Asymmetric Catalysis at Chiral Metal Surfaces

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1. Introduction

The remarkable development in homogeneous enantioselective catalysis reflected by the Nobel prizes in 2001 awarded to Sharpless, Noyori, and Knowles has further spurred the interest in chiral catalysis and with that also the attention to the fascinating properties of chiral surfaces and their applications in enantioselective catalysis. Various strategies have been pursued to design solid enantioselective catalysts, that is, to combine catalytic activity with a suitable stereochemical control of the reaction. Among these approaches, only modification of the catalytic metal surface by a strongly adsorbing chiral compound, termed as a modifier, has as of yet synthetic potential. (Immobilized chiral metal complexes traditionally belong to homogeneous catalysis and will not be discussed here.) The progress in the past years in heterogeneous enantioselective catalysis is indicated by the rapidly growing number of scientific publications and also by the expanding circle of highly enantioselective synthetic applications (for recent general reviews, see refs 1−5). The relevance of chirally modified metals in asymmetric synthesis induced a flourishing of surface science studies aimed at understanding the fundamental properties of chiral surfaces.[6−13]

Presently, there are two main directions in catalysis at chiral metal surfaces. A major group of scientists are engaged in the discovery of new synthetic applications, apparently with only marginal interest in the surface science aspects of the reactions; in some cases, it is not clear at all what the role of the solid surface is. On the other hand, surface scientists focus on the fundamental aspects of idealized chiral surfaces, and the catalytic action under practical conditions remains in the background. We attempt here to combine these two approaches since we are convinced that the use of surface sensitive techniques—and also sophisticated calculations involving the metal surface—will provide a fundamentally different view on how chirally modified solids function and will help replace the trial-and-error type catalyst development by a more rational approach.

Although sufficient references are provided to early results, the emphasis is on new developments in the past 10−15 years and on those applications that offer some synthetic potential, represent a new idea, or help us to understand the origin of enantioselection. At first, a brief overview is provided on the various approaches used in heterogeneous asymmetric catalysis and on the fundamental features of chirally modified metals. The next major part is devoted to the synthetic application of chirally modified metal catalysts categorized by the reaction types. Some interesting phenomena related to the chiral modification of metal hydrogenation catalysts are highlighted in the final part.

2. Strategies in Heterogeneous Enantioselective Catalysis

Several concepts have been advanced and tested for the synthesis of solid materials suitable for enantiospecific

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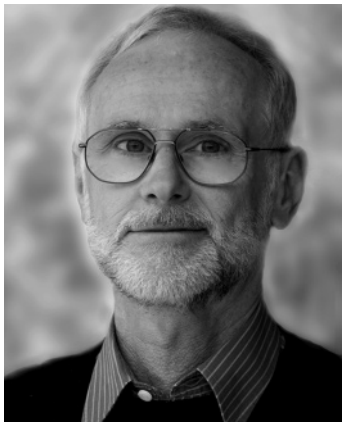


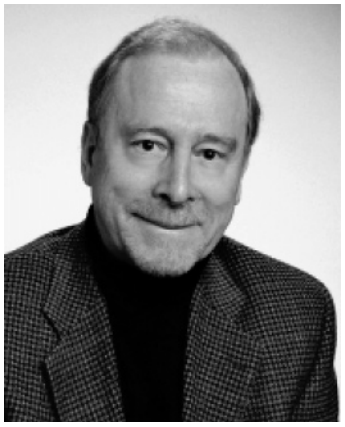
Tamas Mallat received an M.S. degree in 1972 in Chemical Engineering and a Ph.D. in 1976 in Technical Chemistry, both from the Technical University of Budapest, Hungary. He was a postdoctoral associate at Brunel University, London, from 1978 to 1979. He continued his academic carrier at the Organic Chemical Technology Research Group of the Hungarian Academy of Sciences. In 1990, he moved to ETH Zurich, where he is currently a scientist. He was awarded a D.Sc. degree in 1994 by the Hungarian Academy of Sciences. His main scientific interests are the application of heterogeneous catalysts in the synthesis of fine chemicals, including asymmetric catalysis, oxidation, and hydrogenation reactions, and the application of electrochemical methods in catalysis.

Elisabeth Orglmeister studied Chemistry at the University of Vienna, Austria, where she received her Master's Degree in Organic Chemistry in 2002 under the supervision of Edda Goessinger. At ETH Zurich, she continued research in heterogeneous catalysis in the group of A. Baiker; synthetic modifiers were the main topic. During her Ph.D. studies (completed in 2007), she became the mother of two lovely daughters.

adsorption and catalysis.[14−21] From a practical catalysis point of view, the most promising solid enantioselective catalysts are metals modified by the addition of a soluble chiral compound. This approach, which is the main topic of the present review, will be considered in sections 3−5. Other chiral solids that are less attractive for asymmetric synthesis are shortly reviewed here in this section.

2.1. Metal or Metal Oxide on a Chiral Support

An early idea is the deposition of a catalytically active metal or metal oxide onto a chiral support. The application of quartz,[22,23] cellulose,[24] or synthetic chiral polymers[25−28] led to poor enantioselectivities in hydrogenation and dehydration reactions. The disappointing results are understandable when considering that only a fraction of the total surface metal atoms, those at the metal/support interface, are in direct contact with the chiral support, whereas on the rest of the



Alfons Baiker (born 1945) studied Chemical Engineering (1967−71) at ETH Zurich and subsequently joined the group of Prof. W. Richarz, where he completed his doctoral thesis in 1974. During postdoctoral studies (1978–80) with Prof. M. Boudart at Stanford University, California, he completed his Habilitation thesis on ammonia synthesis kinetics. After returning to ETH, he started his own research group, focusing on heterogeneous catalysis and reaction engineering, at the Department of Chemistry and Applied Biosciences and moved up the ranks to become Full Professor in 1990. His research interests, documented in more than 700 publications and numerous patents, are centered around catalyst design and novel catalytic materials, mechanisms and kinetics of catalytic surface processes, asymmetric hydrogenation, selective oxidation, environmental catalysis, chiral surfaces, in situ spectroscopy, and the application of supercritical fluids in catalysis. His goal is to further the scientific basis needed for developing environmentally benign chemical processes, which make optimal use of raw materials and energy.

surface sites the reaction may proceed without any stereochemical control (Figure 1).

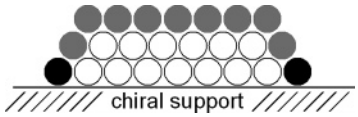


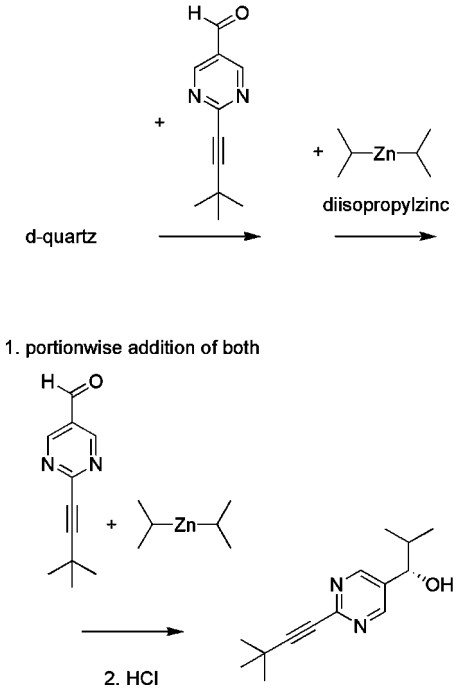
Figure 1. Schematic representation of a metal particle deposited onto a chiral surface. Only the peripheral atoms (black) among the surface-active sites (gray) are in direct contact with the support.

The most famous example is silk-supported Pd[29] that gave 66% optical yield in the hydrogenation of benzylidene oxazolidone, but later, these results could not be reproduced.[30] One may speculate that the use of strongly acidic medium during deposition of Pd onto silk might lead to degradation of the natural organic polymer and that its soluble fragments acted as chiral modifiers on the Pd surface. This explanation would also rationalize the difficulties in the reproduction.

2.2. Naturally Chiral Solids

The application of an intrinsically chiral surface as enantioselective adsorbent[9] seems to be promising, although the following excellent example is very specific. The asymmetric addition of diisopropylzinc in the presence of *d*- and *l*-quartz afforded the (*S*)- and (*R*)-pyrimidyl alkanols as the major enantiomers, respectively (Scheme 1).[31,32] The probable origin of enantioselection is the enantiospecific adsorption of the aldehyde via the electron-rich O- and N-atoms on the chiral surface of quartz, and even a small imbalance [0.6% initial enantiomeric excess (ee)] is multiplied by asymmetric autocatalysis. Interestingly, the potential of quartz as a chiral discriminator is considered to be low as compared to other chiral solids.[33]

Scheme 1. Chiral Pyrimidyl Alkanol Is Produced with >99.5% ee Via Enantiospecific Adsorption on Quartz and Autocatalysis[31]



An intrinsically chiral metal surface may be created by cutting single crystals along specific planes. Kinks at high Miller index metal surfaces (Figure 2) are considered as chiral when the length of the individual steps constituting the kink sites is different and can be defined analogously to the Cahn−Ingold−Prelog rules.[34] Enantiospecific adsorption of the reactant may induce chirality[6,35−38] as evidenced by the different rates of the electro-oxidation of D- and L-glucose on Pt(643) and Pt(431) sites.[7] Chiral molecules may adsorb enantiospecifically at chiral kink sites also on a macroscopically achiral surface that contains equal amounts of *R* and *S* kinks.[39] Major obstacles for synthetic application of this approach are the low population and limited stability of ideal chiral kink sites.[9,40,41]A symmetry analysis of metal crystals displayed that stepped bcc surfaces are also chiral even in the absence of kinks and they are more stable and better suited to asymmetric catalysis than kinks,[42] although the majority of the surface sites is still achiral and should provide racemic products.

2.3. Synthesis of a Chiral Solid in the Presence of a Chiral Auxiliary

Electrodeposition in the presence of a chiral compound may lead to a catalytically active chiral surface. When a CuO film was electrodeposited onto an achiral Au(001)[43,44] or Cu(111)[45] surface, the chiral orientation in the oxide film was controlled by the chirality of hydroxy or amino acids present in the deposition solution. Small differences in the rate of electro-oxidation of (*R*,*R*)- and (*S*,*S*)-tartrate provided the experimental proof for chiral recognition at the CuO film.

The concept of generating a solid surface in the presence of a chiral organic molecule may be an attractive route for the preparation of practical enantioselective catalysts. There are several reports on the synthesis of metal nanoparticles or supported metals in the presence of a chiral auxiliary (termed as ligand, modifier, or colloid stabilizer), but there is yet no evidence to the superiority of these surfaces in enantioselective catalysis, as compared to conventional chirally modified metals.[46−49]

3. Chirally Modified Metals: Fundamental Aspects

The addition of a strongly adsorbing chiral molecule to a (supported) metal catalyst is by far the simplest and most elegant approach to create a catalytically active chiral metal surface (for early reviews, see refs 30 and 50−55). Continuous progress in the past decades led to some synthetically useful solid catalysts. The subsequent discussion in this section is confined to the best understood application of chirally modified metals, the hydrogenation of unsaturated compounds.

3.1. Efficient Chirally Modified Metal Systems

The concept of chiral modification has been applied primarily to the Pt group metals and Ni, and there are only a few catalyst systems that afford high enantioselectivity (>90% ee). Commonly used modifiers are the naturally occurring cinchona alkaloids and tartaric acid (TA) (Figure 3). The only synthetic modifier that offers better than 90% ee is pantoylnaphthylethylamine (PNEA) (Figure 3).[56]

The Raney Ni−TA−NaBr system has been established as the choice for the hydrogenation of unfunctionalized and β-functionalized ketones,[57−59] particularly β-ketoesters and β-diketones (Figure 4). Platinum modified by cinchona alkaloids is the best catalyst for the hydrogenation of activated ketones. Better than 90% ee has been reported for α-ketoesters,[60,61] ketopantolactone,[62] pyrrolidine-triones,[63] α-ketoacetals,[64,65] α-ketoethers,[66] α-diketones,[67] and α,α,α-trifluoromethyl ketones[56,68] (Figure 5). Chirally modified Pd has the broadest application range, including the highly selective hydrogenation of α,β-unsaturated carboxylic acids[69] and 2-pyrones[70] (Figure 6). Beyond hydrogenations, Pd is the choice for heterogeneous enantioselective hydrosilyla-

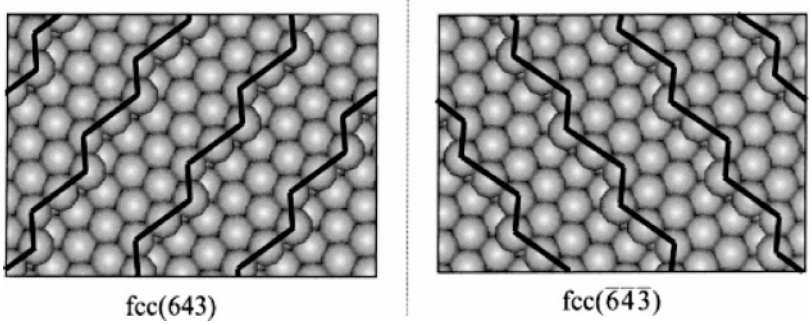
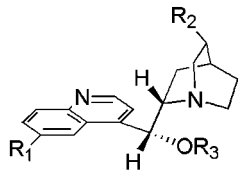
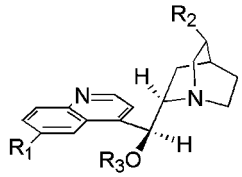


Figure 2. Ball models of the mirror images of the chiral fcc(643) surfaces; the step edges are marked. Reprinted with permission from ref 6. Copyright 2001 American Chemical Society.

	Abbr.	R_1	R_2	R_3
				
Cinchonidine	CD	H	Vinyl	H
10,11-Dihydrocinchonidine	HCD	H	Et	H
O-Methyl-cinchonidine	MeOCD	H	Vinyl	Me
O-Methyl-dihydrocinchonidine	MeOHCD	H	Et	Me
Quinine	QN	OMe	Vinyl	H
				
Cinchonine	CN	H	Vinyl	H
Quinidine	QD	OMe	Vinyl	H

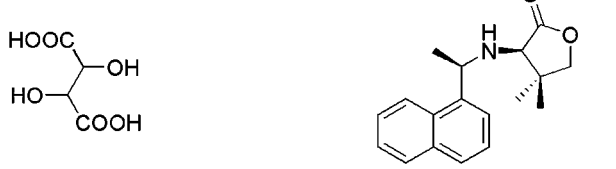


Figure 3. Best chiral modifiers for hydrogenations on Pt group metals and Ni: cinchona alkaloids and their simple derivatives, TA, and PNEA.

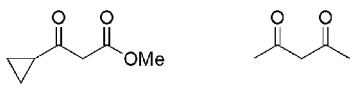


Figure 4. Outstanding examples on the hydrogenation of β-ketoesters and β-diketones on the Ni−TA−NaBr system.

tion,[71] enol isomerization,[72] and allylic substitution[73] reactions. Reports on the application of other Pt group metals are sporadic, and the enantioselectivities are less attractive.

