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Catalysis Today 100 (2005) 159–170

CATALYSIS TODAY

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Reflections on chiral metal surfaces and their potential for catalysis

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Abstract

Principal possibilities for imparting chirality to a metal surface are surveyed and an attempt is made to assess their potential for heterogeneous asymmetric catalysis. Most possible strategies for creating catalytically active enantiodifferentiating sites on metal surfaces possess inherent limitations concerning potential application in practical asymmetric catalysis. Among the various possibilities known today for bestowing chirality to a metal surface only chiral modification by adsorbed chiral organic molecules (chiral modifiers) has gained practical relevance in catalysis, though its application range is still relatively narrow, confined to asymmetric hydrogenation of C=O and C=C bonds in specific substrates. Opportunities and limitations of this approach are discussed using the enantioselective hydrogenation of ketopantolactone over cinchona-modified platinum as an example.

Keywords: Chiral surface; Chiral modification; Metal surface; Asymmetric catalysis; Enantioselective hydrogenation; Platinum; Ketopantolactone

1. Introduction

The increasing demand of the chemical and pharmaceutical industry for enantiomerically pure compounds has spurred research concerned with their production. A survey by Frost and Sullivan estimates that in 2002 of the $7 billion in revenues of the global chiral technology market, 55% was generated by traditional technologies (chiral pool and separation), 35% by chemocatalysis, and 10% by biocatalysis. In 2005, the worldwide revenues are projected to increase to $9.5 billion, indicating the fast growth of this market [1]. Among the various methods applied for production of pure enantiomers [2], catalysis is unique in the sense that with a small amount of optically active catalyst a large quantity of chiral product can be synthesized. In the past years, we have witnessed tremendous progress in homogeneous enantioselective catalysis, culminating in the Nobel Prizes in Chemistry of 2002 awarded to Knowles [3] and Noyori [4] for their work on enantioselective hydrogenation reactions and Sharpless for his work on enantioselective oxidation reactions [5]. A variety of transition metal complexes with chiral ligands have been synthesized that are powerful working horses in asymmetric synthesis [6].

A comparable development has not taken place in chiral heterogeneous catalysis due to various reasons, the most important being the difficulty to create well-defined catalytically active and stable chiral sites on a solid surface. The creation or preparation of chiral surface structures that combine high catalytic activity and stereochemical control is often biased by geometrical constraints and the intrinsic heterogeneity of surfaces. Nevertheless, the inherent technical advantages connected with catalyst separation, reuse and regeneration, are fostering research in this area. Several comprehensive reviews [7–12] discuss possible strategies for the preparation of heterogeneous enantioselective catalysts. The most obvious strategy is the immobilization of effective chiral transition metal complexes on a suitable support material. Using this "heterogenization" strategy researchers try to merge the advantages of homogeneous with that of heterogeneous catalysis. Various immobilization techniques have been applied embracing simple impregnation, grafting, tethering, and encapsulation. Although these methods have led to remarkable success in some cases, the catalytic performance of the immobilized chiral transition metal complexes is often biased by several factors, such as surface heterogeneity,

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doi:10.1016/j.cattod.2004.12.001

leaching of the active complex, sterical constraints imposed by the surface, and side reactions occurring on the support.

Another strategy that has been pursued is molecular chiral imprinting. Work on imprinted materials such as polymers, amorphous metal oxides and zeolites has been covered in recent reviews [13,14]. However, the practical implementation of catalysts based on molecular chiral imprinting has been hindered by their severe limitations imposed by the intrinsically low number density of active sites, site heterogeneity and possible surface reconstruction under reaction conditions.

Less attention has been devoted so far to the creation of chiral sites on metal surfaces. Here, I consider possible strategies for creating catalytically active enantiodifferentiating sites on metal surfaces and make an attempt to assess their potential for asymmetric catalysis. This assessment is certainly subjective and by no means all-inclusive. In the first part, I will discuss principal possibilities for imparting chirality to metal surfaces. Then the focus is laid on the most successful approach to induce enantiodifferentiation on catalytically active metal surfaces, namely, the chiral modification of metals by adsorbed chiral organic compounds (modifiers). Some characteristic features, opportunities and limitations will be discussed using the enantioselective reduction of ketopantolactone to (*R*)-pantolactone over cinchona-modified platinum as an example.

2. Principle possibilities for inducing chirality on metal surface

2.1. Chiral metal surfaces that are chiral due to their surface structure

Metals have achiral bulk structures. Supported polycrystalline metal particles, as used in heterogeneous catalysis are normally not perfectly symmetric structures, they contain defects such as kinks, some of which may be chiral. However, in the absence of additional chiral information the number of left- and right-handed kink sites or other chiral structures is equal and consequently the surfaces of such catalyst particles are achiral and do not yield enantiomeric excess.

However, metal surfaces exposing chiral sites of one handedness can be created by cutting metal single crystals along specific planes. McFadden et al. [15] have shown in their pioneering work on silver single crystal surfaces that high Miller index surfaces that expose kinked steps are chiral. They oriented and cut a silver single crystal to expose the Ag(643) on one side and the Ag($\bar{6}\bar{4}\bar{3}$) surface on the other side. The authors proposed a system for naming these surfaces as Ag$(643)^R$ and Ag$(643)^S$, respectively, in analogy with the Cahn–Ingold–Prelog rules used in the nomenclature of organic stereoisomers. Fig. 1a shows how the chirality of this type of surfaces arises from the chiral structure of the steps and kinks on the example of fcc(643) and fcc($\bar{6}\bar{4}\bar{3}$) surfaces [16]. These surfaces are non-superimposable mirror images of one another and are therefore chiral [17,18].

The chirality of this type was evidenced by the direction of the splitting of the low energy electron diffraction (LEED) spots. In principle, it could be expected that such chiral surfaces exhibit enantiospecific properties in the sense that they interact differently with the two enantiomers of a chiral molecule. Interestingly, in their original work McFadden et al. [15] could not observe any enantiospecificity in the desorption kinetics of the enantiomers of a chiral alcohol ((*R*)-2-butanol and (*S*)-2-butanol) on chiral silver single crystal surfaces by means of TPD. The first indication of enantiospecific properties of chiral single crystal surfaces was provided by Sholl [19] via molecular simulation of the adsorption of chiral hydrocarbons on chiral Pt surfaces. First experimental observations came from electrochemical studies by Attard and co-workers [20,21] who showed that the electro-oxidation of D- and L-glucose on achiral Pt(111) and Pt(211) surfaces did not reveal any enantioselectivity, whereas the chiral Pt(643) and Pt(531) surfaces indicated enantiospecificity in the electro-oxidation kinetics of glucose. More recently, Gellmann et al. [22] added further examples to the growing list of observation of enantiospecificity.

