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Recent advances in Rh-catalyzed asymmetric hydroformylation using phosphite ligands

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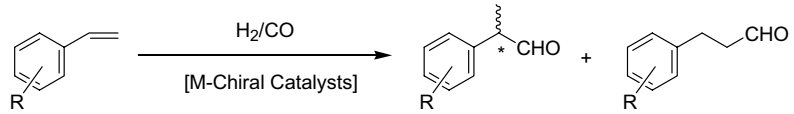
Abstract—This review covers the recent advances in Rh-catalyzed asymmetric hydroformylation using phosphite ligands in the most emerging period for this area of research (1996 to February 2004).

Contents

1. Introduction

The metal-catalyzed asymmetric hydroformylation of alkenes (Scheme 1) has attracted much attention as a potential tool for preparing enantiomerically pure aldehydes,[1] which are important precursors for synthesizing biologically active compounds, biodegradable polymers and liquid crystals.[1c] Since the early 1970s, transition metal complexes based on rhodium and platinum have been used as catalysts in asymmetric hydroformylation. Pt/diphosphine catalysts yield high enantioselectivities, but the chemo- and regioselectivities are low.[2] In general, Rh/diphosphine catalysts have higher catalytic activities and regioselectivities in branched aldehydes, but the ee's do not exceed 60%.[3] Over the last decade, two new types of ligands, diphosphite[4] and phosphite–phosphine[5] ligands, have emerged as suitable ligands for the Rh-asymmetric



Scheme 1. Model metal-catalyzed asymmetric hydroformylation of styrene (R = H) and derivatives.

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hydroformylation, yielding better activities and selectivities than the phosphine-based catalytic systems. Most of the research published in the last decade has been dedicated to Rh-phosphite catalytic systems.

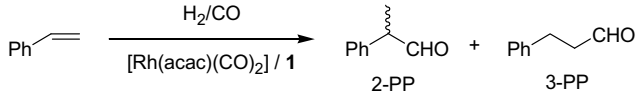
Phosphite ligands are extremely attractive for catalysis because they are easy to prepare from readily available alcohols. The availability of many alcohols allows the synthesis of many series of chiral ligands that can be screened in the search for high activity and selectivity. Another advantage of phosphite ligands is that they are less sensitive to air and other oxidizing agents than phosphines.

Several reviews have been published about the hydroformylation process[1e,6] and to a lesser extent about the asymmetric modification of this type of reaction.[1] The scope of this review is narrower, focusing on the Rh-catalyzed asymmetric hydroformylation using phosphite ligands in the most emerging period for this area of research (1996 to February 2004). In the first section we will cover the results obtained using diphosphite ligands. In the next sections, we will present the results using heterodonor phosphite ligands, emphasizing the results obtained with the phosphite–phosphine ligands. We also discuss any reported mechanistic aspects concerning the hydroformylation results.

2. Diphosphite ligands

The first report on asymmetric hydroformylation using diphosphite ligands revealed no asymmetric induction.[7] In 1992, Takaya and co-workers published the results of the asymmetric hydroformylation of vinyl acetate (ee's up to 50%) using chiral diphosphites with a binaphthol backbone.[8] In the same year, there was an important breakthrough when Babin and Whiteker at Union Carbide patented the asymmetric hydroformylation of various alkenes with ee's up to 90%, using bulky diphosphites **1a–c** derived from homochiral (2*R*,4*R*)-pentane-2,4-diol (Fig. 1, Table 1).[4a] Their results clearly showed that (a) the presence of bulky substituents at the *ortho*-positions of the biphenyl moieties is necessary for good regio and enantioselectivities and (b) the presence of methoxy substituents in the *para*-positions of the biphenyl moieties always produced better enantioselectivities than those observed for the corresponding *tert*-butyl-substituted analogs.

Table 1. Rh-catalyzed asymmetric hydroformylation of styrene using diphosphites **1a–c**[a]



Entry	Ligand	*T* (°C)	% 2-PP[b]	% Ee[c]
1	**1a**	70	95	44
2	**1b**	70	93	61
3	**1c**	70	82	14
4	**1b**	25	98	90

[a] [Rh(acac)(CO)$_2$] = 0.0135 mmol; ligand/Rh = 4; substrate/Rh = 1000; Toluene = 15 mL; $P_{H_2/CO}$ = 130 psi.
[b] Regioselectivity for 2-phenylpropanal.
[c] Enantiomeric excess.

Inspired by the excellent early results obtained with the Union Carbide type-ligands **1a–c**, other research groups have recently studied different modifications in these

