

VI RUSSIAN CONFERENCE  
ON CATALYTIC REACTION MECHANISMS  
(Moscow, October 1–5, 2002)

# Mechanisms of Asymmetric Heterogeneous Catalysis<sup>1</sup>

D. Yu. Murzin, P. Mäki-Arvela, and T. Salmi

Laboratory of Industrial Chemistry, Åbo Akademi, Turku Åbo, Finland

e-mail: dmurzin@abo.fi

Received October 9, 2002

**Abstract**—Asymmetric catalysis plays an important role in present-day production of pharmaceuticals. It can be predicted that enantioselective catalysis will dominate in the future, replacing conventional stoichiometric methods. Heterogeneous catalysts offer several advantages compared to their homogeneous counterparts. In the present review mechanisms of asymmetric heterogeneous catalysis are discussed and the different ways of chirality transfer are addressed. Enantioselection is possible over chiral supports and chiral metals exhibiting intrinsic chirality, as well as over modified metal supported catalysts. The interactions between a reactant and a modifier are very specific being critical for achieving high enantioselectivities.

## INTRODUCTION

Optically active drugs, fragrances, and agrochemicals are of extremely high importance and due to the natural chirality of the human body interact differently with different enantiomers. One of the awful examples of the detrimental influence of the wrong isomer is the administration of thalidomide to pregnant women at the beginning of the 1960s. This drug was produced in the racemate form, and the wrong enantiomer led to birth defects [1, 2]. The importance of research in the field of asymmetric catalysis is recognized by the fact that the Nobel Prize in chemistry in 2001 was given to Knowles, Noyori, and Sharpless, who investigated asymmetric homogeneous oxidations and hydrogenations. Not only the scientific community, but also the business world is nowadays fully aware of the benefits of optically active drugs. It is reflected in the fact that the sales of optically active drugs have grown over threefold over the period 1994–1999, reaching US\$115 billion in 1999 [3, 4].

There exist different methods of preparing optically active compounds like kinetic resolution, enzymatic and microbial transformations, and asymmetric synthesis and catalysis [5]. Asymmetric synthesis uses stoichiometric amounts of reactants producing stoichiometric amounts of waste. In asymmetric catalysis, very selective homogeneous metal–ligand complexes are used; however, these ligands are difficult to separate and reuse. The easy separation of heterogeneous catalysts makes them industrially very attractive. Enantioselectivity is often lower over heterogeneous catalysts than over the homogeneous counterparts [6], and the range of reaction types is still quite limited [7]. The selectivity in several reactions using modified heterogeneous catalysts has reached high levels (over 95%). Modified heterogeneous catalysts are, however, very

reactant and modifier specific. Further progress suffers from our lack of deeper knowledge of the reaction mechanism.

Several kinds of reviews have been written in enantioselective heterogeneous catalysis. Two general reviews deal with all types of enantioselective reactions over heterogeneous catalysts [8, 9]. The application of enantioselective catalysts for the production of fine chemicals was recently reviewed by Blaser *et al.* [5]. Most articles devoted to enantioselective catalysis deal with hydrogenation reactions. Some other reactions to be mentioned are carbene addition [in ref. 9<sup>[49]</sup>], isomerization, dehydration [in ref. 9<sup>[8]</sup>], [in ref. 9<sup>[16]</sup>], [in ref. 9<sup>[41]</sup>], [in ref. 10<sup>[104]</sup>], [10, 11], cyclopropanation over heterogenized homogeneous metal complexes [12], epoxidation [13], and alkylation over heterogenized chiral auxiliaries [14]. The immobilization of the metal complexes has been reviewed by Blaser *et al.* [8], where the different heterogenization methods for making covalent bonds, like grafting, solid state synthesis, and copolymerization, are described. Several types of reactions, i.e., hydrogenation, addition, hydroformylation, epoxidation, and dihydroxylation, are carried out over heterogenized metal complexes [8]. Enantioselective hydrogenations over Ni–tartaric acid (Ni–TA) and Pt–cinchonidine (Pt–CD) catalysts (Fig. 1) have been reviewed [in ref. 16<sup>[10]</sup>], [17], [18]. More specific reviews exist on hydrogenation of  $\beta$ -ketoesters over modified Ni catalysts [19, 20] and  $\alpha$ -ketoesters [21], activated ketones on platinum [22], on hydrogenation of platinum group metals [23], and the design of new modifiers for platinum metal [24, 25].

The crucial questions for enantiodifferentiation over heterogeneous metal catalysts are, What is the nature of a chiral site, and how does the enantiodifferentiation take place on the metal surface? There are several ways to transfer the chirality: (a) to have metals supported on chiral matrices, (b) to use chiral metal surfaces, and

<sup>1</sup> This article was submitted by the authors in English.

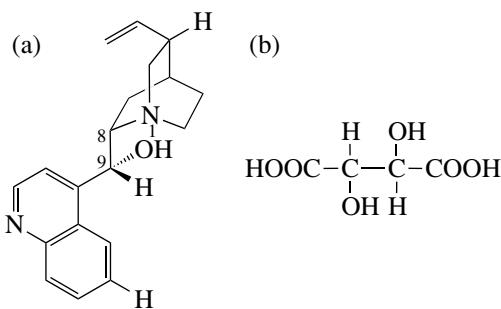


Fig. 1. (a) Cinchonidine and (b) tartaric acid as modifiers.

(c) via adsorbing a chiral modifier on the metal surface (Fig. 2) [15].

There exist different approaches to revealing enantiodifferentiation in heterogeneous catalysis. The tools to elucidate the reaction mechanism are kinetic experiments and modeling [26], as well as molecular modeling [24], combined with physicochemical measurements and advanced surface science techniques for investigating the adsorption of modifiers, specifically, on defined metal surfaces (Fig. 3). New ideas for enantiocontrol, like extended chiral surfaces, two-dimensional organization and complex adsorption phases of modifiers, have been developed via surface science adsorption studies [27]. The aim of this review is to describe the most important catalyst and reaction parameters affecting enantioselectivity and to try to elucidate the reaction mechanism. The focus is on alkaloid modified enantioselective hydrogenations.

The three ways of chirality transfer, i.e., the application of chiral supports, chiral metals exhibiting intrinsic chirality, and modified metal supported catalysts will be discussed below.

