Asymmetric Hydroformylation†

Francine Agbossou, Jean-François Carpentier, and André Mortreux*

Laboratoire de Catalyse Hétérogène et Homogène, Groupe de Chimie Organique Appliquée, URA CNRS 402, Ecole Nationale Supérieure de Chimie de Lille, B.P. 108—59652 Villeneuve d'Ascq Cedex, France

Received March 10, 1995 (Revised Manuscript Received May 19, 1995)

Contents

I. Introduction

Since its discovery by Roelen in 1938,[1] hydroformylation has developed into an extremely important industrial process, and now several million tons per year of oxo products are produced via this method worldwide. Also, hydroformylation is one of the most versatile methods for the functionalization of C=C bonds and can be seen consequently as a very powerful synthetic tool for the preparation of fine chemicals. In this area, the demand of pharmaceutical and agrochemical industries for enantiomerically pure compounds is rapidly increasing.[2] Thus, the application of many simple optically active aldehydes arising from *asymmetric hydroformylation* as synthetic intermediates for the production of sophisticated pharmacologically active molecules is now of great interest and was reviewed in 1991[3] and 1993.[4] In this field, the hydroformylation reaction of vinyl aromatics lends itself to the synthesis of intermediates toward optically active nonsteroidal antiinflammatory agents which are functionalized 2-arylpropanoic acids (Scheme 1). As well, several chiral aldehydes prepared by hydroformylation of simple olefins can be conveniently transformed into optically active α-amino acids. The challenge of asymmetric hydroformylation concerns not only the enantioselectivity (maximal asymmetric induction and minimal racemization of the optically active products) but also the chemoselectivity (hydroformylation *vs* hydrogenation) and the regioselectivity (branched *vs* linear aldehyde). Scheme 2 illustrates the different ways in which enantioselectivity can be achieved in hydroformylation reactions.[5] In the case of monosubstituted alkenes, enantioselection can occur only through the branched aldehyde formation. For α,α-disubstituted alkenes, enantioselection can occur by C−H *or* C−C bond formation, whereas for α,β-disubstituted and trisubstituted alkenes, both C−H *and* C−C bond formation can lead to enantioselectivity, which may or not occur in the same extent.

The first reports on asymmetric hydroformylation appeared in 1972, and concerned the hydroformylation of styrene and related olefins in the presence of cobalt (the traditional metal for industrial oxo processes) catalysts modified by a chiral Schiff base,[6] and rhodium complexes bearing chiral monophosphine ligands.[7,8] For the cobalt catalytic system applied to styrene, the main reaction was hydrogenation into ethylbenzene (over 52%) and the best branched *vs* normal (b/n) ratio for the aldehydes was 59/41. Moreover, optical yields obtained were in every case very low (<3% ee). Only moderate success has been obtained with the rhodium−chiral monophosphine systems,[7,8] since despite better chemo- and regioselectivities, the enantioselectivities were still rather low. For example, the hydroformylation of styrene in the presence of rhodium complexes modified by (+)-benzylmethylphenylphosphine gave 88% of the mixture of aldehydes (b/n = 90/10) with 18% ee.[7] In

* Address correspondence to Professor A. Mortreux. Telephone: (33).20.43.49.93. Fax: (33).20.43.65.85.

† This paper is dedicated to the memory of Professor Francis Petit, deceased December 30, 1992, and his friend Professor Hidemasa Takaya, deceased October 4, 1995.

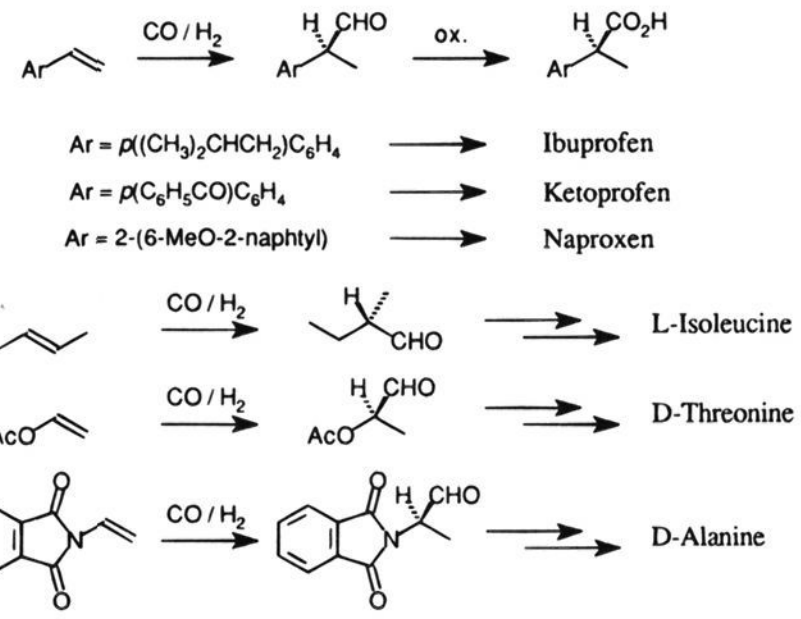
0009-2665/95/0795-2485$15.50/0

Francine Agbossou (formally Niedercorn) was born in Bouzonville, France. She graduated in 1979 from the University of Nancy and started her doctorate work with B. Castro on metalloporphyrins. Then, in 1981, she obtained a permanent position with the "Centre National de la Recherche Scientifique" (CNRS) at the "Institut de Recherches sur la Catalyse" in Villeurbanne. She received her Ph.D. degree in 1985 with I. Tkatchenko for work on metalloporphyrin chemistry. Right after, she moved to the "Laboratoire de Chimie de Coordination du CNRS" in Toulouse to do work in homogeneous catalysis. From 1988 to 1989, she spent 18 months with the group of John Gladysz at the University of Utah as a Postdoctoral Research Associate. In 1991, she moved to the "Laboratoire de Catalyse Hétérogène et Homogène du CNRS" and joined the group of F. Petit and A. Mortreux to develop research in asymmetric catalysis. Her current interests focus on asymmetric homogeneous and heterogeneous catalysis, chiral organometallic complexes and their application in organic synthesis, and computational chemistry.

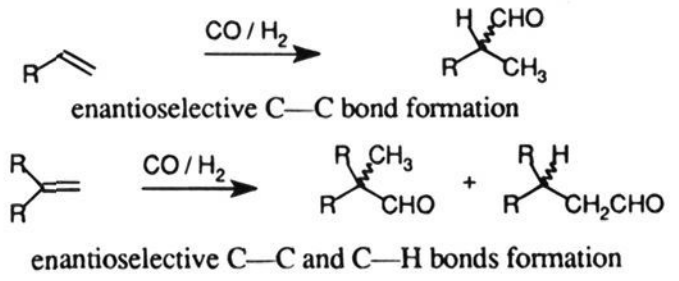
Jean-François Carpentier was born in 1967. He graduated from Ecole Nationale Supérieure de Chimie de Lille in 1989 and received his Ph.D. degree from the University of Lille in 1992 under the direction of F. Petit, for work on carbonylation reactions with alkyl formates. He currently holds a permanent position at the Centre National de la Recherche Scientifique (CNRS). His research interests involve the field of asymmetric homogeneous catalysis including hydrogenation and carbon–carbon bond formation processes, and heterogeneized homogeneous systems.

André Mortreux was born in the North of France in 1943. His chemical education includes a M.S. degree from Lille University in 1965, and a Science Doctorate (Doctorat d'Etat) in chemistry from Poitiers University in 1975, working under Professor M. Blanchard. During his thesis, devoted mostly to catalytic reactions of alkynes via heterogeneous catalysis, he discovered (1972) the first homogeneous catalyst for alkyne metathesis. After a postdoctoral position with Professor F. G. A. Stone in Bristol (UK), he moved back in Lille University where he joined his friend Professor F. Petit who had started research in homogeneous catalysis. André Mortreux is currently full professor at the University of Lille. His research topics include the synthesis of classical or electrogenerated transition metal catalysts for hydrocarbon activation and functionalization (olefins and alkynes metathesis and polymerization, diene oligomerization and telomerization). He is also developing the use of CO and methyl formate as building blocks for the synthesis of specialities and fine chemicals. The design of new phosphorus ligands (AMPP) derived from the amino acid chiral pool for asymmetric catalysis is one of its major interest, including hydrogenation of C=O and C=C bonds, as well as C–C bond formation.

Scheme 1



Scheme 2



view of these poor results obtained with chiral monophosphines associated with rhodium, authors rapidly directed their efforts toward chiral bisphosphines which are the ligands of choice in asymmetric hydrogenation.[9] Thus, DIOP, one of the most promising chiral diphosphines at that time, was first associated with rhodium complexes in 1973[10] and one year later with platinum–tin combinations.[11]

Other metals have been used in asymmetric hydroformylation like ruthenium, iridium, and palladium, but the catalytic properties were rather disappointing.[12] For these metals as for cobalt-based catalytic systems, no substantial progress has been reported in the field of asymmetric hydroformylation since the last review on this subject.[12] Consequently, this review deals only with the two metal systems that have shown the most promise, platinum- and rhodium-based systems, and which have accordingly retained almost total attention of researchers over the last two decades.

This review is an attempt to present the state of the art in the application of platinum and rhodium

systems in asymmetric hydroformylation. The first and second parts present the synthetic aspects of asymmetric hydroformylation with platinum and rhodium catalysts, respectively. Within each part, the results are compiled first according to a classification of the ligands involved to give the reader an idea of the diversity of both the ligands and the substrates. In particular, selected results obtained during the asymmetric hydroformylation of styrene, a substrate which can be considered as a model compound for vinyl aromatic substrates that could be used for the synthesis of antiinflammatory drugs, are summarized in two tables (Tables 1 and 2, respectively).[13] Then, for both metals, the influence of main reaction parameters including temperature, pressure, and composition of the catalytic system are examined.

In a third part, similarities and differences between platinum and rhodium as well as a comparison between the more successful systems is undertaken, and important elements that are beneficial for high selectivities are presented. From this analysis, an attempt at rationalization is made on the basis of models (stereochemical models and molecular modeling) that have been proposed to explain the regio- and the enantioselectivities observed. Finally, some spectroscopic properties attributed to participating catalytic species are presented.

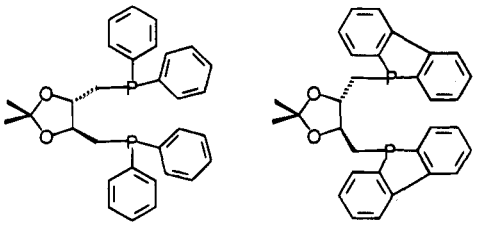
II. Platinum-Catalyzed Asymmetric Hydroformylation

A. Description of Catalytic Systems

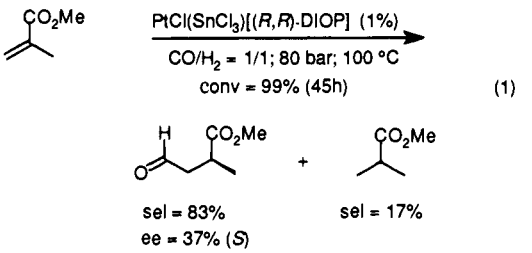
1. Systems Based on DIOP and Related Ligands

Historically, because of its large importance and easy availability, DIOP was the first chiral ligand used in the platinum–tin-catalyzed hydroformylation (Chart 1). At the early stage of research, irreproducible and sometimes contradictory results were reported in the literature on the hydroformylation of butenes and vinyl aromatic compounds.[14–18] The origin of these conflicting results is nowadays quite established and is discussed in more details in the related section II.B. Classically, DIOP–$PtCl_2$–$SnCl_2$ systems are characterized by a rather good catalytic activity compared to other platinum-based systems. Nevertheless, aldehyde formation is usually accompanied by hydrogenation, and sometimes extensive isomerization or polymerization of the substrate. The regioselectivity of hydroformylation is strictly dependent on the nature of the substrate. For instance, *exo*-methylene compounds such as methacrylic acid derivatives[19,20] or 2-arylpropene compounds[21] afforded exclusively the "less-branched" isomeric aldehyde (eq 1). In contrast, significant amounts of branched aldehydes could be obtained from styrene and 2-butenes.[22–24]

Chart 1

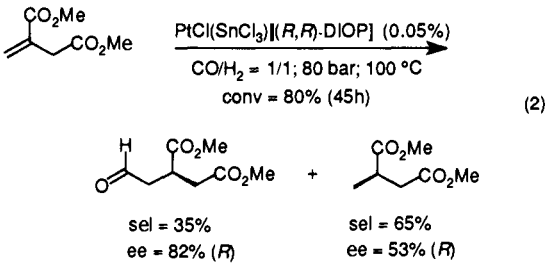


(*S,S*)-DIOP (*S,S*)-DBP-DIOP



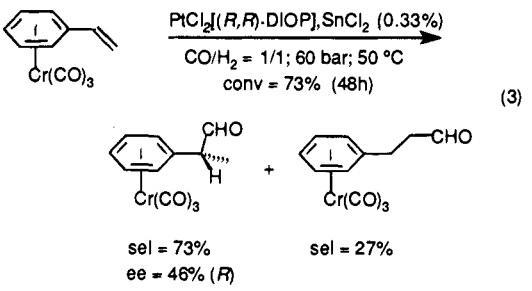
(1)

The enantioface discrimination of DIOP is fair and traditionally led to moderate ee's that ranged from 10 to 50%. Nevertheless, many experiments showed that the Pt–DIOP catalytic active species for hydroformylation and/or the Lewis acid stannous chloride present under the reaction conditions are also effective catalysts for *in situ* racemization of the aldehydes.[23] Consequently, most of the results reported do not exactly reflect the intrinsic enantioselectivity of the DIOP systems. Regardless, enantiomeric excesses as high as 82% were obtained for the hydroformylation of dimethyl itaconate (eq 2),[19] but did not exceed 26% for vinyl aromatic compounds such as styrene (Table 1, entry 1).[21,22,25] In this field,



(2)

it was shown that conversion of styrene and related arylalkenes into their tricarbonylchromium complexes increased the rate of platinum–tin–DIOP-catalyzed hydroformylation, the regioselectivity for branched aldehydes, and the enantioselectivity (eq 3).[26]



(3)

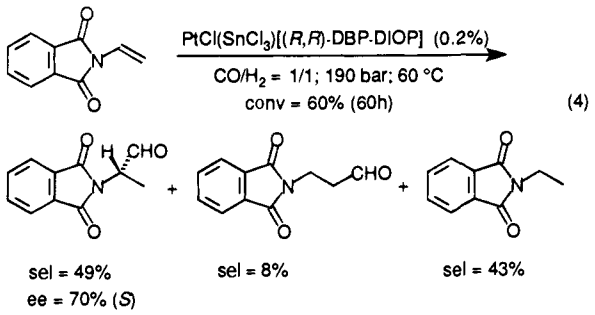
A few years later, after the appearance of DIOP–$PtCl_2$–$SnCl_2$ systems, the possibility of using DBP-DIOP (Chart 1), an analogue of DIOP whose diphenylphosphino groups are substituted by 5*H*-benzo[*b*]phosphindole substituents (dibenzophosphole, DBP), was investigated. A marked increase in the regio- and the enantioselectivity was observed during hydroformylation of butenes[17] and styrene[22,27] when DBP-DIOP was used in place of DIOP (Table 1, entry

Table 1. Asymmetric Hydroformylation of Styrene by $PtCl_2$(ligand)/$SnCl_2$ Systems[a]

entry	ligand	CO/H_2, atm/atm	conversn, %[b] (reacn time, h)	selectivity to aldehydes, %	regioselectivity (*b*/*n*)[c]	ee, % (config)	turnover frequency[d]	ref
1	(*R*,*R*)-DIOP	45/45	90 (10	90	23/77	26 (*S*)[e]	81	22
2	(*R*,*R*)-DBP-DIOP	90/90	100 (16)	80	77/23	64 (*S*)	22	28
3	(*R*,*R*)-DBP-DIOP polymerized	90/90	62 (24)	81	62/38	65 (*S*)	9	28
4	(*S*,*S*)-DIOP-($pNMe_2$)$_4$	35/35	35 (46)	100	42/58	8 (*R*)	7.6	30
5	(*R*,*R*)-BCO-DPP	70/140	100 (3)	83	43/57	25 (*S*)	277	34
6	(*R*,*R*)-BCO-DBP	70/140	95 (2.3)	67	80/20	85 (*S*)	277	34
7[f]	(*R*,*R*)-BCO-DBP	70/140	20 (180)	nr	nr	80 (*S*)	1.3	34
8	(*S*,*S*)-BDPP	40/40	56 (60)	96	40/60	72 (*S*)	18	36
9	(*S*,*S*)-BDPP-($pNMe_2$)$_4$	35/35	18 (48)	100	37/63	7 (*S*)	3.7	30
10	(*S*,*S*)-CHIRAPHOS	40/40	47 (21)	74	62/38	45 (*R*)	33	24
11	(*S*,*S*)-CHIRAPHOS-($pNMe_2$)$_4$	35/35	13 (96)	98	61/39	37 (*R*)	1.3	30
12	(*S*)-BINAP	40/40	37 (52)	97	33/67	69 (*S*)	14	40
13	(*S*,*S*)-BPPM	80/80	40 (4)	98	35/65	77 (*S*)	39	43
14[f]	(*S*,*S*)-BPPM	80/80	100 (150)	nr	33/67	>96 (*S*)	<2.6	43
15	(*S*,*S*)-BPPM polymerized	80/80	9 (50)	100	34/66	55 (*S*)[e]	0.9	41
16	(*S*,*S*)-DBP-BPPM	80/80	20 (4)	nr	76/24	40 (*S*)	<20	43
17[f]	(*S*,*S*)-DBP-BPPM	80/80	56 (95)	nr	77/23	>96 (*S*)	<2.4	43
18	(*R*,*S*)-EPHOS	65/100	54 (36)	92	41/59	36 (*S*)	1.3	46
19	(*S*)-Ph,Ph-ProNOP	52/78	100 (36)	98	40/60	42 (?)[g]	2.7	47,48
20	(*S*)-Cy,Cy-oxoProNOP	52/78	70 (160)	96	35/65	56 (*S*)	0.4	47

[a] Reaction conditions: temperature = 50–60 °C except entry 11 (T = 100 °C); solvent = benzene or toluene except entries 14 and 17 (1,2-dichlorobenzene); $SnCl_2/Pt$ = 1–3; styrene/Pt = 1000–2000 except entries 2–3 and 13–17 (S/C~400) and entries 18–20 (S/C~100). [b] Styrene conversion including aldehydes and ethylbenzene. [c] Ratio of branched to linear products. [d] Average value calculated over the whole reaction time (mol of aldehydes/mol of Pt)/h. [e] Corrected value according to ref 27. [f] Reaction conducted in the presence of triethyl orthoformate. [g] See text.