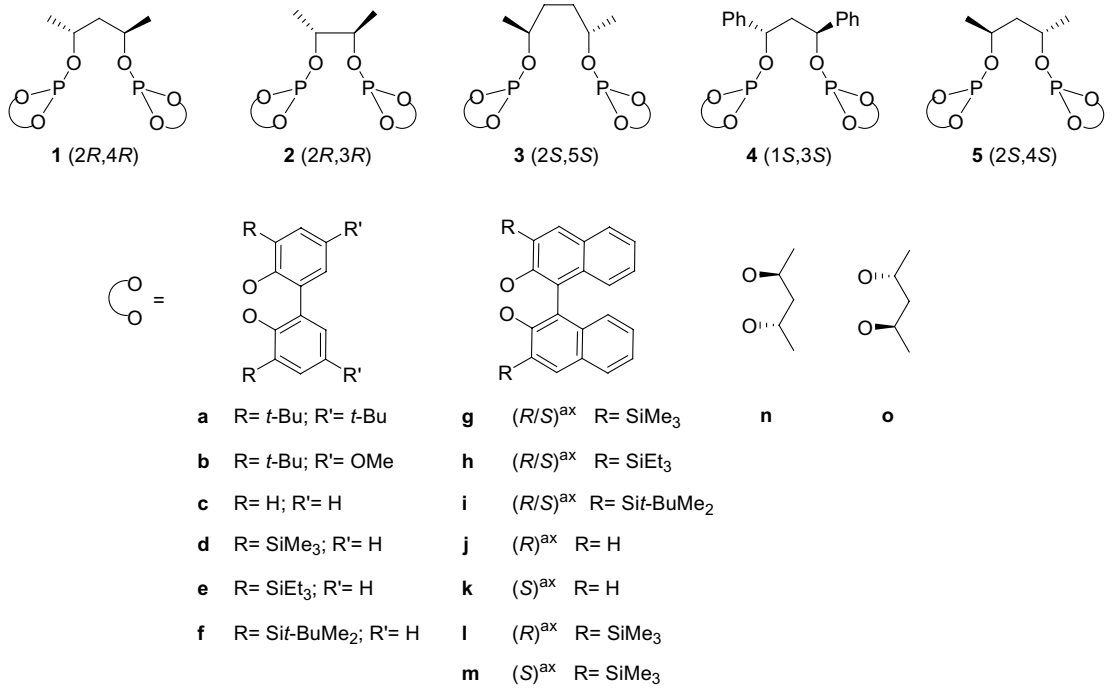


Figure 1. Diphosphite ligands **1–5**.

types of ligand (Fig. 1).[4b,9] In this context, they studied the influence of the bridge length, several phosphite moieties and backbone substituents, and the possibility of a cooperative effect between stereogenic centers on the performance of the catalysts.

The influence of the bridge length was studied with diphosphite ligands based on (2*R*,4*R*)-pentane-2,4-diol (ligands **1a** and **1b)**, (2*R*,3*R*)-butane-2,3-diol (ligands **2a** and **2b)**, and (2*S*,5*S*)-hexane-2,5-diol (ligands **3a** and **3b)**. In general, ligands **1**, which have three carbon atoms in the bridge, provided higher enantioselectivities than ligands **2** and **3**, which have two and four carbon atoms in the bridge, respectively.[9a]

The effect of different phosphite moieties was studied with ligands **1d–o**. In general, sterically hindered phosphite moieties are necessary for high enantioselectivities.[4b,9b] Thus, ligands **1j**, **1k**, **1n**, and **1o** show low asymmetric induction (ee's up to 20%). Also, the results of using ligands **1d–i** indicated that varying the *ortho*-substituents on the biphenyl and binaphthyl phosphite moieties has a great effect on asymmetric induction. The optimal steric bulk in the *ortho*-positions therefore seems to be obtained with trimethylsilyl substitutents (i.e., ligand **1d** provided ee's up to 87% at 20 bar of syn gas and 25 °C). This result is similar to the previously reported best result obtained with **1b**.

The influence of the backbone substituent was studied by comparing ligands **1a** and **1b** with ligands **4a** and **4b** (Fig. 1). Surprisingly, the latter ligands, which have a more sterically hindered phenyl group, provided lower enantioselectivities than ligands **1**.[9a]

A possible cooperative effect between the different stereogenic centers was studied using ligands **1l–o** and **5l–o**. Initially, van Leeuwen et al. studied the cooperative effect between the chiral ligand bridge and the axially chiral binaphthyl phosphite moieties by comparing ligands **1l**, **1m**, **5l**, and **5m**. The hydroformylation results clearly indicate a cooperative effect that leads to a matched combination for ligand **1m** with (S^{ax},2*R*,4*R*,S^{ax})-configurations (ee's up to 86%) (Table 2).[4b] Later, Bakos et al. with ligands **1n**, **1o**, **5n**, and **5o** found a similar cooperative effect between the chiral ligand bridge and the chiral phosphite moiety.[9b] However, the matched combination afforded poorer results (ee's up to 17%) than those obtained with bulky biaryl phosphite ligands **1b**, **1d**, and **1m** (ee's up to 90%) due to the lower steric bulk of the Bakos' ligands (vide supra).

Table 2. Rh-catalyzed asymmetric hydroformylation of styrene using diphosphites **1l**, **1m**, **5l**, and **5m**[a]

Entry	Ligand	TOF[b]	% 2-PP[c]	% Ee[d]
1	**1l**	28	95	38 (*S*)
2	**1m**	17	88	69 (*S*)
3	**5l**	4	91	23 (*S*)
4	**5m**	45	94	40 (*R*)
5[e]	**1m**	11	92	86 (*S*)

[a] [Rh(acac)(CO)$_2$] = 0.02 mmol; ligand/Rh = 2.2; substrate/Rh = 1000; Toluene = 20 mL; $P_{H_2/CO}$ = 10 bar. T = 25 °C.
[b] TOF in mol styrene × mol Rh^{-1} × h^{-1} determined after 1 h reaction time.
[c] Regioselectivity for 2-phenylpropanal.
[d] Enantiomeric excess.
[e] T = 15 °C.