### CHIRAL SUPPORTS

Enantiodifferentiation is possible over metal catalysts supported on chiral carrier materials [15], like quartz, silk, and polymer [in ref. 15<sup>[5]</sup>]. Different metals, like Cu, Ni, and Pt on chiral quartz, were able to dehydrogenate racemic 2-butanol [in ref. 8<sup>[15]</sup>], with a chiral arrangement of crystals responsible for the kinetic resolution. Pd supported on chiral silk was able to yield in enantioselective hydrogenation of the C=C

bond up to 66% enantiomeric excess (*ee*) (*ee* =

$$\frac{[R] - [S]}{[R] + [S]} \times 100$$

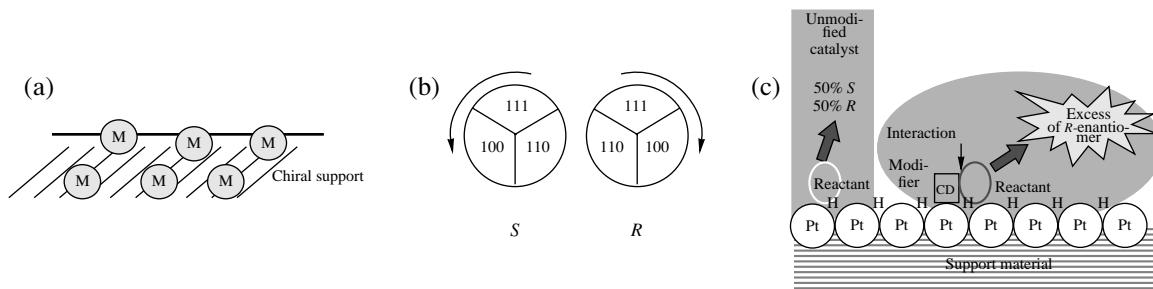
) [in ref. 8<sup>[16]</sup>]. Another example is the utilization of metal colloids encased in a polysaccharide and their application in enantioselective hydrogenation of C=C and C=N bonds [in ref. 15<sup>[7]</sup>].

### CHIRAL SURFACES OF CATALYTIC SURFACE ATOMS

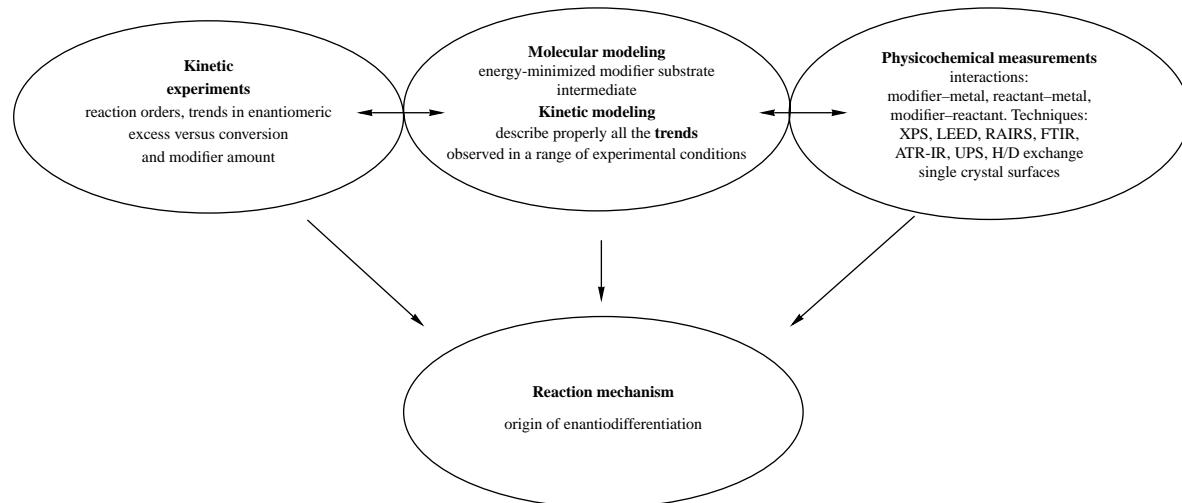
A totally different route is to utilize catalytic surfaces that are intrinsically chiral, e.g., those containing high Miller index surfaces. In such a case no additional chiral template is needed. Gellman *et al.* were the first to prepare pure metal surfaces that are intrinsically chiral [in ref. 28<sup>[53]</sup>]. Experimental evidence for this can be found in the field of electrooxidation of D- and L-glucose [in ref. 28<sup>[55, 56]</sup>] and enantiospecific desorption of *R*-3-methylcyclohexanone [29]. Moreover (*R*)- and (*S*)-naphthylethylamines, known as modifiers, have shown enhanced desorption rates from {643}<sup>R</sup> and {211} platinum surfaces [30]. Naturally, chiral metal surfaces as enantiospecific adsorbents are discussed [in ref. 28<sup>[52]</sup>]. It was supposed [31] that on the surface of fcc metals chiral kinked places exist or can be formed, which play a key role in the metal and chiral substrate interactions. Upon adsorption, the surface chirality changes as a consequence of discriminating adsorption. Enantiodifferentiation over supported Ru and Rh catalysts without addition of any modifier was experimentally confirmed in citral and nerol hydrogenation in 2-pentanol and 3-pentanol as solvents [32]. The maximum *ee* was about 40% in nerol hydrogenation over Rh/Al<sub>2</sub>O<sub>3</sub> catalyst. It was demonstrated recently by STM [in ref. 28<sup>[16]</sup>] that the adsorption of chiral molecules can bestow chirality onto extended flat metal terraces, which could be the reason for enantioselectivity in precious metal catalyzed hydrogenation, as proposed in [32].

### MODIFIED CATALYST SYSTEMS

The two most intensively investigated modified catalytic systems are Ni catalysts modified with  $\alpha$ -hydroxy and  $\alpha$ -amino acids and Pt or Pd modified with cinchona alkaloids. Typical modifiers are tartaric acid (TA) for Ni and cinchonidine (CD) for Pt. Ni and Pt modified catalysts are suitable for hydrogenating C=O bonds, whereas C=C bonds are hydrogenated over Pd-CD catalysts. Moreover, synthetic vinca-type alkaloids have been used with Pd metal for hydrogenating C=O and C=C double bonds. Ni-TA catalysts have successfully been applied in enantioselective hydrogenation of  $\beta$ -ketoesters, 1,3- $\beta$ -diketones, 2-alkanones, and  $\beta$ -ketosulfones [19] (Table 1), whereas hydrogenation of methyl esters of  $\alpha$ -,  $\gamma$ -, and  $\delta$ -keto acids yielded low enantioselectivities [in ref. 20<sup>[61]</sup>], indicating that the distance between the two carbonyl groups in the substrate is critical. The highest enantioselectivities over Pt-CD catalysts have been obtained with  $\alpha$ -keto esters [in ref. 21<sup>[3]</sup>, [31], [in ref. 22<sup>[30]</sup>], [in ref. 24<sup>[25]</sup>],  $\alpha$ -keto acetals [in ref. 22<sup>[55]</sup>], cyclic imidoketones [in ref. 24<sup>[65]</sup>], 1- and 4-substituted pyrrolidine-2,3,5-triones [in ref. 24<sup>[66]</sup>], and 2,4-diketo acid derivatives [in ref. 22<sup>[53]</sup>] (Table 1). Lower enantiomeric excesses (*ees*) were obtained with  $\alpha$ -keto amides (60% *ee*) [34] and 1-phenyl-1,2-propanedione (60–70% *ee*) [35], [in ref. 22<sup>[28]</sup>]. Pd-CD



**Fig. 2.** Transfer of chirality using (a) a metal M on chiral matrices, (b) a chiral metal, and (c) a modified catalyst.



