions during a period of work at the KTH in Sotckholm in Prof. C. Moberg's lab.

Scheme 1.3

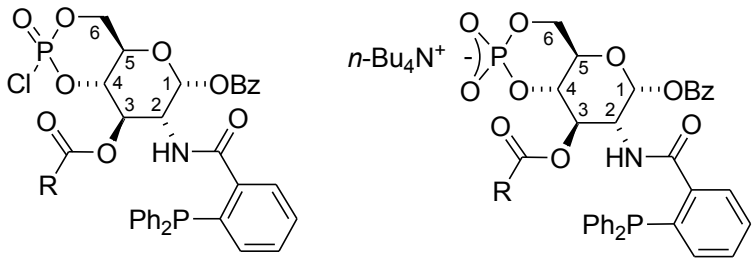


Catalyst re-cycle through conventional separation methods is often the major hinder to the industrial application of homogeneous catalysis.

Nowadays, the methodology of choice for solving this problem is the *multiphasic homogeneous catalysis*.[22] This strategy requires heterogenization of the catalyst, through either its anchorage to a solid support or its selective immobilization in a liquid phase (*e.g.* RTIL) immiscible with the products phase. In these conditions, the catalyst is easily recycled at the end of the reaction by simple phase separation.

Of course, this approach requires suitable tagging of the catalyst, because precise physical properties are necessary for its efficient heterogenization.

To pave the way for further studies and to proof the possibility of performing multiphase catalysis with ligands based on carbohydrates, the last part of this thesis treated the preliminary synthesis and the application in ionic liquid Pd-catalyzed AAA of a new promising 4,6 phosphate based ligand class (**Figure 7**) that could show either a neutral or ionic behaviour.



R= *o*-C_6H_4-PPh_2: **naplephos-a'**
R= $CHPh_2$: **naplephos-h'**

R= *o*-C_6H_4-PPh_2: **naplephos-a"**
R= $CHPh_2$: **naplephos-h"**

Figure 7

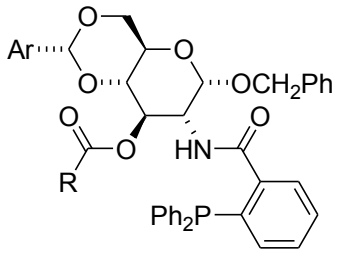
[22] *Multiphase Homogeneous Catalysis*, 1st ed.; Eds: B. Cornils, W.A. Herrmann, I.T. Horvarth, W. Leitner, S. Mecking, H. Olivier-Borbigou, D. Vogt, Wiley-VCH: Weinheim, Germany, **2005**.

CHAPTER 2
RESULTS AND DISCUSSION

2.1 LIGANDS DESIGN

2.1.1 NAPLEPHOS BASED LIGANDS

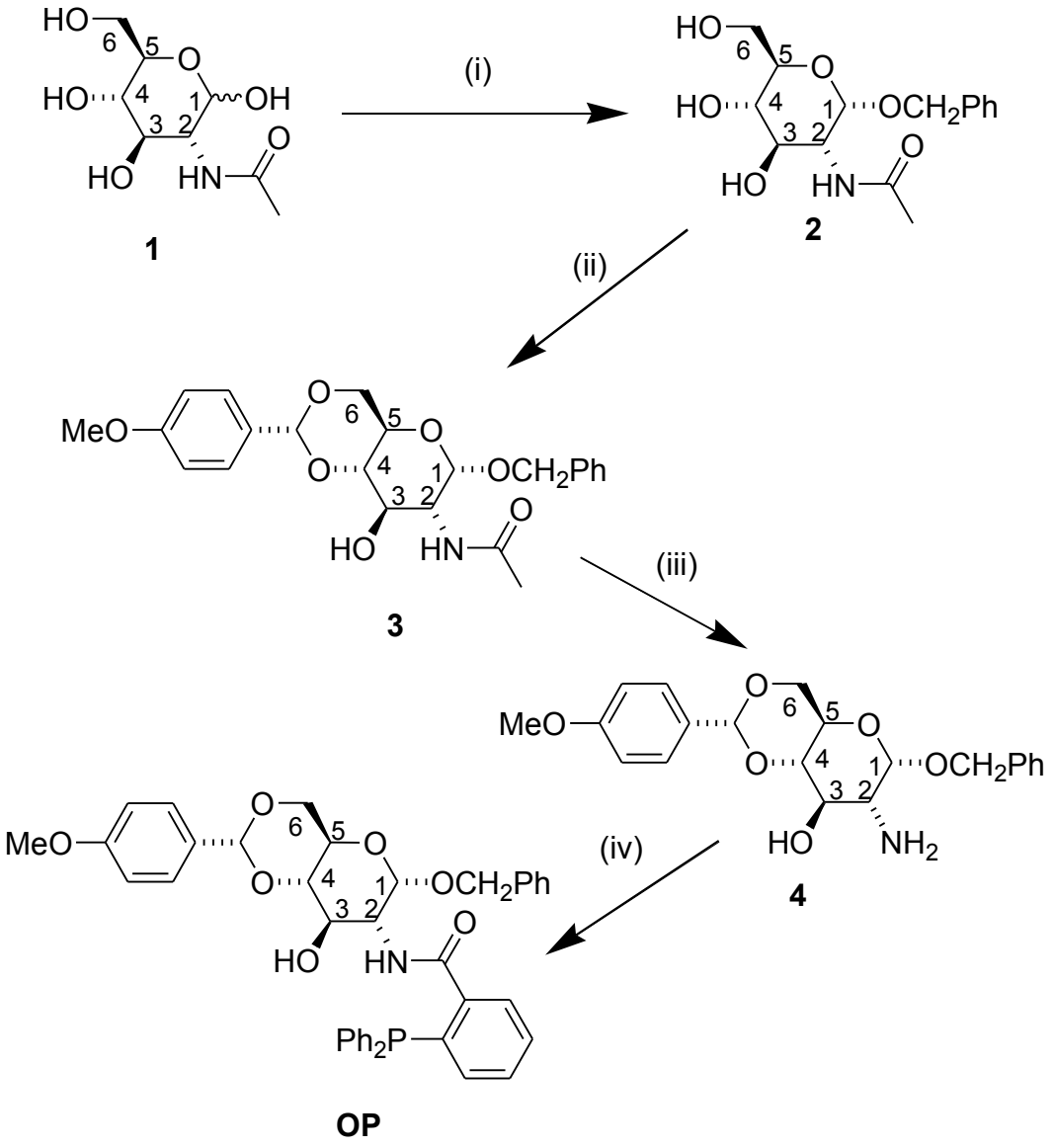
The distinctive structure of the **naplephos** ligands (**Figure 8)** is clearly defined, and is optimised for both synthetic convenience and catalytic performance (**Scheme 1.2**).



naplephos

Figure 8

Starting from inexpensive N-acetylglucosamine, C1 is selectively benzylated at the α-position ((i) in **Scheme 2**.1), thus avoiding a tedious separation of anomers. Positions 4 and 6 are protected with a 4-MeO-benzylidene ring ((ii) in **Scheme 2.1**), which stabilises the chair conformation of the sugar ring, with possible consequent benefit for the outcome of the catalysis.[1] At the same time, this protection can also be easily removed if a different functionalisation is desired.



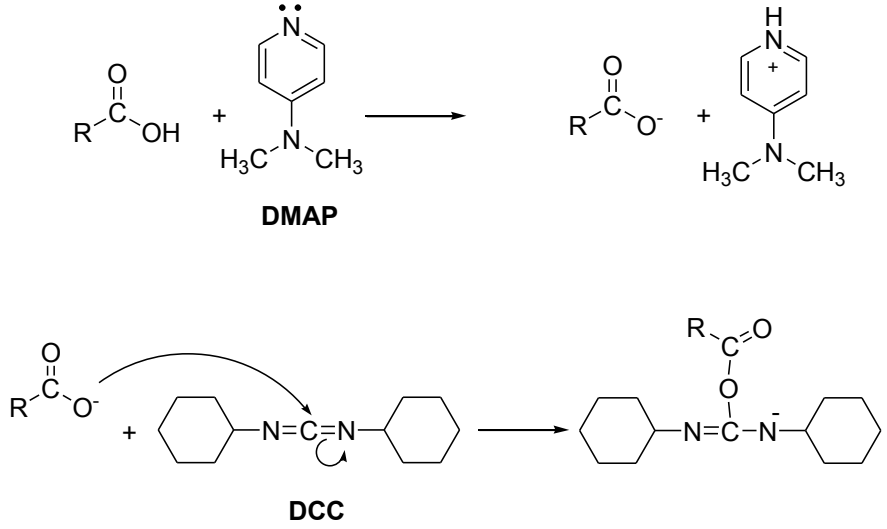
Reagents and conditions: (i) BzOH, AcCl, reflux; (ii) 4-MeO–C6H4–CHO, ZnCl2, 120°C; (iii) EtOH, KOH; (iv) Dry DCM, o-C_6H_4–PPh_2–CO_2H, *N,N′*-Dicyclohexylcarbodiimide (DCC), 4-Dimethylaminopyridine (DMAP); See experimental section for details.

Scheme 2.1

Position -2 is then deprotected by a classical basic hydrolysis ((iii) in **Scheme 2.1**), then a rigid coordinating diphenylphosphinoamido arm is introduced by simple condensation with (2-diphenylphosphino)benzoic (or naftoic sometimes) acid ((iv) in **Scheme 2.1**). This reaction is selective towards the amino function due to its higher nucleophilicity, and introduces the essential coordinating feature of the "privileged" Trost

[1] Benessere, V.; De Roma, A.; Ruffo, F. *ChemSusChem* **2008***, 1, 425*.

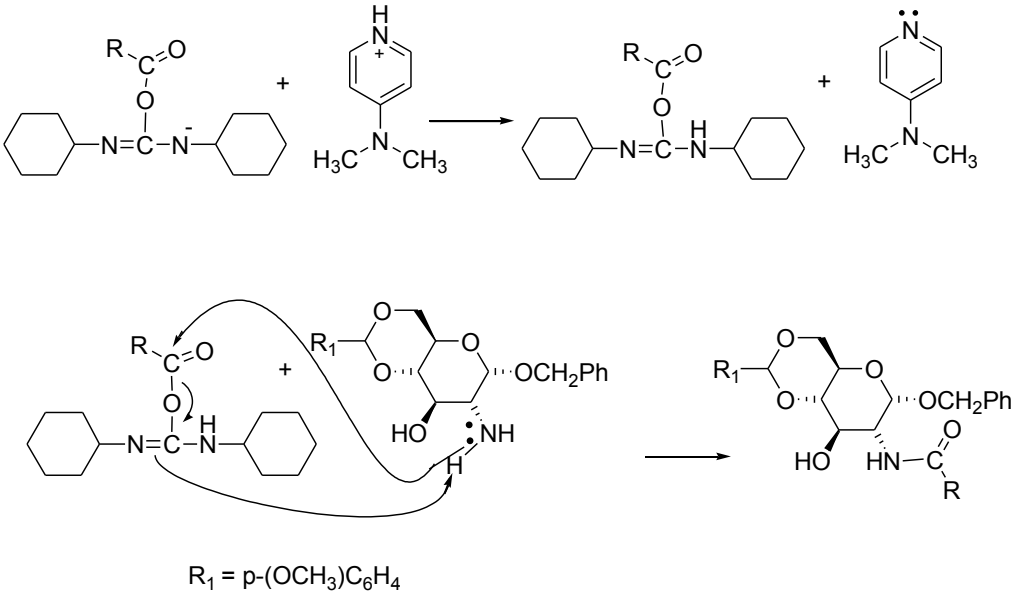
ligand[2] in the molecule. In this step, DCC and DMAP activate the carboxylic group of the (2-diphenylphosphino)benzoic acid, according to the mechanism described below. The nucleophilic catalyst (DMAP) deprotonates the acid, increasing its nucleophilicity, and hence its reactivity towards DCC (**Scheme 2.2**).



Scheme 2.2

The reaction intermediate is protonated by the DMAP cation present in solution, then the amino function attacks the carbonylic carbon, forming the amido group (**Scheme 2.3**).

[2] *ChemFiles, Asymmetric Catalysis, Privileged Ligands and Complexes, Vol. 8, Aldrich Chemical*, **2008.**

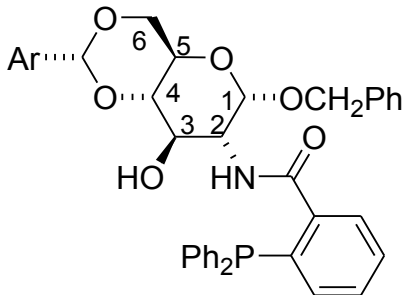


Scheme 2.3

The synthetic intermediate **OP** in **Scheme 2.1** is the key intermediate for the syntesis of the whole ligands library. The last step is a condensation (with a mechanism analogue to that mentioned before) of a carboxylic acid on C3 (**Scheme 2.4**). The ester R group is the only variable ((v) in **Scheme 2**.**4**), and is chosen according to the type of catalytic reaction. As mentioned above, when R is again a diphenylphosphino function, the corresponding **naplephos-a** was already productively applied in both the Pd-catalysed desymmetrisation of meso-diols[1] (ee up to 98%) and the Cu-catalysed addition of dialkylzinc to enones[3] (ee up to 95%).

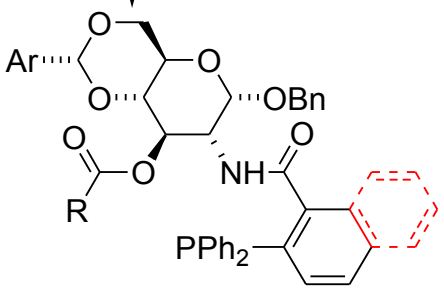
[3] (b) De Roma, A.; Ruffo, F.; Woodward, S. *Chem. Commun*. **2008**, *5384*;

a, R= o-C_6H_4-PPh_2
b, R= Me
c, R= CH_2Ph
d, R= CH_2Cy
e, R= t-Bu
f, R= (R)-CHEt(Ph)
g, R= (S)-CHEt(Ph)
h, R= $CHPh_2$
i, R= $CMePh_2$
j, R= $CHCy_2$
k, R= Ph
l, R= $CH_2C_6F_5$
m, R= $CH_2Ph(2,5\text{-bis-}Me)$
n, R= $CH_2Ph(3,5\text{-bis-}Me)$
o, R= o-Py o', R + naftoic in 2
p, R= o-Chinaldic p', R + naftoic in 2
q, R= CH_2NMe_2
r, R= CH_2NEt_2
s, R= NMe_2
t, R= NEt_2
u, R= $N(isoprop)_2$
v, R= $N(But)_2$



OP

(v)



naplephos

(v) Dry DCM, RCO_2H, DCC, DMAP. See experimental section for details.

Scheme 2.4

We synthesyzed three sub-classes of ligands with different stereoelectronic feature:

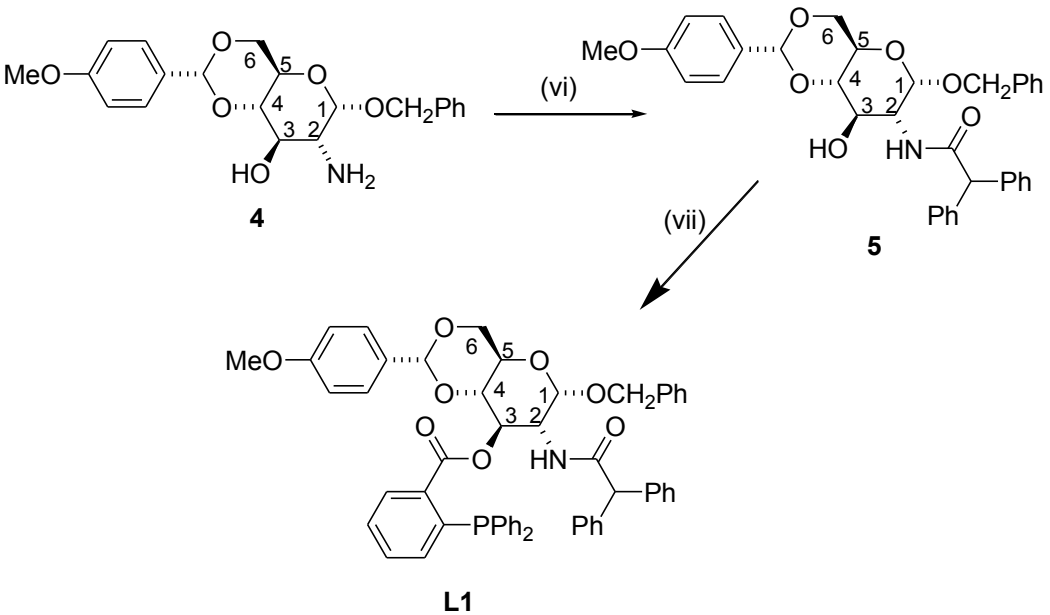
- R was selected among simple and readly available alkyl and aryl groups (**b–n**, see **Scheme 2.4**), with position 3 having just a steric control effect.[4]
- R was selected among simple derivates of picolinic acid (**o, o', p, p'**), with position 3 having a sp^2 N atom with coordination capability.
- R was selected among simple derivates of an aminoester, with position 3 having sp^3 N atom with different stereoelectronic features (**q-v**).

[4]Benessere, V.; Ruffo, F. *Tetrahedron Asymm.*, **2010**, *21*, 176.

Finally, after having recognized **naplephos-h** as the most effective ligand in the asymmetric allylic alkylation (see **section 2.3**), a family of analogue ligands were prepared in order to enlighten effects due to the local inversion of configuration and to outline the effect of position 1 on the catalytic activity (secondary stereochemical effect): these ligand had the following stereochemical feature:

1. inverted groups at C2 and C3 (L1).
2. Nap-h based on allose (L2).
3. Nap-h with alfa-OMe group in position 1 to reduce the steric hindrance of this position (L3).

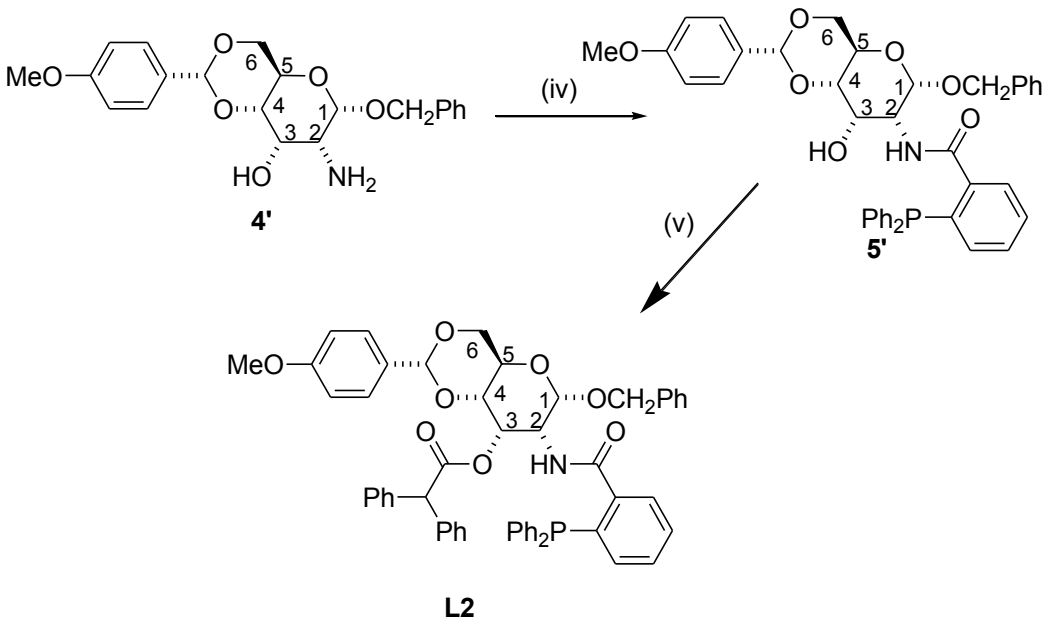
The synthetic procedure for the ligand L1, compared to the synthesis of the analogue, just invert the order of the two condensation reactions (**scheme 2.5).**



(vi) Dry DCM, Ph_2CHCO_2H, DCC, DMAP. (vii) Dry DCM, o-C_6H_4–PPh_2–CO_2H, DCC, DMAP; See experimental section for details.

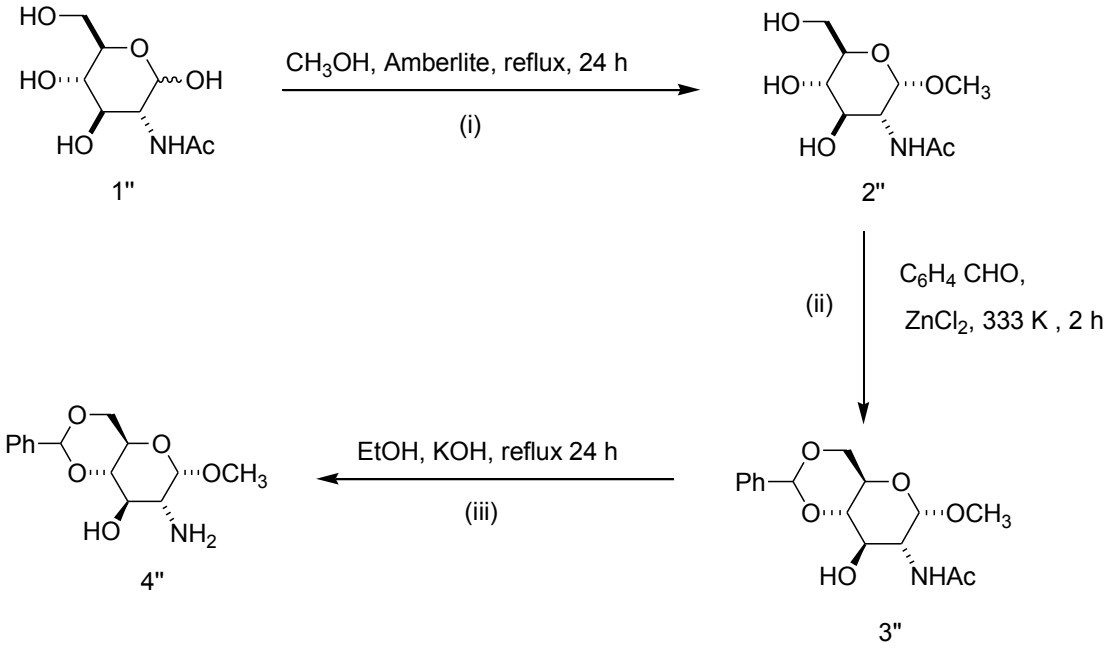
Scheme 2.5

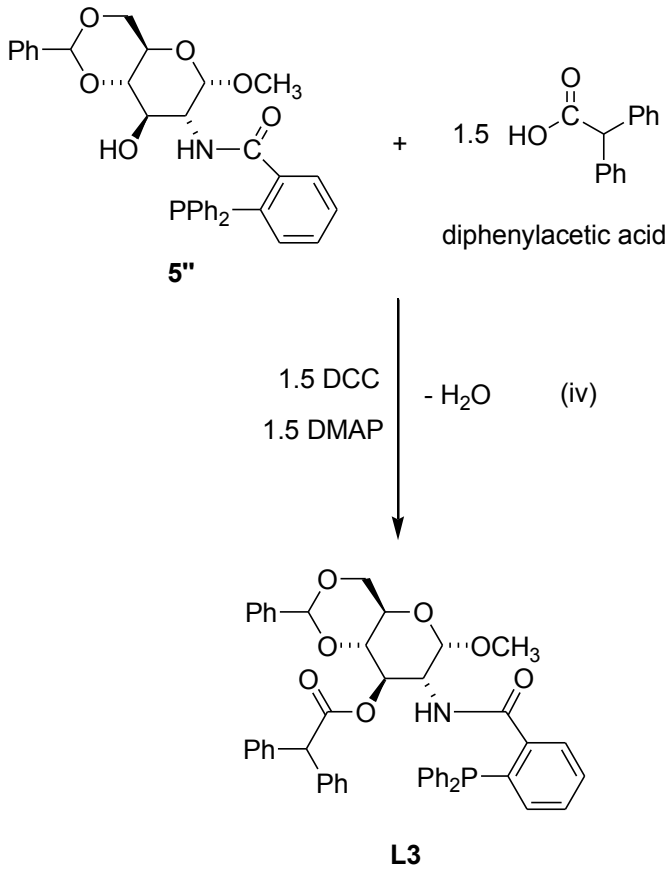
The synthetic procedure for the ligand L2, starts from the amine 4' based on allose and proceeds with the same two condensation steps of standard nap-h.



Scheme 2.6

The synthetic procedure for ligand L3 is different from the standard procedure of nap-h just in the first step where the glycosilation was perform in the presence of an acid resin in methanol (**scheme 2.7**).





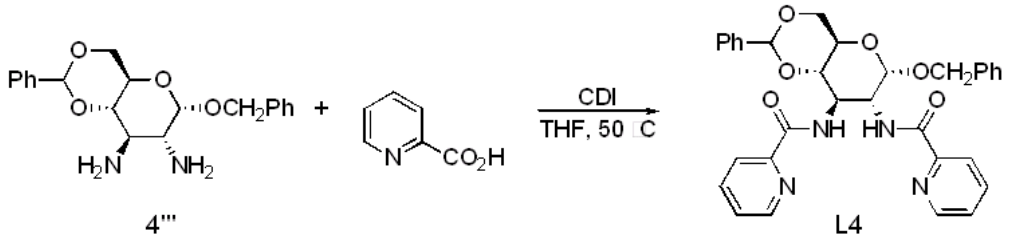
Scheme 2.7

2.1.2 BISPYRIDYLAMIDES BASED LIGANDS[5]

Bispyridylamides, which still are the most efficient ligands for the Mo catalyzed process, are easily prepared from a picolinic acid derivative and a chiral enantioenriched 1,2-diamine.[4] By comparing the results of reactions using ligands with substituted pyridine nuclei it was found that derivatives with π-donor substituents resulted in particularly high enantioselectivities and high branched to linear ratios.[5]

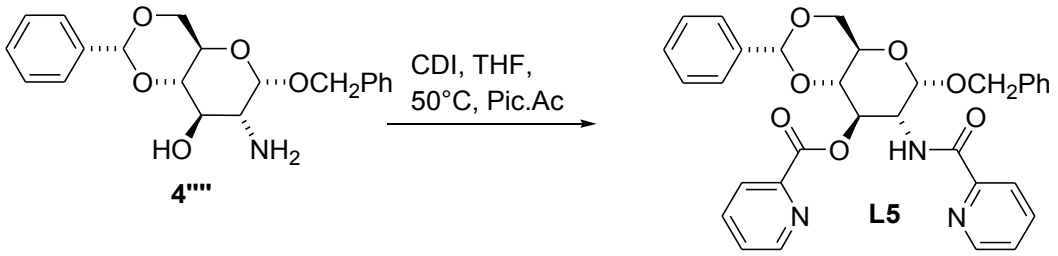
[5] Benessere, V.; Del Litto, R.; Ruffo, F.; Moberg, C. *Eur. J. Org. Chem.* **2009**, 1352.

