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Review

# Carbohydrates as building blocks of privileged ligands

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ABSTRACT

"Privileged ligands" are chiral auxiliaries of wide applicability in asymmetric catalysis. In the previous decades, their effective three-dimensional structures have often been reproduced by using building blocks from a "chiral pool", such as the carbohydrates. This strategy has provided unique ligand moieties which combine the performance of "privileged ligands" with increased flexibility and accessibility. This review gives an overview of the research within this field, giving emphasis to the best results obtained with each ligand type.



## 1. Introduction

The fascinating chemistry of life is based upon asymmetric interactions, which occur through chiral recognition. Hence, a wide number of biologically active molecules, such as aminoacids, carbohydrates and vitamins, exists as a single enantiomer. The same concept holds true for important manufactured products, such as pharmaceuticals, agrochemicals, flavours and fragrances.

Since only one enantiomer has the desired biological property, recent regulations demand the production of the only active enantiomer, strongly disfavouring commercialisation of racemates.

Four general approaches (Fig. 1) are commonly pursued for producing enantiopure compounds, and all of them are based upon the consideration that chiral compounds can be artificially produced only in the presence of another chiral agent [1].

Three strategies, namely (i) the resolution of enantiomers through diastereomeric separation, (ii) the use of natural molecules as chiral building blocks, and (iii) enantioselective synthesis via chiral auxiliaries, usually require large use of solvents and several steps, leading to the formation of by-products, and, in general, undesired consumption of resources.

The fourth approach, the *enantioselective catalysis*, is the most effective one. In this case, the great benefit is that control of stereochemistry requires a little quantity of a chiral catalyst, which can be either of natural origin (*bio-catalysts*) or synthetic (*chemo-catalysts*). The former are active and selective, but extensive application in production is often hindered by their costs.

Over the years, *homogeneous chemo-catalysts* based on metal centres dressed with suitable chiral ligands have attracted increasing academic and industrial interest because relevant reaction

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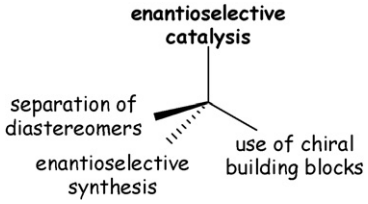



**Fig. 1.** Strategies for the synthesis of chiral molecules.

parameters, such as activity, selectivity and catalyst life can often be rationally optimised [2].

Therefore, *homogeneous enantioselective catalysis* is today a fundamental technology for the production of fine chemicals.

Beside the choice of the active metal, crucial for its effective application, is the accurate design of the chiral ligand, which must possess a well-defined three-dimensional structure, capable of directing the stereochemistry of the reaction. For this reason, in 2003, Jacobsen coined the appealing term "privileged", for the selection of a few ligands of broad applicability, used on a regular basis for the synthesis of chiral molecules, and for discovering new enantioselective processes [3] (in brackets, Fig. 2). The original class of "privileged" ligands has gradually been extended to several other efficient structures, and in 2008 Aldrich Chemical Company has catalogued those shown in Fig. 2 [4].

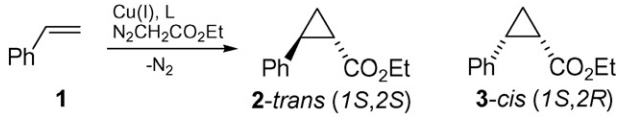
At the same time, several research groups demonstrated that highly performing ligands can be attained by simple modification of molecules from the *natural chiral pool*, such as carbohydrates [5]. This strategy is based upon the assumption that sugars are both abundant (therefore easily available) and "naturally chiral", which avoids the complicated resolution of racemates. Furthermore, carbohydrates are highly functionalised and their chemistry is extremely well developed. This latter feature is particularly attractive because modular ligands with similar structural motifs can be created, thus making possible the generation of libraries.

This strategy is expected to be especially productive when carbohydrates are used as building blocks of "privileged" ligands, aiming to amplify the scope of their application. The introduction of privileged moieties into a sugar backbone promises to afford unique ligand structures, which combine efficiency with convenience and flexibility [6]. This has been demonstrated on several occasions, and, today many "privileged" ligands of Fig. 2 do possess a corresponding sugar version.

Given this premise, this review aims to give an overview of the synthesis and the use in asymmetric catalysis of *carbohydrate-based ligands, which reproduce the structural and the stereochemical coordination motifs of privileged ligands*. We underline that the scope of the review is limited to the "privileged" ligands collected in Fig. 2. Hence, many effective ligands based on carbohydrates will therefore not be included in this review because they do not match this strict feature. However, other recent reviews [5] cover recent advances in the field of sugar-based ligands, though none of them is focussed on the specific profile herein presented.

## 2. Carbohydrates as building blocks of privileged ligands

The following paragraphs describe "privileged ligands" based on carbohydrate scaffolds. They are listed according to the alphabetical order of the original "privileged ligands" described by Jacobsen (in brackets in Fig. 2), along with structurally similar molecules. For example, the review starts with "BOX" type ligands, which will be followed by the related PHOX and PYBOX structural types. "Privileged ligands" of second generation are described thereafter.




**Scheme 1.** Asymmetric cyclopropanation of styrene **1** catalysed by Cu complexes of BOX type ligands.

### 2.1. BOX type ligands

The extreme versatility of bisoxazolines (BOX) is well documented [4]. This class of ligands was reproduced (**L1**–**L11** in Fig. 3) by using a glucose scaffold [7–9].

Structures **L1**–**L4** were found in a twist-like conformation while the benzylidene derivatives **L5**–**L11** adopt the alternative chair-like geometry. The latter were prepared with a wide range of functional groups in the crucial 3-*O* position.

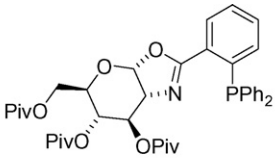
All the ligands were assessed in the cyclopropanation of styrene **1** promoted by Cu(I) (Scheme 1).

Within the family **L5**–**L11**, the enantioselectivity was found to be significantly dependent upon the electronic features and, mostly, the steric hindrance of the 3-*O* substituent, *i.e.* increase of hindrance had a detrimental effect on the ee's, and acyl groups were more effective than alkyls. Thus, in the presence of **L6** the cyclic products **2** and **3** (*cis*:*trans* 21:79) were obtained, respectively, in 82 and 93% ee.

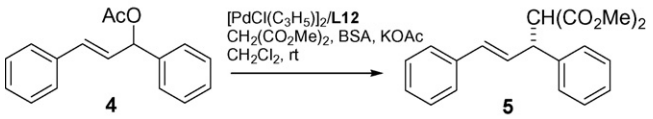
However, steric effects could be overlaid by conformational effects, and another beneficial combination was achieved when the bulky pivaloyl groups were introduced in a twist-like conformed ligand (**L3**). In this case, products **2** and **3** were isolated in 94 and 84% ee.

### 2.2. PHOX type ligands

Phosphinooxazolines (PHOX) are highly flexible ligands of $C_1$ symmetry, successfully used in several metal-catalysed reactions [4]. The sugar based PHOX derivative **L12** was obtained from *N*-acetylglucosamine [10]. Its use in the prototypical Pd-catalysed enantioselective allylation of dimethylmalonate afforded the product (R)-**5** in 98% ee (Scheme 2).




