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P-Donor Ligands: Xylose- and Mannitol-based Ligands

Carbohydrates, with their rich array of stereochemical and functional groups, are a popular source of starting materials for organic synthesis, and particularly for the synthesis of new ligands to be used in homogeneous catalysis. This chapter describes the synthesis of two families of phosphorous derivative ligands based on carbohydrate skeletons and their catalytic response towards the metal-catalysed hydrogenation of imines and enamides.

Chapter *3*

3.1. Introduction

Chiral auxiliaries, reagents and ligands derived from natural products like amino acids and carbohydrates are often used to direct the steric course of asymmetric transformations [1]. In asymmetric catalysis, chirality is transferred from a chiral ligand attached to the metal center to a prochiral substrate. The synthesis of chiral ligands that can effectively transfer chirality, then, is of great importance. One of the most commonly used strategies for obtaining chiral ligands is to transform readily available natural homochiral compounds. Carbohydrates are part of the "chiral pool", carry several stereogenic centres and can be easily obtained enantiopure at a reasonable price. They are highly functionalised, however, in most cases, many or all of the hydroxy groups have to be protected or even removed if the ligand is to be effective for metal-catalysed reactions. This means that it is essentially the backbone and the bulky shape of the whole molecule that transfers the chirality from the ligand to the final product [2].

Scheme 1 shows how versatile carbohydrates can be in synthesizing ligands containing phosphorus functions by a highly flexible route in which the key step is to introduce the phosphorous moiety by reacting the corresponding alcohol with diarylchlorophosphines or lithium diphenylphosphides [3].

A review of the literature shows that carbohydrates were first used to prepare chiral phosphorus ligands in 1978, when Sinou [4], Cullen [5] and Thompson [6] independently reported the synthesis and application of new tertiary phosphorus compounds related to monosaccharides with pyranose or furanose structures in some catalytic hydrogenation processes (Figure 1).

Not much later, in the early 80s Bruner [7] described the synthesis of new phosphorus ligands traced back to mannitol, xylose and glucose. The monophosphinite **6**, phosphinite-phosphite **7** and diphosphite **8** were prepared starting from 1,2:5,6-di-*O*-isopropyldidene-mannitol in a one step procedure by

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reaction with chlorophosphorus compounds (Figure 2). The phosphine-phosphinite **9** and the monophosphine **10** were synthesised from D-xylose derivatives and monophosphine **11** from D-glucose (Figure 2).
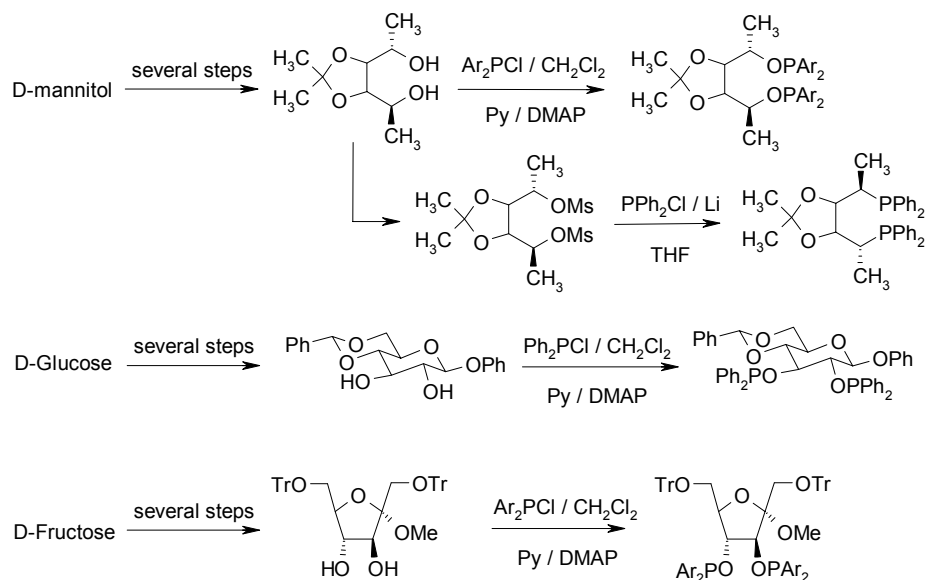
Scheme 1

Jackson [8] reported the synthesis and application of diphosphinite **12** in metal-catalysed hydroformylation and hydrocyanation reactions (Figure 2). This ligand was prepared from tartaric acid. Although tartaric acid is not a carbohydrate, it is one of most important starting materials for a variety of highly selective chiral ligands with C_2-symmetry [2,9].

It is noteworthy that, in the last decade, the synthesis and development of new ligands based on carbohydrate skeletons has undergone a huge increase and many reports discuss the impressive results obtained in several metal-catalysed processes [2,10].

Figure 1
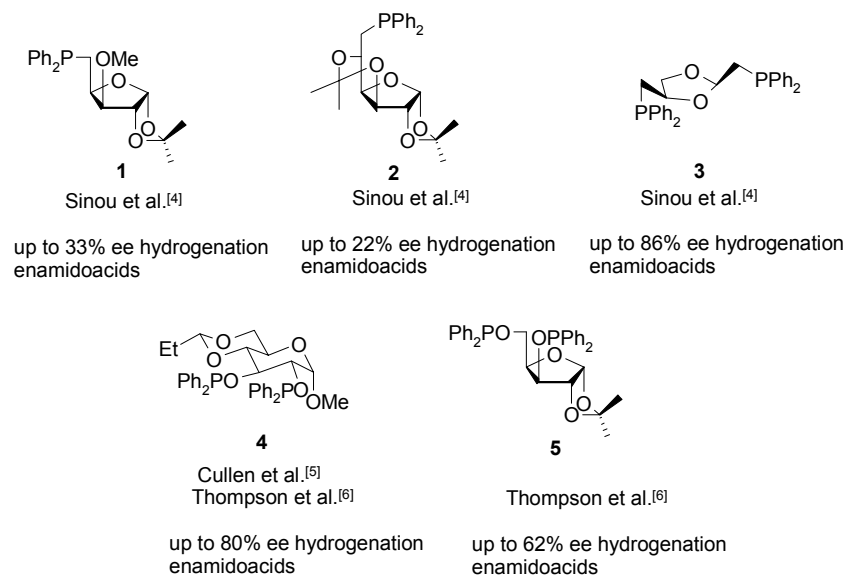

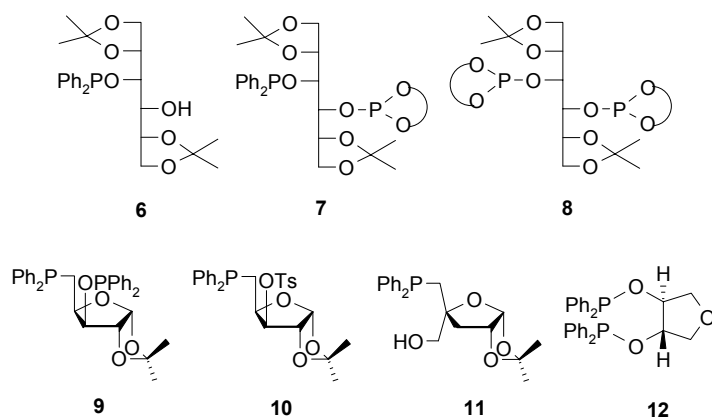**Figure 2**

Based on carbohydrates, ligands with C_1- and C_2-symmetry have been synthesised and successfully used in asymmetric catalysis. C_1-symmetric ligands may be traced back mainly to pyranoses (Figure 3).
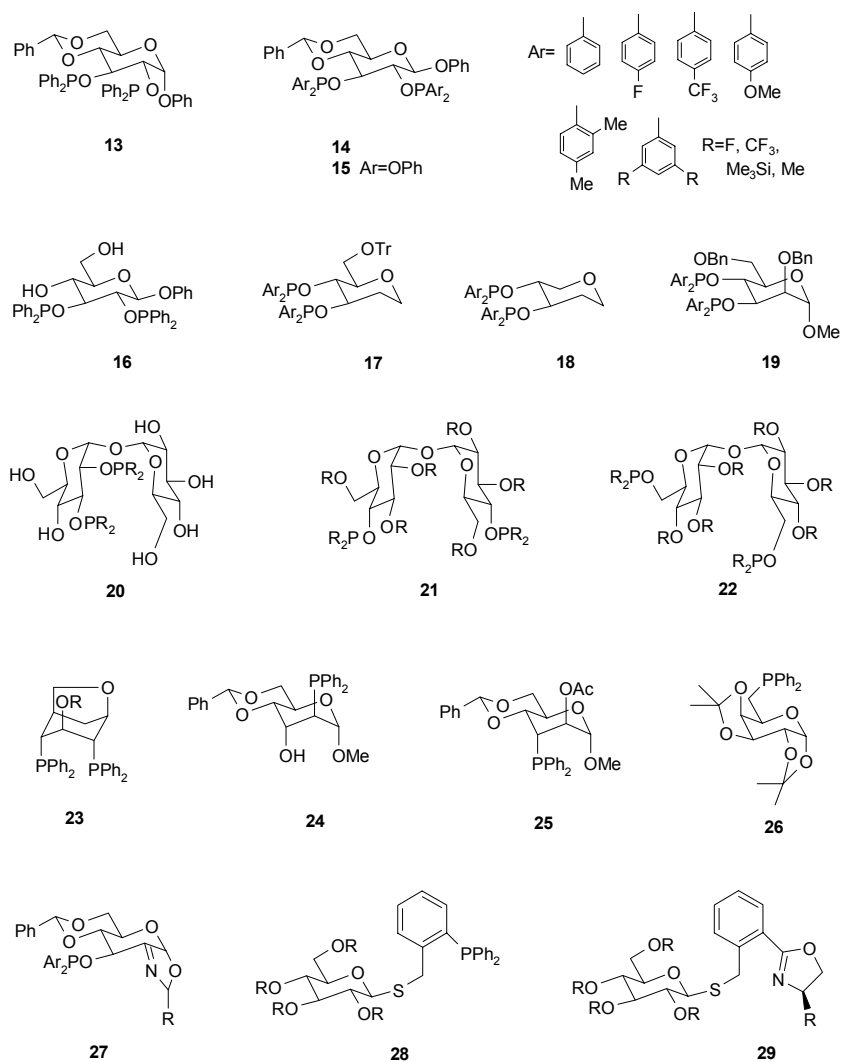
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Figure 3. C_1-symmetric pyranoside ligands derived from carbohydrates

The pyranoside ligands **13** and **14** (Figure 3) differ in the configuration of the anomeric carbon. While diphosphinite **13** (α-OPh) provided enantioselectivities in the hydrogenation of enamidoacids up to 80%, the diphosphinite **14** (β-OPh)

provided values as high as 96% [11]. Besides, diphosphinite **14** (Ar=Ph) was also successfully used in Rh-catalysed hydroformylation of styrene. However, the analogous phosphite **15** showed disappointing enantioselectivities in the hydroformylation of vinyl acetate [12].

In addition, Rajanbabu realized that the diphosphinites **16** and **17-19** (Figure 3) promoted the formation of opposite enantiomers in the Rh-catalysed hydrogenation of dehydroamidoacids with no significant variation in the enantiomeric excess [3a,13]. These pyranoside ligands, whose phosphorus functionalities are located at C2 and C3 or at C3 and C4, were indeed pseudo-enantiomers. Rajanbabu also performed an in-depth study with this family of ligands on how the electronic properties of the ligands affected the selectivity and rates of processes such as Ni-catalysed hydrocyanation of vinylarenes [3b,10g] or Rh-catalysed asymmetric hydrogenations of dehydroamidoacids [3a,10g]. The tuning of the electronic properties of the chelating atoms is related to a variation in the enantiomeric excess, although the reason why enantioselectivity depends on the electronic properties of ligands has still to be explained. However, some studies by Koenig [14] and Achiwa [15] show that more electron-rich phosphines enhance not only the activity of the catalyst by strengthening the d-σ^* interaction but also the enantioselectivitity. One possible explanation is that the more electron-rich phosphines increase the d-π^* back-donation between the metal and the coordinated unsaturated substrate and, therefore, the η^2 chelation between the metal and C=X becomes more rigid and leads to high enantioselectivity.

As mentioned in Chapter 1, it is assumed that diphosphines give the best rates of imine hydrogenation, therefore, other phosphorous ligands have scarcely been used in the reduction of C=N. So there are few examples in the literature in which diphosphinites **14** (Ar=Ph), **16**, **18** and diphosphite **15** promote the transformation of imines into chiral amines with rhodium systems giving conversions higher than 97% [16] (Figure 3). However, only the system

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[Rh(COD)**18**]BF$_4$ gave 72% ee when BnNH$_2$ was used as additive. With [Rh(COD)**14**]BF$_4$ and [Rh(COD)**16**]BF$_4$, the same enantiomeric excess (28%) was obtained, which demonstrated that the free hydroxyl groups at positions C-4 and C-6 do not have any influence on the catalytic results. Disappointingly, only 1% ee is reported for the system [Rh(COD)**15**]BF$_4$.

How to recover and reuse the catalyst after the catalytic reaction is still an unsolved problem in homogeneous catalysis [17], and in many cases, if the catalyst shows enough activity it is not later reused. Carbohydrates have a polyhydroxylic nature, which could favour their solubility in water and make it possible to work with a recyclable and environmentally friendly two-phase system using water-soluble catalysts. In an attempt to use ligands based on carbohydrates in biphasic systems, Uemura [18] and Rajanbabu [19] reported the diphosphinites **20-22** (Figure 3).

While the preparation of phosphinites or phosphites derived from monosaccharides is synthetically ease because it takes advantage of the many hydroxyl functionalities of carbohydrate skeletons, synthesizing phosphines is more difficult. However, some examples of monophosphines have been introduced in Figure 2, where the phosphine functionality is attached to a primary carbon. The introduction of a phosphorus atom into the secondary carbon of carbohydrates by nucleophilic replacement competes with undesired elimination reactions. Nevertheless, Vasella [20] reported the synthesis of diphosphine **23** and its application in the Ru-catalysed hydrogenation of β-ketoesters and Rh-catalysed hydrogenation of enamidoacids with moderate results (Figure 3).

Ligands with only one donor function have been dealt with less in the literature, because it has been generally accepted that chelating ligands give higher enantioselectivities. However, Sinou [4] and Bruner [7] reported the successful application of monodentate ligands **1**, **2**, **10** and **11** in asymmetric catalysis (Figures

1 and 2). In addition, monophosphines **24**, **25** and **26** [21] have recently been synthesized (Figure 3).

With the "hemi-labile ligands" phosphinoaminosugar **27** [18], phosphinothiosugar **28** [22] and oxazolinethiosugar **29** [18] enantioselectivities up to 96% were achieved in the Pd-catalysed allylic substitution (Figure 3).

Just a few examples of C_1-furanoside ligands for enantioselective catalytic transformations are known in the literature (Figure 4).

Rajanbabu reported the diphosphinite **30** [21b] derived from fructose, which was very efficient in the Ni-catalysed hydrocyanation of olefins, as well as the monophosphinite **44** [21b] and its use in hydrovinylation (Figure 4).

Bruner et al. [7a] reported moderate enantioselectivities (up to 35%) with phosphine-phosphinite **31** in the rhodium-catalysed hydrogenation of (Z)-α-acetamidocinnamic acid (Figure 4).

Kagan and Börner synthesized hydroxyphosphines **33** and **34** [23], which have a tetrahydrofuran backbone, from L-ascorbic acid (Figure 4).

Van Leeuwen et al. [24] reported the synthesis and use of a family of diphosphites related with structure **35** in the rhodium-catalysed hydroformylation of styrene. In the last few years, our group at the Rovira i Virgili University has made an important contribution to developing many different types of phosphorous ligands such as diphosphites **36-38** [25], phosphoroamidite-phosphites **39-40** [26], phosphine-phosphite **41** [27] and diphosphines **42-43** [10h,28] with a furanose structure and xylo-, gluco- or ribo- configuration (Figure 4).

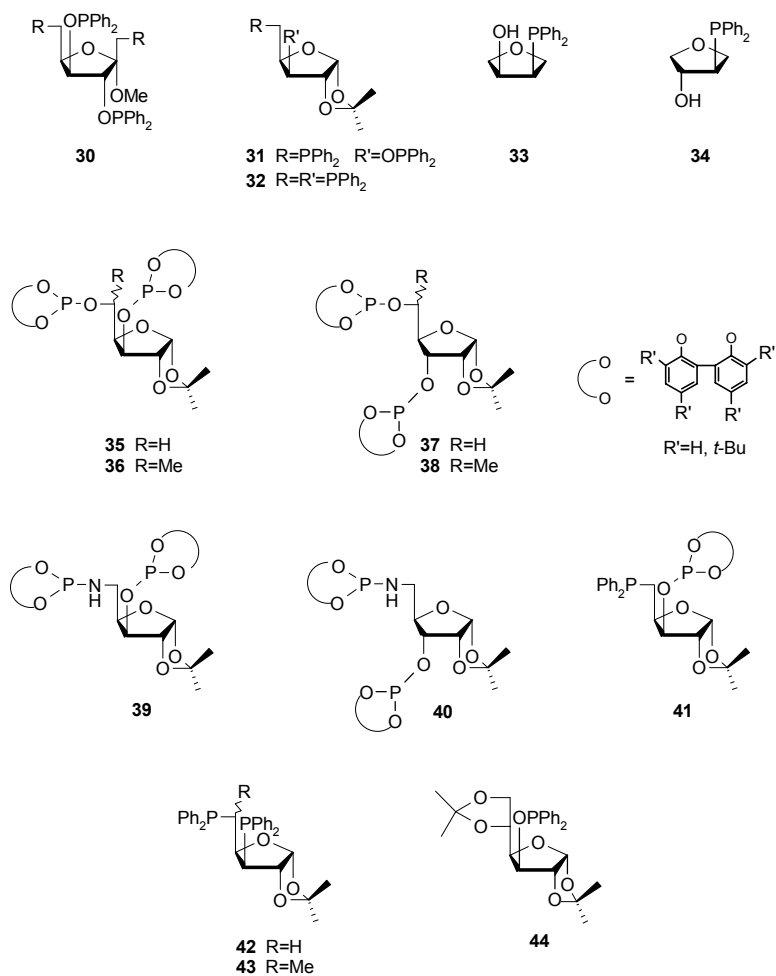**Figure 4.** C_1-symmetric furanoside ligands **30-44** derived from carbohydrates

Ligands derived from glucose introduce a new stereogenic center at the C-5 position close to one of the coordinating phosphorous atoms. This new stereocenter enhances the enantioselectivity; for instance, in the Rh-asymmetric hydroformylation of styrene the ee rose from 61% to 90% when ligand **36** [25a] was used instead of ligand **35** [24].

The chiral diphosphite **35** [25b], based on a xylose backbone, and the diphosphite **37** [25c], based on a ribose backbone, were tested in the asymmetric hydrogenation and hydroformylation of prochiral olefins. It was concluded that the configuration of the product is controlled by the configuration of the stereogenic carbon atom C-3.

The phosphoroamidite-phosphites **39-40** [26] gave enantioselectivities up to 65% in the Rh-catalysed hydroformylation of styrene.

The phosphine-phosphite **41** proved to be an excellent ligand in the asymmetric hydrogenation of α,β-unsaturated carboxylic acid derivatives. Systems generated *in situ* from [Rh(COD)$_2$]BF$_4$/**41** [27a], showed better activities and enantioselectivities (>99% ee) than the Rh/diphosphine **42** [28a] and diphosphite **35** [24] counterparts (under mild conditions: 1 bar of H$_2$ pressure, room temperature).

The phosphines **42-43** were tested in the rhodium-catalysed asymmetric hydroformylation of styrene and other vinyl arenes, and provided regioselectivites on the branched hydroformylated product up to 97% with ee's up to 58% [10h].

All these examples illustrate that chiral C_1-diphosphinite, diphosphite and phosphoroamidite ligands based on carbohydrate skeletons with furanose structures are potentially very useful in catalytic processes.

C_2-symmetric chiral ligands are particularly useful as mediators of stereochemical information. The introduction of this symmetry element means that: (1) both faces of the ligand become equivalent; (2) the number of the competing diastereomeric transition states is reduced significantly; (3) the C_2 symmetry element often also simplifies the synthesis of ligands.

C_2-symmetric ligands are mainly derived from mannitol. Phospholanes **45** [29] and **46** [30], examples of monodentate ligands, have been reported by Zhang and Rajanbabu, respectively (Figure 5).