The key component of chirally modified metals is the modifier that generates chiral sites by its adsorption on the metal surface. In most cases, the chiral modifier is simply added to the reaction mixture containing the catalyst. Several procedures have been developed for fine-tuning the chiral modification step, in particular for the Raney Ni−TA system,[57,74−76] but these pretreatments are not inevitable to induce enantioselectivity. The pool of efficient chiral modifiers is tiny, and the individual modifiers seem to be highly specific to the metal. For example, α-hydroxy-carboxylic acids work excellently with Ni but not with Pt,[77] and cinchonidine (CD) is the best modifier for Pt but useless for Ni and Ru.[78,79] The origin of almost enzymatic specificity is

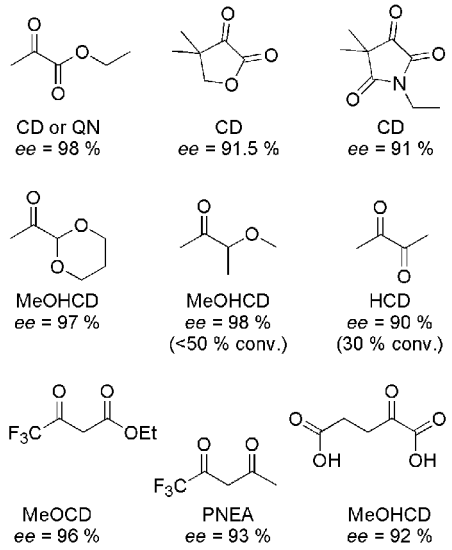


Figure 5. Hydrogenation of these ketones represents the most selective applications of chirally modified Pt (as Pt/Al_2O_3; for abbreviations of the modifiers below the formula, see Figure 3).

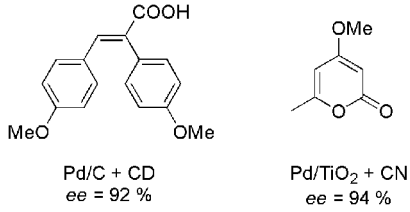


Figure 6. Pd modified by CD or CN is highly selective in the hydrogenation of C=C bonds functionalized in the α-position.

probably due to deviations in the adsorption of substrate and modifier, but the details are as of yet poorly understood.

3.2. Origin of Enantioselection

There are analogies between a soluble transition metal complex possessing ligands as the source of chiral information and a metal surface where the adsorbed modifier controls the stereochemical outcome of the surface reaction. The latter catalyst system is, however, far more complex and structurally less defined. The chiral modifier interacts with not one single transition metal atom but an ensemble of surface metal atoms (Figure 7),[80] and the metal surface imposes substantial geometrical constraint for the modifier−substrate interaction. In addition, homogeneous catalysts typically have a single type of active site, while the surface geometry of practical metal catalysts is intrinsically heterogeneous, containing various types of surface sites with different coordination (terrace, step, edge, kink, vacancy, and adatom) and thus different adsorption properties. Typically, the adsorption strength and geometry change with coverage and coadsorption of other compounds (substrate, solvent, and hydrogen). As a result, the mechanistic models developed for chiral transition metal complexes provide only strongly limited help to understand the functioning of chirally modified metals.

An essential deviation from asymmetric catalysis by chiral complexes is that truly in situ spectroscopic investigations are rare in heterogeneous asymmetric catalysis and yet are limited to the study of substrate−modifier interactions.[81,82] The adsorption mode of the modifier and substrate on the metal surface during their interaction is only speculated based on ex situ measurements[83−101] and theoretical calcula-

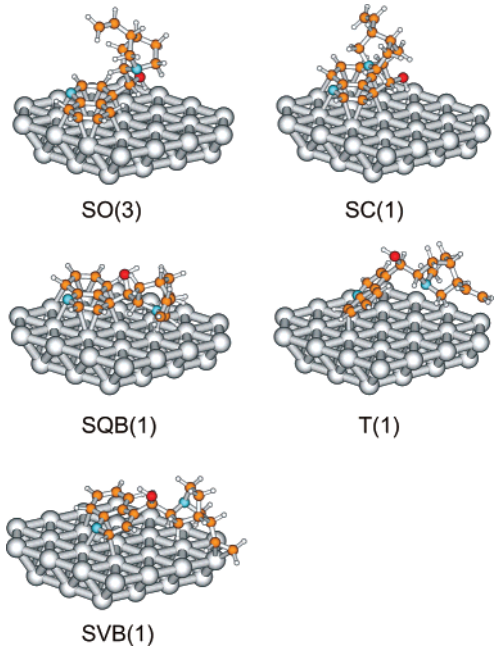


Figure 7. Representative, stable adsorption modes of CD on a Pt 38 cluster used for simulation of a Pt(111) surface.[80] SO(3): parallel adsorption in a quinoline-bound Open(3) conformation; the OH group interacts with Pt, and the quinuclidine N points toward the surface. SC(1): parallel adsorption in a quinoline-bound Closed-(2) conformation; the quinuclidine N points toward the quinoline ring. SQB(1): parallel adsorption mode bound via the quinoline ring and the quinuclidine N. T(1): tilted Closed(1) conformation bound via the quinoline ring "upside down". SVB(1): "upside down" adsorption of Closed(2) conformation bound via the vinyl group; this is the most stable adsorption mode, but the vinyl group is hydrogenated rapidly under reaction conditions.

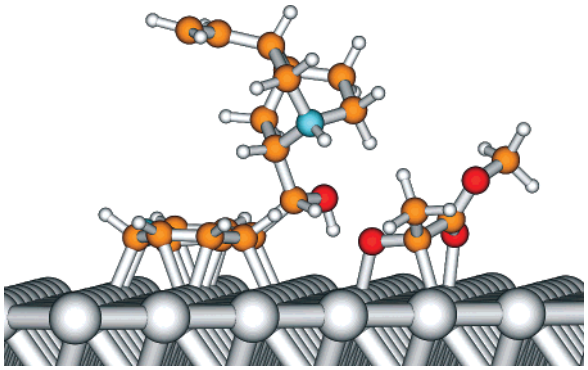


Figure 8. Proposed relative surface structures of CD and methyl pyruvate, both adsorbed on a Pt 31 cluster (DFT calculations), which allow an H-bonding interaction (not shown).[113] Note that such interactions can occur due to the conformational flexibility of the quinuclidine moiety.

tions.[102−112] Hence, it is not astonishing that remarkably different mechanistic models have been proposed for the most studied reactions, and even the basic elements of the origin of enantioselection are debated.

(i) The majority of scientists agree that direct modifier−substrate interactions on the metal surface are responsible for enantioselection. The variations in the details of molecular interactions will be discussed in the subsequent sections; here, only one example is shown in Figure 8 for illustration.[113]

(ii) Another concept is supramolecular chirality at the metal surface. The first version, the so-called template model from Wells' group,[114,115] assumed that ordered arrays of CD on the Pt surface are responsible for enantiodifferentiation

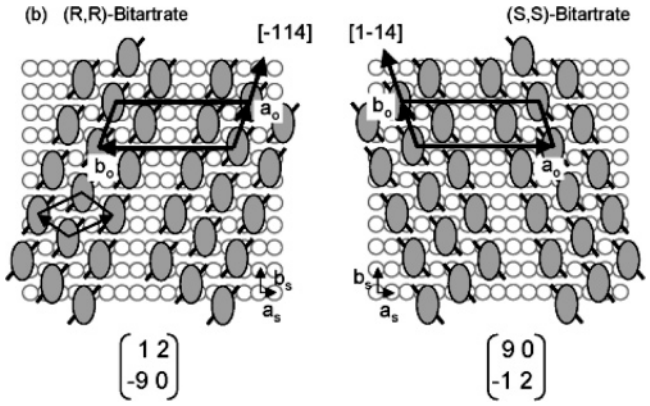


Figure 9. Adsorption models of the bitartrate phases of the two enantiomers on Cu(110). Reprinted with permission from ref 121. Copyright 2004 American Chemical Society.

in pyruvate hydrogenation. Later, the authors found by LEED and XPS[116] that quinoline and 10,11-dihydrocinchonidine (HCD) did not form ordered arrays, and they revised the model to emphasize the role of 1:1 type substrate−modifier interactions that can explain important catalytic observations, for example, the "ligand acceleration".[117] Subsequent surface sensitive spectroscopic and scanning tunneling microscopy (STM) studies confirmed the disordered adsorption of cinchona alkaloids and other amine type modifiers on Pt.[83,96,118]

More recently, STM detection of long-range ordered patterns of α-hydroxycarboxylic acids on Cu and Ni single-crystal surfaces (Figure 9) led to the revival of the concept, assuming that the origin of enantioselection on the Ni−tartrate system is the adsorption of the β-ketoester substrate on the chiral assemblies of metal atoms left free by the ordered modifier.[119−122] The relevance of long-range ordering on the small and irregular particles of practical metal catalysts is, however, questionable. It is more probable that direct substrate−modifier interactions controlled by hydrogen bonding and steric effects[57,123] are at the origin of better than 98% ee[124] achieved on Raney Ni. Jones and Baddeley have recently found by reflection absorption infrared spectroscopy (RAIRS) that ordered arrays of glutamic acid on Ni(111) are catalytically unimportant and that one-to-one molecular interactions seem to control the enantioselection.[97]

It has been shown that single-crystal surfaces covered by ordered superstructures of chiral molecules possess enantioselective adsorption properties.[125−129] It is possible that ordered structures of simple chiral molecules leaving chiral empty sites for the adsorption of another molecule are important in enantiospecific adsorption at single-crystal surfaces, but we assume that the contribution of molecular interactions to the observed small enantioselection is more important.

(iii) Adsorbate-induced restructuring of metal single-crystal surfaces[130] and the remarkable changes in the shape and size of colloidal[131,132] and supported metal[133] particles during catalytic reactions are well-known phenomena. The analogous enantiospecific surface restructuring of achiral Cu, Ni, and Ag single-crystal surfaces under the molecular adsorbate layer of various chiral compounds has been demonstrated by STM analysis.[119,134−138] Enantiospecific restructuring by chiral adsorbates involves both the physical and the electronic structure of the underlying metal surface.[95,139] Tungler and others[120,140] proposed that enantiospecific surface restructuring induced by chiral adsorbates may be relevant in asym-

metric catalysis over chirally modified metals, but convincing experimental evidence for this assumption is missing.

(iv) In polycrystalline metal catalysts, the amount of left- and right-handed chiral kink sites is equal and the metal surface is macroscopically achiral. In theory, a chiral modifier can adsorb selectively on the (*R*)- or (*S*)-kink sites, leaving the opposite types of sites exposed to interact with the substrate.[7,140] This concept that is analogous to selective chiral poisoning of soluble metal complexes[141] cannot rationalize the high enantioselectivities achieved with chirally modified Ni, Pt, and Pd. The fraction of chiral surface sites that might be generated by selective poisoning is low, and racemic product would be formed on the rest of the active sites. Besides, the model contradicts key experimental observations, such as the indiscriminative and structure insensitive adsorption of chiral amine and amino alcohol type modifiers[7,83,89] and their high mobility along the metal surface.[96,98]

4. Asymmetric Reactions at Chirally Modified Surfaces

Enantioselective hydrogenation of unsaturated functional groups is the most studied application of chirally modified metal catalysts. Below, the hydrogenation of C=O, C=C, and C=N bonds is discussed in the order that corresponds to the attractiveness of the results from a synthetic point of view. There are only sparse studies on other reaction types; nevertheless, these excellent examples demonstrate the general applicability of chirally modified metals as solid enantioselective catalysts.

4.1. Hydrogenation of Ketones

4.1.1. α-Functionalized (Activated) Ketones

Catalysts, Reaction Conditions. The discovery of α-ketoester hydrogenation on cinchona-modified Pt by Orito's group in the late seventies initiated a new wave of interest in chirally modified metals.[142−144] The application range of this catalyst system has been extended to several other ketones possessing an electron-withdrawing functional group in α-position, as illustrated with the outstanding examples in Figure 5 (see also some recent reviews).[3,5,145] Presently, this is the most studied and understood reaction class in heterogeneous enantioselective catalysis, and hydrogenation of pyruvate esters has emerged as a commonly used test reaction.

Despite the extensive efforts of many research groups to invent new catalyst systems, the most used catalyst is still supported Pt modified by a cinchona alkaloid, preferentially CD or its *O*-methyl derivative *O*-methyl-cinchonidine (MeOCD) (Figure 3). Other chirally modified metals[78,79,146] including Rh,[49,147−152] Ru,[77,153] Pd,[154−159] and Ir[160−162] are usually inferior to Pt in ketone hydrogenation.

The efficient chiral modifiers of Pt possess an extended aromatic ring that allows strong adsorption on the metal surface ("anchoring moiety"), a basic N atom that interacts with the ketone, and one or more stereogenic centers in the neighborhood of the other two functions to induce enantioselectivity and to provide the necessary conformational rigidity.[163−167] A broad range of alkaloids and derivatives,[153,168−180] various chiral amines,[146,181−184] amino alcohols,[185−190] amides and amino-phenols,[191] alcohols and diols,[191,192] amino acids and derivatives,[191,193,194] hydroxyacids,[77] and organotin compounds[151,195,196] have been tested to extend the circle of useful

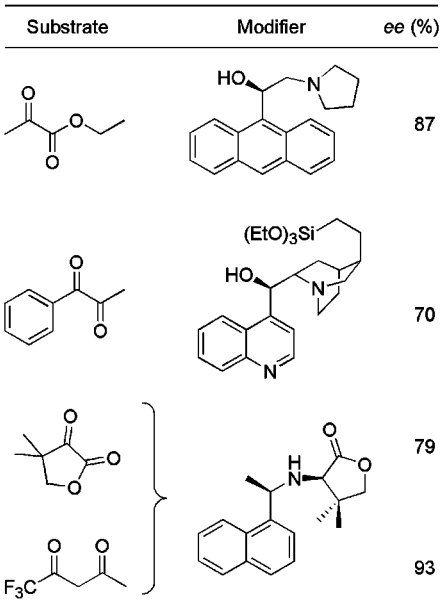
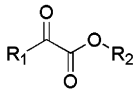
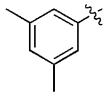
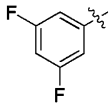
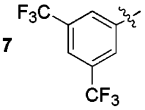
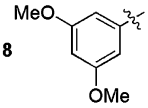
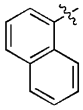


Figure 10. Best synthetic modifiers designed for the hydrogenation of an α-ketoester,[188] a 1,2-diketone,[178] ketopantolactone,[191] and an α-fluorinated ketone.[56]

catalysts. Some outstanding synthetic modifiers are shown in Figure 10. The reactions are usually performed under mild conditions, at or slightly below room temperature (r.t.), and at 1−10 bar[61,197,198] (sometimes up to 100 bar); the preferred media are toluene, acetic acid, and chlorinated solvents.[1,3,5,145] The importance of surface morphology and catalyst pretreatment is discussed separately in section 5.1. The modifier/substrate molar ratio (M/S ratio) necessary to obtain the highest enantioselectivity is relatively low as compared to other metals; it may be reduced to as low as 4 ppm.[199] This advantageous situation is attributed to the strong adsorption of CD on Pt[87,90] and to the relatively low activity of Pt in the saturation of the aromatic ring ("anchoring moiety") of the modifier[200−205] whose side reaction weakens the adsorption on the metal surface.[163] The feasibility of continuous flow operation has also been shown,[199,206−210] including the application of supercritical solvents.[211] Continuous operation with feeding of the modifier in trace amounts can afford better than 90% ee at very high reaction rates [turnover frequency (TOF) = 84000 h^{-1}].[212]

α-Ketoesters. The Pt−cinchona system is highly efficient in the hydrogenation of α-ketoesters and transforms them to the corresponding alcohols with excellent yields and up to 96−98% ee.[60,61,198,213−217] The steric and electronic effects in the substrates are relatively small when Pt is modified by CD,[218] but they are more pronounced when additional bulkiness is introduced in the modifier.[198,217] The probable explanation for the changes shown in Table 1 is that the methoxy and phenoxy groups of quinine (QN) and PhOCD, respectively, occupy a part of the chiral sites available for adsorption of the ketone, and also the position of the quinuclidine N atom is shifted.[219] Variation of the aryl substituent at the keto side reveals interesting electronic effects (Table 1, entries 3 and 5−8). With all three modifiers, the electron-releasing methoxy groups lead to the highest ee and the electron-withdrawing CF_3 groups to the lowest ee. In α-ketoesters, the keto-carbonyl group is already activated by the ester function, and apparently, additional activation from the ketone side is detrimental to the enan-