**L12**




**Scheme 2.** Asymmetric allylic alkylation of 1,3-diphenylpropenylacetate **4** catalysed by the Pd complex of **L12**.

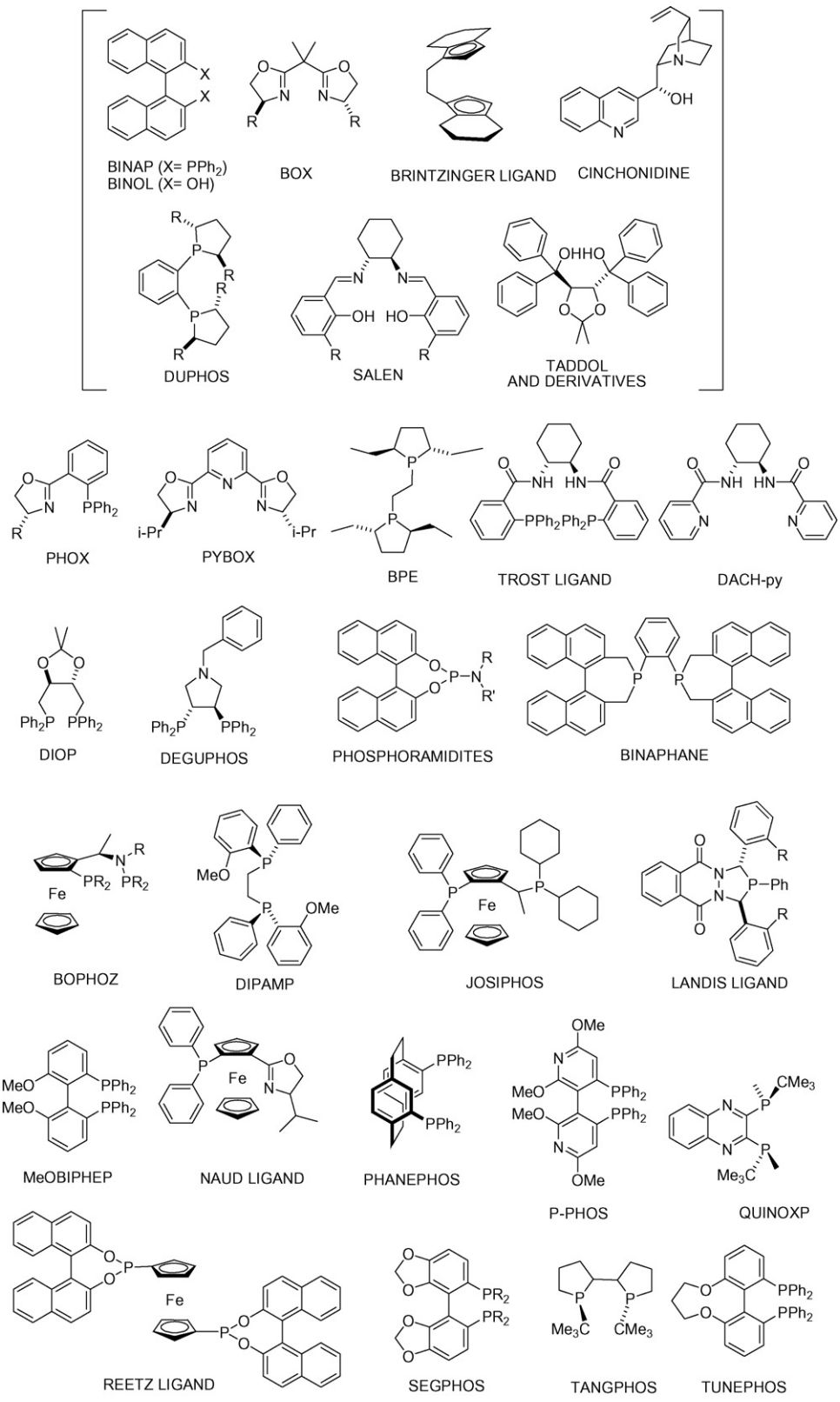



**Fig. 2.** The privileged ligands according to Ref. [4].

### 2.3. PYBOX type ligands

This important family of tridentate ligands has very recently been implemented with a carbohydrate version. Ligand **L13** (Fig. 4) was obtained in simple steps from glucosamine [11a].

Application of **L13** in the copper-catalysed enantioselective alkynylation of imines (*e.g.* **6**) led to the product **7** with ee's up to 99% (Scheme 3).

A thiooxazoline version of **L13** was proposed by the same authors [11b]. Its use in the cyclopropanation of styrenes

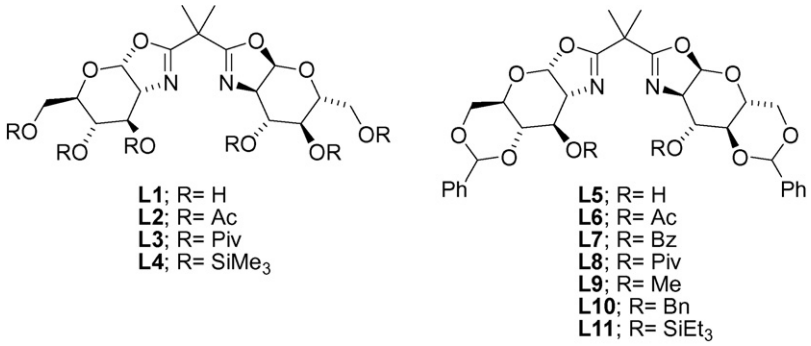



**Fig. 3.** BOX type ligands.

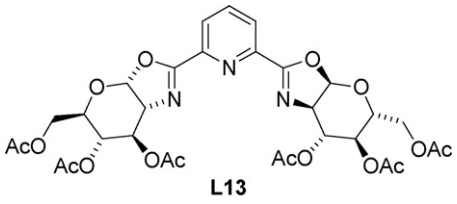
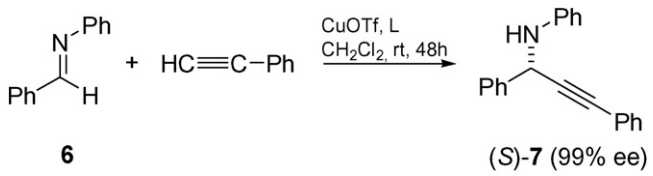
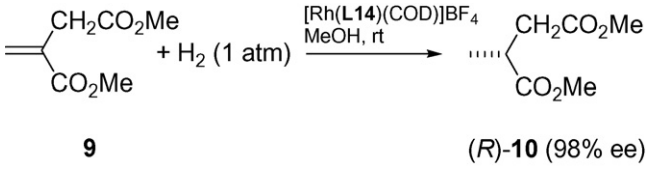


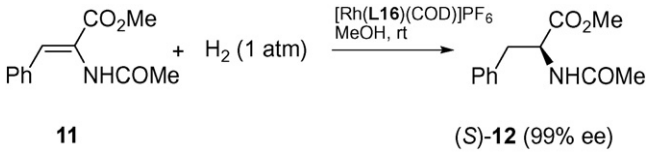

**Fig. 4.** PYBOX type ligand.




**Scheme 3.** Asymmetric alkynylation of imine **6** catalysed by the Cu complex of **L13**.




**Scheme 5.** Asymmetric hydrogenation of the dimethyl ester of itaconic acid **9** catalysed by the Rh complex of **L14**.