The well-known diphosphines (R,R)-DIOP (**47**) [31], and DUPHOS (**48a**) [32], which are among the most efficient ligands used in catalysis, also present C_2-symmetry.

45 **46** **47**

48a R=Me R'=H
48b R=Me R'=OH
48c R=CH$_2$OH R'=H

49a R=Me R'=OH
49b R=CH$_2$OH R'=H

50 R = PPh$_2$
51 R = OP(OPh)$_2$

52 R = Ph
53 R= OPh

54

55

56a R=TBDPS
56b R= OTIPS
56c R=Tr
56d R=Ts

57

58a R=TBDPS
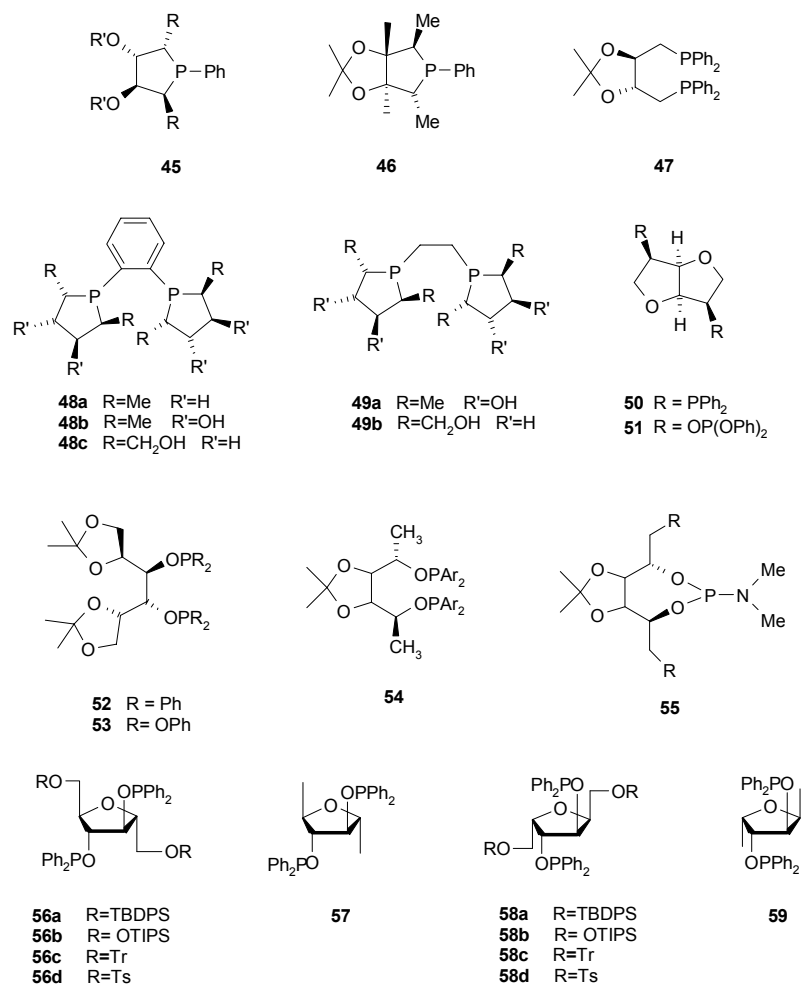**58b** R= OTIPS
58c R=Tr
58d R=Ts

59

Figure 5. C_2-symmetric ligands **45-59** derived from carbohydrates

Several groups have synthesized a wide variety of DuPHOS-analogues (**48b-c**) [33] and BPE-analogues (**49b**) [34], in which the characteristic 2,5-dimethylphospholano ring is substituted by other phospholano rings prepared from mannitol and free hydroxyl groups are incorporated to solubilize the ligands in water (Figure 5).

The diphosphine **50** [35] and diphosphite **51** [36] are responsible for the high enantioselectivities achieved in some asymmetric hydrogenation processes.

Other ligands also prepared from D-mannitol are diphosphite **53** [33], diphosphinites **52** and **54** [37], and phosphoroamidite **55** [38] (Figure 5).

Recently, our group [39] designed two new families of diphosphinites derived from D-mannitol (**56-57**) and L-iditol (**58-59**) with a tetrahydrofuran backbone and C_2-symmetry (Figure 5). These ligands have been used in rhodium-catalysed hydrogenation of prochiral olefins to obtain useful chiral precursors of amino acids and have proved to be very active as well as enantioselective. These two families have the same configuration at C3 and C4, but opposite configurations at C2 and C5. The enantioselectivity of the process is closely influenced by these secondary stereocenters, which shows that the D-mannitol derivatives **56-57** were more enantioselective than the L-iditol derivatives **58-59**. However, the absolute configuration of the resulting product is the same for all the D-mannitol and L-iditol ligands, which shows that it is independent of the configuration of C2 and C5. It is difficult to establish a general pattern for the influence of the protecting groups of the primary alcohols, but it seems that the TBDPS is the most suitable protecting group to achieve high enantioselectivities.

As far as we know, no Ir(I) catalysts bearing diphosphinite or diphosphite ligands based on carbohydrates have been reported in the asymmetric hydrogenation of imines. We felt, therefore, that it would be interesting to investigate the catalytic behavior towards the iridium-catalysed reduction of C=N of some ligands, which provided good results in other hydrogenation processes. So,

the C_1-symmetric diphosphinite **5** [6] and diphosphites **35** [24] based on D-xylose (Figures 1 and 4) were tested in the catalytic reduction of ketimines. In addition, we planned to enlarge the family of C_2-phosphinites related to structure **56a** based on D-mannitol (Figure 5), by preparing new ligands with different electronic properties. We also prepared new C_1- ligands traced back to D-xylose and D-mannitol to check their ability to reduce imines and enamides.

3.2. Results and Discussion

3.2.1. Xylose-based ligands

As stated in Chapter 1, Börner and co-workers [16] found that electron-rich dialkylphosphines provided worse conversions than the more electron-poor diphosphinites in the rhodium-catalysed hydrogenation of acyclic imines, in contrast to what was expected. So, ligands with more π-accepting properties like diphosphinites and diphosphites may be able to satisfactorily reduce prochiral imines. In accordance with this, we proposed to check the catalytic capability of diphosphinite **5** [6] and diphosphites **35a** and **35b** [24] (Figure 6) in the reduction of acyclic and cyclic ketimines with iridium precursors.

In the course of our studies we also isolated the monodentate ligand **60** (Figure 6), and since interesting results have recently been reported in the reduction of enamides with monodentate ligands [40], we decided to test the monophosphinite **60** in the asymmetric rhodium-catalysed reduction of enamides.

Figure 6

3.2.1.1. Synthesis and characterization of ligands 5, 35a-b and 60

Ligands **5** and **35a-b** were prepared satisfactorily by using the general procedures described in the literature [3,6,11,24]. The diol 1,2-*O*-isopropylidene-D-xylofuranose (**61**) was converted into the corresponding phosphinite or phosphite by treatment with R_2PCl/pyridine and purified by flash column chromatography under inert atmosphere with dry and degassed solvents (Scheme 2).

Scheme 2. Synthesis of ligands **9**, **35a-b** and **60**

PPh$_2$Cl was commercially available, but the phosphorochloridites **62a-b** ((RO)$_2$PCl) were prepared from the corresponding diol and PCl$_3$ in good yields (Scheme 3). The bis(2,4-dimethylphenyl)chlorophosphine (**63c**) was prepared from dichloro(diethylamino)phosphine and the Grignard reagent bis(2,4-dimethylphenyl)magnesiumbromide. The resulting diarylaminophosphine was then treated with anhydrous HCl.
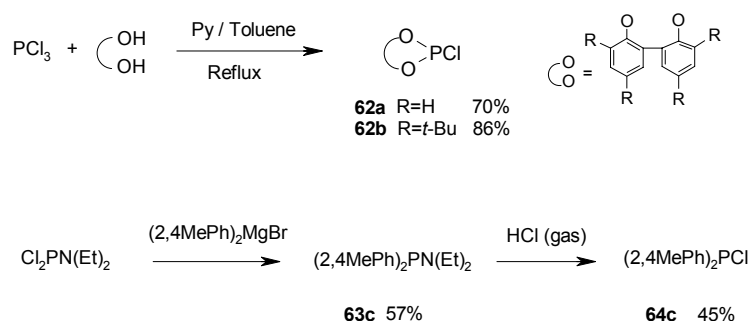
Scheme 3. Synthesis of **62a-b**, **63c** and **64c**

When **61** was treated with an excess of bis(2,4-dimethylphenyl)chlorophosphine (**64c**), the phosphorylation of the primary alcohol took place selectively to give the compound **60** as the major product (Scheme 2).

Various assays increasing the phosphorus reagent excess or forcing the conditions did not make it possible to obtain the diphosphinite derivative. A considerable number of side products containing phosphorus were also detected in the reaction mixture. One of these side compounds in particular had a peculiar ^{31}P{^{1}H} NMR pattern of two sets of doublets with a large coupling constant (*J*=237 Hz), which indicated a possible P-P bond. Although this compound was not isolated in pure form and could not be completely and unambiguously characterised, the ^{1}H NMR spectrum showed a compound, which incorporated xylose backbone and

aromatic groups. Section **3.2.2** (pags. 120-123) will propose and discuss in depth a feasible structure for a similar compound with a mannitol backbone.
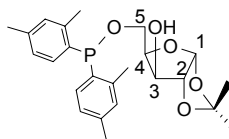
Thus, we reasoned that when the nucleophilic attack of the primary hydroxyl group is rate limiting and other side reactions compete, the phosphitylation reaction is completely selective for less hindered primary hydroxyl group.

Ligands **5**, **35a-b** and **60** were unequivocally characterized by NMR and MS techniques. The spectroscopic data of **5** and **35a-b** were in agreement with the published bibliographic data [7,24].

The $^{31}P\{^{1}H\}$ NMR spectrum of ligand **60** showed only one signal instead of the two signals expected for a disubstituted compound (Table 1).

The $^{13}C\{^{1}H\}$ NMR spectrum revealed that C5 appeared as a doublet at 67.8 ppm with a coupling constant $^{2}J_{C5-P}$=20.5 Hz, but that C3 appeared as a singlet at a similar chemical shift to C3 in compound **61**. These findings indicated that the phosphorus moiety was introduced only at the primary alcohol. Besides, the ^{1}H NMR and $^{13}C\{^{1}H\}$ NMR spectra showed signals corresponding to aromatic rings and methyl groups. The methyl groups attached to the aromatic rings did not become equivalents, and appeared as four different signals. In the $^{13}C\{^{1}H\}$ NMR spectrum, the signals corresponding to the *ortho*-methyl groups appeared as doublets due to the coupling with the phosphorus atom, with a coupling constant $^{3}J_{CH3-P}$=8.4 Hz.
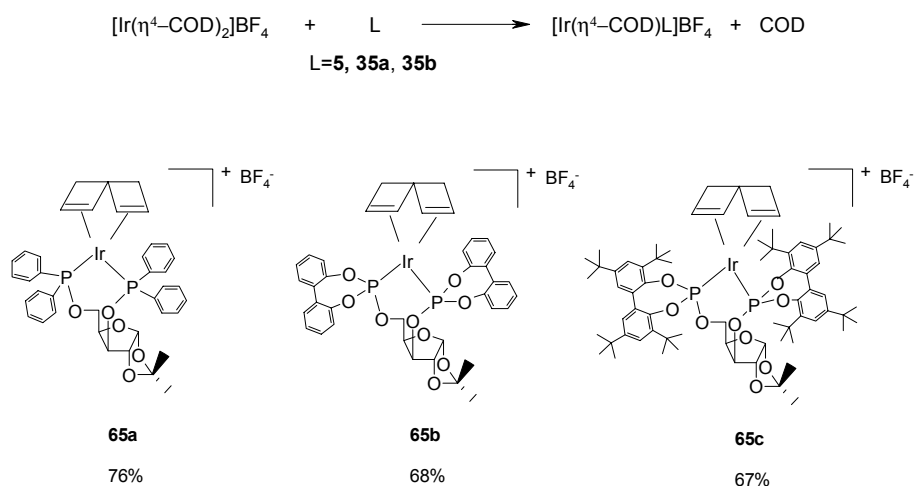
The MS FAB shows a peak at m/z 430.2 corresponding to M^{+}. The elemental analysis of C and H fits the molecular composition $C_{24}H_{31}O_{5}P$.

Table 1. Selected spectroscopic NMR data for ligand **60** recorded in CDCl$_3$

	^{1}H NMR (ppm)		^{31}C$\{^1$H$\}$ NMR (ppm)
Arom	7.15-7.07	Arom	136.0-130.1
H1	5.82 (s)	C1	104.9
H2	4.47 (s)	C2	85.4
H3	4.31 (br)	C3	75.9
H4	4.24 (br)	C4	79.0 (d)
			$^3J_{C4,P}$=7.6 Hz
H5/H5'	4.19 (m)	C5	67.8 (d)
			$^2J_{C5,P}$=20.5 Hz
C(C$\underline{H}_3$)$_2$	1.49 (s), 1.32 (s)	$\underline{C}$(CH$_3$)$_2$	111.8
		C($\underline{C}$H$_3$)$_2$	27.1, 26.5
2,4-C$\underline{H}_3$	2.42 (s), 2.34 (s),	2,4-$\underline{C}$H$_3$	21.5 (s), 21.4 (s), 20.4
	2.31 (s), 2.28 (s)		(d), 20.2 (d) $^3J_{\underline{C}H3,P}$=8.4
			Hz
O$\underline{H}$	2.82		
^{31}P$\{^1$H$\}$ NMR (ppm)	108.9		

3.2.1.2. Synthesis of [Ir(η^4-COD)L]BF$_4$ (65a-c)

The corresponding cationic Ir(I) complexes **65a-c** were prepared by reaction in dichloromethane of [Ir(η^4-COD)$_2$]BF$_4$ (COD=cyclooctadiene) with the ligands **5**, **35a** and **35b** (Scheme 4). Complexes **65a-c** were isolated as a moderately air-stable powder by adding ethyl ether [28a].

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$$[Ir(\eta^4\text{–COD})_2]BF_4 \quad + \quad L \quad \longrightarrow \quad [Ir(\eta^4\text{–COD})L]BF_4 \quad + \quad COD$$

L=**5, 35a, 35b**

65a

76%

65b

68%

65c

67%

Scheme 4. Synthesis of iridium complexes **65a-c**

The elemental analysis of C and H matched the stoichiometry $[Ir(\eta^4\text{-}$ COD)L]BF$_4$ (L= **5**, **35a-b**). The FAB mass spectra for complex **65c** showed the highest ion at a m/z value of 1367.3, which corresponds to the cationic mononuclear species. Moreover, the loss of cyclooctadiene is also observable. The $^{31}P\{^1H\}$ NMR spectra showed two doublets due to the $^{31}P\text{-}^{31}P$ coupling. These doublets are sharp in the case of complex **65a**, but broad for complexes **65b-c**. The ^1H and $^{13}C\{^1H\}$ NMR spectra of **65b-c** are in agreement with the published bibliographic data [25b].

3.2.2. Mannitol-based ligands

As mentioned in the Introduction, our group has recently developed a new family of C_2-symmetry ligands based on the monosaccharide D-mannitol with a

tetrahydrofuran structure (**56-59**) (Figure 5), which provided encouraging results in the rhodium-catalysed asymmetric hydrogenation of α,β-dehydroamino acids. These ligands have the following general structural characteristics (Figure 7): (1) they are "tailor-made" ligands, which make it possible to modify the carbohydrate skeleton and the phosphorus moiety easily and independently; (2) they have C_2-symmetry; (3) the presence of other stereocenters, in addition to those that anchor the phosphorous moiety, influences the conformational flexibility and, therefore, the asymmetric induction; (4) the phosphorus unit may be phosphinite, phosphite, phosphoroamidite or even phosphine, leading to a considerable number of ligands; (5) the size of the chelate can vary from 5 to 7 members depending on the phosphorus functions, and gives organometallic complexes with considerable conformational flexibility; (6) the primary alcohols can be functionalised with bulky protecting groups so that their influence on the enantiocontrol can be studied; (7) it may be possible to recover the catalyst after use by immobilising the ligand in a solid support (polymer, silicagel, etc.) or by introducing polyhydroxilate or perfluorate chains to solubilise the ligand in water or supercritical fluids.
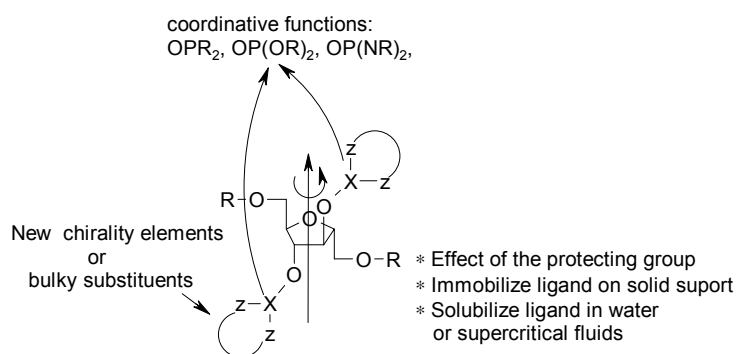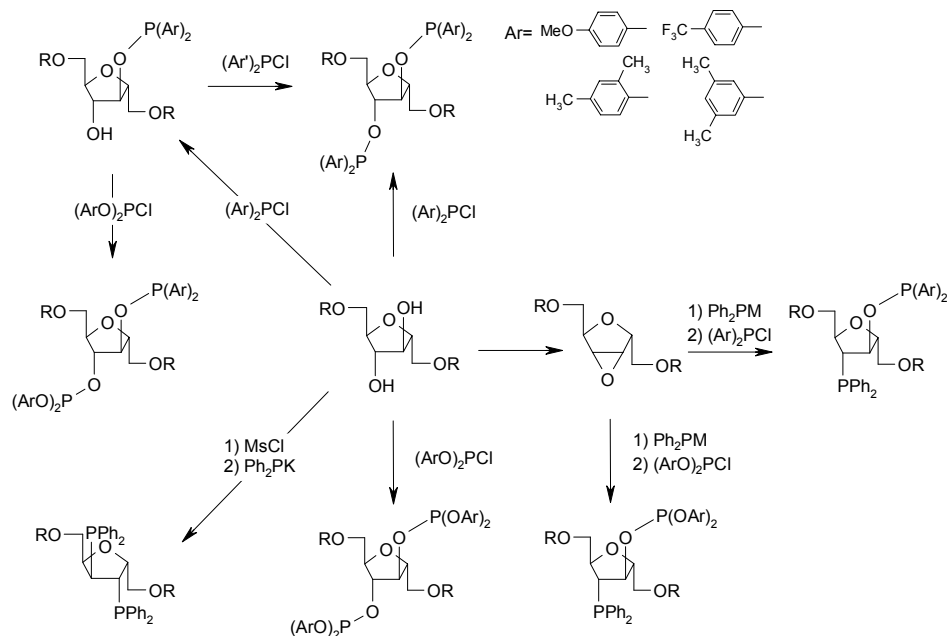

Figure 7

Scheme 5 illustrates some of the ligands that can be prepared from the protected 2,5-anhydro-D-mannitol.

Scheme 5

Strategies for controlling regio- or stereoselectivity in catalytic reactions have usually involved designing or manipulating the catalyst steric enviroment, even though the electronic properties of ligands can have profound effects on the selectivity and rates of fundamental catalytic processes [3].

So it is important to investigate both the electronic and the steric effects. Our aim was to enlarge this new family of C_2-diphosphinites by synthesising a set of diphosphinites (**66a-c**), related to ligand **56a,** with different modifications on the aryl groups attached to the phosphorus atoms (Figure 8).

The monodentate ligand **67** was also unexpectedly obtained, as occurred with the xylose derivative ligand **60**. So compound **67** enabled us to investigate the synthesis of new non-symmetrical ligands by introducing a second phosphorous moiety. Thus the C_1-symmetric ligands **68**, **69a-b** were also prepared (Figure 8).