2). This interesting catalytic system was used also for the asymmetric hydroformylation of a variety of olefins such as vinyl acetate, norbornene, and *N*-vinylphthalimide (eq 4).[28] A similar modification of

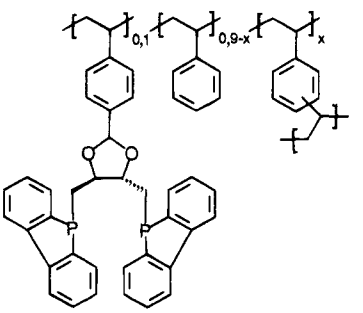


DIOP using binaphthophospholyl (BNP) substituents was very recently reported.[29] The platinum complex of DIOP-BNP in the presence of $SnCl_2$ exhibited an interesting catalytic activity in the hydroformylation of styrene. Under optimum conditions, hydratropaldehyde could be obtained in 50% yield (*b*/*n* = 68/32, 26% hydrogenation into ethylbenzene) and enantiomeric excesses up to 44%.

Almost at the same time, chiral ligands closely related to DIOP and DBP-DIOP attached to linear and to cross-linked polymers were synthesized (Chart 2). Hydroformylations utilizing the corresponding platinum–tin catalysts showed comparable rates and gave nearly the same optical yields as their homogeneous analogues (Table 1, entry 3).[22,28] However, lower branched to normal ratios were obtained, especially with the cross-linked polymer. The major advantage of these systems is the ability to recover and to reuse the catalyst, almost without loss in rate or selectivity.

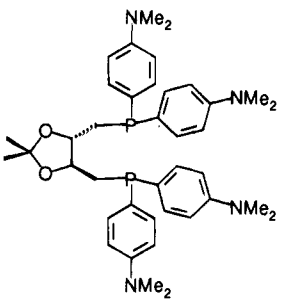
Asymmetric hydroformylation catalyzed by $PtCl(SnCl_3)$(L–L)* complexes of other derivatives of the DIOP ligand, such as tetra-*p*-amino-functionalized

Chart 2

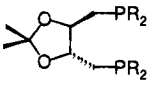


Polymer Bound (*S*,*S*)-DBP-DIOP

Chart 3



(S,S)-DIOP-($pNMe_2$)$_4$

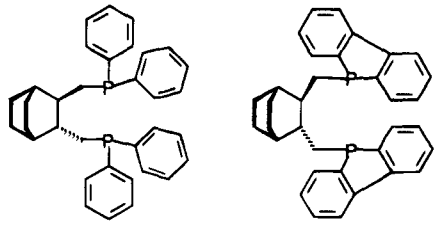


R = Ethyl: (*R*,*R*)-Et-DIOP

R = Cyclohexyl: (*R*,*R*)-Cy-DIOP

DIOP[30] or ligands bearing dialkylphosphino residues in place of the diphenylphosphino groups[31] (Chart 3), were also investigated. Unfortunately, only discouraging results were obtained, since these systems, especially those based on Et- and Cy-DIOP, brought about a loss of catalytic activity and selectivity with respect to the DIOP system (Table 1, entry 4). An interesting feature of the DIOP-($pNMe_2$)$_4$ system is the reversal in the prevailing product configuration as a function of temperature during hydroformylation of styrene. Similar behaviors are discussed in more detail in section II.B.1.

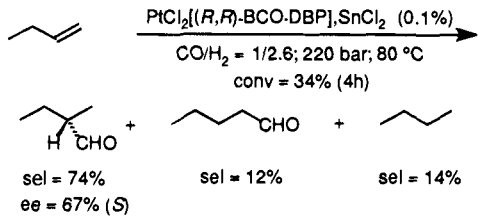
Chart 4



(*R,R*)-BCO-DPP (*R,R*)-BCO-DBP

Numerous investigations of different complexes containing the DIOP ligand have shown that the chelate ring is conformationally labile, both in solution and in the solid state.[32] Therefore, it appeared probable that ligands related to DIOP having C_2 symmetry and forming a seven-membered coordination ring, but with a more rigid skeleton, should improve enantioselectivities while maintaining the high catalytic activity observed for the DIOP ligand. In this way, the use of the platinum(II) complexes of the BCO-DPP and BCO-DBP ligands (Chart 4) in combination with $SnCl_2$ resulted in significant improvements of the catalytic properties.[33,34]

Both systems showed very high catalytic activities, and turnover frequencies up to 280 h^{-1} at 50 °C were achieved for the hydroformylation of styrene.[35] The level of regioselectivity and of asymmetric induction of BCO-DPP was similar to that of analogous DIOP systems (Table 1, entry 5). Interestingly, according to the nature of the olefinic substrates studied, the prevailing absolute configuration for the resulting aldehyde was either identical or opposite to that found with DIOP. The results obtained from the BCO-DBP catalytic system are by far more interesting, since this ligand displayed a very high capacity for enantioface discrimination. Actually, the ee for 1-butene is the highest so far reported (67% ee, eq 5) in the presence of platinum catalysts, while styrene could be hydroformylated in 85% ee (Table 1, entries 6 and 7).[34] Worth noting is the fact that the latter



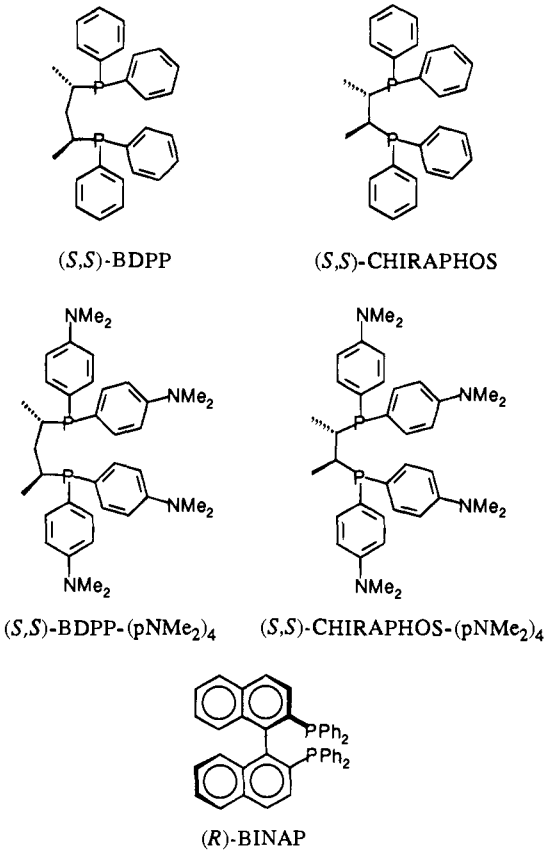
value was not improved by carrying out the reaction in the presence of triethyl orthoformate, which converts the aldehyde as formed into the corresponding configurationally stable diethyl acetal. This indicated that there was no racemization of the optically active aldehyde and that the results reported are indicative of the intrinsic enantioselectivity of the catalyst.

Another interesting feature of the BCO-DBP system is its high regioselectivity, as indicated by the ratio between the linear and the branched product resulting from the hydroformylation of styrene (b/n = 80/20) and of (*Z*)- and (*E*)-2-butenes (b/n = 87/13). Moreover, for these last substrates, due to the presence of the dibenzophosphole substituents, BCO-DBP also exhibited a lower isomerizing activity compared to the BCO system. Systematically, BCO-DBP displayed better or at least identical regio- and enantioselectivities than the DBP-DIOP system, but still suffered from competitive hydrogenation.

2. Systems Based on Other C_2 Symmetry Ligands

Other chiral ligands having C_2 symmetry have been associated with platinum–tin catalytic systems for asymmetric hydroformylation. All are diphosphines which form either five- (CHIRAPHOS and its tetra-*p*-dimethylamino derivative), six- (BDPP and its tetra-*p*-dimethylamino and BNP derivatives) or seven-(BINAP) membered metallacycles (Chart 5).

Chart 5



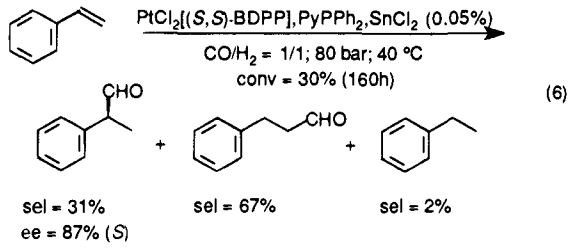
(*S,S*)-BDPP (*S,S*)-CHIRAPHOS

(*S,S*)-BDPP-(pNMe$_2$)$_4$ (*S,S*)-CHIRAPHOS-(pNMe$_2$)$_4$

(*R*)-BINAP

Among these ligands, BDPP is probably the one that has received the greatest attention. When applied to vinylidene carboxylic esters hydroformylation, the normal aldehyde was obtained exclusively in 70–80% selectivity, but the enantioselectivity was still moderate and the best ee's did not exceed 40%.[36] Similarly, deltacyclene could be selectively converted into the corresponding *exo* aldehyde, but only in 16% ee.[37] In the case of styrene, the regioselectivity into hydratropaldehyde always ranged from 25 to 40%. Classical $PtCl(SnCl_3)$(BDPP) systems, under appropriate reaction conditions, led to a relatively high enantiomeric excess (Table 1, entry 8),[36] but this value could be significantly improved by the use of mixed-phosphine systems involving the combination of BDPP with either triphenylphosphine (89% ee)[38] or 2-(diphenylphosphino)pyridine (87% ee) (eq 6).[39]

Unfortunately, in both cases, the yields to the desired product were too low to be of practical interest.



(6)

The use of BDPP-BNP, an analogue of BDPP whose diphenylphosphino groups are substituted by binaphthophospholyl (BNP) moities, was recently investigated.[29] Despite interesting catalytic activity and chemo- and regioselectivity into the desired branched aldehyde, the enantioselectivity of the reaction was consistently low (up to 24% ee).

The asymmetric hydroformylation of styrene in the presence of $PtCl(SnCl_3)$[BDPP-$(pNMe_2)_4$] was strongly temperature dependent and provided good enantioselectivities into both enantiomers of hydratropaldehyde, 57% ee in the *R* product at 100 °C and 61% ee in the *S* product at 30 °C.[30] This reversal is presented in more details in sections II.B.1. and IV. Nevertheless, the behavior of this system was almost similar to that of BDPP and afforded poor reaction rates and above all low regioselectivities into the branched aldehyde (Table 1, entry 9).

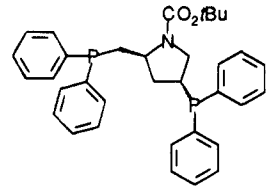
When CHIRAPHOS was used as the chiral ligand, a remarkable decrease in catalytic activity with respect to the DIOP-system was observed for the hydroformylation of a variety of olefins, and most of the reactions required large induction periods.[24] Although hydrogenation of the olefins accompanied hydroformylation, as usually observed with platinum–tin catalytic systems, aldehydes could be nevertheless generally produced in more than 70% selectivity. The regio- and the enantioselectivity of the CHIRAPHOS system were always higher than that of the DIOP system, but in the case of styrene, the corresponding values for hydratropaldehyde did not exceed 62% and 45%, respectively. These results could not be improved by the use of the tricarbonylchromium complex of styrene.[26] The enantioselectivity during the hydroformylation of styrene in the presence of the tetra-*p*-dimethylamino derivative of CHIRAPHOS was also strongly influenced by temperature (but not reversed), but the overall behavior of the system is similar to that of its nonsubstituted analogue (Table 1, entries 10 and 11).[30]

Surprisingly, in contrast with the rhodium-catalyzed asymmetric hydroformylation which is developed below, atropoisomeric ligands have been very little studied in combination with platinum–tin systems. While $PtCl_2$[(*S*)-BINAP] in the presence of stannous chloride was found to be totally inefficient when tricarbonylchromium complex of styrene was used as the substrate,[26] quite interesting results were obtained from free styrene (Table 1, entry 12).[40] Once again, the performances of this system are strongly temperature dependent.

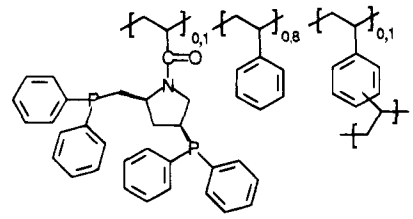
3. Systems Based on Non-C_2 Symmetry Ligands

Among the chiral phosphines used in asymmetric hydroformylation, which do not have a C_2 axis of symmetry, BPPM and closely related derivatives have received much attention (Chart 6).

Chart 6

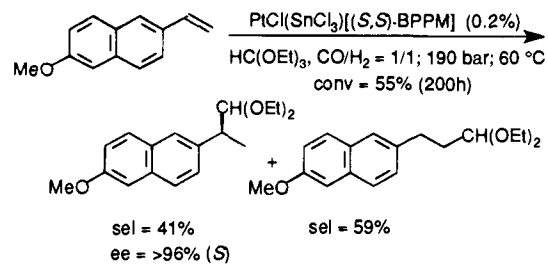


(*S*,*S*)-BPPM



Polymer Bound (*S*,*S*)-BPPM

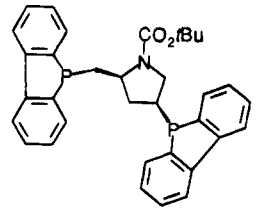
A variety of prochiral olefins, including potentially interesting vinyl aromatic compounds, could be hydroformylated by the $PtCl_2$[(*S*,*S*)-BPPM]–$SnCl_2$ system.[37,41,42] Although the branched to normal ratios were low (*b*/*n* ~29/71 to 37/63), the selectivity to aldehydes was high, and high enantiomeric excesses were achieved (60–80% ee) (Table 1, entry 13). However, the latter values were often lowered as a result of product racemization under the reaction conditions. This undesirable side reaction could be avoided by carrying out the hydroformylation in the presence of triethyl orthoformate as the solvent.[42] In these conditions, aldehydes are converted to acetals which are far less susceptible to racemization (*vide infra*). Although the reaction rates were considerably lower than in a classical aromatic solvent, enantiomerically pure acetals were obtained in high selectivities with almost all the olefins tested, including styrene (Table 1, entry 14) and 2-vinyl-6-methoxynaphthalene, a key intermediate in the synthesis of the antiinflammatory (*S*)-naproxen (eq 7). The branched to normal ratios were not affected by the presence of triethyl orthoformate.



