

The enantioselective hydrogenation of *N*-acyl dehydroamino acids

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The historical development of asymmetric hydrogenation of *N*-acyl dehydroamino acids and their derivatives is reported. Both homogeneous and heterogeneous catalysis are illustrated by selected examples. Catalysis by water soluble complexes and transfer hydrogenation are also treated in this review. The mechanism of catalytic hydrogenation, its elementary steps and the origin of enantioselection are discussed.

Keywords: asymmetric hydrogenation, amino acid precursors, transition metal complexes, homogeneous catalysis, heterogeneous catalysis, water soluble complexes, mechanism, catalytic cycles, origin of enantioselection

1. Introduction

The field of asymmetric synthesis in modern organic chemistry is one of the most important pathways to optically pure compounds. Among those methods transition metal catalyzed reactions are often the most effective route to achieve high enantiomeric purity. Especially asymmetric catalytic hydrogenation is a fundamental and multivariably applicable tool in enantioselective synthesis.

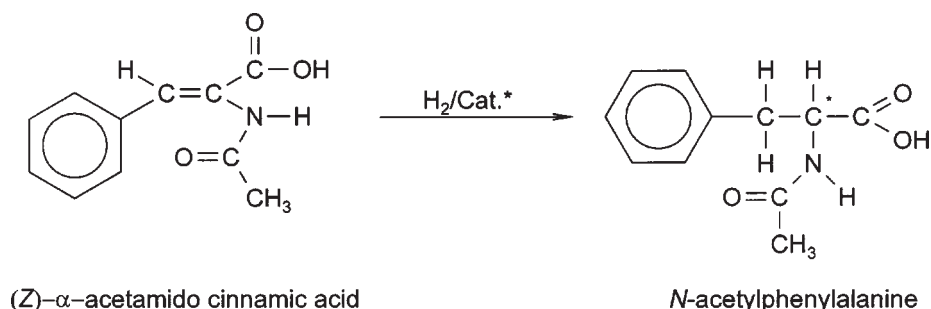
In the mid-sixties the awareness of the potential need for optically pure substances suddenly increased, since it was known that two enantiomers could be totally different in their pharmaceutical effect. The thalidomid scandal certainly is the best known example. The discovery of L-DOPA as an effective drug in treatment of Parkinson's disease gave an new impetus for the industrial development of enantioselective hydrogenation catalysts. It was soon recognized that only the *L*-isomer had the desired therapeutic effect [1].

Many pharmaceutically active substances – like L-DOPA – consist of amino acids. Synthesizing natural – and also non-natural – amino acids in high enantiomeric purity is a challenging problem for modern chemistry. The enantioselective hydrogenation of prochiral enamides is often the crucial step in amino acid synthesis. Therefore the development of highly efficient organometallic hydrogenation

catalysts has been an important task of research in chemistry during the last years [2].

In the late sixties the hydrogenation of α -acetamido cinnamic acid with palladium adsorbed on poly-amino acids gave optical yields of 1–5% [3–5]. Shortly after that a development took place that led to much higher enantioselectivities. Rhodium complexes of phosphine-ligands were used to hydrogenate prochiral enamides [6,7]. Tertiary phosphines with the stereogenic centre at the phosphorus or phosphines which were asymmetric at a neighbouring carbon atom were the first ligands that gave *ee*'s of 60% [8]. With a chiral phosphine containing phenyl-, *o*-anisyl- and cyclohexyl moieties Knowles et al. even achieved up to 90% optical purity in hydrogenating acylamino cinnamic acids [9].

A great progress was made when it was recognized that chelating bisphosphines were more effective ligands. Kagan et al. developed the DIOP-ligand [10–13] (DIOP = 2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane) which first yielded 70–80% *o.y.* and later on was optimized to give up to 90% *o.y.* [14,15]. Knowles et al. also began to work on new bisphosphines and developed the DIPAMP-ligand [16–18] (DIPAMP = 1,2-bis(*o*-anisylphenylphosphino)ethane) which was applied in the industrial L-DOPA synthesis at Monsanto [1].



Scheme 1.

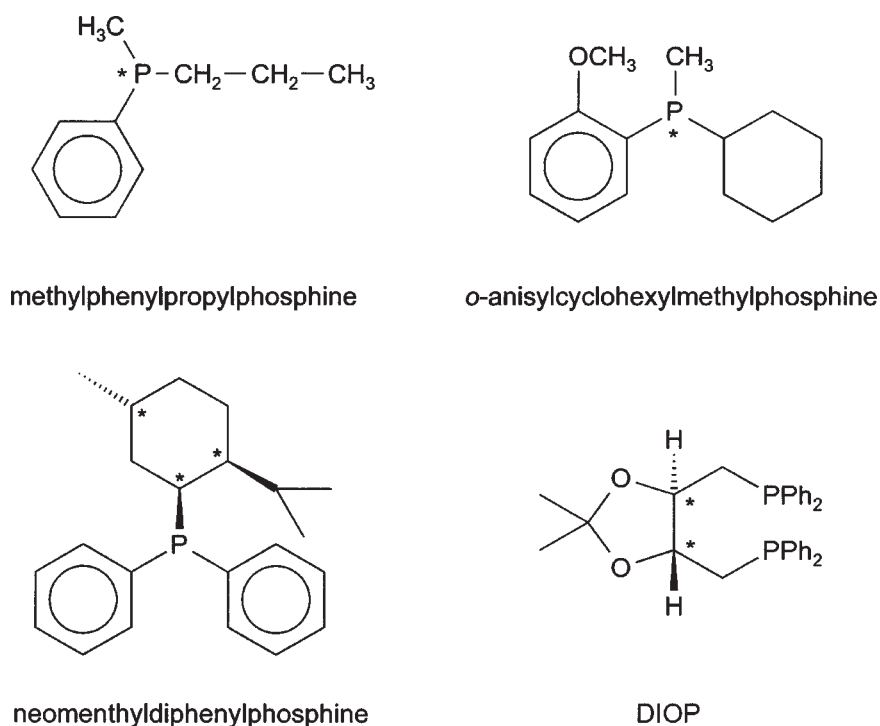


Figure 1.

A wide range of bisphosphine ligands was developed the following years for almost every imaginable hydrogenation problem. A milestone certainly was the development of Noyori's BINAP-ligand (BINAP = 2,2'-bis(diarylphosphino)-1,1'-binaphthyl) in the eighties [19,20]. A cationic Rh-BINAP complex effects enantioselective hydrogenation leading to almost 100% *ee*. An even broader applicability is achieved with Ru-BINAP complexes [21, 22].

During the last years ligands were developed with abilities to hydrogenate even sterically demanding substrates like β,β -disubstituted enamides with high optical purities. Burk et al. synthesized new electron-rich phospholanes which yielded excellent *ee*-values [23–26].

2. Homogeneous catalytic hydrogenation

2.1. Rhodium complexes

In the late sixties and early seventies it was discovered that soluble rhodium-phosphine complexes had great abilities in hydrogenating acrylic acids and unsaturated amino acid precursors. At first chiral tertiary monophosphines with the stereogenic centre at the phosphorus were used [6,7]. Low optical yields about 15% could be obtained. A progress was made when Morrison et al. used tris(neomenthylidiphenylphosphine)-rhodium(I) chloride in benzene-ethanol to hydrogenate (*E*)- β -methylcinnamic acid. With 61% *ee* they achieved the so far highest degree of asymmetric bias accomplished with a chiral hydrogenation catalyst [8]. Subsequently Knowles et

al. introduced the *o*-anisylcyclohexylmethylphosphine ligand yielding an optical purity of 85–90% in the hydrogenation of various acylphenylalanine precursors [9].

A break-through was the development of novel bisphosphine-rhodium complexes. The first efficient bisphosphine ligand was (–)-2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane (= DIOP), developed by Kagan et al. [10,11]. The best optical yields obtained with a [Rh(COD)(DIOP)]⁺ClO₄[–] complex were about 90–92% in the hydrogenations of several enamides (turnover frequencies from 0.02 to 0.07 s^{–1}) [12–15]. Later on various hydroxy groups were introduced to the DIOP ligand by Boerner et al. This new hydroxy bisphosphines produced as their rhodium catalysts *ee*'s comparable to their parent catalysts [27,28].

Simultaneously Knowles, Vineyard et al. achieved excellent *ee*'s up to 96% in the reduction of α -acylamino acrylic acids using 1,2-bis(*o*-anisylphenylphosphino)ethane (= DIPAMP) [16–18]. They also revealed that the (*Z*)-isomers were hydrogenated with greater enantiomeric excess than the (*E*)-isomers and the rates were 15–100 times faster. For the first time the steric demands on the substrate were examined. Another route was pursued by Japanese and Canadian workgroups. They examined the hydrogenation abilities of a new class of bisphosphines derived from ferrocene [29–32]. With (*S*)- α -[(*R*)-1',2-bis(diphenylphosphino)ferrocenyl]ethyl dimethylamine (= BPPFA) α -acetamido cinnamic acid was hydrogenated with 93% *o,y*.

Fryzuk and Bosnich synthesized the chiral 2,3-bis(diphenylphosphino)butane ligand (= CHIRAPHOS) which as its rhodium complex was able to hydrogenate alanine, phenylalanine, leucine, tyrosine and DOPA precursors with high

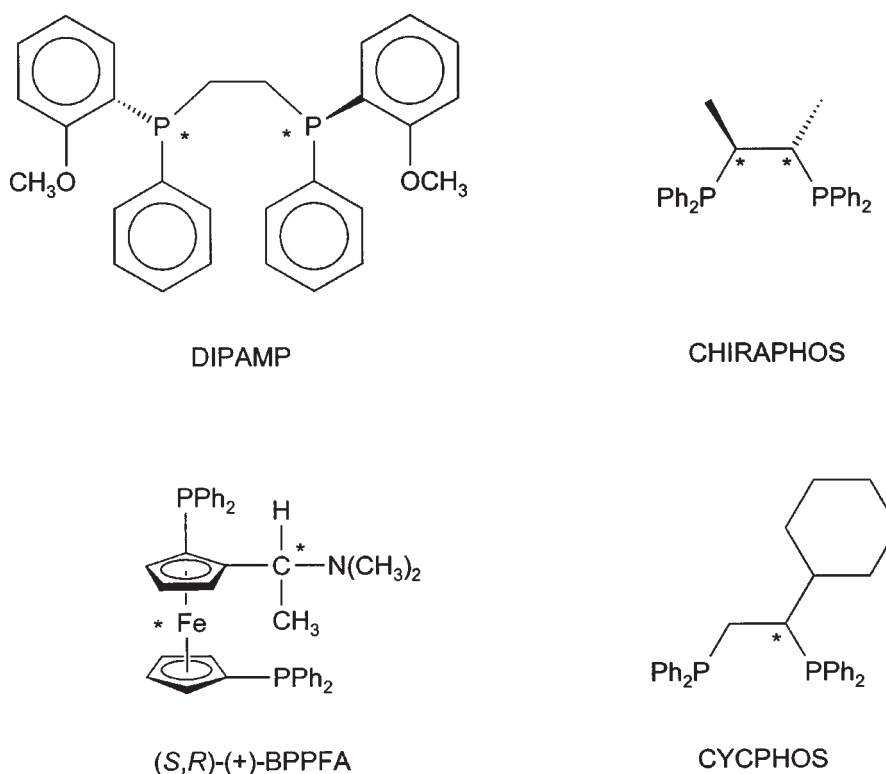


Figure 2.

and partly very high enantioselectivities. For example, *N*-benzamido cinnamic acid was hydrogenated in THF with 99% *o.y.* The leucine precursor *N*-acetamido isopropylacrylic acid was reduced in THF to its corresponding amino acid with approximately 100% *o.y.* [33]. These high enantioselectivities were obtained at room temperature with low H₂-pressure (1 bar H₂) in 24 h.

