Tetrahedron: Asymmetry Vol. 2, No. 9, pp 843-866, 1991
Printed in Great Britain

0957-4166/91 $3.00+.00
Pergamon Press plc

TETRAHEDRON: ASYMMETRY REPORT NUMBER 6

Enantioselective Synthesis Using Chiral Heterogeneous Catalysts.

Hans-Ulrich Blaser

Central Research Services, CIBA-GEIGY AG, R 1055.6
CH-4002 BASEL, Switzerland

(*Received* 17 *June* 1991)

Abstract: The application of solid chiral catalysts for the enantioselective synthesis of chiral molecules is reviewed. An attempt has been made to discuss critically the scope and limitations of these catalytic systems and their value for the synthetic organic chemist. The different catalytic systems described in the literature are tabulated and the enantioselectivities observed for different reactions are summarized according to the functional group which is transformed. Conclusions concerning synthetic and commercial-scale applications and some ideas on the mode of action of chiral solid catalysts are presented.

Table of contents

1. Introduction

Enantioselective synthesis is a topic of undisputable importance in current chemical research and there is a steady flow of articles, reviews and books on almost every aspect involved. The present overview is an updated and revised version of a recent survey[1] and will concentrate mainly on the *synthetic application* of heterogeneous catalysts for the enantioselective preparation of a variety of chiral molecules. From a technical point of view, enantioselective heterogeneous catalysts are often preferable to homogeneous catalysts because of their handling and separation properties. From a synthetic point of view, there are interesting reactions that are efficiently catalyzed by chiral heterogeneous catalysts. Finally, from a theoretical or conceptional point of view, enantioselective catalysis with chiral solids is a fascinating and challenging area of chemistry because, compared to soluble catalysts, there is an additional structural dimension involved. Also included are enantioselective electrochemical reactions and reactions in a chiral crystalline environment. On the other hand, immobilized homogeneous complexes or bio-catalysts are not discussed since the problems that arise differ in many respects and require different strategies and methods to solve them.[2] In the course of the preparation of this manuscript several reviews covering various aspects of heterogeneous enantioselective catalysis have been found to be very informative and are recommended for further information.[3-15]

An enantioselective catalyst has two functions: First, it has to perform what one could call the chemical catalysis, here named *activating function*. Second, it has to control the stereochemical outcome of the reaction and we term this the *controlling function*. The two functions can be performed by the same or by two different agents. Table 1 shows a classification of different types of enantioselective systems described in the literature where an inherently chiral or a chirally modified solid catalyst is involved (see also Tables 2-5). Two extreme cases can be distinguished: the reaction is either catalyzed at the surface of a "hard" solid (e.g. a metal) or it can occur inside a "soft" material (e.g. an organic polymer). In the first case, the modifier or support probably controls the adsorption of the substrate and thus the stereochemistry. In the second case, the activation and the stereocontrol occur inside a three dimensional network comparable to an enzyme.

TABLE 1. Classification of chiral heterogeneous catalytic systems.

Activation	Control	Reaction type
metallic surface	modifier or support	hydrogenation hydrogenolysis isomerization dehydrogenation electrochemistry
metal salt or oxide	modifier	polymerization isomerization epoxidation
chiral metal salt	chiral metal salt	polymerization carbene addition SN_2 reaction
metallic surface	polymer	hydrogenation electrochemistry
chiral polymer	chiral polymer	nucleophilic addition epoxidation
hv or none	crystal	addition reactions dimerization reduction Wittig reaction

2. Historical background

In the last 60 years a great number of different chiral heterogeneous catalysts have been described. This paragraph gives some historical background and an overview on the catalytic systems that have evolved. The catalysts are numbered according to their function: H, hydrogenation catalysts, Table 2; E, electrochemical systems, Table 3; B, base catalysts, Table 4; M, miscellaneous catalysts, Table 5.

Early attempts of what was then called "absolute or total asymmetric synthesis" with chiral heterogeneous catalysts used nature (naturally!) both as a model and as a challenge. Hypotheses on the origin of chirality on earth and early ideas of the nature of enzymes strongly influenced this period.[16] The following approaches were tried: First, existing heterogeneous catalysts were modified by the addition of naturally occuring chiral molecules (the structures of important modifiers are depicted in Fig. 1). Second, chiral solids such as quartz or natural fibres were used as supports for metallic catalysts. Both approaches proved to be successful and even if the optical yields were, with few exceptions, very low or not even determined quantitatively the basic feasibility of heterogeneous enantioselective catalysis was established.

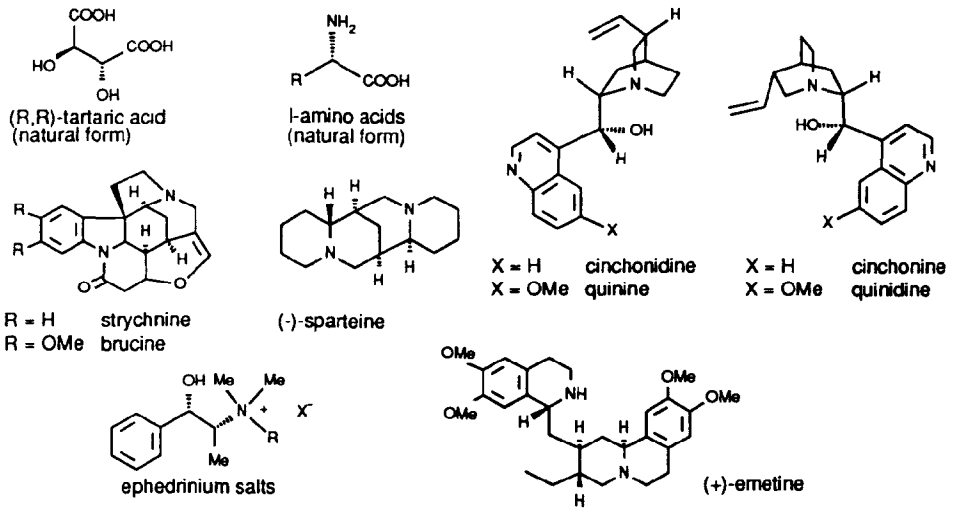


Fig. 1. Structures of the most important chiral modifiers. Not shown are the sugars and biopolymers used. In some cases the naturally occuring compound was derivatized for best effects.

It is not clear whether the ZnO/fructose catalyst **B1** described by Erlenmeyer[17] in 1922 was really heterogeneous but it is the earliest reported example of the combination of a modifier and a catalyst. Much later, Lipkin[18] described in 1939 a Pt catalyst modified with hydrocinchonine **H2** (as salt of the substrate β-methyl-cinnamic acid). Nakamura[19] in 1940 and later Isoda[20] and Izumi[6] chose chiral acids to modify Pt- and Ni-catalysts **H4, H7** eventually leading to the best known enantioselective heterogeneous catalytic systems: Ni/tartrate/NaBr catalysts **H9** which are able to hydrogenate β-ketoesters with optical yields as high as 92%.[3,6,26,79] Other modifiers were not very effective and were not further investigated. A notable exception are the cinchona alkaloid modified Pt catalysts **H14** first described by Orito[21] for the asymmetric hydro-

genation of α-ketoesters with optical yields reaching 95%.[22] Alkaloid modified electrochemical systems **E1**[23] as well as Pd/cinchona catalysts **H15**[24,25] have also been reported to give moderate enantioselectivities.

The use of chiral supports was first reported by Schwab[27] in 1932: Cu, Ni, Pd and Pt on quartz **H1** were used to dehydrogenate racemic 2-butanol. At low conversions, a measurable optical rotation of the reaction solution indicated that one enantiomer of the substrate had reacted preferentially (ee≈10%). Because left- and right-handed quartz gave the opposite optical rotations it was deduced that the chiral arrangement of the crystal was indeed responsible for this kinetic resolution (for a review see Klabunovskii[10]).

Later, biopolymers such as natural fibres like silk fibroin **H5** (1956, Akabori[28]) and cellulose **H12** (1970, Harada[29]), or polysaccharides **H8** (1959, Balandin[30]) were employed as chiral carriers or as protective polymer for several metals. With the exception of Pd/silk fibroin **H5**, where ee's up to 66% were reported,[20] the optical yields observed for hydrogenation catalysts from natural or synthetic chiral supports were very low and it was later found that the results observed with silk fibroin were not reproducible.[6] The use of synthetic polyamines **B5** was first reported by Tsuboyama[31] in 1962. This led to the development of polypeptides **M5**[32] and **M10**[110] as catalysts for the epoxidation of chalcones (ee's up to 99%) and of polymer coated electrodes **E5** for the oxidation of phenyl sulfides (ee's up to 93%).[23]

In recent years several new types of enantioselective solid catalysts were developed and described to be effective for the stereocontrol of various reaction types: Chiral crystals **M2** (1969, Schmidt[33]), metal tartrates **M4** (1979, Marchetti[34]), **M7**[50] and **M8**[86], chiral crystalline hosts **M6** (1983, Tanaka[35]) and **M9**[71], and finally a heterogeneous modification of the Sharpless epoxidation using titanium-pillared montmorillonite **M10** (1990, Choudary[36]).