Table 1. Steric and Electronic Effects in the Hydrogenation of α-Ketoesters on 5 wt % Pt/Al_2O_3 Modified by CD, QN, and *O*-Phenyl-cinchonidine (PhOCD) (Toluene, 10 bar, r.t.)[217]

Entry	Substrate		CD *ee* (%)	QN *ee* (%)	PhOCD *ee* (%)
					
1	Me	Et	80 (*R*)	21 (*R*)	21 (*S*)
2	*tert*-Bu	Et	56 (*R*)	12 (*R*)	41 (*S*)
3	Ph	Et	86 (*R*)	79 (*R*)	57 (*S*)
4	Ph	*tert*-Bu	95 (*R*)	89 (*R*)	78 (*S*)
5		Et	92 (*R*)	75 (*R*)	52 (*S*)
6		Et	87 (*R*)	76 (*R*)	68 (*S*)
7		Et	66 (*R*)	47 (*R*)	48 (*S*)
8		Et	94 (*R*)	84 (*R*)	73 (*S*)
9		Et	86 (*R*)	60 (*R*)	31 (*S*)

tioselection. This conclusion is supported by the observation that hydrogenation of the deactivated ketone acetophenone on the Pt−CD system is poorly selective, but introduction of electron-withdrawing CF_3 groups in the phenyl ring [in 3,5-bis-(trifluoromethyl)acetophenone] enhanced the ee up to 60%.[220]

The numerous mechanistic concepts advanced in the past years will be presented here as an illustration to the role of surface science aspects in understanding the enantioselection at metal surfaces. The models usually consider CD as the source of chirality, with only a few attempts to extension to other modifiers.[111,118,164,188,221]

There is a general consensus that adsorption of the modifier on Pt generates chiral sites for adsorption of the ketone. Two major adsorption modes of CD have been identified by various surface science techniques: a weakly adsorbed species with the quinoline ring being in a tilted position and a strongly adsorbed ("flat") π-bonded species where the aromatic ring is oriented nearly parallel to the surface (Figure 7).[87,88,90,91,93,94,100,222−224] It is commonly assumed, but not proven, that the "flat" species interacts with the ketone during hydrogenation and the tilted modifier is only a spectator species. Note that calculations indicate far more possibilities for adsorption of CD on Pt,[80,106] due to the conformational complexity of the alkaloid (various open and closed conformers)[225−227] and to the multiple functional groups that can interact with Pt (quinoline ring, quinuclidine N, and the C═C function) (Figure 7). Interestingly, Bartók et al. proposed recently that the reason for the inversion of the major enantiomer by replacing CD with cinchonine (CN) would not be the different stereogenic centers in the diasteromers but rather the different orientation of the quinoline rings of the alkaloids toward Pt (flat vs tilted).[228] This interpretation, however, contrasts to recent time-resolved STM studies on Pt(111) and Pd(111) single crystals that revealed similar adsorption geometries but different mobilities (adsorption strength) of CD and CN.[98]

No clear conclusion could be deduced from spectroscopic measurements on the adsorption geometry of pyruvates during hydrogenation.[85,229] According to DFT calculations,[105] interaction of the keto-carbonyl group with the metal surface leads to rehybridization of the carbonyl C atom[230,231] and the loss of the "planarity" of the adsorbed pyruvate molecule (Figure 8), which simplified geometry is a general assumption in the mechanistic models. In addition, the *cis* position of the two carbonyls is energetically favored.

A major source of difficulties in the spectroscopic analysis of the substrate−modifier−metal interactions is the numerous side reactions of activated ketones,[232] including the Pt-catalyzed decarbonylation[233,234] and oligomerization,[86,235] and the amine-catalyzed aldol reaction and cyclization.[236]

In the absence of reliable experimental evidence, most mechanistic ideas are based on assumptions and (at best) calculations. In most cases, the models assume two interactions between the amine type modifier and the ketone: an N−H−O[116,237−241] or N−C type attractive interaction[242−244] and a second attractive or repulsive interaction that directs the adsorption of the ketone on Pt.[239,245]

The first concept based on an N−H−O type H-bond between the protonated amine modifier and the keto-carbonyl O atom is traced back to 1993,[237,246] and the model was improved remarkably throughout the years.[239] The main feature of this model was corroborated later by sophisticated calculations[105,113,247] and in situ spectroscopic measurements.[81,82] To explain the source of H in the complex, originally it was assumed that in acidic medium the protonated quinuclidine N is involved in the N−H−O bond, while in aprotic medium (e.g., in toluene) the basic quinuclidine N atom interacts with the half-hydrogenated state of the ketone.[164,248] It has been demonstrated recently that the Pt−hydrogen system is acidic and can protonate pyridine[249−251] and CD.[110] Thus, we assume that the protonated modifier always is the interacting species and it is unnecessary to postulate the stabilization of the half-hydrogenated state of the ketone by the amine modifier.[252]

A less clear point is the nature of the second interaction that ensures the preferred adsorption mode of the ketone on the *re* or *si* face. Stimulated by the steric and electronic effects in the hydrogenation of α-ketoesters (Table 1) and trifluoromethyl ketones,[253] we now assume that not a repulsive interaction[85,229] but the directing effect of the activating functional group determines the adsorption mode of the ketone. This directing effect is related to the electronic environment of the preadsorbed chiral modifier and is largely independent of the steric bulkiness on any side of the ketone.[217,253] Thus, the activating functional group enhances the reactivity of the ketone and also guides its adsorption mode in the neighborhood of the chiral modifier. This concept can rationalize why the excellent performance of cinchona-modified Pt is limited to the hydrogenation of activated ketones. The illustration in Figure 11 is based on the stereochemical outcome of the hydrogenation reactions and the presence of CD on Pt as a protonated species,[110] independent of the reaction medium. The (*R*)-product is

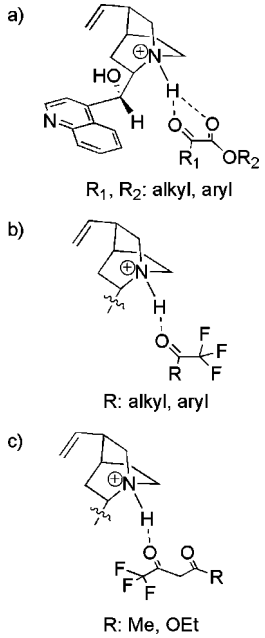


Figure 11. Interaction of CD (protonated by the Pt−H system)[110] with (a) an α-ketoester, (b) a trifluoromethyl ketone, (c) a trifluoromethyl-β-ketoester (R = OEt), or a trifluoromethyl-β-diketone (R = Me). According to Baiker et al.,[217] these adsorption modes result in the formation of the major enantiomer by hydrogen uptake from the Pt surface.

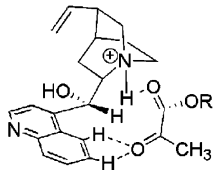


Figure 12. Two-point H-bonding model applied for CD and methyl pyruvate.[241,245]

formed with CD in the hydrogenation of α-ketoesters (Scheme 11a) and simple aliphatic and aromatic trifluoromethyl ketones (Figure 11b). In contrast, hydrogenation of a trifluoromethyl β-ketoester and a β-diketone gives the (*S*)-alcohol as the major enantiomer (Figure 11c). It seems that the carbonyl group is a stronger directing function than the activating trifluoromethyl group and inverts the adsorption mode relative to that of simple trifluoromethyl ketones. This hypothesis can also interpret the unusual electronic effects in the hydrogenation of aromatic α-ketoesters (Table 1), namely, that activation of the carbonyl group should come from only one side due to the critical role of the electronic effect in enantioselection. Note that the role of the OH function of cinchona alkaloids is not yet clear, as will be discussed below.

A different idea was proposed by McBreen, assuming a H-bond between the quinuclidine N of CD and the ester carbonyl of the substrate.[241,254,255] The latest version, the "generalized two-point H-bonding model", assumes a second, bifurcated H-bond involving two aromatic H atoms of the modifier at 5′- and 6′-positions and the O atom of the keto-carbonyl group (Figure 12).[241,245] According to this model, the cinchona alkaloids quinidine (QD) and QN, which contain a methoxy group in the 6′-position (Figure 3), should be ineffective in contrast to the experimental observations (see, for example, Table 1). In addition, the interacting complex is suggested to be valid for the hydrogenation of all activated ketones on Pt. This extension is challenging

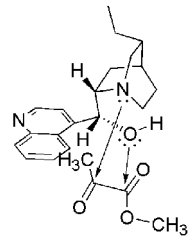


Figure 13. Schematic illustration to the formation of a six-membered ring between CD and methyl pyruvate, according to Augustine.[261]

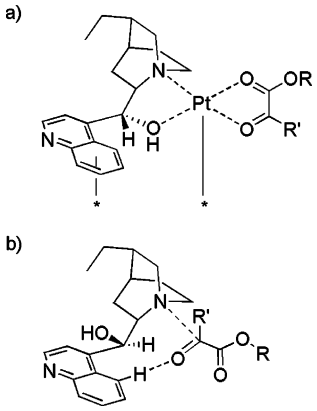


Figure 14. Mechanistic models for the hydrogenation of α-ketoesters on CD-modified Pt suggested by Bartók's group.[198,263]

since many important details of the substrate−modifier interaction and adsorption of the ketones are unknown. For example, protection of the OH function of CD has barely any influence on the enantioselectivity in pyruvate hydrogenation,[256] but it can increase[257] or decrease[258] the ee in the hydrogenation of fluorinated ketones, and even the opposite enantiomer is produced in (small) excess in the reduction of 1-phenylpropane-1,2-dione,[259] aryl-substituted acetophenones,[258] and α-hydroxyketones.[260]

A popular concept is the nucleophilic attack of the quinuclidine N atom on the keto-C atom of the substrate. The model originating from Augustine[242,261] predicts two attractive interactions between the quinuclidine N and the O atoms of CD and the two carbonyl C atoms of the α-ketoester (Figure 13). The formation of the rigid six-membered ring complex on the Pt surface is unlikely due to steric hindrance, particularly when the O-methyl derivative of CD (MeOCD) is used. In addition, neither methylation nor removal of the OH function of CD hinders the enantioselection in pyruvate hydrogenation,[163] contradicting the equal importance of the two interacting functions of CD.

Bartók advanced several models for α-ketoester hydrogenation with the major common point that the quinuclidine N atom acted as an electron pair donor.[198,243,262−265] In an early version, the N and O atoms of CD and the two carbonyl O atoms interact with a surface Pt atom (Figure 14a).[243,263] This surface complex may be considered as an analogy to three-dimensional metal−ligand−substrate interactions in homogeneous catalysis, but it is disfavored on a metal surface due to steric effects. According to the most recent version, the second substrate−modifier interaction that controls the adsorption of the ketone is a H-bond involving an aromatic H of the quinoline ring (Figure 14b).[198] The critical point here is the efficiency of QN and QD as modifiers that cannot be explained by this model, as discussed previously in relation to McBreen's model.[241,245]

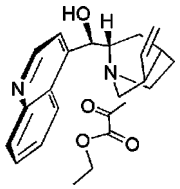
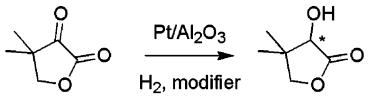


Figure 15. "Shielding model": during adsorption of the complex formed in solution, CD is located above, not beside, the adsorbed ethyl pyruvate.[272]

Scheme 2. Enantioselectivities in the Hydrogenation of Ketopantolactone on Pt Modified by CD, *N,O*-Dimethyl-cinchonidine (*N,O*-DMeOCD·Cl),[275] and NED[192]



modifier	*ee* (%)
CD	91.5 (*R*)
N,O-DMeCD·Cl	44.5 (*S*)
NED	25 (*R*)

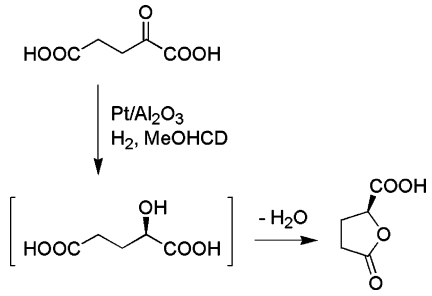
The nucleophilic attack of the quinuclidine N might lead to a zwitterionic intermediate with the activated ketone and provide the basis for enantioselection, as suggested by Sun and co-workers[244] and later by Bartók's group.[228,266,267] Although the model has been justified by NMR analysis in acetone solution,[266−268] it seems that the experimental evidence is based on erroneous interpretation of the signals.[269] Steric hindrance against the interaction of the amine modifier with cyclic ketones and the regioselectivity of the hydrogenolysis of the hypothetical zwitterionic intermediate are further critical points to be considered.[269]

Margitfalvi also predicts an N−C type interaction between the quinuclidine N and the C atom of the ketone, but he rejects the strong adsorption of CD on Pt via the quinoline ring. Instead, his "shielding model"[270−272] postulates the formation of a complex in solution between the α-ketoester and the alkaloid, the subsequent adsorption of the complex on the metal surface (Figure 15), and desorption of the alkaloid and product after hydrogen uptake. The model is disfavored due to energetic[240] and kinetic[273] considerations, and it contradicts the experimental observations corroborating the strong, almost irreversible adsorption of CD on Pt.[90,93]

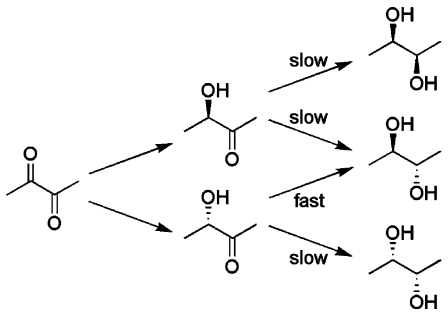
Other Activated Ketones. *Ketopantolactone.* Despite the rigid structure of ketopantolactone, its hydrogenation is very similar to that of acyclic α-ketoesters, with up to 91.5% ee to (*R*)-pantolactone on CD-modified Pt.[62,274] This similarity, however, disappears when using other modifiers. 1-Naphthyl-1,2-ethanediol (NED)[192] and quaternary cinchonidinium salts[275] are moderately selective in ketopantolactone hydrogenation (Scheme 2) but give racemic products in pyruvate hydrogenation. In the case of cinchonidinium salts, the probable origin of enantioselection is an electrostatic interaction between the cinchonidinium cation and the free electrons of the keto-O atom.[275] Note that the mechanistic models developed for pyruvate hydrogenation are based on the early observation that quaternary cinchonidinium salts are ineffective as modifiers.[163]

α-*Ketoacids.* Alumina-supported Pt modified with *O*-methylated CD gives up to 92% ee in the hydrogenation of

Scheme 3. Hydrogenation of 2-Oxoglutaric Acid on Pt Modified by *O*-Methyl-10,11-dihydrocinchonidine (MeOHCD) Gives 92% ee (in Water, at 25 bar and 0 °C)[277]



Scheme 4. Enantioselective Hydrogenation Combined with Kinetic Resolution, Affording up to 90% ee to (*R*)-3-Hydroxybutane-2-one (Pt/Al_2O_3, HCD)[67]



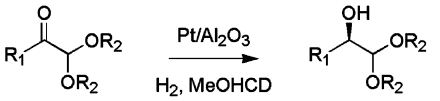
α-ketoacids; other metals perform poorly (Scheme 3).[276,277] The reactions require polar (aqueous) medium, and the loss of ee with K or Na salts of α-ketoacids[276] indicates the importance of acid−base type substrate−modifier interactions. The enantioselection obtained with quaternary cinchonidinium salts[276] extends the circle of the mechanistic differences between the hydrogenation of α-ketoacids and α-ketoesters.

