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Advances in Enantioselective Hydrogenation in the Presence of Chiral Complexes of Rhodium, Palladium, and Cobalt

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Data on the enantioselective hydrogenation of the C=C and C=O bonds in prochiral compounds in the presence of homogeneous and heterogeneous chiral complexes of rhodium, palladium, and cobalt are surveyed. They are examined from the standpoint of the influence of the structure of the ligand on the asymmetric effectiveness of the complex.
The bibliography includes 90 references.

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I. INTRODUCTION

A new field of homogeneous catalysis—enantioselective reactions under the influence of chiral metal complex catalysts—has arisen recently and has been developing successfully. Such processes became possible after Wilkinson's rhodium—phosphine catalysts were converted in 1968 into chiral catalysts[1-4] by introducing into them chiral phosphines, the method of synthesis of which had just been developed. In the first studies[5,6] it was already shown that catalysts based on rhodium—phosphine chiral complexes exhibit an appreciable enantioselectivity not only in hydrogenation but also in many other reactions. Subsequently catalytic systems were found which effect asymmetric syntheses on the basis of certain prochiral substrates with an optimum yield reaching up to 95-99%.[4,7] These studies dealt mainly with the hydrogenation of the C = C bond in prochiral compounds, leading to optically active aromatic hydrocarbons or acids. The enantioselective hydrogenation of the C = O and C = N bonds in the presence of rhodium complexes as well as the use of chiral complexes of cobalt, nickel, and palladium as hydrogenation catalysts have been less thoroughly studied.

The enantioselective hydrogenation of acylaminoacrylic acids is of special interest as a method of synthesis of optically active natural aminoacids. In the study of this reaction, which is of practical importance and at the same time serves as a model, attention was concentrated on the selection of an effective ligand for rhodium complexes.

In the synthesis of new chiral ligands the availability of the initial optically active compounds is a decisive factor. At the present time mainly two types of phosphine ligands are used: those which are chiral at the phosphorus atom (P-chiral) and those which are chiral at the alkyl group of the phosphine (C-chiral). Monophosphine P-chiral ligands were used in the first studies, but the large number of stages in their synthesis and the need to resolve the racemic phosphine into enantiomers led to the wide use of C-chiral phosphines, which proved to be just as effective and which can be synthesised from readily available natural products.

This review represents an attempt at a systematic account of studies on the enantioselective hydrogenation reactions catalysed by homogeneous (and heterogeneous) metal complex catalysts containing transition metals and chiral ligands; the influence of the structure of the ligand on the optical yield is discussed. We may note that the reviews of studies in this field published previously[1-4] are extremely incomplete and are already obsolete.

Mention should be made of the principal definitions used in asymmetric catalysis. The efficiency of the asymmetric reaction is defined in terms of the optical yield (p, %):

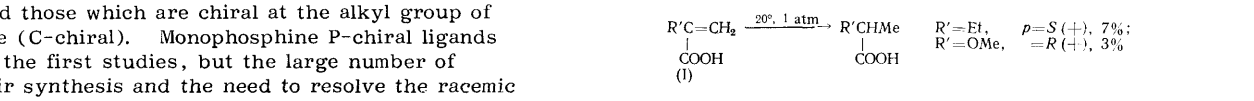
$$p = \{([R] - [S] / [R] + [S])\} \cdot 100$$

which represents the excess of one of the enantiomers in the product. The optical yield is determined experimentally from the ratio of the specific optical rotation of the reaction product to the specific optical rotation of the pure compound: $p = \{[\alpha]_{prod}/[\alpha]_{opt.pure\ comp.}\} \times 100$.

In this review the optically active product is characterised by the configuration, the sign of the optical rotation, and the optical yield; in terms of an abbreviated notation, we have, for example, $R(-)$, 25%. In a kinetically controlled process the optical yield does not vary with the degree of conversion; however, in practice p frequently changes in opposition to the overall specific rate of hydrogenation v and the efficiency of the enantioselective reaction can therefore be usefully characterised also by the rate of formation of the excess of one of the enantiomers w_R: $w_R = pv$ (mmol min^{-1}) per gramme of the catalyst.

II. CATALYSTS WITH P-CHIRAL LIGANDS

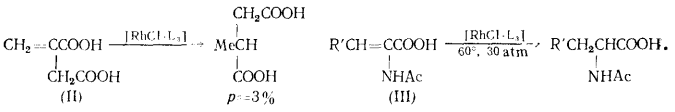
Enantioselective hydrogenation in the presence of Wilkinson's catalysts containing chiral phosphines was first achieved[5] in the hydrogenation of unsaturated acids in the presence of a rhodium complex containing the P*MePhR ligand with a chiral phosphorus atom P*:



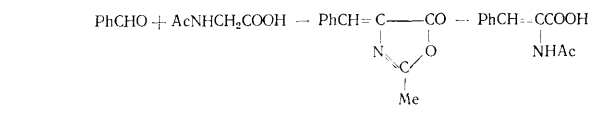
The catalyst was obtained *in situ* by mixing solutions of S(+)-P*MePh(n-Pr) and [Rh(hexa-1,5-diene)Cl]. The replacement of Et by MeO in the prochiral substrate reverses the sign of the enantioselectivity and leads to an R-product[6]. Presumably the methoxy-group is involved in coordination [as in the hydrogenation of methyl acetoacetate in the presence of the Ni-modified (+)-tartaric acid[7,8]], as a result of which the conformation of the immediate complex is inverted. In

the hydrogenation of α-substituted styrenes [PhC(R′) = CH_2, R′ = Et, Pr, iso-Pr, OEt, α-naphthyl, Br, or benzyl] in the presence of complexes containing other phosphines [P*MePhR, R = Pr, benzyl, iso-Bu, or t-Bu), a yield p = 12 to 14% was obtained[9].

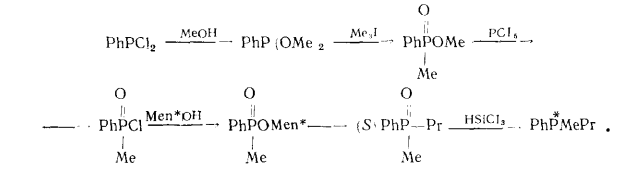
Almost simultaneously with the paper of Horner et al.[5], the communication of Knowles and Sabacky[10] was published, presenting data on the hydrogenation of atropic acid (I, R′ = Ph) [p = (+), 15%] and itaconic acid (II):



The hydrogenation was carried out in a benzene–methanol mixture in a mixture of complexes containing the P*MePhR ligands, where R = Pr, iso-Pr, cyclohexyl, or *o*-anisyl. The complex with the ligand containing the *o*-anisyl group proved to be particularly effective: cyclohexyl-*o*-anisylmethylphosphine (CAMP) (here and henceforth the abbreviations adopted for ligands names in the original literature are employed). The complex is active in the hydrogenation of *N*-acylaminoacrylic acids (III), which can be readily obtained by the Erlenmeyer synthesis for substituted ligands via an intermediate azlactone, for example:



The optically active P-chiral monophosphine is synthesised in accordance with a mechanism involving a stage where the racemate is resolved into the enantiomers:

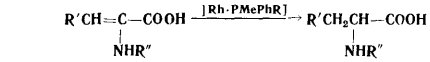


where Men* is the optically active methyl group. P*MePh-*o*-anisyl and P*Me-cyclohexyl-*o*-anisyl were obtained analogously. The complex is synthesised *in situ* by adding a solution of the ligand to the complex [RhCl(hexa-1,5-diene)]. All the hydrogenation reactions of the prochiral substrates are performed at 25 °C at a pressure of 2–3.5 atm in methanol with added NaOH. The results[11–13] are presented in Table 1. A patent[11] mentions also the possibility of using in this reaction the complexes of other metals (Ir, Ru, Os, Pd, and Pt) and the synthesis of optically active aminoacids (without indicating, however, the optical yields of the products).

The synthesis of optically active 3,4-dihydroxyphenylalanine (DOPA)—the preparation for the treatment of Parkinson's disease[13]. In relation to DOPA, asymmetric catalysis was first used for the industrial application of an asymmetric reaction in order to obtain a valuable product despite the difficulty of the preparation of the catalyst, which is the complex [Rh(hexa-1,5-diene)Cl.(+)P*MePh-*o*-anisyl], and the impossibility of regenerating it. The starting compound for the synthesis of L-DOPA was 4-acetoxy-*N*-acylamino-3-methoxycinnamic acid. A DOPA derivative was obtained with p = 60% and "pharmaceutically pure" DOPA was isolated from it after hydrolysis and recrystallisation. A DOPA derivative has been obtained with the yield p = 70.7% from *N*-acylamino-4-hydroxy-3-methoxycinnamic acid using the complex with P*Me-cyclohexyl-*o*-anisyl at 60 °C,[13] the addition of NEt_3 increasing p to 72%.

The high efficiency of rhodium (and also iridium and osmium) complexes with chiral diphosphine ligands in the hydrogenation of prochiral dehydroaminoacids and also α-(trifluoromethyl)vinyl acetate[14] has been reported[13]. Complexes having the general formula RR′P–CH_2–CH_2–PRR′, where R = *o*-anisyl or ethoxyphenyl and R′ = phenyl or tolyl, are obtained *in situ* from $[Rh(COD)Cl_2]BF_4$ (where COD = cyclo-octadiene) in methanol; the hydrogenation is carried out at 50 °C under a pressure of 4 atm. After recrystallising the products, the aminoacids phenylalanine (Phe), DOPA, and tryptophan (Trp) were obtained with optical yields of 92.8, 90.9, and 93.5% respectively.