(7)

Similar observations were made during the hydroformylation of styrene from a polymer-supported catalytic system where the chiral ligand BPPM has been incorporated into a polystyrene resin (Chart 6).[41,42] In benzene, chemo-, regio-, and enantioselec-

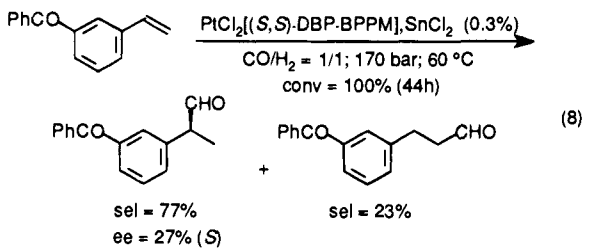
Chart 7



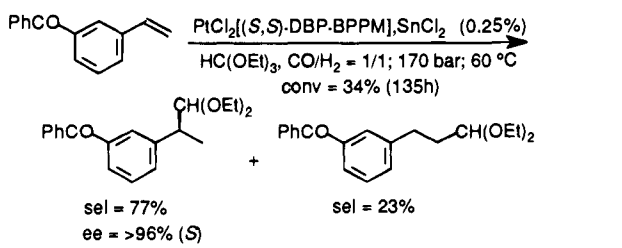
(*S,S*)-DBP-BPPM

tivities were almost similar to that obtained with homogeneous BPPM-based catalysts, and the performances, except somewhat lower reaction rates, were maintained upon recycling of the catalyst (Table 1, entry 15).[41,42] When the reaction was carried out in the presence of triethyl orthoformate, only a poor conversion was obtained, but with the product distribution and enantiomeric excesses (>98%) the same as achieved in the homogeneous case.[42]

On the basis of the observations made on DIOP related ligands, some derivatives of BPPM bearing either diphenylphosphino or dibenzophosphole (DBP) substituents were synthesized (Chart 7). It was shown that the introduction of two DBP groups (DBP-BPPM, Chart 7) resulted in a considerable increase of the branched to normal ratio while maintaining a quite good enantioface discriminating ability.[43] Hence, by carrying out the hydroformylation of various vinyl aromatic compounds in triethyl orthoformate, the DBP-BPPM system gave virtually complete enantioselectivity with high *b*/*n* ratios (Table 1, entries 16 and 17). This catalytic system was successfully applied to the synthesis of pharmaceutical precursors. Typical examples carried out without and in the presence of triethyl orthoformate are illustrated in eqs 8 and 9. It is worth noting that there is considerable question, however, whether the high enantiomeric excesses reported are reproducible,[44] and contradictory opinions are still appearing in the literature about this point.[4,30,34,45] Regardless, hydroformylation reactions conducted in triethyl orthoformate were extremely low.



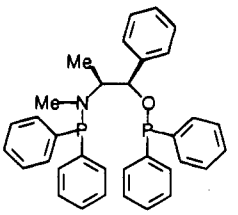
(8)



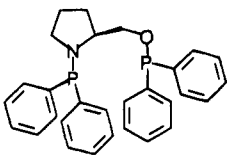
(9)

Another class of ligands, the aminophosphine–phosphinites, derived from natural amino alcohols such as EPHOS, Ph,Ph-ProNOP, and Cy,Cy-oxo-ProNOP (Chart 8), was simultaneously evaluated by

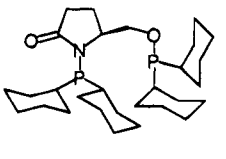
Chart 8



(*R,S*)-EPHOS



(*S*)-Ph,Ph-ProNOP



(*S*)-Cy,Cy-oxoProNOP

two independent groups in the enantioselective hydroformylation of styrene.[46–48] The corresponding platinum complexes in the presence of stannous chloride were often highly selective into aldehyde, but they exhibited very low activities and gave quite poor branched to normal ratios (*b*/*n* ≈ 29/71 to 55/45). Although some discrepancy exists between the two groups concerning the absolute configuration of the prevailing enantiomer of hydratropaldehyde, the ee values were consistent. Namely, classical enantiomeric excesses ranged from 20 to 56%, the best results being observed with Cy,Cy-oxo-ProNOP[47] (Table 1, entries 18–20).

B. Influence of Reaction Parameters

1. Temperature

As mentioned several times in the previous section, the behavior of platinum-based enantioselective hydroformylation catalysts could be strongly influenced by the reaction temperature. Specific reports on such phenomenona are devoted to the study of the platinum–tin systems of BDPP,[36,39] BINAP,[40] and tetra-*p*-amino substituted derivatives of DBPP, DIOP, and CHIRAPHOS.[30] As expected, the reaction rates of both catalytic pathways, *i.e.* hydroformylation and hydrogenation, increased with temperature, but the latter was generally favored. Consequently, the chemoselectivity into aldehydes was almost always optimal at low temperature, although a wide temperature range (usually up to 80 °C) usually existed where chemoselectivity was not affected. A similar trend was also observed for the regioselectivity into the branched aldehyde. However, the variation trend of the branched to normal ratio (*b*/*n*) was more gradual, and temperature effects could be generally observed from ambient temperature. An example of this typical behavior in the case of the asymmetric hydroformylation of styrene in the presence of PtCl(SnCl$_3$)[(*S,S*)-BDPP-(pNMe$_2$)$_4$] is illustrated in Figure 1 (curve ○).

The enantioselectivity is also specially temperature dependent. The typical behavior is for enantioselectivities to improve at low temperature. For example, the enantiomeric excess of (*S*)-hydratropaldehyde increased from 68% to 86% upon decreasing the reaction temperature from 80 to 40 °C in the hydroformylation of styrene with PtCl(SnCl$_3$)[(*R,R*)-BCO-

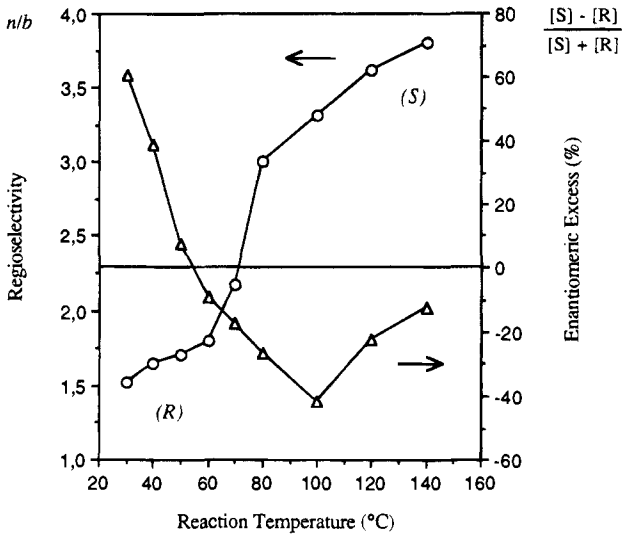


Figure 1. Regioselectivity (○) and enantioselectivity (△) of hydroformylation products of styrene in the presence of $PtCl(SnCl_3)[BDPP\text{-}(pNMe_2)_4]$ as a function of reaction temperature.

DBP].[34] Furthermore, the *in situ* racemization of the optically active aldehyde increased with increasing temperature, and so contributed also to the decrease of the optical yields.[42] This phenomenon also probably accounts for the conflicting results reported for the hydroformylation of 2-butenes.[23] The change in absolute configuration of hydratropaldehyde has been observed in the 20−125 °C temperature range for the hydroformylation of styrene in the presence of various catalytic systems.[30,36,39,40] The example of the $PtCl(SnCl_3)[(S,S)\text{-}BDPP\text{-}(p NMe_2)_4]$ catalyst is illustrated in Figure 1 (curve △). According to the nature of the catalytic system, this uncommon phenomenon was suggested to be due either to the restricted rotation of the phenyl rings (BINAP),[40] or the existence of competing reaction pathways via the diastereomeric intermediates (*p*-aryl-substituted ligands),[30] or a change in the conformation of the chelate ring, or finally to kinetics effects (BDPP).[36,39] A similar reversal of product configuration as a function of reaction temperature was also reported for the hydroformylation of 1-butene with $PtCl(SnCl_3)$[DIOP],[23] but in this particular case, the isomerization of the substrate to 2-butene along with the decomposition of the catalyst was considered to be responsible for the switch in product enantiomer.

2. Catalytic System—Precursor

The insertion of tin(II) chloride into the Pt−Cl bond results in the formation of $PtCl(SnCl_3)$(P−P) type catalyst containing a strongly *trans*-activating $SnCl_3$ ligand, which plays a key role in the reactivity of the catalytic species.[49,50] Although this insertion is generally recognized to be easy and almost quantitative when 1 equiv of both reactants were placed under the catalytic reaction conditions, the catalytic performances of preformed $PtCl(SnCl_3)$(P−P) complexes when compared to *in situ* generated $PtCl_2$(P−P)/$SnCl_2$ species were sometimes different.[28] In particular, the use of *in situ* $PtCl_2$(DIOP)/$SnCl_2$ systems was possibly one important reason for the nonreproducibility of the results reported for the hydroformylation of 1- and 2-butenes.[15,17,18] From an asymmetric point of view, somewhat better results were obtained in the presence of an excess of $SnCl_2$,[36] and most studies are because this observation usually carried out by using an average Sn/Pt ratio of 2−3. For the catalytic system $PtCl_2$(DIOP) modified by $SnCl_2$,[16,22] an increase of the chiral ligand to metal ratio only brought about a decrease of the catalytic activity and had practically no influence on the enantioselectivity of the reaction.

Various cocatalysts have been used in place of stannous chloride. Thus, tin(II) fluoride in combination with $PtCl_2$(BDPP) offered an efficient catalytic system of unusual thermal stability for the enantioselective hydroformylation of styrene.[39] Conversely, $SnCl_4$, $CuCl_2$, or CuCl gave catalytic systems with a rather moderate activity and above all poor enantioselectivity.[38] The behavior of the zerovalent platinum complex $Pt(C_2H_4)$(DIOP) in combination with either CH_3SO_3H as a promoter[51] or $PtCl_2$(DIOP) as a cocatalyst[25] was also investigated, but no significant improvement could be achieved.

3. CO/H_2 Pressure

The partial and to a lesser extent the absolute pressures of CO and H_2 can also considerably influence the activity, as well as the chemo- and the enantioselectivity of the catalysts. Although each catalytic system/substrate combination should be considered as a particular case, general remarks emerge from the analysis of the results reported during asymmetric hydroformylation of a variety of olefins with $PtCl(SnCl_3)$(DIOP):[14,16,19,22,23] (*i*) the hydroformylation rate increases with decreasing $p(CO)$ and particularly with increasing $p(H_2)$; (*ii*) the selectivity to hydroformylation decreases with increasing $p(H_2)$ and with decreasing $p(CO)$; (*iii*) the isomeric ratio is almost unchanged; (*iv*) the enantiomeric excess of the aldehyde increases while increasing $p(H_2)$ and decreasing $p(CO)$. The preformed $PtCl(SnCl_3)$(BDPP) system showed a similar behavior during the hydroformylation of styrene,[36] since for instance the enantiomeric excess increased from 63% to 73% with increasing $p(H_2)$ from 40 to 80 atm. Conversely, this effect of the pressure became negligible in the presence of an excess of $SnCl_2$.

The negative influence of carbon monoxide partial pressure on the reaction rate and on the enantiomeric excess has been attributed to the existence of different catalytic species, each one having its own peculiarity of activity and enantioselectivity.[23] In fact, catalytic species bearing carbon monoxide and phosphorus ligands in different relative ratios could be present at the same time.

4. Solvent

It is generally recognized that the best results in asymmetric hydroformylation are achieved in sol-

vents of medium polarity, and accordingly most of the experiments so far reported have been conducted either in benzene or toluene. In spite of these statements, a few studies have shown that in some cases catalytic activity, selectivity toward aldehyde formation, and regio- and enantioselectivity are greatly affected by the nature of the solvent.[30,39,42] Even between the above-mentioned solvents, differences are expected as for example the ee's for hydratropaldehyde decreased from 37 to 27% by using benzene in place of toluene with $PtCl(SnCl_3)[(S,S)$-BDPP-$(pNMe_2)_4)$.[30] However, the general trend for hydroformylations of styrene conducted in solvents other than benzene, toluene, or chlorobenzene (dichloromethane, 1,2-dichloroethane, hexane, THF, MEK, ethanol, etc.) was to give comparable b/n ratios, but somewhat lower rates and lower enantiomeric excesses.

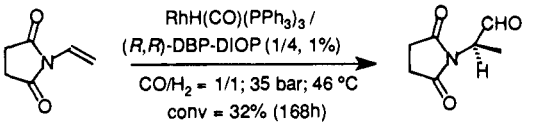
III. Rhodium-Catalyzed Asymmetric Hydroformylation

A. Description of the Catalytic Systems

1. Systems Based on DIOP and Related Ligands

The use of DIOP (Chart 1) with rhodium catalyst precursors was first reported in 1973 for the asymmetric hydroformylation of aromatic olefins.[10] Among those substrates, styrene gave branched and linear aldehydes in 69/31 ratio and 23% ee in the absence of solvent (Table 2, entry 1). Then, up to 1982, the original DIOP ligand was investigated in the presence of various rhodium precursors $(RhH(CO)(PPh_3)_3$,[52-58] $RhCl(CO)(DIOP)$,[59] $[RhCl(C_2H_4)_2]_2$,[59,60] $[Rh(CO)_2Cl]_2$[55,61-63] in the hydroformylation of a variety of olefins (aliphatic olefins,[52,55,57,62] aryl olefins including styrene (Table 2, entry 2),[53-55,57,59,61,62] vinyl acetate,[63] enamides,[58] and 1,3-dienes[56]). The chemoselectivities to aldehydes were quite good even though very dependent on the structure of the substrate. The highest ee observed for styrene was 23%;[55] for *cis*-butene, 28%;[52,55] for vinyl acetate, 23%;[63] and for *N*-vinylsuccinimide, 20%.[58] The effect of several reaction parameters[58,59,61,63] (catalyst precursor, pressure of CO and H_2, temperature, conversion, ligand/rhodium ratio, solvent) on chemo-, regio-, and enantioselectivities (enantiomeric excesses and prevailing configuration) has been investigated and is presented in the related section. Nevertheless, in these rhodium–DIOP catalytic systems, the enantiomeric excesses remained rather low. However, theories on the mechanism of the asymmetric induction were presented very early[52,54] but were sometimes conflicting. Some of them are presented below.[54,64]

During the period 1973–1982, some improvements were obtained with the synthesis of the first analogue of DIOP, DBP-DIOP[55,57,58,62,65] (Chart 1) which, when associated to rhodium, conducted generally to higher selectivities than DIOP (Table 2, entry 3) (eq 10).[58]



sel ~ 100%
ee = 41% (*R*) (10)

DIOP and its derivative DBP-DIOP were attached to a 20% cross-linked polymer (Chart 2) leading in the presence of rhodium to highly selective hydroformylation, with higher b/n ratios than with their soluble counterparts.[55,57] However, for styrene, racemization of the branched aldehyde was expected in the reaction conditions so that a real comparison with homogeneous systems was not possible. Nevertheless, for the hydroformylation of *cis*-butene, a 28% ee was obtained, which was equivalent to those of their soluble counterparts (27% ee).