**Fig. 3.** Different tools to elucidate the reaction mechanism and the origin of enantiodifferentiation.

catalysts have been used in the hydrogenation of hydroxymethylpyrone (85% *ee*) [36], *E*- $\alpha$ -phenylcinnamic acid (72% *ee*) [37], and 2-methyl-2-pentenoic acid (66% *ee*) [38]. Moreover, hydrogenation of isophorone over a (–)-dihydroapovincaminic acid ethyl ester modified Pd catalyst yielded up to 55% *ee* [in ref. 39<sup>[100]</sup>].

### MODIFIER STRUCTURE

The modifier structure is crucial in both Ni-TA and Pt-CD systems. The most effective modifier structures are displayed in Tables 2 and 3. In Ni-TA the presence of four functional groups is necessary. Two carboxylic acid groups adsorb on the Ni surface, whereas –OH is able to make a hydrogen bond with the carbonyl group of the reactant, methyl aceto acetate (MAA). Other modifiers for Raney nickel catalyst have been (*S*)-alanine, (*S*)-valine, (*S*)-leucine, (*S*)-malic, (*S*)-2-aminobutyric, (*R,R*)-TA [in ref. 19<sup>[38]</sup>], (*S*)-glutamic acid, (*S*)-ornithine, and (*S*)-lysine [in ref. 19<sup>[32]</sup>].

The crucial factor in the alkaloid modifier is the anchoring group and the basic nitrogen group in the vicinity of the stereogenic center [40]. An extended, flat anchoring group is important for enantiodifferentiation, whereas benzene and pyridine groups exhibited no

enantiodiscrimination. The existence of nitrogen is not necessary in the anchoring group; e.g., (2*S*, 1*R*)-N-[1-(1-naphthyl)ethyl]-2-aminopropionic acid ethyl ester exhibited 82% *ee* [in ref. 22<sup>[70]</sup>], and it is the most efficient modifier for ethyl pyruvate (EP) hydrogenation under low hydrogen pressures. The alkylation of quinuclidine nitrogen leads to a loss of *ee* in EP hydrogenation [40]. In the hydrogenation of 1-phenyl-1,2-propanedione over 11-(triethoxysilyl)-10,11-dihydrocinchonidine as a modifier yielded higher *ees* (70%) than those obtained with CD (56%) [35]. Modifiers giving moderate *ees* are prepared from *L*-tryptophane [in ref. 22<sup>[68]</sup>],  $\beta$ -isocinchonine [in ref. 22<sup>[85]</sup>], and chiral binaphthol moiety [41], and low *ees*, from brucine, strychnine, codeine, and ephedrine [in ref. 37<sup>[19]</sup>]. In the hydrogenation of carboxylic acids over Pd-CD catalysts, the presence of a hydroxyl group at C<sub>9</sub> [in ref. 22<sup>[79]</sup>] and quinuclidine N [in ref. 22<sup>[78]</sup>] is crucial for enantiodifferentiation, because there is an interaction between the hydroxyl group in CD and the carboxyl group in the carboxylic acid.

It can be summarized that an extended aromatic system is required to form an adsorption complex with the Pt surface; in addition, a chiral amino function

**Table 1.** The highest *e*es in the hydrogenation of different substrates with modified catalysts

Ni-TA catalyst	<i>ee</i> (%), ref.	Pt-CD	<i>ee</i> (%), ref.
	91 [20]		98 [in ref. 22 <sup>[30]</sup> ]
	91 [20]		98 [33]
	85 [20]		97 [in ref. 22 <sup>[55]</sup> ]
	71 [20]		91 [in ref. 24 <sup>[65]</sup> ]
			86 [in ref. 22 <sup>[53]</sup> ]

capable of interacting with the keto group of the adsorbed substrate is needed to induce sufficient enantiocontrol. The sense of asymmetric induction is controlled by the absolute configuration at the C<sub>8</sub> and C<sub>9</sub> carbon atoms of the cinchona modifier. Substitution of the C<sub>9</sub> hydroxyl group with bulky substituents significantly lowers the enantioselectivity, whereas structural modifications of the quinuclidine C<sub>3</sub> substituent were reported to have only a moderate effect on the *ee* in the hydrogenation of EP.

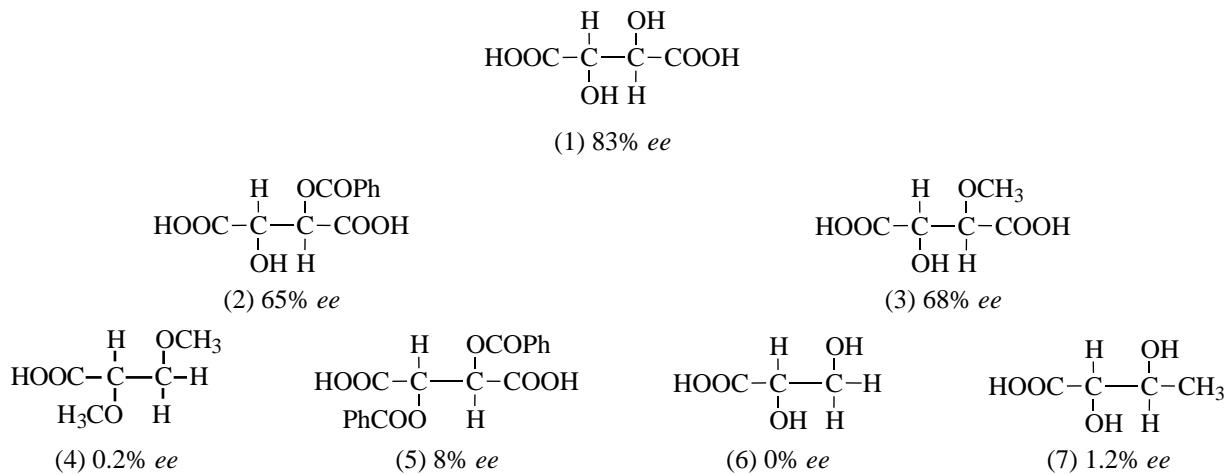
### CATALYST PROPERTIES

The catalyst properties, such as metal selection [in ref. 23<sup>[45]</sup>], metal particle size (Fig. 4) [43], [in ref. 16<sup>[10]</sup>] and catalyst modification (*in situ* [21, 42], premodification [19], [in ref. 23<sup>[12]</sup>], time [in ref. 44<sup>[6]</sup>], temperature [43], pH [19]), and the presence of comodifiers [in ref. 44<sup>[37]</sup>], [19] and additives (water, carboxylic acid) [in ref. 19<sup>[23]</sup>], [in ref. 20<sup>[75]</sup>] can be crucial for enantioselectivity. This is understandable taking into account that these parameters influence not only the reactant-modifier interactions, but also the adsorption (geometry and electronic properties) of organic molecules on the catalyst surface. For instance, relatively large metal particles are suitable for enantiodifferentiation, which reflects the fact that metal crystallites should accommodate large organic molecules providing sufficient space for them to adsorb and interact. Not surprisingly, the optimum metal particle size for enan-

tioselection increases with an increase in the reactant size.