Further, we investigated the catalytic behavior of the bidentate ligands **56a**, **66a-c**, **68** and **69a-b** towards the asymmetric iridium- and rhodium-catalysed C=N and C=C reductions, as well as the monodentate ligand **67** in the asymmetric rhodium-catalysed C=C reduction.
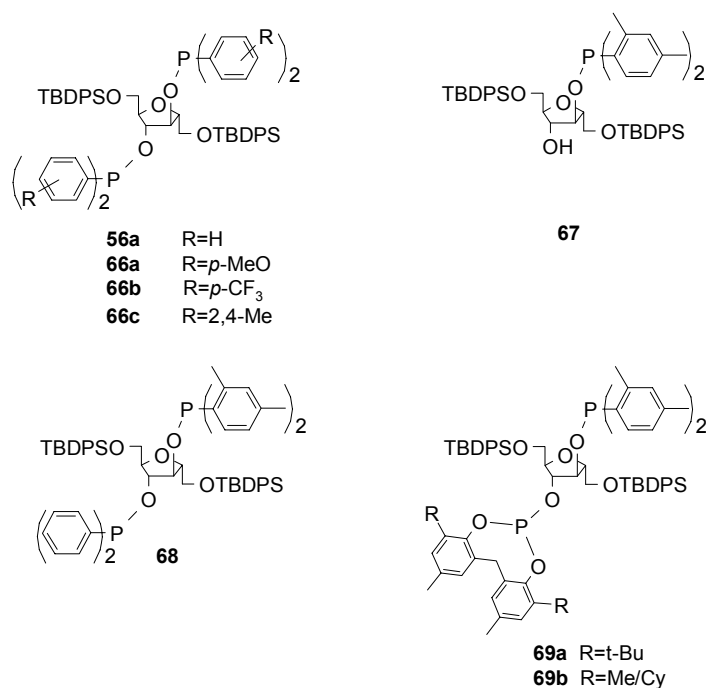

56a R=H
66a R=*p*-MeO
66b R=*p*-CF₃
66c R=2,4-Me

67

68

69a R=t-Bu
69b R=Me/Cy

Figure 8

### 3.2.2.1. Synthesis and characterization of ligands 66a-c, 67, 68, 69a-b

The chiral backbone of these ligands is the 2,5-anhydro-D-mannitol (**70**) in which the two primary alcohols were appropriately protected with tert-butyl-diphenylsilyl group by standard methods (Scheme 6). The resulting diol is then converted into the corresponding diarylphosphinite ligands by treatment with R_2PCl/base [3] or with R_2PNEt_2 [41] and purified by flash column chromatography under inert atmosphere using dry and degassed solvents. By these methods, the series of C_2-diphosphinites **66a-c** were synthesised in one step (Scheme 6).
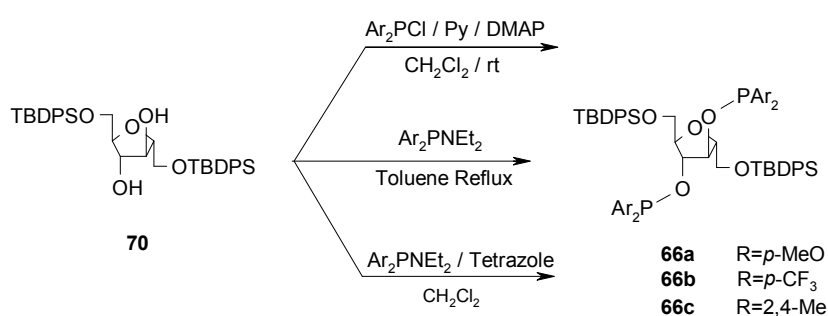
Scheme 6

To synthesise these new ligands various diaryldiethylaminophosphines (**63a-c**) and diarylchlorophosphines (**64a-c**) had to be prepared first, in accordance with the Rajanbabu protocol (Scheme 7) [3].

Grignard reagents (ArMgBr), formed by the reaction of magnesium with the correspoding aryl bromides, were treated with Et_2NPCl_2 to give the aminophosphine intermediates (**63a-c**), which were isolated and characterised. Finally, HCl bubbling replaced the amino moiety by a chlorine atom to give the diarylchlorophosphines (**64a-c**).
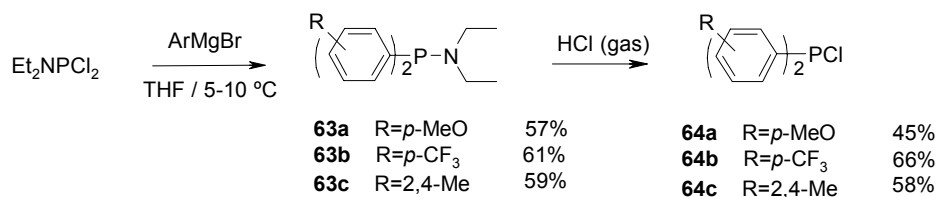
Scheme 7

It was more difficult than expected to synthesise the desired ligands. When the diol **70** was reacted with the chlorophosphine **64a** in the stardard conditions described by Rajanbabu, the starting material was totally converted but a complex and inseparable mixture of compounds was obtained. Many other unidentified side phosphorus compounds were obtained and the amount of ligand **66a** was less than 10% measured by RMN (Table 2, entry 1) [3].

Table 2. Synthesis of ligands **66a** and **66b**
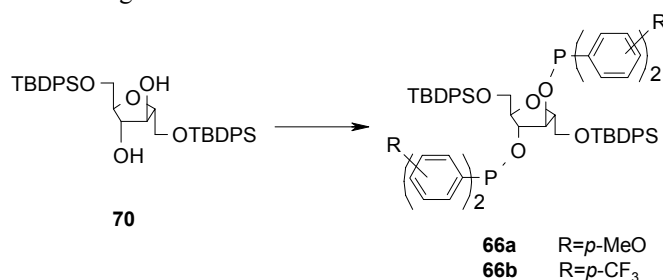
Entry	Reagents	Solvent	T [°C]	Time [h]	Conv. [%]	Yield [%]
1[a]	**64a** / Py / DMAP	CH$_2$Cl$_2$	rt	16	100	Not isolated[b]
2	**63a**	Toluene	110	24	100	23
3	**63b**	Toluene	110	24	100	28
4	**63a** / Tetrazole	CH$_3$CN/CH$_2$Cl$_2$	rt	1/2	100	59

[a] Py=pyridine, DMAP=dimethylaminopyridine [b] Ligand **66a** could not be isolated in pure form from the reaction mixture by column chromatography

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Ligands **66a** and **66b**, however, were isolated by an unoptimized direct reaction of the aminophosphine **63a** or **63b** (Table 2, entries 2 and 3) with diol **70** in refluxing toluene [41]. Although all the starting material disappeared, ligands **66a** and **66b** were obtained in low yields (23% and 28%, respectively) after purification by column chromatography under argon. Many other side compounds were formed under these reaction conditions. These phosphorous compounds seem not to be very stable under purification conditions (silica or even alumina).

In an atempt to find milder reaction conditions, aminophosphine **63a** was treated with the weak acid 1*H*-tetrazole before **70** was added [42]. The reaction to form ligand **66a** worked considerably better and the yield increased to 59% (Table 2, entry 4). By slightly modifying the general synthetic procedure used in the phosphitylation of nucleotides, we found a suitable method for attaching phosphorylate functions to carbohydrates to give phosphinites. The mechanism is probably similar to the one reported for the phosphitylation of nucleotides using phosphoroamidites (($RO)_2PN(i\text{-}Pr)_2$) as a phosphorus reagent [43]. Protonation of the diarylaminophosphine **63** by the weak acid 1*H*-tetrazole, followed by nucleophilic attack by the tetrazolide ion, gives the 1-arylphosphanyl-1*H*-tetrazole (**71**) (Scheme 8). Subsequently nucleophilic attack of hydroxyl groups from **70** on **71** gives the desired protected phosphinite ligands **66**.

With regard to the synthesis of diphosphinite **66c**, Table 3 shows the reaction conditions tested to attach the bis(2,4-dimethylphenyl)chlorophosphine moiety to the mannitol backbone. Although not all the assays were successful at forming **66c**, we found reaction conditions that were suitable for preparing and isolating diphosphinite and monophosphinite ligands **66c** and **67**, but not selectively.

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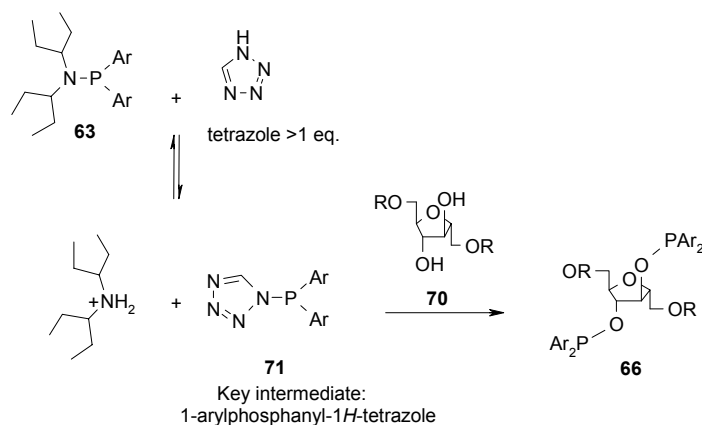
Scheme 8

When diol **70** reacted with diarylchlorophosphine **64c** and pyridine/DMAP in CH$_2$Cl$_2$ gave a mixture in which the major product did not correspond to either **66c** or **67** (Table 3, entry 1). The spectroscopic analysis revealed that the unidentified compound was the phosphine oxide **72** (Table 3, entry 1). The MS spectrum showed the highest m/z at 1120.4, which fits with the molecular composition C$_{70}$H$_{82}$O$_5$P$_2$Si$_2$. The loss of the *tert*-butylphenyl group was also observable at m/z 881.3 (M$^+$-TBDPS). ^{31}P{^{1}H} and ^{1}H NMR revealed a C_2-symmetric compound. However, the chemical shift of the phosphorus atom did not agree with the expected chemical shift for phosphinite compounds. The phosphorus signal appeared at 16.9 ppm in the ^{31}P{^{1}H} NMR spectrum in agreement with the chemical shift of some phosphine oxides ((CH$_3$)$_2$CHCH$_2$P(O)Ph$_2$ δ^{31}P=20 ppm; (CH$_3$CH$_2$)$_2$CHP(O)Ph$_2$ δ^{31}P=38 ppm; (C$_6$H$_{11}$P(O)Ph$_2$ δ^{31}P=33 ppm) [44]. It has long been known that some phosphinite esters undergo "self-isomerization" to the corresponding phosphine oxide [45]. Normally isomerization can be effected by heating and is catalysed by impurities in the reaction mixture or by adding small quantities of iodine or R'X. Indeed, because of the ease of the isomerization

process, it has frequently been difficult to isolate phosphinite esters. Early attempts to prepare methyl- and benzyldiphenyl-phosphinite esters [46] led only to the corresponding phosphine oxides. An attempt to reduce the compound **72** with HSiCl$_3$ did not proceed.

Table 3. Synthesis of ligands **66c** and **67** and formation of **72**
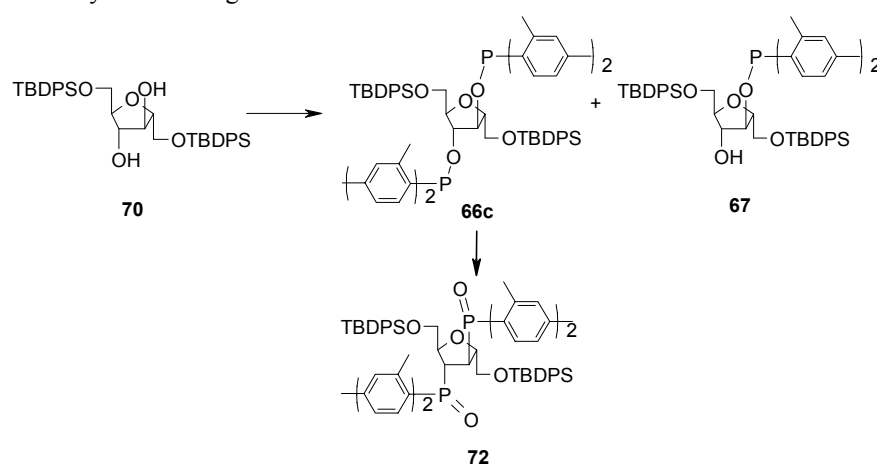
Entry	Reagent	Solvent	T^a [ºC]	Time [h]	Ratio **66c/67**
1[a]	**64c** / Py / DMAP	CH$_2$Cl$_2$	rt	16	--
2	**64c** / Et$_3$N	THF	rt	16	0/1
3	**63c**	Toluene	110	24	--
4	**63c** (4eq)/Tetrazole (5.6eq)	CH$_2$Cl$_2$/CH$_3$CN	rt	3	1/3
5	**63c** (4eq)/Tetrazole (5.6eq)	CH$_2$Cl$_2$/CH$_3$CN	60	7	--
6	**63c** (8eq)/Tetrazole (11.2eq)	CH$_3$CN	rt	24	1/1

[a] Py=piridine, DMAP=dimethylaminopyridine

When the reaction conditions were slightly modified using THF instead of CH$_2$Cl$_2$, and Et$_3$N instead of pyridine at room temperature (Table 3, entry 2), only one phosphine moiety was introduced to give the monodentate ligand **67** in a 48%

yield. A considerable amount of a side product was observed, whereas it was not in CH_2Cl_2.

  This side product was isolated and characterised, and the $^{31}P\{^1H\}$ NMR spectrum showed a set of two doublets at +42.6 ppm and –44.2 ppm with a large coupling constant of 234 Hz. This indicated that there was probably a P-P bond of two unequal phosphorous atoms. Besides, the ^1H and $^{13}C\{^1H\}$ NMR spectra showed a C_2-symmetric compound, following the pattern observed in previous ligands with this symmetry element, two protons of the tetrahydrofuran ring and two protons of the exocyclic methylene group, as well as four singlets associated to four different methyl groups of the aromatic rings. The bidimensional HMQC spectrum ^{31}P-^1H showed the correlation between the two different phosphorus atoms and the aromatic and methyl groups (Figure 9).
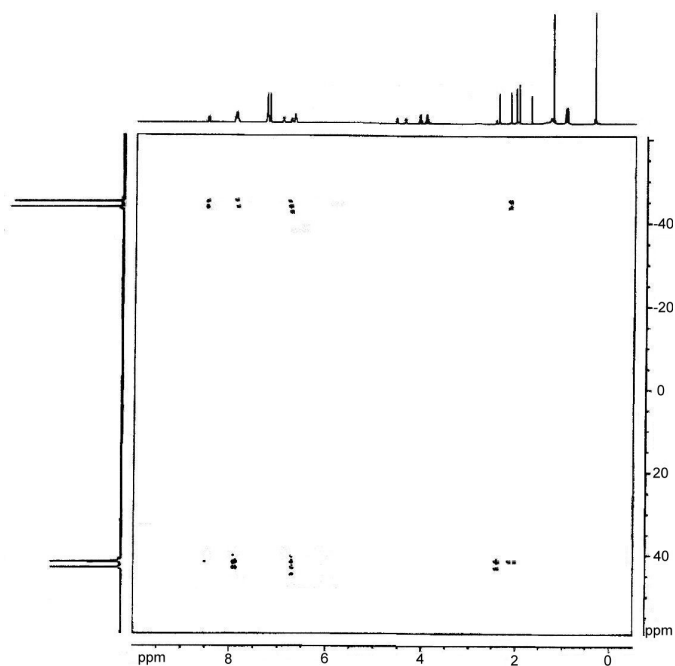

Figure 9. HMQC ^{31}P-^1H spectrum

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The MS analysis showed that the highest peak, at m/z 1120.5, corresponded to a compound with a molecular composition of $C_{70}H_{82}P_2O_5Si_2$. A feasible structure, which fits all these experimental data, is proposed in Figure 10.
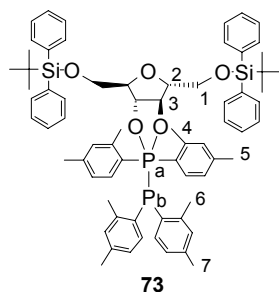

73

Figure 10

However, as can be observed in the ^{31}P-^{1}H spectrum (Figure 9), the couplings between Pa-H3 and Pa-C3 through the oxygen atom were not detectable. The ^{31}P-^{1}H and ^{31}P-^{13}C couplings depen on the molecular geometry and in particular of the dihedral angle, the hybridisation of phosphorus (P^{III}, P^{IV+}, P^{V}), the hybridisation of carbon, and the substituents attached to these atoms [47]. There are several experimental Karplus type curves for the geometrical dependence of ^{31}P-^{1}H couplings, mainly in derivatives of trivalent phosphorus [47]. Thus, it is possible that the geometrical arrangement of the molecule and its dihedral angles give values of $^{3}J(P\text{-}O\text{-}C\text{-}H3)$ and $^{2}J(P\text{-}O\text{-}C3) \approx 0$ Hz.

There are several examples in the literature of compounds of the type R_2P-$P(O)R_2$ [47] (R=Ph, $J_{P\text{-}P}$=224 Hz, δP^{III}=21.6 ppm and δP^{V}=-36.9 ppm) with P^{III} and P^{V} that have coupling constants and chemical shifts similar to those shown by **73**. Examples of P^{V} compounds of the type $P(OR)_2R_3$ or $P(OR)_5$ [47] show the following chemical shifts: $P(OEt)_2(Ph)_3$ δP^{V}=-55 ppm; $P(OMe)_5$ δP^{V}=-67 ppm;

P(OPh)$_5$ δP^V=-85 ppm, which are also in agreement with the chemical shift of P^V in compound **73**.

Scheme 9 shows a plausible mechanism for the formation of compound **73**. Firstly, the expected nucleophilic attack of one hydroxyl group on the diarylchlorophosphine takes place. Subsequently, however, it is the attached phosphorus atom that acts as a nucleophile toward a second molecule of the diarylchlorophosphine. Under specific reaction conditions it may be possible to favour the selective attack of the phosphorus atom, and not the remaining hydroxyl group, on a second electrophile reagent. The bulkiness of the bis(2,4-dimethylphenyl)chlorophosphine reagent may be responsible for the selectivity observed, increasing the difference in the reaction rate between the two hydroxyls.

Phosphorus atom, like all elements of the third period, is characterized by having rather diffuse frontier orbitals, which favour long-range interactions and the formation of P-P bonds [48]. They can also act as both nucleophiles or electrophiles. Finally, the nucleophilic attack of the oxygen atom on P^{IV+} gives compound **73** by removing HCl.
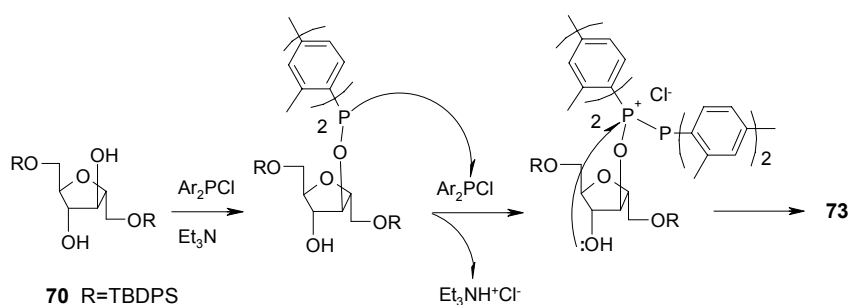
Scheme 9

In an attempt to prevent compound **73** from forming and to continue exploring new synthetic procedures of preparing **66c** and **67**, we also tried to build
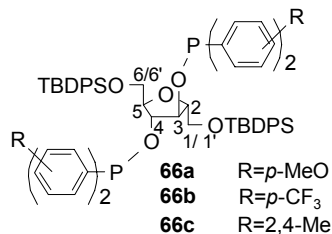
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the bond P-O directly from the corresponding aminophosphine **63c** in toluene at 110°C [41]. However, a complicated mixture of compounds was obtained which could not be purified (Table 3, entry 3).

Treating diol **70** with the aminophosphine **63c** and 1*H*-tetrazol in the standard conditions [42] it was possible to obtain a mixture of di- and monosubstitute ligands. Ligands **66c** and **67** were isolated by column chromatography in a ratio 1/3 (Table 3, entry 4). Several attempts were made to force the reaction into the total conversion of the disubstituted compound **66c** (Table 3, entries 4-6). When the temperature and reaction time were increased, only the starting material was recovered. This seems to indicate that the reaction is reversible in this conditions (Table 3, entry 5). When we used a higher number of equivalents of aminophosphine **63c** and 1*H*-tetrazole the ratio was 1/1, but we could not exclusively obtain the disubstituted compound **66c**.

