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Recent Advances in Enantioselective Hydroformylation

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Contents

1. Introduction

The hydroformylation reaction is one of the oldest processes which makes use of soluble transition metal catalysts and is one of the largest volume industrial applications of these catalysts. Several reviews have been published dealing with the hydroformylation process,[1] and also with the asymmetric modification of this reaction.[2] The two more updated reviews concerning the latter aspect cover the literature reports published up to the end of 1992.[3] In the last two years, some major breakthroughs have been achieved in this field, particularly in the area of the rhodium catalyzed enantioselective hydroformylation. This stimulated us to write this review with the aim of providing a critical presentation of these recent results. Reference to the general features of asymmetric hydroformylation and comparisons with the results obtained since 1992 will be made throughout the text in an effort to rationalize the most important achievements.

The review covers the articles which have appeared in the literature up to the end of 1994 with reference to reports where enantioface discrimination of the substrates is involved. A few papers published in early 1995 have been cited as well and some unpublished results from the laboratories of the authors have been entered where appropriate.

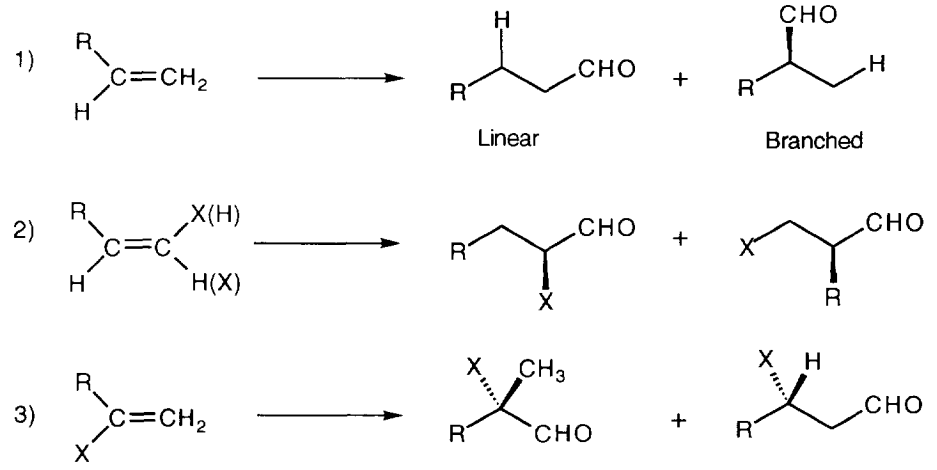
2. Enantioselective Hydroformylation

2.1 General Features

Hydroformylation provides for the one carbon chain-elongation of an olefinic substrate through addition of hydrogen and carbon monoxide to the double bond. In the course of the reaction, new stereogenic carbon atoms may be produced. According to the structure of the substrate, there are several possibilities for accomplishing this goal. The ones of practical significance are illustrated in Chart 1.

Chiral aldehydes can be obtained: 1) by insertion of carbon monoxide onto the more substituted sp^2-carbon of a linear terminal olefin; 2) by insertion of carbon monoxide onto any one of the two carbons of an internal olefin; 3) by insertion either of carbon monoxide or of hydrogen onto the more substituted sp^2-carbon of a vinylidenic olefin.

Chart 1. Possible routes to chiral aldehydes by asymmetric hydroformylation



In the first two entries and in the first case of the third entry the stereocenter originates from the formation of a new carbon-carbon bond. This process is sometimes referred to as asymmetric α-induction and is by far the most common case. In the second case of the last entry, a carbon-hydrogen bond is responsible for the origin of the stereogenic carbon of the less branched aldehyde. This process is sometimes referred to as asymmetric β-induction.

2.2 Scope and Limitations

From Chart 1 it is readily apparent that asymmetric hydroformylation of olefins holds enormous potential for the synthesis of optically active aldehydes. These are valuable intermediates in the preparation of a large variety of biologically active compounds. Unfortunately, among the enantioselective reactions catalysed by transition metals, hydroformylation is one of the most difficult to achieve for several reasons. There are chemoselectivity problems because hydrogen is one of the reactants and hydroformylation catalysts are additionally able to promote hydrogenation and double bond migration. There are problems of regioselectivity since the reaction involves addition of unsymmetrical termini to the double bond of a normally non-symmetrical

substrate. And, obviously, there are problems of stereoselectivity related to the efficiency of the transfer of the chiral information from the catalysts to the substrate. This depends on the extent of the diastereotopic interactions developed in the transition state of the first irreversible step of the catalytic cycle, where the relative configurations of the enantiomeric aldehydes are determined. A balance is necessary for obtaining efficient asymmetric hydroformylation and this requires that favourable conditions for each kind of selectivity have to be met at the same time.

A further limitation arises from the fact that under hydroformylation conditions enolizable chiral aldehydes may undergo racemization. For most aliphatic substrates this is not a serious problem and the enantiomeric purity of the product is only marginally affected even when the reaction is run for a long time at fairly high temperatures. On the contrary, the extent of racemization can be severe when the aldehydes have an additional electron withdrawing substituent like an aryl group on the α-carbon atom. It is advisable to run hydroformylation of vinylarenes under mild conditions and to complete the reaction in a short time in order to minimize racemization phenomena. This calls for chiral catalysts of high activity and these are not always compatible with a high regio- and stereoselectivity. As an alternative, the aldehyde must be promptly removed from the hydroformylation catalyst by addition of a suitable scavenger to the reaction medium. Orthoformate esters have been sometimes employed to this purpose, but their use is not free from drawbacks.[4]

2.3 Metal Catalysts

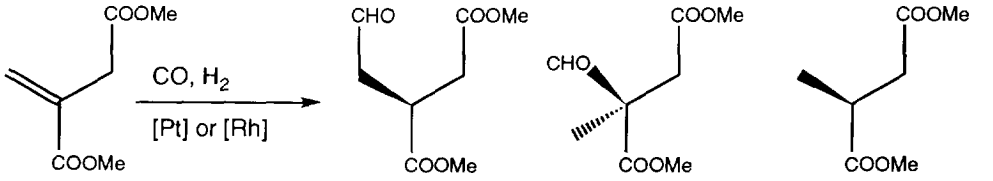
Almost all transition metals have been examined for catalytic activity in hydroformylation and the majority of them have been found active to some extent. As to asymmetric hydroformylation is concerned, however, only rhodium and heterodinuclear platinum-tin catalysts deserve to be considered. Rhodium catalysts were introduced in hydroformylation about thirty years ago.[5] Rhodium complexes with chiral phosphines were the catalysts used in the first successful attempts at asymmetric hydrofomylation carried out by different groups in the early seventies.[6] The use of platinum-tin catalysts in hydroformylation was first reported by Orchin in 1975.[7] These catalysts were promptly addressed towards asymmetric reactions.[8]

Rhodium and platinum behave differently and under some respect they are complementary. As a general rule, rhodium catalysts are more active and more chemoselective whereas platinum catalysts have been considered so far more stereoselective. ***Furthermore, most Pt-catalysts are active only at a fairly high pressure (more than 80 bars), whereas Rh-catalysts are usually active, albeit less selective, even at atmospheric pressure.*** Depending on the structure of the substrate, the tendency of platinum catalysts to favour the linear isomer can be very pronounced, and this is possibly the main difference to rhodium catalysts.

These concepts are clearly apparent from the following examples. The first one is shown in Chart 2 and is concerned with the hydroformylation of dimethyl itaconate which provides the highest enantioselectivity so far recorded in a β-induction process. Only the less branched aldehyde, in high e.e, but in low yield, is obtained with platinum, the major reaction product being the hydrogenated product.[9] The more branched isomer is by far predominant with rhodium: it is obtained in high yield, but the e.e. is very poor.[10]

The second example refers to the asymmetric hydroformylation of alkyl α-N-acylaminoacrylates and is shown in Chart 3. Platinum-tin complexes with DIOP give only the hydrogenated product **3** and no aldehyde is formed.[11] On the contrary, in the presence of rhodium complexes with chelating diphosphine ligands like DIOP, the reaction takes place with complete positional selectivity affording as the exclusive aldehydic product the more

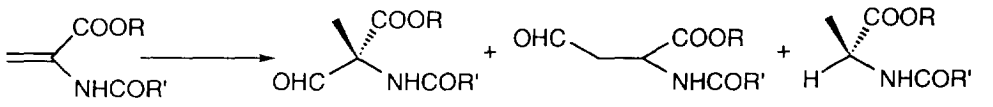
Chart 2. Hydroformylation of dimethyl itaconate



Pt Catalyst	83.6% e.e. 19% yield	– –	51.4% e.e. 73% yield
Rh Catalyst	n.d. 6% yield	9.1% e.e. 80% yield	n.d. 11% yield

branched isomer **1**. Notably, no trace of the less hindered aldehyde **2** was detected. Although the chemoselectivity of the reaction is strongly dependent on the nature of the phosphine ligand and on the operative conditions, under optimised conditions chemical yields up to 95% and e.e. up to 60% can be obtained. The regiospecific insertion of carbon monoxide onto the more substituted carbon has been attributed to the polarization of the double bond and to the chelation control operated by the acylamido group.[12] Even if not exceptional, this enantioselectivity has been for some years the highest in all Rh-catalysed hydroformylations. It is even now the highest in the Rh-catalysed hydroformylation of a vinylidenic olefin.