### KINETIC EFFECTS

Kinetic measurements and the trends in *ee* as a function of hydrogen pressure, modifier amount, and temperature, are very valuable, as highlighted by Blackmond [26]. The main kinetic regularities are summarized in Table 4. The Ni-TA, Pt-CD, and Pd-CD catalyst systems differ from each other in the choice of optimum reaction conditions and solvent. The enantioselective hydrogenation of EP on Pt exhibited 20–100 times higher rates than the unmodified reaction [23], [in ref. 22<sup>[86]</sup>], [in ref. 40<sup>[28]</sup>], [in ref. 22<sup>[102]</sup>]. Many mechanisms that have been proposed for EP hydrogenation thus include the concept of rate acceleration. Recent results with ethyl-benzoylformate [33] over Pt-CD and with methyl pyruvate over Ir-CD [in ref. 23<sup>[45]</sup>], however, have shown lower or equal rates for modified and unmodified catalysts. Although rate acceleration was assumed to be an essential feature of enantioselective hydrogenation over Pt-CD, no rate enhancement was observed in the hydrogenation of ethyl nipecotinate over Pd-CD catalysts [in ref. 10<sup>[38]</sup>], [in ref. 23<sup>[51]</sup>] and in the hydrogenation of trifluoroacetophenone derivatives [45]. A decrease in the rate in enantioselective hydrogenation of hydroxymethylpyrone [46] and of 2-methyl-2-pentenoic acid over CD modified Pd/Al<sub>2</sub>O<sub>3</sub> [38] has been reported. The enhanced

**Table 2.** The effect of modifier structure on the *ee* in the hydrogenation of MAA [27]

Numbers: (1) (*R,R*)-TA, (2) (*R,R*)-O-benzoyl-TA, (3) (*R,R*)-O-methyl-TA, (4) (*R,R*)-O,O'-dimethyl-TA, (5) (*R,R*)-O,O'-dibenzoyl-TA, (6) (*S*)-glyceric acid, (7) (*2R,3R*)-2,3-dihydroxybutyric acid.

rate in enantioselective hydrogenation of MAA has been interpreted by the polarization of carbonyl groups in the presence of a TA modifier [in ref. 44<sup>[62]</sup>].

The solvent affects the conformation [in ref. 24<sup>[41]</sup>] and solvation of the modifier [47] and can promote side reactions [22]. The population density of the Open(3) conformer of the CD varies depending on solvent polarity [in ref. 24<sup>[41]</sup>]. Open(3) and Closed(1) conformers of CD made by molecular modeling are shown in Fig. 5. In EP hydrogenation, an attempt was made to correlate *ee* with the population density of the CD Open(3) conformer; however, the supposition that the population density of the Open(3) conformer changes as a function of solvent polarity cannot explain the experimental data, as is shown in [48]. Thus, there must be specific substrate-modifier interactions, and solvation in the transition state should be taken into account.

## PHYSICOCHEMICAL BACKGROUND OF REACTION MECHANISM

Several mechanistic models have been proposed for hydrogenation of  $\alpha$ -ketoesters [24], [8], [21], [in ref. 21<sup>[71]</sup>], [in ref. 21<sup>[46]</sup>] unsaturated carboxylic acids [in ref. 22<sup>[79]</sup>], [in ref. 23<sup>[51], [66]</sup>], hydroxymethylpyrone [36], and  $\beta$ -ketoesters [20]. Mechanistic models are based on experimental results, kinetic and molecular modeling, and physicochemical measurements regarding all the reaction participants (modifier, reactant, catalyst surface). Thus, basic knowledge of the adsorption of both reactant and modifier and their conformation [in ref. 22<sup>[82]</sup>], [in ref. 24<sup>[26]</sup>] and intermolecular interactions [in ref. 22<sup>[78]</sup>], [in ref. 24<sup>[26]</sup>] is crucial in order to be able to understand the mechanism for enantioselection.

## MODIFIER-SUBSTRATE INTERACTIONS

Theoretical calculations via molecular modeling can give an energy-minimized structure of the modifier–substrate intermediate, which is supposed to resemble the corresponding transition complexes [24]. The chirality can be predicted by calculating the relative stability of the reactant–modifier complexes [24], although neglecting the adsorptive interactions with the catalyst surface. Such models are valid for relatively flat metal surfaces like Pt(111) or Pt(110) [in ref. 22<sup>[93]</sup>]. Another simplification is that the presence of solvent and possible hydrogen bonding interactions are excluded in the molecular modeling [26]. It was shown that in EP hydrogenation a hydrogen bond can be formed between EP and CD, i.e., between the tertiary nitrogen in CD and the oxygen at the  $\alpha$ -carbonyl group of the reactant either in the presence of a half-hydrogenated state of  $\alpha$ -ketoester or after protonation of the tertiary nitrogen in CD, which is possible in acetic acid [16]. The hydrogen bonding interactions are assumed to be relatively weak compared to the adsorption strength of the modifier and reactant. The 1 : 1 interaction between quinuclidine nitrogen and EP was assumed, because the alkylation of quinuclidine nitrogen resulted in complete loss of enantiodifferentiation [in ref. 24<sup>[20]</sup>]. Interactions between EP and CD have been studied not only theoretically, but also by NMR [in ref. 18<sup>[24], [25]</sup>] and circular dichroism [in ref. 15<sup>[39]</sup>]. A complex formation between EP and CD was observed.

The interactions between unsaturated acid and CD confirmed by FTIR have a stoichiometry of 2 : 1 or 1 : 1. The hydrogen bond  $-\text{OH}$  and  $\text{HOOC}-$  can be formed between CD and carboxylic acid. Moreover, the interaction between  $\text{NH}^+ \dots -\text{O}-\text{C}=\text{O}$  has been confirmed [50]. Different types of stereochemical models that

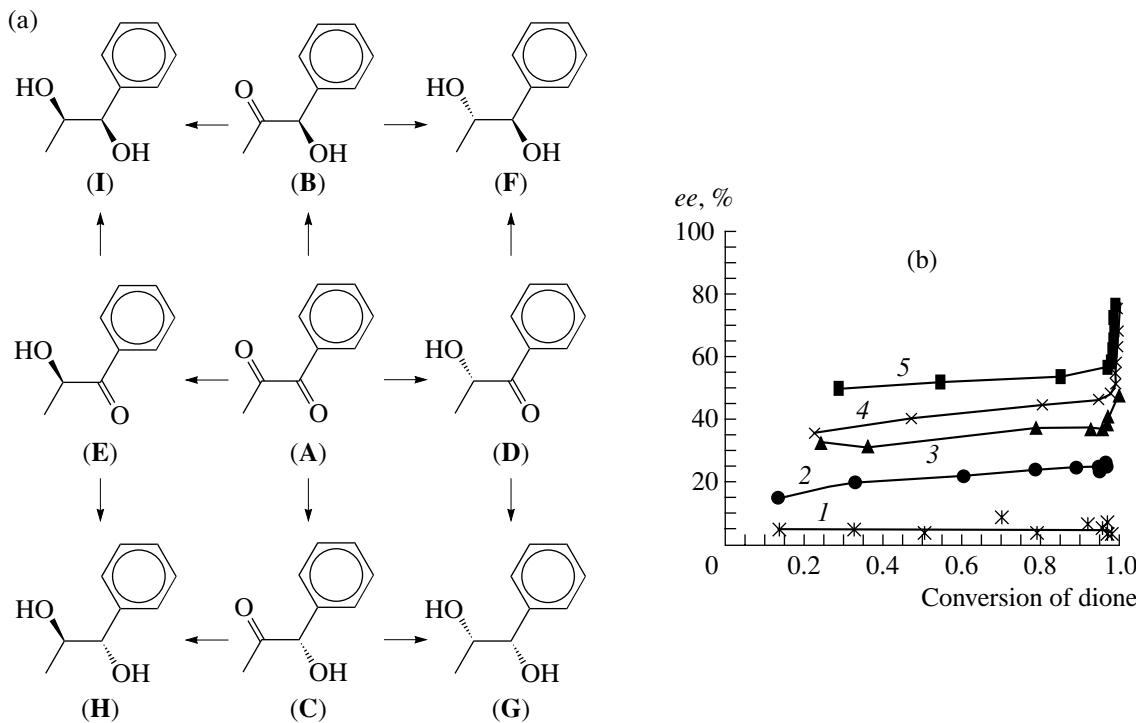
**Table 3.** The highest *e*es in the hydrogenation of carbonyl bond over modified Pt catalysts

