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Journal of Molecular Catalysis A: Chemical 173 (2001) 231–247

JOURNAL OF MOLECULAR CATALYSIS A: CHEMICAL

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Catalysis with supported palladium metal, selectivity in the hydrogenation of C=C, C=O and C=N bonds, from chemo- to enantioselectivity

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Abstract

The selectivity characteristics of Pd catalysts in heterogeneous hydrogenations are discussed, especially the stereochemical issues in the reduction of C=C, C=O and C=N bonds. Special attention was paid to diastereoselective and enantioselective reactions.

Keywords: Palladium; Hydrogenation; Chemoselectivity; Diastereoselectivity; Enantioselectivity

1. Introduction

Pd has a unique character among precious metals as a hydrogenation catalyst. Trimm [1] demonstrated this property in his book with a table, where the different non-reacting and reacting functional groups were displayed. In most cases Pd was the appropriate catalyst, which was selective, for example, in the reduction of C≡C bond to C=C, or of C=C in the presence of C=O and C≡N. In the scientific and patent literature, one can find innumerable examples of chemoselective heterogeneous hydrogenations carried out with Pd containing catalysts [2–7].

Besides these advantageous properties of Pd namely that it hydrogenates, for example, the C=C double-bond with high reaction rates, it has to be mentioned that Pd has strong double-bond isomerization activity too. These characteristics are decisive in the case of stereoselective reductions where the ratio of products with different space structures depends not only on the rate of their formation, but on the isomerization rate of the double-bond as well. Comparing Pd and Pt catalysts, the latter have usually much less isomerization activity than Pd. In spite of the isomerization activity of Pd, it is used in several diastereoselective hydrogenations, where C=C and C=N bonds are saturated, for example, in the preparation of chiral amines and amino acids [8].

Another advantage of Pd is that it can be modified easily in order to increase its selectivity. The change of the support, and of the reducing agent, the use of selective poisons, alloying with other metals are all useful methods [9]. Pd is relatively non-sensitive to catalyst poisons what is demonstrated by that the S–S bond could be hydrogenated with Pd catalyst [10]. The good chemoselectivity of Pd stands out too in the hydrogenation of the aromatic ring of phenol and its derivatives, as the products are cyclohexanone or its derivatives [11].

The first attempts to carry out enantioselective heterogeneous catalytic hydrogenations were made with Pd catalysts, on silk fibrin and on optically active

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1381-1169/01/$ – see front matter
PII: S1381-1169(01)00152-2

quartz as support materials [12,13]. These results could not be reproduced since that time, but the modified catalysts, among others Pd containing catalysts too, brought good results in this field [14,15].

2. Chemoselectivity of Pd catalysts

In the chemistry of hydrogenations catalyzed by Pd one can meet often with peculiar phenomena. The unsaturated ketones, even the conjugated ones, can be hydrogenated to the saturated carbonyl compound with perfect selectivities on Pd, but the α,β-unsaturated aldehydes, like cinnamic aldehyde, are hydrogenated on Pd to the saturated alcohol. Pd is a good catalyst for hydrodehalogenation, but in some cases, one can avoid the cleavage of the halogen even with Pd catalyst by appropriate choice of the solvent or by the modification of the catalyst [9].

In the petrochemical industry, Pd on alumina catalyst with low metal loading is used for the selective hydrogenation of acetylenic compounds, besides olefinic ones. In the hydrogenation of alkynes, the Pd catalysts have good chemoselectivity, if they are on low surface area support or selectively poisoned (Lindlar catalyst).

Several authors, among others Siegel, Smith, Mitsui, Augustine, compared the different noble metal catalysts in double-bond hydrogenation and tried to explain their behavior [16–19]. Over Pd facile double-bond isomerization takes place, giving a mixture of olefins from which the saturated products are produced. On Pd π-allyl adsorption of olefins are proposed as an alternative to the 1,2-σ_2-adsorption of the Horiuti-Polanyi mechanism, the peculiar catalytic behavior of Pd can best be accounted for invoking the intermediary of a π-allyl-adsorbed species.

Delbecq and Sautet [20] published a theoretical approach for the explanation of the selectivity differences of Pt and Pd catalysts in the hydrogenation of α,β-unsaturated aldehydes. They studied the adsorption geometry of acrolein, crotonaldehyde, methyl crotonaldehyde and cinnamaldehyde on Pt and Pd surfaces by means of semiempirical extended Hückel calculations. They have found that the adsorption mode of an ethylenic aldehyde on a metal surface is strongly dependent on the nature of the metal and the type of the exposed crystal face. The low selectivity towards unsaturated alcohol has two basic reasons: the one is that the C=O π-system is not utilized in the molecular adsorption, the C=C bond is only involved in the chemisorption. The second basic reason for poor C=O hydrogenation is an η_4-adsorption, where both double-bonds are involved in a quasi-planar situation, the hydrogenation of the C=C bond is favored for kinetic reasons, this is the typical case for a Pd catalyst. Pd is therefore, intrinsically a poor catalyst for selective hydrogenation of α,β-unsaturated aldehydes.

3. Stereoselectivity of Pd catalysts

Detailed investigations were carried out among others with Pd catalysts in the hydrogenation of substituted cycloalkenes with respect to the stereoselectivity of the reaction [21]. In the explanation of Siegel the initially adsorbed olefin must desorb in the form of another isomer, and then be readsorbed. Hussey [22], however supposed that the olefin exists as *cis*- and *trans*-1,2-σ-diadsorbed alkanes on the surface and the interconversion between these permits the formation of a product mixture with a composition close to the equilibrium one. Mitsui et al. [18] studied the hydrogenation of 2-methyl methylenecyclohexane at various catalyst: reactant ratios. With large amount of catalyst rapid isomerization was observed. They supposed that in the hydrogenation of olefins containing an exocyclic double-bond, the product-determining step is not the hydrogen transfer, but the adsorption of the reactant on the catalyst and the formation of the half-hydrogenated state. The characteristic reaction of the exocyclic double-bond on Pd is its fast migration into the ring, which can occur via the half-hydrogenated state (Horiuti-Polanyi mechanism) or via the π-allyl complex.

The stereoselectivity of Pd catalysts in the hydrogenation of alkynes towards *cis*-alkenes is also high [23]. Bases usually increase; acids decrease the stereoselectivity in this reaction.

4. Diastereoselective hydrogenations with Pd catalysts

The asymmetric catalytic hydrogenation over metal catalyst is a useful method for the preparation of

various chiral compounds. These reactions involve the saturation of prochiral C=C, C=N and C=O double-bonds [8].

