C_1 and C_2-symmetric carbohydrate phosphorus ligands in asymmetric catalysis

Sergio Castillón,* Carmen Claver* and Yolanda Díaz*

Received 9th March 2005
First published as an Advance Article on the web 9th May 2005
DOI: 10.1039/b400361f

Carbohydrates are increasingly used as starting materials for the synthesis of enantiopure ligands. They contain a considerable number of stereocenters, and compounds with all possible configurational combinations are readily available. This *tutorial review* focuses on ligands obtained by the introduction of phosphorus functionalities (mainly phosphinite, phosphite or phosphine) into a carbohydrate framework. They are classified according to their structural features. In this review, ligands are organised as C_1 ligands with a pyranoside or furanoside structure, and C_2 ligands. Particular attention is paid to water soluble ligands prepared from carbohydrates. General methods for the preparation of the ligands are presented in order to show how the backbones can be obtained from simple carbohydrates. The catalytic results obtained in commonly studied processes are presented in tables in order to facilitate the comparison between the ligands. The advantages and limitations of the use of ligands based on carbohydrates are discussed.

1. Introduction. Chiral ligands derived from carbohydrates

The design and synthesis of new ligands is a key step in the development of asymmetric catalysis. Of particular interest in the design of new ligands is the search for new structural arrangements. Carbohydrates are abundant and cheap molecules that are present in nature as enantiomerically pure compounds. They form a large family of compounds with considerable structural variety that combines a great number of carbon backbones with a high density of functional groups. Carbohydrate chemistry is well developed and it allows the performance of many transformations in a direct and efficient way by using well established and tested procedures. Sometimes, however, tedious protection and deprotection procedures are required. The solubility of carbohydrates in water makes them particularly attractive for reactions where water is used as the solvent.

Because of these structural properties, carbohydrates have been used for decades as starting materials to synthesise enantiomerically pure compounds. Thus, carbohydrates, together with amino acids, are the most prominent members of the "chiral pool". Carbohydrates have been mainly used as chiral templates for the synthesis of enantiomerically pure organic compounds by using stereoselective transformations (the "chiron" approach).[1] Carbohydrate derivatives have also been used as synthons to obtain chiral ligands for catalysis, although this was much less explored until very recently.[2]

Departament de Química Analítica i Química Orgànica i Química Física i Inorgànica, Facultat de Química, Universitat Rovira i Virgili, C/ Marcel.li Domingo s/n, 43007 Tarragona, Spain

Sergio Castillón

Sergio Castillón obtained his PhD from the University of Zaragoza in 1982 under the supervision of Prof. J. Vilarrasa. After 2 years of postdoctoral research in the ICSN, Gif-sur-Yvette (France), in G. Lukacs's group, he moved in 1984 to the Faculty of Chemistry of Tarragona (U. Barcelona) as Associated Professor. In 1995 he became full professor at the same Faculty, now University Rovira i Virgili. He was Director of the Chemistry Department in the period 1995–97. His research interest includes development of new synthetic methods, stereoselective synthesis of natural products and asymmetric catalysis.

Carmen Claver

Carmen Claver is Professor of Inorganic Chemistry at the University Rovira I Virgili in Tarragona (Spain), a position she has held since 1991. She received her PhD in 1978 from the University of Zaragoza (Spain) working in the field of organometallic chemistry with Luis A. Oro. Her research is aimed at the development of novel transition metal homogeneous catalysis, covering the synthesis of ligands and complexes, characterization of intermediates and focusing mainly on their application in asymmetric catalysis and polymerisation processes.

Thus, the usual need to protect carbohydrates to control the reactivity in a given position can be advantageously used to obtain a variety of structures which modify the environment of the coordinating functions introduced.

C_2-symmetric ligands are some of the most successful ligands in asymmetric catalysis. However, as carbohydrates generally have C_1-symmetry, most ligands synthesised from them also have C_1-symmetry. Recently, however, significant C_2 ligands have been obtained from carbohydrates, and these will be presented in an additional section of this review.

In addition, most carbohydrates, and in particular the most commonly used pentoses and hexoses (Scheme 1), can be easily and selectively obtained in the pyranose or the furanose form. This multiplies the types of backbones that can be obtained from a single compound, and therefore we have used this as an additional criterion for ligand classification.

In addition, the presence of hydroxyl functions in carbohydrates facilitates the synthesis of oxygenated phosphorus functions such as phosphinites, phosphonites and phosphites.

In this context, the review will be organised as follows:

C_1 ligands

–Pyranoside ligands

–Furanoside ligands

C_2 ligands

The first chiral ligands derived from carbohydrates wee reported in the late 70's by Sinou and Descotes[3] who synthesised the monophosphines (**1**, **2**) and the diphosphine **3** (Fig. 1) from D-xylose and D-glucose. They were all tested in asymmetric rhodium-catalyzed hydrogenation, and using a Rh/**3** catalytic system they obtained 85% ee in the hydrogenation of α-acetamidocinnamic and α-actamidoacrylic acids.

In the same year, Cullen[4] and Thompson[5] reported the first diphosphinite derived from glucose with a pyranoid skeleton (**4**), and Thompson described the first diphosphinite derived from xylose with a furanoid skeleton (**5**) (Fig. 1). They also studied the application of these ligands in asymmetric hydrogenation and their work led to a new family of ligands which turned out to be highly efficient for chiral induction in several metal-catalysed processes.

Yolanda Díaz

Yolanda Díaz obtained her PhD from the Universidad Rovira i Virgili (Tarragona) in 1997. After postdoctoral research in 1998 with professor Frank E. McDonald in Emory University (Atlanta, USA) she joined the Faculty of Chemistry of the University Rovira i Virgili, where she is currently Associate Professor of Organic Chemistry. Her research interests include the development of methodology for the stereoselective synthesis of nucleoside analogues and glycoconjugates. She has also been involved in the synthesis of carbohydrate-derived chiral ligands and their application in asymmetric hydrogenation.

2. Ligands with C_1 symmetry

2.1. Ligands with a pyranoside backbone

Most of the ligands with a pyranoside structure have been prepared from glucose and, more specifically, from a glucopyranoside. The main structural features of glucopyranoside ligands are the following (Fig. 2): a) The anomeric group blocks the pyranoside form and their configuration, α or β can be controlled; b) various substituents (R) can be present in the anomeric group, including coordinating heteroatoms (X = S); c) phosphorus functions can be attached to 2,3-OH and 3,4-OH to give 1,2-diphosphinites or 1,2-diphosphites, or they can be attached to 4,6-OH to give 1,3 derivatives; d) the conformational freedom of 1,2-diphosphinite or 1,2-diphosphite derivatives depends on the nature of the 4-OH and 6-OH protecting groups. e) The absence of protecting groups from the hydroxyl groups not bonded to the phosphorus atoms helps to solubilize the ligands and the corresponding complexes in water.

The first carbohydrate derived ligand prepared, the diphosphinite **4** described by Cullen[4] and Thompson,[5] belongs to this family. This ligand provided enantioselectivity up to 80% in the hydrogenation of α-acetamidoacrylic acids and their esters (entry 1, Table 1).

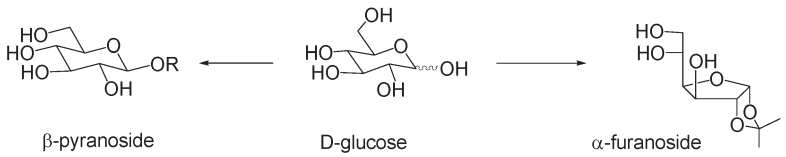
Later, Selke *et al.* studied systematically the effect of the substituents in the anomeric position, and found that when this group was in β position, as in ligand **6** (R′ = Ph), the ee in the hydrogenation of acetoamidocinnamic derivatives **II** and **I** increased to 91% and 96%, respectively (entries 2, 3, Table 1) (Fig. 3).[6] They also demonstrated the importance of the all-equatorial arrangement in vicinal diphosphinite hexapyranoside ligands, if enantioselectivities are to be high in rhodium-catalysed asymmetric hydrogenation.