Modifier	Substrate, <i>ee</i> (%), ref.	Modifier	Substrate, <i>ee</i> (%), ref.
	EP and methyl pyruvate, 98% [in ref. 22 <sup>[30]</sup> ], [in ref. 24 <sup>[25]</sup> ] 1-phenyl-1,2-propanedione, 60% [60]		EP, 93% [40]
	EP, 82% [25]		EP, 67% [40]
	EP, 75% [25]		EP, 58% [25]
	1-phenyl-1,2-propanedione, 70% [35]		EP, 0% [25]

have one hydrogen bond or two hydrogen bonds between the TA and the reactant have been developed [in ref. 19<sup>[52c]</sup>], [20]. For MAA the two-hydrogen bond model has been developed, whereas the one-hydrogen bond model is valid for 2-alkanones. It could be stated that the modifier–substrate interactions resemble lock-and-key interactions in enzymatic catalysis; therefore, enantio-differentiation is so substrate and modifier specific.

#### ADSORPTION MODES OF SUBSTRATE AND MODIFIER

In asymmetric catalysis, however, the specificity of heterogeneous catalysis should also be taken into account. Detailed information about adsorption modes of reactants and modifiers are of immense importance in revealing the reaction mechanism. *In situ* XANES measurements showed that EP is perpendicularly



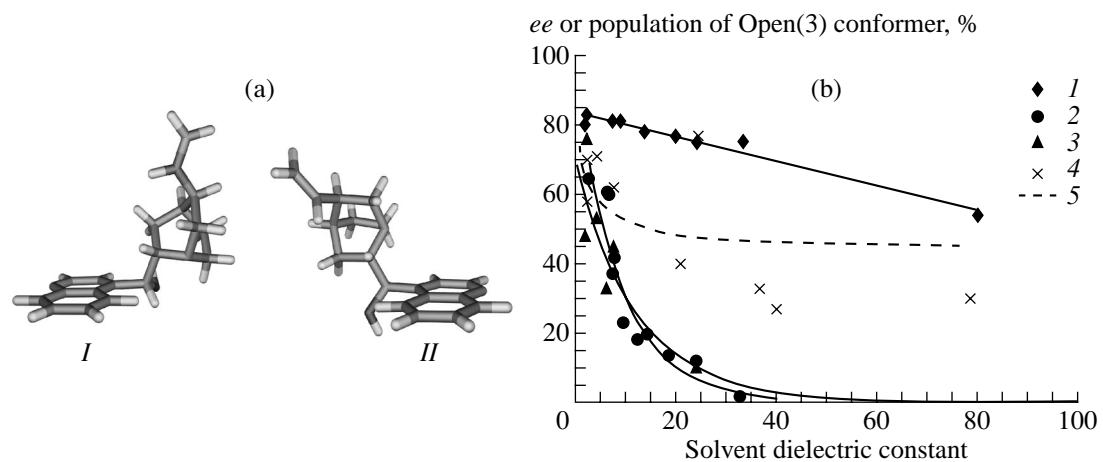
**Fig. 4.** (a) Reaction scheme of 1-phenyl-1,2-propanedione hydrogenation; A: 1-Phenyl-1,2-propanedione and main product, B: (R)-1-Hydroxy-1-phenylpropanone. (b) The *ee* of B in the hydrogenation of 1-phenyl-1,2-propanedione; symbols: Pt/Al<sub>2</sub>O<sub>3</sub> from chloride (1) 2.5 wt % Pt (1.2 nm), (2) 5 wt % Pt (1.3 nm), (3) 7.5 wt % Pt (1.9 nm), (4) 10 wt % Pt (3.1 nm), and (5) 15 wt % Pt (4.0 nm) [43].

adsorbed to the Pt surface in the absence of hydrogen [in ref. 22<sup>[108]</sup>]. Two adsorption modes of EP are distinguished, namely, B-bonded EP based on catalytic experiments and lone-pair bonded EP identified under low temperature UHV work [in ref. 22<sup>[108]</sup>]. Lone-pair bonded EP is considered to be a precursor state of the final  $\pi$ -bonded species, which are relevant in the transition state complex. According to Ferri *et al.* [in ref. 22<sup>[94]</sup>], an EP adsorbs in a parallel way on a Pt surface with two carbonyl groups in *trans* position. The dihedral angle for an EP *s-trans* conformer is 180° [in ref. 22<sup>[107]</sup>]. Moreover, polymerization of EP on a Pt surface was observed by STM, NEXAFS, XPS, TPR, and via catalytic measurements [in ref. 22<sup>[109]</sup>] in the absence of hydrogen and CD.

The adsorption of CD on Pt and TA on Ni has been investigated too. 10,11-dihydrocinchonidine is adsorbed on a Pt(111) surface without decomposition in a disordered state based on LEED, XPS, and UPS measurements [51]. H/D exchange experiments [in ref. 23<sup>[13]</sup>, [20]] and an *in situ* ATR-IR study of CD adsorption on Pt/Al<sub>2</sub>O<sub>3</sub> [52] indicate that CD interacts with Pt through its quinoline moiety. Analogous results have been obtained for adsorption of 10,11-dihydrocinchonidine on a Pt(111) surface [in ref. 40<sup>[29]</sup>]. Tilted adsorption of CD has been confirmed by IR [53]. Under such conditions, which favor CD adsorption parallel to the Pt surface, the activity and enantioselectivity of a Pt

catalyst increases. Chemisorption of CD on the catalyst surface is essential, since, in continuous hydrogenation of 1-phenyl-1,2-propanedione in a fixed bed reactor, the *ee* of the product decreases slowly when the feed of the modifier is stopped [54], [in ref. 22<sup>[43]</sup>] (Fig. 6).