In some hydrogenations, the chirality inducing group is removed after having fulfilled its task in the reduction step, while in others, it becomes the part of the product molecule. A good chiral auxiliary has high asymmetric induction effect and is recoverable.

In heterogeneous reactions, the conformation of a substrate adsorbed on a catalyst might be different from that of the same substrate in solution. Aromatic groups and polar groups such as C=O, NH_2, NH and OH could interact with the catalyst, and preferred conformation of the substrate might be considerably different from the most stable conformation in solution. The classical empirical stereocorrelations proposed for homogeneous reactions are therefore, not always successful for rationalization of steric course of heterogeneous catalytic hydrogenations. However, similar rules are still useful as a way to consider the steric course of heterogeneous reactions.

4.1. Diastereoselective hydrogenations of olefinic double-bonds in chiral molecules

For the hydrogenation of olefinic double-bonds the catalyst most often used are supported palladium, platinum oxide and Raney nickel.

4.1.1. N-acyl-α,β-dehydroamino acids

Diastereoselective hydrogenation of dehydroamino acid derivatives containing an appended chiral auxiliary has provided a useful, preparative approach to make various optically active amino acids.

Heterogeneous catalytic hydrogenation of chiral *N*-acyl-α,β-dehydroamino acid esters and amides were carried out. The chiral alcohol used was (−)-menthol [24–26], the chiral amines used were 2-phenyl-propylamine [27], α-methylbenzylamine [28,29], α-ethylbenzylamine. The catalyst were palladium on carbon, palladium on alumina and Raney nickel. The hydrogenation product was hydrolyzed to give an optically active amino acid (Fig. 1). The optical purity of the resulting amino acid was poor (<40%).

Chiral 2,3-dehydroamino acid derivatives were hydrogenated with complete stereoselectivity over Pd/C (Fig. 2) and then were converted to unusual chiral

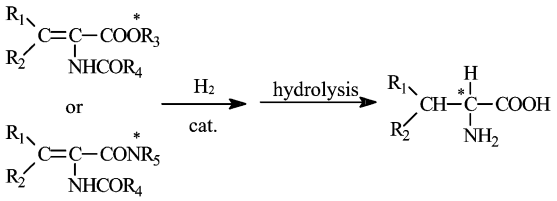


Fig. 1. Hydrogenation of chiral *N*-acyl-α,β-dehydroamino acid esters and amides.

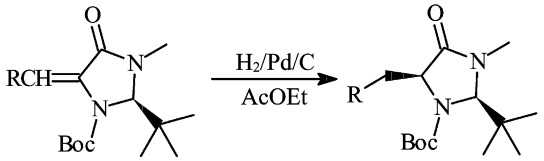


Fig. 2. Hydrogenation of chiral 2,3-dehydroamino acid derivatives to unusual chiral amino acids.

amino acids [30]. Presumably, the addition of the hydrogen molecule occurred from the face opposite to the *tert*-butyl group with complete selectivity.

4.1.2. Dehydrodi-, tri-, tetrapeptides

The asymmetric catalytic hydrogenation of chiral dehydrotripeptides that contain a dehydroalanine and proline residue, over Pd/C was thoroughly studied (Fig. 3) [31].

In all reactions, the absolute configuration of the resulting alanine was (*R*). The optical yield of the resulting alanine was up to 93%, and the chemical yield was in the range 86–97% (Table 1).

The results showed that amino acid in the C-terminal position had much larger contribution in determining the absolute sense and degree of asymmetric induction in producing the (*R*)-alanine moiety than the N-terminal amino acid. C-terminal (*S*)-proline derivatives gave (*R*)-alanine in every cases, regardless of the absolute configuration of the N-terminal residue. The presence of proline *tert*-butyl

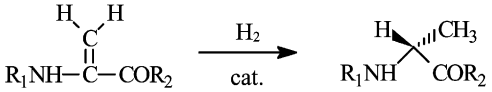


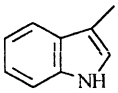
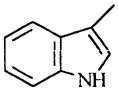
Fig. 3. Hydrogenation of chiral dehydrotripeptides.

Table 1
Chemical and optical yield in the hydrogenation of chiral dehydrotripeptides (Fig. 4)

R_1	R_2	Yield (%)	e.e. (%)
Boc[a]-Gly-	-(*S*)-pro-NH*t*Bu	96	84
Boc-(*S*)-Val-	-(*S*)-pro-NH*t*Bu	97	87
Boc-(*R*)-Val-	-(*S*)-pro-NH*t*Bu	97	81
Boc-(*S*)-Ile-	-(*S*)-pro-NH*t*Bu	97	90
Boc-(*R*)-Phe-	-(*S*)-pro-NH*t*Bu	92	89
Boc-(*R*)-Pro-	-(*S*)-pro-NH*t*Bu	96	89
Boc-(*R*)-Ser-	-(*S*)-pro-NH*t*Bu	86	82
Boc-(*R*)-Ser(*t*Bu)-	-(*S*)-pro-NH*t*Bu	96	93
Boc-Gly-	—(*S*)—Pro—N⟨	92	43
Boc-(*S*)-Val-	—(*S*)—Pro—N⟨	96	74

[a] *Tert*-butyloxycarbonyl.

Table 2
Chemical and optical yields in the hydrogenation of dehydrodiketopiperazines (Fig. 4) (R_2=H)

R_1	R_3	Yield (%)	e.e. (%)
Me	Me	48	99
$AcNH(CH_2)_5$	Me	45	97
Me	*i*Pr	8	96
Me	*i*Bu	47	98
*i*Pr	*i*Bu	61	>99
*i*Bu	*i*Bu	69	98
$AcNH(CH_2)_5$	*i*Bu	22	95
Me	Ph	56	88
*i*Pr	Ph	63	94
*i*Bu	Ph	52	90
$AcNH(CH_2)_5$	Ph	26	77
Me	$PhCH_2CH_2$	55	98
*i*Bu	$PhCH_2CH_2$	52	97
Me		49	71
*i*Bu		18	66

amide as the C-terminal amino acid in the reactants appeared to be an important factor in performing an effective asymmetric induction by the heterogeneous hydrogenation.

4.1.3. Dehydrodiketopiperazines

The Pd catalyzed hydrogenation of dehydrodiketopiperazines containing dehydro-α-aminobutyric acid, dehydrovaline, dehydroleucine, dehydrophenylalanine, dehydro-2-amino-5-phenylpentanoic acid and dehydrotryptophan residues generally obtained high levels of asymmetric induction (Fig. 4) (Table 2) [32–34].