The diphosphinite ligands **66a-c** displayed the expected pattern for C_2-symmetric compounds. The $^{31}P\{^1H\}$ NMR spectra displayed only one signal between 110.5-115.1 ppm, which agreed with the expected chemical shift for phosphinite compounds. Simple ^1H and $^{13}C\{^1H\}$ NMR spectra showed three groups of signals in the region corresponding to the tetrahydrofuran backbone (H1/H1'=H6/H6'; H2=H5; H3=H4 and C1=C6; C2=C5; C3=C4) (Table 4). The most significant difference in the chemical shift was observed for H3 and C3, which appear at higher δ than in diol **70** (Δδ=0.6-0.8 in ^1H NMR spectra and Δδ=5-6 ppm in ^{13}C NMR spectra). The couplings between H3 and the phosphorus atom are observable through the oxygen $^3J(P\text{-}O\text{-}CH)$. Also some signals in the $^{13}C\{^1H\}$ NMR spectra show multiplicity due to the coupling with the phosphorus atom ($^2J(P\text{-}O\text{-}C3)$ and $^3J(P\text{-}O\text{-}C\text{-}C2)$). However, the value of the coupling constants could not always be determined because the NMR spectra were second-order spectra. The signals were unambiguously assigned by bidimensional experiments (HSQC and COSY) and the proposed structures were also confirmed by MS

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spectrometry. Table 4 collects the ^{1}H, ^{13}C{^{1}H} and ^{31}P{^{1}H} NMR data for ligands **66a-c**.

Table 4. [1]H, ^{13}C{^{1}H} and ^{31}P{^{1}H} NMR data for ligands **66a-c** recorded in CDCl$_3$

^{1}H NMR (ppm)	66a[a]	66b	66c
Arom	7.76-6.63	7.65-7.25	7.55-6.70
H1/H1'	3.89 (dd) / 3.19 (dd) $^2J_{H1H1'}$=11.2 Hz, $^3J_{H1H2}$=4 Hz	3.82 (dd) / 3.62 (dd) $^2J_{H1H1'}$=11.2 Hz, $^3J_{H1H2}$=4 Hz	3.65 (dd) /3.54 (dd) $^2J_{H1H1'}$=10.8 Hz, $^3J_{H1H2}$=5.2 Hz
H2	4.39 (m)	4.18 (m)	4.09 (m)
H3	5.18 (m)	5.01 (m)	4.66 (m)
C(C$\underline{H}_3$)$_3$	1.13 (s)	1.05 (s)	0.74 (s)
MeO	3.17 (s) / 3.16 (s)	--	--
CF$_3$	--	--	--
2,4-C$\underline{H}_3$	--	--	2.14 (s), 2.13 (s), 2.12 (s), 2.11 (s)
^{13}C{^{1}H} NMR (ppm)			
Arom	160.7-113.9	134.3-125.3	141.0-126.7
C1	64.1	63.6	64.2
C2	84.5	83.4	84.5
C3	85.0 (m)	86.2 (m)	85.5 (m)
C($\underline{C}$H$_3$)$_3$	27.0	27.0	27.0
$\underline{C}$(CH$_3$)$_3$	19.4	19.5	19.4
MeO	55.3 / 55.2	--	--
CF$_3$	--	122.7	--
2,4-$\underline{C}$H$_3$	--	--	21.4 (b), 20.7 (d, $^3J_{C\text{-}P}$=7.74Hz), 20.52 (d, $^3J_{C\text{-}P}$=6.84Hz)
^{31}P{^{1}H} NMR (ppm)	115.1	110.5	102.6

[a] ^{1}H NMR spectrum of **54a** was recorded in C$_6$D$_6.$

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It is important to note that the phenyl rings attached to the phosphorus atom did not become equivalent, showing two different signals for the CH_3O and four different signals for the 2,4-CH_3 groups. The FAB MS analysis of **66a** and **66c** showed that the highest values of m/z were at 1129.3 and 1121.6 respectively, which corresponded to the M^+.

The structural elucidation of monodentate ligand **67** is supported by ^1H, $^{13}C\{^1H\}$ and $^{31}P\{^1H\}$ NMR spectra (Table 5) as well as by the bidimensional COSY, HSQC and HMBC experiments and MS spectroscopy.

Table 5. ^1H, $^{13}C\{^1H\}$ and $^{31}P\{^1H\}$ NMR data for ligand **67** recorded in $CDCl_3$

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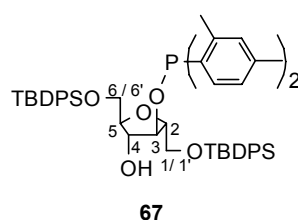
	^1H NMR (ppm)		$^{13}C\{^1H\}$NMR (ppm)
Arom	7.59-6.87	Arom	138.1-127.6
H1/H1'; H6/H6'	3.73-3.52 (m)	C1 / C6	64.7 / 64.1
H2	3.99 (br)	C2	83.9 (d, $^3J_{C2P}$=6 Hz)
H3	4.47 (m)	C3	86.0 (d, $^2J_{C3P}$=18 Hz)
H4	4.31 (br)	C4	78.0 (d, $^3J_{C4P}$=4.5 Hz)
H5	3.99 (br)	C5	85.0 (s)
C(C$\underline{H}_3$)$_3$	0.96 (s), 0.94 (s)	C(C$\underline{H}_3$)$_3$	27.2, 27.0
		$\underline{C}$(CH$_3$)$_3$	21.4, 21.5
2,4-C$\underline{H}_3$	2.30 (s), 2.17 (s),	2,4-$\underline{C}$H$_3$	20.5 (d, $^3J_{C\text{-}P}$=12.2Hz),
	2.11 (s), 2.06 (s)		20,3 (d, $^3J_{C\text{-}P}$=12.3Hz),
			19.6 (s), 19.5 (s)
OH	2.79 (br)		
$^{31}P\{^1H\}$NMR (ppm)	102.7		

The most relevant difference with respect to bidentate ligand **66c** is that monodentate ligand **67**, obviously, did not present C_2-symmetry. Therefore, the ^{1}H and ^{13}C$\{^1$H$\}$ NMR spectra showed 6 groups of signals corresponding to the tetrahydrofuran backbone. Moreover, while C3 in ^{13}C$\{^1$H$\}$ NMR spectrum displayed an increase of 6.3 ppm with regard to the diol **70**, C4 only varied by 1.69 ppm. The ^{31}P$\{^1$H$\}$ NMR spectrum showed one signal at 102.7 ppm in agreement with the expected chemical shift.

The two upfield-shifted resonances for two *t*-butyl groups in a ratio 9:9 in the ^{1}H NMR spectrum indicated that these groups were not equivalent. Neither were the two phenyl rings attached to the phosphorus atoms equivalent. They showed four signals in a ratio 3:3:3:3 attributed to the 2,4-CH$_3$ groups. A correlation between the proton of the hydroxyl group and H4 was observed in the COSY spectrum.

The FAB MS analysis showed the highest m/z value at 881.46 corresponding to the M$^+$.

Because of increasing interest in chiral non-C_2-symmetric bidentate ligands with electronically different phosphorus atoms [49], diphosphinites carrying two phosphorous atoms with quite different electron densities or phosphinite-phosphite are an attractive choice. Therefore, as well as testing the monodentate ligand **67** in catalysis, we decided to explore the synthesis of non-symmetrical ligands by introducing a second different phosphorous moiety (Scheme 10).

Three ligands with C_1 symmetry were prepared by standard methods [6,24]. The non-symmetrical diphosphinite **68** was obtained in moderate yield by reaction of **67** with diphenylchlorophosphine and triethylamine.

The phosphinite-phosphite ligands **69a** and **69b** were isolated after purification in 40% yield and 32% yield, respectively, after reaction of **67** with two different phosphorochlororidites ((RO)$_2$PCl) in a mixture of toluene and pyridine.

The phosphorochlororidites used had very bulky groups at the *ortho* position of the phenyl groups, but they incorporated a methylene group between the aromatic rings to give more flexible structures than those related to the bisphenol moieties [24] used in the synthesis of xylose ligands **35a-b** (Schemes 2 and 3).
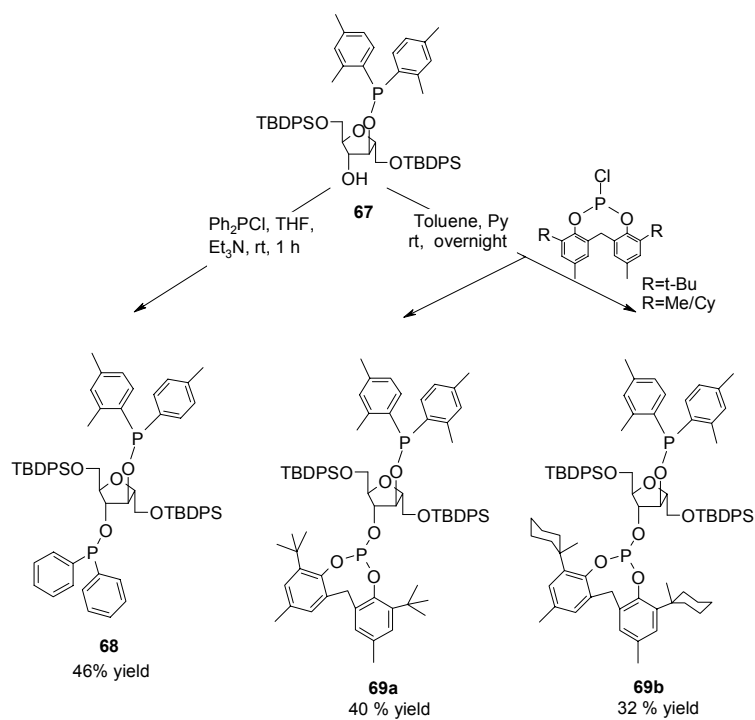
Scheme 10

The ligands **68** and **69a-b** were characterized by NMR techniques (^{1}H, ^{13}C{^{1}H}, ^{31}P{^{1}H} and HSQC) showing C_1-symmetry pattern. Tables 7 and 8 summarize the NMR data for these ligands

Table 6. ^{1}H and ^{31}P{^{1}H} NMR data of **68**, **69a** and **69b** recorded in CDCl$_3$

| **68** | R=Ph | **69a** | R= | **69b** | R= |
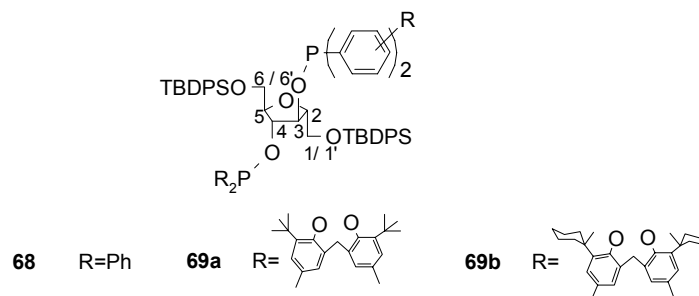
^{1}H NMR (ppm)	**68**	**69a**	**69b**
Arom	7.67-6.91	7.69-6.73	7.71-6.74
H1/H1	3.75-3.57 (m)	3.98-3.72 (m)	4.01-3.74 (m)
H6/H6'	3.75-3.57 (m)	3.98-3.72 (m)	4.01-3.74 (m)
H2	4.17-4.11 (m)	4.30 (m)	4.30 (m)
H3	4.89-4.79 (m)	4.92 (m)	4.85 (m)
H4	4.89-4.79 (m)	5.79 (m)	5.67 (m)
H5	4.17-4.11 (m)	4.67 (m)	4.62 (m)
SiC(CH$_3$)$_3$	1.10 (s), 1.00 (s)	1.04 (s), 0.98 (s)	1.05 (s), 0.97 (s)
2,4-CH$_3$	2.25 (s), 2.23 (s), 2.19 (br), 2.14 (br)	2.31 (br, 2.28 (br), 2.26 (br), 2.26 (br)	2.36 (br), 2.28 (br), 2.24 (br), 2.29 (br)
CH$_2$	--	4.13 (d), 3.15 (d) ^2J=12.2 Hz	4.12 (d), 3.15 (d) ^2J=12.8 Hz
C(CH$_3$)$_3$	--	1.29 (s), 1.22 (s)	--
p-CH$_3$Ph	--	2.26 (s), 2.19 (s)	2.27 (s)
Cyclohexyl	--	--	1.54-1.12
CH$_3$-Cy	--	--	1.16 (s), 1.09 (s)
^{31}P{^{1}H}NMR (ppm)	114.2, 102.7	127.9, 102.8	127.8, 103.2

The incorporation of a second different unit of phosphorus was corroborated by a second signal in the ^{31}P{^{1}H} NMR spectrum shifted in the region

for phosphite compounds and by the displacement of C4 in the $^{13}C\{^1H\}$ NMR spectrum ($\Delta\delta$=7.61 ppm in ligand **68** and 2.2 ppm in ligand **69a**) with regard to monodentate ligand **67**. Signals in the ^1H and $^{13}C\{^1H\}$ spectra corresponding to aromatic, *t*-butyl, cyclohexyl and methyl fragments confirmed that a new phosphorus fragment had been incorporated. In ligands **69a** and **69b**, the two protons of the bridged methylene group appeared as diastereotopics with $\Delta\delta\approx1$ppm in their chemical shift.

The FAB MS analysis of **69a** showed a peak at m/z 1249.12 corresponding to the M^+ ($C_{77}H_{94}O_7P_2Si_2$).

Table 7. $^{13}C\{^1H\}$ NMR data of **55** and **56a** recorded in $CDCl_3$

$^{13}C\{^1H\}$NMR (ppm)	68	69a
Arom	139.3-127.9	145.6-126.8
C1 / C6	64.1 (s), 63.9 (s)	64.3, 63.9
C2	84.3 (m)	85.2
C3	85.6 (m)	85.9 (m)
C4	85.6 (m)	80.3 (m)
C5	84.3 (m)	85.4
SiC(CH$_3$)$_3$	26.8	27.0 (s), 26.9 (s)
SiC(CH$_3$)$_3$	19.4	19.4
2,4-CH$_3$	21.3, 20.7 (d), 20.6 (d) $^3J_{C-P}$=13.7Hz	21.3 (s), 20.8 (d), 20.6 (d) $^3J_{C-P}$=13.7Hz
CH$_2$	--	34.8
C(CH$_3$)$_3$	--	31.2 (s), 31.1 (s)
C(CH$_3$)$_3$	--	19.5 (s)
p-CH$_3$Ph	--	21.5 (s), 21.4 (s)

3.2.3. Asymmetric Hydrogenation of Imines

As has been discussed in Chapter 1, the asymmetric hydrogenation of imines is of interest for obtaining enantiomerically enriched amines. Rhodium and iridium cationic systems bearing diphosphines have proved to be highly effective at reducing ketimines. Therefore, only few rhodium/diphosphinite or rhodium/diphosphite systems have been used in the reduction of acyclic imines [16].

Xylose- and mannitol-diphosphinites (**5, 56a, 66a-c, 68**), xylose-diphosphites (**35a-b**) and mannitol-phosphinite-phosphites (**69a-b**) have been used in the iridium-catalysed asymmetric hydrogenation of acyclic and cyclic ketimines to evaluate their potential as ligands in the reduction of C=N (Figure 11).
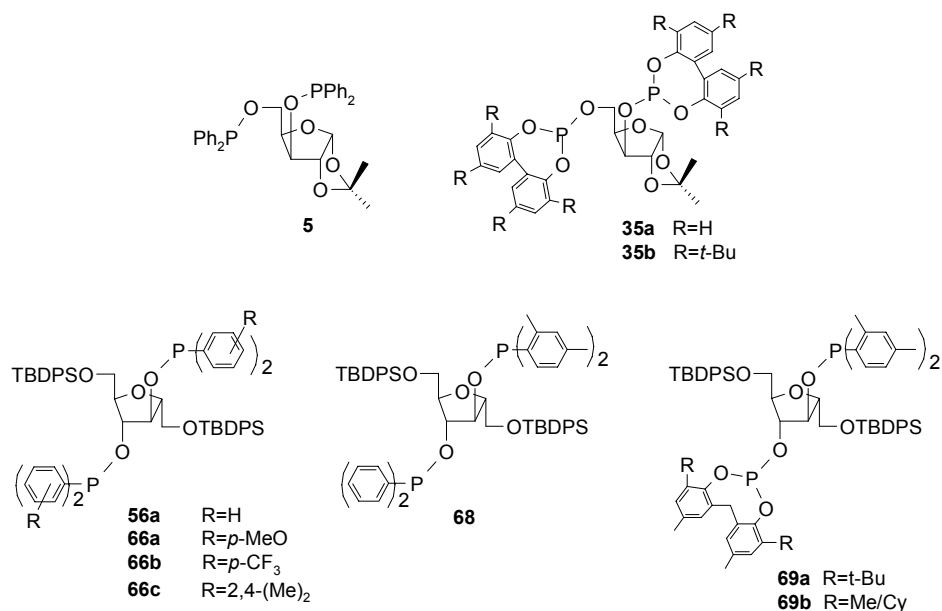

Figure 11

Two acyclic imines were chosen as model substrates to be reduced, *N*-(phenylethylidene)benzylamine (**74**) and *N*-(phenylethylidene)aniline (**76**). The reduction of cyclic imine 6,7-dimethoxyl-1-methyl-3,4-dihydroisoquinoline (**78**), in which the geometry of the C=N double bond is fixed to *E*-configuration was also studied (Scheme 11).

74	R=Bn	R'=Ph		**75**	R=Bn	R'=Ph
76	R=Ph	R'=Ph		**77**	R=Ph	R'=Ph

$$[H_2]$$
$$[Ir] / L$$
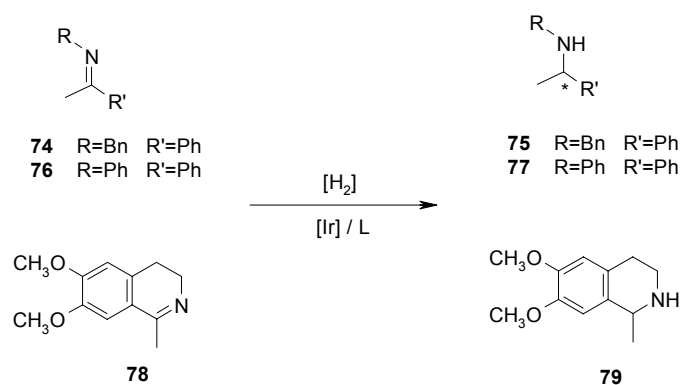
Scheme 11

First, we focused on the asymmetric hydrogenation of a representative non-cyclic ketimine, *N*-(phenylethylidene)benzylamine (**74**). Imine **74** has been reduced satisfactorily (ee higher than 78%) mainly with iridium systems based on diphosphines such as BINAP [50] or cationic iridium precursors containing NP ligands such as diphenylphosphinooxazolines [51] ligands and more recently with an iridium system formed by [Ir(COD)Cl]$_2$ and a phosphine oxide as ligand [52]. Besides, rhodium catalysts containing diphosphinites gave enantioselectivities up to 72% [16].

The hydrogenation of **74** was carried out using the cationic iridium complexes **65a-c** as catalytic precursors. The catalytic precursors [Ir(COD)(L)]BF$_4$ (**65a-c**; L= **5**, **35a**, **35b**) (Scheme 4, p. 112) were tested at several hydrogen

pressures and with various solvents. Catalysts **65a-c** were active at 25-100 bar of hydrogen and 25ºC and provided complete hydrogenation into amine **75** in 16 hours. The cationic iridium precursor **65b** did not provide enantioselectivity in any conditions, even when different solvents (MeOH, CH$_2$Cl$_2$) and pressures were tested. Only with catalyst precursors **65a** and **65c** were moderate ee obtained, 46 and 21%, respectively. However, we found that in the hydrogenation of **74** with these catalytic systems, the ee values were not reproducible, even when the conditions were strictly maintained. It has been previously reported that ee's obtained in the asymmetric hydrogenation of *N*-(phenylethylidene)benzylamine are poorly reproducible [16,53].

Having established in the above experiments the conditions in which imine **74** is most likely to be reduced, we performed a broad ligand screening. We were also interested in investigating the reproducibility of the results in the hydrogenation of imine **74** with other catalytic systems.

The criteria for choosing the most appropriate precatalyst were how it affected the activity and the enantioselectivity of the system. So we studied the influence of the catalyst precursor. Imine **74** was reduced by systems generated *in situ* from both [Ir(COD)Cl]$_2$ and [Ir(COD)$_2$]BF$_4$ by adding diphosphinites (**56a**, **66a-b**, **68**) and phosphinite-phosphite (**69a**) (Table 8).

These systems were active in reducing imine **74** and provided conversions between 70-100% within 16 hours at 70 bar of H$_2$ pressure in CH$_2$Cl$_2$. However, hydrogenolysis products were also detected together with the desired secondary amine **75**, because of the cleavage of the nitrogen-benzylic bond, which decreased selectivity [54]. The [Ir(COD)$_2$]BF$_4$/L systems provided worse selectivities than [Ir(COD)Cl]$_2$/L with values lower than 85% (Table 8, entries 6-10).