Interestingly, the hydroformylation results obtained with ligands **1b** and **1d**, which have conformationally flexible axially chiral biphenyl moieties, are similar to those obtained with ligand **1m**, which have conformationally rigid binaphthyl moieties. This indicates that diphosphite ligands containing the conformationally flexible axially chiral biphenyl moieties predominantly exist as single atropoisomer in the [HRh(CO)$_2$(diphosphite)] complexes when the right bulky substituents in the *ortho*-positions are present (vide infra).[4b] It is therefore not necessary to use expensive conformationally rigid binaphthyl moieties to reduce the degrees of freedom of the system.

To investigate whether a relationship exists between the solution structures of the hydridorhodium diphosphite species [HRh(CO)$_2$(diphosphite]][10] and catalytic performance, van Leeuwen et al. extensively studied the rhodium–diphosphite complexes formed under hydroformylation conditions by high pressure NMR (HP-NMR) techniques. It is well known that these complexes have a trigonal bipyramidal (TBP) structure. Two isomeric structures of these complexes, one containing the diphosphite coordinated in a bis-equatorial (**ee**) fashion and one containing the diphosphite in an equatorial–axial (**ea**) fashion, are possible (Fig. 2).[1e]

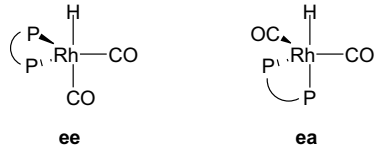


Figure 2. Bis-equatorial (**ee**) and equatorial–axial (**ea**) coordination modes of diphosphite ligands in the [HRh(CO)$_2$(diphosphite)] complexes.

Van Leeuwen's studies using diphosphite ligands **1** and **5** indicated that the stability and catalytic performance of the [HRh(CO)$_2$(diphosphite)] species depend strongly on the configuration of the 2,4-pentanediol ligand backbone and the chiral biaryl phosphite moieties. Thus, for example, ligands **1b**, **1d**, and **1m**, which form well-defined stable bis-equatorial (**ee**) complexes, lead to good enantiomeric excesses, whereas enantioselectivities were low with ligands **1l** and **5m**, which form unidentified mixtures of complexes and ligand decomposition.[4b,11]

In the last few years, various authors, inspired by the great importance of the BINOL-derived ligands for asymmetric catalysis,[12] have followed the path opened by Takaya et al.[8] in the development of new diphosphite ligands based on binaphthol for the Rh-catalyzed asymmetric hydroformylation of styrene (Fig. 3).[13] In general, ligands **6–9** have shown good regioselectivities

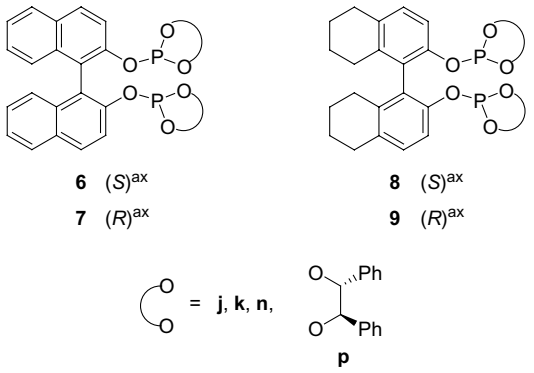


Figure 3. Diphosphite ligands based on binaphthol.

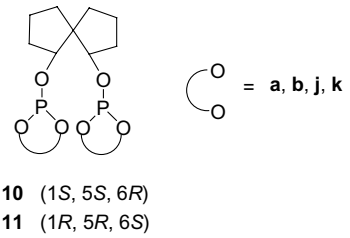


Figure 4. Diphosphite ligands with spiro backbone.

in 2-phenylpropanal (up to 87%) and low-to-moderate enantioselectivities (ee's up to 37%).

In 1998, Chan et al. developed a new class of diphosphite ligands with *cis trans*-spirol backbone for the asymmetric hydroformylation of styrene and other vinyl arenes (Fig. 4).[14] These ligands showed high regioselectivities (up to 97% in the branched aldehyde) and moderate-to-good enantioselectivities (ee's up to 70%). The hydroformylation results indicated once again that the presence of bulky substituents in the *ortho*-positions of the biphenyl moieties is necessary for high enantioselectivity, while the sense of enantioselectivity is controlled by the configuration of the biaryl phosphite moieties. Moreover, no cooperative effect between the spiro backbone and the phosphite moiety was observed.

Another important source of chiral diphosphite ligands studied for asymmetric hydroformylation are sugar derivatives. The first report in this field, by van Leeuwen et al. in 1995, showed the potential of this type of backbone (ee's up to 65%).[15]

In 1998, Selke et al. tested a series of diphosphite ligands **12** (Fig. 5) with β-D-glucopyranoside backbone in the Rh-catalyzed asymmetric hydroformyl-ation of vinyl acetate, allyl acetate and *p*-methoxystyrene.[16] In general, good regioselectivities in branched product (>90%) and low-to-moderate enantioselectivities (ee's up to 36%) were obtained.

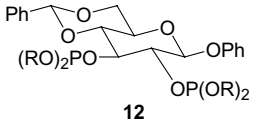


Figure 5. Diphosphite ligands with β-D-glucopyranoside backbone.

An important breakthrough in this area came with the use of a series tunable furanoside diphosphite ligands **13**–**18** (Fig. 6) in the Rh-catalyzed hydroformylation of vinyl arenes.[4c–e,17] The modular construction of these ligands allows sufficient to fine tune (a) the different configurations of the carbohydrate backbone and (b) the steric and electronic properties of the diphosphite substituents. These ligands show both excellent enantioselectivities (up to 93%) and regioselectivities (up to 98.8%) under mild conditions (Tables 3 and 4).