In some reaction, excellent optical purities of the resulting amino acids (>99%) were reported. Lower asymmetric induction could be achieved with dehydrophenylalanine and dehydrotryptophan. Solvent, temperature and catalyst effects on enantiomeric excesses were found to be small. The wide range in chemical yields most likely reflects the experimental difficulties in the separation of the two amino acids.

Heterogeneous catalytic hydrogenation of dehydrodi-, tri- and tetrapeptides ususally resulted lower optical yields, as compared to the hydrogenation of dehydrodiketopiperazine derivatives.

4.1.4. Reactions giving optically active amino acids

The asymmetric heterogeneous catalytic hydrogenation of the carbon–nitrogen double-bond affording optically active amino acids has been extensively studied. Some of the reactants used are oximes and hydrazones, but most of the reactions are carried out using Schiff's bases of α-keto acid derivatives. Enantiomeric excesses obtained by this approach are generally low.

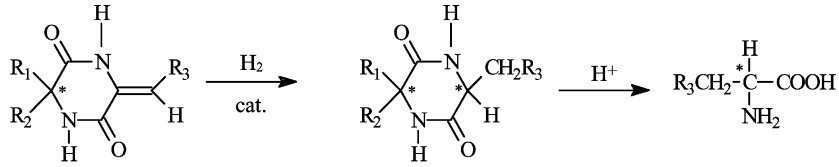


Fig. 4. Hydrogenation of dehydrodiketopiperazines.

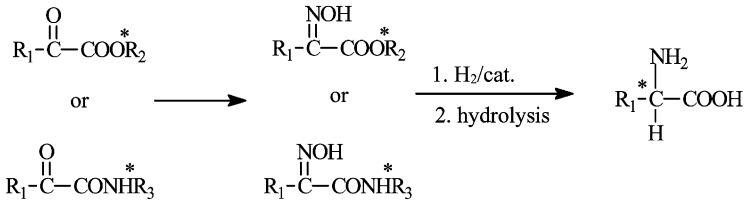


Fig. 5. Hydrogenation of oximes of α-keto acid esters or amides.

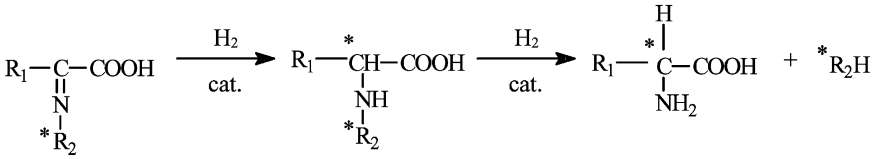


Fig. 6. Hydrogenation of Schiff's base prepared from α-keto acid and its derivative and an optically active amine or amino acid followed by hydrogenolysis.

4.2. Oximes and hydrazones of α-keto acid derivatives

Hydrogenation of oximes prepared from (−)-menthyl esters of pyruvic acid, α-ketobutyric acid and benzoylformic acid resulted in corresponding amino acids with low optical purity (*R*)-α-aminobutyric acid (8–21%). (*R*)-phenylglycine (44–49%) (Fig. 5) [35]. The catalyst used was palladium on carbon or palladium hydroxide on carbon.

4.3. Imines of α-keto acid derivatives

Hydrogenation of C=N double-bond of Schiff's base, prepared from α-keto acid and its derivative and an optically active amine or amino acid, followed by hydrogenolysis, results in an optically active amino acid (Fig. 6).

This method is often called asymmetric transamination. Generally, palladium catalysts are used in both hydrogenation and hydrogenolysis processes. Asymmetric induction arises during the catalytic hydrogenation of the C=N double-bond and the configuration produced changes only slightly or not at all during the hydrogenolysis. In the chiral amine, the N atom is most often linked to a benzylic position, and as a result the auxiliary can be removed by catalytic hydrogenation.

Optically active alanine, α-aminobutyric acid, phenylglycine and glutamic acid were prepared by the hydrogenation of Schiff's bases of the corresponding α-keto acids and (*S*)-α-methylbenzylamine (Me(−)), (*S*)-α-ethylbenzylamine (Et(−)) and (*R*)-α-(naphtyl)ethylamine (Naph(+)) with modest to poor selectivities [36,37]. A considerable substituent effect on the alkyl group increased, the optical purity of the resulting amino acid decreased (Table 3).

4.3.1. Diastereoselective hydrogenation of Schiff's bases to secondary amines

In the following, the asymmetric hydrogenation of Schiff's bases made of chiral amine and prochiral ketone will be discussed.

Table 3
Optical yield in the hydrogenation Schiff's bases prepared from the corresponding α-keto acids (RCOCOOH) and optically active amines

R	Amine	Amino acid	Optical yield (%)
CH_3	Me(−)	(*S*)-Alanine	67
	Et(−)	(*S*)-Alanine	52
	Naph(+)	(*R*)-Alanine	83
C_2H_5	Me(−)	(*S*)-Butyrine	44
	Et(−)	(*S*)-Butyrine	33
C_6H_5	Me(−)	(*S*)-Phenylglycine	30
	Et(−)	(*S*)-Phenylglycine	24
$CH_2C_6H_5$	Me(−)	(*S*)-Phenylalanine	14
	Et(−)	(*S*)-Phenylalanine	10
$(CH_2)_2COOH$	Me(−)	(*S*)-Glutamic acid	12
	Et(−)	(*S*)-Glutamic acid	6

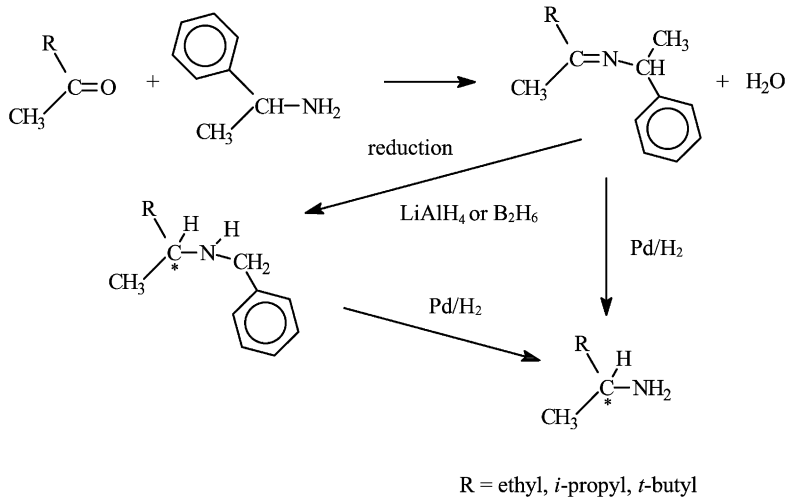


Fig. 7. Asymmetric hydrogenation of Schiff's bases made of prochiral ketones and a chiral amine.