Subsequently, Rajan-Babu improved the performance of diphosphinite **6** by modifying its electronic properties. Introducing different substituents in the P-aryl groups made these ligands excellent inductors of enantioselectivity in several catalytic processes.[7,8] For instance, in the hydrogenation of several *Z*-acetamidocinnamic acids and esters, the enantioselectivity ranged between 97–99% when 3,5-dimethylphenyl groups were present (entry 4, Table 1).[7] The structure of the precatalyst and intermediates has been studied in order to rationalize the effect of electronic density from the ligand in the Rh-catalyzed asymmetric hydrogenation.[7b]

Diphosphinite **6** (R = 3,5-di-trifluoromethylphenyl) also gave excellent results in the Ni-catalyzed hydrocyanation of vinylarenes and ee up to 91% were obtained (Scheme 3).[8]

The complex **7**[9] (R_2P = Ph_2P) contains a ligand with a diphosphinite function at positions 2,3 and two free hydroxyl groups in positions 4 and 6 of a β-pyranoside. When this complex was supported on silica a 95% ee was achieved in the hydrogenation of **II** using methanol as the solvent (entry 6, Table 1). In this reaction, the enantioselectivity was strongly influenced by the nature of the solvent. That is, when the solvent was changed, the enantioselectivity also changed.

One of the limitations of the ligands prepared from the chiral pool is that only one enantiomer is accessible. Sunjic *et al.*,[10] however, observed that diphosphinite **11** behaved as a pseudo-enantiomer of **12**. Indeed, it provides the opposite



Scheme 1 Pyranoside and furanoside structures obtained from D-glucose.

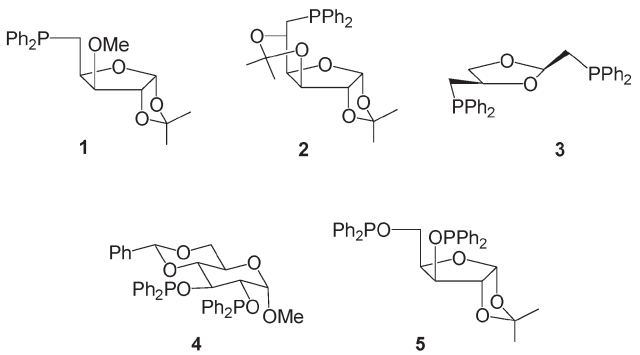
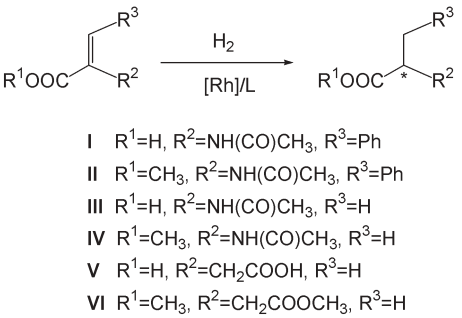


Fig. 1 First chiral ligands prepared from carbohydrates



Scheme 2 Hydrogenation of dehydroamino acids and esters, and itaconic acid derivatives.

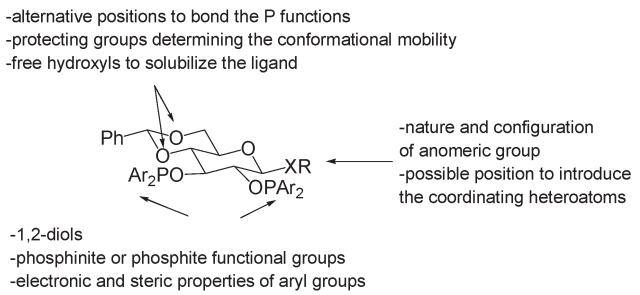


Fig. 2 Positions where structural diversity can be introduced in ligands **4**.

enantiomer in the rhodium-catalyzed hydrogenation of *Z*-acetamidocinamic acid, although the ee was higher (90%, *S*)

Table 1 Hydrogenation of unsaturated acids and esters with pyranoside carbohydrate ligands[a]

Entry	Substrate	Ligand	ee	Reference
1	III	**4**	80(*S*)	4
2	II	**6**	91(*S*)	6
3	I	**6**	96(*S*)	6
4	I	**6**[b]	99(*S*)	7
5	II	**6**[b,c]	94.4(*S*)	11
6	II	**7**[d]	95(*S*)	9
7	II	**8a**[b]	93(*R*)	11
8	II	**8b**[b]	98.3(*R*)	11
9	I	**11**	63(*R*)	10
10	I	**12**	90(*S*)	10
11	II	**17**[e]	88[f](*S*)	17
12	IV	**18**[b]	93	19
13	IV	**19**[b,e]	61	19
14	IV	**20**[b]	83(*S*)	18
15	IV	**21**[b,e]	49%(*S*)	18
16	V	**24**	92(*S*)	20

[a] See Scheme 2. [b] Ar = 3,5-di-methylphenyl. [c] 98.2% ee when Ar = 3,5-di-TMS [d] Catalyst supported on silica. [e] Reaction in water. [f] 99.9% in the presence of sodium dodecylsulfate.

for the Rh/**12** than for the Rh/**11** catalytic system (63% ee, *R*) (entries 9,10, Table 1). In the same way, Rajan-Babu observed that pyranoside derivatives containing phosphorus bonded to the 3,4 hydroxyl groups (**8–10**) could be considered as pseudo-enantiomers of the ligands with phosphorus bonded to the 2,3 hydroxyl groups (**6**). In fact, in the hydrogenation of *Z*-α-acetamidocinnamic acids the Rh/**8–10** catalytic system provided the enantiomer *R*, while the Rh/**6** catalytic system gave the enantiomer *S*. Enantioselectivities were higher than 95% when these catalytic systems were used (entries 7, 8, Table 1).[11]

Selke *et al.*[12] also prepared the diphosphites **6** (R_2 = diol). For the rhodium-catalysed hydroformylation of vinyl acetate, allyl acetate and styrene, they studied the influence of the substituents on phosphorus on the enantioselectivity. In all cases, the ee was found to be very low. The results were best in the hydroformylation of the allyl acetate (36% ee) when R_2 = 3,3′-diphenyl-biphenyl-2,2′-diol. This result confirmed van Leeuwen's postulate that diphosphites derived from vicinal diols are less useful than analogous ligands derived from chiral 1,3-diols for asymmetric hydroformylation. See for instance the results obtained with ligand **37** in the following section.

If glucosamine is used as the starting material a number of interesting structural modifications can be introduced. The aminophosphinite **13** (OR = β-OMe), and in particular the derivative of *allo* configuration where Ar = 3,5-dimethylphenyl, R′ = Ac, were successfully used in the Ni-catalyzed hydrovinylation of styrene, achieving an ee up to 81% with yield and selectivity to the branched isomer of 89% (Scheme 4).[13]

Uemura[14] took advantage of the presence of a nitrogen atom in the glucosamine to prepare the oxazoline/phosphinite ligand **15**, related to **13**, which maintains the basic structure of glucose protected with a 4,6-*O*-benzylidene group. This ligand was used in the palladium-catalyzed allylic alkylation of