The study of as-prepared chiral surfaces and their interaction with chiral probe molecules is doubtless extremely gratifying because fundamental insight into chiral recognition on a metal surface can be gained that is hardly accessible by any other approach. However, there are a number of arguments, which renders these chiral surface sites probably not applicable to real catalysis. First of all, the population of chiral kinks, which can be created by this method, is far too low for efficient asymmetric catalysis. Consequently, the major part of the metal surface is achiral favoring the corresponding competing racemic reaction. An open question is also the stability of the chiral kinks under real reaction conditions, as used in asymmetric catalysis on metals. It is likely that under such conditions the chiral kinks will reconstruct and lose the chiral information. Finally, another problem that may impede practical application of this approach is the ‘‘size mismatch’’ between the chiral centers and the organic molecules, which may bias chiral recognition.

2.2. Selective poisoning of chiral surface sites of specific handedness

Another possibility to impart chiral recognition to an achiral metal surface is the selective poisoning by a strongly adsorbed chiral organic molecule. Such a chiral modifier may interact differently with chiral metal sites of opposite handedness. As a consequence chiral sites of one handedness can be poisoned selectively, leaving the sites with the opposite handedness exposed for the interaction with a reactant. This scenario is illustrated in Fig. 1b [23].

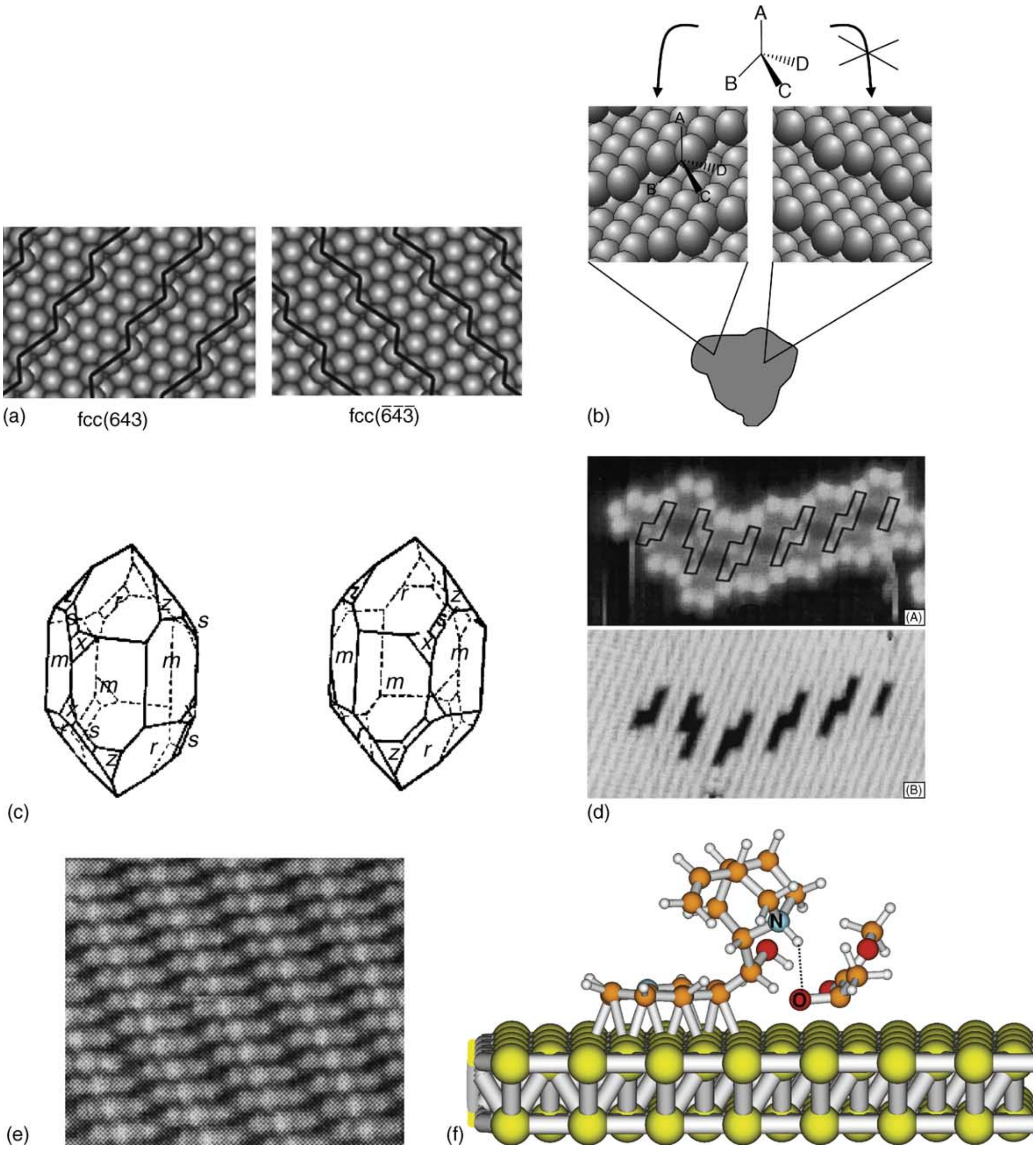


Fig. 1. Illustration of principal possibilities for imparting chirality on metal surfaces. (a) Ball models of fcc(643) and fcc($\bar{6}\bar{4}\bar{3}$) surfaces with step edges highlighted (after Sholl et al., reprinted with permission from [16]). The structures are non-superimposable mirror images of one another. (b) Selective adsorption of a chiral molecule on chiral sites of one handedness (selective blocking) on a racemic surface of a metal particle [23]. (c) Chirality induced by chiral support. The mineral quartz, SiO_2, that has been applied in the original work by Schwab et al. [25] occurs in left- and right-handed variants depending on the orientation of structural helices (after Dana, reprinted with permission from [24]). (d) Surface reconstruction induced by adsorbed chiral molecule. Creation of chiral sites on achiral terraces through adsorption induced reconstruction. The example shows the STM image of adsorbed hexa-*tert*-butyl-decacyclene ($C_{60}H_{66}$) on a Cu(110) surface (top), which results in the creation of chiral kink sites (bottom) (reprinted with permission from [36]); even without reconstruction the adsorption of a chiral molecule may lead to a ‘‘chiral footprint’’ [37]. (e) Supramolecular chirality on non-chiral terraces by self-assembly of chiral molecules. The example shows the STM image of adsorbed (*R*,*R*)-tartaric acid on Cu(110) (reprinted with permission from [38]). The adsorption pattern destroys all symmetry planes of the underlying metal surface, leaving shaped ensembles of surface atoms free. (f) Generation of a chiral site on achiral metal surface by adsorption of chiral organic molecule (modifier). The enantiodifferentiation of a co-adsorbed prochiral reactant occurs as a result of the interaction with the chiral modifier. The example shows the calculated structure of the enantiodifferentiating diastereomeric complex proposed for the enantioselective hydrogenation of methyl pyruvate over platinum modified by cinchonidine (reprinted with permission from [39]). The hydrogen bonding interaction [40,41] between the nitrogen atom of the quinuclidine moiety of cinchonidine and the oxygen of the α-carbonyl group of methyl pyruvate is marked as dotted line.