Riley and Shumate hydrogenated with the 1,2-bis(diphenylphosphino)-1-cyclohexylethane ligand (= CYCPHOS) an even wider range of amino acid precursors. They converted manifold amido acrylic acids with optical yields up to 98% at low pressure hydrogenations (1 bar H₂) at room temperature (25 °C) [34].

Brunner and Pieronczyk developed a chelating bisphosphine ligand with a norbornene backbone bearing the chiral information. Their 2,3-bis(diphenylphosphino)norbornene (= NORPHOS) could be readily separated in its enantiomers using the NORPHOS oxides and gave 96% *ee* in hydrogenating (*Z*)- α -acetamidocinnamic acid [35,36]. Later on Kyba and Davis discovered that the double bond in the norbornene backbone of NORPHOS is hydrogenated itself under the used conditions. The reduction of the NORPHOS to the so called RENORPHOS ligand occurs upon catalyst activation so that the ligand on the operating catalyst is RENORPHOS, regardless of the precursor [37]. Boerner et al. synthesized a hydroxy derivative of NORPHOS but the achieved *ee*'s were lower than those of NORPHOS [38,39].

In 1977 Kumada et al. followed a new route to introduce chiral information in a ligand. They used the atropiso-

meric binaphthyl backbone for their 2,2'-bis(diphenylphosphinomethyl)-1,1'-binaphthyl (= NAPHOS) which carried an axial element of chirality only [40]. The *ee*'s obtained thereby were not too high, at best 54% in hydrogenating acetamido cinnamic acid at 50 bar H₂ in 15 h. Grubbs and DeVries also used an atropisomeric binaphthyl backbone but in combination with diphosphinite moieties. The activity of this catalyst system was low and it reacted only under high pressure of 95 bar hydrogen [41]. The following years atropisomeric ligands were neglected until in 1980 Noyori et al. developed their famous 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (= BINAP) ligand. BINAP was accessible in (*S*)- and (*R*)-conformation, so that both enantiomers of hydrogenation products could be obtained by choosing handedness of the ligand chirality. (*Z*)- α -benzamido cinnamic acid was reduced to *N*-benzoylphenylalanine with 100% *ee* in 97% chemical yield [19,20]. BINAP surely is one of the most commonly applicable ligands, with even more capabilities in ruthenium catalysis as will be mentioned later on.

In general (*E*)- and (*Z*)-isomeric enamides are hydrogenated differently by most of the mentioned catalysts. Frequently the (*Z*)-isomer is hydrogenated more selectively. More bulky substrates like β,β -disubstituted enamides are seldom used for catalytic hydrogenation experiments due to often unsatisfactory results. Achiwa was one of the first who tried to reduce these sterically demanding compounds, thereby creating two chiral centres in the resulting products [42]. Using a cationic rhodium complex of 1-*tert*-butoxycarbonyl-bis{(2-diphenylmethyl)-

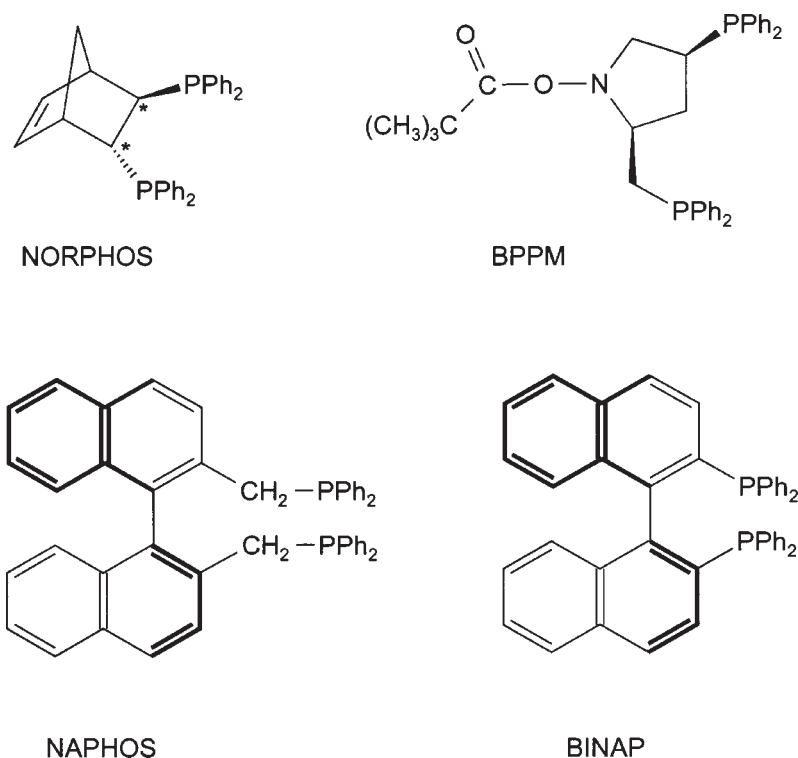


Figure 3.

4-diphenylphosphino}pyrrolidine (= BPPM) he obtained threo- β -methylaspartic acid with > 99% diastereoselectivity and an *ee*-value of 58% in quantitative chemical yield (50 bar H₂, 80 °C in ethanol).

In the early eighties the application of the so far developed catalysts was investigated. DIPAMP was applied in the total synthesis of mucronine B [43] and of leu-enkephalin [44]. Various ligands like BPPM, DIOP and DIPAMP were used to synthesize enantioselectively chiral amino acids and oligopeptides from dehydropeptides [45].

In the mid-eighties Nagel et al. developed a new bisphosphine ligand which showed great abilities in hydrogenating (*Z*)- α -acetamido cinnamic acid [46–49]. With rhodium complexes of 3,4-bis(diphenylphosphino)pyrrolidine (= PYRPHOS) they achieved 99% *ee* in hydrogenating (*Z*)- α -acetamido cinnamic methyl ester at room temperature (57–45 bar H₂) and even 100% *ee* with a cinnamic acid derivate substituted in 3- and 4-position (3-methoxy, 4-hydroxy) [50]. One of the advantages of PYRPHOS is the possibility of obtaining derivatives at its N-ring atom. Manifold protecting groups can be introduced and the ligand can also be easily purified by recrystallization of the amino hydrochloride. At 1 bar PYRPHOS reaches reaction rates similar to NORPHOS (turnover frequencies about 0.008 s⁻¹) but it is possible to enhance its hydrogenation rates by increasing the H₂-pressure to 50 bar without loss of enantioselectivity. Then it reacts about fifty times faster. In the PYRPHOS ligands a relative high rigidity is achieved by one five membered ring fused to the five membered chelate ring imposing a minimal steric strain. This is believed to allow a relative fast equilibrium with substrate

molecules which in turn allows a high turnover frequency at high pressure without loss of enantioselectivity.

In the late eighties Selke et al. obtained good results with carbohydrate phosphinites as ligands in rhodium catalyzed hydrogenation. Phenyl 4,6-*O*-(*R*)-benzylidene-2,3-*O*-bis(diphenylphosphino)- β -D-glucopyranoside (= Ph- β -GLUP) provides enantioselectivities of 96–99% *ee* in asymmetric hydrogenation of *N*-acylaminoacrylic acids [51–53].

Recently new spiro phosphinite ligands were developed by a Chinese workgroup. This new chiral phosphinite ligands, namely 1(*R*),5(*R*),6(*R*)-1,6-bis(diphenylphosphinoxy)-spiro[4.4]nonane (= *R*-spirOP) and 1(*S*),5(*S*),6(*S*)-1,6-bis(diphenylphosphinoxy)spiro[4.4]nonane (= *S*-spirOP), have a rigid spiro backbone which mimics the skewed position of the binaphthyl rings in BINAP. With *R*-spirOP a very high *ee* of over 99.9% was reached in hydrogenation of 2-acetamido acrylic acid methyl ester at 1 bar H₂, 25 °C and a substrate to catalyst ratio of 100 [54].

In the beginning of the nineties a new example of atropisomeric bisphosphine ligands was synthesized. The cationic rhodium complexes of (*R*)-(-)- and (*S*)-(+)-(dicyclohexylphosphino)-6,6'-dimethyl-1,1'-biphenyl ligands (= BICHEP) were able to hydrogenate (*Z*)- α -acetamido and (*Z*)- α -benzamido cinnamates rapidly to the corresponding amino acid derivatives in high optical yield of about 92–99% *ee* [55].

From 1990 up to now Burk et al. developed new electron rich bisphospholane ligands. With their 2,5-disubstituted 1,2-bis(phospholano)ethane (= BPE) and 1,2-bis(phospholano)benzene (= DuPHOS) ligands they fre-

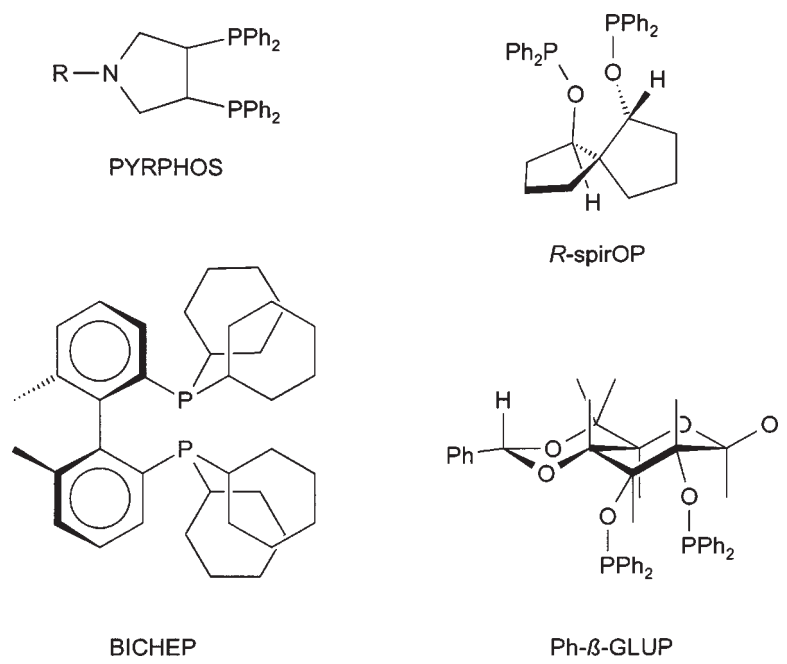


Figure 4.