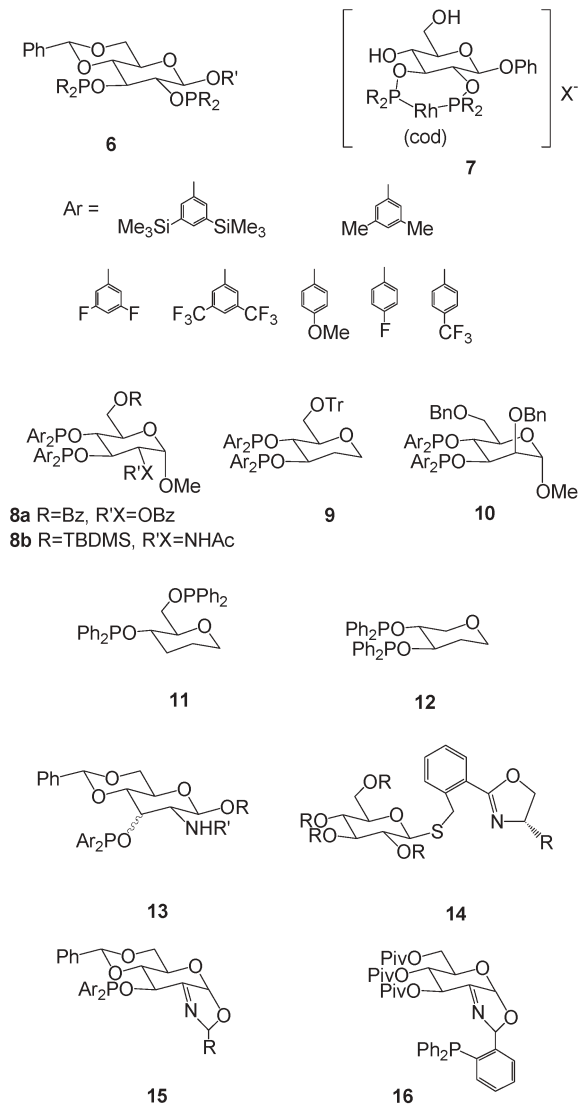
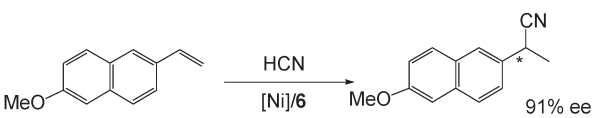
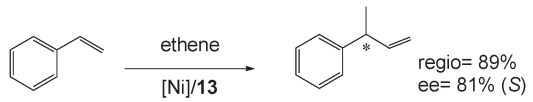


Fig. 3 C_1-symmetric ligands with a pyranoside backbone.



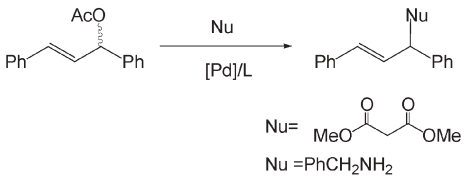
Scheme 3 Hydrocyanation of 6-methoxy-2-vinylnaphtalene with the catalytic system Ni/**6**.



Scheme 4 Ni-catalyzed hydrovinylation of styrene.

1,3-diphenyl-acetoxypropen-1-ene and provided an enantiomeric excess as high as 96% (entry 2, Table 2). The related phosphine/oxazoline ligand **16** was reported by Kunz and also afforded excellent results in the same reaction (98% ee)(entry 3, Table 2).[15]

Table 2 Allylic alkylation and amination of 1,3-diphenyl-3-acetoxypropene



Entry	Ligand	Alkylation	Amination	Ref.
1	**14**	97%		16
2	**15**	96%		14
3	**16**	98%		15
4	**30b**	58(*S*)	67(*R*)	31
5	**31**	42(*S*)	66(*R*)	31
6	**35c**	90(*S*)	97(*R*)	31
7	**36c**	5 (*R*)	—	31
8	**35c**[a]	97%		32
9	**37b**	95%		36
10	**47**	99%(*R*)		42*b*
11	**53**	63%(*S*)		42*b*

[a] Catalysis performed with palladium nanoparticles stabilized with ligand **35c**; ee determined at 56% of conversion; ee of the unreacted isomer was 89%.

An interesting ligand in which all the coordinating heteroatoms are present in the anomeric group is the S/N ligand **14**, developed by Pregosin.[16] The chiral oxazoline group is derived from amino acids, as usual, and the sulfur atom is part of a thioglycoside. This ligand gave an ee of 97% in the palladium-catalyzed allylic alkylation of 1,3-diphenyl-acetoxypropen-1-ene with diethyl malonate (entry 1, Table 2).

Other authors used the ligands developed by Cullen, Selke and Rajan-Babu in which the hydroxyl groups were unprotected to perform those catalytic processes in water.

Uemura prepared the rhodium complex **17** that incorporated diphosphinite ligands derived from α,α-trehalose and β,β-trehalose.[17] Complex **17** (Fig. 4), which incorporated a ligand derived from β,β-trehalose, can be related to **7** (Fig. 3) by replacing the anomeric phenyl group by a glucose moiety, what increases its solubility in water. Complex **17** provided an ee of 88% when methyl *Z*-α-acetamidocinnamate was hydrogenated in water, but it increased to 99.9% in the presence of sodium dodecyl sulfate (entry 11, Table 1). When the reaction was performed in the biphasic system AcOEt/water, the ee was 87% and the catalyst was recovered simply by phase separation at the end of the reaction. The ligands derived from β,β-trehalose gave better results than the ligands derived from α,α-trehalose, in agreement with what was observed for ligands **4** and **6**.

Almost simultaneously, Rajan-Babu prepared a series of diphosphinites **20**–**23**,[18] derived from α,α-trehalose in which the phosphinite functions were at positions 2,3 of a sugar unit (**21**, **22**) or at positions 6,6′ (**22**), or 4,4′ (**23**) of both sugar units. The catalytic system Rh/**20** (R,R′ = cyclohexylidene, Ar = 3,5-di-Me-C_6H_3) provided an ee of 83% in the hydrogenation of methyl α-acetamidoacrylate (entry 14, Table 1), but it dropped to 49% when the reaction was performed in water using the catalytic system Rh/**21** (R,R′ = H, Ar = 3,5-di-Me-C_6H_3). One possible explanation for this

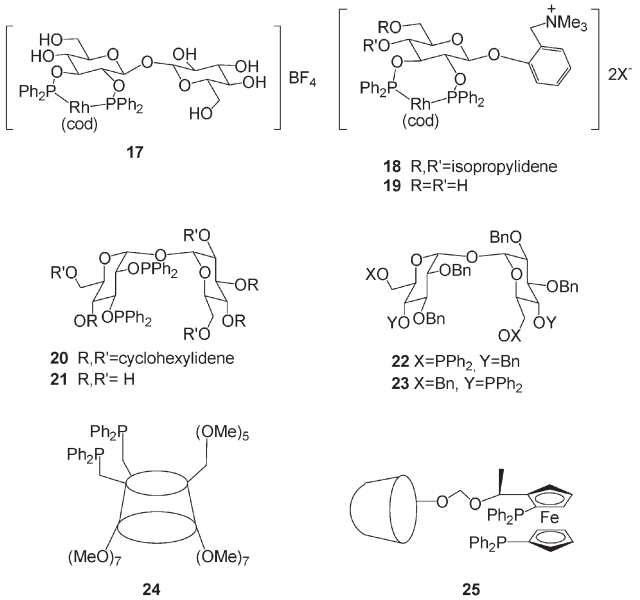


Fig. 4 C_1-symmetric water soluble ligands: a) with a pyranoside backbone (**17–23**), b) based on cyclodextrines (**24**, **25**).

decrease in enantioselectivity is the intervention of protonolysis of the putative Rh–C bond before the final reductive elimination.[18]

Later, Rajan-Babu modified the complex **7** by introducing an ammonium substituent in the anomeric phenyl group of the ligand, and prepared the rhodium complexes **18**, **19**.[19] Complex **18** was tested in the hydrogenation of dehydroamino acids and ee's were slightly lower than those obtained for the corresponding complexes without the ammonium group in organic solvents (entry 12, Table 1). Although the solubility of this complex in water was sufficient to complete the hydrogenation reaction, it required long reaction times and the ee's were very low. Complex **19** was used in the hydrogenation of methyl *Z*-α-acetamidoacrylate in water as the solvent to give a 61% ee. When the product was left in contact with water for long periods of time under the reaction conditions, the enantioselectivity decreased rapidly. These complexes also showed similar trends to that observed for ligand **21**.

Recently, phosphorus functionalities have been incorporated into cyclodextrins in order to take advantage of the properties of cyclodextrins as water-soluble chiral supports. Ligand **24**[20] contains phosphine in two of the positions 6 of a β-cyclodextrin, while in **25**[21] the cyclodextrin merely serves to solubilize a chiral ferrocenylphosphine in water. The Rh/**24** catalytic system has been tested in the hydrogenation of substrates I–VI (Scheme 2) with ee's up to 92%, but only organic solvents were used for these reactions.[20]

2.2. Ligands with a furanoside backbone

Ligands with a furanoside backbone are usually prepared from xylose or glucose. The main structural features of furanoside ligands are the following (Fig. 5): a) The anomeric position is usually blocked with a 1,2-*O*-isopropylidene group to give a bicycle, which restricts the conformational freedom. b) Phosphorus functions can be attached to 3,5-OH (xylose and glucose) and 5,6-OH (glucose) to give 1,3-diphosphinites/diphosphites or 1,2 derivatives. Phosphino derivatives with a furanoside backbone have been prepared.