Assuming that the exposed chiral site is catalytically active, enantiomeric excess can be induced. A consequence of this approach is that only half of the number of the chiral sites of the racemic surface can contribute to catalytic activity and stereochemical control. Although this strategy for the creation of chiral surface sites may be applicable for intrinsically chiral solids with high population density of chiral sites, the application to metal surfaces is limited by the low density of defect structures. To the best of my knowledge, today there exists no example where this strategy has led to a useful asymmetric metal catalyst. Nevertheless, it cannot be excluded that selective poisoning plays a role in some metal catalyst modified by a chiral organic molecule. It is expected that an asymmetric catalyst functioning on this principle shows a rate deceleration compared to the racemic catalyst because the active site density is drastically reduced as a result of the selective poisoning. In case the population density of chiral sites on an achiral surface is sufficiently high, the application of this strategy to create enantioselective metal surfaces with catalytic potential could become feasible.

2.3. Chirality induced by chiral support

The use of naturally occurring chiral materials as support has been one of the very first attempts of heterogeneous enantioselective catalysis. In principle, any crystals that lack a center of symmetry provide chiral surfaces. Though many such acentric materials are known, quartz (Fig. 1c [24]) is probably the most abundant in nature. The chirality of quartz arises from the helical arrangement of corner-linked SiO_4 tetrahedra in the bulk structure. Depending on the sense of that helix, left- or right-handed quartz structures result. Thus, it is not surprising that some of the first attempts to induce chirality on a metal catalyst made use of quartz as a support. In 1932, Schwab and Rudolph [25] used quartz as a chiral support for Cu, Ni and Pt catalysts and demonstrated that in the dehydrogenation of racemic 2-butanol one of the enantiomers had reacted preferentially. Albeit the enantiomeric excess (ee) of these quartz-supported metal catalysts was low (<10%) the study provided some support for this concept. A shortcoming of this and other studies is that powdered quartz crystals were used instead of well-defined single crystals. Powdering a natural chiral crystal inevitably blends right- and left-handed domains so that some of the chiral specificity is lost [26]. The strategy pioneered by Schwab has later been picked up by several researchers with variable success ([27,28] and references therein). Chiral materials like silk, fibroin or cellulose have been applied as supports. The best-known example is a Pd/silk catalyst that afforded 66% optical yield in the hydrogenation of benzylidene oxazolidone [29]. Recently, it was claimed that Pt and Pd supported on chitosan and wool afford up to 100% ee in the hydrogenation of simple unfunctionalized ketones [30,31]. However, these results proved to be irreproducible [32].

The choice of a chiral support may be guided by using chiral indices of crystalline surfaces as a measure of enantioselective potential. Chiral crystal surfaces lack mirror or glide plane symmetry. Recently Downs and Hazen [33] described a procedure to calculate chiral indices I_C of any two-dimensional periodic atomic surface based on atomic displacements from ideal mirror or glide plane symmetries. Such chiral indices define the intrinsic chirality of a surface as the extent to which that surface is non-superimposable on its enantiomer. Achiral surfaces invariably have $I_C = 0$. The authors showed that achiral crystals often display strongly chiral surfaces. The (214) surface of calcite and the (110) surface of diopside were identified to be promising targets for future studies. Interestingly, the intrinsically chiral surfaces of quartz were found to display relatively low chiral indices. Whether the use of chiral indices can really guide the choice of a chiral support for catalytic applications is questionable because it does not take into account the structural properties of the reacting molecule that is decisive for enantioselection.

Summarizing, we can state that there exists some evidence that chiral induction by the support can bear some potential for asymmetric catalysis, however, it seems that the crucial factors for success have not yet been resolved. One obvious shortcoming of the work in this field is that little attention has been given to the fact that the chiral information of the support can probably only be conveyed to metal atoms which are in close contact to the support. This would call for special preparation techniques, where the metal is brought on the chiral support as an epitaxial grown film. An interesting study toward this aim has been reported by Asthagiri and Sholl [34], who examined theoretically Pt adsorption on the stepped $SrTiO_3(620)$ and $SrTiO_3(622)$ surfaces using plane-wave density functional theory. Based on their calculations they suggest that the growth of thin metal films on chiral metal oxides may be a viable approach to producing cheap chiral metal surfaces. However, an experimental proof of concept needs to be given before a solid assessment concerning its practical potential can be made. There are many factors that affect the structure of thin metal films grown on oxidic support materials, among which lattice mismatch and the interfacial adhesion strength between the metal and metal oxide have been identified to be of particular importance [35]. These factors are largely determined by the choice of the chiral support material. Whether this approach is viable for producing chiral metal catalysts is difficult to judge based on the sparse information presently available. Nevertheless, both transfer of chiral information from support to the active metal particles and accessibility of chiral sites would benefit from such structural optimization.

2.4. Surface reconstruction induced by adsorbed chiral molecule

When a chiral molecule interacts strongly with an achiral flat metal surface the interaction could in principle lead to a reconstruction of the metal surface. In general, the binding of adsorbates will induce a restructuring of the surface only if the gain in the adsorption energy of the molecule on the disrupted surface, compared to adsorption on the non-restructed surface overcompensates the energy required to break the metal bonds.

A net driving force may be expected for molecules with high adsorption energy, as it is often the case with large molecules. In some cases, height corrugations of adsorbed molecules measured by STM indicated that underneath the molecular adsorbed layer restructuring of the metal surface occurred. Clear evidence emerged from an STM study [36] of the adsorption of hexa-*tert*-butyl-decacyclene (HtBDC) on a Cu(110) surface which revealed the creation of chiral kink sites as a result of surface reconstruction upon adsorption (Fig. 1d). Although presently there seems to be no feasible possibility to make use of this potential method for creating chiral sites on a metal surface, it should be kept in mind when interpreting the adsorption behavior of large chiral modifiers.