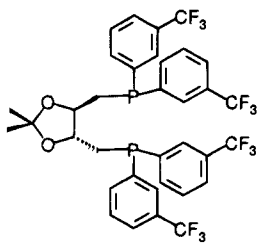
Another way of modifying the DIOP ligand was to introduce various substituents at the phenyl ring of the PPh_2 moiety (1-naphthyl, 2-naphthyl, *m*-CF_3-C_6H_4, Chart 9).[66] These new ligands were synthesized and compared to DIOP and DBP-DIOP in the asymmetric hydroformylation of vinyl esters.[66] High regioselectivities into 2-acetoxypropanal (75–95%)

Table 2. Asymmetric Hydroformylation of Styrene Catalyzed by Rhodium/Ligand Systems[a]

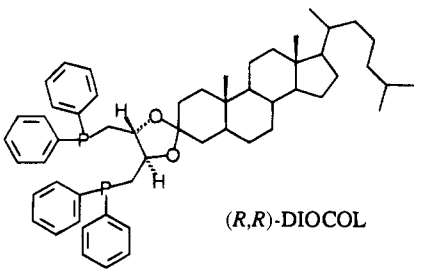
entry	ligand/rhodium precursor[b]	P, atm	*T*, °C	conversn, %[c] (reacn time, h)	regioselectivity (b/n)[d]	ee, % (config)	turnover frequency[e]	ref
1	(*R,R*)-DIOP/$RhH(CO)(PPh_3)_3$	1	40	15 (192)	69/31	23 (*R*)[f]	2.3	10
2	(*S,S*)-DIOP/$[RhCl(C_2H_4)_2]_2$	50	70	7 (12)	73/27	14 (*S*)[f]	18	59
3	(*R,R*)-DBP-DIOP/$[RhCl(CO)_2]_2$	100	80	81 (28)	89/11	30 (*S*)[f]	56	65
4	(*R,R*)-CBDBP/$Rh_4(CO)_{12}$	50	80	nr	86/14	27 (*S*)[f]	14	62
5	(*S,S*)-CHIRAPHOS/$[RhCl(NBD)]_2$	80	100	80 (3)	94/6	24 (*R*)	365	24
6	(*S*)-phosphepine/$Rh(acac)(CO)_2$	50	60	96 (3)	93/7	12 (*R*)	16	79
7	UC-P_2*/$Rh(acac)(CO)_2$	45	40	98 (5)	94/6	67 (*S*)	82	84
8	xylofuranoseP_2/$Rh(acac)(CO)_2$	9	40	51 (15)	92/8	51 (*S*)	14	85
9	(*R,S*)-EPHOS/$RhCl(CO)$((*R,S*)-EPHOS)	1	40	63 (111)	90/10	31 (*R*)	2.3	70
10	(*R*)-(SMe-PPh_2)naphthyl/$[Rh(COD)(OMe)]_2$	60	60	100 (4)	88/12	2.5 (nr)	125	88
11	(*R*)-Me_2BINAS/[Rh(COD)L]X	80	80	100 (24)	84/16	15 (*S*)	17	87
12	(−)-menthoxyPPy/$[Rh(C_8H_{12})L]ClO_4$	50	70	100 (4)	88/12	6 (*R*)	125	89
13	(*S,R*)-BINAPHOS/$Rh(acac)(CO)_2$	100	60	100 (43)	88/12	94 (*S*)	46	93
14	(*S,R*)-BIPHEMPHOS/$Rh(acac)(CO)_2$	100	60	100 (42)	90/10	94 (*S*)	24	92

[a] Reaction conditions: solvent = benzene or toluene; styrene/Rh = 400–4400. CO/H_2 = 1/1. [b] Ligand/rhodium ratio = 1–4, except entry 1, L/Rh = 10. [c] Styrene conversion including aldehydes and ethylbenzene. Selectivity to aldehydes was generally close to 100% or not reported. [d] Ratio of branched to linear products. [e] Average value calculated over the whole reaction time (mol of aldehydes/mol of Rh)/h. [f] Corrected value according to ref 27.

Chart 9

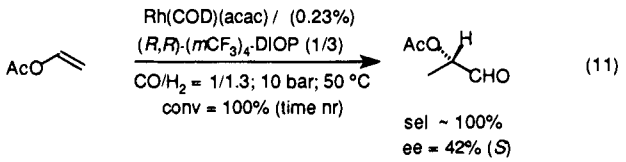


(*R,R*)-DIOP-$(mCF_3)_4$



(*R,R*)-DIOCOL

and moderate enantioselectivities were obtained for vinyl acetate (eq 11).

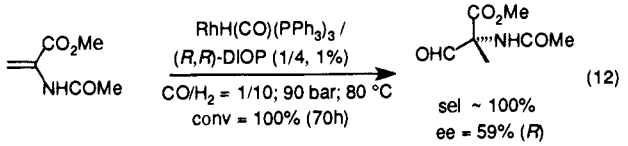


(11)

The extent of asymmetric induction varied widely and depended primarily on the ligand structure and on the ligand to rhodium ratio (maximum ee at a ratio of 3/1 or 4/1). In this example, the presence of the CF_3 group allowed a rate increase of 3–8-fold *vs* DIOP. The best results were obtained for vinyl acetate with DBP-DIOP (51% ee at 80 °C with a ligand to rhodium ratio of 6/1). In addition, (*R,R*)-DBP-DIOP gave 2-acetoxypropanal with a configuration opposite to that provided by (*R,R*)-DIOP, although they have the same chiral backbone.[66] Such phenomena are discussed in more details in section IV. Compared to results prior to 1981, the hydroformylation of vinyl esters proceeded with higher efficiencies than with aliphatic olefins. An explanation of that behavior was the greater ability for the substrate to complex with the metal, perhaps functioning as a bidentate ligand by coordination through the carbonyl oxygen as well as through the olefinic double bond.[66]

From then on, DIOP and several new DIOP-type ligands were investigated in the asymmetric hydroformylation of many substrates including unsaturated nitrogen compounds,[67,68] aromatic olefins,[24,26,31,68–71] aliphatic olefins,[31,37,68,69,72] *N*-acyl-1-aminoacrylic acid derivatives,[73,74] unsaturated carboxylic acids and esters,[20,68,75] and vinyl ferrocene.[76]

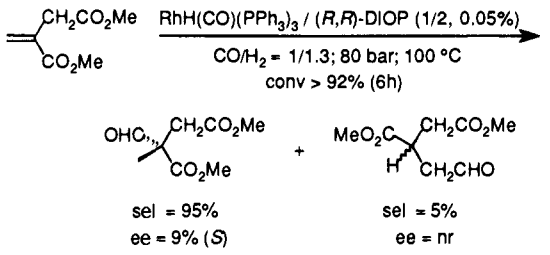
The asymmetric hydroformylation of substituted *N*-vinylphthalimides in the presence of DIOP and DIOCOL, a steroidal-substituted DIOP analogue (Chart 9), occurred with complete chemo- and regioselectivities toward the more branched aldehydes, but the isolated products were racemic.[67,68] The same reaction conducted with *N*-allylphthalimide was less regioselective (b/n = 37/63) but a 1.5% ee could be determined for the more substituted aldehyde. Aryl olefins, model substrates in many works, were reacted in the presence of various rhodium catalysts precursors associated to DIOP[24,26,69–71] and related ligands.[31,69] The DIOP derivatives Et-DIOP and Cy-DIOP (Chart 3) gave low activities and low enantiomeric excesses (<11%), even in the case of complete regioselectivities (styrene, b/n = 100/0, 0.2% ee, Et-DIOP).[31] Now, for simple terminal olefins, rhodium–alkyl-DIOP catalysts allowed mainly the formation of linear aldehydes with even lower enantiomeric excesses (<5% ee).[31] We have described the hydroformylation of styrene (b/n = 64/36, 18% ee) with electrogenerated rhodium–DIOP active species.[70] In that case, the effect of the reduction process in producing the active species was weak compared to a classically formed catalyst (styrene, b/n = 65.5/34.5, 16% ee) (*vide infra* for AMPP ligands). Further, tricarbonyl(η^6-styrene)chromium and related compounds using rhodium–DIOP-based catalysts gave aryl aldehydes in high regioselectivities ("Rh-DIOP", tricarbonyl(η^6-styrene)chromium, b/n = 90/10, 20% ee).[26] Lower enantiomeric excesses were achieved during the hydroformylation of vinylferrocene ("Rh-DIOP", b/n = 71/29, 12% ee).[76] Recently, higher enantioselectivities (in the 11–59% ee range) were reached with asymmetric hydrogenation type substrates, the dehydro amino acid derivatives, and interesting synthetic intermediates could be obtained.[73,74] Under typical oxo conditions (80 °C, 80–100 atm, H_2/CO = 1/1) with $[RhL_2Cl]_2$ (L = CO, C_2H_4 or L_2 = COD, NBD), $RhCl_3$, or $Rh_6(CO)_{16}$ as catalyst precursors, only hydrogenation and polymerization were observed without any formation of aldehydes.[74] Nevertheless, in the presence of $HRh(CO)(PPh_3)_3$ and 1–6 equiv of DIOP, complete regioselectivity affording in high yield the more substituted aldehyde was obtained for the hydroformylation of methyl *N*-acetamidoacrylate in up to 59% ee (eq 12).[74]



(12)

This study devoted to dehydro amino acid compounds showed that the extent of aldehyde formation increased as the basicity of the ligand decreased and as the size of the chelate ring of bidentate ligands increased. Selectivities higher or equal to 90% were reached only with DIOP and strictly related ligands such as DIOCOL.[74] The influence of several parameters on the extent of asymmetric induction was investigated and is presented below. It was also proposed, as previously mentioned,[66] that the possible chelation of the substrate might be responsible for the regio- and enantioselectivities observed.[74] The same authors extended their studies toward the hydroformylation of three other dehydro amino acids with $HRh(CO)(PPh_3)_3$/DIOP or DIOCOL catalysts.[73] Again the reaction was highly chemoselective (90–97%) and totally regioselective toward the more substituted formyl derivative (isolated yields 80–90%). Nevertheless, as for other trisubstituted alk-

enes that are traditionally extremely difficult to effectively hydroformylate due to steric hindrance, the reactions rates were very low (average turnover ~2 h^{-1}). Under optimal conditions the highest ee recorded was 46%, whereas the side hydrogenation reaction gave almost racemic products. (*R,R*)-DIOP promoted the preferential formation of the (*R*) aldehydes, and such mechanistic considerations are presented in section IV. At the time of their research, the authors presented the highest ee's ever reported in asymmetric hydroformylation based on rhodium catalysts.[73,74] Other activated olefins, *i.e.* unsaturated dicarboxylic esters, were also hydroformylated in the presence of rhodium–DIOP catalysts.[75] In that case, the main reaction under oxo conditions was always hydrogenation, except for dimethyl itaconate (eq 13). For the phenyl-substituted olefin (a trisubstituted olefin) no reaction took place at all (neither hydroformylation nor hydrogenation).



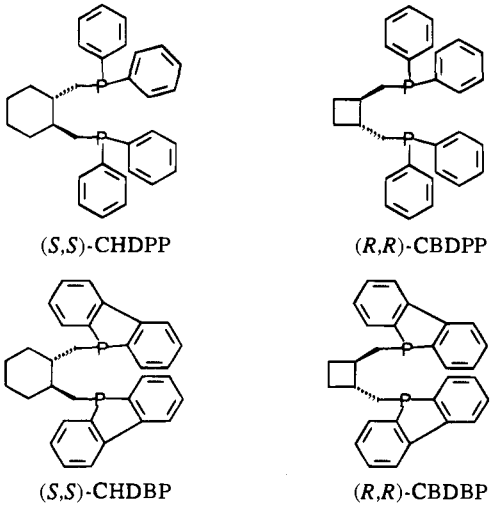
(13)

From all the studies conducted on DIOP and related ligands, we can conclude that DBP-DIOP was generally the best ligand of that family when associated to rhodium and that the higher ee's were obtained with substrates that were also the best ones for asymmetric hydrogenation.

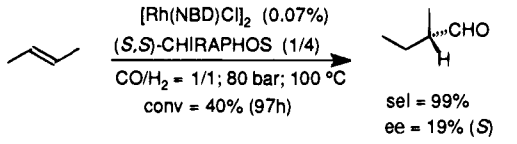
2. Systems Based on Other C_2 Symmetry Ligands

In this section we successively describe results obtained with bisphosphines and bisphosphites. Thus, after DIOP, but quite early on, CHDPP, CBDPP, and their dibenzophosphole derivatives, CHDBP and CBDBP (Chart 10), were applied to the hydroformylation of aryl olefins (styrene and phenyl-2-propene) and butenes (1-butene and *cis*-2-butene).[62,69] The highest ee's reported for these four substrates were associated to CBDBP (Table 2, entry 4). Afterward,

Chart 10

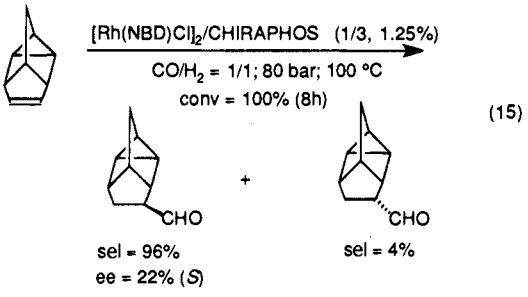


DIPAMP was investigated in the hydroformylation of *N*-vinylimides[58] but no asymmetric induction was reported. Then, in 1985, the effect of CHIRAPHOS (Chart 4) on the rhodium-based asymmetric hydroformylation of various olefins was evaluated (butenes (eq 14), styrene (Table 2, entry 5), phenyl-2-propene, and norbornene).[24] The Rh–CHIRAPHOS system was less active than the Rh–DIOP one, but was more regio- and enantioselective. For 2-butenes and styrene the regioselectivities into branched aldehydes were very high (up to 100%) and the ee's were moderate (eq 14).



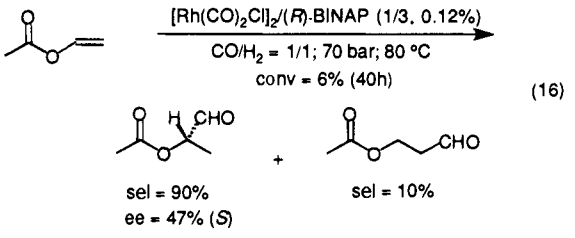
(14)

CHIRAPHOS was also used in the hydroformylation of methacrylate derivatives with rhodium catalysts.[20] When methyl methacrylate was hydroformylated in the presence of $[Rh(CO)_2Cl]_2$–CHIRAPHOS, the more branched aldehyde predominated but the enantioselectivity was quite low (3% ee) in contrast with platinum-based systems (55% ee).[20] For methacrylonitrile and methacrylamide, regardless of the reaction conditions used, only hydrogenation occurred with the Rh–CHIRAPHOS catalytic system. Generally, hydrogenation was the only side reaction, no polymerization being observed with rhodium.[20] Recently, CHIRAPHOS–rhodium catalysts were applied in the hydroformylation of deltacyclene.[37] The *exo*-formyl product was produced (93–98% selectivity) with up to 22% ee (eq 15).



(15)

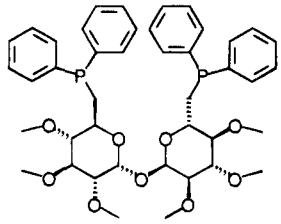
BINAP (Chart 4), the outstandingly efficient ligand in asymmetric hydrogenation,[9] was used for the first time in asymmetric hydroformylation with rhodium catalysts in 1989 for tricarbonylchromium complexes of arylalkenes.[26] The yield into aldehydes was high (>90%) with a good regioselectivity (*b*/*n* = 93/7) but a low enantioselectivity (7% ee). Further in 1992, BINAP was applied with moderate success in the hydroformylation of vinyl acetate (eq 16).[77] BINAP



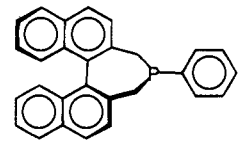
(16)

and CHIRAPHOS were used also for the hydro-

Chart 11



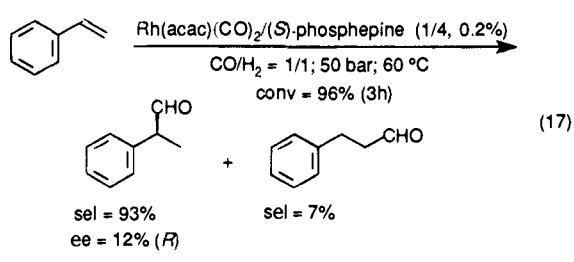
α,α-TREDIP



(*S*)-phosphepine

formylation of methyl *N*-acetamidoacrylate.[74] CHIRAPHOS conducted only to racemic hydrogenation while BINAP allowed asymmetric hydroformylation with 45% selectivity into aldehydes, but only 7% ee was reported for the more substituted aldehyde.[74] These two chiral ligands were also used recently to hydroformylate α-methylene-γ-butyrolactone.[78] The best results were obtained with BINAP but enantiomeric excesses did not exceed 36%, and the yields into the aldehyde lactone were impractically low.

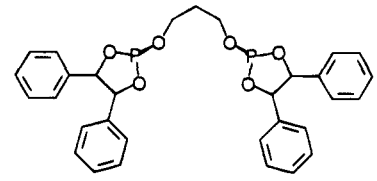
Also, new bisphosphines derived from trehalose (TREDIP, Chart 11) were evaluated in asymmetric hydroformylation.[71] The TREDIP ligands conducted to high regioselectivities when associated to rhodium for the hydroformylation of styrene (b/n = 98.4/1.6) but with very low enantioselectivities ("vanishingly small" as reported in the communication).[71] A new atropoisomeric monophosphine ligand with a dinaphthyl core (phosphepine, Chart 11) was synthesized very recently and applied to the rhodium-based hydroformylation of styrene (Table 2, entry 6) (eq 17).[79] The branched aldehyde was formed in high chemo- and regioselectivity, but the ee was low. Decreasing the reaction temperature to 30 °C improved both regio- and enantioselectivities up to 95% and 20%, respectively.