The results of using the biphenyl-based ligands **13**–**18a**–**d** (Table 3) showed that

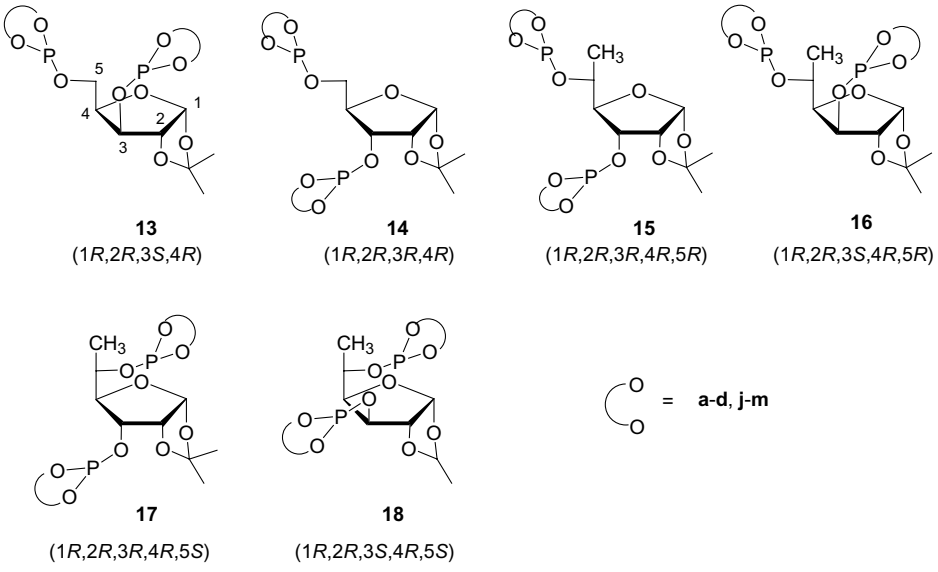


Figure 6. Furanoside diphosphite ligands **13**–**18**.

(a) The presence of a methyl substituent in C-5 is necessary for high enantioselectivities and has a positive effect on rate (entries 3–12 vs 1 and 2).
(b) The level of enantioselectivity is influenced by a cooperative effect between stereocenters C-3 and C-5. Accordingly, ligands **16** and **17** provide better enantioselectivities than ligands **15** and **18** (Table 3, entries 6 and 8 vs 4 and 10).
(c) The absolute configuration of the product is governed by the configuration at the C-3 stereogenic center. Accordingly, ligands **13**, **16**, and **18**, with *S*-configuration at C-3, gave (*S*)-2-phenylpropanal (Table 3, entries 1, 5, 6, 9, 10, and 12) while ligands **14**, **15**, and **17**, with *R*-configuration at C-3, gave (*R*)-2-phenylpropanal (Table 3, entries 2–4, 7, 8, and 11).

Table 3. Rh-catalyzed asymmetric hydroformylation of styrene using diphosphites **13**–**18a**–**d**[a]

Entry	Ligand	TOF[b]	% 2-PP[c]	% Ee
1	**13b**	5	97	60 (*S*)
2	**14b**	5	97	61 (*R*)
3	**15a**	14	97.1	46 (*R*)
4	**15b**	13	97.2	58 (*R*)
5	**16a**	19	98.4	74 (*S*)
6	**16b**	18	98.6	90 (*S*)
7	**17a**	16	98.7	76 (*R*)
8	**17b**	17	98.3	89 (*R*)
9	**18a**	15	97.4	52 (*S*)
10	**18b**	12	97.6	64 (*S*)
11	**15d**	10	98.1	62 (*R*)
12	**16d**	11	98.8	93 (*S*)

[a] $[Rh(acac)(CO)_2] = 0.0135$ mmol; ligand/Rh = 1.1; substrate/Rh = 1000; Toluene = 15 mL; $P_{H_2/CO} = 10$ bar; $T = 20$ °C; $P_{CO}/P_{H_2} = 0.5$.
[b] TOF in mol styrene × mol $Rh^{-1} \times h^{-1}$ determined after 1 h reaction time.
[c] Regioselectivity for 2-phenylpropanal.

(d) As observed with the previously mentioned ligands **1a**–**d**, there is an influence on the substituents in the biaryl phosphite moieties. Thus, ligands **16b** and **16d** and **17b** and **17d**, with either methoxy substituents or trimethylsilyl groups, always produced the best enantioselectivities.

Furthermore, the results of using the binaphthyl-based ligands **13**–**18j**–**m** (Table 4) suggested that the absolute configuration of the product outcome is controlled by the configuration of the biaryl moieties. This suggests that the configuration of fluxional biphenyl moieties in ligands **15**–**18a**–**d** is controlled by the configuration of the C-3 stereogenic center. The results also indicate a cooperative effect between the chiral sugar backbone stereocenters (C-3 and C-5) and the axial chiral binaphthyl phosphite moieties. This cooperative effect, together with the previously observed cooperative effect between the backbone stereocenters C-3 and C-5, controls enantioselectivity.

