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Tunable furanoside diphosphite ligands. A powerful approach in asymmetric catalysis

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A series of highly tunable furanoside diphosphite ligands, derived from readily available D-(+)-xylose and D-(+)-glucose, are discussed. Their modular nature allows a facile systematic variation in the configuration of the stereocentres at the ligand bridge and in the biaryl substituents. This enabled to select a ligand for each particular reaction that provided enantioselectivities that are comparable to those of the best catalysts previously reported in different asymmetric reactions.

Introduction

Asymmetric reactions catalysed by transition metals are one of the most efficient methods for preparing a wide range of enantiomerically pure compounds.[1] To achieve the highest levels of reactivity and selectivity in catalytic enantioselective reactions, different reaction parameters must be explored and adjusted. In this optimization process, a careful selection and design of the chiral ligand is perhaps the most crucial step since the best ligand strongly depends on each particular reaction. Although much progress has been made in this area in the last few years, as is demonstrated by the large amount of relevant literature,[1] there is no straightforward way of predicting, *a priori*, which ligand will provide the highest selectivity. Therefore, the design of new ligands for efficient asymmetric catalysis is still mainly empirical (based on trial-and-error).

For many years a large number of chiral ligands, mainly P- and N-containing ligands with either C_2- or C_1-symmetry, have been successfully applied in asymmetric catalysis.[1] Diphosphines have played a dominant role among the P-ligands, but recently a group of less electron-rich phosphorus compounds – phosphite ligands – has received much attention. Phosphite ligands have been successfully applied in many transition-metal-catalysed reactions such as hydrogenation, hydroformylation, hydrocyanation and allylic alkylation.[2] These ligands are extremely attractive for catalysis because they are easy to prepare from readily available starting materials and are also less sensitive to air than phosphines.[3] However, a systematic evaluation of the effectiveness of these phosphite ligands is hampered by the lack of systematically designed series of them having a similar backbone.[4] Such a task becomes significantly more facile if readily modulable chiral ligands are at hand. Carbohydrate-based ligands are particularly useful for addressing this need.[2f–i,k,5] They are readily available and highly functionalised with several stereogenic centres. This allows the systematic regio- and stereoselective introduction of different functionalities. Series of chiral ligands can be synthesised and screened in the search for high activities and selectivities for

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each type of reaction. This tuning of the ligand structure allows a rational design of ligands which also provides valuable information about the origin of the selectivity. In this way, we are not simply subject to the winds of chance when designing new generations of catalysts.

In this context, in the last few years, we have developed a new class of highly modular 1,2-protected diphosphite ligands with furanoside backbones (Fig. 1) that promote a wide range of catalytic asymmetric reactions.[2f–h,k,6]

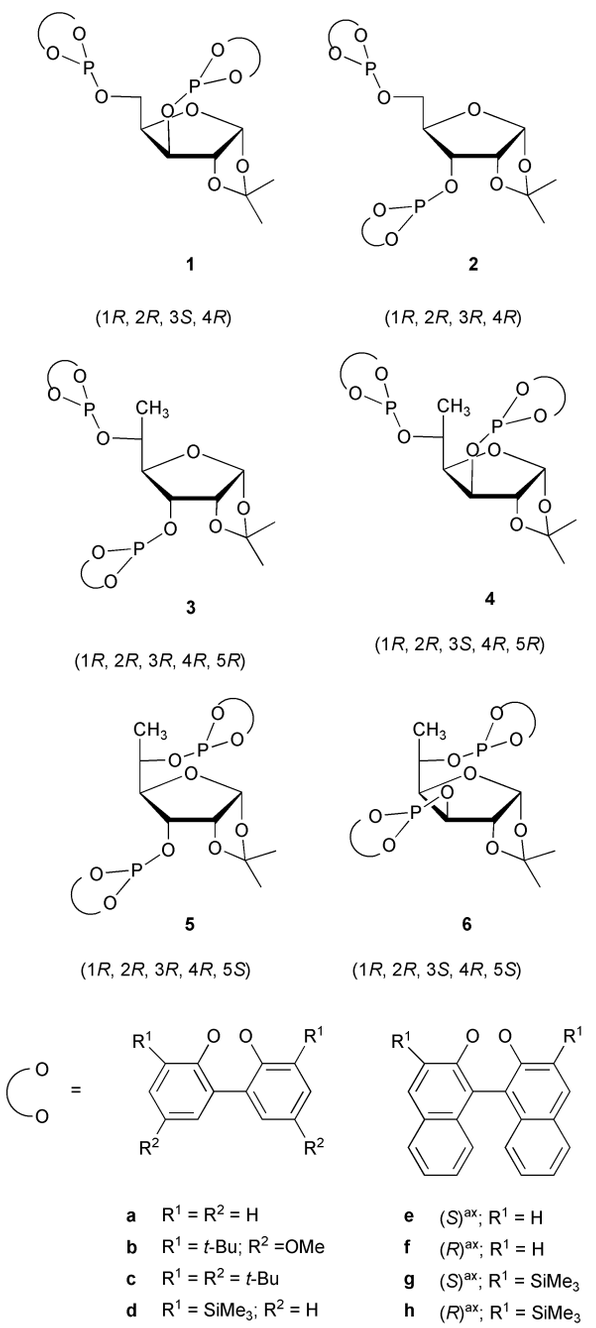


Fig. 1 Furanoside diphosphite ligands **1**–**6**.

