Chapter 5

ASYMMETRIC HYDROGENATION OF 2-OXOCARBOXYLIC ACID ESTERS AND UNSATURATED CARBOXYLIC ACIDS ON MODIFIED PT AND PD CATALYSTS

Abstract

Although the "Orito reaction", a highly effective enantioselective heterogeneous hydrogenation of 2-oxocarboxylic acid esters on Pt-alumina catalysts modified with cinchona alkaloids, was elaborated long ago, only during the 90's did a rapid growth of studies occur in this area. The reaction received strong development in experimental and theoretical aspects. Now about 300 papers have been published on the elaboration of the new catalytic systems with natural and synthetic chiral modifiers. Based on a number of *alpha,beta*-dicarbonyl-groups, a number of types of substrates and a number of new catalysts supported on zeolites were found. Based on detailed mechanistic studies, practical processes, such as the syntheses of the pharmaceutical, (*R*)-(-)-pantolactone, were accomplished with enantioselectivities above 95%.

5.1. General

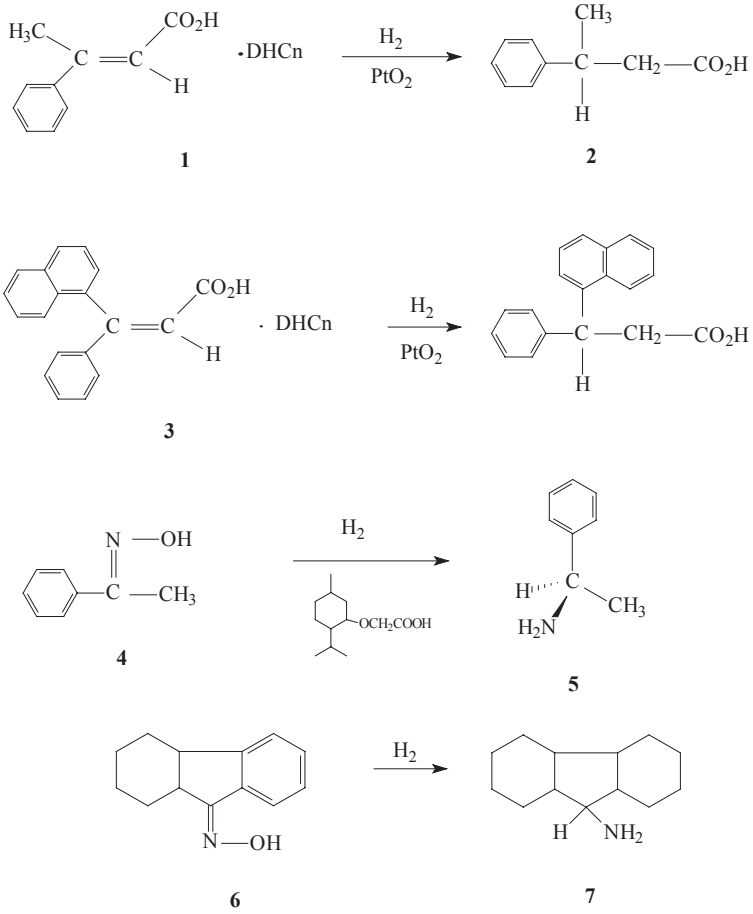
The most efficient enantioselective heterogeneous hydrogenation catalysts to date are the Raney nickel catalysts, modified with tartaric acid, for the hydrogenation of the C=O group of 3-oxocarboxylic acid esters; the alumina supported platinum catalysts, modified with cinchonas, for the hydrogenation of the C=O group of 2-oxocarboxylic acid esters (and *alpha*-keto lactones); and supported palladium catalysts, modified with cinchona and other compounds, the for hydrogenation of C=C bond in prochiral unsaturated carboxylic acids. The latter two catalytic systems have been studied intensively, especially recently, and produced extremely high enantio-selectivities, quite comparable with results attained with the chiral metal-complex catalysts. As for Ni catalysts, it took about fifty years to improve the first results on asymmetric hydrogenation of C=O and C=C bonds in prochiral compounds (ethyl methyl ketone, 2-phenylcinnamic acid) on metal-quartz catalysts (see, Chapters 1 and 2, and Schwab et al. [1], Terent'ev et al. [2], Klabunovskii et al. [3], and others [4-12]), and increase from the first *ee* of 0.1% to the *ee* of 98.6%, from the hydrogenation of ethyl 3-cyclopropyl-3-oxopropionate on Raney Nickel, modified with (2*R,3R)*-tartaric acid (Nakagawa et al. [13]).

Enantioselective heterogeneous hydrogenations on platinum-alumina catalysts modified with cinchonidine (Cnd) is an asymmetric organic reaction

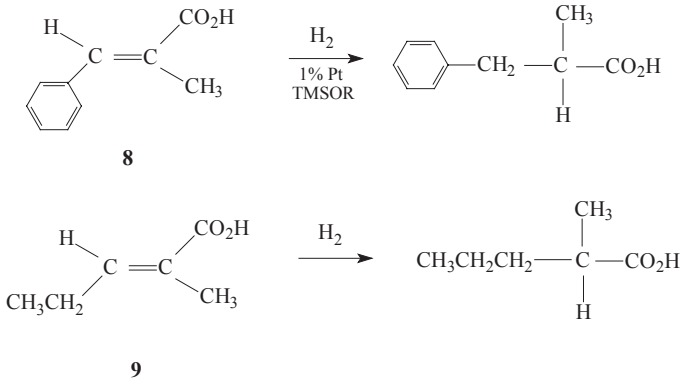
that has become a very intensively studied heterogeneous process. That can be explained by high enantioselectivities and enhanced reaction rates leading to important chiral compounds with high enantiomeric purity, up to 98%. The catalyzing metal, platinum, may be supported on a diverse range of materials including silica, titania, and charcoal, but only with alumina are the best results obtained for the enantioselective hydrogenation of the oxo-group in 2-oxocarboxylic acid esters, mainly pyruvates. High enantiomeric excesses are comparable to the effectiveness of chiral homogeneous complex catalysts when 5% Pt-alumina catalyst is modified with cinchona alkaloids having a particular stereostructure, like cinchonidine, or better 10,11-dihidrocinchonidine (DHCnd), or 9-methoxy-10,11-dihydrocinchonidine (MeODHCnd). There are many reviews summarizing the recent studies of this catalytic system and the mechanism of the enantioselective heterogeneous hydrogenation [14-28].

The first attempts to use the asymmetric hydrogenation of prochiral compounds with C=C and C=N bonds over chiral modified heterogeneous Pt and Pd catalysts were not effective. Lipkin and Stewart [29] found that the (+)-10,11-dihidrocinchonidine salt of 3-methyl-3-phenylacrylic acid (*beta*-methylcinnamic acid), **1**, can be hydrogenated over Adams PtO_2 at 3 bar hydrogen in ethanol solution into 3-phenylbutanoic acid, **2**, with an *ee* of 8-9%. A lower enantioselectivity was observed in the hydrogenation of the (+)-10,11-dihidrocinchonidine salt of the 3-(1-naphthyl)-3-phenylacrylic acid [*beta*-(*alpha*-naphtyl)cinnamic acid], **3**. Similarly, in the hydrogenation of the C=N bond in acetophenoxime, **4**, on Pt-black at room temperature (RT) in the presence of menthoxyacetic acid modifier, (*R*)-(1-phenylethyl)amine, **5**, was obtained with an *ee* of 9.22%, and the hexahydrofluorenon oxime, **6**, was hydrogenated into amine **7**, with an optical rotation of $[\alpha]_{589} = +6.8^{o}$ [30] (Scheme 5.1.).

Smith et al. [31-33] elaborated a new type of the enantioselective modified heterogeneous catalysts by attaching chiral silyl ethers to Pt and Pd surfaces. They found an effect of such "siliconation" on the catalytic activities and selectivities of highly dispersed Pd and Pt catalysts. Chiral alkoxytrimethylsilanes, R^*OSiMe_3, appeared to partly decompose on Pd and form residues which impart enantioselectivity to the catalytic surfaces. Three different types of 1% Pd-silica catalysts were prepared with modification by the silyl ethers of (1*R*)-(-)-nopol, (1*R*)-(-)-myrtenol, and (1*S*)-*endo*-(-)-borneol and were assessed by the liquid phase hydrogenations of the prochiral acids, 2-methyl-3-phenylacrylic acid (*alpha*-methylcinnamic acid), **8**, and (*E*)-2-methylpent-2-enoic acid, **9** (Scheme 5.2.). The resulting catalysts possed enantioselective activity in hydrogenation of C=C bonds with an *ee* of 22.5%. Asymmetric hydrogenations of prochiral compounds containing C=C and C=O bonds also were successful using immobilized chiral complexes [34,35].



Scheme 5.1.



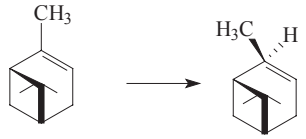
Scheme 5.2.

Immobilization via entrapment is a frequently used method of heterogenization. Mesoporous solids like silicas with pore diameters in the range of 2-25 nm were used by Raja et al.[36] for heterogenization of cationic Rh and Pd complexes with chiral ligands: $[Rh(COD)X]^+CF_3SO_3^-$ and $[Pd(allyl)X]^+CF_3SO_3^-$ in the enantioselective hydrogenation of methyl benzoylformate into methyl mandelate in methanol solution at 40°C and 20 bar hydrogen. Chiral ligands, X, used in Rh complexes are: (*S*)-(-)-2-aminomethyl-1-ethylpyrrolidine (1); (1*R*,2*R*)-(+)-1,2-diphenyl-ethylenediamine (2); and (*S*)-(+)-1-(2-pyrrolidinylmethyl)pyrrolidine (3). For Pd complexes only ligand (3) was used. The examinations showed that homogeneous Rh complexes with ligands (1) and (2) revealed no asymmetric effects. Only the more constrained ligand (3) gave *ee*'s of 53-55% for Rh and Pd complexes. Rh and Pd complexes with ligand (3) immobilized on silicas showed high enantioselectivities (*ee* of 94%) only on silicas with pores size 38-60 A°.

A rhodium complex with chiral phosphane ligand was also intercalated into sodium hectorite by cation exchange (Sento et al.[37]). The intercalated compound was characterized by FTIR, XRD, and TEM and the basal spacing of the compound was estimated to be 2.29 nm. This novel heterogenized catalyst exhibited a characteristic chiral as well as size recognition of the substrate molecule (like the "Tailor-made compounds" method used earlier by Balandin [38] in the hydrogenation of tripticene derivatives over Ni) and was used in enantioselective hydrogenation of the itaconates (methylenesuccinic acid esters).

Selectivity of smectite-intercalated chiral Rh-complexes depended on the interlayer spacing of the swollen clay (Sento et al.[39]). Smectites possessing the tilting angle of 90° (the elevation angle of the longitudinal straight chain to the layer plane of the smectite) modified with both chiral $[Rh(COD)(S,S\text{-DIOP})]ClO_4$ complex (A) and bulky quaternary dimethyldioctadecylammonium bromide (B) as structural tuning guests were novel host-guest catalysts. With a mixture of catalysts {18.3 (A) + 42.8 (B)-LiTN} included into Li-taeniorite {where "TN" is $Li[Mg_2Li](Si_4O_{10})F_2 \times H_2O$} at 20°C in methanol, the hydrogenation of the C=C bond in (1*R*)-(+)-alpha-pinene, **1** (Scheme 5.3.), produced an excess of *exo*-pinane with 92% selectivity in comparison to an *ee* of 87.5% from the hydrogenation with the homogeneous [Rh(DIOP)] catalyst. The hydrogenation of the C=O bond in 4-*tert*-Bu-cyclohexanone, **2**, revealed a diastereoselectivity (*cis/trans* ratio) of 99.6% in comparison with 98.6% for the corresponding homogeneous catalyst.

Copolymerization is also a frequent method of heterogenization. A water-soluble polymer was prepared by coupling a chiral phosphane, PPM, to polyacrylic acid and used for the immobilization of $[Rh(NBD)_2]OTf$. At 22 bar of hydrogen in water or in a biphasic (water-AcOEt) system, this catalyst accomplished the enantioselective hydrogenation of the precursor of *N*-AcPhe with an *ee* of 89 % (Malmstrom et al. [40]).



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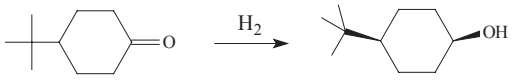

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Scheme 5.3.

Poly[(*S*)-glycidylmetacrylate]co-ethyleneglycol dimethacrylate, an enantiopure copolymer, was transformed into optically active polyamino alcohols. This copolymer was used as a ligand of a Ru complex catalyst in the asymmetric hydrogenation of acetophenone (Herault et al. [41]).

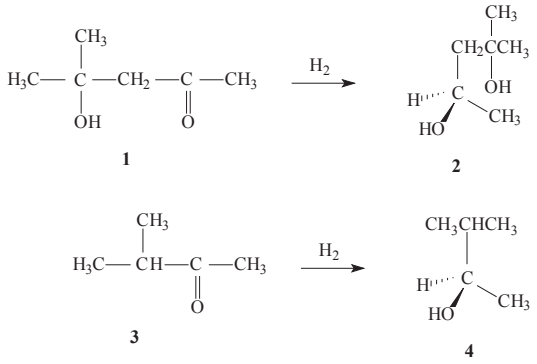
A polymerizable rhodium complex, [Rh{(+)-DIOP}(A)], {where (A) is the deprotonated form of the ligand ethyl 2-acetoacetoximethacrylate}, was obtained by the reaction of [Rh(COD)(A)] with (+)-DIOP at -80^{0}C. Supported chiral complexes have been obtained by the copolymerization of [Rh{(+)-DIOP}(A)] with *N,N*-dimethylacrylamide. The enantioselective hydrogenation of the precursor of (*S*)-phenylalanine methyl ester produced the amino acid with an *ee* of 67%. (Mastrorilli et al. [42]).

Another approach is to build up a polymer network around a complex. Pavlov et al.[43] studied a chiral liquid crystal matrix, in which the Wilkinson catalyst, [$RhCl(PPh_3)_3$] was embedded in cholesteryltridecanoate and catalyzed the enantioselective hydrogenation of 2-acetamidocinnamic acid into *N*-acetylphenylalanine with an *ee* of 60% (see details in Chapter 3).

The heterogenized [Rh(BPPM)] complex embedded in micelles in a membrane reactor (Dwars et al.[44]) proved to be enantioselective in the hydrogenation of precursors of *alpha*-amino acids.

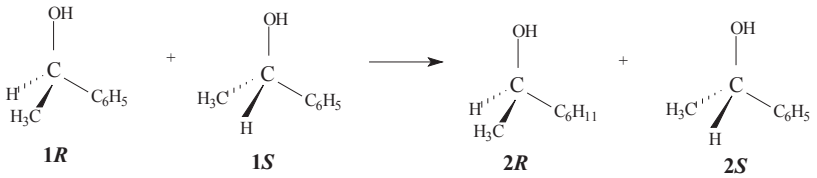
Recently important results were obtained using catalysts supported on chiral natural materials containing polypeptides and polysaccharides. According to Yin et al. [45] a wool-Pd complex at 30^{0}C and 1 bar hydrogen was found to catalyze the asymmetric hydrogenation of 4-hydroxy-4-methylpentan-2-on (diacetone alcohol), 1, into (*R*)-2-methylpentane-2,4-diol, 2, with an *ee* of 73% and 3-methylbutan-2-one, 3, into (*R)*-3-methylbutan-2-ol, 4, with an *ee* of 100% (Scheme 5.4.).

The optical yields were greatly affected by the Pd content in Pd-wool complexes. The catalyst could be used several times without appreciable change in *ee*.



Scheme 5.4.

Yuan et al. [46] found that a Pt-silica catalyst bound with chitin (poly-*N*-acetylglucosamine) is active at 30°C and 1 bar hydrogen in the kinetic resolution of racemic 1-phenylethanol, (1*R* and 1*S*), producing (*R*)-(+)-1-cyclohexylethanol, (2*R*) (Scheme 5.5).



Scheme 5.5.

The optical selectivity of the product amounted to 100% under optimal conditions (unfortunately, the *ee* was calculated only from the optical rotation of the product mixture), but was greatly affected by the circumstances (Pt content of the silica-chitin complex, reaction temperature, solvent, conversion and the amount of added HCl). The catalyst proved to be very stable and the optical selectivity was maintained at 100% upon reuse (see also Blaser [47,48]).

Yin et al.[49] have found a similar catalyst based on a Pd-silica complex bound with chitosan (polyglucosamine) that is highly enantioselective at ambient conditions in the hydrogenation of acetophenone, propiophenone, 3-methylbutan-2-one and 4-methylpentan-2-one into their corresponding alcohols with *ee*'s of 99-100 %.

Padgett, Beamer et al. [50,51] prepared a novel type of catalysts composed of Pd supported on specifically prepared silica gels which had been precipitated from Na silicate with HCl in the presence of sulfates of cinchonidine (Cnd), cinchonine (Cn), quinidine (Qnd), and quinine (Qn). These catalysts proved to be enantioselective in the hydrogenation of 2-methylcinnamic acid with *ee*'s of approximately 3% (see the structure of cinchona alka-

loids used for the enantioselective hydrogenation of *alpha*-keto esters in Scheme 1.6. in Chapter 1).

Later, several groups studied another type of catalysts composed of Pt (and Pd) supported on alumina and modified with cinchona alkaloids. Striking results were obtained using this new type of modification of Pt catalysts with cinchona alkaloids. Platinum supported on carriers, mainly alumina, and modified with alkaloids, exhibited very high enantioselectivities in the hydrogenation of 2-oxocarboxylic esters into 2-hydroxycarboxylic esters. It is interesting to note that before the discovery of this reaction, Orito's group [52-56] in 1976-1977 studied a supported Ni-Kieselguhr (1:1) catalyst modified with (2*R,3R*)-tartaric acid and promoted with 1% noble metals (Pt, Pd, Rh, or Ru) in the hydrogenation of methyl acetoacetate (MAA) to MHB and found small increases in *ee*'s (for catalysts promoted with above mentioned metals the *ee*'s were 61.9%, 55.3%, 55.6%, and 49.5%, respectively) in comparison with the catalyst without these promoters, from which an *ee* of 53.2% was obtained [52] (in this book *ee* values are corrected in comparison with data given in papers).

Later, in 1979, Orito et al.[57-61] studied novel catalysts containing noble metals (Pt-alumina and Pt-charcoal modified with cinchonidine) in the hydrogenation of MePy, MeBf, and EtBf. Optical yields in the hydrogenation of ethyl benzoylformate, EtBf, to (*R*)-(-)-ethyl mandelate reached 89.5% [57,58].

The chemical yield of methyl mandelate reached 87-92% and the *ee* changed, depending on the nature of the solvent, from 61.5% in $MeCO_2Me$ up to 81.9% in $EtCO_2Me$ [57,61]. EtBf was hydrogenated on Pt-C-Cnd with a somewhat larger *ee* in comparison to MeBf [58]. Enantioselective ability of the catalysts strongly depend on the condition of preparation, such as the conditions of reduction of charcoal supported H_2PtCl_6 and the nature of the carrier. Thus, maximum optical yield was observed only when using the commercial charcoal "Norit Extra" of Japanese origin and when the reduction of the Pt-salt supported on the charcoal was performed in sodium formate solution. If after reduction the catalyst was treated with acetic acid and heated in flowing hydrogen, the optical yield was raised 4-5%. The role of AcOH as a solvent will be considered later (see Part 5.5.).

Using alumina instead of charcoal as a carrier of Pt yielded no advantages in the hydrogenation of EtBf, but in the hydrogenation of MePy with addition of alkaloids, Pt-alumina proved to be more effective then Pt-C with the best *ee* being 86.6% [57-61]. Modification of 5% Pt-alumina catalysts with Cn and Qnd were less effective than modification with Cnd and Qn and resulted in configurational enantiomer (*S*)-(+)-MeLa instead of (*R*)-(-)-MeLa. This fact indicated that the configuration of the resulting hydroxy ester is determined by the configuration of the C-8 and C-9 centers in the alkaloid molecules.

Procedures for the preparation of such catalysts for asymmetric hydrogenations are very simple. For example, 5% Pt on carbon catalyst is simply treated with a 1% alcoholic solution of Cnd at 25^0C. The product is washed and used in the hydrogenation of MeBf in benzene solution at 60 bar hydrogen and 25^0C.

Orito's works [57-61] did not attract any attention for a long time; only ten years later did great interest arise in this system now called "Orito reaction", because it was developed by Orito in the National Chemical Laboratory of Industry (Tokyo). Since then detailed studies of these chiral modified Pt and Pd catalytic systems have been performed by several groups: Blaser (Novartis, at present Solvias Basel)[22,26-28,62-78], Baiker (ETH, Zurich)[17-21,79-118], Perez (Coll. France, Paris)[119], Nitta (Techn. College, Niihama)[120-140], Wells and Hutchings (Univ. Hull and Univ. Cardiff)[23,24,141-154,276], Margitfalvi (Centr. Res. Inst. Acad. Sci., Budapest)[155-162], Tungler and Sheldon (Techn. Univ, Budapest and Univ. Delft)[163-167,230], Bartok (Univ. Szeged)[168-195], Reschetilowski (Techn. Univ., Dresden)[196-201], Smith (Southern Illinois Univ., Carbondale)[31,33,171,173,202-204], Augustine (Seton Hall Univ., South Orange)[205-206], and Blackmond (Univ. Hull)[207-212]. Other metal catalysts modified with tartaric acid were studied by the groups of Izumi and Tai (Inst. Protein Res., Univ. Osaka)[213-219], Klabunovskii (Inst. Org. Chem, Acad. Sci., Moscow)[2,7,9,43,167,220-223], and Yasumori (Inst. Tech., Tokyo)[224-226].

The research works mentioned above were aimed mainly in the following directions:

- stereochemical control of the reaction determining the absolute configuration of the products and chirodiastaltic interactions [182]
- effect of the modifier structure
- conditions of the reactions and the properties of the catalysts: the nature and structure of metal catalysts and carriers
- detailed mechanism of the reaction.

The exclusive stereospecificity of this reaction was examined using the system of Pt-alkaloid-ethyl pyruvate. It was found that the optical yield and the rate of the reaction strongly depend on many parameters:

a) properties of catalysts
   - size of catalyst crystallites
   - nature of precursors and the preparation mode of the catalyst
   - preliminary treatment of catalyst

b) procedure of modification of catalysts
   - the structures of alkaloid molecules
   - condition and mode of modification
   - quantities of the alkaloid added

c) structure and purity of substrate molecules

d) effect of solvents
e) conditions of reaction
- temperature and hydrogen pressure
- hydrogen concentration in the solution and the extent of conversion.

Large enantioselective effects were observed only in the cases of Pt-alumina-*alpha*-keto ester systems. *Beta*-keto esters or *beta*-diketones can not be hydrogenated enantioselectively by this catalytic system. The best conditions of the reaction were the following: a solution at 25°C, hydrogen pressure up to 10 bar, Pt crytallites larger than 2 nm and supported on *gamma*-alumina, 10,11-dihydrocinchonidine (DHCnd) or 9-methoxy-10,11-dihydrocinchonidine (MeODHCnd) as best modifiers. Under optimum conditions the reaction rate was high and the optical yield of *alpha*-hydroxy esters reached above 95%.

The mechanism of hydrogenation of pyruvates consists of the addition of dihydrogen to the adsorbed '*trans*' form of pyruvate leading to (*R*)-(-)- or (*S*)-(+)-lactates, depending on the stereostructure of the alkaloid-modifier. The great peculiarity of this reaction is the sharp increase in the rate of hydrogenation in the presence of modified catalyst, both when the catalysts was preliminarily treated with the alkaloid or when the modifier was added simply to the reaction mixture. This alkaloid *in situ* effect is explained by the phenomenon of "ligand acceleration" (Jacobsen, Sharpless et al. [227]).

Recently great interest arose in the process of preparation of optically active 2-hydroxycarboxylic acids and their esters. Especially concerning the preparation of lactic acid (and lactates) and mandelic acid (and mandelates) using heterogeneous asymmetric hydrogenation of the corresponding 2-oxocarboxylic acids and esters over Pt-alumina catalysts in the presence of cinchona alkaloids as chiral modifying agents. Enantiomeric excesses of the products in this process reached above 95% in the best cases.

Using cinchonidine as a modifier of Pt-alumina catalysts, the reaction resulted in the formation of products with preponderances of one enantiomer of the resulting 2-hydroxycarboxylic acid or ester of (*R*)- configuration. But in many papers devoted to this process there is some confusion in the assignment of configuration to the optically active acid (or ester) [167]. Even the same authors (Blaser, Orito, Baiker) in many of their own papers gave either correct or incorrect assignments of the sign of optical rotation to the configuration of lactate or mandelate.

It is well known from monographs (for example, see [228]) that (*S*)-lactic acid and its lactates (MeLa, EtLa), and (*R*)-mandelic acid and its mandelates (MeMn, EtMn) have (+)-rotations (at 589 nm), while the (*R*)-enantiomers have the (-)-rotation. Thus, (*S*)-(+)-lactates correlate configurationally with (*S*)-(+)-mandelates and (*S*)-(+)-butan-2-ol. Similar correlations apply to

enantiomers (*R*)-(-)-mandelic and (*R)*-(-)-lactic acids. These correct correlations were accepted e.g. in the papers by Minder, Baiker et al.[92], and Orito et al. [57,58,60]. On the other hand the incorrect (*R*)-(+) and (*S*)-(-) correlations were published by Orito et al.[59], Sutherland, Wells et al. [141], Reschetilowski et al. [197,200], Blaser et al.[62,65], Wehrli, Baiker et al.[78,80], Zuo [229], and Tungler et al.[230]. To avoid these confusions and to emphasize that (-)-rotating 2-hydroxycarboxylic acids and their esters have (*R*)-configuration, while (+)-rotating enantiomers have (*S*)-configuration, in this book the corrections will be inserted into all cited papers (interesting to note that most salts of (*S*)-(+)-lactic acid are levorotatory, therefore $[\alpha]_{589}$ of L-(+)-lactic acid is -13.5°, if it is measured in an 1.5 N NaOH solution).