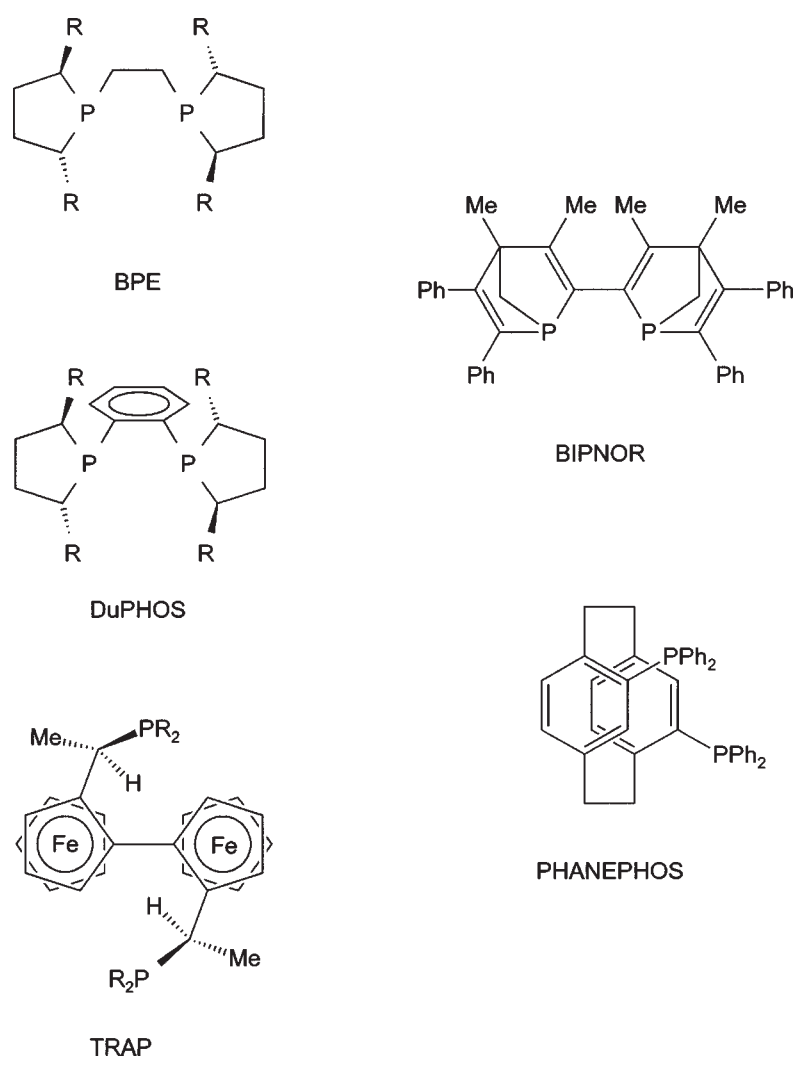


Figure 5.

quently reached over 99% *ee* in rhodium catalyzed hydrogenation of manifold acetamidoacrylates [24,25,56,57]. Remarkably the DuPHOS ligand is able to hydrogenate (*Z*)- and (*E*)-isomers in equally high enantioselectivities. Therefore it was applied in the more difficult hydrogenation of β,β -disubstituted substrates, but the obtained *ee*-values were not as high as before. Only when the more flexible BPE ligand was used the *ee*'s increased again to over 99% [26,58,59].

Ito also hydrogenated β,β -disubstituted α -acetamido acrylates using his 2,2''-bis[1-(dialkylphosphanyl)ethyl]-1,1''-biferrocene (= TRAP) ligands, but he achieved at best 88% *ee* [60].

A new bisphosphine ligand having two chiral, nonracemizable bridgehead phosphorus centers was developed by Mathey et al. The rhodium complex of 2,2',3,3'-tetraphenyl-4,4',5,5'-tetramethyl-6,6'-bis-1-phosphanorborna-2,5-dienyl (= BIPNOR) yielded over 98% *ee* in the hydrogenation of (*Z*)- α -acetamido cinnamic acid at 25 °C and 3 bar H₂ [61,62].

Pye and Rossen synthesized a new planar chiral bisphosphine ligand that is based on a paracyclophane, the (4,12-bis(diphenylphosphino)-[2.2]-paracyclophane (= PHANEPHOS). The rhodium complex of PHANEPHOS hydrogenated 2-acetamido acrylic acid methyl ester with 99.6% *ee* at room temperatures by simply passing a stream of H₂ through a solution of precatalyst and the substrate in methanol. Other dehydroamino acids gave lower *ee*'s at room temperature and needed to be cooled down to -10 °C or -45 °C to give high enantioselectivities [63,64].

2.2. Ruthenium and other transition metal complexes

Aside from rhodium, ruthenium is certainly the other important central atom for enantioselective hydrogenation catalysts of dehydroamino acids.

When Noyori et al. developed their BINAP ligand in the beginning of the eighties they first applied it as its rhodium complex and obtained good results as mentioned above. But soon it was recognized that the ruthenium complex of BINAP could be applied in a much wider range of hydrogenation experiments [65,66].

At first [Ru₂Cl₄(BINAP)₂](NEt₃) was used to hydrogenate (*Z*)- α -benzoylaminocinnamic acid. An optical yield of 92% had been achieved where under identical conditions with a Rh-BINAP complex up to 100% *o.y.* could be obtained [67,68]. But in more complex experiments like the synthesis of morphine derivatives the Ru-catalysis proved to be superior. The asymmetric hydrogenation of (*Z*)-*N*-acyl-1-alkylidenetetrahydroisoquinolines yielded 96–100% *ee* at room temperature (4 bar H₂). Unfortunately the (*E*)-isomer was inert to such catalytic conditions [21,69–72].

It is remarkable that Ru-BINAP yields the opposite enantiomer of the product than Rh-BINAP, respectively [67,73].

Good results were obtained with Ru-BINAP in the enantioselective synthesis of β -amino acids. Some enamido esters were hydrogenated by [Ru(OCOCH₃)₂-BINAP]

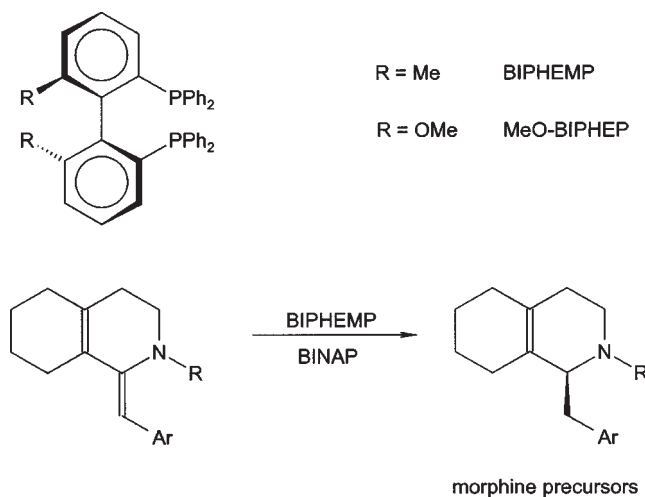
with partly very high *ee*'s. For example, (*E*)-methyl-3-acetamido-2-butenolate was hydrogenated at room temperature and 1 bar H₂ in 19 h with an *ee*-value of 96%. The (*Z*)-isomer on the contrary only yielded 5% *ee* under the same condition [74].

The broadest applicability of the BINAP ligand surely lies in its ability to hydrogenate various classes of ketones with very high *ee*'s. This shall not be discussed here.

Aside BINAP, the most applied ligand in Ru-catalysis, other ligands were used as their Ru-complexes too. In 1972 James et al. published the results of their attempt to hydrogenate α -acetamido acrylic acid using a bi-nuclear ruthenium complex containing a bridging (+)-DIOP ligand. They achieved 60% *o.y.* at 30 °C and 1 bar H₂ with 10⁻³ M of their catalyst in one day [75]. Later on they optimized the catalytic reaction and obtained 97% *ee* in the hydrogenation of *Z*- α -acetamido cinnamic acid using {RuCl₂ [(*S,S*)-CHIRAPHOS]}₂ at 30 °C and 1 bar H₂ [76].

In 1992 Genet et al. reduced α -acetamido acrylic acid to *N*-acetyl alanine using a ruthenium complex of (*R,R*)-DIPAMP, achieving in 72 h an *ee* of 35% at 50 °C and 12 bar H₂ [77].

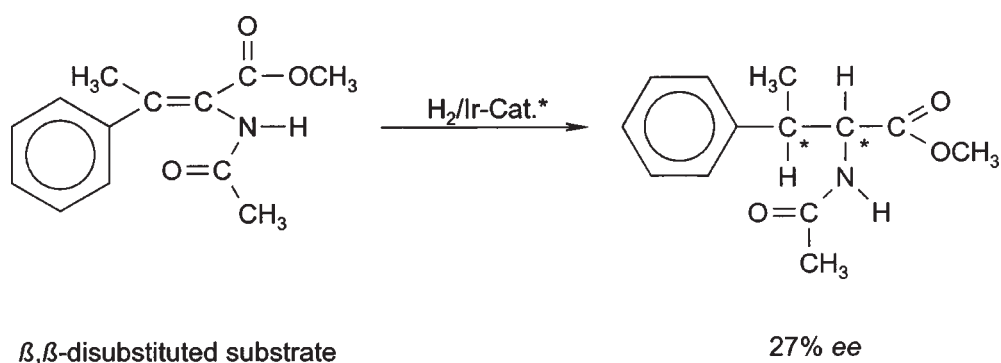
Other atropisomeric ligands are the 6,6'-dimethyl- and 6,6'-dimethoxy-bis(diphenylphosphino)biphenyls (= BIPHEMP and MeO-BIPHEP). They gave high *ee*'s in hydrogenation of *N*-acetyl- and *N*-formyl-(*Z*)-enamides which are morphin precursors (up to 98% *ee* at 100 °C and 60 bar H₂) [78]. Noyori obtained for the same substrate at 30 °C and 100 bar H₂ 97% *ee* with his Ru-BINAP [69].



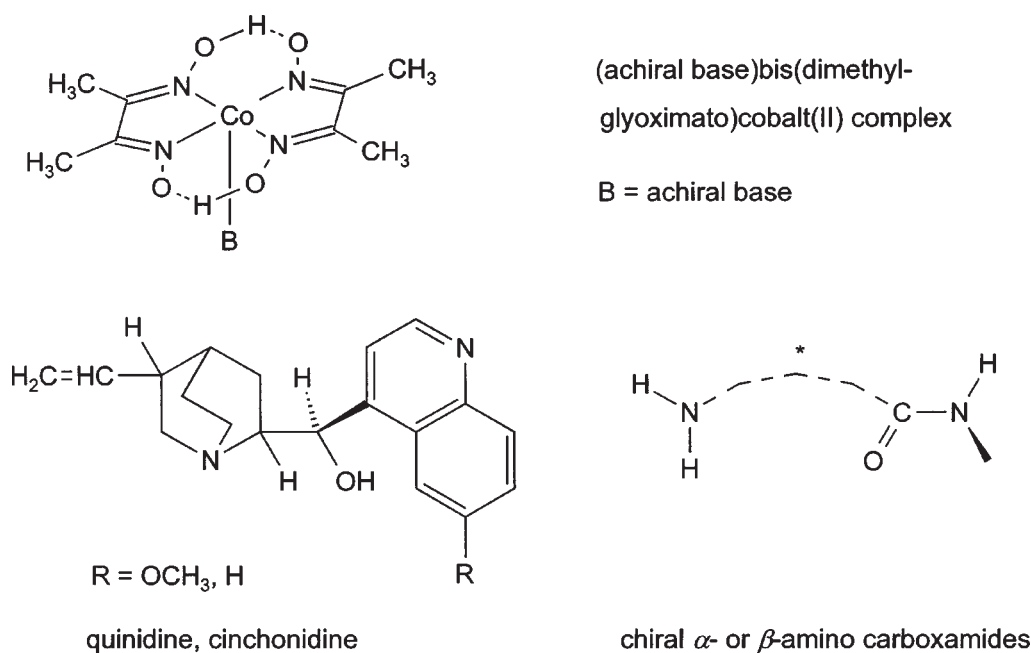
Scheme 2.

Many ligands are applied in Ru-catalysis but usually they are used in enantioselective hydrogenation of alkenes and ketones [79]. Generally spoken Ru-complexes are not as successful in hydrogenating amino acid precursors as Rh-complexes actually are.

Other transition metals aside from rhodium and ruthenium are rarely used in asymmetric hydrogenation of dehydroamino acids, and only few examples of iridium or cobalt complexes are known.



Scheme 3.



Scheme 4.

In the eighties Oro et al. developed a chiral iridium complex containing a COD-, a benzonitrile and a (-)-neomenthyl-diphenylphosphine ligand. This iridium complex showed the ability to hydrogenate sterically demanding substrates like tetrasubstituted alkene moieties in prochiral α,β -didehydro amino acids [80,81]. At 20 °C and 1 bar H₂ it gave in 48 h 27% *ee* in hydrogenating *N*-acetamido- β -methyl- β -phenyl-acrylic acid methyl ester. This result is remarkable in respect of being an early example for the hydrogenation of a sterically demanding β,β -disubstituted substrate.

