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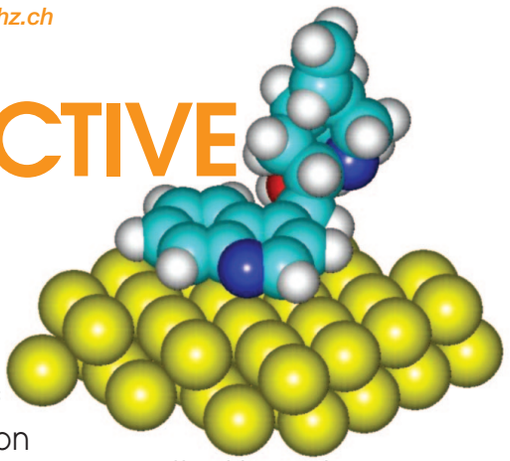
SOLID ENANTIOSELECTIVE CATALYSTS



A brief overview on various strategies used to develop solid enantioselective catalysts and on the probable mechanisms of their functioning is presented. Currently, only metal hydrogenation catalysts modified by strongly adsorbed chiral compounds have some practical importance.

The increasing demand for enantiomerically pure intermediates, fine chemicals and pharmaceuticals led to a rapid development in asymmetric catalysis in the past decades (1). Numerous sophisticated homogeneous metal complex catalysts have been discovered that offer practically useful routes for the synthesis of chiral compounds (2, 3).

Though heterogeneous catalysts have several inherent technical advantages (easy separation, handling and reuse), their enantioselectivity is generally lower and the application range is (yet) narrow, mainly confined to some hydrogenation reactions. Various approaches have been applied to design solid enantioselective catalysts, i.e. to combine catalytic activity with a suitable stereochemical control of the reaction (4-7). The potential and limitations of these approaches are described in the first part of this review. The second, major part will focus on the application of chirally modified metal hydrogenation catalysts that represents as yet the only synthetically useful approach in heterogeneous asymmetric catalysis.

Solid asymmetric catalysts and chiral surfaces

Metal on a chiral support

According to this early strategy, a chiral material of natural origin, e.g. quartz, silk fibroin, or cellulose, is used as a support for a metal or metal oxide catalyst (8, 9). The best known example is a Pd/silk catalyst that afforded 66% optical yield in the hydrogenation of benzylidene oxazolidone. Recently, Pt and Pd supported on chitosan and wool were proposed as new enantioselective catalysts, which would afford up to 100% enantiomeric excess (*ee*) in various hydrogenation reactions including the hydrogenation of simple, unfunctionalized ketones (10, 11). These results, however, proved to be irreproducible (12).

A fundamental limitation of this strategy is that only a small fraction of the surface metal atoms is in direct contact with the support; on the rest of the surface sites the reaction proceeds without any stereochemical control.

Chiral metal surface

Creating a solid surface with intrinsic chirality is the only approach in which the stereochemical control is not separated from the catalytic activity. It has been shown that kink sites of high Miller index metal surfaces may be considered as chiral (13-15). Two such surfaces that are not superimposable can be defined analogously to the Cahn-Ingold-Prelog rules (e.g. $(643)^R$ and $(643)^S$). Adsorption or desorption of sufficiently big molecules on these sites may be enantiospecific though the measured difference of adsorption energies was minor (14). The rate of electrooxidation of D- and L-glucose varied significantly with the chirality of Pt(643) and Pt(431) sites - another experimental evidence for the enantiospecific properties of chiral surfaces (15). Stability of the ideal chiral kink sites is of key importance; their distortion due to, for example, thermal roughening (spontaneous diffusion) has to be considered (16).

It has long been speculated that the metal surface may restructure under the molecular adsorbate layer (17). An STM analysis of the adsorption of hexa-*tert*-butyl-decacyclene (Figure 1) on a Cu(110) surface provided the first convincing evidence in this direction (18). Adsorption of the propeller-shaped molecules generated chirality on extended, flat terraces of the single crystal surface. This restructuring increases the adsorbate-metal interaction and seems to be the driving force for the formation of self-assembled monolayers.

Metal modified by a soluble chiral compound

Modification of a metal hydrogenation catalyst by a naturally occurring chiral compound is another classical method: the first successful attempts were published about 60 years ago (for recent reviews see (19, 20)). Continuous progress led to the presently known most efficient chiral solid catalysts affording up to 98.5% *ee* in the hydrogenation of ethyl pyruvate to lactate. The active site should be considered as an ensemble of surface metal atoms that adsorb and activate the reactants.