In summary, both the (*S*)- and (*R*)-enantiomers of the product can be obtained with excellent regio and enantioselectivity. These results are among the best ever reported for the asymmetric hydroformylation of vinyl arenes.[4,5]

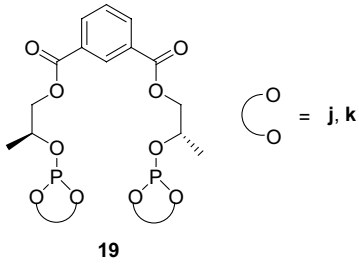
Table 4. Rh-catalyzed asymmetric hydroformylation of styrene using diphosphites **13**–**18j**–**m**[a]

Entry	Ligand	TOF[b]	% 2-PP[c]	% Ee
1	**13j**	126	80	44 (*R*)
2	**13k**	85	83	37 (*S*)
3	**15j**	178	86	20 (*R*)
4	**15k**	158	84	5 (*S*)
5	**16j**	165	85	60 (*R*)
6	**16k**	153	85	25 (*S*)
7	**16m**	149	84	68 (*S*)

[a] $[Rh(acac)(CO)_2] = 0.0135$ mmol; ligand/Rh = 1.1; substrate/Rh = 1000; Toluene = 15 mL; $P_{H_2/CO} = 10$ bar; $T = 40$ °C; $P_{CO}/P_{H2} = 0.5$.
[b] TOF in mol styrene × mol $Rh^{-1} \times h^{-1}$ determined after 1 h reaction time.
[c] Regioselectivity for 2-phenylpropanal.

The characterization of the rhodium complexes formed under hydroformylation conditions by NMR techniques and in situ IR spectroscopy showed that there is a relationship between the structure of the $[HRh(CO)_2(P–P)]$ (P–P = **13**–**18**) species and their enantiodiscriminating performance. In general, enantioselectivities were highest with ligands with a strong bis-equatorial (**ee**) coordination preference, while an equilibrium of species with bis-equatorial (**ee**) and equatorial–axial (**ea**) coordination modes considerably reduced the ee's.[4d,e]

In 2001, Freixa and Bayón reported the first example of chiral macrocyclic diphosphite ligands for a fairly efficient asymmetric hydroformylation of several vinyl arenes (Fig. 7).[18] Thus, ligand **19j** provided good enantioselectivities (ee's up to 76%), but moderate regioselectivities in favour of the branched aldehyde were obtained (regioselectivity up to 83%).

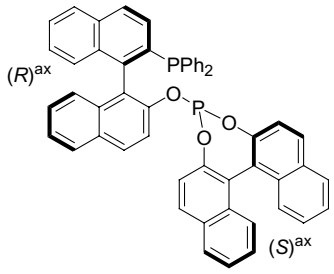


19

Figure 7. Macrocyclic diphosphite ligands **19**.

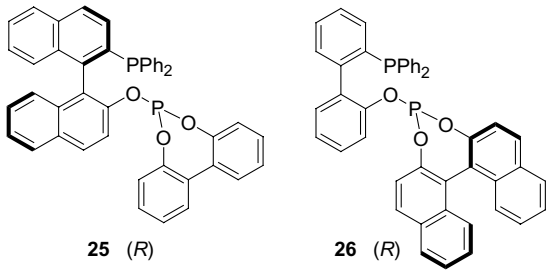
3. Phosphite–phosphine ligands

The first report on asymmetric hydroformylation using phosphite–phosphine ligands was by Takaya et al. in 1993.[19] With the aim of combining the effectiveness of the BINOL chemistry for asymmetric catalysis and the effectiveness of the phosphite moiety for asymmetric hydroformylation, they developed the (*R*,*S*)-BINAPHOS ligand **20**, which turned out to be a very efficient ligand (Fig. 8).



(*R*,*S*)-BINAPHOS **20**
(ee's up to 95%)

Figure 8. (*R*,*S*)-BINAPHOS ligand.



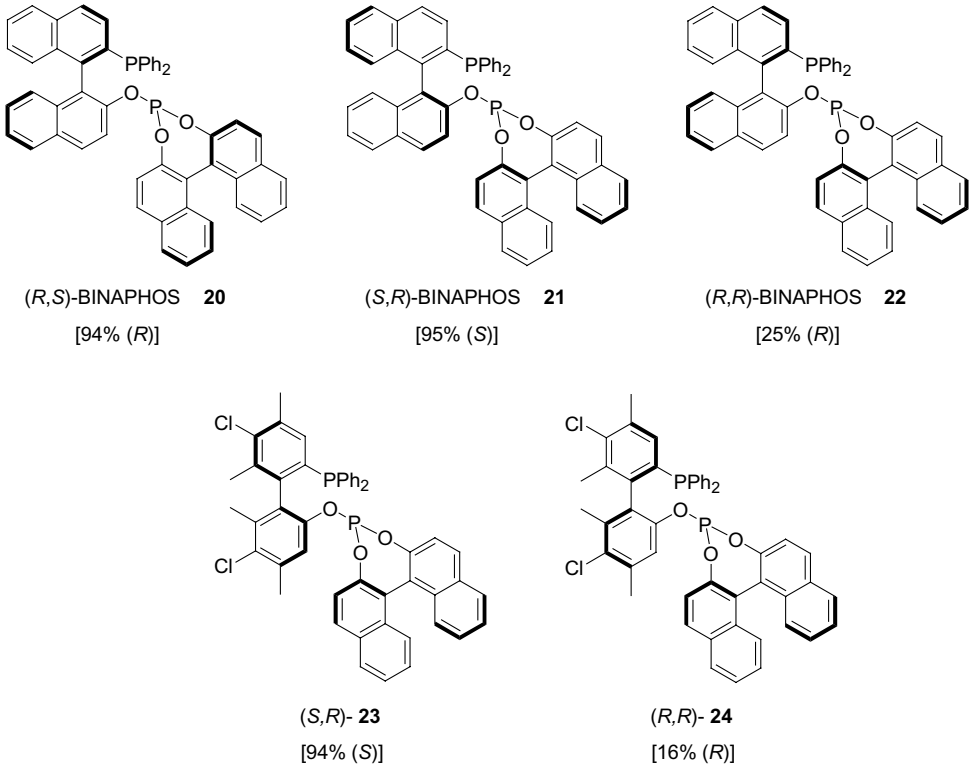
25 (*R*) **26** (*R*)

Figure 10. BINAPHOS related ligands **25** and **26**.