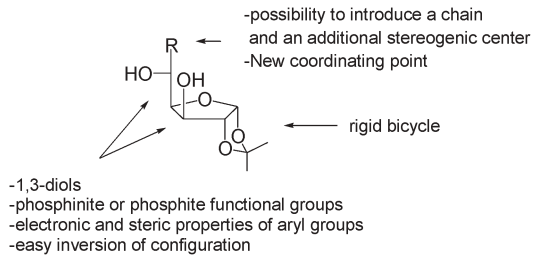


Fig. 5 Structural features of C_1 symmetric furanoid ligands.

Although ligand **5**[5] (Fig. 1) was one of the first reported ligands derived from carbohydrates, there are only a few examples of ligands with a furanoside structure. Starting from D-xylose, Brunner[22] prepared **5** and other ligands such as hydroxyl/phosphine **27** and the phosphine/phosphinite **28**.

Recently, diphosphinites **5** and **26** (Fig. 6) were used in rhodium and iridium-catalyzed asymmetric hydrogenation of prochiral substrates. Curiously, the enantiomeric excess in the hydrogenation of methyl α-acetamidoacrylate (**IV**) was 76% (*R*) with the Rh/**26** catalytic system and 78% (*R*) with the Ir/**5** catalytic system. The enantiomeric excess was dependent on both the absolute configuration of the C-3 stereocenter of the carbohydrate backbone and on the nature of the metal precursor. The catalytic systems Rh/**5** and Ir/**26** gave very low ee's.[23]

Diphosphinite **29**,[24] reported by Rajan-Babu, was probably the first ligand with a furanoside structure that provided excellent results in asymmetric catalysis. This ligand can be obtained from fructose in three steps and provided an enantiomeric excess as high as 89% (95% at 0 °C) in the Ni-catalyzed hydrocyanation of styrene. Like ligand **6**, results were best when Ar = 3,5-di-trifluoromethyl-phenyl.

It is possible to easily introduce different functional groups in ligands derived from xylose. Ligands **30–32** and **35**,**36** are representative examples.

The hydroxy/thioether ligand **30a** (X = OH, R = Ph) gave an ee as high as 61% in the conjugated addition of $ZnEt_2$ to cyclohexenone catalyzed by $Cu(OTf)_2$ (Scheme 5).[25a]

When the thioether/phosphite ligand **30b** (X = $OP(OR)_2$)[25b] was used in the iridium-catalyzed hydrogenation of itaconic acid, the enantiomeric excess was 53%. The related phosphine/phosphite ligand **31**, however, gave excellent results in the rhodium-catalyzed enantioselective hydrogenation of dehydroamino acids, and provided enantiomeric excesses higher than 99% (entries 1,2. Table 3).[26] Ligand **31** is a promising ligand for asymmetric hydrogenation. Mechanistic studies have shown that the absolute configuration of the major enantiomer of the hydrogenated product is mainly controlled by the configuration of the phosphite moiety, and that the presence of bulky substituents in the biphenyl moiety has a great effect in the enantioselectivity.

The diphosphine **32**[27] was used at room temperature in the rhodium catalyzed hydrogenation of α-acetamidocinnamic and itaconic acids, and methyl acetamidoacrylate, and gave conversions of 100% with ee's of 89%, 62% and 91%,

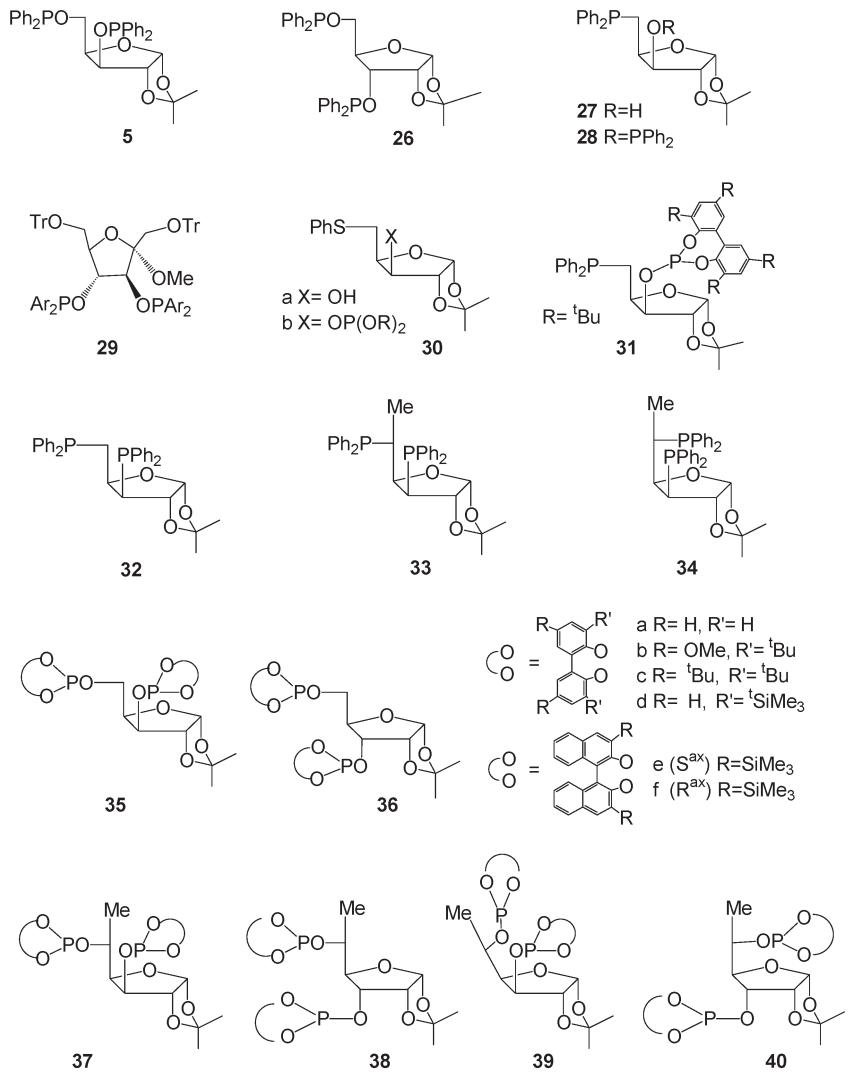
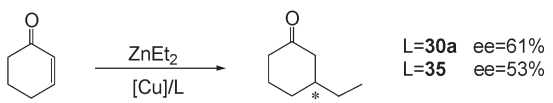


Fig. 6 C_1 symmetric ligands derived from carbohydrates with a furanoside structure.



Scheme 5 Copper-catalyzed addition of $ZnEt_2$ to cyclohexenone.

Table 3 Hydrogenation of dehydroamino acids and esters with furanoside carbohydrate ligands

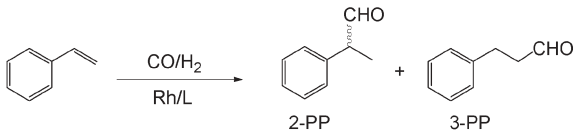
Entry	Substrate	Ligand	ee	Reference
1	II	**31**	98.8(*R*)	26
2	IV	**31**	>99(*R*)	26
3	I	**32**	89(*S*)	27
4	IV	**32**	92(*S*)	27
5	V	**32**	62(*R*)	27
6	IV, II	**33**	98(*S*)	38*a*
7	IV, II	**34**	53(*S*)	38*a*

respectively. At 0 °C the ee in the hydrogenation of methyl acetamidoacrylate rose to 98% but the conversion decreased to 11%.

Diphosphite **35**, with a *xylo* configuration, was initially prepared by van Leeuwen[28] and also used in the rhodium-catalyzed hydroformylation of styrene, providing an enantiomeric excess of 53% (entry 4, Table 4). Subsequently, diphosphinite **36**, with a *ribo* configuration, was also prepared in order to study how the configuration of the position 3 of the furanose ring influenced the enantioselectivity of the reaction. In the rhodium catalyzed hydroformylation of styrene the diphosphite **36** provided the same ee as the diphosphite **35** but with opposite configuration (entry 5, Table 4).[29a] However, when these phosphites were used in the Rh-catalysed hydrogenation of substrates **I**, **IV** and **V** (Scheme 2) the configuration of the major enantiomer was similar in both cases and the ee's were low (50%).