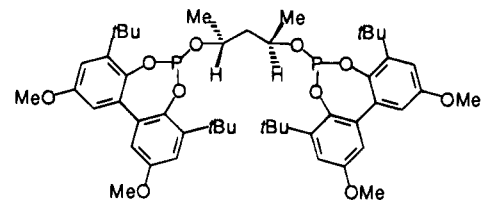
(17)

Recently, a new class of ligands specially designed for asymmetric hydroformylation has appeared, the bisphosphinites[80] and the bisphosphites[77,81,82] (Chart 12). The first reported were bis(dioxaphospholane) ligands which, when applied to the hydroformylation of styrene gave hydratropaldehyde with a b/n ratio of 75/25 but as a racemic mixture.[82] Then, a patent reported on the synthesis of a bisphosphite (named UC-P_2*) which, in solution with Rh(acac)$(CO)_2$, catalyzed the hydroformylation of styrene to give after oxidation 2-phenylpropionic acid in 60% ee.[83] However, the latter value could not really account for the intrinsic efficiency of this hydroformylation catalytic system, since a 90% ee was claimed for the asymmetric hydroformylation of styrene into hydratropaldehyde (Table 2, entry 7). Thus, on the strength of

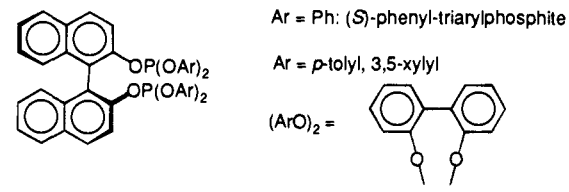
Chart 12



bis(dioxaphospholane)



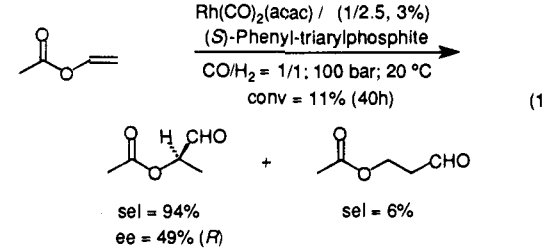
(*R*,*R*)-UC-P_2*



(*S*)-bis(triarylphosphite)

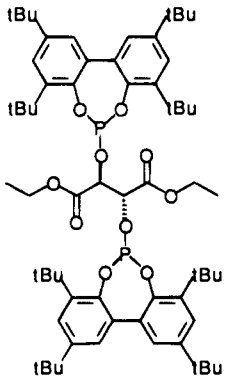
the good regio- and enantioselectivities reported, the UC-P_2* system should be considered as one of the best practical asymmetric hydroformylation catalysts for vinyl arenes. A series of new chiral diphosphites closely related to the UC-P_2* ligand was recently synthesized and evaluated in the asymmetric hydroformylation of styrene.[84] These chiral ligands are based on butane-2,3-diol, pentane-2,4-diol, hexane-2,5-diol, diphenylpropane-1,3-diol, and *N*-benzyltartaramide as chiral bridges and phosphorus moieties derived from 2,2′-bis(phenols). The catalytic results were strictly consistent with those aforementioned for the UC-P_2* system. Namely, high regioselectivities (b/n > 95/5) and high conversions (> 99%) to 2-phenylpropanal were found under mild conditions (25−40 °C), with up to 67% ee.

In 1992, chiral bis(triaryl phosphite) ligands derived from binaphthol bearing various substituents at the phosphorus atom were synthesized (Chart 12).[77] Their use in association with rhodium in the hydroformylation of vinyl acetate under various conditions led to the formation of 2-acetoxypropanal in high regio- and stereoselectivities (eq 18). To reach these high enantioselectivities, an excess of ligand was required (ligand/Rh = 2.5). The effect of several reaction parameters is presented in the related section (*vide infra*).

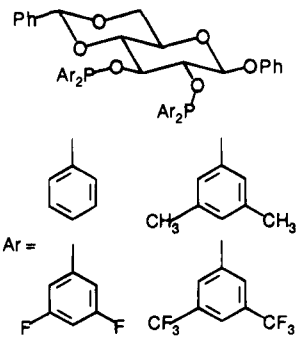


(18)

Chart 13

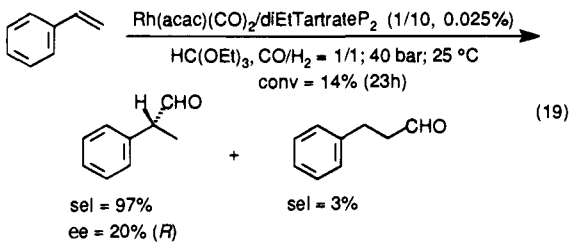


Diethyl tartrate derived ligand



Carbohydrate-phosphinites

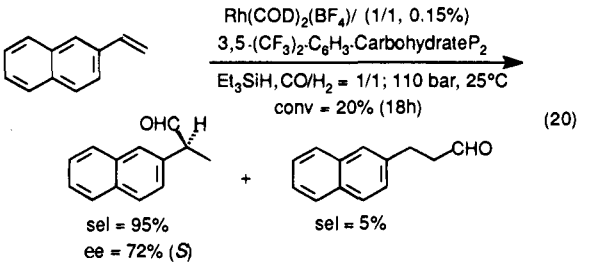
Other chiral bisphosphites (which do not necessarily have a C_2 axis of symmetry but which are closely related to the previous ligands) were synthesized starting from 1,2:5,6-diisopropylidene-D-mannitol, L-α,α,α,α,-tetramethyl-1,3-dioxolan-4,5-dimethanol and L-diethyl tartrate, which are inexpensive optically active diols (Chart 13).[81] These ligands were investigated in the hydroformylation of styrene. The catalytic activity increased with the bulkiness of the ligand. Thus, with a *tert*-butyl-substituted ligand, enantiomeric excesses up to 20% were obtained under quite mild reaction conditions (eq 19).[81] Again, it was



(19)

found that the extent of asymmetric induction was closely related to the reaction conditions applied and is developed in the corresponding section. These results were very recently improved by using new chiral diphosphites derived from other sugar backbones (mannopyranoside and glucopyranoside derivatives) and phosphorus moieties similar to those found in the UC-P_2* and related ligands (*vide supra*, Charts 12 and 13).[85] Enantioselectivities up to 64% were obtained with stable hydridorhodium diphosphite dicarbonyl catalysts ($HRhPP(CO)_2$) in the hydroformylation of styrene. High regioselectivities (up to 97%) to the branched aldehyde were found at relatively mild reaction conditions (Table 2, entry 8).

In 1994, phosphinites derived from carbohydrates (Chart 13) were synthesized and used for rhodium based asymmetric hydroformylation of olefins.[80] The hydroformylation of 2-vinylnaphthalene using [(diphosphinite)Rh(COD)]BF_4 as the catalyst and Et_3SiH as the solvent gave the branched aldehyde in 95/5 *b*/*n* ratio and 72% ee with only 5% hydrosylilation as the secondary reaction (eq 20). The enantiomeric excesses were strikingly dependent on the nature of the solvent. Other substrates were investigated (styrene, vinyl acetate, and 4-methylstyrene) but the enantioselectivities were lower (up to 30% ee).



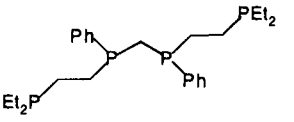
(20)

3. Systems Based on Miscellaneous Ligands

In this category of catalytic systems we will find successively bisphosphines of non-C_2 symmetry, C_2 symmetry sulfur ligands, and heterobidentate ligands. Among the classical phosphines only BPPM (Chart 6) received any attention and was used in the hydroformylation of *N*-vinylphthalimide,[58] tricarbonylchromium complexes of arylalkenes,[26] and methyl *N*-acetamidoacrylate (the main reaction in this case was hydrogenation, 94%).[74] The enantioselectivities were rather low (4.2%, 14%, and 10% respectively for the three substrates). For tricarbonyl (η^6-styrene)-chromium, the corresponding aldehydes were obtained with a *b*/*n* ratio of 95/5.

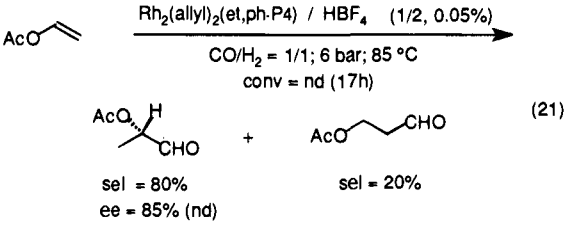
The use of a binucleating tetraphosphine, et,ph-P4 (Chart 14) was recently reported for the hydro-

Chart 14



et,ph-P4

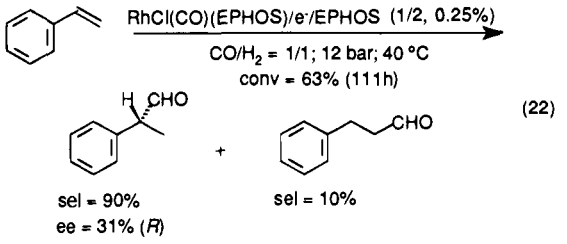
formylation of various vinyl esters.[45] Typically, vinyl acetate was converted to aldehyde with a branched to linear regioselectivity of 4:1, and an enantiomeric excess of 85% (eq 21). The catalytic system based on cationic rhodium dinuclear species is quite selective to aldehyde and appears very stable, but somewhat slow.



(21)

Several aminophosphine–phosphinite rhodium systems were investigated for the hydroformylation of styrene.[70] Among these ligands, a diphosphine derived from ephedrine, (*S*,*R*)-EPHOS (Chart 8) was applied in the hydroformylation of styrene in the presence of classical rhodium precursors and electrogenerated rhodium catalysts.[70] The results were strinkingly dependent on the nature of the catalyst precursor and on the reaction conditions used. Namely, replacing classical catalyst precursors by electrogenerated rhodium species resulted in a significant increase of the enantioselectivity from ca. 18% to 31% ee, respectively (Table 2, entry 9) (eq 22). Moreover, strong differences in the catalytic behavior of the (*S*,*S*) and (*S*,*R*) diastereomers of the EPHOS

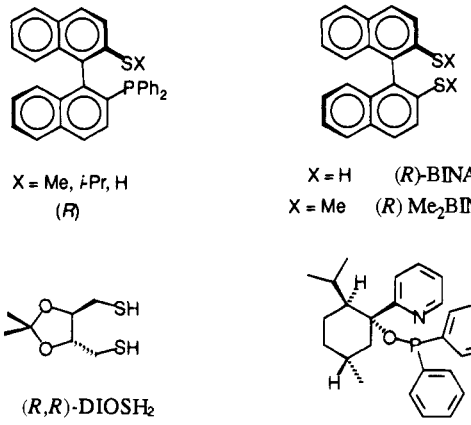
ligand were observed. Thus, the (*S,S*) diastereomer gave hydratropaldehyde of opposite configuration in lower enantioselectivity (7% ee), with a lower activity.



(22)

Dithiolate ($DIOSH_2$[86] and BINAS[87]) and P–S ligands (*S*-alkyl-(*R*)-2-(diphenylphosphino)-1,1′-binaphthyl-2′-thiol)[88] (Chart 15) were used by two

Chart 15

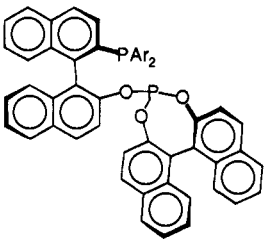


groups in the hydroformylation of styrene. Unfortunately, only low enantiomeric excesses were obtained (max. 17% ee) (Table 2, entries 10 and 11). Recently, a chiral bidentate P,N ligand bearing pyridine and [(diphenylphosphino)menthyl]oxy residues (Chart 15) was associated to rhodium to investigate the asymmetric hydroformylation of various substrates (styrene (Table 2, entry 12), 2-vinylnaphthalene, methyl acrylate, and vinyl acetate).[89] An important point of this article is that the ee values reported for the hydroformylation of methyl acrylate (up to 92% ee) are erroneous.[90] Consequently, the efficiency of this catalytic system, as revealed by the results obtained with other substrates, appear quite poor (maximum 12% ee for vinyl acetate).

4. Systems Based on Phosphine–Phosphite Ligands

The major breakthrough in the rhodium asymmetric hydroformylation was made very recently by the introduction of the binaphthyl core in phosphine–phosphite ligands giving the so called BINAPHOS asymmetric inducers.[91–93] The first BINAPHOS-type ligands synthesized (Chart 16) were reported in 1993 and were investigated in the hydroformylation of a variety of olefins (vinyl acetate, *N*-vinylphthalimide, arylalkenes, and simple olefins).[93] The enantioselectivities obtained were in the 73–95% ee range, the highest ever reported so far for rhodium-based catalysts, and the branched to normal ratios ranged from

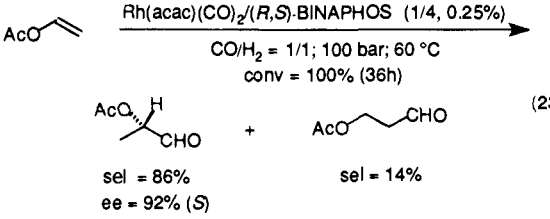
Chart 16



Ar = Ph, (*R,S*)-BINAPHOS

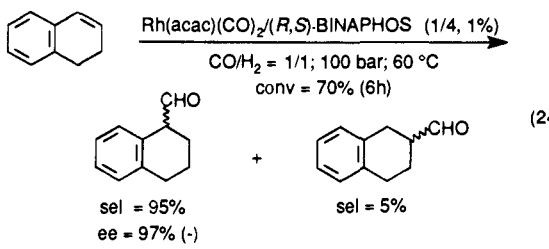
Ar = 3,5- $Me_2C_6H_3$, (*R,S*)-3,5-Me_2 -BINAPHOS

85/15 to 98/2 according to the nature of the substrate (eq 23).



(23)

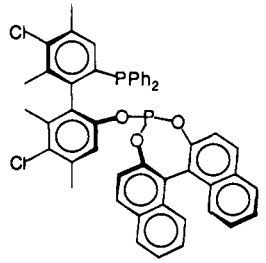
A marked dependence of the enantioselectivities on the structures of the phosphite moieties relative to that of the 2-(diphenylphosphino)1,1′-binaphthyl backbone was observed. The highest ee's were always obtained with the (*R,S*) ligand and its enantiomer (*S,R*), while the (*R,R*) equivalents gave lower values (Table 2, entry 13). Then, the same ligands were applied to the hydroformylation of internal olefins (butenes, phenylpropenes, indene, and 1,2-dihydronaphthalene).[91] The lowest asymmetric induction (48% ee) was obtained with *trans*-butene and the highest (97% ee) with 1,2-dihydronaphthalene (eq 24). The *b*/*n* ratios were very high (92/8 to 98/2).



(24)

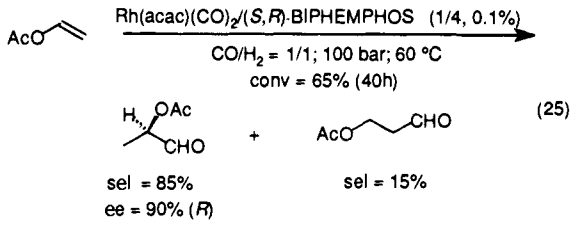
In 1994, the synthesis of new chiral phosphine–phosphite ligands was described, BIPHEMPHOS (Chart 17).[92] Their rhodium(I) complexes were efficient catalysts for the asymmetric hydroformylation of various olefins (*cis*-butene, styrene (Table 2, entry

Chart 17



(*S,R*)-BIPHEMPHOS

14), vinyl acetate (eq 25), 1-hexene, indene, and 1,2-dihydronaphthalene). The enantioselectivities for the (*S,R*)-BIPHEMPHOS are in the same range as for the first reported (*R,S*)-BINAPHOS ligands,[93] The (*R,R*) diastereomer gave much lower enantioselectivities.



(25)

This is a promising new class of efficient ligands for asymmetric hydroformylation of a variety of substrates and we can expect the publication of new phosphine–phosphites in the future.

B. Influence of Reaction Parameters

1. Temperature

A systematic study of the effect of the temperature is not reported and optimization of the reaction conditions corresponded more to a specific tuning involving all the reaction parameters, some of them being more important in their effect than others. Nevertheless, a variation of temperature usually affected the enantioselectivities of the reactions, and generally a decrease of temperature corresponded to an increase of the ee's even if the reaction rates decreased accordingly. For instance, during the hydroformylation of vinyl acetate with DIOP–Rh, lowering the temperature from 80 to 50 °C increased significantly the ee's from 24 to 42% ee.[66] Another example was the parallel increase of ee and *b*/*n* ratio (12 to 20% and 93 to 95%, respectively) for reactions based on a styrene–Rh–phosphepine association when decreasing the temperature from 60 to 30 °C.[79] The same effect was observed for the methyl *N*-acetamidoacrylate–Rh–DIOP catalytic system.[74] Thus, on going down from 60 to 30 °C, the ee increased from 47 to 59%. That effect of temperature is generally less important on the *b*/*n* ratios. Now, when the decrease of temperature is associated with an increase of the ligand to rhodium ratio (from 1 to 4) and with an increase of the hydrogen partial pressure (from 1/1 to 4/1), the hydroformylation of benzyl *N*-acetamidoacrylate led to an increase of 32 to 46% ee in the presence of Rh–DIOP catalytic systems.[73]

2. Catalytic System—Precursor

There is a quite long list of rhodium complexes used as catalyst precursors ($Rh_4(CO)_{12}$, $[Rh(NBD)Cl]_2$, $[Rh(CO)_2Cl]_2$, $Rh(CO)_2(acac)$, $HRh(CO)(PPh_3)_3$, $[Rh(COD)_2]BF_4$, etc.), and all of them conducted, when associated to a chiral ligand, to asymmetric induction to some extent. Nevertheless, there can be a difference if two different rhodium complexes are used as catalysts precursors, all the reaction conditions being the same. As already mentioned, we also observed that when starting from $RhH(CO)(PPh_3)_3$ or electrogenerated species for which no HCl is produced during the catalytic process, rather than chlororhodium precursors like RhCl(CO)(EPHOS), the catalytic systems were more enantioselective and slightly more active.[70] In fact, since halides are well-known inhibitors for hydroformylation, halide-containing rhodium complexes are very poor starting materials.