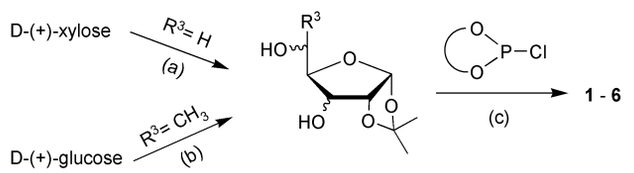
In this paper, we report the opportunities these ligands provide for improving the performance of three types of asymmetric catalytic reactions: hydroformylation, hydrogenation and allylic alkylation.

The modular construction of these ligands allows sufficient flexibility to fine-tune (a) the different configurations of the carbohydrate backbone and (b) the steric and electronic properties of the diphosphite substituents in order to improve the selectivity of these reactions. In this way, we studied the effect of the stereogenic carbon atom C-3 on the sugar backbone with ligands **1** and **2** whose configuration of C-3 is opposite. Ligands **3**–**6** provided an insight into the effect of a new stereocentre at the carbon atom C-5. These ligands include the four diastereomers that can be obtained by varying the configuration of C-3 and C-5. We used them to systematically study what effects these configurations have and whether there are any cooperative effects between them.

We also studied how attaching different groups to the *ortho*- and *para*-positions of the biphenyl moieties affects enantioselectivity with ligands **1**–**6(a**–**d)**. Finally, we used the series of enantiomerically pure binaphthol-based ligands **1**–**6(e**–**h)** to determine whether there is a cooperative effect between the stereocenters of the ligand backbone and the configuration of the biaryl phosphite moieties

Synthesis of diphosphite ligands

Diphosphite ligands **1**–**6** were synthesized very efficiently in one step from the corresponding diols, which were easily prepared on a large scale from D-(+)-xylose and D-(+)-glucose (Scheme 1). Therefore, reacting the corresponding diol with 2 equiv. of the desired *in situ* formed phosphorochloridites in the presence of base afforded ligands **1**–**6** as white air-stable solids.



Scheme 1 Synthesis of ligands **1**–**6**: (a) refs. 7 and 8, (b) ref. 2*f*, (c) refs. 2*f*,*k* and 6*c*.

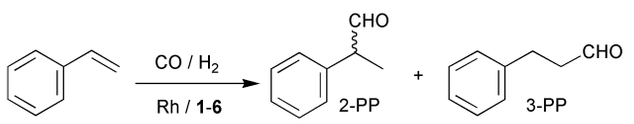
Asymmetric hydroformylation

The rhodium-catalysed asymmetric hydroformylation of alkenes has attracted much attention as a potential tool for preparing enantiomerically pure aldehydes under mild and clean reaction conditions. Chiral aldehydes are important precursors for synthesising biologically active compounds, biodegradable polymers and liquid crystals.[9]

In the last ten years, several studies have reported a remarkable improvement in the rhodium-catalysed asymmetric hydroformylation based on the use of diphosphite[2a,b] or phosphine–phosphite[2c,d] (Binaphos) ligands. At this time, Binaphos is the only ligand with a wide scope in this reaction.

In this section, we show how the modularity of diphosphite ligands **1**–**6** was exploited to improve the regio- and enantioselectivity of the rhodium-catalysed hydroformylation of styrene, which is usually used as a model substrate (Scheme 2).[10]

Initial experiments with ligands **1a**–**c** provided low-to-good regio- and enantioselectivities (Table 1, entries 1–3).[8]



Scheme 2 Hydroformylation of styrene with compounds **1**–**6**.

Ligands **1b** and **1c**, which have sterically demanding groups at the *ortho* positions of the biphenyl moieties, resulted in higher regio- and enantioselectivities than the less sterically encumbered unsusbtituted ligand **1a**. Ligands **2**, whose configuration of carbon atom C-3 is opposite to that of ligands **1**, followed the same trend (Table 1, entries 4 and 5) but the sense of the enantioselectivity was reversed.

Since ligands **1** and **2** have a phosphorus moiety bound to the non-stereogenic centre C-5, we examined whether introducing a new stereocentre at the C-5 position would improve the enantioselectivity. We therefore tested diphosphite ligands **3**–**6**.[2f,6c,11]

Table 1 Asymmetric hydroformylation of styrene catalysed by [Rh(acac)(CO)$_2$] / diphosphite **1** and **2**.[a]

Entry	Ligand	TOF[b]	% Conv.[c]	% 2-PP[d]	% ee[e]
1	**1a**	40	17	84	4 (*S*)
2	**1b**	50	20	95	51 (*S*)
3	**1c**	53	20	95	39 (*S*)
4	**2b**	41	19	96	53 (*R*)
5	**2c**	55	23	98	45 (*R*)

[a] Reaction conditions: T = 40 °C, P = 25 bar, styrene (13 mmol), [Rh(acac)(CO)$_2$] (0.0135 mmol), ligand/Rh = 1.1, toluene (15 mL), P_{CO}/P_{H_2} = 1. [b] TOF in mol styrene × mol Rh^{-1} × h^{-1} determined after 1 h reaction time by GC. [c] % Conversion measured by GC after 5 h. [d] Regioselectivity for 2-phenylpropanal. [e] % Enantiomeric excess measured by GC using a FS-Cyclodex β-I/P column.

In a first set of experiments, ligands **3**–**6(b**,**c)** were used to investigate how the configurations of the stereogenic carbon atoms C-3 and C-5 affect the selectivity. We expected their configurations to be important because they are close to the metal. These ligands constitute the four diastereomers that can be obtained by varying the configuration of the C-3 and C-5 atoms in the backbone in combination with two different bulky 2,2′-biphenyl moieties. The selectivity results with these ligands can be summarised as follows (Fig. 2):

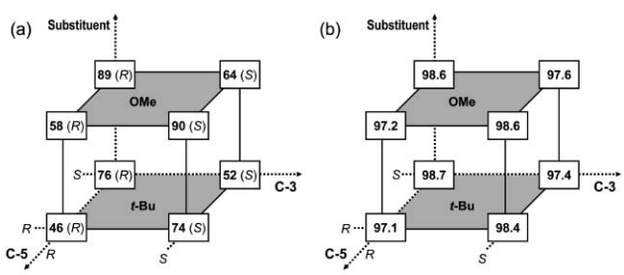


Fig. 2 Visual representations of: (a) enantioselectivities and (b) regioselectivities obtained with catalysts containing ligands **3**–**6(b**,**c)**, at selected reaction conditions (P = 10 bar, T = 20 °C).