3. Heterogeneous enantioselective catalytic systems

In this chapter we summarize what is known about chiral heterogeneous catalytic systems (somewhat arbitrarily divided into four different classes) in terms of characterization, influence of structural and preparation parameters and related aspects. Because the preparative application of these catalysts is the main topic of the present review (see next chapter), the description of the catalysts is very condensed and we refer to pertinent references for more detailed information.

Before discussing the various chiral catalysts the problem of *substrate specificity* should be mentioned: It is quite common that very selective catalysts are highly substrate specific, i.e. are only effective with certain substrates. A case in point are the enzymes which often accept only one single substrate (the "natural" substrate) whereas even slightly modified molecules react with lower rates and/or lower selectivities. More often the specificity of a given catalyst is connected with certain substrate classes or types. Naturally, a catalyst is much more useful and convenient if the substrate specificity is low i.e. when as many transformations as possible are catalyzed with high selectivity. Enantioselective heterogeneous catalysts are usually selective for a given class of compounds e.g. Ni/tartrate **H9** for the hydrogenation of β-functionalised ketones[3,6] or polypeptide coated electrodes **E5** for the oxidation of aryl sulfides.[23] But specificity for one single substrate has also been reported.[37] When the activating and controlling function are separate, these have to be optimally matched in order to give an effective enantioselective catalyst, e.g. tartrate is only a good modifier with Ni but not with Pt[25] whereas cinchona alkaloids lead to selective catalysts with Pt, Rh or Pd but not with Ni or Ru.[25,37,38]

3.1 Hydrogenation catalysts

Hydrogenation is arguably the most important synthetic application of enantioselective catalysts because of its potential to produce a large variety of chiral functional groups. It is therefore not surprising that the largest number of catalytic systems has been described for this reaction type. Even though Table 2 shows an impressive number of entries, a closer inspection reveals that there are really only two families of synthetically useful catalytic systems: Ni catalyst modified with tartate/NaBr **H9** and Pt (Pd) catalysts modified with cinchona alkaloids **H14, H15**. These are also the only ones that have been investigated systematically. In the next few paragraphs we will summarize important results concerning these catalysts. All the other catalytic systems listed are either not very selective or not easily reproducible or both; as mentioned above, they are interesting from a historical and some also from a conceptual perspective.

TABLE 2. Enantioselective heterogeneous hydrogenation catalysts

Year[1)]	Cat.[2)]	Activation / Control	Reduced function (best ee)	Ref.
1932	H1	Cu, Ni, Pd, Pt / quartz	CH-OH dehydrog. (≈10)	9,10,27
1939	H2	PtO_2 / cinchonine	C=C (8)	18
1939	H3	Raney Ni / glucose	C=C (≈10)	94,95
1940	H4	Pt black / chiral acids	C=N (18)	18
1956	H5	Pd / silk fibroin	C=N (30), C=C (66)	20,28
1958	H6	Raney Ni / camphor	C=O (24)	20
1958	H7	(Raney) Ni / amino acid	C=O (10), C=N (5), C=C (50)	3,20
1959	H8	Pd, Pt-colloid / polysaccharide	C=O (1), C=N (n.d.)	9,30
1964	H9	(Raney) Ni / tartrate/(NaBr)	C=O (92), C=C (17)	3,26,79,112
1966	H10	Pd/C / amine or amino acid	C=O (8), C=N (10), C=C (4)	97-99
1967	H11	Pd, Ni, Ru / polypeptide	C=C (6)	100,101
1970	H12	Pd / cellulose	C=C, C=O (<1)	29a
1970	H13	Pd/ion exch.resin / amino acid	C=C, C=O (<1)	29b
1979	H14	Pt / cinchona alkaloid	C=O (95), C=N (15), C=C (11), C-Cl (25)	21,22,25,37
1985	H15	Pd / cinchona alkaloid	C=C (30), C-Cl (50)	24,37
1985	H16	Pt / zeolite/chiral amine	C=C (n.d.)	102
1987	H17	Pd/C / cyclodextrine	C=O (1)	103

1) First description 2) number of catalyst system

Tartaric acid (tartrate) modified (Ni) catalysts **H9**. This is by far the best studied family of heterogeneous enantioselective catalysts. Good reviews are available and cover almost every aspect of these catalytic systems.[3,6,8,13,15,39] Since most investigations have been carried out only with methyl acetoacetate as substrate, most of the following statements can only be generalized with caution.

Substrates: β-functionalised ketones ***2-4***, β-diketones ***5*** and methylketones ***6*** are preferred substrates.[3,6] (For substrate numbers see Tables 6 - 14).

Modifier: Tartaric acid is clearly superior to α-amino acids or other α-hydroxy acids.[3,6]

Catalyst: Freshly prepared Raney nickel is the preferred catalyst for preparative purposes. Supported Ni catalysts are suitable.[3,6,8] Bimetallic and noble metal catalysts have been studied.[8,15]

Modifying conditions: Modifier concentration, pH, temperature, time and sometimes modification procedures are crucial for a good catalyst performance.[3,6] Treating the modified catalyst with ultra sound has recently been reported to lead to enhanced activity and enantioselectivity.[26]

Co-modifiers: NaBr enhances the optical yields by 10-30%, other modifiers have been studied.[3,6]

Solvent and additives: Aprotic semipolar solvents, especially methyl propionate, give the highest ee's. But other trends have been reported.[6,13] The addition of weak acids increases the ee's, especially pivalic acid in the hydrogenation of methyl ketones,[69] while water is detrimental.[3,6] The reaction can also be carried out in the gas phase but optical yields are lower.[39]

Reaction conditions: Temperatures between 60-100 °C and H_2 pressures between 80-120 bar usually give good enantioselectivities. No simple correlation has been found between optical yield and p or T.[3,6]

Cinchona modified (Pt) catalysts **H14, H15**. A more extended summary can be found elsewhere[1]. With few exceptions all the following statements are strictly valid only for the hydrogenation of α-ketoesters ***1c*** and ***1h***.

Substrates: Preferred substrates are α-ketoesters ***1***.[38]

Modifier: Naturally occuring cinchona alkaloids with only slight modifications give the best results.[21,40] The modifier concentration has a large influence on the enantioselectivity and activity.[38,45]

Catalyst: Both commercially available and experimental Pt catalysts on various supports are suitable.[21,38,41] Catalyst preparation and catalyst structure have been shown to be important.[40,42,43] Rh catalysts give moderate ee values, Pd, Ru and Ni are not effective.[38] Pd is effective for the dehalogenation of the dichlorobenzazepinone ***28***.[22]

Catalyst pretreatment: Treatment in hydrogen at 300-400 °C and/or soaking in a solution of the modifier often leads to a marked improvement of catalyst activity and enantioselectivity.[21,38,41,44]

Solvent and additives: Generally, good optical yields are obtained in solvents with dielectric constants between 2 and 10.[25,38,46] The best results have been reported in acetic acid (95% ee for ethyl pyruvate).[22] The addition of amines and weak acids can affect both activity and enantioselectivity.[21,22]

Reaction conditions: Temperatures between 20-50 °C and pressures >10 bar give good enantioselectivities. Usually higher pressures lead to slightly higher ee's and an increase in rate, while an increase of the temperature also leads to higher rates but to a lower selectivity.[25,38,44]

3.2 Electrochemical systems

There are two reasons for including electrochemical reactions here: First, electrochemical and catalytic reductions have many common features.[47] Second, electrochemical methods have been used to determine the amount of adsorbed tartrate on Ni[13] and it might be possible to study the adsorption behavior of certain modifiers on metallic electrodes as model for metallic surfaces using methods recently described.[48] The different types of chirally modified electrodes are listed in Table 3. We can keep our comments short because an excellent review by Tallec[23] gives a thorough discussion of scope and limitations of enantioselective electrochemistry. Three types of systems have given acceptable results: metal electrodes with strongly adsorbing chiral modifiers **E1**, chiral electrolytes **E2** and electrodes coated with polypeptides **E5**. There are not many systematic investigations on the influence on the various system parameters. But the following factors can be expected to affect the enantioselectivity of a given reaction: *substrate structure, electrode material, electrode pretreatments* (especially for polymer coated electrodes), *modifier structure, modifier concentration, solvent, electrolyte, pH and buffer system, voltage and temperature*. Tallec concludes in his review that, with few exceptions, enantioselective electrochemistry is at the moment not a competitive method for the preparation of chiral molecules.