Chart 3. Hydroformylation of α-Acylaminoacrylic Acid Esters



1 **2** **3**

2.4 Enantioselective Hydroformylation of Styrene

The contrasting behaviour of rhodium and platinum-tin catalysts is readily apparent also from the data reported in Tables 1 and 2 which summarize the state of art in the hydroformylation of styrene by the end of 1992. This reaction has attracted particular attention since it provides a straightforward method for the preparation of arylpropionic acids, an important class of non-steroidal anti-inflammatory agents. The synthesis of two important representative drugs of this family, Ibuprofen and Naproxen, is sketched in Chart 4.

Table 1 collects selected results obtained with rhodium catalysts. The structures of the chiral ligands are reported in Chart 5. High conversions and high branched selectivities can be easily obtained, but the e.e.'s are always low irrespective of the phosphine ligand employed. It was a bit frustrating that after twenty years of asymmetric hydroformylation of styrene with this metal the best result obtained was as low as 31%!

On the contrary, as it appears from Table 2, with platinum the stereoselectivities are consistently higher, in some cases even excellent, but the chemical yields of the branched aldehyde are always unsatisfactory. This is in part due to the fact that in the Pt-catalysed hydroformylation of vinylarenes the linear aldehyde is normally the

In summary, after more than twenty years of investigations in the field of asymmetric hydroformylation, at the end of 1992 we had only the possibility to attain high chemical yields at the expenses of the optical yields or vice versa.

2.5 Determination of the enantiomeric excess

The enantiomeric purity of the chiral aldehydes obtained in asymmetric hydroformylation experiments can be determined with a variety of methods. The procedure of choice, when feasible, is the GC analysis of the aldehyde, as well as of the relevant alcohol or acid, on a suitable chiral capillary column. When the determination of e.e. is preceded or followed by a blank of the racemic compound, this method proved to be the most reliable and reproducible one in our hands. This procedure can be used routinely in the case of styrene and other aliphatic substrates of low molecular weight with complete satisfaction. Chiral phase HPLC analysis is a valid alternative when the products cannot be analysed by GC. Chromatographic methods provide as well a powerful tool for the monitoring of the selectivity along the reaction to check for the occurrence of racemization.

The e.e.'s of several aldehydes have been determined by NMR in the presence of chiral shift reagents. The method is substantially reliable, albeit less handy and accurate than chromatography. Care should be paid to the identification of the enantiotopic protons to be integrated. A comparison with a blank of the racemic aldehyde can aid to avoid misleading conclusions.

Chromatographic and NMR methods have overridden the traditional polarimetric determinations, which have been in use for a long time since the outset of asymmetric hydroformylation. From a qualitative point of view, polarimetry is still now very useful for establishing the configuration of the chiral aldehyde. For a quantitative determination, however, it can be considered reliable only if the aldehyde is properly purified by distillation and the amount of by-products, even achiral, in the sample is as low as possible. Deviations from linearity of the optical rotations induced by the presence of achiral contaminants are not infrequent and the effect can be surprisingly large.[22] The rotations reported in the literature must be carefully checked and the determinations obtained by this way should be better referred to as optical purity rather than as e.e. Despite these drawbacks, we strongly recommend to check always if the hydroformylation product is optically active.

3. Enantioselective Hydroformylation with Rhodium Catalysts

3.1 Catalytic Cycle and Mechanistic Aspects

The catalytic cycle generally accepted for the hydroformylation of terminal olefins with rhodium-chelate diphosphine catalysts is summarized in a over-simplified way in Chart 6. Only the reaction path leading to the branched aldehyde is reported with reference to only one of the possible diastereomeric intermediates. Moreover, not all the equilibria occurring in solution are considered. Despite of this crude picture, the scheme should allow some meaningful comments on the origin of the selectivity in the course of the catalytic cycle.

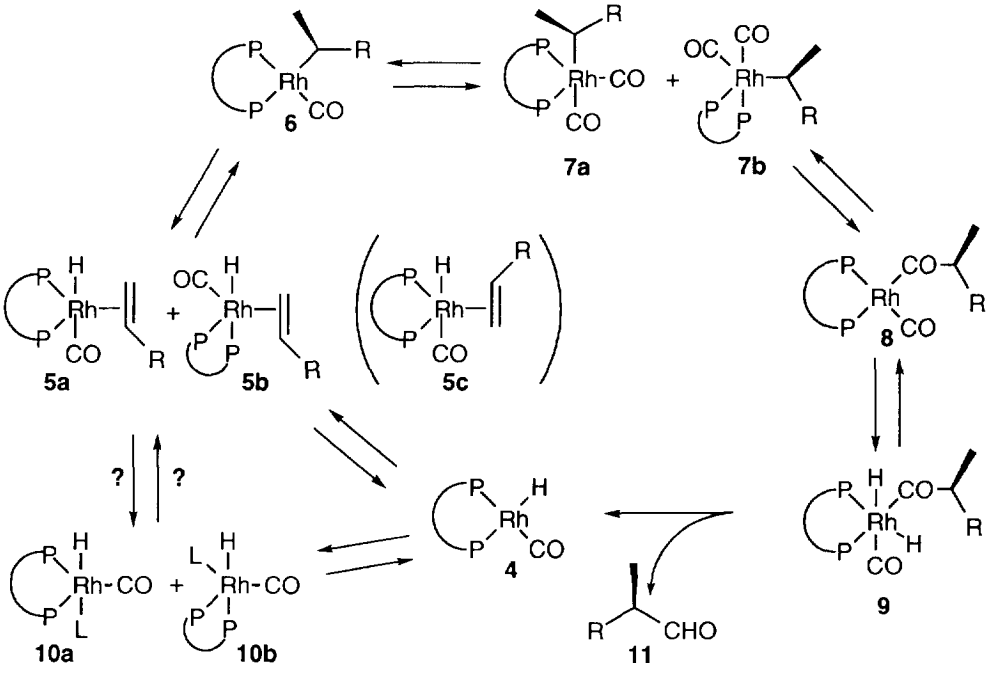
It is clearly apparent that several different complexes may coexist under hydroformylation conditions and most of them are reasonably catalytically active species. It is obvious that, in order to increase the chemo-, regio- and stereoselectivity of the reaction, their number (or the relative concentrations of most of them) should be reduced as low as possible. This goal can be in part achieved, sometimes with remarkable success, by selecting the most appropriate combination catalytic precursor-supporting ligands and, to a lower extent, by a careful choice of the reaction conditions.

For instance, when PPh_3 is employed as ligand, the hydroformylation of aliphatic terminal olefins can be driven quite efficiently towards the linear aldehyde operating at PPh_3:Rh ratio as high as 50:1 or higher.[23] The

excess PPh_3 shifts the equilibria towards catalytic species containing two phosphine ligands. It is assumed that these fairly hindered derivatives should favour the formation of a linear rather than a branched alkyl rhodium intermediate on purely steric grounds. Conversely, improved branched selectivities have been recorded upon reducing the PPh_3:Rh ratio or upon increasing the CO partial pressure. Both these operations should favour a reaction channel where fairly unhindered dicarbonyl rhodium intermediates play a major role. Kinetic[24] and NMR[25] evidences in support to this assumption have been provided.

Unfortunately, these tricks are of little value in asymmetric hydroformylation where chelating biphosphine are consistently used as ligands because monodentate phosphine are poor inducers. Until two years ago, with these catalysts the regioselectivity was "substrate-dependent" since it was basically dictated by the electronic polarization of the double bond of the olefin and/or by the occurrence, if any, of chelation control operated by the substrate.