For example, in the aforementioned reaction over cinchona-modified Pt an ensemble of about 15-20 metal atoms is required to accommodate the bulky modifier, reactant and hydrogen (21). In most cases the chiral modifier is simply added to the reaction mixture containing the supported Pt or Pd catalyst.
The modifier adsorbs on the metal surface - together with hydrogen and reactant - and its interaction with the reactant during hydrogen uptake induces enantiodifferentiation.
Prereduction of the catalyst with hydrogen before use, sometimes at elevated temperature, or a short pretreatment of the catalyst with the chiral modifier may increase the *ee*, though no unambiguous explanation for the improvements has yet been found. A more demanding pretreatment procedure is applied for optimizing the performance of the Ni-tartaric acid-NaBr catalyst system (22). The technique of preparing an effective modified Ni catalyst has been improved remarkably during the past decades. It has been shown that Ni powder and supported Ni are almost as good precursors as Raney Ni. Large Ni crystallites are most favorable for enantiodifferentiation, whereas the Al-enriched disordered Ni domains should be removed from Raney Ni by a chemical or physical treatment (23).
The latest technique includes ultrasonication of Raney Ni in water followed by modification with tartaric acid and NaBr at 100 °C and a pH of 3.2. The modification procedure is strongly corrosive and produces large amounts of nickel- and bromide-containing waste, - a major drawback for industrial application. Besides, the activity of modified Ni is rather low. For example, full conversion of β-ketoesters at 100 bar and 60-100 °C (typical conditions) required up to 48 h even at a catalyst/reactant ratio of 23 wt% (24). For comparison, hydrogenation of ethyl pyruvate or ketopantolactone over the Pt-cinchonidine system is ten- to hundredfold faster even at ambient temperature.

Chirally modified zeolite

Various acidic zeolites are good catalysts for alcohol dehydration. Modification of zeolite H-Y with chiral dithiane-1-oxides enhanced the rate of butan-2-ol dehydration to but-1-ene and but-2-ene, and induced a small ee (6-7%) in the kinetic resolution of the racemic mixture (25). The increased activity of modified zeolite is attributed to a specific interaction of the chiral modifier dithiane-1-oxide with an extra-framework Al site (X_3Al^+) and the Brønsted acid site associated with a framework Al site (Figure 2) (26).

Heterogenized homogeneous catalysts

Heterogenization of proven homogeneous catalysts offers a combination of high enantioselectivity of the soluble complex with the technical advantages of using a solid catalyst. A wide variety of efficient techniques have been proposed (27-31) including:
(i) covalent bonding of the catalyst to an inorganic solid or an organic polymer,
(ii) encapsulation into zeolites and sol-gel materials (ship-in-a-bottle complex),
(iii) synthesis of chiral polymeric ligands,
(iv) heterogenization via ion exchange,
(v) intercalation into layered materials (e.g. hydrotalcites),
(vi) use of chiral catalytic membranes,
(vii) immobilization via H-bonding to silica, and
(viii) heterogenization via thin film technology.
The topic belongs traditionally to homogeneous catalysis as the active species originates from a soluble, homogeneous catalyst.

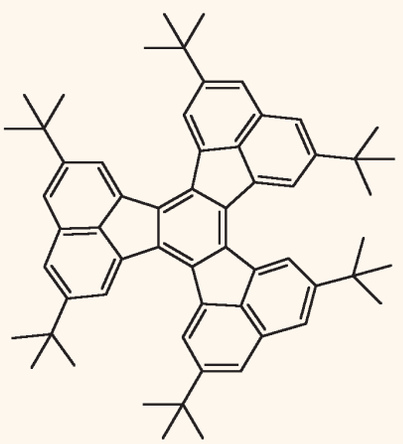


Figure 1 - Structure of the propeller-shaped hexa-tert-butyl-decacyclene that induced chiral restructuring of Cu(110)