Most of these systems did not provide enantiocontrol in the hydrogenation of **74**. Only the system formed by [Ir(COD)$_2$]BF$_4$ and phosphinite-phosphite **69a** gave a noteworthy ee of 73% (Table 8, entry 10). Moreover, it is important to note

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that whereas no enantioselectivity was achieved using [Ir(COD)Cl]$_2$/**69a**, the system formed by [Ir(COD)$_2$]BF$_4$/**69a** proved to be superior in terms of enantioselectivity, and produced the chiral amine **75** rather effectively (Table 8, entries 5 and 10). The findings show that the precatalysts are important if a high degree of enantioselectivity is desired [55].

Table 8. Hydrogenation of **74** with Ir/L catalytic systems. Effect of the precatalyst [a]
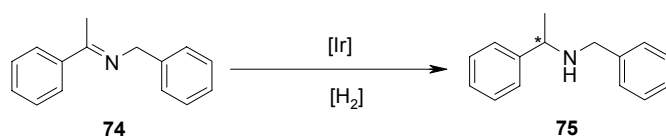
Entry	Precatalyst	Conv [%]	Selec [%]	Ee[b] [%]
1	[Ir(COD)Cl]$_2$/**56a**	100	95	0
2	[Ir(COD)Cl]$_2$/**66a**	74	85	0
3	[Ir(COD)Cl]$_2$/**66b**	93	92	5 (-)
4	[Ir(COD)Cl]$_2$/**68**	100	90	0
5	[Ir(COD)Cl]$_2$/**69a**	100	90	0
6	[Ir(COD)$_2$]BF$_4$/**56a**	82	76	9 (-)
7	[Ir(COD)$_2$]BF$_4$/**66a**	70	68	0
8	[Ir(COD)$_2$]BF$_4$/**66b**	85	76	11 (-)
9	[Ir(COD)$_2$]BF$_4$/**68**	82	68	6 (+)
10	[Ir(COD)$_2$]BF$_4$/**69a**	100	85	73 (-)

[a]Reaction conditions: 1% mol [Ir], 1.25 % mol ligand, 70 bar H$_2$, 16 h, 25ºC, CH$_2$Cl$_2$ [b] absolute configuration was not determined

The mannitol-based ligands **69a-b** have C_1-symmetry, bulky groups in the *ortho* positions of the aryl rings and combine the electronic properties of phosphinite and phosphite functionalities. The seven-membered Ir(I)-chelate based

on phosphinite-phosphite ligands **69a-b** provided better results than the more conformationally flexible eight-membered Ir(I) chelate based on diphosphinite **5** or diphosphite **35b**. So, the accurate tuning of structural and electronic parameters makes the Ir(I)/mannitol-based phosphinite-phosphite systems the most suitable of all the catalysts tested in this study to reduce imine **74** satisfactorily.

We also studied the effect of temperature and additives on both activity and enantioselectivity in the hydrogenation of **74** using the catalyst [Ir(COD)$_2$]BF$_4$/**69a-b** (Table 9). Several reports have shown that additives may improve catalytic activity and enantioselectivity [56]. Halides [57] and amines are the most widely used additives [50].

When **74** was hydrogenated with the catalyst [Ir(COD)$_2$]BF$_4$/**69a** at shorter reaction times or at lower temperatures (0ºC) (Table 9, entries 2 and 3), the activity of the catalytic system and the optical yield decreased. After half an hour, conversion was only 24% resulting in a TOF[h^{-1}]=48 (TOF= turnover frequency) (Table 9, entry 2). The lower enantiomeric excess obtained at shorter times or lower temperatures suggests that the catalytic species responsible for enantiocontrol needs longer times or higher temperatures to be formed.

The results obtained with catalysts [Ir(COD)$_2$]BF$_4$/**69a** and [Ir(COD)$_2$]BF$_4$/**69b** are depend heavily on the presence of iodide ions. Addition of Bu$_4$NI deactivates the catalyst and causes a sharp decrease in conversion and enantioselectivity (Table 9, entries 1, 4, 9, 10).

I$_2$ also had a dramatic effect on the selectivity and enantioselectivity of the catalytic system. The selectivity in the desired amine **75** decreased spectacularly and favoured the hydrogenolysis of amine **75** (Table 9, entries 5, 11). Besides, the ee dropped to almost zero when the experiments were carried out in the presence of 10% mol of I$_2$ at 25ºC (Table 9, entries 5 and 11). The combination of a lower temperature (0ºC) and the addition of I$_2$ resulted in a considerable variation in the

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optical yield, favoring the formation of the opposite enantiomer in 76% ee (Table 9, entry 6).

Table 9. Hydrogenation of **74** with [Ir(COD)$_2$]BF$_4$ / **69a**, **69b**. Study of the effect of temperature and additive[a]
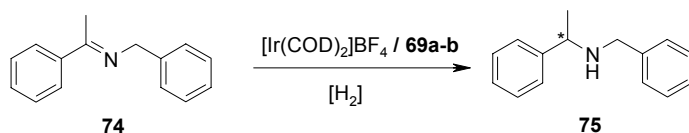
Entry	Ligand	Additive[b]	Temp. [ºC]	Time [h]	Conv [%]	Selec [%]	Ee[c] [%][c]
1	**69a**	--	25	16	100	85.5	73 (-)
2	**69a**	--	25	0.5	24	100	68 (-)
3	**69a**	--	0	2	4.3	100	40 (-)
4	**69a**	Bu$_4$NI	25	16	9.5	100	16 (-)
5	**69a**	I$_2$	25	16	100	17	1.4 (-)
6	**69a**	I$_2$	0	2	1.4	100	76 (+)
7	**69a**	Phthalimide	25	16	100	89	75 (-)
8	**69a**	BnNH$_2$	25	16	97	91	76 (-)
9[d]	**69b**	--	25	2	17	93	52 (-)
10	**69b**	Bu$_4$NI	25	16	9	100	11 (-)
11	**69b**	I$_2$	25	16	100	87	0
12	**69b**	Phthalimide	25	16	63	100	54 (-)
13	**69b**	BnNH$_2$	25	16	91	81	58 (-)

[a] Reaction conditions: 1% mol catalyst, 1.2% mol ligand, 70 bar H$_2$, 25ºC, 16h, CH$_2$Cl$_2$ [b] 10% mol additive [c] absolute configuration was not determined [d] 30 bar H$_2$

These findings allow us to speculate about the role of the iodide. Since the imine is coordinated to the metal by one of the two enantiotopic faces, the addition of iodide must influence the opposite coordinating mode of the imine [58], which is more selective at low temperatures when the conformational mobility of the system is reduced.

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The addition of amine derivatives did not have a very strong influence, at least at 25ºC, and both conversion and enantioselectivity were maintained (Table 9, entries 7, 8, 12, 13). This indicates that amines, which are also the reaction products, do not deactivate the catalyst and conversion of the substrate is almost total.

A rather broad ligand screening was also carried out with *N*-aryl imine **76**, which has a more constrained structure and is less basic than imine **74**. Imine **76** is very efficiently hydrogenated by iridium systems bearing the ferrocenyl-phosphine (*R,R*)-f-binaphane (ee up to 84%) and by the cationic iridium complexes with diphenylphosphinooxazolines (ee up to 89%) [51b,59].

The homogeneous catalysts were based on iridium and modified by adding different diphosphinite, diphosphite and phosphinite-phosphite ligands. The effect of pressure and temperature on the conversion to the amine, the optical yield and the effect of additives on these parameters were also investigated.

Initially we studied the hydrogenation of **76** at different pressures and temperatures using the complex [Ir(COD)**5**]BF$_4$ (**65a**) as catalyst precursor (Table 10). Enantioselectivities were best (57%) at low pressures (Table 10, entries 1-3). Curiously, a higher substrate/catalyst ratio and a lower temperature decrease the enantioselectivity (Table 10, entries 4 and 6). This dependence of the enantiomeric excess on the temperature has also been observed in the hydrogenation of **74**, which agrees with the hypothesis that the most enantioselective species needs higher temperatures if it is to be formed.

When Bu$_4$NI was used as additive at 0ºC, the enantioselectivity fell sharply and promoted the opposite enantiomer (Table 10, entry 7). Similar behaviour was also observed in the hydrogenation of **74** with [Ir(COD)$_2$]BF$_4$/**69a** at 0ºC, when I$_2$ was added (Table 9, entry 6).

Table 10. Hydrogenation of imine **76** using complex [Ir(COD)**5**]BF$_4$ (**65a**) as catalyst[a]
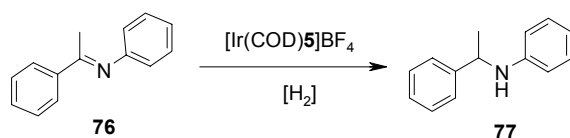
Entry	P [bar]	T [°C]	Additive	Conversion [%]	ee [%]
1	10	25	-	83	57 (*S*)
2	25	25	-	95	56 (*S*)
3	50	25	-	92	38 (*S*)
4[b]	50	25	-	20	22 (*S*)
5	85	25	-	98	30 (*S*)
6	25	0	-	85	20 (*S*)
7[c]	25	0	Bu$_4$NI	96	15 (*R*)

[a] Reaction conditions: 1% mol catalyst, 18 h, CH$_2$Cl$_2$ [b] 0.1% mol catalyst [c] 25% mol additive, 5 h

Imine **76** was also satisfactorily reduced to secondary amine **77** by systems generated *in situ* from [IrCODCl]$_2$/L and [Ir(COD)$_2$]BF$_4$/L (L=**35a-b**, **56a**, **66a-c**, **68**, **69a**) at 70 bar of H$_2$ pressure in CH$_2$Cl$_2$. Whereas the catalysts [IrCODCl]$_2$/L provided no noteworthy enantioselectivities (up to 10%), the [Ir(COD)$_2$]BF$_4$/L systems proved to be more enantioselective and gave ee values as high as 70% (Table 11, entry 5).

The catalytic system [Ir(COD)$_2$]BF$_4$/diphosphites **35a-b** were active in the hydrogenation of imine **76** (Table 11, entries 1 and 2), and selectively provided the amine **77.** They did not achieve enantioselectivity under these conditions, however.

Table 11. Hydrogenation of imine **76** using [Ir(COD)$_2$]BF$_4$ / L catalytic system. Effect of the additive [a]
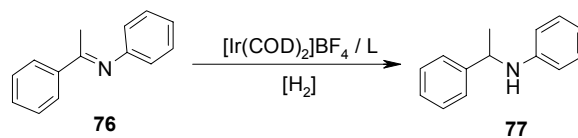
Entry	Ligand	Time [h]	Additive[b]	Conv. [%]	Selec [%]	Ee[c] [%]
1	**35a**	16	--	40	100	0
2	**35b**	16	--	100	100	5 (-)
3	**56a**	16	--	100	100	65 (+)
4	**66a**	0.25	--	26	100	nd[d]
5	**66a**	1	--	98	100	70 (+)
6	**66a**	16	--	100	100	70 (+)
7	**66b**	16	--	100	100	31 (-)
8	**66c**	1	--	6	100	15 (-)
9	**68**	16	--	98	99	3 (+)
10	**69a**	16	--	99	100	0
11	**35a**	16	Bu$_4$NI	78	100	0
12	**35a**	16	I$_2$	100	100	0
13	**35b**	16	Bu$_4$NI	100	100	46 (-)
14	**35b**	16	I$_2$	100	100	31 (-)
15	**35b**	16	Phthalimide	49	96	9 (-)
16	**35b**	16	BnNH$_2$	10	71	7 (-)
17	**56a**	16	Bu$_4$NI	42	100	19 (-)
18	**56a**	16	I$_2$	100	100	10 (-)
19	**56a**	16	Phthalimide	98	100	66 (+)
20	**56a**	16	BnNH$_2$	52	97	42 (+)
21	**66a**	16	Bu$_4$NI	71.1	100	19 (+)
22	**66a**	16	I$_2$	100	100	5 (-)
23	**66a**	16	Phthalimide	99.3	100	70 (+)
24	**66a**	16	BnNH$_2$	43.6	94	52 (+)
25	**66b**	16	Bu$_4$NI	100	100	12 (+)
26	**66b**	16	I$_2$	100	100	4 (-)
27	**66b**	16	Phthalimide	99	100	9 (-)
28	**66b**	16	BnNH$_2$	25	90	10 (-)
29	**68**	16	Bu$_4$NI	58	100	15 (+)

[a] Reaction condititions: 1% mol [Ir(COD)$_2$]BF$_4$], Ratio 1% mol Ligand, 70 bar, 25ºC, 16 h, CH$_2$Cl$_2$ [b] 4% mol additive [c] absolute configuration was not determined. [d] not determined

The systems [Ir(COD)$_2$]BF$_4$/diphosphinite (**56a**, **66a-b**) afforded enantioselectivities between 31-70% (Table 11, entries 3-7), whereas the Ir(I) systems carrying the diphosphinite ligand **66c**, which introduces methyl groups into the aromatic rings to increase either the electron density on phosphorus or the steric hindrance, only afforded 6% conversion and 15% ee in 1 hour (Table 11, entry 8).

The cationic iridium complex with C_1-diphosphinite **68** and phosphinite-phosphite **69a** provided racemic mixtures (Table 11, entries 9 and 10).

The most striking result in Table 11 is the value of ee obtained with [Ir(COD)$_2$]BF$_4$ and the more electron-donor ligand **66a** (up to 70%) (Table 10, entries 5 and 6). The substrate was almost completely reduced within 1 hour. The more electron-donor properties of ligand **66a,** which incorporates a methoxy group into the aromatic rings, may be the reason for this higher activity.

Whereas [Ir(COD)$_2$]BF$_4$/**56a** provided an ee of 65% under these conditions (Table 11, entry 3)**,** the catalyst based on [Ir(COD)$_2$]BF$_4$ and the less donor ligand **66b** gave low enantioselectivities and promoted the formation of the opposite enantiomer (Table 11, entry 7).

It should be pointed out that of all the ligands presented in this study, diphosphinite ligands provided the best results for the iridium-catalysed reduction of the *N*-aryl imine **76** affording moderate ee's (Table 10, entry 1: Ir(I)/diphosphinite **9** up to 57%; and Table 11 entries 3, 5, 7: Ir(I)/diphosphinite **66a** up to 70%)).

The seven-membered Ir(I)-chelate based on the mannitol derivative ligand **66a** provided better results than the eight-membered Ir(I)-chelate based on the xylose derivative ligand **9**. Of the mannitol derivative diphosphinites, the more electron donor diphosphinite **66a** provided more enantioselective Ir(I) catalysts (Table 11, entry 5).

These findings suggest that the electronic parameters of the ligands have a considerable effect on the enantiomeric excess. Imine **76**, which is less basic than

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imine **74**, may require more electron donor catalytic systems able to increase the d-π* back-donation between the metal and the coordinated imine, resulting in a more rigid metal-imine η^2 chelation and enhancing the optical yield [14,15].

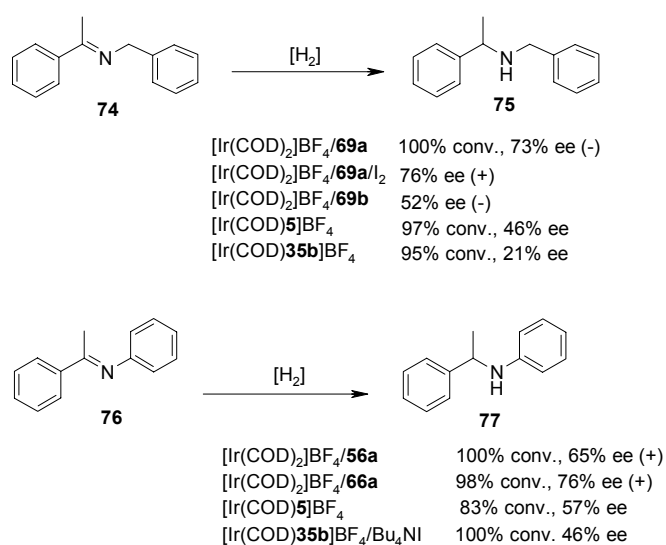The effect of adding halide ions or amine derivative to these catalytic systems was also examined.

The addition of Bu$_4$NI or iodine to the catalyst [Ir(COD)$_2$]BF$_4$/**35a** improved conversion but did not modify the ee (Table 11, entries 1, 11 and 12). However, when Bu$_4$NI was used as additive together with [Ir(COD)$_2$]BF$_4$/**35b**, the optical yield increased to 46% ee (Table 11, entries 2 and 13). Iodine also improved the enantiomeric excess, but not as much as Bu$_4$NI (Table 11, entry 14). Phthalimide and benzylamine were also used as additives, but they promoted the deactivation of the catalytic system, probably by poisoning the catalyst (Table 11, entries 15 and 16). This confirms the importance of additives in the asymmetric hydrogenation of imines and shows for the first time that diphosphite ligands with iridium systems can also provide ee in this process.

When Bu$_4$NI or I$_2$ were added to [Ir(COD)$_2$]BF$_4$/**56a, 66a-b**, the enantioselectivity dropped sharply (Table 11, entries 17, 18, 21, 22, 25, 26), favouring the formation of the reduced product with the opposite configuration. This behaviour seems to be general for the hydrogenation of acyclic imines **74** and **76** with these catalytic systems when iodine derivatives are used as additives.

The [Ir(COD)$_2$]BF$_4$/**68** catalyst became enantioselective when Bu$_4$NI was added achieving 15% ee (Table 11, entries 9 and 29).

In general, when amines were used as additives there was no notable effect on the enantioselectivity. Nevertheless, the addition of benzylamine slowed the reaction down considerably and the activity of the catalytic system decreased, probably because of an irreversible coordination of the primary amine that occupied free sites and poisoned the catalyst.

To sum up, the combination of the electronic and structural characters of the ligands and Ir(I) complexes must be optimal for each *N*-aryl imine, which shows the limited substrate scope of this reaction. Nevertheless, in general when iodine derivatives are added to the Ir(I)/L catalysts in the reduction of both imines, the formation of the opposite enantiomer is promoted. Scheme 12 collects the best results obtained here in the asymmetric reduction of imines **74** and **76** with Ir(I) / *P*-donor ligands based on D-xylose and D-mannitol backbones.


[Ir(COD)₂]BF₄/**69a**	100% conv., 73% ee (-)
[Ir(COD)₂]BF₄/**69a**/I₂	76% ee (+)
[Ir(COD)₂]BF₄/**69b**	52% ee (-)
[Ir(COD)**5**]BF₄	97% conv., 46% ee
[Ir(COD)**35b**]BF₄	95% conv., 21% ee

[Ir(COD)₂]BF₄/**56a**	100% conv., 65% ee (+)
[Ir(COD)₂]BF₄/**66a**	98% conv., 76% ee (+)
[Ir(COD)**5**]BF₄	83% conv., 57% ee
[Ir(COD)**35b**]BF₄/Bu₄NI	100% conv. 46% ee

Scheme 12

We next turned our attention to the hydrogenation of imine **78**. This substrate is one of the most typical cyclic imines reported in the literature and is reduced principally by iridium and rhodium complexes with diphosphines at high H₂ pressure [60,49b,56a].

A preliminary screening of the reduction of **78** with both [M(COD)Cl]₂ and [M(COD)₂]BF₄ (M=Rh or Ir) using diphosphinites (**56a, 66a-c**) and diphosphinite-

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phosphite ligands (**69a-b**) showed that, although all the systems were active, the enantiomeric excesses were lower than 10% in almost all cases. Table 12 collects some of the results obtained in the hydrogenation of **78** by $[M(COD)Cl]_2$ and $[M(COD)_2]BF_4$ (M=Rh or Ir) using diphosphinites (**56, 66a-c**) and diphosphinite-phosphite ligands (**69a-b**).

Table 12. Hydrogenation of **78** with $[M(COD)Cl]_2$ and $[M(COD)_2]BF_4$ (M=Rh or Ir)./ **56a**, **66a**, **69b**[a]
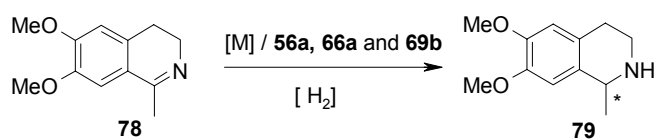
Entry	Ligand	Precursor	Conv. [%]	Ee[b] [%]
1	**56a**	$[Ir(COD)Cl]_2$	34	3 (+)
2	**66a**	$[Ir(COD)Cl]_2$	84	15 (+)
3	**69b**	$[Rh(COD)_2]BF_4$	2	30 (-)
4[c]	**69b**	$[Ir(COD)_2]BF_4$	43	4 (+)

[a] 1% catalyst, 1.2% mol Ligand, 70 bar, 25ºC, 16 h, CH_2Cl_2. [b] absolute configuration was not determined. [c] 20 h

The Ir(I) catalysts based on diphosphinite **56a** did not achieve enantioselectivity. However, the catalyst $[Ir(COD)_2]BF_4$, which bears the more donor diphosphinite ligand **66a**, gave an ee of 15%.