A totally different catalyst system was used by Ogho et al. Since the beginning of the seventies they developed various bis(dimethylglyoximato)cobalt(II) complexes (= Co(dmgl)₂) containing two additional ligands, one of them chiral. The chiral information was not introduced by bisphosphine ligands as usual but by optically active bases like amino alcohols or amino carboxamides. As chiral amino alcohols quinine, quinidine, cinchonidine and ephedrine derivatives were applied. The amino carboxamides consisted of α - and β -amino carboxamides like propi-

onamides or quinuclidinecarboxamides with strongly varying substituents. Tertiary phosphines (tributyl- or triphenylphosphine) or benzylamine were used as achiral base. It is interesting that the chirality inducing ligand did not contain any phosphorus at all.

At first a Co(dmgl)₂-quinine complex was able to hydrogenate methyl α -acetamido acrylate and α -phenylacetamido acrylate with *o.y.* of 19% and 7%, respectively, at room temperature and atmospheric pressure of H₂ (molar ratio of substrate to cobalt complex about 8) [82,83]. Later on a Co(dmgl)₂ complex with triphenylphosphine as achiral base and 2-acetoxy-3-dimethylamino-3-phenyl-(1-phenylethyl)propionamide (= DHP-*O*-Ac-(*S,S*)*R*) as chiral base reached under similar conditions an *ee*-value of 34% [84]. With *N*-[(*R*)-1-phenylethyl]-2-quinuclidine-carboxamides (= QC-(*S*)*R* or QC-(*R*)*S*) as chiral bases up to 42% *ee* were achieved [85]. It must be mentioned that the chemical yields of those hydrogenation reactions were not very high, ranging from 45 to 65%.

The hydrogenation of hydantoin derivatives was much more successful. Soon 79% *ee* could be reached in hydro-

generating *N,N'*-dimethyl-5-benzylhydantoin with $\text{Co}(\text{dmg})_2$, triphenylphosphine and QC-(*S*)*R* [85,86]. The chemical yield of 93% was now satisfactory.

A catalyst system consisting of $\text{Co}(\text{dmg})_2$, tributylphosphine and (*S*)-*N*-[(*R*)-1-phenylethyl]-2-quinuclidinecarboxamide was applied successfully in the synthesis of the pharmaceutically interesting piperazine alkaloid (2*S*,5*S*)-2,5-dibenzyl-1,4-dimethylpiperazine [87].

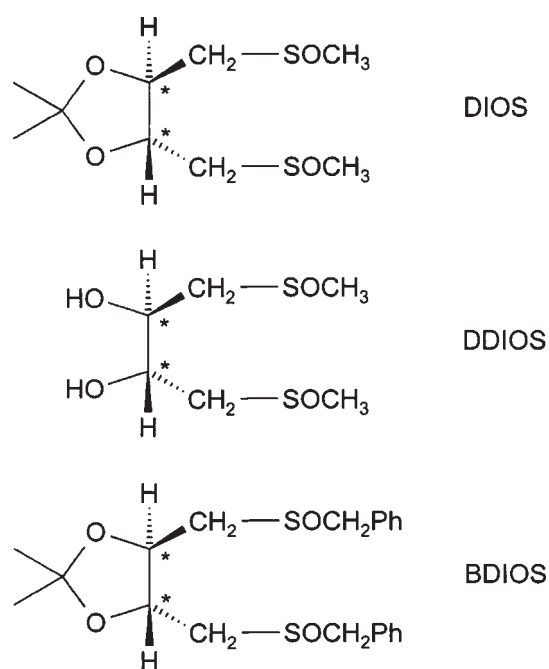
2.3. Water soluble complexes

One of the disadvantages of homogeneous catalysis is the difficulty to separate products from catalysts without destruction of the latter. Often the catalysts cannot be reused due to this difficulty. A possible solution was sought in the two-phase catalysis with an aqueous phase bearing the catalyst and an organic phase bearing the products.

To carry out enantioselective hydrogenations in water as sole solvent is also interesting with regard to comparison of the results with those of enzymatical catalyzed reactions which are usually performed in aqueous phase.

Therefore it is understandable that the introduction of water solubility into transition metal complexes is an area of increasing interest. Water as solvent bears several advantages: easy separation of the catalysts, no toxicity, no harmfulness to environment, applicability in biological processes and last but not least its low price. To achieve water solubility of organic ligands highly polar groups such as amino, carboxylic acid, hydroxy, sulfonate or oligomeric chains containing many hetero atoms must be introduced.

Already in 1977 James et al. synthesized chiral water soluble sulfoxide ligands. Their ligands were patterned after Kagan's DIOP but did not contain bisphosphine moieties. The three new chelating ligands were (2*R*,3*R*)-2,3-*O*-iso-

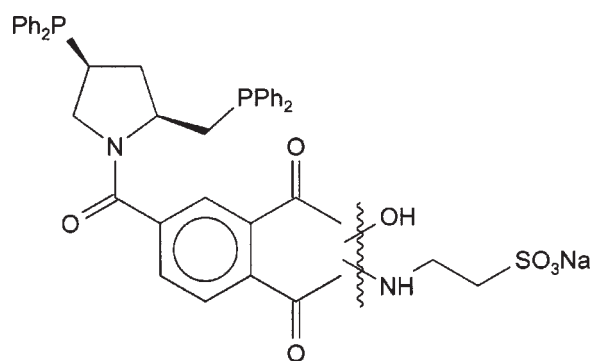


Scheme 5.

propylidene-2,3-dihydroxy-1,4-bis(methyl sulfinyl)butane monohydrate (= DIOS), (2*R*,3*R*)-2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(benzyl sulfinyl)butane monohydrate (= BDIOS) and (2*R*,3*R*)-2,3-dihydroxy-1,4-bis(methyl sulfinyl)butane (= DDIOS).

These ligands showed a good solubility in water but unfortunately the hydrogenation experiments were carried out only in *N,N*-dimethylacetamide (dma). RuCl_2 (DIOS) (DDIOS) was applied to hydrogenate 2-acetamido acrylic acid at 55 °C and 3.2 bar H_2 with dma as solvent but only 7.2% *ee* could be reached [88].

Sinou, Amrani et al. developed in 1985 a water soluble bisphosphine derived from 2-[(diphenylphosphino)methyl]-4-(diphenylphosphino)pyrrolidine (= PPM) which was developed by Achiwa.



water soluble PPM

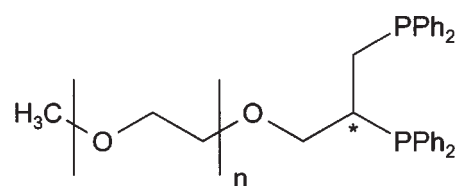
Scheme 6.

The ligand was acylated with trimellitic anhydride acid chloride and treated with sodium hydroxide or sodium taurinate to give the water soluble bisphosphine. A rhodium complex of the ligand reached at best 60% *o.y.* in hydrogenation of α -acetamido cinnamic acid in an aqueous solution of sodium hydrogenphosphate (1 bar H_2 , 25 °C). The enantioselectivity is about 20% lower than in ethanol [89].

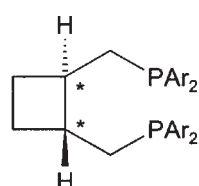
They also used tetrasulphonated cyclobutane-DIOP and sulphonated CHIRAPHOS for hydrogenations in aqueous-organic two-phase solvent systems. 88% *ee* could be achieved with sulphonated CHIRAPHOS in hydrogenating α -acetamido cinnamic acid in water-ethyl acetate at 25 °C and 10 bar H_2 . Sulphonated cyclobutane-DIOP gave lower *ee*'s: only 35% in water-ethyl acetate for α -acetamido cinnamic acid vs. 91% using the non-sulphonated ligand in ethanol [90].

Sinou, Amrani et al. also developed polyoxa-1,2- and 1,4-bisphosphines containing a bis(diphenylphosphinoethyl) and a DIOP moiety, respectively [91].

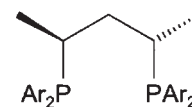
The *ee*'s decreased dramatically when water instead of ethanol was used as solvent. Both ligands yielded in water



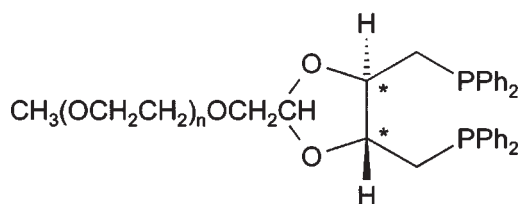
polyoxa-1,2-bisphosphine



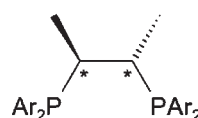
cyclobutane-DIOP



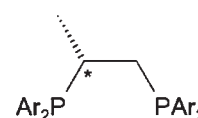
SKEWPHOS



polyoxa-1,4-bisphosphine



CHIRAPHOS



PROPPOS

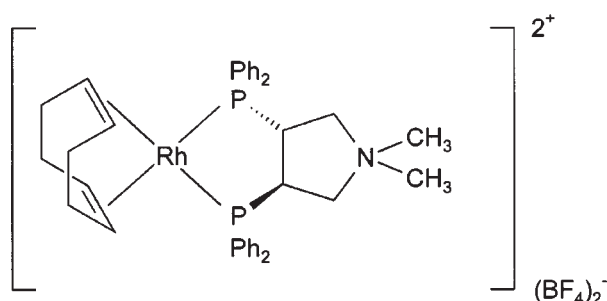
Ar = sulphonated aromate

Scheme 9.

Scheme 7.

at best about 30% *ee* in hydrogenating α -acetamido cinnamic acid (25 °C, 1 bar H₂) [92].

The first ligand that did not show decreasing *ee*'s in water was developed by Nagel et al. in 1986. The above mentioned PYRPHOS ligand was quarternized at its nitrogen atom and thereby made water soluble.



quarternized PYRPHOS

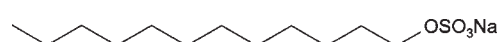
Scheme 8.

The PYRPHOS rhodium complex gave with 90% *ee* the so far highest enantioselectivity obtained in water in hydrogenating the sodium salt of α -acetamido cinnamic acid (22 °C, 50 bar H₂) [47].

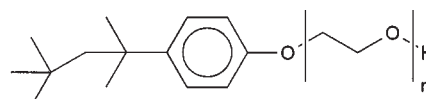
In the late eighties and the beginning nineties Sinou and the Hungarian group of Toth worked together on chiral sulphonated phosphines. Aside the already known sulphonated CHIRAPHOS and cyclobutane-DIOP they also sulphonated SKEWPHOS and PROPPOS with oleum and applied those new water soluble ligands to hydrogenation of olefinic compounds. As before, the tetrasulphonated CHIRAPHOS yielded the highest *ee*'s. The other ligand gave frequently lower *ee*'s with various substrates [93–97].

Toth, Hanson and Davis made their favoured ligands DIOP, SKEWPHOS and CHIRAPHOS water soluble by introducing quarternary amino moieties into the phenyl rings at the phosphorus. They obtained complexes of the kind [Rh(diene)[ligand(*p*-NMe₃)₄][BF₄]₅. Again CHIRAPHOS was the most successful ligand. With α -acetamido cinnamic acid as substrate at 25 °C and 14 bar H₂ it reached in water *ee*-values up to 94% [98–100].

