Chapter 7

PRACTICAL ASYMMETRIC CATALYTIC REACTIONS

Abstracts

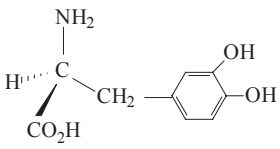
This chapter summarizes some of the most characteristic results obtained with the use of mainly homogeneous metal complex catalysts either in the industry or in processes recommended for practical use. These are large scale processes of asymmetric synthesis of the herbicide metolachlor, synthesis of optically pure menthol with the use of chiral iridium and rhodium phosphine complexes, consideration of the synthesis of ethyl 2-hydroxybutyrate as a monomer for the preparation of biodegradable polyesters with use of heterogeneous chiral modified nickel catalyst, the manufacturing of (*R*)-pantolactone by means of a possible catalytic systems for enantioselective hydrogenation of ketopantolactone, and catalytic systems for the preparation of other pharmaceuticals.

7.1. Asymmetric metal complex catalysts in industry

There are many pharmaceuticals, fragrants, and agrochemicals in which desirable biological properties are strongly related to a given configuration of an enantiomer included in the given compound. In many cases the pharmaceuticals are used as racemic compounds, where one enantiomer is an active component and another is an "isomeric ballast", but it is not always safe, as in the case of racemic thalidomide, in which the *S*-enantiomer proved to be a teratogen and therefore, a tragedy for mothers who took the racemic mixture. Therefore in practical manufacturing, it is desirable to synthesize only one enantiomer.

The preparation of enantiomerically pure compounds can be realized by methods of separation of racemic mixtures into enantiomers, by asymmetric synthesis using chiral auxiliaries, or better by using chiral homogeneous or heterogeneous catalysts. Below will be considered only the last two methods.

At first practical asymmetric catalysis used pure amino acids having biological activity. Thus the process elaborated at first by Monsanto Co. (St. Louis) (Knowles et al.[1ab]) consisted of the asymmetric synthesis of (*S*)-*DOPA* (see as **1** in Scheme 7.1.) served as a landmark in industrial synthesis based on the asymmetric catalytic hydrogenation of the precursor dehydroamino acid. The rhodium complex with the ligand *DIPAMP*, **2**, proved to be more effective as the catalyst in the asymmetric synthesis of this remedy against Parkinson disease. VEB ISIS Chemie Ltd.[2] elaborated this synthesis with a Rh-complex using ligand **3**.



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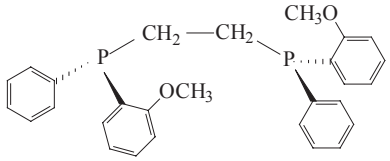

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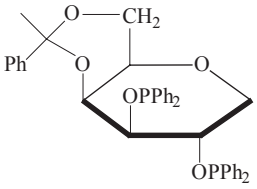

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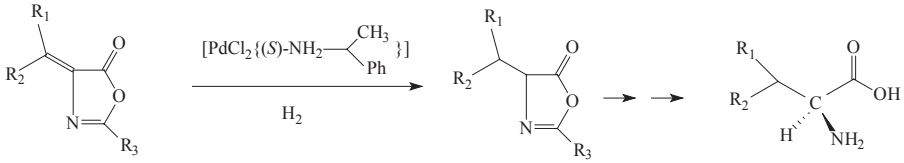
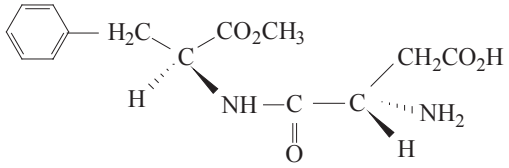
Scheme 7.1.

Another method of synthesis of (*S*)-*DOPA* and other *alpha*-amino acids was elaborated using hydrogenation of a precursor corresponding to the azlactone of substituted acrylic acids on a [$PdCl_2${(*S*)-(1-phenylethyl)-amine)}] complex that was prepared *in situ (*Karpeiskaya et al.[3]) (Scheme 7.2.).



Scheme 7.2.