Chirality upon adsorption of a molecule can also be created without disruption of metal atoms from the lattice, slight displacement of some surface atoms from the equilibrium position in the absence of the adsorbate may suffice. This has been suggested by Raval and co-workers [37] for explaining the creation of chiral sites upon adsorption of (*R*,*R*)-tartaric acid on an Ni(110) surface, relevant for the enantioselective hydrogenation of β-ketoesters over tartaric acid modified Ni catalysts. Using reflection adsorption infrared spectroscopy, scanning tunneling microscopy, and periodic density functional theory calculations they uncovered that (*R*,*R*)-tartaric acid is adsorbed in its bitartrate form. Calculations indicated that adsorption of bitartrate displaces neighboring Ni surface atoms which leads to a ‘‘chiral footprint’’ for which all local mirror symmetry planes are destroyed. This chiral ensemble of metal atoms may be the active site, combining catalytic activity and enantiodifferentiation. The formation of this chiral footprint is energetically favored compared to the mirror adsorption site. The energy difference was suggested to be sufficient to enable the same local chiral reconstruction and motif to be sustained over 90% of the system, resulting in an overall highly chiral metal surface. Note that in contrast to the reconstruction discussed above no metal–metal bond breaking occurs in this case, that is, the metal atoms are not removed from the lattice. Depending on the degree of displacement of the atoms, the ‘‘footprint’’ can change from almost non-chiral to very chiral in the case of strong displacements from the symmetric arrangements.

2.5. *Supramolecular chirality*

Supramolecular chirality can be bestowed to a metal surface if a chiral molecule (modifier) forms long-range ordered patterns on the metal surface in a fashion that the symmetry planes of the underlying metal surface are destroyed. A nice example of extended surface chirality from supramolecular assemblies has been shown by Raval and co-workers [38] who studied the adsorption of (*R*,*R*)-tartaric acid on Cu(110) by electron energy loss spectroscopy (EELS), low energy diffraction (LEED) and scanning tunneling microscopy (STM) (Fig. 1e). The adsorbed phase was found to consist solely of bitartrate in which both acid groups have deprotonated to yield carboxylate moieties. The adsorbed layer destroys existing symmetry elements of the underlying metal and bestows chirality to the modified surface. The created chiral channels exposing bare metal atoms were speculated to be responsible for imparting enantioselectivity by forcing the orientation of incoming reactant molecules. Switching the chirality of the modifier (*S*,*S*-tartaric acid) changed the handedness of both the adsorbed surface phase and the channels, forcing an incoming reactant to dock in the opposite sense. The authors also showed that the adsorption of chiral molecules at surfaces does not automatically lead to the creation of chiral phases, as demonstrated by the various achiral phases formed by (*R*,*R*)-tartaric acid on Cu(110). Factors constraining the expression of chirality at an extended two-dimensional surface were discussed.

2.6. *Chirality induced by adsorbed chiral organic molecule (modifier)*

Finally, the chiral information can be imparted to an achiral catalytically active metal surface by adsorption of suitable chiral organic molecules (chiral modifiers) that interact with co-adsorbed prochiral reactants in such a way that enantiodifferentiation occurs. In this approach, the metal surface has two main functions: it provides the active sites and simultaneously serves for adsorptive anchoring of the chiral modifier. This scenario is illustrated in Fig. 1f, which shows the 1:1 interaction between co-adsorbed cinchonidine (modifier) and methyl pyruvate, which has been proposed to be responsible for the high enantioselectivity of the platinum-catalyzed asymmetric hydrogenation. Hydrogen-bonding has been identified to be crucial for the enantiodifferentiating modifier-reactant interaction [40,41], albeit other bonding types may be feasible.

In a sense, the organic chiral modifier has a similar function as the chiral ligands in a transition metal complex, providing the stereochemical control by direct interaction with the reactant. However, there are obvious differences, first of all the active metal surface imposes considerable geometrical constraint for the interaction between co-adsorbed modifier and reactant. The chiral modifier generally interacts with an ensemble of metal atoms on the surface and its adsorption geometry may change depending on surface coverage. Consequently the relative geometrical position of the chiral modifier to the surface metal atoms is usually much less well defined than that of a chiral ligand in a metal complex. Consequently, a homogeneous chiral transition complex is normally not a good model for mimicking the enantiodifferentiating interaction occurring on a chirally modified metal catalyst. Nevertheless, there are some common features. The enantiodifferentiation of a chiral modifier is strongly dependent on its structure, critical are both the structure of the anchoring moiety (responsible for adsorption) as well as the structure of the chiral part and their relative positions. Strong adsorption of the modifier is favorable for high surface coverage, however, some mobility facilitates easier orientation for proper interaction with the co-adsorbed reactant. Recent time-resolved STM studies uncovered that cinchonidine molecules adsorbed on a Pt(111) surface are rather immobile at room temperature, but become mobile in the presence of hydrogen [42].

Among all principal possibilities for imparting chirality to a metal surface discussed above, the chiral induction by direct interaction of the modifier with the reactant has been the only one so far which has gained practical relevance in heterogeneous enantioselective catalysis. However, till now the application is limited to asymmetric hydrogenation.

Though first successful applications of this method have been reported about 60 years ago, major progress has been made more recently. The state of the art has been summarized in several reviews [43–56]. Today, three catalytic systems are known that bear some practical potential, the nickel–tartaric acid [28,43–6,48], the platinum–cinchona [23,28,46–55], and the palladium–cinchona [46,48,56] systems. Depending on the system, the chiral modifier is either brought onto the metal surface in a special pretreatment step or simply added to the reaction mixture. Each catalyst system is only efficient in the hydrogenation of specific substrates. Extension of the scope of substrates has proven to be possible, within a certain limit of structural variation. Today various substrates are known that can be hydrogenated using these catalytic systems reaching in some cases high enantioselectivity and the list of successful applications is growing steadily. Fig. 2 summarizes substrates that can be hydrogenated over these catalyst systems with good to high enantiomeric excess (ee).

In the following I will discuss some opportunities and limitations of this strategy using an example of practical interest, the enantioselective hydrogenation of ketopantolactone to (*R*)-pantolactone (Scheme 1), which is an intermediate in the synthesis of vitamin B5 and co-enzyme A.

