Chiral Catalyst Immobilization and Recycling

Edited by D. E. De Vos
I. F. J. Vankelecom
P. A. Jacobs

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Preface

For the most part of human history, nature has monopolized chirality. Over the last decades, however, enantioselective catalysis has become the godly finger of mankind, its own instrument for synthesis of natural compounds, and for synthesis of new molecules with a substantially beneficial impact on health and environment. The field is growing at an incredible pace in academia, which continuously produces new ligands and catalysts. Additionally, large scale preparation of single enantiomers has now become an objective within reach for industry.

In such an era, books are doomed to get outdated like boulders drowning in a rising tide. However, the mere example of Ojima's book, which was published in 1993 by VCH, demonstrates that clear overviews by world experts can be an enlightening guide for scores of chemists around the world. For the present book as well, it was a prime ambition of the editors to gather leading scientists from all over the globe. We feel honored by the outstanding contributions that our authors have delivered, and we owe special thanks to all these scientists.

As enantioselective catalysis is being integrated in process schemes throughout the chemical industry, issues such as separation and reuse of expensive catalysts now come to the foreground. Thus, the publication of this book itself reflects a certain technical maturity but will hopefully also entice chemists and chemical engineers to contribute to this challenging subarea of technical chemistry.

In an introductory chapter, Blaser and his colleagues draw on their wide experience to give us a perspective on the challenges ahead, both for researchers in industry and in academia. The biggest challenge might well be, as they suggest, for people from universities and companies to look together for solutions. The next four chapters present general approaches to immobilization and recuperation of enantioselective catalysts. While Jacobs presents the major types and uses of inorganic supports in Chapter 2, Bergbreiter provides the organic polymer counterpart in Chapter 3. The focus is on the availability and preparation of the support materials, and on strategies to immobilize enantioselective catalysts. Liquid biphasic catalysis is addressed in Chapter 4. Hanson tackles specific issues, such as the ligand modifications that are required to confine a soluble catalyst to a single liquid phase. Chapter 5 is an exception in that it discusses enzyme catalysis. Based on his own experience in penicillin antibiotics syn-

thesis, Rasor compares a spectrum of methods that can lead to economical reuse of enzymes, a topic amply illustrated with realistic figures.

The remaining chapters highlight specific reactions. Hydrogenations over modified metallic surfaces are discussed in Chapters 6 to 8. Wells and Wells give a comprehensive overview of the present understanding of alkaloid modified Pt and Pd, and carefully balance the sometimes conflicting viewpoints in literature. Baiker highlights the strategies, *e.g.* computational methods, that can lead to the successful rational design of new synthetic modifiers for Pt hydrogenation catalysts. The Japanese contribution of Tai and Sugimura shows in detail the evolution of the modified Ni catalysts, starting from a very moderate enantioselectivity in the early days, up to the excellent e.e.'s and profound understanding that have been achieved in recent years.

Catalysis with heterogenized metal complexes or ligands is the focus of Chapters 9 to 11. Bayston and Polywka introduce the important group of phosphine ligands for enantioselective hydrogenations and hydroformylations. The Salvadori group evaluates, based on its rich experience in the field, heterogenized epoxidation and dihydroxylation catalysts, for instance of the Jacobsen and Sharpless types. Finally, the group of Brunel discusses the variety of heterogenized, enantioselective catalysts that can be used to create new carbon-carbon bonds.

Ultimately, Chapter 12 deals with heterogeneous diastereoselective synthesis. An increasing number of recent publications shows that, in certain cases, this strategy can be an economically attractive alternative to enantioselective catalysis.

Finally, we thank Nico Wuestenberg for his skillful assistance in handling files of bewildering formats as well as the publishing editors of VCH for their fruitful collaboration. Two of the editors (DEDV and IFJV) are indebted to F.W.O. Vlaanderen for post-doctoral fellowships.