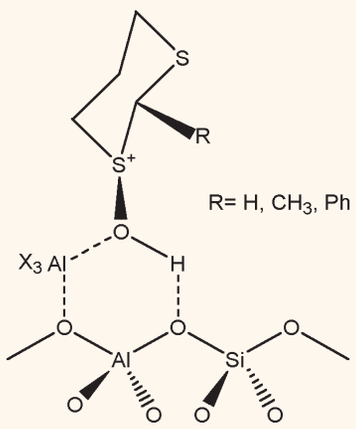


Figure 2 - Chiral active site on zeolite H-Y modified with a dithiane-1-oxide

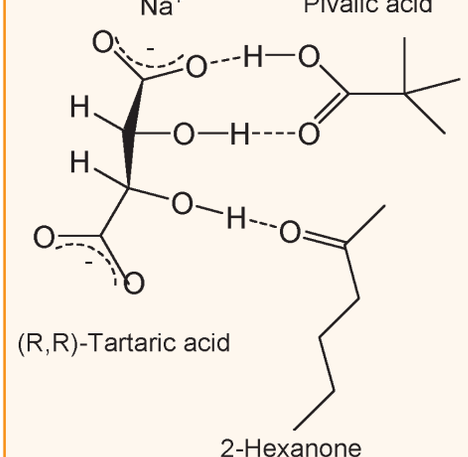


Figure 3 - Interaction of a 2-ketone (2-hexanone) with the deprotonated tartaric acid modifier and pivalic acid co-modifier over the Ni surface (top-view)

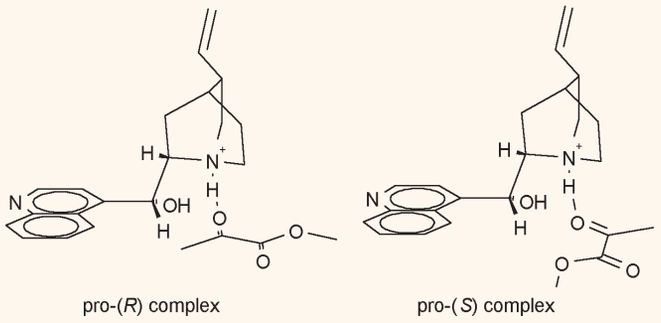


Figure 4 - A feasible mechanistic model for enantiodifferentiation in the hydrogenation of ethyl pyruvate to lactate over cinchonidine-modified Pt (top-side view)

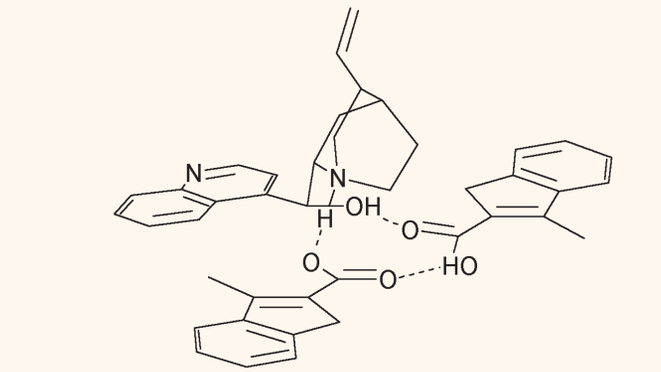


Figure 5 - Interaction of cinchonidine with an α,β-unsaturated carboxylic acid dimer on the Pd surface (top-side view)

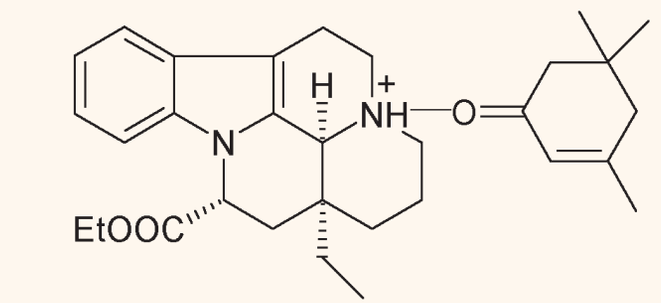


Figure 6 - Proposed model for enantiodifferentiation in the hydrogenation of isophorone on Pd chirally modified by dihydro-apovincaminic acid ethyl ester (top view)

Chirally modified metal hydrogenation catalysts

Chirally modified nickel

Hydrogenation of β-ketoesters is highly efficient over the Ni-tartaric acid-NaBr system (32-36). Fine tuning of catalyst modification conditions resulted in quantitative yield to the corresponding β-hydroxyesters and good to excellent enantioselectivities. Variation of the alkyl chain length next to the keto-carbonyl group of the substrate had only minor effect on *ee*. The outstanding *ee* with the cyclopropyl function was explained by steric and kinetic effects (37).