We report here the preparation of the new ligands and their use in Mo-catalyzed allylic alkylations Ligands **L4** was prepared from previously described diamino derivatives **4'''**[**Errore. Il segnalibro non è definito.**] and the picolinic acid in the presence of carbonyl diimidazole (DCI) in 90% yield (**scheme 2.8**).



scheme 2.8

In order to verify the importance of the bispyridylamides backbone we also synthesized a bispyridylamides ligand with an aminoalchol structure (L5), starting from 4'''' with the same condensation procedure described above (scheme 2.9).



scheme 2.9

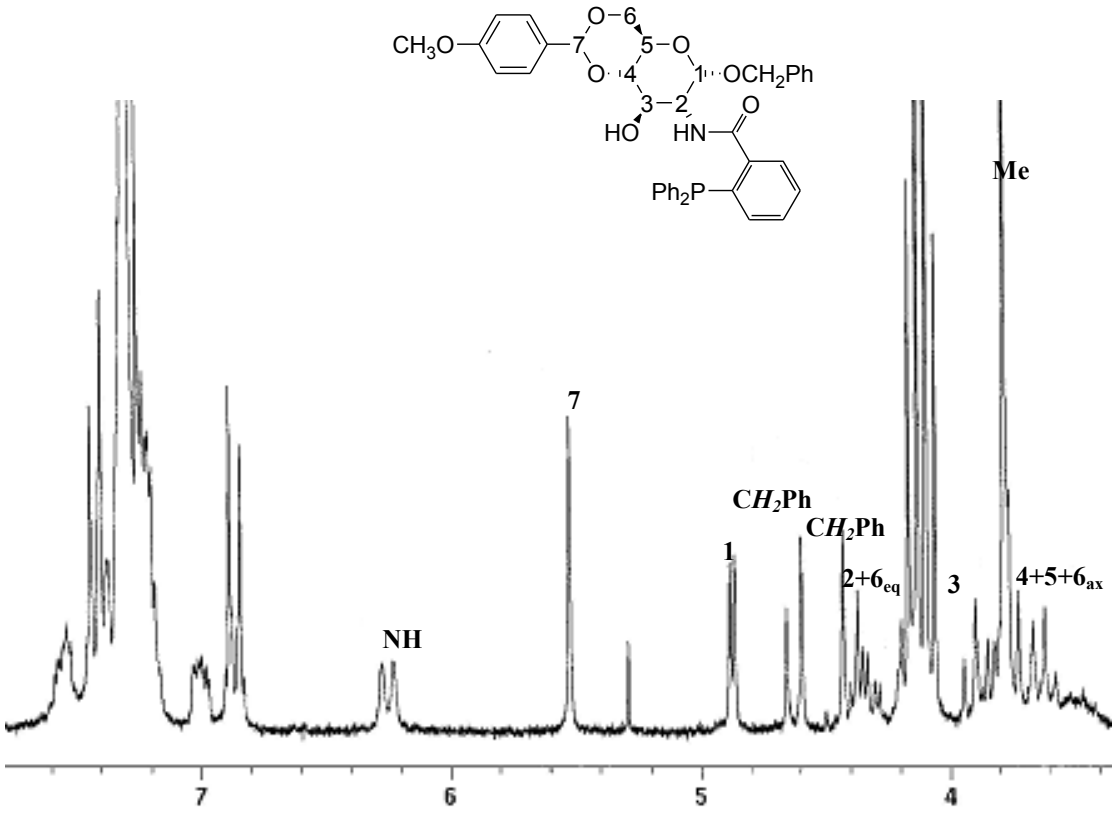
2.2 ^{1}H NMR CHARACTERIZATION OF THE LIGANDS

All the ligands, **naplephos(a–v)** and **L1-5**, were characterised via NMR spectroscopy. The sugar protons were assigned according to both their expected chemical shifts and the consistence of the coupling constants within the glucose ring.

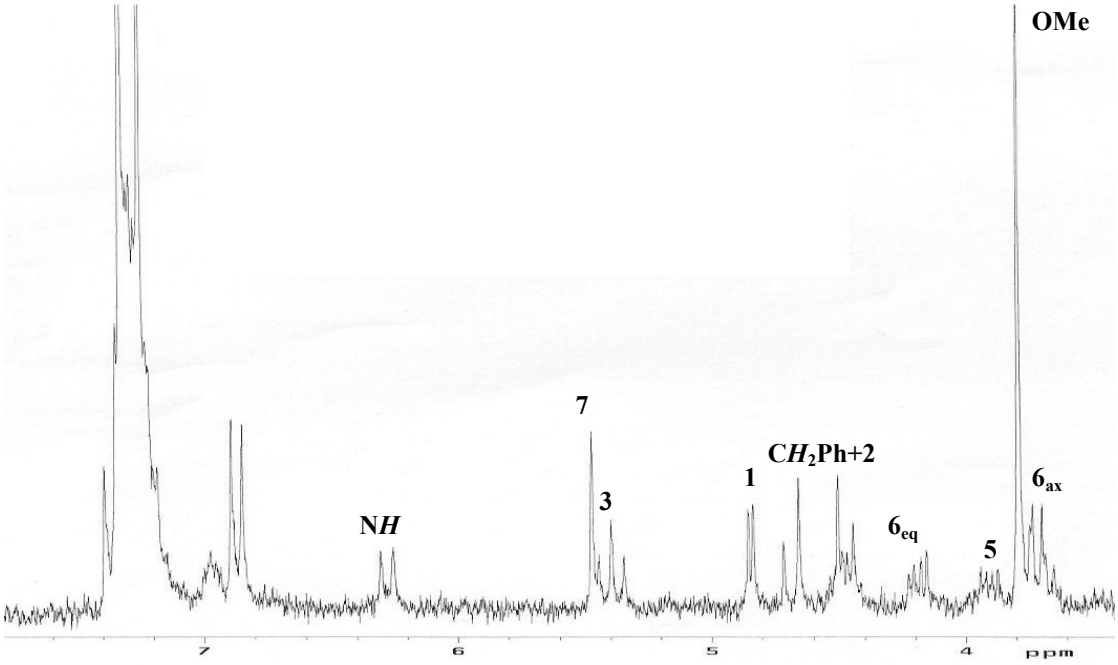
The functionalization on C2 and C3 is easily recognized: the signal of the proton on the functionalized carbon is found at higher frequences ($\Delta\delta \approx 2$ ppm) compared to the precursor.

The ^{1}H NMR spectra of **OP** and of all the ligands **naplephos(a–v)** and **L1-5** are reported in succession.

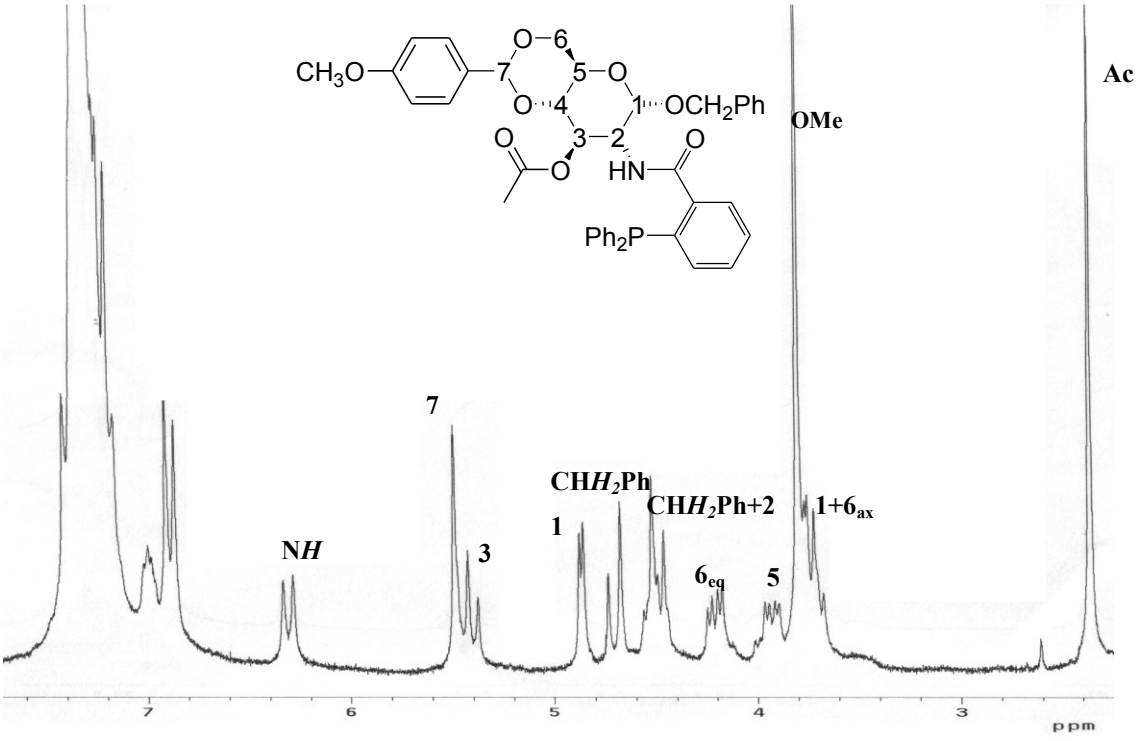
^{1}H NMR spectrum (300 MHz) of the **OP intermediate**



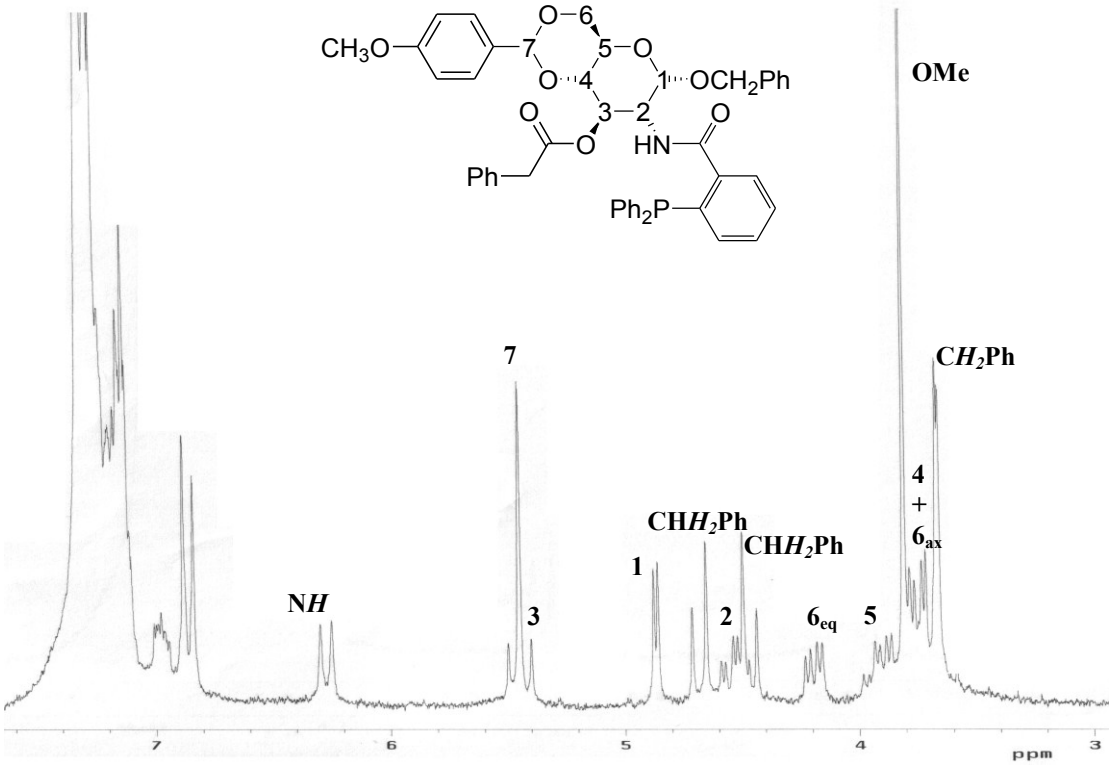
^{1}H NMR spectrum (300 MHz) of **naplephos-a**



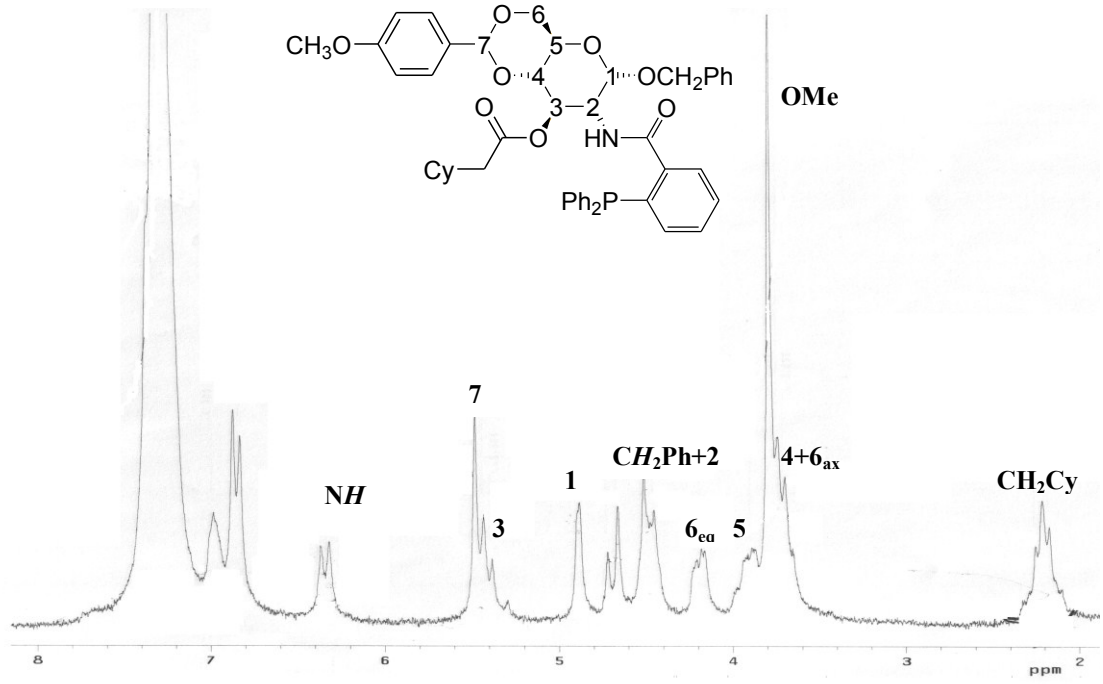
^{1}H NMR spectrum (300 MHz) of **naplephos-b**



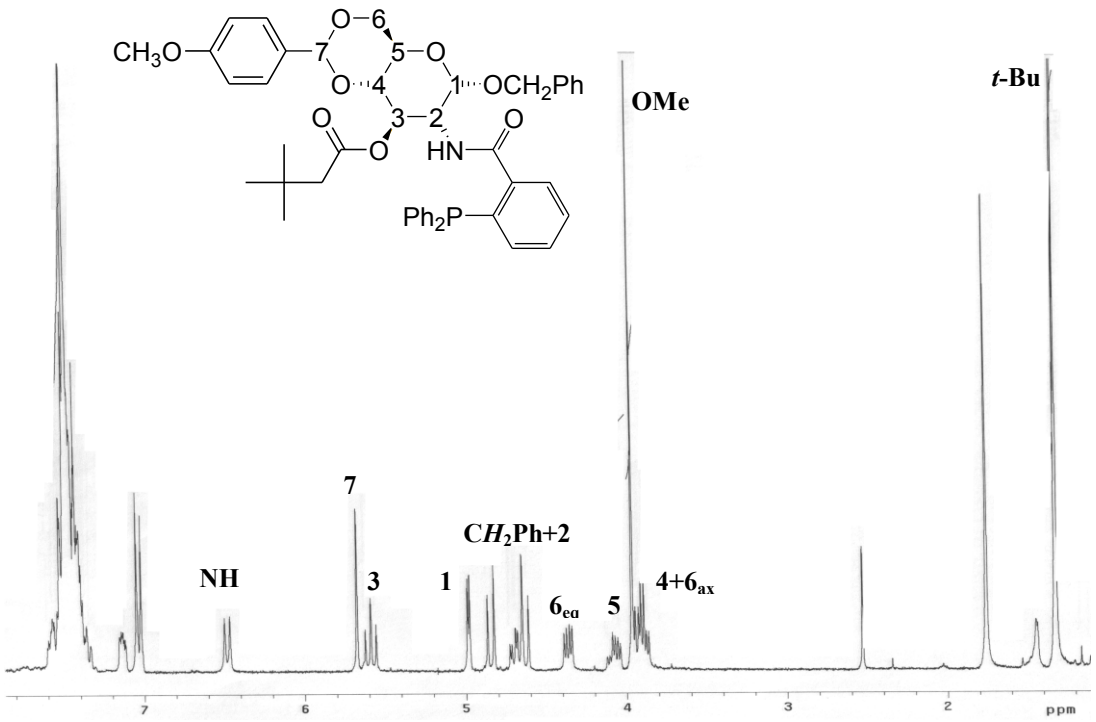
^{1}H NMR spectrum (300 MHz) of **naplephos-c**



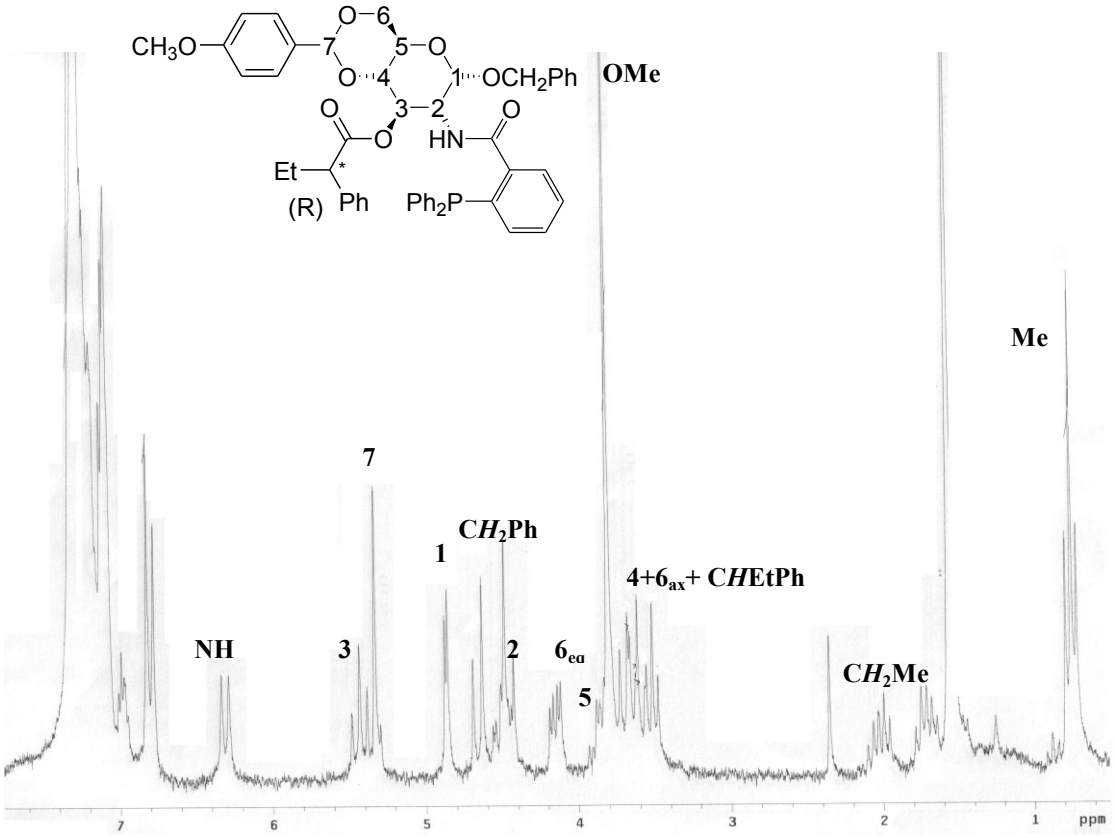
^{1}H NMR spectrum (300 MHz) of **naplephos-d**



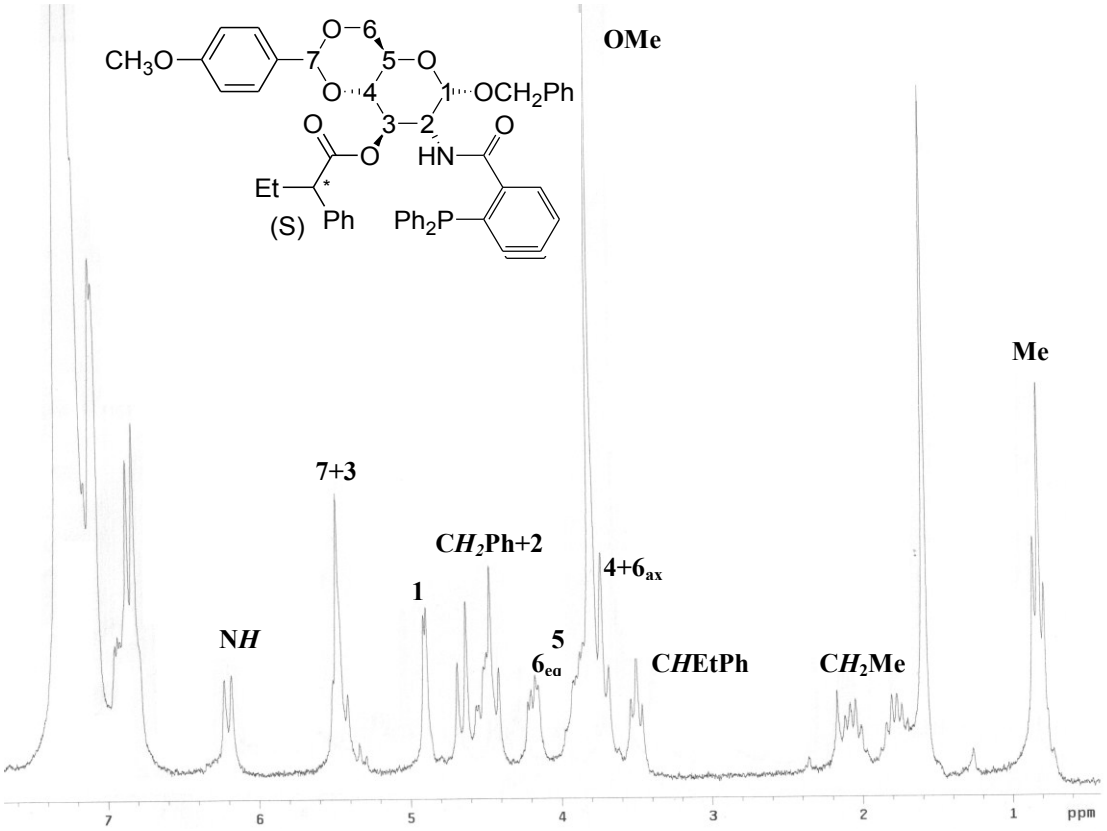
^{1}H NMR spectrum (300 MHz) of **naplephos-e**



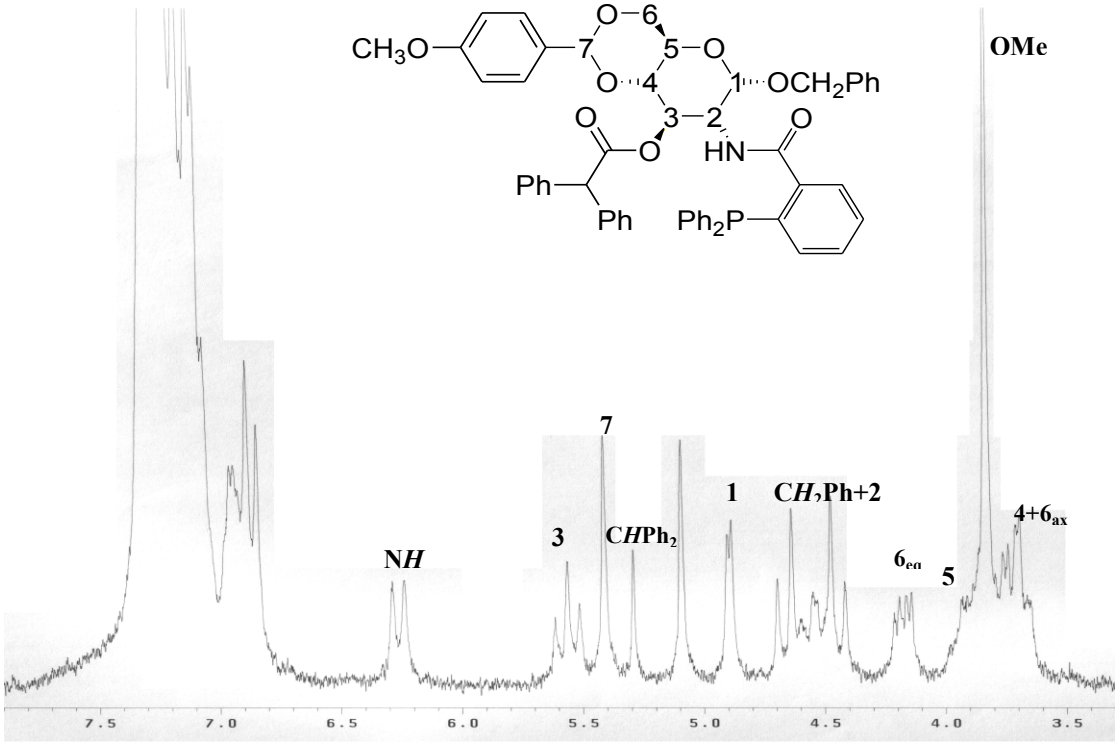
^{1}H NMR spectrum (300 MHz) of **naplephos-f**



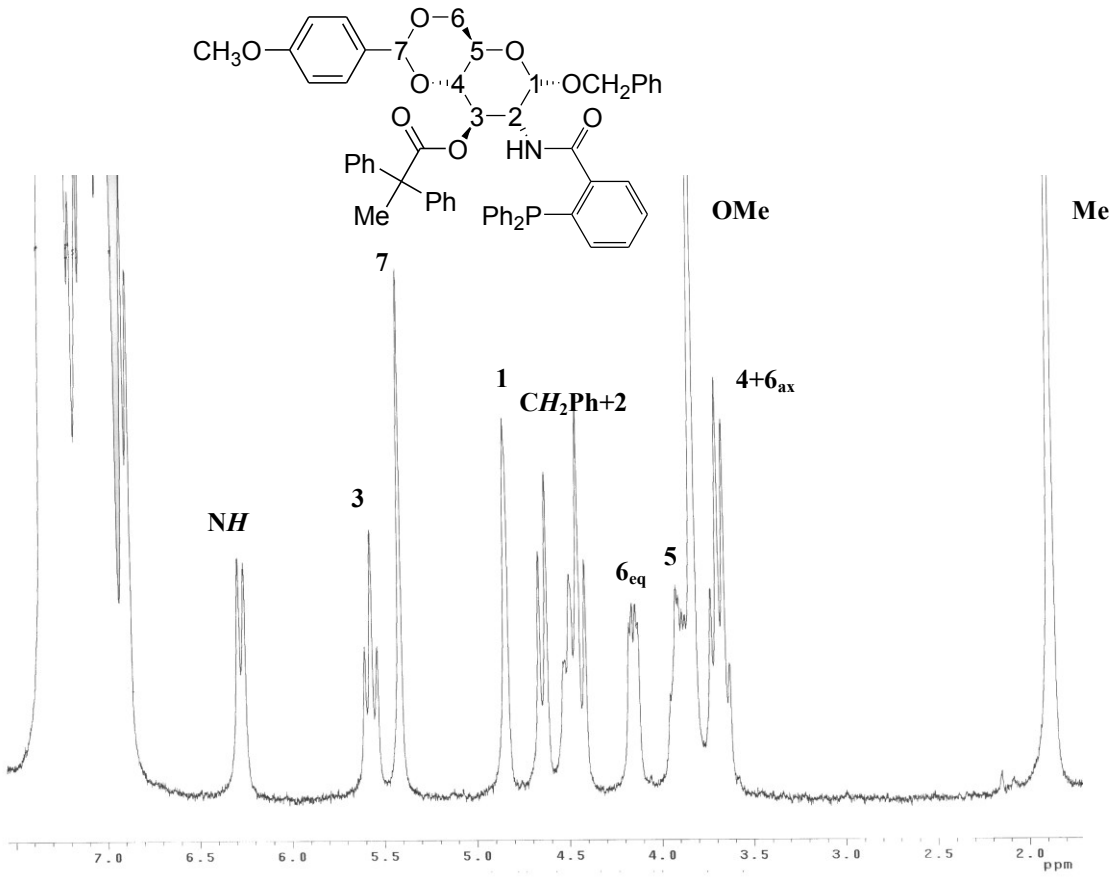
^{1}H NMR spectrum (300 MHz) of **naplephos-g**