Dirk E. De Vos
Ivo F.J. Vankelecom
Pierre A. Jacobs

Leuven,
March 9, 2000

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List of Abbreviations

AA	Acetoacetate
7-ACA	7-Amino-cephalosporanic acid
Acac	Acetylacetone
AC-SR	Acetic acid type silicone rubber
AD	Asymmetric dihydroxylation
AdA	1-Adamantanecarboxylic acid
7-ADCA	7-Aminodeacetoxycephalosporanic acid
AE	Asymmetric epoxidation
Aib	α-Aminoisobutyric acid
AIBN	α,α'-Azoisobutyronitrile
6-APA	6-Aminopenicillanic acid
AQN	Anthraquinone
B/n	Branched/normal
BDPP	2,4-Bis(diphenylphosphino)pentane
BDPP-DS	Disulfonated 2,4-bis(diphenylphosphino)pentane
BDPP-MS	Monosulfonated 2,4-bis(diphenylphosphino)pentane
BDPP-TrS	Trisulfonated 2,4-bis(diphenylphosphino)pentane
BDPP-TS	Tetrasulfonated 2,4-bis(diphenylphosphino)pentane
BINAP	2,2′-Bis(diphenylphosphanyl)-1,1′-binaphthyl
BINAPHOS	[2-Diphenylphosphino-1,1′-dinaphthalen-2′-yl][1,1′-dinaphthalene-2,2′-diyl]phosphite
BINAS	Sulfonated NAPHOS
BINOL	1,1′-Bi(2-naphthol)
BIPHLOPHOS	4,6,4′,6′-Tetrachloro-2,2′-bis-(diphenylphosphinomethyl)-1,1′-biphenyl
BISBI	2,2′-Bis-(diphenylphosphinomethyl)-1,1′-biphenyl
BPPM	1-*tert*-Butoxycarbonyl-4-diphenylphosphino-(2-diphenylphosphino-methyl)pyrrolidine
*i*BuA	Isobutyric acid
CAL-B	Lipase from *Candida antarctica*, type B
CD	Cinchonidine
CLB	4-Chlorobenzoate ester
CLEC	Cross-linked enzyme crystal

CN	Cinchonine
COD	*cis,cis*-1,5-cyclooctadiene
m-CPBA	*meta*-Chloroperoxybenzoic acid
CPG	Controlled pore glass
CRL	Lipase from *Candida rugosa*
CSD	Crystal size distribution
D_c	Crystal diameter
DABCO	1,4-Diazabicyclo[2.2.2]octane
D-AOD	D-Amino acid oxidase
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
d.c.	Dielectric constant
d.e.	Diastereomer excess
DHCD	9-Deoxy-10,11-dihydrocinchonidine
DIOP	1,4-Bis(diphenylphosphino)-1,4-dideoxy-2,3-O-isopropylidene-threitol
DIPAMP	1,2-Bis[(o-methoxy)phenylphosphino]ethane
DMI	Dimethylitaconate
DNi	Nickel prepared by the thermal decomposition of nickel formate
DOPA	(3-(3,4-Dihydroxyphenyl)-alanine)
DPEN	1,2-Diphenylethylenediamine
DPP	Diphenylpyrazinopyridazine diether
DP-PHAL	Diphenylphthalazine diether
DVB	Divinylbenzene
E_A	Activation energy
e.d.a.	Enantiodifferentiating ability
EDCA	Ethyldicyclohexylamine
e.e.	Enantiomeric excess
EGDMA	Ethylene glycol dimethacrylate
EL	Ethyl lactate
EMR	Enzyme membrane reactor
E-region	Enantiodifferentiating region on the catalyst
EtAc	Ethyl acetate
EtPy	Ethyl pyruvate
GA	Glycolic acid
Gl-acylase	Glutaric acid acylase
h_8-BINAP	Octahydro-BINAP
HCD	10,11-Dihydrocinchonidine
HDMS	Hexadimethylsilazane
HEMA	Hydroxyethyl methacrylate
HNi	Nickel prepared by the hydrogenation of NiO
HP	4-Hydroxy-2-pentanone
HQ	10,11-Dihydroquinine
HQD	10,11-Dihydroquinidine
i	Intrinsic e.d.a.
IPB	Insoluble polymer-bound
Kg	Kieselguhr
LDH	Layered double hydroxide