While the catalyst $[Ir(COD)_2]BF_4$/phosphinite-phosphite ligand **69b** provided 43% conversion and a racemic mixture, $[Rh(COD)_2]BF_4$/**69b** was less active but gave 30% ee (Table 12, entry 3, 4).

3.2.4. Asymmetric Hydrogenation of Enamides

The rhodium-catalysed asymmetric hydrogenation of α-arylenamides has recently attracted considerable attention [61]. Impressive results have been achieved with rhodium catalysts and diphosphines such as Me-DUPHOS [61b], Me-BPE [61], (R,R)-binaphane [62] and DIOP [61g], with enantioselectivities as high as 99%. Many groups have recently reported the use of monodentate ligands such as monophosphoramidites [40a,63], monophosphonites [64] and monophosphites [40g,d-f] as highly efficient ligands for the rhodium-catalysed enantioselective reduction of enamides.

Diphosphinites (**56a, 66a-b, 68**), diphosphites (**35a-b**), phosphinite-phosphite (**69a**) and monophosphinites (**60**, **67**) have been used in the rhodium-catalysed asymmetric hydrogenation of α-arylenamides (Figure 12).
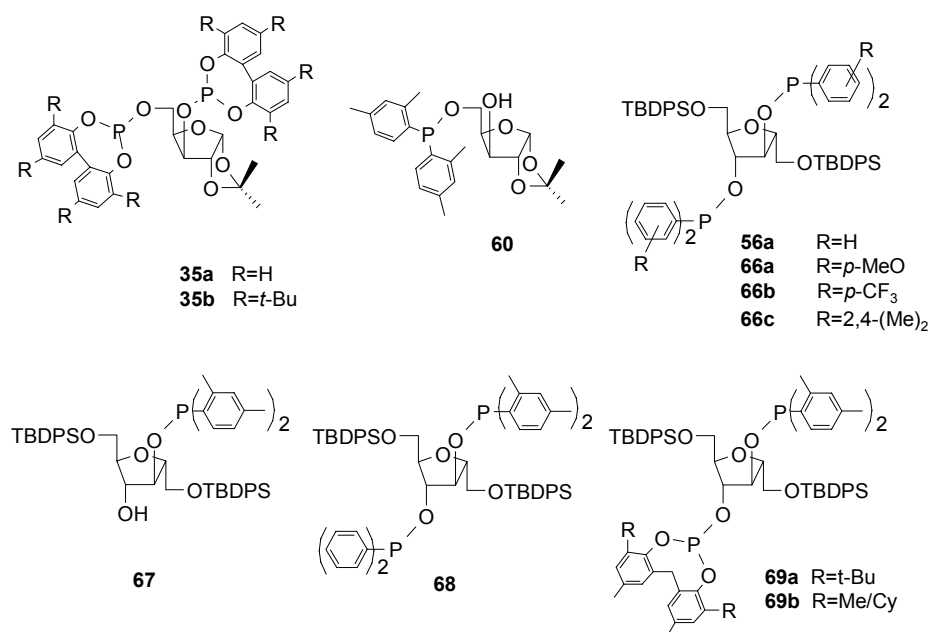

Figure 12

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Initial experiments focused upon α-arylenamide **80**, and then went on to examine the tetrasubstituted α-arylenamide **82** (Scheme 13).

Firstly, several experiments were performed to screen the optimal conditions for hydrogenating *N*-acetylphenylethenamine **80.** Several rhodium catalyst precursors were checked: $[Rh(NBD)_2]PF_6$ (NBD=nobornadiene); $[Rh(COD)_2]X^-$ (COD=1,5-cyclooctadiene, X=BF$_4$ or OTf); $[Rh(COD)Cl]_2$; with bidentate ligands at 3.5 bar of H$_2$ pressure in CH$_2$Cl$_2$. Table 13 collects the most interesting results.

80 R=H
82 R=Me

81 R=H
83 R=Me
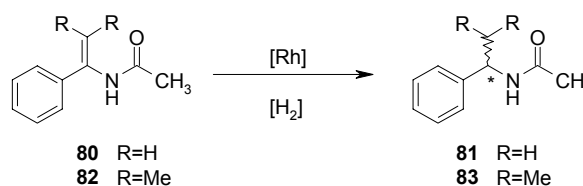
Scheme 13

$[Rh(NBD)_2]PF_6$ and $[Rh(COD)_2]X^-$ (X=BF$_4$ or OTf) were found to be more effective catalyst precursors than a neutral Rh species $[Rh(COD)Cl]_2$) [61a,d,e]. They provided the reduced product **81** in high conversions and selectivities, and moderate enantioselectivities (Table 13). In general, the differences in the ee values achieved with different cationic Rh(I) precursors are not considerable. In the literature, it is generally accepted that the well known hydrogenation with cationic rhodium(I) of the diolefin COD takes place more slowly than the hydrogenation of NBD [65] and the hydrogenation of this diolefinic ligands must takes place before the prochiral substrate [66]. In general, the differences between the rhodium(I) precursors containing COD or NBD ligands were not great. However, the catalysts $[Rh(NBD)_2]PF_6$/**35b**/**56a**/**68** were more active than the analogues precatalysts bearing COD instead of NBD (Table 13, entries 3, 4, 5, 7, 13, 14).

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Table 13. Hydrogenation of **80** with Rh(I)/L. Effect of precursor[a]
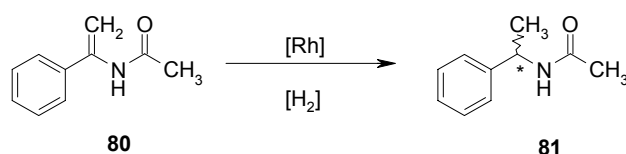
Entry	Ligand	Precursor	Conv [%]	Selec [%]	ee[b] [%]
1	**35a**	[Rh(NBD)₂]PF₆	98	95	0
2	**35a**	[Rh(COD)₂]BF₄	>99	>99	3 (+)
3	**35b**	[Rh(NBD)₂]PF₆	95	83	32 (+)
4	**35b**	[Rh(COD)₂]BF₄	31	79	35 (+)
5	**56a**	[Rh(NBD)₂]PF₆	100	100	48 (−)
6	**56a**	[Rh(COD)₂]BF₄	99	99	44 (−)
7	**56a**	[Rh(COD)₂]OTf	59	96	40 (−)
8	**66a**	[Rh(NBD)₂]PF₆	>99	99	33 (−)
9	**66a**	[Rh(COD)₂]BF₄	95	99	35 (−)
10	**66a**	[Rh(COD)₂]OTf	90	99	28 (−)
11	**66b**	[Rh(COD)₂]BF₄	99	98	22 (+)
12	**66b**	[Rh(COD)₂]OTf	95	93	50 (+)
13	**68**	[Rh(NBD)₂]PF₆	>99	98	20 (−)
14	**68**	[Rh(COD)₂]BF₄	41	90	20 (−)
15	**69a**	[Rh(NBD)₂]PF₆	99	98	22(−)
16	**69a**	[Rh(COD)₂]BF₄	>99	99	31 (−)
17	**69a**	[Rh(COD)₂]OTf	>99	98	27 (−)
18	**69a**	[Rh(COD)Cl]₂	8	39	25 (−)

[a] Reaction conditions: 1% mol [Rh(olefin)₂]X, 0.5% mol [Rh(COD)Cl]₂, 1.2% mol ligand, 3.5 bar H₂, CH₂Cl₂, 25ºC, 16 h [b] absolute configuration was not determined.

The systems based on [Rh(COD)Cl]₂ bearing diphosphites **35a-b** or diphosphinites **56a, 66a-b** and **68** gave low conversions and selectivities and values of ee<5% in almost all cases.

While Rh(I)/**35a** catalysts provided racemic mixtures (Table 13, entries 1, 2), Rh(I)/**35b** produced the reduced product **81** with optical yields up to 35%. (Table 13, entries 3, 4). %. It seems that bulky *tert*-butyl groups must be present in the *ortho* positions of the biphenyl moiety of diphosphite **35b** if enantioselectivities are to be provided, as was previously found in the hydrogenation of dehydroaminoacid derivatives [27b] and in imine reductions (see section 3.2.3).

The electronical variation of the diphosphinite ligands **56a**, **66a-b** in the Rh-catalysed reduction of **80** did not cause dramatic changes in the enantioselectivity (Table 13, entries 5-12). Nevertheless, Rh(I)/**56a** generally gave slightly higher ees than the more electron donor catalyst Rh(I)/**66a** or the less electron donor catalyst Rh(I)/**66b** (Table 13, entries 6, 9 and 11).

The catalyst based on $[Rh(COD)_2]X$ ($X=PF_6$ or BF_4) bearing the C_1-diphosphinite **68** provided ee's up to 20%. However, the activity of the system was higher when the counterion PF_6 was used instead of BF_4 (Table 13, entries 13 and 14).

Although the **69a**-$[Rh(olefin)_2]X$ (olefin=NBD or COD; $X=PF_6$, BF_4 or OTf) catalysts satisfactorily reduced the α-arylenamide **80** with high conversions (>99%), the enantioselectivities were only between 22-31%. The catalyst $[Rh(COD)Cl]_2$/**69a** provided an ee of 25%. The conversion and selectivity, however, were low (Table 13, entry 18).

We next turn our attention to the asymmetric hydrogenation of **80** catalysed by rhodium-monodentate phosphinite complexes. Recently many papers have described highly enantioselective Rh catalysts containing chiral monodentate phosphonites [40d,64], phosphites [40d-g] or even phosphoroamidites [40a,67]. However, as far as we know there are no reports of the Rh(I)-catalysed asymmetric hydrogenation of α-arylenamides using monophosphinite ligands.

Initially, we performed a screening in order to establish the most suitable rhodium precursor. Surprisingly, whereas the catalysts $[Rh(olefin)_2]X$

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(olefin=NBD or COD; X=PF_6, BF_4 or OTf) bearing the monophosphinites **60** or **67** did not provide any noteworthy enantioselectivities, [Rh(COD)Cl]$_2$/**60** or **67** catalysts gave ee's up to 76 and 63%, respectively (Table 14, entries 1-4 and 9-12). However, the conversions and the selectivities achieved using the neutral rhodium precursor were very low (Table 14, entries 4 and 12).

As expected, when the hydrogen pressure was increased, the conversion was higher or even complete within 16 hours, and the selectivity of the desired compound **81** was total (Table 14, entries 5, 6 and 13). Moreover, at higher H_2 pressure the enantiomeric excess was maintained or improved.

A slight improvement was observed when the experiment was carried out at low temperature (0ºC), even though the reactivity of the catalytic system was decreased (Table 14, entry 8).

The fact that the selectivity of the process depends on the hydrogen pressure suggests that there is a possible isomerization process under the catalytic conditions. Rhodium catalysts should favor the isomerization of α-arylenamide **80** to imine **84**, which is also capable of being reduced to give secondary amine **81** (Scheme 13). Whereas at high H_2 pressure both compounds **80** and **84** were reduced satisfactorily, at low H_2 pressures only **80** is reduced to give a mixture of the desired amine **81** and imine **84**.

Table 14. Hydrogenation of **80** and **82** with Rh(I)/monophosphinites **60** and **67**
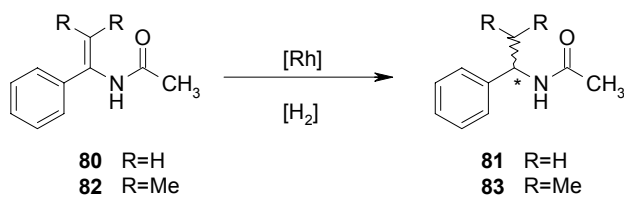
Entry	Enamide	Ligand	Precursor	H₂ [bar]	Conv [%]	Selec [%]	ee[b] [%]
1	**80**	**60**	[Rh(NBD)₂]PF₆	3.5	21	68	5 (+)
2	**80**	**60**	[Rh(COD)₂]BF₄	3.5	nd	nd	nd
3	**80**	**60**	[Rh(COD)₂]OTf	3.5	97	95	9 (+)
4	**80**	**60**	[RhCODCl]₂	3.5	6	52	76 (+)
5	**80**	**60**	[RhCODCl]₂	30	86	100	75 (+)
8[c]	**80**	**60**	[RhCODCl]₂	30	1	100	82 (+)
6	**80**	**60**	[RhCODCl]₂	70	100	100	79 (+)
7[d]	**80**	**60**	[RhCODCl]₂	70	100	100	75 (+)
9	**80**	**67**	[Rh(NBD)₂]PF₆	3.5	99	97	18 (-)
10	**80**	**67**	[Rh(COD)₂]BF₄	3.5	15	73	19 (-)
11	**80**	**67**	[Rh(COD)₂]OTf	3.5	10	59	19 (-)
12	**80**	**67**	[RhCODCl]₂	3.5	11	9	63 (-)
13[e]	**80**	**67**	[RhCODCl]₂	30	100	100	82 (-)
14	**82**	**60**	[Rh(NBD)₂]PF₆	30	62	100	14 (+)
15	**82**	**60**	[Rh(COD)₂]BF₄	30	66	100	0
16	**82**	**60**	[RhCODCl]₂	30	1	76	17 (+)
17	**82**	**67**	[Rh(NBD)₂]PF₆	30	21	100	5 (+)

[a] Reaction conditions: 1% mol [Rh(olefin)₂]X, 0.5% mol [Rh(COD)Cl]₂, 2.5% mol ligand, 3.5 bar H₂, CH₂Cl₂, 25°C, 16 h [b] absolute configuration was not determined [c] 0°C, 7 h [d] 50°C [e] 2.7% mol ligand, 24 h
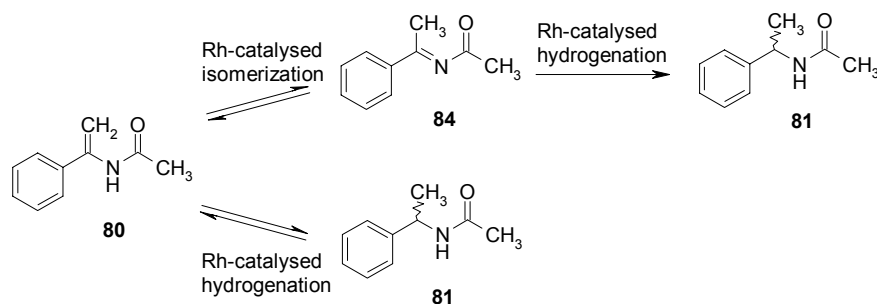
Scheme 14

Although moderate to good enantioselectivities were obtained for the hydrogenation of α-arylenamides without substituents in the β-position, the β-substituted-α-arylenamide **82** was reduced with very low enantioselectivities (Table 14, entries 14-17).

3.3. Conclusions

It has been reported for the first time that *N*-aryl imine **74** can be efficiently hydrogenated by iridium catalysts bearing the D-mannitol derivative ligands phosphinite-phosphite **69a-b**. The catalytic systems Ir(I)/**69a** reached 100% conversion and 73% ee. Besides, the Ir(I)/D-xylose derivative ligand diphosphinite **5** succeeded in hydrogenating **74**. The optical yield, however, was only 46%.

In addition, the new C_2-mannitol diphosphinite ligands (**56a, 66a-b**) proved to be well suited for the Ir(I)-catalysed hydrogenation of *N*-aryl imine **76** and enantioselectivities were as high as 70%. Moreover, the iridium catalyst based on a diphosphite ligand can satisfactorily reduce imine **76** with ees up to 46% in the presence of Bu$_4$NI. Bulky *tert*-butyl groups in the *ortho* positions of the biphenyl

moiety of diphosphite **35b** have an extremely positive effect on enantioselectivity, as was previously found in the hydrogenation of dehydroaminoacid derivatives [27b].

The combination of the electronic and structural properties of the ligands and Ir(I) complexes must be optimal for each *N*-aryl imine.

The hydrogenation of imine **78** with rhodium and iridium systems bearing diphosphine and phosphinite-phosphite D-mannitol derivative ligands was not as successful as the hydrogenation of **74** and **76.** Conversions and enantioselectivities were low.

The catalytic systems Rh(I)/D-mannitol derivative diphosphinites reduced α-arylenamide **80** effectively but enantioselectivities were only moderate (up to 50%). However, the [Rh(COD)Cl]$_2$/D-mannitol and D-xylose monophosphinites proved to be more enantioselective systems, and provided ee's up to 82%.

3.4. Experimental Section

General Comments. All reactions were carried out in an argon atmosphere using standard Schlenk techniques. Solvents were distilled and degassed prior to use.

^{1}H, ^{13}C{^{1}H}, ^{31}P{^{1}H} and ^{19}F{^{1}H} NMR spectra were recorded on a Varian Gemini spectrometer at 300 and 400 MHz. Chemical shifts were reported relative to tetramethylsilane for ^{1}H and ^{13}C{^{1}H} as internal reference, H$_3$PO$_4$ 85% for ^{31}P{^{1}H} and trichlorofluoromethane for ^{19}F{^{1}H} as external references. Elemental analyses were carried out on a Carlo Erba Microanalyser EA 1108. VG-Autospect equipment was used for FAB mass spectral analyses with 3-nitrobenzylalcohol as matrix. EI mass spectra were obtained on an HP 5989 A spectrometer at an ionizing voltage of 70 eV. Optical rotations were measured on a

Perkin-Elmer 241 MC polarimeter. Melting points were determined in an open capillary tube with a Tottoli-Büchi 510 melting point apparatus and are uncorrected. Single hydrogenation reactions were carried out in a Berghof or Parr 100 ml stainless steel autoclave and multi-screening hydrogenations were performed in a home-made 96-micro-titer plate in Bayer AG (Leverkusen-Germany)). The catalytic reactions were monitored by GC on a Hewlett-Packard 5890A. Conversion was measured in an Ultra-2 (5 % diphenylsilicone/95% dimethylsilicone) column (25 m x 0.2 mm Ø). The enantiomeric excess of *N*-(phenylethylidene)benzylamine (**21a**) was determined by ^{1}H NMR (with mandelic acid as the resolution agent) or by chiral chromatography after derivation into the trifluoroacetamide compound.. The enantiomeric excess of *N*-(phenylethylidene)aniline (**22a**) was determined by chiral chromatography after derivation into the acetamide compound. The enantiomeric excess of the 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline imine (**23a**) was determined by chiral chromatography.

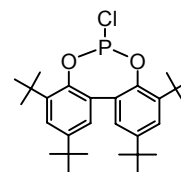### 2,2'-Biphenylphosphorochloridite (62a) [24]
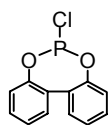
A 100-ml three-necked, round-bottomed flask equipped with a dropping funnel was filled with 6.2 ml of dry pyridine (76.5 mmol) and 1.34 ml of recently distilled PCl$_3$ (15.3 mmol). 1.2 g of 2,2'-bisphenol (6.4 mmol) was dissolved in 45 ml of dry toluene and added dropwise to the PCl$_3$/pyridine solution at 0ºC. When the addition was complete, the reaction mixture was refluxed overnight. The pyridine salts formed were removed by filtration under argon atmosphere. The reaction mixture was concentrated at reduced pressure. The product **62a** was used without purification in the following reaction step (1.1 g, 70% yield).

NMR ^{1}H (400 MHz, CDCl$_3$, ppm) 7.38-7.11 (m, 8H, arom.). **NMR ^{31}P** (161.9 MHz, CDCl$_3$, ppm) 180.6.

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4,4',6,6'-Tetra-*tert*-butyl-2,2'-biphenylphosphorochloridite (62b) [24]

A 50-ml three-necked, round-bottomed flask equipped with a dropping funnel was filled with 3 ml of dry pyridine (37.1 mmol) and 750 μl of recently distilled PCl_3 (8.25 mmol). 3 g of 4,4',6,6'-Tetra-*tert*-butyl-2,2'-bisphenol (7.3 mmol) wa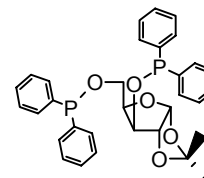s dissolved in 15 ml of dry and degassed toluene and added dropwise to the PCl_3/pyridine solution at 0ºC. When the addition was complete, the reaction mixture was refluxed overnight. The pyridine salts formed were removed by filtration under argon atmosphere. The reaction mixture was concentrated at reduced pressure. The product **62b** was used without purification in the following reaction step (3.47g, 86% yield).