Chart 6. Catalytic Cycle of Rh-catalysed Hydroformylation



More recently, however, unprecedently high proportions of linear aldehydes have been obtained on aliphatic substrates using suitable diphosphite ligands.[26] Ligands of the same type provide as well a quite high branched selectivity with aryl substituted olefins.[27] According to the results reported later by other authors,[28] under hydroformylation conditions these diphosphites may produce a single pentacoordinate rhodium carbonyl complex such as **10a** (L=CO) where both the P-atoms coordinate at the equatorial sites. Since the olefin should then take up the last equatorial position, regiodiscrimination should arise from differences in the reaction rates, either of formation or of consumption, between a couple of pentacoordinated olefin rhodium complexes **5a** and **5c** (Chart 6).

A similar argument may hold for enantioselectivity. In their pioneering work on asymmetric hydroformylation of butenes,[2b] Pino and coworkers advanced the proposal that enantioselection occurs at an

Chart 4. Hydroformylation of vinylarenes

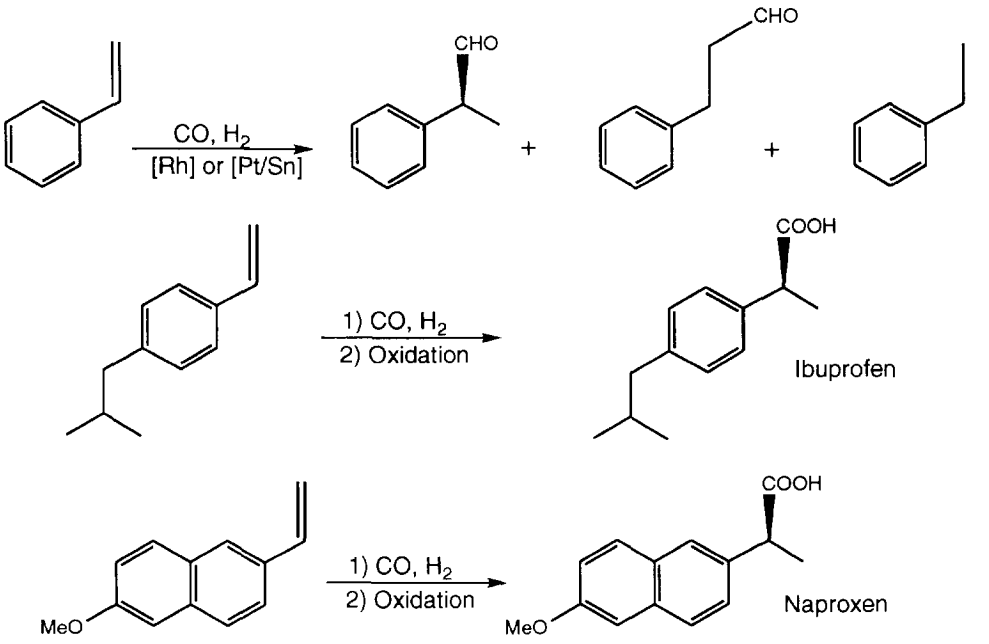


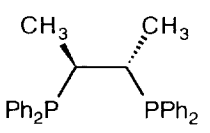
Table 1. Enantioselective Hydroformylation of Styrene with Chiral Rhodium Catalysts

ligand	$P(H_2)$ bars	P(CO) bars	Temp. (°C)	conv.,% (t, h)[a]	b/l, %[b]	e.e., %[c] (config.)	Ref.
(R,R)-DIOP	65	65	80	n.r.[d]	68/32	12 (R)	13
(R,R)-DIOP-DBP	65	65	80	n.r.[d]	89/11	25 (R)	13
(S,S)-CHIRAPHOS	40	40	100	80(3)	94/6	24 (R)	14
(R,S)-EPHOS	6	6	40	63(111)	90/10	31 (R)	15
(R,R)-DIOP-Et	40	40	80	58(2.5)	100	0.2 (S)	16

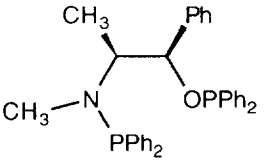
[a]Styrene converted in %; time in h in parenthesis. [b]2-phenylpropanal/3-phenylpropanal in %. [c]Enantiomeric purity of 2-phenylpropanal in %; absolute configuration in parenthesis. [d]Not reported.

prevailing product. The regioselectivity can be shifted in the favour of the branched product introducing a dibenzophospholyl group (DBP) in the place of diphenylphosphinyl in the chiral ligand. The effect is remarkable and the regioisomer ratio can be even reversed. Unfortunately, the chemoselectivity is not yet satisfactory and therefore, only in the best cases does the chemical yield of the branched isomer exceed 50%. Finally, we have to add that controversial opinions[4c,17a,44] have been expressed on the reproducibility of the results obtained by Stille and co-workers in the hydroformylation of styrene, where more than 96% e.e. has been claimed by using Pt-$SnCl_3$/BPPM or BPPM-DBP in the presence of ethyl orthoformate as a scavenger.[4a,18]

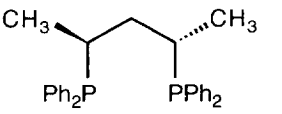
Chart 5. Chiral Phosphorus Ligands



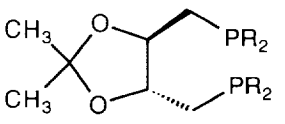
CHIRAPHOS



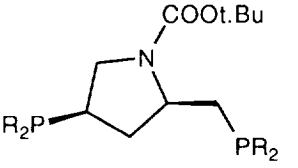
EPHOS



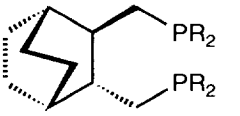
BDPP



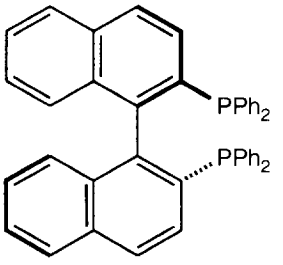
DIOP R = Ph
DIOP-Et R = Et
DIOP-DBP R_2 = DBP



BPPM R = Ph
BPPM-DBP R_2 = DBP



BCO R = Ph
BCO-DBP R_2 = BDP



BINAP

DBP =

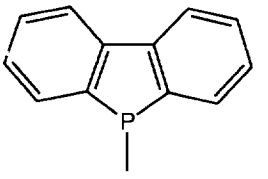


Table 2. Enantioselective Hydroformylation of Styrene with Chiral Platinum Catalysts

ligand	$P(H_2)$ bar	P(CO) bar	T, °C	conv.,% (t, h)[a]	S, %[b]	b/l,%[c]	e.e.,%[d] (config.)	Ref.
(R,R)-DIOP	40	40	80	70(1)	73	38/62	4 (S)	14
(R,R)-DIOP-DBP	234	80	36	>90(55)	65	82/18	80 (S)	19
(S,S)-CHIRAPHOS	40	40	80	47(9)	74	38/62	45 (R)	14
(R,S)-EPHOS	97	65	50	54(36)	93	41/59	36 (S)	20
(S)-BINAP	40	40	50	37(52)	97	33/67	69(S)	21
(R,R)-BCO	150	70	50	100(3)	90	43/57	25 (S)	17
(R,R)-BCO-DBP	150	70	50	95(23)	75	80/20	85 (S)	17
(2S, 4S)-BPPM	96	96	60	100(6)	>98	31/69	70 (S)	4a
(2S, 4S)-BPPM[e]	96	96	60	100(150)	>98	50/50	>96 (S)	4a
(2S, 4S)-BPPM-DBP	86	86	60	42(48)	n.r.[f]	74/26	7 (n.r.)	18
(2S, 4S)-BPPM-DBP[e]	86	86	60	56(95)	n.r.	77/23	>96 (n.r.)	18

[a]Styrene converted in %; time in h in parenthesis. [b]Selectivity in aldehydes with respect to the styrene converted. [c]2-phenylpropanal/3-phenylpropanal in %. [d]Enantiomeric purity of 2-phenylpropanal in %; absolute configuration in parenthesis. [e]Triethyl orthoformate was used as solvent and the corresponding acetals were obtained. [f]Not reported.

early stage of the catalytic cycle, before or during the formation of the alkyl-rhodium intermediate. Although some experimental results are not easy to fit within this picture, no alternative hypothesis has been substantiated so far. In the first case, the stereochemical outcome of the reaction should be determined by the diastereotopic interactions developed between the incoming olefin and the catalyst **4** in the binding step. In the second case, the enantioselectivity should originate from the different rates at which the two couples of diastereoisomers **5a** and **5b** insert the olefin into the Rh-H bond. While most attention has been paid so far to the binding step, more recent results seem to support better the assumption that pentacoordinated intermediates are significantly involved in the determination of the stereoselectivity of the reaction. It is our feeling that the role of these species in addressing the stereochemical fate of the reaction has been probably underestimated so far and we expect that further evidences on this point will be soon provided.