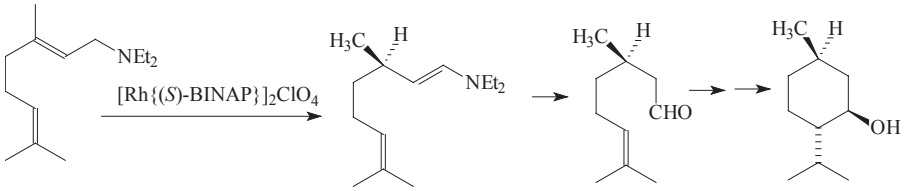
A lot of chiral diphosphines were used as ligands for Rh- and Ru-complexes as catalysts in the asymmetric hydrogenation of different dehydroamino acids as amino acid precursors and particularly in the almost optically pure *alpha*-phenylalanine for the manufacture of the sweetener *Aspartame* (Scheme 7.3.).



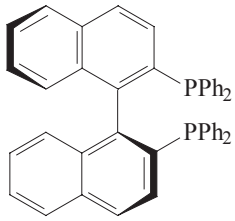
Scheme 7.3.

Another important example for practical asymmetric synthesis is the manufacture of (-)-menthol produced by Tagasago Co. (Tani et al.[4]) on a

scale of more than 1000 tons per year according to process in Scheme 7.4. involving the asymmetric hydrogenation of *N,N*-diethylgeranylamine over a Rh-complex containing the chiral ligand, *BINAP* (Scheme 7.5.), first into (+)-citronellal and then into (-)-menthol with high chemical and optical yields [4].

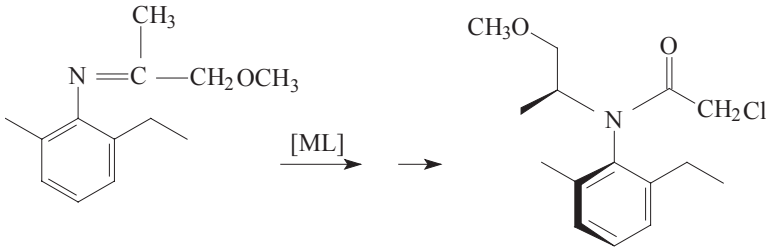


Scheme 7.4.



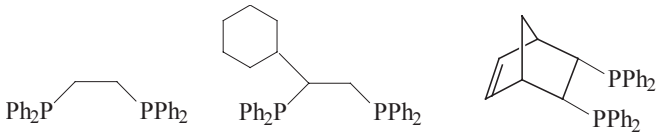
Scheme 7.5.

Rhodium and ruthenium complexes with chiral diphosphine ligands (L) are mainly active in hydrogenation of functionalized alkenes or ketones. In the hydrogenation of C=N bonds these complexes were less effective. And the first attempts to hydrogenate the imine precursor of the important herbicide *Metolachlor* (trade name DUAL) was not very successful (Scheme 7.6.).



Scheme 7.6.

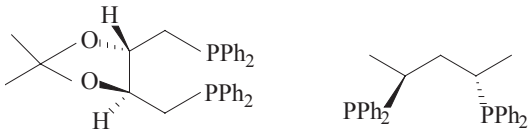
Rh complexes with chiral diphosphines (*DiPhos, NorPhos* and *CycPhos*) (Scheme 7.7.) were used to hydrogenate this imine precursor with an *ee* of not more than 50% [5].



DiPhos CycPhos NorPhos

Scheme 7.7.

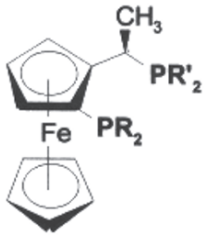
Iridium complexes of *DIOP* and *BDPP* ligands (Scheme 7.8.) proved to more effective catalysts. The highest optical yields were obtained with [Ir(bdpp)] catalysts.



DIOP BDPP

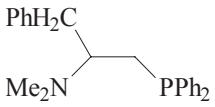
Scheme 7.8.

Even though [Ir(DIOP)] and [Ir(BDPP)] catalysts showed much higher activities than the best Rh complexes, they are were still far below the requirements [6,7]. The commercial production of the biologically active (*S*)-enantiomer was made possible by the Ir complexes of ferrocenyl-diphosphine ligands [7,8] (Scheme 7.9.). Especially the catalysts with R=C_6H_5 and R'= 3,5-diMeC_6H_5 groups gave very good results.



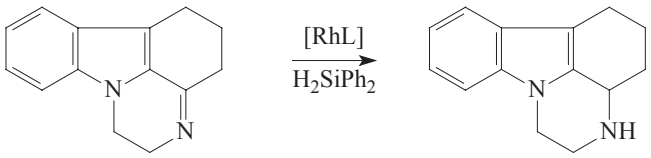
Scheme 7.9.