NMR [1]**H** (400 MHz, $CDCl_3$, ppm) 7.46 (d, *J*=2.4Hz, 2H, arom.), 7.17 (d, *J*=2.4Hz, 2H, arom.), 1.47 (s, 18H, *o*-C$_4$H$_9$), 1.35 (s, 3H, *p*-C$_4$H$_9$). **NMR** [13]**C** (100.6 MHz, $CDCl_3$, ppm) 147.8 (C arom.), 145.7 (C arom.), 140.6 (C arom.), 132.8 (C arom.), 126.9 (CH arom), 125.0 (CH arom.), 35.7 (C), 34.9 (C), 31.7 (CH_3), 31.1 (CH_3). NMR [31]P (161.9 MHz, $CDCl_3$, ppm) 172.1.

3,5-bis(diphenylphosphinite)1,2-*O*-isopropylidene-D-xylofuranose (5) [6]

A total of 500 mg of 1,2-*O*-isopropylidene-D-xylofuranose (**61**) (2.6 mmol) was dissolved in dry and degassed THF (10 ml) to which 2 ml of dry pyridine (24 mmol) was added. 1 ml (5.28 mmol) of chlorodiphenylphosphine was added. The reaction mixture was stirred for 3 h. at room temperature. Ethyl ether (55 ml) was then added and the pyridine salts were precipitated and removed by filtration under argon atmosphere. Evaporation of the solvent gave 1.1 g (80% yield) of compound **5** as a yellow foam.

NMR [1]**H** (400 MHz, $CDCl_3$, ppm) 7.55-7.24 (m, 20H, arom.), 5.91 (d, [3]*J*=3.2Hz, 1H, CH), 4.59 (m, 1H, CH), 4.44 (m, 2H, CH), 4.09 (m, 2H, CH_2), 1.40 (s, 3H,

CH$_3$), 1.23 (s, 3H, CH$_3$). **NMR ^{13}C** (100.6 MHz, CDCl$_3$, ppm) 141.4-127.7 (arom.), 111.3 (<u>C</u>(CH$_3$)$_2$), 104.5 (CH), 83.2 (d, ^3J=24Hz, CH), 81.5 (d, ^2J=75.6Hz, CH), 79.6 (t, ^3J=27.2Hz, CH), 66.6 (d, ^2J=75.6Hz, CH$_2$), 26.6 (CH$_3$), 26.1 (CH$_3$). **NMR ^{31}P** (161.9 MHz, CDCl$_3$, ppm) 116.9, 115.1.

3,5-Bis[1,1'-biphenyl-2,2'-diyl)phosphite]-1,2-*O*-isopropylidene-D-xylofuranose (35a) [24]
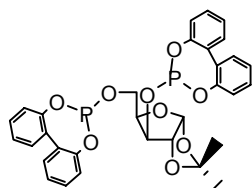
A total of 380 mg of 1,2-*O*-isopropylidene-D-xylofuranose (**61**) (2 mmol) was dissolved in dry and degassed- toluene (12 ml) to which 1 ml of dry pyridine (12 mmol) was added. In 30 min the solution was added to a solution of **1** (5 mmol) in 5 ml of dry and degassed toluene and 1 ml of pyridine (12 mmol) at 0ºC. The reaction mixture was stirred for 2 h at room temperature. Filtration under argon atmosphere followed by evaporation of the solvent gave a yellow foam which was purified by flash column chromatography under argon atmosphere (dry and degassed toluene), affording 925 mg (75% yield) of compound **35a** as a white powder.

$[\alpha]_D^{20}$ = + 0.045º (c=1, CH$_2$Cl$_2$). **NMR ^{1}H (**400 MHz, CDCl$_3$, ppm) 7.31-6.95 (m, 16H, arom.), 5.79 (d, $^3J_{H,H}$=3.6Hz, 1H, CH), 4.63 (dd, $^3J_{H,P}$=9.6Hz, $^3J_{H,H}$=2.8Hz, 1H, CH), 4.52 (d, $^3J_{H,H}$=3.6Hz, 1H, CH), 4.36 (td, $^3J_{H,H}$=6.8Hz, $^3J_{H,H}$=2.8Hz, 1H, CH), 4.2 (t, $^3J_{H,P}$=6.9Hz, 2H, CH$_2$), 1.33 (s, 3H, CH$_3$), 1.15 (s, 3H, CH$_3$). **NMR ^{13}C** (100.6 MHz, CDCl$_3$, ppm) 149.9-121 (arom.), 112.3 (<u>C</u>(CH$_3$)$_2$), 105.0 (CH), 79.1 (CH), 76.9 (d, $J_{P,C}$=18Hz, CH), 61.7 (d, $J_{P,C}$=178.8Hz, CH$_2$), 26.9 (CH$_3$), 26.4 (CH$_3$). **NMR ^{31}P** (161.9 MHz, CDCl$_3$, ppm) 140.5, 139.3.

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3,5-Bis[(3,3',5,5'-tetra-*tert*-butyl-1,1'-biphenyl-2,2'-diyl)phosphite]-1,2-*O*-isopropylidene-D-xylofuranose (35b) [24]
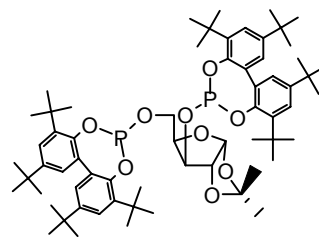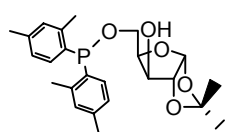
A total of 500 mg of 1,2-*O*-isopropylidene-D-xylofuranose (**61**) (2.6 mmol) was dissolved in dry and degassed toluene (12 ml) to which 1 ml of dry pyridine (12 mmol) was added. The solution was added in 30 min to a solution of **3** (7.3 mmol) in 20 ml of dry and degassed toluene and 1 ml of pyridine (12 mmol) at 0ºC. The reaction mixture was stirred overnight at room temperature and the pyridine salts were removed by filtration under argon atmosphere. Evaporation of the solvent gave a white foam which was purified by flash column chromatography under argon atmosphere (dry and degassed- mixture of hexane/ethyl acetate 20:1), affording 2.2 g (78% yield) of compound **35b** as a white powder.

$[\alpha]_D^{20}$= + 0.838º (c=1, CH_2Cl_2). **MS FAB m/z (%)**: 1066.62 (1.67, M$^+$). **HRMS L-SIMS:** m/z, [$C_{64}H_{92}O_9P_2$] **Calculated** 1067.3574, **Found** 1067.6269. **NMR** ^{1}**H** (400 MHz, $CDCl_3$, ppm) 7.43-7.13 (m, 8H, arom.), 5.53 (d, $^3J_{H,H}$=3.2Hz, 1H; CH), 4.71 (dd, $^3J_{H,P}$=7.2Hz, $^3J_{H,H}$=2.4Hz, 1H, CH), 4.26 (dt, $^3J_{H,H}$=6.4Hz, $^3J_{H,H}$=2.4Hz, 1H, CH), 4.04 (m, 2H, CH_2), 3.92 (d, $^3J_{H,H}$=3.2Hz, 1H, CH_2), 1.47 (s, 18H, C(CH$_3$)$_3$), 1.46 (s, 9H, C(CH$_3$)$_3$), 1.45 (s, 9H, C(CH$_3$)$_3$), 1.38 (s, 9H, C(CH$_3$)$_3$), 1.35 (s, 27H, C(CH$_3$)$_3$), 1.33 (s, 3H, CH$_3$), 1.10 (s, 3H, CH$_3$). **NMR** ^{13}**C** (100.6 MHz, $CDCl_3$, ppm) 146.9-124.3 (arom.), 111.9 (C(CH$_3$)$_2$), 104.9 (CH), 84.2 (CH), 79.0 (CH), 76.4 (CH), 61.9 (CH$_2$), 35.6 (C(CH$_3$)$_3$), 35.5 (C(CH$_3$)$_3$), 32.4 (C(CH$_3$)$_3$), 32.3 (C(CH$_3$)$_3$), 31.6 (C(CH$_3$)$_3$), 26.9 (CH$_3$), 26.6 (CH$_3$). **NMR** ^{31}**P** (161.9 MHz, $CDCl_3$, ppm) 143.3, 134.7.

3-hydroxy-5-bis-*O*-(4-methoxyphenylphosphino)1,2-*O*-isopropylidene-D-xylofuranose (60)
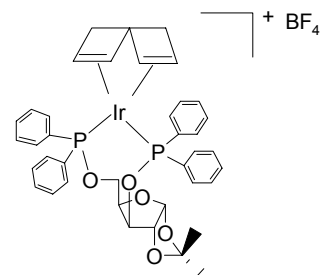
A flask equipped with a magnetic stirrer was charged with 260 mg (1.35 mmols) of the 1,2-*O*-isopropylidene-D-xylofuranose (**61**), 7 ml of anhydrous THF and 0.34 ml (8.7 mmol) of anhydrous pyridine. A solution of 800 mg (2.89 mmols) of bis-(2,4dimethylphenyl)-chlorophosphine (**64c**) in 3 ml of anhydrous THF was added. The mixture was stirred at room temperature. Anhydrous Et$_2$O was added to facilitate the precipitation of the salts formed and filtered under argon. Purification by column chromatography under argon gave 203 mg (35% yield) of compound **60** as a foam.

$[\alpha]_D^{20}$= - 0.134° (c=0.67, CH$_2$Cl$_2$). **Elemental Analysis calculated for C$_{24}$H$_{31}$O$_5$P$_1$** (%): C, 66.96; H, 7.26, **Found (%)**: C, 66.25; H, 7.28. **MS FAB m/z (%)**: 430.17 (4.16, M$^+$). **HRMS L-SIMS:** m/z, [C$_{24}$H$_{31}$O$_5$P] **Calculated** 430.1909, **Found** 430.1896. **NMR ^{1}H** (400 MHz, CDCl$_3$, ppm) 7.15-7.08 (m, 6H, arom.), 5.82 (br, 1H, CH), 4.47 (br, 1H, CH), 4.31 (br, 1H, CH), 4.24 (br, 1H, CH), 4.19 (m, 2H, CH$_2$), 2.82 (br, 1H, OH), 2.41 (s, 3H, CH$_3$), 2.35 (s, 3H, CH$_3$), 2.31 (s, 3H, CH$_3$), 2.28 (s, 3H, CH$_3$), 1.49 (s, 3H, CH$_3$), 1.32 (s, 3H, CH$_3$). **NMR ^{13}C** (100.6 MHz, CDCl$_3$) 136.0-130.1 (CH, C, arom.), 111.8 (C), 104.9 (CH), 85.4 (CH), 79.0 (d, ^3J=7.6 Hz, CH), 75.9 (CH), 67.8 (d, ^2J=20.5 Hz, CH), 27.1 (CH$_3$), 26.5 (CH$_3$), 21.5 (CH$_3$), 21.4 (CH$_3$), 20.5 (d, ^3J=8.4 Hz, CH$_3$),20.3 (d, ^3J= 8.4 Hz, CH$_3$) **NMR ^{31}P** (161.9 MHz, CDCl$_3$, ppm) 108.9.

[Ir(COD)(5)]BF₄ (65a)

To a chilled (-80ºC) solution of [Ir(COD)₂]BF₄ (150 mg, 0.3 mmol) with dry and degassed dichloromethane (4 ml), a solution of **5** (250 mg, 0.4 mmol) with dry and degassed dichlorometane (5 ml) was added dropwise.The solution was al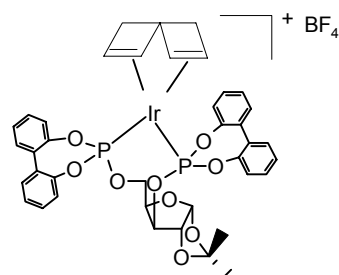lowed to warm to 0ºC and stirred for 15 min. Ethyl ether (30 ml) was then added to precipitate the desired compound **65a** as a pale purple solid (322 mg, 76% yield).

Elemental analysis calculated for.C₄₀H₄₄O₅P₂IrBF₄ (%):C 50.80; H 4.69, **Found** (%):C 50.65; H 4.85. **NMR ³¹P** (161.9 MHz, CDCl₃, ppm) 103.5 (d, $^2J_{P;P}$=78Hz), 101.0 (d, $^2J_{P;P}$=78Hz).

[Ir(COD)(35a)]BF₄ (65b) [25b]

To a chilled (-80ºC) solution of [Ir(COD)₂]BF₄ (104 mg, 0.2 mmol) with dry and degassed dichloromethane (4 ml), a solution of **35a** (128 mg, 0.2 mmol) with dry and degassed dichlorometane (5 ml) was added dropwise. The solution was allowed to warm to 0ºC and stirred for 15 min. Ethyl ether (30 ml) was then added to precipitate 68.3mg (68% yield) of the compound **65b** as a white solid.

Elemental analysis calculated for C₄₀H₄₀O₉P₂IrBF₄ (%): C 47.77; H 4.01, **Found** (%): C 47.45; H 4.09. **NMR ³¹P** (161.9 MHz, CDCl₃, ppm) 105.1 (br), 103.5 (br).

[Ir(COD)(35b)]BF₄ (65c) [25b]

To a chilled (-80ºC) solution of [Ir(COD)₂]BF₄ (103.3 mg, 0.2 mmol) with dry and degassed dichloromethane (4 ml), a solution of **35b** (213.7 mg, 0.2 mmol) with dry and degassed dichlorometane (5 ml) was added dropwise.The solution was allowed to warm to 0ºC and stirred for 15 min. Ethyl ether (30 ml) was then added to precipitate 194.8 mg (67% yield) of compound **65c** as a purple solid.

Elemental analysis calculated for C₇₂H₁₀₄O₉P₂IrBF₄ (%): C 59.45; H 7.21, **Found (%):** C 59.57; H 7.86. **NMR ³¹P** (161.9 MHz, CDCl₃, ppm) 112.01 (d, $^2J_{P;P}$=50Hz), 110.6 (d, $^2J_{P;P}$=50Hz).

(diethylamino)-bis(4-metoxyphenyl)phosphine (63a) [10g]

A flask fitted with a mechanical stirrer and an addition funnel was charged with 0.43 g (18 mmol) of magnesium turnings, 6 ml of THF and 6 ml of Et₂O. An iodine crystal was added to facilitate the initiation of the reaction. To this cooled suspension (0°C) 2.14 ml (17.1 mmol) of 4-bromo-anisole in 3 ml of anhydrous Et₂O was added. The reaction was allowed to warm to 22-28 °C and was stirred overnight. The reaction was then transferred into an addition funnel via canula and washed with 5 ml of THF to ensure that all the Grignard reagent had been transferred. The flask containing the addition funnel was charged with 1.2 ml (8.2 mmol) of Et₂NPCl₂ and 7 ml of THF and cooled to 0°C and the Grignard reagent was added for half an hour. The reaction mixture was stirred for 2 hours at 5-10°C. Then the reaction mixture was concentrated to the minimum amount in a vacuum pump. To the mixturee was added dry hexane (60 ml) and the solution was

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filtered through dry celite under argon. A total of 1.48 g (57.2% yield) of the expected compound **63a** was obtained as a syrup.

NMR ^{1}**H** (400 MHz, CDCl$_3$, ppm) 7.48 (dd, *Jortho*= 8.8 Hz, J_{PH}= 6.4 Hz, 4H, arom.), 6.88 (m, 4H, arom.), 3.81 (s, 6H, CH$_3$O), 3.06 (q, ^3J=7.2 Hz, 2H, CH$_2$), 0.96 (t, ^3J=7.2 Hz, 3H, CH$_3$). **NMR** ^{31}**P** (161.9 MHz, CDCl$_3$, ppm) 59.5.

(diethylamino)-bis(4-trifluoromethylphenyl)phosphine (63b) [10g]

Prepared following the procedure described for **63a**. A total of 1.95 g (61.4% yield) of the expected compound **63b** was obtained as a syrup.
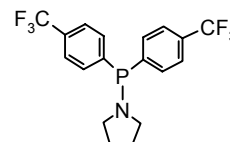
NMR ^{1}**H** (400 MHz, CDCl$_3$, ppm) 7.48 (m, 4H, arom.), 7.37 (m, 4H, arom.), 2.99 (m, 2H, CH$_2$), 1.38 (t, ^3J=6.8 Hz, 3H, CH$_3$). **NMR** ^{31}**P** (161.9 MHz, CDCl$_3$, ppm) 59.4.

(diethylamino)-bis(2,4-dimethylphenyl)phosphine (63c) [10g]

Prepared following the procedure described for **63a**. A total of 1.37 g (59% yield) of the expected compound **63c** was obtained as a syrup.
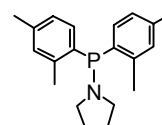
NMR ^{1}**H** (400 MHz, CDCl$_3$, ppm) 7.04 (m, 2H, arom), 6.94 (m, 4H, arom), 3.11 (m, 4H, CH$_2$), 2.29 (s, 6H, CH$_3$), 2.28 (s, 6H, CH3), 0.86 (t, 6H, CH$_3$). **NMR** ^{31}**P** (161.9 MHz, CDCl$_3$, ppm) 47.2.
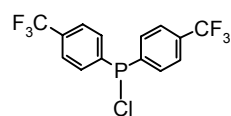
bis(4-methoxyphenyl)chlorophosphine (64a) [10g]

A flask fitted with a mechanical stirrer and an addition funnel was charged with 0.43 g (18 mmol) of magnesium turnings, 6 ml of THF and 6 ml of Et$_2$O. An iodine crystal was added to facilitate the initiation of the reaction. To this cooled suspension (0°C) 2.14 ml (17.1 mmol) of 4-bromo-anisole in 3 ml of anhydrous Et$_2$O was added. The

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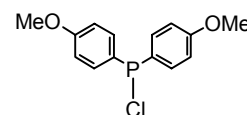
reaction was allowed to warm to 22-28 °C and was stirred overnight. The reaction was then transferred into an addition funnel via cannula and washed with 5 ml of THF to ensure that all the Grignard reagent had been transferred. The flask containing the addition funnel was charged with 1.2 ml (8.2 mmol) of Et_2NPCl_2 and 7 ml of THF and cooled to 0°C and the Grignard reagent was added for half an hour. The reaction mixture was stirred for 2 hours at 5-10°C. The reaction mixture was concentrated to the minimum amount in a vacuum pump. To the mixturee was added dry hexane (60 ml) and the solution was filtered through dry celite under argon. The filtrated dry HCl gas was passed through the solution for 1 hour. The reaction was mildly exothermic. The mixture was degassed by bubbling argon and the solid precipitate was filtered under argon. The filtrate was concentrated in a vacuum pump to give 1 g (45% yield) of compound **64a** as a syrup.

NMR **¹H** (400 MHz, CDCl₃, ppm) 7.48 (t, *Jortho*= 8.4 Hz, J_{PH}= 8.4 Hz, 4H, arom.), 6.88 (d, *Jortho*= 8.4 Hz, 4H, arom.), 3.75 (s, 6H, CH₃O). **NMR** **³¹P** (161.9 MHz, CDCl₃, ppm) 84.2.

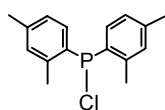**bis(4-(trifluoromethyl)phenyl)chlorophosphine (64b)** [10g]

Prepared following the procedure described for **64a**. A total of 1.93 g (66% yield) of the expected compound **64b** was obtained as a syrup.

NMR **¹H** (400 MHz, CDCl₃, ppm) 7.33 (m, 8H, arom.). **NMR** **³¹P** (161.9 MHz, CDCl₃, ppm) 76.3.

bis(2,4-dimethylphenyl)chlorophosphine (64c) [10g]

Prepared following the procedure described for **64a**. A total of 1.4 g (58.3% yield) of the expected compound **64c** was obtained as a syrup.
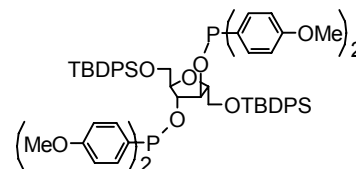
NMR **¹H** (400 MHz, CDCl₃, ppm) 7.40 (d, *Jmeta*= 4.4 Hz, 2H,

arom.), 7.2 (m, 4H, arom.), 2.5 (d, J_{PH}= 2 Hz, 6H, CH$_3$), 2.4 (s, 6H, CH$_3$). **NMR**
^{31}P (161.9 MHz, CDCl$_3$, ppm) 75.6.