α-*Ketoamides.* Hydrogenation of α-ketoamides on CD-modified Pt/Al_2O_3 is not an attractive route to the corresponding chiral alcohols (34−60% ee),[278−280] but reduction of cyclic imidoketones, such as pyrrolidine-2,3,5-triones, affords up to 91% ee (Figure 5).[63,281]

α-*Diketones.* The high enantioselectivity in the hydrogenation of α-diketones on cinchona-modified Pt is due to a combination of enantioselective reaction and kinetic resolution.[67,282] In the complex reaction route (Scheme 4), the medium ee in the first step is increased up to 90% via further transformation of the hydroxy-ketone intermediate to the 1,2-diol. The synthetic potential of the method is limited by the low chemical yield, usually less than 30%. Other reactions investigated are the hydrogenation of hexane-3,4-dione,[283] 1-phenyl-1,2-propanedione (>90% ee),[284] and cyclohexane-1,2-dione (81% ee).[285] Supported Pt in the presence of CD is the best choice also for this reaction class; replacement of Pt by other Pt group metals[79,162] and that of CD by other cinchona derivatives or analogous chiral amino alcohols[176,177] diminished the enantioselectivity.

There is no unambiguous conclusion yet concerning the reaction mechanism.[107,108,259] The striking similarity between the hydrogenation of α-hydroxy- and α-alkoxy-ketones[66,260,286] indicates that both O atoms of the substrate act as H-bond acceptors toward the protonated N of the modifier.[285] The protection of the OH function of the alkaloid by methylation leads to a dramatic loss of enantioselection or even to inversion of the major enantiomer.[177,260] Contrary to these

Scheme 5. Structural Effects in the Hydrogenation of α-Keto Acetals (5 wt % Pt/Al_2O_3, AcOH, MeOHCD, 25 °C, and 60 bar)[65]



R_1	R_2	*ee* (%)	rate ($mmol \cdot g^{-1} \cdot min^{-1}$)
Me	Me	96	53
Me	$(CH_2)_3$	97	42
Me	Et	91	5.8
Me	Bu	85	1.8
Ph	Me	89	1.5
$PhO(CH_2)_3$	Me	93	5
$Me_2NOC(CH_2)_2$	Me	80	0.7
$MeO_2C(CH_2)_2$	Me	50	<0.1

observations, theoretical calculations showed that bifurcated H-bonded complexes not involving the OH function of CD are energetically favored as compared to cyclic modifier−substrate complexes involving both interacting functions of the 1,2-amino alcohol type modifier.[112]

α-*Ketoacetals.* Hydrogenation of α-keto acetals belongs to the most selective reactions on chirally modified Pt.[64,65,287,288] The enantioselection is good even in the presence of additional functional groups (Scheme 5).[65] Pyruvaldehyde acetals are highly reactive, but the reaction rate drops with increasing bulkiness of the substrate.

α-*Fluorinated Ketones.* The Pt-catalyzed hydrogenation of α-fluorinated ketones is characterized by unusually strong structural effects. The best modifiers are CD, MeOCD, and PNEA (Figure 3) for some fluorinated *β*-diketones.[56,289] Protection of the OH function of CD (in MeOCD) may be advantageous[257,290] or detrimental[258,291,292] to enantioselection as mentioned previously, and this effect is as of yet poorly understood. For example, replacement of CD by MeOCD increased the ee from 31 to 77% in the hydrogenation of 1,1,1-trifluoro-2,4-pentanedione[257] but diminished it from 55 to 17% in the hydrogenation of 1,1,1-trifluoro-acetophenone,[292] using otherwise identical conditions.

The method shows the biggest potential in the hydrogenation of fluorinated aromatic ketones,[267,291−293] *β*-diketones,[56,257,289] and *β*-ketoesters,[68,294] but even within these groups, the good enantioselectivity is not general (Figure 16). A unique example is the dynamic kinetic resolution of racemic ethyl 2-fluoroacetoacetate where 82% ee to the (2*S*,3*R*)-alcohol was obtained due to the spontaneous racemization of the unreacted ketone.[294] This is the only example in the literature where a single F atom activates the keto group. Reduction of aliphatic fluorinated ketones is moderately selective[292] and complicated by striking solvent effects that are difficult to rationalize.[253,266] Some reactions are fast (average TOF of 1500−2100 h^{-1}),[68] while others are difficult to bring to completion[289] or there is no reaction at all at r.t.[267]

A few mechanistic proposals analogous to those developed for pyruvate hydrogenation are available,[266,267,295,296] but some important observations cannot easily be rationalized by them. As discussed previously, a key element of enantioselection is the directing effect of the CF_3 group that controls the adsorption of the ketone on the *re* or *si* face,[253] although this effect is not very strong, as a carbonyl group in the substrate "overwrites" it (Figure 11).[217] It is very probable

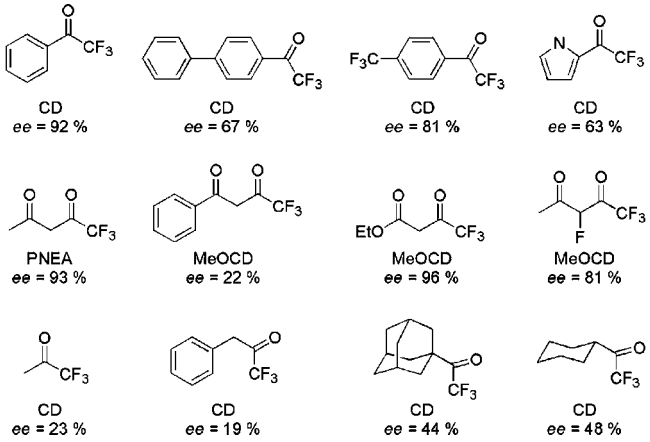


Figure 16. Structural effects in the hydrogenation of fluorinated ketones on Pt/Al_2O_3 modified by CD, MeOCD, and PNEA.

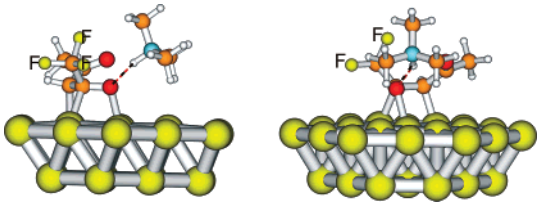


Figure 17. Side and front views of the calculated structure for the interaction of 1,1,1-trifluoro-2,4-pentanedione with an amine type modifier, for example, CD. The protonated amine (simulated here by Me_3NH^+) is coordinated to the di-*σ*-adsorbed, deprotonated enolate on a Pt 31 cluster. Reprinted with permission from ref 297. Copyright 2006 American Chemical Society.

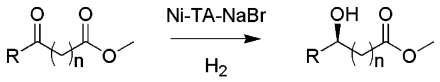
that the amino function of the modifier interacts with the ketone and the different performance of CD and MeOCD indicates that the OH group of the alkaloid may or may not be important in the substrate−modifier interactions. There is experimental evidence in favor of an N−H−O type H-bond. In the hydrogenation of 1,1,1-trifluoro-2,4-diketones, addition of the amine type modifier (CD or PNEA) induced high ee and also enhanced the chemoselectivity up to 100% toward the hydrogenation of the activated carbonyl group to an OH group.[257,297] NMR and IR spectroscopy proved the formation of an ion pair between the protonated amine modifier and the enolate form of the substrate.[297] DFT calculations including the simulation of the amine−enolate interaction on the Pt surface showed that only the activated carbonyl is in direct contact with the metal and can be hydrogenated, which adsorption geometry explains the high chemoselectivity (Figure 17). An intriguing point in this model is that not the ketone but an enol type species is the reactive form on chirally modified Pt, in contrast to all existing models for ketone hydrogenation.

4.1.2. *β*-Functionalized Ketones

The extensive research initiated by Japanese scientists several decades ago evolved the Raney Ni−TA−NaBr system to the best heterogeneous enantioselective catalyst for the hydrogenation of *β*-functionalized and unfunctionalized ketones to alcohols; other metals are far less efficient. Details of this development and the critical role of catalyst modification can be found in numerous reviews.[30,53,55,57−59,123,298−302]

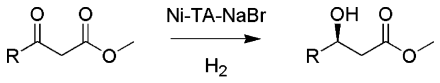
TA-modified Ni is mainly used for the hydrogenation of *β*-ketoesters. The importance of the *β*-position of the ester group is illustrated in Scheme 6, and some outstanding examples are collected in Scheme 7.[124,301] TA is the most

Scheme 6. Structural Effects in the Hydrogenation of Ketoesters on the Raney Ni−TA−NaBr Catalyst System (THF + AcOH, 100 °C, 90 bar)[57]



n	*ee* (%)
0	2
1	83
2	38
3	0

Scheme 7. Structural Effects in the Hydrogenation of *β*-Ketoesters on the Raney Ni−TA−NaBr System, at 60 °C[124,301]



R	*ee* (%)
Me	86
Et	94
i-Pr	96
cyclopropyl	>98
Bu	91
cyclobutyl	94

suitable chiral modifier among the various hydroxy and amino acids tested. Crucial requirements that the modifier has to fulfill are the presence of two carboxyl groups and at least one hydroxyl group.[57] The original, time-consuming, and corrosive catalyst preparation technique has been improved remarkably in the past years.[74,75,303−307] A general obstacle is the relatively low activity of Ni as compared to that of Pt group metals; completion of the reactions requires high pressure and elevated temperature. In an extreme case, in the hydrogenation of racemic 3-cyclopropyl-2-methyl-3-oxopropanoate, 93% ee and high diastereomer ratio were obtained by dynamic kinetic resolution but the conversion was only 23% after 1 day at 80 °C.[308]

Other useful substrates are *β*-ketoalcohols and *β*-ketoethers (68−70% ee), *β*-ketosulfones (67−71% ee), and *β*-diketones.[57] In the latter substrate class, kinetic resolution enhances the enantioselectivity of the first reaction step and gives 90−91% ee to the (*R*,*R*)-diol.

According to the "two-point interaction" model advanced several years ago by Japanese scientists, TA adsorbs on Ni as a dianion and interacts with the keto form of the *β*-ketoester via H-bonding (Figure 18).[58,309] The carboxylate groups anchor the modifier to the surface, and the OH groups interact with the keto form of the substrate. This complex cannot explain the good enantioselectivity achieved with

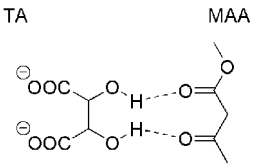
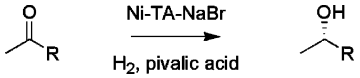


Figure 18. "Two-point interaction" model for the hydrogenation of methyl acetoacetate (MAA) on Ni modified by (*R*,*R*)-TA; hydrogen uptake from the surface (from "below").[57]

Scheme 8. Hydrogenation of 2-Alkanones over Raney Ni Modified by (*R*,*R*)-TA and Pivalic Acid (in THF, at 60 °C)[301,318]



R	*ee* (%)
Et	63
i-Pr	85
Bu	80
pentyl	71
hexyl	80

monohydroxy-dicarboxylic acid type modifiers (e.g., 70% ee with malic acid),[301] but STM studies support the concept that all four functional groups of TA are involved in the modifier−surface and modifier−substrate interactions.[310] Adsorption of methyl acetoacetate with the molecular plane parallel to the Ni surface[310] and that of TA as bitartrate ions[119] were also confirmed by surface science studies. The reactivity of the keto form of the substrate is indicated by the good enantioselectivity in the hydrogenation of methyl α,α-dimethylacetoacetate, an ester that cannot exist in the enol form,[309] and by the low enantioselectivity in the reduction of cyclic *β*-ketoesters that are present dominantly as enols in solution.[311] Earlier, Yasumori suggested the enol form of acetoacetate as the reactive species,[312] but the enol (beside the keto form) was detected on Ni(111) only at relatively high coverage.[310]

Several other models have been proposed to rationalize some important aspects of *β*-ketoester hydrogenation.[53,120] To account for the positive effect of acid additive on the enantioselectivity, Osawa et al. assumed that the acid additive forms a complex with TA through a sodium ion.[301] The formation of a six-membered ring involving only one OH function of TA was proposed for *β*-ketoester hydrogenation over mixed nickel-cerium oxides.[313] Raval and co-workers considered the surface restructuring of Ni atoms induced by modifier−metal interactions[95,119,314] and the formation of long-range ordered adsorption patterns of TA[122,315,316] as the origin of enantioselection. Ordered arrangements of TA on Ni(111) were confirmed, but methyl acetoacetate did not interact with the chirally modified surface (at r.t.).[317] See also the discussion in section 3.2.

4.1.3. Other Ketones

2-Alkanones. TA-modified nickel is the only useful metal catalyst for the hydrogenation of unfunctionalized aliphatic ketones, although good enantioselection requires more than a stoichiometric amount of an achiral acid additive.[318−321] In the hydrogenation of 2-alkanones, addition of the bulky pivalic acid allowed up to 85% ee (Scheme 8). It seems that branching in the α-position of the ketone (3-methyl-2-butanone) and the acid additive (pivalic acid) leads to the highest enantioselectivities. The role of the bulky pivalic acid is to prevent the adsorption of the ketone on the other side ("key-lock" system), as visualized by the "one-point interaction" model in Figure 19.[58,301,322] Later, the one-point and two-point interaction models were extended to a generalized mechanistic concept that can account for the enantioselectivity of TA-modified Ni in ketone hydrogenation in the presence of additional acids.[57,58] Gas-phase hydrogenation

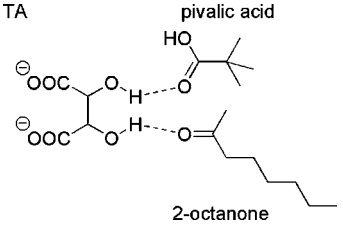
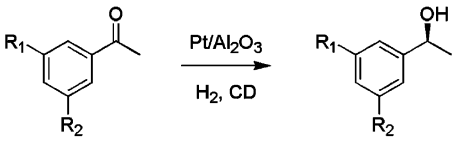


Figure 19. "One-point interaction" model for the hydrogenation of 2-octanone on Ni modified by (*R*,*R*)-TA and pivalic acid; hydrogen uptake from the surface (from "below").[57]

Scheme 9. Effect of Aryl Substituents in Acetophenone Hydrogenation[220,258]



R_1	R_2	*ee* (%)
H	H	17
H	CF_3	44
CF_3	CF_3	69.5*

* optimized value

of 2-butanone is also feasible when the catalyst (Ni/Y zeolite) is premodified ex situ with TA.[323]

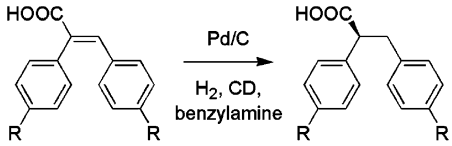
3-Alkanones. The Ni−TA−NaBr system is also effective in the hydrogenation of 3-alkanones, but in these reactions, a more bulky carboxylic acid additive is necessary.[324] Enantioselectivities in the range of 25−44% ee were achieved by using more than 1 equiv of 1-methyl-1-cyclohexanecarboxylic acid. The lower efficiency of the catalyst system in the hydrogenation of 3-alkanones, as compared to that of 2-alkanones, is attributed to the smaller difference between the steric bulkiness of the alkyl groups on the two sides of the keto group.