TABLE 3. Enantioselective electrochemical systems.

Year	Cat.	Electrode / Control	Reduced function (best ee)	Ref.
1970	E1	Hg / alkaloid	C=C (48), C=N (19), C-Br (45), C=C (20)	23
1973	E2	Hg / chiral electrolyte	C=O (26)	"
1982	E3	Ni / tartrate	C=O (6)	"
1983	E4	graphite / polypeptide	C-Br (17), C=C (43), S oxidation (20)	"
1983	E5	Pt / polypeptide	S oxidation (93)	"

3.3 Basic catalysts; miscellaneous catalyst types

Reactions catalyzed by solid bases were obvious candidates for testing hypotheses on the nature and the mode of action of enzymes. Bredig used aminated cellulose B2 as a model because an enzyme was thought to consist of "a specific active function and a colloidal carrier".[49] With few exceptions, none of these enantioselective catalysts has been investigated systematically up to now or has been shown to be useful for the synthetic chemist. This is probably the main reason why not much is known on the structure of the tested catalysts or how the catalyst structure affects its catalytic performance. In the case of the synthetic polypeptides M5 it was shown that the following factors had an effect on the catalytic performance for the epoxidation of chalcones: *the type of amino acid, the substituent at the terminal amine, the degree of polymerization and the organic solvent.* From these and other observations it was proposed that the "helical content" of the polymeric catalyst might be of importance.[11,12] For several metal tartrates the crystal structure has been determined (Zn tartrate M7 is amorphous[50]) but little is known about the surface of the particles where the activation of the substrates and the stereocontrol is thought to occur. A fascinating development is the use of chirally modified clays or zeolites as illustrated by the titanium-pillared montmorillonite M10 as heterogeneous catalysts for the Sharpless epoxidation.[36]

TABLE 4. Solid enantioselective base catalysts.

Year	Cat.	Activation / Control	Reaction type (best ee)	Ref.
1922	B1	ZnO / d-fructose	C=C Br_2 addition (~50)	17
1932	B2	amino cellulose	C=O HCN addition (22)	49
1955	B3	LiO / quartz	alkylation (n.d.)	9,104
1957	B4	Al_2O_3 / alkaloid	isomerization (n.d.)	105
1962	B5	polyamine	C=O HCN addition (21), polymerization (n.d.)	31,108
1984	B6	$Ca(OH)_2$ / chitosan	sugar formation (n.d.)	106

Enantioselection by a chiral crystalline environment is not really catalysis by solids. Reactions in the solid state will have drawbacks like heat and mass transport problems which will limit their applications. But some of the reactions described give quite good optical yields and are also very interesting from a theoretical point of view. This is especially the case when *achiral* molecules crystallize in a *chiral* structure (like the well known quartz) which then can undergo stereocontrolled reactions.[51] If the right- and left-handed crystals are separated "à la Pasteur" or can be produced preferentially by seeding,[52] products with an enantiomeric excess can be obtained. This fact has also been used as a mechanistic tool in order to demonstrate that hydrogenation reactions can occur in the solid phase via a spillover mechanism.[53] Different effects are probably

operative when a transformation in the presence of an optically active host like M6, M9 leads to high optical induction only if the reaction is carried out in the solid state but not in solution. Chiral micelles[54] or liquid crystals[55] as controlling medium for asymmetric synthesis have also been described but enantioselectivities are much lower. This indicates that an efficient transfer of chirality in the product determining step requires a highly ordered environment which is more likely to be found in the crystalline state. At the moment there is really no way to predict which reaction can be carried out in this fashion.

TABLE 5. Miscellaneous solid catalytic systems.

Year	Cat.	Activation / Control	Reaction type (best ee)	Ref.
1932	M1	Ag, Cu, Ni / quartz	isomer. (n.d.), dehydr. (<1)	10,27,104
1969	M2	(hv) / crystalline environment	various reactions (93)	33,52,107
1977	M3	$TiCl_3/AlR_3$ / chiral polymer	polymerization (37)	119
1979	M4	Cd-tartrate	polymerization (30)	34
1980	M5	polypeptide	epoxidation (97)	12,32
1983	M6	crystalline cyclodextrin	C=C red. (91), C=C XY addition (100)	35,70,72,109,113-115
1984	M7	Zn-tartrate, Cu-tartrate	epoxide ring opening (85)	50
1985	M8	Cu-tartrate	cyclopropanation (46)	86
1989	M9	none / crystalline host	Wittig reaction (57), C=O red. (59)	71,81
1990	M10	Ti-pillared clay / diethyltartrate	epoxidation (98)	36
1990	M11	polymer supported polypeptide	epoxidation (99)	110

4. Enantioselective transformations of functional groups.

This part is devoted to applications of enantioselective heterogeneous catalysts in order to solve synthetic problems both on a laboratory and on a commercial scale. An attempt is made to discuss the state of the art of the application of these catalytic systems. Before describing the various asymmetric reactions (organized according to the functional group that is transformed) we will mention a few points which are of general importance to chemists involved in the development of new or improved catalysts and also to their colleagues who will use them for practical applications.

Substrate specificity. This has already been discussed above.

Synthetic applications. As a rule, synthetic chemists will consider only those new reactions and catalysts for preparative purposes where the enantioselectivity reaches a certain degree (e.g. >80%) and where the catalyst is readily available or easy to prepare. For heterogeneous catalysts this is often a problem because many of the reported catalysts are not commercially available or their preparation requires experience and know-how which is lacking in most organic laboratories. In addition, important catalyst preparation variables and structural features are frequently either not known or not well described. It is therefore of interest that two types of modified Nickel catalysts are now commercially available: a Raney nickel/tartrate/NaBr from Degussa[56] and a nickel powder/tartrate/NaBr from Heraeus[57,58]. As already pointed out, commercial Pt catalysts are suitable for the enantioselective hydrogenation of α-ketoesters.[21,38] With some catalytic experience, both systems are relatively easy to handle and give reproducible results if care is taken to work with purified substrates. The general applicability for most of the other catalytic systems has not yet been demonstrated.

Process development. We have found that the process development for an enantioselective hydrogenation

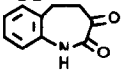
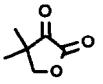
reaction using modified catalysts is more demanding than for a classical heterogeneous hydrogenation because additional reaction parameters are involved. This statement can probably be extended to other catalytic enantioselective syntheses. Some approaches which have been found useful (screening concepts, the use of statistical optimization methods etc.) have been described.[1] In addition, we have found that rigorous quality control (substrate, catalyst, solvent etc.) is necessary to guarantee reproducibility.[25]

Production scale applications. In addition to good enantioselectivity and availability, a viable production catalyst has to meet further requirements e.g. activity, productivity, price, handling and separation.[59] Heterogeneous catalysts have an inherent advantage concerning handling and separation whereas the other criteria can only be judged case by case. For the nickel/tartrate system in the hydrogenation of β-ketoesters, productivity and price of the modified catalyst can be a problem. Successful attempts to re-use the catalyst either by coating with a polymer[60] or by adding certain amines[61] have been reported.

4.1 Enantioselective transformations of the C=O group

Reduction of α-ketoacid derivatives. Cinchona modified Pt catalysts are the only heterogeneous catalysts that are of preparative value for the reduction of α-ketoacid derivatives ***1***. The corresponding hydroxy derivatives are formed with good to very good optical yields (see Table 6). One reason for this success is probably the extensive investigation and optimization of the effects of the catalyst, the solvent, the modifier and the reaction conditions.[1,21,22,25] The other entries in Table 6 have been included to illustrate a few points: Ni/tartrate catalysts which show high enantioselectivity for β-ketoesters and or electrochemical reduction in presence of cinchona alkaloids lead to almost racemic products (***1a/e***) whereas the strychnine modified electroreduction gives mandelic acid in moderate optical yield. The Ni/camphor system for the hydrogenation of ***11*** is of interest because camphor is an unusual type of modifier.

TABLE 6. Optical yields obtained for the reduction of α-ketoacid derivatives $R_1COCOOR_2$ using modified hydrogenation catalysts and electrochemical systems.