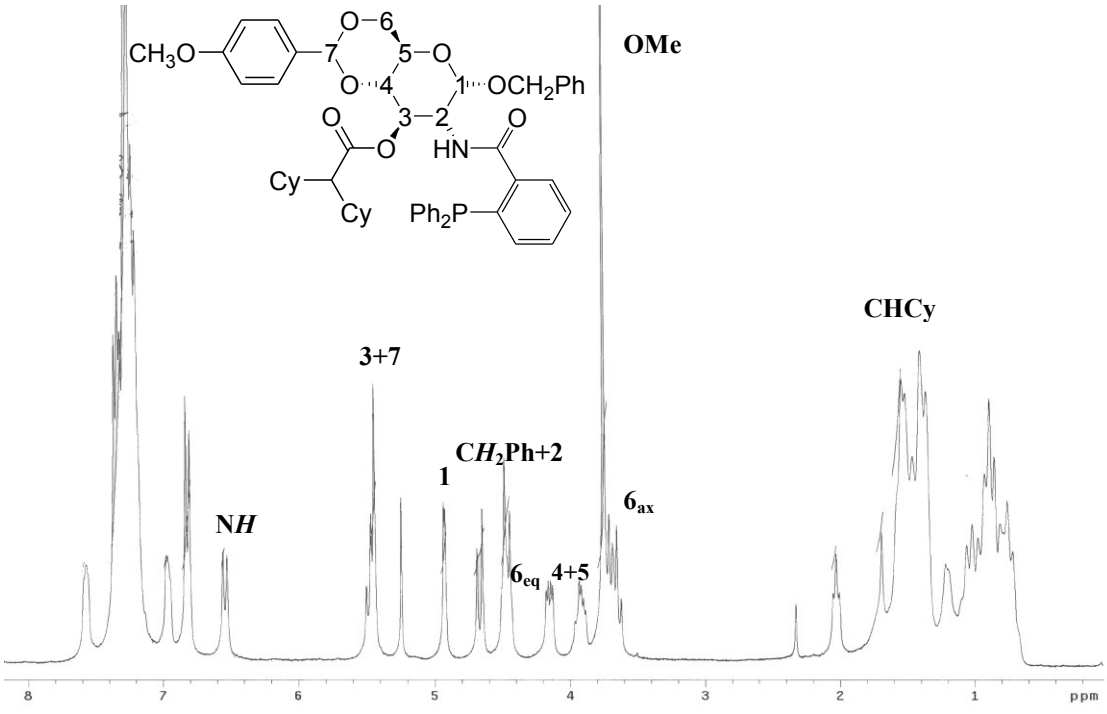
^{1}H NMR spectrum (300 MHz) of **naplephos-h**



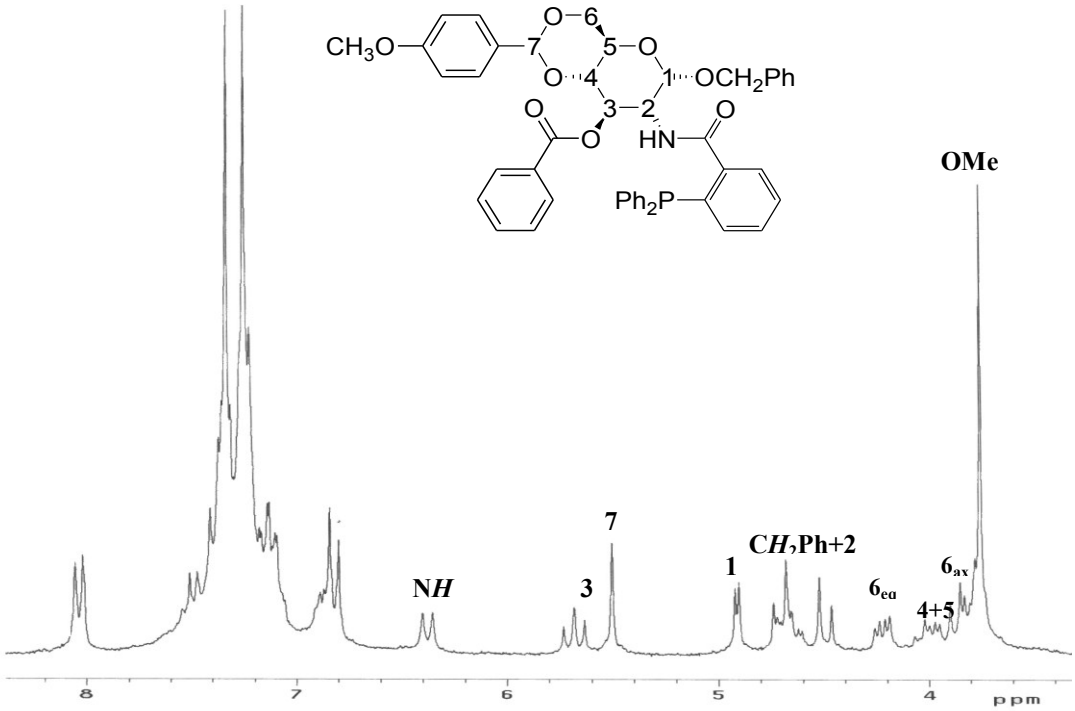
^{1}H NMR spectrum (300 MHz) of **naplephos-i**



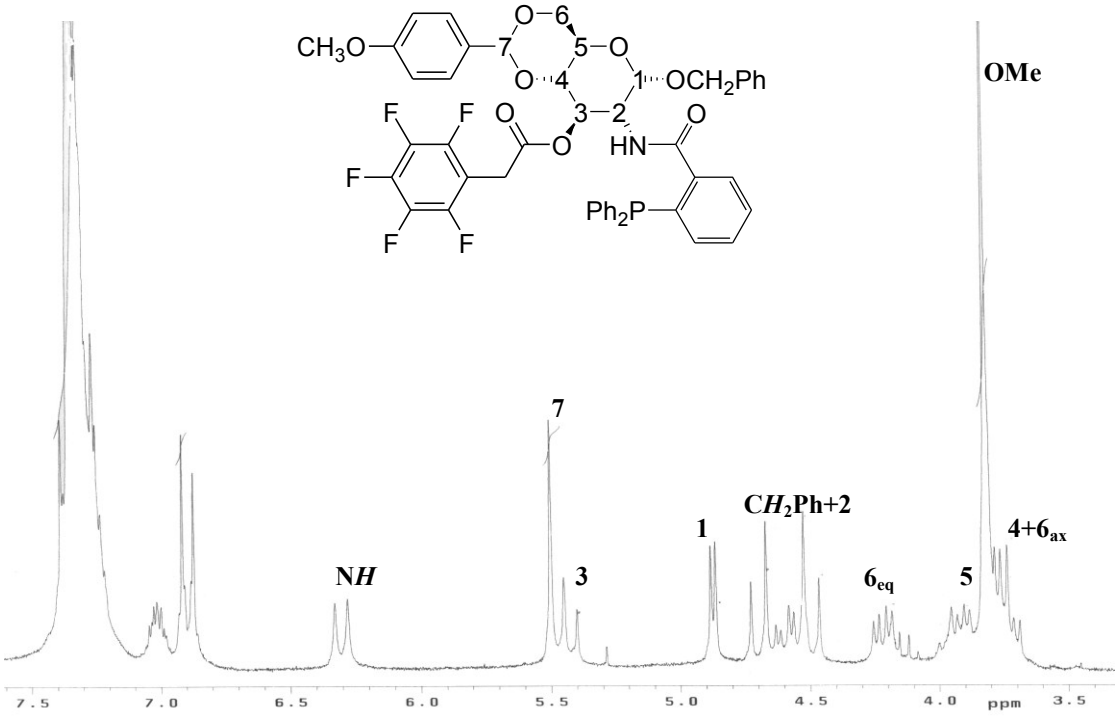
^{1}H NMR spectrum (300 MHz) of **naplephos-j**



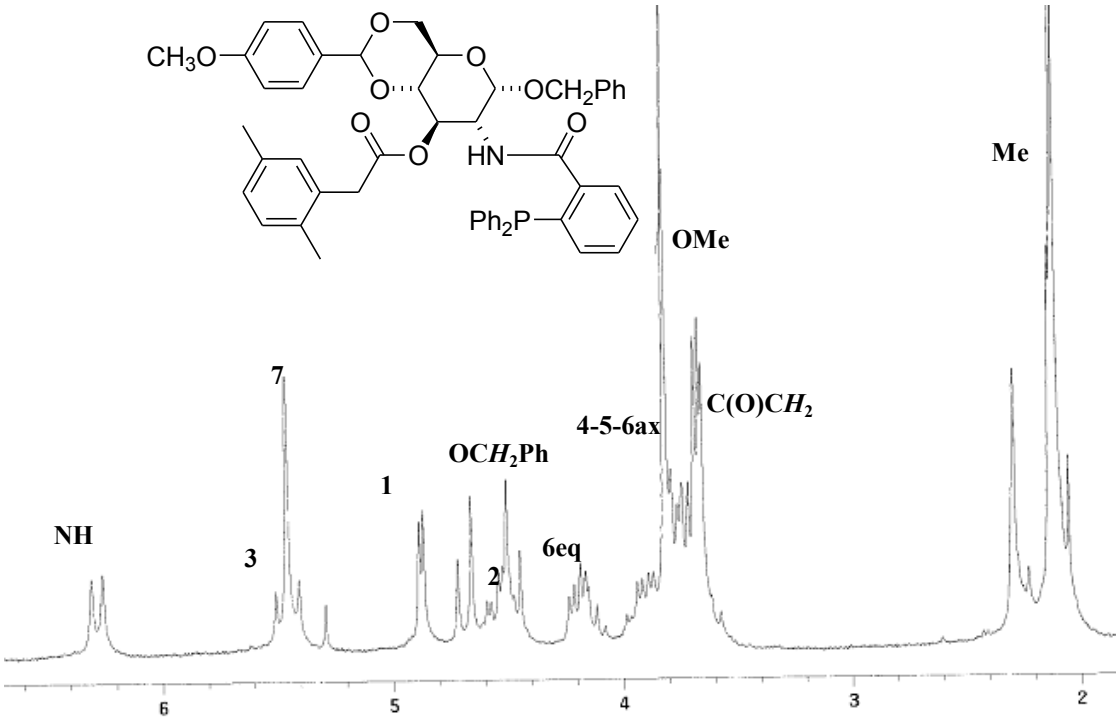
^{1}H NMR spectrum (300 MHz) of **naplephos-k**



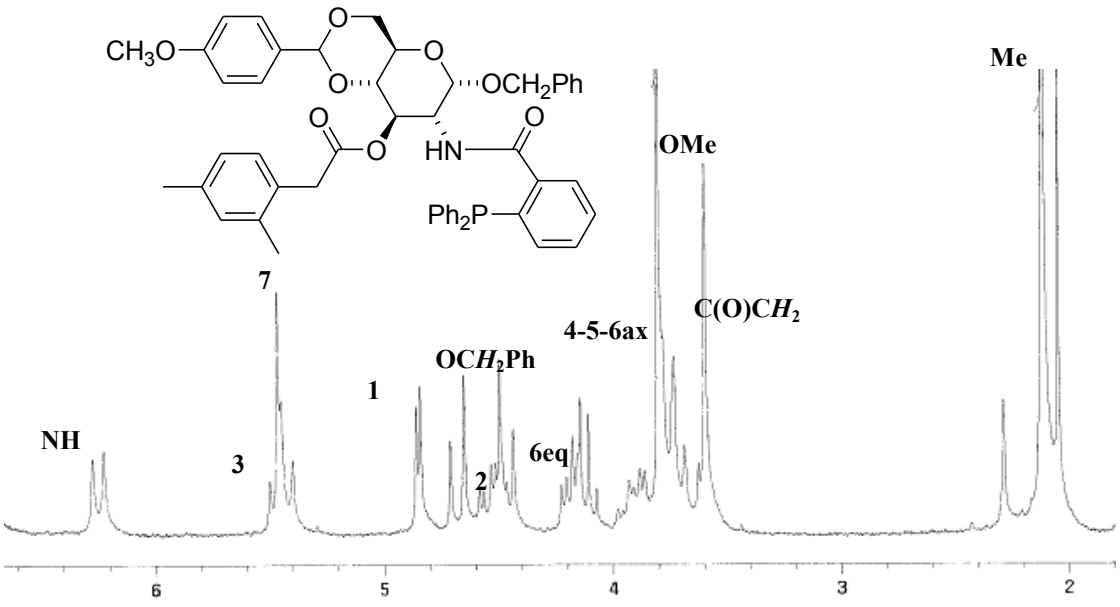
^{1}H NMR spectrum (300 MHz) of **naplephos-l**



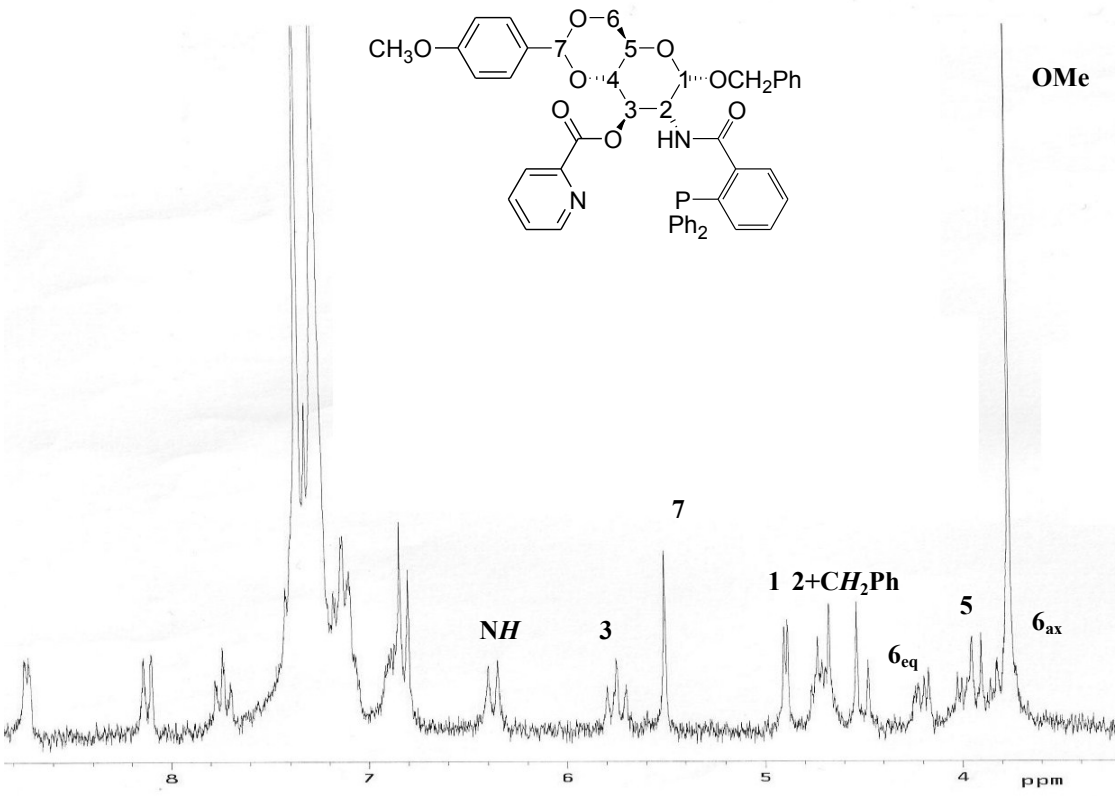
^{1}H NMR spectrum (300 MHz) of **naplephos-m**



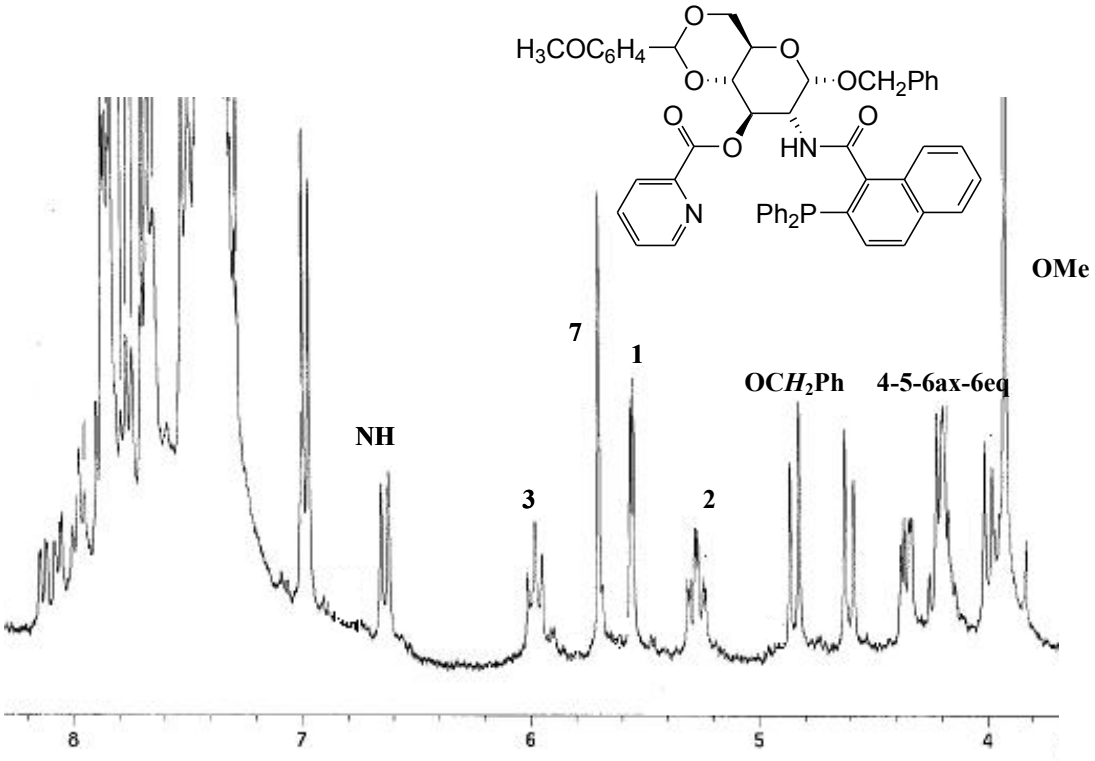
^{1}H NMR spectrum (300 MHz) of **naplephos-n**



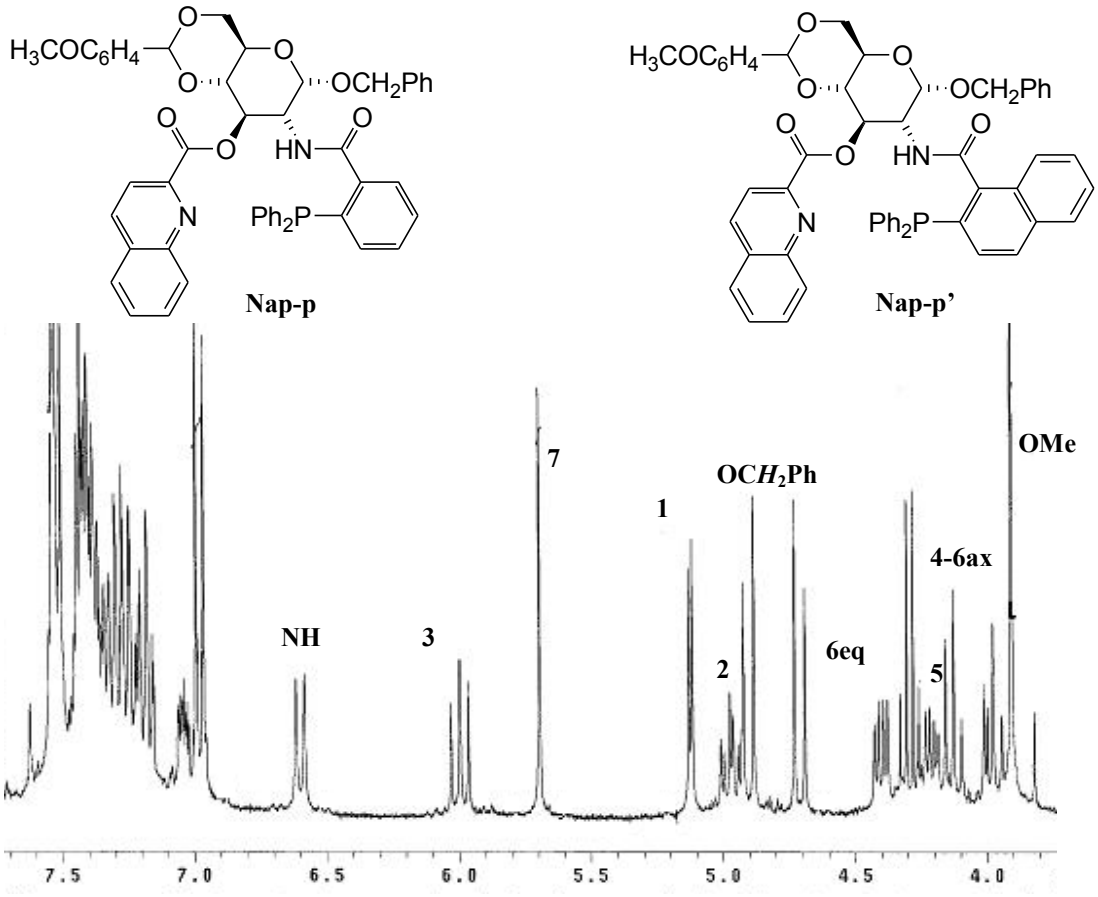
^{1}H NMR spectrum (300 MHz) of the **naplephos-o**



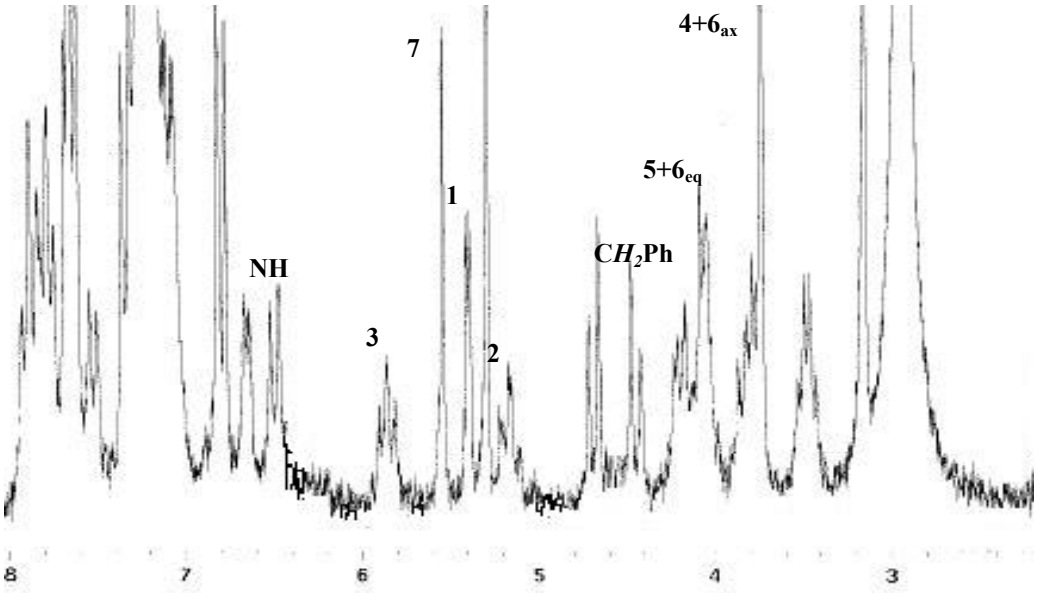
^{1}H NMR spectrum (300 MHz) of the **naplephos-o'**



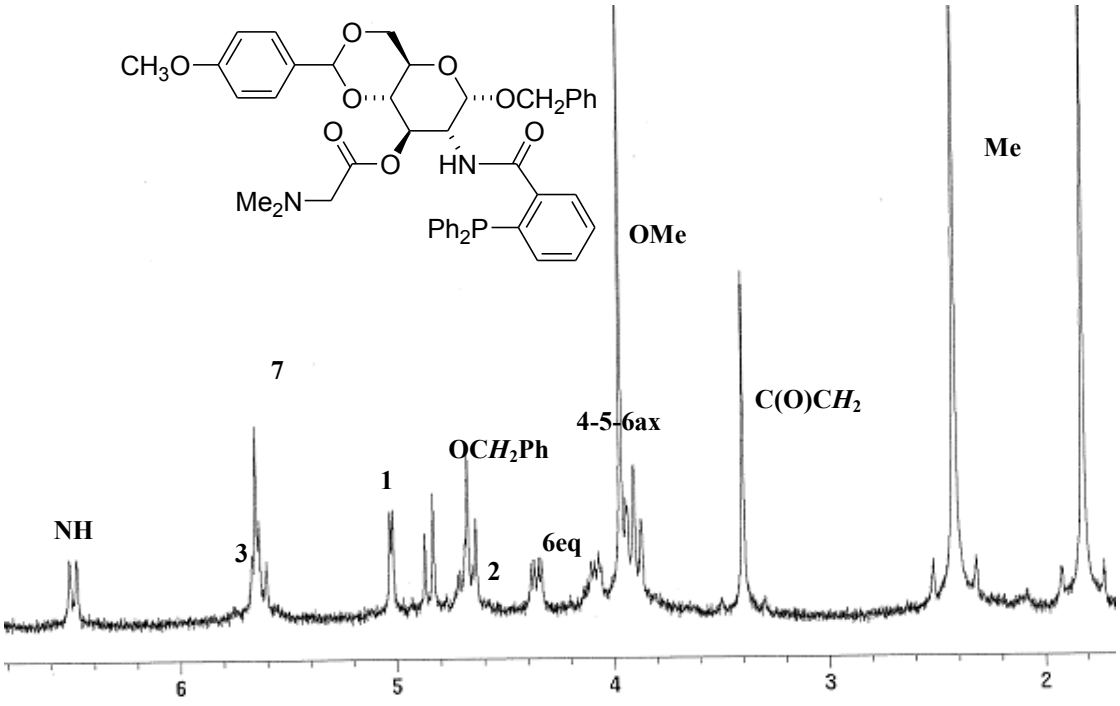
^{1}H NMR spectrum (300 MHz) of the **naplephos-p**



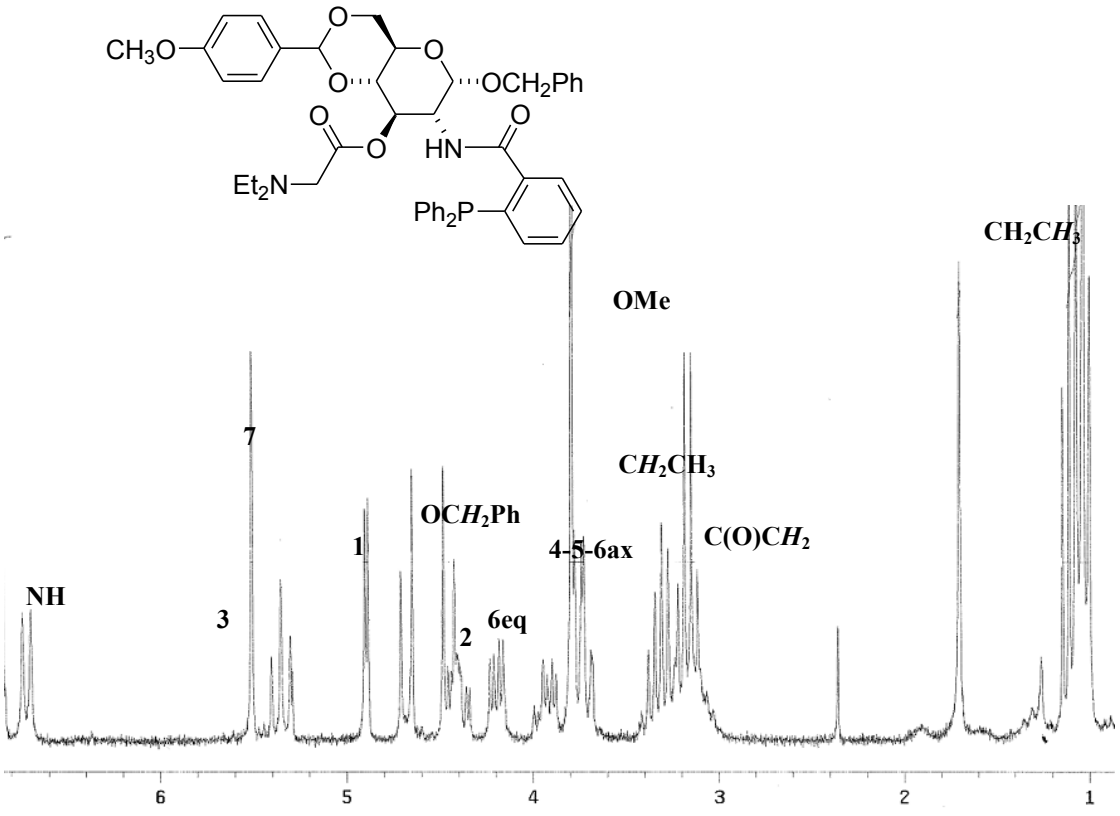
^{1}H NMR spectrum (300 MHz) of the **naplephos-p'**