Aromatic Ketones. Another demanding reaction is the hydrogenation of unfunctionalized aromatic ketones. Hydrogenation of acetophenone on a CD-modified Pt cluster supported on MCM-41 gave 49% ee at 40% conversion, but the enantioselectivity decreased with conversion and the catalyst slowly deactivated.[325] Platinum modified with an organotin compound (24% ee)[195] and Pd/C in the presence of (*S*)-proline (23% ee)[326] were even less selective. The enantioselection improved by ring substitution of acetophenone. The reduction of 3,4-dimethoxyacetophenone on Pt/SiO_2 modified by a chiral organotin compound gave 39% ee,[196] and 69.5% ee was obtained in the hydrogenation of 3,5-bis(trifluoromethyl)acetophenone[258] on CD-modified Pt/Al_2O_3. The latter reaction, including some other acetophenone derivatives,[220] resembles the hydrogenation of activated ketones, but here, the carbonyl group is activated by electron-withdrawing groups at the aromatic ring (Scheme 9). Theoretical calculations confirmed this relation,[296,327] including the similarity of the probable reaction mechanism.[258]

4.2. Hydrogenation of C=C Bonds

Chirally modified metals are effective only in the hydrogenation of functionalized olefins and aromatic compounds, and the best choice is usually supported Pd modified by a cinchona or vinca alkaloid.[2,328,329]

Scheme 10. Best Examples on the Hydrogenation of Aryl-Substituted Alkenoic Acids (5 wt % Pd/C, CD, 0.8 equiv Benzylamine, 1 bar, r.t.)[69]



R = H *ee* = 81 %
R = OMe *ee* = 92 %

4.2.1. Unsaturated Carboxylic Acids and Esters

The first report on the hydrogenation of α,β-unsaturated carboxylic acids dates back to the early sixties,[330] and continuous improvement mainly by Nitta[331−336] resulted in a highly selective transformation of some aryl-substituted acids (Scheme 10).[69,337] The only useful catalyst is cinchona-modified Pd; other metals[28,338,339] and modifiers[340,341] are poorly selective. Under optimized conditions, a base (benzylamine) in an almost equivalent amount is added to deprotonate the carboxylic acid and thus weaken the adsorption of the product on Pd.[342] Another handicap is the relatively small substrate/modifier ratio of 25, which may be due to the weak adsorption of CD on Pd.[92] The addition of CD diminishes the reaction rate, which is a typical feature of Pd-catalyzed hydrogenations. The method was applied for the synthesis of L-DOPA via reduction of the corresponding cinnamic acid derivative (44% ee).[343]

According to Nitta, the probable origin of enantioselection in the hydrogenation of aromatic unsaturated acids is the formation of a 1:1 acid:CD complex via two H-bonds (Figure 20).[344] In the strongly polar medium necessary for high

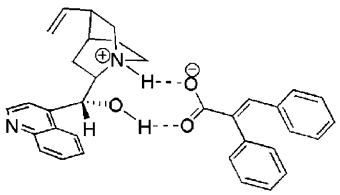


Figure 20. Probable key interaction (1:1 complex) leading to enantioselection in the hydrogenation of α-phenylcinnamic acid on CD-modified Pd.[344]

enantioselectivity, the substrate is present mainly as a monomer, and a similar monomer−dimer equilibrium was implicitly assumed on the Pd surface. Another important element of the model is the adsorption of CD nearly parallel to the metal surface via the quinoline ring, and the existence of this π-bonded species (beside a tilted species) was confirmed later by attenuated total reflection infrared (ATR-IR) spectroscopy.[92]

The enantioselectivities are less impressive in the hydrogenation of aliphatic α,β-unsaturated carboxylic acids when there is no aryl substituent in the β-position.[345] The ee varies in the range of 20−66%, depending on the functionalization of the C=C bond.[154,346−349] The addition of up to 2 equiv of benzylamine increases the enantioselectivity, and the presence of two carboxyl groups in the substrate diminishes the enantioselectivity.[350] A major reason for the sometimes disappointing enantioselectivity is the rapid isomerization of the alkenoic acid on the Pd surface, which as a side reaction is accelerated by the amine type modifier.[351,352] Good enantioselectivities can be achieved only when the double

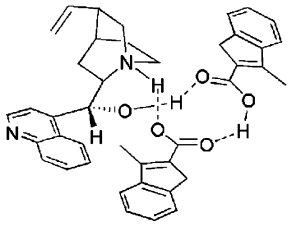
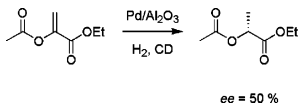


Figure 21. Empirical mechanistic model for the hydrogenation of α,β-unsaturated carboxylic acids; H uptake from the Pd surface ("bottom-side *syn* addition") affords the major enantiomer.[346,354,355]

Scheme 11. Synthesis of (*R*)-Ethyl 2-Acetoxypropionate on CD-Modified Pd (DMF, 1 bar, r.t., 5 min)[359]



bond migration is slow (internal C═C bond), or it is not possible at all (α-phenyl-cinnamic acid derivatives).

The enantioselectivity decreases with increasing solvent polarity,[353] indicating that in this case the acid dimer may be the reactive species. An empirical model that can predict the major enantiomer of the product in the hydrogenation of aliphatic α,β-unsaturated carboxylic acids (including indene carboxylic acids) is shown in Figure 21.[346,354,355] The quinoline ring of CD and the acid dimer lie close to parallel to the Pd surface, and their interaction is stabilized by two H-bonds, involving the quinuclidine N and OH functions of CD. The acid dimer is in *trans* arrangement, and one of the C═C bonds points toward the neighboring quinoline ring of CD. Spectroscopic studies confirmed the dominance of acid dimer−CD interactions in solution in the concentration range relevant for alkenoic acid hydrogenation.[356,357] Ab initio calculations showed that the 2:1 complex is energetically favored and can adsorb on the metal surface easier than the 1:1 complex.[355]

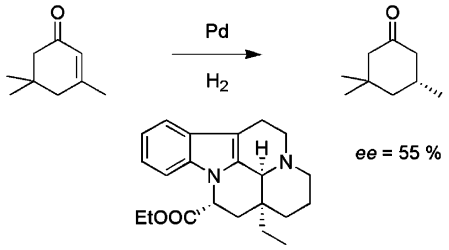
A closer supervision of the hydrogenation of all acrylic acid derivatives reveals that a phenyl substituent in β-position inverts the adsorption mode of the substrate on Pd,[358] but indene-carboxylic acid seems to be an exception (Figure 21). The directing effect of the phenyl group is probably related to steric effects.

Early mechanistic studies revealed that in the hydrogenation of unsaturated carboxylic acids the origin of enantioselection is acid−base type interactions and the efficiency of cinchona-modified Pd is lost by transformation of the carboxyl group to an ester.[154,353,354] The Pd−cinchona system may still be effective, however, if there is an additional functional group in the molecule in α-position to the C═C group, whose function may be to interact with the alkaloid. Examples include the hydrogenation of an enol ester (Scheme 11),[359] an enamine (24% ee),[360] and an N-acetyl dehydroamino acid ester (33% ee).[361−364]

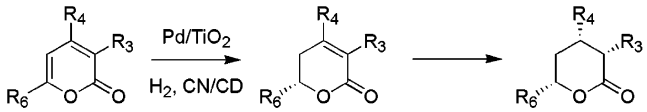
4.2.2. Unsaturated Ketones

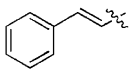
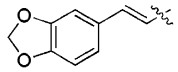
A large part of the available data is related to reactions carried out in the presence of stoichiometric amount of proline.[365−371] Tungler et al.'s pioneering work has indicated that proline acts as a chiral auxiliary that reacts with isophorone and the adduct is hydrogenated diastereoselectively. Interestingly, it has recently been proposed that the origin of enantioselection is kinetic resolution of the racemic hydrogenation product by interaction with proline in the homogeneous phase and the Pd surface is not involved in the enantiodifferentiating step.[372] In any case, the topic does not belong to enantioselective reactions over chirally modified metals.

Scheme 12. Hydrogenation of Isophorone on Pd Black Modified by DHVIN (MeOH + AcOH, 50 bar, r.t.)[375]



Scheme 13. Hydrogenation of 2-Pyrone Derivatives over Pd/TiO_2 Modified by CD (Entry 1) or CN (Entries 2−7) and the ees to the Dihydro Intermediate (2-Propanol, 1 bar, r.t)[70]



Entry	R_3	R_4	R_6	*ee* (%)
1	H	OH	CH_3	85 (*S*)
2	H	OCH_3	CH_3	94 (*R*)
3	H	OCH_2CH_3	CH_3	85 (*R*)
4	CH_3	OCH_3	CH_3	75 (*R*)
5	H	OCH_3		89 (*R*)
6	H	OCH_3		90 (*R*)
7	H	CH_3	CH_3	-

The best ees achieved in the hydrogenation of α,β-unsaturated ketones on chirally modified Pd are around 50%. CD-modified Pd black is the choice for the hydrogenation of an exocyclic alkenone, 2-benzylidene-1-benzosuberone, to the corresponding saturated ketone (54% ee).[373] A similarly efficient modifier for Pd is the vinca alkaloid derivative (−)-dihydroapovincaminic acid ethyl ester (DHVIN),[374] which gives up to 55% ee in the hydrogenation of isophorone (Scheme 12).[375−377] Other modifiers were less selective in this thoroughly investigated test reaction.[159,378−381] On the basis of the observation that addition of a weak acid improved the ee, it was speculated that enantioselection might be attributed to interaction of the keto O atom of isophorone with the protonated aliphatic N atom of the bulky modifier adsorbed parallel to the Pd surface.

4.2.3. Pyrones

Hydrogenation of the pseudo-aromatic 4-hydroxy, 4-alkoxy, and 4-methyl derivatives of 2-pyrones to the corresponding dihydro- and tetrahydropyrones is highly selective on cinchona-modified Pd; the structural effects are illustrated in Scheme 13.[70] Partial hydrogenation of the 4-hydroxy derivative (entry 1) was slow and complicated by the saturation of the quinoline ring of the cinchona alkaloid.[382] Continuous feeding of the modifier during reaction sustained

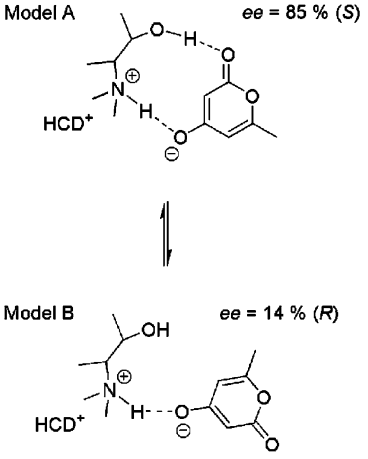


Figure 22. Schematic models for the interaction of protonated CD (HCD^+) with the deprotonated 4-hydroxy-6-methyl-2-pyrone (top-side view on the Pd surface).[384]

the initial good ee (85%) with an overall M/S ratio of around 5 mol %.[383] Replacement of the acidic OH function by a methyl or methoxy group (entries 2−7) eliminated this difficulty: The reactions were fast even under ambient conditions, affording good yields and 75−94% ees to the corresponding dihydropyrones. Only in one case (entry 7), the separation between the uptakes of 2 equiv of hydrogen was poor due to the missing stabilization by the methoxy group at the 4-position (an indication to the pseudo-aromatic character of the molecule), and the tetrahydropyrone formed with 99% de.

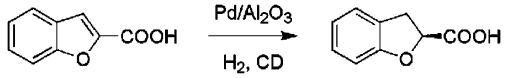
Catalytic experiments with CD and its O- and N-methyl derivatives revealed various competing interactions between the 2-pyrones and the alkaloid modifier, and the dominance of these interactions depended on the substrate, modifier, and reaction conditions.[384,385] The mechanistic models (Figure 22) suggested for the hydrogenation of the acidic 4-hydroxy-2-pyrone derivatives were supported by NMR and FTIR investigations and theoretical calculations. The origin of enantioselection in the best solvent acetonitrile is the bidentate complex (model A). A more flexible and less effective monodentate interaction (B) is dominant in strongly interacting protic solvents and for reactions where the O atom of the alkaloid is protected (MeOCD). Note that in the latter case even the opposite enantiomer forms in excess. Various other interacting complexes are feasible for the nonacidic 4-methoxy and 4-methyl derivatives, although these assumptions need further confirmation.[385]

4.2.4. Aromatic Compounds

The attempts for the enantioselective hydrogenation of aromatic compounds on Rh[386,387] and Ni[388−390] were barely successful, and the ee remained in the single-digit region. Cinchona-modified Pd is more promising for the hydrogenation of furan and benzofuran carboxylic acids, although the enantioselectivities are medium at best (Scheme 14).[391] The reactions are relatively slow, and the competing hydrogenation of the quinoline ring of CD necessitates high M/S ratios (2−15 mol %). Clearly, cinchona alkaloids and other modifiers that possess an aromatic ring as the "anchoring moiety" are not suitable for demanding hydrogenation reactions, particularly not on Pd and Rh, which are highly active in this side reaction.[286,383]

Spectroscopic measurements and ab initio calculations indicated that the origin of enantioselection is an acid dimer−

Scheme 14. Hydrogenation of Benzofuran Carboxylic Acid on 5 wt % Pd/Al_2O_3 by Stepwise Feeding of CD in the First 7 h (Cumulative M/S Ratio: 4.5 mol %, 2-Propanol, 30 bar, r.t., 23 h)[391]



Y = 29 %
ee = 50 %

Scheme 15. Pd-Catalyzed Hydrodehalogenation of an α,α-Dichloro Compound in the Presence of CN [in THF, at 3 bar and r.t.; Catalyst/Substrate Ratio (C/S), 60 Mass %; M/S, 47 mol %][400]

ee = 50 %

CD interaction analogous to that suggested for alkenoic acid hydrogenation (Figure 21).[392] The 1:1 type interaction is thermodynamically disfavored, and adsorption of the rigid complex on the Pd surface is hindered by geometrical constraints. The 2:1 stoichiometry is also supported by the almost equal efficiency of 1,2- and 1,3-amino alcohol and amino phenol type modifiers.[393]

4.3. Hydrogenation of C═N Bonds

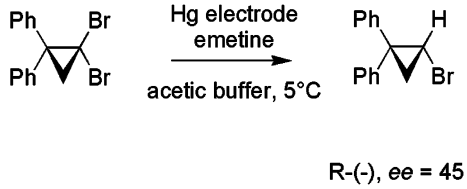
Enantioselective saturation of C═N bonds is a challenging reaction, and only chirally modified Pd revealed some enantioselectivity. Around 20% ee was achieved in the hydrogenation of a Schiff base on Pd/SiO_2 modified by L-alaninol or L-phenylalaninol[394] and in the reduction of an N-alkyl-α-iminoester on cinchona-modified Pd/Al_2O_3.[395] The enantioselectivity was slightly higher in some other reactions but only when the "modifier" was applied in a stoichiometric amount.[362,396] From a synthetic point of view, these reactions are uninteresting, and the weak interactions allowing only poor enantioselection are difficult to interpret.

4.4. Hydrodehalogenation

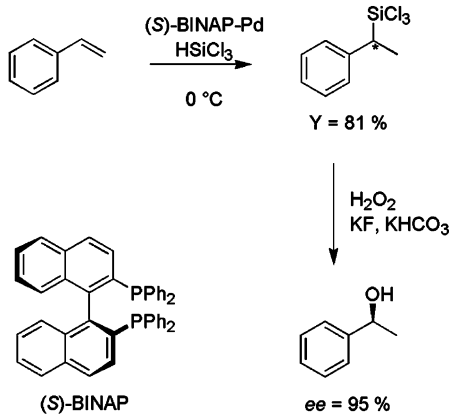
Supported Pd, commonly used in the presence of a base, is a highly active and chemoselective catalyst for the hydrogenolysis of carbon−halogen bonds.[397−399] Palladium was also outstanding in the enantioselective hydrodehalogenation of α,α-dichlorobenzazepin-2-one (Scheme 15).[400] CN-modified $Pd/BaSO_4$ in the presence of NBu_3 as a HCl acceptor afforded the monochloride with high chemoselectivity and up to 50% ee. The reaction could not be generalized to other α,α-dihalogen compounds and to other modifiers beyond the cinchona family. The unusually high catalyst and modifier concentrations necessary to obtain the best optical yield further limit the attractiveness of the method. The performance of various cinchona derivatives indicated that the crucial substrate−modifier interaction that controlled the enantioselection involved hydrogen bonding between the OH function of the modifier and the carbonyl group of the lactam; involvement of the quinuclidine N of the alkaloid was excluded.