Table 1. Hydrogenation of aminoacid precursors in the presence of rhodium catalysts with monophosphine ligands[10–13]:



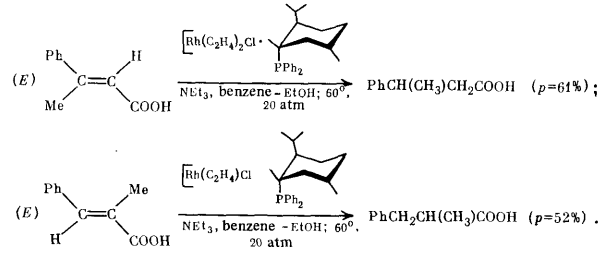
R	R′	R″	Product: amino-acid	Product: p, %
Pr	H	PhCO	Ala	6
o-Anisyl	H	PhCO	Ala	32
o-Anisyl	Ph	Ac	Phe	45
Pr	Ph	Ac	Phe	14.5
Pr	3-MeO-4-(OH)C_6H_3	Ac	DOPA	28
Cholesteryl	3-MeO-4-(OH)C_6H_3	Ac	DOPA	1.1
iso-Pr	3-MeO-4-(OH)C_6H_3	Ac	DOPA	20
Benzyl	3-MeO-4-(OH)C_6H_3	Ac	DOPA	8
m-Anisyl	3-MeO-4-(OH)C_6H_3	Ac	DOPA	0.1
o-Anisyl	3-MeO-4-(OH)C_6H_3	Ac	DOPA	46
o-Anisyl	3-MeO-4-Ac-C_6H_3	Ac	DOPA	50
Methylcyclohexyl-*o*-anisylphosphine*	3-MeO-4-(OH)C_6H_3	Ac	DOPA	70.7
Methylcyclohexyl-*o*-anisylphosphine**	3-MeO-4-(OH)C_6H_3	Ac	DOPA	65

* Ligand with 90% purity.

** Ligand with 80% purity.

III. CATALYSTS WITH C-CHIRAL LIGANDS

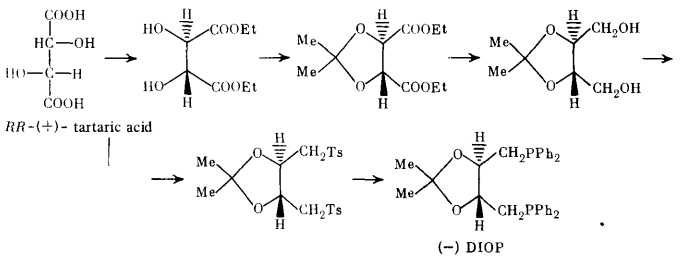
Catalysts of this type have come to be widely used. The first attempt to employ a complex containing a C-chiral ligand $PPh(CH_2C^*HCH_3C_2H_5)_2$, obtained from natural isopentyl alcohol, was unsuccessful[1]. Successful enantioselective hydrogenation was achieved[1,15,16] in 1971 using rhodium complexes with comparatively readily synthesised C-chiral ligands based on menthol; PPh_2Men (MDPP) and neomenthyldiphenylphosphine (NMDPP), the latter being more effective in the hydrogenation of compound (I, R = Ph) (p = 28%); other examples are given below:



The difference between the effects of complexes with these phosphines has been explained[1] by the fact that menthol and neomenthol are diastereoisomers with different properties and that the phosphines obtained from them exhibit different

capacities for coordination. MDPP apparently forms a more stable complex with rhodium than NMDPP, which is the reason for its lower efficiency.

A very effective and readily available diphosphine ligand (DIOP) was synthesised[17] from (+)-tartaric acid via the scheme



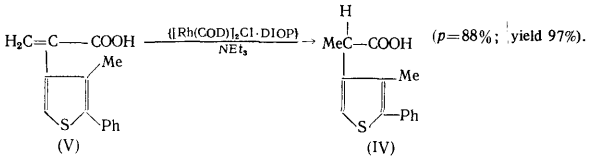
The comparative simplicity of the synthesis and the high enantioselectivity of the reaction of the complex containing DIOP attracted attention to this ligand and it became a common readily available reagent used in many preparative syntheses of optically active compounds.

The complex is obtained under conditions ruling out contact with air by adding a solution of the ligand mixed with NEt_3 to a benzene solution of $[RhCl(CoCt)_2]$ (CoCt = cyclooctene). The hydrogenation of prochiral compounds containing the C = C bond at room temperature and atmospheric pressure leads to the formation of products with very high optical yields. The following results were obtained already in the first study[17]: $p = 63\%$ for (I, R′ = Ph) and $p = 72\%$ for (III). With increase of the ratio P/Rh above two, the activity of the complex disappears as a consequence of the formation of the catalytically inactive complex $[Rh(DIOP)]^+Cl^-$. The complex [Rh-DIOP] is particularly active in the asymmetric synthesis of aminoacids by hydrogenating their precursors—substituted acrylic acids or their amides. The use of methyl esters or *N*-benzoyl derivatives as well as aliphatic acids reduces *p*, while the azlactone of *N*-acetamidocinnamic acid, benzoylhydanatoin, and dehydrobenzoylvaline are not hydrogenated at all.

The optical yields of the aminoacids obtained were enhanced further by recrystallising the products. Thus phenylalanine with $p = 88\%$ was obtained after a single crystallisation from crude *N*-acetylphenylalanine ($p = 72\%$); the overall yield was 66%. The catalyst based on (−)-DIOP leads to unnatural aminoacids of the D-series. In order to obtain the natural L-aminoacids, it is necessary to employ (+)-DIOP, which is synthesised from synthetic *SS*(−)-tartaric acid, which significantly reduces the practical value of the synthesis of aminoacids by this procedure. The chiral diarsine which is an analogue of DIOP makes it possible to obtain the natural aminoacid isomers but with low optical yields[18].

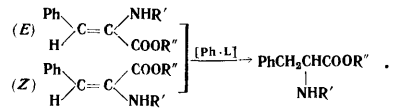
The DIOP ligand is a typical C-chiral diphosphine. The high enantioselectivity of the complex based on it can be accounted for by the configurational rigidity of the ligand molecule and the *trans*-position of the dioxolan ring relative to the chelate unit. This model of the complex explains satisfactorily its asymmetric activity[19]. The presence of the carboxy-group in compound (III) increases *p* under the influence of [Rh.DIOP], while the introduction of the ester group reduces the optical yield as a consequence of the weakening of the coordination of the substrate molecule. Bulky groups, for example adamantyl or bornyl groups, have a particularly marked effect[19].

The complex [Rh.DIOP] has been used in the synthesis of the anti-inflammatory compound (+)-(IV) by hydrogenating compound (V). Although compound (V) contains the sulphur atom of the thiophen ring, the hydrogenation proceeds smoothly and the optical yield is higher than in the hydrogenation of atropic acid [an analogoue of compound (V)], in the presence of this complex[20]:



The influence of the *E*,*Z*-isomerism of the substrate on enantioselectivity has been studied mainly in relation to the hydrogenation of substituted acrylic acids in the presence of rhodium complexes of DIOP[21] and bis(ethylidenephenylanisylphosphine) (EPAP).[14] Table 2 shows that there is a significant difference between the enantioselectivity of the hydrogenation of the *E*- and *Z*-isomers of *N*-acylaminoacrylic acids. Esterification of the acid in general reduces *p* for both *E*- and *Z*-isomers. The asymmetric hydrogenation of the latter is more effective than that of the *E*-isomers.

Table 2. Enantioselective hydrogenation of *E*,*Z*-isomers of acylaminocinnamic acids and their esters in the presence of rhodium complexes with the DIOP and EPAP ligands[14] [the optical yields (*p*,%) are quoted]:



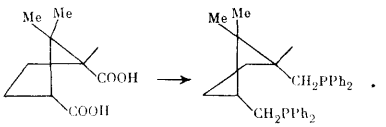
Substrate	R′	R″	Ligand DIOP	Ligand EPAP	Substrate	R′	R″	Ligand DIOP	Ligand EPAP
Z	Ac	H	81	94	*Z*	PhCO	Me	37.5	—
E	Ac	H	—	47	*Z*	PhCO	H	70	93
Z	Ac	Me	55	96	*E*	PhCO	H	25	39
E	Ac	Me	—	23	*E*	PhCO	Me	5.3	—

Table 3. Comparative catalytic efficiences of chiral rhodium complexes with various ligands in the enantioselective hydrogenation of prochiral *Z*- and *E*-substrates [the configurations and optical yields (*p*,%) of the corresponding products are quoted][124].

Substrate	Ligand Camphos	NMDPP	MDPP	CAMP	DIOP
Atropic acid	*S*; 6.1	*S*; 29.6	0	—	*S*; 44
(*E*) α-Methylcinnamic acid	*R*; 15.2	*R*; 60	*S*; 16.8	*R*; 12	*S*; 25
(*Z*) α-Methylcinnamic acid	*S*; 11.0	*R*; 25.2	0	*R*; 24	*R*; 33
(*E*) α-Phenylcinnamic acid	*S*; 11.8	*S*; 34.4	*R*; 27.2	*S*; 24	*R*; 15
(*Z*) α-Phenylcinnamic acid	*S*; 13.9	*S*; 9.1	*S*; 3.2	*R*; 1.5	*S*; 1
(*E*) β-Methylcinnamic acid	*S*; 9.7	*S*; 61.8	*S*; 1.2	*S*; 37	*R*; 14
(*Z*) β-Methylcinnamic acid	*R*; 11.4	*R*; 31.2	*S*; 30.6	*R*; 13	*S*; 28
Itaconic acid	*R*; 10.7	*R*; 8.1	*R*; 18.1	—	—
Mesaconic acid	*R*; 1.8	*R*; 5.9	*S*; 7.2	—	—

Table 3 shows that, when a monodentate molecule (α,β-unsaturated acids or esters) is hydrogenated, the influence of the *E*,*Z*-isomerism becomes less definite. The same picture has been observed also in hydrogenation in the presence of rhodium–amide catalysts[22,23] (see Table 10 below).