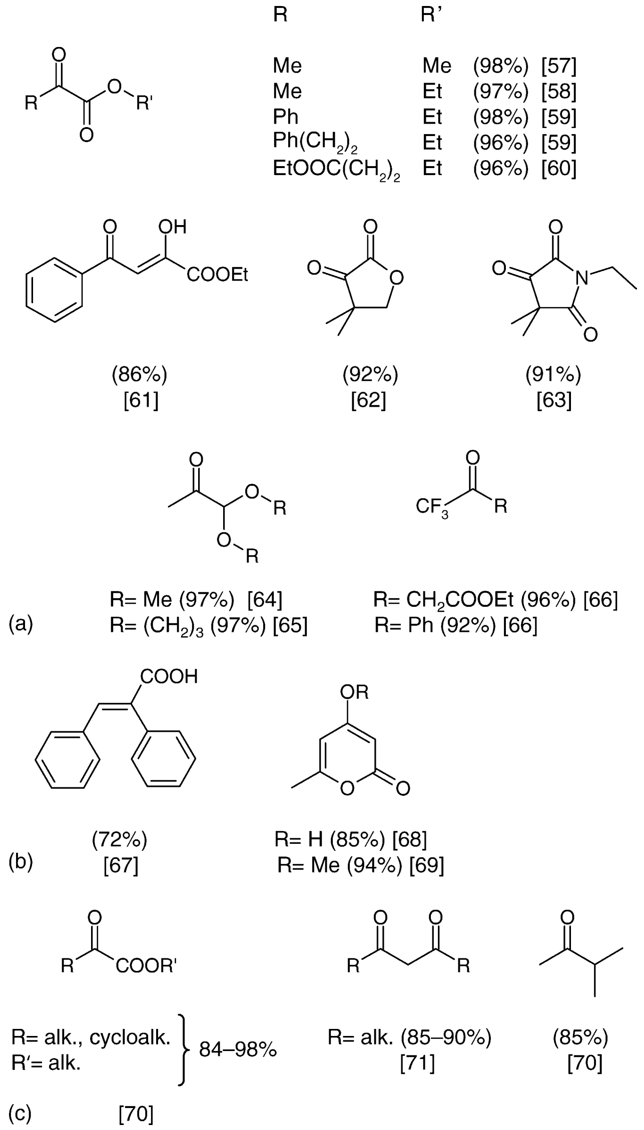
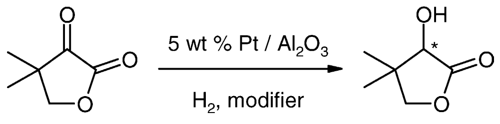


Fig. 2. Substrates affording good to high enantiomeric excess when hydrogenated under optimal conditions over (a) Pt–cinchona and (b) Pd–cinchona, and (c) Ni–tartaric acid systems. For details the reader is referred to the cited references. *Sources*: [57–71].

Heterogeneous catalytic enantioselective hydrogenation of ketopantolactone over cinchona-modified platinum was first reported in 1987 [72]. It was virtually an extension of Orito et al.'s [73] pioneering work on the enantioselective hydrogenation of alkyl pyruvates on platinum–cinchona reported in 1979. However, the enantiomeric excess (52%) in the ketopantolactone hydrogenation was far below that Orito reached for the hydrogenation of ethyl pyruvate (92%). Motivated by industrial interest almost ten years later we have revisited this reaction benefiting from the remarkable progress that has been made in the understanding of the platinum–cinchona system during this period.

There are several factors affecting the performance of the platinum–cinchona system, including structure and concentration of modifier, structure of reactant, pretreatment and properties of the supported platinum catalyst, solvent, and reaction conditions (reactant/modifier ratio, hydrogen pressure, temperature). Understanding of the interactions



Scheme 1. Enantioselective hydrogenation of ketopantolactone to (*R*)- or (*S*)-pantolactone over chirally modified platinum.

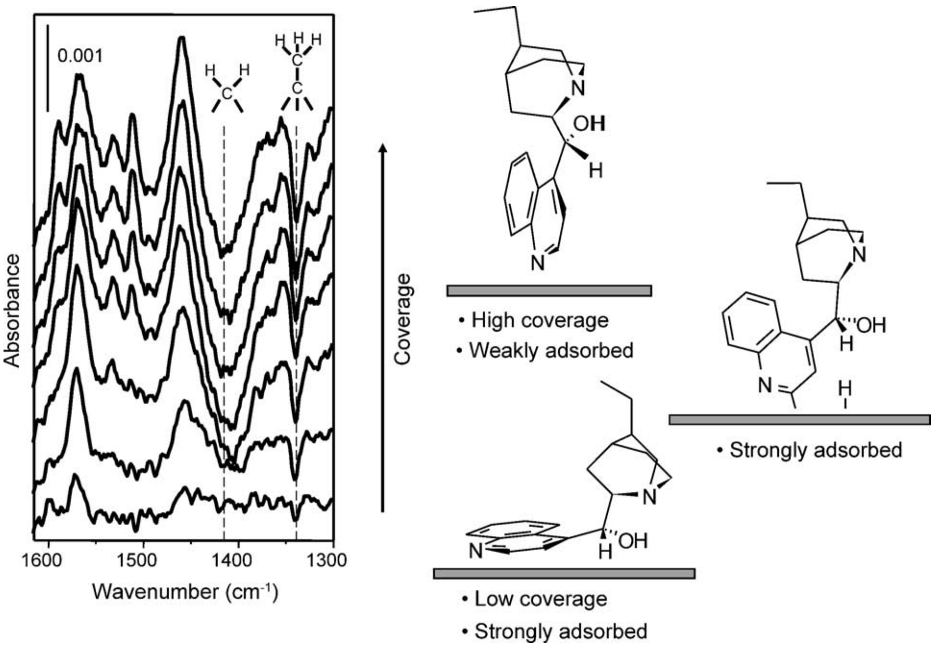


Fig. 3. Dependence of adsorption mode of cinchonidine on surface concentration, as revealed by ATR-IR spectroscopy. ATR-IR spectra (left) measured in situ while flowing solutions of cinchonidine (modifier) at different concentration in hydrogen-saturated dichloromethane over Pt/Al_2O_3 [74,75]. The spectrum of adsorbed cinchonidine changes with increasing coverage. Negative bands are due to solvent decomposition products that are displaced from the surface by cinchonidine. The right panel shows the changing adsorption mode of the cinchonidine species as suggested from ATR-IR spectroscopy.

occurring between platinum surface, modifier, solvent, reactants and product is essential to improve the performance of this catalytic system. Though some of these interactions have been targeted by spectroscopic and theoretical studies much remains to be done.