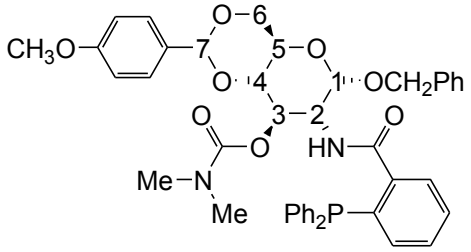
Spettro ^{1}H NMR (200 MHz) del legante **naplephos-q**

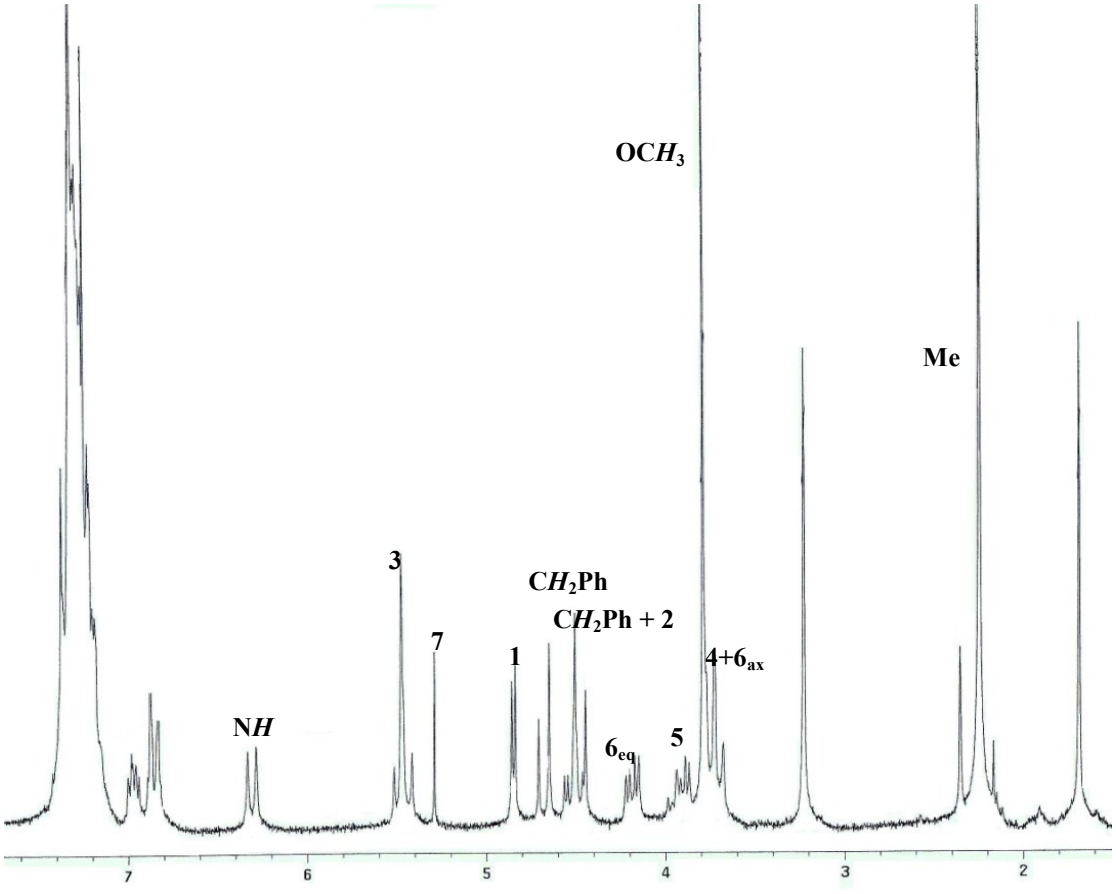


Spettro ^{1}H NMR (200 MHz) del legante **naplephos-r**

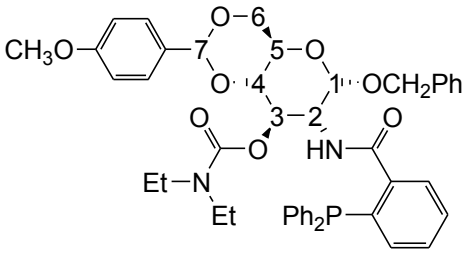


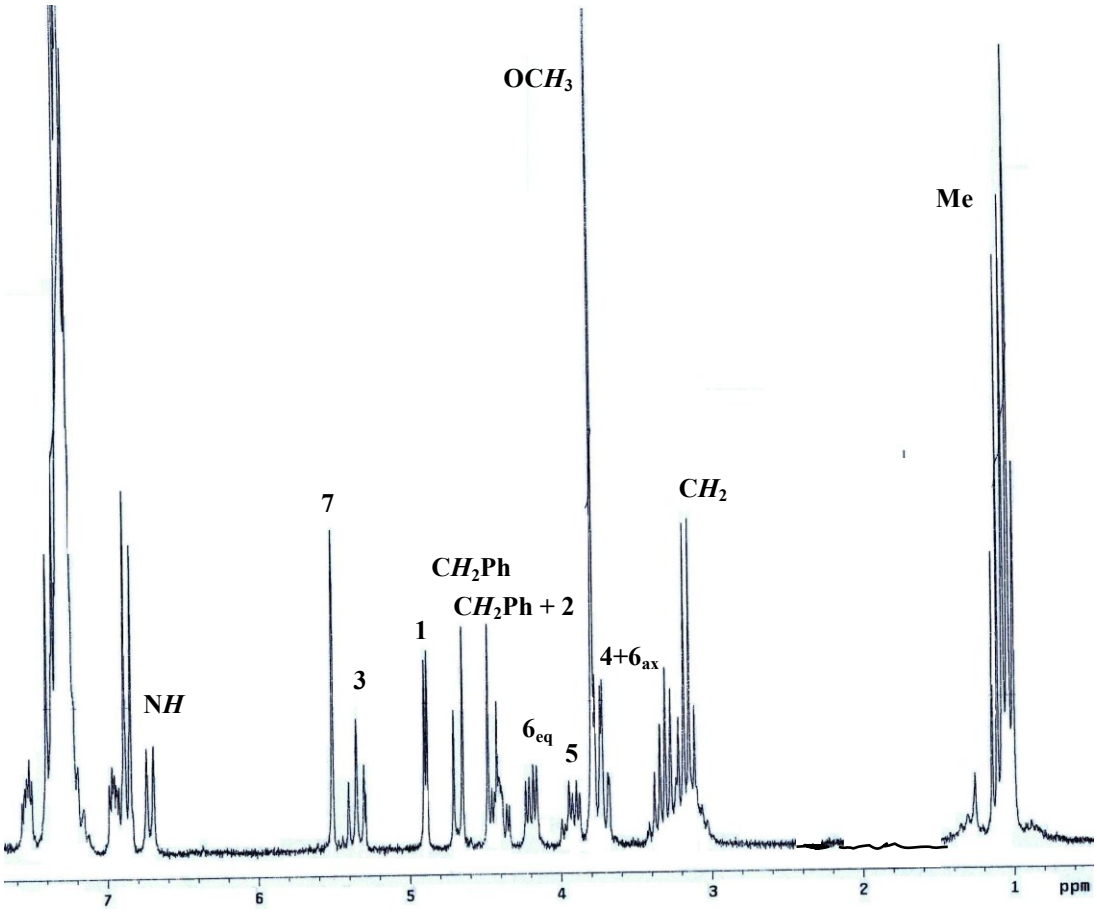
Spettro ^{1}H NMR (200 MHz) del legante **naplephos-s**



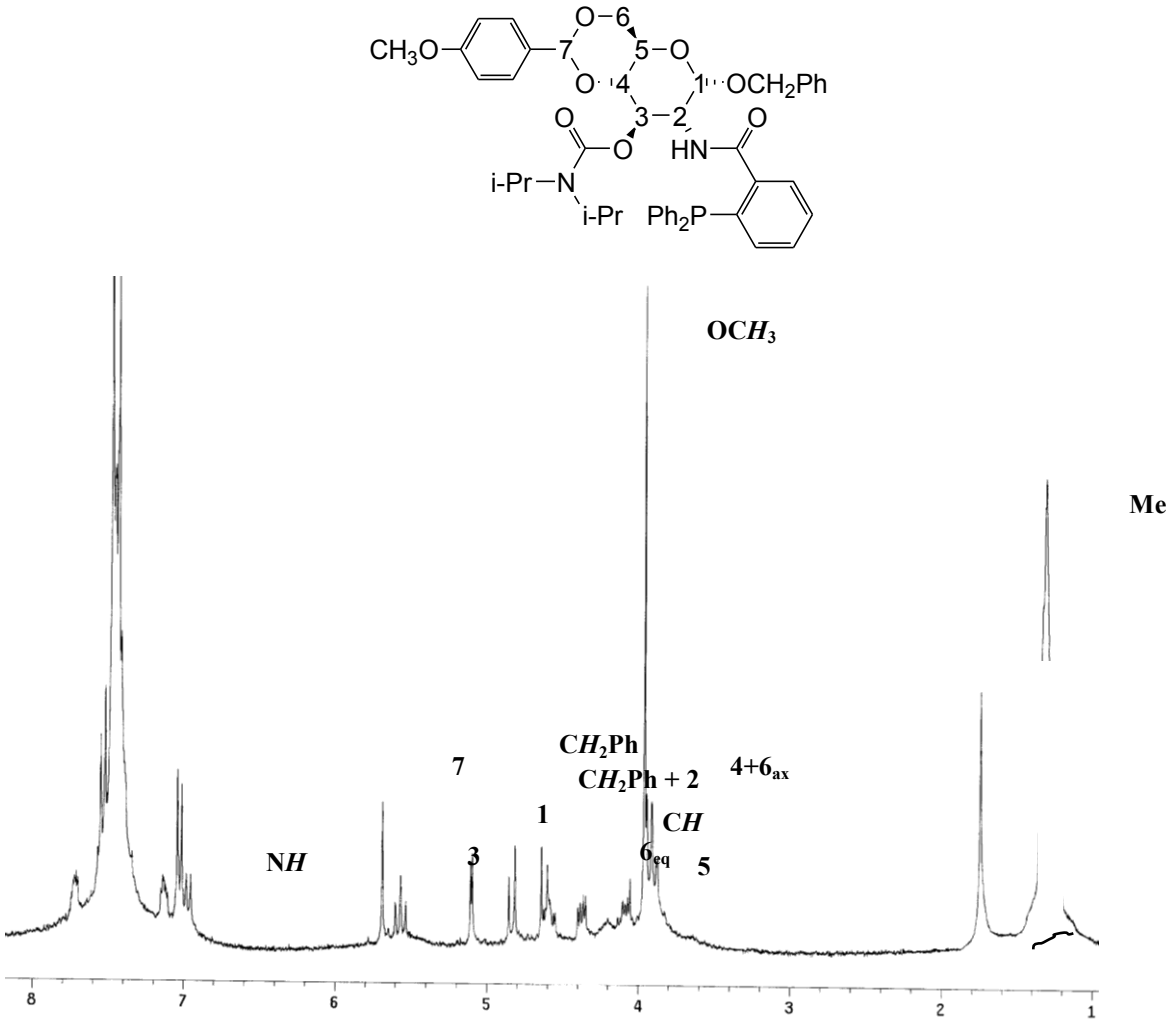


Spettro ^{1}H NMR (200 MHz) del legante **naplephos-t**

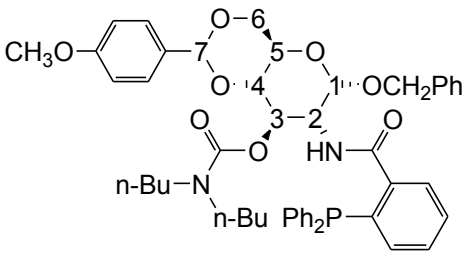


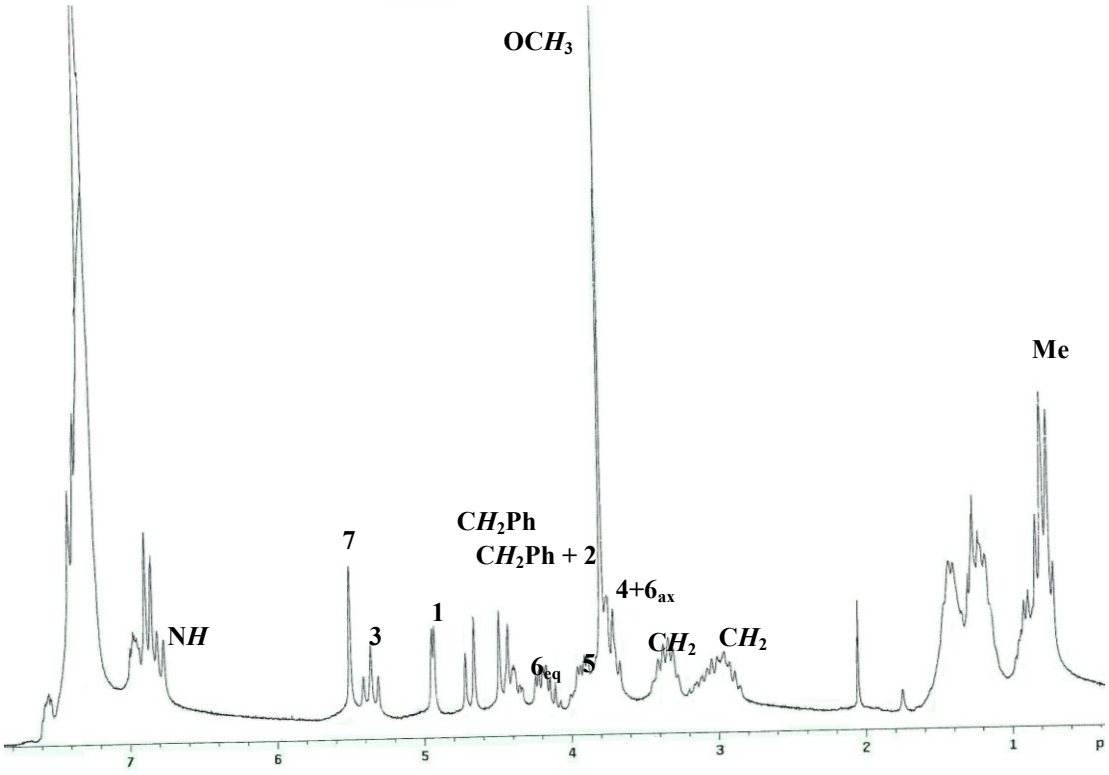


Spettro ^{1}H NMR (200 MHz) del legante **naplephos-u**

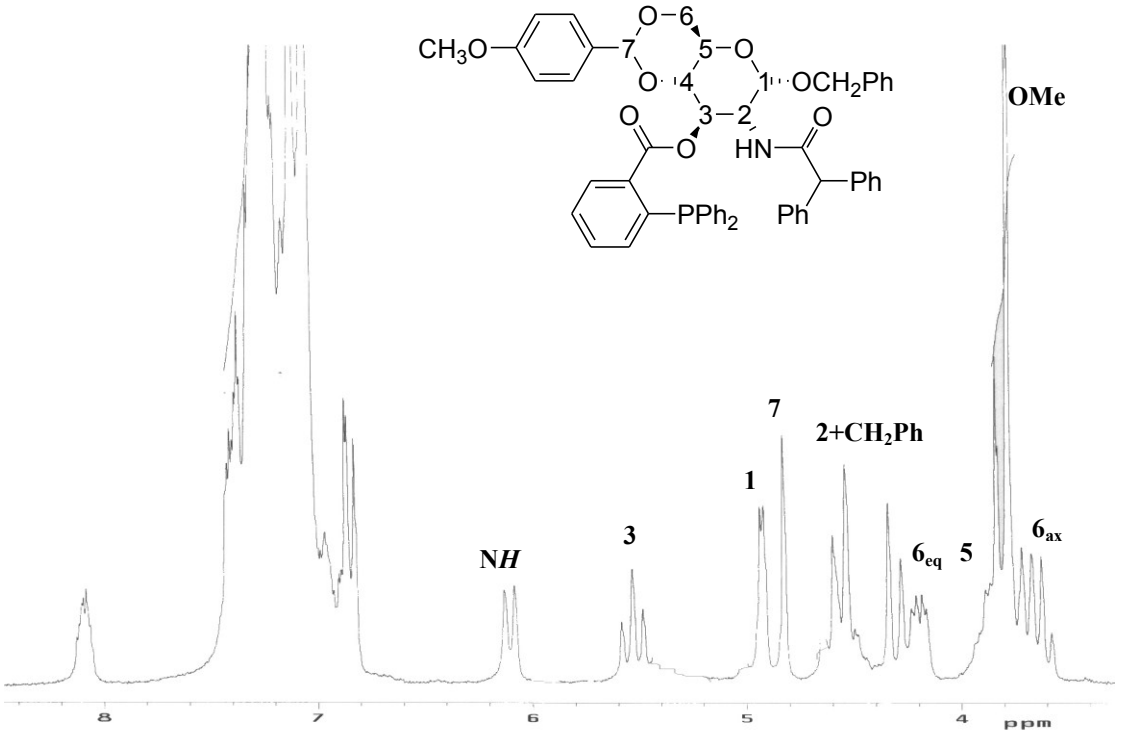


Spettro ^{1}H NMR (200 MHz) del legante **naplephos-v**

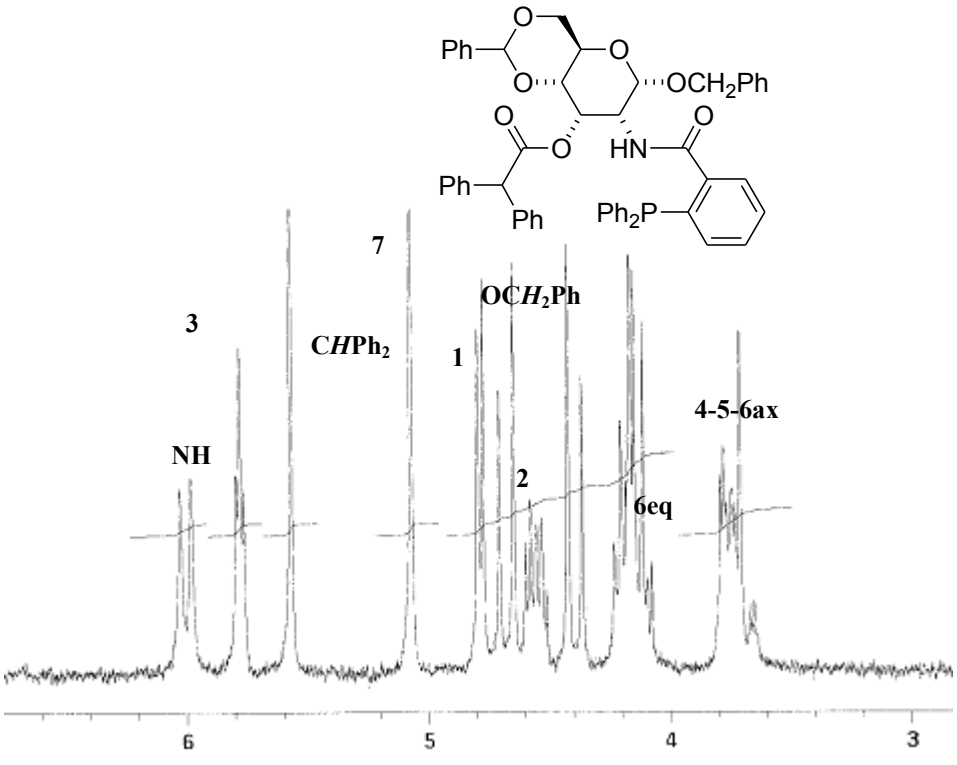




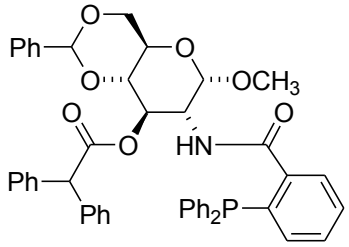
^{1}H NMR spectrum (300 MHz) of the **L1**

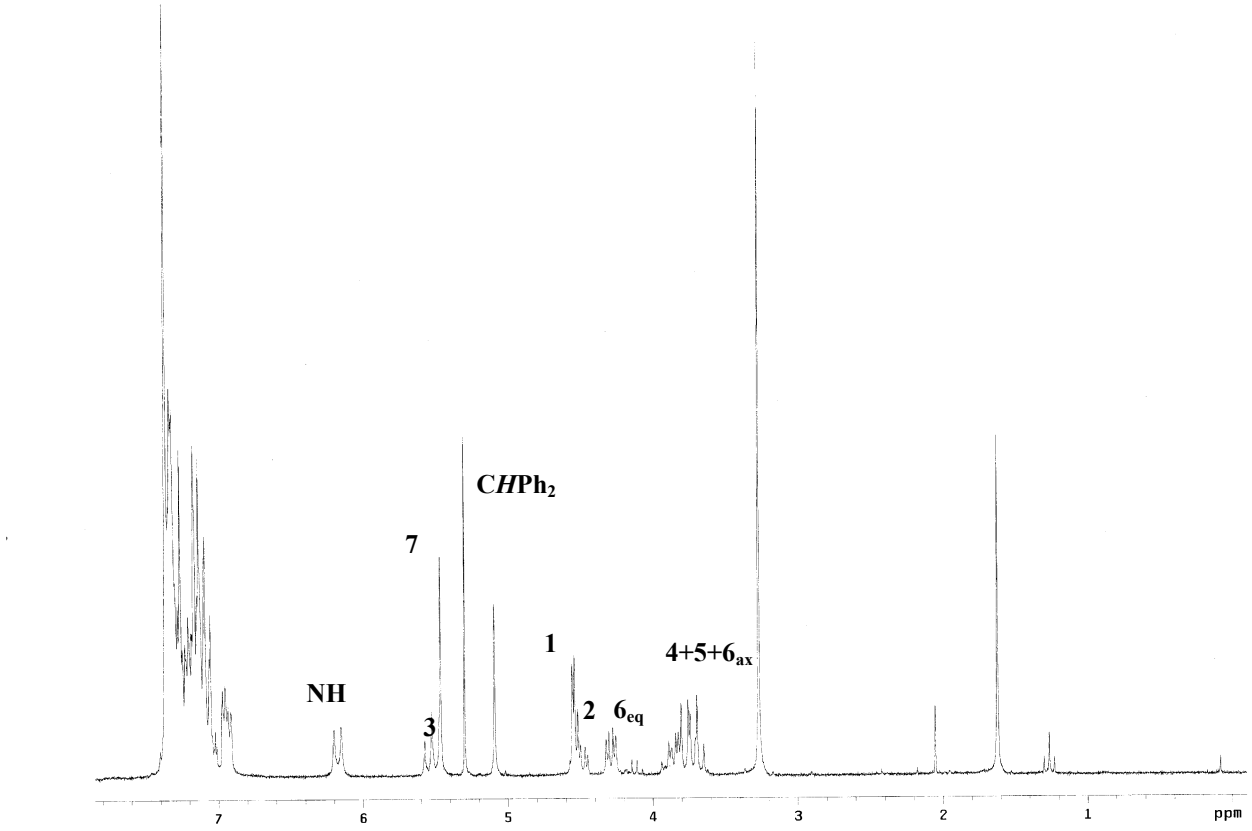


^{1}H NMR spectrum (300 MHz) of the **L2**

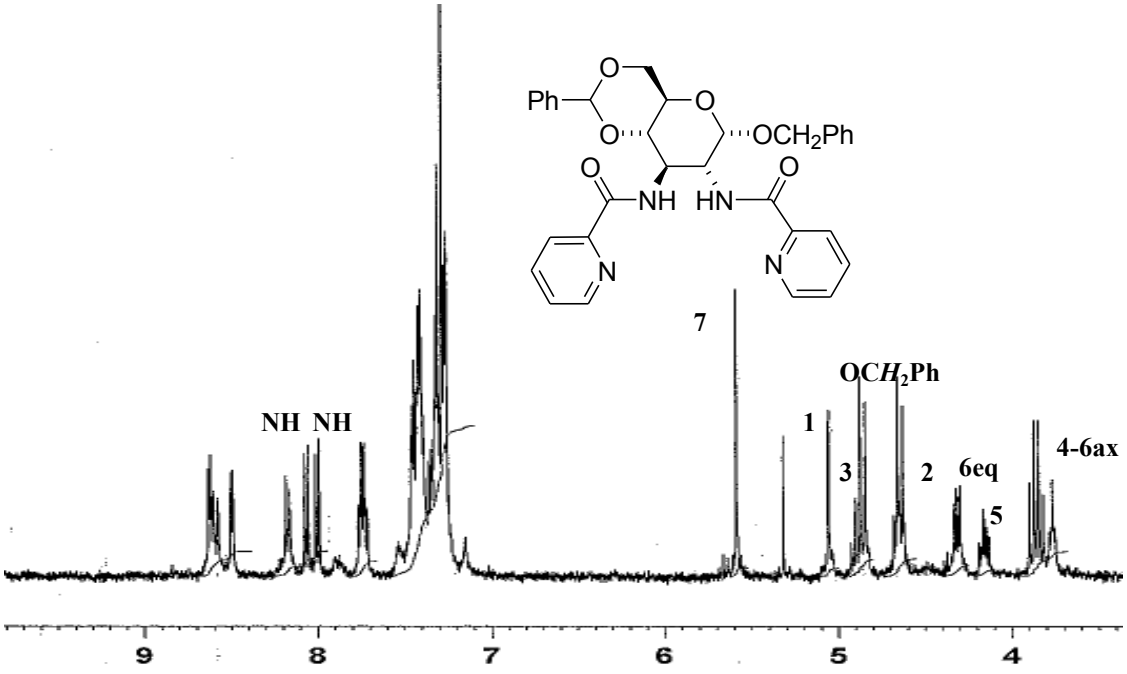


^{1}H NMR spectrum (300 MHz) of the **L3**

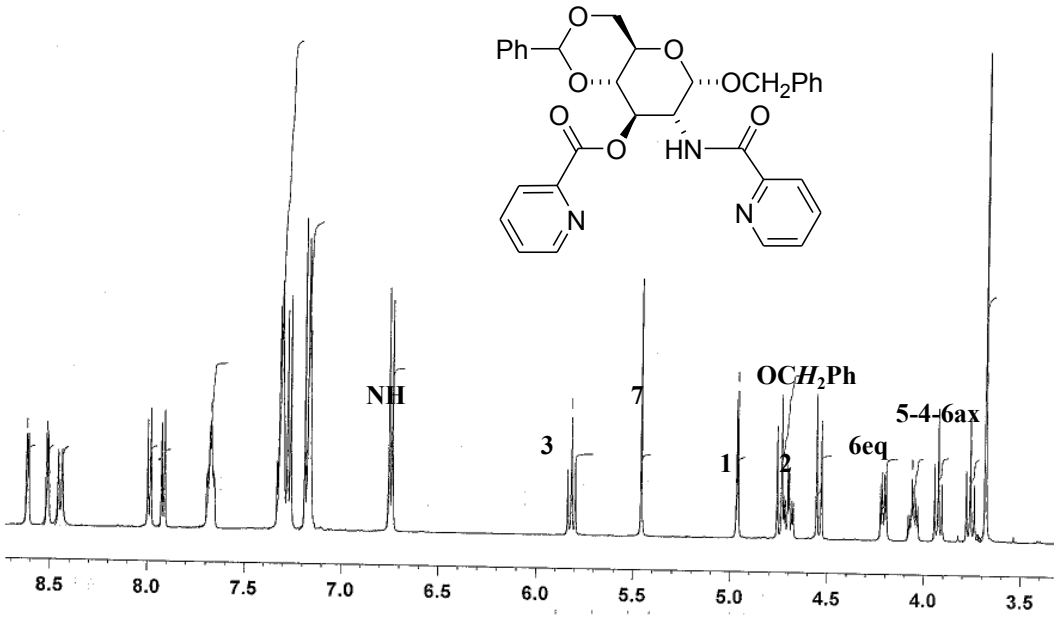




^{1}H NMR spectrum (300 MHz) of the **L4**



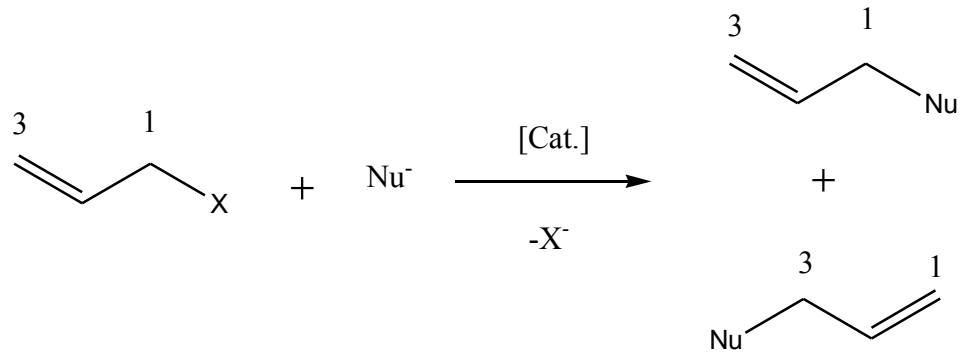
^{1}H NMR spectrum (300 MHz) of the **L5**



2.3 THE HOMOGENEOUS PHASE Pd-CATALYSED ASYMMETRIC ALLYLIC ALKYLATION (AAA)

2.3.1 GENERAL CONSIDERATION

AAA (**Scheme 2.10**) has several applications in the field of target molecules synthesis of fine chemistry.[6] As a matter of fact this reaction is involved in really versatile processes and are widely employed in the enantioselective formation of carbon-carbon or carbon-heteroatom bonds of optically active compounds,[7] useful in biological, pharmaceutical or flavours field.