**Scheme 6.** Asymmetric hydrogenation of the methyl ester of *Z*-acetammidocinnamic **11** catalysed by the Rh complex of **L16**.

(Scheme 1) was less fruitful, leading to a product with moderate ee's.

### 2.4. DUPHOS type ligand

This remarkable class of privileged ligands has received notable attention during the last two decades [4]. Two sugar versions of DUPHOS are identified, the classes of ligands known as ROPHOS and BASPHOS [12], both using D-mannitol (**8**) as carbohydrate source (Scheme 4).

The ligands are advanced versions of DUPHOS aimed at (i) displaying additional hemilabile coordinating ability, (ii) introducing a secondary interaction site with the substrate, (iii) helping solubility in water of the catalyst and (iv) generally improving the flexibility of the chiral structure [13,14].

Although both ligand types were originally prepared by the same group [14,15], other authors [13] have simultaneously compared their use and performance in catalysis. For sake of clarity the two classes will be discussed separately.

The first reported example of a ROPHOS type ligand was **L14** in Fig. 5 [15].

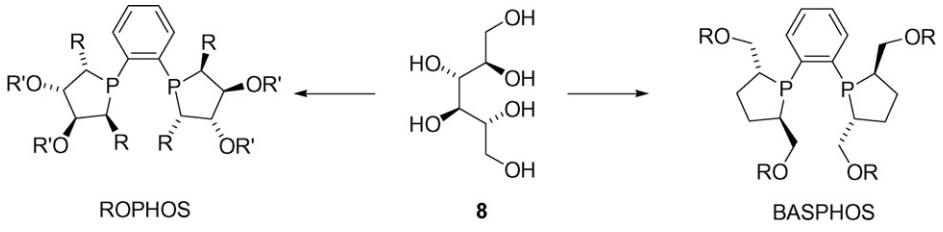
Ligand **L14** was assessed [15] in the rhodium catalysed hydrogenation of functionalised alkenes with excellent results (*e.g.* as illustrated for the dimethyl ester of itaconic acid **9** in Scheme 5).

Deprotected versions of **L14** were subsequently prepared through a simplified synthetic procedure (**L15** and **L16** in Fig. 5), and examined along with their parent compounds **L20** and **L21** in the enantioselective hydrogenation of dehydroaminoacids and esters (*e.g.* **11** in Scheme 6) [16]. High enantioselectivities (up to >99% ee) were reported for **L15** and **L16**.

Rhodium complexes of the same ligands were used [16] in water to hydrogenate itaconic acid derivatives without decrease of enantiomeric excess (Scheme 7).

Another independent report simultaneously described a synthetic strategy for the synthesis of **L20** and its diastereomeric form **L22** (Fig. 5) where the configurations at C2 and C5 are inverted [17].

The two ligands were successfully examined as chiral auxiliaries in the Pd-catalysed asymmetric allylation reaction described by Scheme 2 [18]. The enantioselectivity depended mainly on the




**Scheme 4.** The structure of D-mannitol **8**, the precursor of ROPHOS and BASPHOS.

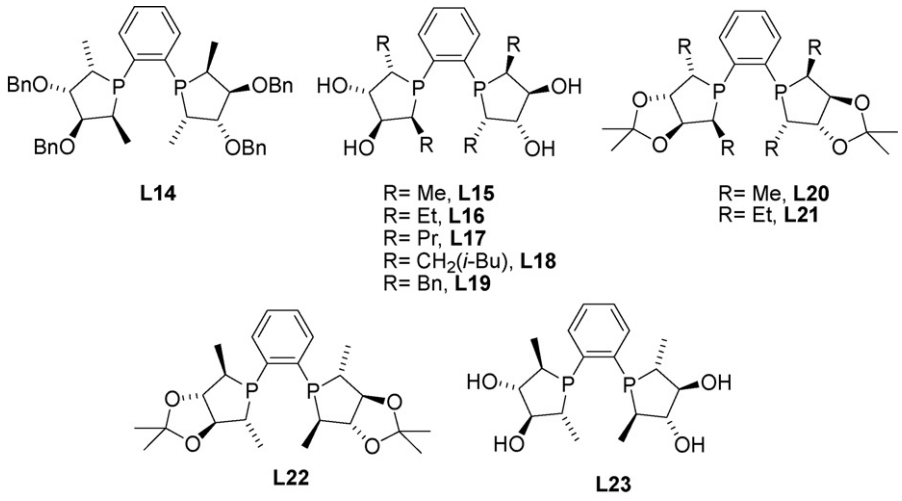
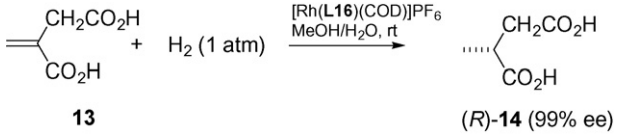



**Fig. 5.** ROPHOS type ligands.




**Scheme 7.** Asymmetric hydrogenation of itaconic acid **13** catalysed by the Rh complex of **L16**.

absolute stereochemistry of the P-carrying carbon atoms, and, remarkably, the two ligands induced preferential formation of the opposite enantiomers of **5**, *i.e.* up to 94% of *S* configuration for **L22**, and up to 99% of the *R*-product with **L20**. The same authors reported an improved synthesis of the hydroxospecies **L15** and **L16** along with the diastereomeric form **L23** (Fig. 5) [19].

Contrary to an earlier report [16], the isopropylidene derivatives **L20**, along with **L22**, were excellent ligands for the Rh-catalysed asymmetric hydrogenation of dehydroaminoacids. As expected, the two ligands gave opposite selectivity. Notably, the deprotected ligands **L15** and **L23** allowed one to perform the same reaction under aqueous biphasic conditions. For instance, the rhodium catalyst [Rh(**L23**)(COD)]$BF_4$ was re-cycled four times without loss of activity (100% conversion) and enantioselectivity (90%).

A more systematic study of both diastereomers **L20** and **L22** in the rhodium catalysed asymmetric hydrogenation of different kinds of unsaturated compounds was reported later [20].

Ligands with longer chains at C2 and C5 were also prepared (**L17**, **L18** and **L19** in Fig. 5) [21]. They were also effective in the Rh-catalysed enantioselective hydrogenation of acetamidocinnamic and itaconic acids mentioned above, with ee's up to 99%. The determination of the X-ray crystal structure of the complex [$PdCl_2$(**L20**)] disclosed the $C_2$ symmetry adopted by the coordinated ligand, and its spatial orientation was correlated to the outcomes of catalytic experiments.

BASPHOS ligand **L24** (Fig. 6) was not isolated, and was prepared through a convenient procedure involving the use of the metal centre as a protector group [14].

In this way the pre-catalyst [Rh(**L24**)(COD)]$BF_4$ was obtained and tested in the hydrogenation of 2-acetamido acrylic acid **15** and its methyl ester **16**, in water as solvent (Scheme 8). Excellent enantioselectivity was achieved in both cases.