Finally, we like to stress that it is a wise choice to avoid the use of catalytic precursors containing strongly coordinating ancillary ligands such as PPh_3. This may subtract part of the metal in the form of probably inactive species like **10** and would introduce unnecessary complications in the path from **4** to **5**.

3.2 Chiral Ligands Containing Phosphorus Donors

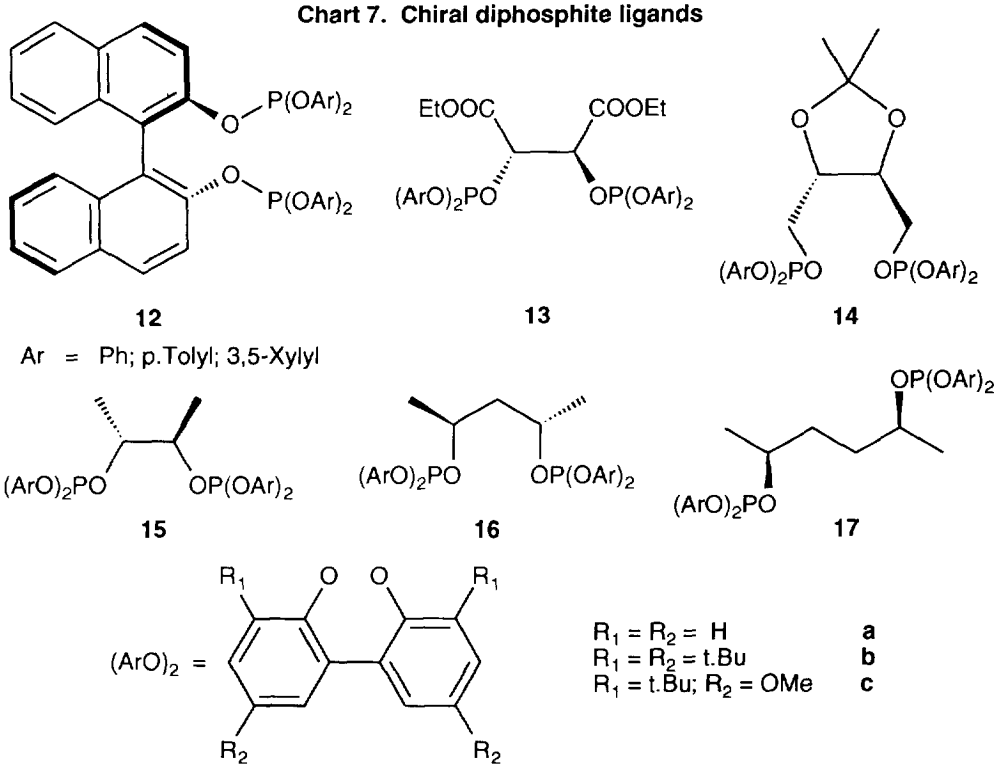
The most significant advances in enantioselective hydroformylation in the last two years have been achieved using chiral ligands containing phosphorus donors. Chiral chelating phosphites attracted particular attention, but also phosphinites, phosphacyclic compounds and other more exotic phosphorus derivatives have been introduced with variable success.

The beneficial effect of phosphites on the catalytic activity and/or regioselectivity of rhodium catalysed hydroformylation has been claimed since long in the patent literature.[29] Their use attracted increasing attention after the publication of the first report on the peculiar effect of bulky phosphites on the catalytic activity.[30] More recently quite high regioselectivities have been obtained in the hydroformylation of functionalised as well aryl substituted olefins with rhodium-diphosphite catalysts.[26,27] In spite of these favourable figures, the outset of asymmetric hydroformylation with chiral diphosphites was far from encouraging since at the first attempt a stereorandom reaction was observed.[31] Two years later Takaya was more successful and obtained about 50% e.e. in the hydroformylation of vinyl acetate with bis(triarylphosphite) ligands derived from atropisomeric 1,1'-binaphthol such as **12** (Chart 7).[32] The BINAP-based catalyst afforded a similar stereoselectivity (46% e.e.), but was by far less active.

Lower stereoselectivities, up to 20%, were recorded on styrene with 1,2- and 1,4-diphosphite ligands **13** and **14** (Chart 7) derived from tartaric acid. A remarkably high share of branched isomer was observed in this reaction.[33] A patent by Union Carbide, which was cleared soon later, provided decisive arguments for making this area one of the hottest topic in enantioselective catalysis.[34] The patent reports on the preparation of a set of fairly bulky diphosphites derived from suitable chiral diols. It is claimed that Rh-complexes with these ligands are able to hydroformylate styrene at room temperature and moderate pressure in up to 90% e.e. with more that 98% branched selectivity. Other vinylarenes behave similarly whereas aliphatic olefins gave less appealing results. The diphosphites **16** (Chart 7), derived from the chiral backbone of 2,4-pentanediol, were the most efficient ligands.

These "first generation" chiral phosphites are characterized by the presence of equivalent phosphorus donors and by a C_2 symmetry. These features have mantained constant in several cases and the number of phosphite ligands of this kind, even with C_3 symmetry,[35] experienced a fairly rapid growth.[36]

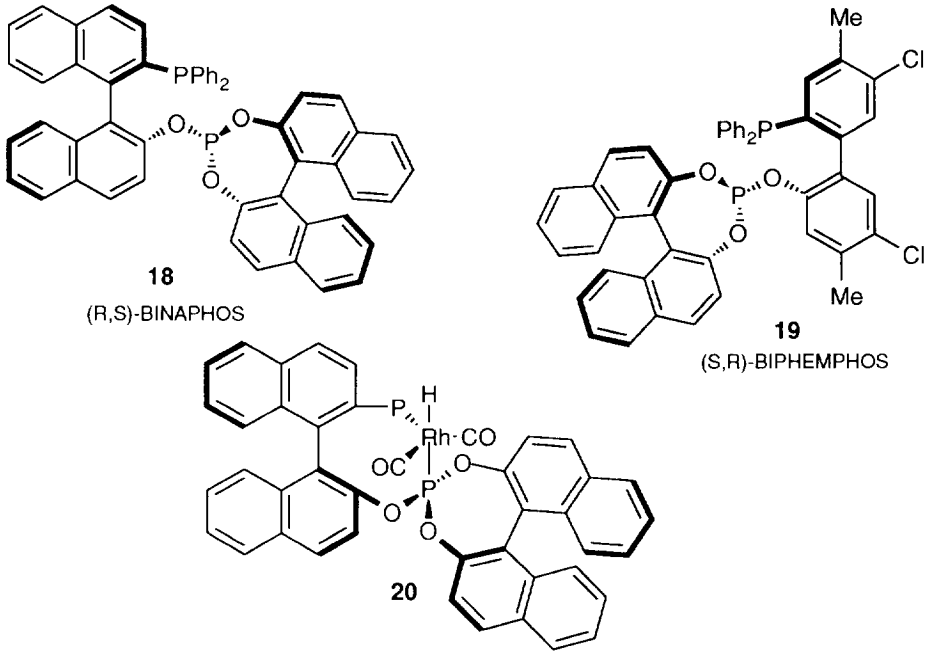
Chart 7. Chiral diphosphite ligands



Further studies by van Leeuwen and coworkers have shown that hydrido-rhodium-diphosphite complexes display a fluxional behaviour in solution. The interconversion between complexes having the two phosphorus centers in equatorial-equatorial or equatorial-axial positions (compounds **5a** and **5b**, Chart 6) in a trigonal bipyramidal structure is at the basis of this behaviour.[28] The preferred coordination geometry depends substantially on the structure of the chiral carbon backbone connecting the diphosphite units. Diphosphites such as **15**, derived from 1,2-diols produce highly fluxional seven-membered ring chelates with an equatorial-axial disposition of the P-atoms. They produce only modest enantioselectivities in the hydroformylation of styrene. Even poorer results were obtained with phosphite ligands **17** based on chiral 1,4-diols, which give equatorial-equatorial nine-membered chelate complexes. On the contrary, ligands like **16**, derived from chiral 1,3-diols, produce fairly stable Rh-complexes where the P-atoms coordinate preferentially in diequatorial mode like in structure **5a** (Chart 6). These complexes are quite efficient catalysts in the asymmetric hydroformylation of styrene and afford the branched aldehyde in up to 76% e.e. and in more than 90% isolated yield.[37]