Both phosphites **35** and **36** were used in the $Cu(OTf)_2$-catalyzed conjugated addition of diethylzinc to cyclohexenone (Scheme 5).[29b] The best result was obtained with diphosphite **35**, which afforded an enantiomeric excess of 53%, although this was lower than that for **30a**. Phosphite **35** was also tested in the iridium-catalyzed hydrogenation of imines and provided an ee of 57%.[30] In all cases, the best results were obtained when

Table 4 Hydroformylation of styrene with the Rh/**32–40** catalytic systems



Entry	Ligand	2-PP (%)	ee (%)	Reference
1	**32**	97	51 (*S*)	38*b*
2	**33**	97	58 (*S*)	38*b*
3	**34**	97	44 (*S*)	38*b*
4	**35**	92	53 (*S*)	28
5	**36**	96	53 (*R*)	29*a*
6	**37b**	98.6	90 (*S*)	33*a*
7	**37d**	99	93 (*S*)	33*b*
8	**38b**	97	58 (*R*)	33*a*
9	**39b**	97	64 (*S*)	33*a*
10	**40b**	98	89 (*R*)	33*a*

the phosphite function incorporated a 5,5′-dimethoxy-3,3′-di-*tert*-butyl-2,2′-biphenol unit.

Ligands **30b**, **31**, **35** and **37** were tested in the Pd-catalyzed allylic alkylation of 1,3-diphenyl-acetoxypropen-1-ene with dimethyl malonate and in the corresponding amination using benzyl amine. In both processes the best results were obtained with the catalytic system Pd/**35c**, achieving 90% and 97% of ee[31] (entries 4–9, Table 2).

Palladium nanoparticles stabilized by ligand **35c** were recently prepared from $[Pd_2(dba)_3]$. These particles were used as catalysts in the allylic alkylation of 1,3-diphenyl-acetoxypropen-1-ene with diethyl malonate as nucleophile. The kinetic resolution was excellent because after two hours, only one enantiomer was transformed. The ee was 97% in the transformed product and 89% in the remaining enantiomer at a conversion of 56% (entry 8, Table 2).[32] This is the first example of kinetic resolution using nanoparticles, and remarkably they behave differently from molecular catalysts, which transformed all the starting material to provide the allylation product with an ee of 90%.

In the ligands **30–32**, **35**, **36** presented above, with a *xylo* or *ribo* configuration, only one of the coordinating heteroatoms is bonded to a stereogenic center in the carbohydrate backbone, while the second heteroatom is bonded to a primary carbon. Binding the second coordinating heteroatom to another stereogenic center might improve the asymmetric induction. Starting from the 1,2-isopropyliden-D-glucofuranoside, the deoxygenation of position 6 afforded a diol similar to that with *xylo* configuration, but where both hydroxyl groups were bonded to stereogenic centers. The four diastereomers **37–40** were obtained by modifying the configuration of these diols and introducing the phosphorus functions. These diphosphites were tested in the rhodium-catalyzed hydroformylation of styrene (entries 6–10, Table 4), and the catalytic system Rh/**37b** provided an ee of 90% and a regioselectivity into the branched aldehyde of 99%. It was also demonstrated that the configuration of position 3 of the sugar ring determines the configuration *R* or *S* of the main enantiomer, while position 5 helps to increase the ee.[33*a*] The ee was increased to 93% when the biphenol fragment had Me_3Si groups instead of *tert*-butyl groups (ligand **37d**).[33*b*] These results are among the best that have ever been reported, behind the very successful BINAPHOS developed by Takaya and Nozaki.

Curiously, in the enantioselective hydrogenation of dehydroamino esters **II**, **IV**, and **VI** (see Scheme 2) it was the catalytic system Rh/**38d** which afforded excellent results: ee's were higher than 99% at 5 °C and 30 bars of hydrogen pressure (Table 5).[34] The configuration of the major enantiomer obtained using the catalytic system Rh/**38d** is predominantly controlled by the configuration of the biaryl at the phosphite moieties. A comparison of the behaviour of Rh/**37c–40c** catalytic systems in the asymmetric hydrogenation of **II**, **IV** and **VI** showed that the configuration of the major enantiomer obtained is the same, suggesting a similar spatial arrangement around the metal center in the active catalytic species. Interestingly, also in this case the presence of an additional stereogenic center at C5, with regards to the ligands **35** and **36**, increased the enantioselectivity. Unlike the results observed in hydroformylation,[33] the configuration of the major enantiomer produced in the hydrogenation reaction with the biphenyl-based ligands is not controlled by the configuration of the stereogenic carbon atom C-3. Similar behaviour was also observed for ligands **35–36**.

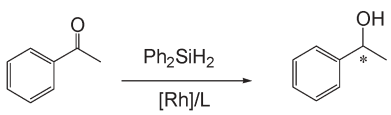
Diphosphite **38** and phosphine/phosphite **31** are both excellent ligands for asymmetric hydrogenation. However, the ligand **37**, which is structurally related to **31**, did not give enantioselectivity. Further mechanistic studies will be necessary to explain these results.

This type of ligands has also provided excellent results in other catalytic processes. For instance, an ee of 84% was obtained in the conjugated addition of $ZnEt_2$ to cyclohexenone catalyzed by Cu/**37**.[35] Furthermore, in the allylic alkylation of 1,3-diphenyl-3-acetoxypropene with diethyl malonate as nucleophile and Pd/**37b** as catalyst, the ee obtained was 95% (entry 9, Table 2).[36]

Both the diphosphites derived from xylose (**35**) and glucose (**37**) were tested as ligands in the Rh-catalyzed hydrosilylation of acetophenone (Scheme 6). The results, however, were only modest, with an ee of 45% when the diphosphite **35** was used.[37] The diphosphites derived from xylose provided better enantioselectivity than those derived from glucose.

Table 5 Hydrogenation of dehydroamino acids and esters, and dimethyl itaconate with furanoside phosphite carbohydrate ligands **37–40**[34]

Entry	Ligand	II(ee%)	IV (ee%)	VI (ee%)
1	**37c**	2(*S*)	3(*S*)	2(*R*)
2	**38c**	91(*S*)	92(*S*)	90(*R*)
3	**39c**	29(*S*)	29(*S*)	32(*R*)
4	**40c**	67(*S*)	71(*S*)	70(*R*)
5	**38d**	>99(*S*)	>99(S)	>99(*R*)



Scheme 6 Rhodium catalyzed hydrosilylation of ketones.

Diphosphines **33** and **34** were used as ligands in the Rh-catalyzed hydrogenation of dehydroamino acids.[38a] The catalytic system Rh/**33** proved to be the most efficient, providing an ee of 98% in the hydrogenation of methyl α-acetamidocinnamate (**II**), and acetamidoacrylate (**IV**) (see Scheme 2) (entry 6, Table 3), while the system Rh/**34** only gave 53% ee (entry 7, Table 3).

2.3. Synthesis of C_1 chiral ligands

The general procedures for the synthesis of the most important ligands from glucose are shown in Scheme 7. The general strategies are based on the synthesis of diols, which reacts with Ar_2PCl or $(RO)_2PCl$ in basic medium to give the corresponding phosphinite or phosphite functions. In the synthesis of pyranoside derivatives, one first has to decide whether α or β glycosides are desired. This is important when the coordinating functions are at positions 2 or 3; thus, it was found than **6** provides better results than **4** in the hydrogenation of dehydroamino acids.