The preparation of *Metolachlor* proved to be the second example (after the synthesis of (-)-menthol) of using an asymmetric catalysis on a large scale 100,000 tons per year *Metolachlor* was produced in optically active form using this procedure.



Scheme 7.10.

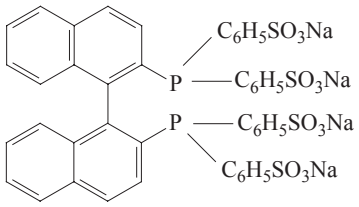
The Rh-complex of the chiral diphosphine ligand, (*S*)-*PhePhos (*Scheme 7.10.), was used as catalyst for the reductive hydrosilylation of the C=N bond of the imine precursor of the antidepressant, *Pyrazidol,* with an *ee* of 73% [9] (Scheme 7.11).



Scheme 7.11.

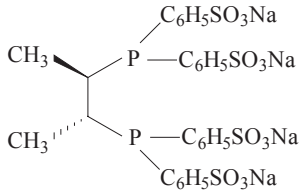
7.2. Heterogenized metal complex catalysts

The easy separation of a solid catalysts from the reaction mixture is one of the main advantages offered by heterogeneous catalysts. The cost of most chiral homogeneous metal complexes used as catalysts is very high; therefore, their heterogenization is highly desirable. But many attempts to obtain effective heterogenized complex catalysts have been unsuccessful [2]. The first successful step for the synthesis of reusable catalysts was the creation of water-soluble chiral ligands. High enantioselectivity was found for a water-soluble Ru-complex containing sulfonated chiral diphosphine *BINAP* (Scheme 7.12.).



Scheme 7.12.

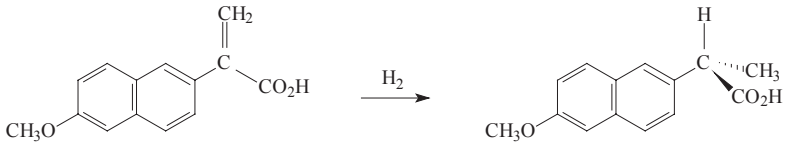
Using this homogeneous metal complex catalyst allowed hydrogenation in water-organic biphasic systems. In this case the catalyst was dissolved in water and could be used repeatedly, while the substrate remained in the organic solution [10]. Accordingly, the complex $[Rh(COD)Cl]_2$, with sulfonated diphosphine, *ChiraPhos* (Scheme 7.13.), is an effective catalyst for the hydrogenation of dehydro-*N*-acetylalanine into (*S*)-*N*-acetylalanine with an *ee* of 20-60% in water solution at 25^0C and 1-6 bar of hydrogen [11-14].



Scheme 7.13.

Davis et al.[13-14] described a new type of effective chiral catalysts, the so called "supported aqueous-phase catalysts". This hydrophilic complex is supported on a hydrophilic solid to create a large interface between the catalytic species and the organic reactants. The hydrophilicity of the ligands and the support creates an interaction sufficient to maintain immobilization of the sulfonized *BINAP* ligand (Scheme 7.12.) in a layer on the carrier.

The complex [Ru(*BINAP*-$4SO_3Na$)(benzene)Cl]Cl was supported on a solid carrier of controlled pore size porous glass [14]. In the process of heterogenization the complex was bounded covalently to the carrier. Sometimes such catalysts revealed enantioselectivity close to those of the homogeneous complex. In the case of the synthesis of the anti-inflammatory drug, *(S)-Naproxen*, the C=C bond of the precursor was hydrogenated (Scheme 7.14.) with high effectiveness.

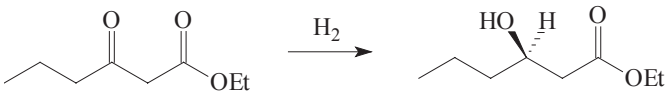


Scheme 7.14.

The homogeneous catalyst $[Ru(OAc)_2(BINAP)]$ also resulted in this synthesis with a chemical yield of 92% and an *ee* of 97%. Immobilization of Ru-complexes with phenyl-sulfonated groups on porous glass allowed for the synthesis of *Naproxen* in a MeOH-ethylene glycol solvent mixture at 20^0C

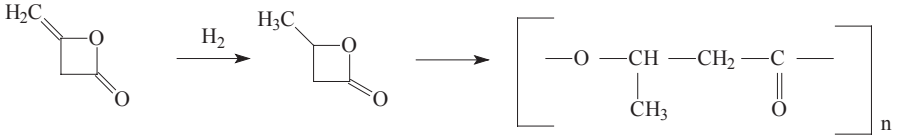
and 100 bar with an *ee* of 89.1% and in an ethylene glycol solvent with an *ee* of 94.8% without decreasing enantioselectivity upon repeated use of catalyst.