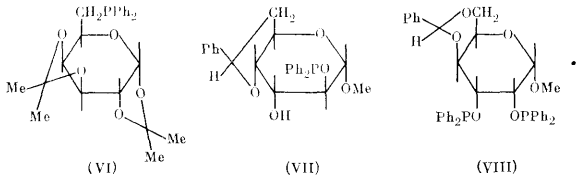
Table 3 presents comparative data on the catalytic efficiency of complexes with various ligands, including the diphosphine Camphos, obtained from (+)-camphoric acid[24]:



Thus interesting data have been obtained in the study of the simultaneous effect of the C- and P-chiral centres in the phosphine. Such a ligand was first used in the asymmetric dimerisation of olefins in the presence of the complex [NiP*Me-t-Bumen*]. The rhodium complex [Rh(COD)Cl. .P*MePhMen*], containing both the optically pure (i.e. C- and P-chiral) ligand(A) and the ligand(B) 87% epimerised at the P centre, has been used for hydrogenation[25]. The optical yields in the presence of the complexes with (A) and (B) were 13.5 and 27.5% for the *R*- and *S*-isomers in the hydrogenation of itaconic acid and 67.1 and 70.6% respectively for the *R*- and *S*-isomers in the hydrogenation of *E*-β-methylcinnamic acid. Apparently the presence of the ligands (A) and (B) in the catalytic complexes leads to enantiomeric products in both cases which indicates a significant influence of the P-chiral centre in the ligand of the rhodium complex on the stereochemistry of the products.

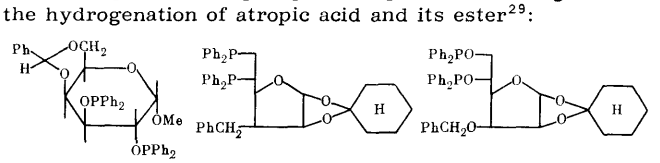
Rhodium complexes with chiral phosphinites (Camphinit) are also extremely effective catalysts[26]. A special comparison of the catalytic effect of the complexes [Rh.Camphos] and [Rh.Camphinit] demonstrated their similar enantioselectivities, the complex with phosphinite being more suitable for the hydrogenation of substrates without COOH or NHAc groups[26]. In this connection, the use of natural monosaccharides for the synthesis of both phosphines and phosphinites is extremely promising.

Ligands based on galactose (VI) and altrose (VII) have been synthesised[27]:

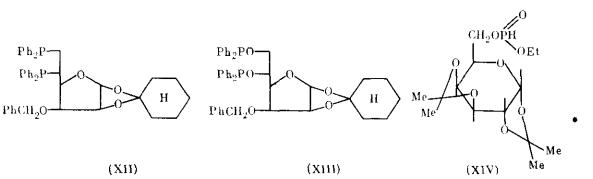


(VI) (VII) (VIII)

The catalyst was obtained *in situ* by the reaction of compound (VI) or (VII) with $[Rh(COD)Cl_2]_2$. The hydrogenation was carried out at 20 °C and atmospheric pressure. The hydrogenation of tiglic acid gave a higher optical yield (39%) than the hydrogenation of *N*-acetamidocinnamic and itaconic acids (1.7 and 2.7%). Catalysts containing diphosphonites based on glucopyranose (VIII) or galactopyranose (IX) are more effective[28]. In the presence of the complex of compound (VIII), *N*-acetamidocinnamic acid and its methyl ester give products with $p = 71$ and 60% respectively. Comparison of the enantioselectivities of the rhodium complexes of diphosphines and diphosphinites derived from glucofuranose [compounds (X) and (XI)] and idofuranose [compounds (XII) and (XIII)] demonstrated their similar efficiences in the hydrogenation of substituted acrylic acids; the enantioselectivity of the complexes with phosphinites proved to be higher in the hydrogenation of atropic acid and its ester[29]:

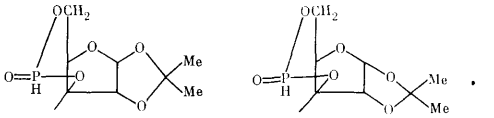


(IX) (X) (XI)



(XII) (XIII) (XIV)

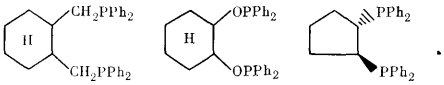
The chiral palladium complexes ($L_2PdCl_2PdL_2$), based on the acid galactose phosphite (XIV), also exhibit enantioselectivity in hydrogenation although it is weaker than that of the rhodium complexes. When compound (XIV) is treated with (−)-phenylethylamine, the derivative (XV) with a chiral P atom is formed and reacts with bis(π-palladium chloride) to produce a more effective complex. Palladium complexes with the cyclic phosphites (XVI) and (XVII) also exhibit an appreciable enantioselectivity[30–32].



(XVI) (XVII)

The efficiency of this palladium complex in the hydrogenation of citraconic acid is noteworthy, while in the presence of rhodium complexes with a wide variety of ligands the acid cannot by hydrogenated enantioselectively[1].

Cyclic diphosphines and diphosphinites (XVIII)–(XX) have also been used to synthesise rhodium complexes:



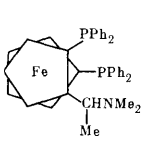
(XVIII) (XIX) (XX)

Table 4. Comparison of the enantioselectivities of rhodium complexes with the ligands (XIX), (XX), and DIOP in the hydrogenation of prochiral unsaturated compounds [the configurations and optical yields (p,%)] are quoted[35].

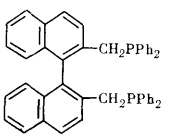
Substrate	t, °C	Ligand		
		(XIX)	(XX)	DIOP
α-Ethylstyrene	50	*R*; 33	*R*; 60	*S*; 24.5
cis-2-Phenylbut-2-ene	50	*S*; 14.4	—	—
Atropic acid	50	*S*; 0.7	0	*S*; 6.3
Methyl atropate	50	*S*; 4.5	*S*; 20	*R*; 7
N-Acetamidocinnamic acid	0	*S*; 68.5	*S*; 12	*R*; 63
Methyl-*N*-acetamidocinnamate	50	—	*S*; 43	*R*; 55
N-Acetamidoacrylic acid	−20	*S*; 78.5	0	*R*; 73
N-Acetamido-*p*-hydroxycinnamic acid	50	*S*; 48.5	—	—

The compound *trans*-(+) (XIX) and the complex [RhCl(hexa-1,5-diene)$_2$] form a chelate which has a rigid structure and in its presence the enantioselective hydrogenation of prochiral precursors of aminoacids proceeds with an extremely high efficiency[34]. The contraction of the ring and the binding of $P(Ph_3)$ groups directly to the ring increase the enantioselectivity of the complex [ligand-(+)-*trans*-(XX)].[35] Even the hydrogenation of α-ethylstyrene, which has no polar groups, proceeds with a high efficiency in this instance. In the hydrogenation of unsaturated acids the yield p is low, but it increases somewhat in the hydrogenation of the esters. Table 4 presents the values of p obtained using complexes with the ligands (XIX) and (XX) and for comparison also with DIOP.

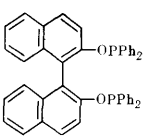
Isomeric atropisomericphosphines constitute another type of chiral ligands. The ferrocenyl derivatives of mono- or diphosphines, which exhibit simultaneously planar and central chirality of type (XXI), have been used in a complex with [RhCl(hexa-1,5-diene)] in the hydrogenation of acetamidocinnamic acids. The complexes (particularly the cationic complex) exhibit a very high enantioselectivity in the synthesis of the most important aminoacids—phenylalanine, tyrosine, and DOPA. The optical yield depends greatly on the polarity of the medium and on the presence of the NMe_2 group in the ligand[36] (Table 5). Tamao et al.[37] were the first to use the atropisomeric ligands (XXII) and (XXIII). The complex with compound (XXIII) proved to be more effective, the aminoacid esters and not the free aminoacids being formed in a high optical yield[38]:



(XXI)



(XXII)



(XXIII)

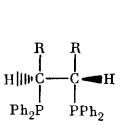
Table 5. Hydrogenation of acylacrylic acids in the presence of rhodium catalysts with atropisomeric ligands[36]:

$$RR'C{=}C(NHAc)COOR'' \xrightarrow[25°,\ 95\ atm]{[Rh(CO)Cl\text{-}C]} RR'CH{-}CH(NHAc){\cdot}L]OOR'' .$$

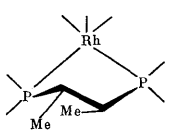
R	R′	R″	Ligand	Product	p, %	Solvent
H	Ph	H	(XXIII)	Phe	9	—
H	Ph	Me	(XXIII)	MePhe	76	—
H	H	H	(XXIII)	Ala	6	—
H	H	Me	(XXIII)	MeAla	76	—
Ph	Me	Et	(XXIII)	ethyl β-methylcinnamate	44	—
H	Ph	H	(XXI)	Phe	93	MeOH
H	Ph	H	(XXI)	Phe	92	EtOH—H_2O
H	Ph	H	(XXI)	Phe	89	MeOH—H_2O
H	4-$AcOC_6H_4$	H	(XXI)	Tyr	8	MeOH
H	4-$AcOC_6H_4$	H	(XXI)	Tyr	38	EtOH
H	4-$AcOC_6H_4$	H	(XXI)	Tyr	87	MeOH—H_2O
H	3-MeO-4-$AcOC_6H_3$	H	(XXI)	DOPA	36	EtOH
H	3-MeO-4-AcO-C_6H_3	H	(XXI)	DOPA	86	MeOH—H_2O
H	3,4-$(CH_2O_2)C_6H_3$	H	(XXI)	DOPA	52	MeOH—H_2O

* The NHAc group in the initial substrate has been replaced by H.