Treating D-glucose with acid in methanol gives the α-glycoside **C**, from which the formation of the 4,6-*O*-benzylidene provides the diol precursor for **4**. Selective protection of positions 2,6 give the diol precursor for **8**. Synthesis of ligands **6**, **18** and **19**, and complex **7**, requires the 4,6-*O*-benzylidene-β-glycoside **B**, which is prepared in four steps from glucose. Complex **7** was prepared by a controlled hydrolysis of the complex containing ligand **6**. This is a general strategy to obtain a complex with a free hydroxyl, as will be seen below. Synthesis of 1,2-dideoxy- and 1,2,3-trideoxy derivatives **9** and **11** starts from the commercially available tri-*O*-acetyl-glucal (**D**, R = Ac). After hydrolysis, selective protection of 6-OH, and reaction with Ar_2PCl gives the phosphinite **9**. The synthesis of **11** requires selective protection of hydroxyl groups at positions 4,6, deoxygenation of 3-OH, deprotection and formation of the diphosphinite functions. Ligand **12** was obtained from xylal by double bond hydrogenation and the formation of the phosphinite functions.

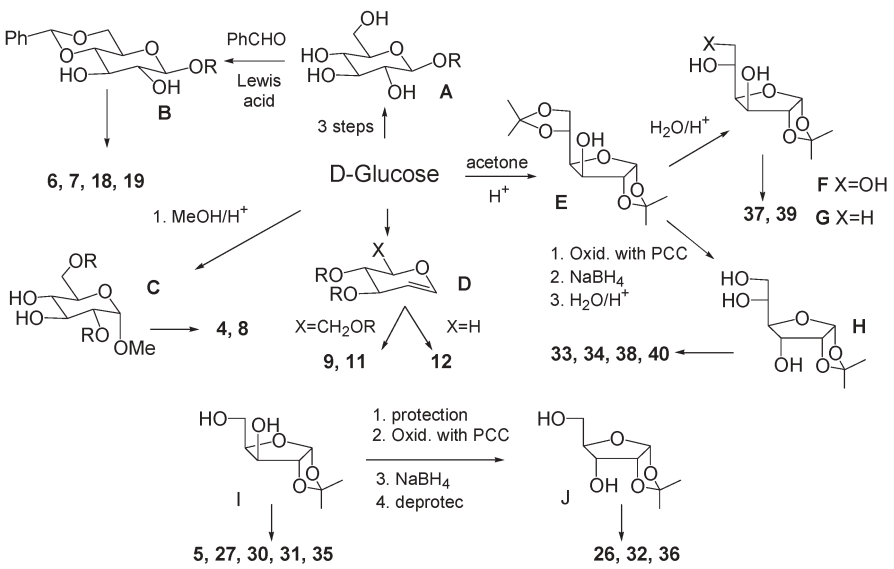
The synthesis of furanoside derivatives **33**, **34**, **37–40** starts from the commercially available 1,2-5,6-diisopropylidene derivative **E** which, after selective hydrolysis of 5,6-isopropylidene acetal and deoxygenation of 6-OH, affords **F** and **G**, which is the precursor for **37** (Scheme 7). The formation of **39** requires inversion of the configuration at position 5 in **E**, which is done by reacting $LiAlH_4$ with the epoxide obtained by tosylation of 5-OH followed by treatment in basic medium. Oxidation of **E** with pyridinium chlorochromate and reduction with $NaBH_4$ inverts the configuration of C-3 to give **H**, from which ligands **38** and **40** are obtained by procedures similar to those used for the synthesis of **37** and **39**.

Diphosphines **33** and **34** were obtained from the diol precursors of **40** and **38**, respectively, by tosylation and reaction with $KPPh_2$ through an S_N2 reaction. Xylose derivatives **5**, **27**, **30**, **31** and **35** were obtained directly from the commercially available diol **I**. Protection of 5-OH, inversion of the configuration of C-3, in the same way as for **E**, and subsequent deprotection provided the diol precursors for **26**, **32**, and **36**.

3. Ligands with C_2 symmetry

C_2-symmetric ligands belong to the most efficient ligands in asymmetric hydrogenation and other metal-catalyzed processes. In the sections above, we have presented a set of C_1-symmetric ligands derived from carbohydrates that are readily available and lead to the highest enantioselectivities in asymmetric catalysis. Here we will present some important carbohydrate-based ligands with C_2 symmetry.

C_2-symmetric ligands have mainly been prepared from D-mannitol. Particularly important are those with a phospholane structure. In analogy with DUPHOS, A. Börner described the preparation of ligands **41** and **42**[39] (Fig. 7) in which the 2,5-dimethylphospholane ring, characteristic of DUPHOS, was replaced by a phospholane ring derived from mannitol. The ligand performance was similar to that of DUPHOS and provided ee's higher than 98% in the hydrogenation of



Scheme 7 General procedures for the synthesis of C_1-symmetric ligands containing pyranoside and furanoside structures.

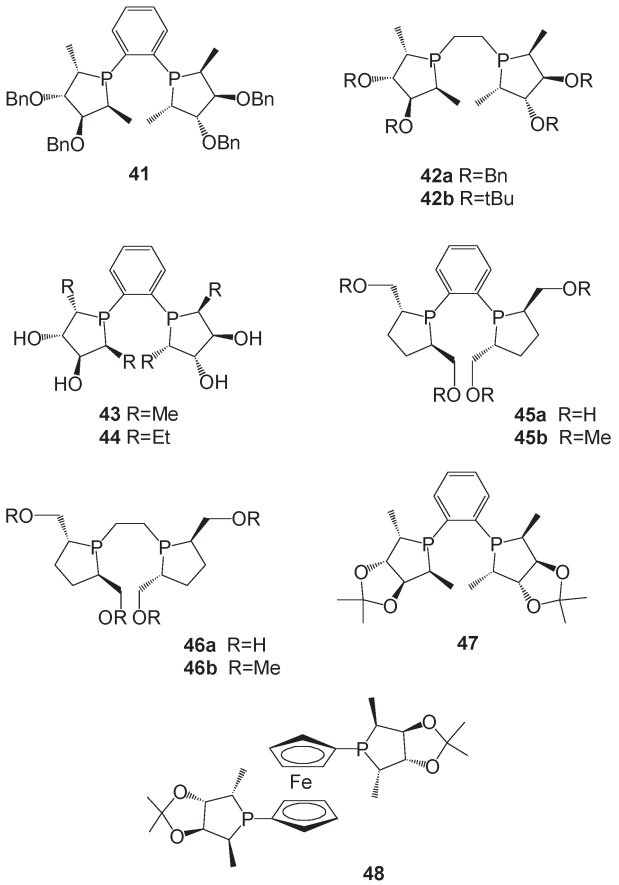


Fig. 7 C_2-symmetric ligands containing phospholane units (DUPHOS analogues) obtained from carbohydrates (**41–48**).

acetamido cinnamates, acrylates and itaconic acid (entries 1–3, Table 6). This is one of the most significant structural innovations in carbohydrate-derived ligands since the early examples described above.

Researchers interested in this type of ligand were attracted by the possibility of solubilizing DUPHOS in water by incorporating hydroxyl groups in the phospholane ring. With this aim, ligands **43** (RoPHOS), **44**,[40] **45**[40b,41] and **46**[41] were prepared (Fig. 7). Ligand **43** gives ee's up to 99% in the rhodium-catalyzed hydrogenation of methyl acetamidoacrylate (entry 4, Table 6). However, the enantioselectivity was found to be strongly dependent on the nature of the solvent, and decreases when the amount of water increases. The catalytic system Rh/**44** gives ee's higher than 99% in pure water (entry 5, Table 6). The catalytic system can be recovered by extracting the reaction product with diethyl ether, and the remaining solution can be reused since it still contains the catalyst. However, the activity of the system Rh/**44** decreases after three runs.

Ligand **45a** (BASPHOS)[41] was prepared by Holz and Börner and the Rh/**45a** complex was tested on the hydrogenation of the α-acetamidoacrylic acid and the corresponding methyl ester (**III**, **IV**), to obtain 99.6% (entry 6, Table 6) and 93.6% ee respectively.[53a] Rajan-Babu showed that the catalytic system Rh/**45a** gives an ee higher than 99% in pure water for the hydrogenation of **IV**, and could be reused five times with no loss in activity or enantioselectivity (entry 6, Table 6).[40b] This ligand was also tested in the hydrogenation of substrates **I**, **II** and **V**, in methanol as solvent providing 79.5%, 95.8% and 97% ee, respectively.[41b] Higher enantioselectivities were observed with the catalyst based on the ligand **45b**, characterized by four methoxy groups and a phenylene bridge. When the methyl groups were replaced by the larger benzyl or tetrahydropyranyl groups, ee values were found to be lower. When the rigid 1,2-phenylene bridge was replaced by the more flexible ethylene bridge (ligands **46**), the enantioselectivity decreased considerably. The best results in the Rh-catalyzed hydrogenation of *Z*-α-acetamidocinnamic acid (**I**) α-acetamidoacrylic acid (**III**) were also obtained using ligands **43** and **44**. The catalytic system Ru/**45b** gave an ee of 96.2% in the asymmetric reduction of β-ketoesters, as shown in Scheme 8.