Extensive studies of the adsorption of cinchonidine on platinum model catalysts revealed that three main adsorption modes can be distinguished, strong adsorption via π-bonding of the quinoline moiety nearly parallel to the surface, and two weaker adsorbed CD species where the quinoline moiety is tilted towards the surface [74–76]. The main findings of these studies are summarized in Fig. 3. Interesting information concerning the adsorption mode of the modifier also emerged from adsorption studies on platinum single crystal surfaces under ultrahigh vacuum conditions [77,78]. These studies also revealed a tendency of the modifier to adsorb flat at room temperature. Thus, today there is considerable experimental evidence (see [23] and references therein) for the validity of the previously made assumption that in the crucial enantiodifferentiating complex the quinoline part of cinchonidine is adsorbed parallel via π-bonding [40,41].

A crucial factor for the performance of chirally modified metal catalysts is the chemical and thermal stability of the adsorbed modifier under reaction conditions. It has been shown that cinchona alkaloids can undergo partial hydrogenation during enantioselective hydrogenation leading to some loss in enantioselectivity [28]. This behavior has been traced to the hydrogenation of the quinoline anchoring part of the modifier resulting in lower adsorption strength. The loss in enantioselectivity can be substantial, depending on the relative rates of the desired enantioselective hydrogenation and the partial hydrogenation of the modifier. As long as some free modifier molecules exist in the reaction mixture, the weakly adsorbed partially hydrogenated modifier species will be replaced by the strongly adsorbing fresh modifier species. In the cases, where the rate of the desired enantioselective hydrogenation is not much faster than that of the hydrogenation of the modifier, continuous addition of a small amount of fresh modifier to the reaction solution can avoid or at least suppress loss of enantioselectivity [79]. Thus, in a sense the ineffective chirally modified sites (covered with weakly adsorbed partially hydrogenated modifier) are ‘‘repaired’’ in situ. This is an important feature for practical application. Note that such a simple ‘‘repair mechanism’’ seems not to exist for chiral solid catalysts based on other concepts.

Theoretical calculations aimed at revealing the structure of a possible enantiodifferentiating complex formed upon interaction of the chiral modifier cinchonidine and ketopantolactone indicated hydrogen bonding between the nitrogen atom of the quinuclidine moiety and the oxygen atom of the α-keto group of ketopantolactone [80]. Fig. 4 shows the proposed structures of the enantiodifferentiating adducts leading upon hydrogenation to (*R*)- and (*S*)-pantolactone, respectively. The stability of the pro-(*R*) complex, was calculated to be higher (2.2 kcal/mol) than that of the corresponding pro-(*S*) complex, which if thermodynamics controls would translate in an ee $> 90\%$, favoring (*R*)-pantolactone. The formation of the hydrogen

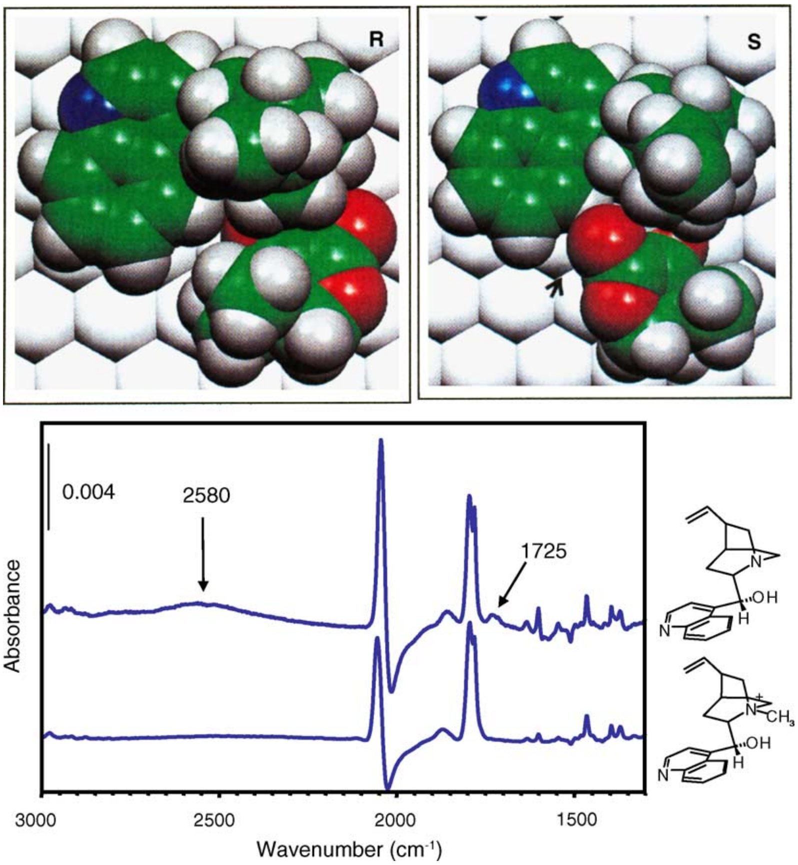


Fig. 4. Top: Models of enantiodifferentiating complexes formed on cinchonidine-modified platinum during asymmetric hydrogenation of ketopantolactone. The complex leading to (*R*)-pantolactone on hydrogenation is calculated to be 2.2 kcal/mol more stable [80]. Bottom: ATR-IR evidence for hydrogen bonding interaction between quinuclidine nitrogen of cinchonidine and oxygen atom of α-keto group of ketopantolactone [81]. The two vibrations indicative for the hydrogen bonding are observed at 2580 and 1725 cm^{-1}, respectively. Note that no hydrogen bonding was observed when cinchonidine was substituted by *N*-methyl-cinchonidine chloride.

bonding between cinchonidine and ketopantolactone was recently evidenced by ATR-IR studies [81]. Blocking of the nitrogen lone pair by applying *N*-methyl-cinchonidine instead of cinchonidine precluded hydrogen bond formation. The importance of the hydrogen bonding has recently also been corroborated for the enantioselective hydrogenation of ethyl pyruvate over platinum modified by cinchonidine using in situ ATR-IR spectroscopy [82].