In the last few years, a wide range of structural variations has been reported. In this context, in 1997, Nozaki et al. used ligands **20**–**22** and found that the sense of enantioselectivity is governed by the configuration of the binaphthyl bridge, whereas the enantiomeric excess depends strongly on the configuration of both binaphthyl moieties (Fig. 9).[5a] Enantioselectivity is therefore higher when the configurations of the two binaphthyl moieties are opposite (i.e., diastereoisomers *R*,*S* or *S*,*R*). Similar trends were observed with ligands **23** and **24**, which have a chiral biphenyl bridge.

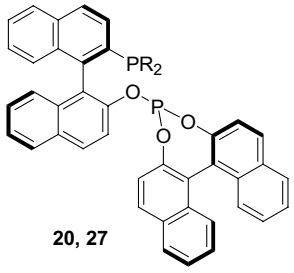
To understand further the role of the chirality at the bridge and the axial chirality at the phosphite moiety in transferring the chiral information to the product outcome, ligands **25** and **26** were studied (Fig. 10).[5a] Ligand **25**, which has an (*R*)-binaphthyl in the bridge, provides an ee of 83% (*R*). This value is close to the (*R*,*S*)-BINAPHOS value (94% (*R*) ee). This suggests that, in the formation of the Rh-complex, the binaphthyl bridge controls the conformation of the biphenyl phosphite moiety. Likewise, ligand **26** provides an ee of 69% (*S*), which suggest that the binaphthyl phosphite moiety also controls the conformation of the biphenyl bridge upon coordination to rhodium. However, the control by the binaphthyl bridge is more efficient than that of the binaphthyl phosphite moiety.

The effect of several substituents in the phosphine moiety has been extensively studied by Nozaki's group (Fig. 11). Their results indicate that both regio and enantioselectivity can be increased by suitable choice of the aryl phosphine group. The best combinations of regio and enantioselectivity were therefore obtained with ligands **27a** and **27b**.[20]



(*R*,*S*)-BINAPHOS **20** [94% (*R*)]
(*S*,*R*)-BINAPHOS **21** [95% (*S*)]
(*R*,*R*)-BINAPHOS **22** [25% (*R*)]
(*S*,*R*)- **23** [94% (*S*)]
(*R*,*R*)- **24** [16% (*R*)]

Figure 9. Rh-catalyzed asymmetric hydroformylation of styrene using ligands **21**–**24**. Enantioselectivities obtained at 100 bar of syn gas and 60 °C are shown in brackets.



Ligand	R	%2-PP	%ee
20	C_6H_5	90.6	95.2 (*R*)
27a	3-MeO-C_6H_4	95.0	97.5 (*R*)
27b	3-^{i}PrO-C_6H_4	94.0	98.3 (*R*)
27c	3-$C_6F_{13}CH_2CH_2$-C_6H_4	92.7	90.6 (*R*)
27d	3-Me-C_6H_4	93.4	94.1 (*R*)
27e	3,5-(MeO)2-C_6H_3	87.5	92.2 (*R*)
27f	4-MeO-C_6H_4	88.8	91.7 (*R*)

Figure 11. Rh-catalyzed asymmetric hydroformylation of styrene using ligands **20** and **27**.

The characterization of the rhodium complexes formed under hydroformylation conditions by NMR techniques and in situ IR spectroscopy showed that there is a relationship between the structure of the [$HRh(CO)_2$(BINAPHOS)] species and their enantiodiscriminating performance. Thus, (*R*,*S*) and (*S*,*R*)-BINAPHOS ligands show high equatorial–axial (**ea**) coordination preference with the phosphite moiety in the axial position. Meanwhile, the characterization of the (*R*,*R*)- and (*S*,*S*)-BINAPHOS ligands suggests that there is either a structural deviation of the monohydride complexes from an ideal TBP structure or an equilibrium between isomers.[5a,21]

Highly cross-linked polymer-supported-BINAPHOS ligands were effective for the hydroformylation of styrene and other functionalized olefins (ee's up to 89%). Recovery and reuse of the catalyst was possible at low stirring conditions.[22]

Perfluoroalkyl-substituted BINAPHOS ligand **27c** was also developed for asymmetric hydroformylation of vinyl arenes in $scCO_2$. With this ligand high regio and enantioselectivity (ee's up to 93.6%) were achieved without the need of hazardous organic solvents.[5b,23]

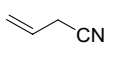
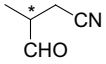
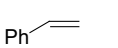
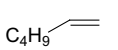
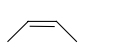
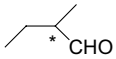
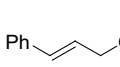
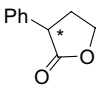
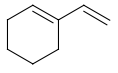
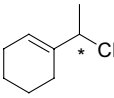
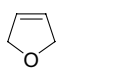
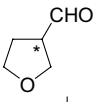
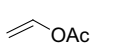
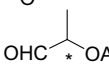
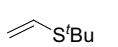
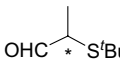
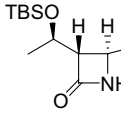
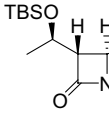
In summary, BINAPHOS is the most important ligand for asymmetric hydroformylation. Thus, this ligand provides higher enantioselectivities than diphosphine and diphosphite ligands for a wide variety of both functionalized and internal alkenes (Table 5).