Scheme 2.10

AAA often proceed under much milder conditions than ordinary S_N2 or S_N2' reactions, and with different chemo-, region- and stereoselectivies. Typical leaving groups are acetates and carbonates, rather then the more reactive halides or sulfonates, which may be a considerable advantage in the synthesis of complex multifunctional compounds.

---

[6] (a) *Encyclopedia of Reagents for Organic Synthesis*, L.A. Paquette, Ed.: J. Wiley and Sons: Sussex, England, **1996** (b) J.Tsuji, *Tetrahedron Lett*. **1965,** 4387. (c) B.M.Trost, T.J.Fullerton, *J.Am.Chem.Soc*, **1973**, *95*, 292. (e) Trost, B. M.; Tang, W.; Toste, *J. Am. Chem. Soc.* **2005**, *127*, 14785.

[7] B. M. Trost *Chem. Pharm. Bull.* **2002** *50*(1*) 1-14* and reference within.

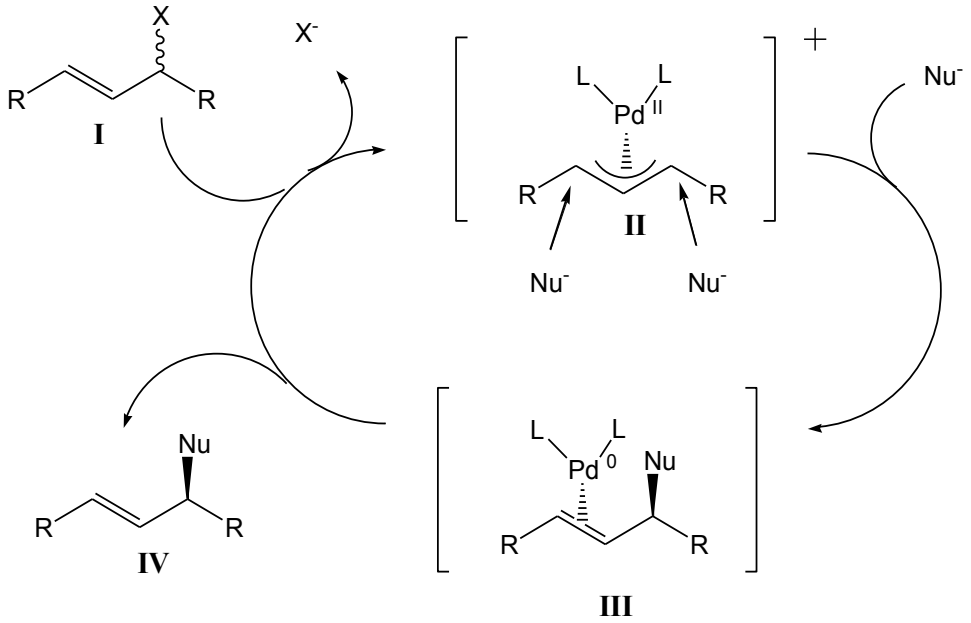
By changing the metal or the ligand, it is often possible to tune the reactivity or selectivity of the catalyst, according to the specific requirement of a particular application. A variety of transition metal complexes derived from Pd, Ni, Ru, Rh, Ir, Mo, W, and other elements are known to catalyze AAA. The most widely used are Pd catalyzed reactions with "soft" nucleophiles, such as stabilized carbanions or amines.

The variety of enantiodiscrimination mechanisms and bond types makes AAA promoted by Pd a good solution to simplify the synthetic strategy of elaborate intermediates and chemicals.

2.3.2 REACTION MECHANISM

The mechanism of Pd catalyzed AAA with soft nucleophiles has been firmly estabilished, and a detailed picture of the catalytic cycle can be drawn[8] **(Scheme 2.11)**.

[8] (a) Tsuji, J.; *Organic synthesis with Pd compounds. Sprinter, Berlin heidelberg New York,* **1980** (b) Trost B.M.; Verhoeven T. R.; in : Wilkinson G.; Stone F.G.; Abel E.W.;(eds) *Comprehensive organometallic chemistry. Pergamon, Oxford, chap 8* **1982***;* (c) Godleski S.A. in: Trost B.M.; Fleming I.; Semmelhack M.F.; (eds) *Comprehensive organic synthesis, Pergamon, Oxford, vol4, chap 3.3*, **1991** (d) Frost C.G.; Howart J., Williams J.M.J.; *Tetrahedron asymmetry,* **1992**, 3, 1089 (e) Tsuji J.; *Palladium reagnts and catalysts, innovation in organic synthesis, Wiley, Chinchester.* **1995** (f) Heumann A., in: Beller M.; Bolm C. (eds) *transition metals for organic synthesis, Wiley-VCH, Weinheim, vol1, chap 2.15*; **1998** (g) Consiglio G.; Waymouth R.M.; *Chem Rev* **1989** 89, 257 (h) Hayashi T. in: Ojima I. (ed) *Catalytic assymmetric synthesis, VCH, New York, chap 7.1***, 1993** (i) Trost B.M., Van Vranken D.L., *Chem Rev* **1996** 96, 395



Scheme 2.11

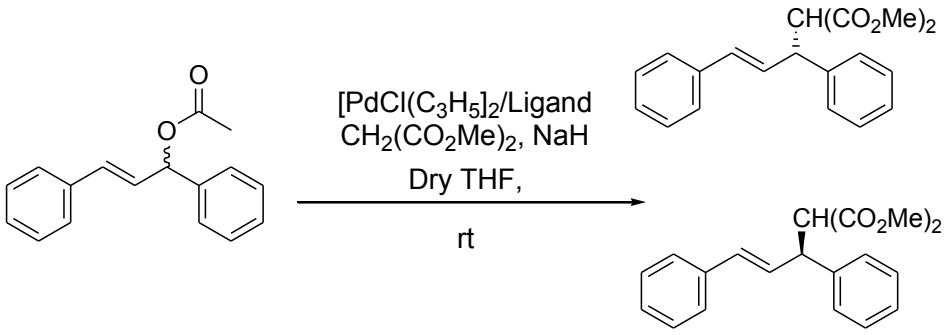
An allylic substrate **I,** tipically an acetate or a carbonate, react with the catalyst, which enters the catalytic cycle at the Pd (0) oxidation level. Both Pd(0) and Pd (II) can be used as precatalysts, because Pd(II) is easily reduced in situ to activate Pd(0) form. The reaction is initiated by formation of a π-complex which eliminates X^- to produce an (η^3-allyl)Pd(II) complex. The product of this oxidative addition can be a cationic complex **II**, or a neutral complex if the resulting anion X^- coordinates to the Pd. The equilibrium between cationic and neutral forms depends on the nature of the ligands as well as on other factors such as the solvent and the anion. Bidentate ligands usually favour the cationic form, which is more reactive towards nucleophiles, because of the strong preference of Pd(II) for a square-planar coordination geometry. Allyl complexes **II** can isomerize in various way (π-σ-π isomerization, apparent allyl rotation, Pd(0)-catalyzed allyl exchange), and this can have important consequences for the course of the reaction. If **I** has identical substituent at C1 and C3, starting from either enantiomer the same allyl-palladium complex is formed. Therefore, the first part of the catalytic cycle leading to this intermediate usually is irrelevant for the

stereoselectivity of the overall reaction. The two termini of the free allyl are enantiotopic; if the catalyst is chiral, they become diastereotopic in the allyl-metal complex and, therefore, may hexibit different reactivities.

The electrophilic Pd(II) center activates the allyl system for nucleophilic attack at the allyl termini. Addition of the nucleophile at C1 or C3 generates an unstable Pd(0)-olefin complex **III**, which readly relases the final product **IV** and undergoes oxidative addition to another substrate molecule.

2.3.3 CATALYTICAL TESTS ON rac-1,3-DIPHENYL-2-PROPENYL ACETATE

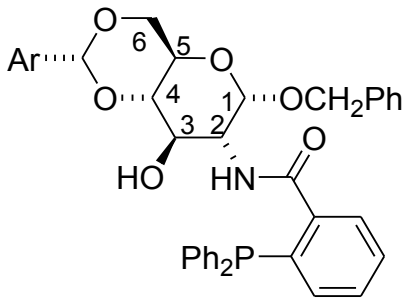
All the ligands synthesized were tested in the asymmetric allylic alkylation of *rac*-1,3-diphenyl-2-propenyl acetate with Sodium dimethylmalonate (**Scheme 2.12)** (see experimental section for detailes):



Scheme 2.12

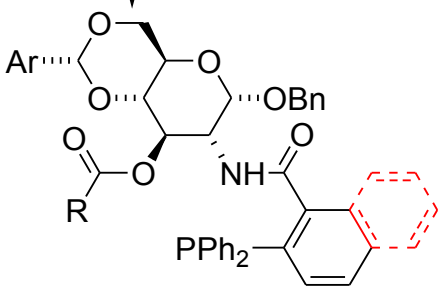
The results are reported in the following table (**Table 2.1**):

a, R= o-C_6H_4-PPh_2
b, R= Me
c, R= CH_2Ph
d, R= CH_2Cy
e, R= t-Bu
f, R= (R)-CHEt(Ph)
g, R= (S)-CHEt(Ph)
h, R= $CHPh_2$
i, R= $CMePh_2$
j, R= $CHCy_2$
k, R= Ph
l, R= $CH_2C_6F_5$
m, R= CH_2Ph(2,5-bis-Me)
n, R= CH_2Ph(3,5-bis-Me)
o, R= o-Py o', R + naftoic in 2
p, R= o-Chinaldic p', R + naftoic in 2
q, R= CH_2NMe_2
r, R= CH_2NEt_2
s, R= NMe_2
t, R= NEt_2
u, R= N(isoprop)$_2$
v, R= N(But)$_2$

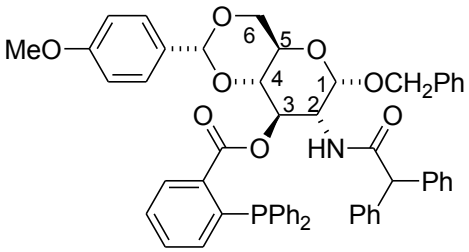


OP intermediate

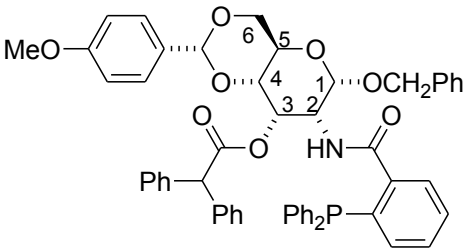
(v)



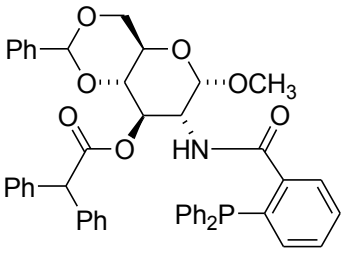
naplephos



L1



L2



L3

No.	Ligand	Cone angle[a] (°)	Charton parameter[a]	Conversion (%)[b]	Time (h)	ee (S)[c] (%)
1	**naplephos b**	87	0.52	>99	8	39
2	**naplephos c**	106	0.70	>99	5	85
3	**naplephos d**	115		>99	2	87
4	**naplephos e**	118	1.24	>99	2	89
5	**naplephos f**	121	1.18	>99	2	91
6	**naplephos g**	121	1.18	>99	2	86
7	**naplephos h**	126	1.25	>99	2	91
8	**naplephos i**	136		>99	18	80
9	**naplephos j**	144		>99	18	80
10	**naplephos k**			>99	18	45
11	**naplephos l**			50	18	60
12	**naplephos m**	160		>99	5	60
13	**naplephos n**	160		70	24	63
14	**L1**			>99	2	0
15	**naplephos a**			>99	2	-33 (R)
16	**OP**			80	18	50
17	**naplephos o**			>99	18	70
18	**naplephos o'**			>99	18	-50 (R)
19	**naplephos p**			>99	18	70
20	**naplephos p'**			60	18	-20 (R)
21	**naplephos q**			>99	18	70
22	**naplephos r**			>99	18	73
23	**naplephos s**	87		>99	12	30
24	**naplephos t**	106		>99	18	61
25	**naplephos u**	118		>99	18	90
26	**naplephos v**			>99	18	52

Reaction conditions: rt, 0.25 mmol of substrate, 0.75 mmol of dimethylmalonate, 0.75 mmol of NaH, 0.0050 mmol of $[Pd(\mu\text{-}Cl)(\eta^3\text{-}C_3H_5)]2$, 0.022 mmol of ligand.

[a] Relative to the R substituent at the carbonyl α-position. Taken, respectively, from Refs. 8 and 9(a),(b).

[b] Evaluated by NMR spectroscopy of the crude reaction mixture.

[c] Determined by HPLC on Chiracel OD-H, using 2-propanol/hexane 2:98, 1.0 mL/min, UV, 254 nm. (R) 9.6min., (S) 10.3 min.

Table 2.1

After some preliminary runs, the ligand/Pd ratio was conveniently set to 2:1 in most of the experiments (see below). All the reactions were complete within a few hours, affording the expected product as the only one. A neat trend was observed, in that both the conversion and the enantioselectivity showed a clear dependence upon the steric hindrance of the ester substituent in 3 (**Table 2.1** also reports both the cone angles[9] and the Charton parameters[10] of some R group). The gradual increase in the dimension of the R group along the series **naplephos-b** through **naplephos-h** (entries 1–9) enhances the performance of the catalyst, reaching a maximum which corresponds to a cone angle within 120–126° (entries 5–7). Further enlargement decreases both the activity and the selectivity (entries 8–9). The presence of an additional stereocenter in the ester group R has little effect on the catalyst performance. In fact, similar enantioselectivity and conversion rate were observed when using **naplephos- f** and **naplephos-g** (entry 5 vs entry 6), which only differ in the configuration of this substituent [R = (R)-CH(Et)Ph and (S)-CH(Et)Ph, respectively]. In other words, the significant steric role of the substituent is independent of its configuration. **Naplephos-k** and **naplephos-o** have similar hindrance, but differ for the coordinating ability of Py versus Ph. The similarity of the performance of this two ligands (same activities, mediocre enantioselectivity) confirm what was demonstrated by study on naplephos **o-v** ligands (entry 17-26), i.e. tuning of the steric hindrance on the C3 is more important than tuning the electronic proprieties on the same group for this ligands, in this case N sp^2 or sp^3. According to this behaviour when we use different steric hindrance also on a sp^3 N atom we just have significant enhancement in ee with more bulky group (entry 23-26).

[9] Taken from: http://www.bu.edu/qale/.
[10] (a) Charton, M. *J. Am. Chem. Soc*. **1969**, *91, 615*; (b) Charton, M. *J. Am. Chem. Soc*. **1975***, 97, 3691*. (c) Sigman, M. S.; Miller, *J. J. J. Org. Chem*. **2009**, *74, 7663*.

A particular, but not efficient, chiral pocket is active when ligand **naplephos o'-p'** are used: in this case we have a different enantiomer (+R), probably because the steric hindrance on C2 change the isomer of the phosphinoamide. Ligand **L1** gave no enantioselection, probably because different active species are involved.

Thus, best results were obtained with **naplephos-h** [R=$CHPh_2$], which has afforded the product in 91% ee under the given experimental conditions. **Naplephos-h** was therefore selected for further refinement of the results, as reported in **Table 2.2.**

No.	Nucleophile	L/Pd	Additive	Conversion[b] (%)	Time (h)	ee[c] (S) (%)
1[a]	$NaCH(CO_2Me)_2$	1.1/1	-	>99	18	80
2[a]	$NaCH(CO_2Me)_2$	2/1	-	>99	2	91
3[a]	$NaCH(CO_2Me)_2$	4/1	-	>99	0.2	96
4[d,a]	$NaCH(CO_2Me)_2$	2/1	-	>99	2	90
5[e]	$NaCH(CO_2Me)_2$	2/1	-	>99	2	93
6[a]	$NaCH(CO_2Me)_2$	2/1	Bu_4NBF_4[f]	70	4	95
7[a]	$BSA/CH_2(CO_2Me)_2$	2/1	KOAc[g]	>99	5	70
8[a]	$BSA/CH_2(CO_2Me)_2$	2/1	LiOAc[g]	>99	5	86

[a] Reaction conditions: rt, 0.25 mmol of substrate, 0.75 mmol of nucleophile, 0.0050 mmol of $[Pd(\mu\text{-}Cl)(\eta^3\text{-}C_3H_5)]_2$.
[b] Evaluated by NMR spectroscopy of the crude reaction mixture.
[c] Determined by HPLC on Chiracel OD-H, using 2-propanol/hexane 2:98, 1.0 mL/min, UV, 254 nm. (R) 9.6min., (S) 10.3 min.
[d] The catalyst was treated with a stoichiometric amount of $AgBF_4$ prior the addition of the reagents.
[e] Reaction conditions: rt, 0.10 mmol of substrate, 0.30 mmol of nucleophile, 0.0050 mmol of of $[Pd(\mu\text{-}Cl)(\eta^3\text{-}C_3H_5)]_2$.
[f] 0.75 mmol.
g 0.010 mmol.

Table 2.2

The performance of the catalyst could be greatly improved upon by increasing the ligand/Pd ratio (entries 1–3), and the conversion was complete in only 10 min with an ee of 96% when 4 equiv of ligand was

added (entry 3). The addition of a tetrabutylammonium salt (entry 6) increased the enantioselectivity although the reaction rate did decrease. The performance of the catalyst was nearly identical when the chloride ion was preliminarily precipitated as a silver salt (entry 4), while the generation of the nucleophile by using BSA resulted in lower reaction rates and ee's (entries 7 and 8).

2.3.4 INTERPRETATION OF THE RESULTS AND STUDY OF THE COMPLEX

A key argument for the interpretation of the results collected in **Tables 2.1** and **2.2** is the strong dependence of the catalyst's performance on (i) the ligand/palladium ratio (entries 1–3 of **Table 2.2**) and (ii) the steric hindrance of the R group at the 3-position. Therefore, some experiments were addressed to study the coordination modes of **naplephos-h** as a function of the ligand/Pd ratio. In the first test, 1 equiv of **naplephos-h** was added to a THF-d8 solution of the cationic precursor $[Pd(THF\text{-}d8)_n(\eta^3\text{-}C_3H_5)]^+(TfO^-)$.[11,12] The following pieces of diagnostic evidence were observed in the NMR spectra of the resulting complex:

– A shift at high frequency (δ 8.82) of the NH signal in the proton spectrum with respect to the free ligand (δ 7.70).

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[11] Prepared by mixing $[Pd(\mu\text{-}Cl)(\eta^3\text{-}C_3H_5)]_2$ with a stoichiometric amount of AgOTf in 0.6 mL of THF-d8. After filtering AgCl, **naplephos-h** was added to the solution affording the complex. The decision to generate a cationic species by removing the chloride ion from the solution aimed at simulating the catalytic conditions. In fact, it is likely that in the presence of a large excess of sodium ions coming from the malonate salt, precipitation of NaCl occurs, affording cationic Pd compounds, as also proposed by other authors (see reference 11)

[12] (a) Tollabi, M.; Framery, E.; Goux-Henry, C.; Sinou, D. *Tetrahedron: Asymmetry* **2003**, *14, 3329*; (b) Konovets, A.; Głegola, K.; Penciu, A.; Framery, E.; Jubault, P.; Goux-Henry, C.; Pietrusiewicz, K. M.; Quirion, J. C.; Sinou, D. *Tetrahedron: Asymmetry* **2005**, *16, 3183*; (c) Amatore, C.; Jutand, A.; Mensah, L.; Ricard, L. *J. Organomet. Chem*. **2007***, 692, 1457*; (d) Marinho, V. R.; Rodriguez, A. I.; Burke, A. J. *Tetrahedron: Asymmetry* **2008***, 19, 454*.

– The presence of a single resonance at δ 23.3 in the P spectrum.
– A shift at high frequency from δ 169.4 to δ 173.2 of the amido carbonyl group in the carbon spectrum.

According to previous literature,[13] all these features do clearly indicate P,O-chelation through the amide carbonyl function at the 2-position (see **Figure 9** for the [Pd(η^3-allyl)(**P,O-naplephos-h**)]$^+$ complex), and, hence, in the presence of only 1 equiv of ligand, the active species are plausibly cationic chelated complexes [Pd(η^3-allyl)(**P,O-naplephos**)]$^+$.

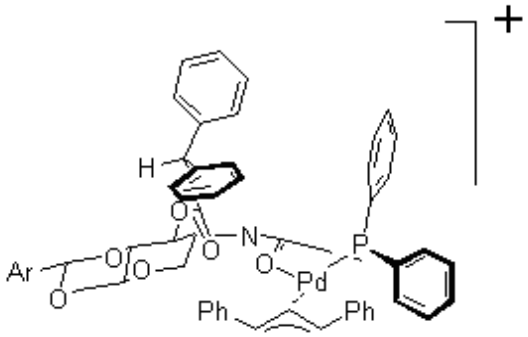


Figure 9

More interesting within this context is what happened upon the addition of the second equivalent of ligand to [Pd(η^3- C_3H_5)(**P,Onaplephos-h**)]$^+$, because these are the conditions which largely favour both conversion and ee (e.g., entry 1 vs entry 2 of **Table 2.2**). The immediate phosphorous spectrum displayed the signal of the free ligand at δ -9.5, along with the aforementioned signal at δ 23.3. On standing, the former signal gradually decreased, while a new singlet at δ 28.5 grew. After a few hours this was by far the prevailing species.

[13] (a)Głegola, K.; Framery, E.; Goux-Henry, C.; Pietrusiewicz, K. M.; Sinou, D. *Tetrahedron* **2007**, *63, 7133* (b) Tollabi, M.; Framery, E.; Goux-Henry, C.; Sinou, D. *Tetrahedron: Asymmetry* **2003**, *14, 3329* (c) Butts, C. P.; Crosby, J.; Lloyd-Jones, G. C.; Stephen, S. C. *Chem. Commun*. **1999**, *1707* (d) Mahadik, G. S.; Knott, S. A.; Sezezepura, L. F.; Peters, S. J.; Standard, J. M.; Hitchcock, S. R. *J. Org. Chem.* **2009***, 74, 8164.*

The contemporaneous shift of the NH signal from δ 8.82 to the original region at around δ 7.7 was also observed. This finding strongly indicates competitive coordination of two phosphines in a C2-symmetrical fashion affording a more active catalytic species when the ligand/Pd ratio is equal to two or higher. By combining these pieces of evidence with the aforementioned dependence of the enantioselectivity on the hindrance of R, the results can be interpreted by assuming that two phosphines coordinate as illustrated in **Figure 10** which represents the most active π-allyl intermediate of the catalytic cycle.[14] According to the mechanism proposed by Pfaltz for C2-symmetrical ligands,[15] the enantioselectivity originates from the different rates of nucleophilic attacks (i and ii) at the allyl carbon termini. These are governed by the rotation[16] of the allyl fragment to give (S)-product and (R)-product, respectively, coordinated in an η^2-fashion in $\mathbf{P_1}$ and $\mathbf{P_2}$. In this case, it is clear how the attainment of $\mathbf{P_2}$ is hampered by steric repulsion between the substituents on the (R)-product and R, and, as a consequence, a gradual increase of the cone angle of R regularly favours the formation of (S)-product.

[14] Tsuji, J. *Palladium Reagents in Catalysis. In Innovation in Organic Synthesis; Wiley: New York,* **1995**

[15] Pfaltz, A.; Lautens, M.. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; *Springer: Berlin*, **1999**; *Vol. 2, Chapter 24;*

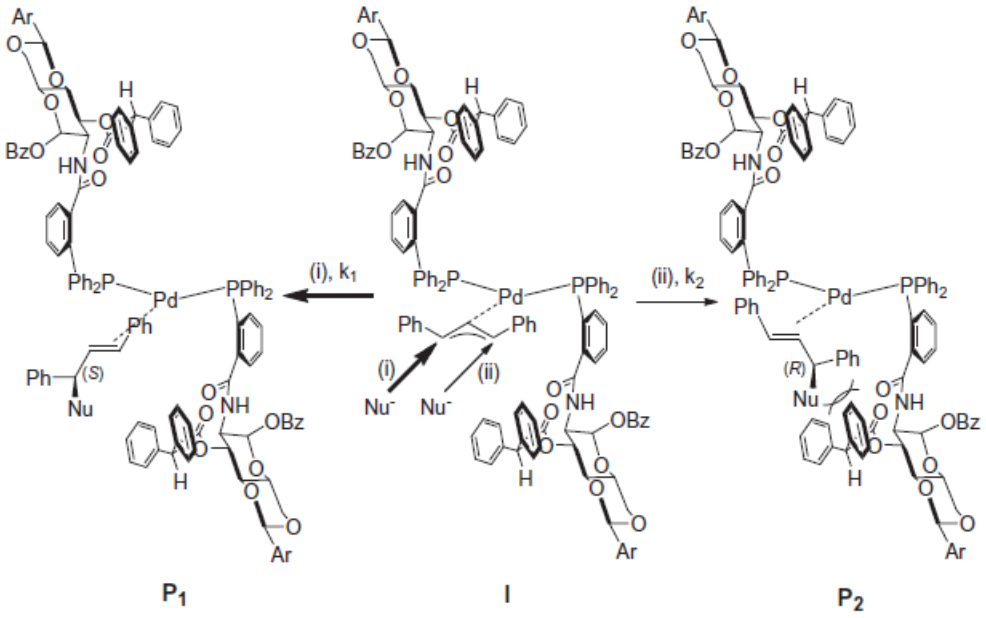


Figure 10

Furthermore, in the P,P-coordination mode, the N–H units are available for hydrogen-bond interactions with the carbonyl nucleophile, an additional feature which can be beneficial for both rate and selectivity.[16] This is also in agreement with the fact that the R group is sterically effective, but stereochemically inactive (see above, entry 5 vs entry 6), and with the observation that the enantioselectivity of the reaction is mainly governed by the pocket created by the chiral ligands.

[16] Butts, C. P.; Filali, E.; Lloyd-Jones, G. C.; Norrby, P.-O.; Sale, D. A.; Schramm, Y. *J. Am. Chem. Soc.* **2009**, *131, 9945.*

2.3.5 FURTHER REFINEMENT IN USE OF NAPLEPHOS LIGANDS[17]

As mentioned in the Introduction, *naplephos* ligands have already been investigated in the asymmetric allylic alkylation of 1,3-diphenylpropenylacetate with dimethylmalonate. In a recent paper, we described how both the steric hindrance in 3 and the ligand:Pd ratio are decisive for the enantioselectivity of the reaction. In fact, *naplephos-h* produces the (*S*)-product in ee's up to 96% by increasing the ligand:Pd ratio up to 4:1, with dry THF as solvent, and $Na(CHCO_2Me)_2$ as the nucleophile (Table 1).

Although in these conditions the reaction is fast and selective, we were strongly motivated to assess the performance of the ligands in other conditions, aiming to (i) use lower and more convenient ligand:Pd ratios, (ii) reduce the impact of the process, (iii) save precious chemicals, (iv) confirm the versatility of the ligands, (v) re-cycle the metal catalyst. The first conditions can be in principle satisfied by using dichloromethane as solvent, since the reactions can be performed in milder conditions by generating the nucleophile with BSA.