Selke et al. obtained very good results in 1992 when they started to use micelle-forming amphiphiles to support enantioselective hydrogenation in water as solvent. The micelles built micro-heterogeneous systems of colloidal dimensions. They applied rhodium complexes of Achiwa's BPPM, Kagan's DIOP and their own Ph- β -GLUP-OH. As surfactants they chose sodium dodecylsulfate (= SDS) and Triton X-100.



sodium dodecylsulfate (= SDS)



Triton X-100

n = 9-10

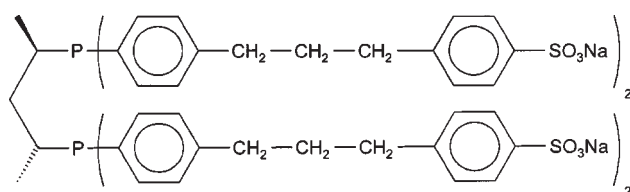
Scheme 10.

With various α -acetamido cinnamates as substrates they reached at 25 °C and 1 bar H₂ *ee*-values of 97–98% [101,102]. The influence of different types of surfactants – nonionic, anionic, cationic and zwitterionic amphiphiles – were examined in detail by Oehme, Paetzold and Grassert in 1993 [103]. They also worked with polymeric surfac-

tants to enforce the formation of micelles under the critical (micelle-forming) concentration of the amphiphiles. These polymeric micelles enclosed the organometallic catalysts but were not covalently bound to them. Nevertheless this is not any more a true homogeneous catalysis because the polymer-surrounded catalyst is not soluble but only swells in water and can be separated by filtration [104]. These polymeric micelles already represent a borderline case to polymer-attached catalysts.

Davis and Wan derived a water soluble ligand from Noyori's BINAP by sulphonating the aromatic substituents at the phosphorus. The rhodium complex of this ligand achieved in water at best 70% *ee* in hydrogenating 2-acetamido acrylic acid at room temperature under 1 bar H₂. As its ruthenium complex it reached under otherwise similar conditions 68% *ee* with 2-acetamido acrylic acid and 87% *ee* with 2-acetamido cinnamic acid as substrate (substrate to catalyst ratio 18 and 75, respectively) [105,106].

Bakos, Hanson et al. synthesized a SKEWPHOS derivative that showed qualities of surface activity. It was not sulphonated directly at the phosphorus substituents but contained a three membered carbon chain between the phenyl rings at the phosphorus and the *para*-sulphonated phenyl rings at the end. These tentacles ought to support the two-phase catalysis.

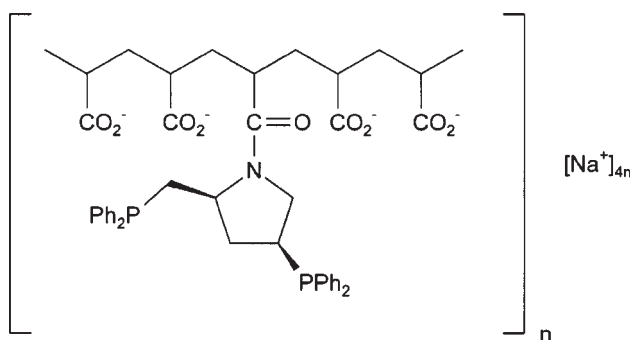


modified SKEWPHOS

Scheme 11.

In a two-phase solvent system consisting of water-ethyl acetate the rhodium complex of this new ligand gave 69% *ee* at 25 °C and 1 bar H₂ [107].

Andersson and Malmstroem acylated the Achiwa-ligand PPM using water soluble polyacrylic acid. In water-



polyacrylic acid-PPM

Scheme 12.

ethyl acetate they obtained 74% *ee* hydrogenating (*Z*)- α -acetamido cinnamic acid [108].

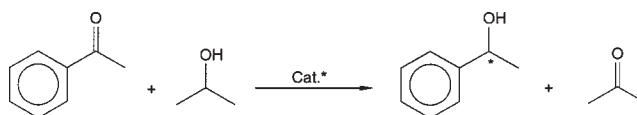
In general hydrogenations in water as a solvent frequently lead to lower enantioselectivities than in organic solvents. This can be explained by assuming that water is not only a solvent but is engaged in the coordination sphere of the metal atom [109].

2.4. Transfer hydrogenation

The use of elementary hydrogen implies a special apparatus for hydrogenation experiments. Herein lies an undeniable advantage of a non-gaseous hydrogen source. In transfer hydrogenation reactions most of the reagents employed as hydrogen donors are organic molecules such as primary or secondary alcohols and formic acid and its salts [110,111].

Transfer hydrogenations are very successfully used for enantioselective reduction of prochiral ketones and imines [112–116].

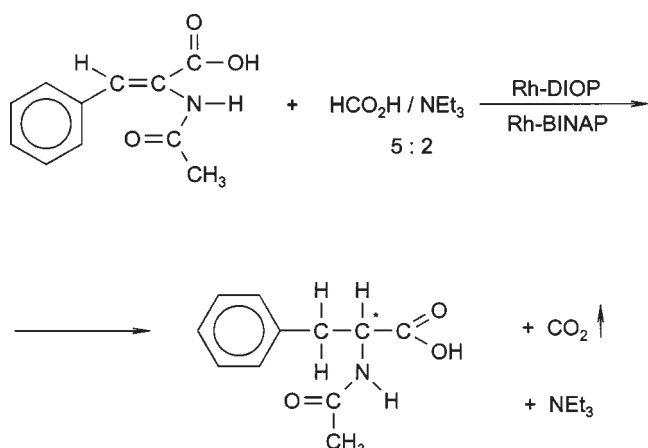
Only few examples are known where unsaturated carboxylic acids are hydrogenated via transfer hydrogenation. Hereby itaconic acid is the most successfully hydrogenated substrate. Dehydroamino acids are seldom submitted to transfer hydrogenation therefore only few examples can be quoted here.



transfer hydrogenation of acetophenone

Scheme 13.

Brunner et al. were the first group to use formic acid as hydrogen source for catalytic transfer hydrogenation of some dehydroamino acids. They used rhodium complexes of the bisphosphines NORPHOS, PROPHOS, BPPFA and DIOP as catalysts. Addition of sodium formate led to the increase of the enantioselectivity. The highest *ee* was achieved with (*Z*)- α -acetamido cinnamic acid as substrate and NORPHOS as ligand at 120 °C. In most of the other cases the *ee*-values are much lower [117]. Later on the catalytic reaction was developed further. With DIOP and BPPM as ligands and a mixture of formic acid and triethylamine (5:1) as hydrogen source (*Z*)- α -acetamido cinnamic acid could be hydrogenated with 50% and 70% *ee*, respectively, under very mild conditions. This was the first example in asymmetric transfer hydrogenation with enantioselectivities as high or partly even higher than the corresponding hydrogenations with elementary hydrogen [118,119]. In 1993 Leitner, Brown and Brunner also examined mechanistic aspects of rhodium-catalyzed transfer hydrogenation of α,β -unsaturated carboxylic acids using this hydrogen source [120].

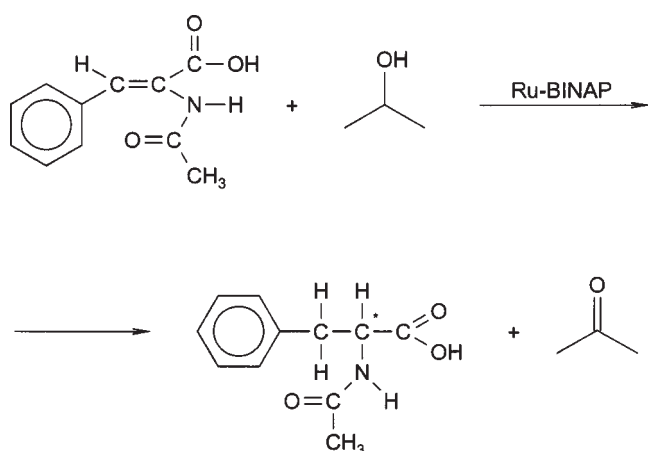


transfer hydrogenation of acetamido cinnamic acid
with the azeotrope formed by formic acid / triethyl amine

Scheme 14.

Ruthenium complexes of DIOP, BPPM, BINAP and other ligands were also applied to enantioselective transfer hydrogenation. With Ru-BINAP very high *ee*'s were achieved in hydrogenation of itaconic acid, but with acetamido cinnamic and acetamido acrylic acid the *ee*'s are lower with 56% and 40%, respectively [121].

Saburi et al. also applied Ru-BINAP to hydrogenate α -acetamido cinnamic acid but they used alcohols as a hydrogen source. An *ee* of 96% could be reached with 2-propanol, but unfortunately the chemical yield was only 57% (reaction temperature 50 °C). 100% chemical yield could be achieved at refluxing temperature of THF-alcohol mixture (alcohols: 2-propanol, ethanol) but the *ee*'s decreased to 67%. Nevertheless the reported enantioselectivities are the highest we found for dehydroamino acids as substrates in transfer hydrogenation [122].



transfer hydrogenation of acetamido cinnamic acid
with 2-propanol as hydrogen source

Scheme 15.

The work of Sinou et al. (1991) provides an example for a combination of transfer hydrogenation and catalysis in aqueous phase. They report about transfer hydrogenation of unsaturated substrates with formates in presence of water using a sulphonated cyclobutane-DIOP derivative. An *ee*-value of 43% was obtained in the reduction of α -acetamido cinnamic acid with ammonium formate as hydrogen source at 50 °C in water as solvent [123]. This value surpassed the *ee* achieved with molecular hydrogen in water or a two-phase solvent system using the same catalyst and substrate [94].

3. Heterogeneous catalytic hydrogenation

Heterogeneous catalysis bears certain advantages with regard to separation of products from catalyst and reuse of the latter. In comparison to homogeneous catalysis the field of heterogeneous catalysis is relatively old. Some of the first enantioselective hydrogenations were carried out on surface modified palladium.

In the late sixties Beamer et al. worked on hydrogenation of α -acetamido cinnamic acid using modified palladium. The chiral information was introduced by poly-*S*-leucine, poly-*S*-valine, poly- γ -benzyl-*S*-glutamate and poly- β -*S*-aspartate which were applied on the palladium surface. The optical yields were with 5–6% very low [3–5]. Harada used modified cellulose-palladium catalysts but his optical purities were only about 0.15% [124].

The early heterogeneous hydrogenations reached only low enantioselectivities and when in the seventies the first successful homogeneous hydrogenation catalysts were developed the heterogeneous pathway was neglected for the following years. Many attempts focussed on polymer fixation of homogeneous catalysts, however.

In the mid-seventies Stille et al. developed polymer-attached DIOP catalysts. They synthesized new polymers which swelled in the polar solvents that were necessary to dissolve the substrates. 2-*p*-styryl-4,5-bis(tosyloxymethyl)-1,4-dioxolane was copolymerized (radically) with hydroxyethyl methacrylate and then treated with sodium diphenylphosphine to give the bisphosphine ligand. Since hydroxyethyl methacrylate contains ethylene glycol dimethacrylate, a cross-linked copolymer was obtained. Hydrogenation of α -acetamido cinnamic acid in ethanol-benzene gave an optical yield of 86% at 25 °C and 1–2.5 bar H₂. This is a slightly higher result than that of the homogeneous case under otherwise similar conditions [125,126]. The polymer supported catalyst could be easily separated from the product by filtration.