In an earlier study, the solvent was found to have a decisive influence on the conformation of cinchonidine which in turn affects the structure of the enantiodifferentiating complex [83]. The conformation ‘‘Open (3)’’ adopted in the enantiodifferentiating complex in the model calculations is favored in apolar solvents. Interestingly, the enantiomeric excess achieved in ketopantolactone hydrogenation shows qualitatively a similar dependence on solvent polarity as the population density of conformer ‘‘Open (3)’’ [83], as illustrated in Fig. 5. Though this appears to be an oversimplified correlation, it indicates that at least part of the observed solvent effect in the enantioselective hydrogenation over cinchona-modified platinum is attributable to the conformational change of the cinchona alkaloid induced by solvent polarity. It should be stressed that beside the solvent polarity there are other factors that can affect the conformation of the modifier, such as specific interactions between modifier and solvent (e.g. hydrogen bonding). Furthermore, with less rigid substrates than ketopantolactone as, e.g. alkyl pyruvates, the solvent polarity can also affect the conformation of the substrate [49].

After optimization of the reaction conditions an enantiomeric excess of 92% could be achieved in the enantioselective hydrogenation of ketopantolactone to (*R*)-pantolactone [62]. This was particularly striking at that time because it was the first substrate possessing a rigid *cis* conformation of the carbonyl groups. Previous models of ethyl pyruvate hydrogenation [40,41] assumed that in the enantiodifferentiating complex the α-ketoester exists in *trans*-conformation, though it has been shown later that an enantiodifferentiating complex containing the α-ketoester in *cis* conformation is feasible [84].

A chiral switch of the produced enantiomer of pantolactone can be achieved by substituting cinchonidine by the near-enantiomer cinchonine or by applying *O*-phenyl-cinchonidine [85] (Fig. 6). The switch in the stereochemical outcome of the hydrogenation occurring when cinchonidine is replaced by cinchonine is observed with most substrates

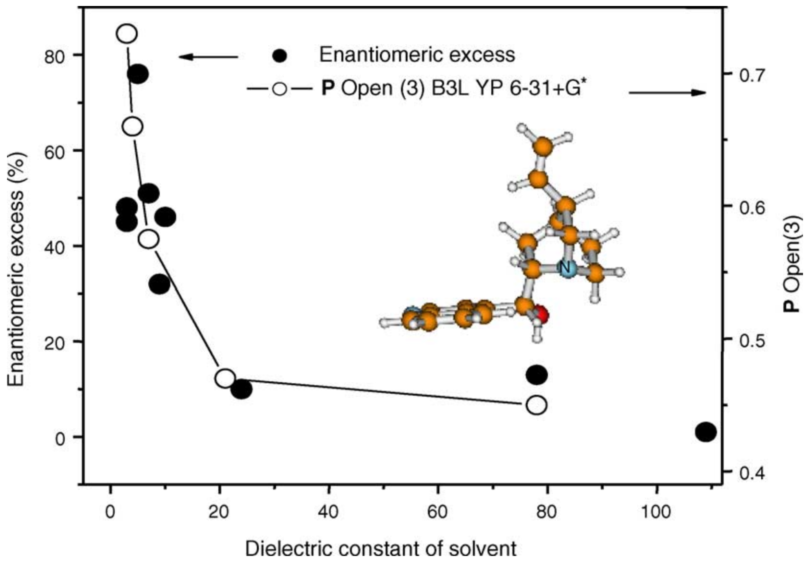


Fig. 5. Combined plot of population (**P**) of conformer ‘‘Open (3)’’ of cinchonidine (right axis) and enantiomeric excess achieved in hydrogenation of ketopantolactone to (*R*)-pantolactone over cinchonidine-modified platinum (left axis) vs. dielectric constant of solvent [83]. The axis scale is arbitrarily chosen. The population ‘‘**P** Open (3)’’ has been calculated by density functional theory in combination with a reaction field model which showed good agreement with **P** Open (3) derived from NMR techniques.

and can be traced to the opposite chirality of the diastereomers cinchonidine and cinchonine at C-8 and C-9, respectively. In contrast, the switch in the favored product enantiomer observed when applying *O*-phenyl-cinchonidine instead of cinchonidine has been proposed to originate from a change in the adsorption mode of the modifier [85]. Recent ATR-IR studies and theoretical calculations indicate that *O*-phenyl-cinchonidine is more weakly adsorbed than cinchonidine, though both are adsorbed via the quinoline anchoring moiety [86]. Thus, a switch in the stereochemical outcome can be caused by a change in the stereogenic part of the modifier or alteration of the adsorption mode (adsorption

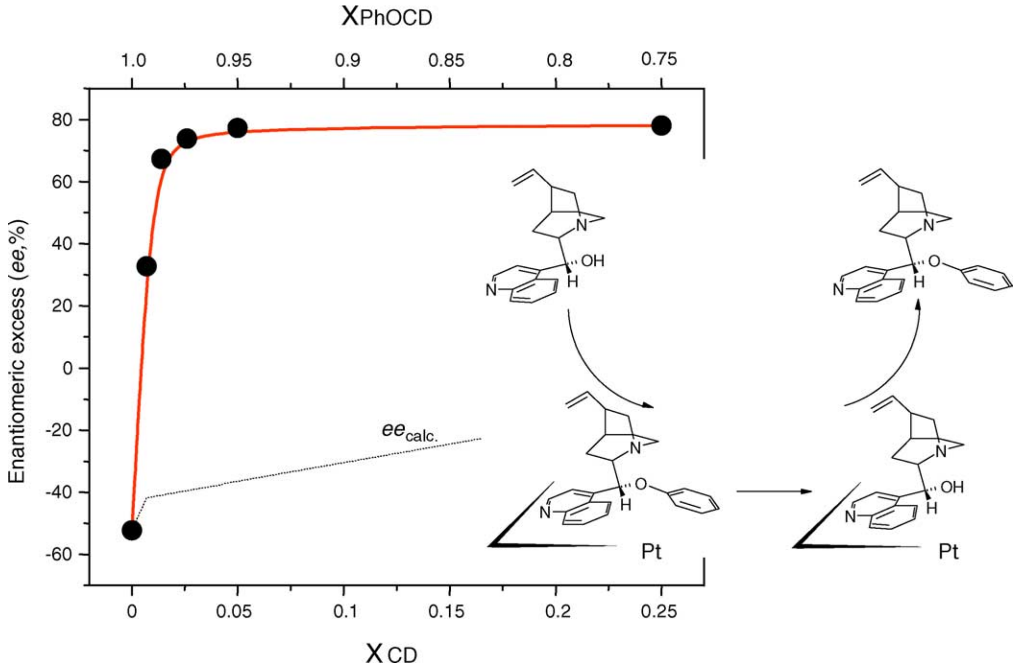


Fig. 6. Switching of the sense of enantiodifferentiation in ketopantolactone hydrogenation by subtle structural change of modifier structure [85]. Cinchonidine as modifier affords (*R*)-pantolactone as major enantiomer, whereas *O*-phenyl-cinchonidine favors the production of (*S*)-pantolactone. Adding a low amount of cinchonidine ($X_{\mathrm{CD}} < 0.05$) to a reaction mixture containing a Pt catalyst modified by *O*-phenyl-cinchonidine already affords a change from (*S*)-pantolactone to (*R*)-pantolactone as the major product. This non-linear behavior is attributed to the much stronger adsorption of CD compared to *O*-phenyl-cinchonidine. The dotted line (ee_{calc}) represents the theoretical curve for ee when the system would behave ideally linear.