5.2. Properties of catalysts

5.2.1. Nature of metal

The use of catalysts modified with cinchonidine (Cnd) based on Rh-alumina or Ir-alumina yields moderate *ee*'s (around 30%) in the enantioselective hydrogenation of pyruvates. Catalysts composed of Pd-C and Ru-alumina were found to produce lower enantioselectivities and Raney Ni modified with (2*R*,3*R*)-tartaric acid was inactive for this reaction (Blaser et al. [62]). Platinum catalysts were found to be most suitable. The enantioselectivity strongly depends on the conditions of the preparation, even on the conditions of the reduction of H_2PtCl_6. Thus a high optical yield (*ee* of 89.5%) was reached using commercial "Norit Extra" carbon and preparing the catalyst by reduction of the Pt-salt with sodium formate (Orito et al. [58]). If, after reduction, the catalyst was treated with acetic acid and heated in flowing hydrogen, the optical yield from hydrogenation of EtBf increased by 4-5%.

5.2.2. Nature of carrier

Using alumina instead of carbon as the carrier of Pt has no advantage in the hydrogenation of EtBf, but in the hydrogenation of MePy, with addition of alkaloids, Pt-alumina was more effective than Pt-C producing the best *ee* of 86.6%.

Activated carbons were oxidized different ways for the preparation of Pt-C catalysts. Such catalyst were modified with (-)-Cnd and used in the hydrogenation of MePy. After activation, their catalytic activities depend on the concentration of remaining surface oxygen measured by XPS (Fraga et al.[231]).

Farkas and Tungler et al. [232] studied the support effects in the enantioselective hydrogenation of isophorone over Pd catalysts prepared on different carbon supports with different specific surface areas and on activated carbons with different surface chemistries. The Pd catalysts, obtained by different reduction methods of the catalyst precursors had different dispersions, and the

low dispersions turned out to be advantageous for high enantioselectivity in the hydrogenation of the C=C bond in isophorone.

Various Pd-black catalysts modified with DHVin differing in their preparation method showed different *ee's* from the hydrogenation of isophorone (Farkas and Tungler et al. [233]).

Solvent	5% Pt-C *ee* (%)	5% Pt-alumina *ee* (%)	Addition of 0.1 g alkaloid
None	74.0	-	None
MeOH	64.6	32.6	None
MeOH	71.2	86.6	Cnd
EtOH	78.7	83.2	Cnd
iPrOH	72.2	80.6	Cnd
EtOH	76.6	-	Qn
MeOH	-	82.4	Qn

Table 5.1. Asymmetric hydrogenation of methyl pyruvate (MePy) to (*S*)-(+)-methyl lactate (MeLa) on 5% Pt-C and 5% Pt-Alumina catalysts modified with supplemental addition of different alkaloids in different solvents (according to Orito et al. [59]).

The hydrogenation of MePy to (*R*)-(-)MeLa proceeded somewhat less effectively; the *ee* values increased from 64% to 73.1% in the series of solvents, THF, MeOH, AcOEt, and iPrOiBu, But it was found that hydrogenation without solvent was even somewhat more effective yielding an *ee* of 74%. The addition of 0.1 g of Cnd to that reaction mixture did not affect the *ee* value, whereas addition of Cnd or Qn in the presence of solvent increased *ee* (Table 5.1.).

5.2.3. Zeolites as carriers

The steric structure of the matrix-carrier can make an additional contribution to the asymmetric reaction, especially if the carrier contains chiral characteristics. Thus, Smith et al. [202] showed that *alpha*-cyclodextrin as the host compound can induce asymmetric reactions in the reduction of acetophenone and Tanaka et al. [234] showed that the pyridine-borane-cyclodextrin system induces chirality with an *ee* of 91%. Pd supported on a copolymer of *beta*-cyclodextrin-epichlorhydrin hydrogenates 2-methylpent-2-enoic acid with an *ee* of 9.3% whereas Pt supported on *beta*-cyclodextrin polymer produced an optical yield of up to 15.7% (Smith et al. [202]).

Zeolites can be used as supports for the preparation of chiral heterogeneous catalysts in different ways [235]:

a) anchoring chiral complexes by covalent bonds

b) encapsulating large chiral complexes
c) modifying zeolites with chiral compounds

Method a) was used by Corma et al. [236-239] to prepare heterogenized hydrogenation catalysts. Proline based ligands were anchored through their silanol groups to the walls of modified USY zeolite producing a "super-micropore" system with 1.2-3 nm pore sizes. Rh complexes of these immobilized ligands were active catalysts in the enantioselective hydrogenation of 2-acetamidocinnamic acid to *N*-acetylphenylalanine.

Method b) consists of the encapsulation of voluminous complexes within the micropores of zeolite. It was used in the enantioselective epoxidation on a Mn(III)Salen complex-zeolite catalytic system [240-242].

Method c) is exemplified in the chiral modification of surfaces of zeolites with chiral compounds. Sundarababu et al. [243] modified NaX and NaY zeolites with (-)-ephedrine and used them in the asymmetric photolysis of ketones with *ee*'s above 10%. A strange behavior of the nature of carriers for the configuration of products in the latter reaction was observed: the NaY-(-)-ephedrine zeolite system gave (+)-rotating products, while the NaX-(-)-ephedrine zeolite system gave (-)-rotating products. Zeolite H-Y modified with (*R)*- or (*S*)-dithiane-1-oxide showed catalytic activity in the asymmetric decomposition of racemic 2-butanol (Hutchings) [244].

This result raised hopes of modifying zeolite supported metals by chiral compounds and using these catalysts in asymmetric hydrogenations. Nitta et al. [132] used Ni catalysts supported on Zeolite Y (specific area 550 m^2/g) in the asymmetric hydrogenation of the *beta*-keto ester MAA to MHB. The catalysts (Ni:Zeolite Y = 1:1) were prepared by precipitation of Ni on the Zeolite, followed by calcination and reduction of the resulting catalyst in a hydrogen stream. Modification of the catalyst was carried out in an aqueous solution of tartaric acid at pH 5.1. This catalyst produced an *ee* of 45.6% in the hydrogenation of MAA to MHB at 10 bar hydrogen and 60^0C. For comparison, under the same conditions, a catalyst composed of Ni-silica modified with (2*R,*3*R*)-tartaric acid gave MHB with an *ee* of 56.2%. Also modified Ru ion-exchanged zeolite catalysts were used in the enantioselective hydrogenation and diastereoselective hydrogenations of cyclic *beta*-keto esters [245-247].

The first example of an enantioselective hydrogenation reaction in the gas phase was published byHutchings's group [153,154,244]. They accomplished the asymmetric decomposition of racemic 2-butanol with rather good diastereoselectivity using a Y zeolite modified with chiral dithiane oxide.

Reschetilowski et al. [196-201] elaborated a novel Pt catalysts supported on zeolites, which proved to be rather enantioselective, effective, and stable in the liquid phase hydrogenation of EtPy. Pt-zeolite (5%) was prepared by impregnating the zeolite with an aqueous solution of $H_2Pt(OH)_6$ + HNO_3. The resulting material was calcinated and reduced in flowing hydrogen at

250^{0}C [199,201] or at 200^{0}C [200]. However, more effective catalysts resulted from Pt on zeolite Y or ZSM-35, with ratios of Si:Al = 2.5-5, when 1-5 mg of Cnd were added to the reaction solution during hydrogenation of EtPy. At 70 bar hydrogen and 20^{0}C (*R*)-(-)-EtLa was obtained with an *ee* of 86.1% in AcOH solution. It was found that other zeolites (mordenite and erionite) were also effective supports for Pt over which (*R*)-(-)-EtLa was obtained with an *ee* of 85-87%. At the same time catalysts based on zeolite Beta and ZSM-5 were less effective (see Table 5.2.) in the catalytic production of (*R*)-(-) EtLa. In Table 5.2. the Si:Al ratio changes from 2.5 to 15 and ZSM-35 showed the highest *ee* (68%) in the hydrogenation of EtPy to (*R*)-(-)-EtLa.

	zeolite Y	ZSM-35	zeolite Beta	ZSM-5
Si/Al ratio	2.5	5	12.5	15
Pore size (nm)	0.71	0.35-0.54	0.55-0.76	0.51-0.56
Particle size (nm)	2.9	9.6	12.0	8.7
ee (% of (*R*)-(-)EtLa)	62	68	53	47

Table 5.2. Characteristics of zeolites used for the preparation of 5% Pt-zeolite catalysts.

Reschetilowski et al. [200] also gives a comparison of the efficacy of Pt-zeolite-Cnd catalysts in the hydrogenation of EtPy based on alumina enriched with zeolite Y or ZSM-35 and silica enriched Zeolite Beta or ZSM-5 as carriers (Fig.5.1.).

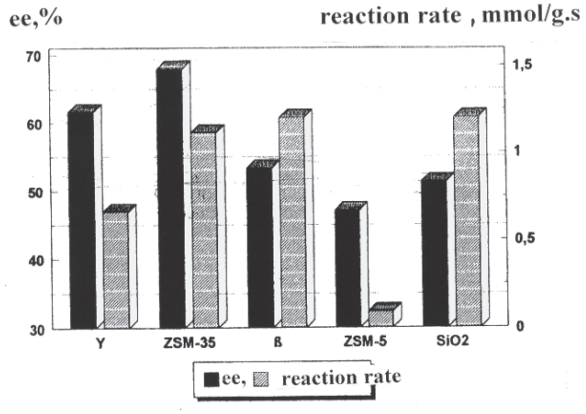


Figure 5.1. A diagram for comparison of enantioselectivity and reaction rate in the hydrogenation of EtPy on Pt-containing catalysts (according to Reschetilowski et al.[200])

Figure 5.1. shows that the best *ee* values were obtained on catalysts based on alumina enriched zeolites like ZSM-35 and zeolite Y. Optical yields did not depend on the amounts of catalysts but increased sharply with diminishing amounts of added Cnd reaching an optimal value with the addition of 1 mg Cnd per 100 mg of catalyst.

Repeated hydrogenations of up to 20 cycles were achieved without diminishing *ee's* (about 75%) on a sample of 5% Pt-ZSM-35 contingent upon the addition of a new portion of Cnd (1.2 mg) in each cycle, even though the amount of catalyst was reduced by one-fourth after each filtration (Reschetilowski [199-201]).

Table 5.3. shows dependence of the *ee* values on the polarities of solvents in the hydrogenation of EtPy on Pt-zeolite catalysts in comparison with Pt-alumina-Cnd catalysts.

Solvent	dielectric	5% Pt/Y		5% Pt/ZSM-35		5% Pt/γ-Al_2O_3	
	constant	r_o	*ee*	r_o	*ee*	r_o	*ee*
methanol	32.63	0.37	61.6	1.1	69.8	1.08	75.1
ethanol	24.3	0.42	67.7	1.2	64.5	2.28	75.0
acetone	20.7	0.57	69.8	1.17	73.3		
propan-2-ol	20.1	0.88	64.3	2.01	71.3	3.05	76.7
butan-2-ol	15.5	0.84	68.7	1.69	72.3		
dichloromethane	9.08	0.69	76.3	1.09	75.0	2.20	81.4
acetic acid	6.15	0.56	83.9	0.69	86.1		
cyclohexane	2.02	0.80	74.5	1.79	77.5	2.94	79.9
hexane	1.89	0.74	71.3	2.07	74.7		

Table 5.3. Influence of solvents polarity on the *ee* (%) and the reaction rate (mmol/ sec·g cat) in hydrogenation of EtPy on supported Pt catalysts (200 mg) modified with Cnd (40 mg) (Reschetilowski et al. [200]).

Using 5% Pt-Zeolite Y-Cnd (cyclohexane, 30 bar hydrogen, 20-30°C) Boehmer and Reschetilowski et al. [198] showed almost the same *ee* values (82-84%) on Pt catalysts based tge cationic modified zeolites, HNaY, CaNaY, NaY, MgNaY, and (Nd-Pr)NaY, with relative proton activities of 10.2, 5.2, 0.0, 5.6, and 7.0, respectively, while the reaction rate constant increased in this series as shown in Figure 5.2.

A very stable sample of 5% Pt supported on zeolite ($H_{0.7}Na_{0.3}Y$) in AcOH solution gave ten cycles of hydrogenations of EtPy with an *ee* of 85-87% and gave 15 cycles in cyclohexane with an *ee* of 70-78% (Reschetilowski [199,201], Bartok [311]).

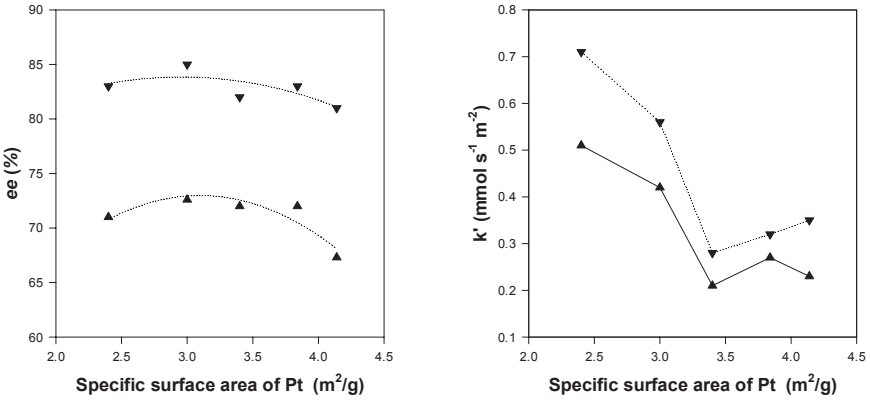


Figure 5.2. Dependence of the enantiomeric excess, *ee*%, (left) and the initial reaction rate constant, k', (right) of ethyl lactate on the specific surface area of platinum and the relative proton activity of the modified zeolites during the hydrogenation of ethyl pyruvate on 5% Pt-zeolite catalysts modified with Cnd in acetic acid (▼) and in cyclohexane (▲) [198]. The catalysts from left to right were: Pt/HNaY (10.2), Pt/CaNaY (5.2), Pt/NaY (0), Pt/MgNaY (5.6), and Pt/(Nd-Pr)NaY (7.0) (proton activities are given in parentheses).

5.2.4. Effect of crystallite size on enantioselectivity

Both the metal particle size and the crystallite size of supported metal catalysts have decisive effects on enantioselectivity, but other parameters of the reaction often become important as well; for example, the nature of the metal, the nature of the support, the method of preparation, the salt used for preparation, the mode of catalyst reduction, and the nature of catalyst pretreatment, such as high temperature heating or sintering.

Bartok et al. [174] recommended that the pretreatment of Pt-alumina (Engelhard 4759) in hydrogen at 400°C must be carried out before the modification with Cnd or DHCnd to avoid hydrogenation of the quinoline skeleton, which will lead to a decrease of optical yield and, in fact, caused the hydrogenation of EtPy to stop at approximately 70% conversion.

Mastalir et al. [248] prepared highly dispersed Pt nanoparticles immobilized in swelling clay minerals modified with DHCnd. The modified smectites were impregnated with H_2PtCl_6 and reduced with $NaBH_4$. TEM images revealed the formation of ultrafine, monodispersed Pt nanoparticles with mean crystallite sizes of 0.8 nm (montmorillonite) or 1.2 nm (synthetic hectorite). Both catalysts proved to be mildly enantioselective in the asymmetric hydrogenation of ethyl pyruvate to (*R*)-ethyl lactate. The low catalytic per-

formance was ascribed to steric reasons. The constrained environment between the layers prevents the formation of the proper chiral active sites for enantioselective hydrogenation.

For the preparation of Pt-C catalysts activated carbon was oxidized either in the presence or absence of a liquid phase. The catalyst was modified with (-)-Cnd and was used in the hydrogenation of MePy. The catalytic activity depended on the concentration of surface oxygen remaining after activation as measured by XPS (Fraga et al. [231]).

Farkas et al.[232] studied the support effects in the enantioselective hydrogenation of isophorone over Pd catalysts prepared on different carbon supports with different specific surface areas and with different surface chemistries. In the cases of Pd catalysts different precursors resulted in different dispersions after reduction. The low dispersion proved to be advantageous for high enantioselectivity in the hydrogenation of the C=C bond in isophorone.

Various Pd-black catalysts modified with DHVin and differing in their preparation method showed different *ee*'s in the hydrogenation of isophorone (Farkas et al.[233]).

Enantioselective efficacy of heterogeneous metal catalysts depends on many factors, one of which is crystallinity. The effect of metal crystallinity was studied by several groups: Gross and Rys [249], Sachtler [250], and Nitta [131] used Ni catalysts, Klabunovskii [3,25,220,222] studied Ru catalysts, Blaser and Baiker [63] used Pt, while Nitta [128] and Zuo [229] studied Pd catalysts**.** These investigations revealed very important regularities in the hydrogenations of C=O and C=C bonds in prochiral keto esters and olefinic acids.

It is well known that increasing crystallinity of the metals is beneficial for obtaining higher *ee*'s in C=O hydrogenations (Klabunovskii [3,8,9,220] and Sachtler [250,251]).

The effect of crystallite size on the optical yield was first observed by Vedenyapin et al. [222] in the hydrogenation of ethyl acetoacetate into ethyl 3-hydroxybutyrate during progressive loading of Ru in Ru-silica catalysts that had been modified with (2*R,*3*R*)-tartaric acid. The reaction proved to be structure sensitive. The most effective catalyst proved to be the one with a 4.5 nm crystallite size, while catalysts with crystallite sizes 1.6 and 8.0 nm revealed lower asymmetric abilities. The sizes of the Ru crystallites were increased by increasing reduction times of the catalysts during their preparations.

Similar structure sensitivities was found by Gross and Rys [249]. They found that the enantioselectivities of Raney nickel catalysts were increased by increasing the temperature and time of NaOH etching of Ni-Al. Nitta et al. studied the Pd-TiO_2-Cnd catalyst system in the hydrogenation of 2-phenyl-

cinnamic acid [120-130] and the Ni-silica-Tart catalyst system in the hydrogenation of MAA [131-140].

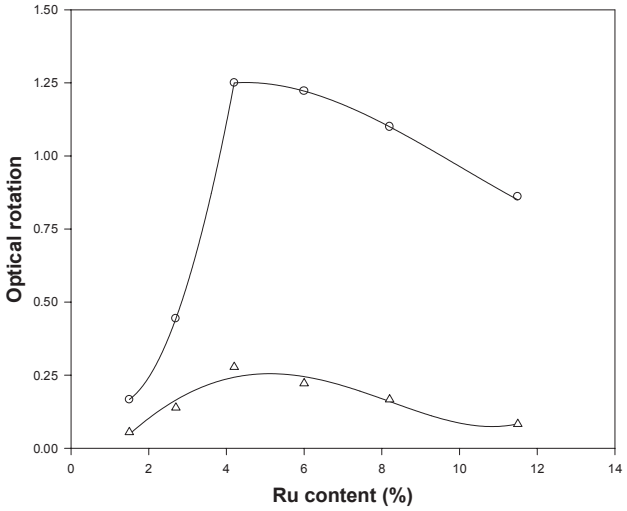


Figure 5.3. Effect of loading of Ru on enantioselectivity in the hydrogenation of ethyl acetoacetate into ethyl 3-hydroxybutyrate over Ru-silica catalysts modified with (2*R*,3*R*)-tartaric acid (reduction time: 0.5 (upper curve) or 5 h (lower curve); crystallite sizes after 0.5h reduction time were: 1.6 nm (at 1.5% Ru), 4.5 nm (at 4.2% Ru) or 8 nm (at 11.5% Ru) (according to Vedenyapin et al. [222]).

Also, they compared [131] enantioselectivities in hydrogenation of MAA over Raney Ni-Tart at 60^0C and 10 bar hydrogen in AcOEt solutions to enantioselectivities of amorphous Ni-boride (Ni-B) and Ni-phosphide (Ni-P) catalysts (prepared by reduction of Ni-salts with $NaBH_4$ or NaH_2PO_2, respectively) and found that a mean crystallite size of 6-8 nm produced *ee* values of 55%, which are comparable to Raney Ni prepared from Ni-Al alloy or from decomposition of Ni-formate. Ni-B and Ni-P catalysts have very small crystallite sizes and exhibit lower enantioselectivities (Figure 5.4.). The Figure also contains data (as curve 4) from the paper by Gross and Rys [249].

According to Molvinger et al. [252] Ni-boride modified with (1*R*,2*S*)-(-)-norephedrine produced catalysts that can hydrogenate acetophenone to (*R)*-(+)-1-phenylethanol with an *ee* of 90%. This catalyst can be recycled with no loss of performance. Such excellent enantioselectivity is connected with the formation of 1,2,3-oxazaborilidene anchored to the surface of Ni-boride. In addition to acetophenone, 4-methylpentan-2-one and isophorone were also hydrogenated (with lower *ee*'s) to products with (*S*)-configurations.

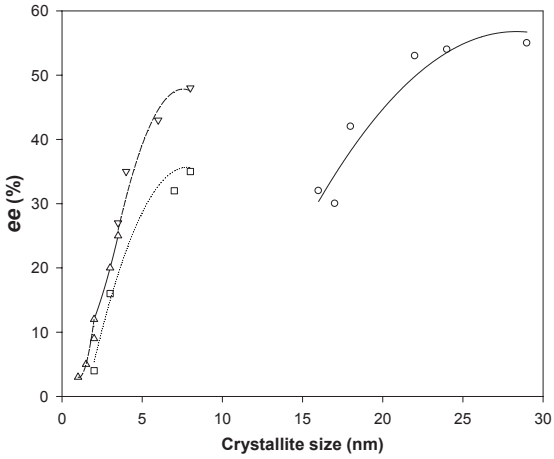


Figure 5.4. Dependence of optical yields on mean crystallite size of nickel in various catalysts in the enantioselective hydrogenation of methyl acetoacetate over RNi (□), Ni-B (Δ), Ni-P (∇) [131] or RNi (o) [249] catalysts.

As Nitta et al. [136,137] have found, amorphous Ni catalysts revealed low enantioselectivities and only catalysts with crystallite sizes around 10.0 nm revealed rather high *ee*'s. Increasing Ni loading on the support increases the *ee* associated with Ni crystallite diameter on carriers [131]. In general, as noted by Fish and Ollis [10,11] through electrochemical studies of this reaction on chirally modified Ni-catalysts, reactions of molecules adsorbed on an optically selective metal surface site require more area than one adsorbed on an optically non-selective site. Therefore optically selective centers of Ni catalyst must consist of an ensemble of Ni atoms large enough to adsorb both modifier and reactant on one nickel crystallite. A similar stereochemical model of orientation of adsorbed modifier molecules of (2*R,*3*R*)-tartaric acid and ethyl acetoacetate on the edge of nickel crystallite catalyst was proposed by Klabunovskii and Vedenyapin [220] and discussed by Izumi [215,218] and Tai [214].

The conditions of preparation of catalysts from its precursor Ni-salts affect the crystallite size and crystallite size distribution. Therefore small amounts of the additives, such as, Pt or Pd salts, have a favorable effect during reduction of the catalysts and the process of its formation [138]. Orito et al. [52-56] were first to show that enantioselectivity in the hydrogenation of MAA into MHB over Ni catalysts supported on Kieselguhr and modified with (2*R,*3*R*)-tartaric acid can be increased from 53% to 62% after including in the composition of the catalyst 1% of a noble metal, the best being Pt or Pd. Loading of the metal on Kieselguhr is of importance; only the

Ni:Pt:Kieselguhr ratio of 1:0.01:1 produced an an *ee* above 90% (see Chapter 4, part 4.3.).

Although the method of purification of Kieselguhr used for preparation of these catalysts was not indicated [52-56], likely the carrier contained some additives favorable for stereoselective reactions because pure silica gel used as the carrier was found to be less effective than Kieselguhr. In the case of Ni-silica-Tart, the increased loading of Ni from 20% to 75% gave increased mean crystallite sizes from 6 to 9 nm that resulted in hydrogenation of MAA to *ee*'s of 47.3% and 57.2%, respectively. Moreover, according to Nitta [138], the addition of $PdCl_2$ during preparation of the catalyst from a Ni-salt-precursor improved the reduction of the Ni-salt and subsequent enantioselectivity.

Optimal crystal sizes can be arranged by changing the temperature of catalyst treatment. Thus, the reduction by Orito et al. [52,54] of Ni-silica-Tart catalysts at 300°C proved to be mild enough to provide high *ee*'s but reduction made by Sachtler [250,251] at 400°C was too severe for Ni-alumina catalysts. Therefore crystallite size distribution seems to have a very important role in determining enantioselectivity of supported catalysts. Catalysts with larger crystallite size and with narrower crystallite size distribution produce higher *ee*'s, because smaller crystallites have higher catalytic activities but lower enantioselectivities (according to Nitta et al. [136]). On the other hand, catalysts with large crystallites produce only low catalytic activity; therefore in the case of supports such as silica, which give moderate crystallites of nickel around 6.0 to 10.0 nm, higher reduction temperatures (400°C) seem to be suitable for the preparation of catalysts with high enantioselectivities.

Another problem hindering true evaluation of the role of crystallinity of metal catalyst consists of the inhibition effect of the product. Namely, the predominant product of the reaction, (*R*)-(-)-3-hydroxybutyrate, can decrease enantioselectivity of the reaction owing to the fact that the relative adsorption coefficient of the (-)-enantiomer on modified chiral Ni centers is somewhat larger than those of the racemic product, (found by Chernyshova et al.[253] and by Neupokoev et al. [254]). Therefore, introducing (*R*)-(-)-ethyl 3-hydroxybutyrate (EHB) [253,254] into the reaction mixture of ethyl acetoacetate (EAA) or (-)-methyl3-hydroxybutirate (MHB) [134] into the reaction mixture of methyl acetoacetate (MAA) will diminish optical activity of the resulting 3-hydroxybutyrates. So, in order to make an accurate evaluation of the effect of crystallite size, the extent of asymmetric reaction needs to be controlled (for details see later in Part 5.5.).