MA	Malic acid
MAA	Methyl acetoacetate
MA-Mni	Malic acid modified Ni
McA	1-Methyl-1-cyclohexanecarboxylic acid
O-MeDHCD	*O*-Methyl derivatives
Me-DUPHOS	1,2-Bis(2,5-dimethylphospholano)benzene
MEPY	Methyl pyroglutamate
MePy	Methyl pyruvate
MHB	Methyl 3-hydroxybutanoate
MMA	Methyl methacrylate
MNi	Modified nickel
MP	Methyl pyruvate
MPC	Methyl piperazine-2-carboxylate
MPr	Methyl propionate
MTS	Micelle-templated silica
MVK	Methyl vinyl ketone
NAPHOS	2,2′-Bis-(diphenylphosphinomethyl)-1,1′-binaphthyl
NEA	1-(1-Naphthyl)ethylamine
NMO	*N*-Methylmorpholine-*N*-oxide
NORPHOS	2,3-Bis(diphenylphosphino)bicyclo[2.2.1]hept-5-ene
N-region	Non-enantiodifferentiating region on the catalyst
OX-SR	Oxime type SR
1P	Interaction through one hydrogen bond
2P	Interaction through two hydrogen bonds
PA	Pivalic acid
PAA	Phenylacetic acid
PCL	Lipase from *Pseudomonas cepacia*
PD	2,4-Pentanediols
PDHCD	2-Phenyl-9-deoxy-10,11-dihydrocinchonidine
PDMS	Polydimethylsiloxane
PEG	Polyethylene glycol
PGA	Penicillin G amidase, also called Penicillin acylase
PHAL	Phthalazine
PhIO	Iodosylbenzene
PHN	Phenantryl
PHPG	D-*p*-Hydroxyphenylglycine
PLE	Esterase from pig liver
PNE	*(R)*-2-(1-Pyrrolidinyl)-1-(1-naphthyl)ethanol
PPL	Lipase from porcine pancreas
c-Pr	Cyclopropyl group
PYCA	2-Pyrrolidone-5-carboxylate
PYR	Diphenylpyrimidine diether
QD	Quinidine
QN	Quinine
RNi	Raney nickel catalyst
RNiA	Acid-treated Raney nickel

RNiH	Raney-type leaching at high temperature
RNiL	Raney-type leaching at low temperature
RNiU	Ultrasound-irradiated RNi
SALEN	Bis(salicylidene)ethylenediamine
SAP	Supported aqueous phase
SAPC	Supported aqueous phase catalyst
SDS	Sodium dodecyl sulfate
SEM	Scanning electron microscopy
SLP	Supported liquid phase
SPC	Supported nickel catalyst
SR	Silicone rubber
TA	Tartaric acid
TADDOL	2,3-*O*-Isopropylidene-1,1,4,4-tetraphenyl-threitol
TAH_2	Free acid of TA
TAHNa	Monosodium salt of TA
$TANa_2$	Disodium salt of TA
THF	Tetrahydrofuran
Ti-PILC	Titanium-pillared montmorillonite
TMC	Transition metal complexes
TOF	Turnover frequency
TON	Turnover number
TPE	1-(9-Triptycenyl)-2-(1-pyrrolidinyl)ethanol
U	Units
xyl	Xylene

1 Enantioselective Heterogeneous Catalysis: Academic and Industrial Challenges

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1.1 Introduction

The trend towards the application of single enantiomers of chiral compounds is undoubtedly increasing. This is especially the case for pharmaceuticals but also for agrochemicals, flavors and fragrances [1, 2]. Among the various methods to selectively produce one single enantiomer of a chiral compound, enantioselective catalysis is arguably the most attractive method. With a minute quantity of a (usually expensive) chiral auxiliary, large amounts of the desired product can be produced. Homogeneous metal complexes with chiral ligands are currently the most widely used and versatile enantioselective catalysts. From an industrial point of view, however, catalysts that are not soluble in the same phase as the organic reactant have the inherent advantage of being easily separated and often having better handling properties. Such catalysts can be truly heterogeneous, i.e. insoluble, or they can be soluble in a second phase that is immiscible with the organic one [3–6]. Here, we will use the term 'heterogeneous catalyst' for both cases.