strength). Tuning of the modifier structure involving both the stereogenic part as well as the anchoring moiety is a powerful approach for searching a suitable enantiodifferentiating modifier for a specific substrate [87]. However, it is noteworthy to mention that for ketopantolactone hydrogenation cinchonidine proved to be a more effective modifier than all modifiers synthesized so far with systematic variation of anchoring group and stereogenic regions [88].

A very striking feature of the ketopantolactone–cinchona–platinum system is that only trace amounts of cinchonidine are necessary for enantiodifferentiation, in fact a cinchonidine/ketopantolactone ratio of 276,000 was found sufficient to induce enantioselectivity [62]. This observation triggered the idea to perform the enantioselective hydrogenation in a continuous fixed-bed reactor by adding a trace amount (ca. 200 ppm) of cinchonidine to the reactant feed consisting of ketopantolactone, solvent and hydrogen [89]. This concept led to significant process intensification; in fact with a small tubular reactor (size of a pencil) more than 14 kg (*R*)-pantolactone per hour could be produced. The continuous reactor operation has later been successfully applied for the asymmetric hydrogenation of other substrates [90–92] and some criterion were discussed which have to be fulfilled for successful application of continuous operation. Thus, the ultimate goal of a heterogeneous enantioselective catalytic process based on the concept of chirally modified metals has become feasible for practical application.

3. Conclusions and outlook

In the past decade, we have witnessed a considerable gain in knowledge how chirality can be imparted to a metal surface. Fundamental studies have unraveled several possible mechanisms for chiral induction on metal surfaces. Here I have made an attempt to assess the potential of the different possibilities for creating chirality on metal surfaces for asymmetric catalysis. Though such an assessment may be premature I feel that it reflects roughly what can be expected in the nearer future. The most evident limitations of possibilities discussed in Sections 2.1–2.5 are the generally low number density and structural stability of the chiral sites. The major part of the metal surface exposes metal atoms, which lack chiral recognition. Assuming that on such metal sites the competing racemic reaction would prevail it seems that the achievable enantiodifferentiation for a catalytic process is rather low. Another practical limitation is the relatively demanding procedure for the creation of the chiral metal surface structures in these approaches. Nevertheless, in some cases there might be potential possibilities to overcome these intrinsic limitations originating from the fact that metals are achiral materials.

Judging from the presently available knowledge gathered about the principal possibilities for imparting chirality to a metal surface, it seems that the chiral modification of metals by adsorbed chiral organic modifiers is most promising for catalytic applications. Considerable effort has been expended in the past two decades by several groups to gain some understanding of the functioning of catalytic systems based on this strategy. Crucial factors for efficient asymmetric hydrogenation have been identified and the scope of reactants has been remarkably increased. Nevertheless, research in this field has shown that each reaction system (consisting of reactants, catalyst, modifier, and solvent) behaves very specifically and as a result of this there are relatively few general principles that can be applied in the exploration of new catalytic systems. An obvious general requirement is that the metal surface should expose only active chiral sites affording the desired enantiomer, whereas achiral active sites (leading to racemic product) and chiral sites yielding the undesired enantiomer should be avoided. Unfortunately, this ideal situation is difficult to realize in practical heterogeneous asymmetric catalysis.

In order to understand the functioning of a chirally modified metal catalyst all interactions between the different components of the reaction system have to be understood, which is of course a very demanding task. However, if this level of understanding can be reached, the method gives access to process opportunities that are usually not achievable in homogeneous asymmetric catalysis, such as demonstrated for the continuous asymmetric hydrogenation of ketopantolactone in a fixed-bed reactor.

An intrinsic limitation of the method is imposed by the fact that the surface of supported metal catalysts is heterogeneous and that the adsorption mode of modifier and reactants is prone to change with conditions such as surface coverage, solvent and temperature. This factor strongly limits a rational design of such catalyst systems because several competing structurally different enantiodifferentiating complexes can coexist on the metal surface during reaction, which can impair achieving high enantioselectivity. This is definitely an inherent drawback compared to enantioselective catalysis by transition metal complexes with well-defined chiral ligands and active sites. Nevertheless the steadily growing number of reactants that can be hydrogenated with high enantioselectivity demonstrates that this difficulty can be overcome.

Another limitation of these catalytic systems is that as yet they were only found suitable for asymmetric hydrogenation, extension of this concept to other classes of asymmetric reactions seems possible but is not straightforward. Up to today it seems that the application of this method is confined to reactions at low temperature in reducing atmosphere due to inherent problems with stability and adsorptive anchoring of the chiral modifier.

Interestingly, efforts towards extension of the scope of suitable modifiers have not resulted yet in modifiers that show a better performance than the original cinchona alkaloids. However, these studies have greatly contributed to a better understanding of the reaction mechanism. Although considerable progress towards this aim has been made in the past decade several important fundamental and practical aspects are still awaiting clarification. As examples, hardly anything is known about the dynamics of the surface processes leading to enantiodifferentiation or the catalytic behavior of other chirally modified transition metals. Compared to research in homogeneous asymmetric catalysis the effort made is still modest and so is the accumulated understanding of the governing reaction mechanisms. Nevertheless, the present state of the art clearly indicates that the chiral modification of metal catalysts bears a potential for asymmetric catalysis that renders research in this field rewarding. The impressively growing number of publications dealing with chiral metal surfaces shows that this research field has become very dynamic and vital. It is likely that this effort will lead not only to a better understanding of enantiodifferentiation on metal surfaces but also give access to new opportunities for creating chiral sites. Both challenges may drive asymmetric heterogeneous catalysis to blossom.

Acknowledgements

The author thanks all his former and present co-workers for their intellectual and experimental contributions. Their names appear in the references. Financial support of our work by the Swiss National Science Foundation is gratefully acknowledged.

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