(a) The sense of the enantiodiscrimination was predominantly controlled by the configuration at C-3. Accordingly, ligands **4** and **6**, with *S* configuration at C-3, gave (*S*)-2-phenylpropanal, while ligands **3** and **5**, with *R* configuration at C-3, gave (*R*)-2-phenylpropanal.

(b) A cooperative effect was observed between stereocentres C-3 and C-5. That is, when the configuration of C-3 was *S*, changing C-5 from *R* (ligand **4b**) to *S* (ligand **6b**) resulted in a decrease in enantioselectivity from 90% *S* to 64% *S*. However, when the configuration of C-3 was *R*; changing C-5 from *R* (ligand **3b**) to *S* (ligand **5b**) increased the enantioselectivity from 58% *R* to 89% *R*. This behaviour was also observed for ligands **3**–**6(c)**.

From (a) and (b), we can see that either (*S*)- or (*R*)-2-phenylpropanal enantiomers can be obtained with excellent regio- and enantioselectivities, under very mild reaction conditions, by suitably selecting the diastereoisomeric ligands **4** or **5**, respectively. These results are among the best that have been reported for the asymmetric hydroformylation of vinyl arenes.[2a–c]

We also found that the substituents in the *para* positions of the biphenyl moieties effected the enantioselectivity, but regioselectivities were hardly affected (Fig. 2). Ligands **3**–**6(b)** with methoxy substituents always produced better enantioselectivities than those with the corresponding *tert*-butyl-substituted analogs (ligands **3**–**6(c)**). To check whether this behaviour could be attributed to steric problems with the *tert*-butyl groups in *para*, we synthesised two new ligands **3d** and **4d** without these groups, but still containing bulky substituents (trimethylsilyl groups) in the *ortho* positions of the biphenyl moieties. The results,[12] which were similar to those we obtained with ligands **3b** and **4b**, suggested that bulky substituents in the *para* positions had a negative effect on enantioselectivity.

Table 2 Asymmetric hydroformylation of styrene catalysed by [Rh(acac)(CO)$_2$]/diphosphite **3b**–**f** and **4b**–**h**.[a]

Entry	Ligand	TOF[b]	% Conv[c]	% 2-PP[d]	% ee[e]
1	**3b**	131	64	99	49 (*R*)
2	**4b**	98	49	97.8	78 (*S*)
3	**3c**	165	81	96	36 (*R*)
4	**4c**	134	66	97.3	62 (*S*)
5	**3d**	147	73	95	30 (*R*)
6	**4d**	151	72	96	76 (*S*)
7	**3e**	158	77	84	5 (*S*)
8	**4e**	153	78	85	25 (*S*)
9	**3f**	178	83	86	20 (*R*)
10	**4f**	165	82	85	60 (*R*)
11	**4g**	149	73	84	68 (*S*)
12	**4h**	99	52	86	30 (*S*)

[a] Reaction conditions: T = 40 °C, P = 10 bar, styrene (13 mmol), [Rh(acac)(CO)$_2$] (0.0135 mmol), ligand/Rh = 1.1, toluene (15 mL), P_{CO}/P_{H_2} = 0.5. [b] TOF in mol styrene × mol Rh^{-1} × h^{-1} determined after 1 h reaction time by GC. [c] % Conversion measured by GC after 5 h. [d] Regioselectivity for 2-phenylpropanal. [e] % Enantiomeric excess measured by GC using a FS-Cyclodex β-I/P column.

To further investigate how enantioselectivity was influenced by the groups attached to the biaryl moieties, ligands **e**–**h** containing different enantiomerically pure binapthyl moieties were also tested (Table 2. Note that in this case these experiments were carried out at 40 °C; For comparative purposes we also include the results using ligands **3**, **4(b**–**d)** at 40 °C). In this case, ligands **3** and **4** were chosen since they include two different combinations of the stereocentres C-3 and C-5. Ligands **4** have the combination of configurations on C-3 and C-5 required to induce the highest enantioselectivity, while ligands **3** have an inappropriate configuration of carbon atoms C-3 and C5 (*vide supra*).

Low enantioselectivity was found with ligand **4e**, which has an unsubstitituted (*S*)-binaphthyl moiety (Table 2, entry 8). Changing the configuration of the binaphthyl moieties from (*S*) to (*R*) (ligand **4f**) increased activity and enantioselectivity (entry 8 vs 10). Moreover, the sense of the enantioselectivity was reversed; the (*S*) enantiomer was obtained with **4e** and the (*R*) enantiomer was obtained with **4f**. Ligands **3e** and **3f**, whose configuration of carbon atom C-3 is opposite to those of ligands **4**, followed the same trend as catalyst precursors Rh/**4e** and Rh/**4f** (entries 7 and 9). However, the enantiomeric excesses were smaller because of the inappropriate configuration of carbon atoms C-3 and C-5. If we compare these four results, we find a cooperative effect between the stereogenic centres of the ligand backbone and the stereogenic binaphthyl phosphite moieties. This cooperative effect, together with the previously observed cooperative effect between the backbone stereocentres C-3 and C-5 controls enantioselectivity. From this, we can also conclude that the excellent enantioselectivity found with ligands **4b**,**d** and **5b**,**d** (*vide supra*) was due to the preferential formation of the complex [HRh(L–L)(CO)$_2$] (L–L = **1**–**6**) with the required conformation for optimal chiral cooperativity that induces the highest enantioselectivity (see the section on the characterisation of [HRh(L–L)(CO)$_2$] complexes). We also found that the sense of the enantioselectivity was controlled by the configuration of the biaryl phosphite moieties. This suggests that the configuration of fluxional biphenyl moieties in ligands **3**–**6(b**–**d)** is controlled by the configuration of the stereogenic centre C-3.