This reaction was later more deeply investigated [19] by using [Rh(**L24**)(NBD)]$SbF_6$ as pre-catalyst. The catalyst was re-cycled four times, and in the sequential runs 99% ee and 100% conversions were obtained. This work also describes a synthetic strategy for

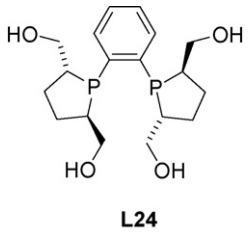
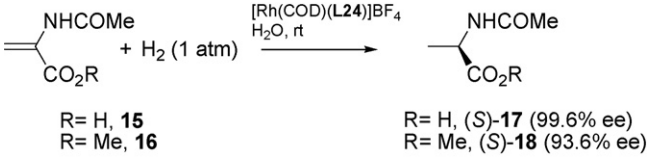



**Fig. 6.** BASPHOS type ligand **L24**.




**Scheme 8.** Asymmetric hydrogenation of 2-acetamidoacrylic acid **15** and its methyl ester **16** catalysed by the Rh complex of **L24**.

the isolation of **L24**, which previously [19] was attained only upon coordination to the metal centre.

The three BASPHOS type ligands **L25**–**L27** (Fig. 7) were then assessed in the hydrogenation of acetamidocinnamic or itaconic acids and their esters, and their performance was compared to that of **L24** and of the original DUPHOS molecule [22].

The enantioselectivity of the reaction spanned from 8 to 99% ee, with the best results obtained with **L27**. This means that, in comparison to DUPHOS molecule, the 2,5-dioxy functionalisation of BASPHOS ligands affects the enantiofacial discriminating prop-

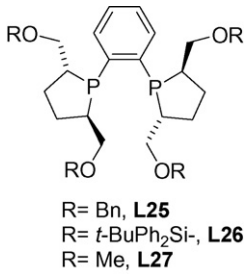



**Fig. 7.** BASPHOS type ligands **L25**–**L27**.

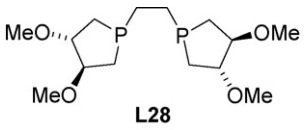



**Fig. 8.** BPE type ligand **L28**.

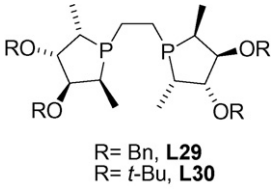



**Fig. 9.** BPE type ligands **L29**–**L30**.

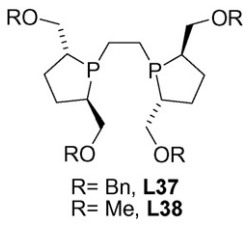
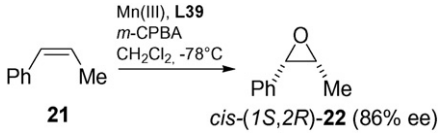



**Fig. 11.** BPE type ligands **L37**–**L38**.




**Scheme 10.** Asymmetric epoxidation of *cis*-β-methylstyrene **21** catalysed by the Mn complex of **L39**.

erties more than simple alkyl groups, making the catalyst more sensitive to changes in the geometry of the prochiral alkene.

Detailed kinetic studies on the hydrogenation of 3-acetoamidobutenoates by rhodium complexes bearing several diphosphines also demonstrated that the presence of oxymethyl functions in ligand **L27** significantly slow the hydrogenation of the *E*-substrate with respect to Et-DUPHOS [23,24].

Excellent enantioselectivity was achieved also in another catalytic reaction, *i.e.* the ruthenium catalysed hydrogenation of β-oxocarboxylates (**19** in Scheme 9) [22].

Use of this large bouquet of BASPHOS ligands in both Rh [25] and Ru [26,27] catalysed hydrogenations was the object of patents over the years.

### 2.5. BPE type ligands

The privileged BPE ligand, the aliphatic counterpart of DUPHOS, is also a very effective ancillary ligand for asymmetric catalysis [4]. The first sugar version was **L28** in Fig. 8, derived from tartaric acid [28]. The corresponding rhodium complexes were tested in the hydrogenation α-acetammidocynnamic acid and afforded the corresponding aminoacid with poor enantioselectivity.

Lately, this seminal approach inspired the synthesis of the improved versions **L29** and **L30** (Fig. 9) from D-mannitol **8**, which were presented along with ROPHOS **L14** and similarly show the oxo groups at C3 and C4 [15]. Their use in the asymmetric hydrogenation of functionalised alkenes provided the product with high enantioselectivity, *e.g.* compound **10** was isolated in 98.9 and 99.1% ee, respectively, with **L29** and **L30**.

This version of the ligand was further refined, and the following modifications **L31**–L**36** [29,30] were very efficiently used for hydrogenating dehydroaminoacids (Fig. 10).

The oxo-functionalisation was also placed at C2 and C5 positions (**L37** and **L38** in Fig. 11) in close analogy with BASPHOS ligands **L25** and **L27** [22]. However, they showed reduced enantiodiscriminating properties in comparison with these latter ligands, plausibly due to the more flexible ethylene bridge between the two phosphorus atoms.

### 2.6. SALEN type ligands

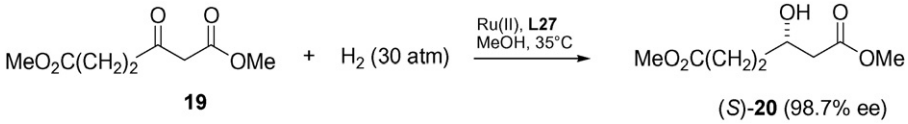
Since the early reports of Jacobsen and Katsuki on the asymmetric epoxidation of alkenes promoted by Mn, complexes containing salen ligands have found increasing application in enantioselective catalysis [4].

The corresponding sugar versions (**L39** and **L40**, Fig. 12) were prepared by using suitable 2,3-D-glucodiamines and 2,3-D-mannodiamines as building blocks.

Cationic and neutral manganese(III) complexes of both deprotonated ligands were prepared [31].

The glucose-based complexes catalysed the epoxidation of *cis*-β-methylstyrene **21** by using *m*-chloroperbenzoic acid (Scheme 10) affording the *cis* epoxide **22** as the major product (*cis*/*trans* 95/5), with high conversions (up to 99% within 30′) and good ee's (86%).

On the other hand, mannose derivatives gave lower conversion yields (up to 59% within 180′), reduced *cis*/*trans* ratio (80/20) and




**Scheme 9.** Asymmetric hydrogenation of the β-oxocarboxylate **19** catalysed by the Ru complex of **L27**.

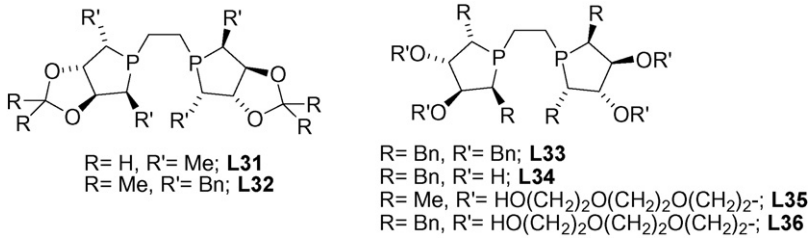



**Fig. 10.** BPE type ligands **L31**–**L36**.

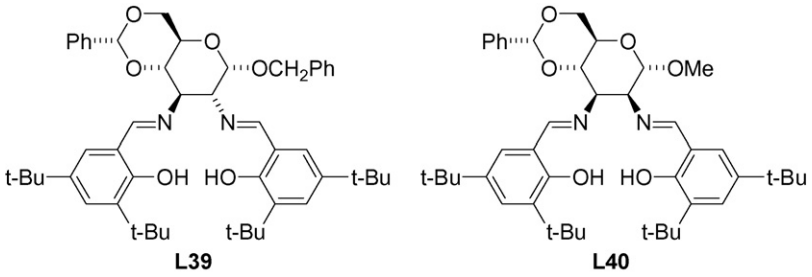



**Fig. 12.** SALEN type ligands.

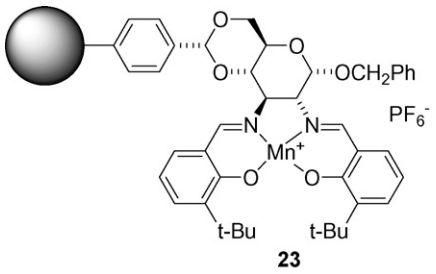



**Fig. 13.** The supported catalyst **23**.

poor enantioselectivity (ee up to 50%). Furthermore, mannose ligands induced opposite selectivity with respect to the corresponding glucose ligands. These differences were explained in terms of the different local geometry imposed by the ligands (pseudo-$C_2$ for **L39** and pseudo-$C_s$ for **L40**) around the metal centre.