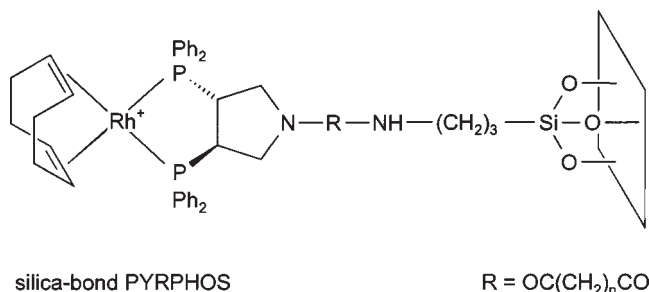
Later on they introduced optically active alcohol sites into the polymer by copolymerization of methyl vinyl ketone and reducing it to a chiral alcohol by enantioselective hydrosilylation. They suggested a participation of the polymer-bound alcohol. Those systems yielded about 70% *ee* in hydrogenating α -acetamido acrylic acid (25 °C, 1 bar H₂) [127,128]. Even 77% *ee* were achieved by the reduc-

tion of α -acetamido cinnamic acid with racemic alcohol sites in the polymer support [129].

Stille et al. also attached cyclohexylmethylphenylphosphine and Achiwa's PPM ligand to their cross-linked polymer matrix. The first system provided complete conversion of acylamino acrylic acid to *N*-acetylalanine, but in only 13% *ee* [130]. The polymer-bound PPM ligand was more successful. It reached 90% *o.y.* in hydrogenating α -acetamido cinnamic acid at 20 °C and 55 bar H₂ [131].

In 1985 Kinting et al. developed silica-supported rhodium complexes for asymmetric hydrogenation. They prepared ω -triethoxysilylalkyldimethylphosphines differing in spacer length and anchored them onto macroporous silica. 80% was the highest optical yield achieved with a spacer length of three carbon atoms in hydrogenation of α -acetamido cinnamic acid at 25 °C and 1 bar H₂. Unfortunately a high level of catalyst leaching could not be avoided during the recycling process [132].

Nagel and Kinzel achieved outstanding results when they attached the highly efficient PYRPHOS ligand to silica. 1-amino-3-(triethoxysilyl)propane was coupled to a dicarboxylic acid derivative; the resulting monoamide could be bound to the nitrogen atom of the PYRPHOS ligand backbone using the methods of peptide synthesis. α -acetamido methylcinnamate was hydrogenated with 100% *ee* at room temperature under 50 bar H₂-pressure (molar ratio substrate/catalyst = 2200) [133].

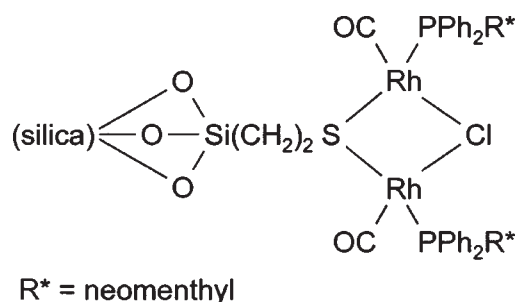


Scheme 16.

Selke published in 1986 his work about immobilization of cationic Rh-complexes of Ph- β -GLUP on cation exchangers. Commercially available exchangers such as sulphonated styrene-divinylbenzene (2%) copolymer were used. He achieved generally high *ee*'s over 90% hydrogenating various α -acetamido cinnamic acids under mild conditions. It was surprising that in all cases the enantioselectivities of the heterogenized catalyst were higher than those of the homogeneously applied catalyst. Recycling of the catalyst was possible and leaching effects were low. Nevertheless a decreasing activity of the catalyst was observed [134]. Some years later Selke and Capka attached the Ph- β -GLUP ligand to silica-based cation exchangers. Various commercial silicas were functionalized with spacer-carrying arylsulphonic acid (SiO₂)–O–Si(CH₂)₃–O–C₆H₄–SO₃H. The immobilized cationic Rh-complex of Ph- β -GLUP again yielded high enantioselectivities of about 95%

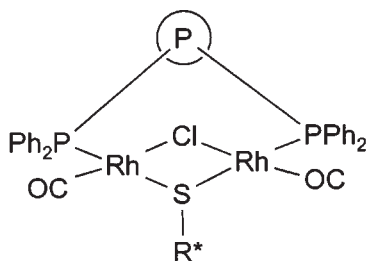
ee with α -acetamido methylcinnamate as substrate. The catalyst activity could be increased five times by preloading the exchangers with alkali or ammonium ions. Inorganic supports can be used in polar and nonpolar organic solvents due to their inability to collapse but the ionic binding of the catalyst is not as strong as a covalent binding on an organic support and therefore there is always the danger of catalyst leaching [135].

Eisen and Blum developed new silica-bound μ -thiolato- μ -chlorodicarbonylbis(neomenthyl)diphenylphosphine)dirhodium complexes.



Scheme 17.

Hydrogenating α -acetamido methylcinnamate to (*R*)-(-)-*N*-acetylphenylalanine methyl ester in presence of the silica-bound catalyst they reached 95% *ee* using a high pressure of 70 bar and 120 °C but the chemical yield was only 5.8%. Surprisingly, decreasing the pressure to 7 bar the chemical yield could be increased to 69% but then the enantioselectivity falls to 17% *ee*. They assumed that at high pressures the active site of the catalyst was saturated with hydrogen and therefore the approach of the substrate was restricted and more selective. On the other hand there were not enough hydrogen molecules activated by the chiral catalyst at too low a pressure resulting in an optimum at 7 bar [136,137]. Later on Eisen and Blum also bound different dirhodium complexes on divinylbenzene-crosslinked polystyrene resins but the optical as well as the chemical yields were not very high [138].



R* = neomenthyl, pinyll

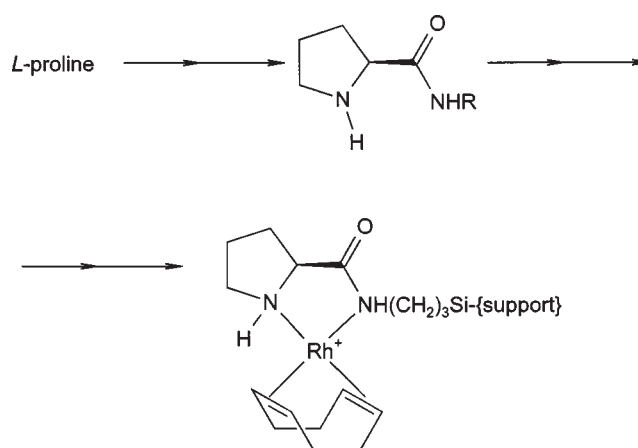
(P) = divinylbenzene-crosslinked polystyrene resin

Scheme 18.

Toth, Hanson and Davis immobilized water soluble amine-functionalized SKEWPHOS and CHIRAPHOS derivatives on strongly acidic cation exchange resins (Nafion-H and Amberlyst-H). Various α -acetamido cinnamic acid derivatives were hydrogenated under 14 bar H_2 and at 20 °C. On Nafion-H the *ee*-values were only little lower or similar in comparison to homogeneous catalysis but on Amberlyst-H the enantioselectivities were quite low. In general CHIRAPHOS yielded the higher *ee*'s. The reaction times could be improved immensely by using a new immobilization technique were the Nafion-H beads were smaller and therefore more active [139,140].

Brunner et al. immobilized the ligands DIOP and NORPHOS on a multitude of supports. $BaSO_4$, cellulose, silica gel, alumina, AgCl and charcoal were impregnated with rhodium complexes of DIOP and NORPHOS. They also applied the cationic complexes to the strongly acidic ion exchangers DOWEX HCR-S and DOWEX MSC-1 and to the weakly acidic ion exchangers SERDOLIT CW-18 and SERVACEL CM-32. All those systems were used for hydrogenation of α -acetamido cinnamic acid in water/ethanol as solvent under comparable conditions. On $BaSO_4$, cellulose and alumina DIOP gave *ee*'s from 53 to 60%. Only on silica gel the *ee* was 69%. NORPHOS yielded on $BaSO_4$, cellulose and silica gel *ee*-values from 56–68% on the first run. The enantioselectivities increased to 75% *ee* on further runs probably due to reduction of the catalyst to the already mentioned RENORPHOS. On AgCl both ligands achieved only relatively low *ee*'s. On charcoal they reached up to 60% *ee*. The ion exchanger supported catalysts showed large differences in their hydrogenation abilities depending strongly on the solvent. Under optimized conditions *ee*-values up to 87% were achieved in methanol but esterification of the free acid with solvent molecules takes place [141].

In the beginning of the nineties Corma, Iglesias, del Pino and Sanchez obtained very good results using zeolites as heterogeneous supports. A *N*-based chiral ligand derived from natural L-proline was anchored on silica and on a modified USY zeolite which contained supermicropores and mesopores.

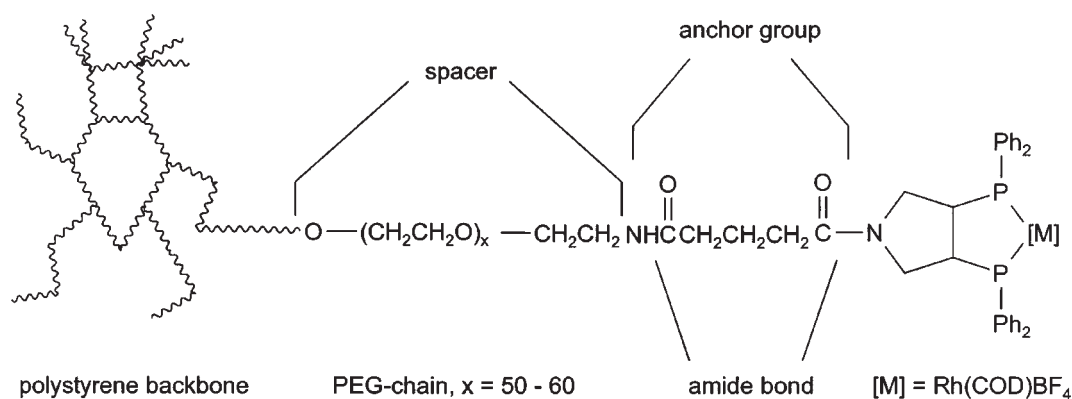


Scheme 19.

Those systems yielded excellent enantioselectivities of 92% and 99% *ee*, respectively, with α -benzamido ethyl cinnamate as substrate and silica and USY zeolite as supports (65 °C and 5 bar H_2). Generally the *ee*-values were higher when the zeolite was used as a support. Remarkably the supported ligand yielded higher *ee*'s than the homogeneously applied actually did [142,143].

In 1993 Fritz and Dengler synthesized a chiral support to which they attached an achiral rhodium complex. Their idea was to avoid the difficult and expensive synthesis of chiral ligands for rhodium catalysis and therefore to introduce the chiral information over an optically active polyepichlorohydrine which shows a helical topology. In THF α -acetamido cinnamic acid was hydrogenated with 30% chemical yield and an *ee* of 35% (catalyst/substrate = 100) [144].

Recently, Nagel and Leipold introduced the new concept of interphases to asymmetric hydrogenation of amino acid precursors. Interphases are defined as penetration of a stationary phase and a mobile phase in molecular dimensions without building a homogeneous mixture. The widely applicable PYRPHOS ligand was bound to a polymer matrix (TentaGel from Rapp). TentaGel consists of cross-linked polystyrene containing polyethyleneglycol arms which are functionalized with amino groups at their ends. The amino



Scheme 20.

groups of the TentaGel and those of the PYRPHOS ligand were connected over dicarboxylic acids as anchoring groups using the methods of peptide coupling. To reach high mobility of the catalyst it is necessary to swell the polymer. The best swelling was obtained in halogenated solvents like CH_2Cl_2 or CHCl_3 or dipolar aprotic solvents (DMF, acetonitrile) but these solvents are not optimal for catalytic hydrogenation. The solvation of the metal complex is not satisfactory in alcohols which are the best solvents with regard to hydrogenations. However, mixtures of toluene and methanol showed to be a suitable solution. In those solvent systems *ee*-values of 97% could be reached hydrogenating α -acetamido cinnamic acid at 8 bar H_2 and 25 °C [145].