To produce supported Ni catalysts with constant loading, Nitta [137] used as a carrier the layered silicate, chrysotile, and prepared the compound, Ni-chrysotile, $Ni_3(OH)_4Si_2O_5$. The reduction of this compound gave homogeneously dispersed *Ni-on-silica* catalyst. The crystallite size of these catalysts were controlled by the changing of the reduction temperature, while the

general loading of Ni remained constant. In the hydrogenation of MAA these catalysts gave *ee*'s from 22% to 35%, when the crystallite sizes increased from 5 to 6.5 nm, and *ee*'s from 30% to 40% at crystallite sizes 8 and 10.5 nm.

5.2.5. Enantioselective hydrogenation of C=C bond in unsaturated carboxylic acids

Until now there were not many examples of asymmetric hydrogenation of C=C bonds on Ni-Tart and Pt-Cnd catalytic systems. Bartok et al.[171-173,183] found that the Na-salt of (*E*)-2-phenylcinnamic acid gave sodium (*S*)-(+)-2,3-diphenylpropionate with an *ee* of 17%, whereas the hydrogenation of the acid gave only 0.21 %. Although Perez et al.[119] showed earlier that the latter chiral acid can be prepared with an *ee* of 30.5% using the Cnd modified Pd-C catalyst instead of Ni. This finding indicated that Pd-catalysts modified with Cnd are favored for asymmetric hydrogenations of C=C bonds in prochiral unsaturated acids.

Indeed, as it was mentioned above, Smith [31-33] accomplished the enantioselective hydrogenation of unsaturated carboxylic acids using Pt or Pd catalysts modified with chiral silyl ethers.

Quite recently in the asymmetric hydrogenation of **(***E***)-**2-methylpent-2-enoic acid in hexane over Engelhard Pd-alumina catalysts (E 40692 and E 5220), modified with Cnd, were used. Deuteriumation experiments showed that double bond migration and *E-Z* isomerization occurs during deuteriumation, but these processes are less important at the higher pressure of hydrogen (40 bar) and in the presence of modifier Cnd (Salladie-Cavallo et al.[255]).

Aminocinnamic acid derivatives on catalysts modified with Cnd or DHVin proceeded with low *ee's*. Only in the diastereoselective hydrogenation of *N*-acetyl-dehydrophenylalanyl-(*S*)-prolinanilide into dipeptide was a higher *ee* (68%) achieved (Tungler et al. [166]).

The mechanism of enantioselective hydrogenation of unsaturated carboxylic acids over cinchona modified Pd catalysts was studied in the hydrogenation of tiglic acid (2-methylbut-2-enoic acid) into 2-methylbutanoic acid. Applications of the derivatives of Cnd, modified at the C_9-OH group and the quinuclidine *N*-atom, proved that both functional groups are involved in the enantiodiscriminating step. Addition of the strong base DBU to tiglic acid prior to hydrogenation revealed that one Cnd molecule interacts with the dimer of tiglic acid on the metal surface. Calculation showed that the acid dimer-Cnd intermediate is stabilized by hydrogen bonding revealing both the OH group and the quinuclidine *N*-atom of Cnd (Borszeky et al. [84]).

Nitta et al.[120-130] have found that Pd-titania modified with Cnd is the most suitable catalyst for hydrogenation of 2-phenylcinnamic acid because titania is a nonporous carrier and gave metal crystallites of the proper size.

This catalyst was reduced in flowing hydrogen at 200^0C in order to increase the crystallite size of Pd. In this case, the first results on hydrogenation of (*E*)-2-phenylcinnamic acid reached an of *ee* 44%. With the addition of 7% water to the solvent mixture of EtOAc and EtOH the *ee* reached 58% (Nitta et al. [121,122]).

In optimal conditions the hydrogenation of (*E*)-2-phenylcinnamic acid proceeded with an *ee* of 72% (Nitta et al. [128]), whereas the hydrogenation of the C=C bond in isophorone on Pd modified with (-)-dihydroapovincaminic acid ethyl ester, (-)-DHVin, reached an *ee* of 55% (Tungler, Nitta et al.[129]). The differences in *ee* values were explained by the interactions between modifier and the reactant and by their different basicities.

Thus, there are some important differences between the asymmetric hydrogenations of C=O and C=C bonds :

1) For C=O hydrogenations solvents should be dry; on the other hand, for C=C hydrogenations the addition of water is favorable and increases *ee* values.

2) For C=C hydrogenations the reactions with unmodified catalyst were much faster then those with modified catalyst, such as with Cnd. This is quite different from results reported for the hydrogenation of *alpha*-keto esters on Pt-alumina, where the addition of the modifier alkaloid leads to chiral products and strongly accelerates the reaction (Bartok et al. [171,172], Tungler, Nitta et al. [129]).

The structure of Pd catalyst proved to be of decisive influence for accomplishing good enantioselectivity (Nitta [128]). Pd metal particles located in micropores of the support proved to be inaccessible to the bulk molecules of the modifier and reactant and to the intermediate complex [Modifier-Reactant] resulting in low *ee*'s. Therefore, using nonporous carriers are preferable for enantioselective reactions. But high metal dispersion on the surface of the catalyst is also detrimental to enantioselectivity (Tai [214]).

Nitta et al. [131-140] showed in a number of papers that *ee* values in the hydrogenation of MAA increased with increasing crystallite size of Ni. This effect confirmed the data of Klabunovskii et al. [220,222] who obtained results for a Ru-silica catalyst modified with (2*R,*3*R*)-tartaric acid in the hydrogenation of EAA into ethyl 3-hydroxybutyrate that could be explained by the increasing fraction of the metal surface atoms occupying regular crystal faces large enough (Fu et al. [251], Klabunovskii [220]) to have enough area to accommodate the large molecules of reactants and modifiers. The same suggestions were made later to explain hydrogenation of EtPy on Pt-alumina-Cnd catalysts (Wehrli et al. [63,69,78,80]). They found that the dispersion of Pt should be lower than 0.2 for good *ee*'s, and that the modifier cinchona alkaloid is anchored with the quinoline ring on the Pt surface (see below, on "Template model" of Wells et al.[141-152]).

In contrast, Zuo et al. [229,256] prepared highly efficient Pt nanocluster catalysts stabilized with polyvinylpyrrolidone polymer (PVP) modified with Cnd and noted that achievement of high *ee*'s in the formation of MeLaPd requires the existence of very small crystallite sizes. On finely dispersed catalysts MePy and EtPy were hydrogenated into (*R*)-lactates with *ee*'s of 97.6% and 92.2% , respectively. Zuo et al.demonstrated that the reaction is structure insensitive on clusters of about 1.4 nm, which is quite different from conventional supported chiral catalysts.

However, according to LeBlond et al. [257], MePy and EtPy were hydrogenated into lactates with the same *ee*'s, which is different from Zuo et al. [229]. Moreover, Zuo et al. [229] erroneously reported (*R*)-(+)-lactates instead of the correct correlations: (*R*)-(-) and (*S*)-(+) lactates[167].

The pore diameter limitation also was found for Pd-Cnd catalysts active in the C=C hydrogenation of (*E*)-2-phenylcinnamic acid. On a 5% Pd-silica catalyst the *ee*'s increased with increasing average pore diameter of silica, and the conclusion was that Pd metal particles should be located in pores large enough to accommodate the bulky alkaloid-modifier molecules and the substrate forming intermediate complex {modifier-reactant} that have been identified on the surface of Pd-titania catalyst (Nitta et al. [126]). Palladium metal particles in smaller pores are difficult to modify and they behave therefore as non-selective centers.

The comparison of a number of Pd-supported catalysts on non-porous and porous materials confirmed that non-porous ultrafine carriers like titania, seem to be most suitable for hydrogenation of (*E*)-2-phenylcinnamic acid. Thus, for porous and non-porous supports results of hydrogenation were as follows: on SiO_2 49.1% and 30.7%, on TiO_2 62.0% and 29.4%, respectively (Nitta et al. [128]).

The effect of Pd loading was also very important for accomplishing high *ee*'s. It was found that only a 5% Pd-titania catalyst (non-porous titania) gave the best *ee* (58.6%) with the highest rate of reaction. Catalysts with 20% Pd on titania or Pd-black gave only *ee*'s of 17.3% and 8.0%, respectively; thus the most effective catalyst proved to be a 5% Pd-titania-Cnd with a Pd dispersion of 0.2.

In general, the reactions of enantioselective hydrogenations of *beta*-keto esters on modified Ni or of *alpha*-keto esters on modified Pt are structure sensitive reactions. In both reactions, enantioselectivities increase with increasing crystallite size of Ni or Pt.

In the case of Pd catalysts supported on non-porous carriers, like SiO_2 or TiO_2, *ee's* depend on dispersion as found in the case of Pd-TiO_2-Cnd in the hydrogenation of (*E*)-2-phenylcinnamic acid (Nitta et al.[128]). These results showed that the reaction is mildly structure sensitive in the dispersion range higher than 0.2, but at lower Pd dispersions, it is similar to Pt and Ni catalysts

in the enantioselective hydrogenation of C=O bonds in *alpha*- and *beta*-keto esters (Figure 5.5.).

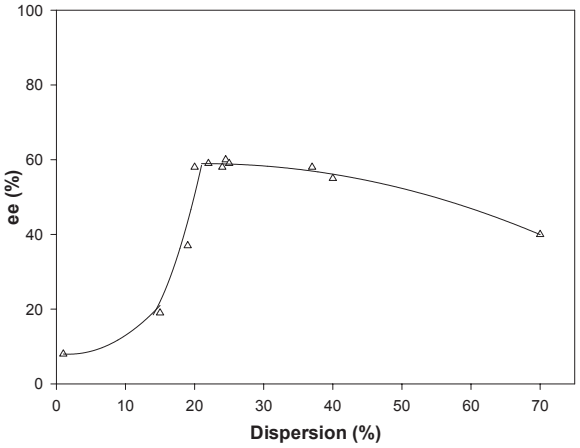


Figure 5.5. Correlation between the dispersion of palladium and the enantioselectivity in the hydrogenation of (*E*)-2-phenylcinnamic acid on Pd-TiO_2 catalyst modified with cinchonidine (according to Nitta et al. [128]).

On the other hand, the sharp decrease of *ee* at dispersions lower than 0.2 is similar to that observed in enantioselective hydrogenation on Pd modified with a bulky vinca alkaloid, according to Tungler and Nitta et al. [129].

The behavior of Pd catalyst in hydrogenation of (*E*)-2-phenylcinnamic acid can be explained in terms of the adsorption mode of the intermediate complex [modifier-substrate] on the Pd surface. The adsorption of the bulky Cnd molecule on large Pd crystallites hinders the C=C bond's approach to the Pd active center and it leads to a diminishing of the *ee* and the rate. If the molecule to be hydrogenated is small enough, as in the case of the hydrogenation of isophorone on Pd modified with vinca alkaloid (Tungler [164,165,230,258-260]), the *ee* increased with decreasing Pd crystallite sizes, and Pd-black (crystallite sizes 0.1 nm) proved to be a more effective catalyst than Pd-C with crystallite sizes around 0.5 nm [258]. The same holds true for the comparison of the strong hindrances in the hydrogenation of the C=O bond in pyruvate and the C=C bond in (*E*)-2-phenylcinnamic acid. Borszeky et al. [84] proposed an arrangement of an adduct {Cnd-acid dimer, 1:1} on the flat Pd crystallite surface for the hydrogenation of tiglic acid (Nitta et al. [128]).

Thus, enantioselective hydrogenation of pyruvates on Pt clusters supported on alumina modified with Cnd as well as finely dispersed colloidal Pt-PVP (according to Boennemann et al. [261], Koehler et al. [262,263], and Zuo et al. [229,256]) exhibits less structure sensitivity with the best *ee*'s occurring over very

small clusters, which contradicts results on the common Pt-alumina catalysts with particle sizes of 3-4 nm.

Solvent-stabilized Pt and Pd nanoparticles, of sizes 2.3-2.8 and 2.7-3.8 nm, respectively, have been prepared by metal vapor synthesis routes and modified with Cnd. These catalysts were used in the hydrogenation of EtPy, and the Pd catalysts produced EtLa of inverse configuration, that is, instead of the expected (*R*)-EtLa, the (*S*)-EtLa was obtained. The Pt particle size distribution showed a higher degree of monodispersity after use in catalysis (Collier et al. [264]).

Vorlop et al. [265,266] suggested a novel strategy for heterogenizing homogeneous and colloidal chiral catalysts based on the three-dimensional entrapment of catalyst by electrostatic attraction between a polyelectrolyte and an active metal in the polymeric matrix. Based on this method, they entrapped chirally stabilized Pt-colloid in alginate (polymannuronate) and conducted twenty-five hydrogenation cycles of EtPy.

A rather effective catalyst proved to be the system of rhodium nanoclusters stabilized with polyvinylpirrolidone (PVP) and supported on finely dispersed oxides (gamma-alumina, silica, or titania) and modified with Cnd (Huang et al. [267]). With this system EtPy was hydrogenated at 25^0C and 70 bar hydrogen in THF with a TOF of 58.6 min^{-1} and an *ee* of 65.4%.

Rhodium nanoclusters stabilized by PVP, supported on TS-1, and modified with Cnd, Cn, or Qn (4 mmol/L) were used for the hydrogenation of EtPy at 5^0C and 70 bar hydrogen with an *ee* of 63.1% (Ma et al. [268]).

A similar catalytic system based on finely dispersed PVP-stabilized Pt-nanoclusters supported on conventional carriers and modified with Cnd accomplished the enantioselective hydrogenation of 2,2,2-trifluoroacetophenone into the (*R*)-alcohol at 20 bar hydrogen in a mixture of *o*-dichlorobenzene and ethanol (Zhang et al. [269]). The same catalyst was not very effective in the asymmetric decomposition-hydrogenation of racemic 3-hydroxybutan-2-one. The enantiomeric excess reached a maximum *ee* > 40% at a molar ratio of the modifier to reactant of about 1:650 in dichloromethane-ethanol solvent (Zuo et al. [270]).

Finely dispersed PVP-stabilized iridium, supported on alumina and modified with Cnd produced only an *ee* of 34.1% in the hydrogenation of MePy at 10^0C and 40 bar hydrogen in alcohol or AcOH (Zuo et al. [271]).

A rhodium nanocluster stabilized with PVP and modified with Cnd or Qn (4.3 mmol/L in THF) was active in the enantioselective hydrogenation of EtPy at 25^0C and 50 bar hydrogen with a TOF of 941 h^{-1} and an *ee* of 42.2% (Huang et al. [272]).

According to Boennemann [261], colloidal Pt-alumina catalyst, was prepared by reducing an aqueous solution of Pt salt in the presence of protonated DHCnd with the addition of the stabilizing colloid PVP (MW 10.000 [262,263]). Particle sizes of the resulting catalysts ranged from 1.5 to 4

nm and the hydrogenation of EtPy at room temperature and 1 bar hydrogen resulted in an *ee* of 76%. The enantioselectivity increased with diminishing dispersion. A catalyst of 1% Pt-alumina-Cnd with a particle size of 3.5 nm was compared with a Pt-PVP-Cnd catalyst system in the hydrogenation of EtPy and the *ee*'s were 34% and 42%, respectively.

The statement of Baiker [21,63] that good enantioselectivity can be achieved with Pt particle sizes above 3-4 nm is based on obtaining large ensembles where modifier and reactant can adsorb best on the large crystallites. Indeed, in the hydrogenation of EtPy on Pt-alumina-Cnd (room temperature and 70 bar hydrogen) Blaser et al. [69] found a maximal *ee* of 80% at 0.2 dispersion which diminished to 30% with dispersion increasing to 0.8 simultaneously with the rate of reaction.

With this conclusion (according to Zuo et al. [229,256]) the structure sensitivity originated from the structure of the surface of the catalysts, but stereochemical hindrances of reacting molecules probably confused this effect. On other samples of Pt-alumina cluster catalyst with crystallite sizes of 1.1-3.3 nm, prepared by adsorption of clusters [Pt-PVP] on Al_2O_3 with further rinsing of PVP from surface of catalyst, *ee*'s were found to be lower, at about 8%, for particles of 3-3.5 nm in comparison with *ee*'s of 88-90% for particles of 1.5 nm. In this case, in the hydrogenations of MePy, a very high *ee* was found: (*R*)-methyl lactate was obtained with an *ee* of 97.6%.

The role of crystalline size of Ni-Tar modified catalysts was studied also by Fu, Sachtler et al [251]. Increasing the loading of metal on the surface of the carriers resulted in increasing particle sizes; however, Ni catalysts changed their exact composition of large and small particles during modification in solutions of tartaric acid due to the leaching of small particles (this process was absent in the modification of Ru-silica catalysts [220,222]). It was suggested [251] that the "true" method for studying this effect is at constant metal loading for Ni on silica, modified with (2*R*,3*R*)-tartaric acid and active in the hydrogenation of MAA. Sachtler [250,251] proposed that the effect of loading on *ee* consists of pore diffusion and therefore the studies of crystallite size can be investigated only at constant loading. The change in nickel particle size was accomplished using the method in which larger particles grow at the expense of smaller ones during the formation and decomposition of Ni-tetracarbonyl at temperatures above 50°C.

$$Ni + 4CO \rightleftharpoons Ni(CO)_4$$

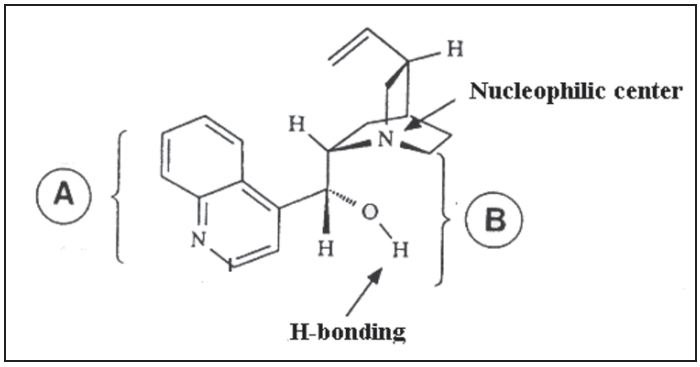
Hydrogenations of MAA were carried out both in gas-phase and liquid phase with flowing hydrogen. Optical yields were 8-15% in the former and 30-32% in the latter cases, and no significant structure sensivities were observed. In the range of 4-10 nm no influence of particle size was seen in the *ee*'s of the methyl 3-hydroxybutyrate product [251]. The results were considered confirmation of the “dual site model" (Sachtler [250]), which states that one sort

of Ni atoms (or ions) on the surface coordinates the two molecules of modifier (tartaric acid) formatting two five membered chelate rings. The role of the other Ni atoms consists of adsorption of a dihydrogen molecule and dissociating it into hydrogen atoms.

According to Wehrli et al. [63], dispersion of crystallites in Pt-silica-Cnd catalysts from 0.3 to 0.8 (characterized by CO adsorption) produced *ee*'s in range of 65% to 35%. in the enantioselective hydrogenation of EtPy. Increasing the particle size was achieved by increasing the temperature of the reduction of the catalyst. Wehrli et al. [80] also found highest *ee'*s from catalysts prepared from Pt salts deposited on alumina by reducing them with formate or with HCHO. Catalysts reduced in flowing hydrogen gave the highest dispersion, 0.05, and the lowest enantioselectivity. Thus they concluded that attainment of highest *ee's* (80%) in the hydrogenation of EtPy required the Pt-alumina-Cnd catalyst to have crystallite sizes of 3-4 nm [80].

5.3. The structure of the modifiers

Although cinchona alkaloids and especially cinchonidine, Cnd, proved to be the most effective chiral modifier for the catalytic system of Pt-alumina, in the liquid phase enantioselective hydrogenations of the carbonyl group in pyruvic acid esters, efforts to understand the mechanism of action of this catalyst system has continued to the present. The efforts may be divided into two categories: finding natural modifiers other than cinchona alkaloids and examining new effective amino alcohols, which are modeled after the structure of known cinchona modifiers.



Scheme 5.6. The different parts of the cinchonidine (Cnd) molecules.
Part A: adsorbs on the surface of Pt.
Part B: asymmetric region of the molecule.

Elucidating the reasons for the efficacy of alkaloids as modifiers of Pt catalysts and searching for new modifiers with structures similar to the alkaloids of the cinchona alkaloid group is of great interest from the theoretical and practical points of view. The strategy for the search of structures of

new modifiers must correspond to the basic requirements: to adsorb strongly on the surface of the metal (Part A of the cinchonidine molecule in Scheme 5.6.) and to match the stereochemical interaction through H-bonding of the substrate (Part B) with the nucleophilic center of the N-atom of the quinuclidine moiety of Cnd.

To these requirements the alkaloids of the cinchona group correspond moderately well owing to the their peculiar structure. The quinoline group of the Cnd molecule provides strong adsorption of the modifier on the surface of Pt while the stereochemically important part of molecule provides energetic and stereochemical interactions with the pyruvate molecule through the *N*-1 atom of quinuclidine ring.

Modifier structure			Solvent	*ee*	Configuration
C8	C9	R_1		(%)	
Cinchonidines					
H	OH	CH=CH2	EtOH	76	*R*
H	OH	CH_2CH_3	EtOH	79	*R*
H	OH	CH_2CH_3	AcOEt	81	*R*
H	OH	CH_2CH_3	PhMe	83	*R*
H	OMe	CH_2CH_3	EtOH	78	*R*
H	OH	CH_2CH_3	AcOEt	80	*R*
H	OH	CH_2CH_3	PhMe	81	*R*
H	OAc	CH_2CH_3	EtOH	20	*R*
H	H	CH_2CH_3	EtOH	44	*R*
H	OH	CH_2OH	EtOH	≈80	*R*
Cinchonines					
H	OH	$CH=CH_2$	EtOH	56	*S*
H	OH	$CH=CH_2$	MeOH	58	*S*
H	OH	CH_2CH_3	MeOH	54	*S*

Table 5.4. The effect of the structure of modifier alkaloids, cinchonidine (Cnd) and cinchonine (Cn), on the enantioselective hydrogenation of ethyl pyruvate into ethyl lactate over 5% Pt-alumina.
Reaction conditions: EtPy (10.9 g), 5% Pt-alumina (100 mg), modifier alkaloids (10 mg), solvent (20 mL), temperature 25-30^{0}C, 70-100 bar hydrogen (mainly according to Blaser [69]).

Recently a number of studies by the groups of Orito [57-60], Blaser [62,64,68,69,71,72], Baiker [17-19,79,88,90,92,104,105,111], Wells [23,141,147,148], Tungler and Sheldon [164,230,258,259], and Bartok [169] were devoted to searching for principal methods of selection of new effective modifiers. Most detailed studies were made using the model reaction of the asymmetric hydrogenation of ethyl pyruvate over Pt-alumina catalysts modified with cinchona alkaloids. Structural alterations at various parts of the cinchonidine molecule led to significant changes in enan-

tioselectivity. Table 5.4. summarizes the data (mainly according to Blaser [69]) on the enantioselective hydrogenation of EtPy over 5% Pt-alumina catalysts modified with alkaloid derivatives of Cnd or Cn.

For hydrogenation of both pyruvates and MeBf (methyl benzoylformate) Modification of Pt-alumina catalysts with Cn, Qn, or Qnd was less effective than modification with Cnd. Modifying with Cnd and Qn resulted in the (*S*)-(+) isomer of MeLa rather then the (*R*)-(-) isomer as in the case of modifying with Cn. This indicated that the absolute configuration of the resulting hydroxy ester is determined by the configurations at the C_8 and C_9 centers in the alkaloid molecules (see Scheme 5.6.).

Detailed investigations of the effects of structural changes in the Cnd and Cn modifier molecules on the enantioselectivity of hydrogenations of EtPy revealed that derivatives of Cnd yielded (*S*)-(+)-EtLa, while derivatives of Cn yielded (*R*)-(-)-EtLa.

The alkaloids Cnd and Cn are diastereomers that differ only in their configurations at C_8 and C_9, and this difference results in the formation of lactate products with opposite configurations. This was shown by the interaction of the pyruvate molecule with just the C_8 and C_9 centers of the alkaloids.

The next important conclusion concerned the role of the OH-group at the C_9 center in Cnd. Changing the OH for OAc or for H (annihilation of the chiral C_9 center) strongly diminished the *ee* values of EtLa [69]. However, Blaser et al.[68] found that methylation of the OH group in DHCnd resulted in the most efficient modifier of Pt-alumina catalysts reaching an *ee* value of 94%, which was the highest value ever reported for an enantioselective hydrogenation of EtPy over these catalytic systems. Table 5.5. summarizes the data from the hydrogenation of EtPy in different solvents.

In the hydrogenations of ethyl pyruvate, maximal optical yields of 91-94 % were achieved, especially if the reaction was carried out in AcOH or propionic acid instead of the more commonly used toluene or ethanol. It was a very important observation that the *ee* depended on the acidity of acids used as solvents (conditions of reaction are the same as in Table 5.4.).

The nature of groups at C_3 do not affect *ee* values, because the vinyl-group at C_3 in Cnd is hydrogenated in a few minutes after the beginning of the reaction into an ethyl-group forming 10,11-dihydrocinchonidine (DHCnd), which proved to be an even more effective modifier than Cnd itself. Therefore, most investigators preferred using the Pt catalysts modified with DHCnd.

Alkylation of the N-atom at the N-1 center in the quinuclidine part of Cnd completely annihilates enantioselectivity of the catalyst, which indicates the crucial role of the N-1 atom in the formation of an active intermediate complex [69].