Aiming to help the re-cycling of the catalyst, the Mn glucose complex was anchored to a Stratosphere-CHO resin by employing ring positions not involved in coordination, *i.e.* C4 and C6 in Fig. 13 [32].

The supported catalyst **23**, which contained 0.16–0.18 mmol of Mn per gram, was examined in the asymmetric epoxidation of *cis*-β-methylstyrene by using four oxidants, namely *m*-chloroperbenzoic acid, $H_2O_2$, NaClO and ($n$-$Bu_4N$)$HSO_5$, with a substrate:catalyst ratio of 25:1. Significant leak of metal from the matrix occurred during its use, which prevented efficient re-cycling of the catalyst. This was ascribed to the cleavage of the benzylidene ring under the severe oxidation conditions.

Ligand **L39** was also used [33] for inducing enantioselectivity in a yttrium promoted *trans*-acylation between enolesters and chiral secondary alcohols, in comparison with other salen-type ligands. Product **25** was obtained in enantiomeric excess of 61% in reaction of Scheme 11.

### 2.7. TROST type ligands

The TROST ligand is a powerful chiral auxiliary [4], especially in asymmetric allylic alkylations for the enantioselective formation of C—C, C—O, C—S and C—N bonds.

Three different sugar versions of the ligand were prepared over the years, with the aim of both reproducing the high performance of the original Trost ligand and optimising the synthetic procedure. The following main structural types can thus be recognised (**L41**–**L42**, **L43**–**L45** and **L46** in Fig. 14).

Early studies [34] led to the synthesis of the bis(phosphinoamides) **L41** and **L42**, obtained by condensation of the 2,3-diamino precursors with 2-diphenylphosphinobenzoic acid. The ligands were examined in the Pd-catalysed asymmetric desymmetrization of *meso*-2-cyclopenten-1,4-diol biscarbamate **26** (Scheme 12).

Bis(phosphinoamides) yielded the product **27** with high ee's (up to 97%), and, remarkably, with opposite enantioselectivity according to the nature of the sugar (*R*,*S* with **L41** and *S*,*R* with **L42**). Nevertheless, their multi-step synthesis does not encourage their use, and, hence, the corresponding bis(phosphinoesters) **L43**–**L45** were alternatively selected [35], since they are immediately available from commercial sources. Unfortunately, their activity was less satisfying, because the ee of the product did not exceed 82%.

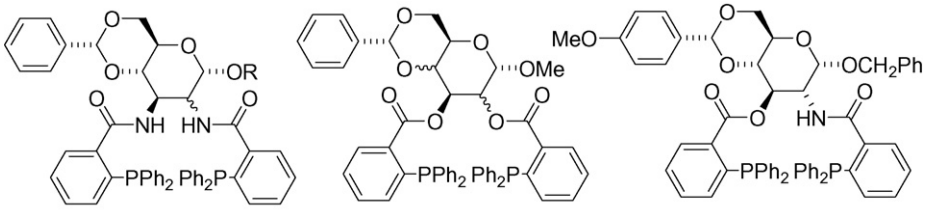
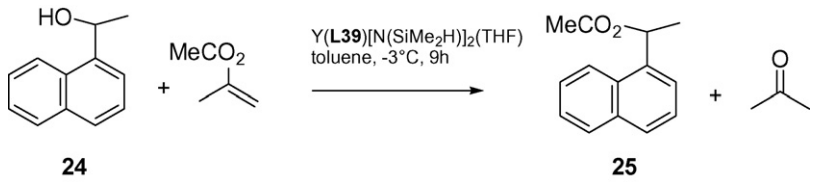
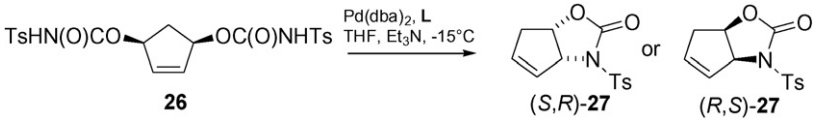



**Fig. 14.** TROST type ligands **L41**–**L46**.

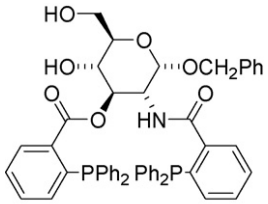



**Scheme 11.** Asymmetric acylation 1-(1-hydroxyethyl)-naphthalene **24** catalysed by the Y complex of **L39**.



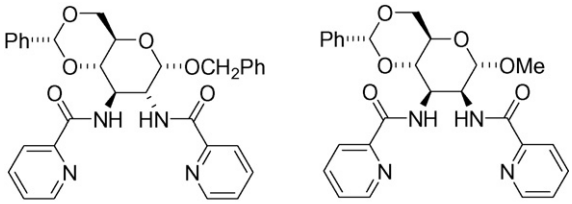

26 (S,R)-27 (R,S)-27

**Scheme 12.** Asymmetric desymmetrization of the bis(carbamate) of *meso*-2-cyclopenten-1,4-diol **26** catalysed by Pd complexes of TROST type ligands.




**L47**

**Fig. 15.** TROST type ligand **L47**.




**L48** **L49**

**Fig. 16.** DACH-py type ligands.

Synthetic convenience and high catalytic performance were obtained by preparing the mixed (phosphinoamide–phosphinoester) ligand **L46** [36]. In fact, the synthesis requires only four simple steps from inexpensive N-acetylglucosamine, and the corresponding Pd complex was as active as the one containing the analogous bis(phosphinoamide) **L41** (ee of up to 98%).

By simple treatment with formic acid the de-protected version **L47** was obtained (Fig. 15).

Its polarity was exploited [36] for application in *biphasic homogeneous catalysis* [6]. In fact, differently from the original Trost ligand, the presence of free hydroxyls resulted in prompt dissolution of **L47** (and of the corresponding Pd complex) in the ionic liquid BMIM[$BF_4$] (1-butyl-3-methylimidazolium tetrafluoroborate). Catalysis of Scheme 12 was performed by adding the substrate and triethylamine to a solution of the catalyst in this solvent at 298 K. After 30 min the organic product was extracted with diethyl ether, while the catalyst phase was re-cycled for further runs. The first four cycles shown high reproducibility, giving elevated conversion (99%) and similar enantioselectivities (ca. 55% ee). This was lower than that observed by using **L46** in traditional homogeneous solution, a result which was explained in terms of the different polarity between THF and the ionic liquid.