To prepare the catalyst precursor the major effect was always brought by the ligand to rhodium ratio. Thus, in the beginning of the research in asymmetric hydroformylation, the first effect on using chiral bisphosphines associated to rhodium was the parallel decrease in the activities with the amount of ligand added,[58,59,63] as classically observed with oxo achiral catalysts.[94] Nevertheless, ratios in the 2–6 range were necessary to reach appreciable enantioselectivities.[63,66,73] But the major effect observed on the enantioselectivities was always related to the structure and the properties of the chiral ligand (see Table 2 for examples). For rhodium-based hydroformylations, the presence of a phosphine (chiral bisphosphines for asymmetric hydroformylation,[59] or simple phosphines for the classical oxo reaction[94]) allowed the elimination of the secondary hydrogenation reaction leading thus to highly chemoselective catalytic systems. This side reaction remained only for substrates that are particularly easy to hydrogenate.[74,75] For those substrates, the chemoselectivity was very dependent on the reaction conditions.

The catalyst performed better in mediums of low polarity[73,74] and the best solvents are benzene, toluene, ethyl benzene, and hexane. The use of coordinating solvents such as THF resulted in a decrease of both enantioselectivity and rate.[77,80] Racemization of the aldehyde has also been reported to be a major problem, so that some reactions were performed in triethyl orthoformate to trap the aldehyde as the corresponding acetal as already mentioned for platinum systems.[3,30,34,43] However, in the case of rhodium catalysts and in contrast with platinum–tin systems, quite often no conclusions can be made from running such experiments.[80,81] Also, long reaction times conducted sometimes to a decrease of the ee's attributed to a racemization of the chiral aldehyde produced in the reaction conditions,[58] or to an evolution of the catalyst with time leading to less or nonenantioselective active species.[81]

3. CO/H_2 Pressure

Generally the effect of the hydrogen and carbon monoxide partial pressures and total pressure were not systematically explored and often several reaction parameters were varied at the same time, so that it is rather difficult to conclude about that effect. Nevertheless, the mixture commonly used is H_2/CO 1/1 at a total pressure going from 1 to 100 atm. However, in a few cases the effect of the partial and total pressure has been carefully reported.[59,63,66] Thus, the *b*/*n* ratio for the hydroformylation of styrene in the presence of rhodium/TREDIP slightly decreased when increasing the H_2/CO mixture from 1/1 to 2/1 (98.4/1.6 and 97.7/2.3, respectively).[71] The stereoselectivity of the reaction was also slightly affected by a variation of the partial pressure of hydrogen and carbon monoxide for the reaction conducted with DIOP and vinyl acetate,[63] as well as

with styrene.[59] Hydrogen-rich mixtures (up to 10/1) increased the amount of aldehyde formation for the hydroformylation of methyl acetamidoacetate and the ee's (from 11% to 59% ee), but lowering the total pressure favored the hydrogenation reaction for this substrate.[73,74]

IV. Discussion. Mechanistic Considerations

A. Platinum and Rhodium Systems: Comparison

1. Catalytic Performances

According to the observations made from the above description of the catalytic systems, it appears clearly that the behaviors of platinum- and rhodium-based hydroformylation systems are quite different with regard to their properties, *i.e.* chemo-, regio-, and enantioselectivities and rates. For comparison purposes, we propose to divide the reported systems into three families closely related to their properties: platinum–tin systems, classical rhodium systems, and phosphine–phosphite–rhodium systems. In order to illustrate the behavior of these three families, the best results obtained during hydroformylation of simple and functionalized aliphatic olefins and vinyl aromatic substrates have been selected and are presented in Tables 3 and 4.

Generally, hydroformylations conducted in the presence of platinum–tin associated to a chiral diphosphine are more enantioselective than the corresponding classical rhodium systems, but they have the disadvantage of undergoing competitive hydrogenation (Tables 1, 3, and 4). Platinum systems also led to lower branched to normal ratios and quite often the linear isomer is the major one. Consequently, the yields into the desired chiral aldehyde are often low, although this important factor has been greatly improved with the introduction of dibenzophosphole (DBP) substituents (Table 1, compare entries 1 and 2, 5 and 6, 13 and 16). Another negative point is the racemization of the chiral aldehyde produced under hydroformylation reaction conditions. To avoid this side reaction, experiments could be performed in the presence of triethyl orthoformate to trap the aldehyde produced, but under these conditions the rates were despairingly low (Table 3, entries 2, 8, 11, and 14).

In contrast, classical rhodium-catalyzed hydroformylations present generally a complete chemoselectivity, except for a few substrates particularly activated for hydrogenation or polymerization (Table 2; Table 3, entries 3, 12, and 15; and Table 4, entries 3, 7, 14, and 17). Moreover, the regioselectivity to the branched aldehyde is in most cases very good. Unfortunately, the enantioselectivities are always by far lower with classical rhodium systems than with platinum–tin combinations. Thus, the highest ee reported was 78% for the hydroformylation of 2-vinylnaphthalene (Table 3, entry 12).

The major advance was made with the appearance of the third family, a new class of unsymmetrical bidentate ligands, the phosphine–phosphites with a binaphthyl core which is systematically superior to any other rhodium system as far as the comparison is possible. So, even if in some cases platinum–tin systems present a higher enantioselectivity than the

Table 3. Best Platinum and Rhodium-Based Systems for Asymmetric Hydroformylation of Vinyl Aromatic Substrates[a]

substrate	entry	catalytic system	T, °C	CO/H_2, atm/atm	conversn, % (react time, h)	selectivity to aldehyde, %	regio-selectivity[b] (b/n)	ee, % (config)	turnover frequency[c]	ref
styrene	1	Pt/(*R,R*)-BCO-DBP	40	70/150	98 (10)	67	80/20	86 (*S*)	66	34
	2[d]	Pt/(*S,S*)-DBP-BPPM	60	85/85	56 (95)	nr	77/23	>96 (*S*)	<2.4	43
	3	Rh/(*R,R*)-DBP-DIOP	80	50/50	81 (28)	100	89/11	30 (*S*)	111	65
	4	Rh/(*S,R*)-BIPHEMPHOS	60	50/50	99 (42)	100	90/10	94 (*S*)	24	92
4-methoxystyrene	5	Pt/(*S,S*)-BPPM	60	90/90	65 (8)	>98	38/62	73 (*S*)	65	42
	6	Rh/(*S,R*)-BINAPHOS	60	50/50	100 (34)	100	87/13	88 (*S*)	29	93
4-isobutylstyrene	7	Pt/(*S,S*)-DBP-BPPM	60	85/85	45 (37)	>80	67/33	39 (*S*)	3.3	43
	8[d]	Pt/(*S,S*)-DBP-BPPM	60	85/85	7.5 (215)	>90	67/33	>96 (*S*)	0.05	43
	9	Rh/(*S,R*)-BINAPHOS	60	50/50	100 (66)	100	88/12	92 (*S*)	4.5	93
2-vinylnaphthalene	10	Pt/(*S,S*)-BPPM	60	90/90	66 (18)	nr	35/65	78 (*S*)	25	42
	11[d]	Pt/(*S,S*)-DBP-BPPM	60	85/85	73 (145)	>90	77/23	>96 (*S*)	1.4	43
	12	Rh/(−)-Menthoxy-PPy	100	40/40	100 (16)	100	100/0	78 (*R*)	31	89
2-vinyl-(6-methoxynaphthalene)	13	Pt/(*S,S*)-BPPM	60	90/90	90 (9)	nr	41/59	81 (*S*)	70	42
	14[d]	Pt/(*S,S*)-DBP-BPPM	60	85/85	50 (182)	>90	77/23	>96 (*S*)	0.3	43
	15	Rh/carbohy-phosphinite	25	55/55	73 (18)	nr	94/6	39 (nr)	<27	80

[a] Reaction conditions: substrate/catalyst = 200–2000. [b] Ratio of branched to linear products. [c] Average value calculated over the whole reaction time (mol of aldehydes/mol of Pt or Rh)/h. [d] Reaction conducted in the presence of triethyl orthoformate. Hydroformylation products were recovered as the corresponding diethyl acetals.

Table 4. Best Platinum and Rhodium-Based Systems for Asymmetric Hydroformylation of Olefinic Substrates[a]

substrate	entry	catalytic system	T, °C	CO/H_2, atm/atm	conversn, % (reactn time, h)	selecticity to aldehyde, %	regioselectivity[b] (b/n)	ee, % (config)	turnover frequency[c]	ref
vinyl acetate	1	Pt/(*S,S*)-BPPM	60	90/90	70 (40)	100	30/70	80 (nr)	7.6	42
	2[d]	Pt/(*S,S*)-BPPM	60	90/90	25 (240)	nr	60/40	>98 (nr)	0.5	42
	3	Rh/(Et,Ph)-P4	90	3/3	nr	nr	80/20	85 (nr)	125	45
	4	Rh/(*R,S*)-BINAPHOS	60	50/50	99 (36)	100	86/14	92 (*S*)	11	93
N-vinylphthalimide	5	Pt/(*S,S*)-BPPM	60	90/90	52 (46)	85	33/67	73 (*R*)	4.2	42
	6[d]	Pt/(*S,S*)-BPPM	60	90/90	46 (240)	nr	33/67	>96 (*R*)	0.8	42
	7	Rh/(*R,R*)-DBP-DIOP	48	17/17	35 (96)	nr	nr	38 (*R*)	0.4	58
	8	Rh/(*S,R*)-BINAPHOS	60	50/50	98 (90)	100	89/11	85 (*R*)	3.3	93
1-butene	9	Pt/(*R,R*)-BCO-DBP	80	70/150	34 (4)	86	14/86	67 (*S*)	73	34
	10	Rh/(*R,S*)-BINAPHOS	30	35/35	nr (67)	100	21/79	83 (nr)	23	100
(*Z*)-2-butene	11	Pt/(*R,R*)-BCO-DBP	80	70/150	67 (21)	98	87/13	30 (*R*)	31	34
	12	Rh/(*R,S*)-BINAPHOS	60	50/50	nr (44)	100	100/0	82 (*S*)	10	91
(*E*)-2-butene	13	Pt/(*R,R*)-BCO-DBP	80	70/150	65 (30)	97	87/13	29 (*R*)	21	34
	14	Rh/(*S,S*)-CHIRAPHOS	100	40/40	40 (97)	nr	99/1	19 (*S*)	6	24
	15	Rh/(*R,S*)-BINAPHOS	60	50/50	nr (45)	100	100/0	48 (*S*)	0.5	91
dimethyl itaconate	16	Pt/(*R,R*)-DIOP	50	40/200	80 (45)	35	0/100	82 (*R*)	12	19
	17	Rh/(*R,R*)-DIOP	100	40/40	93 (6)	77	95/5	9 (*S*)	238	75

[a] Reaction conditions: substrate/catalyst = 200–2000. [b] Ratio of branched to linear products. [c] Average value calculated over the whole reaction time (mol of aldehydes/mol of Pt or Rh)/h. [d] Reaction conducted in the presence of triethyl orthoformate. Hydroformylation products were recovered as the corresponding diethyl acetals.

rhodium phosphine–phosphite catalysts, the gain in chemo- and regioselectivity as well as in catalytic activity justify the supremacy of these new systems (Table 3, entries 4, 6, and 9; and Table 4, entries 4, 8, 10, 12, and 15). This is the first time that a system is usable for a wide range of different substrates with almost equal capabilities for asymmetric hydroformylation. As a consequence of the higher chemo- and regioselectivities of rhodium catalysts, the development of new ligands for asymmetric hydroformylation has been quite flourishing over the last five years for their application in rhodium-based reactions rather than in platinum ones.

2. Possible Correlations

Another point of interest that could emerge from the whole results described in the previous sections is the relations and regularities that might exist between the observed asymmetric induction and the intrinsic characteristics of the catalytic system, *i.e.* the nature of the substrate, the type of the ligand and of the metal center. Accordingly, Table 5 presents the results obtained for the rhodium- and platinum-catalyzed hydroformylation of various olefins in the presence of diphosphines of comparable geometry. For this purpose, (*R,R*)-DIOP and (*R,R*)-BCO-DPP, ligands changing only by their chiral backbone and giving both seven-membered metallacycles, as well as their dibenzophosphole (DBP) analogues, have been retained. As a basis, it is assumed that for the large majority of the substrates studied, the absolute configuration of the product is connected to the prevailing reacting enantioface.[12] Thus, several remarks can be made on the influence of the structure of the substrate, of the type of the ligand and of the metal on asymmetric induction, although the results should be compared carefully because of the slightly different reaction conditions used. First, comparing the direction of enantioselectivity for the six systems, it appears that the prevailing chirality of the products varies widely on the nature of the substrate. Although some regularities do exist for specific classes of substrates such as mono- or disubstituted aliphatic olefins,[12] this comparison clearly indicates that the chirality of the ligand is not the only factor determining the configuration of the prevailing product, as it is now well established for asymmetric hydrogenation.[9] On the other side, by comparing the results obtained on changing the carbon skeleton of the ligand, it seems that a correlation might exist between the chirality of the phosphine and the prevailing chirality of the aldehydes, at least for platinum systems. Actually, as one goes from (*R,R*)-BCO-DBP to (*R,R*)-DBP-DIOP in association with platinum complexes, the absolute configuration of all the products remains the same. A similar trend is observed from the diphenylphosphino ligands, except for 1-butene. Changing the nature of the substituent on the phosphine ligand (diphenylphosphine *vs* dibenzophosphole) also considerably affects the results since for the three associations studied (Pt–BCO, Pt–DIOP, Rh–DIOP), the absolute configuration of almost half of the products are opposite. Finally, the

Table 5. Platinum and Rhodium-Catalyzed Asymmetric Hydroformulation of Olefinic Substrates with DIOP and BCO Ligands and their DBP Derivatives

substrate	Pt/(*R,R*)-BCO-DPPP[b]		Pt/(*R,R*)-DIOP[c]		Rh/(*R,R*)-DIOP[c]		Pt/(*R,R*)-BCO-DBP[b]		Pt/(*R,R*)-DBP-DIOP[d]		Rh/(*R,R*)-DBP-DIOP[c]	
	regioselectivity[b] (*b*/*n*)	ee, % (config)	regioselectivity[a] (*b*/*n*)	ee, % (config)	regioselectivity[b] (*b*/*n*)	ee, % (config)	regioselectivity[b] (*b*/*n*)	ee, % (config)	regioselectivity[a] (*b*/*n*)	ee, % (config)	regioselectivity[b] (*b*/*n*)	ee, % (config)
1-butene	40/60	7.7 (*S*)	6/94	25 (*R*)	8/92	6 (*R*)	14/86	67 (*S*)	15/85	39 (*S*)	32/68	16 (*S*)
(*E*)-2-butene	75/25	1.6 (*S*)	51/49	13 (*S*)	100/0	3 (*S*)	87/13	29 (*R*)	71/29	1.8 (*R*)	nr	2 (*S*)
styrene	42/58	23 (*S*)	38/62	4 (*S*)	71/29	10 (*R*)	77/23	68 (*S*)	79/21	65 (*S*)	90/10	25 (*S*)
2-phenyl-propene	0/100	12 (*S*)	0/100	7 (*S*)	0/100	1.4 (*R*)	0/100	16 (*R*)	0/100	12 (*R*)	79/21	1.8 (*R*)
vinyl acetate					100/0	15 (*S*)			77/23	60 (*S*)	100/0	38 (*R*

[a] Ratio of branched to linear products. [b] Results taken from ref 34. [c] Results taken from refs 24 and 63. [d] Results taken from refs 17, 28, and 34. [e] Results taken from refs 58, 62, 66, and 69.

change in the metal center induces strong modifications to the catalytic behavior as illustrated in Table 5 with (*R,R*)-DIOP and (*R,R*)-DBP-DIOP systems, and as reported for (*R,R*)-CHIRAPHOS.[24] From this analysis, we can conclude that no rationalization is possible for these systems, which were nevertheless the more promising for such a study because of their closely related structures and the large amount of data available. However, typical trends were found in restricted areas and prompted Consiglio and Pino to develop the model which is described below.