From a mechanistic point of view, it is interesting to consider the early work on the electrochemical reduction of 1,1-dibromo-2,2-diphenylcyclopropane (Scheme 16).[401] The

Scheme 16. Enantioselective Electrochemical Monohydrodehalogenation on Emetine-Modified Hg[401]



Scheme 17. Enantioselective Synthesis of 1-Phenylethanol Via Hydrosilylation of Styrene on BINAP-Stabilized Pd Nanoparticles[71]



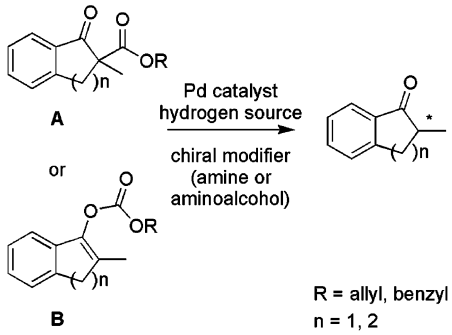
chemo- and stereoselective hydrogenolysis was carried out on a mercury electrode modified with different alkaloids, among which emetine performed best. Here, the authors attributed the stereochemical control to an interaction between the protonated N atom of the adsorbed alkaloid and the cycloalkyl bromide. Another application of chirally modified Hg is the enantioselective hydrodehalogenation of 3,3-dichloro-4,4-diphenyl-succinimide (26.5% ee with strychnine).[402]

4.5. Hydrosilylation

Catalytic asymmetric hydrosilylation of olefins[403] and the subsequent oxidation of the organosilicon compounds with retention of configuration[404,405] is a viable route to optically active alcohols. The Pd-catalyzed transformation of terminal olefins to 2-alkylsilanes in the presence of monodentate phosphine ligands is characterized by high rate and excellent regio- and enantioselectivity.[406,407] Spurred by the outstanding performance of chiral Pd complexes, chirally modified Pd nanoparticles were also tested in the hydrosilylation of styrene.[71] Colloidal Pd, stabilized by adding (*R*)- or (*S*)-BINAP [2,2′-bis-(diphenyl-phosphino)-1,1′-binaphthyl], catalyzed the reaction with trichlorosilane under very mild conditions (Scheme 17). Oxidation of the chiral organosilane with hydrogen peroxide gave (*R*)- or (*S*)-1-phenyl-ethanol, respectively, with high enantioselectivity.

For comparison, Pd complexes coordinated with BINAP are ineffective in hydrosilylation of olefins, probably because a bisphosphine chelate complex cannot offer a coordination site for the activation of the olefin.[408,409] This is a strong indication that hydrosilylation carried out with the Pd nanoparticle−BINAP system is a truly heterogeneous reaction involving metallic surface sites. In fact, racemic hydrosilylation catalyzed by colloidal or supported metals is well-demonstrated in the literature. In addition to Pt group metals and Ni, even bimetallic compositions with significant synergic effect between the components have been recommended as effective catalysts.[410−416]

Scheme 18. Pd-Mediated Enantioselective Formation of 2-Methylindan-1-one or 2-Methyltetral-1-one by Hydrogenolysis/Decarboxylation of β-Keto-ester A or Deprotection/Decarboxylation of Enol Carbonate B



4.6. Enol Isomerization (Domino Reactions)

The tautomeric equilibrium between ketones and enols is the basis of enantioselective protonation, a special route to optically active carbonyl compounds.[417−419] When a stereogenic carbon is in the α-position to the carbonyl group, addition of a base or acid catalyzes the deprotonation−protonation reaction, and both steps can be carried out enantioselectively. In enantioselective protonation, the transfer of the proton from a chiral source may be kinetically favored to either of the enantiofaces of the prochiral enol. The enol may be produced by various routes, including deprotection−decarboxylation of enol carbonates[72,420−422] and hydrogenolysis−decarboxylation of β-keto esters.[72,422−428] These two routes are usually performed as one-pot domino (cascade) reactions induced by homogeneous or heterogeneous catalysts; the latter is the topic of this section. An illustrative example is shown in Scheme 18. Removal of the benzyl or allyl group on Pd under hydrogenation conditions is followed by decarboxylation. The crucial step is then asymmetric protonation of the prochiral enolate, immediately after it has been produced, by using an amino alcohol or amine as the chiral protic source, or chiral modifier in our terms.

Many variations have been published for the cascade reactions; some substituted β-ketoesters (**1**,[72,422,424,428] **3**,[424] **5**,[423] **6**,[426,427] **7**,[426] and **8** + **9**[425]) and enol carbonates (**2a**,[72,421,422,424] **2b**,[420,422,424] and **4**[422,424]) as typical starting compounds are shown in Figure 23. The source of chirality is frequently a cinchona alkaloid, ephedrine, or 2-hydroxy-3-aminobornane, but a broad range of other amino alcohols and secondary amines have been applied successfully. The amount of chiral modifier varies between stoichiometric and catalytic; the latter requires a careful adjustment of the reaction conditions.[427] The absolute configuration of the ketone depends on the configuration of the carbon carrying the amino group, not the OH group, of the modifier.[422] The characteristics of supported Pd have a major influence on the reaction rate and enantioselectivity, but the origin of this effect could not be found.[423,428] Racemization on the Pd surface can diminish the enantioselectivity.[423]

There are only a few mechanistic studies available on the Pd-catalyzed cascade reactions.[72,421,425,426] In the first step starting from β-ketoesters, hydrogenolysis of the benzyl or allyl group gives the ketoacid intermediate that decarboxylates rapidly (Scheme 19).[72] The decarboxylation product is

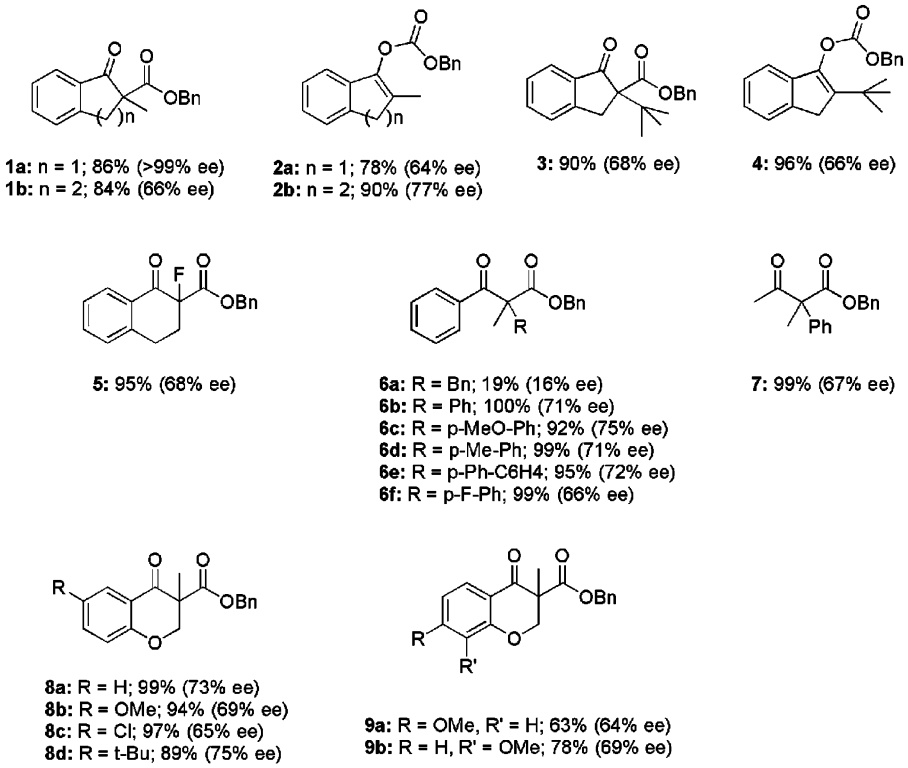
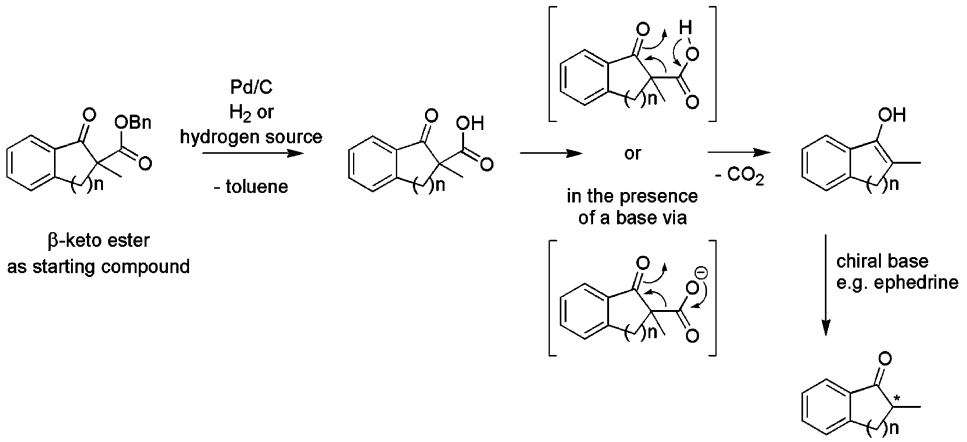


Figure 23. Starting compounds **1**−**9** have been used in the domino deprotection−decarboxylation−tautomerization sequence over heterogeneous Pd catalysts. Yields and the highest ees (in brackets) are given, and references can be found in the text.

Scheme 19. Feasible Reaction Mechanism for the Pd-Catalyzed Cascade Reaction[72]



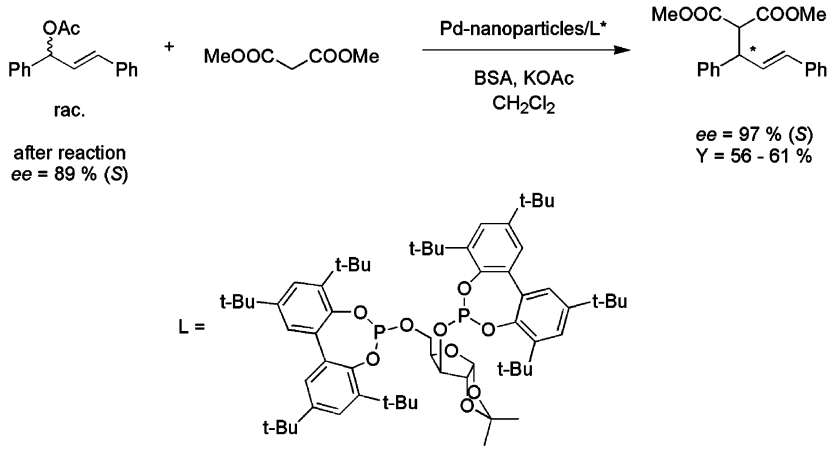
the enol, when the solvent (e.g., acetonitrile) is able to stabilize it via hydrogen bonding. The decarboxylation can proceed intramolecularly via a sigmatropic reaction, or it may be induced by the basic N atom of the amino alcohol by abstraction of the acidic proton; involvement of the Pd surface is also feasible.[426] Ketonization (protonation) of the enol may proceed via O-protonation, C-protonation, or a cyclic mechanism. A cyclic transition state might rationalize the role of the hydroxyl group of the amino alcohol modifier.[421]

Although some fundamental elements of the reaction route and the mechanism are known, the role of the metal surface in the enantioselection is unclear. Cinchona alkaloids (5−10 mol %) are good (homogeneous) catalysts of enantioselective decarboxylation,[429] but the reaction can also occur on the Pd surface where the acid is adsorbed (and activated) as a carboxylate after its formation. Arguments in favor of the latter route are the strong adsorption of carboxylic acids on Pd as carboxylates[430] and the facile decarboxylation of alkanoic acids on Pd(111) (the dominant crystallographic face on polycrystalline Pd) already at r.t.[431] Strong adsorption of CD on the Pd surface via the quinoline ring is also proven.[92] It seems that the prerequisites of enantioselection on the metal surface exist, but there is no experimental evidence yet for the participation of Pd in the enantioselective reaction step.

4.7. Allylic Substitution

Palladium complexes are first choice catalysts for asymmetric allylic substitution reactions, but many other metals have been used as well.[432,433] Since its discovery in 1965,[434] allylic substitution has been rarely attempted heterogeneously,[435−437] and up to now, only two cases of enantioselective allylic substitution on chirally modified metals have been reported.[73,437] Jansat et al.[73] compared the efficiency of Pd nanoparticles stabilized by a chiral diphosphite[438,439] and the related chiral homogeneous complex in the alkylation of *rac*-3-acetoxy-1,3-diphenyl-1-propene with dimethylmalonate (Scheme 20). The enantioselectivity of the hetero-

Scheme 20. Enantioselective Allylic Alkylation on Pd Nanoparticles Stabilized by a Chiral Xylofuranoside Diphosphite [r.t., 24−168 h; BSA, *N*,*O*-Bis(trimethylsilyl)acetamide][73]



geneous reaction was higher (97 vs 90% ee), and the yield was considerably lower than that of the homogeneous process.

A critical question is whether the alkylation reaction was catalyzed by the metal surface or small amounts of dissolved Pd were the active species. Discrimination between homogeneous and heterogeneous catalysis is a delicate task,[440,441] since the heteroatom-containing ligand may facilitate the leaching and the dissolved metal can (partially) redeposit at the end of the reaction, as reported for some Pd-catalyzed heterogeneous Heck[442−444] and Suzuki[445−447] reactions. In the case of the allylic alkylation reaction in Scheme 20, an indication for heterogeneous catalysis is the different kinetic behavior of the colloidal and molecular systems. The heterogeneous reaction could not be run to completion; instead, a high kinetic resolution occurred. The (*R*)-enantiomer reacted twice as fast as the (*S*)-enantiomer with the Pd complex while a kinetic preference by a factor of 12−20 was observed for colloidal Pd, resulting in strong enrichment in substrate and product over the metal surface. This kinetic resolution might be attributed to the enhanced stereoselectivity that is inherent to a heterogeneous system (shielding from one side), exploited already earlier.[435]

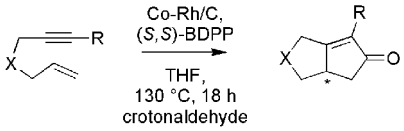
The reaction in Scheme 20 (with diethylmalonate instead of dimethylmalonate) was carried out by another group in water using (*R*)-BINAP-modified Pd/C.[437] With this catalyst system, the yield (21%) and ee (80% to the (*R*) product) were significantly lower.