As for the catalyst recycle, a proven alternative is the use of an unconventional solvent, such as an inexpensive ionic liquid, capable of selectively dissolving the metal catalyst.

On these basis, the allylic alkylation of 1,3-diphenylpropenylacetate with dimethylmalonate was first performed in dry dichloromethane by setting the naplephos:Pd ratio to 1:1, and by generating the nucleophile in the presence of BSA and a pinch of lithium acetate.

[17] Benessere, V., Lega, M., Ruffo, F., **in press**

no.	ligand	cone angle[a] (°) (Charton parameter)[a]	conditions	conversion[c] (%)	time (h)	ee(S)[b] %
1	**naplephos-c**	106 (0.70)	[c]	99	5	85
2	**naplephos-c**	106 (0.70)	[d]	99	18	88
3	**naplephos-f**	121 (1.18)	[c]	99	2	91
4	**naplephos-f**	121 (1.18)	[d]			
5	**naplephos-g**	121 (1.18)	[c]	99	2	86
6	**naplephos-g**	121 (1.18)	[d]			
7	**naplephos-h**[a]	126 (1.25)	[c]	99	2	91
8	**naplephos-h**	126 (1.25)	[d]	99	18	96
8	**naplephos-i**[a]	136	[c]	99	18	80
8	**naplephos-i**	136	[d]	99	18	96
9	**naplephos-j**[a]	144	[c]	50	18	80
10	**naplephos-j**	144	[d]	99	18	76

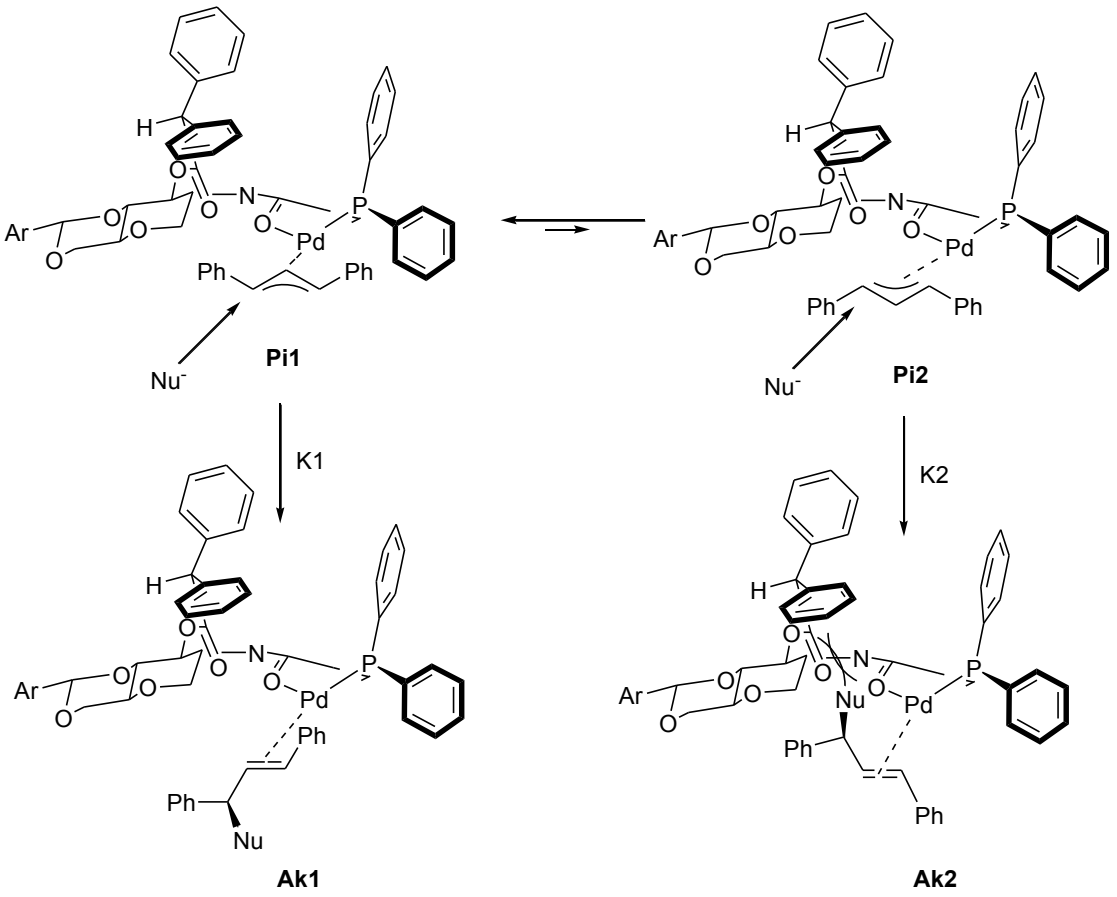
[a]Relative to the R substituent in the carbonyl α position. Respectively taken from references 8 and 9.
[b]Evaluated by NMR spectroscopy of the crude reaction mixture.
[c]Reaction conditions: RT, THF, 0.25 mmol of substrate, 0.75 mmol of dimethylmalonate, 0.75 mmol of NaH, 0.0050 mmol of $[Pd(\mu\text{-}Cl)(\mu^3\text{-}C_3H_5)]_2$, 0.022 mmol of **naplephos**.
[d]Reaction conditions: RT, dichloromethane, 0.25 mmol of substrate, 0.75 mmol of dimethylmalonate, 0.75 mmol of BSA, 0.0050 mmol of $[Pd(\mu\text{-}Cl)(\mu^3\text{-}C_3H_5)]_2$, 0.010 mmol of **naplephos**, pinch of LiOAc.

Table 2.3

A comparison of the results (Table 2.3) with those obtained in THF (Table 2.1-2.2) discloses two important trends. First, analogous steric effects hold true in the two solvents, in that the higher ee is achieved with *naplephos-h* (ee 96%), while more or less crowded ligands produce a less enantiorich product.

Furthermore, the effect of the ligand concentration is reversed. When ligand:Pd ratios higher than 1:1 were used in dichloromethane, both conversion and enantioselectively were depressed. This effect is reproducible, although its origin is not yet clearly explained (nota).

The steric effect can be reasonably elucidated on the grounds of both literature results and molecular models. It is likely (stessa nota) that the ligands coordinate Pd through the phosphorous atom and the amido carbonyl oxygen in position 2, and, hence, oxidative addition of the acetate affords the two diastereomeric π-allyl intermediates **P1** and **P2** (Scheme 2.13).



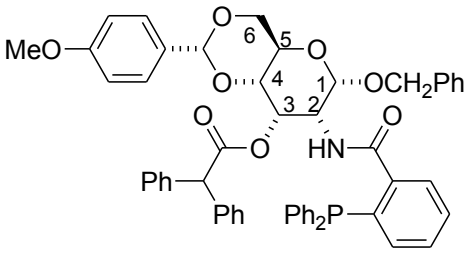
Scheme 2.13

On the grounds of the acknowledged mechanism, nucleophilic attack of malonate takes place preferentially at the allyl carbon atom *trans* to P, with formation of the corresponding alkene products **Ak1** and **Ak2**. Enantioselectivity ensues from the diverse rates of nucleophilic attack. By assuming that the geometry of the transition state of the attack is close to that of **Ak1** and **Ak2**, it is reasonable that $K_1 > K_2$, because **Ak2** is selectively hindered by the ester substituent in 3. Thus, a bulky R group (*i.e.*, R= $CHPh_2$) helps the enantioselectivity, although undue hindrance (*e.g.*, R= $CHCy_2$) reduces the catalyst's performance, plausibly because it hampers the carbonyl coordination, and the steric control moves away from the catalytic centre.

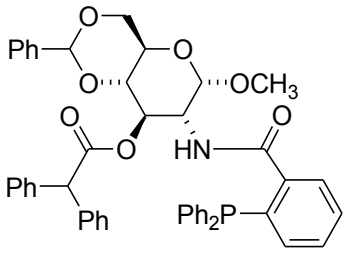
Addition of one equivalent of *naplephos-h* to a CD_2Cl_2 solution of π-$[PdCl(\pi^3\text{-allyl})]_2$ results in immediate formation of the expected

diastereomeric couple of π-allyl species [Pd(P,O-*naplephos-h*)(π^3-allyl)]Cl. Further addition of ligand simply results in the growth of the signal pertaining to the free ligand.

We also investigated other different modifications on the structure of naplephos ligands and in particular we changed the relative absolute configuration of the C3 using a ligand based on allose (**L2**), and the bulky group in position 1 (**L3**) substituting the benzyl group with a methyl group in order to define some secondary steric effect on the catalysis that can influence the performance not just near the catalytic centre but from the backbone. Results are reported in the table below.



L2



L3

no.	ligand	cone angle[a] (°) (Charton parameter)[a]	conditions	conversion[c] (%)	time (h)	ee(S)[b] %
1	**naplephos-h**	126 (1.25)	[d]	99	18	96
2	**L2**	126 (1.25)	[d]	20	18	0
3	**L3**		[d]	99	18	83

Table 2.4

As it's clear from the analysis of the Table 2.4 when we use ligand **L2** with the same steric parameters but a different absolute configuration only at C3 we can observe a dramatic change of catalytic activity due to the different orientation of the bulky group that doesn't have the effect to produce the other enantiomer gives rise to a complete different active specie.

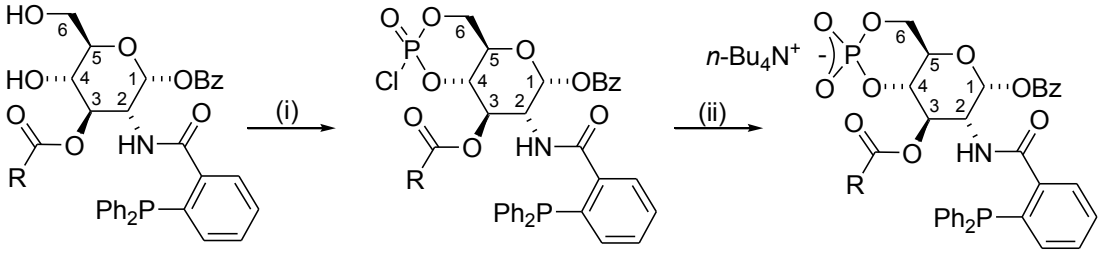
No important effects, but there is an effect, are observed when we change the group in position 1 (**L3**).

2.4 NAPLEPHOS IN MULTIPHASE CATALYSIS: PRELIMINARY WORK[17]

Ionic liquids are among the most promising green solvents.[18] Though their use does not require specific tagging of the catalysts, in several occasions their affinity for the ionic liquid demonstrated to improve fruitfully with the polarity of the ligands. This also inhibits leaching of the catalyst in the organic product phase, and increases the possibility of further catalyst re-cycles.

This approach has been pursued during this thesis, by providing selected *naplephos* ligands of appropriate tags (Figure 3), whose choice has been dictated by at least three important considerations. First, the tag must be polar or ionic, for securing solubility in the ionic solvent. Then, its structure must preserve the conformational rigidity of the glucose chair, as the benzylidene ring is able to do. Furthermore, the synthesis must be straightforward and easy to carry out.

We devised an approach which combines these benefits by introducing a 4,6-phosphate moiety within the sugar ring, as depicted in Scheme 2.14



R= *o*-C_6H_4-PPh_2: **6**
R= $CHPh_2$: **7**

R= *o*-C_6H_4-PPh_2: **naplephos-a'**
R= $CHPh_2$: **naplephos-h'**

R= *o*-C_6H_4-PPh_2: **naplephos-a"**
R= $CHPh_2$: **naplephos-h"**

(i) $POCl_3$, Et_3N, dichloromethane, 298 K; (ii) *n*-Bu_4NOH, water/dioxane, 298 K

Scheme 2.14

By reacting the 4,6-deprotected precursors **6** and **7** with $POCl_3$ in dry dichloromethane, the corresponding 4,6-oxychlorophosphate compounds *naplephos-a'* and *naplephos-h'* were isolated in high yield. Subsequent controlled hydrolysis of the P-Cl bond in a water/dioxane mixture afforded the ionic products *naplephos-a"* and *naplephos-h"* as their tetra-*n*-butylammonium salts.

The ligands were characterised through NMR spectroscopy. As anticipated, the 4,6-phosphate ring assumes a chair conformation, which is clearly revealed by the coupling constants within the sugar protons. In *naplephos-a'* and *naplephos-h'* the phosphorous atom in the phosphate ring is stereogenic, and two diastereomers can be observed in solution. However, given the significant distance of this stereochemical motif from the active catalytic centre, its presence is not expected to have any control in the enantioselectivity of the process to be catalysed.

Most important, both neutral and cationic phosphate ligands display high solubility in the ionic liquid used for most of the experiments, BMIM[BF_4], as well as in common organic solvents (THF, dichloromethane, chloroform or toluene). It is interesting to note that, from preliminary catalytic results, the 4,6-phosphate species *naplephos-h'* and *naplephos-h"* induce very similar enantioselectivities, thus demonstrating that the presence of the phase-tag has no effect on the stereochemistry of the reaction, but a great effect on the physical-chemical properties of the catalyst.

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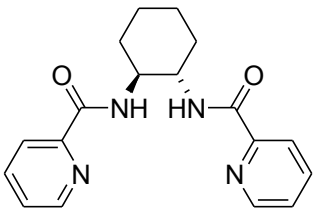
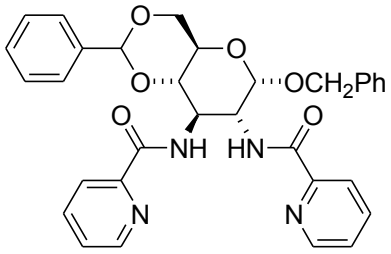
2.5 Mo-CATALYSED AAA PROMOTED BY μW

Catalysts containing palladium have been most extensively employed in synthetic applications,[22] but may lead to undesired products when unsymmetrically substituted allyl derivatives are used.[23]



Moberg's ligand



L4

Figure 11

Thus, whereas palladium complexes as a rule afford the achiral linear products from monosubstituted allylic substrates,[24] complexes based on Ir and Mo have a preference for formation of the branched chiral products. With the introduction of (*R**,*R**)-1,2-diaminocyclohexane (**Figure 11**)[25] as ligand by Trost,[26] highly enantioselctive Mo-catalyzed allylations became possible. Although Ir catalysts have a wider scope,[27] catalysts containing Mo have become attractive due to the lower cost of molybdenum as compared to iridium and the robustness of the in situ formed catalytic system.[28] These factors together with our simple experimental protocol using microwave irradiation, allowing the catalytic reactions to be run within less than 10 minutes in air using stable, crystalline, commercially available $Mo(CO)_6$ as catalyst precursor,[29] have made Mo catalysts viable alternatives to those based on Pd and Ir for a variety of applications.

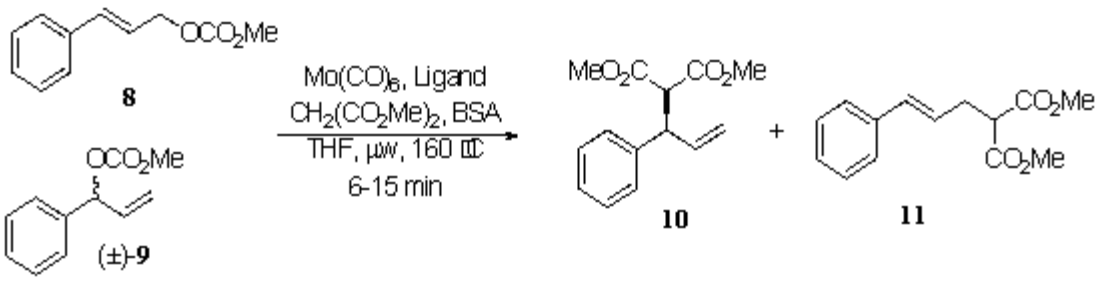
Bispyridylamides, which still are the most efficient ligands for the Mo catalyzed process, are easily prepared from a picolinic acid derivative and a chiral enantioenriched 1,2-diamine.[30] By comparing the results of

reactions using ligands with substituted pyridine nuclei it was found that derivatives with π-donor substituents resulted in particularly high enantioselectivities and high branched to linear ratios.[31] C_2-Symmetric 1,2-diaminocyclohexanes have commonly been used as ligand precursors together with picolinic acid derivatives. In the search for more easily available diamines, Lloyd Jones, Kocovsky and co-workers used asymmetric diamines derived from naturally occurring amino acids.[32] The ligands obtained provided catalysts, some of which exhibited high enantio- and regioselectivity and high reactivity.

Carbohydrates are other examples of useful naturally occurring starting materials for ligand synthesis, and they are particularly attractive as they are available in several stereoisomeric forms.[33] α-D-Glucose[34] and α-D-mannose[35]derivatives with amino substituents in the 2- and 3-positions of the carbohydrate have been described and have successfully been used for the preparation of ligands which have been applied in metal-catalyzed enantioselective processes. Inspired by the structural analogy between *trans*-cyclohexanediamine and the glucose derivative and by the possibility to obtain a chiral cis-substituted ligand from mannose, we decided use the two 1,2-diamines for the preparation of bispyridylamides.

The catalytic reactions were performed using our previously developed experimental conditions. Thus, $Mo(CO)_6$, ligand, allylic carbonate **8**, dimethyl malonate, and *N*,*O*-bis(trimethylsilyl)acetamide were mixed in THF and heated at 160 °C in the microwave cavity under air. After completed reaction, conversions and branched to linear ratios were determined by ^{1}H NMR spectroscopy and gas chromatography, respectively, and enantioselectivities by chiral HPLC. First the three types of ligands were assessed using 4 and/or 10 mol % Mo, a nucleophile to substrate ratio of 1.1:1, and a ligand to metal ratio of 1.3:1. The results of these initially performed reactions are shown in Table 2.5. In reactions

using **L4** and **L4'**, (*R*)-(+)-dimethyl 3-phenyl-1-butene-4,4-dicarboxylate was formed as the major product, whereas the opposite enantiomer was obtained in reactions with **L4''**. Higher catalyst loadings resulted not only in higher reactivity but also in higher regioselectivity (entries 1 and 4 vs 2 and 5, respectively). In contrast to results obtained with ligands derived from 1,2-diaminocyclohexane, the *p*-chloro-substituted derivative (entry 3) gave the product with lower enantioselectivity than **L4**. The enantioselection of ligands prepared from the *pseudo*-C_2-symmetric 2,3-*gluco* derivatives **L4** and **L4'** turned out to be far superior to that of *pseudo*-C_s-symmetric 2,3-*manno* diamide **L4''**(38-40% ee, entries 3 and 4). **L4** was thus the ligand of choice, exhibiting higher reactivity and providing higher enantioselectivity (99% ee) and higher branched to linear ratio (49/1 using 10 mol % catalyst) than **L4'** and **L4''**. Reactions using this ligand were therefore studied in more detail.



Scheme 2.15

Table 2.5. Molybdenum-catalyzed asymmetric substitutions of **4** using ligands **L4-4'-4''**.[a]

Entry	Ligand	Cat.(%)	Conversion[a] (%)	Regiosel.[b] (**10**/**11**)	Ee[c] (%)
1	**L4**	10	96	49/1	99 (*R*)
2	**L4**	4	50	8/1	99 (*R*)
3	**L4'**	4	42	12/1	87 (*R*)
4	**L4''**	10	76	14/1	38 (*S*)
5	**L4''**	4	41	5/1	40 (*S*)

[a] Reactions were run at 160 °C for 6 min. with ligand:metal = 1.3:1 and Nu:**4** = 1.1:1.[b]Determined by GC-MS. [c] Determined by HPLC using a Daicel OD-H (0.46 cm Ø x 25 cm) column.

The following catalytic reactions using **L4** were performed employing the same procedure as that used in the initial reactions, but equimolar amounts of nucleophile and substrate, and lower ligand to metal ratios (1.1:1) were used. These conditions allowed isolation of pure products by bulb-to-bulb distillation; in some reactions the product was isolated by chromatography, which resulted in lower yields. Again, lower amounts of catalyst resulted in lower conversion and lower regioselectivity (Table 2.6, entries 1-3), although the enantioselectivity remained high (99% ee). With 4 mol % catalyst, the conversion was merely 50% after 6 minutes (entry 3). Prolonged reaction times resulted in further product formation, which however ceased after 15 minutes (entries 4 and 5), probably due to decomposition of the catalyst; this decomposition could not be prevented by higher ligand loading (entry 6). With 1 mol % catalyst somewhat lower enantioselectivity (94% ee) and very low regioselectivity were observed (entry 7). The best result, obtained with 10% catalyst loading, (entry 1) allowed the product with a branched to linear ratio of 49/1 to be isolated in 90% yield (99% conversion).

Table 2.6 Molybdenum-catalyzed asymmetric substitutions of **8** using ligand **L4**.[a]

Entr	Cat.(%)	Mo/Lig	Time	Conversion[b]	Yield (%)	Regiosel.[c](**10**/**11**)	Ee[d]
1	10	1/1.1	6	99	90[e]	49/1	99
2	5	1/1.1	15	78	38[f]	9/1	99
3	4	1/1.1	6	50	35[f]	8/1	99
4	4	1/1.1	15	65	33[f]	8/1	99
5	4	1/1.1	30	65	35[f]	8/1	99
6	4	1/1.5	15	50	35[f]	8/1	99
7	1	1/1.1	30	10	7[f]	1.5/1	94
8	10	No Lig	6	25	n. d.[g]	4/1	-

[a] Reactions were run at 160 °C with ligand:metal = 1.1:1 and Nu:**4** = 1:1. [b] Determined by ^{1}H NMR. [c] Determined by GC-MS. [d] Determined by HPLC using a Daicel OD-H (0.46 cm Ø x 25 cm) column. [e] Isolated by bulb-to-bulb distillation. [f] Isolated by chromatography on silica gel (eluent 1/1 Peth.ether/DCM). [g] not determined.

Mo-catalyzed allylic alkylations are known to proceed via π^3-allyl molybdenum complexes, which are formed by oxidative addition of the allylic carbonate to ligated Mo(0).[37] The reactions proceed stereospecifically by syn displacement of the carbonate.[38] For this reason diastereomeric allyl complexes are formed from the two enantiomers of branched carbonates such as **9**. In order to achieve high enantioselectivity in reactions with branched racemic substrates, equilibration of the diastereomeric allyl complexes via $\pi^3 \square \pi^1 \square \pi^3$ isomerization therefore needs to be rapid in relation to nucleophilic attack, which also occurs by a syn mechanism. Under certain conditions equilibration is incomplete, resulting in modest memory effects and, as a consequence, in lower enantioselectivities than in reactions with linear substrates.[39]

The results from reactions with *rac*-**9** using the present catalytic system are shown in Table 2.7. The branched substrate **9** gave the product with lower enantio- and regioselectivity than the linear substrate, but the conversion remained high when the catalyst loading was decreased from

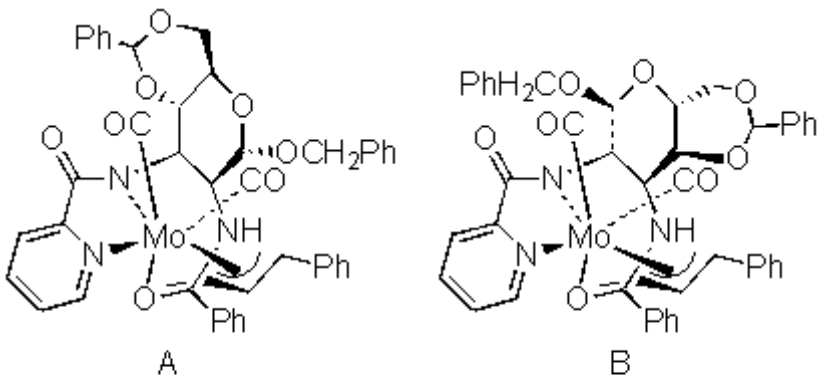
10 (entry 1) to 5 mol % (entry 2). With a further decrease of the amount of catalyst, the conversion decreased and with 1% catalyst merely 15% conversion was observed after 30 minutes (entry 4). No major difference was observed between reactions run in THF and in toluene (entries 2 and 3).

Table 2.7. Molybdenum-catalyzed asymmetric substitutions of *rac*-**9** using ligand **L4**.[a]

Entr	Cat.(%)	Mo/Lig.	Time	Conversion[b]	Yield	Regiosel.[c](**6**/**7**)	Ee[d]
1	10	1/1.1	6	99	82[f]	8/1	96
2	5	1/1.1	15	99	90[f]	8/1	95
3	5	1/1.1	15[e]	99	85[f]	8/1	96
4	1	1/1.1	30	15	12[g]	8/1	80
5	10	No Lig	6	50	n. d.[h]	5/1	-

[a] Reactions were run at 160 °C with ligand:metal = 1.1:1 and Nu:**5** = 1:1. [b] Determined by ^{1}H NMR. [c] Determined by GC-MS. [d] Determined by HPLC using a Daicel OD-H (0.46 cm Ø x 25 cm) column. [e] Reaction run in toluene. [f] Isolated by bulb-to-bulb distillation. [g] Isolated by chromatography on silica gel (eluent 1/1 Peth.ether/DCM). [h] not determined.

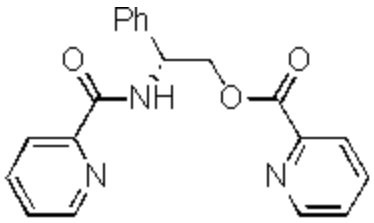
In the π^3-allyl complex obtained after oxidative addition of the allylic carbonate, the ligand has been shown to coordinate to Mo in a tridentate manner via one pyridine nitrogen, one deprotonated amide nitrogen, and one carbonyl oxygen atom.[40] Assuming the same configuration at the metal center as that found for the complex containing ligand in Figure 11, two modes of coordination (A and B, Figure 12) are possible for asymmetric ligand **L4**, and thus two complexes leading to the observed product, due to the lack of twofold rotational axis.



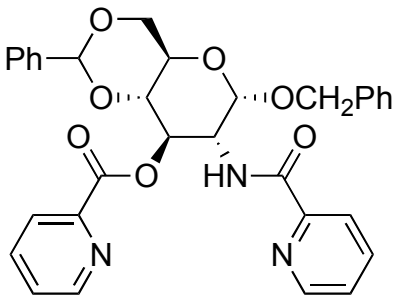
Diastereomeric complexes differing in the mode of coordiantion of **L4** to Mo

Figure 12

A catalytic run failed when the pyridylamide derived from a 4,6-*O*-benzylidene-2-amino-2-deoxyglucoside scaffold was used (Figure 13). This suggests that the NH function in position 3 is essential for the reaction, and, hence, diasereomer A should be the actual allyl intermediate. Although a catalyst containing (*R*)-1-(2-pyridinecarboxamido)-2-(2-pyridinecarboxy)-1-phenylethane (**L5'**), an ester–amide, has been shown to exhibit some activity in Mo-catalyzed allylic substitutions, no product formation was observed when monoamide **L5**, derived from a 2-amino-4,6-*O*-benzylidene-2-deoxyglucoside scaffold, was used as ligand.



L5'



L5

Figure 13

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CHAPTER 3
CONCLUSIONS

The simple functionalisation of commercially available N-acetylglucosamine provides the efficient library of chiral ligands **naplephos (Figure 3.1)**.