Modifier	Solvent	ee (%)	rate (mol g_{cat}^{-1} min^{-1})
DHCnd	ethanol	82	< 0.1
DHCn	toluene	87	0.11
DHCn	acetic acid	92	0.12
MeODHCnd	ethanol	82	-
MeODHCnd	toluene	88	0.08
MeODHCnd	acetic acid	94+1	0.16
MeODHCnd	propionic acid	91	0.11
MeODHCnd	butyric acid	89	0.09
MeODHCnd	isobutyric acid	86	0.07
MeODHCnd	nonanoic acid	82	0.07
MeODHCnd	triethylamine	3	0.02
MeODHCnd	piperidine	4	0.007
MeODHCnd	morpholine	7	0.004
MeODHCnd	quinoline	30	<0.001
DHCnD	acetonitrile	28	0.007

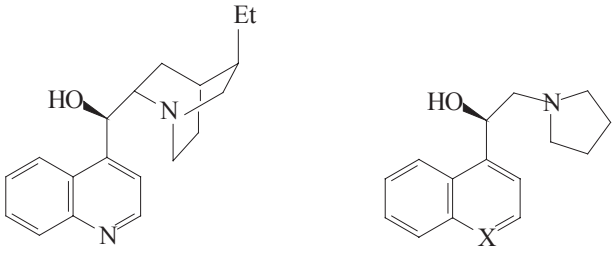
Table 5.5. Hydrogenation of ethyl pyruvate on 5% Pt-alumina modified with 10,11-dihydrocinchonidine (DHCnd) or 10,11-dihydro-O-methylcinchonidine (MeODHCnd) in various solvents at room temperature and 100 bar hydrogen (according to Blaser et al.[68,69]).

The aromatic system of the quinoline nucleus provides strong adsorption of the alkaloid molecule on the Pt surface. Even partial hydrogenation of the quinoline nucleus diminishes *ee* values by as much as 50% during the formation EtLa [21,69].

From these data it is clear that high enantioselectivity in the hydrogenation of pyruvate over modified Pt-alumina catalysts results from modifier molecules that have the structure of heteroaromatic alcohols, like R_1-CH(OH)-CH_2-R_2, where R_1 is the quinolyl group and R_2 is the quinuclidyl group.

5.3.1. Modifiers with structures similar to cinchona alkaloids

In accordance with the general stereochemical requirements, Baiker et al.[17-19,21,79,88,90,92,104,105,111] prepared a number of optically active modifiers, such as (*R*)-2-(1-pyrrolidyl)-1-(1-naphthyl)ethanol (PNE, 2a in Scheme 5.7.) with structures similar to the structures of cinchonidine alkaloids.



1 2

Scheme 5.7. The structures of DHCnd (1) and similar amino alcohols with naphthyl (2a, X = CH) and quinolyl (2b, X = N) aromatic groups.

Table 5.6. shows that the enantioselectivity in the hydrogenation of EtPy into (*S*-)-(+)-EtLa on 5% Pt-alumina modified with PNE, was 75%, which is similar to the 73% measured at lower pressure on a Cnd modified catalyst.

Modifier	H_2 pressure (bar)	Reaction time (h)	Conversion (%)	*ee* (%)
1	1	1.0	100	73
1	75	0.5	100	87
2a	1	1.0	100	68
2a	10	0.2	100	75
2a	25	1.0	99	47
2a	75	0.5	100	46
2b	1	1.0	100	48
2b	25	0.5	98	55
2b	75	0.5	100	66

Table 5.6. Comparison of the effect of modifiers DHCnd (**1** in Scheme 5.7**.**) and amino alcohols with naphthyl (**2a**) and quinolyl (**2b**) aromatic groups in the enantioselective hydrogenation of ethyl pyruvate on 5% Pt-alumina at various hydrogen pressures adapted data from Wang et al.[90]

The quinoline group, however, proved to be less effective than the naphthyl group (*ee* = 48-66%). The modifier PNE could be used as an additive to the reaction mixture without the usual preliminary procedure of modifying the catalyst. At optimal concentrations the relationship of EtPy to PNE was found to be equal to 30,000. Suggesting flat adsorption of EtPy and PNE on the Pt (111) facet, in which the complex molecule [Platinum-EtPy-PNE] requires an area of about 20 Pt surface atoms, results in 10% PNE being sufficient for full coverage of the surface.

The effect of solvent on the use of this model modifier is similar to that found for the Cnd modifier and the most effective solvent proved to be

nonpolar ones (toluene, heptane) and also AcOH, which caused protonation of the *N*-1 center in PNE. With increasing temperatures, the *ee* reached a maximal value at 0^0C. Increasing the hydrogen pressure from 10 bar to 25 bar, decreased *ee's* from 72% to 60%, and 54% was measured at 40-70 bar. This decrease was a consequence of the partial hydrogenation of the aromatic quinoline ring (Figure 5.6.).

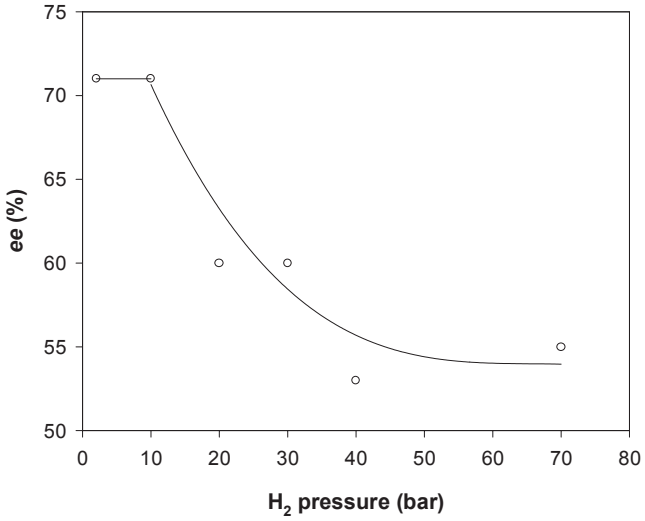


Figure 5.6. Enantiomeric excess as a function of hydrogen pressure in the hydrogenation of EtPy over 5% Pt-alumina-PNE in acetic acid at 25^0C (according to Minder et al.[92]).

This was a result of the weakening of the adsorption of the modifier on Pt due to breaking the definite orientation of the intermediate complex [Platinum-Modifier-Substrate]. Another picture was observed in the case of the Cnd modifier (Figure 5.7.).

At the beginning of the reaction the additional adsorption of the vinyl group of the alkaloid takes place, weakening the orientation of the modifier. However, during the course of the reaction this group is hydrogenated and the resulting DHCnd proved to be a more effective modifier than the original Cnd and increased *ee*. On the other hand, the partial hydrogenation of the quinoline ring of the Cnd weakened the adsorption of the modifier and diminished the *ee* of the resulting EtLa.

Indeed, the importance of this anchored group was revealed by an increase of *ee* from 48 to 66% when the naphthyl group in PNE was replaced with a quinoline group [90] (compare reactions at 75 bar in Table 5.6.)

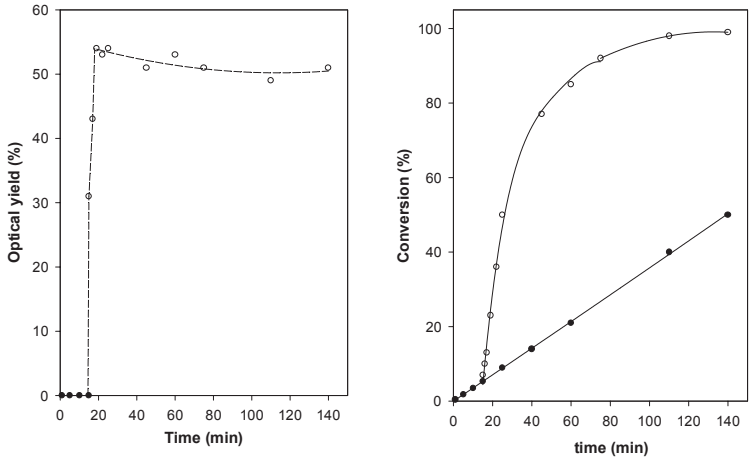


Figure 5.7. Effect of the addition of the modifier Cnd to the hydrogenation of ethyl pyruvate on 5 % Pt-alumina catalyst (mainly according to Baiker [21]). Optical yield (left) and conversion (right) with (o) and without (●) Cnd modifier.

To elucidate the stereochemical action of the PNE modifier the enantioselective hydrogenation of EtPy on 5% Pt-alumina in the presence of modifier-fragments of the PNE molecule were studied, and it was found that other structures close to the structure of Cnd can yield high catalytic and enantioselective activities during the hydrogenation of pyruvates. For example, Blaser et al.[62] found that some chiral amines, like 1-phenylethylamine and some amino alcohols, like ephedrine can reveal low to moderate enantioselectivities in the hydrogenation of pyruvates. But the most effective modifiers proved to be structures similar to PNE, which give good adsorption on the Pt surface and contain the aromatic part of the molecule as well as a chiral center with OH- and amino-groups that can react with the keto esters as shown in Table 5.7.

Table 5.7. demonstrates the crucial role of the large flat aromatic part of the modifier molecules, especially in the case of the anthracenyl-group (*ee* = 83%). But in the case of the tripticenyl moiety the enantioselectivity falls almost to zero, probably due to steric hindrances and the difficulties of the pí-bonding interactions with the surface Pt atoms [88]. However, according to Balandin and Klabunovskii (see review by Skvarchenko et al. [273]) tripticene derivatives, despite their steric molecular hindrances, could be hydrogenated

on Ni catalysts, which likely have more homogeneous crystallite surfaces than platinum catalysts.

		H_2 pressure (bar)	*ee* (%)
10,11-Dihydrocinchonidine		75	87
(*R*)-5-(1-naphtyl)-(*N*-methyloxazolidine)		75	49
Ar	R		
1-Naphthyl	pyrrolidin-1-yl	1	68
4-Quinolyl	pyrrolidin-1-yl	75	48-66
Phenyl (1*S*)	pyrrolidin-1-yl	75	4
4-Pyridyl	pyrrolidin-1-yl	75	0
2-Naphthyl	pyrrolidin-1-yl	1	42
9-Anthracenyl	pyrrolidin-1-yl	10-75	83
1,9-Tripticenyl	pyrrolidin-1-yl	-	< 5
1-Naphthyl	dimethylamino	1	62
1-Naphthyl	di-isobutilamino	1	49
1-Naphthyl	morpholino	75	32
1-Naphthyl	methylamino	1	48
1-Naphthyl	amino	75	8
1-Naphthyl	(1*S*)-(1-phenylethyl)amino	25	32

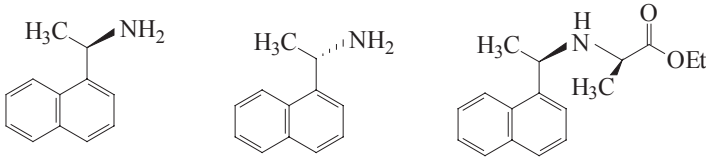
Table 5.7. Effect of the aromatic part of the (1*R*)-1-aryl-2-(pyrrolidin-1-yl)ethanol type modifier molecules, (Ar-CH(OH)-CH_2R), on enantioselectivities in the hydrogenation of EtPy on 5% Pt-alumina catalyst (summarized data [88,111]).

Results received by Blaser, Baiker, et al. [69,90] confirmed that the most effective modifiers could be the compounds that contain an aromatic part of the molecule as in PNE. Indeed, molecules similar to PNE, containing the quinoline group instead of the naphthyl group, gave results close to those received with PNE (see Table 5.6.). These results showed that the center *N*-1 in the pyrrolidine ring did not play a crucial role in revealing enantioselectivity. Therefore the point of view of Augustine et al.[205,206] that the molecule of Cnd adsorbs in a perpendicular mode on the Pt surface seems not born out, rather the aromatic ring adsorbs parallel to the surface. Thus the use of (*R*)-(+)-1-(2-naphthyl)ethanol did not give a chiral product [97].

In the molecule PNE, which is simpler than the Cnd molecule, there is only a C7 center (see Scheme 5.7.), which is similar to the C9 center in Cnd, and proves to be enough for the creation of an effective modifier of Pt-alumina catalysts yielding EtLa with an *ee* of 70%. The function of the *N*-1 center is to give close bonding of the modifier to the pyruvate molecule in-

volving the rigid quinuclidine ring in Cnd or the more flexible cycle in PNE. But in both cases the required sequences of centers, Ar-CH(OH)-CH-N-, is fulfilled. Protonation of *N*-1 in PNE during reaction in AcOH solution gave increased enantioselectivity (Schwalm et al. [97]).

Minder [104] used the commercially available (*R*)-(+)- or (*S*)-(-)-1-(1-naphthyl)ethylamines (see Scheme 5.8., enantiomers **1** and **2**), which proved to be rather effective modifiers if the reaction is carried out at lower hydrogen pressures.



1 **2** **3**

Scheme 5.8.

With these modifiers an interesting interaction was observed in the hydrogenation of EtPy with the formation of compound **3** (Scheme 5.8.). That compound can itself act as a modifier of Pt catalyst in enantioselective hydrogenations (Table 5.8.) and can serve as a model by revealing the nonlinear effect of an autocatalytic process (see Avalos et al.[4], Girard et al. [5], Kagan et al. [6], Blackmond [211,212], and Soai [274]).

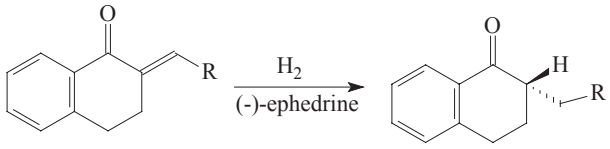
Modifier	pressure (bar)	conversion (%)	*ee* (%)
1	72-75	48	51 (*R*)
	22-25	54	55 (*R*)
2	72-75	52	53 (*S*)
	22-25	59	58 (*S*)
3	21-25	83	55 (*R*)

Table 5 8. A comparison of the chiral modifiers, (*R*)-(+)- and (*S*)-(-)-1-(1-naphthyl)ethylamines, in the enantioselective hydrogenation of ethyl pyruvate in AcOH at room temperature (reaction time is 1 h, mol reactant to mol modifier ratio is 1500). Adapted data from Minder et al.[104]

The structures of other modifiers similar to Cnd confirmed once more that modifier requirements for inducing enantioselectivity are an aromatic system and an amino-group. Results show that chiral catalytic systems can be prepared not only with cinchona alkaloids as modifiers but also with simpler amines and amino alcohols allowing the hydrogenation of the *alpha*-keto esters with *ee*'s up to 80% and, importantly, at lower hydrogen pressures [21].

5.3.2. Modifiers with structures different from cinchona alkaloids

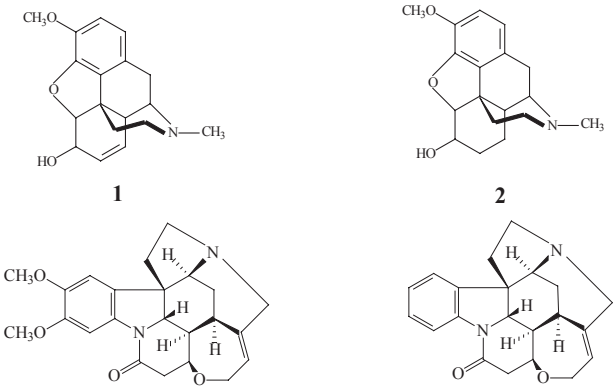
Torey et al.[275] showed that in *alpha, beta*-unsaturated ketones (see Scheme 5.9.) the C=C bond can be asymmetrically hydrogenated over 10% Pd-C catalyst in MeCN solution with the addition of 0.5 equivalent of (-)-ephedrine at RT with an *ee* of 19-30%.



Scheme 5.9.

The hydrogenation of the EtPy on Pt-alumina modified with tartaric acid, 1-phenylethylamine or menthol was not enantioselective [22,26,62] and only ephedrine was an effective modifier with ee's of 5-25%.

Griffiths et al.[147] described attempts to use alkaloids (Scheme 5.10.) as modifiers like codeine (**1**), 7,8-dihydrocodeine (**2**) (*ee* = 3%), brucine (**3**), and strychnine (**4**). With brucine (but not with strychnine) *ee*'s of 10-12% were produced over 6.3% Pt-silica.



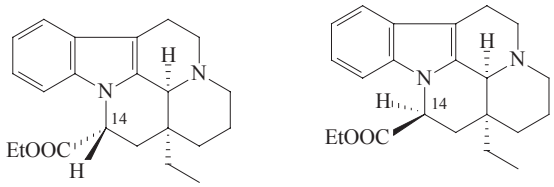
Scheme 5.10.

Enantioselective hydrogenation of MePy at RT and 10 bar of hydrogen over 6.3% Pt-silica modified with brucine resulted in (*S*)-MeLa with an *ee* of 20%, but no enantioselectivity was found in the hydrogenation of butane-2,3-dione. According to Wells et al.[276] brucine adsorbs on a Pt surface to form cavities for the enantioselective adsorption of MePy but not for the diketone. On the other hand, Pt catalyst modified with the morphine alkaloid, oxycodone, works as an enantioselective catalyst in the hydrogenations of both MePy and

the diketone at 10 bar and 20°C with *ee*'s of 15% and produces (*R*)-enantiomers in each cases.

A new modifier prepared from L-triptophane proved to be effective in the enantioselective hydrogenation of EtPy over Pt catalyst supported on commercial alumina. The greatest enantioselective action was found by the modifier (*S*)-3-(1-methylindol-3-yl)-2-(methylamino)propan-1-ol. At ambient conditions an *ee* value of 43% was found. A slight increase of pressure led to a dramatic drop in *ee*. An interesting inversion of the sense of enantioselectivity was observed with this modifier when the reaction was carried out in AcOH instead of toluene (Szollosi et al. [175]).

Tungler, Sheldon et al. [164,230,258] found a novel modifier for Pd-carbon catalysts that proved to be active in the enantioselective hydrogenation of C=C and C=O bonds. This modifier, the alkaloid dihydrovinpocetine (the ethyl ester of (-)-dihydroapovincaminic acid, DHVin) possesses quite a different structure from the cinchona alkaloids (Scheme 5.11.).



Scheme 5.11. The structures of the (-)-dihydrovinpocetine (left) and (+)-dihydrovinpocetine (right) alkaloids.

Vinpocetine is a synthetic medicine which is used in the treatment of oxygen-deficiency of the brain and is quite available (trade mark "Cavintone"). DHVin was prepared by hydrogenation of vinpocetine and consisted of a mixture of diastereomers at the C14 centers: (-)- and (+)-stereoisomers in the ratio of 91:8. The catalytic system of 5% Pd-C-DHVin proved to be enantioselective in the hydrogenation of the C=C bond in isophorone and the C=O bond in methyl pyruvate, which also was enantioselectively hydrogenated on Pt-alumina-DHVin catalyst.

The properties of the Pd-C-DHVin catalytic system are quite different from the cinchona alkaloid modified Pt catalysts. Thus, in the hydrogenation of the C=C bond in isophorone into the saturated ketone on 5% Pd-Carbon-DHVin, the *ee* values and rates of reaction changed in opposite directions and the effect of ligand acceleration, that was observed in the Pt-alumina-Cnd catalytic system, was absent. Also a very strange dependence of *ee* on the nature of supports was observed: *ee*'s increased in the following order: Al_2O_3 (5%), SiO_2 (6%), carbon (10%), $BaSO_4$ (16%), and TiO_2 (22%). Pd-black without support was the most efficient catalyst (*ee* 38%); enantioselectivity

increased with dispersion of Pd and its maximal value was observed at 0.2-0.4 dispersion in the case of Pd-black-DHVin catalyst.

From the hydrogenation of isophorone different catalyst supported on carbon and modified with DHVin produced an unusual set of changes of *ee* values and absolute configurations of product depending on the nature of the catalytic metal and diminishing in the following order: 10% and (*R*) on Pd, 2.1% and (*R*) on Ir, 1.9% and (*R*) on Pt, 0.83% and (*S*) on Rh, and 0.3% and (*S*) on Ru.

Very interesting results were observed in studies of competing influence of modifiers DHVin and Cnd upon their simultaneous addition to one sample of catalyst in the enantioselective hydrogenation of EtPy at RT and 50 bar. Thus when increasing amounts of DHCnd were added to a Pt-alumina catalyst that was originally modified with DHVin, *ee* values of the resulting EtLa changed from 25% (*R*) (no DHCnd added) to 50% (*S*) (2 mmol Cnd added), which indicated that DHCnd is more strongly adsorbed and displaced DHVin from the active Pd centers.

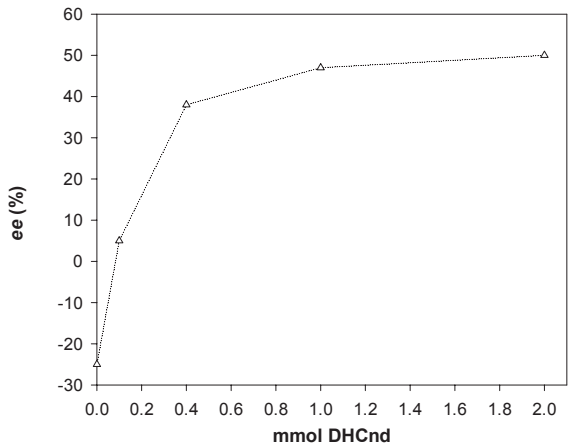


Figure 5.8. Enantiomeric excess values in the enantioselective hydrogenation of ethyl pyruvate into (*R*)-(-)- and (*S*)-(+)-EtLa on Pt-alumina catalyst modified with DHVin with increasing addition of DHCnd at RT and 50 bar (according to Tungler, Sheldon [230]).

The asymmetric inductions of (-)-DHVin and Cnd as chiral modifiers were compared in the Pd catalyzed hydrogenation of the C=C double bonds of 2-phenylcinnamic acid and isophorone. The differences in their effects and behaviors were attributed to the differences in the interactions between the modifier and reactant and their different basicities (Tungler et al. [129]).

Prominent nonlinear effects in enantioselectivity were observed when EtPy was hydrogenated over Pt-alumina in the presence of two cinchona alkaloid modifiers, Cnd and Qnd, which alone afford excesses of opposite enantiomers of EtLa. The changes in reaction rate and *ee* varied strongly with the type and amount of the alkaloid and with the order of their addition to the reaction mixture. Under ambient conditions in AcOH as solvent, Cnd afforded an *ee* of 90% to (*R*)-EtLa, but addition of an equimolar amount of Qnd to the Cnd modified catalyst reduced the *ee* to only 88%, even though Qnd alone provided 94% *ee* to (*S*)-EtLa. This results can be explained by preferential adsorption of Cnd on the surface of Pt via the quinoline rings, which lie approximately parallel to the Pt surface. In this position the Cnd molecule can interact with EtPy during H-uptake and control enantioselectivity. On the other hand, the weaker adsorbing Qnd adopts mainly a position with the quinoline plane tilted relative to the Pt surface, and this species cannot be involved in the enantioselective reaction (Huck et al. [277]).

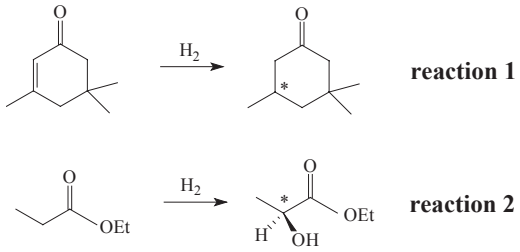
Farkas et al.[278] compared the esters (-)-DHVin and (+)-DHVin with (-)-dihydro-apovincaminic acid as chiral modifiers in the enantioselective hydrogenation of EtPy and isophorone.

(*S*)-Proline based chiral modifier esters and amides containing aromatic rings were used in the enantioselective hydrogenation of isophorone and EtPy (Sipos et al.[279]).

Pd-C modified with (*S*)-proline[2-(2-naphthyl)ethyl] ester resulted in an *ee* of 23% for (*S*)-dihydroisophorone upon the hydrogenation of its C=C double bond in MeOH, and Pt-alumina modified with the 3-ethylindol derivative of (*S*)-prolineamide gave only an *ee* of 5% upon the hydrogenation of the C=O of EtPy in MeOH.

Sipos et al.[280,281] considered the characteristics of Pd-titania catalysts modified with (-)-DHVin in the enantioselective hydrogenation of isophorone. They used supports that were different in crystalline forms and in surface areas.

Pt-alumina modified with DHVin proved to be less effective than that modified with Cnd for the hydrogenation of EtPy; *ee* reached only 30% (Tungler, Sheldon [230]).



Scheme 5.12.

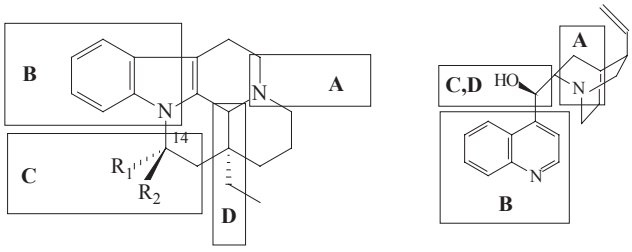
The hydrogenation of isophorone (reaction 1) and EtPy (reaction 2) were the studied reactions (Scheme 5.12.) using different Pd- and Pt-catalysts, modified with (-)-DHVin and (+)-DHVin (Table 5.9.) [258].

Reactions	Catalysts	Modifiers		
		(-)-DHVin *ee* (%)	(+)-DHVin *ee* (%)	DHCnd *ee* (%)
reaction 1	0.3 g Pd black	40	10	20
	0.5 g Pd powder	19	6	10
	0.1 g Pd/C	10	4	3
reaction 2	0.1 g Pt/Al_2O_3	30	14	72
	0.1 g Pt/C	27	13	55

Table 5.9. A comparison of enantioselective hydrogenation of isophorone (reaction 1) on Pd and ethyl pyruvate (reaction 2) on Pt catalysts modified with DHVin isomers and DHCnd (according to Tungler, Sheldon [230]).
Conditions: 100 cm^3 methanol, 0.1 g modifier, 0.5 g acetic acid, 0.05 mol isophorone or 0.1 mol EtPy.