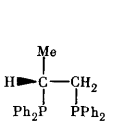
A highly effective complex is formed also when[39] the five-membered chelate ring, formed, for example, from ligand (XXIV), has a fixed conformation[39] with two asymmetric carbon atoms and equatorial methyl groups [compound (XXV)]. The cationic complex [Rh.(XXV)]$^+$.ClO_4^- (XXVI) also exhibits a high enantioselectivity. However, it has been shown[39] that the complex with the ligand (XXVII), having a single asymmetric carbon atom, is no less effective. The most typical results, using the complex [Rh.(XXIV)] (Chiraphos) in the hydrogenation of substituted aminoacrylic acids, are presented in Table 6.



(XXIV)



(XXV)



(XXVII)

It is seen that the complex exhibits an exceptionally high enantioselectivity in the case of aminoacids, leucine and phenylalanine having been obtained with $p = 100\%$. The disadvantages of the method include the necessity to synthesise the ligand from $S(+)$-lactic acid, which is difficult to obtain in a pure form. King et al.[40] attempted to eliminate this disadvantage and synthesised compound (XXII, R = Ph) from the enantiomers of mandelic acid.

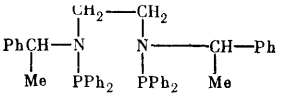
Table 6. Enantioselective hydrogenation in the presence of the complex [Rh.Chiraphos] [the optical yields (p, %) are quoted][39,40]:

$$R'CH{=}C(NHR'')COOH \xrightarrow{[Rh\cdot L]} R'CH_2{-}CH(NHR'')COOH .$$

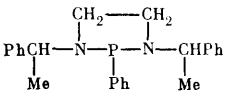
Substrate	R′	R″	Aminoacid product	Solvent	
				THF	EtOH
Z	H	Ac	AcAla	88	91
Z	Ph	Bz	BzPhe	99	95
Z	Ph	Bz	BzPhe	83	—
Z	Ph	Ac	AcPhe	74	89
Z	iso-Pr	Ac	AcLeu	100	93
Z	HOC_6H_4	Bz	BzTyr	92	—
E	HOC_6H_4	Bz	BzTyr	80	88
Z	4-AcO-3-$MeOC_6H_3$	Ac	DOPA	80	83
—	Ph	Ac	AcPhe *	82	—
—	Ph	Bz	BzPhe *	86	—

* L = (XXIV), R = Ph; in the remaining cases R = Me.

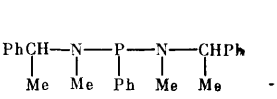
Morrison and Masler[16] were the first to report an attempt to employ chiral aminophosphines. A series of diaminodiphosphines have been synthesised[41] using S-α-phenylethylamine and the high efficiency of complexes with the ligands (XXVIII)-(XXX) has been demonstrated:



(XXVIII)



(XXIX)

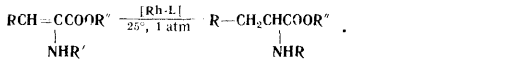


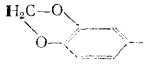
(XXX)

The catalyst was obtained *in situ* by the reaction of [RhCl.$(CH_2{=}CH_2)]_2$ with compound (XXVI). Although the chiral centre in the ligand is remote from the reaction centre, the efficiency of the catalyst proved to be extremely high and comparable to that of [Rh.DIOP], the data for which are presented in brackets in Table 7.[41] The high efficiency of the complex with ligand (XXVIII), particularly when a polar solvent is used, has been explained[42] by the ionisation of the complex and the formation of a hydrogen bond between the solvent and substrate molecules. This has been confirmed by the finding that the cationic complex [RhL_2(Solv)].BF_4 is still more active than the chlororhodium complex; aminoacids are formed with $p = 82.5\%$. A high yield can be achieved both by the coordination of the polar groups in the substrate to the metal and by the interaction of the substrate with the ligand containing functional groups other than the

phosphine group. This has been shown in the hydrogenation of itaconic acid for which complexes containing chiral phosphines have been in general not particularly effective, although in certain cases the optical yield reached 53%.[20]

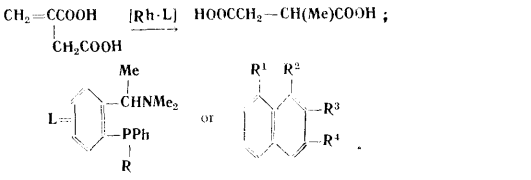
Table 7. Enantioselective hydrogenation in the presence of complexes containing aminophosphine ligands [the configurations and optical yields (p,%) of products are quoted][41]:



R	R′	R″	Configuration; p,%	Ligand
H	Ac	H	R; 73 (73)	(XXVIII)
Ph	Ac	H	R; 84 (82)	(XXVIII)
Ph	Ac	H	82.5	(XXVIII)
Ph	Ac	Me	R; 49 (55)	(XXVIII)
Ph	Bz			
	Ac	H	R; 68 (64)	(XXVIII)
		H	R; 75 (79)	(XXVIII)
H	Ac	H	S; 7.5	(XXIX)
Ph	Ac	H	0	(XXIX)
Ph	Ac	H	R; 19.7	(XXX)

The influence of the structures of a series of aminophosphine complexes of rhodium has been studied[43]. The results presented in Table 8 have been obtained under comparable conditions for the ratio L/Rh = 2.

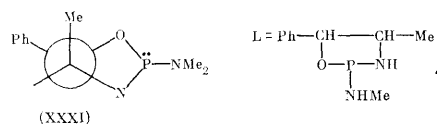
Table 8. Enantioselective hydrogenation in the presence of rhodium complexes containing aminophosphine ligands [the configurations and optical yields (p,%) of products are quoted][43]:



Ligand						Neutral complex	Cationic complex
configuration	R	R^1	R^2	R^3	R^4		
S	Ph	—	—	—	—	R; 18	R; 18
SS	Bu	—	—	—	—	S; 20	S; 17
S	—	H	$CHMeNMe_2$	PPh_2	H	R; 41	R; 43
—	—	PPh_2	$CHMeNMe_2$	H	H	S; 20	—
R	—	H	PPh_2	$CHMeNMe_2$	H	S; 5	0
R	—	H	H	$CHMeNMe_2$	PPh_2	S; 3.5	S; 15

The maximum yield was obtained in the presence of a complex with ligand (XXX), whose effect is comparable to that of [Rh.DIOP]. The introduction of a chiral P centre into the ligand [the aminophosphine (XXIX)] leads to the inversion of the configuration of the product, which occurs also when the H atom in the amino-group is replaced by Me, for example in the diphosphine derivative 1,2-bis(diphenylphosphinoamino)cyclohexane[45]. The replacement of the chiral α-phenylethyl group in compound (XXVIII) by the pinanyl group reduces the enantioselectivity of the catalyst[44]. The monoaminophosphines (XXIX) and (XXX) are less effective than the diphosphines. An attempt has been made[42] to repeat the results of Florini et al.[41] who used the ligands (XXIX) and (XXX). Despite the data of Florini et al.[41], the effect of the complex with compound (XXIX) could not be reproduced[42].

The derivatives of oxazaphospholan (XXXI) have been synthesised from (−)-ephedrine and used as ligands in palladium complexes of the following type[46]:

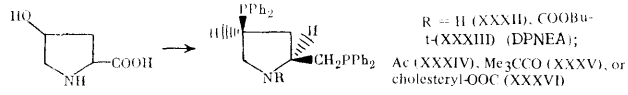


(XXXI)

The presence of chiral C and P centres in ligand (XXXI) was established by circular dichroism[46]. The hydrogenation of *N*-acetamidocinnamic acid, its azalactone and dimethyl itaconate took place with yields of 16.4, 4.0, and 9.9% respectively. The complex is one of the few chiral palladium complexes capable of effecting asymmetric hydrogenation. The low optical yield in the reaction is apparently associated with the partial decomposition of the complexes in the reaction.

A new synthesis of a chiral rhodium complex involving the substitution of one ligand in the coordination sphere of the triphenylphosphine complex by chiral α-phenylethylamine has been achieved[47]. The complex exhibits enantioselectivity in the hydrogenation of *N*-acetamidocinnamic acid (p = 20.2%) and its methyl ester (p = 11.8%). The optical yield increases with increase of the ratio amine/$RhCl(PPh_3)_3$ to a definite limit.

Ligands having two phosphine groups and the NH and NR groups have been obtained[48] from hydroxyproline[48]:



The catalyst was obtained *in situ* by the interaction of the ligand with the complex [Rh.hexa-1,5-diene]Cl; its efficiency was investigated in the hydrogenation of substituted aminocinnamic acids; the complex with compound (XXXIII) is more effective than that with (XXXII). NEt_3 influences the optical yield for complexes with a substituted NH-group, whereas in the case of [Rh.(XXXII)] this influence is absent as a consequence of the interaction of the free NH group in the ligand with the COO group in the substrate molecule. The [Rh.(XXXIII).NEt_3] system exhibits a greater enantioselectivity (p = 80–90%) when the reaction is carried out in ethanol than in methanol or water, which indicates the more effective interaction of the complex with the substrate in a less polar solvent[48]. Other substrates normally employed yielded the following results: p = 15 and 24% were obtained for (Z)-α-methylcinnamic acid and dimethyl itaconate in the presence of [Rh.(XXXIII)], and p = 29.5% was obtained in the presence of [Rh.(XXXVI)].[49] In addition, hydrogenation of olefins in the presence of the last complex yielded hydrocarbons:

$$CH_2=C(Et)R \rightarrow MeCH(Et)R$$

R = n-Bu, p=5.8 %, R=Ph, p=24.7%

If the NH-group of the ligand is acylated [compounds (XXXIV) and (XXXV)], the addition of Et_3N impairs the enantioselectivity and can actually lead to a configuration of the product which is the opposite to that obtained in the presence of the complexes with compounds (XXXII) and (XXXIV) (Table 9)[50]. The activity of the complexes of compounds (XXXIV) and (XXXV) in the hydrogenation of benzyl derivatives of the alanine precursor, which is of great interest for peptide synthesis, has been studied[50].