These results provide some interesting clues into the design of efficient chiral ligands for asymmetric hydroformylation, but the conclusions that one may be induced to draw seem to contrast with the recent reports by Takaya and coworkers. In a series of brilliant papers, they have shown that atropisomeric diaryl-core phosphinophosphito ligands (Chart 8) are excellent chiral inducers in the rhodium catalysed hydroformylation of olefins. Asymmetric inductions higher than 90% are consistently obtained with terminal[38] as well as internal olefins[39] with (S,R)- or (R,S)-BINAPHOS **18**, a binaphthyl-core ligand. Much lower enantioselectivities are

Chart 8. Atropisomeric phosphinophosphito ligands



P-Phenyl substituents omitted for clarity

Table 3. Hydroformylation of olefins with atropisomeric phosphinophosphito ligands

[*% of branched aldehyde*; e. e. (config.)[a]]

Substrate	Ligand (S,R)-**18**	Ligand (S,R)-**19**	Notes
Styrene	*88*; 94 (S)	*90*; 94 (S)[b]	a) Configurations obtained with the (R,S)-enantiomers have been reversed.
p.Me-styrene	*86*; 95 (+)		
p.MeO-styrene	*87*; 88 (+)		
p.i.Bu-styrene	*88*; 92 (S)		
p.Cl-styrene	*87*; 93 (+)		b) Unchanged regioselectivity, but much lower e.e. (16%) was obtained with (R,R)-**19**.
Vinyl acetate	*86*; 92 (R)	*85*; 90 (R)	
1-Hexene	*24*; 75 (S)	*23*; 85 (S)	
Vinylphthalimide	*89*; 85 (R)		
Z-2-Butene	*c* ; 82 (R)	*c* ; 85 (R)	c) Only 2-methylbutanal is formed.
E-2-Butene	*c* ; 48 (R)		
E-Phenylpropene[d]	*97*; 92 (S)		d) The prevailing regioisomer has the formyl group at the benzylic position.
Indene[d]	*92*; 83 (+)	*92*; 88 (+)	
Acenaphtylene[d]	*96*; 97 (+)	*95*; 96 (+)	

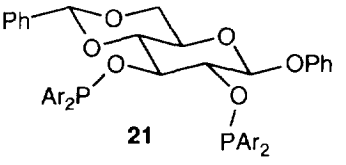
obtained with the (R,R)-diastereoisomer. Among terminal olefins, vinylarenes afford e.e.'s and branched selectivities higher than simple aliphatic substrates. The catalysts tolerates the presence of further functional groups in the substrate and vinyl acetate and vinyl phthalimide could be hydroformylated in high e.e. (Table 3).

Treatment of [Rh(acac){(R,S)-BINAPHOS}] with a 1:1 mixture of hydrogen and carbon monoxide leads to the formation of a single monohydrido carbonyl complex. On the basis of multinuclear NMR, this compound has been attributed the trigonal bipyramidal structure **20** reported in Chart 8, where the phosphite donor takes up selectively the apical position. This complex is remarkably stable since it exists as a single isomer even at 60°C and apparently is involved in the catalytic cycle. According to previous authors, the preference between apical-equatorial and equatorial-equatorial coordination modes should be basically determined by the natural bite angle of the ligand. Consistently, molecular mechanics calculations have revealed that BINAPHOS has a natural bite angle of 90.4° which is perfectly compatible with the observed geometry.

Comparable enantio- and regio- selectivities can be obtained with BIPHEMPHOS **19**, a similar phosphinophosphito ligand based on the axially chiral biphenyl backbone.[40] Even in this case ligands with opposite configurations of the axially chiral elements are by far more efficient than the corresponding diastereoisomers. The work performed with these atropisomeric ligands has been summarized in a short review in Japanese[41] and a full paper on BINAPHOS is in preparation.[42]

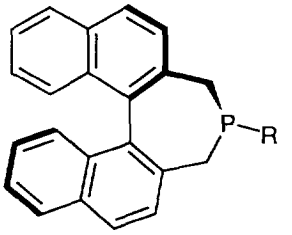
As it has been recently pointed out in a series of papers,[43] electronic effects may be quite significant in the determination of a favourable asymmetric bias in asymmetric reactions catalysed by transition metal complexes. In the rhodium-catalysed hydroformylation of olefins, vicinal carbohydrate phosphinites like **21** (Chart 9) provide high regio- and chemo-selectivities for the branched aldehyde, but the enantioselectivity is moderate. In the case of 6-methoxy-2-vinylnaphthalene, however, an increase of the e.e. from 10% to 38% is observed when electron-deficient aryl groups containing two fluorine atoms or two trifluoromethyl substituents are introduced onto the phosphorus centers in the place of plain phenyls. The stereoselectivity improves further, up to 51% and 72% when apolar solvents like hexane and triethylsilane, respectively, were used.[44] These ligands are very tunable, in the sense that they are quite sensitive to the olefin structure and give unusually large differences of e.e.'s on similar substrates. The highest e.e. with 2-vinylnaphtalene did not exceed 39% and the asymmetric induction was even lower with other olefins, such as styrene and vinyl acetate. Application of these biphosphinite ligands to the hydroformylation of 2-vinylnaphthalenes with Pt-catalysts, gave much poorer results than with rhodium.[44]

Chart 9. Bis-phosphinite and phosphepine ligands



21

Ar = C_6H_5
Ar = 3,5-$C_6H_3(CF_3)_2$
Ar = 3,5-$C_6H_3F_2$
Ar = 3,5-$C_6H_3(CH_3)_2$



22

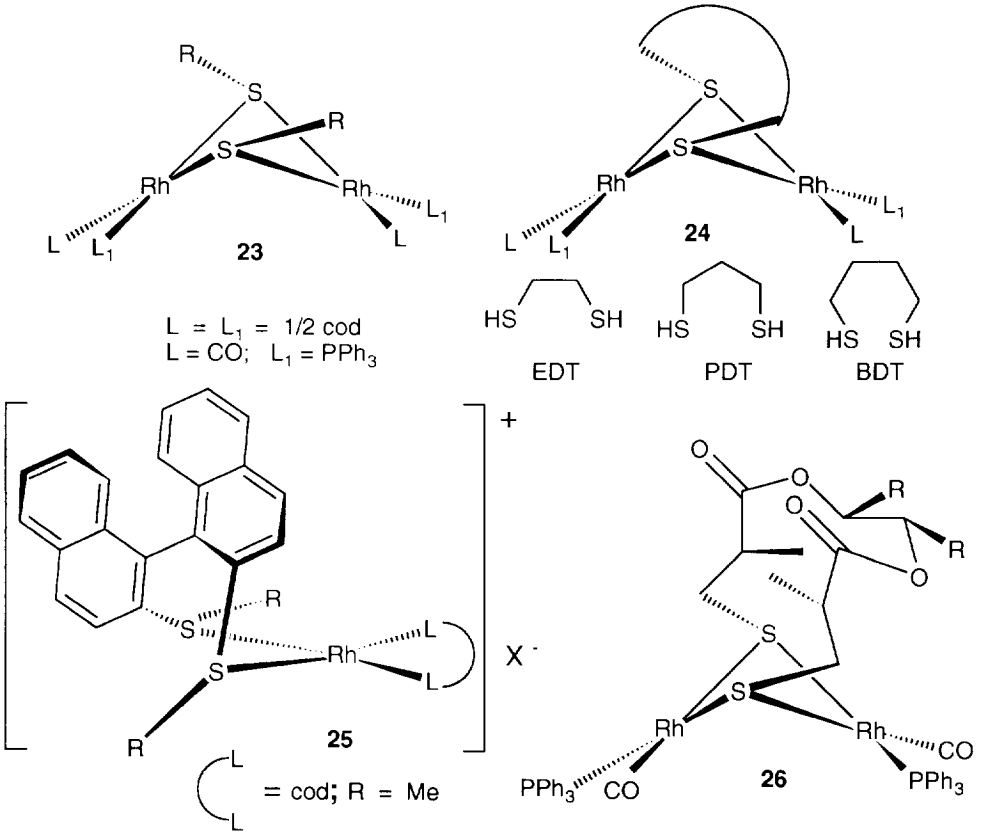
R = Ph; Me

Phospholanes are an emerging class of chiral auxiliaries in the Rh-catalysed asymmetric hydrogenation[45] and phosphole ligands display a peculiar pattern of selectivity in the Rh-catalysed hydroformylation.[46] Despite these promising figures, the use of chiral phosphacyclic ligands in the hydroformylation with Rh-catalysts has been fairly neglected so far and only one report on this topic has appeared in the last two years. The atropisomerically pure dinaphthophosphepine **22** has been obtained by resolution of the racemate and tested in the asymmetric hydroformylation of styrene in conjunction with $Rh(acac)(CO)_2$ as catalyst precursor. The branched aldehyde was obtained in 95% selectivity and, in the best case, a 20% e.e. was recorded.[47] Albeit modest, this enantioselectivity is one of the highest ever obtained in the hydroformylation of styrene with a monodentate ligand as the chiral auxiliary.