Interaction of DHVin with EtPy to form and association was confirmed by circular dichroism in which it was found that the *N*-atom in DHVin reacted with the C=O group in pyruvate; the dichroic effect was increased when the *N*-atom was protonated by the addition of AcOH, analogous to the same effect in the case of Cnd. Adsorption on Pt through the heteroaromatic group and by the indole group of DHVin proceeds similarly to the adsorption of Cnd. The much stronger adsorption of the quinoline group in Cnd than the indol group in DHVin explains the greater effectiveness of catalysts modified with Cnd than with DHVin.

Comparison of the active parts in DHVin (left in Scheme 5.13) and Cnd (right) show their similarities.



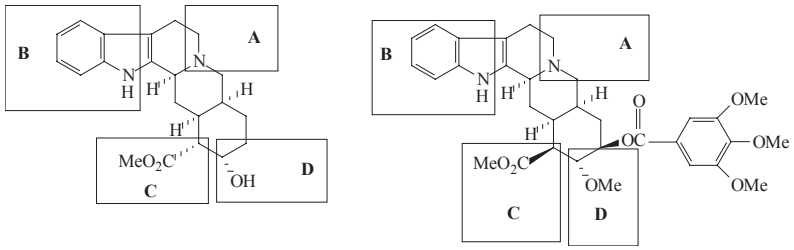
Scheme 5.13.

In DHVin it is possible to mark the four groups responsible for asymmetric reaction as A, B, C, and D, shown in Scheme 5.13. according to Tungler [164].

The effect of addition of AcOH in the hydrogenation mixture with Pt-catalyst modified with both DHCnd and DHVin can be explained by interaction of the basic center *N*-1 (region A) with the substrate molecule. The indole ring (in DHVin) and quinoline ring (in Cnd) (region B) are responsible for the coordination of the modifiers with metal centers on the surface of the catalyst.

The roles of regions C and D are less definite. (-)-DHVin and (+)-DHVin stereoisomers have different configurations at C-14 and different optical rotations, but as modifiers they lead to the same configuration of products.

Structures close to DHVin and DHCnd with regions A, B, C, and D can be identified in yohimbine and reserpine, too (Scheme 5.14.).



Scheme 5.14.

The effectiveness of these compounds as modifiers should be evaluated in future experiments. It is of interest that electrochemical reduction of the C=C bond in cumarin in the presence of yohimbine leads to the (*R*)-(+)-ketone with an *ee* of 13 % (see Chapter 6).

5.4. Structure of substrate

There are many classes of substrate structures involved in heterogeneous enantioselective hydrogenation on modified metal catalysts. They consist of 2-oxocarboxylic acids and their esters, ketones, diketones, keto lactones, unsaturated acids, oximes, and amides. Enantioselectivities of heterogeneous chirally modified metal catalysts are determined in an important way by the matched interactions between the functional groups of the substrate and the modifier.

For example, the Pt-alumina-alkaloid catalytic systems proved to be the best for enantioselective hydrogenations of 2-oxocarboxylic acids and their esters, especially the pyruvates (Blaser [22], Baiker [17-20]), and the formates (Orito et al.[57,58]), originally studied in the "Orito Reaction" (see Bartok et

al.[169]). And recently very high *ee*'s were obtained in hydrogenations of pyruvaldehyde dimethyl acetal (Torok et al.[282] and Studer et al.[76]), ketopantolactone (Schuerch et al.[20]), substituted pyrrolidine-trione (Kunzle et al. [87]), and ketoglutarates (Balazsik et al.[283] and Felfoldi et al.[177]). The highest *ee*'s, 96-98.6%, were obtained with 2-oxoesters over 5% Pt-alumina catalyst modified with HCnd or MeO-DHCnd (Blaser [68]). And also, the hydrogenation of formates gave high *ee*'s; EtBf was hydrogenated with a somewhat larger *ee* than MeBf, 89.5% [58] versus 81.9% [57].

Recently reported have been several syntheses of chiral esters that have practical applications for the preparation of natural products and chiral synthones. Many good results were achieved due to special conditioning of the catalysts and adjustments of the solvents. Further, the reaction has been extended to include the hydrogenation of functionalized compounds; for example, carboxylic acids containing a C=C bond have been hydrogenated with chirally modified Pd catalysts supported on a new type of carriers (Smith et al.[202] and Nitta et al.[124]). And in the hydrogenation of the C=C bond in 2-phenylcinnamic acid recent amazing results were obtained over a Pd-TiO_2 modified catalysts that considerably extended the possibility of the given catalytic systems**.**

5.4.1. Hydrogenation of ketones

Hydrogenation of diketones and ketones proved to be not very effective (Vermeer et al.[150]); hydrogenations of the diketones, butane-2,3-dione and hexane-3,4-dione, on 6.5% Pt-silica-Cnd at 10 bar and 20^0C in CH_2Cl_2 solution produce *ee*'s of only 33% and 38%, respectively, although trifluoroacetophenone gave 56% (Bodmer et al. [99,100]). Likewise, Torey et al.[275] found that hydrogenation of the C=C side chain in an unsaturated cyclic ketone over Pd-charcoal catalyst modified with (-)-ephedrine at 0^0C in MeCN resulted in a product with an *ee* of only 36%.

The hydrogenation of a nonactivated ketone, acetophenone, over Pt supported on carbon and modified with Cnd was not very effective, producing an *ee* of only 20% (Perosa et al.[284]). However, electron-withdrawing groups in the aromatic ring increased the reaction rate and enantiomeric excess. Derivatives of acetophenone in the *o*-, *m*- and *p*-positions gave higher *ee*'s; for example, hydrogenation of 3,5-bis(trifluoroacetyl)acetophenone under ambient conditions over Pt-alumina-Cnd catalyst yielded a product with an *ee* of 60%. An interesting unprecedented behavior in this reaction was observed: addition of Cnd into the reaction media slowed down all hydrogenation reactions (Hess et al.[285]).

Von Arx et al.[286] studied the hydrogenation of 4-oxoisophorone (2,6,6-trimethylcyclohex-2-en-1,4-dione) over Pt-alumina and Pd-alumina catalysts modified with Cnd and discovered (over Pt-alumina-Cnd) the first example of an unprecedented selectivity in hydrogenation of a sterically hin-

dered C=O bond in an *alpha, beta*-unsaturated diketone to an unsaturated alcohol (3,5,5-trimethylcyclohex-2-en-4-ol-1-one) with an *ee* of 14%.

Pyrone derivatives, 3,6-dimethyl-4-hydroxy-2-pyrone and 4-methoxy-6-methyl-2-pyrone, were hydrogenated over 5% Pd-titania modified with Cnd and Cn. During the reaction the quinuclidine *N*-atom of the alkaloid modifier can interact with the acidic OH group of 3,6-dimethyl-4-hydroxy-2-pyrone [113].

Solvent effects were studied in the enantioselective hydrogenation of 1-phenylpropane-1,2-dione over Pt-alumina-Cnd catalyst. The *ee* values and reaction rates are dependent on the hydrogen solubilities and dielectric constants in different solvents. The highest *ee*, 65%, of (*R*)-1-hydroxy-1-phenylpropanone was obtained in toluene. It decreased non-linearly with increasing solvent dielectric constant becoming close to zero in MeOH (Toukonitty et al.[287])

In the second hydrogenation step during the asymmetric hydrogenation of cyclohexane-1,2-dione over Pt-alumina-Cnd an enantiomeric excess of over 80% of (1*R*,2*R*)-*trans*-cyclohexane-1,2-diol was obtained due to kinetic resolution (Sonderegger et al.[288]).

Ethyl methyl ketone and methoxyacetone were transaminated with benzylamine over Pd-C catalyst in the presence of chiral modifiers like L-Ala, L-alaninol, or L-Ala-OR with *ee*'s of 20% in cyclohexane solvent. When the (*S*)-(-)-(1-phenylethyl)amine was the chiral transamination agent, the hydrogenation resulted in (*S*)-1-methoxypropan-2-amine with an *ee* of 70% (Gobolos et al.[289]).

Ethyl nipecotate (ethyl piperidine-3-carboxylate) was prepared with an *ee* of 24% by enantioselective hydrogenation of ethyl 1,4,5,6-tetrahydronicotinate over DHCnd modified Pd-C catalyst in solution (DMF, AcOH + water) and with an *ee* of 19% over Pd-TiO_2 in DMF solution. As Blaser et al.[290] noted, this example is the first asymmetric hydrogenation of a heterocyclic *alpha, beta*-unsaturated ester with significant *ee*'s using a chirally modified heterogeneous catalyst.

Compared to homogeneous chiral transition metal complexes, enantioselective hydrogenation of aromatic and heteroaromatic compounds over modified metal catalysts has the greater potential.

Maris et al. [112] hydrogenated furan-2-carboxylic acid over a Cnd modified 5% Pd-alumina catalyst at RT and 30 bar hydrogen in a solvent. (*S*)-tetrahydrofuran-2-carboxylic acid was obtained with an *ee* of 32%. When benzofuran-2-carboxylic acid was hydrogenated slowly, the *ee* increased to 50% at 29% chemical yield. The potential application of the method is limited by the competing hydrogenation of the quinoline rings of Cnd, which necessitate the presence of only small amounts of Cnd during the reaction. The reaction mechanism is analogous to that applied for *alpha,beta*-unsaturated carboxylic acids (see below, Part 5.7.). The *ee* values were lower in the

hydrogenation of methylfuran carboxylic acids but 100% *de* values were achieved.

Diastereoselective hydrogenations of the bornyl and menthyl esters of furan-2-carboxylic acid in EtOH over 10% $Pd(OH)_2$-C catalyst at 20°C and 50 bar hydrogen were studied [291,292]. The optically active esters were reduced with $LiAlH_4$ and the *de* values of the resulting tetrahydrofuryl-alcohols were measured. The *de* value of the bornyl ester was 24%, and of the menthyl ester was 20%.

Exocyclic *alpha,beta*-unsaturated ketones can be enantioselectively hydrogenated. For example, (*E*)-2-benzilidene-1-benzosuberone was hydrogenated to (*S*)-2-benzyl-1-benzosuberone with an *ee* of 20% in AcOEt or acetonitrile at ambient conditions over Pd-C catalysts in the presence of (*S*)-proline (Fogassy et al.[293]) or with an *ee* of 53.7% in toluene over Pd black modified with Cnd (Fogassy et al.[294]).

On chiral modified metal catalysts very important results were obtained from the hydrogenation of ketopantolactone to pantolactone (see also, Chapter 7) with *ee*'s up to 79% (Baiker [17-20,82]). A very important role has been shown for the application of new type of modifiers other then the cinchona alkaloids by modeling their molecular structures (Schuerch [20]). Of interest is the elaboration of the effective preparation of intermediates and synthones for the syntheses of novel drugs via asymmetric hydrogenation of the keto ester, ethyl 2-oxo-4-phenylbutyrate to ethyl (*R*)-2-hydroxy-4-phenylbutyrate. An example is the preparation of benazepril (Blaser et al.[71-73]) (see also Chapter 7, reaction 7.31 and 7.32) using modified Pt-alumina-Cnd catalyst or the $[\{Rh(NBD)Cl\}_2(Norphos)]$ complex.

Unfortunately, the best *ee* (96%) obtained with the use of latter homogeneous complex was obtained only at a low substrate/catalyst ratio of 50. The heterogeneous catalyst, on the other hand, revealed an *ee* of 95%, high activity, and high productivity. The main problem accompanying the high rate and *ee* value was the substrate quality.

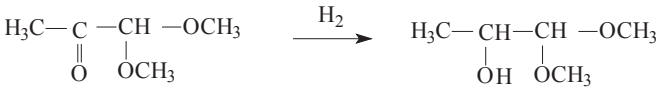
The main results from enantioselective hydrogenations on Pt-alumina were received from hydrogenations of pyruvates (the most promising model substrates), which procduced *ee*'s above 95%. Recently, however, some new examples of substrates were described revealing excellent enantioselectivities.

Bartok, Balazsik et al.[176,177,283] studied the enantioselective hydrogenation of 2-oxoglutaric acid and dialkyl 2-oxoglutarates over cinchona modified Pt/Al_2O_3 catalysts. They found that the hydrogenation of the keto-group in alkyl 2-oxoglutarates at 20°C and 10 bar hydrogen in AcOH solution over 5% Pt-alumina modified with MeO-DHCnd gave, with subsequent cyclization, the furane derivatives, (*R*)-alkyl-5-oxotetrahydrofuran-2-carboxylates (chiral building blocks for further syntheses), with *ee*'s of 93%. Increasing the hydrogen pressure to 20 bar gave products with somewhat higher *ee*'s, 94-96%. Modifying the catalysts with Cnd or Cn instead of

MeO-DHCnd produced products with *ee*'s of 83% (*R*)**,** and 66% (*S*), respectively. Similar to the hydrogenation of EtPy on alkaloid-modified Pt-alumina, the general rate increased from 0.12 to 1.41 mmol/min·g catalyst after addition of the alkaloid modifier to the reaction mixture.

Unfortunately the report of Bartok, Balazsik et al. [283] did not indicate the *ee* of the hydroxyglutarate produced in initial catalytic hydrogenation step; therefore, it can not be excluded that the high *ee* of the cyclized product was obtained as a result of the diastereomeric cyclisation of hydroxyglutarate rather than as a result of the catalytic hydrogenation of the keto-group in 2-oxoglutarate. Felfoldi et al.[176] studied the modifier concentration dependence of the rate and enantioselectivity of hydrogenation of the diethyl 2-oxoglutarate and pyruvaldehyde dimethyl acetal over Pt-alumina modified with cinchona alkaloids. Using the Engelhard catalyst (E4759) in AcOH at ambient conditions an optical yield of 95-97% was achieved.

Bartok's group [282] described the first application of the heterogeneous cinchona modified Pt catalysts for the highly enantioselective synthesis of a chiral building block of an acetal with an *ee* of 96.5% using the hydrogenation of pyruvic aldehyde dimethyl acetal to lactaldehyde dimethyl acetal (Scheme 5.15.).



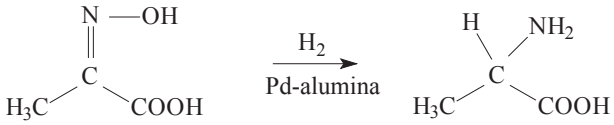
Scheme 5.15.

The reaction was carried out at 20°C and 1 bar hydrogen in AcOH solution over 5% Pt-alumina catalyst modified by Cnd or Cn. In the presence of Cnd-modifier, the (*R*)-product with an *ee* of 96.5% and a rate of 0.81 mol/g·catalyst·min was obtained, while with Cn as the modifier, the (*S*)-acetal with 88% *ee* and 0.72 mol/g·catalyst·min was formed. Increasing the hydrogen pressure decrease the values of *ee's* and increases the rates of reactions indicating a ligand acceleration mechanism; thus, the highest optical yields were obtained at the highest reaction rate.

Another example of high enantioselectivity (*ee* 97%) in the hydrogenation of pyruvaldehyde dimethyl acetal was found by Studer, Blaser et al.[76] carrying out the reaction on 5% Pt-alumina modified with MeO-DHCnd in AcOH as solvent at 60 bar and 25°C. This reaction was also studied by Torok, Bartok et al.[282]**,** under mainly the same conditions but at 10 bar hydrogen and with Cnd as the modifier and resulted in products with *ee's* of 96.5 %(*R*)- and 88% (*S*)-isomers.

Very interesting results were obtained by Borszeky, Mallat, Baiker et al. [108-110] in the enantioselective hydrogenation of nitrogen containing substrates. It was found [108] that on Pd-alumina catalyst modified with Cnd, Cn, or ephedrine, the C=N bond in pyruvic acid oxime can be hydrogenated into

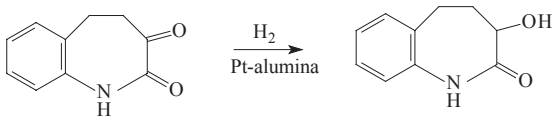
alanine (Scheme 5.16.) at 0-45^{0}C and 10 bar hydrogen in polar solvents with *ee*'s of 14.1% (*S*)-isomer (Cnd), 12% (*R*)-isomer (Cn), or 26% (*S*)-isomer (ephedrine), respectively.



Scheme 5.16.

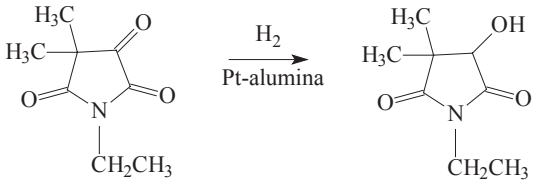
Enantioselectivity increased with higher temperatures and higher alkaloid to oxime ratios. The presence of the alkaloid modifier resulted in a decrease of the reaction rate by a factor of as much as 140, compared to the "racemic" hydrogenation without modifier. On 5% Pt-alumina-Cnd catalyst, at 60 bar, 20^{0}C, in AcOH, they showed [109,110] that pyruvamides with different amido groups gave modest *ee*'s with the best *ee* of 60% being observed only for trifluoroethyl pyruvamide.

In a similar way the hydrogenation of the cyclic imidoketone (Scheme 5.17.) proved to be enantioselective resulting in a product with an *ee* of 47%.



Scheme 5.17.

Kunzle, Baiker et al. [87] synthesized a cyclic imidoketone, 1-ethyl-4,4-dimethylpyrrolidine-2,3,5-trione (a structural analog of ketopantolactone), and hydrogenated it over 5% Pt-alumina-Cnd at 15^{0}C in toluene solution into (*R*)-1-ethyl-3-hydroxy-4,4-dimethylpyrrolidine-2,5-dione (Scheme 5.18.) with an *ee* of 91%.

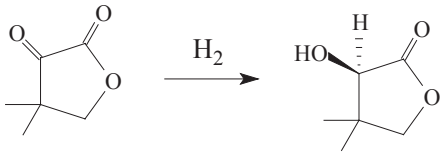


Scheme 5.18.

In polar solvents (EtOH or DMF), its *ee* dropped to 20%, but in AcOH its *ee* reached 70%, similar to the hydrogenation of ketopantolactone. The high concentration of hydrogen on the Pt surface favored increasing the *ee*;

therefore, a hydrogen pressures of 30 bar was chosen as the optimal value. With the Cnd concentration of 3 mg/l and the substrate to modifier ratio of 70,000, the optical yield reached 91%.

This process is used in the industrially important reaction, the hydrogenation of ketopantolactone (KPL) (4,4-dimethyltetrahydrofuran-2,3-dione) into pantolactone (PL) [(*R*)-(-)-3-hydroxy-4,4-dimethyltetrahydofuran-2-one] (Scheme 5.19.).



Scheme 5.19.

A very effective process for hydrogenating KPL using Rh and Ru chiral complex catalysts will be considered in Chapter 7. Here the enantioselective heterogeneous hydrogenation of KPL will be examined in connection with the question of mechanism of heterogeneous hydrogenation of the C=O bond on chirally modified Pt catalysts. In KPL the keto-carbonyl group is activated like the *alpha*-keto group in *alpha*-keto esters. The homogeneous hydrogenation of KPL on chiral Rh-complex catalysts proved to be very effective and similar to the hydrogenation of pyruvate in which *ee* values reached above 90% under very mild conditions using chiral metal complex catalysts [295-298]. Chapter 7 will give in detail results of the asymmetric synthesis of PL via hydrogenation of KPL using metal complexes with chiral phosphane ligands and producing *ee*'s up to 98%, which are of practical interest. Here we can note that Ru(II)- and Rh(I)-arene complexes were very effective in the enantioselective hydrogenation of activated carbonyl groups [108]. The use of Rh-complexes with a new chiral ligand (*S*)-dicyclopentylphosphane-dicyclopentylphosphinite-pyrrolidine allowed the hydrogenation of KPL into PL with an *ee* of 96% at 20°C and 96.9% at 70°C. The Rh-complex supported on silica gave PL with an *ee* of 91%, which is the same value obtained using the unsupported homogeneous catalyst.

The first enantioselective heterogeneous hydrogenation of KPL was reported in a Japanese patent (Niwa [299]). Over a 5% Pt/C catalyst previously modified with Cnd in ethanolic solution at reflux, KPL was hydrogenated in benzene at 60 bar to (*R*)-PL with an *ee* of 36%. Later, a Pd/C catalyst modified with Cnd proved to be more effective and gave (*R*)-PL with an *ee* of 52% (see Baiker [17-20]). Even more effective proved to be a Pt-alumina-DHCnd catalysts that produced (*R*)-(-)-PL with an *ee* of 79% under optimal conditions (22°C and 70 bar) in toluene at low concentrations of alkaloid (Schuerch et al.[20]).

The main characteristics of the process of hydrogenation of KPL are quite similar to those of the hydrogenation of pyruvates. These characteristics are similar positive influences of preliminary catalyst treatments at elevated temperatures in flowing hydrogen gas, the use of solvents of low polarity, and the existence of relatively high Pt surface hydrogen concentrations. All these factors strongly work for higher enantioselectivity.

5.4.2. Effect of variables on the hydrogenation of ketopantolactone

Effect of hydrogen pressure. The optical yield of KPL from hydrogenation on Cnd modified Pt-alumina increased with increasing hydrogen pressure from 1 bar (50% *ee*) to 30 bar (75% *ee*). Above 30-40 bar the *ee* values reached a plateau. This picture is similar to that observed for the hydrogenation of pyruvates (Schuerch [20], Sun [109] and Garland [67]). It was found that for high *ee*'s it is necessary to create high hydrogen concentrations on the Pt surface. Therefore *ee* values from the hydrogenation of KPL will be considerable lower when the catalyst is cooled in flowing nitrogen after heat treatment in flowing hydrogen. It was found [209,258], that *ee*'s depend considerably on the concentration of molecular hydrogen in the liquid phase rather than on the hydrogen pressure in the gas phase if the reaction proceeds under kinetic conditions rather than under diffusion control. Values of *ee* from the hydrogenation of EtPy on Pt-alumina increased in the initial period of reaction at constant pressure of 6 bar and 30^0C by increasing the gas-liquid mass-transfer of hydrogen. Good *ee* values could be obtained provided the catalyst is properly preconditioned and traces of oxygen and water are removed (see Johnston et al. [144] and Margitfalvi et al. [162]).

Effect of reaction temperature. Increasing the temperature of the hydrogenation of ketopantolactone in the range of 7-27^0C leads to a maximum *ee* of 78%, while increasing the temperature of the hydrogenation of pyruvates results in decreasing enantioselectivity.

Effect of substrate concentration and degree of conversion. In the concentration range of 0.05-2 mmol/L of KPL the influence of concentration on the rate of reaction and on *ee* is very small. On the other hand, in the hydrogenation of pyruvates there is another picture. There the rates and *ee*'s increase with extent of conversion up to 20% (Wang [211]) at least in the initial period of the reaction (Singh et al. [207,208]). No such changes occurred in the hydrogenation of KPL. That is, there is no such dependence if the reaction is carried out under "standard condition" (hydrogen pressure 70 bar). But at atmospheric pressure in toluene solution an increasing *ee* of 20-35% was obtained during the degree of conversion of 5% to 90% (Singh [207]).

Effect of modifier concentration. A broad maximum of *ee* (75-80%) has been observed as a function of the concentration of HCnd (in standard conditions of 150 mg of catalyst, 3.9 mmol KPL, 7^0C, 70 bar, toluene solvent).

The maximum corresponds to a low molar ratio of DHCnd to Pt of 0.065. For the hydrogenation of pyruvates this ratio is equal to 0.5 (Garland et al. [67]). Thus under standard conditions the best results obtained the product (*R*)-(-)-PL with an *ee* of 75% (if the catalyst was preliminarily treated with hydrogen but not with nitrogen!). Kunzle et al. [114] showed the enantioselective hydrogenation of KPL over Pt-alumina-Cnd in a fixed bed reactor by continuously feeding the chiral modifier, Cnd, in *ppm* concentrations to the reactant stream. The reaction proceeded at RT and 40 bar hydrogen with a rate of 94 mmol/g catalyst·h and an *ee* of 83.4%. In the same conditions EtPy was hydrogenated with 23 mmol/g cat·h and resulted in an *ee* of 89.9%.

Effect of solvents. The nature of solvent plays an important role in the asymmetric hydrogenation of KPL. As observed during the hydrogenation of pyruvates, *ee* values decreased with increasing solvent polarity (Blaser et al. [68]). The same effect was observed in the hydrogenation of KPL. A high *ee* of 78% was obtained in apolar media such as toluene. In polar solvents like ethanol *ee* values dropped almost to zero. Strangely, although acetic acid was the best solvent for enantioselective hydrogenation of pyruvates, for KPL it gave an *ee* of only 35% (Schuerch et al. [20]).

Rate acceleration. A very peculiar feature of the hydrogenation reaction of pyruvates over Pt-alumina catalysts consists in the sharp increase in the rate of reaction and in the *ee* of the product immediately after introducing a small amount of alkaloid into the reacting solution. It is the well known effect of "ligand acceleration" (Garland et al. [66]) for enantioselective hydrogenation of pyruvates. The same picture was observed for the hydrogenation of KPL. The rate increased by 4-25 times in comparison with the reaction in the absence of alkaloid modifier. Adding merely 2-20 mg of Cnd to the reaction mixture increased the rate of reaction and reduced the reaction time from 25 min to 3.5 min and produced PL with an *ee* above 70% under standard reaction conditions (0.15 g of 5% Pt-alumina catalyst, 19.5 mmol KPL, 25 ml toluene, 70 bar hydrogen, and 12^0C).