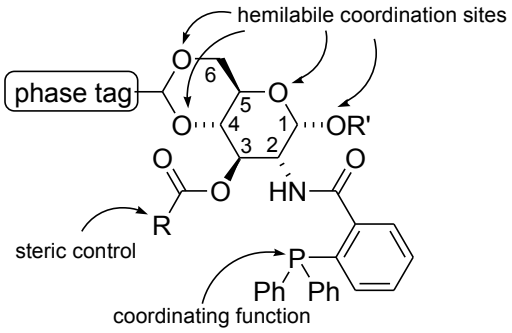
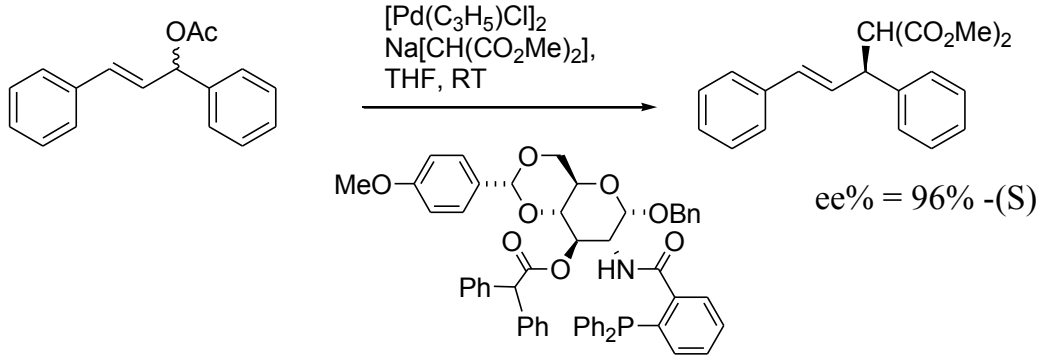


Figure 3.1

Along with an anomeric α-benzyl group and the rigid benzylidene ring in C4 and C6, the distinctive feature of the ligands is a coordinating diphenylphoshino arm in the equatorial 2-position. Esterification at the 3-position with readily accessible carboxylic acid RCO_2H allows to functionalise the ligands with fine control of the steric hindrance. The experimental work carried out during this thesis project demonstrated that the basic structure **naplephos,** alredy successfully employed in the copper-catalyzed 1,4 addition of dialkyl zinc on conjugated enones and in the Pd-catalysed asymmetric desymmetrization of meso-2-cyclopenten-1,4-diol biscarbamate, may be effectively adapted to the Pd-allylic alkylation of the *rac*-1,3-diphenyl-2-propenyl acetate, leading up to 96% ee% (**Scheme 3.1**).



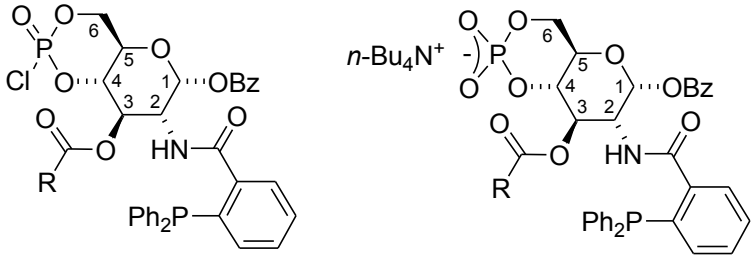
[Pd / Ligand / Substrate / Nucleophile = 1 / 4 / 25 / 75]

Scheme 3.1

An NMR study of the foundamental intermediate involved in this reaction was carried out, providing useful information on the reaction mechanism and its stereochemical control.

Further investigation proved the versatility of these structure that can display both PP and PO coordination motifs to be active in THF and DCM respectively.

We also demonstrated the possibility to perform multiphase catalysis in ionic liquids through simple modification of this class of ligand and to pave the way for further study that can confirm the catalyst re-cycle (**Figure 3.2**).

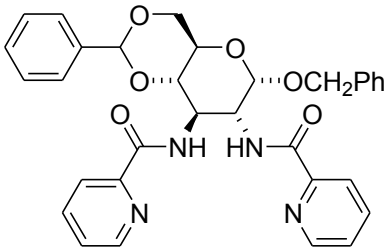


R= *o*-C_6H_4-PPh_2: **naplephos-a'**
R= $CHPh_2$: **naplephos-h'**

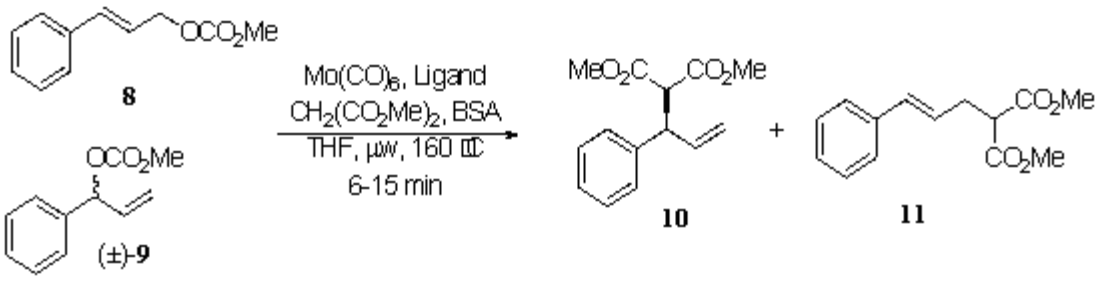
R= *o*-C_6H_4-PPh_2: **naplephos-a"**
R= $CHPh_2$: **naplephos-h"**

Figure 3.2

Bis(pyridine-2-carboxamides) were conveniently prepared from 1,2-diamines obtained from á-D-glucose according to known procedures and shown to serve as efficient ligands in Mo-catalyzed microwave-mediated asymmetric allylic alkylations. The two types of structures allowed the comparison of ligands having the amide arms in *trans* and *cis* positions in the six-membered ring. The former type of ligands proved to be more successful, providing the product, (+)-(*R*)-dimethyl 3-phenyl-1-butene-4,4-dicarboxylate, with 99% enantiomeric excess and with a branched/linear ratio of 49:1 in 90% isolated yield under optimized conditions.



L4



Scheme 3.2

CHAPTER 4
EXPERIMENTAL SECTION

4.1 GENERAL CONSIDERATIONS

NMR spectra were recorded in $CDCl_3$ ($CHCl_3$, δ 7.26, and $^{13}CDCl_3$ δ 77, as internal standards) with a 200 and 300 MHz spectrometers (Varian Model Gemini, at the CIMCF of the "Università degli studi di Napoli Federico II"), or with a 270 MHz spectrometer (JOEL EX270, at the "University of Nottingham"). The following abbreviations were used for describing NMR multiplicities: s, singlet; d, doublet; dd, double doublet; t, triplet; dt, double triplet; m, multiplet; app, apparent. Specific optical rotatory powers [α] were measured with a Perkin– Elmer Polarimeter (model 141) at 298 K and 589 nm in chloroform (c 1.0 g/100 mL) (at the "Università degli studi di Napoli Federico II"). Microwave heating was performed by using a Smith Creator single-mode cavity from Biotage (KTH Sweden, Prof. Moberg's Lab). Benzyl-4,6-O-[(4-MeO)-benzylidene]-2- deoxy-2-amino-a-D-glucoside (intermediate **4** of **Scheme 2.**1), and the **naplephos-a** were prepared according to literature methods[1]. THF and MTHF were distilled from $LiAlH_4$, dichloromethane from CaH_2, toluene and Et_2O from Na. All the substrates and products of the catalysis were prepared according to literature,[2] isolated and characterized by NMR.

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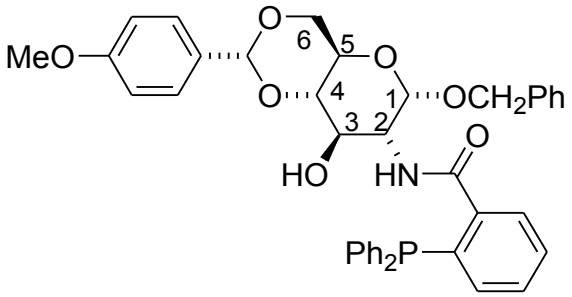
[2] (b)A. de Roma, F. Ruffo, S. Woodward**.** *Chem Commun (Camb).* ***2008****;(42):5384-6* and reference within.

4.2 PREPARATION OF THE OP INTERMEDIATE



OP intermediate

A solution of **4** (1.2 g, 2.0 mmol), 2-diphenylphosphinobenzoic acid (2.0 mmol), 4-dimethylaminopyridine (0.024 g, 0.20 mmol) and 1,3-dicyclohexylcarbodiimide (0.82 g, 4.0 mmol) in dry Dichloromethane (20 mL) was stirred for 12 h at room temperature under an inert atmosphere to afford a suspension. The residue was removed by filtration. The resulting solution was evaporated under vacuum, and the residue was chromatographed on silica gel (2:1 ethyl acetate/hexane) affording the pure product as a white solid (yield: 85%).

Detailed presentation of physical data for **5**: [α] = +6.7 (c 1, $CHCl_3$); selected 1H NMR data: 6.41 (d, 1H, $^3J_{NH–H2}$ = 9.2 Hz, NH), 5.70 (s, 1H, OCHO), 5.05 (d, 1H, $^3J_{H1–H2}$ = 4.2 Hz, H1), 4.80 (d, 1H, $^2J_{gem}$ = 11.7 Hz, C*H*HPh), 4.58 (d, 1H, CH*H*Ph), 4.52 (dt, 1H, $^3J_{H2–H3}$ = 10.2 Hz, H2), 4.35 (dd, 1H, $^3J_{H6eq–H5}$ = 4.2 Hz, $^2J_{H6eq–H6ax}$ = 9.0 Hz, H6eq), 4.07 (t, 1H, $^3J_{H3–H4}$ = 10.2 Hz, H3), 4.02 (dt overlapped, 1H, $^3J_{H5–H4}$ = $^3J_{H5–H6ax}$ = 9.9 Hz, H5), 3.97 (s, 3H, OMe), 3.91 (t, 1H, H4), 3.80 (t, 1H, H6ax); selected 13C NMR data: δ = 170.0, 102.2, 97.4, 82.0, 70.9, 70.0, 69.2, 63.3, 55.5, 55.2. Anal. Calcd for C40H38NO7P: C, 71.10; H, 5.67; N, 2.07. Found: C, 0.89; H, 5.45; N, 2.11.

4.3 GENERAL PROCEDURE FOR THE PREPARATION OF THE LIGANDS

A solution of **OP INTRMEDIATE** (1.2 g, 2.0 mmol), the appropriate RCO_2H acid (2.5 mmol), 4-dimethylaminopyridine (0.24 g, 2.0 mmol) and 1,3- dicyclohexylcarbodiimide (0.82 g, 4.0 mmol) in dry dichloromethane (10 mL) was stirred for 12 h at room temperature under an inert atmosphere affording a suspension. The residue was removed by filtration. The resulting solution was evaporated under vacuum, and the residue was chromatographed on silica gel (1:2 ethyl acetate/hexane) affording the pure product as a white solid (yield: 80– 85%).
Naplephos s-v where synthesized by adding TEA and the chloride derivate of the acid, in refluxing toluene for a day; the work up and the yields were the same.

Detailed presentation of physical data for **naplephos-b**:[α] = -7.9 (c 1, $CHCl_3$); selected ^{1}H NMR data: 6.30 (d, 1H, $^3J_{NH–H2}$ = 9.4 Hz, NH), 5.49 (s, 1H, OCHO), 5.42 (t, 1H, $^3J_{H3–H2} = {}^3J_{H3–H4}$ = 9.8 Hz, H3), 4.86 (d, 1H, $^3J_{H1–H2}$ = 3.4 Hz, H1), 4.70 (d, 1H, $^2J_{gem}$ = 11.8 Hz, CHHPh), 4.50 (m, 2H, CHHPh and H2), 4.21 (dd,1H, $^3J_{H6eq–H5}$ = 4.0 Hz, $^2J_{H6eq–H6ax}$ = 10.0 Hz, H6eq), 3.92 (dt, 1H, $^3J_{H5–H4} = {}^3J_{H5–H6ax}$ = 9.6 Hz, H5), 3.80 (s, 3H, OMe), 3.76 (t, 1H, H4), 3.75 (t, 1H, H6ax), 2.36 (s, 3H, Me); selected 13C NMR data: 260 δ = 169.0, 166.3, 99.3, 95.1, 76.6, 67.7, 66.3, 60.6, 52.8, 50.2, 18.7. Anal. Calcd for $C_{42}H_{40}NO_8P$: C, 70.28; H, 5.62; N, 1.95. Found: C, 70.48; H, 5.59; N, 1.88.

Detailed presentation of physical data for **naplephos-c**: [α] = +7.8 (c 1, $CHCl_3$); selected ^{1}H NMR data: δ = 6.27 (d, 1H, $^3J_{NH–H2}$ = 9.8 Hz, NH),

5.41 (t, 1H, $^{3}J_{H3–H2} = {}^{3}J_{H3–H4}$ = 9.9 Hz, H3), 5.40 (s, 1H, OCHO), 4.87 (d, 1H, 3JH1–H2 = 3.4 Hz, H1), 4.68 (d, 1H, $^{2}J_{gem}$ = 11.6 Hz, CHHPh), 4.60 (dt, 1H, H2), 4.47 (d, 1H, CHHPh), 4.19 (dd, 1H, $^{3}J_{H6eq–H5}$ = 4.4 Hz, $^{2}J_{H6eq–H6ax}$ = 9.8 Hz, H6eq), 3.92 (dt, 1H, $^{3}J_{H5–H4} = {}^{3}J_{H5–H6ax}$ = 10.0 Hz, H5), 3.81, (s, 3H, OMe), 3.76 270 (t, 1H, H4), 3.72 (t, 1H, H6ax), 3.65 (app d, 2H, CH2Ph); selected 13C NMR data: δ = 172.3, 168.7, 101.6, 97.9, 79.8, 70.8, 70.4, 69.0, 63.4, 55.5, 52.9, 41.5. Anal. Calcd for $C_{48}H_{44}NO_8P$: C, 72.62; H, 5.59; N, 1.76. Found: C, 72.87; H, 5.50; N, 1.65.

Detailed presentation of physical data for **naplephos-d**: [α] = +20.8 (c 1, $CHCl_3$); selected 1H NMR data: 6.35 (d, 1H, $^{3}J_{NH– H2}$ = 10.0 Hz, NH), 5.48 (s, 1H, OCHO), 5.43 (t, 1H, $^{3}J_{H3–H2} = {}^{3}J_{H3– H4}$ = 9.4 Hz, H3), 4.88 (d, 1H, $^{3}J_{H1–H2}$ = 4.2 Hz, H1), 4.68 (d, 1H, $^{2}J_{gem}$ = 11.6 Hz, CHHPh), 4.47 (m, 2H, CHHPh and H2), 4.18 (dd, 1H, $^{3}J_{H6eq–H5}$ = 4.2 Hz, $^{2}J_{H6eq–H6ax}$ = 9.2 Hz, H6eq), 3.89 (dt, 1H, 280 $^{3}J_{H5–H4} = {}^{3}J_{H5–H6ax}$ = 9.6 Hz, H5), 3.79 (s, 3H, OMe), 3.74 (t, 1H, H4), 3.70 (t, 1H, H6ax), 2.21 (m, 2H, CH_2Cy); selected 13C NMR data: δ = 173.0, 164.4, 99.6, 97.5, 94.0, 75.4, 65.9, 64.9, 59.4, 51.4, 49.9, 38.3, 30.9, 28.9, 21.9. Anal. Calcd for $C_{48}H_{50}NO_8P$: C, 72.07; H, 6.30; N, 1.75. Found: C, 71.69; H, 6.36; N, 1.82.

Detailed presentation of physical data for **naplephos-e**: [α] = _-.2 (c 1, $CHCl_3$); selected 1H NMR data: δ = 6.47 (d, 1H, $^{3}J_{NH–H2}$ = 9.6 Hz, NH), 5.67 (s, 1H, OCHO), 5.59 (t, 1H, $^{3}J_{H3–H2} = {}^{3}J_{H3–H4}$ = 10.0 Hz, H3), 4.98 (d, 1H, $^{3}J_{H1–H2}$ = 3.6 Hz, H1), 4.84 (d, 1H, $^{2}J_{gem}$ = 11.7 Hz, CHHPh), 4.68 (dt, 1H, H2), 4.63 (d, 1H, CHHPh), 290 4.22 (dd, 1H, $^{3}J_{H6eq–H5}$ = 4.5 Hz, $^{2}J_{H6eq–H6ax}$ = 9.9 Hz, H6eq), 4.08 (dt, 1H, $^{3}J_{H5–H4} = {}^{3}J_{H5–H6ax}$ = 10.2 Hz, H5), 3.96 (s, 3H, OMe), 3.91 (t, 1H, H4), 3.89 (t, 1H, H6ax), 1.29 (s, 9H, t-Bu); selected ^{13}C NMR data: δ = 180.7, 168.4, 101.3, 98.2, 79.6, 70.5,

70.0, 69.0, 63.4, 55.5, 52.8, 39.2, 27.3. Anal. Calcd for $C_{45}H_{46}NO_8P$: C, 71.13; H, 6.10; N, 1.84. Found: C, 71.46; H, 6.29; N, 1.89.

Detailed presentation of physical data for **naplephos-f**: [α] = -16.6 (c 1, $CHCl_3$); selected ^{1}H NMR data: 6.30 (d, 1H, $^3J_{NH-H2}$ = 9.6 Hz, NH), 5.43 (t, 1H, $^3J_{H3-H2} = {}^3J_{H3-H4}$ = 10.0 Hz, H3), 5.33 (s, 1H, OCHO), 4.86 (d, 1H, $^3J_{H1-H2}$ = 3.6 Hz, H1), 4.65 (d, 1H, 300 $^2J_{gem}$ = 11.4 Hz, CHHPh), 4.49 (dt, 1H, H2), 4.45 (d, 1H, CHHPh), 4.15 (dd, 1H, $^3J_{H6eq-H5}$ = 4.4 Hz, $^2J_{H6eq-H6ax}$ = 9.8 Hz, H6eq), 3.81 (dt, 1H, $^3J_{H5-H4} = {}^3J_{H5-H6ax}$ = 10.0 Hz, H5), 3.80 (s, 3H, OMe), 3.72 (t, 1H, H4), 3.66 (t, 1H, H6ax), 3.51 (t, 1H, $^3J_{H-H}$ = 7.4 Hz, CHEtPh), 2.10 (m, 1H, CHHMe), 1.71 (m, 1H, CHHMe), 0.75 (t, 3H, $^3J_{H-H}$ = 8.0 Hz, Me); selected ^{13}C NMR data: δ = 174.6, 168.5, 101.2, 98.1, 79.4, 70.4, 69.8, 68.9, 63.3, 55.5, 53.5, 52.7, 26.5, 12.2. Anal. Calcd for $C_{50}H_{48}NO_8P$: C, 73.07; H, 5.89; N, 1.70. Found: C, 73.22; H, 5.83; N, 1.61.

Detailed presentation of physical data for **naplephos-g**: [α] = +41.1 (c 1, $CHCl_3$); selected ^{1}H NMR data: 6.38 (d, 1H, $^3J_{NH-H2}$ = 9.5 Hz, NH), 5.66 (s, 1H, OCHO), 5.64 (t, 1H, $^3J_{H3-H2} = {}^3J_{H3-H4}$ = 10.4 Hz, H3), 5.07 (d, 1H, $^3J_{H1-H2}$ = 3.6 Hz, H1), 4.82 (d, 1H, $^2J_{gem}$ = 12.0 Hz, CHHPh), 4.70 (dt, 1H, H2), 4.61 (d, 1H, CHHPh), 4.35 (dd, 1H, $^3J_{H6eq-H5}$ = 4.8 Hz, $^2J_{H6eq-H6ax}$ = 10.4 Hz, H6eq), 4.07 (dt, 1H, $^3J_{H5-H4} = {}^3J_{H5-H6ax}$ = 9.6 Hz, H5), 3.97 (s, 3H, OMe), 3.94 (t, 1H, H4), 3.92 (t, 1H, H6ax), 3.68 (t, 1H, $^3J_{H-H}$ = 7.2 Hz, CHEtPh), 2.52 (m, 1H, CHHMe), 1.93 (m, 1H, CHHMe), 0.98 (t, 3H, $^3J_{H-H}$ = 7.2 Hz, Me); selected ^{13}C NMR data: δ = 170.6, 164.4, 97.4, 95.2, 75.5, 66.3, 64.8, 59.3, 51.3, 49.7, 48.8, 2.9, 8.1. Anal. Calcd for $C_{50}H_{48}NO_8P$: C, 73.07; H, 5.89; N, 1.70. Found: C, 71.93; H, 320 5.68; N, 1.81.

Detailed presentation of physical data for **naplephos-h**: [α] = -23.0 (c 1, $CHCl_3$); selected 1H NMR data: δ = 6.34 (d, 1H, $^3J_{NH–H2}$ = 9.8 Hz, NH), 5.64 (t, 1H, $^3J_{H3–H2}$ = $^3J_{H3–H4}$ = 10.2 Hz, H3), 5.46 (s, 1H, OCHO), 5.16 (s, 1H, CHPh2), 4.95 (d, 1H, $^3J_{H1–H2}$ = 3.6 Hz, H1), 4.71 (d, 1H, $^2J_{gem}$ = 11.6 Hz, CHHPh), 4.61 (dt, 1H, H2), 4.48 (d, 1H, CHHPh), 4.30 (dd, 1H, $^3J_{H6eq–H5}$ = 4.6 Hz, $^2J_{H6eq–H6ax}$ = 10.2 Hz, H6eq), 3.96 (dt, 1H, $^3J_{H5–H4}$ = $^3J_{H5–H6ax}$ = 9.6 Hz, H5), 3.85 (s, 3H, OMe), 3.75 (t, 1H, H4), 3.75 (t, 1H, H6ax); selected 330 13C NMR data: δ = 173.3, 168.1, 101.3, 97.9, 79.2, 70.7, 70.3, 68.8,63.3, 56.9, 55.5, 52.5. Anal. Calcd for $C_{54}H_{48}NO_8P$: C, 74.55; H, 5.56; N, 1.61. Found: C, 74.10; H, 5.49; N, 1.62.

Detailed presentation of physical data for **naplephos-i**: [α] = - 28.6 (c 1, $CHCl_3$); selected ^{1}H NMR data: δ = 6.25 (d, 1H, $^3J_{NH–H2}$ = 9.6 Hz, NH), 5.55 (t, 1H, $^3J_{H3–H2}$ = $^3J_{H3–H4}$ = 9.4 Hz, H3), 5.39 (s, 1H, OCHO), 4.82 (d, 1H, $^3J_{H1–H2}$ = 3.3 Hz, H1), 4.62 (d, 1H, $^2J_{gem}$ = 11.7 Hz, CHHPh), 4.48 (dt, 1H, H2), 4.42 (d, 1H, CHHPh), 4.13 (dd, 1H, $^3J_{H6eq–H5}$ = 5.1 Hz, $^2J_{H6eq–H6ax}$ = 10.2 Hz, H6eq), 3.89 (dt, 1H, $^3J_{H5–H4}$ = $^3J_{H5–H6ax}$ = 10.2 Hz, H5), 3.85 (s, 3H, OMe), 3.67 (t, 1H, H4), 3.65 (t, 1H, H6ax), 1.85 (s, 3H, Me); selected ^{13}C NMR data: δ = 175.9, 168.3, 101.7, 98.2, 79.4, 71.0, 70.5, 69.0, 63.4, 57.0, 57.6, 52.7, 27.1. Anal. Calcd for $C_{55}H_{50}NO_8P$: C, 74.73; H, 5.70; N, 1.58. Found: C, 72.28; H, 5.81; N, 1.54.

Detailed presentation of physical data for **naplephos-j**: [α] = +14.5 (c 1, $CHCl_3$); selected ^{1}H NMR data: 6.54 (d, 1H, $^3J_{NH–H2}$ = 9.0 Hz, NH), 5.46 (t, 1H, $^3J_{H3–H2}$ = $^3J_{H3–H4}$ = 10.2 Hz, H3), 5.44 (s, 1H, OCHO), 4.92 (d, 1H, $^3J_{H1–H2}$ = 3.3 Hz, H1), 4.66 (d, 1H, $^2J_{gem}$ = 11.7 Hz, CHHPh), 4.48 (m, 2H, CHHPh and H2), 4.14 (dd, 1H, $^3J_{H6eq–H5}$ = 4.8 Hz, $^2J_{H6eq–H6ax}$ = 10.2 Hz, H6eq), 3.92 (dt, 1H, 350 $^3J_{H5–H4}$ = $^3J_{H5–H6ax}$ = 9.6 Hz, H5), 3.74 (s, 3H, OMe), 3.70 (t, 1H, H4), 3.65 (t, 1H, H6ax), 2.02 (t, 1H, $^3J_{H–H}$ = 6.6 Hz,

$CHCy_2$); selected ^{13}C NMR data: δ = 175.7, 167.5, 101.7, 97.9, 79.5, 70.3, 69.3, 68.9, 63.2, 57.4, 55.3, 52.9, 36.5. Anal. Calcd for $C_{54}H_{60}NO_8P$: C, 73.53; H, 6.86; N, 1.59. Found: C, 73.77; H, 6.76; N, 1.55.

Detailed presentation of physical data for **naplephos-k**: [α] = - 2.0 (c 1, $CHCl_3$); selected ^1H NMR data: 6.38 (d, 1H, $^3J_{NH-H2}$ = 9.6 Hz, NH), 5.68 (t, 1H, $^3J_{H3-H2} = {}^3J_{H3-H4}$ = 10.0 Hz, H3), 5.55 (s, 1H, OCHO), 4.91 (d, 1H, $^3J_{H1-H2}$ = 3.6 Hz, H1), 4.71 (d, 1H, $^2J_{gem}$ = 11.8 Hz, CHHPh), 4.66 (dt, 1H, H2), 4.48 (d, 1H, CHHPh), 4.22 (dd, 1H, $^3J_{H6eq-H5}$ = 4.2 Hz, $^2J_{H6eq-H6ax}$ = 9.6 Hz, H6eq), 4.10 (dt, 1H, $^3J_{H5-H4} = {}^3J_{H5-H6ax}$ = 9.6 Hz, H5), 3.85 (t, 1H, H4), 3.83 (t, 1H, H6ax), 3.75 (s, 3H, OMe); selected ^{13}C NMR data: δ = 168.7, 160.1, 101.4, 97.9, 79.5, 70.7, 70.3, 68.8, 63.3, 55.3, 52.7. Anal. Calcd for $C_{47}H_{42}NO_8P$: C, 72.39; H, 5.43; N, 1.80. Found: C, 72.73; H, 5.48; N, 1.84.

Detailed presentation of physical data for **naplephos-l**: [α] = +12.7 (c 1, $CHCl_3$); selected 1H NMR data: 6.26 (d, 1H, $^3J_{NH-H2}$ = 9.2 Hz, NH), 5.47 (s, 1H, OCHO), 5.41 (t, 1H, $^3J_{H3-H2} = {}^3J_{H3-H4}$ = 9.8 Hz, H3), 4.84 (d, 1H, $^3J_{H1-H2}$ = 4.2 Hz, H1), 4.66 (d, 1H, $^2J_{gem}$ = 11.6 Hz, CHHPh), 4.60 (dt, 1H, H2), 4.47 (d, 1H, CHHPh), 4.18 (dd, 1H, $^3J_{H6eq-H5}$ = 4.4 Hz, $^2J_{H6eq-H6ax}$ = 9.6 Hz, H6eq), 3.91 (dt, 1H, $^3J_{H5-H4} = {}^3J_{H5-H6ax}$ = 10.0 Hz, H5), 3.80 (s, 3H, OMe), 3.70 (t, 1H, H4), 3.65 (t, 1H, H6ax); selected ^{13}C NMR data: δ = 168.8, 160.2, 101.4, 97.6, 79.1, 71.9, 70.2, 68.7, 63.2, 55.3, 52.3, 28.0. Anal. Calcd for $C_{48}H_{39}F_5NO_8P$: C, 65.23; H, 4.45; N, 1.58. Found: C, 65.15; H, 4.44; N, 1.50.

Detailed presentation of physical data for **naplephos-m**

selected ^1H NMR data: δ = 6.20 (d, 1H, $^3J_{NH-H2}$ = 9.6 Hz, NH), 5.52 (t, 1H, $^3J_{H3-H2} = {}^3J_{H3-H4}$ = 9.4 Hz, H3), 5.38 (s, 1H, OCHO), 4.83 (d, 1H, $^3J_{H1-}$

$_{H2}$ = 3.3 Hz, H1), 4.68 (d, 1H, $^{2}J_{gem}$ = 11.7 Hz, CHHPh), 4.44 (dt, 1H, H2), 4.41 (d, 1H, CHHPh), 4.11 (dd, 1H, $^{3}J_{H6eq–H5}$ = 5.1 Hz, $^{2}J_{H6eq–H6ax}$ = 10.2 Hz, H6eq), 3.87 (dt, 1H, $^{3}J_{H5–H4}$ = $^{3}J_{H5–H6ax}$ = 10.2 Hz, H5), 3.85 (s, 3H, OMe), 3.64 (t, 1H, H4), 3.62 (t, 1H, H6ax), 1.85 (s, 6H, Me).