4.8. Pauson–Khand Reaction

Various Co, Ti, Ru, and Rh complexes catalyze the Pauson−Khand reaction, the [2 + 2 + 1] cycloaddition of an alkyne, an alkene, and carbon monoxide to form cyclopentenones.[448−450] The enantioselective version of the catalytic reaction is relatively new; the first report on a chiral titanocene complex appeared in 1996.[451] Cobalt nanoparticles usually immobilized on charcoal or silica emerged as a practical, recyclable alternative to homogeneous catalysts.[452−456]

Bimetallic Co−Rh, Co−Ru, and Co−Pd particles are more active than monometallic Co, but the real nature of the synergic effect of the noble metal component is unknown.[457−459] The addition of C_2 symmetrical chiral diphosphine ligands (modifiers) to a Co−Rh/C catalyst induced significant enantioselectivity; the most effective among them was (*2S*,*4S*)-(−)-2,4-bis(diphenylphosphino)pentane [(*S*,*S*)-BDPP].[460] Various enyne substrates were converted using BDPP-modified Co−Rh/C, and the yields and enantioselectivities were comparable to, or even better than, those achieved with homogeneous catalysts (Scheme 21). The commonly used mercury-poisoning experiment indicated that the catalyst was truly heterogeneous. No mechanistic model exists for the interpretation of enantioselection, and also, the functioning of the homogeneous counterpart is poorly understood.[448]

Scheme 21. Intramolecular Pauson−Khand Reactions on Charcoal-Supported Co−Rh Bimetallic Nanoparticles Chirally Modified by (*S*,*S*)-BDPP; Crotonaldehyde Is Used as a Substitute for CO[460]



X	R	yield (%)	*ee* (%)
O	Ph	91	84
O	Bu	75	62
O	Me	85	80
para-tosyl-N	Ph	94	85
$(MeOOC)_2C$	Me	92	56
$(MeOOC)_2C$	Ph	89	64
$(EtOOC)_2C$	Me	93	87
$(EtOOC)_2C$	Ph	94	51

Gaseous CO is commonly replaced by an aldehyde that decarbonylates on the transition metal. An attractive, atom-economic solution is the use of an α,β-unsaturated aldehyde as the source of CO and the alkene reactants.[450]

4.9. Hydroformylation

Enantioselective hydroformylation of olefins with synthesis gas is a demanding reaction, which also needs careful control of the chemoselectivity to avoid hydrogenation and isomerization and the regioselectivity, which is the ratio of branched to linear aldehydes.[461,462] Very recently, Chinese scientists have uncovered a new method using highly dispersed Rh/SiO_2 and chiral diphosphine modifiers.[463] The highest enantioselectivity was achieved with BINAP (72% ee) in the hydroformylation of vinyl acetate at 60 °C and 50 bar. The chemoselectivity was also excellent−100% to the branched aldehyde. A strong limitation to practical applica-

tion is the very low conversion of only 5%; at higher conversion, the enantioselectivity dropped. Good performance of the catalyst required an astonishingly high modifier/Rh molar ratio of around unit, although the (expected) strong adsorption of the chiral modifier on Rh was proved by ^{31}P MAS NMR and by the competitive adsorption of CO. Even more unusual is the "steplike" correlation between the BINAP/Rh ratio and the enantioselectivity; the racemic product formed below a BINAP/Rh ratio of 0.6, but the maximum ee was obtained at a ratio of 0.9 or above. It was speculated that enantioselection occurred only when all unmodified sites were eliminated at sufficiently high BINAP concentrations.

5. Chirally Modified Metals: Special Aspects

In this section, we discuss some phenomena that have attracted great interest in the past years, and they will probably remain in the focus in the near future due to the unsatisfactory understanding of their origin.

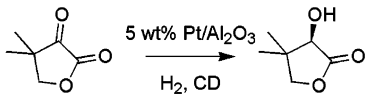
5.1. Structure Sensitivity—Catalyst Restructuring

A fundamental difference between homogeneous catalysis with chiral metal complexes and heterogeneous catalysis at chirally modified metal surfaces is the replacement of the central metal atom—the active site—by the metal surface. Obviously, the surface structure should have a strong influence on the adsorption of substrate and modifier and on their interaction resulting in enantioselection, but studies in this direction are in an early stage.

An illustration to the complex and poorly understood role of metal surface is the sometimes dramatic influence of catalyst pretreatments. Effective and widely used procedures are (i) the corrosive pretreatment of Raney Ni,[55,76,300,306] (ii) prereduction of supported Pt[143,203,293] and Pd[69,391,395,464] in hydrogen at elevated temperature in the gas phase or in solution, and (iii) ultrasonication of Pt,[56,465−467] Pd,[347,369] and Ni[468−470] in solution in the presence of the modifier. These empirically developed techniques are highly catalyst specific. Taking the example of the hydrogenation of pyruvate esters on cinchona-modified Pt, 95−98% ee was obtained without any pretreatment on small Pt nanoparticles stabilized by polyvinylpyrrolidone[60] and on a commercial Pt/Al_2O_3,[287] and on Pt/Al_2O_3 only after a hydrogen treatment at 400 °C with[471,472] or without[61] a subsequent sonication step in solution. The only conclusion that may be deduced is that there are several alternative routes toward a highly selective, chirally modified surface.

In the case of Raney Ni, the positive effect of catalyst pretreatment in acidic medium in the presence of bromide ions has been attributed to corrosive restructuring (etching).[53,55] The remarkable selectivity enhancement after reductive heat treatment of supported Pt was originally attributed to complete reduction of surface metal oxides.[144] Because M^0 sites are considered as the real active sites of all reactions discussed in section 4, it is understandable that prereduction of the supported Pt group metal catalyst stored under air influences the performance. Complete prereduction of Pt requires forcing conditions only for very small particles on oxide supports.[473,474] For most other cases, the dominant effect of heat treatments is probably adsorbate (hydrogen, and oxgen, and in situ produced water)-induced restructuring of the metal particles,[475] a phenomenon thoroughly investigated by surface scientists.[476−479] The effect of adsorbate-induced restructuring of Pt/Al_2O_3 is illustrated in Scheme 22. Pretreatment in the gas phase in flowing hydrogen doubled the enantioselectivity as compared to the oxidative treatment in air under otherwise identical conditions.[475] Redispersion of the Pt particles was clearly detectable by high-resolution transmission electron microscopy (HRTEM), and the change in enantioselectivity after reductive and oxidative treatments showed excellent reversibility: The last treatment always controlled the ee. Restructuring of the metal particles changes the relative abundance of special surface sites[480,481] that influences the adsorption of the reaction components. Also, sonication of the catalyst prior to the enantioselective reaction leads to severe structural changes as indicated by the shifts in the metal particle size distributions.[216,471] Unfortunately, the sites responsible for the higher or lower enantioselectivity could not be identified in these studies.

Scheme 22. Reversible Effects of Reductive and Oxidative Catalyst Treatments at 400 °C in a Flow-Through Reactor on the Subsequent Hydrogenation of Ketopantolactone (Toluene, 70 bar, −9 °C, 2 h[475a]



pretreatment	conv. (%)	*ee* (%)
no	99	46
H_2	87	89
air	97	46
H_2 → air	99	44
H_2 → air → H_2	95	89

[a] After oxidative pretreatment at 400 °C, the catalyst was reduced by hydrogen at r.t. at the beginning of ketopantolactone hydrogenation.

The importance of surface morphology of small supported Pt particles was confirmed by Attard's work on Bi- and S-poisoned Pt/graphite catalysts.[482,483] A cyclic voltammetric analysis indicated that surface step sites were more enantioselective than terraces. A limitation of the study was that bismuth and tin poisoning also influenced the extent of side reactions (e.g., pyruvate dimerization), and surface impurities might hinder the unambiguous localization of the observed shifts in enantioselectivity. This limitation is probably valid to many other studies where the highly reactive ethyl pyruvate is used as a model substrate since hydrogenation of this compound is complicated by extensive side reactions.[232] Reductive and oxidative pretreatments of Pt/Al_2O_3 are accompanied by the removal[484] or formation[485,486] of impurities on the metal surface, and these treatments strongly influence the adsorption of cinchona alkaloids.[7,90,487] We assume that the contradictory observations on the effect of metal particles size on enantioselectivity in various reactions are partly due to different surface impurities originating from catalyst preparation and to side reactions that are also structure sensitive (for examples on pyruvate hydrogenation, see refs 46, 238, 481, and 488−491).

Selectivity enhancement induced by restructuring of the metal particles during transformation of the substrate is an intriguing phenomenon that demonstrates the structure sensitivity of enantioselective reactions. Although there are numerous reports on the variation of enantioselectivity at low conversion ("initial transient period")[79,100,233,264,492−494] or during long-term use of chirally modified metals,[197,209,211,305,495−504]

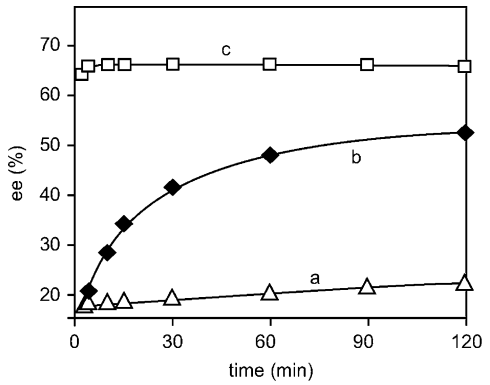


Figure 24. Variation of ee with time during the hydrogenation of 3,5-bis(trifluoromethyl)acetophenone to the corresponding alcohol on CD-modified Pt/Al_2O_3 (toluene, 1 bar, r.t.). Curve a, no catalyst pretreatment; curve b, catalyst is prereduced in H_2 at 400 °C; and curve c, catalyst is prereduced in H_2 at 400 °C, and then, the reaction mixture was stirred under N_2 for 1 h before H_2 was introduced.[505]

there is only one example where metal restructuring was verified as the origin of the phenomenon.[505] In the hydrogenation of 3,5-bis(trifluoromethyl)acetophenone, the intrinsic enantioselectivity of CD-modified Pt was low but increased continuously with time (Figure 24, curve b). Stirring the slurry under nitrogen before introducing hydrogen tripled the initial selectivity (Figure 24, curve c). A considerable redistribution of the Pt particles during preconditioning was evidenced by TEM, but no correlation between the particle size and ee could be deduced. It is very probable that the quinoline fragment of CD ("anchoring moiety") is responsible for the restructuring since replacement of CD by quinoline led to almost the same effect; that is, the chirality of the modifier did not play a role. Reductive treatment at elevated temperature activated the catalyst for the subsequent restructuring in the liquid phase (compare curves a and b in Figure 24).

To sum up, we consider the structure sensitivity of enantioselection as a field where scientific understanding would require studies on well-defined (single crystal) surfaces. It is difficult to find unambiguous correlations between enantioselectivity and surface structure when conventional metal catalysts are applied, which possess heterogeneous structures (broad range of particle size and shape) with inevitable surface impurities.

5.2. "Ligand Acceleration"

The higher reactivity of chirally modified metals compared to the unmodified metals, frequently termed as "ligand acceleration" based on the analogous phenomenon in homogeneous catalysis, is a widely debated feature of these catalysts. In the light of classical heterogeneous catalysis, the early observation is indeed fascinating: Quinoline and its derivatives are well-known poisons of metal hydrogenation catalysts,[506,507] but the addition of CD, a bulky quinoline derivative that adsorbs strongly and occupies a large fraction of active sites, increases remarkably the rate of ethyl pyruvate hydrogenation on Pt/Al_2O_3.[78,117,492,495,508−510] Later, rate acceleration induced by the addition of CD was perceived in the hydrogenation of several other activated ketones on Pt,[65,66,267,274,276,293,297,511,512] Pd,[341] Rh,[49,148−150,152] and Ir[161] and also in the presence of other chiral modifiers.[169,187,190,191,341,513] On the other hand, there are numerous examples where the modified and unmodified reactions run with comparable rates, or even the latter is faster significantly. The relative rate on modified and unmodified metals may vary within a substrate class[267] or by small, apparently unimportant changes in the modifier structure,[180,514] and these deviations cannot be attributed to mechanistic differences.

Before discussing the origin of the phenomenon, we have to address the confusion in the literature concerning the definition of "ligand acceleration". In homogeneous catalysis, a ligand-accelerated reaction means that the enantioselective cycle is faster relative to the racemic cycle.[515] Analogously, in heterogeneous catalysis, the modifier enhances the rate at the enantioselective surface sites over the rate at the unmodified sites that afford racemic product. The modifier occupies a fraction of surface sites and thus generates chirally modified surface sites, but the number of modified and unmodified sites is unknown. Hence, from the overall or apparent reaction rate, we cannot deduce the intrinsic rate at the modified sites that would be important to understand the phenomenon at the molecular level. In other words, macroscopic observation of rate acceleration indicates unambiguously the phenomenon, but a lower overall reaction rate after addition of the modifier cannot exclude some "ligand acceleration" at the molecular level (which might be the case on chirally modified Pd).[154,347,378,379,383,391,464,516]

Interpretation of the rate acceleration is complicated by numerous side reactions, particularly in the hydrogenation of α-ketoesters.[232] The byproducts may occupy an unknown fraction of the active sites and makes the interpretation of the relative rates even more ambiguous. It was suggested[483,517,518] that the major role of cinchona modifiers would be to suppress catalyst deactivation due to pyruvate polymerization on Pt[86] and alumina.[519] The simplest way to avoid this complication is to consider those reactions where the kinetic data are not distorted by poorly controlled side reactions. In contrast to the transformation of acyclic α-ketoesters, hydrogenation of ketopantolactone is not complicated by the aldol reaction due to the missing α-H atom, and decarbonylation by Pt was barely detectable by ATR-IR spectroscopy.[81] The rate acceleration induced in this reaction by various chiral modifiers on Pt[191,274] and Rh[152] clearly contrast the concept that "ligand acceleration" would be linked to catalyst deactivation and not to the enantiodifferentiating step.

In the hydrogenation of acetophenone and trifluoromethylacetophenone derivatives on CD-modified Pt/Al_2O_3, the conversion rates and enantioselectivities varied strongly with the nature of the aromatic substituents.[220,291] The different reactivities were traced to the electronic (and steric) effect of the substituents and to hydrogen-bonding interactions between the quinuclidine N atom of the alkaloid and the carbonyl group of the substrate.[296,327] Theoretical calculations revealed a linear correlation between the logarithm of the reaction rate and the highest occupied molecular orbital and lowest unoccupied molecular orbital stabilization ΔE_{orb} of the carbonyl compounds, relative to the reference compound (Figure 25). The relative orbital stabilization is defined as the sum of two numbers: the difference between the energy of the antibonding orbital of the reference compound acetophenone and that of the substituted acetophenone, and the corresponding energy difference for the bonding orbitals. The more stabilized the orbitals of the substituted acetophenone are, the larger ΔE_{orb} and the reactivity of the molecule are. According to these calculations (where the metal surface was not involved), the origin of "ligand acceleration" is the lowering of the π-orbitals in the

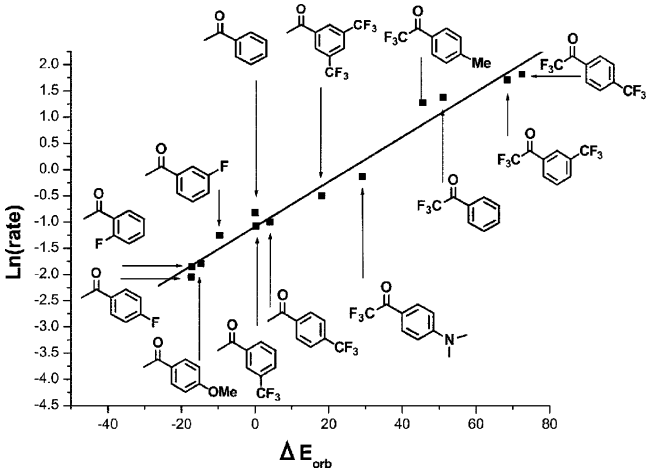


Figure 25. Linear correlation between the logarithm of the hydrogenation rate (mmol h^{-1}) of acetophenone and 2,2,2-trifluoroacetophenone derivatives and the relative orbital stabilization ΔE_{orb} (see the text). Reprinted with permission from ref 327. Copyright 2002 Royal Society of Chemistry.

diastereomeric complex of the substrate and modifier. In the pro(*R*) and pro(*S*) complexes, the carbonyl π-orbitals are differently stabilized, which results in different intrinsic rates in the formation of the two enantiomers. It remains, however, to be proven that the concept can be extended to other substrates and reaction types.

5.3. Inversion of Enantioselectivity

Variations in the catalyst composition or the reaction conditions may have a large influence on the enantioselectivity of chirally modified metals and sometimes even the sense of enantioselection changes. (Application of the opposite enantiomer, another diastereomer, or another chiral compound as modifier may give the opposite enantiomer of the product in excess, but this case is not considered here.) The switch in chirality provides valuable hints to the nature of modifier−substrate−metal surface interactions, with the supplementary advantage that the information is related to truly in situ conditions. The observed inversions may be classified according to the parameter varied: (i) solvent composition, including variations in polarity[253,258,266,520,521] and addition of an acid[258,259,262,522] or water;[523] (ii) modifier concentration;[242,362,524,525] (iii) temperature of catalyst modification (Ni−glutamic acid system);[30] (iv) catalyst support (C or Al_2O_3);[521] (v) cleaning of the continuous reactor (removal of the soluble fraction of the modifier);[526] (vi) size of the ester group in the substrate (Me or Et ester);[521] (vii) reaction time (probably induced by transformation of the modifier during reaction);[194,524] and (viii) structure of the modifier while preserving the stereogenic centers, including protection of the OH function of CD by methyl[177,258,259,291,344] or other bulkier groups[152,174,180,219,258,260,527,528] and protection of both N and OH functions.[275] The inversion induced by replacing CN with β-isocinchonine[265] does not belong here since the latter compound represents a new modifier with an additional stereogenic center.[529]

In many cases, the enantioselectivities are low and interpretation of the inversion is barely possible due to the corresponding small energy difference. The examples discussed below in more detail elucidate some aspects of the reaction mechanisms.