Contrary to the Pt-CD system, direct detection of the adsorbed TA on an Ni surface by physicochemical methods has not yet been successful [20]. TA chemisorbs corrosively on an Ni surface [55, 56] by forming a complex between TA and Ni during the modification. The corrosive chemisorption of TA leaches out the smaller Ni particles, decreasing the Ni dispersion. Ni leaching depends on the modification temperature, time, and pH [in ref. 27<sup>[14]</sup>]. XPS measurements [in ref. 20<sup>[41]</sup>, [42]] have confirmed that Ni is preserved in a metallic state after exposing the modified catalyst to air, while the unmodified catalyst is oxidized. TA<sup>2-</sup>/Na<sup>+</sup> adsorption might protect metallic Ni. Interactions between Cu, Ni, and the modifier TA have been recently investigated by adsorbing the modifier on a well-defined metal surface and investigating the interactions with surface science techniques, e.g., STM, LEED, RAIRS, and XPS-ESCA under UHV conditions. These results have been combined with *ab initio* calculations [27, 28, 57]. As is well known, STM and LEED give information about the adsorption geometry and two-dimensional order, whereas RAIRS reveals the molecular orientation and XPS gives the chemical com-



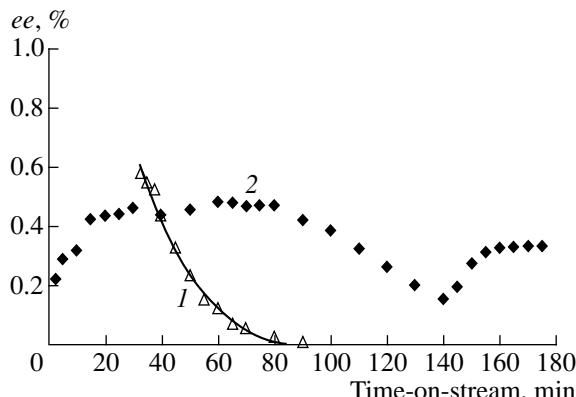
**Fig. 5.** (a) Open(3) (*I*) and Closed(1) (*II*) conformers of CD. (b) Experimentally observed *ees* and population of Open(3) conformer of CD as a function of the solvent dielectric constant; symbols: *ee* in the hydrogenation of (*I*) EP [in ref. 10<sup>[46]</sup>], (2) 1-phenyl-1,2-propanedione [48], (3) ketopantolactone [in ref. 24<sup>[41]</sup>], (4) experimentally determined (NMR [in ref. 24<sup>[41]</sup>]) population of Open(3) conformer, and (5) modeled population (B3LYP 6-31+G\*) [in ref. 24<sup>[41]</sup>].

position on the surface. It was demonstrated that over a Cu(110) surface (*R,R*)-TA created an extended chirality, i.e., self-organization of several of the modifier molecules. The adsorption mode varies noticeably with temperature and modifier coverage. At room temperature, a monotartrate structure is predominant, whereas a slow change from monotartrate to bitartrate takes place at higher temperatures. A bitartrate structure is adsorbed at 130°C. Higher temperatures also enhance the formation of two-dimensional ordered structures,

which destroy all the mirror symmetry elements on the metal. On an Ni(110) surface, a bitartrate form of adsorbed TA, which was observed at low coverages at 25°C, forms a chiral footprint over four Ni atoms at the metal surface by destroying the local mirror planes [28]. Still, a question remains: How are these surface science results under ultrahigh vacuum conditions connected to the real catalytic results? There exist some similarities; i.e., higher *ees* were obtained with larger

**Table 4.** Kinetic regularities in the hydrogenation of different substrates

Reactant/Catalyst	$P_{\text{opt}} \times 10^5$ , Pa	$T_{\text{opt}}$ , °C	Reactant order	$\text{H}_2$ order	Suitable solvent	<i>ee</i> as a function of conversion	Rate acceleration	Optimum metal particle size, nm
EP/Pt-CD	>20 [in ref. 22 <sup>[102]</sup> ]	<50 [in ref. 23 <sup>[25]</sup> ], [in ref. 21 <sup>[10]</sup> ]	0 [in ref. 23 <sup>[25]</sup> ]	1 [in ref. 40 <sup>[25]</sup> ], [in ref. 23 <sup>[25]</sup> ]	Toluene, acetic acid [16], [in ref. 22 <sup>[119]</sup> ], [in ref. 40 <sup>[14]</sup> ]	Increases to the steady state value [25]	20–100 [23]	>3 [16]
1-Phenyl-1,2-propanedione/Pt-CD	5	0–15 [61]	0.7 [61]	0 [61]	Ethyl acetate	Increases to the steady state value, >90% conversion increases, kinetic resolution [60]	1.3 [61]	4 [43]
Carboxylic acid/Pd-CD	1 [62]	25 [62]	Not studied	Not studied	Polar solvents [in ref. 23 <sup>[65]</sup> ], [in ref. 23 <sup>[63]</sup> ]	Not studied	Declinement [38, 23]	Not studied [23]
MAA/Ni-TA	1 [44]	60 [44]	0.3 [44]	<0.1 [44]	Tetrahydrofuran [63]	Increases to the steady state value [20]	Enhanced rate [in ref. 44 <sup>[62]</sup> ]	>20 [20]

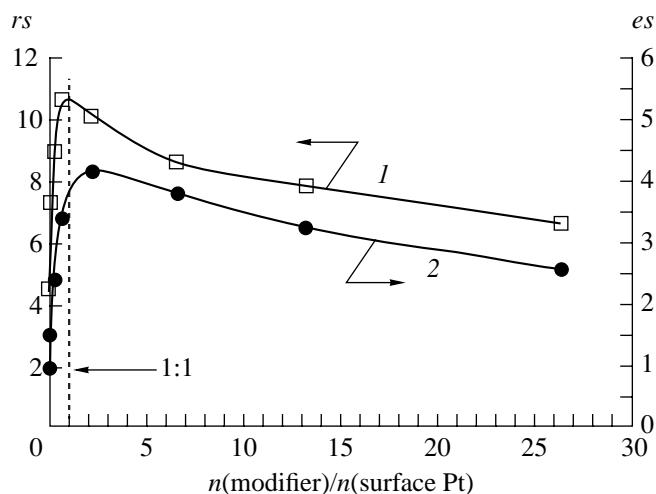


**Fig. 6.** *ee* of (R)-1-hydroxy-1-phenylpropanone in the hydrogenation of 1-phenyl-1,2-propanedione (A) in two transient experiments: (1) the catalyst was premodified with CD, after which the reactant-solvent mixture was fed into reactor (*ee*), and (2) the catalyst was not premodified, and, after 60 min of time-on-stream, the CD feed was stopped and switched on again after 140 min. Inlet concentrations were  $c_{0A} = 0.015 \text{ mol/dm}^3$  and  $c_{0M} = 10^{-4} \text{ mol/dm}^3$ , respectively, and a space time ( $t$ ) of 44 s was used [54].

Ni particles [58], [in ref. 44<sup>[56]</sup>] and at submonolayer coverages of the modifier. The optimum TA coverage for maximizing *ees* was 0.2–0.3 on a nickel surface, which enables the adsorption of substrate on the metal surface [20], [in ref. 44<sup>[17]</sup>].