Detailed presentation of physical data for **naplephos-n**
selected ^{1}H NMR data: δ = 6.24 (d, 1H, $^{3}J_{NH–\ H2}$ = 9.6 Hz, NH), 5.51 (t, 1H, $^{3}J_{H3–H2}$ = $^{3}J_{H3–H4}$ = 9.4 Hz, H3), 5.31 (s, 1H, OCHO), 4.87 (d, 1H, $^{3}J_{H1–H2}$ = 3.3 Hz, H1), 4.67 (d, 1H, $^{2}J_{gem}$ = 11.7 Hz, CHHPh), 4.45 (dt, 1H, H2), 4.46 (d, 1H, CHHPh), 4.12 (dd, 1H, $^{3}J_{H6eq–H5}$ = 5.1 Hz, $^{2}J_{H6eq–H6ax}$ = 10.2 Hz, H6eq), 3.88 (dt, 1H, $^{3}J_{H5–H4}$ = $^{3}J_{H5–H6ax}$ = 10.2 Hz, H5), 3.84 (s, 3H, OMe), 3.64 (t, 1H, H4), 3.61(t, 1H, H6ax), 1.88 (s, 6H, Me);

Detailed presentation of physical data for **naplephos-o**:
selected 1H NMR data: 6.4 (d, 1H, NH), 5.75 (t, 1H, H3), 5.45 (s, 1H, OCHO), 4.90 (d, 1H, H1), 4.66 (dt, 1H, H2), 4.60 (d, 1H, CHHPh), 4.47 (d, 1H, CHHPh), 4.20 (dd, 1H, $H6_{eq}$), 3.90 (dt, 1H, H5), 3.85 (t, 1H, H4), 3.70(s, 3H, OMe), 3.65 (t, 1H, $H6_{ax}$);
selected ^{13}C NMR: 168.6, 164.9, 159.9, 149.9, 147.5, 140.5, 140, 113.5, 101.4, 97.7, 79.1, 71.5, 70.3, 68.7, 63.2, 55.2, 52.5.

Detailed presentation of physical data for **naplephos-o':** selected 1H NMR data: δ 6.64 (d, 1H, NH-C2, $^{3}J_{NH-H2}$ = 9.6Hz), 5.98 (t, 1H, H3, $^{3}J_{H3-H4}$ = 19.2Hz, $^{3}J_{H3-H2}$ = 9.9Hz), 5.70 (s, 1H, H7), 5.55 (d, 1H, H1, $^{3}J_{H1-H2}$ = 3.9Hz), 5.27 (dt, 1H, H2), 4.84 (d, 1H, C*H*HPh, $^{2}J_{gem}$ = 11.4Hz), 4.60 (d, 1H, C*H*HPh), 4.38-4.17 (m, 3H, H5, $H6_{eq}$, $H6_{ax}$), 3.99 (t, 1H, H4, $^{3}J_{H4-H5}$= 9.9Hz), 3.92 (s, 3H, OCH_3).
selected ^{13}C NMR: 169.4, 164.9, 160.2, 150.2, 148.0, 143.4, 142.5, 113.7, 101.7, 98.5, 79.8, 71.3, 70.9, 69.0, 63.5, 55.5, 52.9.

Detailed presentation of physical data for **naplephos-p:**

selected ^{1}H NMR (300MHz): δ 6.59 (d, 1H, NH-C2, $^{3}J_{NH-H2}$ = 9.6Hz), 5.99 (t, 1H, H3, $^{3}J_{H3-H4}$ = 19.8Hz, $^{3}J_{H3-H2}$ = 9.9Hz), 5.69 (s, 1H, H7), 5.12 (d, 1H, H1, $^{3}J_{H1-H2}$ = 3.6Hz), 4.96 (dt, 1H, H2), 4.90 (d, 1H, C*H*HPh, $^{2}J_{gem}$ = 11.7Hz), 4.71 (d, 1H, C*H*HPh), 4.40 (dd, 1H, $H6_{eq}$, $^{3}J_{H6eq-H5}$ = 4.5, $^{3}J_{H6eq-H6ax}$ = 10.2 Hz), 4.18 (dt, 1H, H5, $^{3}J_{H5-H4}$= 9.6Hz), 4.12 (t, 1H, H4), 3.97 (t, 1H, $H6_{ax}$), 3.91 (s, 3H, OCH_3).

selected ^{13}C NMR: 168.2, 165.1, 160.0, 147.8, 121.8, 114.5, 113.9, 101.6, 98.9, 79.7, 71.6, 71.0, 68.1, 63.2, 55.0, 52.5.

Detailed presentation of physical data for **naplephos-p':**

selected ^{1}H NMR (200MHz): δ 6.52 (d, 1H, NH-C2, $^{3}J_{NH-H2}$ = 9.0Hz), 5.86 (t, 1H, H3, $^{3}J_{H3-H2}$ = 10.1Hz, $^{3}J_{H3-H4}$ = 19.5Hz), 5.54 (s, 1H, H7), 5.42 (d, 1H, H1, $^{3}J_{H1-H2}$ = 3.6Hz), 5.16 (dt, 1H, H2), 4.71 (d, 1H, C*H*HPh, $^{2}J_{gem}$ = 12.0Hz), 4.42 (d, 1H, C*H*HPh), 4.24-3.96 (m, 2H, H5, H_{6eq}), 3.82-3.92 (m, 2H, H4, H_{6ax}), 3.75 (s, 3H, OCH_3).

selected ^{13}C NMR: 168.3, 165.1, 160, 149.8, 147.7, 142, 113.5, 101.8, 98, 72.3, 70.2, 68.4, 67.7, 55.7, 54.2.

Detailed presentation of physical data for **naplephos-q**

Selected ^{1}H NMR (300MHz): δ 6.58 (d, 1H, NH-C2, $^{3}J_{NH-H2}$= 9Hz), 5.55 (s, 1H, H7), 5.28 (t, 1H, H3, $^{3}J_{H3-H4}$= $^{3}J_{H3-H2}$= 10.2Hz), 4.75 (d, 1H, H1, $^{3}J_{H1-H2}$= 3.6Hz), 4.62 (s, 1H, C*H*HPh, $^{2}J_{gem}$= 11.4Hz), 4.41 (d, 1H, C*H*HPh), 4.35 (dt, 1H, H2), 4.20 (dd, 1H, $H6_{eq}$, $^{3}J_{H6eq-H5}$= 4.8Hz, $^{2}J_{gemH6eq-H6ax}$= 10.2Hz), 3.90 (dt, 1H, H5, $^{3}J_{H5-H6ax}$= $^{3}J_{H5-H4}$= 10.2Hz), 3.83 (s, 3H, OCH_3), 3.71 (m, 2H, $H6_{ax}$+4), 2.80 (s, 3H, Me).

Detailed presentation of physical data for **naplephos-r**

selected ^{1}H NMR (200MHz): δ 6.70 (d, 1H, NH-C2, $^{3}J_{NH-H2}$= 9.4Hz), 5.50 (s, 1H, H7), 5.30 (t, 1H, H3, $^{3}J_{H3-H4}$= $^{3}J_{H3-H2}$= 10.4Hz), 4.80 (d, 1H, H1, $^{3}J_{H1-H2}$= 3.6Hz), 4.65 (d, 1H, C*H*HPh, $^{2}J_{gem}$= 11.8Hz), 4.42 (d, 1H, C*H*HPh), 4.35 (dt, 1H, H2), 4.25 (dd, 1H, $H6_{eq}$, $^{3}J_{H6eq-H5}$= 4.6Hz, $^{2}J_{gemH6eq-H6ax}$= 10.2Hz), 3.94 (dt, 1H, H5, $^{3}J_{H5-H6ax}$= $^{3}J_{H5-H4}$= 10.2Hz), 3.78 (s, 3H, OCH_3), 3.72 (m, 2H, $H6_{ax}$+4), 3.25 (4H, CH_2Me), 1.07 (6H, CH_2*Me*).

Detailed presentation of physical data for **naplephos-s:**

Selected ^{1}H NMR (300MHz): δ 6.56 (d, 1H, NH-C2, $^{3}J_{NH-H2}$= 9Hz), 5.49 (s, 1H, H7), 5.32 (t, 1H, H3, $^{3}J_{H3-H4}$= $^{3}J_{H3-H2}$= 10.2Hz), 4.85 (d, 1H, H1, $^{3}J_{H1-H2}$= 3.6Hz), 4.68 (s, 1H, C*H*HPh, $^{2}J_{gem}$= 11.4Hz), 4.46 (d, 1H, C*H*HPh), 4.39 (dt, 1H, H2), 4.18 (dd, 1H, $H6_{eq}$, $^{3}J_{H6eq-H5}$= 4.8Hz, $^{2}J_{gemH6eq-H6ax}$= 10.2Hz), 3.93 (dt, 1H, H5, $^{3}J_{H5-H6ax}$= $^{3}J_{H5-H4}$= 10.2Hz), 3.80 (s, 3H, OCH_3), 3.72 (m, 2H, $H6_{ax}$+4), 2.80 (s, 3H, Me).

Detailed presentation of physical data for **naplephos-t:**

selected ^{1}H NMR (200MHz): δ 6.72 (d, 1H, NH-C2, $^{3}J_{NH-H2}$= 9.4Hz), 5.51 (s, 1H, H7), 5.35 (t, 1H, H3, $^{3}J_{H3-H4}$= $^{3}J_{H3-H2}$= 10.4Hz), 4.89 (d, 1H, H1, $^{3}J_{H1-H2}$= 3.6Hz), 4.68 (d, 1H, C*H*HPh, $^{2}J_{gem}$= 11.8Hz), 4.47 (d, 1H, C*H*HPh), 4.37 (dt, 1H, H2), 4.20 (dd, 1H, $H6_{eq}$, $^{3}J_{H6eq-H5}$= 4.6Hz, $^{2}J_{gemH6eq-H6ax}$= 10.2Hz), 3.93 (dt, 1H, H5, $^{3}J_{H5-H6ax}$= $^{3}J_{H5-H4}$= 10.2Hz), 3.79 (s, 3H, OCH_3), 3.71 (m, 2H, $H6_{ax}$+4), 3.27 (4H, CH_2Me), 1.07 (6H, CH_2*Me*).

Detailed presentation of physical data for **naplephos-u:**

selected ^{1}H NMR (200MHz): δ 7.84 (d, 1H, NH-C2, $^{3}J_{NH-H2}$= 9Hz), 5.52 (s, 1H, H7), 5.40 (t, 1H, H3, $^{3}J_{H3-H4}$= $^{3}J_{H3-H2}$= 10.0Hz), 4.93 (d, 1H, H1, $^{3}J_{H1-H2}$= 3.4Hz), 4.67 (d, 1H, C*H*HPh, $^{2}J_{gem}$= 11.6Hz), 4.45 (d, 1H,

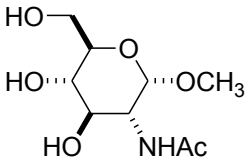
C*H*HPh), 4.38 (dt, 1H, H2), 4.20 (dd, 1H, $H6_{eq}$, $^{3}J_{H6eq-H5}$= 4.6Hz, $^{2}J_{gemH6eq-H6ax}$= 10Hz), 4.04 (m, 1H, C*H*i-Pr), 3.96 (m, 1H, H5, $^{3}J_{H5-H6ax}$= 9.8Hz), 3.79 (s, 3H, OCH_3), 3.72 (m, 2H, $H6_{ax}$+4), 1.14 (m, 12H, Mei-Pr).

Detailed presentation of physical data for **naplephos-v:**
Selected ^{1}H NMR (200MHz): δ 6.79 (d, 1H, NH-C2, $^{3}J_{NH-H2}$= 8.8Hz), 5.50 (s, 1H, H7), 5.36 (t, 1H, H3, $^{3}J_{H3-H4}$= $^{3}J_{H3-H2}$= 9.6Hz), 4.93 (d, 1H, H1, $^{3}J_{H1-H2}$= 3.4Hz), 4.67 (d, 1H, C*H*HPh, $^{2}J_{gem}$= 11.8Hz), 4.45 (d, 1H, C*H*HPh), 4.38 (m, 1H, H2), 4.20 (dd, 1H, $H6_{eq}$, $^{3}J_{H6eq-H5}$= 4.2Hz, $^{2}J_{gemH6eq-H6ax}$= 10.2Hz), 3.96 (m, 1H, H5, $^{3}J_{H5-H6ax}$= 10.2Hz), 3.79 (s, 3H, OCH_3), 3.72 (m, 1H, $H6_{ax}$+4), 3.35 (m, 6H, NCH_2n-Bu), 0.80 (m, 14H, CH_2CH_2CH_3n-Bu).

Detailed presentation of physical data for **L1**: selected ^{1}H NMR data: 6.15 (d, 1H, NH), 5.74 (t, 1H, H3), 4.95 (d, 1H, H1), 4.85 (s, 1H, OCHO), 4.55 (dt, 1H, H2), 4.50 (d, 1H, CHHPh), 4.15 (d, 1H, CHHPh), 4.05 (dd, 1H, $H6_{eq}$), 3.90 (dt, 1H, H5), 3.85 (t, 1H, H4), 3.70(s, 3H, OMe), 3.60 (t, 1H, $H6_{ax}$);

Detailed presentation of physical data for **L2**
selected 1H NMR data: δ = 6.08 (d, 1H, $^{3}J_{NH–H2}$ = 9.8 Hz, NH), 5.77 (t, 1H, $^{3}J_{H3–H2}$ = $^{3}J_{H3–H4}$ = 2.5 Hz, H3), 5.56 (s, 1H, OCHO), 5.07 (s, 1H, CHPh2), 4.95 (d, 1H, $^{3}J_{H1–H2}$ = 3.6 Hz, H1), 4.71 (d, 1H, $^{2}J_{gem}$ = 11.6 Hz, CHHPh), 4.61 (dt, 1H, H2), 4.48 (d, 1H, CHHPh), 4.30 (dd, 1H, $^{3}J_{H6eq–H5}$ = 4.6 Hz, $^{2}J_{H6eq–H6ax}$ = 10.2 Hz, H6eq), 3.96 (dt, 1H, $^{3}J_{H5–H4}$ = $^{3}J_{H5–H6ax}$ = 9.6 Hz, H5), 3.85 (s, 3H, OMe), 3.75 (t, 1H, H4), 3.75 (t, 1H, H6ax).

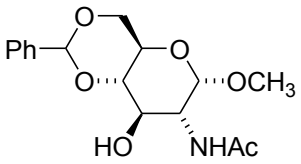
Synthesis of 1-*methyl-2-acetamide-2-deoxy-α-D-glucopiranoside*



2''

A suspension of N-acethyl-D-glucosamine-α-OMe (**1''**) (6.0 g, 27 mmol) in methanol (140 mL) and Amberlite (10 g) was refluxed for 24 hours. At the end of the reaction a brown precipitate is present. This precipitate was remover by filtration and the crude solution was cooled at RT, washed with Et_2O and dryed under vacuum. (yield: 85%).

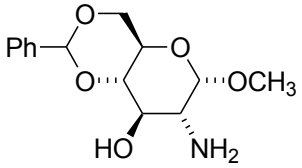
Synthesis of 1-*methyl-2-acetamide-3-hydroxy-4,6-O-benzylidene-α-D-glucopiranoside*



3''

Compaund **2''**, **(**7.0 g**,** 30 mmol), and dry $ZnCl_2$ (7.01 g, 205 mmol), dust, were sospende in benzaldehyde (37.6 mL) and stirred for 2 hours at 70 °C. 600 mL of water were added under stirring and the precipitate was filtrated, washed with water and petroleum ether (yield: 52 %).

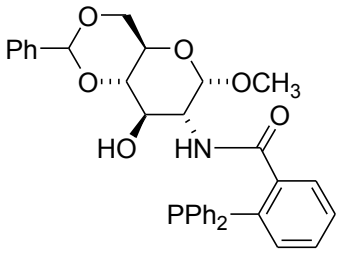
Synthesis of 1-*methyl-2-amine-3-hydroxy-4,6-O-benzylidene-α-D-glucopiranoside*



4''

Compaund **3''**, (3.2 g, 9.9 mmol) was added to a warm solution of KOH (28 g, 500 mmol) in ethanol (63 mL) and refluxed for 24 hours. Water was added and entracte 3 times with DCM. The crude product was then passed on Na_2SO_4 and dryed under vacuum. White solid (yield: 72%).
selected ^{1}H NMR (200 MHz) : δ = 5.49 (s, 1H, C*H*Ph), 4.62 (d, 1H, H1, $^3J_{H1\text{-}H2}$ = 3.4 Hz), 4.24 (dd, 1H, H2, $^3J_{H2\text{-}H3} = {}^3J_{H3\text{-}H4}$ = 8.6 Hz) 3.74-3.62 (m, 2H, H4, H5, $^3J_{H4\text{-}H5}$ = 9.6 Hz) , 3.39 (t, 1H, H3), 3.40 (s, 3H, OCH_3), 2.7 (dd ,1H , NH_2C2, $^3J_{NHC2\text{-}H2}$ = 6 Hz) .

Synthesis of **5''**



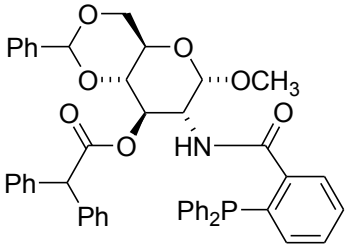
5''

A solution of **4''** (1.3 g, 4.5 mmol), 2-diphenylphosphinobenzoic acid (2.0 mmol), 4-dimethylaminopyridine (0.024 g, 0.20 mmol) and 1,3-dicyclohexylcarbodiimide (0.82 g, 4.0 mmol) in dry Dichloromethane (20 mL) was stirred for 12 h at room temperature under an inert

atmosphere to afford a suspension. The residue was removed by filtration. The resulting solution was evaporated under vacuum, and the residue was chromatographed on silica gel (2:1 ethyl acetate/hexane) affording the pure product as a white solid (yield: 85%).

selected ^{1}H NMR (200 MHz) : δ = 6.24 (d, 1H, NH-C2, $^{3}J_{NH-H2}$ = 9.2 Hz), 5.57 (s, 1H, H7) , 4.61 (d, 1H, H1, $^{3}J_{H1-H2}$ = 3.6 Hz), 4.27 (dd, 1H, $H6_{eq}$, $^{3}J_{H6eq-H5}$ = 4 Hz, $^{2}J_{H6eq-H6ax}$ = 9.6 Hz), 4.36 (dt, 1H, H2), 3.85 (td ,1H,H5, $^{3}J_{H6ax-H5}$ = 9.6 Hz), 3.752 (t , 1H, $H6_{ax}$), 3.67-3.63 (m, 2H, H3,H4 $^{3}J_{H3-H4}$ =$^{3}J_{H2-H3}$ = 7.8 Hz), 3.22 (s, 3H, CH_3O).

Synthesis of **L3**



L3

A solution of **5''** (0.50 g, 8.4 mmol), the Ph_2CHCO_2H acid (2.5 mmol), 4-dimethylaminopyridine (0.24 g, 2.0 mmol) and 1,3-dicyclohexylcarbodiimide (0.82 g, 4.0 mmol) in dry dichloromethane (10 mL) was stirred for 12 h at room temperature under an inert atmosphere affording a suspension. The residue was removed by filtration. The resulting solution was evaporated under vacuum, and the residue was chromatographed on silica gel (1:2 ethyl acetate/hexane) affording the pure product as a white solid (yield: 80– 85%).

Detailed presentation of physical data for **L3**

Risonanze selezionate ^{1}H NMR (200 MHz) : δ = 6.18 (d, 1H, N*H*-C2, $^{3}J_{NH-H2}$ = 10 Hz) , 5.52 (t, 1H, H3, $^{3}J_{H3-H4}$ =$^{3}J_{H2-H3}$ = 9.8 Hz) , 5.46 (s, 1H, H7) 5.09 (s, 1H, C*H*Ph$_2$), 4.54 (d, 1H, H1, $^{3}J_{H1-H2}$ = 3.4 Hz) , 4.48 (dd, 1H, H2), 4.29 (dd, 1H, H6$_{eq}$, $^{3}J_{H6eq-H5}$ = 4 Hz, $^{2}J_{H6eq-H6ax}$ = 9.6 Hz) , 3.89 (dt, 1H, H5).

Synthesis of Ligands L4: A suspension of picolinic acid (138 mg, 1.12 mmol) and 1,1_-carbonyldiimidazole (182 mg, 1.12 mmol) in dry tetrahydrofuran (2 mL) was heated in a flamedried flask at 50 °C under nitrogen for 1 h. Then the appropriate diamine (0.56 mmol) was added, and the mixture was stirred at the same temperature for 2 h. The solvent was removed under vacuum and the residue extracted with dichloromethane. The organic phase was extracted with water (3.5 mL) and the aqueous phases were combined and extracted with dichloromethane (2.5 mL). The col lected organic phases were dried with sodium sulfate, and the solvent was evaporated to afford ligands **L4** (245 mg, 77%) . Use of the ligands in the catalytic reactions did not require any further purification. Recrystallization of **L4** from methanol afforded 136 mg (43%) of the product.

Detailed presentation of physical data for **L4**

Selected ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.53 (d, *J* = 4.4 Hz, 1 H, H6-py), 8.52 (d, *J* = 10.4 Hz, 1 H, NH), 8.38 (d, *J* = 4.7 Hz, 1 H, H6-py), 8.10 (d, *J* = 10.4 Hz, 1 H, NH), 7.97 (d, *J* = 7.8 Hz, 1 H, H3-py), 7.90 (d, *J* = 7.8 Hz, 1 H, H3-py), 7.66–7.62 (m, 2 H, H4-py), 7.36–7.30 (m, 4 H, H5-py and Ph H), 7.28– 7.16 (m, 8 H, Ph), 5.50 (s, 1 H, OCHO), 4.97 (d, *J* = 3.6 Hz, 1 H, H1), 4.81 (q, *J* = 10.4 Hz, 1 H, H3), 4.77 (d, *J* = 12.2 Hz, 1 H, C*H*HPh), 4.58 (dt, *J* = 10.4, 3.6 Hz, 1 H, H2), 4.54 (d, *J* = 12.2 Hz,

1 H, CH*H*Ph), 4.22 (dd, *J* = 10.2, 4.9 Hz, 1 H, H6eq), 4.06 (dt, *J* = 9.9, 4.9 Hz, 1 H, H5), 3.86 (dd, *J* = 10.2, 9.9 Hz, 1 H, H6ax), 3.76 (t, *J* = 10.3 Hz, 1 H, H4) ppm.

Selected ^{13}C NMR (100 MHz, $CDCl_3$):

δ = 165.5, 165.1, 149.9, 149.8, 148.7, 148.3, 137.6 (2 C, overlapped), 137.4 (2 C, overlapped), 129.3, 128.8, 128.6, 128.4, 128.3, 126.7, 126.5, 126.4, 122.7, 122.6, 102.2, 97.5, 80.3, 70.2, 69.5, 64.6, 53.4, 50.7.

Synthesis of Ligand L5: A solution of picolinic acid (520 mg, 4.2 mmol), 4-(dimethylamino)pyridine (48 mg, 0.43 mmol) and 1,3 dicyclohexylcarbodiimide (890 mg, 4.3 mmol) in dry dichloromethane (7 mL) was added to a solution benzyl 2-amino-2-deoxy-4,6-*O*-(4 methoxybenzylidene)-α-D-glucopyranoside, (2.0 mmol) in the same solvent (7 mL). The resulting mixture was stirred at room temperature under an inert gas for 12 h to afford a yellow suspension. The precipitate was removed by filtration. The resulting yellow solution was concentrated under vacuum, and the residue was chromatographed on silica gel (ethyl acetate/hexane, 1:5) to afford the pure product as a white solid (yield: 777 mg, 65%).

Detailed presentation of physical data for **L5**

Selected ^{1}H NMR (300 MHz, $CDCl_3$, 298 K): δ = 8.60 (d, *J* = 4.8 Hz, 1 H, H6-py), 8.55 (d, *J* = 5.1 Hz, 1 H, H6-py), 8.48 (d, *J* = 9.9 Hz, 1 H, NH), 8.05 (d, *J* = 7.5 Hz, 1 H, H3-py), 7.95 (d, *J* = 7.8 Hz, 1 H, H3-py), 7.71 (t, *J* = 7.8 Hz, 2 H, H4-py), 7.40–7.10 (m, 9 H, H5-py and Ph H), 6.80 (d, *J* = 8.4 Hz, 2 H, Ph), 5.85 (t, *J* = 9.9 Hz, 1 H, H3), 5.50 (s, 1 H, OCHO), 5.01 (d, *J* = 3.6 Hz, 1 H, H1), 4.73 (m, 2 H, H2, C*H*HPh), 4.58 (d, *J* = 12Hz, 1 H, CH*H*Ph), 4.25 (dd, *J* = 10.2, 4.5 Hz, 1 H, H6eq), 4.11

(dt, J = 10.2, 4.5 Hz, 1 H, H5), 3.96 (t, J = 9.6 Hz, 1 H, H6ax), 3.82 (t, J = 10.2 Hz, 1 H, H4), 3.70 (s, 3 H, OCH3) ppm.
Selected ^{13}C NMR (75.3 MHz, $CDCl_3$): δ = 164.7, 164.6, 160.3, 150.1, 149.4, 148.5, 147.8, 137.3, 137.0, 136.8, 129.7, 128.6, 128.4, 128.3, 127.7, 127.0, 126.5, 125.7, 122.3, 113.8, 101.7, 97.6, 79.6, 71.9, 70.2, 69.1, 63.5, 55.4, 52.6 ppm.

4.4 GENERAL PROCEDURE FOR THE Pd-AAA CATALYTIC REACTION

With the sodium salt of dimethylmalonate: a solution of [Pd(μ-Cl)- (η^3-allyl)]$_2$ (0.0020 g, 0.0050 mmol) and the appropriate **naplephos** (0.022 mmol) in 0.5 mL of dry THF was stirred under nitrogen for 0.5 h. A solution of substrate (0.25 mmol) in 0.5 mL of the same solvent was then added. After stirring the resulting light yellow solution for additional 0.5 h, a solution of the sodium salt of dimethylmalonate (0.116 g, 0.750 mmol) (and the additive when present) in 4mL of dry THF was added. After the required reaction time, the system was quenched by the addition of aqueous ammonium chloride. The product was extracted with dichloromethane and, after drying over sodium sulphate, the product was isolated by column chromatography on silica gel (dichloromethane).

With BSA/dimehylmalonate: a solution of [Pd(μ-Cl)- (η^3-allyl)]$_2$ (0.0020 g, 0.0050 mmol) and the appropriate naplephos (0.022 mmol) in 0.5 mL of dry dichloromethane was stirred under nitrogen for 0.5 h. A solution of substrate (0.25 mmol) in 0.5 mL of the same solvent was then added. After stirring the resulting light yellow solution for additional 0.5 h, a solution of dimethylmalonate (0.0997 g, 0.750 mmol), BSA (0.152 g, 0.750 mmol) and a pinch of the acetate salt in 2 mL of dry

dichloromethane was added. After the required reaction time, the system was quenched by the addition of aqueous ammonium chloride. The organic phase was dried over sodium sulphate, and the product was isolated by column chromatography on silica gel (dichloromethane).

4.5 GENERAL PROCEDURE FOR THE Mo-AAA CATALYTIC REACTION PROMOTED BY μW

Two different stock solutions were prepared: solution N, containing the nucleophile, was prepared by adding dimethyl malonate (880 μL, 7.7 mmol) to a suspension of 60% NaH in mineral oil in tetrahydrofuran (10 mL), and solution S, containing the substrate, was prepared by dissolving the allylic carbonate (4 or 5) (7.1 mmol) in THF (10 mL). Then the appropriate ligand (0.034 mmol) and Mo(CO)6 (6.9 mg, 0.026 mmol) were transferred to a flame-dried SmithProcessVialTM. Solution N (1 mL), solution S, and BSA 311 (208 μL) were added in this order, and the suspension was heated in the microwave cavity at 160 °C for the desired time. The brown solution obtained was diluted with Et_2O to a total volume of 10 mL, resulting in a dark precipitate. A sample of the solution was filtered through silica gel and analysed by 1H NMR spectroscopy and GC-MS to determine the conversion and the regioselectivity.

The crude product was then purified either by bulb-tobulb distillation or by chromatography on silia gel (eluent: petroleum ether/DCM, 1:1). The *ee* was determined by HPLC using a Daicel OD-H (0.46 cm i.d. _ 25 cm) column. The structures of the products were confirmed by comparison with published spectroscopic data and GC-MS analyses.