Substrate	R_1	R_2	Cat.[1)]	Activation	Control	ee (%)	Ref.
1a	Ph	H	E1	Hg electrode	strychnine	19	23
	"	"	"	"	quinidine	2	"
1b	Ph	Et	H14	Pt/Al_2O_3	cinchonidine	89	21
1c	Me	Et	"	"	dihydrocinchonidine	89(95)[2)]	22,38
1d	nPr	Et	"	"	"	57	25
1e	Me	Me	"	"	"	90	"
	"	"	H9	RaneyNi	tartrate	2	3
1f	$PhCH_2CH_2$	Me	H14	Pt/Al_2O_3	dihydrocinchonidine	85	25
1g	"	Et	"	"	"	83(91)[2)]	22,25
1h	"	nBu	"	"	"	82	25
1i	"	iBu	"	"	"	80	"
1k	CH_2COOEt	Et	"	Pt/C	cinchonidine	43	"
1l	$(CH_2)_2COOEt$	Et	H6	RaneyNi	camphor	24	20
1n			H14	Pt/Al_2O_3	dihydrocinchonidine	47	25
1m			H14	Pt/C	cinchonidine	52	118

1) catalytic system, see Tables 2-5 2) solvent: toluene (acetic acid)

As already mentioned in the preceding section the type and structure of the Pt catalysts strongly affect the catalytic performance but certain commercially available catalysts are well suited for the hydrogenation of α-ketoesters even in larger scale reactions. This was demonstrated for the synthesis of an important intermediate for the angiotensin-converting enzyme inhibitor BENAZEPRIL (see Fig. 2) where the hydrogenation of the α-ketoester ***1g*** has been developed and scaled-up into a production process (10-200 kg scale, chemical yield >98%, ee 79-82%).[25] Compared to a classical heterogeneous hydrogenation process there are only two differences: the catalyst has to be pretreated in hydrogen at 300-400 °C before the reaction and the modifier 10,11-dihydrocinchonidine has to be added to the reaction solution. Some α-ketoesters are not very stable and there are observations that the substrate quality can be of importance.[25]

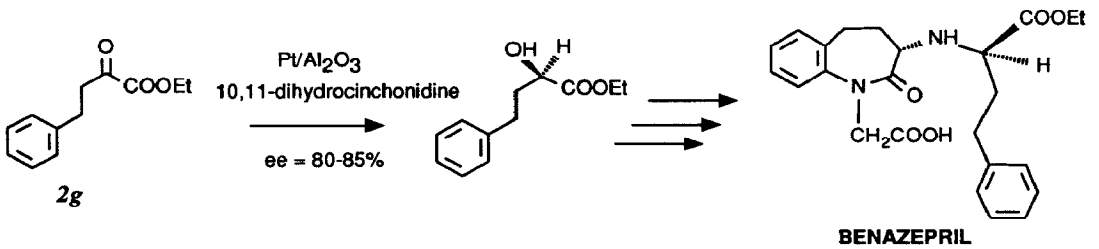


Fig. 2. Synthesis of the angiotensin-converting enzyme inhibitor BENAZEPRIL.[88]

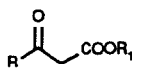
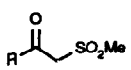
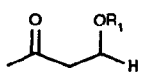
The cinchona modified platinum catalysts are at the moment among the most selective catalytic systems known for the synthesis of α-hydroxy acid derivatives. Other alternatives are homogeneous Rh and Ru diphosphine complexes where the best optical yields are between 76 and 96 %,[62,80a] stoichiometric reductions with chiral borohydrides[63] and biocatalytic transformations[64]. These last two methods give even higher optical yields (up to 100%) but generally only one enantiomer of the α-hydroxy ester is easily accessible.

Hydrogenation of β-functionalized ketones and various methyl ketones. Historically, the hydrogenation of β-ketoesters has been the first reaction catalyzed by a chirally modified heterogeneous catalyst with high and reproducible optical yields. The development of the tartrate/NaBr modified Raney Nickel catalyst and its application for several types of ketones has been described extensively.[3,6] Tables 7 and 8 demonstrate that aliphatic ketones with an oxygen function such as an ester (***2a-h***), a sulfoxide (***3a-c***), a hydroxy (***4a***), or an ether (***4b***) group in β-position can be reduced to the corresponding secondary alcohol in good to high optical yields using this modified Ni catalyst. Cyclic β-ketoester derivatives are hydrogenated less selectively with optical yields between 9 and 15 %.[65] The hydrogenation of β-diketones ***5a-e*** is more complex because when the second keto group is also reduced several types of selectivity problems are involved. The resulting diols can be obtained in fair chemical and acceptable to very high optical yields.[26,66-68] Few other heterogeneous catalytic systems have been described for the enantioselective reduction of these substrates.

Several types of methyl ketones ***6*** can be reduced with moderate to good optical yields using a variety of solid catalytic or control systems (Table 9). From a practical point of view, the Ni/tartrate catalyzed hydrogenation of aliphatic methyl ketones ***6a/c-g*** in presence of pivalic acid or its sodium salt with ee's up to 80% is probably synthetically useful.[3,69] At the moment, all other transformations are interesting only from a theoretical and conceptual point of view. Aromatic methyl ketones ***6b/i/k/o*** are reduced with enantioselectivi-

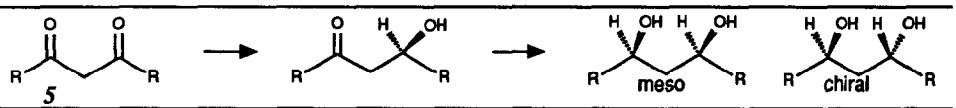
ties up to 90% as inclusion complexes in cyclodextrines or other chiral hosts. In these cases, the optical induction is only high if the reaction is carried out in the solid state whereas it is small or zero in solution.[70-72] Good results are obtained for acetyl pyridines ***6l-n*** (note the effect of the acetyl position!) with a Hg electrode modified by the addition of strychnine or brucine, on the other hand, a tartrate modified Ni-electrode reduced 2-heptanone ***6e*** with only 6% ee.[23]

TABLE 7. The highest optical yields obtained for the hydrogenation of different β-functionalised ketones using modifed hydrogenation catalysts.

Substrate		R	R_1	Cat.	Activation	Control	ee(%)	Ref.
	**2a**	CH_3	CH_3	H9	RaneyNi	tartrate	85	3
	2b	"	C_2H_5	"	"	"	88	"
		"	"	H14	Pt/C	cinchonidine	5	38
2	**2c**	"	n-C_3H_7	H9	RaneyNi	tartrate	88	3
	2d	"	i-C_3H_7	"	"	"	88	"
	2e	"	n-C_8H_{17}	"	"	"	88	"
	2f	C_2H_5	CH_3	"	"	"	86	"
	2g	n-C_8H_{17}	CH_3	"	"[1)]	"	91	26
	2h	n$C_{11}H_{23}$	C_2H_5	"	"	"	92	79
	**3a**	C_2H_5		H9	RaneyNi	tartrate	71	3
	3b	n-C_5H_{11}		"	"	"	68	"
	3c	n-C_8H_{11}		"	"	"	67	"
3								
	**4a**	H		H9	RaneyNi	tartrate	70	3
	4b	CH_3		"	"	"	68	"
4								

1) modified catalyst treated with ultrasound

TABLE 8. Hydrogenation of β-diketones to β-hydroxyketones and β-diols by tartrate modified Raney Nickel H9.



5

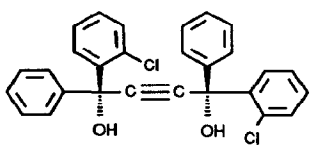
	R	Conversion (%)	Yield (%)	ee (%)	meso/chiral	chiral (%)[1)]	ee (%)	Ref.
5a	CH_3	100	90	73				67
	"	70	-	-	8/92	-	98	"
	"	100	-	-	13/87	65	86	67,68
	"	100	7	-	8/92	86	91[2)]	26
5b	CH_3CH_2	-	-	-	20/80	30[3)]	100[3)]	68
5c	$CH_3(CH_2)_2$	-	-	-	15/85	11[3)]	100[3)]	"
5d	C_6H_5	-	-	-	23/77	20[3)]	100[3)]	"
5e	$(CH_3)_2CH$	100	17	59	20/80	66	85[4)]	66
	"	100	6	-	25/75	72	90	26

1) chemical yield 2) modified catalyst treated with ultra sound 3) after recrystallization
4) after recrystallization: yield 29%, ee 100%

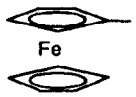
TABLE 9. Optical yields for the reduction of methyl ketones $RCOCH_3$ using hydrogenation catalysts, modified electrodes and inclusion complexes.