3.3 Chiral ligands containing sulfur donors

The first report on the use of achiral sulfur ligands in hydroformylation was published as early as in 1983,[48] when the dinuclear complexes $[Rh_2(\mu\text{-}SR)_2(CO)_2(PR_3)_2]$ such as **23** were found active catalysts for the hydroformylation of alkenes under mild conditions (5 bars and 80°C). Catalytic systems of this type can be easily prepared by reaction of $[Rh_2(\mu\text{-}SR)_2(cod)_2]$ with a suitable phosphorus donor under hydroformylation conditions. Ten years later, the first dinuclear dithiolato rhodium complexes $[Rh_2\{\mu\text{-}S(CH_2)_nS\}(cod)_2]$, **24**,

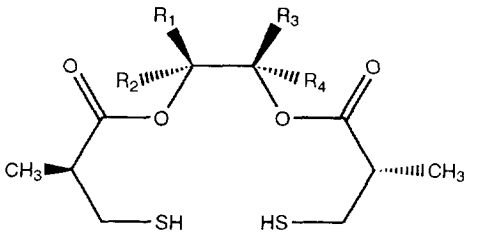
Chart 10. Rhodium complexes with sulfur donors used in hydroformylation



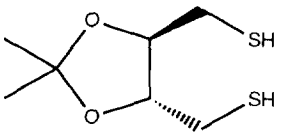
were synthesized from suitable achiral dithiols.[49] These derivatives are as well active hydroformylation catalysts in the presence of PPh_3. The complex **24** with the ligand BDT is active even at low pressure, whereas the ones derived from the fairly rigid ligands EDT and PDT require at least 30 bars of syn-gas to be active.[50]

It has been proposed that the dinuclear framework of $[Rh_2(\mu\text{-}SR)_2(CO)_2(PR_3)_2]$ is retained throughout all the steps of the catalytic cycle.[51,52] Support to this assumption comes from IR evidence and from the occasional recovery of the starting dinuclear complex at the end of the process when the catalytic reaction has run in mild conditions.[50,51,53] The dinuclear nature of all the intermediates has been, however, criticized[54] and the existence of a cooperative effect between the two metal centers is still controversial.[55] Despite this limitation, during the last two years these dinuclear thiolato complexes have attracted increasing attention as catalysts in asymmetric hydroformylation because of their versatility. In fact, they give the possibility to exploit both the single and the double enantioselection process by properly locating the chiral information either onto the sulfur or onto the phosphorus ligand or onto both of them.

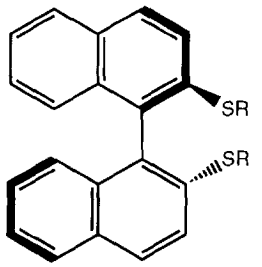
Chart 11. Chiral sulfur ligands used in enantioselective hydroformylation



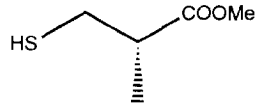
27 R = H MMP-EG
28 R_2,R_3 = Me; R_1,R_4 = H MMP- DHBR
29 R_1,R_4 = Me; R_2,R_3 = H MMP- DHBS



31 DIOS



30 R = H BINAS
31 R = Me Me_2BINAS



32 MMP-M

Following a few preliminary reports,[56] the first paper on the asymmetric hydroformylation with a Rh-catalyst containing a sulfur ligand as a chiral inducer appeared in 1993.[57] Enantiopure 1,1'-binaphtalene-2,2'-dithiol (BINAS, **30**) was used as the bridging ligand for rhodium and the complex **24** $[Rh_2(\mu\text{-BINAS})(cod)_2]$ was found to display a good catalytic activity in the hydroformylation of styrene in the presence of two moles of PPh_3. Operating at 30 bars of pressure, the branched aldehyde was obtained in high chemical yield and in more than 90% regioselectivity, but in less than 10% e.e. In the absence of PPh_3, the complex still mantains its catalytic activity and provides a slightly higher stereoselectivity, but is less active and regioselective.

Similar results have been obtained with the dinuclear complex $[Rh_2(\mu\text{-DIOS})(cod)_2]$.[58] A complete conversion of styrene into aldehydes at 30 bars and 65 °C was obtained in a few hours, but the regioselectivity and the e.e. were poor. At 30 °C and 80 bar, the regioselectivity in 2-phenylpropanal reached 96%, but e.e. did not improve.

Table 4. Hydroformylation of Styrene with Catalytic Precursors containing Sulfur Ligands

Cat. Prec[a]	Sulfur ligand	Phosphorus ligand[b]	P[c] bar	T °C	conv., % t (h)[d]	b/l, %[e]	e e,% (con.)[f]	Ref
24	BDT	(-)BDPP	30	65	90(24)	94/6	42(S)	59
24	(+)BINAS	-	30	80	77(20)	56/44	11(S)	57
24	(+)BINAS	PPh_3 (1)	30	60	100(2)	92/8	7(S)	57
25	(+)Me_2BINAS	-	30	80	98(24)	51/49	6(S)	57
25[g]	(+)Me_2BINAS	-	80	80	100(24)	84/16	15(S)	57
24	(-)DIOS	-	30	80	65(22)	64/36	5(S)	58
24	(-)DIOS	PPh_3(4)	6	80	98(4)	83/17	4(S)	58
24	(-)DIOS	PPh_3(4)	30	65	97(3)	91/9	4(S)	58
24	(+)DIOS	(+)BDPP(2)	30	65	100(24)	90/10	4(S)	59
24	(+)DIOS	(-)BDPP(2)	30	65	98(24)	90/10	13(R)	59
24	(-)DIOS	(+)BDPP(2)	30	65	50(24)	93/7	34(S)	59
24	(-) DIOS	(-)BDPP(2)	30	65	40(24)	92/8	13(R)	59
26	MMP-EG	PPh_3 (2)	6	80	>95 (3)	80/20	34(R)	60
26	MMP-DHBR	PPh_3 (2)	6	80	>95 (3)	48/52	20(S)	60
26	MMP-DHBS	PPh_3 (2)	6	80	>95 (3)	72/28	5(R)	60
23	MMP-M	PPh_3 (2)	6	80	>95 (3)	63/37	2(S)	60
26	MMP-EG	PPh_3 (2)	6	60	>95 (8)	90/10	53(R)	60
26	MMP-EG	PPh_3 (2)	6	50	>95 (20)	89/11	14(R)	60
26[h]	MMP-EG	PPh_3 (2)	6	50	>95 (20)	94/6	58(R)	60

[a]Type of complex used as catalytic precursor. [b]In parenthesis the P/Rh ratio. [c]In all cases $P(H_2) = P(CO)$. [d] Styrene converted in % , time in h in parenthesis. [e] 2-phenylpropanal/3-phenylpropanal in %. [f]Enantiomeric excess of 2-phenylpropanal in %, absolute configuration in parenthesis.[g]Three additional equivalents of the dithioether ligand were added. [h]Solvent was $HC(OEt)_3$ and the corresponding diethyl acetals were obtained.