Inspired by the excellent results of the BINAPHOS ligands, other authors have recently developed new phosphite–phosphine ligands for asymmetric hydroformylation.

In 1996, Börner and co-workers developed a series of chiral sugar phosphine–phosphite ligands, **28**–**32**, with axial and central chirality for the Rh-catalyzed asymmetric hydroformylation of allyl acetate (Fig. 12).[30] Their results clearly indicated that both central and axial chirality are responsible for the stereochemical outcome of this reaction. Enantioselectivities of up to 44% ee were obtained using ligand **31**.

In 2000, van Leeuwen et al. developed a series of phosphite–phosphine ligands **33** and **34** containing a

Table 5. Several substrates efficiently hydroformylated using Rh-BINAPHOS system

Substrate	Product	% Ee[a]	Ref.
		66	24
		98.3	20
		90	20
		89.9	20
		88	25
		97	26
		68	27
		92	5a
		90	28
		89[b]	29

[a] Enantiomeric excess.
[b] Diastereomeric excess.

stereogenic phosphine moiety and a phosphite moiety with axial chirality (Fig. 13).[31] These ligands were applied in the Rh-catalyzed asymmetric hydroformylation of styrene, with good regioselectivities (up to 92%) and enantioselectivities (ee's up to 62%). They found that the absolute configuration of the product is governed by the stereogenic center at the ligand backbone. Their results also showed a cooperative effect between the binaphthol moiety and the group attached to the stereocenter in the backbone. In the [$HRh(CO)_2$(PP)]

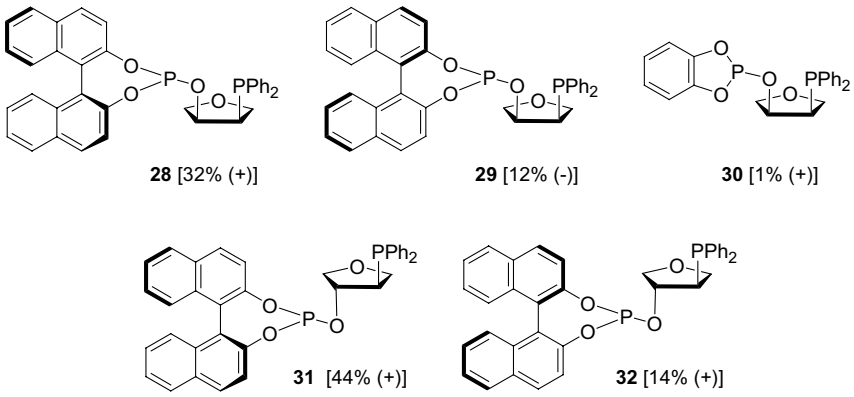


Figure 12. Furanoside phosphine–phosphite ligands **28**–**32**. Enantiomeric excess is shown in brackets.

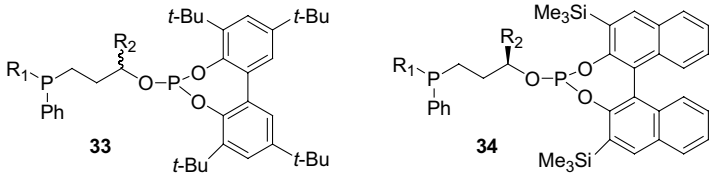


Figure 13. Phosphine–phosphite ligands developed by van Leeuwen and co-workers.

(PP = **33**, **34**) complexes, the ligands coordinated in an equatorial–axial (**ea**) coordination mode with the phosphine moiety in the axial position. This contrasts with the coordination mode for the complex $[HRh(CO)_2(BINAPHOS)]$ but is in agreement with the results of Takaya et al., who found that, also for BINAPHOS, the equatorial coordinated group has the largest influence in enantiodiscrimination.

In 2001, Claver et al. also developed a series of phosphine–phosphite ligands **35** with furanoside backbone related to diphosphite **13** (Fig. 14).[32] These ligands showed low-to-moderate enantioselectivities in the Rh-catalyzed asymmetric hydroformylation of styrene (ee's up to 49). As previously observed, enantioselectivity was best when bulky susbtituents were present in the *ortho*-positions of the biphenyl moieties. The HP-NMR studies indicate that the $[HRh(CO)_2(\mathbf{35})]$ complexes exist in two diastereomeric equatorial–axial (**ea**) forms in fast exchange, which may account for the lower enantioselectivities than those obtained with the BINAPHOS system.

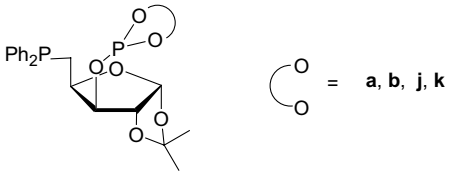


Figure 14. Phosphine–phosphite ligands **35** with furanoside backbone.

Recently, Faraone et al. synthesized a series of phosphite–phosphine ligands **36** for the asymmetric hydroformylation of styrene (Fig. 15).[33] These ligands showed

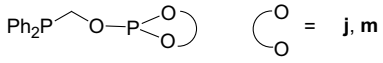


Figure 15. Phosphite–phosphine ligands **36**.

low enantioselectivities (ee's up to 20%). These low enantioselectivities are explained by monodentate coordination of the ligand under hydroformylation conditions.