Substrate	R	Cat.	Activation/Red. agent	Control	ee (%)	Ref.
6a	CH_3CH_2	H9	RaneyNi	tartrate	49	3
	"	M6	BH_3.pyridine	crystalline β-cyclodextrine	47	70
6b	$C_6H_5(CH_2)_2$	"	"	"	89	"
6c	$CH_3(CH_2)_2$	H9	RaneyNi	tartrate	66	3
6d	$CH_3(CH_2)_3$	"	"	"	80	69
6e	$CH_3(CH_2)_4$	E3	RaneyNi electrode	"	6	23
6f	$CH_3(CH_2)_5$	H9	RaneyNi	"	80	69
6g	$(CH_3)_2CH$	"	"	"	63	3
6h	$(CH_3)_3C$	"	"	"	74	"
6i	C_6H_5	E2	Hg electrode	N-Me_2ephedrinium chloride	20	23
	"	M6	BH_3.pyridine	β-cyclodextrine	91	70
6k	$o(CH_3)C_6H_4$	M9	$BH_3.(CH_2NH_2)_2$	crystalline host[1)]	59	71
6l	o	E1	Hg electrode	strychnine	48	23
6m	m	"	"	"	0	"
6n	p	"	"	"	40	"
6o	Fc[2)]	M6	$NaBH_4$	crystalline β-cyclodextrine	52	72
6p	Fc[3)]	"	"	"	84	"

1)



2) Fc =



3) ferrocenyl-phenylketone

The preparative application of Raney Nickel modified with tartrate/NaBr has been described to be easy and reproducible.[3,6] Our own experience has shown that the modification step is somewhat delicate and requires careful control of the modification conditions. As already mentioned, modified Ni catalysts are now commercially available. Several examples have been described where the enantioselective hydrogenation is a key step in the preparation of chiral target molecules.

The first example, a multistep synthesis of several isomers of the sex pheromone of the pine sawfly (Fig. 3), starts with the nickel catalyzed hydrogenation of methyl 2-methyl-3-oxobutyrate ***2i*** with fair stereoselectivity.[73] Recently a new synthesis was published starting with the enantioselective hydrogenation of methyl acetoacetate with the same catalytic system.[74] In the same publication interesting results on the biological activity of the different diastereomers and mixtures thereof were described.

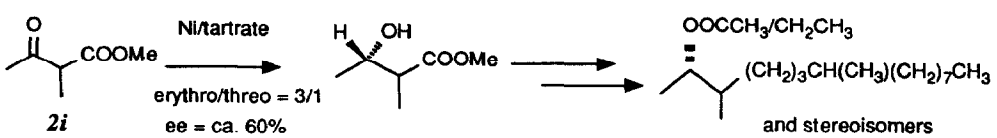


Fig. 3. Synthesis of the sex pheromone of the pine sawfly.

The same catalyst system was also reported to lead to biologically active C_{10}-C_{16} 3-hydroxyacids starting from the corresponding ketoesters with optical yields of 83-87%. The optical purity could be increased to >99% with a simple recrystallization.[75]

A convenient and efficient ligand synthesis for homogeneous enantioselective hydrogenation catalysts was described starting with the stereoselective hydrogenation of acetylacetone ***5a***[76] (Fig. 4). The hydrogenation was developed by Izumi's group and commercialized by Wako Pure Chemicals Ind..[3,77] Kawaken Fine Chemicals Co. has also indicated that similar catalytic reactions are under development and that certain optically pure intermediates will be produced.[78]

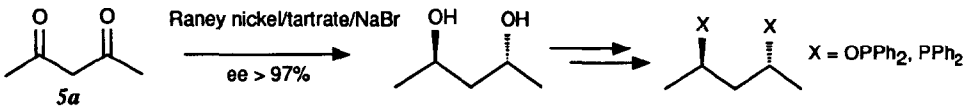


Fig. 4. Synthesis of diphosphine ligands

Finally, Raney nickel modified by (R,R)-tartaric acid/NaBr has been shown to be an efficient catalyst for the asymmetric hydrogenation of an intermediate ***2k*** in the synthesis of tetrahydrolipstatin, a pancreatic lipase inhibitor (Fig. 5) developed by Hoffmann-LaRoche (100% chemical yield, ee 90-92%, 6-100 kg scale).[79]

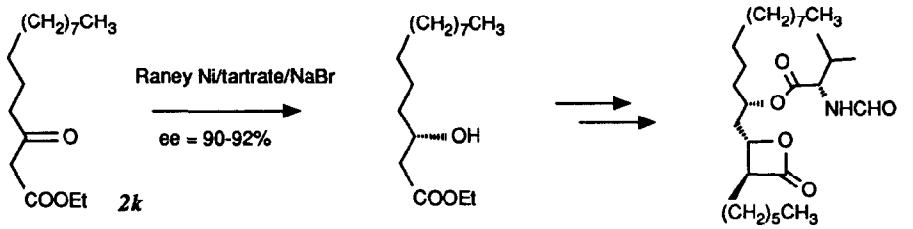
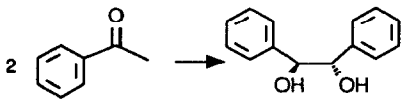
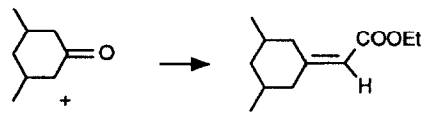
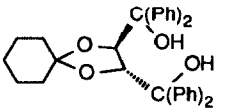


Fig. 5. Synthesis of tetrahydrolipstatin.

For some time, the tartrate modified Ni catalysts have been the most selective catalysts for the asymmetric hydrogenation of β-functionalized ketones. Recently, homogeneous Ru-BINAP catalysts have been reported to lead to even higher optical yields.[80a] The choice of the preferred catalyst for a desired transformation can only be made on a case by case basis.

Miscellaneous reactions of ketones. A few more enantioselective transformations of carbonyl groups that are of potential preparative interest are mediated by heterogeneous systems (Table 10). Examples are the cyanohydrine formation ***8*** catalyzed by a synthetic chiral polymer[31] or the electrochemical pinacole formation ***7***.[23] The Wittig reaction of the substituted cyclohexanone ***9*** carried out in a crystalline chiral host is claimed to be the first case using an external source of chirality with good optical yields.[81] At the moment these results may not be useful for the synthetic chemist since the scope and applicability of these catalysts remains to be established. On the other hand, C-C bond forming reactions are central to organic synthesis and these enantioselective examples might lead to new ideas for solving similar problems.

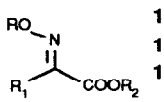
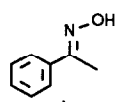
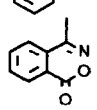
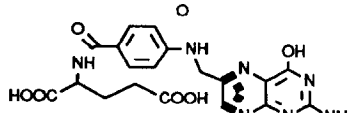
TABLE 10. Optical yields for various transformation of ketones using inclusion complexes, modified catalysts and electrodes.

Reaction	Cat.	Activation	Control	ee (%)	Ref.
7 	E2	Hg electrode	N,N-dimethyl-ephedrinium chloride	26	23
8 	B5		(S)-isobutylimine polymer	21	31
9  $(C_6H_5)_3P$=CHCOOEt	M9	none	 crystalline host	57	81

4.2 Enantioselective reductions of the C=N group

The enantioselective reduction of various compounds with a C=N function has been of interest for a long time since chiral amines and especially amino acids are very important natural products. Not unexpectedly, oximes where among the first class of compounds that were used as substrates for asymmetric hydrogenation

TABLE 11. Optical yields for the reduction of C=N bonds using hydrogenation catalysts and modified electrodes.

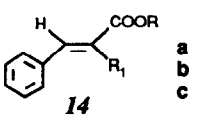
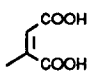
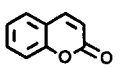
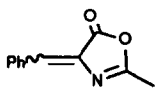
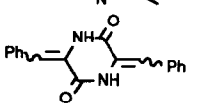
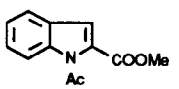
Substrate		R	R_1	R_2	Cat.	Activation	Control	ee (%)	Ref.
10 	**10a**	Ac	$PhCH_2$	Et	H5	Pd	silk fibroin	26	28
	10b	H	$Ph(CH_2)_2$	Et	H14	Pt/C	cinchonidine	~15	25
	10c	H	CH_3	H	E4	C electrode	poly-L-valine	6	23
		"	"	"	H10	Pd/C	ephedrine	10	97
	10d	H	C_6H_5	H	E1	Hg electrode	strychnine	19	23
11 					H4	Pt black	menthoxy acetic acid	18	19
12 					E1	Hg electrode	strychnine	~5	23
13  L-folic acid					E2	Hg electrode	N-methyl-cinchonium iodide	~20	111

catalysts.[19,28] The results summarized in Table 11 are therefore rather disappointing because even the most selective catalysts give optical yields <30%. With the exception of homogeneous catalysts for the hydrogenation of imines[82] there are to our knowledge no recent results with better selectivities for this type of transformation. An alternative strategy that promises more success might be the diastereoselective hydrogenation of chiral oximes or imines.[83]

4.3 Enantioselective transformations of the C=C group

Enantioselective Reductions. The asymmetric hydrogenation of C=C bonds by homogeneous noble metal catalysts is one of the catalytic success stories of recent years. Many functionalized olefins can now be hydrogenated with optical yields >90% using soluble or immobilized Rh and Ru diphosphine complexes.[80a] Compared to these catalysts that have been all developed in the last ten years the performance of the older heterogeneous systems listed in Table 12 is not very impressive. There are two exceptions: The hydrogenation of the oxazolinone derivative ***17*** with optical yields of 66% using the by now historical Pd/silk fibroin catalyst[20] and the electroreduction of the coumarin ***16*** with a poly-valine coated electrode with 43% ee.[23] As already mentioned, the Pd/silk catalyst is not easily reproducible and also the coating of an electrode is probably not a routine operation. Therefore, at this time there is no heterogeneous system for the enantioselective reduction of C=C bonds that is preparatively useful.