Ligand **L46** was also effectively used in another enantioselective reaction, *i.e.* in the copper(I) catalysed 1,4-addition of $ZnR_2$ to linear aliphatic enones (87–95% ee) [37]. A representative reaction is reported in Scheme 13.

Under the same reaction conditions the original Trost ligands were ineffective. This suggests that **L46** acts as a polyfunctional ligands, allowing the simultaneous coordination of the copper catalyst (via phosphorus) and the zinc nucleophile (via oxygen), as found in related architectures [38].

### 2.8. DACH-py type ligands

DACH-py ligands find their most effective application in the enantioselective allylic alkylation promoted by Mo complexes [4]. This reaction is complementary to that promoted by Pd catalysts, because Mo usually favours the attack on the substituted carbon atom of the allyl moiety, thus promoting the formation of chiral branched products.

The corresponding sugar versions (**L48** and **L49**, Fig. 16) were conveniently prepared from 2,3-D-glucodiamine and 2,3-D-mannodiammine [39].

The ligands were assessed in molybdenum-catalysed asymmetric allylic alkylations using both (*E*)-3-phenyl-2-propenyl (**30**) and *rac*-1-phenyl-2-propenyl methyl carbonates (**31**) and dimethyl malonate as nucleophile under microwave irradiation (Scheme 14).

High enantioselectivity (99% ee, *R*) and high regioselectivity (49/1 in favour of the branched isomer **32**) were observed in reactions of the linear substrate **30** in the presence of 10 mol% of a catalyst prepared from **L48**. Somewhat lower enantioselectivity (up to 96% ee) was obtained from the branched racemic carbonate **31** using the same ligand.

On the other hand, mannose ligand **L49** was less effective, and promoted formation of the opposite enantiomer in lower ee.

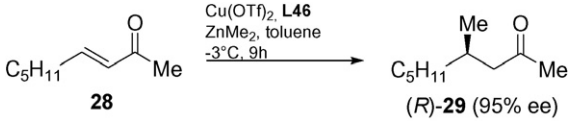
### 2.9. DEGUPHOS type ligands

This classical ligand belongs to the wide family of chiral structures known as catASium [4]. The distinctive structural feature is the presence of the coordinating functions $-PPh_2$ in the *trans* vicinal positions of a five-member ring originating from tartaric acid. A large class of related ligands derived from arabinitol has been patented [40] (*e.g.* **L50** in Fig. 17).

### 2.10. DIOP type ligands

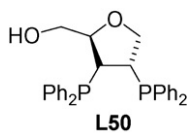
The distinguished architecture of the pioneering DIOP ligand [4] also presents the coordinating functions ($-CH_2PPh_2$) in the *trans* adjacent positions of a five-member ring obtained from tartaric acid.

Within this review, only ligands displaying this privileged moiety will be described, although sugar rings with a larger number of atoms have also been employed for producing related effective ligands [41].



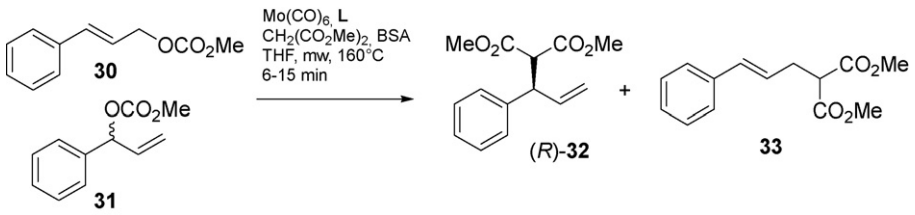

28 (*R*)-**29** (95% ee)

**Scheme 13.** Asymmetric 1,4-addition of dimethylzinc to *E*-non-3-en-2-one **28** catalysed by the Cu complex of **L46**.

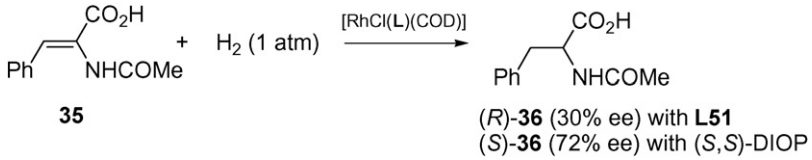



**L50**

**Fig. 17.** DEGUPHOS type ligand.




**Scheme 14.** Asymmetric allylic alkylation of *E*-3-phenyl-2-propenyl methylcarbonate **30** and *rac*-1-phenyl-2-propenyl methylcarbonate **31** catalysed by Mo complexes of DACH-py type ligands.




**Scheme 15.** Asymmetric hydrogenation of *Z*-acetamidocinnamic acid **35** catalysed by Rh complexes of **L51** and (*S*,*S*)-DIOP.

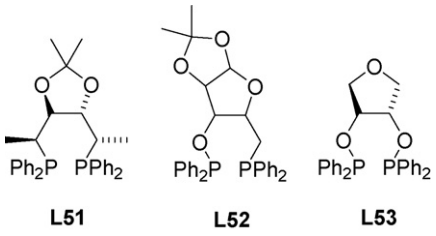



**Fig. 18.** DIOP type ligands **L51**–**L53**.

The first reported modification of DIOP was **L51**, in which new chiral centres adjacent to the phosphorus atoms were introduced by using D-mannitol (**8**) as building block [42].

The ligand was screened in some test-reactions, namely the reduction of C=C double bonds (Scheme 15) and the hydrosilylation of acetophenone. Although **L51** was somewhat less effective than the original DIOP, an interesting effect of the two new stereogenic centres on the reactivity pattern was disclosed. Thus, **L51** promoted preferential formation of the same enantiomer as (*S*,*S*)-DIOP in the hydrogenation of **15** to give **17** (*S*), while the selectivity of the two ligands was opposite when **35** was used as substrate (Scheme 15).

Lately, ligand **L52** (Fig. 18) was prepared from xylose and used in the same hydrogenation reaction with moderate results [43]. The DIOP version **L53** was prepared from (*R*,*R*)-tartaric acid in a few simple steps, and again examined in the Rh-catalysed hydrogenation of functionalised alkenes, though with poor selectivity [44].

Several carbohydrate-based DIOP ligands with the general structure **L54** (Fig. 19) were prepared from α-D-fructose, which showed similar steric hindrance, while the electronic properties were systematically varied (X, Y=H, 3,5-$(CF_3)_2$, 3,5-$Me_2$, 4-MeO, 3,5-$F_2$) [45].

Use of the ligands in the asymmetric hydrocyanation of 6-methoxy-2-vinylnaphthalene **37** (Scheme 16) afforded the product with unprecedented enantioselectivity (Scheme 16).

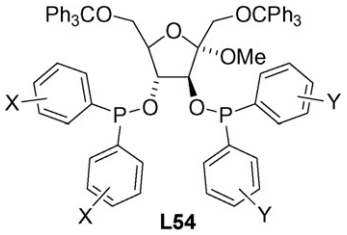
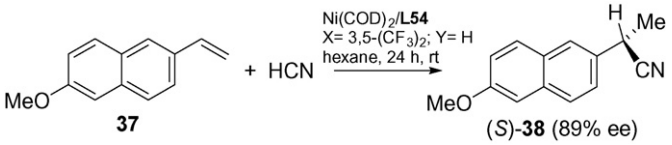



**Fig. 19.** DIOP type ligands **L54**.




**Scheme 16.** Asymmetric hydrocyanation of 6-methoxy-2-vinyl-naphthalene **37** catalysed by the Ni complexes of **L54**.