Table 9. Hydrogenation of acylacrylic acids in the presence of rhodium complexes containing heterocyclic diphosphines(L): [50]

$$RCH{=}CCOOR' \xrightarrow[NHR'']{[Rh\cdot L]} R{-}CH_2{-}\underset{NHR''}{CHCOOR'}$$

R	R′	R″	Configuration of product; p, %	L	Solvent
Ph	H	Ac	S; 6	XXXII	ethanol
Ph	H	Ac	R; 30	XXXIII	methanol
Ph	H	Ac	R; 91	XXXIII	ethanol + NEt_3
Ph	Me	Ac	S; 7	XXXIII	ethanol
Ph	Me	Ac	R; 15	XXXIII	ethanol + NEt_3
3,4-$CH_2O_2C_6H_3$	H	Ac	R; 83	XXXIII	ethanol + NEt_3
3,4-$CH_2O_2C_6H_3$	H	Ac	R; 32	XXXIII	ethanol
3-MeO-4-$AcOC_6H_3$	H	Ac	R; 86	XXXIII	ethanol + NEt_3
4-$AcOC_6H_4$	H	Ac	R; 87	XXXIII	ethanol + NEt_3
H	H	$PhCH_2COO$	R; 57	XXXIV	ethanol
H	H	—	S; 8	XXXIV	ethanol + NEt_3

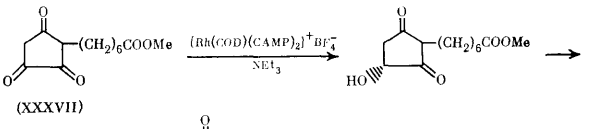
The efficiences of [Rh.(XXXIII)] and other rhodium-phosphine complexes have been compared in the hydrogenation of itaconic acid[51]. At 20 °C and a pressure of 20 atm in the presence of the complex [Rh.(XXXIII)]with added NEt_3, methylsuccinic acid was obtained with $p = 92\%$. This high optical yield was achieved after converting the complex into the cationic form $[L.Rh(COD)]^+ClO_4^-$ † with the ratio NEt_3 : itaconic acid = 1. For the neutral complex, p increases from 78.8 to 90.6% with increase of this ratio, i.e. in fact when the complex is converted into the cationic form. Thus the role of NEt_3 reduces to activating the carbonyl substrate and the formation of the carboxylate anion, which then interacts with rhodium in the coordination sphere of the complex and is converted into a cationic complex[51]. Comparative hydrogenation of itaconic acid in the presence of a number of complexes showed that, in the series of the chiral ligands PMePhPr-n,[10] NMDPP,[1] MDPP,[1] Camphos[20], PMePhMen,[25] DIOP,[16] BPPA,[43] Amphos[43], and DPNEA [48,51] the last proved to be the most effective; the optical yield reaches 92% in the presence of the complex with the ligand (XXXIII) (DPNEA).

The enantioselective hydrogenation of the C = O and C = N bonds has been less well studied than the hydrogenation of the C = C bond. Wilkinson's catalyst is known to be relatively inactive in the hydrogenation of the C = O bond and also it induces the decarbonylation of aldehydes. However, the use of cationic rhodium complexes with phosphine ligands made it possible to achieve the hydrogenation of certain ketones and Bonvicini et al.[52] reduced ketones for the first time under the influence of the rhodium complex with the P-chiral ligand $PMePhCH_2Ph$ (the PMePhEt ligand proved to be relatively ineffective according to Tanaka et al.[53] owing to the small difference between the bulks of the phosphine groups). The reaction was performed at 20 °C and atmospheric pressure in anhydrous ethanol[52]. The catalyst is in general relatively inactive and the overall rate of reaction decreases in the course of the hydrogenation. Phenylbutanol ($p = 8.6\%$) and 2-butanol ($p = 1.9\%$) were obtained from the corresponding ketones. The optical yields are small but are comparable to those obtained in the presence of the same complex in the hydrogenation of prochiral C = C substrates[6]. The introduction of DIOP into the complex in place of the P-chiral phosphine permits the enantioselective hydrogenation not only of the C = O but also of the C = N bond[54].

The use of the cationic rhodium (and also iridium) complex[55] $[Rh(COD)(CAMP)_2]^+BF_4^-$ with the CAMP ligand in the hydrogenation of ketones at 75 °C and 6 atm in isobutyric acid solution with added 0.1% of water is much more effective[10]: the ketones MeCOR (R = ET, Hex, iso-Bu, Bz, or Ph_2CH) give rise to alcohols with optical yields of 12, 14, 14, 19, and 32% respectively. The antiparallel variation of p and of the overall rate of reaction has been observed[55]. Methyl acetoacetate reacts much faster than ketones in alcohol (25°, 34 atm) with formation of methyl β-hydroxybutyrate ($p = 56\%$). The yield p is greatly influenced by the hydrogen pressure, temperature, the added water, and the nature of the solvent. It has been shown for the hydrogenation of 2-octanone (75 °C, 6 atm) that p increases from 0.3 to 12% in the series of solvents tetrahydrofuran (THF) < ethyl acetate < dimethylacetic acid < acetic acid. When the reaction is carried out in isobutyric acid, an increase of the water content in the solvent to 8% reduces sharply the optical yield (from 10–14 to 5%).[55]

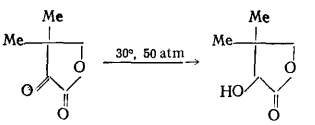
The complex (Rh(norbornadiene).(XXVIII)] is able to catalyse the hydrogenation of ketones (25°, 12 atm): the corresponding alcohols were obtained with $p = 17$ and 8% respectively from acetophenone and hexyl methyl ketone[41]. The complex [Rh(XX)] exhibits an appreciable enantioselectivity[35]. The hydrogenation of acetophenone at 80 °C leads to the corresponding alcohol with $p = 22\%$, while that of propiophenone gives rise to the alcohol with $p = 3.5\%$. The enantioselective dehydrogenation of the racemic α-phenylethyl alcohol takes place in the presence of the complex $[RuCl_2 \cdot PPh_3 \cdot (neomenthylPPH_2)]$. From this it follows that a rigorous determination of the degree of asymmetric synthesis in each individual case requires a detailed study in order to be able to show that the enantioselective reaction does not occur.

The hydrogenation of the intermediate (XXXVII) in the synthesis of prostaglandin (XXXVIII), which is a reaction of practical importance, has been achieved[56] in the presence of the complex [Rh.CAMP] ($p = 68\%$):



(XXXVII) (XXXVIII)

The complexes of the ligands (XXXIII) and (XXXVI) are capable of hydrogenating enantioselectively the keto-group in the pyruvates MeCOCOOEt and MeCOCOOBu-n with $p = 62$–65%.[49] Ketopanthoyl-lactone is hydrogenated to R(−)-panthoyl-lactone (XXXIX) with a high optical yield ($p = 86.7\%$).[57]

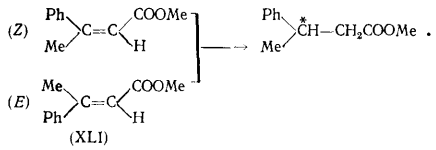


(XXXIX)

† COD = 1,5-cyclo-octadiene (Ed. of Translation).

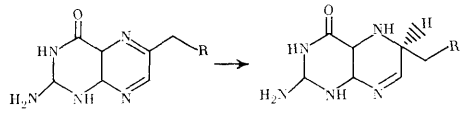
IV. RHODIUM AND PALLADIUM CATALYSTS CONTAINING AMIDES AND AMINES

Chiral rhodium-amide catalysts, capable of the enantioselective hydrogenation of unsaturated acids[22,23] as well as acetamidoacrylic acid[58], are obtained *in situ* when $[(Py)_3.RhCl]$ is treated with $NaBH_4$ in a solution of an optically active amide. With decrease of the concentration of the chiral amide to 5% in solution in the methyl ether of diethylene glycol, the enantioselectivity of the catalyst is preserved, which shows that, instead of the solvation of the complex by the chiral solvent, the chiral (apparently ionic) complex $[(Py)_2(amide)RhCl(BH_4)]^+Cl^-$ (XL) is formed. Various amides have been investigated as ligands (Table 10). The interesting fact (see Table 10, Nos.7–10) that the *Z,E*-isomerism of the substrate has almost no influence in this instance on the enantioselectivity is striking[22]



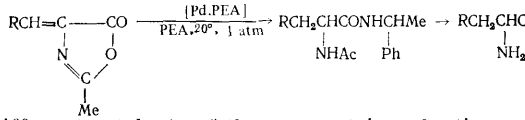
(XLI)

Apart from this model reaction involving the hydrogenation of compound (XLI), the application of the complex with the amide (XL) made it possible to hydrogenate the C = C bond in the precursor of the aminoacid (III, R = Ph) and to obtained acetylphenylalanine with $p = 75.3\%$ and an overall yield of 66%.[56] Another example of a reaction of practical importance is the synthesis[59] of folic acid (XLII) under the influence of the rhodium complex containing α-phenylethylformamide as the chiral ligand, via the reaction:

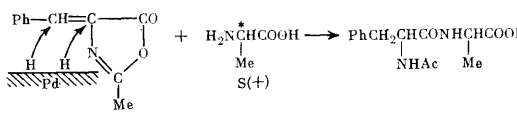


(XLII)