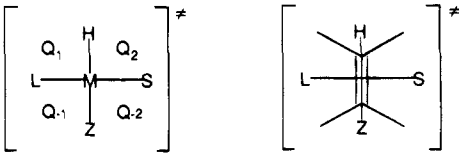
B. Attempts at Rationalization: Models

1. Stereochemical Model

The model of Pino and Consiglio[12] is based on the commonly accepted catalytic cycle for the hydroformylation reaction[94] and the following hypotheses: (*i*) asymmetric induction occurs during the insertion of the π-complexed olefin into the M−H bond leading to the intermediate alkyl−metal complexes; (*ii*) the metal approached by the substrate in the transition state is a chiral center; and (*iii*) the double bond of the substrate in the transition state and the M−H bond are approximately coplanar. Thus, a simple planar representation of these transition states can be obtained (Scheme 3). The space for accommodating the substituent(s) of the olefinic double bond of the substrate is divided in four quadrants defined by two mutually perpendicular planes containing three different sized groups of a particular ligand (L > S, Z > H).[95] In this model, the different free energies for the four possible transition states arising from the superposition of the substrate are governed by steric interactions. Thus, in the more favored intermediate, the larger substituent of the olefin would occupy preferentially the quadrant in which more space is available (Q_2). In practice, the relative positions of the ligand L (Large) and S (Small) on the metal are established from the experimental results obtained during the hydroformylation of a given simple substrate.

Thus, this model has been used to predict the regio- and the enantioselectivity of particular catalytic systems based essentially on DIOP or DBP-DIOP in association with rhodium complexes,[12,24,73] and on DIOP, DBP-DIOP, BCO-DPP, and BCO-DBP in combination with platinum−tin associations.[19,20,24,34] The level of predictability is generally high, although strictly dependent on the nature of the substrate. In the hydroformylation of simple olefins such as butenes, 2-methyl-1-butene, 2,3-dimethyl-1-butene, and norbornene in the presence of rhodium and platinum−tin catalytic systems modified either by DIOP or by CHIRAPHOS,[24] the model gives correct qualitative information about both regio- and enantioselectivity.

Scheme 3



The reliability of the predictions is surprisingly good in view of the simplicity of the model and of the relatively small (<10%) regioselectivities and enantiomeric excesses found in many cases. In particular, the latter values were explained on the basis of the relatively large space available in quadrants Q_1 and Q_2 of DIOP-based systems, which results in activated intermediate complexes of slightly different free energy. For these aliphatic hydrocarbons, the only attractive interaction between substrate and catalyst is believed to occur at the double bond, and this can account for the high reliability of this model based on repulsive interactions only.

Conversely, the model fails in many cases when applied to olefins containing a conjugated aromatic ring or functional substituents bearing an heteroatom which can coordinate to the metal. Almost all wrong predictions concern such substrates. For instance, the application of this model to the platinum-catalyzed hydroformylation of unsaturated esters,[19] and vinyl aromatic derivatives like styrene and 2-phenylpropene[24] led to laborious discussions that could not explain the observed regioselectivity and hardly the enantioface discrimination. In other cases, like the hydroformylation of dehydro amino acid compounds in the presence of a rhodium catalyst modified by DIOP,[73] the efficiency of the predictions was strongly dependent on the one-sided choice of the bulkiness of the substituent. In fact, in the presence of such substrates, strong attractive interactions between substituent(s) of the olefin and catalytic complex and electronic effects undoubtedly play a significant role which limits the application of the model.

2. Molecular Modeling

More recently, a molecular modeling approach of the asymmetric hydroformylation reaction in the presence of platinum complexes modified by BPPM and DBP-BPPM ligands (Charts 6 and 7) has been used to examine the differential stabilization of the initially formed platinum alkyl complexes.[96] In the case of a simple aliphatic olefin, *i.e.* 1-pentene, it was found, as expected, that the olefin insertion was governed by steric interactions which destabilize the branched intermediate (+5 kcal/mol over the normal product), in agreement with both experiments and the above model developed by Consiglio and Pino. The case of styrene is more complex: for BPPM, it was found that the normal, phenethyl product is preferred over the branched α-methyl styryl product. Conversely, for DBP-BPPM, the reverse preference was found. The regioselectivity of the DBP-BPPM catalyst could be explained on the basis of a favorable π-stacking interaction (7 kcal/mol) between the phenyl ring of the α-methyl styryl and a dibenzophosphole substituent of the phosphine. Moreover, it was suggested that experimental choice of solvent is likely to affect the degree of π-stacking and therefore the regioselectivity and probably by extension the enantioselectivity. Thus, this study points to the fact that electronic interactions among substrate, catalyst, and their environment must be considered as important factors for numerous systems.

3. Miscellaneous

The intermediacy of metal−alkyl complexes in the classical hydroformylation reaction in the presence of platinum[50] and rhodium[97] complexes has been established. Nevertheless, in the platinum-catalyzed enantioselective hydroformylation, despite several attempts to characterize the intermediates present in catalytically active solutions,[30] only catalyst precursors of the type $PtCl_2$(L−L) were detected. Therefore, most of the explanations proposed for the observed regio- and enantioselectivity are based on analogous hypothetical intermediates, as mentioned in the above model studies. Other approaches were made to explain the variations in the extent of enantioselectivity and the configuration of the prevailing product with temperature (*vide supra* sections II.B.1 and III.B.1). Most of the work devoted to the platinum−tin systems presents, on the basis of literature[98] or NMR analysis,[40] reactions via different conformations of the complex.[36,39,40] In this way, it was recognized that DIOP can assume different conformations.[32] However, a reversal of product configuration was also observed in spite of a conformationally stable chelate ring, *i.e.* in the presence of *p*-dimethylamino-substituted DIOP (*vide supra* section II.B.1).[30,99] In that case, it was assumed that reaction may proceed via competing paths. It is noteworthy that the coexistence of different catalytic species, each one having its own peculiarity of regio- and enantioselectivity, as well as of activity, has also been invoked to explain the observed dependence of the optical yield upon the carbon monoxide and hydrogen partial pressure (*vide supra* section II.B.3).[23]

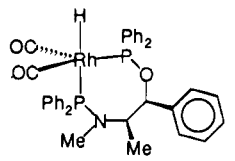
Similar assumptions were made to explain the inversion of configuration of the rhodium-based hydroformylation product of styrene by using diphenylphosphino (DPP) and dibenzophosphole (DBP) derivatives of the same chiral backbone, DIOP.[69] An interpretation of the level of asymmetric induction along with the inversion of configuration has been proposed with the help of an X-ray determination of an iridium complex, IrCl(1,5-COD)((−)-DBP-DIOP),[69] compared to an earlier reported structure, IrCl(1,5-COD)((+)-DIOP).[32a] Thus, it was found that although the difference in the conformations of the chelate ring around the metal is small, upon comparison of the two iridium complexes, the steric environment around the olefin coordination site is greatly changed leading thus to higher ee's with DBP-DIOP than with DIOP and to the observed inversion of configuration.[69]

C. Model Complexes—Catalytic Intermediates

Contrary to platinum−tin systems, the spectroscopic detection of catalytic intermediates has been more successful in the case of rhodium complexes. To the best of our knowledge, spectroscopic data were reported only twice for rhodium−chiral bisphosphine complexes placed under oxo conditions, but in the absence of substrate.[70,93] Two additional examples have appeared in the course of the final preparation of this manuscript.[84,85] In each case a monohydrido complex could be visualized by NMR.

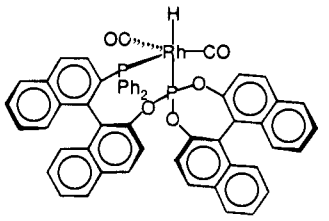
For the two older examples described, slightly different arrangements of the ligands around the

Scheme 4



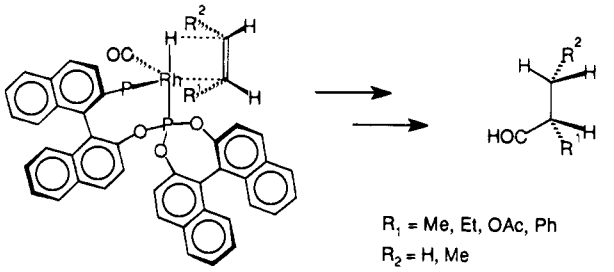
$RhH(CO)_2[(S,R)\text{-EPHOS}]$

Scheme 5



$RhH(CO)_2[(S,R)\text{-BINAPHOS}]$

Scheme 6



rhodium atom were proposed. Thus, in the first example reported, when a solution of $[Rh(\mu\text{-CO})(CO)((S,R)\text{-EPHOS})]_2$ was treated with a 1:1 mixture of hydrogen and carbon monoxide (1 atm), the ^1H and ^{31}P NMR data suggested the existence of a major hydridorhodium complex in equilibrium with the starting dimer.[70] A trigonal structure was proposed with the geometry shown in Scheme 4. In the second example described, when complex Rh(acac)((*S,R*)-BINAPHOS) was treated under the same oxo conditions, the complex formed was also assigned a trigonal-bipyramidal structure, as shown in Scheme 5.[93] The solution containing this hydrido complex was placed under a pressure of a mixture of H_2/CO and led to asymmetric hydroformylation of *p*-methylstyrene in the same extent as the *in situ* prepared catalyst (100 atm, substrate/Rh: 300, 60 °C, 20 h, 82% yield, 94% ee into the branched aldehyde), thus suggesting that the hydrido species observed is a catalytically active one involved in the catalytic cycle. Following these observations, a model was proposed for the coordination of the olefin to be hydroformylated to the hydridocarbonyl rhodium complex, ordering the large and small substituents of the olefin according to Scheme 6. The configuration of the produced chiral aldehydes is in good agreement with the model for four substrates (1-butene, *cis*-2-butene, vinyl acetate, and styrene).[100] Comparing the two hydridorhodium species, it appears that the hydride is located *trans* to the more basic phosphorus atom in one case (Scheme 4),[70] and in the second case, *trans* to the less basic phosphorus moiety (Scheme 5).[93] This suggests that steric factors exert a major influence compared to electronic considerations. Regardless, in both EPHOS and BINAPHOS hydridorhodium complexes, the aminophosphine–phosphinite and the phosphine–phosphite adopt equatorial–axial coordination to the rhodium center, respectively.

Conversely, the latest NMR and IR studies recently conducted on new hydridorhodium complexes showed that bidentate coordination of the chiral diphosphite ligand to the rhodium center may also take place in a bis-equatorial way.[84,85] Namely, in the first series of chiral diphosphites derived from butanediol-, pentanediol, hexanediol, diphenylpropanediol, and dihydroxy-*N*-benzyltartaramide (*vide supra*, section II-I.A.2),[84] spectroscopic data revealed that diphosphite ligands giving rise to a seven-membered chelating ring adopt mainly equatorial–axial coordination to the rhodium. In contrast, diphosphites which form eight- and nine-membered rings with rhodium lead to equatorial–equatorial coordination to the rhodium center. However, it is to be noticed that this series of complexes usually reveals a fluxional behavior. Diphosphites of the second series, presenting a sugar bone and 2,2′-biphenyl-1,1′-diyl phosphochloridites (*vide supra*, section III.A.2), also adopt a bis-equatorial coordination to the rhodium.[85] By comparing the structure of the complexes present in solution as well as the relative stability of the complexes to the results of catalysis, a relation between the trigonal-bipyramidal structure and the enantioselectivity of the $HRhPP(CO)_2$ complex was found. Thus, the highest enantioselectivities are obtained with undistorted, trigonal-bipyramidal hydridorhodium (bis-equatorial) diphosphite complexes.

This last trend may appear inconsistent with the high enantioselectivities exhibited by the equatorially–axially coordinated eight-membered hydridorhodium complexes derived from BINAPHOS ligands. However, it is noteworthy that all the above chiral ligand–Rh(I) systems described in this section, and especially the BINAPHOS system which is the best catalytic system so far reported for the asymmetric hydroformylation of styrene (Table 2, entries 9 and 13), present highly assymmetric structures around rhodium. This factor was pointed out to be the most important one to achieve high enantioselectivities.[85,93] More, it was also suggested that the formation of a single catalytic species may also contribute.[70,85,93] Therefore, it is probable that future developments will focus on the design of ligands having highly assymmetric structures. Another point of interest concerns the effect of the configuration of the diastereomers. Actually, we have previously mentioned (*vide supra* sections III.A.3 and 4) that both *diastereomers* of EPHOS and phosphine–phosphite ligands (BINAPHOS, BIPHEMPHOS), when associated to rhodium, contributed to strongly different results, since both the enantiomeric excesses and the prevailing configuration of the product changed. Thus, it would be of great interest to study all the diastereomers for a given non-C_2 symmetry ligand, in order to determine the more efficient one. In addition, some improvements are expected from the optimization of the electronic properties of the phosphorus atom. This last point is accessible through fine tuning of the substituents as already reported for asymmetric hydroformylation[47,70,93] and hydrogenation processes.[101]

V. Abbreviations

BCO-DPP	[bicyclo[2.2.2]octane-3,4-diylbis(methylene)]bis[diphenylphosphine]
BCO-DBP	[bicyclo[2.2.2]octane-3,4-diylbis(methylene)]bis[5*H*-benzo[*b*]phosphindole]
BDPP	2,4-bis(diphenylphosphino)pentane
BDPP-(pNMe$_2$)$_4$	2,4-bis[bis[*p*-(dimethylamino)phenyl]phosphino]pentane
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
BINAPHOS	[2-(diphenylphosphino)-1,1′-binaphthalen-2′-yl] [1,1′-binaphthalen-2,2′-diyl] phosphite
BINAS	1,1′-binaphthalene-2,2′-dithiol
BIPHEMPHOS	[5,5′-dichloro-2-(diphenylphosphino)-4,4′,6,6′-tetramethylbiphenyl-2′-yl] [1,1′-binaphthalen-2,2′-diyl] phosphite
BPPM	*N*-(*tert*-butoxycarbonyl)-4-(diphenylphosphino)-2-[(diphenylphosphino)methyl]pyrrolidine
CBDBP	1,2-bis[(5*H*-benzo[*b*]phosphindolyl)methyl]cyclobutane
CBDPP	1,2-bis[(diphenylphosphino)methyl]cyclobutane
CHDBP	1,2-bis[(5*H*-benzo[*b*]phosphindolyl)methyl]cyclohexane
CHDPP	1,2-bis[(diphenylphosphino)methyl]cyclohexane
CHIRAPHOS	2,3-bis(diphenylphosphino)butane
CHIRAPHOS-(pNMe$_2$)$_4$	2,3-bis[bis[*p*-(dimethylamino)phenyl]phosphino]butane
COD	1,5-cyclooctadiene
Cy-DIOP	2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(dicyclohexylphosphino)butane
Cy,Cy-oxoProNOP	1-(dicyclohexylphosphino)-2-[[(dicyclohexylphosphino)oxy]methyl]pyrrolidinone
DBP-BPPM	*N*-(*tert*-butoxycarbonyl)-4-(dibenzophospholyl)-2-[(dibenzophospholyl)methyl]pyrrolidine
DBP-DIOP	2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(5*H*-benzo[*b*]phosphindolyl)butane
DIOCOL	2,3-*O*-(5′α-cholestan-3′,3′-ylidene)-2,3-dihydroxy-1,4-bis(diphenylphosphino)-butane
DIOP	2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
DIOP-(mCF$_3$)$_4$	2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis[bis[*m*-(trifluoromethyl)phenyl]phosphino]butane
DIOP-(pNMe$_2$)$_4$	2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis[bis[*p*-(dimethylamino)phenyl]phosphino]butane
DIOSH$_2$	2,3-*O*-isopropylidene-2,3-dihydroxybutane-1,4-dithiol
DIPAMP	1,2-bis[(*o*-methoxyphenyl)phenylphosphino]ethane
Et-DIOP	2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diethylphosphino)butane
EPHOS	1-phenyl-1-[(diphenylphosphino)oxy]-2-[*N*-methyl-*N*-(diphenylphosphino)amino]propane
Menthoxy-PPy	2-[3-[(diphenylphosphino)oxy]menth-3-yl]pyridine
NBD	norbornadiene
NMDPP	neomenthyldiphenylphosphine
nr	not reported
Phosphepine	4-phenyl-4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1′,2′-*e*]phosphepine
Ph,Ph-ProNOP	1-(diphenylphosphino)-2-[[(diphenylphosphino)oxy]methyl]pyrrolidine

Acknowledgments. We wish to thank Hervé Bricout, graduate student in our group, for his help to set up this manuscript.