TABLE 12. Optical yields for the reduction of C=C bonds using hydrogenation catalysts and modified electrodes.

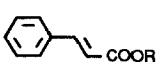
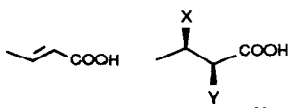
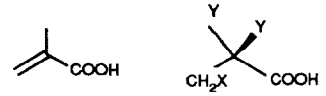
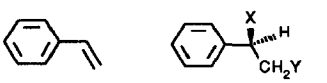
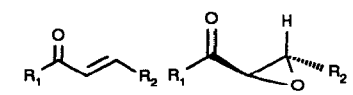
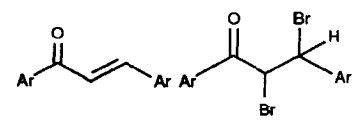
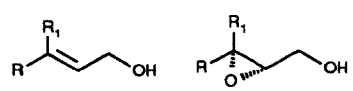
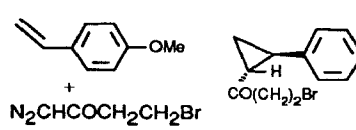
	Substrate		Cat.	Activation	Control	ee (%)	Ref.
		R R$_1$					
		a H Ph	H15	Pd/C	cinchonidine	30	24
		b Na Ph	H9	RaneyNi	tartrate	17	112
		c H NHAc	H11	Pd	poly-S-leucine	5	101
14							
15			E4	C electrode	poly-L-valine	21	23
16			E4	C electrode	poly-L-valine	43	23
17			H5	Pd	silk fibroin	66	20
			H7	RaneyNi	tyrosine	50	"
18			H5	Pd	silk fibroin	23	28
19			H14	Pt/C	cinchonidine	11	25
20			H9	RaneyNi	tartrate	5	96

Addition reactions to C=C bonds. Three types of reactions have been reported to proceed with fair to

very good optical yields in the presence of a heterogeneous catalyst or in the crystalline state (Table 13).

The first type is the addition of XY across various substituted C=C bonds. With the exception of the early example ***21a*** using a ZnO/fructose catalyst reported by Erlenmeyer,[17] all these reactions occur as inclusion complexes in crystalline cyclodextrins which obviously limits their practical application. In the case of the acrylic acids ***22*** and ***23*** the optical yields for the addition of HX or Cl_2 are very good and these inclusion complexes might have interesting potential for asymmetric transformations which are otherwise not possible.

TABLE 13. Optical yields for various addition reactions to C=C bonds using crystalline cyclodextrins or modified catalysts.

	Substrate → Product			Cat.	Activation	Control	ee (%)	Ref.
		R	X Y					
21		H	Br Br	B1	ZnO	D-fructose	~50[1]	17
		H	Br Br	M6	-	β-cyclodextrin	40	115
		Et	Br H	"	-	α-cyclodextrin	46	114
		H	Cl Cl	"	-	β-cyclodextrin	37	115
22			Br H	M6	-	α-cyclodextrin	58	109
			Cl H	"	-	"	64	"
23			Cl Cl	M6	-	α-cyclodextrin	100	35
			Cl Cl	"	-	β-cyclodextrin	88	"
24			OH Cl	M6	-	α-cyclodextrin	14	113
		R1	R_2					
25		**a** Ph	Ph	M5	poly-L-alanine		96	12
			"	M11	poly-L-leucine supported		97	110
		b "	p-MeOPh	"	on polystyrene[2]		90	"
		c "	p-NO_2Ph	"			99	"
		d "	o-MeOPh	"			76	"
		e "	p-ClPh	"			99	"
		f p-MeOPh	Ph	"			87	"
		g p-ClPh	"	"			99	"
26				M2	-	chiral crystal	6	33
		R_1	R					
27		**a** H	Me	M10	Ti-PILC[3]	diethyl tartrate	95	36
		b H	nPr	"			94	"
		c H	Ph	"			98	"
		d Me	$Me_2C{=}CH(CH_2)_2$	"			98	"
28				M8	Cu	tartrate	46	86

1) after several recrystallizations 2) 2% crosslinked 3) Ti-pillared montmorillonite (pillared clay)

The second reaction type is the epoxidation of olefins ***25a-g*** and ***27a-d***. Chalcone ***25a*** can be oxidized using H_2O_2 with very high optical yields in a two-phase reaction system in the presence of a poly amino acid derivative as chiral catalyst.[12,32] This catalyst has been used to prepare chiral flavonoid ***25h*** intermediates enantioselectively (Fig. 6).[84] Recently, a polymer supported version of the catalyst has been described for several substitued chalcones ***25a-g*** with even better selectivities and a moderate substituent effect.[110] Another recent development is the the use of titanium-pillared montmorillonite as heterogeneous catalyst for the Sharpless epoxidation of various allylic alcohols ***27a-d***.[36] Interestingly, the original version of Sharpless was stoichiometric in titanium but when 3-4 Å zeolites are added, the reaction can be carried out in a catalytic fashion. The role of the molecular sieve is assumed to be the removal of water that is known to be detrimental for the catalytic activity.[85] At this time it is not clear whether the montmorillonite plays a similar role and, more importantly, whether the preparation of this unusual catalyst can be reproduced without difficulty. Because the Sharpless reaction is widely used in preparative chemistry a heterogeneous version with such good selectivity could be a tremendous advantage.

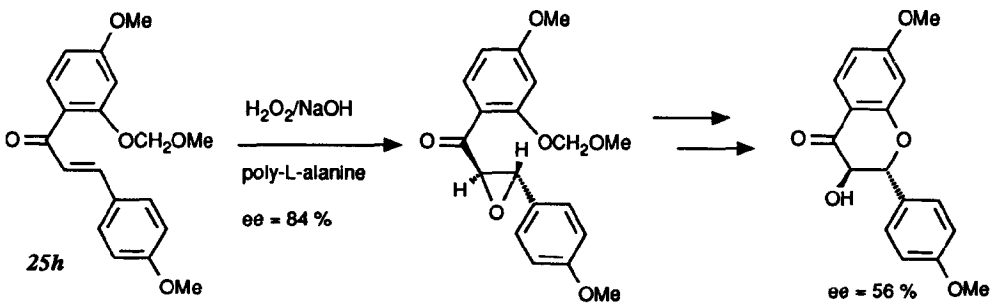


Fig. 6 Synthesis of flavonoids

Finally, Cu-tartrate has been described for the cyclopropanation reaction ***28*** with moderate optical yield, giving an intermediate in a steroid synthesis.[86] The enantioselective cycloclopropanation reaction is usually carried out in the presence of soluble Cu or Co complexes with very elaborate ligands (for a recent overview see Pfaltz[80b]) so it is rather surprising that a simple tartrate salt is so effective.

4.4 Miscellaneous enantioselective transformations

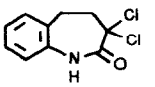
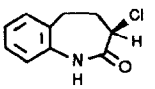
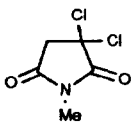
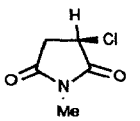
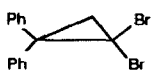
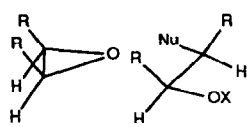
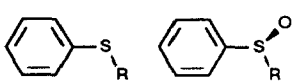
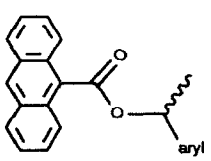
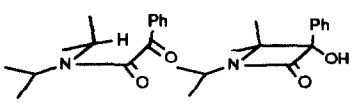
The catalytic mono-hydrodehalogenation of geminal dihalogen compounds is a well known reaction[87] but very few examples exist where one of the two enantiomeric mono-halogen compounds is produced selectively. The dehalogenation reactions ***29-31*** either by hydrogenation with cinchona modified Pd or Pt catalysts or by electroreduction in the presence of various alkaloids have been described to give moderate to fair optical yields. The enantioselective hydrodechlorination of the the α,α-dichlorobenzazepinone-2 ***29*** could be a potential alternative intermediate in the established synthesis for the ACE inhibitor BENAZEPRIL (see Fig. 2) where the racemic α-bromobenzazepinone-2 is used.[37,88] At the moment the enantioselectivity of both the catalytic and the electrochemical system is too low to be of practical use.