In the presence of palladium- or rhodium-based metal complex catalysts incorporating α-phenylethylamine (PEA), enantioselective reductive aminolysis of the azlactones of substituted acylaminoacrylic acids take place with formation of the corresponding aminoacid amides and, after their hydrolysis, of the aminoacids[60]:



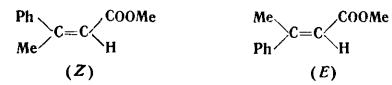
Different catalysts of the asymmetric reductive aminolysis of azlactones have been obtained by the reduction of $PdCl_2$ or $RhCl_3$ in aprotic solvents containing *S*(−)-PEA, H_2, $NaBH_4$, and *S*(−)-α-phenylethylaminoborane have been used as the reductants[60]. In *trans*-$Pd(PEA)_2Cl_2$-*S*(−)-α-phenylethylaminoborane system the excess of the *SS*-amide formed on reduction was 53%. An important component of the catalytic system is the chiral nucleophile, which can be PEA or S-alanine. In the latter case the reaction leads to the formation of a dipeptide, which is of considerable practical interest because dipeptides are assimilated by organisms more readily than aminoacids:



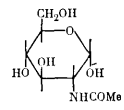
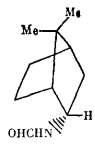
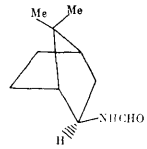
V. CHIRAL COBALT HYDROGENATION CATALYSTS

The development of effective chiral hydrogenation catalysts without platinum metals is of special interest. Cobalt complexes are extremely active dissymmetric catalysts capable of hydrogenating both C = C and C = O bonds. Two types of catalysts are known. They are based on $Co(CN)_5$ or $Co(DMG)_2$ (where DMG = dimethylglyoxime) and contain chiral ligands. The complex with $Co(CN)_5$, containing coordinated isoleucine as the aminoacid L, exhibited a weak enantioselectivity ($p \cong 0.1\%$) in the hydrogenation of atropic acid (I, R = Ph).[62] The replacement of the coordinated aminoacid by *R*(−)-propylenediamine increases *p* to 1.1%, while the introduction of *S*(+)-*N,N'*-dimethylpropylenediamine makes it possible to obtain a product with $p = 7.1\%$ from (I, R = Ph). The low enantioselectivity is apparently associated[63] with the difficulty of achieving the coordination of the substrate in the complex. It has been noted that amines with opposite configurations lead to the same *S*-acids.[64,65]

Table 10. Enantioselective hydrogenation of *E*- and *Z*-methyl β-methylcinnamates in the presence of rhodium—amide catalysts[22,23]:



(*Z*) (*E*)

№	Ligand: formula	optical purity	Substrate (XLI)	Configuration of product; *p*, %
1	PhCH(Me)CH_2NHCHO	100	*E*	*S*; 57
2	ditto	96	*E*	*R*; 48
3	ditto	100	*E*	*S*; 55
4	$(PhCH(Me)NHCO)_2$	—	*E*	*S*; 45
5	$MeCH(OH)CONH_2$	92	*E*	*R*; 16
6		99	*E*	*R*; 14
7		96	*Z*	*S*; 45
8	ditto	96	*E*	*S*; 40
9		100	*Z*	*S*; 28
10	ditto	100	*E*	*S*; 22

It is known that the complex $[Co(DMG)_2.amine]$ is active in the hydrogenation of the carbonyl group and azo-, azoxy-, and nitro-groups. A high enantioselectivity in the hydrogenation of the C = O bond has been observed for this complex after the introduction into its composition of a chiral

aminoalcohol or amine. Thus [Co(DMG)$_2$.quinine] exhibited a high enantioselectivity in the hydrogenation of benzil[66]:

$$\underset{S(+)\text{-benzoin}}{\text{PhCO—COPh} \rightarrow \text{PhCH(OH)COPh}}\ ;\quad p = 61.5\%\ .$$

The reaction proceeds under mild conditions (room temperature and atmospheric pressure). The ratio substrate/Co = 10–20, quinine/Co = 2, and the solvent is benzene or THF. In a polar solvent p decreases. Under the reaction conditions, enantioselective separation of the racemic benzoin does not occur and the chirality of the product therefore rises at the catalytic stage[66].

The hydrogenation of the ketones of the type PhCOCOR also leads to $S(+)$-benzoins. Since the product readily racemises, the true value of p was found by extrapolating the time variation of p to the time $\tau = 0$. The hydrogenation of diacetyl and ethylphenyl glyoxylate is accompanied by reductive dimerisation, which also leads to chiral products; this shows that the intermediate chiral complex reacts with the second substrate molecule without the dissociation of the Co–C bond[67]. The results are presented in Table 11.

Table 11. Enantioselective hydrogenation of α-diketones and α-ketoesters in the presence of the complex [Co(DMG)$_2$. .quinine][67].

Substrate	t, °C	Product			
		formula	yield, %	$[\alpha]_D$	p, %
PhCOCOPh *	−10	PhCH(OH)COPh	95	(+)0.86	*S*; 73
PhCOCOMe	20	PhCH(OH)COMe	88	(+)0.88	*S*; 56
MeCOCOMe	30	MeCH(OH)COMe	—	(−)0.2	*R*; 2.5
MeCOCOMe	20	MeCH(OH)COMe	54	(−)2.44	*R*; 30
PhCOCOOEt	30	PhCH(OH)COOEt	32	(+)0.28	*S*; 13.7
PhCOCOOPr-iso	—	PhCH(OH)COOPr-iso	62	(+)0.18	*S*; 11.5

* The reaction was carried out in toluene and in the remaining cases in the absence of a solvent.

The introduction of various chiral amines and aminoalcohols into the complex as ligands showed that the configuration of benzoin formed on hydrogenation of benzil is determined by the coordination of the C*–NH$_2$ and C*–OH centres in the ligand molecule: one amino-group is insufficient for enantioselective hydrogenation. For example, when brucine, O-acetylquinine, or α-phenylethylamine is introduced into the complex, the latter is incapable of effecting the enantioselective reaction, while the introduction of quinine, quinidine, or cinchonidine is approximately equally effective ($p \approx 33\%$). In the sequence *N*-methylephedrine > ephedrine > ψ-ephedrine the yield p decreases from 28 to 7.8%. These data indicate the diminution of the efficiency of the catalyst for the threo-disposition of the amino- and hydroxy-groups in the ligand[68]. The introduction of an additional amine (or triphenylphosphine) into the complex as well as the decrease of the reaction temperature to −10 °C made it possible to increase p to 78%. The base is then coordinated in the axial position, displacing the chiral aminoalcohol. The use of the aminoalcohol hydrochloride increases p, while the increase of the basicity of the amine greatly reduces p (Table 12). It has been suggested[69] that the chiral aminoalcohol is not linked directly to the complex Co(DMG)$_2$ and the entire complex thus resembles an oxidoreductase enzyme in which the catalytic and specific centres are separated. In this case the chiral aminoalcohol corresponds to the apoenzyme. The independence of p of the overall rate of the reaction, which can increase by an order of magnitude while p remains unaltered, is regarded as confirmation of this view[69]. However, one should note that this conclusion by the authors is not entirely convincing, since the reaction kinetics were not investigated and the process was inferred from the initial velocity.

Table 12. The influence of the amine (B) introduced into the complex [Co(DMG)$_2$.Q] on the optical yield and rate of hydrogenation of benzil[68,69].

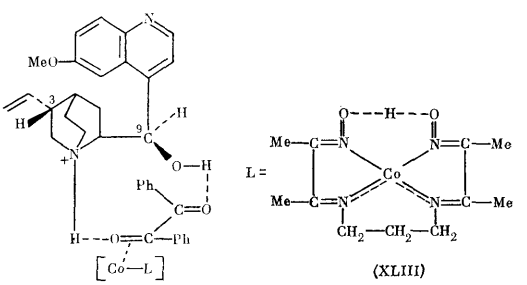
Q	B	B/Co	Q/Co	Q·HCl/Co	p, %	v *
Quinidine	Benzylamine	1	1	0	*R*; 48	6.0
Quinidine	Benzylamine	1	3	0	*R*; 51	12.0
Quinine	—	0	1	1	*R*; 61.5	1.5
Quinine	Benzylamine	1	0	1	*S*; 59	6.5
Quinine	Benzylamine	1	1	1	*S*; 61	13.6
Quinine	Triphenylphosphine	1	1	1	*S*; 61.5	0.3

* v is the rate of reaction expressed in millimoles of absorbed hydrogen per second per mole of catalyst.

If the hydrogenation is carried out at the interface in such a way that the benzene layer contains the substrate and quinine and the aqueous layer consists of a solution of the complex containing the amine (ammonia or aminoacid), then the course of the asymmetric reaction shows that the aminoalcohol does not enter directly into the cobalt complex. The chiral agent can be either in the benzene layer (quinine) or in the aqueous layer (ascorbic acid, aminoacid)[70].

This unusual mechanism of the reaction involving chiral cobalt complexes has been investigated for the chelate[71,72] formed *in situ* from compound (XLIII), quinine, and benzylamine in solution in a propanol-toluene mixture.

Scheme 1



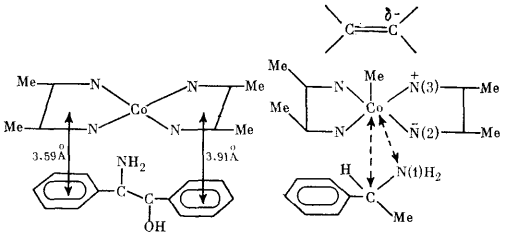
(XLIII)

The hydrogenation was carried out below −8 °C for 24 h. The products of the reactions involving methyl benzoylformate, benzoin, and methylpyruvate were obtained in yields of up to 48, 79, and 48% respectively.