In this overview, we will first discuss the situation and requirements for the industrial application of a catalytic method and more specifically of heterogeneous catalysts. Thereafter, the present scope and limitations of different types of enantioselective heterogeneous catalysts are documented (with reference to the appropriate chapters in this book) and assessed from an application point of view. Based on this analysis, academic and industrial challenges are then defined.

1.2 The Industrial Process in General and the Specific Prerequisites for Chiral Catalysts

In order to understand the challenges facing the application of chiral catalysts in the fine chemicals industry, one not only has to understand the essential industrial require-

ments but also how process development is carried out and which criteria determine the suitability of a catalyst [1, 2].

1.2.1 Characteristics of the Manufacture of Enantiomerically Pure Products

The manufacture of chiral fine chemicals such as pharmaceuticals or agrochemicals can be characterized as follows (numbers given in parentheses reflect the experience of the authors):

- Multifunctional molecules produced via multistep syntheses (from 5 to over 10 steps for pharmaceuticals and 3 to 7 steps for agrochemicals) with short product lives (often less than 20 years).
- Relatively small-scale products (1–1000 t/y for pharmaceuticals, 500–10000 t/yr for agrochemicals), usually produced in multipurpose batch equipment.
- High purity requirements (usually >99% and <10 ppm metal residue in pharmaceuticals).
- High added values and therefore tolerance of higher process costs (especially for very effective, small-scale products).
- Short development time for the production process (< few months to 1–2 years), since marketing time affects the profitability of the product. In addition, development costs for a specific compound must be kept low, since process development often starts at an early phase when the chances of product success are low.
- At least in European companies, chemical development is carried out by all-round organic chemists, sometimes in collaboration with technology specialists.

1.2.2 Process development: Critical Factors for the Application of (Heterogeneous) Enantioselective Catalysts

The first decision to be made at the start of process development is the choice of a strategy that promises the best answer in the shortest time. This strategy will depend on a number of considerations: the goal of the development, the know-how of the investigators, the time frame, the available manpower and equipment etc. In process development, there is usually a hierarchy of goals (or criteria) to be met. It is useful to divide the development of a manufacturing process into different phases:

Phase 1: Outlining and assessing possible synthetic routes on paper.
Phase 2: Demonstrating the chemical feasibility of the key step, often the enantioselective catalytic reaction.
Phase 3: Optimizing the key catalytic reaction.
Phase 4: Optimizing the overall process.

In the final analysis, the choice whether a synthesis with an enantioselective catalytic step is chosen depends very often on the answers to two questions:

- Can the costs for the overall manufacturing process compete with alternative routes?
- Can the catalytic step be developed in the given time frame?

Presuming that enantioselective catalysis is the method of choice, the next question in the context of our treatise is whether to choose homogeneous or heterogeneous catalysis.

Table 1.1 gives a very condensed summary of the strong and weak points of the two classes of catalysts. This table is a somewhat subjective view of the authors and mirrors their personal experiences. Moreover, the importance of the various factors changes for any specific catalytic transformation and, in some cases, might well be just the opposite!

1.2.3 Important Criteria for Enantioselective Catalysts

As a consequence of the peculiarities of enantioselective catalysis described above, the following critical factors often determine the viability of an enantioselective process:

Enantioselectivity, expressed as enantiomeric excess (e.e., %). The enantioselectivity of a catalyst should be in the range of 99% for pharmaceuticals if further enrichment is not possible (this is relatively rare). E.e.'s >80% are acceptable for agrochemicals or if further enrichment is easy, e.g. via recrystallization or via separation of diastereomers later in the synthesis; in our experience, this is very often the case.

Catalyst productivity, given as turnover number (TON), determines catalyst costs. In our experience, TONs for (homogeneous) enantioselective hydrogenation reactions ought to be >1000 for small-scale, high-value products and >50000 for large-scale or less expensive products. For C-C coupling reactions and probably also for some other reaction types with high added value or for very inexpensive catalysts, lower TONs

Table 1.1. Strong and weak points of homogeneous and heterogeneous catalysts.