French authors studied the asymmetric induction of different reduction methods of Schiff's bases: reduction with $LiAlH_4$ or with B_2H_6 and catalytic hydrogenation over Pd on carbon catalyst [38] (Fig. 7, Table 4).

The use of $LiAlH_4$ gave poor optical yields. Moderate enantioselectivities, depending on the reactant structure, could be achieved with B_2H_6 or with Pd on carbon.

4.3.2. Diastereoselective hydrogenations of the carbonyl group

Several studies on asymmetric catalytic hydrogenations of α-keto acid derivatives have been performed [39,40] only a few reports appeared on α-keto amids.

Asymmetric catalytic hydrogenations of chiral pyruvamides were carried out using palladium on carbon as a catalyst to give lactamides with the diastereoisomeric purities of up to 62% [41].

Table 4
Asymmetric hydrogenation of Schiff's bases made of prochiral ketones and a chiral amine (Fig. 7)

R	Configuration of product amine	e.e. (%) with different reduction methods		
		$Pd(OH)_2/C$	$LiAlH_4$	B_2H_6
Et	*S*	28	10	20
*i*Pr	*R*	55	10	50
*t*Bu	*R*	56	5	60

N-[(*R*)-lactoyl]-(*S*)-amino acid isobuthyl esters were obtained through the catalytic hydrogenation of *N*-pyruvoyl-(*S*)-amino acid (alanine, valine and leucine) isobutyl esters over Pd/C [42].

A linear correlation was found between the dielectric constant of the solvent and the optical purity of the product, this ratio increased with the decrease of dielectric constant. This effect could be explained by the chelation mechanism (Fig. 8) [43–49], the interaction of the two carbonyl groups in the substrates with the catalyst.

4.4. Summary of the general aspects of diastereoselective heterogeneous catalytic hydrogenations of C=C, C=O and C=N bonds in chiral compounds

- the catalyst most often used is palladium on active carbon or if it is necessary $Pd(OH)_2$ on carbon support,
- the asymmetric induction depends above all on the structure of the reactant (rigid ring structure gives higher diastereoselectivity),
- reaction conditions (temperature, polarity of the solvents, etc.) influence the selectivity also, but lesser extent,
- Prelog and Cram rule is less applicable in these heterogeneous catalytic reactions than in the homogeneous ones.

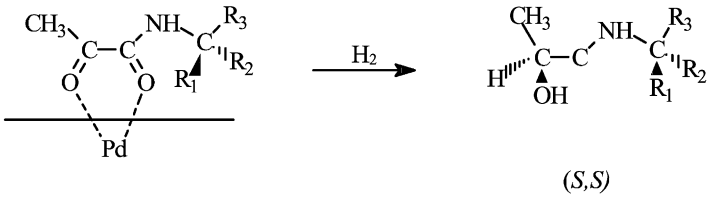


Fig. 8. Chelation mechanism of hydrogenation of chiral pyruvamides.

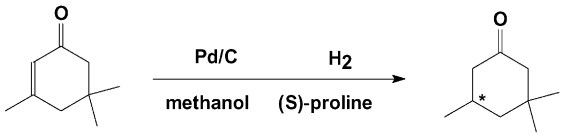


Fig. 9. Asymmetric hydrogenation of isophorone.

4.5. Asymmetric hydrogenations with (S)-proline as chiral auxiliary

(*S*)-proline proved to be an excellent homogeneous chiral catalyst in some reactions, among others in the Robinson-type condensation of α,β-unsaturated ketones. It was supposed that this property could be used in heterogeneous hydrogenations too. (Figs. 9 and 10) [50–55].

The hydrogenation of isophorone with Pd catalysts, in the presence of stoichiometric (*S*)-proline, in methanol as solvent on room temperature resulted in dihydroisophorone with enantiomeric excesses up to 80%. After the uptake of one mol hydrogen the chemical yield of dihydroisophorone decreased significantly and the major product was the alkylated proline (Fig. 11).

In the hydrogenation of acetophenone with Pd, stoichiometric (*S*)-proline and methanol as solvent, the enantiomeric excess was around 20%.

The kinetic investigation of the above mentioned reactions, circular dichroism spectroscopic studies, the assignation of the side-product alkylated proline led to the conclusion, that these reactions are only virtually enantioselective, but they are really diastereoselective according to (*S*)-proline acts as a chiral auxiliary, reacts with the substrate giving an addition and condensation product, this adduct is hydrogenated diastereoselectively. With Pd catalyst (and with Rh) this hydrogenation is not only diastereoselective, but chemoselective as well, this means that the saturation of the C=C double-bond is faster than the hydrogenolysis of the C–O bond. With Pt catalyst, the main product is the alkylated proline, because Pt is not chemoselective in this reaction.

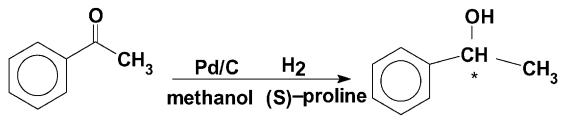


Fig. 10. Asymmetric hydrogenation of acetophenone.

4.6. Enantioselective hydrogenations with modified catalysts

The most sophisticated way of asymmetric heterogeneous catalytic hydrogenation is the use of chirally modified catalysts. The first such effective systems, however, involved Ni and Pt catalyst, but not Pd. In spite of this fact we think, that a short presentation of the Ni and Pt mediated enantioselective hydrogenations is necessary, in order to understand the later developed Pd catalyzed reactions.

4.6.1. Tartrate/NaBr modified Raney Nickel catalyst

The hydrogenation of the carbonyl group of the β-ketoesters has been the first reaction catalyzed by a chirally modified heterogeneous catalyst with high and reproducible optical yields. Izumi and his coworkers discovered this reaction in the early sixties.