4. Theory of enantioselective catalytic hydrogenation of dehydroamino acids with soluble rhodium complexes

4.1. Mechanism

The mechanisms of enantioselective hydrogenation are very complicated. Many aspects and certain elementary steps are well investigated but being isolated from each other they often do not help to provide a general mechanism. Nevertheless plausible ideas of catalytic cycles exist.

Rhodium catalysts are much more examined than ruthenium catalysts and five-ring chelates more than six- or seven-membered. For this reason we will discuss mechanistic aspects mostly for rhodium complexes.

Especially DIPAMP and CHIRAPHOS rhodium complexes were examined in detail by Halpern and Landis in the mid-eighties [146,147]. They developed and nearly proved a whole catalytic cycle. Halpern and Landis described the coordination of substrate to the activated complex and its further reaction in two different cycles: the “Minor Manifold” and the “Major Manifold” which are diastereomeric to each other.

The catalyst precursors are turned into bis-solvent complexes which are actually the catalytic active species. The substrate displaces the solvent molecules and chelates the rhodium side-on with its double bond and with one electron pair of the oxygen of its amido group. The substrate coordination is reversible. Two diastereomeric substrate complexes exist of which one is predominant (“major” substrate complex). The more stable “major” substrate complex does not lead to the main product but the less stable “minor” diastereomer because the latter reacts much faster with hydrogen to a suggested dihydrido complex. The oxidative addition of hydrogen is believed to be the first irreversible step in the catalytic cycle and therefore dictates the enantioselection. The octahedral geometry of the dihydrido complex requires completely different structural properties of the ligands compared to the square planar geometry of the substrate complex. Accordingly not the preferred geometry of the substrate complex is crucial

but the required geometry of the dihydrido complex. Unfortunately the dihydrido complex could not be directly observed by conventional analytic methods in contrast to the other intermediates. Recently, Bargon and Eisenberg reported on new possibilities of detecting the dihydride step using *para*-hydrogen to enhance NMR sensitivity (ParaHydrogen Induced Polarization = PHIP). Certain metal dihydrido complexes could be proved and there is a hope to solve the problem soon [148–154].

The dihydrido complex immediately reacts to the hydrido alkyl complex which at last eliminates the product and rebuilds the bis-solvent complex.

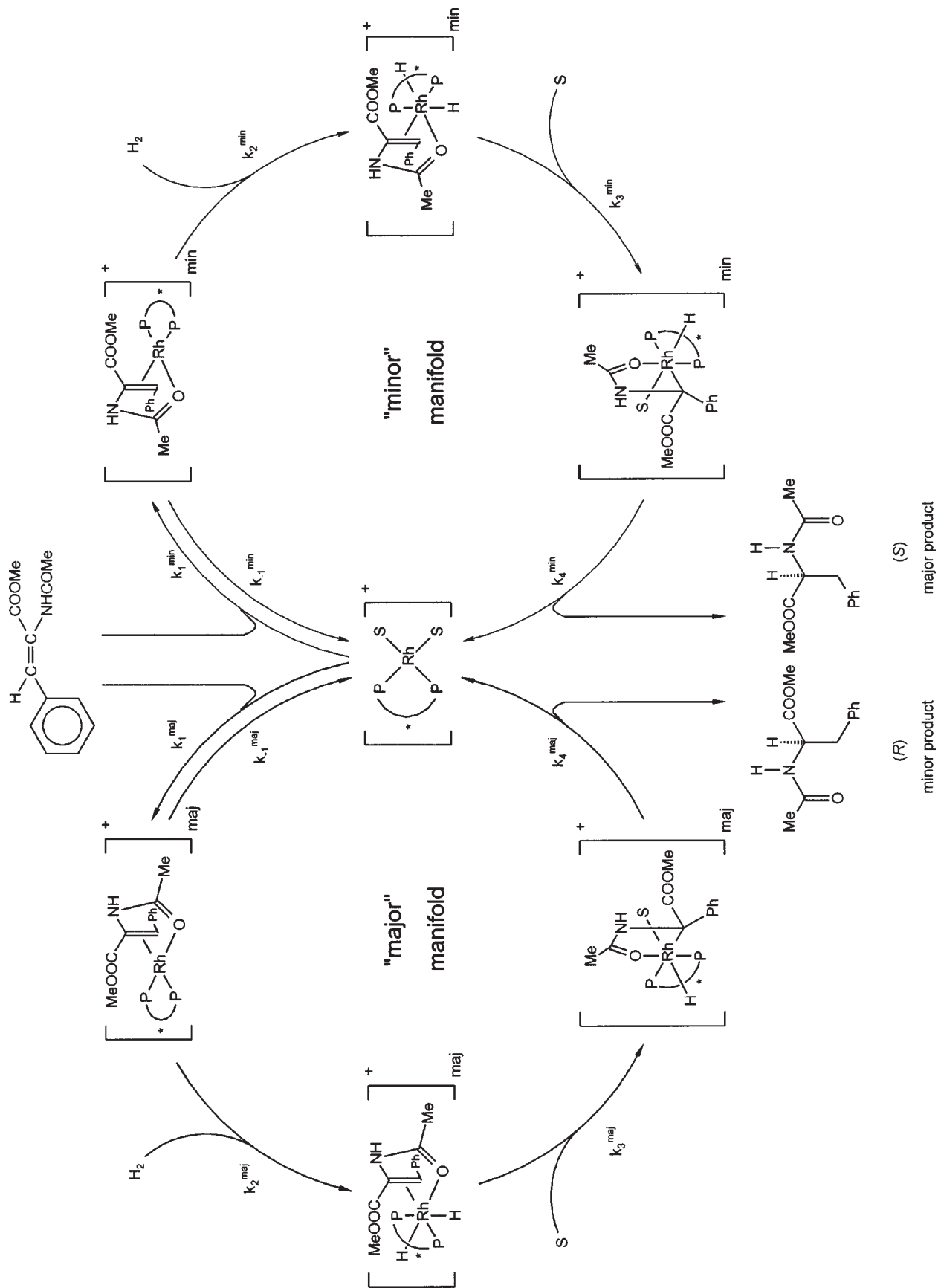
The kinetic model detailed by Halpern and Landis is able to describe the dependence of the enantioselectivity on the reaction temperature and the hydrogen pressure. Two extreme cases are easy to understand. In the case of low hydrogen pressure the hydrogenation step is slow compared to the binding and dissociation of the substrate. An undisturbed equilibrium is established between the major and the minor substrate complex partly without dissociation and recoordination [155]. The minor substrate complex reacts much faster with hydrogen yielding the predominant product enantiomer. In the case of high hydrogen pressure only the rate constants for the formation of the substrate complexes are of interest. Because the rate constant for the coordination of the substrate leading to the minor substrate complex is somewhat greater than the rate constant associated with the building of the predominant (major) substrate complex, the predominant enantiomer in the hydrogenated product is the same as in the low pressure case but the *ee* is much lower. Obviously in the pressure range in between there is a strong dependence of the enantioselectivity on the hydrogen pressure. The rate of the substrate coordination step is more temperature dependent than the rate of the hydrogen activation. That means, that an increase in temperature gives an increase in enantioselection in the intermediate pressure range. Or increased temperatures can be used to offset the detrimental influence of increased hydrogen pressure on the enantioselection to give higher overall rates.

The catalytic cycle of Halpern and Landis is proved only for DIPAMP and CHIRAPHOS ligands but it seems plausible that the elementary reaction steps are transferable to other systems whereas the kinetics sometimes are differing.

The single reaction steps shall be discussed in the following sections where also the occurring differences shall be considered.

4.1.1. Catalyst precursors and building of the solvent complex

Catalytic hydrogenations can be carried out in two different modes: with a definite previously prepared catalyst precursor or with an *in situ* prepared catalyst. Though there is no difference in principle between these two modes *in situ* hydrogenations demand a slightly different considera-



Scheme 21.

The most common catalyst precursors are cyclooctadiene (= COD) or norbornadiene (= NBD) complexes of rhodium(I) which also contain the chelating chiral ligand and a non-coordinating anion like BF_4^- or SbF_6^- . COD complexes are more stable than NBD complexes.

Starting the hydrogenation at first the diene component is hydrogenated to cyclooctene or norbornene which both have a lower affinity to rhodium than the educts and can be replaced by two coordinating solvent molecules. Bis-solvent complexes are very labile and represent an active catalyst intermediate. They react immediately to the two diastereomeric substrate complexes (only α -acetamido acrylates shall be considered as substrates). On this occasion it becomes important that the substrate complexes are more stable than the complexes of cyclooctene and norbornene so that the substrate cannot be displaced by the olefins resulting from hydrogenation of the bisolefins of the precursors.

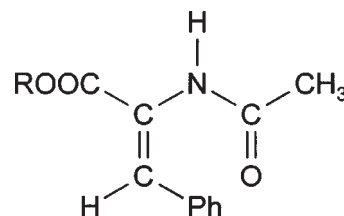
The hydrogenation of the coordinated bisolefin can lead to an induction period. With regard to five-ring chelate ligands this does not include any problems because complexes of those ligands hydrogenate α -acetamido acrylates quite slowly so that the bisolefins are completely hydrogenated before a considerable amount of substrate (which is submitted in excess) has a chance to react. But catalysts containing seven-membered chelate-rings show much faster hydrogenation rates. The possibility exists that a great quantity of substrate is already hydrogenated by the first free active catalyst molecules just before all of the bisolefin is split off the remaining rhodium complexes. Then the determined reaction rates (which are always over-all rates) will be too low because not every rhodium complex gets a chance to hydrogenate the substrate [156,157].

In situ catalysts are often prepared from a dimeric rhodium chloro complex – which also contains COD or NBD – and the bisphosphine ligand. Thereby usually more ligand than rhodium is applied to avoid catalytic active but achiral rhodium species which are spoiling the *ee*'s. This results in a small contamination of the catalyst with a complex containing two bisphosphine ligands. This contamination is considered catalytically inactive. In many cases a consequence of *in situ* preparation is the presence of chloride anions which possibly are able to coordinate to rhodium thereby influencing the catalysis. In methanol as solvent chloride seems to be non-coordinating. At least PYRPHOS catalysts show under *in situ* conditions no differing kinetics and enantioselectivity. Solvents in which chloride anions are less solvated may show a dependence of the catalysis on the chloride content because chloride now may interact with the rhodium complexes.

To build the actually active rhodium species two solvent molecules shall coordinate to the complex. This implies that the solvent has the ability of coordination. The mechanism proposed by Halpern cannot operate in totally non-coordinating solvents, but for the substrates discussed here these solvents are of little use.

4.1.2. Coordination of substrate

As substrates only dehydroamino acids and their derivatives shall be examined here. These α -acetamido acrylates are ideal substrates for asymmetric catalytic hydrogenations. The most common substrates surely are (*Z*)- α -acetamido cinnamates because of the ease of their preparation.



(*Z*)- α -acetamido cinnamates

Scheme 22.

For a catalyst containing a common bis(diphenylphosphino) ligand the ideal substrate has to fulfill special structural requirements. The double bond which shall be hydrogenated must lie in the right distance to another coordinating group (here the oxygen of the amido group). Thus the substrate is able to build a stable $5\frac{1}{2}$ -membered chelate ring with the metal. This stability often leads to approximate zero order in substrate during catalysis. The effect is more pronounced for catalysts containing 1,2-bisphosphanes, which give a five-membered chelate ring, than for ligands giving six- or seven-membered rings, which are sterically more demanding. PYRPHOS complexes show zero order in substrate during hydrogenation; its derivatives with two or three methoxy substituents in one phenyl ring at each phosphorus are sterically crowded and therefore no longer show zero order in substrate [158].