The same Ni-tartaric acid-NaBr system is the best choice also for the hydrogenation of unfunctionalized 2- and 3-ketones to the corresponding alcohols (33). A major improvement was achieved by the application of pivalic acid as co-modifier in higher than stoichiometric amount. This additive enhanced the ee from 2 to 80-85% in the reduction of various 2-ketones. The proposed model (Figure 3) assumes that one of the carboxylate anions and the neighboring OH group of tartaric acid form a complex with pivalic acid. The position of 2-alkanone over the Ni surface is fixed by a H-bond with the other OH group of tartaric acid and by the steric effect of the *t*-butyl group of pivalic acid.

Transformation of 3-alkanones to 3-alkanols requires slightly different conditions (23). Discrimination between the ethyl and another alkyl group is considerably more difficult than the differentiation between a methyl and a longer chain alkyl group. This is the probable explanation for the relatively low *ee* of 44% in the hydrogenation of 3-octanone, as compared to 80% *ee* reported for 2-octanone.

Chirally modified platinum

The Pt-cinchona alkaloid system was discovered in 1979 by Orito *et al.* (38) for the hydrogenation of α-ketoesters to α-hydroxyesters. Since then remarkable progress has been achieved in understanding the mechanism of enantiodifferentiation and broadening the scope of the reaction (for recent reviews see (19-21, 39, 40)).

In the past years, a broad range of α-functionalized, activated ketones has been hydrogenated with good to high enantioselectivities over the Pt/cinchonidine and Pt/O-methyl-cinchonidine catalyst systems, including α-ketoacids, α-ketoamides, α-diketones, ketopantolactone, pyrrolidine-2,3,5-triones, α-ketoacetals, and α-trifluoromethyl ketones. A recent development is the successful hydrogenation of acetophenone derivatives (41).

RIASSUNTO

Catalisi enantioselettiva solida

Viene presentata una breve rassegna delle varie strategie usate per sviluppare catalizzatori enantioselettivi solidi e sul loro probabile meccanismo di funzionamento. Per il momento, hanno una qualche importanza pratica solamente catalizzatori metallici di idrogenazione modificati con ausiliari chirali fortemente adsorbiti.

Electron-withdrawing functional groups in the aromatic ring increased the reaction rate and *ee* up to 60% {3,5 di(trifluoromethyl)acetophenone}.
The good selectivities demonstrate that the Pt/cinchona system is effective even in the absence of a functional group in α-position to the keto-carbonyl group.
A typical feature of the Pt-catalyzed hydrogenation of activated ketones is the remarkable rate acceleration effect of the modifier by a factor of 2-100. In contrast, cinchonidine slows down the hydrogenation of acetophenone derivatives. These observations are critical for understanding the reaction mechanism (42).
The highest substrate/modifier molar ratio of 237,000 and lowest modifier/surface Pt atom ratio of 0.019 were reported for the hydrogenation of ketopantolactone to (R)-pantolactone (92% ee (43)). Note that cinchona alkaloids are cheap and separation of the modifier is not necessary due to the low concentration in the product. The high substrate/ modifier ratio allows hydrogenation in a continuous flow fixed-bed reactor where minute quantities of modifier are added to the feed (44). Ethyl pyruvate hydrogenation in toluene and "supercritical" ethane at ambient temperature afforded an average turn-over frequency (tof) of 2.2 and 15 s^{-1}, respectively, indicating a remarkable solvent effect (45).
Several models have been proposed for the interpretation of enantiodifferentiation in the hydrogenation of α-ketoesters over the Pt-cinchonidine system (40, 46-50). A feasible approach (21) assumes that the quinoline ring system and the two carbonyl groups in *trans* position adsorb parallel to a (flat) Pt surface (Figure 4). The quinuclidine N is not in direct contact with the metal surface but interacts with the keto-carbonyl O-atom via hydrogen bonding. The OH group of cinchonidine is not involved in the modifier-substrate interaction. *Ab initio* calculations indicated that the complex leading to (*R*)-lactate can easily adsorb on a low index Pt surface (typical for polycrystalline Pt with moderate dispersion), and is energetically favored compared to the pro-(*S*)-complex, due to steric hindrance (repulsion) by the quinoline ring. In apolar medium the transition complex corresponds to the (stabilized) half-hydrogenated state of the substrate. Protonation of cinchonidine favors the modifier-substrate interaction, in agreement with the enhancement in enantioselectivity achieved by using acetic acid as solvent (Figure 4). Refined calculations revealed that a bifurcated hydrogen bond is formed in the two diastereomeric complexes and both *cis* and *trans* conformations of ethyl pyruvate can interact with the quinuclidine N atom (51).