Another example of the successful use of these catalysts is in the hydrogenation of butyrylactone (Scheme 7.15.) in ethylene glycol at 85 ^{0}C and 60 bar with an *ee* of 95% [13b] (in homogeneous hydrogenation the *ee* reached 97%).



Scheme 7.15.

Comparison of this new type of catalyst with known catalytic heterogenized systems, for example, Ru-BINAP-catalyst deposited on zeolite-*beta* [12], showed that these catalysts are very effective, despite the metal complex not being covalently bonded to the carrier but distributed in the liquid film on the surface and thus representing a "hybrid genuine" homogeneous-heterogeneous catalytic system (Davis [13,14]).



Scheme 7.16.

Hydrogenation of the C=O bond in diketene to its chiral lactone, followed by its polymerization into a polyhydroxybutyrate-type biodegradable polymer [15,16] (Scheme 7.16.) is a prospective process for the preparation of plastics that are produced by ICI with a process involving fermentation of glucose [17a]. It was found that over the complex [RhCl((*S*)-BINAP) (benzene)]Cl Net_3 in THF at 50 ^{0}C and 100 bar the product were produced with *ee*'s of 90-92% [15].

The preparation of optically active ethyl and methyl 3-hydroxybutyrates was considered in detail in Chapter 4. Here it will be compared with the effectiveness of production of these optically active esters using enzymatic, heterogeneous, and homogeneous catalysts [17].

Table 7.1. presents the main characteristics of the process involving the reduction of *beta*-keto butyrate, i) acted upon by Baker's yeast, ii) using a Raney Ni catalyst modified by (2*R,*3*R*)-tartaric acid + NaBr, and iii) in the presence of a chiral Ru complex containing chiral diphosphine *BINAP*.

As can be seen, all three methods ensure a high effectiveness of the process. The optical yields of 3-hydroxybutyrates (in best instances) reached 85-99%. But all three methods have their own advantages and disadvantages.

In spite of the low productivity of the enzymic process – the large volumes of solution with low concentration of product; the long duration of reaction and the need of additional purification, filtration, and extraction of product from reaction mixture; the instability of the enzyme; and the impossibility of recycling the enzyme - this process is still used in practice.

Characteristics	Enzymic reduction	Heterogeneous hydrogenation	Homogeneous hydrogenation
Substrate (g)	EAA, 40	MAA, 40	MAA, 40
Solvent (ml)	water, 2600	none	MeOH, 40
Catalyst	Baker's yeast	Ni-TA-NaBr	Ru-BINAP
(g)	200	2	0.14
Reductant	Sucrose, 600 g	H_2, 75 bar	H_2, 20 bar
Temperature (^oC)	20	100	20
Reaction time (h)	134	20	40
Product recovering	Filtration extraction distillation	Filtration distillation	Distillation
Chemical yield (%)	59-76	94	99
Optical yield (%)	85	90	99
Configuration of product molecule	(*S*)	*S*) or (*R*)	(*S*) or (*R*)
Productivity g / liter solution x h	0.07	40	12
Repeating of use of catalyst	none	5-30 times	none

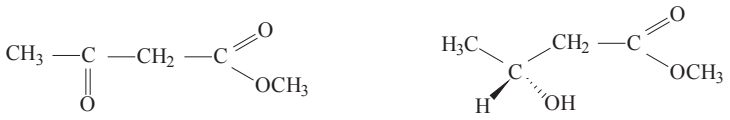
Table 7.1. A comparison of various methods for the synthesis of 3-hydroxy-butyrates by the reduction of *beta*-keto esters.

In spite of the fact that metal-complexes are extremely efficient catalysts (*ee*'s above 91%, high productivity and high turnover numbers), the high price of the precious metal and the expensive synthesis of the chiral diphosphine ligand, like *BINAP* and the impossibility of recycling of the catalysts renders this method impractical for large scale production of butyrates.