Finally, as expected, ligand **4g**, which resulted from introducing bulky trimethylsilyl substituents at the *ortho* position of the (*S*)-binaphthyl moieties in ligand **4e**, improved enantioselectivity (68% ee, entry 11). Surprisingly, ligand **4h**, with bulky trimethylsilyl substituents at the *ortho* position of the (*R*)-binaphthyl moieties, showed lower activity and lower

Table 3 Calculated **ee** : **ea** ratio for $[HRh(L–L)(CO)_2]$ and selected data for enantioselectivity

Ligand	Ratio of **ee** : **ea**[a]	% ee at 40 °C	% ee at 20 °C
3b	85 : 15	49 (*R*)	58 (*R*)
3c	90 : 10	36 (*R*)	46 (*R*)
3d	98 : 2	30 (*R*)	52 (*R*)
4b	100 : 0	78 (*S*)	90 (*S*)
4c	100 : 0	62 (*S*)	74 (*S*)
4d	99 : 1	76 (*S*)	90 (*S*)
4f	75 : 25	60 (*R*)	–
4g	100 : 0	68 (*S*)	81 (*S*)
4h	98 : 2	30 (*S*)	–
5b	100 : 0	77 (*R*)	89 (*R*)
5c	99 : 1	59 (*R*)	76 (*R*)
6b	88 : 12	48 (*S*)	64 (*S*)
6c	89 : 11	31 (*S*)	52 (*S*)

[a] Measured from HP-NMR data.[13]

asymmetric induction than the less hindered ligand **4f** (entry 10 *vs.* 12). This unexpected low enantioselectivity can be explained by considering that the bulky ligand probably reduces its steric congestion in the hydridorhodium complex by adopting a non-favourable conformation that reaches lower enantioselectivities.

Characterisation of $[HRh(L–L)(CO)_2]$ complexes

To obtain information about species $[HRh(L–L)(CO)_2]$, which are known to be the resting state in the hydroformylation reaction,[9] we studied the solution structures of hydridorhodium diphosphite dicarbonyl catalysts $[HRh(L–L)(CO)_2]$ (L–L = **1**–**6**), under syngas pressure by high-pressure NMR (HP-NMR) and *in situ* high-pressure IR (HP-IR) spectroscopy. These complexes are generally assumed to have a trigonal bipyramidal structure and two isomeric structures of these complexes are possible, containing the diphosphite coordinated in a bis-equatorial (**ee**) or an equatorial–apical (**ea**) fashion (Fig. 3). The studies reported below showed that the configurations of the stereogenic carbon atoms C-3 and C-5 and the configuration of the binaphthyl moieties greatly influenced the structure of $[HRh(L–L)(CO)_2]$ and, therefore, the enantioselectivity.[2f,6c]

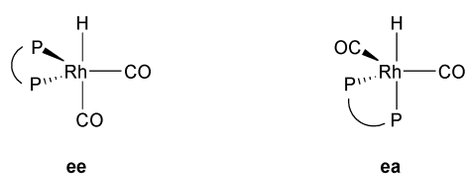


Fig. 3 Equatorial–equatorial (**ee**) and equatorial–axial (**ea**) coordination of diphosphite ligands in the $[HRh(L–L)(CO)_2]$ complexes (L–L = **1**–**6**).

The NMR data for complexes containing ligands **4b**–**d**, **4g** and **5b**,**c** indicate the formation of trigonal bipyramidal (*TBPY*) hydridorhodium dicarbonyl species with equatorial–equatorial (**ee**) coordinating diphosphites (Fig. 3). Further evidence is provided by IR *in situ* measurements. Each spectrum showed two carbonyl vibrations around 2070 and 2010 cm^{-1}, which are characteristic of ee isomers.[9d] Moreover, the formation of only one diastereoisomer was confirmed by variable-temperature NMR.

For complexes containing ligands **3b**–**d**, **4f**, **4h** and **6b**,**c**, NMR and IR spectra indicated an equilibrium between equatorial–equatorial (**ee**) and equatorial–axial (**ea**) species (Table 3).

If we compare the solution structures of the $[HRh(L–L)(CO)_2]$ species with results of hydroformylation (Table 3), we can conclude that the enantiodiscriminating performance is generally highest for ligands with strong bis-equatorial coordination preference. However, this structure/selectivity relationship is not always straightforward and several factors must be considered:

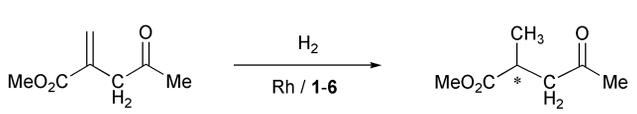
(i) High bis-equatorially coordination preference does not always lead to high selectivity because the enantiodiscrimination depends strongly on the exact ligand structure (*vide supra*). Thus, ligand **4h** which shows high bis-equatorially coordination preference (**ee** : **ea** ratio of 98 : 2) shows very low enantioselectivity (Table 3).