Molecular modeling of the reaction system showed that in the transient complex the basic quinuclidine N-atom of Cnd is bound to the C=O group of KPL via a hydrogen bond interaction that stabilizes the half-hydrogenated state. The interaction favors the formation of (*R*)-PL compared to (*S*)-PL. It was noted (Schuerch et al. [20]) that diastereomeric transition complexes leading to (*R*)-pantolactones are more stable by 8 kJ/mol than the corresponding complex leading to (*S*)-pantolactones. This calculation did not take into consideration the metal surface and concerned only the Modifier-Substrate interactions rather than with the Modifier-Catalyst or Substrate-Catalyst interactions. In this connection, it was suggested that the transition complex is adsorbed on the Pt surface in such a position that the quinoline rings of Cnd and the carbonyl groups of KP are adsorbed on a flat Pt(III) surface facet. This arrangement shows the similarities of the diastereomeric transition complexes when comparing the cyclic lactone, KPL, and the *alpha*-keto

esters in an apolar medium, where the alkaloid is not protonated (Schuerch [20]). But the hydrogenation of pyruvates proceeds with higher *ee* values, when Cnd is protonated (Baiker [21]). For this case, a model was proposed by Schwalm et al. [96-98]. When the protonated Cnd interacts with the carbonyl substrate, the interaction can again be described as hydrogen bonding between the quinuclidine *N*-atom and the *alpha*-carbonyl O-atom.

Molecular modeling of the diastereomeric transition complexes Cnd-PL-Pt also indicated that the complex affording (*R*)-PL is energetically favored with Cnd, whereas the complex leading to (*S*)-PL formation is favored by Cn. The formation of both structures are quite similar to those proposed for the hydrogenation of MePy suggested by Schwalm et al. [98].

5.5. Effect of Solvents and Additives

In different ways solvents influence enantioselective hydrogenation of keto esters on chiral modified Pt-supported catalysts. The effect of solvent on enantioselective hydrogenation involves the solubility of hydrogen, the solubility of the reactant, and the interaction between modifier, reactant, and catalyst surface including the carrier (Singh et al. [207,208]). There are no general regularities of the effects of solvents on the actions of Pt-alumina-Cnd catalyzed enantioselective hydrogenations of pyruvic acid esters. Unfortunately, it is difficult to develop a theory of the effects of solvents but some empirical regularities can be pointed out. In a number of studies, toluene and ethanol were used as the most suitable solvents. It was found (Wehrli et al. [78]) that with increasing solvent polarity both *ee* and reaction rate were found to decrease (see Table 5.10.).

Blaser et al. [68] found that *ee*'s almost linearly decreased with increasing solvent polarity (Table 5.10.). In apolar solvents with dielectric constants in the range of 2 and 6, *ee* values obtained in the hydrogenation of MePy were maximal (Baiker [17-20], Wehrli [78]).

Almost the same dependence of optical yields was observed with the use of an empirical solvent parameter given by Reichardt [300] (see Baiker [17-19]). It is of interest that alcohols with dielectric constants of 15-30, also gave good results, although they partly reacted with the keto ester to give the hemiketal (Minder [94,95]). Using ethanol as a solvent, a good result that led to higher *ee* values in the hydrogenation of EtPy can be explained by the partial formation of AcOH during the prior oxidative treatment of the Pt-alumina catalyst (Minder et al.[94,95], Johnston et al. [144]).

The best *ee* was obtained in solutions of AcOH (dielectric constant 6.15) and with other carboxylic acids with *ee*'s up to 91%. NMR studies showed that in the presence of AcOH the quinuclidine *N*-atom of Cnd is protonated, which favors the interaction between modifier and reactant (Baiker [17-19,94,95]).

Solvent	Dielectric constant	Activity r_o (mol kg^{-1} s^{-1})	Conversion (%)	Optical yield *ee* (%)
cyclohexane	2.02	2.94	100	79.9
toluene	2.38	2.68	100	82.9
trichloroethylene	3.4	0	0	-
chlorobenzene	5.71	2.32	100	83.9
tetrahydrofuran	7.6	2.14	100	81.1
dichloromethane	9.08	2.20	100	81.4
pentan-1-ol	13.9	2.38	95	78.0
propan-2-ol	20.1	3.05	100	76.7
ethanol	24.3	2.28	100	75.0
methanol	33.6	1.08	92.7	75.1
DMSO	46.7	0	0	-
water-ethanol (1:1)	50	1.45	90.7	61.9
water	80.4	0.78	100	54.1

Table 5.10. Effect of different solvents on optical yield (*ee* %, normalized values) and reaction rate, r_0, in the enantioselective hydrogenation of ethyl pyruvate on 5% Pt-alumina catalyst modified with cinchonidine (according to Wehrli et al. [78]).

The effect of acids and bases as solvents (or as additives) in the hydrogenation of EtPy on Pt-alumina-Cnd was studied by Blaser et al. [62,68]. The addition of AcOH to common applied solvents (toluene, ethanol) or using AcOH as the solvent exhibited unusually strong positive effects on *ee*'s, up to 95%, especially with catalysts modified with MeO-DHCnd (Blaser et al. [68]).

Table 5.11. shows that all carboxylic acids as additives are suitable for enantioselective hydrogenation but *ee* and initial reaction rates decrease with increasing chain lengths of the acid molecules. Bases decrease the *ee* values somewhat.

Bartok et al. [180,302,309] found that the alumina support can react with the acetic acid producing aluminum containing oxonium cations. These cations may play a role in the enantioselection in the asymmetric hydrogenation of ethyl pyruvate catalyzed by the platinum-alumina-dihydrocinchonidine catalytic system.

Analogous to the pyruvates, the same decrease in *ee* with increasing solvent polarity was found in the enantioselective hydrogenation of ketopantolactone into pantolactone over Pt-alumina-Cnd catalyst (Schuerch et al. [20]). The most suitable solvent proved to be toluene (*ee* 78%) but in acetic acid solution the strong increase of *ee,* which was observed in the case of pyruvates, was not seen and the optical yield of pantolactone reached only up to 35% (see results in Part 5.4.).

Additive	Amount (g/L slurry)	Modifier	*ee* (%)	Rate (mol g^{-1} min^{-1})
none		MeODHCnd	77	0.08
none		MeODHCnd	73	0.08
none		DHCnd	84	0.1
CH_3COOH	80	MeODHCnd	90	0.13
CH_3COOH	80	MeODHCnd	87	0.09
HCOOH	40	MeODHCnd	91	0.01
CF_3COOH	40	MeODHCnd	87	0.03
C_6H_5COOH	40	MeODHCnd	78	0.08
$(COOH)_2$	40	MeODHCnd	71	0.01
phenol	40	DHCnd	67	0.14
phenol	40	MeODHCnd	72	0.1
quinoline	0.4	DHCnd	88	0.08
quinoline	4	DHCnd	79	0.04
Et_3N	2.8	DHCnd	79	0.05
Pyridine	0.4	DHCnd	83	0.1

Table 5.11. Effect of various acidic and basic additives to solvent toluene on the hydrogenation of ethyl pyruvate over Pt-alumina catalyst modified with 10,11-dihydrocinchonidine (DHCnd) or 10,11-dihydro-O-methylcinchonidine (MeODHCnd) at RT and 100 bar hydrogen pressure (according to Blaser et al. [68]).

Solvent	Chemical yield (%)	$[\alpha]_{589}$ (in EtOH) of the "Scalemic products" *	Optical yield of (*R*) (*ee* %)
AcOH	87	82.4	61.5
EtOH	89	83.2	62.1
iPrOH	90	92.8	69.3
PhMe	87	97.0	72.4
THF	89	97.8	73.0
AcOEt	90	104.7	78.2
iBuOH	88	101.5	75.8
iPrOiPr	89	106.3	79.4
Dioxane	89	107.1	80.0
$EtCO_2Et$	92	107.9	80.0
EtOEt	89	108.4	80.8
PhH	90	109.0	81.4
AcOiPr	91	109.5	81.0
$EtCO_2Me$	92	109.7	81.9

***** "Scalemic products " are optically active mixtures, containing unequal amounts of enantiomers (see in *J. Am. Chem. Soc*., **53**, 1922 (1988)).

Table 5.12. Asymmetric hydrogenation of methyl benzoylformate into (*R*)-(-)-methyl mandelate in different solvents over 5% Pt-C catalyst modified with cinchonidine (according to Niwa,Orito et al. [58]).

Orito et al. [59,60] also showed that the nature of the solvent proved to be important in the hydrogenation of MeBf and MePy on Pt-C and Pt-alumina catalysts modified with Cnd (Tables 5.12. and 5.13.).

The hydrogenation of MePy into MeLa proceeds somewhat less influenced by solvents. In the series of solvents, THF, MeOH, AcOEt, iPrOH, and iBuOH, the *ee*'s of MeLa increased from 64% to 73.1%. But hydrogenation without solvent proved to be somewhat more effective, giving an *ee* of 74.0%, and the addition to the reaction mixture of 0.1 g of Cnd did not affect the *ee*, but in the presence of solvents, the addition of Cnd or Qn did increase *ee*'s (Table 5.13.).

Solvent	5 % Pt-C *ee* % [32]	5 % Pt-Alumina *ee* % [33]	Supplement addition of 0.1 g alkaloid
None	74.0	-	None
MeOH	64.6	32.6	None
MeOH	71.2	86.6	Cnd
EtOH	78.7	83.2	Cnd
iPrOH	72.2	80.6	Cnd
EtOH	76.6	-	Qn
MeOH	-	82.4	Qn

Table 5.13. Asymmetric hydrogenation of methyl pyruvate (MePy) into (*S*)-(+)-methyl lactate (MeLa) on 5% Pt-C and 5% Pt-alumina modified with supplement addition of alkaloids in different solvents (according to Orito et al.[59,60]).

Addition of small amounts of triethylamine (Et_3N) or 20% of Cnd to the solvents gave large improvements in the asymmetric effect (Table 5.14.).

It was found that the initial reaction rate increases with the pK_a of bases added to the reaction mixture in the series of quinoline (pK_a= 5) < quinuclidine (pK_a = 11) < pyrrolidine (pK_a = 16.3) < cinchonidine (pK_a = 8.3).

The effect of Cnd is much higher than by the above mentioned amines despite its lower pK_a, because its specific adsorption on the Pt surface results in simultaneously increasing the reaction rate and the enantioselective effect. Such a result was explained by the "Template effect", which is a mutual adsorption of reactant and modifier molecules on the Pt catalyst surface (Sutherland et al. [141]).

Chernysheva et al.[253] were the first to have obtained evidence of inhibition from the product of the reaction of hydrogenation of ethyl acetoacetate on Raney nickel catalyst modified with (2*R*,3*R*)-tartaric acid into ethyl (*R*)-(-)-3-hydroxybutyrate. Similar results were obtained also in the enantio-

selective hydrogenation of ethyl acetoacetate on Raney Cobalt modified with (2*R*,3*R*)-tartaric acid [220].

Solvent	Conversion (%)	*ee* (%)	Catalyst
none	68	74.0	5% Pt-C-Cnd
MeOH	72	64.6	5% Pt-C-Cnd
MeOH*	-	69.6	5% Pt-C-Cnd
EtOH	72	70.1	5% Pt-C-Cnd
EtOH*	-	74.0	5% Pt-C-Cnd
iPrOH	66	73.0	5% Pt-C-Cnd
THF	68	53.7	5% Pt-C-Cnd
AcOEt	65	68.8	5% Pt-C-Cnd
Benzene	85	80.8	5% Pt-alumina-Cnd
Benzene*	84	85.2	5% Pt-alumina-Cnd
MeOH	79	32.6	5% Pt-alumina-Cnd
MeOH*	86	44.9	5% Pt-alumina-Cnd
MeOH**	84	86.6	5% Pt-alumina-Cnd

* Addition of 0.2 mL Et_3N ** Addition of 0.1g Cnd

Table 5.14. Effect of solvents and additives on the enantioselective hydrogenation of MePy into (*S*)-(+)-MeLa on 5% Pt-C-Cnd and 5% Pt-alumina-Cnd catalysts (0.5 g catalysts, 70 bar, RT) (according to Orito [59,60]).

Nitta et al.[134] also confirmed these effects using Ni-silica catalysts modified with (2*R*,3*R*)-tartaric acid in the hydrogenation of methyl acetoacetate (Figure 5.9.) They showed the effects on optical selectivity of the concentration of methyl (*R*)-(-)-3-hydroxybutyrate, which had been previously added to the reaction mixture.

These observations confirm that the methyl (*R*)-(-)-3-hydroxybutyrate, the product of the reaction, inhibits a fraction of the active centers of the selective reaction on the surface of catalyst and thus diminishes enantioselectivity. An especially strong inhibiting effect was observed after the addition of strongly adsorbing compounds like thiophene to the reaction mixture [106a].

The use of supercritical fluids (SCF's) as solvents is of interest for enantioselective hydrogenation. Baiker [103-105,285] was the first to employ SC-solvents in the enantioselective hydrogenation of ethyl pyruvate over Pt-alumina catalyst modified with Cnd in a solution of ethane under supercritical conditions. The reaction was carried out in an autoclave at 60 bar and 60^0C. It was found that the hydrogenation rate was higher than in toluene solution but the *ee* was approximately the same as in the common solvents. The tem-

perature dependence of *ee* in the formation of (*R*)-(-)-EtLa in SCF was also the same as in common solvents [103].

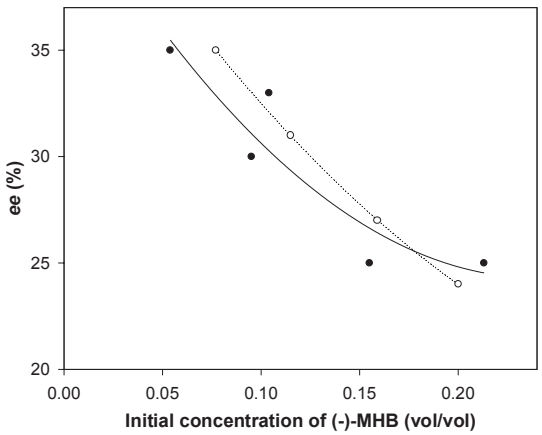


Figure 5.9. Effect of the amounts of previously added methyl (*R*)-(-)-3-hydroxybutyrate to methyl acetoacetate before hydrogenation on Ni-silica catalyst modified with (2*R*,3*R*)-tartaric acid (•) (according to Nitta et al. [134]) and the hydrogenation of ethyl acetoacetate on Raney nickel catalyst modified with (2*R*,3*R*)-tartaric acid (o) (according to Chernysheva et al [253]).

Under supercritical conditions the diffusivity of solutes in SCF is higher than in commonly applied liquids, the viscosity is lower, and mass-transfer is enhanced (Baiker [101,103,303-305]). The comparison of ethane in the supercritical state (SC) and ethanol as solvents in the enantioselective hydrogenation of EtPy over Pt-alumina-Cnd showed that under identical conditions the hydrogenation rate in SC-ethane is increased by a factor of 3.5 with the same *ee*-values. A further advantage of SC-ethane is that the high *ee* value remains constant with increasing catalyst to substrate ratio, which can be important for practical uses of the catalyst in continuous fixed-bed reactors for hydrogenation (see below Figure 5.10.). According to Baiker,Wandeler et al.[101-103, 303-306] the enantioselective hydrogenation of EtPy was studied in a fixed bed reactor over Pt-alumina-Cnd catalyst using supercritical ethane as solvent. Application of SC-ethane revealed good enantioselectivity and very fast conversion of EtPy into EtLa with a TOF 15 sec^{-1} at RT. The phase behavior in the range of 15-50^{0}C and at pressure up to 140 bar showed the multicomponent phase high-pressure reaction system. The rate of hydrogenation in the system composed of ethane-EtPy-hydrogen increased significantly [102,103] when the pressure was increased above 60 bar at 40^{0}C and the density of reaction mixture was 0.3 g/cm^3.

It was found that for enantioselective hydrogenation over modified platinum catalysts the most suitable SC-solvents are ethane and propane as indicated in Table 5.15. [101]. Application of SC-CO_2 in hydrogenation on chiral modified Pt-catalysts proved to be less suitable because CO_2 is partly hydrogenated into CO, which poisons the catalyst [101]. But polymer-supported colloidal Pd nanoparticles as catalysts in supercritical CO_2 ($scCO_2$) revealed TOF's as high as 4 x 10^6 h^{-1} at 15 bar hydrogen, and 50^0C (Niessen et al. [306]).

Solvent	P_{crit} (bar)	$^oC_{crit}$
Xenone	58.0	16.59
CO_2	72.9	31.0
Ethane	48.2	32.3
Propane	96.8	42.0
Butane	36	153
$CClF_3$	28.8	39.0
CF_4	44.6	58.0
CHF_3	62	44.9
$CHCl_3$	63.8	143

Table 5.15. Supercritical fluids (SCF's) most suitable for asymmetric catalytic hydrogenation.

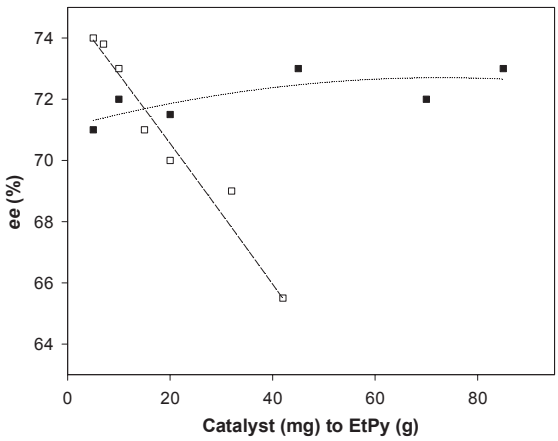


Figure 5.10. Comparative study of enantioselective hydrogenation of EtPy into (*R*)-(-)-EtLa on Pt-alumina-Cnd catalyst as a function of the catalyst to substrate weight ratio in ethanol solution (□, at 60 bar, 22^0C as subcritical solvent) and in the supercritical solvent ethane (■, at 60 bar, 40^0C) (according to Baiker [101-103]).

Table 5.15. shows the other SC-solvents that can be applied in asymmetric hydrogenation. They must be rather inert and can be used in the suitable ranges of pressure and temperatures for practical application.

Figure 5.10. shows an example of the application of SC-ethane as solvent in the hydrogenation of EtPy over Pt-alumina-Cnd catalyst. For all practical purposes the *ee* values of the resulting EtLa did not change with increasing amounts of catalyst if the reaction was carried out in SC-ethane, whereas these values fall sharply in ethanol.

Enantioselective hydrogenation of EtPy on Pt-alumina-Cnd catalyst at 60 bar, 40^{o}C, in supercritical solvent ethane (subcritical condition for ethane are 48.2 bar and 32.2^{0}C) can be compared with hydrogenation in ethanol at 60 bar, 22^{0}C as subcritical solvent (SCF are 61 bar and 241^{0}C) (according to Baiker [102,103]).

5.6. Reaction variables

The kinetics of enantioselective hydrogenation of pyruvates on Pt-alumina (or Pt-silica) catalysts modified with Cnd (or DHCnd) was studied by the groups of Baiker [85,91,102,103], Blaser [66,67,74,75,78], Wells [141,143,146], and Blackmond [207,208,211,212].

A kinetic model for the system of Pt-alumina-Cnd-EtPy was elaborated by Garland [66]. It was based on a two cycle mechanism that proposed increasing the reaction rate on modified centers leading to (*R*)-(-)-ethyl lactate as a result of "ligand acceleration" [227], which is characterized by a high rate (and enantioselectivity) on selective centers, and a slow rate on non-selective centers, both reactions being equilibrated. A mechanistic scheme proposed, was based mainly on a concept suggested earlier by Klabunovskii [25,220,307] for enantioselective hydrogenation of *alpha*-keto esters on tartaric acid-modified Ni catalysts that suggested that two kinds of centers exist on the surface of the catalyst, namely, selective centers leading to chiral products and non-selective centers leading to racemic products.

In kinetic studies zero order was found with respect to the *alpha*-keto ester and first order with respect to hydrogen [78,141]. Apparent activation energies for hydrogenation on Pt-alumina and Pt-silica were found to be 31 kJ/mol and 38 kJ/mol, respectively (Baiker [21]).

Catalytic systems including cinchona alkaloids (or amino alcohols with similar molecular structures) as modifiers proved to be the only successful compounds in asymmetric hydrogenations that provided strong adsorption on the surface of Pt catalyst owing to their aromatic part and their ability to form a hydrogen bond between the tertiary *N*-atom of the quinuclidine moiety of the alkaloid and the oxygen atom of the *alpha*-keto group of the reactant-

pyruvate molecule. In the enantioselective hydrogenation of EtPy on Pt-alumina-DHCnd, Garland et al. [66] found the effect of the lowest concentrations of modifier, DHCnd, added during the reaction to a solution of toluene or ethanol. The modifier concentrations varied between 0 and 0.23 mmol/L corresponding to zero to one DHCnd molecule per one exposed platinum atom on the surface of the catalyst.

Rather important factors influencing enantioselectivity are temperature and hydrogen pressure. Reaction temperatures in the range of 20-50^{0}C are suitable; at higher temperatures optical yields drop drastically.

Hydrogen pressures above 5-10 bar gave good results, but according to recent studies of Blackmond's group [209,257] good stirring of the reaction mixture and the resulting concentration of hydrogen in the reaction mixture determined by the mass transfer coefficient of the system was the important factor rather than the hydrogen pressure in the gas phase. Blackmond's group [207-209,211,212,257] found that the kinetic parameters affected enantioselectivity and the main factor was the high rate of mixing of the reacting liquid phase. Increasing the mass transfer coefficients by stirring the reaction mixture from 400 rpm to 1000 rpm [209,257] assisted in transferring the gas into the liquid, brought the reaction into kinetic control, and resulted in increased enantioselectivity.

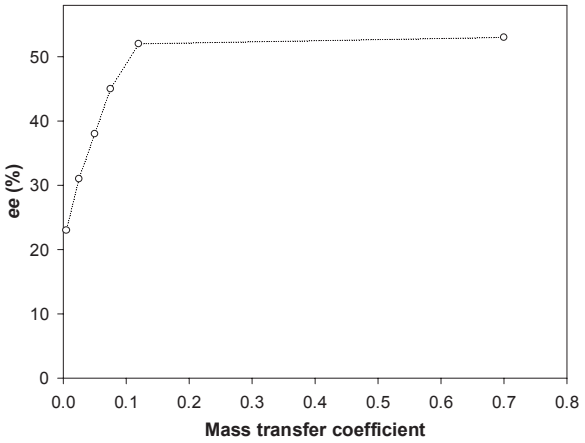


Figure 5.11. Enantioselectivity at 50% conversion as a function of the gas-liquid mass-transfer coefficient (K) in the hydrogenation of ethyl pyruvate on Pt-alumina modified with Cnd at constant pressure in gas phase of 5.73 bar and 30^{0}C (according to Blackmond, Sun et al. [209,257]).

Figures 5.11. and 5.12. demonstrate that enantioselectivity and hydrogen concentration of the solution, vary as a function of the mass transfer coefficient at constant hydrogen pressure. When the rate of mass transfer becomes high

enough, owing to the high speed of the stirring in the reactor, the hydrogen concentration approaches $[H_2]^{sat}$ in solution. Further increasing in coefficient causes no additional increase in enantioselectivity. Hydrogen pressure determined the value of $[H_2]^{sat}$ at a given temperature and, therefore, may set the upper limit on enantioselectivity [209,257]. Thus the hydrogen pressure is a valid kinetic parameter only when efficient mixing allows the solution to approach its solubility limit of hydrogen.

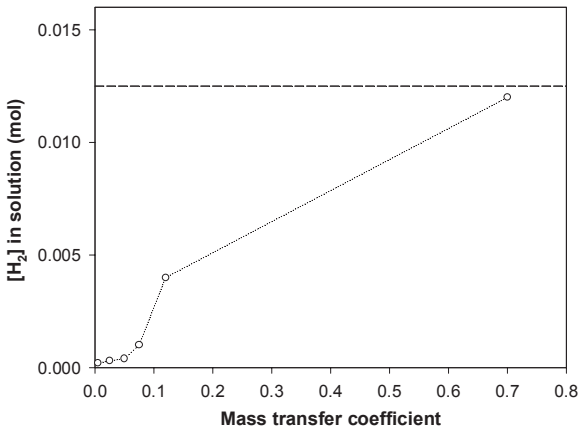


Figure 5.12. Hydrogen concentration of the solution at 50% conversion as a function of the gas-liquid mass-transfer coefficient the $[H_2]^{sat}$ concentration in the liquid phase (broken line) in hydrogenation of ethyl pyruvate on Pt-alumina modified with Cnd at constant pressure in gas phase of 5.73 bar and 30^0C (according to Blackmond, Sun et al. [209,257])

The effect of degrees of conversion on enantioselectivity is also of importance. It was found [207,208] that *ee* increased in the hydrogenation of EtPy on Pt-alumina-DHCnd with increasing conversion over a wide range of reaction temperatures reaching a plateau between *ee* 54-58% at high degrees of conversion. The increase of the stirring rate in an autoclave from 400 to 1000 rpm, increases significantly the optical yield of resulting ethyl lactate from 35% *ee* (*R*) to 60%. Wang et al [211] found the significant increase of *ee* and reaction rate is in accordance with the term "ligand acceleration" that was used by Sharpless [81] to describe the significant rate increase observed in the homogeneous asymmetric dihydroxylation of olefines catalyzed by osmium complexes containing cinchona alkaloid ligands.

The initial transient period (ITP) of the enantioselective hydrogenation of activated ketones (ethyl pyruvate, pyruvaldehyde dimethyl

acetal and methyl benzoylformate) on Pt-alumina modified by cinchonidine or dihydrocinchonidine under mild conditions in toluene was studied by Balazsik et al [308]. The results suggest that the ITP is affected not only by impurities but also by the competitive adsorptions of reactants, modifier and solvent. Consequently, ITP may be considered an intrinsic feature of this type of enantioselective hydrogenations.

In the enantioselective hydrogenation of ethyl benzoylformate to (*R*)-ethyl mandelate over dihydrocinchonidine modified Pt/Al_2O_3 in acetic acid 98% *ee* was achieved. The difference between the rates of racemic and enantioselective hydrogenation was less than in the case of ethyl pyruvate, which indicates that ligand acceleration is not an absolutely necessary prerequisite for achieving high enantioselectivity in the enantioselective heterogeneous hydrogenation of *alpha*-keto esters [309,310].