The tartrate/NaBr modifier Raney nickel catalyst and its application for the reduction of several types of ketones has been extensively studied (Tables 5 and 6) (Fig. 12) [56–58]. The generally accepted working mode of this catalyst system comprises the corrosive chemisorption of the tartaric acid on the Ni surface and the interaction of this adsorbed species with the

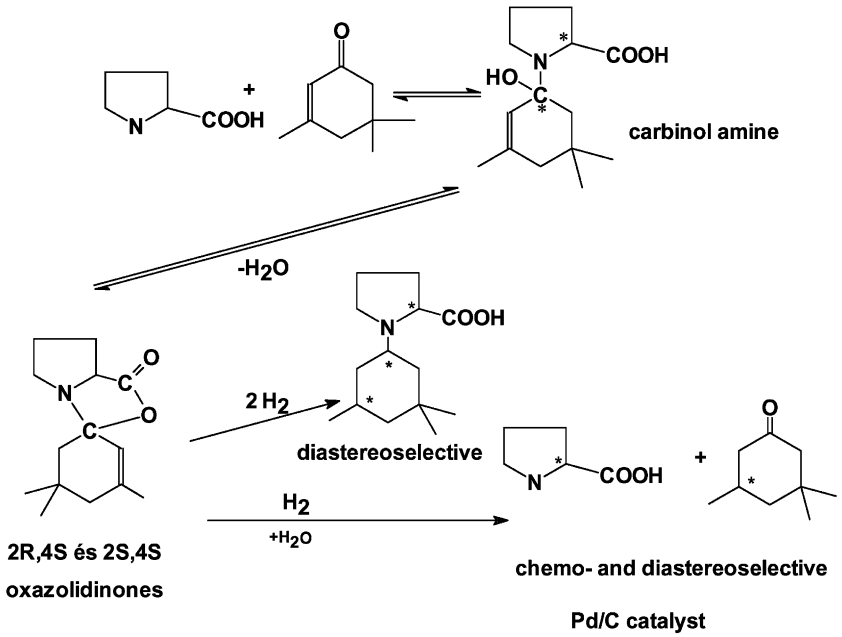


Fig. 11. The reactions taking place during the asymmetric hydrogenation of isophorone in the presence of (*S*)-proline chiral auxiliary.

substrate molecules through hydrogen-bridges between the carbonyl groups of the substrate and the hydroxyl groups of the tartaric acid.

Aliphatic ketones with an oxygen function such as an ester [57,59], a sulfoxide, a hydroxy, or an ether group in β-position can be reduced to the corresponding secondary alcohol in a good to high optical yields. Cyclic β-ketoester derivatives are hydrogenated less selective (e.e. 9–15%) [60].

The hydrogenation of β-diketones is a more complicated issue, because at the reduction of the second keto group diastereoselectivity plays also an

Table 5
The highest optical yields obtained for the hydrogenation of different β-functionalized ketones using modified hydrogenation catalyst

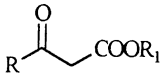
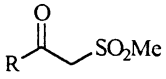
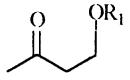
Substrate	R	R_1	e.e. (%)
	CH_3	CH_3	85
	CH_3	C_2H_5	88
	CH_3	n-C_3H_7	88
	CH_3	i-C_3H_7	88
	CH_3	n-C_8H_{17}	88
	C_2H_5	CH_3	86
	n-C_8H_{17}	CH_3	91
	n-$C_{11}H_{23}$	C_2H_5	92
	Cyclopropyl	CH_3	98
	C_2H_5		71
	n-C_5H_{11}		68
	n-C_8H_{11}		67
	H		70
	CH_3		68

Table 6
Hydrogenation of β-diketones to β-hydroxyketones and β-diols (Fig. 12)

R	Conversion (%)	Yield (%)	e.e. (%)	Meso/chiral	Chiral	
					Yield (%)	e.e. (%)
CH_3	100	90	73			
CH_3	70	–	–	8/92	–	98
CH_3	100	–	–	13/87	65	86
CH_3	100	7	–	8/92	86	91
CH_3CH_2	–	–	–	20/80	30	100
$CH_3(CH_2)_2$	–	–	–	15/85	11	100
C_6H_5	–	–	–	23/77	20	100
$(CH_3)_2CH$	100	17	59	20/80	66	85
$(CH_3)_2CH$	100	6	–	25/75	72	90

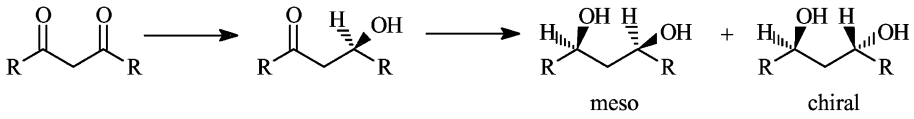


Fig. 12. Hydrogenation of β-diketones to β-hydroxyketones and β-diols.

important role. The resulting diols can be obtained in fair chemical and acceptable to very high optical yields [57,61–63].

The modification of the structure of tartaric acid proved that the modifier molecule has to be containing the two carboxyl and minimum one hydroxyl group [64,65].

4.6.2. Cinchona modified Pt catalyst

The cinchona alkaloid modified platinum catalyst was first described by Orito and his coworkers [66–69] for asymmetric hydrogenation of α-ketoesters (Fig. 13).

The alkaloids used are cinchonidine and its derivatives (Fig. 14). As catalysts, supported platinum [70–76] was found to be suitable. Iridium is also applicable, but exhibits inferior catalytic behavior [77]. Palladium and rhodium show poor performance, and ruthenium and nickel are not effective. The most frequently used supports are alumina, silica and activated carbon.

The cinchona alkaloids modified platinum catalysts were studied primarily in the hydrogenation of α-ketoesters, of ethyl and methyl pyruvate. The best enantiomeric excess was above 95% [78–88]. Later this system was applied efficiently in the hydrogenation of other prochiral reactants (Fig. 15).

Several mechanistic proposals have been made to explain the enantiodifferentiating processes. For example, it was proposed that on tartaric acid/Ni catalysts β-keto esters are hydrogenated on chirally modified nickel according to the Langmuir-Hinshelwood mechanism. Competitive reaction on unmodified sites affords racemic product [89]. It was assumed that the

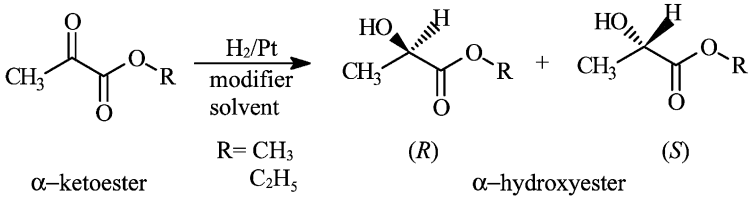
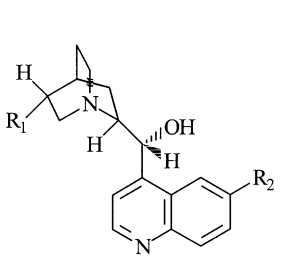
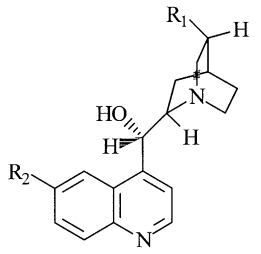


Fig. 13. Hydrogenation of ethyl pyruvate.