Recently attempts to improve the process were described. A catalytic system obtained by *in situ* mixing $[RuCl_2(benzene)]_2$ + BINAP has been used in the hydrogenation of MAA with an *ee* of 95% [39]. The highest activity and enantioselectivity in the production of (*R*)-MHB were measured with the cationic catalyst [RuCl(iPr-Ph)]Cl-BINAP, when the reaction was carried out

in methanol, ethanol or 2-propanol [40]. These solvents, which also acts as proton donors, accelerated the product release from the reaction intermediate. The presence of water in the reaction mixture was found to be detrimental for both activity and enantioselectivity. Despite the somewhat reduced optical yield, *ee* 94%, in comparison to the heterogeneous Ni catalysts modified with (2*R,*3*R*)-tartaric acid, the application of this catalyst is compensated by the high productivity of the process, by the low cost of the catalysts, their easy preparation, and by the possibility of its reuse many times without loss of catalytic activity and enantioselectivity. Therefore the catalyst of this type probably can be recommended for large scale production of alkyl butyrates as monomers for manufacturing biodegradable polyesters.

Another path of manufacture of practical catalysts is using immobilized chiral metal complexes. Thus, the complex [Rh-BINAP] was occluded [18] in an elastomeric type polydimethylsiloxane membrane, which gave a regenerable active membrane-catalyst with the same enantioselectivity as the homogeneous catalyst in the hydrogenation of acetoacetic acid ester into methyl (*R*)-(-)-3-hydroxybutyrate, that can be polymerized into polyester (Scheme 7.17.).

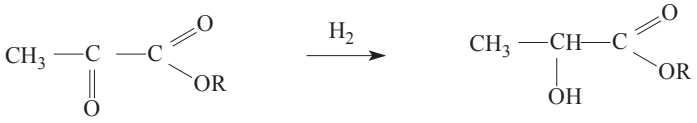


Scheme 7.17.

In contrast to earlier polymer-supported complex catalysts in which complexes were immobilized through electrostatic interaction, covalent bonds, or coordinative bonds, in this case the complex is captured in the elastomer network by occlusion in a dense polymer in the absence of any supplementary chemical bonding and only as result of steric restrictions. In the hydrogenation of methyl acetoacetate by this catalyst an *ee* of 70% was obtained in polyethyleneglycol solution at 60 ^{0}C. After regeneration of the catalyst and reuse, its activity and enantioselectivity were almost unchanged.

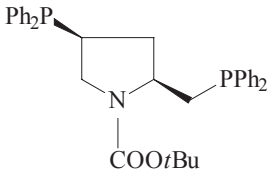
7.3. Asymmetric hydrogenation of *alpha*-keto esters on chiral metal complexes

Neutral Wilkinson type catalysts with chiral ligands are quite effective for the hydrogenation of C=O bonds in prochiral 2-oxocarboxylic acids or their esters and are applied to the asymmetric synthesis of 2-hydroxyesters with rather high *ee*'s of up to 80-95%. The reduction of *alpha*-keto esters, such as alkyl-pyruvates into alkyl-lactates (Scheme 7.18.) on chiral complexes is one of the most important methods of the synthesis of chiral synthones for practical use.



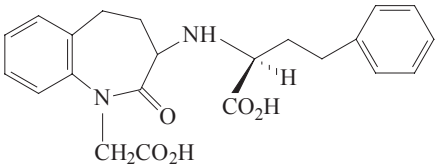
Scheme 7.18.

Thus, on the Rh complex of the *BPPM* ligand (Scheme 7.19.), isobutyl pyruvate was reduced into the lactate with an *ee* of 70% [19-20].

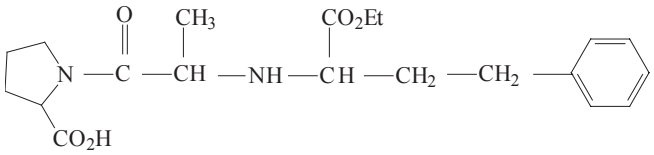


Scheme 7.19.

A comprehensive review of asymmetric hydrogenation, mainly 2-oxo-carboxylic acids and their esters, over heterogeneous catalysts of Pt-alumina modified with alkaloids was presented in Chapter 5 of this book. Here some practical aspects of these catalytic systems will be considered. Thus, ethyl (*R*)-4-phenyl-2-hydroxybutyrate is an important intermediate for the synthesis of the angiotensin-converting enzyme inhibitor *Benazepril* (Scheme 7.20.) [21], and other carboxyalkyl dipeptides like *Enalapril* (Scheme 7.21.) [17c].