A feasible explanation for the special effect of carboxylic acids, leading in extreme cases to inversion of the major

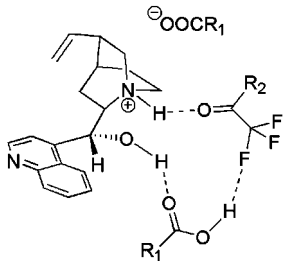


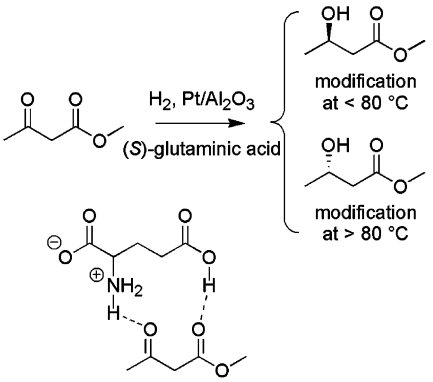
Figure 26. Feasible structure of the modifier−carboxylic acid (R^1-COOH)−substrate interaction without considering the adsorption on the metal surface and using the example of CD and a fluorinated ketone substrate (R^2CO-CF_3).[530]

enantiomer, is the change of the reaction mechanism.[530,531] IR spectroscopy revealed that CD (and probably also other 1,2-amino alcohols) forms 1:1 and 2:1 type acid:modifier complexes that are analogous to the substrate−modifier interactions in the Pd-catalyzed hydrogenation of alkenoic acids.[356,357] These complexes represent the actual modifier that interacts with the substrate as illustrated with one example in Figure 26. The model predicts that changes in enantioselectivity are intrinsically coupled with a lower reaction rate,[530] in agreement with the experimental observations.[259,530]

Inversion of the major enantiomer in the hydrogenation of ethyl pyruvate[262] and ketopantolactone[522] on Pt modified by β-isocinchonine was explained differently. Bartók et al. assumed that in toluene the nucleophilic quinuclidine N of the modifier interacts with the electrophilic C of the keto carbonyl of the substrate, while in acidic medium the protonated N atom interacts with the O atom of the ketone via H-bonding.[262] This interpretation, however, contradicts numerous other experimental observations. The addition of an acid does not induce inversion in these reactions when the parent cinchona alkaloids or other amine type modifiers are used as modifiers.[1,3,165] Besides, both (*R*)- and (*S*)-lactate were produced by β-isocinchonine-modified Pt in toluene by changing the reaction conditions,[262,532] and there was no inversion by acid addition in the hydrogenation of various other α-ketoesters on the same catalyst.[198] It is very unlikely that the reaction mechanism would change within a substrate class. We assume that the exceptional behavior of β-isocinchonine, induced by subtle variations in the reaction conditions or substrate structure, should be attributed to changes in the adsorption mode of this rigid molecule on the metal surface leading occasionally to inversion.

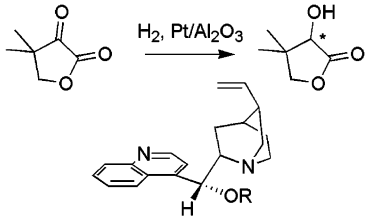
Many years ago, Japanese scientists made the astonishing observation that the performance of Raney Ni modified by (*S*)-glutamic acid strongly depended on the catalyst modification temperature.[30] The (*R*)-enantiomer formed in excess in the hydrogenation of methyl acetoacetate when the catalyst was modified under ambient conditions, but the ee decreased with increasing modification temperature, and above 80 °C, the major product was inverted (Scheme 23). On the basis of RAIRS and STM studies, Baddeley and co-workers attributed the inversion to fundamental changes in the adsorption and interaction of modifier and substrate.[97,533] At r.t. and low surface coverage, glutamic acid adsorbs on Ni(111) in a zwitterionic form, and the subsequently added methyl acetoacetate adsorbs on the modified surface as a diketone with the molecular plane lying parallel to the surface. The modifier and the ketone probably interact via two H-bonds involving the protonated amine and the keto O atom as the dominant interaction. This interaction leads

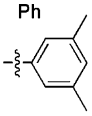
Scheme 23. Inversion of the Major Enantiomer in the Hydrogenation of Methyl Acetoacetate on Raney Ni Modified by (*S*)-Glutamic Acid[a]



[a] The inversion is induced by increasing the catalyst modification temperature.[30] The interacting complex at ambient temperature is shown below (top view).[97]

Scheme 24. Inversion of Enantioselectivity in the Hydrogenation of Ketopantolactone on Pt/Al_2O_3 Modified by Bulky Ether Derivatives of CD ($PhCF_3$, 40 bar, r.t., Full Conversion)[528]



R	*ee* (%)
H	73 (*R*)
Me	40 (*R*)
Et	47 (*R*)
$Si(CH_3)_3$	51 (*S*)
Ph	50 (*S*)
	53 (*S*)

preferentially to the (*R*)-product. When the surface modification is carried out at a higher temperature, the β-ketoester adsorbs in the enol form and the adsorption geometry switches from parallel to approximately perpendicular to the single-crystal surface. Interestingly, ordered arrays of glutamic acid are formed at high surface concentration of the modifier, and this modified surface is catalytically inactive since the β-ketoester cannot adsorb onto Ni.

Protection of the OH group of cinchona alkaloids by methylation is a frequently used approach to clarify the role of this function in the substrate−modifier interaction.[163] The loss of enantioselection or formation of the opposite enantiomer with a small ee is commonly interpreted as evidence for the involvement of the OH group (beside the basic quinuclidine N atom) in the enantiodifferentiating complex. An intriguing case is when the OH group is not involved in the substrate−modifier interaction and the same enantiomer is formed in excess in the presence of CD or *O*-methyl-CD, but with increasing bulkiness of the ether group, the ee gradually decreases or even the opposite enantiomer becomes dominant (Scheme 24). The inversion has been confirmed in the hydrogenation of various activated ketones on Pt[174,180,258,260,527,528] and Rh.[152,286] ATR-IR spectroscopy and DFT calculations indicated that introduction of a bulky ether group restructures the chiral sites available for adsorption of the substrate on the metal surface, partly due to the steric effect of the ether group and partly to the repositioning of the quinuclidine moiety, the interacting function of the modifier.[219] This switch in the sense of enantioselection demonstrates the crucial importance of the adsorption mode and conformation of the modifier during interaction with the substrate, the least understood element of the existing mechanistic models.

5.4. Nonlinear Phenomenon

The nonlinear effect (NLE) in homogeneous asymmetric catalysis is attributed to molecular interactions (associations) between two enantiomers of the auxiliary or ligand.[534,535] The concept has been extended to diastereomers and even to chemically different compounds that give products of opposite configuration.[536−538] This "extended" nonlinearity has been studied in heterogeneous catalysis, with only one exception.[539] We termed the nonlinear behavior of modifier mixtures in heterogeneous catalysis "nonlinear phenomenon" to clearly separate it from NLE in homogeneous catalysis.[539]

Technically, the nonlinear behavior of modifier mixtures can be studied in three different setups. In the classical "static" method, the reaction is simply carried out in a batch reactor using mixtures of two modifiers.[540] A transient method can also be applied in a batch reactor by starting the reaction with one modifier, and after a short period, a second modifier is added in an equimolar amount.[524] According to the third approach, the reaction is carried out in a continuous flow reactor and the "disturbance" induced by a switch from one modifier to another in the feed is followed.[101] The latter two transient methods give insight into the dynamics of modifier competition at the metal surface.

At first, Wells et al.[540] observed some nonlinearity in pyruvate hydrogenation on Pt modified by mixtures of cinchona alkaloids in a batch reactor. They attributed the deviation from the expected (calculated) ee to differences in the adsorption strength of the modifiers. Very recently, this interpretation was corroborated by time-lapse STM studies on a Pt(111) surface.[98] Tungler et al. found a unique behavior of mixtures of dihydrocinchonine and dihydrovinpocetine in the hydrogenation of isophorone: Either the cinchona or the vinca alkaloid controlled the enantioselection, depending on the catalyst used (Pd or Pd/TiO_2).[155] Later, analysis of the nonlinear phenomenon became a common tool to characterize the adsorption of various modifiers under reaction conditions on Pt,[180,188,228,265] Pd,[61,524] and Rh,[152] including the kinetic aspects of the competing enantioselection.[101,541,542]

A systematic study revealed a linear behavior of mixtures of the two enantiomers (*R*,*R*)- and (*S*,*S*)-PNEA (Figure 3) in ketopantolactone hydrogenation on Pt in a batch reactor.[539] This result is in agreement with the majority of the mechanistic models of ketone hydrogenation assuming 1:1 type modifier−substrate interactions and provides indirect evidence against the relevance of long-range ordering of chiral modifiers on the metal surface. A small deviation from the ideal behavior was observed when mixtures of two diastereomers (*R*,*S*)- and (*S*,*S*)-PNEA were used. Considerable nonlinearity was detectable only when the anchoring moieties of the modifiers were different, corroborating the

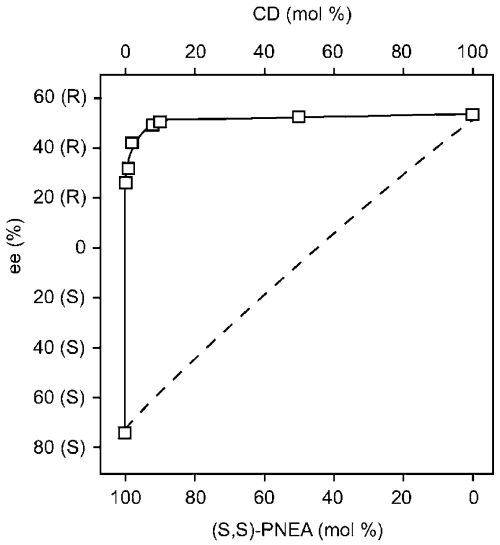


Figure 27. Nonlinear behavior of mixtures of CD and (*S*,*S*)-PNEA (Figure 3) in the hydrogenation of ketopantolactone (Pt/Al_2O_3, acetic acid).[539] The theoretical ee (dashed line) was calculated with the assumption that the molar ratios of the modifiers in solution and on the Pt surface are identical and that the reaction rates and ees are linear combinations of those measured with each modifier alone.

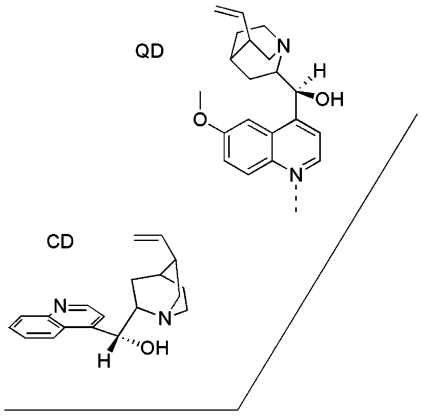


Figure 28. Competitive adsorption of CD (dominant modifier, "parallel" adsorption mode) and QD (inferior modifier, "tilted" adsorption mode) on Pt or Pd.[524,541]

crucial importance of the adsorption strength of the modifiers. In some extreme cases, less than 1 mol % of the more strongly adsorbing modifier in the mixture was sufficient to invert the major enantiomer (Figure 27).[527,539] An essential conclusion from this study is that, although strong adsorption is a crucial requirement for an efficient modifier, there is no positive correlation between the adsorption strength and the enantioselectivity achieved with the modifier alone.[539]

The primary reason for the nonlinear phenomenon is the different adsorption strength of the modifiers on the metal surface.[98,540] The energy difference, however, does not necessarily result in the expected big difference in the surface concentrations of the modifiers.[524] The imbalance is traced to the different adsorption modes of the modifiers, as illustrated in Figure 28 on the example of CD and QD.[541] According to this concept, the dominant modifier CD adsorbs mainly via the quinoline ring being parallel to the metal surface while the inferior modifier QD adsorbs more weakly in a tilted position of the aromatic ring. The latter geometry disfavors the interaction with the ketone substrate in the enantiodifferentiating step; thus, the inferior modifier may be considered mainly a spectator species. When the inferior modifier is used alone, it can adopt parallel adsorption via the aromatic ring system and allow high ee. This interpretation is supported by the competitive hydrogenation of the two modifiers on Pt/Al_2O_3.[541] Hydrogenation of the quinoline ring of CD and QD occurred at similar rates when only one alkaloid was present, indicating a similar, parallel adsorption geometry of the alkaloids via the quinoline rings. In contrast, in an equimolar mixture, the rate of CD hydrogenation was higher by more than an order of magnitude. Recently, the different adsorption modes of CD and QD when they are present simultaneously on Pt have been confirmed by ATR-IR spectroscopy.[101]

The practical importance of the nonlinear phenomenon is that cheap but low purity chiral compounds can be applied as effective modifiers if the impurities adsorb weakly. This fortunate situation allows one to achieve 98% ee with CD, although the alkaloid contains considerable amounts of QD that affords the opposite enantiomer in excess.[61] On the other hand, only traces (<0.1 mol %) of a strongly adsorbing impurity can distort the enantioselectivity and lead to a false conclusion in a mechanistic study. Several cinchona derivatives belong to this category as the parent alkaloids adsorb much stronger on the metal surface.[219,522,527]

6. Summary

The state of art in the practical heterogeneous catalytic synthesis of chiral compounds is reviewed in the light of the fundamental features of chiral surfaces. Despite the remarkable development in the past years, many details of the interaction of substrate and chiral modifier at the metal surface remain to be worked out. We hope that this critical review aids in improving the understanding of enantioselection at the molecular level and provokes further research in this fascinating area of heterogeneous catalysis.

A comparison of the literature of homogeneous and heterogeneous enantioselective catalysis reveals several differences. An important deviation is the relatively narrow application range of enantioselective catalysis at chiral surfaces. We consider this as a sign of the early stage of development and look forward to increasing involvement of synthetic chemists to accelerate the advance. The recent extension of the application of chirally modified metals beyond catalytic hydrogenation has been hopefully only the beginning of a positive development in this direction. From a synthetic point of view, the simple approach of chiral modification of metals provides easy-to-handle catalysts that in some reactions are highly efficient and represent a technically attractive and cheap alternative to soluble transition metal complex catalysts.

7. Abbreviations

ATR-IR	attenuated total reflection infrared (spectroscopy)
BDPP	2,4-bis(diphenylphosphino)pentane
BINAP	2,2′-bis-(diphenyl-phosphino)-1,1′-binaphthyl
CD	cinchonidine
CN	cinchonine
C/S	catalyst/substrate ratio (mass %)
de	diastereomeric excess
DHVIN	(−)-dihydroapovincaminic acid ethyl ester
ee	enantiomeric excess (%)
M	metal
HCD	10,11-dihydrocinchonidine
HRTEM	high-resolution transmission electron microscopy
MeOCD	*O*-methyl-cinchonidine

MeOHCD	*O*-methyl-10,11-dihydrocinchonidine
M/S	modifier/substrate molar ratio
NED	1-naphthyl-1,2-ethanediol
PNEA	pantoylnaphthylethylamine
QD	quinidine
QN	quinine
RAIRS	reflection absorption infrared spectroscopy
r.t.	room temperature
STM	scanning tunneling microscopy
TFA	trifluoroacetic acid
TOF	turnover frequency (h^{-1})
Y	yield (%)

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