(ii) A mixture of bis-equatorial and equatorial–axial species does not always lead to low enantioselectivity, since the product formation can be kinetically controlled. Thus, if one of the diastereoisomeric species inserts the styrene into the Rh–H bond faster than the other species, a good selectivity can be obtained.[14] The results using ligand **4f** clearly show that enantioselectivity was good (Table 3) even with a 75 : 25 mixture of **ee** : **ea** species.

Asymmetric hydrogenation

The asymmetric hydrogenation of prochiral compounds catalysed by chiral transition-metal complexes has been widely used in stereoselective organic synthesis and some processes have found industrial applications.[1b–d] For many years, the scope of this reaction has been gradually extended in both reactant structure and catalyst efficiency. Many chiral diphosphines[1] and diphosphinites[5a,d] have been successfully applied to metal-catalysed asymmetric hydrogenation. Recently, a group of less electron-rich phosphorus compounds – phosphite ligands – has received more attention. However, only Reetz *et al.* have reported a successful enantioselective hydrogenation using phosphite ligands.[2i,j]

In this section, we describe the results for the hydrogenation of dimethyl itaconate with diphosphite ligands **1**–**6** (Scheme 3).[2k,15] This substrate has been studied with a wide variety of ligands carrying different donor groups. We can therefore directly compare the efficacy of different ligand systems.



Scheme 3 Rh-Catalysed hydrogenation of dimethyl itaconate using diphosphite ligands **1**–**6**.

Initial experiments with ligands **1** and **2** provided low (22% (*R*)) to moderate (64% (*R*)) enantioselectivities.[2k] In continued efforts to improve the selectivity, we screened ligands **3**–**6**, related to **1** and **2**, but with a new stereogenic centre at C-5 (Table 4). In this set of ligands, enantioselectivities were best with ligands **3** with *R* configuration on both C-3 and C-5 stereocentres (Fig. 4). Moreover, the enantiomeric excesses depended strongly on the absolute configuration of C-3 of the carbohydrate backbone. This behaviour contrasted with the highly

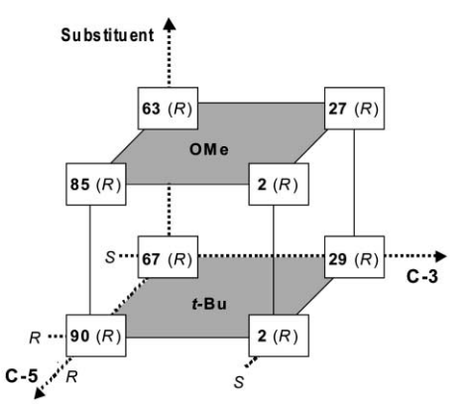


Fig. 4 A visual representation of the enantioselectivities obtained with catalysts containing ligands **3**–**6(b,c)**.

Table 4 Rh-Catalysed asymmetric hydrogenation of dimethyl itaconate using diphosphite ligands **3**–**6**.[a]

Entry	Ligand	% Conv[b] (*t*/h)	% ee[c]
1	**3b**	82 (8)	85 (*R*)
2	**3c**	90 (8)	90 (*R*)
3	**3d**	100 (6)	97 (*R*)
4	**3e**	50 (8)	50 (*S*)
5	**3f**	46 (8)	52 (*R*)
6	**4b**	98 (8)	2 (*R*)
7	**4c**	100 (8)	2 (*R*)
8	**4d**	100 (8)	3 (*R*)
9	**5b**	80 (8)	63 (*R*)
10	**5c**	87 (8)	67 (*R*)
11	**6b**	69 (8)	27 (*R*)
12	**6c**	73 (8)	29 (*R*)

[a] Reaction conditions: $[Rh(cod)_2]BF_4$ (0.01 mmol), Ligand/Rh = 1.1, Substrate/Rh = 100, CH_2Cl_2 (6 mL), T = 25 °C, P = 5 bar. [b] % Conversion measured by GC. [c] % Enantiomeric excess measured by GC using a Chiraldex G-TA column.

cooperative effect between stereocenters C-3 and C-5 in Rh-catalysed hydroformylation, which resulted in a matched combination for ligands with gluco- (ligands **4**) and talofuranoside (ligands **5**) backbone (Fig. 2(a)).

Unlike what happens in the hydroformylation process, the different substituents in the biphenyl moieties have a limited influence on enantioselectivity (Fig. 4 and Table 4). The effect is also different: results are better with ligands containing *tert*-butyl at both *ortho* and *para* positions (ligand **3c**) (Fig. 4), while in the Rh-catalysed hydroformylation reaction the best enantioselectivities were obtained with ligands containing methoxy substituents in the biphenyl moieties (Fig. 2(a)). Ligands with trimethylsilyl in *ortho* positions (**3d**) also provided high enantioselectivity (up to >99% (*R*) at 5 °C).

Finally, if we compare the results for ligands **3e**,**f** (Table 4), which contain stereogenic binaphthyl moieties, we can see that the sense of the enantiodiscrimination is predominantly controlled by the configuration of the biaryl at the phosphite moieties. Accordingly, ligands containing (*S*)-binaphthyl moieties gave the (*S*)-dimethyl 2-methylsuccinate, while ligands containing (*R*)-binaphthyl moieties gave the (*R*) product. This behaviour was also observed for the hydroformylation reaction.