	R_1	R_2		R_1	R_2
cinchonidine	C_2H_3	H	cinchonine	C_2H_3	H
quinine	C_2H_3	OCH_3	quinidine	C_2H_3	OCH_3
dihydrocinchonidine	C_2H_5	H	dihydrocinchonine	C_2H_5	H
dihydroquinine	C_2H_5	OCH_3	dihydroquinidine	C_2H_5	OCH_3

Fig. 14. Cinchona alkaloids.

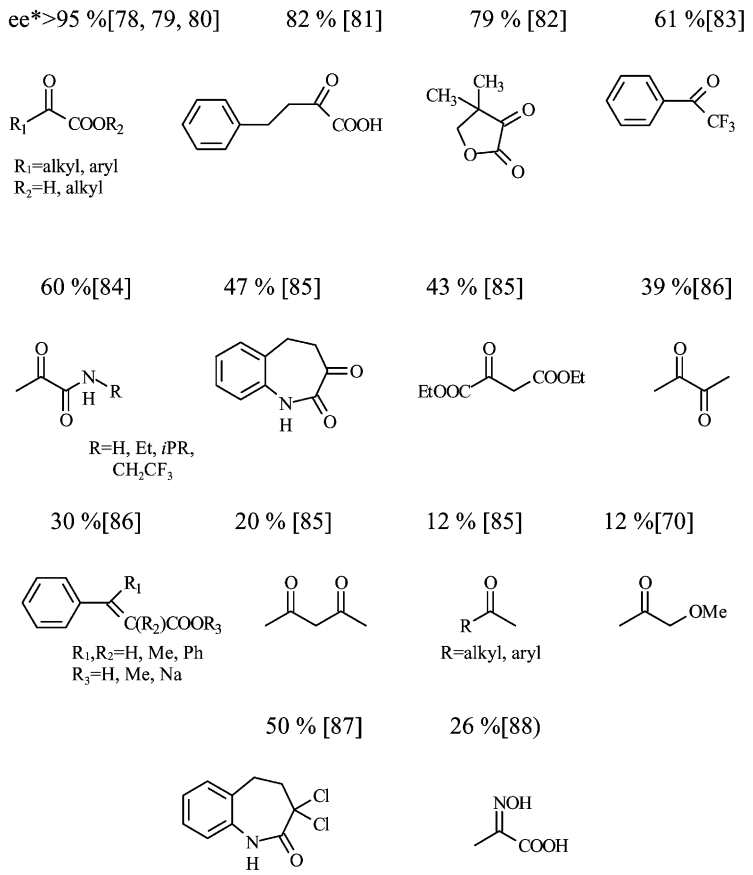
interaction between the modifier and the substrate involves hydrogen bonding through hydroxyl and carbonyl groups.

In addition to the enantioselective effect, cinchona alkaloids produce a rate acceleration also, i.e. this is an example of ligand accelerated catalysis [90]. The model of a non-close packed ordered array of cinchonidine molecules adsorbed on platinum, proposed by Wells and coworkers, was abandoned in their later study [91]. Augustine [92] deduced from the behavior of this system at low modifier concentrations that the chiral sites are formed at the edge and corner platinum atoms, which involve the adsorbed cinchonidine and a metal adatom. The different authors agreed that the quinoline ring of the modifier is responsible for the adsorption on platinum, the quinuclidine part, through the nitrogen atom, interacts with the carbonyl group of the pyruvate, and the product configuration is determined by the C8 and C9 geometry of the modifier molecule. Protonation of the basic nitrogen of the modifier increases the enantiomeric excess. Baiker and coworkers [93–96] carried out molecular modeling calculations in order to find out the likeliest conformation of the substrate-modifier adduct on the platinum surface. Margitfalvi [97,98] concluded from NMR, kinetic measurements and molecular modeling calculations that the interaction between the modifier and the substrate, which also exists in solution, changes the reactivity of the pyruvate and the conformation of the cinchonidine. The quinoline ring of the latter exerts a shielding effect on the pyruvate determining the direction of the entering of the hydrogen.

4.6.3. Enantioselective hydrogenations with modified Pd catalysts

The scope of enantioselective heterogeneous catalytic hydrogenations with chirally modified Pt and Ni catalysts is limited to the above mentioned reactants. The use of chiral auxiliaries in Pd mediated hydrogenations for similar purposes is limited, as it was demonstrated with the example of (*S*)-proline/isophorone. The enantioselectivity was remarkable, but the chemical yield was low. However, in the last decade, several chiral reactions were discovered, which are mediated by Pd catalys.

Some vinca- and morphine-type alkaloids have screened in the hydrogenation of various substrates [99]. A vinca-type alkaloid, dihydroapovincaminic acid ethyl ester (Fig. 16) proved to be an effective chiral additive in the hydrogenation of both C=C and C=O double-bonds.



*ee: enantiomeric excesses quoted correspond to highest values achieved for specific reaction

Fig. 15. Compounds enantioselectively hydrogenated using cinchonidine modified platinum catalyst.

(−)-Dihydroapovincaminic acid ethyl ester is an efficient chiral modifier in the hydrogenation of isophorone over palladium catalyst. Up to 55% e.e. could be achieved under optimized reaction conditions [100,101].

The enantioselectivity of supported Pd catalysts (Pd/C and Pd/TiO_2) depended on the support used, it turned out that lower surface area of the support and smaller dispersion of the active metal are advantageous [102–104].

Further extension of the scope of reactions, including C=C double-bonds, has recentely achieved with chirally modified palladium catalyst (Fig. 17).

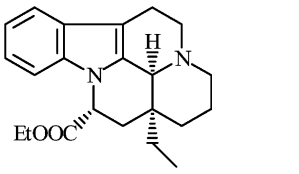


Fig. 16. (−)-Dihydroapovincaminic acid ethyl ester.

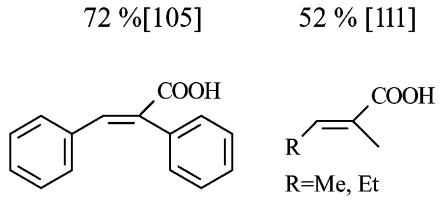


Fig. 17. Compounds enantioselectively hydrogenated using cinchonidine modified palladium catalyst.