The repeated use of Pt-alumina modified by dihydrocinchonidine was studied by Balazsik and Bartok [311] for the enantioselective hydrogenation of ethyl pyruvate under mild experimental conditions in toluene and AcOH. In toluene, depending on the reaction conditions, an increase of *ee* by 10-20% was observed on the reused catalysts. The same effect, however, was not found in AcOH. The phenomenon was attributed to an intrinsic feature of the Pt-alumina-cinchona system, in which the restructuring of the Pt surface may play an important role.

Using electrospray ionization mass spectrometry technology on products from pyruvate hydrogenations Bartok's group identified aluminum containing oxonium cations and new adducts, which were formed by non-covalent interactions [301,312-316]. In the study of enantioselective hydrogenation of EtPy on Pt-alumina, Pt-black, and Pt-(black + alumina) modified with DHCnd in AcOH solution under the mild conditions of RT and 1 bar hydrogen EtLa was produced with an *ee* of 92% accompanied by the following ratios: EtPy/DHCnd > 43,000, EtPy/ $Pt_{surface}$ > 1000, and an extremely low DHCnd/$Pt_{surface}$ ratio (0.0072). It was found experimentally that the quinoline ring of DHCnd gradually hydrogenated during the reaction decreasing the enantioselectivity (Bartok et al. [180]). This reduction of the modifiers during the hydrogenation reaction was published in other articles, too [317,318].

LeBlond et al. [257] applied unprecedented mild conditions for the enantioselective hydrogenation of keto esters, 5.8 bar instead of the commonly used 100 bar, over 1% Pt-alumina catalyst with 25% Pt dispersion, modified with DHCnd. In their standard experiment 1.4 g of 1% Pt-alumina, 400 ml AcOH, and 0.1 mol of EtPy were evacuated and stirred before applying hydrogen.

They achieved 94% *ee*'s for (*R*)-(-)-MeLa and (*R*)-(-)-EtLa under mild conditions (17°C, 5.8 bar hydrogen), and an *ee* of 92% was obtained at 1.3 bar owing to the elaborations of control for low concentrations of the modifiers (DHCnd, DHQ) at the surface of the catalyst and for

implementation of optimal conditions: TOF 4 s^{-1} (at 5.8 bar), turnover numbers EtPy/DHCnd > 28 000, EtPy/$Pt_{surface}$ > 5500.

But for hydrogenation of ethyl 2-oxo-4-phenylbutyrate, which is used in the preparation of pharmaceuticals, the optimal ratio of $Pt_{surface}$/DHCnd was 1 at an *ee* of 91%. It is of interest that the regularities of the heterogeneous enantioselective hydrogenation should be different in solutions and in gas-phase reactions**.**

Hutchings and Wells [153] reported the first gas-phase enantioselective - hydrogenation in a flow reactor, the hydrogenation of a pyruvate esters over Pt supported on *gamma*-alumina, *alpha*-alumina or silica, premodified with the solution of Cnd in dichloromethane. Over 2.5% Pt on *gamma*-alumina or on silica the hydrogenation of MePy at 40°C resulted in (*R*)-(-)-MeLa with *ee's* of 46-51%, while the corresponding values in toluene were 50-70%. Over 1% Pt on *alpha*-alumina (this support has no intraparticle pore structure) the *ee* was only 25%. Thus, these results demonstrate that enantioselective hydrogenations have different behaviors in gas-phase and in liquid-phase.

Because the enantioselective reaction produces a chiral product, which itself can serve as modifier and influence selectivity, it was of interest to investigate the effect of the degree of conversion on the optical yield. Such experiments were studied in the asymmetric hydrogenation of *alpha*-keto esters by Chernysheva et al.[253] and Nitta [134]. It was found [253] that the significant value of the relative adsorption coefficient of (-)-MHB resulted in it inhibiting the enantioselective hydrogenation of MAA (see Figure 5.9.). On the other hand, a decrease in *ee* with degree of conversion could indicate instability of modified centers of catalyst [169,220,307].

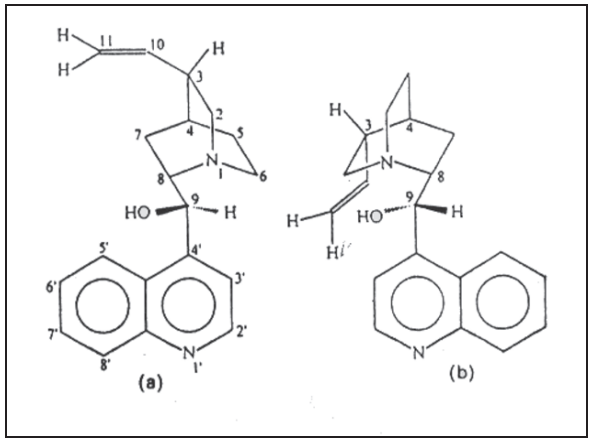
In the case of the Pt-alumina-Cnd-EtPy system, increasing conversion did not change the *ee* even at high conversions. This is in contrast to the Ni catalysts modified with tartaric acid and suggests a different mechanism of enantioselectivity. Also, in both cases the possibility of nonlinear effects must be pointed; that is, increasing enantio-purity of a product of low optical purity upon its exposure to a chiral catalyst (Blackmond [210], Avalos [4], Kagan [5,6]).

5.7. On the mechanism of hydrogenation

The mechanism of enantioselective hydrogenation on nickel catalysts modified with optically active compounds was suggested for the first time by Balandin's group [7-9]. They proposed that the reaction proceeded through an intermediate complex involving catalyst metal atom, (Ni), modifier molecule, (M), and substrate molecule, (S): {Ni-M-S}. Similar models were proposed later by Yasumori et al [224-226] and Izumi and Tai [213-218].

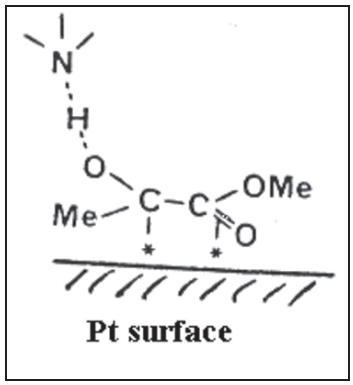
The aims of studies to elucidate the mechanism have been to account for the observed enantioselectivity and the reaction rate enhancement. The

first attempts to account for the detailed mechanism of action of Pt-alumina-alkaloid-pyruvate system were made by Wells' group [141-152].



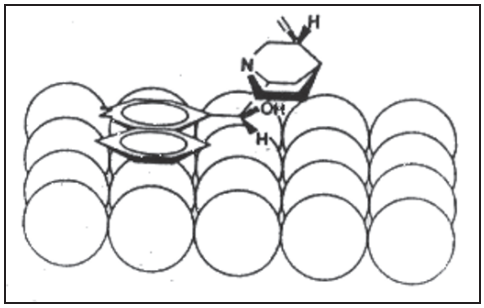
Scheme 5.20. Cinchonidine (a) and cinchonine (b) molecules.

Sutherland et al. [141] developed the 'Template model' based on a geometric explanation of enantioselectivity assuming adsorption of the cinchona alkaloid modifier and methyl pyruvate reactant on the surface of a Pt(III) facet such that the alkaloid modifier is adsorbed by its quinoline ring in such a way that there is a place for adsorption of the pyruvate molecule to form an intermediate active complex which produces, after hydrogenation of the C=O bond in pyruvate, either the (*R*)-(-)-methyl lactate, in the case of using Cnd as modifier, or the (*S*)-(+)-methyl lactate using Cn as modifier (see the modifier structures in Scheme 5.20.).



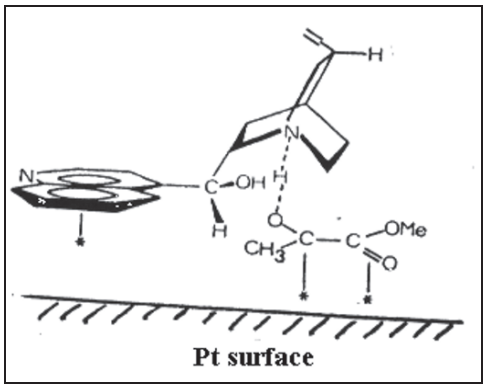
Scheme 5.21. Hydrogen bond between the *N*-base of the alkaloid and the half-hydrogenated state of the pyruvate molecule [141].

This first 'Template model' was later reexamined using LEED and improved to the '1:1 model' (Simons, Wells et al. [149]) as a simpler and better argument which shows that an H-bond is established between the N1-nitrogen of the quinuclidine bicycle and the half-hydrogenated form of pyruvate molecule (Scheme 5.21.).



Scheme 5.22. Cinchonidine molecule adsorbed in the lowest energy conformation on the Pt surface.

Cnd adsorbs on Pt via the aromatic quinoline ring, assuming flat adsorption parallel to the Pt surface over two adjacent Pt atoms. H-D exchange between adsorbed Cnd and a deuteriated solvent showed that all of the H atoms of the quinoline moiety simultaneously exchanged, suggesting that the modifier molecules are chemisorbed on the Pt surface with the *pi*-electron system of the quinoline ring. Scheme 5.22. shows the region of the surface that the modifier molecule obscures. The quinoline ring is spatially well suited to lie above two adjacent surface Pt atoms and the quinuclidine bicycle lies just above the surface, forming an 'overhang'.

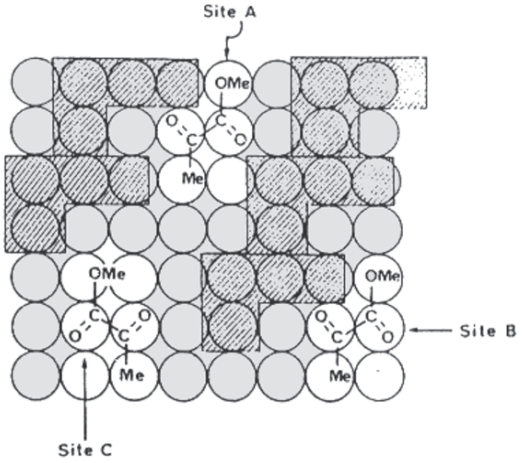


Scheme 5.23. A possible conformation of the modifier Cnd when it is H-bonded to the half-hydrogenated state of MePy (according to Bond, Wells et al.[146]).

Buergi and Baiker [115] used an *ab initio* method to calculate the interactions in the complexes between Cnd-modifier and MePy-reactant complexes that are active in the enantioselective hydrogenation over Pt-alumina catalysts. It was found that the *trans*-MePy complex, resulting in (*R*)-(-)-EtLa upon hydrogenation, is more stable by 7.5 kJ/mol than the corresponding complex leading to the (*S*)-(+)-enantiomer, which corresponds to an *ee* of 92%, in good agreement with the experimental results. Scheme 5.23. shows the schematic representation of the intermediate complex [Cnd-MePy] at the surface of a Pt catalyst.

Each adsorbed Cnd molecule utilizes an L-shaped region of the surface (Scheme 5.24.). Enantioselectivity could be attributed to the establishment of a closely packed 'adlayer' of Cnd molecules.

Scheme 5.24. shows the proposed adsorbed state of the cinchonidine molecule which provides the templated surface for enantioselective hydrogenation. With the half-hydrogenated state of methyl pyruvate stabilized by hydrogen bonding, the geometrical requirements are achieved by rotation about the C8-C9 bond in the cinchonidine molecule.

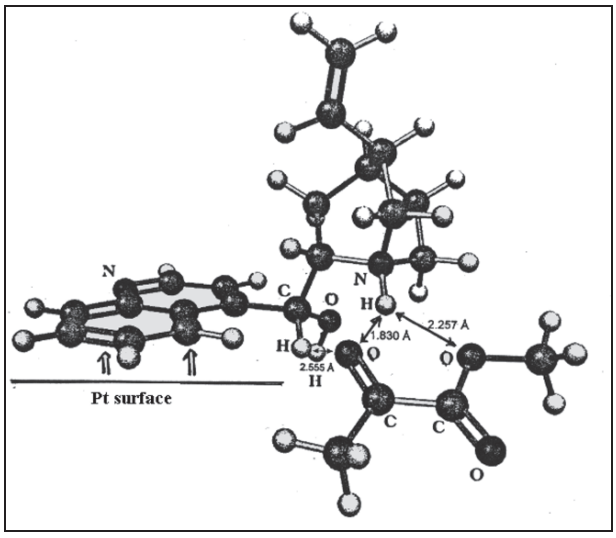


Scheme 5.24. Array of cinchonidine molecules adsorbed on Pt (100) together with two methyl pyruvate molecules.
Site A: asymmetric hydrogenation site according to the 'Template model' resulting (*R*)-(-)-MeLa.
Site B: the '1:1 interaction model' resulting in (*R*)-(-)-MeLa
Site C: racemic hydrogenation site, because there is no interaction with adsorbed cinchonidine molecules (according to Webb, Wells [105]).

Site A in Scheme 5.24. shows the regular adsorption of five Cnd molecules with their 'L-shaped forms' on a Pt area consisting of 7x7 Pt atoms accompanied by adsorption of the methyl pyruvate molecule to be hydrogenated and leading to (*R*)-(-)-methyl lactate.

Site B shows another orientation of MePy leading to (*S*)-(+)-MeLa, the 'adlayer' of Cnd molecules exert steric hindrance for adsorption of the methyl and methoxy groups and therefore make this model less probable.
This was confirmed by experiments with Pt-catalyst modified with Cnd, which resulted in predominantly (*R*)-(-)-MeLa. In this reaction Cnd obscures rather more then one surface Pt atom and the adsorbed Cnd is 'L-shaped' as viewed from the liquid phase and shown on Scheme 5.24. Site C is a *racemic* hydrogenation site because there is no interaction in this case with the adsorbed Cnd molecules.

Baiker et al. [17-19,21] studied the interaction of the *N*-atom of the quinuclidine moiety using quantum chemistry techniques at both *ab initio* and semi-empirical levels as well as molecular mechanics (Schwalm, Baiker et al. [96-98]). The quinuclidine center can act as a nucleophilic center or, after protonation, as an electrophilic center. As a model of both cases the interaction of methyl pyruvate with NH_3 and NH_4^+ were studied theoretically and it was found that the {Pyruvate-NH_4^+} complex is much more stable by 10.5 kJ/mol due to favorable electrostatic interactions. This indicated that in protic solvents, e.g. in AcOH, this structure plays an important role and, indeed, AcOH proved to be the most favorable solvent for this enantioselective reaction.



Scheme 5.25. The calculated structures of complexes formed between protonated cinchonidine and pyruvate adsorbed on a platinum surface (according to Schwalm et al. [98]).

The interactions shown in Scheme 5.25. give a reason for the almost 20-fold rate increase in enantioselective hydrogenation of pyruvate on Pt catalysts that are modified with Cnd at RT and 10 bar hydrogen, because in this catalytic system:

i) the modifier promotes the rate as an alicyclic *N*-base that stabilizes the half-hydrogenated state by H-bonds

ii) the modifier when adsorbed on the Pt surface enhances the surface coverage of hydrogen

iii) the modifier is adsorbed on the Pt surface by its quinoline aromatic part and enhances the activity of the Pt catalyst.

The next part of the specific behavior of the cinchona alkaloids as modifiers resides in their stable conformational structure. The molecules of cinchona alkaloids, e.g. cinchonidine or cinchonine (see Scheme 5.20.), consists of two relatively rigid parts: an aromatic quinoline ring and an aliphatic bicyclic quinuclidine ring, both connected through the hydroxyl-bearing chiral carbon atom, C9.

Conformational changes of the molecule, e.g. Cnd, are possible owing to rotation about the C4'-C9 and C9-C8 bonds. Calculations of the molecular mechanical energy as functions of the two dihedral angles, C3'-C4'-C9-C8 and C4'-C9-C8-N1, showed that of the six possible forms (in unprotonated and in *N*-protonated forms) there are two minimum energy conformations, a 'closed' conformation in which the N1 atom in the quinuclidine bicycle points towards the quinoline ring (the so called ‘closed form’) and an ‘open’ conformation in which the N1 atom points away from the quinoline ring (the so called ‘open form’) (see Scheme 5.25.).

Baiker [17-19,117,118] proposed a mechanism for the reduction of the keto-group, which explains enantioselectivity as an interaction in the hydrogen bonded complex of the alkaloid and the keto ester. According to Margitfalvi [155-162] the keto-compounds and the Cnd molecules form a complex in which one side of the keto-group is shielded by the aromatic ring of Cnd molecule, leaving the other side open for hydrogenation. But this model requires the Cnd molecule in ‘closed form’, in which the *N*-atom of the quinuclidine moiety points towards the quinoline aromatic rings. This model is just opposite to the ‘open’ form conformation in which this N-atom of the quinuclidine moiety points away from the quinoline rings. But it was found experimentally that only the ‘open’ forms of the alkaloids can induce enantioselectivity in the hydrogenation reaction, and the ‘closed forms’ can not play any important role in this process [17-19]. Baiker [118] found an $N^{+}\cdots H\cdots O$ hydrogen bond between the keto ester and Cnd using vibrational spectra. McBreen’s group [319] used vibrational spectra techniques for the analysis of the interaction between a chiral modifier, 1-(1-naphthyl)ethylamine (a modifier molecule with more simple structure than an alkaloid) and the reactant, MePy. In the absence of the modifier and at low MePy concentration, the MePy molecule tends to

adopt 'enediolate' geometry in which the carbonyl groups are in a *cis* conformation and the ester molecule bonds to the surface through both carbonyl oxygen atoms .

Another model proposes nucleophilic catalysis involving the *N*-atom of the Cnd and the C=O group of the pyruvate [205] . This became unpopular in favor of the hydrogen bonding model. One exception is the works of Bartok's group. They found that the DHCD/Pt_{surf} ratio necessary for achieving maximum enantioselectivity is highly solvent-dependent and the large difference may be a reflection of the difference in the reaction mechanism, and they assumed a switch from the nucleophilic mechanism in toluene to the hydrogen bonding mechanism in acetic acid [178,179].

The enantioselective hydrogenation of fluoroketones on cinchonidine modified Pt-alumina in toluene with and without trifluoroacetic acid was also studied, and it was proposed that the compounds responsible for the chiral induction were the intermediate complexes, the structures of which depended on whether hydrogenation was performed with or without TFA [320]. An unexpected change in the sense of enanatioselectivity was observed in the hydrogenation of ethyl pyruvate (EtPy) over *beta*-isocinchonine modified Pt-alumina catalysts, where (*R*)-(-)-ethyl lactate was the major product in toluene, while (*S*)-(+)-EtLt was formed in AcOH [321].

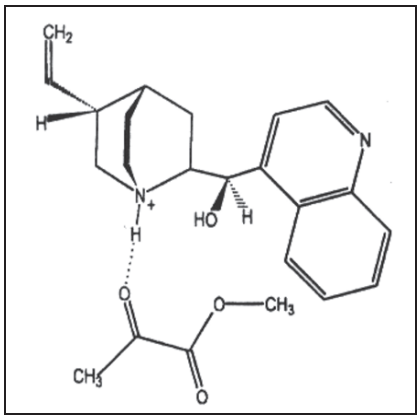
The hydrogenation of trifluoromethylcyclohexyl ketone in toluene or ethanol on Pt-alumina modified by cinchona alkaloids was studied, and depending on the solvents inversion of the enantioselectivity was observed. It was assumed that the structures of intermediates responsible for chiral induction depend mostly on the acidic or non-acidic nature of the hydrogenation medium [99,100,116,322].

In contrast with other reaction mechanism proposals that are based on weak hydrogen bonding, Vayner, Houk et al.[323] proposed that the key interaction is a strong bond between the amine, Cnd, and the carbonyl group of the ester, forming a zwitterion adduct at the platinum surface in acetic acid media [118,324].

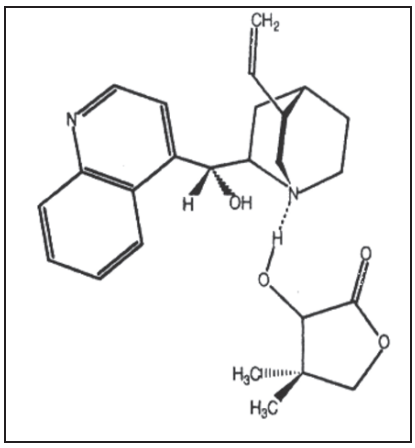
It was noted that in the ''closed' form there exists significant steric hindrance for the quinuclidine-*N* lone pair to participate in interaction with pyruvate, whereas in the 'open' conformation of the Cnd N-lone pair of quinuclidine is more readily accessible to the reactant. Scheme 5.26. shows the model of interaction of Cnd in the 'open' conformation with methyl pyruvate as calculated by Schwalm et al.[98] for the intermediate complex.

Another important aspect is the role of adsorption of the intermediate complex on the Pt active center. In the intermediate complex the pyruvate molecule is bound to the modifier via stabilizing hydrogen bond interactions, N-H···O, between the protonated quinuclidine-N atom and the O-atom of the *alpha*-carbonyl group of pyruvate, or O-H···N-bond for unprotonated system, such as for reactions in toluene solution. In this case, the H-atom can come from dissociatively adsorbed dihydrogen from the Pt-surface. The same

model is valid for the hydrogenation of ketopantolactone into (*R*)-pantolactone (Scheme 5.27.).



Scheme 5.26. Transition complex formed between cinchonidine and the half-hydrogenated state of methyl pyruvate resulting (*R*)-(-)-methyl lactate (according to Baiker et al. [17]).



Scheme 5.27. Transition complex formed between cinchonidine and the half-hydrogenated state of ketopantolactone resulting (*R*)-pantolactone (according Schwalm et al. [98]).

Calculations for this model showed the transition state for (*R*)-pantolactone to be more stable by 8.4 kJ/mol than the corresponding complex leading to (*S*)-pantolactone. According to these calculations, it is possible to produce an *ee*

of 90%, but experimentally only 79% was achieved (Schuerch, Baiker et al. [20]).

Buergi and Baiker [117] studied the influence of different solvents for the conformations of Cnd in the enantioselective hydrogenation of ketopantolactone. They claimed three conformations of Cnd at RT: 'closed (1)', 'closed (2)' and 'open (3)'. The latter structure is the most stable in polar solvents and increases with solvent polarity, as suggested by experiments on the enantioselective hydrogenation to pantolactone with a maximal *ee* of 78% in toluene solution, which is the solvent with the lowest dielectric constant. The increase in dielectric constant in the series of cyclohexane, hexane, diethyl ether and THF, decreases *ee* up to 50% and in EtOH and water even to 15%, in accordance with a decrease in the population of the 'open (3)' conformation of Cnd.

Margitfalvi et al. [160] suggested that the catalytic systems: Pt– and Pd–cinchona alkaloid–keto esters, are the first examples of a new class of heterogeneous catalytic reactions of supramolecular catalysis, where the prochiral group is part of a conjugated double bond system.

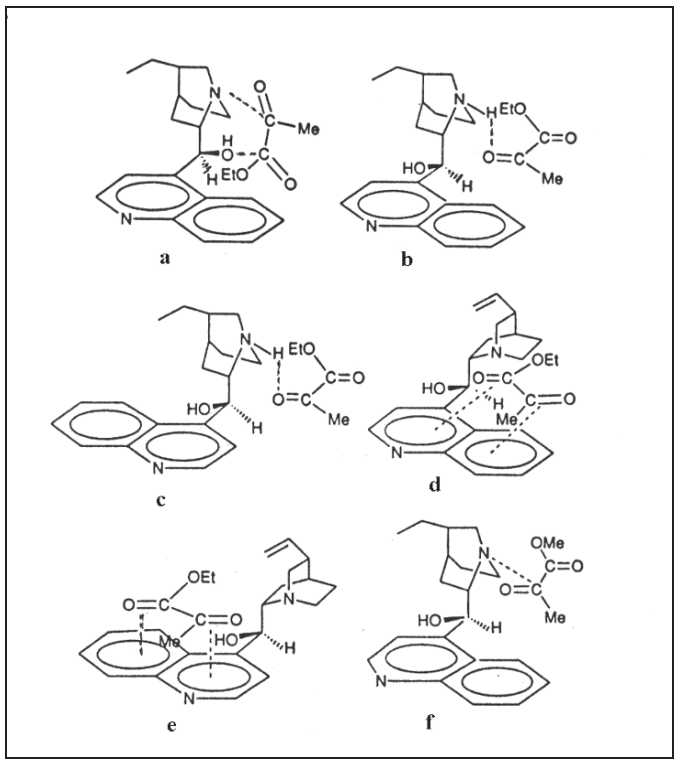
The role of the Pt surface in the formation of intermediates {Pt-surface-modifier-Cnd-reactant-pyruvate} considered in the above cited publications is not enough. According to Blaser et al.[69], an enantioselective center is formed by adsorption of the cinchona alkaloid on well defined platinum ensembles. The effect of crystallite size on the *ee* of the product was discussed earlier in Part 5.2 of this Chapter. The modification process involved only a part of the active centers on the surface of the Pt catalyst, while the absolute configuration of the C8 of the quinuclidine bicycle determined which configuration of the lactate product would be formed preferably. The decisive interaction of the pyruvate takes place with N1, but probably C9 also plays an important role in enantioselectivity because substitution of the OH at C9 for OAc or H decreases or annihilates enantioselectivity, as also was observed after hydrogenation of the quinoline ring in Cnd. As it was proposed by Blaser et al.[69], enantioselective hydrogenation proceeds through the modifier-reactant '1:1 complex' on the Pt surface, as was proposed in the case of the hydrogenation of ethyl acetoacetate on Ni-catalyst modified with (2*R*,3*R)*-tartaric acid (Izumi and Tai [213,219], Yokozeki [325], and Klabunovskii [9,220], see, also Chapter 4).