4. Other heterodonor ligands

Other types of heterodonor ligands containing a phosphite moiety have also been developed for application in asymmetric hydroformylation catalysis. In general these have had little success.

4.1. Phosphite–phosphoroamidites

To the best of our knowledge, only four reports are known in the literature.

The first of these reports used an ephedrine-based phosphite–phosphoroamidite ligand **37** in the hydroformylation of styrene (Fig. 16).[34] These ligands afforded low levels of enantioselectivity (ee's up to 8%).

The second report used a series of phosphite–phosphoroamidite ligands with furanoside backbone **38** (Fig. 16).[35] These ligands showed low-to-moderate enantioselectivities in the Rh-catalyzed asymmetric hydroformylation of styrene (ee's up to 65%). The HP-NMR

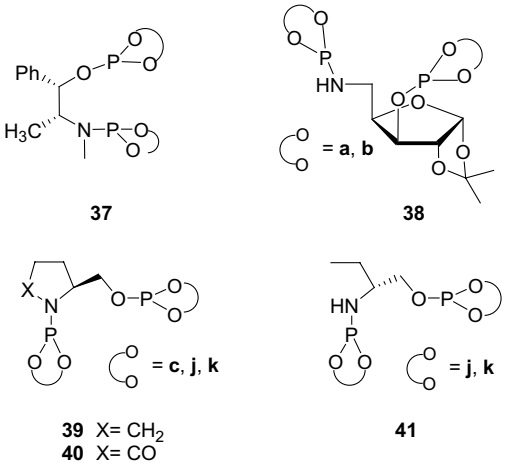


Figure 16. Phosphite–phosphoroamidites ligands **37**–**41**.

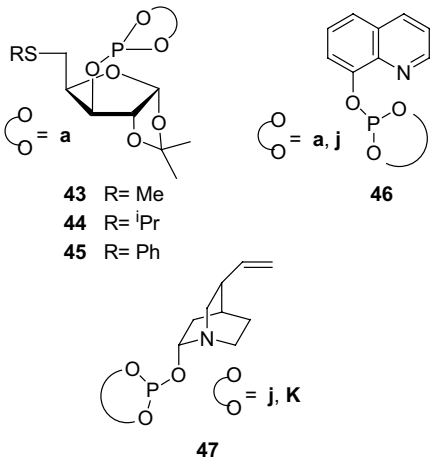


Figure 18. Phosphite–thioether and phosphite–amino ligands **43**–**47**.

and in situ HP-IR spectroscopy studies indicated that the most stable bisequatorial diastereomer of the [$HRh(CO)_2$(**38**)] complexes are in equilibrium with equatorial–axial species.

The third report, which used proline-based phosphite–phosphoroamidite ligands **39c** and **40c** (Fig. 16) in the Rh-catalyzed asymmetric hydroformylation of styrene, obtained poor enantioselectivities (ee's up to 19%).[36]

The last report developed a series of 1,2-phosphite–phosphoroamidite ligands **40j** and **40k** and **41j** and **41k** with chiral binaphthyl moieties (Fig. 16).[37] These ligands were tested in the Rh-catalyzed asymmetric hydroformylation of vinyl acetate with high regioselectivity in the branched aldehyde and low-to-moderate enantioselectivity (ee's up to 32%).

4.2. Phosphite–aminophosphine

So far only Vogt et al. have reported the use of phosphite–aminophosphine in asymmetric hydroformylation. These authors used an ephedrine-based phosphite–aminophosphine ligand **42** with a stereogenic center at the aminophosphine P-atom in the hydroformylation of styrene (Fig. 17).[38] This ligand afforded encouraging levels of regio and enantioselectivity (ee's up to 58%).

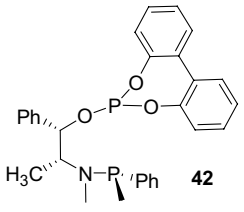


Figure 17. Ephedrine-based phosphite–aminophosphine ligand **42**.

4.3. Phosphite–thioether and phosphite–amino

In the last few years, three reports have used these types of ligands in asymmetric hydroformylation (Fig. 18), but with little success.[39] Enantiomeric excesses are usually negligible. In the case of thioether–phosphite ligands **43**–**45**, the HP-NMR study under catalytic conditions indicated that the thioether moiety is not coordinated in the mononuclear hydride–rhodium complexes. This could explain the low enantiomeric excess obtained with this system and the phosphite–amino systems (Rh-**46** and Rh-**47**).[40]

5. Conclusions

In the last few years, diphosphite and phosphine–phosphite ligands have undoubtedly become some of the most versatile ligands for the enantioselective hydroformylation reaction. Excellent control of selectivity based on the properties of the ligand has been demonstrated. For both types of ligands, complexes with the formula $RhH(PP)(CO)_2$ have been characterized as the resting state of the catalyst. The presence of only one active diastereoisomeric hydridorhodiumcarbonyl species with the Rh–diphosphites (**ee**) or Rh–phosphine–phosphite (**ea**) system precursors is presumably the key to controlling efficient chirality transfer.

For industrial applications, however, the productivity of the catalysts needs to be further improved in order to achieve high turnover numbers and frequencies. It is hoped that the efficiency of the catalyst can be increased and the search for improved ligand systems will be greatly assisted by combinatorial screening methods, to which the readily available phosphite ligand may prove to be well suited.

Acknowledgements

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