	Homogeneous	Heterogeneous
Strong points	Defined on molecular level (close to organic chemistry)	separation, recovery, recycling
	Scope, variability (design?) (commercial) preparation	stability, handling
Weak points	Sensitivity (handling, stability)	characterization (understanding on molecular level)
	Activity, productivity (of many literature procedures)	availability, preparation (needs special know-how), reproducibility diffusion to and within catalyst

might be acceptable. Much lower limits might apply if catalyst reuse is possible without much loss in selectivity and activity.

Catalyst activity. For preparative applications, a useful number is the turnover frequency (TOF) at high conversion. Because this value determines the production capacity, TOFs (especially for high pressure reactions) ought to be $>500\ h^{-1}$ for small-scale and $>10\,000\ h^{-1}$ for large-scale products. For applications in standard equipment, lower TOFs might be acceptable.

Separation should be achieved by a simple operation such as distillation, filtration or phase separation, and at least 95% of the catalyst should be recovered. Methods like ultrafiltration or precipitation (e.g. for separating soluble polymer supports) usually require expensive equipment.

Stability. If the advantage of the heterogeneous catalyst is its recyclability, it has not only to show a stable catalytic performance, but it should also be mechanically stable and the active component must not leach (chemical stability).

Price of catalysts. The catalyst price will only be important at a later stage, when the cost of goods of the desired product is evaluated. For homogeneous catalysts, the chiral ligand often is the most expensive component (typical prices for the most important chiral phosphines are 100–500 \$/g for laboratory quantities and 5000 to >20 000 \$/kg on a larger scale). For heterogeneous systems, the dominant cost elements depend on the type of catalyst.

Availability of the catalysts. If an enantioselective catalyst is not available at the right time and in the appropriate quantity, it will not be applied due to the time limitation of process development. At present, only very few homogeneous catalysts and ligands are commercially available in technical quantities, so that their large-scale synthesis must be part of the process development. The situation for heterogeneous catalyst systems is even more difficult, because their preparation and characterization require know-how that is usually not available in a standard development laboratory.

Which of these criteria will be critical for the development of a specific process will depend on the particular catalyst and transformation, the scale of the process, the technical experience and the production facilities of a company as well as the maturity of the catalytic process.

1.3 The General Challenges

In many areas described in the following chapters, much remains to be done for both academia and industry. A special challenge for both communities is the interdisciplin-

ary nature of the field of heterogeneous enantioselective catalysis. It comprises the preparation of such widely different materials as polymers, inorganic supports, small metal particles, colloids, complex organic molecules and organometallic complexes. We have listed some crucial points which, in our view, are important for progress in heterogeneous enantioselective catalysis. Needless to say, a good dialog between industry and academia is probably the most important factor for the rate of progress, because the different approaches and goals are very often complimentary.

1.3.1 For Academia

Generally, the central task of academic researchers is to find new concepts, catalysts and reactions, to demonstrate proof of concept of a catalytic reaction and to investigate its mechanism.

Development of new concepts, new catalysts and processes. Most of the existing enantioselective catalytic systems lack general applicability. Although some new concepts (such as artificial catalytic antibodies) and technologies (e.g., fluorous biphasic reactions, or immobilization on an aqueous layer on a porous support) have been developed and applied recently, there is a need for new ideas which eventually will lead to new catalysts – hopefully with broader applicability.

Determination of synthetic scope and limitations. Well characterized catalysts with clear scope and limitations are much more likely to be applied by the synthetic chemist (both at the university and industry) who usually has little time and patience for trial and error. In the literature, many new systems are tested only on one or two model substrates under a very narrow set of reaction conditions. For an immobilized catalyst, a realistic comparison with the corresponding homogeneous systems is quite often lacking and, in addition, little information on catalyst activity or productivity is provided.

Characterization, mechanistic investigation, understanding and interpretation. Many of the heterogeneous systems are very difficult to characterize and are not well understood. Improved characterization should lead to better reproducibility, whereas understanding on a molecular level (if possible) can often help to improve existing concepts and develop new catalytic systems.