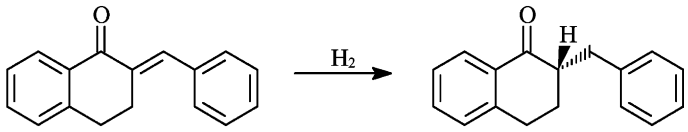


Fig. 18. Hydrogenation of α,β-unsatureted ketones.

Cinchonidine was used as a chiral auxiliary in the saturation of C=C bond of (*E*)-α-phenylcinnamic acid. The reported optical yield of (*S*)-(+)-2,3-diphenylpropionic acid was 30.5%. In the hydrogenation of the same molecule with cinchonidine modified 5% Pd/TiO_2, in the mixture of dimethylformamide and water the highest optical yield was 72% [105–109].

The hydrogenation of (*E*)-α-phenylcinnamic acid in the presence of (−)-DHVIN as a chiral modifier afforded less enantioselectivity (28%) [110].

Baiker et al. [111] proved the existence of bimolecular associates of the unsaturated carboxylic acid substrates in solution, which interact with the basic cinchonidine modifier.

Using (−)-ephedrine in the hydrogenation of (*E*)-2-benzylidene-tetral-1-one (Fig. 18) to induce the chirality, palladium on carbon as catalyst, gave an e.e. of 32% [112].

In contrast with the Pt/cinchonidine/ethyl pyruvate system, where rate acceleration was observed, in the Pd catalyzed chiral hydrogenations the reaction rate is smaller in every case than that of the unmodified reaction.

Enantioselectivity is very sensitive to the method of Pd catalyst preparation, this is valid for the other, the most effective modified catalytic systems also: Pt/chinconidine and Raney-Ni/tartaric acid [64,70].

The emergence of new prochiral substrates and chiral modifiers and new enantioselective reactions have created a need for identifying common mechanistic features in all of these reactions: the structural, reactivity- and affinity characteristics of the effective modifiers, the interactive functional groups of the prochiral substrates and the appropriate catalysts. (Fig. 19).

According to circular dichroism spectroscopic investigations and detailed study of the enantioselective hydrogenations the probable processes of enantiodifferentiation could be clarified (Fig. 17). Similar processes can take place in the Pt-cinchona and Ni-tartaric

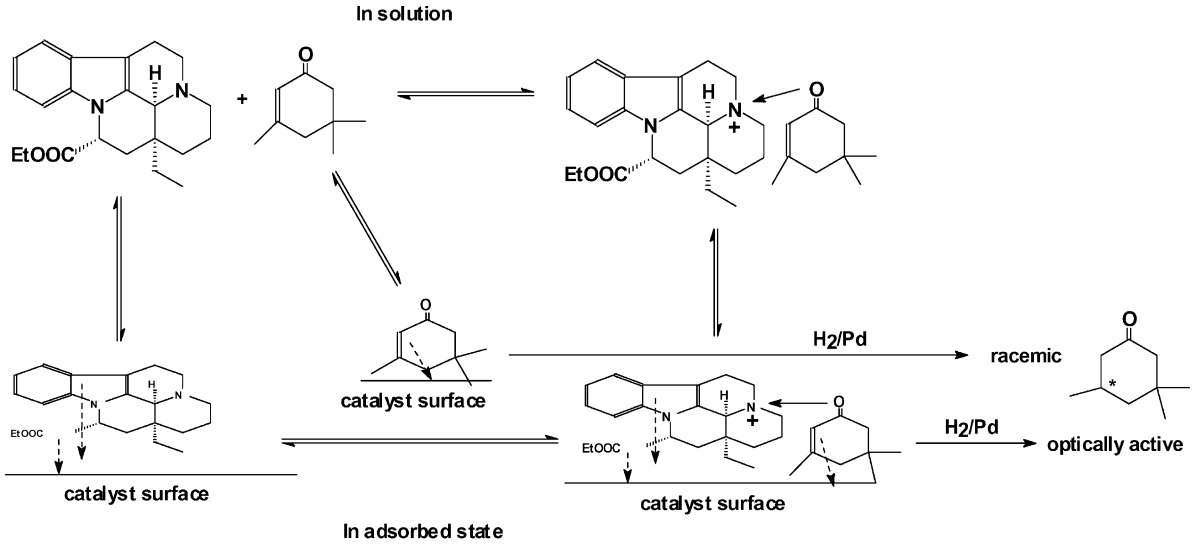


Fig. 19. Possible processes in the enantioselective hydrogenation of isophorone.

acid mediated reactions. The enantiomeric excess of the product depends in every case on the equilibrium constants of adduct forming and adsorption reactions and the relative rates of competing hydrogenations, the chiral and racemic reactions.

(−)-Dihydroapovincaminic acid ethyl ester as a chiral modifier in the asymmetric hydrogenations interacts through the basic N with the carbonyl group of the substrates. The asymmetric effect is greater if the N is protonated by a week acid as acetic acid. Strong acids terminate the interaction, because they form close ion-pairs and the anions exclude the substrate molecules [101,102].

The substrate-modifier interaction exists, according to CD, in solution, probably in the form of aggregates. They may contain in sandwich-like form substrate and modifier molecules, which probably remain in adsorbed state on the surface of the catalyst too. The aggregates may be similar to those described in enantiomer separation processes [113].

The adsorption of the modifier is directed on the surface of the catalyst, it occurs through the heteroaromatic indole part, analogous to the adsorption of cinchonidine through the quinoline ring. The adsorption strength of "quinoline" is stronger on the supported Pt than that of the "indole". This explains why cinchonidine, if it is present, controls asymmetric induction in the hydrogenation of ethyl pyruvate, even in the presence of larger amounts of (−)-dihydroapovincaminic acid ethyl ester. However, on Pd catalysts in the hydrogenation of isophorone, the adsorption of the vinca alkaloid may be stronger, as this modifier controls the enantioselection process.

The difference in the effect of the two epimers (−)- and (+)-dihydroapovincaminic acid ethyl ester can be explained by their shape: in the *cis*-epimer (−), the COOEt-group, occupying an equatorial position, can readily interact with the catalyst surface. This gives an explanation, why enantiomeric excesses induced by (−)-dihydroapovincaminic acid ethyl ester are greater than that of (+)-dihydroapovincaminic acid ethyl ester.

The specificity of a modifier is influenced by: (i) the strength of its adsorption, (ii) the strength and nature of the substrate-modifier interaction in solution, and whether it is preserved in the adsorbed state, and (iii) the 'ligand accelerating' or 'ligand retarding' effect of the modifier on the rate of the asymmetric hydrogenation reactions [101].