The asymmetric ring opening of symmetric epoxides ***32*** by several types of nucleophiles catalyzed by metal tartrates is a new reaction. The optical yields are moderate to good and the best catalyst, Zn-tartrate, should be easily prepared.[50]

Good optical yields are reported for the electrochemical oxidation of hindered arylsulfides *33* using an interesting polypeptide coated graphite or Pt electrode.[23] Because the highest enantioselectivities are obtained with bulky substituents R, this could be a complementary method to the Ti/diethyltartrate catalyzed oxidation reported by Kagan.[89] However, the reproducibility of the electrochemical reaction has been questioned.[23]

The last two transformations are photochemical reactions in chiral crystals. Whereas the kinetic resolution of *34* is probably not of preparative value, the β-lactame formation *35* could be of interest because it is possible to control the crystal chirality be seeding the crystallization solution.[52]

TABLE 14. Optical yields for various reductions, addition and ring formation reactions using chiral crystals, modified catalysts and electrochemical systems.

	Substrate → Product		Cat.	Activation	Control	ee (%)	Ref.
29			H16 H14	$Pd/BaSO_4$ $Pt/BaSO_4$	cinchonine cinchonidine	50 25	37 "
30			E1	Hg electrode	strychnine	26	116
31			E1	Hg electrode	emetine	44	117
32		R = (CH$_2$)$_4$, Nu = nBuS, X = H	B8	Zn-tartrate		85	50
		" PhN "	"	"		52	"
		" N_3 $SiMe_3$	"	"		42	
		(CH$_2$)$_3$ nBuS H	"	"		72	"
		" BzS "	"	"		50	"
		CH_3 " "	"	"		75	"
		" N_3 $SiMe_3$	"	Cu-tartrate		40	"
33		R = Me	E5	Pt electrode	poly-L-leucine	2	23
		iPr	"	"	poly-L-valine	77	"
		nBu	"	C	poly-L-glutamate	20	"
		iBu	"	Pt	poly-L-valine	44	"
		tBu	"	"	"	93	"
		cyhex	"	"	"	54	"
34		dimerisation (kinetic resolution)	M3	hv	chiral crystal	90	107
35			M3	hv	chiral crystal	93	52

5. Mechanistic considerations

Even though it is quite obvious that empirical strategies are effective for improving a catalytic system, understanding how a catalyst works is certainly the ultimate challenge. This is difficult for any heterogeneous catalyst and even more so for an enantioselective one. For the tartrate modified catalysts a large series of mechanistic investigations have been reported by several research groups. These are summarized and commented in recent reviews.[3,6,8,13,15,39] The Pt/cinchona system has also been investigated in some depth and has been reviewed[1] whereas no systematic studies have been carried out for all the other catalytic systems described above. In this paragraph we summarize some ideas on the different types of mechanisms or modes of action that have been proposed for enantioselective heterogeneous catalysts. The experimental facts that support these mechanistic models can be found in the references.

In order to get high enantioselectivities the product determining step of the reaction must occur in a "tightly controlled homochiral environment".[90] This environment is provided by the chiral component of an enantioselective catalyst and it is essential that the activating and the controlling function of the catalyst are close to each other and that the activated catalyst-substrate complex is well defined spatially. Many types of interactions (acid-base interactions, hydrogen bonds, hydrophobic binding, π-π interaction etc.[91]) have been postulated to be able to control the geometry of this activated complex and have been discussed in terms of asymmetric discrimination[92] and molecular recognition[93].

Compared to a soluble, molecularly defined catalytic species, a solid catalyst has an additional dimension that on the one hand makes the system more complex but on the other hand opens up new possibilities. This additional dimension can be a surface of a solid or the inside of a polymer (or a crystal) where the activation of the substrates and/or the stereocontrol of the reaction takes place. The catalyst types listed in Table 1 are combinations of different activation and control agents. For mechanistic purposes it is useful to distinguish between two sets of combinations:

1. - Activation on an achiral surface, stereocontrol by a chiral (low molecular weight) modifier or a chiral support.
   - Activation and stereocontrol by a chiral surface.
2. - Activation on an achiral surface, control by a chiral polymer covering the surface.
   - Activation (if necessary) and control by a chiral polymeric (or crystalline) environment.

In the first case the stereochemistry is controlled by the orientation of the prochiral substrate relative to the surface, i.e. which enantiotopic face of the molecule is oriented towards the surface of the catalyst. In this category there is always a metal (metal crystallite, metal oxide, metal salt) involved which probably provides the necessary binding energy between substrate and catalyst while secondary interactions with the chiral auxiliary (modifier, support, anion) determine the orientation of the substrate. This explaines why in almost every case high optical yields are only obtained if the substrate and the chiral auxiliary have matching functionalities e.g. tartrate - β-ketoester or cinchona alkaloid - α-ketoester. Several detailed mechanisms have been proposed for the hydrogenation of ketones with Ni/tartrate[3,6,15,39] and to a lesser degree for the hydrogenation of α-ketoesters by cinchona modified Pt catalysts.[1,41,45,46] Low molecular modifiers are probably more successful because a chiral support normally can only control those regions of the metal surface that are close to the points of attachment of the metal particle to the support.

If the stereochemistry is controlled by a chiral polymer or a crystal, the situation is much more complex and comparable to enzyme catalysis i.e. activation and orientation of the substrate is thought to occur inside a

three-dimensional network. When this is permeable (swellable organic polymer) the transport of the substrates and products is possible and a catalytic reaction can take place. When the network is crystalline, the crystal has to be destroyed in order to obtain the product (as already mentioned this is not a catalytic reaction in the usual sense). If the activation occurs on a metallic surface surrounded by the polymer (e.g. polymer coated electrode) the contact between the two entities is crucial, explaining the importance of the preparation techniques.[23] For obvious reasons, there is no reaction where a detailed picture of the interactions between substrate and polymeric catalyst has been offered. In the case of the polypeptide catalyzed epoxidation of chalcones, the helical content of the polymeric catalyst has been proposed to be of importance.[12]

6. Conclusions

From a synthetic point of view, there are several reaction types catalyzed by chiral heterogeneous catalysts which are useful to preparative chemists. But it is also evident that the scope of most catalytic systems is rather narrow and very high substrate specificity is observed. Compared to homogeneous or biocatalysis, enantioselectivities are usually lower with some notable exceptions.

From a technical or commercial point of view, enantioselective heterogeneous catalysts would be preferable to homogeneous catalysts because of their handling and separation properties, but only if their catalytic performance is satisfactory. It has been demonstrated that in a few cases this is indeed possible.

From a theoretical or conceptional point of view, enantioselective catalysis with chiral solids is a fascinating and challenging area of chemistry. For the case of the modified hydrogenation catalysts we propose that the metal surface must have a suitable structure to allow exactly the right interactions between the metal, the adsorbed modifier and the adsorbed substrate. This would explain the observed requirements for high enantioselectivity: two functional parts for the modifier (for adsorption on the catalytic surface and for interactions with the substrate) as well as for the prochiral substrate (binding function and reaction site). The polymeric heterogeneous catalysts described in this review can be regarded as enzyme models. The catalysis very likely occurs inside the chiral matrix and the reaction is controlled by supramolecular interactions.

Acknowledgments

I would like to thank E. Broger, K. Deller and J. Strutz for providing information on technical aspects of asymmetric hydrogenations, M. Garland for preliminary results, and A. Togni, F. Spindler and M. Studer for critical discussions during the preparation of this manuscript.

References

1 H.U. Blaser and M. Müller, *Studies in Surface Science and Catalysis* (Heterogeneous Catalysis and Fine Chemicals II), 1991, **59**, 73.

2 For recent reviews see M. Capka, *Collect. Czech. Chem. Commun.*, 1990, **55**, 2803.
F.R. Hartley, in F.R. Hartley, (Ed.), *The Chemistry of the Metal-Carbon Bond*, Vol. 4, John Wiley & Sons, London, 1987, p. 1163.

3 A. Tai and T. Harada, in Y. Iwasawa (Ed.), *Taylored Metal Catalysts*, D. Reidel, Dordrecht, 1986, p. 265.

4 J. D. Morrison (Ed.), *Asymmetric Synthesis*, Vol. 5, Academic Press, New York, 1985.

5 J.D. Morrison and H.S. Mosher, *Asymmetric Organic Reactions*, Amer. Chem. Soc., Washington DC, 1976.

6 Y. Izumi, *Adv. Cat.*, 1983, **32**, 215.

7 H. Brunner, *Topics in Stereochemistry*, 1988, **18**, 129.

8 M. Bartok, in *Stereochemistry of Heterogeneous Metal Catalysts*, chapt. XI, J. Wiley, New York, 1985, p. 511.

9 H. Pracejus, *Fortschr. Chem. Forsch.*, 1967, **8**, 493.

10 E.I. Klabunovskii, *"Asymmetric Synthesis"*, Goskhimizdat, Moscow, 1960, german translation by G. Rudakoff, VEB Deutscher Verlag der Wissenschaften, Berlin, 1963.