This set of ligands were also applied in the Rh-catalysed hydrogenation of other benchmark dehydroamino acid derivatives. The results followed the same trend as observed for dimethyl itaconate, but the activities were somewhat higher.[2k]

Allylic substitution

The palladium-mediated allylic substitution reaction is an efficient synthetic tool for the formation of carbon–carbon and carbon–heteroatom bonds, which is one of the main objectives in modern organic synthetic chemistry.[16] The combination of mixed phosphite–oxazoline,[2e] phosphite–thioether[17] and phosphite–phosphine[18] ligands has been successfully used in the Pd-catalysed allylic substitution, but studies using diphosphite ligands are scarce.[2g,h]

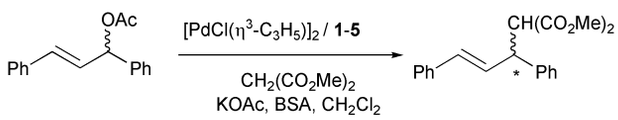
In this section we describe the results with the modular furanoside ligands **1**–**5**, which, to the best of our knowledge, constituted the first example of diphosphite ligands being applied to this process.[2g,h]

Table 5 shows the yield and enantiomeric excess obtained in the palladium(0)-catalysed addition of dimethyl malonate to *rac*-1,3-diphenylacetoxyprop-1-ene (Scheme 4).[19] This reaction was chosen as a model because it has been carried out with a wide variety of ligands carrying different donor groups. This enables us to directly compare the efficacy of several ligand systems.

Table 5 Pd-catalysed asymmetric allylic alkylation using ligands **1**–**5**.[a]

Entry	Ligand	*t*/h	% Conv[b]	% ee[c]
1	**1a**	22	95	20 (*S*)
2	**1c**	1.5	83	90 (*S*)
3	**2b**	22	11	5 (*R*)
4	**2c**	1.5	100	1 (*R*)
5	**3a**	24	50	2 (*R*)
6	**3b**	0.32	100	45 (*R*)
7	**3c**	0.25	100	64 (*R*)
8	**4a**	0.58	60	9 (*S*)
9	**4b**	0.17	100	95 (*S*)
10	**4c**	0.08	100	84 (*S*)
11	**5c**	60	100	52 (*S*)

[a] All reactions were run at room temperature. Diphenylallyl acetate/palladium = 100. Malonate/palladium = 300. Ligand/palladium = 1. Catalyst preparation time is 30 min [b] Conversion determined by GC. [c] Enantiomeric excesses determined by HPLC on a Chiralcel-OD column.



Scheme 4 Allylic alkylation of *rac*-1,3-diphenylacetoxyprop-1-ene with compounds **1**–**5**.

The reaction using xylofuranoside diphosphite ligand **1a**, containing two unsubstituted biphenyl moieties, provided low enantioselectivity (entry 1). Introducing bulky *tert*-butyl substituents in the *ortho* and *para* positions of both biphenyl moieties (ligand **1c**) had a strong positive effect on enantioselectivity (entry 2), which increased from 20 to 90% ee. Furthermore, the *tert*-butyl groups also had a positive effect on activity (entry 1 *vs*. entry 2).

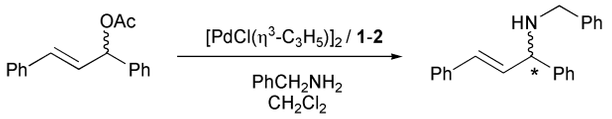
When we used ribofuranoside diphosphite ligands **2b**,**c**, the configuration of the carbon atom C-3 of which is opposite to the configuration of this atom in ligands **1**, enantioselectivities were very low even for the ligands with the bulky *tert*-butyl groups in *ortho* position (entries 3 and 4). Of these two, the presence of methoxy groups at the *para* positions (**2b**) slowed the reaction dramatically, whereas the enantioselectivity was slightly higher.

The reaction using ligand **4a**, which is related to **1a** but has a new stereogenic centre at C-5 with (*R*) configuration, provided only 9% ee (entry 8). As with ligand **1c**, the presence of bulky *tert*-butyl groups in the *ortho*-positions of the biphenyl moiety (ligands **4b** and **4c**) had a positive effect on enantioselectivity and activity (entry 8 *vs*. entries 9 and 10). Also, the presence of methoxy groups in the *para* positions of the biphenyl moieties significantly improved enantioselectivity (ee up to 95%, entry 9).

The trends were similar with ligands **3**, in which the configuration of the carbon atom C-3 is opposite to those of ligands **4**, but enantioselectivities and activities were lower (entries 5–7).

The use of ligand **5c**, which resulted from changing the configuration of C-5 in ligands **3** from (*R*) to (*S*), led to lower activity and slightly lower enantioselectivity than the catalytic system Pd/**3** (entry 11 *vs*. entry 7).

Finally, ligands **1** and **2** were tested in the palladium-catalyzed reaction of 1,3-diphenyl-2-propenyl acetate with benzylamine as a model reaction of the allylic amination (Scheme 5).[2h] In general, the results follow the same trend as that observed for the allylic alkylation, which is not unexpected because the reactions have a similar mechanism.[20] However, the enantiomeric excesses obtained are higher (up to 97% ee), and the reaction rates are much lower.[2h] The higher ee's in the allylic amination can be explained by a later transition state, which results in larger ligand–allyl interaction.[21]



Scheme 5 Allylic aminaion of *rac*-1,3-diphenylacetoxyprop-1-ene with compounds **1**, **2**.

The results obtained with ligands **1**–**5** clearly indicated that stereogenic centre C-5 scarcely affected the enantioselectivity. This suggests that the nucleophilic attack, which is generally accepted as the enantiodiscrimination step,[16,20] takes place *trans* toward the carbon atom C-5 (Fig. 5). We obtained further proof for this hypothesis by studying a series of heterodonor phosphite–thioether and phosphite–phosphine ligands with the same furanoside backbone, where the nucleophilic attack also occurs *cis* to the phosphite moiety at C-3.[2h]

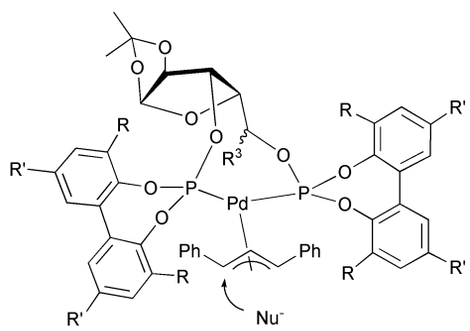


Fig. 5 Nucleophilic attack on the palladium diphosphite allyl intermediate (R^3 = H, CH_3).