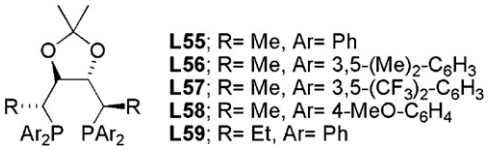


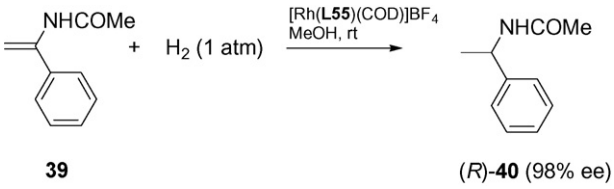

**Fig. 20.** DIOP type ligands **L55**–**L59**.

The diastereomeric version of **L51** (**L55** in Fig. 20) was then independently prepared from D-mannitol **8** by two research groups [18,46]. This ligand was first examined, along with DIOP, **L51** and ROPHOS ligands, in the asymmetric allylic alkylation of Scheme 2 with moderate results [18].

Better results were instead achieved in the asymmetric reduction of several functionalised alkenes, which afforded the products in high ee's (*e.g.* as in Scheme 17) [46,47].

Poorer results were instead obtained by using **L51**. Both groups interpreted this evidence on the grounds of the geometry of the chelate ring in the ground-state conformation of the pre-catalyst. This is stable when the two methyl groups are in an equatorial position, as with **L55**, and is destabilised when they are axially orientated, as in the case of **L51**, possibly resulting in the intervention of other conformations.

The same reaction was examined by using functionalised versions of **L55**, in which the electronic properties were widely varied by using diverse aryl substituents (**L56**–**L59** in Fig. 20) [47]. In




**Scheme 17.** Asymmetric hydrogenation of *N*-(1-phenylvinyl)acetamide **39** catalysed by the Rh complex of **L55**.

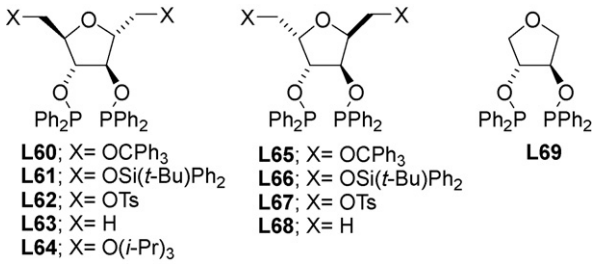
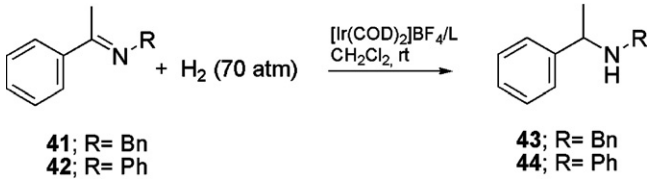



**Fig. 21.** DIOP type ligands **L60**–**L69**.




**Scheme 18.** Asymmetric hydrogenation of imines **41** and **42** catalysed by Ir complexes of **L70**–**L75**.

all cases, the electron rich ligands **L56**, **L58** and **L59** gave quantitative yields and high enantioselectivities, while **L57** afforded systematically the product in nearly racemic form. This detriment of enantioselectivity disclosed the dramatic importance of the electronic features of the chiral ligand.

Another ample family of ligands with a DIOP-like structure was prepared from D-glucosamine and D-glucitol (**L60**–**L69** in Fig. 21) [48]. The straightforward synthetic procedure allowed one to control the configuration in positions 2 and 5, and to introduce different substituents. Ligand **L69**, enantiomer of **L53**, was prepared for assessing the performance of a ligand with the stereochemistry at C3 and C4 as in **L60**–**L68**, but lacking chirality at C2 and C5.

The ligands were studied in the rhodium-catalysed hydrogenation of **9** (Scheme 5), **11** (Scheme 6) and **16** (Scheme 8) under different conditions of pressure and temperatures. In all cases, **L69** afforded the products in poor enantioselectivity.

In the hydrogenation of **11** and **16** the configuration of the main enantiomer (*R*) was determined by that of C3 and C4, which support the coordinating arms. The remote stereogenic centres at C2 and C5 had a matching effect in the case of ligands **L60**–**L64** (ee up to 93%), while their action was detrimental for **L65**–**L68**. An effect of the nature of the substituents at C2 and C5 on the enantioselectivity was also disclosed. On the other hand, configuration at C2 and C5 drove the enantioselectivity in the hydrogenation of **9**, which was prevalently obtained in S and R configurations, respectively, by using **L60**–**L64** and **L65**–**L68** ligands.

More recently, this class of ligands was expanded to include diphosphinites **L70**–**L73** and phosphite–phosphinite **L74**–**L75**, all of them obtained from D-glucosamine (Fig. 22) [49].

The ligands were used in the iridium-catalysed asymmetric hydrogenation of imines **41** and **42**, as in Scheme 18.

The performance of structures **L74**–**L75** was superior to that of **L70**–**L73** in the hydrogenation of **41**, and **L74** promoted its conversion to **43** in 73% ee (−). Instead, conversion of **42** was more effectively carried out in the presence of **L71**, which afforded **44** in 70% ee (+).

Structural variations of DIOP based on carbohydrate scaffolds were also patented for use in asymmetric reactions [50–52].

### 2.11. Phosphoramidite type ligands

Main chirality is introduced in this important class of "privileged ligands" by 1,1-binaphthyl groups. Additional stereogenic centres can however be present on the nitrogen substituents, *e.g.* if R=H and R′=CH(Me)Ph in Fig. 2. This extra chirality derived from a sugar framework in ligands **L76**–**L81** (Fig. 23), which were conveniently prepared from D-xylose [53,54]. The structural types are either bisphosphoramidites or phosphito-phosphoramidite and consist of a 1,2-*O*-protected xylo- or ribo-furanoside backbone with the phosphorus functions at C3 and C5.

This assortment of ligands was also selected in order to study the effects of the configuration of both the stereogenic carbon atom C(3) (*e.g.* **L76** *vs* **L78**), and the binaphthyl group (*e.g.* **L76** *vs* **L77**).

The auxiliaries were examined, along with corresponding species displaying an achiral biaryl moiety in place of the binaphthyl one, in the Pd-catalysed asymmetric allylic alkylation on several substrates with different electronic and steric properties.

The phosphito-phosphoramidite ligands were found to be complementary, in that those with xylo-configuration (**L76** and **L77**) produced better activity and enantioselectivities with encumbering substrates, while ligands based on a ribo-configuration were more effective with unhindered substrates. For example, in the presence of **L77**, amination of **4** produced (*R*)-**45** in 97% ee (reaction a of Scheme 19), and, starting from the same substrate, product (*S*)-**11** was isolated in 98% ee. In this case, a cooperative effect between the configuration of the biaryl moiety and that of the sugar backbone was also disclosed, as in the same reaction the unmatched combination **L76** produced (*S*)-**11** in only 6% ee. On the other hand, the smaller allyl acetate **46** was more conveniently converted into (*S*)-**47** by using **L78**, as in reaction b of Scheme 19.