1.3.2 For Industry

Its main task is to apply the know-how created by basic research to practical problems. For the catalyst user, this means to adapt catalysts and processes to industrial conditions, and for catalyst manufacturers, to make available more well-defined catalysts on a commercial basis.

Development, up-scale and commercialization of industrially useful catalysts and processes. New systems, as described in the literature, are often unsuited for indus-

trial application (exotic solvents, reactions conditions, too low productivity and activity, etc.). Since the industrial chemist knows the specific prerequisites of the process, it is his or her task to determine the technical scope and limitations and to adapt catalytic systems to the technical problems and conditions. In addition, investigation of technical aspects such as catalyst stability, recycling, metal leaching are often necessary.

Toolbox for fast development and commercial availability of catalysts. In many cases, development of technical processes with heterogeneous or immobilized chiral catalysts is very tedious. Automation of both the development of the best suited catalyst as well as the optimization of reaction conditions should improve that considerably. For this endeavor, the ready and easy availability of a large collection of (tunable) catalysts is necessary to get results in a timely manner. Involvement of the catalyst producers and commercial availability of versatile catalysts would certainly help their application.

1.4 Chiral Heterogeneous Catalysts: State of the Art and Future Challenges

In this section, the present scope as well as the specific problems and challenges are analyzed for the most important types of enantioselective heterogeneous catalytic systems. One can roughly distinguish between three types of enantioselective heterogeneous catalysts:

- Heterogeneous catalysts with demonstrated catalytic activities that are rendered chiral by modification with a chiral auxiliary,
- Homogeneous catalysts with demonstrated enantioselectivity and activity modified in such a way as to become heterogeneous (as defined in the introduction),
- Catalysts with no known precedent in these two categories.

1.4.1 Heterogeneous Catalysts Modified with a Chiral Auxiliary

1.4.1.1 Metallic Catalysts on Chiral Supports

Metals supported on chiral biopolymers and natural fibers were the first somewhat successful approach to produce enantioselective heterogeneous catalysts. For a review, see Blaser and Müller [3]. With the exception of Pd/silk fibroin where e.e.'s of up to 66% were reported for the hydrogenation of an oxazolinone derivative, the optical yields were very low. Later, it was found that the results observed with silk fibroin were not reproducible and this approach was practically abandoned.

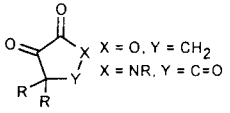
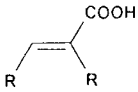
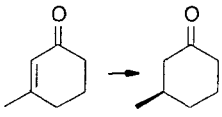
Assessment and challenge. Clearly, fresh ideas would be needed to revive this class of enantioselective catalysts but at the moment, no leads exist for a promising revival.

1.4.1.2 Metallic Catalysts Modified with a Low Molecular Weight Chiral Auxiliary

This is undoubtedly the most successful approach to render an already active catalyst enantioselective, and several recent informative reviews on different aspects have been published [7–12]. The investigation of heterogeneous chiral hydrogenation catalysts started in the late fifties in Japan and has seen a renaissance in the last few years. Despite many efforts, only two classes of modified catalyst systems have been found to be of industrial interest at this time: Ni catalysts modified with tartaric acid and Pt and, to a lesser degree, Pd catalysts modified with cinchona alkaloids and analogs thereof. However, several laboratories are working to expand the scope of this interesting and potentially very versatile class of chiral catalysts.

Since these catalytic systems are covered in Chapters 6–8, we will not discuss but only list reactions and catalysts that have either sufficiently high enantioselectivities for synthetic applications or are of conceptual importance (see Table 1.1). One exception: in two very recent papers the highly selective hydrogenation of a variety of α-ketoacetals with cinchona modified Pt catalysts was described with enantioselectivities up to 97% [13, 14]. Since chiral α-hydroxyacetals are versatile intermediates for a variety of chiral building blocks (e.g., 1,2-diols, α-hydroxy acids, 1,2-amino alcohols), the new enantioselective transformation is also of synthetic significance.

Table 1.2. State of the art for the synthetic application of modified metallic catalysts.