A reaction mechanism, postulating the simultaneous coordination of the substrate, quinine, and hydrogen molecules to a single catalytic centre, was put forward[72] on the basis of the results of a number of studies[63–69]. This unusual mechanism is based on the hypothesis that the chiral centre in the ligand (quinine) is linked to the substrate and not to the metal (Scheme 1). In this connection it was of interest to investigate the influence of the chiral C(3) and C(9) centres on the enantioselectivity by replacing quinine by its

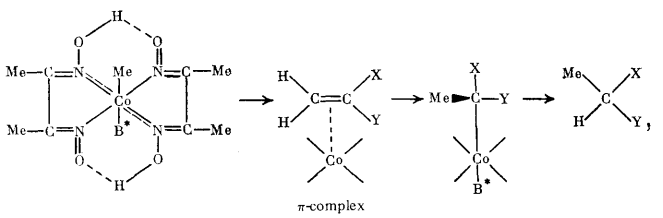
derivative and by diastereoisomers. This situation resembles that of enzyme systems where the centre determining the stereochemistry of the reaction is remote from the catalytically active centre. The observed independence of p of the overall rate of reaction can be understood in terms of this mechanism.

X-Ray diffraction analysis of a model compound—the complex (XLIV) having an analogous structure[73]—showed that N(1) and O(1) are in the *trans*-positions but the OH group in the chiral aminoalcohol is remote from $Co(DMG)_2$ and does not form a hydrogen bond with it: coordination takes place via the amino-group.



(XLIV) (XLV)

A more detailed study of the structure of the complex was performed on the model compound (XLV).[73] α-Phenylethylamine was used as the chiral amine, but one should note that this complex has no chiral catalytic properties. It contains the methyl group, which distinguishes it from the enantioselective catalytic complex, but it was assumed[73] that the methyl group does not influence the properties of the complex. Nor is it clear how hydrogen is activated in such a complex. The study of this model established that the introduction of a chiral amine into the complex [Me.(α-phenylethylamine).$Co(DMG)_2$] results in the deformation of the plane of the $Co(DMG)_2$ molecule. The strong repulsion between the amine and $Co(DMG)_2$ causes a shift of the N(1) atom towards N(2) and the Co plane is then distorted. The polarisation of the N(2) and N(3) atoms in $Co(DMG)_2$ causes the orientation of the prochiral olefin. A mechanism of the hydrogenation of the C=C bond via the formation of π- and σ-complexes was proposed on the basis of a study of the structure of the complex (XLV)[73]:



where B* is the optically active base.

Catalytically active systems of the type of Ziegler–Natta catalysts based on cobalt, namely [$Co(acac)_2$.$AlEt_3$.$P(Ph)_2$-(neomenthyl)] and [$Co(L\text{-}I\ leu)_2$.$AlEt_3$], also exhibit enantioselectivity in the hydrogenation of isomeric 2-phenylbutanes: the optical yields of 2-phenylbutane were 5.4 and 25% respectively[74].

VI. HETEROGENEOUS METAL COMPLEX CATALYSTS LINKED TO A POLYMERIC CHIRAL LIGAND

It is evident that metal complex catalysts linked to a polymeric carrier have many advantages over their soluble analogues. These are mainly the technological usefulness of the catalyst—the ease of its separation after the reaction, the possibility of its re-use and regeneration, and sensitivity to poisoning. It is not easy to draw a line between metallic catalysts on carriers and metal complex catalysts linked to polymeric ligands. Complex formation on the surface of a solid (polymeric) carrier takes place when the carrier exhibits a definite complex-forming capacity. Otherwise, for example, as in asymmetric hydrogenation on metals deposited on quartz crystals, one is dealing with deposited catalysts.

Catalysts can be subdivided into the following groups on the basis of the increase of the strength of the bond between the catalytic centre (metal or complex) and the carrier surface.

1. Metal deposited on an inert carrier (for example, nickel on quartz).

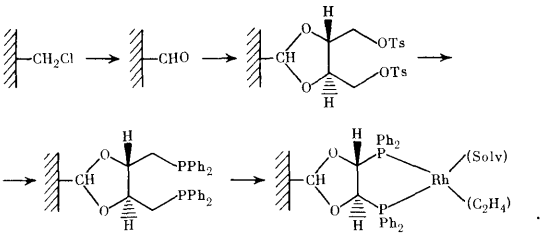
2. Metallic catalyst modified with an optically active organic complex: the complex formed is coordinated to the surface of the catalyst (for example nickel—tartaric acid or nickel—leucine).

3. The complex, which becomes chemically bound to the carrier or metal when a polymeric ligand (a complex forming polymer) is introduced into it (for example, rhodium—polyacrylamide—ethylidenealanine).

A catalyst of the last type is considered below.

Phosphinated polystyrene resins have been used as ligands for metal complex rhodium and platinum hydrosilylation and hydroformylation reactions[75]. The polymeric ligand can be obtained in two ways: (1) by introducing an achiral phosphine into a chiral synthetic or natural polymer; (2) by binding a chiral phosphine to an achiral polymer.

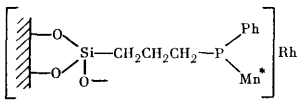
An active chiral metal complex hydrogenation catalyst containing a chiral polymeric ligand was first obtained by Poulin and coworkers[75,76] from Merrifield's resin (polystyrene cross-linked with 2% of divinylbenzene and chloromethylated to an extent of 0.7 mequiv. g^{-1}) bound to DIOP. The chiral polymer was synthesised and the complex [$RhCl(CH_2CH_2)_2$] was immobilised in accordance with the following scheme:



The rhodium complex is formed *in situ*. The hydrogenation was carried out at 20 °C for 12 h in benzene. *R*(−)-2-Phenylbutane with $p = 1.5\%$ was obtained from α-ethylstyrene, while the corresponding soluble complex [Rh.DIOP] gave a product with $p = 15\%$; repeated hydrogenation in the presence of the same catalyst gives a product with $p = 0.6\%$. The relatively inactive *S*(+)-phenyl propionate was also obtained from methyl atropate (the soluble complex gives $p = 7\%$). *N*-Acetamidocinnamic acid, which is insoluble in non-polar solvents, is not hydrogenated at all under the conditions investigated, while in an alcoholic medium the reaction could not be achieved owing to the hydrophobic nature of the polymeric catalyst. Thus the catalyst proved to be relatively unsuitable for hydrogenation, although it exhibited an appreciable enantioselectivity in the asymmetric hydrosilylation of acetophenone by Ph_2SiH_2: the product is *S*(−)-α-phenylethyl alcohol with $p = 29\%$. When the catalyst was re-used, the product with $p = 22\%$ was obtained. For the analogous soluble complex, $p = 28\%$. The use of naphthylphenylsilane as the silylating agent[77] increases the optical yield to 58.5%.

The increase of the ligand/Rh ratio above 2 for the soluble complex results in a loss of enantioselectivity, while that of the polymeric analogue is retained in this instance, an increase of p being observed in other cases. This shows that in the last case the active centres are distributed at fairly long distances from one another and the rigid polymer chain prevents the coordination of the excess diphosphine to rhodium. At the same time it follows from these results that the hydrogenation reaction is much more sensitive to the catalyst structure than hydrosilylation, whereas the enantioselectivities are the same for both the polymeric catalyst and for its soluble analogue.

Immobilised complexes of another type are also active in hydrosilylation. The compound $(EtO)_3Si(CH_2)_2PPhMen$, which reacts with $RhCl_2(CO)$ to form the homogeneous complex (XLVI), has been obtained[77]. Binding of the complex (XLVI) to silica gel yields the complex



(XLVI),

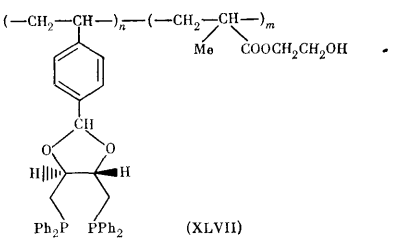
which exhibits enantioselectivity in the hydrosilylation of acetophenone or propiophenone:

$$PhCOR + H_2SiPh_2 \rightarrow \underset{\underset{OSiHPh_2}{|}}{PhCH—R} \rightarrow \underset{\underset{OH}{|}}{Ph—CH—R} .$$

For the optimum ratio Rh/P = 1 : 5, the action of the homogeneous catalyst is comparable to that of the effective [Rh.DIOP] catalyst. It is of interest to note that the alcohol formed has different configurations: S in the former case and R in the latter, although only the S-alcohol is obtained when the complex is re-used or in the presence of an excess of the ligand, apparently as a consequence of the shift of the equilibrium to the left:

$$RhL_n \rightleftarrows RhL_{n-1}Cl + L .$$

The employment of a carrier which swells in polar solvents made it possible to obtain an effective hydrogenation catalyst. A cross-linked polymer containing the DIOP residue, swelling in alcohols and other polar solvents, has been synthesised[78]:



(XLVII)

The catalyst was obtained by the interaction of [RhCl.$(C_2H_4)_2]_2$ with compound (XLVII). Acylaminoacrylic acids were hydrogenated at 1–3 atm, which gave a high optical yield of the product (60–86%), comparable to the value of p for the homogeneous complex containing DIOP (63–81%). The antiparallel variation of p and of the overall rate of reaction was noted.

A somewhat different approach was used in a study[79] where $S(-)$-α-phenylethylamine was introduced as the chiral ligand into a rhodium complex containing PPh_3 groups. Two types of polymeric catalysts were obtained. The catalyst based on the IRC-50 ion-exchange resin was prepared by converting the resin into phenylethylammonium salt and by the reaction with $RhCl(PPh_3)_3$. Hydrogenation of N-acetamidocinnamic acid leads to a 50% yield of R-Phe with 17.7% [?(Ed. of Translation)].