Thus, the main question of the mechanism of reaction consists of the mode of conformation of the alkaloid modifier on the surface of the catalyst. As mentioned above, there are two mechanistic concepts, which can be divided into path I and path II. According to path I, alkaloid modifier (e.g. Cnd) interacts with EtPy adsorbed on the surface of Pt by means of adsorption of the quinoline ring in the 'open' conformation according to the Scheme 5.28. as "***a"*** (Augustine et al.[205,206]), "***b"*** (Baiker, Blaser et al.[77]), "***c"*** (Blaser et al.[74,75]) or "***f"*** (Simons et al.[149]). According to path II, intermediate

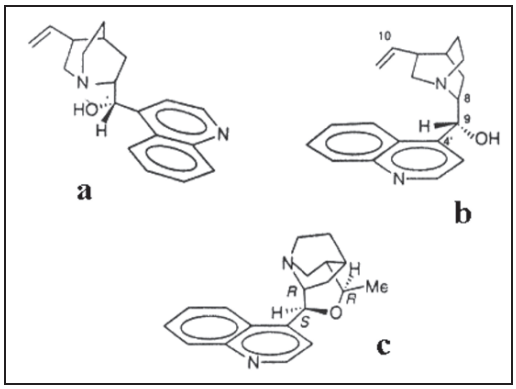
complex, Cnd-EtPy, is formed in solution in 'closed', "***d"*** and "***e"*** conformations (Margitfalvi et al.[159,160]).

The first group of conformations (***a, b, c*** and ***f***) adsorb on the Pt surface by multicenter *pí*-bonds of the quinoline ring and the *sigma, pí*-system of the pyruvate. Another group of conformations (***d*** and ***e***) suggest formation of the intermediate in solution *before* adsorption on the Pt surface.

To choose between these possibilities Bartok et al.[321,326-329] studied the mechanism of hydrogenation using derivatives of cinchonine (instead of cinchonidine used as the common effective modifier in all works earlier) and synthesized *alpha*-isocinchonine as a novel modifier. Scheme 5.29. shows the stable conformations of cinchonine in the 'open' conformation (***a***) and the 'closed' conformation (***b***) and the conformation of *alpha*-isocinchonine, α-iCn (***c***).



Scheme 5.28. The structures of the [cinchonidine-ethyl pyruvate] intermediate complexes (***a***, ***b***, ***c*** and ***f*** are in 'open'-conformations, while ***d*** and ***e*** are in 'closed' conformations (according to Bartok et al. [326]).



Scheme 5.29. The structure of cinchonine (Cn) in 'open' conformation (***a***), Cn in 'closed' conformation (***b***) and *alpha*-isocinchonine (***c***) (according to Bartok et al. [326]).

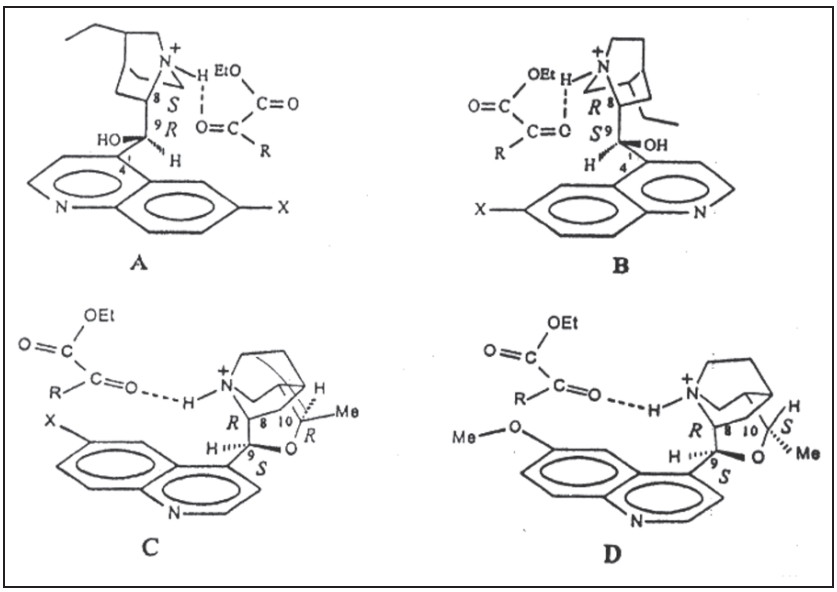
As can be seen, conformational changes in Cn are possible by rotation around the C4'-C9 and C8-C9 bonds. It should be noted, that in the case of adsorption of the quinoline portion of the alkaloid on Pt, rotation along the C'4-C9 bond is possible but hindered. But in the case of α-iCn, rotation along the C8-C9 bond is excluded, therefore, α-iCn exists only in the 'anti-open' steric hindered conformation.

The effect of the action of α-iCn as a modifier with fixed conformation was compared with Cn in the hydrogenation of EtPy on 5% Pt-alumina (RT, 50 bar, AcOH solvent), and it was shown that the catalyst modified with Cnd, Cn, and α-iCn lead to EtLa with 90% (*R*), 67% (*S*), and 69% (*S*), respectively. These *ee* values supported the existence of conformations (b) and (c) in the reaction and discounted the suggestion of Margitfalvi et al.[156-161] on the formation of an intermediate {alkaloid-pyruvate} in solution *before* adsorption on the catalyst and his criticism of the '1:1 model'.

Bartok et al.[169,321,326,327,329,330] also studied the mechanism of the hydrogenation of EtPy and ethyl benzoylformate (EtBf) on 5% Pt-alumina using (8*R*,9*S*,10*R*)-*alpha*-iCn and isocinchona alkaloids, namely *alpha*-isoquinidine [(8*R*,9*S*,10*R*)-α-iQnd] and *gamma*-isoquinidine [(8*R*,9*S*,10*S*)-γ-iQnd], as modifiers with new 10*R* or 10*S* chiral centers, possessing more rigid conformations (Scheme 5.30.).

Using NMR spectra combined with X-ray crystallography and molecular calculations it was shown by Bartok et al.[169] that Cnd, Cn, Qn, and Qnd must exist in their 'anti-open' conformations as modifiers. Rotations around the C4'-C9 and C8-C9 bonds are hindered. Therefore, the alkaloids exist also in the 'anti-open' conformations but they do not have the C8-C9 free rotation and form a rigid structure during adsorption on the surface of Pt-alumina catalyst.

H-D exchange studies of the isoalkaloids confirmed that adsorbed alkaloids undergo H-D exchange only inside the quinoline ring and on the C9 atom. In the quinuclidine skeleton H-D exchange appeared only in the case of Cn and iCn but not in the case of *gamma*-iQnd; therefore, good values of *ee* from the hydrogenation of EtPy were observed with the modifiers Cn (88%, *S*), Qn (90%, *R*), Qnd (89%, *S*), and with the isoalkaloids *alpha*-iCn (88%, *S*) and *alpha*-iQnd (85%, *S*) except *gamma*-iQnd (22%, *S* for EtPy and 9%, *S* for hydrogenation of EtBf). The methyl group at the C10 in *gamma*-iQnd exerts inhibition of rotation around the C9-C10 bond and the OMe group in the quinoline ring which gives an unfavorable steric hindrance in adsorption resulting in diminishing *ee* of the resulting EtLa.



Scheme 5.30. Structures of the '1:1 cinchona alkaloid pyruvate' intermediates:
A: Cinchonidine, Cnd, (X=H) and quinine, Q, (X=OMe) in 'anti-open'
conformations.
B: Cinchonine, Cn, (X=H) and quinidine, Qnd , (X=OMe) in 'anti-open' conformation
C: *alpha*-iCn (X=H) and *alpha*-iQnd (X=OMe) in 'anti-open' complex
D: *gamma*- iQnd in 'anti-open' complex conformation
(Bartok et al.[169]).

Some important conclusions can be drawn from the experimental confirmation of the proposed 1:1 [modifier-reactant] chiral complex based on the 'anti-open' conformation of the alkaloid-modifier, which fully excludes the

concept of the closed conformation in the reacting complex as well as the formation of the [modifier-pyruvate] complex in solution before reaction. Also the new C10 center in the isoalkaloids does not allow the formation of the intermediate form, so the isoalkaloids can be considered novel effective modifiers. Chiral induction is not affected by the new chiral C10 in the isoalkaloids but the Me group at C10 exerts a significant effect on enantioselectivity diminishing the steric adsorption on catalyst surface.

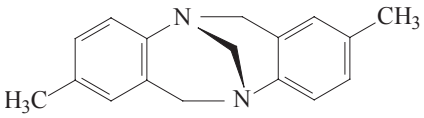
Thus the '1:1 model' proposed earlier by Wells [149] and Baiker [17-19,21] has gained experimental proof using the isoalkaloids as modifiers. Margitfalvi et al.[156,159,162] criticized the 'Template model' because of some experimental uncertainties and put forward a new mechanism based on the "Shielding effect" suggesting that enantioselectivity proceeds through the formation of a weak complex {Cnd-MePy}, not on the surface of the heterogeneous catalyst, but in solution in the liquid phase, such that the modifier, cinchonidine, shields one side of the prochiral site of the reactant and allows the other side to undergo enantioselective hydrogenation after its adsorption on Pt-catalyst (see, Margitfalvi et al. [155-157]).

They fulfilled the experiments and calculations for the confirmations of this aspect of the 'shielding effect' in the system consisting of [Cnd (in closed conformation)-Methyl pyruvate] leading to the (*R*)-(-) methyl lactate. Also they considered these data as confirmation of the 'Shielding effect' from experiments of hydrogenation of the complex in the 'closed form' of methyl pyruvate with chiral Troger's base at 10^0C and 50 bar hydrogen. The molecular model of interaction of *alpha*-keto esters over Pt-alumina-Cnd catalyst was considered by Margitfalvi et al.[331] as an alternative model. The model suggested the formation of a weak complex between the modifier and the substrate in the *liquid phase rather than on the surface of the catalyst*, in which the modifier provides a specific shielding effect, owing to the fact that the alpha-keto ester can interact with the metal surface only on its unshielded side.

If the reactivity of the substrate in the shielded [substrate-modifier] complexes is higher than that of the free keto ester, enantioselectivity can occur. According to Margitfalvi [157-162] the quinuclidine *N*, which aims towards the keto carbonyl group in the keto ester, provides the increased reactivity of the keto carbonyl group. This shielding model, can explain enantioselectivity and rate acceleration effects for almost all substrates used in many examples, for example, hydrogenation of MePy, MBf, ketopantolactone, and trifluoroacetophenone over Pt-alumina-Cnd catalysts.

On the other hand, Tungler et al. [332] considered the selective characteristics of heterogeneous chiral modified catalysts in the enantioselective and diastereselective hydrogenation of C=C, C=O, and C=N double bonds. Because of the absence of interaction between these groups and the tertiary *N*-atom of the Troger's base (Scheme 5.31.), rate acceleration in hydrogenation could not be observed and resulted in an *ee* of only 38.3%.

From this fact the conclusion was drawn that the enantioselective step proceeded in the liquid phase with the use of the Troger's base as the chiral matrix in the 'closed form' of the alkaloid molecule interacting with the reactant molecule followed by hydrogenation of this complex on the Pt surface.



Scheme 5.31. Troger's base.

But according to Margitfalvi [156] the formation of the 'Troger's base-methyl pyruvate' intermediate, with its following hydrogenation on Pt just can be considered as an indication against his suggestion of a 'liquid phase complex formation'. Rather, it is indicative of formation in solution of a diastereomeric compound like the reaction of isophorone with proline studied by Tungler et al.[260] and leading to a modest enantioselective effect. Thus only participation of a heterogeneous catalyst with subsequent formation of stereospecific adsorption on the metal surface can conditions be created for high asymmetric effects.

But as Johnston and Wells [144] noted, this model, which is based on the 'shielding effect', could not be considered true because that complex {Cnd-Pyruvate} can be achieved not only in the liquid phase but also in the gas-phase where the interaction of reactant and modifier before adsorption can not possibly occur. Moreover it is possible to conduct reaction in the liquid phase on a catalyst surface and obtain high enantioselective by such minute quantities of Cnd even though its concentration in solution is extremely low. On the other hand, results received by Bartok [169,321,326] indicated that the reaction can proceed through formation of a complex of pyruvate with Cnd only in the 'open' form adsorbed on the Pt surface owing to bonding to the surface of the quinoline aromatic ring.

The aspects of the mechanism of action of the catalytic system Ptalumina - Cnd-MePy discussed by Margitfalvi et al. [159,162] seemed to be reasonable but they can be applied equally well to processes proceeding on the surface of the catalyst rather than only in the solution above the catalyst.

Additional crucial evidence against a mechanism based on such associations formed in solution is supported by the fact that under these conditions on Pt-alumina-Cnd catalysts C=C prochiral bonds, which are unable to form associations like {Cnd-MePy}, can be enantioselectively hydrogenated with good *ee*'s.

Indeed, Lipkin [29] and Nakamura [30] noted for the first time that the Pt-alkaloid system can be used for the hydrogenation of C=C bonds in methyl-

and naphthylcinnamic acids. Attempts to hydrogenate asymmetrically the C=C bonds in olefinic acids were described also by Schwab et al. [1] and by Terent'ev et al. [2] using tiglic acid and *alpha*-phenylcinnamic acid over Pt and Ni-catalysts supported on optically active quartz crystals but resulting in very small *ee's*, about 0.1%. Klabunovskii and Patrikeev [12,221,223] considered the mechanism of this reaction and suggested that small chiral effects were due to weak asymmetric adsorption of reactant on the surface of optically active quartz crystals (see, Chapter 2).

Therefore, for a long time the modified Pt and Ni metal catalysts were considered effective only for the enantioselective hydrogenation of the carbonyl C=O bond in 2- and 3-oxocarboxylic esters with the particular mechanisms of reactions much different from the others. In 1958 Isoda et al.[333] tried to hydrogenate enantioselectively the azlactone derivative of 2-acetamidocinnamic acid to (*S*)-phenylalanine and described striking results of high efficacy of the action of Pd catalysts modified with (*S*)-tyrosine. The catalyst was prepared by hydrogen treatment of Pd-(*S*)-tyrosine complex at high hydrogen pressure and high temperature and could hydrogenate the azlactone into the amino acid with an *ee* of 65%. Unfortunately, these high results were not confirmed later in the literature.

Then it was shown that catalysts modified with Cnd were effective in the hydrogenation of tiglic acid ((*E*)-2-methylbut-2-enoic) acid on Pd-silica with an *ee* of 22% (Bartok et al.[172]). The detailed studies of Nitta et al. [120,124,125] have shown that enantioselective hydrogenations of (*E*)-2-phenylcinnamic acid into (*S*)-(+)-2,3-diphenylpropionic acid can proceed very effectively with an *ee* above 70% on a catalyst of 5% Pt-titania in the presence of Cnd in polar solutions, especially in the dispersion range below 0.2. In the solvents with low polarities, the optimal Pd dispersions are much lower than those observed in polar and protic solvents. The catalysts with the lowest dispersions, however, exhibit poor selectivities, irrespective of the solvent employed. In the hydrogenation of an (*E*)-2-methylpent-2-enoate and (*E*)-2-methylbut-2-enoic acid, the dispersion dependencies are much milder and independent of the solvent [130].

Baiker et al. [86,107] also hydrogenated 2-methylpent-2-enoic acid on Pt-alumina-Cnd at 20^0C and 50 bar with an *ee* of 52%.

As it have been shown previously (see, Chapter 4) Ni catalysts modified with chiral acids revealed very little effectiveness in enantioselective hydrogenation of C=O bonds in keto esters and C=C bonds in unfunctionalized substrates (see Izumi, Tai [213-215]).

The MePy molecule mostly exists in an anti-carbonyl conformation and cannot interact with modifier-tartaric acid on Ni catalysts through two hydrogen bonds. Therefore on RNi modified with (2*R*,3*R*)-tartaric acid, hydrogenation of MePy leads also to a poor *ee*: 2% (*S*) (rate 0.07

mmol/g·min), whereas MAA hydrogenates with an *ee* of 86% at a rate of 0.48 mmol/g·min (Tai et al.[218], Okamoto et al.[219]).

But using special techniques and reaction variables it was possible to improve the effectiveness of modified Ni catalysts, e.g. using ultrasonic treatment (Tai et al.[216] and Torok et al [170]), and to receive very high optical yields from the hydrogenation of *alpha*-keto carboxylic acids with *ee*'s of 94%. Other examples of the ultrasonic treatments exist [334-341].

Smith et al. [203] succeeded in obtaining impressive data from the hydrogenation of prochiral C=C bonds in carboxylic acids on modified Ni catalyst. They suggested that the failure of C=C containing compounds to display significant enantioselective effect in former works can be explained by the absence of an appropriate binding site to form a complex with the catalysts and with chiral groups of modifiers like intermediate {Catalyst-Modifier-Substrate} in accordance with a scheme suggested by Klabunovskii et al.[3,9,220] for the hydrogenation of ethyl acetoacetate on a number of metal catalysts (Ni, Cu, Ru, Pd, and LaNi) modified with (2*R*,3*R*)-tartaric acid.

Later, using RNi modified with (2*R*,3*R*)-tartaric acid and NaBr Bartok et al.[172] succeeded in the enantioselective hydrogenation of Na-salts of (*E*)- and (*Z*)-2-phenylcinnamic acid, resulting in the (*E*)-substrate producing the 2,3-diphenylpropanoic acid with an *ee* of 17.0% whereas the (*Z*)-and (*E*)-isomers of the free acid resulted in an *ee* of only 0.47% and 0.2%, respectively. The explanation of such differences of behaviors of (*E*)- and (*Z*)-acids consists in their difference of stereochemical and electronic properties. In the (*E*)-acid *the beta*-phenyl group and the -CO_2H group are in conjugative interaction with the C=C bond and are in a coplanar arrangement

The use of Pd catalysts with Cnd as modifier proved to be more effective. Following the first works [29,30], Perez et al.[119] found that hydrogenation of (*E*)- and (*Z*)-isomers of 2- and 3-methylcinnamic acids and 2-phenylcinnamic acid over 5% Pd-C in the presence of cinchona alkaloids in polar solutions was rather effective. It was found that hydrogenation of (*E*)-2-methylcinnamic acid is less effective (*ee* 3.3% *R*) whereas (*E*)-2-phenylcinnamic acid gave an *ee* of 13.3% *S* in the presence of an equivalent amount of substrate and quinine as modifier. But in the case of a small addition of 3% Cnd, the hydrogenation of (*E*)-2-phenylcinnamic acid resulted to the best *ee* of 30.5% *S*.

Nitta et al.[120-128] studied the effect of variables of hydrogenation of substituted cinnamic acids and found striking results. The best *ee* approached 80% [120,126]. It was found that titania was the best support for 5% Pd in the hydrogenation of (*E*)-2-phenylcinnamic acid in the presence of a small amounts of Cnd.

The use of solvents with larger dielectric constants result in hydrogenation over 5% Pd-alumina of higher *ee*'s, up to 53% [121]. All these features are quite different from properties of the Pt-alumina-cinchonidine system in

the hydrogenation of the pyruvates and indicate different mechanisms of these two reactions.

It was found that reactions with *unmodified* catalyst proved to be much faster than those with Cnd modified catalyst, which also is quite different from the results reported for Pt-alumina-Cnd catalysts in the hydrogenation of *alpha*-keto esters. Reuse of catalysts resulted in almost complete loss of *ee* and indicates elution and absence of Cnd from the surface of the catalyst.

Pd-species containing the chiral modifier Cnd are precipitated during preparation of the catalyst only on the exterior surface of the support. Therefore nonporous and ultrafine particles seem to be more suitable as the support materials for this process. This was the case for titania as a support. The same results were found in the hydrogenation of *alpha*-keto esters on Pt-alumina-Cnd catalysts [69]. The best results were obtained using alumina support with relatively small surface area, high pore volume, and rather large pores. Thus the best *ee* obtained in the hydrogenation of the C=C bond in 2-phenylcinnamic acids on 5% Pd-TiO_2-Cnd catalyst was 72% in polar solution (DMF + 10% water) at 10^0C and 1 bar at 100% conversion. In the beginning of the reaction at 20% conversion the *ee* reached 80%.

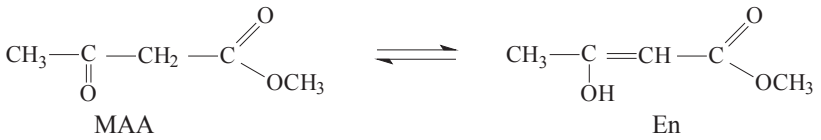
The effect of modifier structure was studied in the hydrogenation of EtPy in MeOH and in (DMF + water) [126]. Heinz et al.[105] showed that a Pt-alumina catalyst modified with (*S*)-(-)-1-(1-naphthyl)ethylamine gave an *ee* of 82% in the hydrogenation of EtPy, whereas modification with Cnd under the same conditions gave only *ee*'s of 73-75%; but in the hydrogenation of the C=C bond in cinnamic acids *ee* values reached only 4-12% [123].

The best modifier for the hydrogenation of substituted cinnamic acids proved to be DHCnd (*ee*, 61% *S*, in DMF + water mixture). Most cinchona alkaloids with the same absolute configuration similar to Cnd also gave the (*S*)-products. It was interesting that other cinchona alkaloids, like quinine (*ee* 10% *S*), norcinchol (*ee* 50% *S*), and *N*-benzilcinchonidinium chloride (*ee* 57% *S*), proved to be less effective. Cinchonine also proved to be much less effective as a modifier and resulted in a product with 28% *R*. These data suggest that the absolute configuration at C8 and C9 in the alkaloid molecule determine the dihydroacid configuration as in the case of hydrogenation of *alpha*-keto esters on Pt-alumina-Cnd catalysts. As was found by Beamer et al.[50,51], the hydrogenation of 2-methylcinnamic acid on Pd supported on silica formed in the presence of the alkaloids Cnd, Cn, Qn, and Qnd, resulted only in the (+)-dihydroacid, indicating the crucial role of the C3 and C4 centers of the cinchona alkaloid molecules in chiral recognition, whereas the C8 and C9 centers in the above mentioned diasteromeric alkaloids affect only the numerical values of the *ee*. Cnd and Qn proved to be more active than Cn and Qnd. Thus the mechanism of asymmetric hydrogenation of the C=C bond is significantly different from hydrogenation of the C=O bond in oxo-carboxylic acids. The data obtained suggested that the mechanism of in-

teraction of phenylcinnamic acid with modifier Cnd shows differences between both mechanisms of hydrogenation of C=O and C=C bonds.

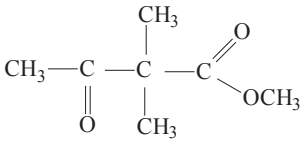
In the system {Cnd-2-phenylcinnamic acid} the alkaloid interacts with the acid *via* two hydrogen bonds [126]. Interaction of the C9-OH group is the crucial influence in the chiral induction. Substitution of OH for OMe will weaken the interaction between modifier and the substrate. A second hydrogen bond between the N-atom in the quiniclidine group and the carboxylic group was revealed by experiments of modification of Pd-titania catalyst with a mixture of (Cnd + 9-MeO-DHCnd). Therefore esterification of the carboxylic group resulted in complete loss of enantioselectivity.

Smith et al [32,33] reported that the hydrogenation of 2-methylcinnamic acid and 2-methylpent-2-enoic acid on 1% Pd-silica catalysts modified with 1-(*S*)-*endo*-bornyloxytrimethylsilane in MeOH at 25^0C results in chiral products with *ee*'s of 22.5% and 11.6%. These results noted that modified Pt and Pd catalysts can hydrogenate enantioselectively systems with 1,3-conjugated bonds, but the transfer of these aspects for hydrogenation of 1,4-double bonds as in methyl acetoacetate (MAA) has definite difficulties because it needs to assume the enol form (En) to react (Scheme 5.32.).



Scheme 5.32.

Although this enol form (En) is confirmed by MNDO calculations (Yokozeki et al.[325]), the reaction of the keto-form (MAA) can not be excluded and, moreover, the formation of the enol (En) as reacting species in the hydrogenation of methyl acetoacetate is not confirmed experimentally.



Scheme 5.33.

First, the correlation of *ee* of the product with the concentration of enol (En) in the original 3-oxocarboxylic ester (MAA) is absent; in different solvents the enol content is much different; second, it was shown that methyl 2,2-dimethyl-3-oxobutyrate (DMB) (Scheme 5.33.), which cannot form an enol,

also can be hydrogenated asymmetrically with an *ee* of 30% on catalyst Ni-Tart (see Smith [203]), while the hydrogenation of methyl acetoacetate under the same conditions results in methyl 2-hydroxybutyrate with an *ee* of 38%.

CONCLUSION

Enantioselective heterogeneous hydrogenations in the liquid phase of *alpha*-keto esters on Pt-alumina catalysts modified with cinchona alkaloids as chiral ligands known as the "Orito reaction", have become common. Over 130 publications considering this system have appeared since 1989, and this reaction is continued to be studied intensively by many groups, such as Baiker and Blaser (Switzerland), Wells, Hutchings and Blackmond (England), Nitta (Japan), Sheldon (Netherlands), Tungler, Bartok and Margitfalvi (Hungary), Reschetilowski (Germany), Smith and Augustine (USA) and Zhou (China). A lot of experimental and theoretical work has dealt with different catalytic systems. Based on studies of the mechanism of reaction, new types of modifiers were elaborated. Optical yields of the resulting hydroxy ester products reached above 95%. It was stated that this reaction is structure sensitive. Enantioselectivities increase with increase of the crystalline size of the supported or bulk platinum catalysts.

Owing to the last experimental and theoretical works in the study of the Orito reaction some insight in the mechanism of the reaction has been gained but full understanding has not yet been achieved. Therefore much more effort is needed in the future, especially in studying the role of the nature of the metal catalysts and the effects of triple intermediate complexes, [Metal-Modifier-Reactant], in enantioselectivity as shown in the case of the enantioselective hydrogenation of *alpha*-keto esters on tartaric acid modified Ni, Cu, and Co catalysts [7].

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