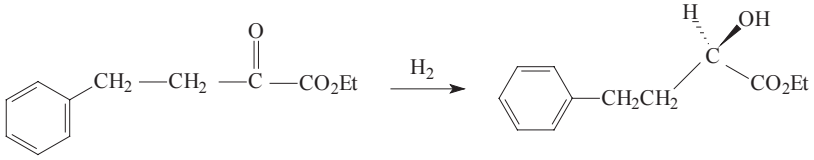


Scheme 7.20.



Scheme 7.21.

The ethyl (*R*)-4-phenyl-2-hydroxybutyrate intermediate was prepared by the enantioselective hydrogenation of a keto ester (Scheme 7.22.).



Scheme 7.22.

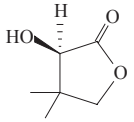
Using $[Rh(NBD)Cl]_2$ and *NorPhos* as chiral ligand, the 4-phenyl-2-oxobutyrate was hydrogenated with an *ee* of 96% [20]. (*R*)-4-phenyl-2-hydroxybutyrate can also be prepared with an *ee* of 73% on 5% Pt-alumina modified with the alkaloid MeODHCnd at 25^0C [21a]. This process has been developed by the Ciba Geigy AG. (Basel) and scaled up for production of up to 200 kg of *Benazepril* with an *ee* of 79-82% [21]. This catalyst gives products with (*R*)-configuration, but *Benazepril* must have (*S,S,S*)-configuration for medical use; therefore, the modifier cinchonidine must be changed to cinchonine giving (*S*)-configuration, but in this case the product will be obtained with a somewhat lower *ee*. The same problem exists in the synthesis of *Enalapril* in which the product must attain the (*S,S,S*)-configurations of all asymmetric centers [17c].

Very promising are supercritical fluids as solvents for asymmetric hydrogenations. Thus, ethyl pyruvate can be hydrogenated into ethyl lactate in supercritical ethane with a 3.5 times increased reaction rate and with the same *ee* as in the common solvent toluene [21b] (see Chapter 5.5 of this book).

7.4. Catalytic synthesis of pantolactone and other pharmaceuticals using chiral homogeneous metal complexes

The methods of preparation of pantolactone via asymmetric hydrogenation of ketopantolactone are of great interest [17a]. Here practical aspects of preparation of pantolactone using homogeneous chiral metal complex catalysts will be considered. The heterogeneous catalysts of this process were considered in Chapter 5.

Pantolactone (PL) [(*R*)-(-)-3-hydroxy-4,4-dimethyltetrahydofuran-2-on], **1** (Scheme 7.23.), is an intermediate in the preparation of several biologically important molecules such as D-(+)-pantothenic acid, **2**, which is a member of B vitamins (Vitamin B_5) and is an important constituent of coenzyme A. The biosynthesis of **2** involves the asymmetric reduction of ketopantolactone, **3**, (KPL) (4,4-dimethyltetrahydrofuran-2,3-dion) to *R*-(-)-PL, because only the *R*-(-)-enantiomer is biologically active.



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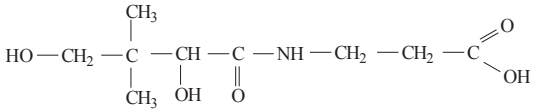

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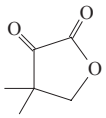

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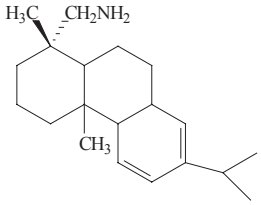
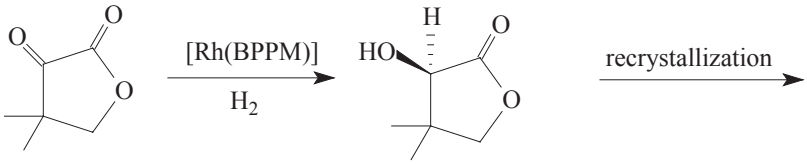


4

Scheme 7.23.