#### KINETICS OF ENANTIOSELECTIVE HYDROGENATION

Only a few reactions exist in which kinetic regularities have been investigated in a broad enough range of reaction conditions. These reactions are hydrogenation of MAA over Ni-TA and  $\alpha$ -ketoesters and 1-phenyl-1,2-propanedione (A in Fig. 4a) over Pt-CD catalysts. The goal in the kinetic approach is to develop a model that could adequately describe all the kinetic trends (reaction orders, *ee* dependence on conversion level, and modifier concentration) under a valid range of conditions. A Langmuir–Hinshelwood type model has been proposed for hydrogenation of  $\beta$ -ketoesters over an Ni-TA catalyst, where the adsorbed substrate reacts with activated hydrogen on an Ni surface [19, 59]. The rate-determining step is the surface reaction between adsorbed MAA and hydrogen. Moreover, a two-site model has been proposed for a system that contains NaBr, where nonmodified sites have been poisoned by this additive [19, 59]. Several kinetic models have been proposed for EP hydrogenation. In the model of Blaser *et al.* [in ref. 22<sup>[102]</sup>], EP adsorbs on a nonmodified site and migrates to a modified site due to (a) attractive interactions between the ketone oxygen and modifier or (b) after fast proton transfer to oxygen. The following step is a slow addition of the second hydrogen atom followed by desorption of the product. Margitfalvi *et al.* [in ref. 21<sup>[46]</sup>], [in ref. 21<sup>[47]</sup>] proposed as a first step for



**Fig. 7.** Regioselectivity (*rs*) (1) and enantioselectivity (2) (*es* =  $[\mathbf{B}]/[\mathbf{C}]$ ) (see compounds in Fig. 4a) in the hydrogenation of 1-phenyl-1,2-propanedione at different molar ratios of CD-to-surface Pt over 0.15 g of catalyst [61].

mation of the CD–EP complex in the liquid phase, after which the activated complex is hydrogenated either via an Eley–Rideal [in ref. 21<sup>[47]</sup>] or a Langmuir–Hinshelwood mechanism [in ref. 21<sup>[46]</sup>]. The complex formation is claimed to be an enantio-differentiation step. The quinoline ring provides a steric shielding, enhancing the enantioselectivity. The Eley–Rideal mechanism can be excluded due to the saturation effect of *ee* with increasing modifier concentration [in ref. 22<sup>[103]</sup>].

A more complicated reaction, hydrogenation of 1-phenyl-1,2-propanedione (Fig. 4a) [60], produces two different regioisomers as predominant products, namely, *R*- and *S*-1-hydroxy-1-phenylpropanone (**B** and **C**) and *R*- and *S*-2-hydroxy-1-phenylpropanone (**D** and **E**). The regioselectivity is defined as  $rs = \frac{[\mathbf{B}]}{[\mathbf{B}] + [\mathbf{C}]}$ . The enantioselectivity (*es*) increases  $\frac{[\mathbf{D}]}{[\mathbf{D}] + [\mathbf{E}]}$  with increasing reactant concentration. The regio- and enantioselectivities as a function of the modifier–surface Pt ratio are displayed in Fig. 7 [61]. The hydrogenation rate exhibited a maximum as a function of the modifier-to-surface Pt ratio. The nonselective phenyl ring hydrogenation took place when there was no, or a negligible amount of, modifier on the metal surface. Based on these kinetic observations, the following assumptions were made regarding the kinetic model: (1) both selective and unselective sites coexist on the catalyst surface, (2) different coverage-dependent adsorption modes prevail for both reactant and modifier, (3) spectators exist in the reaction system (tilted adsorption of modifier), (4) a different number of metal sites are needed for different reactants, (5) interaction between modifier and reactant is necessary, and (6) a

specific solvent effect exists. The kinetic model presented in [61] described well the essential features of enantioselective hydrogenation of 1-phenyl-1,2-propanedione and could be useful in the future for the kinetic modeling of other heterogeneous catalytic reactions involving complex organic molecules.

## CONCLUSIONS

Asymmetric catalysis plays a central role in present-day production of pharmaceuticals. It may be predicted that the role of heterogeneous catalysis in the synthesis of optically pure chemicals will increase in the future. The transfer of chirality from a chiral inducer (chiral support, metal, or modifier) is essential for asymmetric heterogeneous catalysis. The most frequently studied systems are hydrogenation of  $\beta$ -ketoesters on Ni-tartaric acid catalysts and that of  $\alpha$ -ketoesters on cinchonidine modified Pt, although other molecules have also been used.

In case of catalysis with the aid of chiral modifiers, specific interactions between them and the reactants play a key role in enantiodifferentiation. Such interactions resemble lock-and-key interactions in enzymes and are analogously temperature and pH dependent. As the reaction proceeds on the surfaces of heterogeneous catalysts, only particular adsorption modes provide possibilities for the above-mentioned reactant-modifier interactions. A deep understanding of all the interactions between reactant, modifier, and catalyst surface will provide possibilities for the rational synthesis of optically active molecules.

## ACKNOWLEDGMENTS

This work is part of the activities at the Åbo Akademi Process Chemistry Group within the Finnish Centre of Excellence Program (2000–2005) of the Academy of Finland.