In summary, the enantiomeric excesses with ligands **1**–**5** in the asymmetric allylic substitution depend strongly on the absolute configuration of the stereocentre carbon C-3 of the carbohydrate backbone. This behavior is similar to the results obtained for asymmetric hydrogenation, except that the stereochemistry in the carbon atom C-3 that provides good enantioselectivities is reversed. For asymmetric hydrogenation, therefore, the enantioselectivities were best with ligands **3**, while ligands **1** and **4** provided the highest enantiomeric excess in asymmetric allylic alkylation. Note that introducing a stereogenic centre in C-5 had a positive effect on activity, although the enantioselectivity is unaffected. This contrasts with the results from the hydroformylation and hydrogenation reactions where the new stereogenic centre at C-5 improved both activities and enantioselectivities. All these results show that the modular carbohydrate ligands described in this study have several advantages for optimising the selectivities (activity and enantioselectivity) for each particular process.

Conclusions

We have discussed a family of simple and highly modular furanoside diphosphite ligands for enantioselective catalysis. These ligands have two main advantages: (1) they can be prepared in a few steps from readily available D-(+)-xylose and D-(+)-glucose and (2) their modular nature allows a facile systematic variation in the configuration of the stereocentres at the ligand bridge and in the biaryl substituents. This means that it is possible to select a ligand for each particular reaction that provided enantioselectivities that are comparable to those of the best catalysts previously reported in different asymmetric reactions.

Varing the chirality of the sugar backbone stereocentres (C-3 and C-5) and the biaryl moieties in these ligands had a remarkable effect on activity and selectivity in several types of asymmetric catalytic reactions. We found that, for the same series of ligands the effects were completely different depending on the reaction studied. Thus, the best ligands for hydroformylation were **4b**,**d** and **5b**,**d**, with *RR* and *SS* configuration of C-3 and C-5, respectively. The best ligands for hydrogenation were **3c**,**d** with *R* configuration of both C-3 and C-5. Finally, the best ligands for allylic substitution were **1c** and **4b**,**c**. This shows the advantage of the modular carbohydrate ligands described in this study. The many combinations they offer were the key to finding the most suitable ligand for each particular process.

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References

1 See, for example: (*a*) H. Brunner and W. Zettlmeier, in *Handbook of Enantioselective Catalysis*, VCH, Weinheim, 1993; (*b*) R. Noyori, in *Asymmetric Catalysis in Organic Synthesis*, Wiley, New York, 1994; (*c*) *Catalytic Asymmetric Synthesis*, ed. I. Ojima, Wiley, New York, 2000; (*d*) *Comprehensive Asymmetric Catalysis*, ed. E. N. Jacobsen, A. Pfaltz and H. Yamamoto, Springer, Berlin, 1999, vol. 1.

2 See, for example: (*a*) J. E. Babin and G. T. Whiteker (Union Carbide Chem. Plastics Techn. Co.), *World Pat.*, WO 93/03839, 1993; (*Chem. Abstr.*, 1993, **119**, P159872h); (*b*) G. J. H. Buisman, L. A. van deer Veen, A. Klootwijk, W. G. J. de Lange, P. C. J. Kamer, P. W. N. M. van Leeuwen and D. Vogt, *Organometallics*, 1997, **16**, 2929; (*c*) K. Nozaki, N. Sakai, T. Nanno, T. Higashijima, S. Mano, T. Horiuchi and H. Takaya, *J. Am. Chem. Soc.*, 1997, **119**, 4413; (*d*) G. Franciò and W. Leitner, *Chem. Commun.*, 1999, 1663; (*e*) R. Prétôt and A. Pfaltz, *Angew. Chem., Int. Ed.*, 1998, **37**, 323; (*f*) M. Diéguez, O. Pàmies, A. Ruiz, S. Castillón and C. Claver, *Chem. Eur. J.*, 2001, **7**, 3086; (*g*) M. Diéguez, S. Jansat, M. Gomez, A. Ruiz, G. Muller and C. Claver, *Chem. Commun.*, 2001, 1132; (*h*) O. Pàmies, G. P. F. van Strijdonck, M. Diéguez, S. Deerenberg, G. Net, A. Ruiz, C. Claver, P. C. J. Kamer and P. W. N. M. van Leeuwen, *J. Org. Chem.*, 2001, **66**, 8867; (*i*) M. T. Reetz and T. Neugebauer, *Angew. Chem., Int. Ed.*, 1999, **38**, 179; (*j*) M. T. Reetz and G. Mehler, *Angew. Chem., Int. Ed.*, 2000, **39**, 3889; (*k*) M. Diéguez, A. Ruiz and C. Claver, *J. Org. Chem.*, 2002, **67**, 3796; (*l*) K. Selvakumar, M. Valentini, P. S. Pregosin and A. Albinati, *Organometallics*, 1999, **18**, 4591; (*m*) T. Horiuchi, E. Shirakawa, K. Nozaki and H. Takaya, *Tetrahedron: Asymmetry*, 1997, **8**, 57.