VI. References and Notes

(1) Falbe, J. *Carbon monoxide in Organic Synthesis*; Springer Verlag: New York, 1970; *New Syntheses with Carbon Monoxide*; Springer Verlag: New York, 1980.
(2) Collins, A. N.; Sheldrake, G. N.; Crosby, J. *Chirality in Industry*; Wiley: Chichester, 1992.
(3) Botteghi, C.; Paganelli, S.; Schoinato, A.; Marchetti, M. *Chirality* **1991**, *3*, 355.
(4) For a general recent review article on asymmetric hydroformylation, see: Consiglio, G. In *Catalysis in Asymmetric Synthesis*; Ojima, I., Ed.; VCH Publishers Inc.: New York, 1993; pp 273–302.
(5) The hydroformylation of racemic olefins, e.g. 3-methyl-1-pentene, in which an enantiomer-discriminating process may occur, presents a further possibility of obtaining optically active aldehydes. This type of asymmetric hydroformylation has been achieved in the first stage of research and was reviewed in 1982. See ref 12.
(6) Botteghi, C.; Consiglio, G.; Pino, P. *Chimia* **1972**, *26*, 141.
(7) Ogata, I.; Ikeda, Y. *Chem. Lett.* **1972**, 487.
(8) Tanaka, M.; Watanabe, Y.; Mitsudo, T.-A.; Yamamoto, K.; Takegami, Y. *Chem. Lett.* **1972**, 483.
(9) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994; Chapter 2.
(10) Salomon, C.; Consiglio, G.; Botteghi, C.; Pino, P. *Chimia* **1973**, *27*, 215.
(11) Hsu, C. Y. Ph. D. Dissertation, University of Cincinnatti, 1974; *Chem. Abstr.* **1975**, *82*, 154899.
(12) Consiglio, G.; Pino, P. *Top. Curr. Chem.* **1982**, *105*, 77.
(13) It is noteworthy that in the early stage of research (up to 1983), many optical yields for the hydroformylation product of styrene were overestimated, because of an erroneous value for the specific rotation value of pure hydratropaldehyde. Some of these results are reported in this paper, but the ee's have been revalued (lowered) according to the exact specific rotation determined by Pittman,[27] *i.e.* $[\alpha]^{21}_D = 315.8°$ (ca. 1.5 g in 100 mL of benzene) or $[\alpha]^{21}_D = 238°$ (neat) for pure 2-phenylpropanal.
(14) Consiglio, G.; Pino, P. *Isr. J. Chem.* **1976**, *15*, 221.
(15) Consiglio, G.; Pino, P. *Helv. Chim. Acta* **1976**, *59*, 642.
(16) Consiglio, G.; Arber, W.; Pino, P. *Chim. Ind. (Milan)* **1978**, *60*, 396.
(17) Kawabata, Y.; Suzuki, T. M.; Ogata, I. *Chem. Lett.* **1978**, 361.
(18) Haelg, P.; Consiglio, G.; Pino, P. *Helv. Chim. Acta* **1981**, *64*, 1865.
(19) Kollar, L.; Consiglio, G.; Pino, P. *J. Organomet. Chem.* **1987**, *330*, 305.
(20) Consiglio, G.; Kollar, L.; Kölliker, R. *J. Organomet. Chem.* **1990**, *396*, 375.
(21) Consiglio, G.; Roncetti, L. *Chirality* **1991**, *3*, 341.
(22) Pittman, C. U.; Kawabata, Y.; Flowers, L. I. *J. Chem. Soc., Chem. Commun.* **1982**, 473.
(23) Haelg, P.; Consiglio, G.; Pino, P. *J. Organomet. Chem.* **1985**, *296*, 281.
(24) Consiglio, G.; Morandini, F.; Scalone, M.; Pino, P. *J. Organomet. Chem.* **1985**, *279*, 193.
(25) Paganelli, S.; Matteoli, U.; Scrivanti, A. *J. Organomet. Chem.* **1990**, *397*, 119.
(26) Doyle, M. M.; Jackson, W. R.; Perlmutter, P. *Tetrahedron Lett.* **1989**, *30*, 5357.
(27) Consiglio, G.; Pino, P.; Flowers, L. I.; Pittman, C. U. *J. Chem. Soc., Chem. Commun.* **1983**, 612.
(28) Parrinello, G.; Deschenaux, R.; Stille, J. K. *J. Org. Chem.* **1986**, *51*, 4189.
(29) Gladiali, S.; Fabbri, D.; Kollar, L. *J. Organomet. Chem.* **1995**, *491*, 91.
(30) Toth, I.; Guo, I.; Hanson, B. E. *Organometallics* **1993**, *12*, 848.
(31) Consiglio, G.; Rama, F. *J. Mol. Catal.* **1991**, *66*, 1.
(32) (a) Brunie, S.; Mazan, J.; Langlois, N.; Kagan, H. B. *J. Organomet. Chem.* **1976**, *114*, 225. (b) Ball, R. C.; James, B. R.; Trotter, J.; Wang, D. K. W.; Dixon, K. R. *J. Chem. Soc., Chem. Commun.* **1979**, 460. (c) Consiglio, G.; Gramlich, V. *Helv. Chim. Acta* **1979**, *62*, 1016. (d) Balavoine, G.; Brunie, S.; Kagan, H. B. *J. Organomet. Chem.* **1980**, *187*, 125. (e) Ball, R. C.; Trotter, J. *Inorg. Chem.* **1981**, *20*, 261. (f) Payne, N. C.; Stephan, D. W. *J. Organomet. Chem.* **1982**, *228*, 203. (g) Hodgson, M.; Parker, D.; Taylor, R. J.; Ferguson, G. *J. Chem. Soc., Chem. Commun.* **1987**, 1309. (h) Evans, J.; Jones, A. G.; Webster, M. *Acta Crystallogr.* **1989**, *C45*, 595.

(33) Consiglio, G.; Nefkens, S. C. A. *Tetrahedron: Asymmetry* **1990**, *1*, 417.
(34) Consiglio, G.; Nefkens, S. C. A.; Borer, A. *Organometallics* **1991**, *10*, 2046.
(35) These turnover frequencies cannot be compared directly to the values of other platinum systems reported in Table 1. Actually, the corresponding experiments of BCO type systems were carried out under elevated pressure (CO/H_2 = 70/140 atm), and this could also account, at least in part, for the high catalytic rates as shown in section II.B.3 devoted to the influence of pressure.
(36) Kollar, L.; Bakos, J.; Toth, I.; Heil, B. *J. Organomet. Chem.* **1988**, *350*, 277.
(37) Kollar, L.; Wada, T.; Lautens, M. *Tetrahedron: Asymmetry* **1992**, *3*, 1011.
(38) Kollar, L.; Bakos, J.; Toth, I.; Heil, B. *J. Organomet. Chem.* **1989**, *370*, 257.
(39) Kollar, L.; Kégl, T.; Bakos, J. *J. Organomet. Chem.* **1993**, *453*, 155.
(40) Kollar, L.; Sandor, P.; Szalontai, G. *J. Mol. Catal.* **1991**, *67*, 191.
(41) Parrinello, G.; Stille, J. K. *J. Mol. Catal.* **1983**, *21*, 203.
(42) Parrinello, G.; Stille, J. K. *J. Am. Chem. Soc.* **1987**, *109*, 7122.
(43) Stille, J. K.; Su, H.; Brechot, P.; Parrinello, G.; Hegedus, L. S. *Organometallics* **1991**, *10*, 1183.
(44) This problem was pointed out by two reviewers.
(45) Stanley, G. G. In *Catalysis of Organic Reactions*; Marcel Dekker Inc.: New York, 1995; pp 363–372.
(46) Mutez, S.; Mortreux, A.; Petit, F. *Tetrahedron Lett.* **1988**, *29*, 1911.
(47) Naïli, S.; Carpentier, J.-F.; Agbossou, F.; Mortreux, A. *Organometallics* **1995**, *14*, 401.
(48) Bandini, A. L.; Banditelli, G.; Cesarotti, E.; Minghetti, G.; Bovio, B. *Inorg. Chem.* **1992**, *31*, 391.
(49) Gomez, M.; Muller, G.; Sainz, D.; Sales, J.; Solans, X. *Organometallics* **1991**, *10*, 4036.
(50) Scrivanti, A.; Paganelli, S.; Matteoli, U.; Botteghi, C. *J. Organomet. Chem.* **1990**, *385*, 439.
(51) Botteghi, C.; Paganelli, S.; Matteoli, U.; Scrivanti, A.; Ciorciaro, R.; Venanzi, L. M. *Helv. Chim. Acta* **1990**, *73*, 284.
(52) Consiglio, G.; Botteghi, C.; Salomon, C.; Pino, P. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 669.
(53) Stefani, A.; Tatone, D.; Pino, P. *Helv. Chim. Acta* **1976**, *59*, 1639.
(54) Stefani, A.; Tatone, D. *Helv. Chim. Acta* **1977**, *60*, 518.
(55) Fritschel, S. J.; Ackerman, J. J. H.; Keyser, T.; Stille, J. K. *J. Org. Chem.* **1979**, *44*, 3153.
(56) Botteghi, C.; Branca, M.; Saba, A. *J. Organomet. Chem.* **1980**, *184*, C17.
(57) Stille, J. K.; Fristchel, S. J.; Takaishi, N.; Masuda, T.; Imai, H.; Bertelo, C. A. *Ann. N.Y. Acad. Sci.* **1980**, *333*, 35.
(58) Becker, Y.; Eisenstadt, A.; Stille, J. K. *J. Org. Chem.* **1980**, *45*, 2145.
(59) Stern, R.; Hirschauer, A.; Sajus, L. *Tetrahedron Lett.* **1973**, *35*, 3247.
(60) Brown, J. M.; Chaloner, P. A. *J. Chem. Soc., Chem. Commun.* **1980**, 344.
(61) Tanaka, M.; Watanabe, Y.; Mitsudo, T.-a.; Takegami, Y. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 1698.
(62) Hayashi, T.; Tanaka, M.; Ikeda, Y.; Ogata, I. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 2605.
(63) Watanabe, Y.; Mitsudo, T.-A.; Yasunori, Y.; Kikuchi, J.; Takegami, Y. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 2735.
(64) Pino, P.; Consiglio, G.; Botteghi, C.; Salomon, C. *Adv. Chem. Ser.* **1974**, *132*, 295.
(65) Tanaka, M.; Ikeda, Y.; Ogata, I. *Chem. Lett.* **1975**, 1115.
(66) Hobbs, C. F.; Knowles, W. S. *J. Org. Chem.* **1981**, *46*, 4422.
(67) Delogu, G.; Faedda, G.; Gladiali, S. *J. Organomet. Chem.* **1984**, *268*, 167.
(68) Gladiali, S.; Faedda, G.; Marchetti, M.; Botteghi, C. *J. Organomet. Chem.* **1983**, *244*, 289.
(69) Hayashi, T.; Tanaka, M.; Ogata, I.; Kodama, T.; Takahashi, T.; Uchida, Y.; Uchida, T. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 1780.
(70) Pottier, Y.; Mortreux, A.; Petit, F. *J. Organomet. Chem.* **1989**, *370*, 333.
(71) Brown, J. M.; Cook, S. J. *Tetrahedron* **1986**, *42*, 5105.
(72) Gladiali, S.; Chelucci, G.; Marchetti, M.; Azzena, U. *Chim. Ind. (Milan)* **1985**, *67*, 387.
(73) Gladiali, S.; Pinna, L. *Tetrahedron: Asymmetry* **1991**, *2*, 623.
(74) Gladiali, S.; Pinna, L. *Tetrahedron: Asymmetry* **1990**, *1*, 693.
(75) Kollar, L.; Consiglio, G.; Pino, P. *Chimia* **1986**, *40*, 428.
(76) Kollar, L.; Floris, B.; Pino, P. *Chimia* **1986**, *40*, 201.
(77) Sakai, N.; Nozaki, K.; Mashima, K.; Takaya, H. *Tetrahedron: Asymmetry* **1992**, *3*, 583.
(78) Lee, C. W.; Alper, H. *J. Org. Chem.* **1995**, *60*, 499.
(79) Gladiali, S.; Dore, A.; Fabbri, D.; De Lucchi, O.; Manassero, M. *Tetrahedron: Asymmetry* **1994**, *5*, 511.
(80) RajanBabu, T. V.; Ayers, T. A. *Tetrahedron Lett.* **1994**, *35*, 4295.
(81) Buisman, G. J. H.; Kamer, P. C. J.; Van Leeuwen, P. W. N. M. *Tetrahedron: Asymmetry* **1993**, *4*, 1625.
(82) Wink, D. J.; Kwok, T. J.; Yee, A. *Inorg. Chem.* **1990**, *29*, 5006.
(83) Babin, J. E.; Whiteker, G. T. PCT Int. Appl. WO 93 03839, 1993; *Chem. Abstr.* **1993**, *119*, 159872h.
(84) Buisman, G. J. H.; Vos, E. J.; Kamer, P. C. J.; Van Leeuwen, P. W. N. M. *J. Chem. Soc., Dalton Trans.* **1995**, 409.
(85) Buisman, G. J. H.; Martin, M. E.; Vos, E. J.; Klootwijsk, A.; Kamer, P. C. J.; Van Leeuwen, P. W. N. M. *Tetrahedron: Asymmetry* **1995**, *6*, 719.
(86) Masdeu, A. M.; Orejon, A.; Ruiz, A.; Castillon, S.; Claver, C. *J. Mol. Catal.* **1994**, *94*, 149.
(87) Claver, C.; Castillon, S.; Ruiz, N.; Delogu, G.; Fabbri, D.; Gladiali, S. *J. Chem. Soc., Chem. Commun.* **1993**, 1833.
(88) Gladiali, S.; Dore, A.; Fabbri, D. *Tetrahedron: Asymmetry* **1994**, *5*, 1143.
(89) Grazia Arena, C.; Nicolo, F.; Drommi, D.; Bruno, G.; Faraone, F. *J. Chem. Soc., Chem. Commun.* **1994**, 2251.
(90) Personnal communication from Dr. Felice Faraone. In fact, the branched hydroformylation product of methyl acrylate is in equilibrium with its enol form (both tautomers observed in NMR spectroscopy), that quickly results in a racemic mixture. The ee values in this article for substrates other than methyl acrylate are correctly reported.
(91) Sakai, N.; Nozaki, K.; Takaya, H. *J. Chem. Soc., Chem. Commun.* **1994**, 395.
(92) Higashizima, T.; Sakai, N.; Nozaki, K.; Takaya, H. *Tetrahedron Lett.* **1994**, *35*, 2023.
(93) Sakai, N.; Mano, S.; Nozaki, K.; Takaya, H. *J. Am. Chem. Soc.* **1993**, *115*, 7033.
(94) Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry* 2nd Ed.; University Science Books: Mill Valley, CA, 1987; pp 621–632.
(95) L and S represent originally two ligands of different size. It is not indicated if they are sterically unequivalent moieties of the original chiral ligand ((*R,R*)-DIOP for instance) or two distinct entities. Z represent a third ligand which is assumed to be different and larger than H (CO for instance).
(96) Castonguay, L. A.; Rappé, A. K.; Casewit, C. J. *J. Am. Chem. Soc.* **1991**, *113*, 7177.
(97) Tolman, C. A.; Faller, J. W. In *Homogeneous Catalysis with Metal Phosphine Complexes*; Pignolet, L. H., Ed.; Plenum: New York, 1983.
(98) MacNeil, P. A.; Robert, N. K.; Bosnich, B. *J. Am. Chem. Soc.* **1981**, *103*, 2273.
(99) Toth, I.; Hanson, B. E. *Organometallics* **1993**, *12*, 1506.
(100) Takaya, H.; Nozaki, K. *Shokubai* **1994**, *36*, 259 (in Japanese); *Chem. Abst.* **1994**, *121*, 300137x.
(101) See for example: (a) Takahashi, H.; Sakuraba, S.; Takeda, H.; Achiwa, K. *J. Am. Chem. Soc.* **1990**, *112*, 5876. (b) Inoguchi, K.; Sakuraba, S.; Achiwa, K. *Synlett* **1992**, 169. (c) Morimoto, T.; Nakajima, N.; Achiwa, K. *Tetrahedron: Asymmetry* **1995**, *6*, 23. (d) Togni, A.; Breutel, C.; Schnyder, A.; Spindler, F.; Landert, H.; Tijani, A. *J. Am. Chem. Soc.* **1994**, *116*, 4062.

CR9100411