Rajan-Babu[42] described a series of ligands containing a phospholane substructure, among which was the C_2-symmetric ligand **47**. Ligand **47** was tested in the Pd-catalyzed allylic alkylation of 1,3-diphenyl-acetoxypropen-1-ene with dimethyl malonate affording 99% ee (entry 10, Table 2).[42b] The chiral ferrocenyl diphosphine **48**, which incorporate two diphospholane units, gives enantioselectivities higher than 99% with high activity in the Rh-catalyzed hydrogenation of dehydroamino acids derivatives and itaconic acid derivatives (entry 9, Table 6).[43]

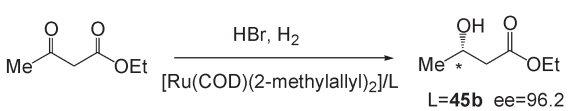
Mannitol was first used in its most simple protected form (1,2:5,6-diisopropylidene-D-mannitol) by Brunner[22] to prepare phosphites **49** (X = $(OR)_2$) (Fig. 8). Diphosphinite **49** (X = Ph_2) was subsequently used in the rhodium-catalyzed hydrogenation of *Z*-α-acetamidocinnamic and α-acetamidoacrylic acids with ee's of 96.4% and 91.6%, respectively (entry 10, Table 6).[44]

A particular case of mannitol-derived diphosphite ligands are those with a 1,4:3,6-dianhydro-D-mannitol structure **50**,[45] where the diol moiety can be a bisphenol or bisnaphthol unit.

Table 6 Hydrogenation of deshydroamino acids and esters, itaconic acid and diester with C_2 symmetry ligands derived from carbohydrates

Entry	Ligand	I ee(%)	II ee(%)	III ee(%)	IV ee(%)	V ee(%)	VI ee(%)	Ref.
1	**41**	93(*S*)	96(*S*)			97(*R*)	98(*R*)	39
2	**42a**	93.5(*S*)	97.5(*S*)			98(*R*)	98.9(*R*)	39
3	**42b**	96.8(*S*)	98.4			96.7	99.1	39
4	**43**	>99(*S*)	>99(*S*)	>99(*S*)	98(*S*)	96(*R*)	>98(*R*)	40
5	**44**	>99(*S*)	>99(*S*)	>99(*S*)	>99(*S*)[a]	>99(*R*)	>99(*R*)	40
6	**45a**	79.5(*S*)	95.8(*S*)	99.6(*S*)	99(*S*)[a]	97(*R*)		40,41
7	**45b**	94.8(*S*)	98.9(*S*)			98(*R*)		41
8	**47**				97(*R*)			41[a]
9	**48**		99.5		99.6	99.5	89.9	43
10	**49**	96.4(*R*)		91.6				44
11	**50**				88.8(*R*)		98.2(*R*)[b]	45
12	**57b**		81(*R*)		85[b](*R*)		48[c](*S*)	48
13	**58b**		59(*R*)		59(*R*)		9[c](*R*)	48
14	**59**		27(*R*)		16(*R*)		4(R)	48

[a] Reaction in water. [b] 98% ee at −10 °C. At −25°, ee = 91%. [c] With **57a**, ee = 48(*S*), with **48a**, ee = 53 (*R*).



Scheme 8 β-Ketoester reduction using Ru based catalysts.

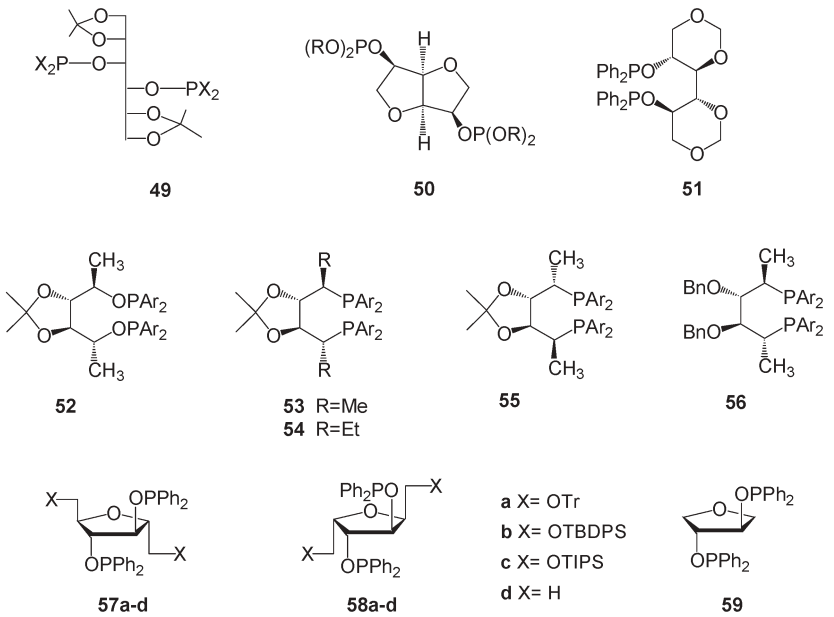


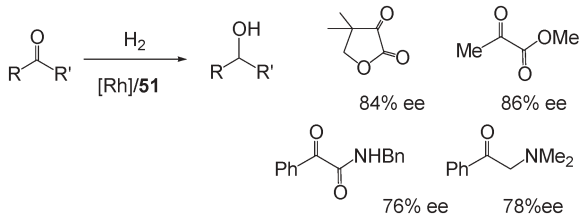
Fig. 8 C_2 symmetric ligands derived from carbohydrates.

The configuration of major enantiomer depends on the chirality of the bisnaphthol unit and on the nature of substituents in the bisphenol unit. Enantioselectivities of 88.8% and 98.2% were obtained in hydrogenation of substrates **IV** and **VI**, respectively (entry 11, Table 6).

Diphosphinite **51**, which results from the selective protection of alcohols 1,3 and 4,6 in mannitol with formaldehyde, was used in the Rh-catalyzed hydrogenation of ketones, α-ketoesters and α-ketoamides. Enantioselectivities were as high as 86% (Scheme 9).[46]

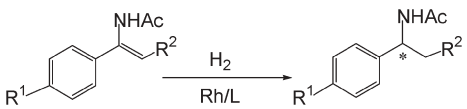
Diphosphinite **52**[42] and diphosphines **53–56** can be considered as modifications of DIOP and were obtained from D-mannitol. Diphosphine **53** was simulateneously reported by Rajan-Babu, who used it as ligand in the PD-allylation (63% ee, entry 11, Table 2),[42b] and by Zhang, who used it in the Rh-catalyzed hydrogenation of α-acetamidostyrene and related enamides achieving ee's higher than 99% (entries 1,2, Table 7).[47] The best results were obtained with the ethyl derivative **54**. Recently, the catalytic systems Rh/**53** and Rh/**56** were used in the hydrogenation of an α-acetamido-β-alkoxystyrene with 84.6% and 98.1% ee, respectively (entries 3,4, Table 7).[47] The Ir/**56** catalytic system was also active in the hydrogenation of cyclic imines providing ee's up to 85%.

Recently, diphosphinites **57a–d** and **58a–d** have been prepared from D-glucosamine and D-glucitol.[48] These ligands were used in the Rh-catalyzed hydrogenation of methyl



Scheme 9 Ketone reduction using Rh based catalysts.

Table 7 Hydrogenation of enamides with diphospholane derivatives.