Substrate	R/R'	Catalyst	Modifier	E.e. (%)	TOF (1/h)[a]	Ref.
CH_3COR	Alk	Ra-Ni	Tartrate/NaBr[b]	70–85	$\ll 1$	[10]
$PhCOCF_3$		Pt/Al_2O_3	Cinchona alkaloid	56	150	[15]
$RCOCOOR'$[b]	R/Alk,H	Pt/Al_2O_3	Cinchona alkaloid	85–98	Low->50000	[7, 8, 16]
$RCOCH(OR')_2$	R/Alk	Pt/Al_2O_3	Cinchona alkaloid	50–97	Low->20000	[13, 14]
 X = O, Y = CH_2 X = NR, Y = C=O	Alk	Pt/Al_2O_3	Cinchona alkaloid	92	50	[17, 18]
$RCOCH_2COOR'$[c]	Alk/Et	Ra-Ni	Tartrate/NaBr	83–98	<1	[19]
$CH_3COCH_2COCH_3$		Ra-Ni	Tartrate/NaBr	91(diol)	1	[20]
	Alk, Aryl	Pd/TiO_2	Cinchona alkaloid	50–72	400	[8, 21]
		Pd black	Vinca alkaloid	53	–	[22]

[a] TOFs for complete conversion, rough estimates. [b] In presence of pivalic acid. [c] Technical applications with R' = Et have been reported.

Assessment and challenges. Several transformations have already been developed for commercial applications or are mature to be used on a technical basis [3, 4]. There are some good and challenging ideas on the mode of action of the chiral catalysts, but by far no mechanism that explains all major effects or allows to design new catalysts. In the case of the Pt–cinchona system, both catalyst and some of the modifiers are available commercially or easy to prepare. Nevertheless, reproducibility is still an issue even here and especially for the Ni catalysts. Furthermore, the preparation procedures (soaking in dilute solutions, extractions etc.) and pretreatments (high temperature prereduction under hydrogen, sonication etc.) are often cumbersome. Besides these technical problems, the sensitivity for catalyst poisons and starting material quality is a major drawback. Last but not least, the scope of these systems is still very narrow, and only very few substrates give satisfactory activities and selectivities.

The challenge for academia is further progress in understanding mechanisms, identifying catalyst poisons and developing new catalytic systems. The challenge for catalyst producers is developing reproducible catalysts that do not need pretreatment and are less sensitive to poisoning, and for industrial process developers, optimizing existing systems with respect to technical applicability.

1.4.1.3 Metal Oxide Catalysts Modified with a Chiral Auxiliary having Low Molecular Weight

Titanium-pillared montmorillonite (Ti-PILC) modified with tartrates was described as a heterogeneous Sharpless epoxidation catalyst [23]. Unfortunately, the results could not be reproduced by other laboratories. Very recently, tantalum tartrate complexes grafted to silica were described with e.e.'s of up to 98% and promising activities for the epoxidation of allylic alcohols. Remarkably, the homogeneous Ta-complex was neither stable nor catalytically active [24]. Metal oxides modified with histamine showed modest efficiencies for the kinetic resolution of activated aminoacid esters ($k_R/k_S \approx 2$) [25]. Silica or alumina treated with diethyl aluminium chloride and menthol catalyzed the Diels-Alder reaction between cyclopentadiene and methacrolein with modest enantioselectivities of up to 31% [26]. Zeolite HY, modified with chiral sulfoxides, had remarkable selectivities for the kinetic resolution of 2-butanol by dehydration ($k_S/k_R = 39$). The enantioselectivity is due to the preferential acceleration of the dehydration of one enantiomer [27]. A NaY zeolite modified with norephedrine allowed the photocyclization of tropolone methyl ether with an e.e. of up to 50%, albeit not in a really catalytic fashion [28].

Assessment and challenges. Although solid acids and bases are increasingly applied for the catalytic synthesis of fine chemicals, chirally modified versions, though potentially interesting because of their variability, are definitely not ready for synthetic applications. In many cases, the preparation of the catalysts is not trivial and not always reproducible. There is very little known about their mode of action, and few new concepts are currently being discussed. Filling this gap is an important fundamental challenge for academic laboratories with a good background in metal oxide catalysis.