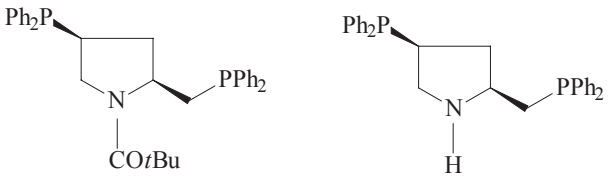
At this time in the industry, the preparation of *R*-(-)-PL is still based partly on the resolution of the racemic pantolactone into its two enantiomers, for example, with the use of dehydroabietylamine, **4** [22]. A more economical preparation of PL might be based on the asymmetric hydrogenation of KPL, using homogeneous or heterogeneous chiral catalysts. Along these lines, a rather effective hydrogenation of KPL to PL using chiral metal phosphine complexes has been realized. This asymmetric hydrogenation can be carried out in quantative yields with high optical purity (*ee* = 86.7%) under optimal conditions using a neutral Rh complex with the chiral phosphine ligand *BPPM* (Scheme 7.19.). The resulting product can be easily purified to pure *R*-(-)-pantolactone in 70-80% yield by recrystallization from a hexane-benzene mixture. The process is shown on Scheme 7.24.



Scheme 7.24.

Reduction of ketopantolactone using Baker's yeast gives an *ee* of approximately 72% [23], but a chiral Rh catalyst has been shown to be superior to Baker's yeast in this process.

High optical yields were obtained using [Rh(hexa-1,5-diene)L] complexes, where L = *BPPM* (Scheme 7.19), or **1** and **2** in Scheme 7.25. [24].



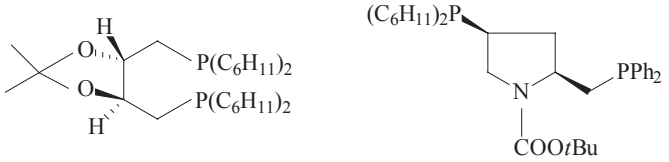
1 2

Scheme 7.25.

The reduction of KPL on [Rh(HD)L] catalysts with *BPPM* and **1** ligands lead to (*R*)-PL with *ee'*s of 54.6 and 59.2%, respectively, while the ligand **2** produces (*S*)-PL with an *ee* of 15.4%. The substituent at the *N*-atoms play an important role in the process because the sense of asymmetric induction depends on the *N*-substituents.

Using cycloocta-1,5-diene (COD) ligand instead of hexa-1,5-diene in the Rh-complexes, increased the *ee* from 54.6% *R* to 80.5% *R* [25] or 86.7% *R* [26] at 30^0C and 50 bar hydrogen pressure in benzene solution if the neutral [RhCl(COD)(BPPM)]Cl complex was used, while the cationic complex, $[Rh(COD)(BPPM)]ClO_4$, gave only 53.5% *R* [27]. In the case of the latter cationic complex, a remarkable solvent effect was observed. In MeOH, which is well known as a poorly coordinating solvent, the sense of asymmetric induction was opposite and (*S*)-(+)-pantolactone with an *ee* of 15.7% was produced [27].

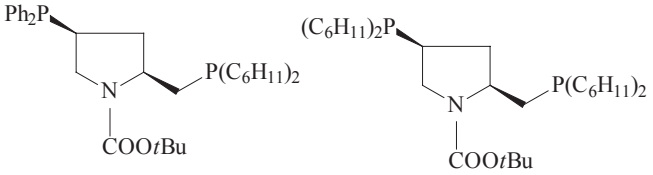
Another type of ligand is the (-)-*Cy-DIOP* (Scheme 7.26.), which is based on ligand *DIOP* (Scheme 7.8.) [28,29]. The cyclohexyl analog is an effective ligand in the hydrogenation of ketopantolactone to a moderate *ee* of 45% [30]. On the other hand, including the cyclohexyl group instead of the phenyl into the *BPPM* produced the very effective *BCPM* ligand and the $[Rh(COD)Cl]_2$ (BCPM) produced (*R*)-(-)-PL with 100% yield and an *ee* of 92 % in THF and at a substrate to catalyst ratio of 1000 [31].



Cy-DIOP BCPM

Scheme 7.26.

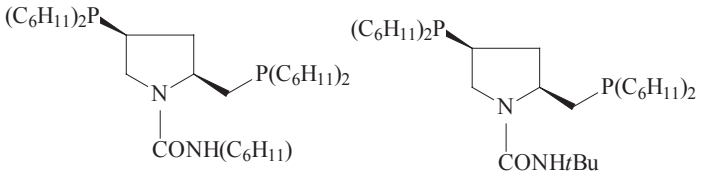
In the hydrogenation of KPL at 50^0C and 50 bar in THF a markedly different effect of the dicyclohexyl-phosphino groups of the ligands at the C2 position was observed on the optical yields of PL.