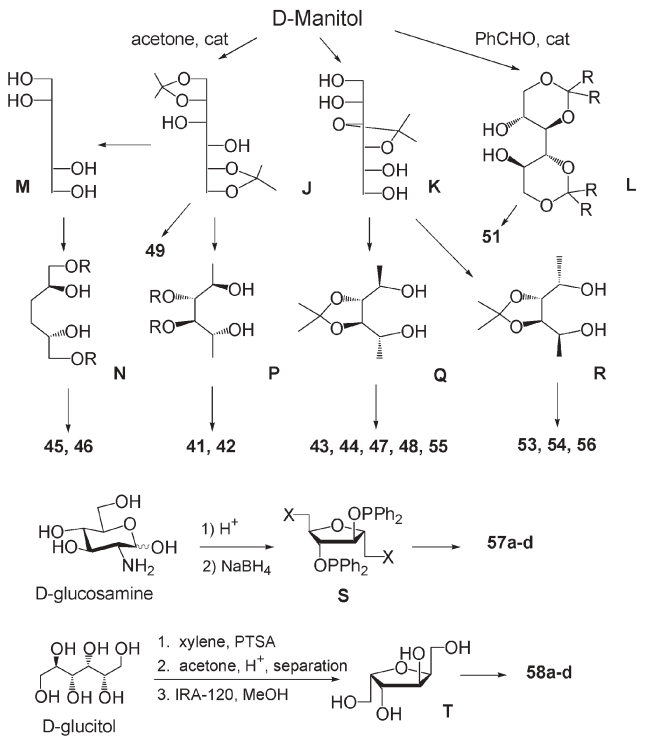


Entry	Ligand	R^2	ee(%)	References
1	**53**	H	98(*R*)	47*a*,*b*
2	**54**	H	99(*R*)	47*c*
3	**53**	OMOM	84.6	47*c*
4	**56**	OMOM	98.1(*S*)	47*c*

acetamidoacrylate, methyl acatamidocinnamate and dimethyl itaconate. Catalytic systems containing the ligand **57c** afforded the best results with an ee of 93% in the hydrogenation of methyl acetamidoacrylate. Ligand **59**, which does not contain substituents at positions 2 and 5 of the tetrahydrofuran ring only gave an ee of 22%. This indicates that the stereogenic centers which are not directly bonded to the coordinating atoms have a strong influence on the selectivity. Substituents X in **57** and **58** also affect the stereoselectivity. The ee's were lower for the dimethyl itaconate than for the other substrates but unexpectedly, the configuration of the major enantiomer, when ligands **57a** and **58a** were used, seems to be determined by the configuration of substituents at carbons 2 and 5 (entries 12–14, Table 6).

Synthesis of C_2 chiral ligands

As mentioned above, most of the chiral ligands derived from carbohydrates with C_2 symmetry are obtained from D-mannitol (Scheme 10). The synthesis of these ligands is based on different protection procedures of the hydroxylic functions in D-mannitol. Thus, the reaction of D-mannitol with acetone gives the diol **J**, while reaction with aldehydes, formaldehyde or benzaldehyde, gives the diol **L**. The



Scheme 10 General procedures of synthesis of C_2 symmetric ligands.

tri-isopropylidene derivative can be obtained by forcing the reaction conditions with acetone. Selective hydrolysis leads to tetrol **K**. Intermediates **J–L** are transformed into diols the **N–Q**, which are precursors for the formation of the ligands using common procedures (see below). Deoxygenation of hydroxylic functions in **J** gives **M**, from which **N** is obtained by selective protection of primary hydroxyl groups. Mesylation of the free hydroxyl groups and reaction with 1,2-diphosphinobenzene or 1,2-diphosphinoethane gives the diphospholanes **45** and **46**, in which the configuration at the hydroxylic positions has been inverted.

The diol **Q** was obtained from **K** by selective tosylation of the primary hydroxyls, treatment in basic medium to give a diepoxide, and reduction with $LiEt_3BH$. Similarly, the diol **R** was obtained from **K** by selective benzoylation of primary hydroxyls, tosylation of the secondary hydroxyls and treatment in basic medium to give a diepoxide whose configuration of the stereogenic centers in the epoxide was opposite to that obtained previously. Further reaction with $LiEt_3BH$ gives **R**. The diol **Q** can be transformed into the dimesylate or the sulfate, from which the diphospholane derivatives **43**, **44**, **47**, **48** and **55** were obtained in a similar way to **45** and **46**. The diphosphines **53** and **56** were obtained from the diol **R** *via* the dimesylate by reaction with $LiPPh_2$. The ethyl derivative **54** was synthesised by the opening of the diepoxide with a methylcuprate, and using a procedure similar to that used in the synthesis of **53**.

Diphosphinites **57** were prepared from diols **S**, which were obtained from glucosamine through a ring contraction reaction induced by $NaNO_2$, reduction of resulting aldehyde and selective protection of the primary hydroxy groups. Similarly, the diols **58** were prepared from glucitol by dehydration in acid medium, recovery of the suitable tetrol by formation of the di-isopropylidene derivative, hydrolysis and protection of the primary hydroxyl groups.

4. Conclusion

In conclusion, a large number of phosphorus based ligands with different backbones have been obtained from carbohydrates in enantiomerically pure form. These ligands have been successfully used in several transition metal catalyzed reactions. Some of the advantages of using carbohydrates as the chiral pool to obtain enantiopure chiral ligands are the following:

•Carbohydrates are mainly C_1-symmetric compounds and consequently C_1-symmetric ligands can be easily obtained. However, D-mannitol is a C_2-symmetric carbohydrate that has allowed the synthesis of numerous C_2-symmetric ligands.

•The availability of various protection procedures means that many different structures can be obtained by simply selecting the appropriate protecting groups. For instance, ligands **6** and **37** can both be obtained from D-glucose in a straightforward manner, or the diphospholane derivatives **41–47** and ligands **49–56**, which were all obtained from D-mannitol.

•The size of the chelate ring with the metal can also be selected by varying the protecting group. See for instance ligands **49–51** or ligands **6** and **37**, and the strong influence that this has on the enantioselective hydroformylation.

•Protecting groups can also be used to tune the behaviour of the ligand in the enantioinduction. See for instance the variation in the results obtained with ligand **6** in the Rh-catalyzed asymmetric hydrogenation, when R′ = Me or Ph.

•The hydroxylic groups in these compounds enable us to introduce phosphorus functions, particularly phosphinites and phosphites can be easily obtained. These allow the electronic (see ligands **6** and **29**) and steric (see ligand **37**) properties of the resulting ligands to be easily tuned. This feature also holds for other diols used as starting materials.

•The high number of stereogenic centers in carbohydrates allows their use in order to obtain analogues of well-know ligands with increased efficiency. For instance, DIOP analogues **53–56**, DUPHOS analogues **41–47**, and gluco-furanoside derivatives **37–40** when compared to the xylose derivatives **35** and **36**, or of the gluco-pyranoside **6** when compared to the ligand **12**.

•Because only two hydroxylic groups are usually bonded to the coordinating phosphorus atoms, the presence of additional hydroxylic groups may facilitate the solubilisation in water. Although there are still many problems for generalising the use of water-soluble ligands derived from carbohydrates in catalysis, the results obtained with the catalytic systems **17** and Rh/**45a** are particularly promising.

The main drawbacks of carbohydrates-based ligands are:

•As often happens with molecules of nature's chiral pool, only one enantiomer is available. This can be partially overcome by considering the relative configuration of the various stereogenic centers in the molecule. See for instance the pairs of ligands **6/9**, **11/12**, **35/36** or **37/38**, which behave like

pseudoenantiomers, although the enantioselectivity is not identical for each pseudoenantiomer.

•Some of the ligands often require long synthetic sequences.

Carbohydrates are cheap and readily available starting materials for the synthesis of enantiopure chiral ligands. Carbohydrate chemistry is well developed and for years to come, it will provide researchers with many more unexplored structures for the preparation of new ligands; as is the case for example for example of natural sugars that contain nitrogen, which have scarcely been studied. In spite of the enormous progress in the last decade as reported above, it is expected that the near future will bring considerable contributions to the field of asymmetric catalysis based on the use of new carbohydrate-based chiral ligands.

Acknowledgements

We thank Prof. P. W. M. N van Leeuwen for interesting suggestions and Dr. C. Godard for the careful reading of the manuscript.

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