Chirally modified palladium

Chirally modified Pd is the best solid catalyst for the enantioselective hydrogenation of olefins that possess an electron-withdrawing group in α-position to the C=C bond. Up to 72% ee has been achieved in the hydrogenation of (E)-α-phenylcinnamic acid, using a Pd/TiO_2 catalyst and cinchonidine (52). For aliphatic α,β-unsaturated carboxylic acids the ee varied between 20 and 53%, depending on the structure of acid (53). A probable explanation for this difference is the isomerization of the C=C bond as a competing side reaction during hydrogenation of aliphatic α,β-unsaturated carboxylic acids (54). Variation of the structure of cinchonidine at the quinuclidine N and the OH group revealed that both functional groups are involved in interactions with the alkenoic acid during enantiodifferentiation (55). On the basis of spectroscopic analysis and *ab initio* calculations an empirical model has been suggested which can predict the configuration of the major product in the hydrogenation of aliphatic alkenoic acids in apolar medium (56).
In the adsorption arrangement shown in Figure 5 the *trans* acid dimer and the quinoline ring system of cinchonidine adsorb parallel to the Pd surface. It is important that one of the C=C double bonds points toward the quinoline ring system. In this position, bottom side *syn* addition of two hydrogen atoms results in the major enantiomer. Pd modified by a vinca-type alkaloid, dihydro-apovincaminic acid ethyl ester is effective in the hydrogenation of α,β-unsaturated ketones to the corresponding cyclic ketone. At best, 55% *ee* was achieved in the hydrogenation of isophorone (57, 58). The authors assumed that a H-bond between the protonated N atom of the alkaloid and the carbonyl O atom of isophorone was responsible for enantioselection (Figure 6).
Ephedrine was used as chiral modifier for Pd in the hydrogenation of some cyclic α,β-unsaturated ketones, tetralone and indanone derivatives, affording 50-93% chemoselectivity to the saturated ketones and up to 36% *ee* (59).
Up to now, the most successful application of supported Pd is the enantioselective hydrogenation of the pseudo-aromatic 2-pyrones (60). In the partial reduction of 4-hydroxy-6-methyl-2-pyrone to the dihydro-derivative, 85% *ee* was obtained over Pd/TiO_2 under very mild conditions. Catalytic and spectroscopic studies and theoretical calculations indicated a mechanistic model involving two H-bonds between the deprotonated reactant and the protonated cinchona alkaloid (61). In the hydrogenation of 4-methoxy-6-methyl-2-pyrone, 94% *ee* and 95% chemoselectivity to the dihydro-derivative were achieved at 80% conversion. The results are comparable to those achieved with homogeneous metal complex catalysts. Replacement of the methoxy group by a methyl group did not hinder the enantioselection but in this case the *cis*-tetrahydro-derivative was obtained with 99% diastereomeric excess (*de*) and 75% *ee* (60).
An interesting feature of the hydrogenation of various 2-pyrone derivatives is that the enantioselectivity is determined by competing substrate-modifier interactions. These interactions may involve the OH function and the quinuclidine N of the alkaloid, and the acidic OH or the carbonyl group of the substrate (62).

FECS Lecture 2004

Professor Andreas Manz will deliver the 2004 FECS Lecture *'Continuous-flow Bioassays, Separations and Isoelectric Focusing on Chip'* during Euroanalysis XIII, European Conference on Analytical Chemistry, in Salamanca, Spain, on 5-10 September 2004.

The Euroanalysis Conference, one of a series of FECS Conferences, promoted by the FECS Division of Analytical Chemistry, will bring together chemists from industry and academia and provide an international forum for the presentation and discussion of a broad spectrum of analytical topics under the banner "The Role of Analytical Chemistry in the Protection of the Citizens", highly interesting for the community of analytical sciences. Further information is on the web at **www.euroanalysis13.com**

Andreas Manz is Head of ISAS - Institute for Analytical Sciences, Dortmund and Berlin, Germany, and professor at the University of Dortmund.

Andreas Manz is one of the pioneers in microchip technology used for chemical applications. The Manz Lab focuses on novel applications of chip technology in analytical chemistry and the life sciences. He has been involved in the development of high speed analysers based on capillary electrophoresis, liquid chromatography and flow injection analysis. Much of his research has been carried out with his group at Ciba-Geigy Ltd. in Basel, Switzerland and at Imperial College in London, UK. Further details of his work are on the web at **www.ansci.de**

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