BCPP BCCP

Scheme 7.27.

The Rh-complexes with chiral ligands of *BPPM* (Scheme 7.19.), *BCPM* (Scheme 7.26.), *BCPP* and *BCCP* (Scheme 7.27.) were studied [32], and it was found that complexes with *BPPM, BCPM* and *BCPP* ligands gave (*R*)-PL with *ee*'s of 81%, 91% and 9%, respectively, while the *BCPP* ligand led to (*S*)-PL with an *ee* of 61%. This may be rationalized by the assumption that one of the Ph_2P-groups in the other ligands controls the chiral induction and accelerates the reaction rate.

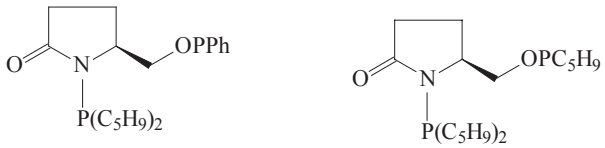


1 2

Scheme 7.28.

In the case of the Rh complexes with ligands **1** and **2** (Scheme 7.28.) was found that a neutral Rh-complexes of these ligands in THF gave pantolactone with an *ee*'s of 41% *S* and 60% *S*, respectively, while both cationic complexes gave an *ee* of 10% and *R*-configuration. Thus it was found [33] that the above Rh complexes are more effective catalysts than [Rh(Alk)(DIOP)] complexes in the asymmetric hydrogenation of ketopantolactone.

In 1990 Petit and the Mortreux's group [34] found that the $[Rh(COD)Cl]_2$ complex with rather simple chiral ligand containing one cyclopentyl and one Ph-groups (**1** in Scheme 7.29) revealed high enantioselectivity: *ee* 90.7% *R*, at 1 bar hydrogen, and with the relationship of substrate to Rh 400.



1 2

Scheme 7.29.

Recently, for the hydrogenation of KPL Mortreux et al.[35] found other more effective ligands for Rh-catalyst containing two cyclopentyl groups. They found very high *ee*'s up to 96.9% at 70 ^{0}C in the case of ligand 2 with a substrate to catalyst ratio of approximately 10 000. As the authors indicated "...to the best of our knowledge, the neutral Rh complex of this new chiral ligand is the most effective catalyst so far reported for the asymmetric hydrogenation of ketopantolactone into (*R*)-(-)-pantolactone..." [35].

As for the mechanism of this reaction, it was noted [33] that the studies revealed that:

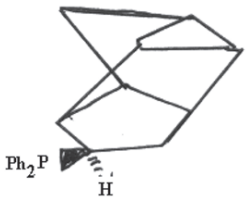
i) the Schrock-Osborn mechanism [36] is not operative since no acceleration by the addition of water was observed

ii) there is a difference between cationic and neutral complexes in that the neutral complexes are much more enantioselective

iii) there is a remarkable solvent effect on the enantioselectivity of pantolactone formation.

A new Rh(I)-complex catalyst bearing two chiral ligands, the (*R,R*)-DIOP and an *N,N'*-co-ligand based on (*R*)- or (*S*)-phenylethylamines, pyrroleimines, or pyrroleoxazolines proved to be enantioselective in the hydrogenation of ketopantolactone into (*R*)-pantolactone at 50 ^{0}C and 50 bar in toluene solution at a relationship of substrate to Rh 200 [37].

In all cases, the investigated Rh-complexes with co-ligands, independently of their configuration, *R*- or *S*-, and their chemical structure, (*R*)-pantolactone was obtained with an *ee* of approximately 30%, while catalyst [Rh-(COD)Cl_2-(*RR*)-DIOP] resulted the (*R*)-pantolactone with an *ee* of 54%. Thus there was no matched-mismatched contributions from chirality of *N,N'*-co-ligands that was explained by formation of monodentate coordination of co-ligand with Rh only by the *N* of the pyrrole ring. Only in the case of a monodentate co-ligand with rigid structure (Scheme 7.30.) combined with the complex [Rh(*RR*-DIOP)Cl] was the (*R*)-pantolactone obtained with an *ee* of 50%.



Scheme 7.30.

For preparation of (*R*)-(-)-pantolactone the enzymic method was applied. Under the action of *ketopantoyl lactone reductase* in Baker's yeast (*R*)-(-)-pantolactone was prepared with high chemical and optical yields [38].

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