In the substrate olefin a H-atom *trans* to the N-atom usually is required. Consequently only (*Z*)-isomers are good substrates. (*E*)-isomers and β,β -disubstituted substrates are sterically hindered and always caused problems when conventional ligands with two aryl substituents at the phosphorus were applied [159]. The aryl substituents need too much space to tolerate any bulky group in (*E*)- β -position. There are, however, ligands which easily can hydrogenate (*E*)-isomers and β,β -disubstituted substrates like Burk's phospholane ligands. The substrate complexes of these ligands were found to be similar to those formulated by Halpern [160], but the phospholanes show different steric properties. Nevertheless these ligands are believed to operate under the same mechanism as CHIRAPHOS and DIPAMP.

The diastereomeric substrate complexes are quite stable and proved by NMR methods. Iridium complexes are often used as model substances because iridium hydrogenates the applied substrates so slowly that the substrate complexes can be examined rather in detail. Brown et al. published manifold work about the binding modes of various substrates to rhodium bisphosphines complexes [155,161–169].

There also exist crystal structures of substrate complexes of rhodium and iridium bisphosphanes which confirm the supposed structure [170–172].

4.1.3. Oxidative addition of hydrogen

The oxidative addition of hydrogen to the substrate complex is thought to be the first irreversible step in the catalytic cycle and therefore all steps afterwards are irrelevant for the enantioselection. Hydrogen is transferred in pairs, both atoms stemming from the same dihydrogen molecule [148]. The hydrogen molecule is cleaved into its atoms during oxidative addition thereby building the assumed dihydride. The octahedral dihydride was not yet proved by NMR, IR, X-ray crystal structure or any other analytic method. Only the above mentioned PHIP phenomenon seems to bear a possibility to trace the dihydride [149]. Nevertheless there are certain model substances like dihydrogen complexes of iron or molybdenum that give an idea of the possible geometry of the rhodium dihydrogen complex, which must be passed on the way to the assumed dihydrido complex. Somewhere between the dihydrogen and the dihydrido complex the transition state of the oxidative addition is passed. It is believed that in many cases this transition state is passed irreversibly. Then the enantioselection is determined here.

When dihydrogen is added to the complex, electrons are pushed into the anti-binding orbital of the H₂-molecule thereby cleaving the H–H-bond. The more electron-rich the central metal atom is the easier it can push electrons into the H₂-orbital. α -acetamido acrylates as substrates are able to give the rhodium a certain basicity via the coordinating electron pair of the amido group. Another source of basicity are the chelating phosphane ligands. Burk's phospholanes are especially electron-rich and consequently excellent and widely applicable ligands. Conventional tetra-aryl bisphosphanes are in contrast electron-poor. The metal ion in the catalyst has an influence too. It seems, that for rhodium more basic ligands are optimal. For ruthenium as metal BINAP, a weakly basic ligand containing only P-aryl bonds, works exceptionally good. There is an influence of the chelate ring size on the oxidative addition of hydrogen, too. Seven membered chelate rings react much faster than five membered rings. If the oxidative addition becomes faster than the following reductive elimination and is reversible the above mentioned transition state does not determine the *ee* anymore (cf. below).

4.1.4. The σ -alkyl complex

Generally the rearrangement of the dihydride to the σ -alkyl complex happens very rapidly. For CHIRAPHOS and DIPAMP as ligands the subsequent reductive elimination takes place also immediately at room temperature. However, the activation entropy for the reductive elimination is negative whereas the activation entropy of the oxidative addition of hydrogen is positive. This leads to a build-up of the σ -alkyl complex at low temperature. Halpern proved this intermediate (for DIPAMP as ligand) with ¹H-NMR at

–30 °C. The alkyl ligand occupies a *cis* position with regard to the remaining H-atom. The sixth coordination site at the Rh(III) is occupied by a solvent molecule. In the well documented case of DIPAMP as ligand only one diastereomer of the σ -alkyl complex can be found. The two diastereomers may have different reactivity in the reductive elimination, but this different reactivity does not influence the enantioselectivity, because the foregoing step (oxidative addition of hydrogen) is irreversible in this case. This may be different for ruthenium complexes. In this case a three dentate coordination of the substrate and the reversibility of the oxidative addition of hydrogen was demonstrated [173].

The reductive elimination of the products is in most cases irreversible. Most of the free reaction enthalpy of the catalytic hydrogenation is liberated at this reaction step (The reverse reaction, the catalytic activation of an alkane, is a formidable task!) The reductive elimination is assisted by two solvent molecules. They complete the valence shell of the rhodium atom after the elimination of the product molecule and are then readily replaced by an olefin molecule to close the catalytic cycle.

For the hydrogenation of α -acetamido cinnamic acid or its methyl ester with 3,4-bis(diphenylphosphino)pyrrolidine (PYRPHOS) as ligand in a rhodium based catalyst the solvent has to show coordinating qualities. Many different solvents can be used. Most often alcohols, especially methanol, are used but acetone or THF works as well. A somewhat slower hydrogenation takes place in acetonitrile, dimethylformamide or in toluene. The coordinating ability of the solvent influences the stability of the bis-solvent complex and therefore the ease of the reductive elimination of the products but also the coordination of the substrate. Obviously a balance has to be met for optimal performance of the catalyst depending on the ligand and the substrate used.

The basicity and the sterical demand of a ligand has also to be balanced. Small and basic ligands promote the oxidative addition of hydrogen but slow down the reductive elimination of the products. Seemingly small differences can have drastic consequences. The rate of the catalytic hydrogenation of acetamido cinnamic acid with a rhodium complex of 3,4-bis(diphenylphosphino)pyrrolidine depends linearly on the hydrogen pressure up to 100 bar. Consequently the oxidative addition of hydrogen is rate determining for the whole catalytic cycle up to 100 bar hydrogen pressure. This is also true if the two equatorial phenyl groups are replaced by methyl groups, the overall rate being somewhat higher. However, if the equatorial phenyl groups are retained and the axial groups are replaced by methyl groups, the picture is different. At low hydrogen pressure (up to 2 bar) the rate is improved. At hydrogen pressures above 2 bar the rate is independent from the hydrogen pressure, because the rate is now determined by the reductive elimination of the product, as expected for a small and basic ligand [48].

4.1.5. Origin of enantioselectivity

There is no universal molecular picture available to explain all aspects of the origin of enantioselection. Molecular modelling today does not improve the situation very much. Different populations of rotational conformations in various parts of the catalyst molecule all contribute to the enantioselection. Attempts have been made to collect data and derive empirical rules. These rules generally have a very limited range of applicability. In the remaining part of the article we will try to recollect and comment these rules.

The ligand of choice contains phosphorus as donating group. Other elements are seldom employed. Chelating bisphosphines are superior to non-chelating ligands. This holds for any metal in the catalyst and is explained by an improved stereochemical rigidity of the catalyst complex. The chelating ring size should be five or seven membered, six membered rings adopt too many conformations providing low levels of chiral discrimination.

Most bisphosphines contain two aryl groups at each phosphorus atom. These aryl groups form a chiral array around the metal atom. The shape of this array is determined by the rigidity of the chelate ring. Five membered rings are inherently relatively rigid. The remaining flexibility of these rings can be directly seen in cases where X-ray structures of complexes contain more than one molecule in the asymmetric unit (CY-CPHOS [34], {1-(*tert*-butoxycarbonyl)-3,4-bis[(2-methoxyphenyl)phenylphosphino]pyrrolidine-PP'}[1,5-cyclooctadiene]rhodiumtetrafluoroborate [174–176]). The chelating ring adopts preferentially a lambda or delta conformation, the envelope conformation is present to a minor extent too. In an achiral ligand lambda and delta conformation are of equal importance. Suitable substitution of the ligand leads to the preference of one form. An additional ring in the ligand backbone which is fused with the chelate ring is helpful (PYRPHOS, NORPHOS, bis(diphenylphosphino)cyclopentane [177]) but not necessary as, e.g., the CHIRAPHOS ligand is showing.

The less rigid seven membered chelate rings always need fused rings to improve stereochemical rigidity. One ring fused to the chelate ring is not enough to ensure very high enantioselectivities as show for example DIOP. These ligands give very active catalysts with moderate to high enantioselectivity which depends strongly on reaction conditions as pressure and temperature and solvent. In water as a solvent most of catalytic hydrogenations with these ligands show lower enantioselectivities than in alcohols. The reason could be the high surface tension of water which compels the complexes to deform their conformation to take up a smaller volume. To lower water's surface tension various attempts were undertaken to hydrogenate in presence of amphiphiles (see Selke et al. in the chapter "Water Soluble Complexes").

Two rings fused to the chelate ring as in BINAP impose a very rigid structure on chelation and lead to a very enantioselective catalyst. Another point in favour of seven membered chelate rings is a bite angle greater than 90°

which gives the ligand a stronger influence on the substrate during catalysis.

As mentioned above most chiral bisphosphines give a chiral array of four aryl groups upon coordination to a metal atom. In the beginning of enantioselective hydrogenation it was believed that an edge-face arrangement of these aryl groups is related to the enantioselection of these catalysts. This arrangement is not present in all X-ray structures of catalysts and furthermore the aryl groups are able to rotate easily. *o*-substituents on the aryl groups influence the edge-face arrangement and can improve the enantioselectivity of the catalysts [174–176].

Another feature is an axial-equatorial displacement of the aryl groups in the catalyst. This arrangement can qualitatively be correlated with enantioselection. The same handedness of the phenyl group array always gives the same sense of enantioselection during hydrogenation [178,179]. We can define an angle as measurement of chirality of the four aryl groups in the following way: As reference plane we choose the plane through the two phosphorus atoms and the rhodium atom. The angle between the P–aryl bond and this reference plane is taken as measurement for axi-ality of the aryl group in question. If we take the average of the two axial groups and subtract the average of the two equatorial groups we obtain an angle as measurement for the chirality of the catalyst. This angle shows a weak correlation with the degree of enantioselection for the hydrogenation of dehydroamino acid derivatives. This angle measurement predicts BINAP as the best known ligand for hydrogenation. A similar correlation was found by Seebach for the enantioselection of epoxidation of olefins with the TADDOL ligands and titanium as catalyst [180].

Another class of ligands does not necessarily contain aryl groups: the phospholanes. But these ligands also contain fused rings. In addition to the five membered chelate ring there are two phospholane rings added in a spiro type manner. This combination of three five membered rings, in some cases an additional six membered aromatic ring in the ligand skeleton and the optimal chiral substitution by alkyl groups can yield excellent enantioselectivities [23–26,56,57,160,181].

Obviously there are different ways to design good chiral ligands and catalysts as only the effective discrimination of the transition state decides the enantioselectivity [182]. As the experience with the very selective but also very specific enzymes tells us, the search for a universally usable highly enantioselective catalyst seems to make sense only for a narrow class of substrates for each ligand. Thus, there is still a need for new effective ligands for enantioselective catalysis in general and asymmetric hydrogenation in particular.

Definitions. enantiomeric excess

$$ee = \frac{E_1 - E_2}{E_1 + E_2},$$

optical purity

$$o.p. = \frac{[\alpha]}{[\alpha]_{\max}}$$

%*o.p.* is also referred to as **optical yield** *o.y.*

Only in the absence of diastereomeric associations between the enantiomers in nonideal solution, the measured optical purity *o.p.* is equivalent to the value of the true enantiomeric excess *ee* [183]:

$$o.p. = \frac{[\alpha]}{[\alpha]_{\max}} \equiv \frac{E_1 - E_2}{E_1 + E_2} = ee.$$

TOF turnover frequency = number of hydrogenated substrate molecules per catalyst molecule and second.

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