The activity of the catalytic system increased when PPh_3 was added to the catalytic precursor, but neither this had a beneficial effect on the stereoselectivity. When the reaction was carried out in triethyl orthoformate, the activity and the selectivity of the catalyst was maintained and the corresponding diethyl acetals were obtained with the same poor e.e. In the aim to increase the stereoselectivity of the (+) and (-)-DIOS system, the chiral diphosphines (+) and (-) BDPP were used as additional chiral ligands. Among the four possible combinations, the best results were obtained with the couple (-)-DIOS and (+)-BDPP (Table 4), which produced (S)-2-phenylpropanal in 43% e.e.[59] An almost identical value was recorded when styrene was hydroformylated by the complex $[Rh_2\{\mu\text{-}S(CH_2)_4S\}(cod)_2]$, containing an achiral bridging dithiolate ligand, in the presence of the chiral diphosphine BDPP. A 94% branched selectivity and 42% e.e. was obtained in this case.[59]

Neutral binuclear rhodium complexes such as **26**, containing the dithiolate ligands MMP-EG, MMP-DHBS and MMP-DHBR (Chart 11), in the presence of PPh_3, are active precursors for the hydroformylation of styrene in fair to good enantioselectivities. The reaction occurs in mild conditions and at pressures as low as 5 bars. The best results were obtained with the ligand MMP-EG (Table 4). In this case the binuclear species can

be recovered from the reaction mixture at the end of the catalytic run. On the contrary, complexes of the ligands MMP-DHBS and MMP-DHBR, which undergo partial polymerization under hydroformylation conditions, yield lower regio- and enantioselectivities. It has been shown in separate experiments that the polymeric species formed from these catalytic precursors, while active, are much less selective than the starting binuclear complexes. Although this result does not provide a decisive evidence, it supports the assumption that the dinuclear unit is retained during the enantiodiscriminating steps of the catalytic cycle. In the case of the ligand MMP-EG, the enantioselectivity increased steadily upon decreasing the reaction temperature. At 50°C, however, extensive racemization of the branched aldehyde takes place because of the low reaction rate. This inconvenient could be prevented by using $CH(OEt)_3$ as the solvent. In these conditions, 94% of 2-phenylpropanal with a 58% e.e. was achieved.[60]

In addition to the dinuclear thiolato-bridged neutral species, cationic mononuclear rhodium complexes containing neutral sulfur ligands like sulfides were also found to be well-suited catalysts for asymmetric hydroformylation.[57] The disulfide-rhodium derivatives $[Rh(BINASMe_2)(COD)]^+X^-$ ($X = BF_4$, ClO_4), **25**, are catalysts as active as the corresponding dithiolato complexes. Up to 96% of branched aldehyde, but in very low e.e. has been obtained running the reaction at room temperature and 80 bars. The stereoselectivity improves up to 15% at 80°C, but the regioselectivity decreases to 84%. Note that, upon coordination to the metal, the sulfur atoms of the sulfides become stereogenic centers and this can result in a mixture of diastereomeric complexes. This fact may explain the poor stereoselectivity of the reaction.

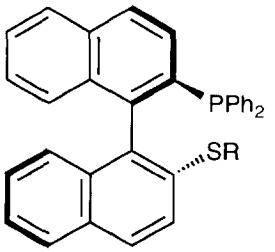
In summary, chiral dithiolate rhodium complexes are an appealing new type of catalytic precursors for enantioselective hydroformylation of olefins. It seems that some degree of flexibility in the backbone of the ligands is required to produce active precursors at low pressure. Likely, at high pressures an equilibrium between the dithiolate species **24** and classical $RhH(CO)_x$ or $RhH(CO)_x(PPh_3)_y$ catalyst occurs, thus reducing the enantioselectivity of the systems. Finally the combined use of chiral dithiolate complexes with chiral diphosphines has evidenced a promising matching effect that deserves further studies.

3.4 Chiral Ligands Containing Heterodonor Atoms

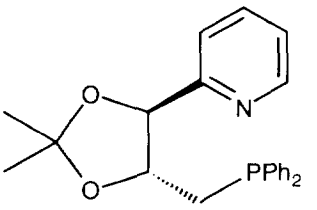
The first successful report on the use of heterobidentate ligands as chiral auxiliaries in asymmetric hydroformylation refers about a P,S-atropisomeric binaphthyl-core derivative and has appeared in the literature only in 1994. Soon later two other reports on chiral P,N-chelates have been published.

In the first paper, the hydroformylation of styrene was performed with cationic rhodium complexes containing the axially chiral P,S-chelators **33** (Chart 12). Chemo- and regio-selectivities were quite satisfactory, but the e.e. was disappontingly low (14%).[61] A result even poorer was obtained when styrene and other functionalised olefins were hydroformylated with *in situ* catalysts containing PYDIPHOS **34** or the relevant P-oxide. In all the cases the e.e.'s recorded were negligible.[62] On the contrary, depending on the structure of the substrate, highly divergent e.e.'s have been achieved using a different bidentate P,N-ligand such as (2-pyridyl)menthyl phosphinite **35** as chiral inducer.[63] While styrene and vinyl acetate gave poor enantioselectivities, 2-vinylnaphtalene was hydroformylated with complete regioselectivity in an amazingly high 78% e.e. Even higher stereoselectivities (up to 92% e.e.) are claimed for methyl acrylate. Since in this case easy racemization of the branched aldehyde through keto-enol equilibration is expected, these last results deserve to be confirmed. As we are aware, they are under current investigation and a further paper on this subject is expected to appear in due course.[64]

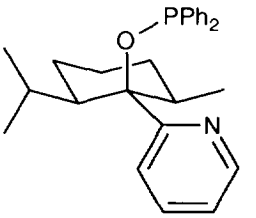
Chart 12. Chiral heterobidentate ligands



33 R = Me; i.Pr



34 PYDIPHOS



35

4. Enantioselective Hydroformylation with Platinum-Tin Catalysts

In comparison with rhodium, the use of platinum-tin catalysts in enantioselective hydroformylation has attracted less attention in recent times as judged from the fairly low number of papers that have appeared in the last two years on this topic. Although no substantial improvement of previous results has been recorded in these investigations, some interesting and uncovered features of these catalysts have been pointed out.

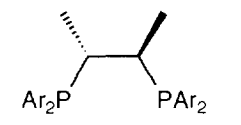
The asymmetric hydroformylation of styrene in the presence of $L_2PtCl(SnCl_3)$ complexes displays a strong dependence from the temperature when chiral chelating diphosphines with *p*-aminosubstituted aryl group such as **36**, **37** and **40** (Chart 13) are used as chiral ligands.[65] With **37** and **40**, an inversion in the configuration of the prevailing enantiomer occurs at relatively low temperatures (53° and 72°C, respectively) and products of comparable and fairly good enantiomeric purities, but opposite configurations can be produced by the same catalyst at different temperatures. A reversal of product configuration with the reaction temperature has some precedent in the Pt-catalysed hydroformylation of styrene[66] and 1-butene[67], but a complete switch of enantioselectivity was never observed. This dramatic effect could be explained either by reaction of different chelate conformations of the complex or by competitive reactions of the diastereomeric adducts of a single chelate conformation. Variable temperature NMR data of the complex with **37** seem to support better the second assumption. These results demonstrate how significant is the determination of the temperature effect on the enantioselectivity for a complete characterization of a chiral catalysts. The paper draws further attention to the relevance of kinetics in the elucidation of the mechanistic aspects of asymmetric catalysis.

An inversion in the enantioselection of the reaction with the temperature has been observed as well when styrene is hydroformylated with a Pt-BDPP complex in the presence of tin fluoride as a co-catalyst.[68] The use of SnF_2 as a promoter produces a catalytic system of unusually high thermal stability which allows the reaction to be run even at 200°C. At this temperature the enantiomeric purity of 2-phenylpropanal of (R) configuration is quite low (5%) as expected, but in the same conditions the (S)-enantiomer was obtained in 24% e.e. after 25 h of reaction when VALPHOS **42** was used in place of BDPP **38** (Chart 13). Given the temperature this is an exceptionally high value. Improved enantioselectivities were recorded for the (S) enantiomer at low temperatures with the BDPP ligand (76% e.e. at 40°C). The stereoselectivity decreased when toluene was substituted by dichloromethane as the solvent. Addition of one equivalent of 2-diphenylphosphinopyridine strongly reduced the reaction rate, but had a beneficial effect on the stereoselectivity that improved up to 87% with no change in the configuration.