Methyl acetoacetate is hydrogenated to $R(-)$-methyl-β-hydroxybutyrate in the presence of a ruthenium complex bound to poly-L-methylethyleneimine (the monomer was obtained from L-alanine).[80,81] The catalyst is obtained *in situ* by adding $RuCl_3$ to a solution of the ligand in an acetate buffer at pH 5.5. The hydrogenation is carried out at 80 to 100 °C and 80 atm. With increase of the ligand/Ru ratio from 2.5 to 10, p increases only slightly (from 0.5 to 5.3%). The antiparallel variation of p and of the overall rate of reaction was noted. The complex [$RuH(PPh_3)$poly-L-glu] is also relatively ineffective in this reaction ($p = 3\%$) and the use of a polymeric ligand—a copolymer of maleic anhydride with S-2-methylbutyl ether—did not lead to the optically active methyl β-hydroxybutyrate[82].

In these examples the manifestation of enantioselectivity by the heterogenised complex is apparently influenced by the chiral structure of the polymeric ligand in the inner sphere of the complex, since it has been shown by the method of the optical rotary dispersion[83] that the polymer does not have a chiral secondary structure. The opposite picture is observed in the case of the complex Cu-poly-L-lysine, in which the helical structure of the polymer plays a decisive role in the manifestation of chiral catalytic properties by the complex[83]. Although this catalyst effects an oxidation and not a hydrogenation reaction, the example is of interest because here the secondary polymer structure has a major influence on the enantioselectivity of the catalyst.

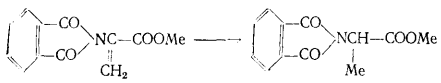
Poly-L-lysine (PLL) has a more rigid helical structure than poly-DL-lysine (PDLL), which has a random uncoiled structure[84,85]. This difference in the secondary structures of the polymers is manifested in the catalytic properties of copper chelates based on them. In the oxidation of D- and L-DOPA (3,4-dihydroxyphenylalanine) in aqueous solution at pH 10.5 in the presence of copper complexes of PLL and PDLL, a difference between the initial rates of oxidation of L- and DL-DOPA in the presence of Cu-PLL was observed. In the helical structure of Cu-PLL four NH_2 groups are coordinated to the copper atom in a plane almost parallel to the axis of the helix, while the amide and OH groups occupy apical positions. The ratio of the rates of oxidation of D- and L-DOPA (v_D/v_L) increases from 1.07 to 1.53 with increase of the fraction of the helical structure of the polymer from 15.6 to 27.6%.[84,85] On the other hand, when the polychelate copper complex of poly-L-α,γ-diaminobutyric acid, which has no helical polymer chain, is used, the specificity of the oxidation vanishes and $v_{DL}/v_L = 1$, which indicates the decisive importance of the helical structure for the manifestation of stereo-selectivity by the polychelate. The distance between the Cu-complexes distributed around the polymer chain is important for the manifestation of the asymmetrising activity. The helical structure of the polymer binds the copper complexes into a three-dimensional structure. The thermodynamic parameters of activation have been determined from the temperature variation of the Michaelis constants, $T\Delta S$ being more negative for L-DOPA than for D-DOPA, indicating a denser transition state with D-DOPA and a correspondingly higher rate of its decomposition.

Metallic hydrogenation catalysts modified by chiral polymers can be assigned to the type of heterogenised metal complex catalysts considered only as a matter of convention.

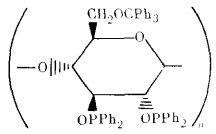
Raney nickel and palladium black have been modified by a chiral copolymer of styrene with D- and L-alanine derivatives of maleimide[86]. The copolymer has three pseudoasymmetric atoms in the chain and in the chiral side group. The question whether the carbon atoms of the polymer chain become chiral was not investigated. Methyl N-acetamidocinnamate was hydrogenated in the presence of nickel and

palladium in solution at atmospheric pressure and 20 °C. The catalysts were modified with 1% solutions of copolymers. *R*(+)-Phe is formed in dioxan, cloroform, and methanol solutions with yields $p = 1.6$ and 1.8%. The change in the acidity of the medium on modification from pH 4 to 9 alters the configuration of the product from *R* to *S*. In acid and neutral media modification apparently results in the formation of imide complexes while in an alkaline medium carboxylate complexes, giving rise to a different stereochemical environment in the complex formed, are produced[86].

Similar studies have been carried out using natural chiral polymers—polysaccharides and proteins. It has been stated that palladium deposited on polysaccharide resins based on dextran and cellulose, can be used in asymmetric hydrogenation[87]. A patent[88] describes the catalyst obtained by treating cellulose with Ph_2PCl and subsequent interaction with $[RhCl(PPh_3)_3]$; the catalyst is active in the reaction

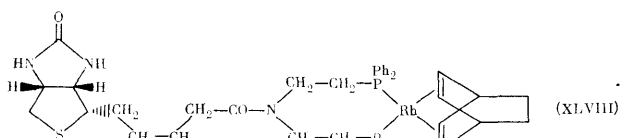


resulting in the formation of the product with $p = 28\%$. The low value of p can be explained[88] by a non-uniform distribution of phosphinite groups in the polymer base. The effect of rhodium catalysts, obtained on the basis of cellulose phosphinite



has been studied in detail[89]. The hydrogenation of α-ethylstyrene to *R*-phenylbutane at 50–120 °C and atmospheric pressure takes place with $p = 57$–77%. An increase of p with increase of the ratio P/Rh to 10 is observed. The antiparallel variation of p and the overall reaction rate has been noted. The re-use of the catalyst leads to a decrease of p to 35%. *N*-Acetamidocinnamic acid is also hydrogenated in the presence of the catalyst with $p = 52\%$ and an overall yield of 17.5% (reaction conditions: P/Rh = 11.5, 50 °C, benzene–ethanol solvent, reaction time 7 days).

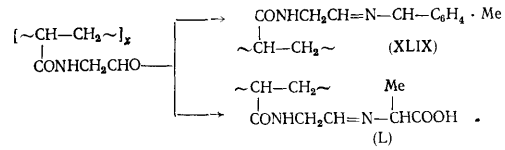
The binding of $Rh(PPh_3)_2$ to proteins leads to the formation of a chiral catalyst for the hydrogenation of *N*-acetamidoacrylic acid[90]. In this case the chiral tertiary structure of the protein (avidin, lysozyme, albumin) creates the necessary chiral environment for the metal complex. The study has been carried out mainly on avidin, whose molecule consists of four identical subunits linked to biotin. The complex is synthesised as follows: biotin is converted into a diphosphine derivative, which gives rise to the complex(XLVIII) *in situ*:



(XLVIII)

The protein and the complex (XLVIII) are added to a solution of the substrate and the reaction is carried out at 1.5 atm and 0 °C for 48 h. Optically active *N*-acylalanine is formed. The complex (XLVIII) is itself a chiral catalyst and the introduction of the protein has little effect on the overall reaction rate. However, whereas in the absence of the protein $p < 2\%$, when one equivalent of avidin is introduced the optical yield rises to 44%. Lysozyme and albumin proved to be relatively ineffective: $p \leq 2$–5%. Preliminary treatment of avidin with biotin reduced sharply the enantioselectivity of the catalyst and p falls to 4%. Hence it follows that the active centre constitutes a formation in which the complex (XLVIII) is linked to the protein via the biotin in the protein molecule.

The catalyst based on a polymer containing aldehyde groups exhibited a high enantioselectivity. The aldehyde groups in the polymer were bound to PEA or alanine with formation of a polymer swelling in organic solvents:



On treatment of compound (XLIX) or (L) with $[Rh(COD).Cl]_2$, enantioselective heterogenised metal complex catalysts are formed and the catalyst based on compound (XLIX) does not differ in its enantioselectivity from low-molecular-weight catalysts containing chiral PEA or Schiff bases, while the catalyst based on compound (L) as well as the complex [Rh.benzylidenealanine] exhibited a very high enantioselectivity: the hydrogenation of methyl-*N*-acetamidocinnamate (50 °C, atmospheric pressure, methanol solvent) results in the formation of *S*-phenylalanine with $p = 94.9$–97.6%.[91]

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Thus an extensive search has been carried out for effective metal complex catalysts based on chiral ligands, mainly phosphines, starting with readily available sources of optically active compounds (tartaric acid, phenylethylamine, menthol, hydroxyproline, and monosaccharides). Highly effective catalysts have been obtained, but these exhibit a high enantioselectivity only for a limited number of substrates and the spectrum of their activity is difficult to guess beforehand. The catalytic systems created on the basis of readily available optically active compounds can be used for the preparative synthesis of certain valuable chiral compounds (for example DOPA in an optically pure state). However, the unsuitability for technological applications of soluble metal complex catalysts limits their applicability and makes it necessary to seek systems incorporating a polymeric ligand, i.e. the catalytically active complex must be bound to a polymer chain or a carrier in order to convert the homogeneous catalyst into an insoluble "heterogenised" catalyst. The present review has shown that promising data have been obtained on these lines.

Despite the advances made in enantioselective hydrogenation, the deficiencies of these investigations should be noted: the studies have been performed with a purely experimental selection of systems and detailed investigations of the reaction mechanism in order to discover the relation between the enantioselectivity and reactivity of the complexes and the relation between the structure of the ligand and the complex, on the one hand, and the structure of the substrate molecule, on the other, have not been made. So far no attempts have been made to find general rules governing the action of chiral metal complex catalysts in a specific reaction, relating, for example, the thermodynamic stability of the complex to its overall activity and enantioselectivity. The discovery of such rules, for example, in asymmetric hydrogenation on metallic catalysts modified with chiral aminoacids, proved to be extremely useful in predicting their enantioselective activity[7].

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