The 'modification' of the modifier helped to clarify further the working mode of these vinca-type chiral modifiers (Fig. 20, Table 7) [114].

The conclusions derived from the above mentioned results.

1. The difference between the effect of α,α-isomers of saturated ester and acid is small suggesting that the ester and the carboxyl group have similar anchoring capabilities.
2. The α,α-isomers of the saturated ester and acid give a larger asymmetric induction than that of the α,β-isomers, suggesting that an equatorial position is preferred for the ester or acid group.
3. Asymmetric induction solely due to the unsaturated modifier compounds (I, II) could be observed only in the Pt catalyzed hydrogenation of ethyl pyruvate, and was much smaller than that of the saturated molecules. A possible explanation for this difference can be that the ester or acid groups can exert their anchoring effect much better if they are not in the plane of the ring they are attached to.
4. The difference in asymmetric induction observed with the two epimeric esters (−)- and (+)-DHVIN was much larger than that with the acid epimers (III and IV). This may be due to the different size of the ester and carboxyl groups.

4.7. Trends in asymmetric heterogeneous catalytic hydrogenation

Some methods of asymmetric heterogeneous catalytic hydrogenation, diastereo- and enantioselective reactions mediated by Pd catalysts were surveyed. There is an acceptable demand that the chemists want to know which are the most promising methods of hydrogenation on solid catalysts for the preparation of optically active compounds.

The most elegant method is the use of chirally modified metal catalysts, among them that of Pd. The disadvantage of such reactions is their specificity; that is to say they can be used only for the enantioselective hydrogenation of a given compound, or at most, of a class of compounds. In this respect, they are similar to the enzymatic systems.

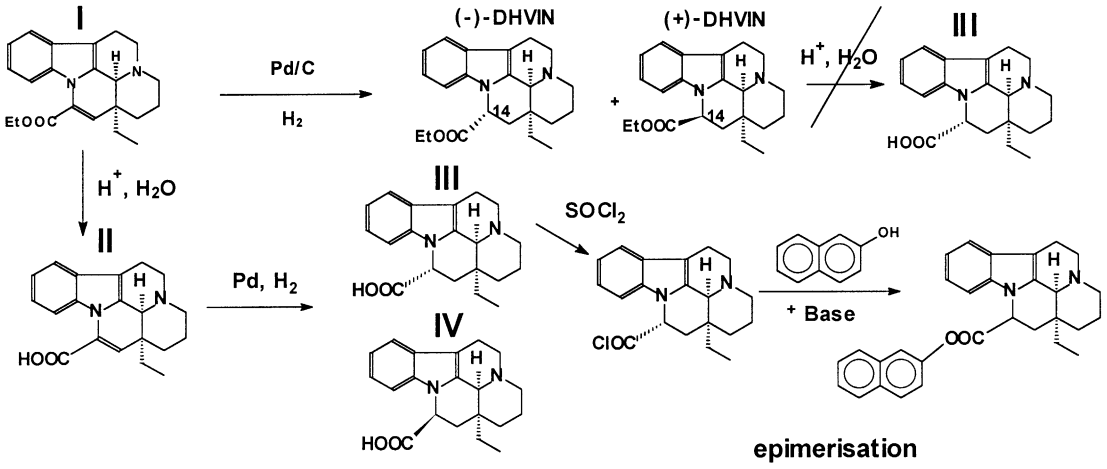


Fig. 20. The reaction-scheme of the preparation of modifiers derived from apovincaminic acid ethyl ester.

Diastereoselective hydrogenations can be applied in that case if the prochiral starting material can easily be synthesized and if necessary, the product can be separated from the residue of the chiral moiety. The synthesis of unusual amino acids serves as a good example.

A prolonged effort is the heterogenization of chiral transition metal complex catalysts for enantioselective hydrogenations. The usual method to 'heterogenize' a homogeneous catalyst has been to attach a ligand to a solid support material and then react these ligands with a metallic species to prepare the supported complex. The disadvantage of such catalysts is the leaching of the precious metal and that it is less active than the corresponding homogeneous species.

Augustine et al. anchored homogeneous complexes, chiral ones too, with heteropoly acid to support materials and used them in enantioselective hydrogenations with success [115–117]. Their results serve as a good basis for investigations of exploiting all possibilities of such anchored catalysts (Table 8).

Among synthetic methods the chemo- and stereoselective hydrogenations, those too which are catalyzed by Pd, play an important role. For practical, industrial application the heterogeneous catalytic reactions are advantageous, independently from that whether they are enantioselective or diastereoselective. It is an often-heard objection that the optical yield in these reactions rarely can compete with that of the homogeneous catalyzed or enzymatic reactions. From

Table 7
Relation between structure, substituents of the modifiers and their asymmetric effect in hydrogenations

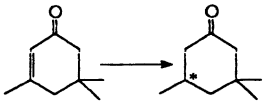
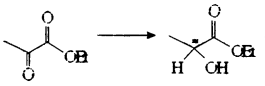
Reaction (mol substrate)		Catalyst (g)	Enantiomeric excess (%) modifiers					
			(−)-DHVIN	(+)-DHVIN	I	II	III	IV
	0.05	Pd black 0.3	55	15	53	41	50	38
	0.1	Pt/Al_2O_3 0.1	30	14	14	7	29	22

Table 8
Perspectives of different hydrogenation methods for the preparation of optically active compounds

Methods	Chiral modification of the catalysts	Use of chiral auxiliaries in the reaction mixture	Anchored homogeneous catalysts	Forming new chiral compound with a chiral reactant and carry out diastereoselective hydrogenation
Examples	Pt/cinchonidine/ethyl pyruvate Pd/cinchonidine/phenyl cinnamic acid	Pd/(*S*)-proline/ isophorone	Rh (DIPAMP)/PTA/Al_2O_3 dehydroaminoacids	Schiff bases from a chiral amine and a prochiral ketone/Pd/C
Optical purity	Good ⇒ excellent	Good	Good ⇒ excellent	Poor ⇒ excellent
Chemical yield	Good	Poor	Good	Acceptable
Scope	Narrow	Narrow	Increasing	Broad
Industrial application possibility	Limited	No	Promising	Hopeful

practical point of view, however, the combination of an asymmetric, less selective catalytic reaction and following resolution of the products can be competitive. Namely, the resolution of the non-racemic mixture of stereomers is simpler.

Acknowledgements

The authors gratefully acknowledge the financial support Hungarian OTKA Foundation under the contract number T 029557 and T 025041, as well as that of the Ministry of Education, FKFP 0017/1999.

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