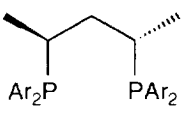
An exceptionally high branched selectivity (36:1) was recorded in the hydroformylation of styrene with platinum complexes containing chiral aminomethylphosphine ligands like **44**. The highest conversion, however, did not exceed 15% and the e.e.'s were modest (up to 31%).[69]

Chelating *bis*-binaphthtophosphole ligands **39** and **41** where two axially chiral binaphthtophospholyl (BNP) groups are connected through a suitable chiral carbon chain of different length have been synthesized by alkylation of binaphthophospholyl anion with the appropriate chiral ditosylate.[70] Due to the easy atropisomerization of the binaphthyl backbone, in solution these compounds exhibit a fluxional behaviour at room temperature. Mononuclear six- or seven- membered chelate platinum complexes containing *bis*-BNP ligands have been obtained as a mixture of diastereoisomers. Upon coordination to the metal, the conformational stability of the ligands increases and separate diastereomeric species can be detected in solution up to 50°C. Upon addition of tin chloride these complexes produce quite active hydroformylation catalysts. Styrene is quantitatively converted even at 32°C with a highly favourable branched selectivity (up to 85%), but the e.e. of 2-phenylpropanal is modest and does not exceed 45% in the best case.[70]

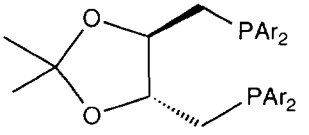
Chart 13. Chiral ligands used in Pt-catalysed hydroformylation



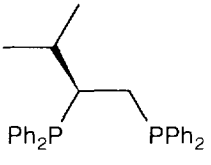
36 Ar = 4-$Me_2NC_6H_4$



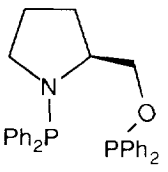
37 Ar = 4-$Me_2NC_6H_4$
38 Ar = PPh_2
39 Ar_2 = BNP



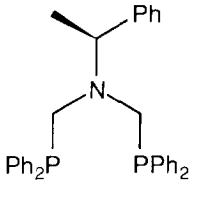
40 Ar = 4-$Me_2NC_6H_4$
41 Ar_2 = BNP



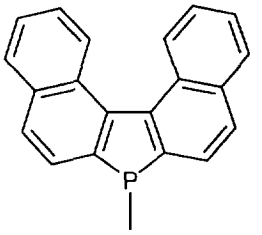
42 VALPHOS



43



44



BNP

Chiral platinum complexes with phosphite-phosphinamide ligands related to proline such as **43** have been prepared and tested in the enantioselective hydroformylation of styrene in combination with tin chloride.[71] High chemoselectivities and fair e.e.'s (40-56%) were obtained, but the branched selectivity was unsatisfactory and the chemical yield of 2-phenylpropanal was always lower than 40%. An apparent discrepancy exists between these results and the ones previously reported by other authors.[72] Opposite configurations have been assigned to the prevailing enantiomer of the chiral aldehyde which has been obtained with a Pt complex containing the same (S)-ligand **43**. Although there are slight differences in the reaction conditions reported in the two papers, it seems highly improbable that they can cause a complete switch in the enantioselection of the reaction.

5. Concluding Remarks

After more than twenty years of disappointing results, remarkable advances have been achieved in the last two years in the enantioselective hydroformylation of olefins with rhodium catalysts. They are basically related to the use of bidentate ligands of novel design, most of which charaterized by a fairly large chelate ring. The most efficient catalysts presently available are derived either from bidentate C_2 symmetry diphosphites of chiral 1,3-diols or from non-symmetrical atropisomeric phosphino-phosphito ligands like BINAPHOS. Upon coordination to rhodium they both provide fairly stable 8-membered chelate ring complexes which both seem to produce a single pentacoordinated hydridocarbonyl derivative under hydroformylation conditions. These complexes are characterized by a different arrangement of the P-donors. The P,P-diequatorial geometry is preferred by symmetrical 1,3-diphosphites whereas only the equatorial-axial isomer is observed with BINAPHOS. The different coordination mode is basically due to the different natural bite angle of the ligands, which is close to 120° for diphosphites[28] and to 90° for BINAPHOS.[38] In the latter case, additionally, the presence of two phosphorus centers of different ligating properties is beneficial because it induces the exclusive formation of the regioisomer where the more apicophilic donor (the phosphite) takes up selectively the axial position.

It has been recently pointed out that a correlation exists between the natural bite angle of chelating diphosphines and the regioselectivity of the rhodium catalysed hydroformylation. For terminal olefins, the amount of the straight-chain aldehyde increases with the angle[73] and high regioselectivities can be attained even with functionalised olefins.[26] With styrene and vinylarenes, similar ligands provide a high branched selectivity.[27,74] This peculiar behaviour has been attributed to the selective chelation of these ligands to the equatorial sites in the trigonal bipyramidal rhodium species involved in the catalytic cycle.

It is our feeling that the efficiency of the novel chiral inducers recently introduced in asymmetric hydroformylaton may rest on a similar, albeit not identical, argument. From the results reported above, it is apparent that both large- and narrow-bite ligands are able to provide high stereoselectivities. Thus, the ligand is important only as far as it promotes the formation of a single pentacoordinated intermediate, while the peculiar coordination aptitude is less significant. In view of the results so far available, 1,7-bidentate phosphorus ligands designed to match exclusively either with an eq-eq or with an eq-ax coordination appear the best candidates for a high enantioselection in asymmetric hydrofomylation with rhodium catalysts.

The initial results obtained upon introduction of chiral ligands with S-donors in the Rh-catalysed process look encouraging. Since their outset, these derivatives have equaled or overtaken the results obtained after twenty years with the old-fashioned phosphine ligands. Dinuclear rhodium complexes with large size chelate ring originated from flexible dithiolate ligands are very efficient hydroformylation catalysts under low gas pressure and seem to hold the promise for improved efficiency in the next future. Unfortunately, the mechanistic details of this catalysis are mostly obscure and this hampers a rational design of new ligands. With the exception of the single case of 2-vinylnaphtalene, the results obtained so far with heterobidentate chelating ligands seem less promising. The variety of the structures available for these derivatives, however, is so wide that their potential is at present basically unexpressed.

Electronic effects seem as well important in determining high stereoselectivities in rhodium-catalysed hydroformylation, but at present a rationale for this behaviour is not obvious. We may only speculate that the presence of electron withdrawing substituents at phosphorus can stabilize non-bonded interactions between the substrate and the catalyst, reducing the number of diastereomeric conformers of comparable energy. Theoretical calculations support the view that π-stacking interactions between the substrate and the aryl substituents at

phosphorus may play a significant role in addressing the regioselectivity in the Pt-catalysed hydroformylation of styrene.[75] The exceptionally large e. e. differences recorded in two separate cases when styrene and 2-vinylnaphtalene were hydroformylated with the same catalyst[44,63] may be possibly ascribed to a similar reason.

The results obtained in the last two years in the enantioselective hydroformylation with platinum are less exciting than with rhodium. In part this is because most efforts have been focussed on rhodium chemistry, where the general expectations were more favourable. In part, this is because platinum is less versatile than rhodium. For example, switching from chelating phosphines to P,S- or S,S-bidentate donors results in a dramatic decrease or complete loss of catalytic activity of platinum complexes.[76] Platinum catalysts seem as well more sensitive than rhodium to temperature variations and sometimes the same catalysts may provide both the enantiomers of the same product. This fact has obvious bearings with respect to the determination of the enantiodetermining step of the reaction and may either confirm or discharge the original proposal by Pino.[2b]

In spite of these recent advances, particularly with rhodium catalysts, several questions still remain open in asymmetric hydroformylation. The hydroformylation of terminal aliphatic olefins, irrespective of the catalysts used, is still far from giving satisfactory e. e.'s. The intimate mechanism of the reaction, both with rhodium and with platinum, is not yet known in its details. In particular, for a rational ligand design, the contribute, if any, of the elusive pentacoordinated intermediates to the determination of the prevaling enantiomer must be clarified.

A common drawback of the catalysts so far available is that usually they associate a high enantioselectivity to a modest catalytic activity or vice versa. In principle this dichotomy may be settled either by reducing the steric constraints or by increasing the donicity of the ligand. In the case of rhodium catalysts, phospholes seem particularly appropriate for this purpose.[46] A few chiral diphospholes have been synthesized recently, but the catalytic behaviour of their rhodium complexes in hydroformylation has been not yet reported.[77] On the other hand, preliminary tests with *in situ* catalysts obtained from *bis*-binaphthophospholes[70] and suitable rhodium procatalysts afforded so far unsatisfactory results.[76]

Finally, we guess that it is a general issue of people involved in asymmetric catalysis that a clear-cut conclusion on the reliability of the results published by Stille and coworkers[4a,18] can be achieved in order to give up any further dispute. We are very much looking forward to reading a decisive report on this controversial point in the next future.

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