The substitution of one phosphito for a phosphoramidite group has a significant effect, *e.g.* in the presence of **L80** product **47** was obtained in only 33% ee and with opposite configuration with respect to that found with the corresponding phosphite-phosphoramidite **L78** (see reaction b of Scheme 19).

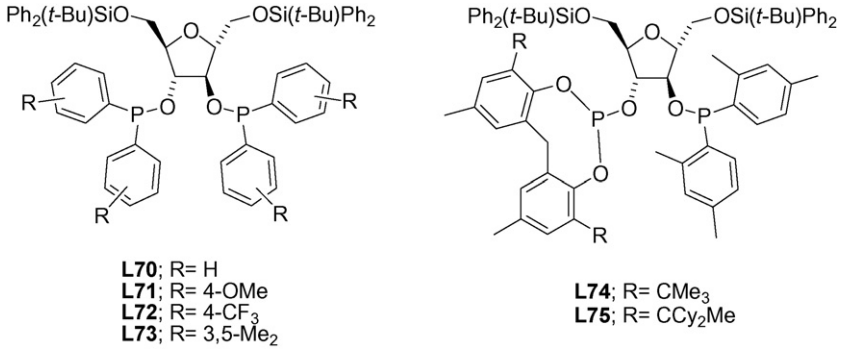



**Fig. 22.** DIOP type ligands **L70**–**L75**.

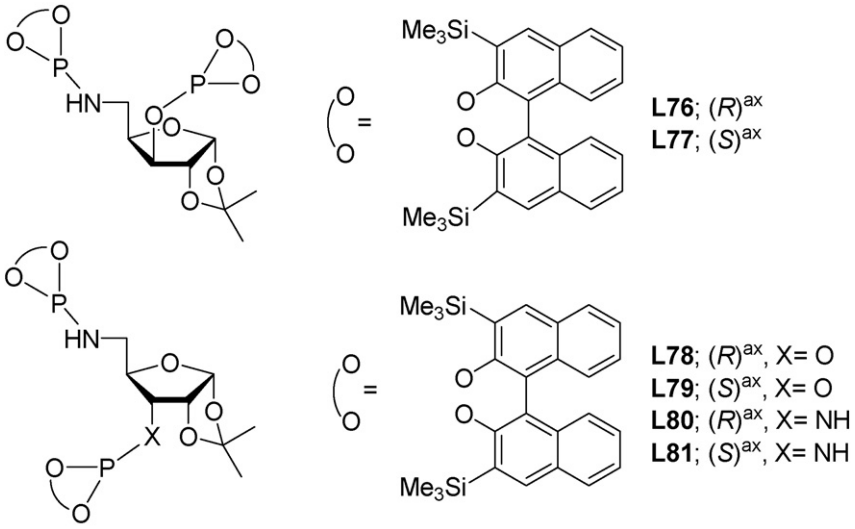
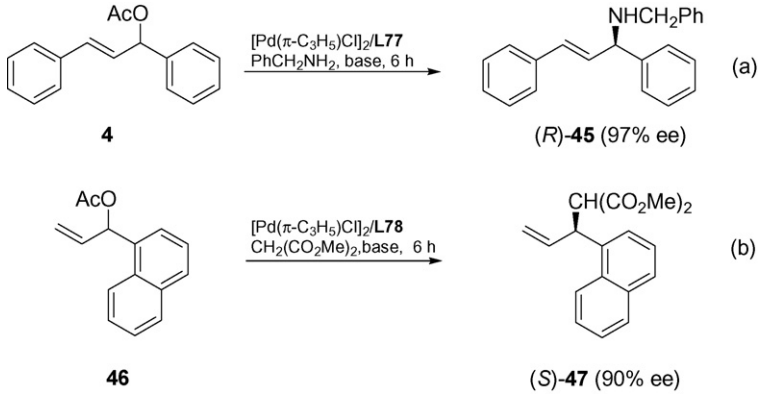



**Fig. 23.** Phosphoramidite type ligands.




**Scheme 19.** Asymmetric allylic amination of 1,3-diphenylpropenylacetate **4** catalysed by the Pd complex of **L77** (a) and asymmetric allylic alkylation of 1-(naphthalen-1-yl)allyl acetate **46** catalysed by the Pd complex of **L78** (b).

Although beyond the purpose of this review, it has recently been demonstrated that introduction of the 1,1-binaphthyl group in phosphite-oxazoline ligands derived from D-glucose affords very effective auxiliaries (**L82**–**L85** in Fig. 24) in the Ir-catalysed asymmetric hydrogenations of alkenes [55].

Thus, the library of ligands, along with corresponding biaryl species, was able to hydrogenate unfunctionalised alkenes with high and unprecedented enantioselectivity, as shown in Scheme 20 for *trans*-α-methylstilbene (**48**).

In the same way, there are related families of ligands, such as diphosphites containing carbohydrate scaffolds and a 1,1-binaphthyl moiety, that have also been successfully applied in asymmetric catalysis [56].

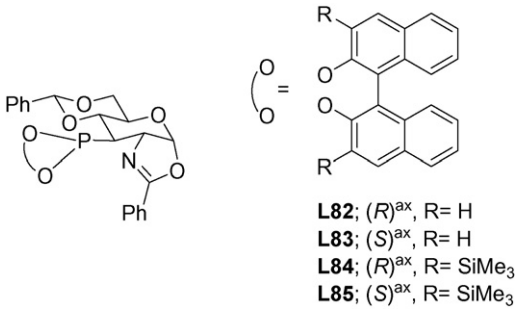
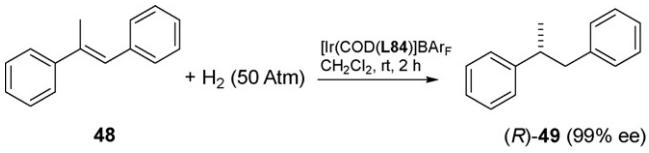



**Fig. 24.** Phosphito-oxazoline type ligands.




**Scheme 20.** Asymmetric hydrogenation of *trans*-α-methylstilbene **48** catalysed by the Ir complex of **L84**.

## 3. Conclusion

This review offers an unprecedented overview of the productive strategy which consists in reproducing "privileged" ligands incorporating carbohydrate scaffolds. Over the years, several authors have demonstrated that this approach yields modular ligand libraries, which combine efficiency with convenience and flexibility. Thus, today, at least eleven privileged architectures have corresponding sugar versions. In many cases, they promote metal-catalysed asymmetric reactions as efficiently as the original privileged structures, leading to chiral products in high ee's. In addition, in some cases, the sugar-based ligands demonstrated even higher ability than the traditional structures, reaching an excellent

level of enantioselectivity in reactions where the latter were not active at all [37]. More than half of the papers quoted have been published since 2000, which also reveals the fast growth of this area of research.

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[6] An additional benefit is that the generous presence of functional groups in sugars can be employed for "tagging" the "privileged" ligands in view of their application in *multiphase homogeneous catalysis*. This methodology allows easy catalyst re-cycling via simple phase separation, and relies on using two immiscible solvents and phase-tagged catalysts, which are soluble in only one of the two solvents (catalyst phase), while being insoluble in the other solvent (reactant/product phase). See: B. Cornils, W.A. Herrmann, I.T. Horvarth, W. Leitner, S. Mecking, H. Olivier-Borbigou, D. Vogt (Eds.), Multiphase Homogeneous Catalysis, 1st ed., Wiley-VCH, Weinheim, Germany, 2005.
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