## REFERENCES

- Muller, G.W., Konnecke, W.E., Smith, A.M., *et al.*, *Org. Proc. Res. Dev.*, 1999, vol. 3, p. 139.
- Takeuchi, Y., Shiragami, T., Kimura, K., *et al.*, *Org. Lett.*, 1999, vol. 1, p. 1571.
- Stinson, S.C., *Chem. Eng. News*, 1994, vol. 72, p. 38.
- Stinson, S.C., *Chem. Eng. News*, 2000, vol. 78, p. 55.
- Blaser, H.-U., Spindler, F., and Studer, M., *Appl. Catal. A*, 2001, vol. 221, p. 119.
- Sheldon, R.A., *Chirotechnology*, New York: Marcel Dekker, 1993.
- Collins, A.N., Sheldrake, G.N., and Crosby, J., *Chirality in Industry II*, New Delhi: Thomson, 1997.
- Blaser, H.-U. and Pugin, B., *Chiral Reactions in Heterogeneous Catalysis*, Jannes, G. and Dubois, V., Eds., New York: Plenum, 1995, p. 33.
- Blaser, H.-U. and Müller, M., *Stud. Surf. Sci. Catal.*, 1991, vol. 59, p. 73.
- Blaser, H.-U., *Tetrahedron Asymm.*, 1991, vol. 2, p. 843.
- Feast, S., Rafiq, M., Siddiqui, H., *et al.*, *J. Catal.*, 1997, vol. 167, p. 533.
- Fraile, J.M., Garcä, J.I., Mayoral, J.A., *et al.*, *J. Catal.*, 1999, vol. 186, p. 214.
- Brunel, D., Sutra, P., and Fajula, F., *Stud. Surf. Sci. Catal.*, 2000, vol. 129, p. 773.
- Abramson, S., Lasperas, M., and Chiche, B., *J. Mol. Catal. A: Chem.*, 2001, vol. 165, p. 231.
- Heterogeneous Catalysis in Organic Chemistry*, Smith, G.V. and Notheisz, F., Eds., New York: Academic, 1999, p. 97.
- Baiker, A., *J. Mol. Catal. A: Chem.*, 1997, vol. 115, p. 473.
- Baiker, A. and Blaser, H.-U., *Handbook of Heterogeneous Catalysis*, Ertl, G., Knözinger, H., and Weitkamp, J., Eds., Weinheim: VCH, 1997, vol. 5, p. 2422.
- Margitfalvi, J., Tälas, E., and Tfirst, E., *Chim. Oggi/Chem. Today*, 2000, p. 45.
- Izumi, Y., *Adv. Catal.*, 1983, vol. 32, p. 215.
- Tai, A. and Sugimura, T., *Chiral Catalyst Immobilization and Recycling*, De Vos, D.E., Vankelecom, I.F.J., and Jacobs, P.A., Eds., Weinheim: Wiley–VCH, 2000, p. 173.
- Blaser, H.-U., Jalett, H.-P., Müller, M., *et al.*, *Catal. Today*, 1997, vol. 37, p. 441.
- Von Arx, M., Mallat, T., and Baiker, A., *Top. Catal.*, 2002, vol. 19, p. 75.
- Wells, P.B. and Wilkinson, A.G., *Top. Catal.*, 1998, vol. 5, p. 39.
- Baiker, A., *J. Mol. Catal. A: Chem.*, 2000, vol. 163, p. 205.
- Baiker, A., in *A Molecular View of Heterogeneous Catalysis*, Derouane, E.G., Ed., Paris: De Boeck Université, 1998, p. 165.
- Blackmond, D.G., *Cattech*, 1998, vol. 6, p. 17.
- Raval, R., *Cattech*, 2001, vol. 5, p. 12.
- Humblot, V., Haq, S., Muryn, C., *et al.*, *J. Am. Chem. Soc.*, 2002, vol. 124, p. 503.
- Ahmadi, A., Attard, G., Feliu, J., *et al.*, *Langmuir*, 1999, vol. 15, p. 2420.
- Stephenson, M.J. and Lambert, R.M., *J. Phys. Chem. B*, 2001, vol. 105, p. 12832.
- Tungler, A., *React. Kinet. Catal. Lett.*, 2001, vol. 74, p. 271.
- Mäki-Arvela, P., Salmi, T., and Murzin, D.Yu., *Stud. Surf. Sci. Catal.*, 2003 (in press).
- Sutynszki, M., Szöri, K., Felföldi, K., *et al.*, *Catal. Commun.*, 2002, vol. 3, p. 125.
- Wang, G.Z., Mallat, T., and Baiker, A., *Tetrahedron Asymm.*, 1997, vol. 8, p. 2133.
- Lindholm, A., Mäki-Arvela, P., Toukoniitty, E., *et al.*, *J. Chem. Soc., Perkin Trans. I*, 2002, p. 2605.
- Huck, W.-R., Bürgi, T., Mallat, T., *et al.*, *J. Catal.*, 2002, vol. 205, p. 213.
- Nitta, Y. and Kobiro, K., *Chem. Lett.*, 1996, p. 897.
- Kun, I., Török, B., Felföldi, K., *et al.*, *Appl. Catal. A*, 2000, vol. 293, p. 71.

39. Tungler, A. and Fogassy, G., *J. Mol. Catal. A: Chem.*, 2001, vol. 173, p. 231.
40. Blaser, H.U., Jalett, H.P., Lottenbach, W., *et al.*, *J. Am. Chem. Soc.*, 2000, vol. 122, p. 12675.
41. Testa, A.C. and Augustine, R.L., *Catalysis in Organic Reactions*, New York: Dekker, 2001, vol. 82, p. 465.
42. Osawa, T., Hayashi, Y., Ozawa, A., *et al.*, *J. Mol. Catal. A: Chem.*, 2001, vol. 169, p. 289.
43. Toukoniitty, E., Mäki-Arvela, P., Kalantar Neyestanaki, A., *et al.*, *Stud. Surf. Sci. Catal.*, 2000, vol. 130, p. 3363.
44. Keane, M.A., *Langmuir*, 1997, vol. 13, p. 41.
45. Vargas, A., Bürgi, T., von Arx, M., *et al.*, *J. Catal.*, 2002, vol. 209, p. 489.
46. Huck, W.-R., Mallat, T., and Baiker, A., *Catal. Lett.*, 2000, vol. 69, p. 129.
47. Gamez, A., Köhler, J., and Bradley, J., *Catal. Lett.*, 1998, vol. 55, p. 73.
48. Toukoniitty, E., Mäki-Arvela, P., Kuusisto, J., *et al.*, *J. Mol. Catal. A: Chem.*, 2003, vol. 192, p. 135.
49. Baiker, A. and Blaser, H.-U., *Handbook of Heterogeneous Catalysis*, Ertl, G., Knözinger, H., and Weitkamp, K., Eds., Weinheim: VCH, 1997, vol. 5, p. 2422.
50. Kubicki, M., Borowiak, T., Gawron, M., *et al.*, *J. Cryst. Spectr. Res.*, 1990, vol. 20, p. 447.
51. Carley, A.F., Rajumon, M.K., Roberts, M.V., *et al.*, *J. Chem. Soc. Faraday Trans.*, 1995, vol. 91, p. 2147.
52. Ferri, D. and Bürgi, T., *J. Am. Chem. Soc.*, 2001, vol. 123, p. 12074.
53. Kubota, J. and Zaera, F., *J. Am. Chem. Soc.*, 2001, vol. 123, p. 11115.
54. Toukoniitty, E., Mäki-Arvela, P., Kalantar Neyestanaki, A., *et al.*, *Appl. Catal. A: Chem.*, 2002, vol. 235, p. 125.
55. Kukula, P. and Červený, L., *Appl. Catal. A*, 2001, vol. 210, p. 237.
56. Webb, G., *Chiral Reactions in Heterogeneous Catalysis*, Jannes, G. and Dubois, V., Eds., New York: Plenum, 1995, p. 61.
57. Lorenzo, M.O., Humblot, V., Murray, P., *et al.*, *J. Catal.*, 2002, vol. 205, p. 123.
58. Wolfson, A., Geresh, S., Landau, M.V., *et al.*, *Appl. Catal. A*, 2001, vol. 208, p. 91.
59. Klabunovskii, E.I., Vedenyapin, A.A., Chankvetadze, B.G., *et al.*, *Proc. 8th Int. Congr. Catal.*, Berlin, 1984, vol. 5, p. 543.
60. Toukoniitty, E., Mäki-Arvela, P., Kuzma, M., *et al.*, *J. Catal.*, 2001, vol. 204, p. 281.
61. Toukoniitty, E., Ševčíková, B., Mäki-Arvela, P., *et al.*, *J. Catal.*, 2003, vol. 213, p. 7.
62. Nitta, Y. and Shibata, A., *Chem. Lett.*, 1998, p. 161.
63. Kukula, P. and Červený, L., *J. Mol. Catal. A: Chem.*, 2002, vol. 185, p. 195.