3 (*a*) M. J. Baker and P. G. Pringle, *J. Chem. Soc., Chem. Commun.*, 1991, 1292; (*b*) M. J. Baker, K. N. Harrison, A. G. Orpen, G. Shaw and P. G. Pringle, *J. Chem. Soc., Chem. Commun.*, 1991, 803; (*c*) L. H. Pignolet, in *Homogeneous Catalysts with Metal Phosphine Complexes*, Plenum, New York, 1983.

4 For representative examples of successful modifications of phosphite ligands for asymmetric catalysis, see refs. 2*a*,*b*,*i* and *j*.

5 See also, for example: (*a*) T. V. RajanBabu and A. L. Casalnuovo, *Pure Appl. Chem.*, 1994, **94**, 149; (*b*) D. S. Clyne, Y. C. Mermet-Bouvier, N. Nomura and T. V. RajanBabu, *J. Org. Chem.*, 1999, **64**, 7601; (*c*) K. Yonehara, K. Ohe and S. Uemura, *J. Org. Chem.*, 1999, **64**, 937; (*d*) H. Park and T. V. RajanBabu, *J. Am. Chem. Soc.*, 2002, **124**, 734; (*e*) R. J. Selke, *Organomet. Chem.*, 1989, **370**, 249; (*f*) T. V. RajanBabu, B. Radetich, K. K. You, T. A. Ayers, A. L. Casalnuovo and J. C. Calabrese, *J. Org. Chem.*, 1999, **64**, 3429; (*g*) M. Diéguez, A. Ruiz and C. Claver, *Chem. Commun.*, 2001, 2702.

6 (*a*) M. Diéguez, A. Ruiz and C. Claver, *Tetrahedron: Asymmetry*, 2001, **12**, 2895; (*b*) M. Diéguez, O. Pàmies, A. Ruiz and C. Claver, *Tetrahedron: Asymmetry*, 2002, **13**, 83; (*c*) M. Diéguez, O. Pàmies, A. Ruiz and C. Claver, *New. J. Chem.*, 2002, **26**, 827.

7 G. J. H. Buisman, M. E. Martin, E. J. Vos, A. Klootwijk, P. C. J. Kamer and P. W. N. M. van Leeuwen, *Tetrahedron: Asymmetry*, 1995, **6**, 719.

8 O. Pàmies, G. Net, A. Ruiz and C. Claver, *Tetrahedron: Asymmetry*, 2000, **11**, 1097.

9 (*a*) M. Beller, B. Cornils, C. D. Frohning and C. W. Kohlpainter, *J. Mol. Catal.*, 1995, **104**, 17; (*b*) F. Agboussou, J.-F. Carpentier and A. Mortreux, *Chem. Rev.*, 1995, **95**, 2485; (*c*) S. Gladiali, J. C. Bayón and C. Claver, *Tetrahedron: Asymmetry*, 1995, **7**, 1453; (*d*) *Rhodium Catalyzed Hydroformylation*, ed. P. W. N. M. van Leeuwen and C. Claver, Kluwer Academic Press, Dordrecht, 2000.

10 The catalysts were prepared *in situ* during 16 h. In general, hydrogenated or polymerized products of styrene were not observed.

11 M. Diéguez, O. Pàmies, A. Ruiz, S. Castillón and C. Claver, *Chem. Commun.*, 2000, 1607.

12 Ligands **3d** and **4d** gave 52% (*R*) and 90% (*S*) ee at 20 °C, respectively.
13 Calculated from the HP-NMR data using the typical value of the *cis* and *trans* phophorus–proton coupling constants as in ref. 2*f* and P. W. N. M. van Leeuwen, P. C. J. Kamer, J. N. H. Reek and P. Dierkes, *Chem. Rev.*, 2000, **100**, 2741.
14 Recent mechanistic studies suggest that the enantioselectivity is determined during the insertion of the olefin into the Rh–H bond, see for example: (*a*) D. Gleich, R. Schmid and W. A. Herrmann, *Organometallics*, 1998, **17**, 2141; (*b*) T. Horiuchi, E. Shirakawa, K. Nozaki and H. Takaya, *Organometallics*, 1997, **16**, 2921 and ref. 2*c*.
15 In general, the catalysts were prepared *in situ* by adding the corresponding ligands to the catalyst rhodium precursor $[Rh(cod)_2]BF_4$.
16 J. Tsuji, in *Palladium Reagents and Catalysis, Innovations in Organic Synthesis*, Wiley, New York, 1995.
17 K. Selvakumar, M. Valentini, P. S. Pregosin and A. Albinati, *Organometallics*, 1999, **18**, 4591.
18 S. Deerenberg, H. S. Schrekker, G. P. F. Van Strijdonck, P. C. J. Kamer, P. W. N. M. van Leeuwen and K. Goubitz, *J. Org. Chem.*, 2000, **65**, 4810.
19 The reactions were carried out in dichloromethane at room temperature in the presence of a catalyst generated *in situ* from π-allyl–palladium chloride dimer $[PdCl(\eta^3\text{-}C_3H_5)]_2$ and the corresponding ligand and a catalytic amount of KOAc.
20 (*a*) B. M. Trost and D. L. van Vranken, *Chem. Rev.*, 1996, **96**, 395; (*b*) M. Johannsen and K. A. Jorgensen, *Chem. Rev.*, 1998, **98**, 1869.
21 (*a*) P. Dierkes, S. Ramdeehul, L. Barloy, A. de Cian, J. Fischer, P. C. J. Kamer, P. W. N. M. van Leeuwen and J. A. Osborn, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 566; (*b*) S. Ramdeehul, P. Dierkes, R. Aguado, P. C. J. Kamer, P. W. N. M. van Leeuwen and J. A. Osborn, *Angew. Chem., Int. Ed.*, 1998, **37**, 3118.