2,3-bis-*O*-(4-methoxyphenylphosphino)-1,6-dideoxy-2,5-anhydro-D-Mannitol (66a)

Procedure A:

A flask equipped with a reflux condenser was
charged with 100 mg (0.156 mmols) of the
1,6-dideoxy-2,5-anhydro-D-Mannitol (**70**). A
solution of 109 mg (0.343 mmols) of
(diethylamino)-bis(4-metoxyphenyl)phosphine (**63a**) in 2.2 ml of anhydrous toluene
was added. The mixture was refluxed overnight and followed by TLC
(Hexane/Ethyl Acetate 5:1 Rf=0,25). The residue was then purified by column
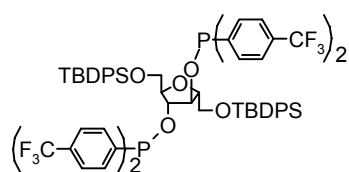chromatography with silica under argon to give 40 mg (22.7% yield) of compound
66a as a foam.

Procedure B:

A solution of 569 mg (1.79 mmols) of (diethylamino)-bis(4-
methoxyphenyl)phosphine (**63a**) and 5.1 ml of a tetrazole (0.45M in CH$_3$CN) was
stirred for 10 minutes at room temperature under argon. A solution of 288 mg (0.45
mmols) of 1,6-dideoxy-2,5-anhydro-D-Mannitol (**70**) in 3 ml of anhydrous
dichloromethane was added and stirred for 30 minutes at room temperature. The
reaction was followed by TLC (Hexane/Ethyl Acetate 5:1 Rf=0.25). The residue
was then purified by column chromatography with silica under argon to give 301.2
mg (59% yield) of compound **66a** as a foam.

$[\alpha]_D^{20}$= 0.065º (c=0.83, CH$_2$Cl$_2$). **MS FAB m/z (%)**: 1129.31 (2.73, M$^+$). **HRMS
L-SIMS:** m/z, [C$_{66}$H$_{74}$O$_9$Si$_2$P$_2$] **Calculated** 1129.4069, **Found** 1129.4430. **NMR**
^{1}H (400 MHz, C$_6$D$_6$, ppm) 7.93 (m, 8H, arom.), 7.67 (m, 8H, arom.), 7.26 (m, 12H,
arom.), 6.84 (m, 8H, arom.), 5.38 (dd, *J*=7.9 Hz, *J*=4 Hz, 2H, CH), 4.59 (m, 2H,

CH), 4.09 (dd, J=10.9 Hz, J=4.2 Hz, 2H, CH$_2$), 3.99 (dd, J=10.9 Hz, J=4.2 Hz, 2H, CH$_2$), 3.37 (s, 6H, CH$_3$O), 3.35 (s, 6H, C$\underline{H}_3$O), 1.32 (s, 9H, CH$_3$), 1.27 (s, 9H, CH$_3$). **NMR ^{13}C** (100.6 MHz, CDCl$_3$) 160.7-113.9 (arom.), 85.0 (m, CH), 84.5 (CH), 64.1 (CH$_2$), 55.25 (CH$_3$O), 55.23 (CH$_3$O), 27.0 (C($\underline{C}$H$_3$)$_3$), 19.4 ($\underline{C}$(CH$_3$)$_3$) **NMR ^{31}P** (161.9 MHz, CDCl$_3$, ppm) 115.1.

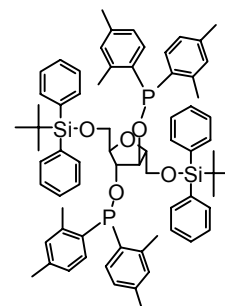## 2,3-bis-*O*-((4-trifluoromethyl)phenylphosphino)-1,6-dideoxy-2,5-anhydro-D-Mannitol (66b)

A flask equipped with a reflux condenser was charged with 213 mg (0.332 mmols) of the 1,6-dideoxy-2,5-anhydro-D-Mannitol (**70**). A solution of 352 mg (0.897 mmols) of diethylamino-bis(4-trifluoromethylphenyl) phosphine (**63b**) in 2.5 ml of anhydrous toluene was added. The mixture was refluxed overnight and followed by TLC. The residue was then purified by column chromatography with silica under argon to give 40 mg (28% yield) of compound **66b** as a foam.

NMR ^{1}H (400 MHz, CDCl$_3$, ppm) 7.65-7.25 (m, 36H, arom), 5.01 (m, 2H, CH), 4.18 (m, 2H, CH), 3.82 (dd, ^2J=11.2 Hz, ^3J=4 Hz, 2H, CH$_2$), 3.62 (dd, ^2J=11.2 Hz, ^3J=4 Hz, 2H, CH$_2$), 1.05 (s, 9H, CH$_3$). **NMR ^{13}C** (100.6 MHz, CDCl$_3$) 134.3-125.3 (arom.), 122.7 (CF$_3$), 86.2 (m, CH), 83.4 (CH), 63.6 (CH$_2$), 27.0 (C($\underline{C}$H$_3$)$_3$), 19.5 ($\underline{C}$(CH$_3$)$_3$) **NMR ^{31}P** (161.9 MHz, CDCl$_3$, ppm) 110.5.

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2,3-bis-*O*-(2,4-dimethylphenylphosphino)-1,6-dideoxy-2,5-anhydro-D-Mannitol (66c)

A solution of 3.4 g (10.9 mmols) of (diethylamino)-bis(2,4-dimethylphenyl)phosphine (**63c**) and 34 ml (15.3 mmols) of a tetrazole (0.45M in CH_3CN) was stirred for 10 minutes at room temperature under argon. To this solution, 878 mg (1.37 mmols) of 1,6-dideoxy-2,5-anhydro-D-Mannitol (**70**) was added and stirred for 2 hours at room temperature. The reaction was followed by TLC (Hexane/Ethyl Acetate 10:1 Rf=0.47). The residue was then purified by column chromatography with silica under argon to give 630 mg (41% yield) of compound **66c** and 446 mg (37% yield) of **67**.

$[\alpha]_D^{20}$= 0.080º (c=0.71, CH_2Cl_2). **NMR ^{1}H** (400 MHz, $CDCl_3$, ppm) 7.55-6.70 (m, 32H, arom.), 4.66 (m, 1H, CH), 4.09 (m, 1H, CH), 3.65 (m, 2H, CH), 3.54 (m, 2H, CH), 2.14 (s, 6H, CH_3), 2.13 (s, 6H, CH_3), 2.12 (s, 6H, CH_3), 2.11 (s, 6H, CH_3), 0.74 (s, 18H, CH_3). **NMR ^{13}C** (100.6 MHz, $CDCl_3$, ppm) 141.0-126.7 (arom.), 85.5 (m, CH), 84.5 (CH), 64.2 (CH_2), 27 (C($\underline{C}H_3$)$_3$), 20.7 (d, ^3J=7.74 Hz, CH_3), 20.5 (d, ^3J=6.84 Hz, CH_3), 20.5 (br, CH_3), 19.4 ($\underline{C}$(CH_3)$_3$). **NMR ^{31}P** (161.9 MHz, $CDCl_3$, ppm) 102.6.

2-*O*-(2,4-dimethylphenylphosphino)-1-6-dideoxy-2,5-anhydro-D-Mannitol (67)

A flask equipped with a magnetic stirrer was charged with 300 mg (0.468 mmols) of the 1,6-dideoxy-2,5-anhydro-D-Mannitol (**70**) and 0.26 ml of anhydrous Et_3N. A solution of 337 mg (1.219 mmols) of bis-(2,4dimethylphenyl)-chlorophosphine (**64c**) in 2 ml of anhydrous THF was added. The mixture was stirred at room temperature. Anhydrous Et_2O was added to facilitate the precipitation of the
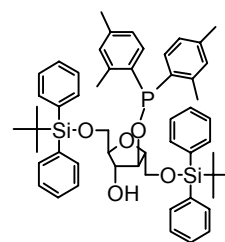
salts formed and filtered under argon. Purification by column chromatography under argon gave 180 mg (48% yield) of compound **67** as a foam and 157 mg (30% yield) of compound **73**.

Spectroscopic Data of 67

$[\alpha]_D^{20}$= 0.178º (c=0.89, CH$_2$Cl$_2$). **MS FAB m/z (%)**: 881.46 (4.39, M$^+$). **HRMS L-SIMS:** m/z, [C$_{54}$H$_{65}$O$_5$Si$_2$P] **Calculated** 881.2357, **Found** 881.2385. **NMR ^{1}H** (400 MHz, CDCl$_3$, ppm) 7.59-6.87 (m, 26H, arom.), 4.47 (m, 1H, CH), 4.31 (m, 1H, CH), 3.99 (m, 2H, CH), 3.69 (m, 3H, CH$_2$), 3.54 (dd, 1H, CH$_2$), 2.79 (s, OH), 2.30 (s, 3H, CH$_3$), 2.17 (s, 3H, CH$_3$), 2.11 (s, 3H, CH$_3$), 2.06 (s, 3H, CH3), 0.96 (s, 9H, CH$_3$), 0.94 (s, 9H, CH$_3$). **NMR ^{13}C** (100.6 MHz, CDCl$_3$, ppm) 138.1-127.6 (CH, C, arom.), 86.0 ($^2J_{C-P}$=18 Hz, CH), 84.9 (CH), 83.9 ($^3J_{C-P}$=6.13 Hz, CH), 78.0 ($^3J_{C-P}$=4.5 Hz, CH), 64.7 (CH$_2$), 64.1 (CH$_2$), 27.2 (C($\underline{\text{C}}$H$_3$)$_3$), 27.0 (C($\underline{\text{C}}$H$_3$)$_3$), 21.44 ($\underline{\text{C}}$(CH$_3$)$_3$),21.45 ($\underline{\text{C}}$(CH$_3$)$_3$), 20.5 (d, ^3J=12.17 Hz, CH$_3$), 20.3 (d, ^3J=12.27 Hz, CH$_3$), 19.6 (s, CH$_3$), 19.5 (s, CH$_3$). **NMR ^{31}P** (161.9 MHz, CDCl$_3$, ppm) 102.7.
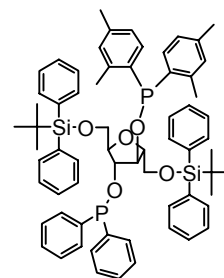
Spectroscopic Data of 73
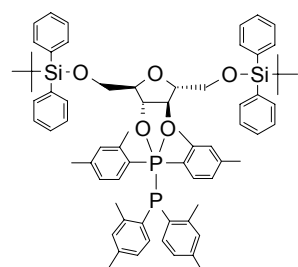
NMR ^{1}H (400 MHz, CDCl$_3$, ppm) 7.73-6.77 (m, 32H, arom.), 4.15 (m, 2H, CH), 4.05 (m, 2H, CH), 3.78 (dd, ^2J=11.2 Hz, ^3J=3.4 Hz, 2H, CH$_2$), 3.66 (dd, ^2J=11.2 Hz, ^3J=3.4 Hz, 2H, CH$_2$), 2.12 (d, J=2 Hz, 6H, CH$_3$), 2.05 (s, 6H, CH$_3$), 1.98 (s, 6H, CH$_3$), 1.88 (d, J=2 Hz, 6H, CH$_3$), 0.97 (s, 18H, CH$_3$). **NMR ^{13}C** (100.6 MHz, CDCl$_3$, ppm) 140.0-127.5 (arom.), 86.3 (CH), 79.4 (CH), 65.5 (CH$_2$), 27.0 (C($\underline{\text{C}}$H$_3$)$_3$), 21.3 (CH$_3$), 21.2 (CH$_3$), 21.9 (CH$_3$), 20.7 (CH$_3$), 19.4 ($\underline{\text{C}}$(CH$_3$)$_3$). **NMR ^{31}P** (161.9 MHz, CDCl$_3$, ppm) 42.6 (d, $^1J_{P-P}$=234.2 Hz, P(III)), -44.2 (d, $^1J_{P-P}$=234.2 Hz, P(V)). **MS m/z (%):** 1120.5 (M$^+$)

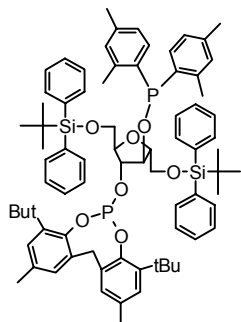**2-*O*-(2,4-dimethylphenylphosphino)-3-*O*-(diphenylphosphino)-1-6-dideoxy-2,5-anhydro-D-Mannitol (68)**

A total of 58 mg (0.06 mmols) of 2-*O*-(2,4-dimethylphenylphosphino)-1-6-dideoxy-2,5-anhydro-D-Mannitol (**67**) was dissolved in 0.5 ml of anhydrous THF and 32 µl of anhydrous Et$_3$N. To this solution, 12.5 µl (0,066 mmols) of chlorodiphenylphosphine was added. The reaction mixture was then allowed to react for 1 hour, following the reaction by TLC (Hexane/Ethyl Acetate 20:1 Rf= 0.36). The salts formed were removed by filtration through celite under argon. Evaporation of the solvent gave a solid, which was purified by column chromatography with silica under an atmosphere of argon to give 29.4 mg (45.9% yield) of compound **68** as a foam.

NMR ^{1}H (400 MHz, CDCl$_3$, ppm) 7.67-6.91 (m, 36H, arom.), 4.89-4.79 (m, 2H, CH), 4.15 (m, 2H, CH), 3.75 (m, 2H, CH$_2$), 3.57 (m, 2H, CH$_2$), 2.25 (s, 3H, CH$_3$), 2.23 (s, 3H, CH$_3$), 2.19 (s, 3H, CH3), 2.14 (s, 3H, CH$_3$), 1.10 (s, 9H, CH$_3$), 1.00 (s, 9H, CH$_3$). **NMR ^{13}C** (100.6 MHz, CDCl$_3$, ppm) 139.3-127.9 (CH, C, arom.), 85.6 (m, CH, CH), 84.3 (m, CH, CH), 64.1 (CH$_2$), 63.9 (CH$_2$), 26.8 (C(CH$_3$)$_3$), 21.3 (CH$_3$), 20.7 (br, CH$_3$), 20.6 (br, CH$_3$), 19.4 (C(CH$_3$)$_3$). **NMR ^{31}P** (161.9 MHz, CDCl$_3$, ppm) 114.2, 102.7.

2-*O*-(2,4-dimethylphenylphosphino)-3-*O*-(4,8-ditert-butyl-2,10-dimethyl-12h-dibenzo[δ,γ][1,3,2]dioxaphosphocine)-1-6-dideoxy-2,5-anhydro-D-Mannitol (69a)

A total of 178 mg (0.202 mmols) of 2-*O*-(2,4-dimethylphenylphosphino)-1-6-dideoxy-2,5-anhydro-D-Mannitol (**67**) was dissolved in 1 ml of anhydrous toluene and 100 µl of anhydrous pyridine and cooled at 0°C. A solution of 100 mg (0,252 mmols) of 4,8-ditert-butyl-6-chloro-2,10-dimethyl-12h-dibenzo[δ,γ] [1,3,2] dioxa_phosphocine in 1 ml of anhydrous toluene and 100 ul of anhydrous pyridine was added dropwise. The reaction mixture was then allowed to warm to room temperature and stirred, following the reaction by TLC (Hexane/Ethyl Acetate 10:1 Rf= 0.55). Purification by column chromatography with silica gave 100 mg (39.6% yield) of compound **69a** as a foam. $[\alpha]_D^{20}$= 0.174º (c=0.42, CH_2Cl_2). **MS FAB m/z (%)**: 1249.12 (3.91, M$^+$). **NMR ^{1}H** (400 MHz, $CDCl_3$, ppm) 7.69-6.73 (m, 30H, arom.), 5.79 (m, 1H, CH), 4.92 (m, 1H, CH), 4.67 (m, 1H, CH), 4.30 (m, 1H, CH_2), 4.13 (d, ^2J=12.4 Hz, CH_2), 3.98-3.72 (m, 4H, CH_2), 3.15 (d, ^2J=12.4 Hz,1H, CH_2), 2.31 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 2.26 (s, 9H, CH_3), 2.19 (s, 3H, CH_3), 1.29 (s, 9H, CH_3), 1.22 (s, 9H, CH_3), 1.04 (s, 9H, CH_3), 0.98 (s, 9H, CH_3). **NMR ^{13}C** (100.6 MHz, $CDCl_3$, ppm) 145.6-126.8 (CH, C, arom.), 85.9 (m, CH), 85.4 (CH), 85.2 (CH), 80.3 (m, CH), 64.3 (CH_2), 63.9 (CH_2), 34.8 (CH_2), 31.2 (C($\underline{C}H_3$)$_3$), 31.1 (C($\underline{C}H_3$)$_3$), 27.0 (C($\underline{C}H_3$)$_3$), 26.9 (C($\underline{C}H_3$)$_3$), 21.5 (CH_3), 21.4 (CH_3), 21.3 (CH_3), 20.8 (d, ^3J=13.7 Hz, CH_3), 20.6 (d, ^3J=13.7 Hz, CH_3), 19.5 ($\underline{C}$(CH$_3$)$_3$), 19.4 ($\underline{C}$(CH$_3$)$_3$). **NMR ^{31}P** (161.9 MHz, $CDCl_3$, ppm) 127.9, 102.8.

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2-*O*-(2,4-dimethylphenylphosphino)-3-*O*-(2,10-dimethyl-4,8-bis(1-methylcyclohexyl)-12H-dibenzo[δ,γ][1,3,2]dioxaphosphocine)-1-6-dideoxy-2,5-anhydro-D-Mannitol (69b)

A total of 145 mg (0.164 mmols) of 2-*O*-(2,4-dimethylphenylphosphino)-1-6-dideoxy-2,5-anhydro-D-Mannitol (**67**) was dissolved in 0.5 ml of anhydrous toluene and 100 μl of anhydrous pyridine and cooled at 0°C. A solution of 100 mg (0.252 mmols) of 6-chloro-2,10-dimethyl-4,8-bis(1-methylcyclohexyl)-12H-dibenzo[δ,γ][1,3,2] dioxaphosphocine in 1 ml of anhydrous toluene and 100 μl of anhydrous pyridine was added dropwise. The reaction mixture was then allowed to warm to room temperature and stirred. To the mixture was then added dry hexane and the solution was filtered under argon. Purification by column chromatography under argon with silica gave 71 mg (32.4% yield) of compound **69b** as a foam.
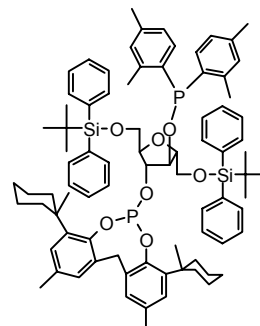
$[\alpha]_D^{20}$= 0.226° (c=0.50, CH₂Cl₂). **MS FAB m/z (%)**: 1328.16 (1.45, M⁺). **NMR ¹H** (400 MHz, CDCl₃, ppm) 7.71-6.74 (m, 30H, arom.), 5.67 (m, 1H, CH), 4.85 (m, 1H, CH), 4.62 (m, 1H, CH), 4.30 (m, 1H, CH), 4.12 (d, ^2J=12.8 Hz, 1H, CH₂), 4.01-3.74 (m, 4H, CH₂), 3.15 (d, ^2J=12.8 Hz, 1H, CH₂), 2.36 (s, 3H, CH₃), 2.29 (s, 2h, CH₃), 2.28 (s, 3H, CH₃), 2.27 (br, 6H, CH₃), 2.24 (s, 3H, CH₃), 1.54-1.12 (m, CH₂), 1.16 (s, 3H, CH₃), 1.09 (s, 3H, CH₃), 1.05 (s, 9H, CH₃), 0.97 (s, 9H, CH₃). **NMR ³¹P** (161.9 MHz, CDCl₃, ppm) 127.8, 103.2.

General procedure for the Ir-catalysed hydrogenation of imines

[Ir(COD)Cl]₂ (0.022 mmol) or [Ir(COD)₂]BF₄ (0.045 mmol) was dissolved in 10 ml of dry, degassed CH₂Cl₂ in a Schlenk tube. The corresponding ligand (0.055 mmol) was then added, followed by the corresponding imine (4.4 mmol for a 100:1

imine:Ir ratio). The solution was transferred under argon to the autoclave via a syringe.

The reaction mixture was stirred overnight at room temperature under 70 bar of H_2 pressure

References

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