11 S. Inoue, *Adv. Polym. Sci.*, 1976, **21**, 78.

12 M. Aglietto, E. Chiellini, S. D'Antone, G. Ruggeri and R. Solaro, *Pure & Appl. Chem.*, 1988, **60**, 415.

13 M.J. Fish and D.F. Ollis, *Cat. Rev.-Sci. Eng.*, 1978, **18**, 259.

14 J. Mathieu and J. Weill-Raynal, *Bull. Soc. Chim. Fr.*, 1968, 1211.

15 E.I. Klabunovskii, *Izv. Akad. Nauk. SSSR, Ser. Khim.*, 1984, 505 (engl. 463).

16 F. Rost, *Angew. Chem.* 1935, **48**, 73.

17 E. Erlenmeyer and H. Erlenmeyer, *Biochem. Zeitschr.*, 1922, **233**, 52.

18 D. Lipkin and T.D. Stewart, *J. Amer. Chem. Soc.*, 1939, **61**, 3295.

19 Y. Nakamura, *Bull. Chem. Soc. Jpn.*, 1941, **16**, 367.

20 T. Isoda, A. Ichikawa and T. Shimamoto, *Rikagaku Kenkyusho Hokuku*, 1958, **34**, 134, 143. C.A., 1958, **54**, 285. See also ref. 6.

21 Y. Orito, S. Imai, S. Niwa and Nguyen G-H, *J. Synth. Org. Chem. Jpn.*, 1979, **37**, 173. Y. Orito, S. Imai and S. Niwa, *J. Chem. Soc. Jpn.*, 1979, 1118, 1980, 670 and 1982, 137.

22 H.U. Blaser, H.P Jalett and J. Wiehl, *J. Mol. Catal.*, 1991, in print.

23 A. Tallec, *Bull. Soc. Chim. Fr.*, 1985, 743.

24 J.R.G. Perez, J. Malthete and J. Jacques, *C. R. Acad. Sc. Paris Serie II*, 1985, 169.

25 H.U. Blaser, M. Garland, H.P. Jalett, M. Müller and U. Pittelkow (Ciba-Geigy AG), unpublished work.

26 A. Tai, T. Kikukawa, T. Sugimura, Y. Inoue and T. Osawa, *Shokubai*, 1990, **32**, 362.

27 G.M. Schwab and L. Rudolph, *Naturwiss.*, 1932, **20**, 362; G.M. Schwab, F. Rost and L. Rudolph, *Kolloid-Zeitschrift*, 1934, **68**, 157.

28 S. Akabori, S. Sakurai, Y. Izumi and Y. Fuji, *Nature*, 1956, **178**, 323. S. Akabori, Y. Izumi, Y. Fuji and S. Sakurai, *Nippon Kagaku Zasshi* 1956, **77**, 1956. S. Akabori, Y. Izumi and Y. Fuji, *Nippon Kagaku Zasshi*, 1957, **78**, 886.

29 a) K. Harada and T. Yoshida, *Naturwiss.*, 1970, **57**, 131. b) K. Harada and T. Yoshida, *Naturwiss.*, 1970, **57**, 306.

30 A.A. Balandin, E.I. Klabunovskii and Y.I. Petrov, *Dokl. Akad. Nauk. SSSR*, 1959, **127**, 557 (engl. 571),

31 S. Tsuboyama, *Bull. Chem. Soc. Jpn.*, 1962, **35**, 1004.

32 S. Julia, J. Masana and J.C. Vega, *Angew. Chem. Int. Ed. Engl.*, 1980, **19**, 929.

33 K. Penzien and G.M.J. Schmidt, *Angew. Chem.*, 1969, **81**, 628.

34 M. Marchetti, E. Chiellini, M. Sepulchre and N. Spassky, *Makromol. Chem.*, 1979, **180**, 1305.

35 Y. Tanaka, H. Sakuraba and H. Nakanishi, *J. Chem. Soc. Chem., Commun.* 1983, 947.

36 B.M. Choudary, V.L.K. Valli and A. Durga Prasad, *J. Chem. Soc., Chem. Commun.* 1990, 1186.

37 H.U. Blaser, S.K. Boyer and U. Pittelkow, *Tetrahedron: Asymmetry*, 1991, in print.

38 H.U. Blaser, H.P. Jalett, D.M. Monti, J.F. Reber and J.T. Wehrli, *Studies in Surface Science and Catalysis* (Heterogeneous Catalysis and Fine Chemicals I), 1988, **41**, 153.

39 W.M.H. Sachtler, *Chem. Ind.* (Catalysis in Organic Reactions), 1985, **22**, 189.

40 H.U. Blaser, H.P. Jalett, D.M. Monti, A. Baiker and J.T. Wehrli, *Studies in Surface Science and Catalysis* (ACS Symposium on Structure-Activity Relationships in Heterogeneous Catalysis, 1990), 1991, **67**, in print.

41 I.M. Sutherland, A. Ibbotson, R.B. Moyes and P.B. Wells, *J. Catal.*, 1990, **125**, 77; J.M. Thomas, *Angew. Chem. Adv. Mater.*, 1989, **101**, 1105.

42 J.T. Wehrli, A. Baiker, D.M. Monti and H.U. Blaser, *J. Mol. Catal.*, 1990, **61**, 207.

43 J.T. Wehrli, A. Baiker, D.M. Monti and H.U. Blaser, *J. Mol. Catal.*, 1989, **49**, 195.

44 P.A. Meheux, A. Ibbotson and P.B. Wells, *J. Catal.*, 1991, **128**, 387.

45 M. Garland and H.U. Blaser, *J. Amer. Chem. Soc.*, 1990, **112**, 7048.

46 J.T. Wehrli, A. Baiker, D.M. Monti, H.U. Blaser and H.P. Jalett, *J. Mol. Catal.*, 1989, **57**, 245.

47 F. Beck, *Chem.-Ing.-Tech.*, 1976, **48**, 1096.

48 M.P. Soriaga, E. Binamira-Soriaga, A.T. Hubbard, J.B. Benziger and K.W.P. Pang, *Inorg. Chem.*, 1985, **24**, 65 and 73.

49 G. Bredig and F. Gerstner, *Biochem. Zeitschr.*, 1932, **250**, 414.

50 H. Yamashita, *Bull. Chem. Soc. Jpn.*, 1988, **61**, 1213.

51 B.S. Green, R. Arad-Yellin and M.D. Cohen, *Topics in Stereochemistry*, 1986, **16**, 131. J.R. Scheffer and M. Garcia-Garibay, in *Photochemistry on Solid Surfaces*, M. Anpo and T. Matsuura (Eds.), Elsevier, Amsterdam, 1989, p. 501.

52 F. Toda, *Topics Curr. Chem.*, 1988, **149**, 211.

53 R. Lamartine, R. Perrin, A. Thozet and M. Perrin, *Mol. Cryst. Liq. Cryst.*, 1983, **96**, 57.

54 J.M. Brown, in *Further Perspectives in Organic Chemistry*, Ciba Foundation Symp. 53, Elsevier, Amsterdam, 1978, p. 149. R. Ueoka, Y. Matsumoto, R.A. Moss, S. Swarup, A. Sugii, K. Harada, J. Kikuchi and Y. Murakami, *J. Amer. Chem. Soc.*, 1988, **110**, 1588 and references cited therein.

55 V.A. Pavlov, N.I. Spitsyna and E.I. Klabunovskii, *Dokl. Akad. Nauk. SSSR, Ser. Khim.*, 1983, 1653 (engl. 1501).

56 K. Deller, Degussa, Hanau, personal communication.

57 J. Strutz, W.C. Heraeus GmbH, Hanau, personal communication.

58 H. Brunner, M. Muschiol, T. Wischert and J. Wiehl, *Tetrahedron: Asymmetry*, 1990, **1**, 159.

59 For a discussion of these problems see R. Sheldon, *Chem. Ind.* (London), 1990, 212. J.W. Scott, *Topics of Stereochemistry*, 1989, **19**, 209.

60 A. Tai, K. Tsukioka, Y. Imachi, Y. Inoue, H. Ozaki, T. Harada and Y. Izumi, *Proc. 8th Int. Congr. Cat.* 1984, V-531

61 A. Tai, K. Tsukioka, H. Ozaki, T. Harada and Y. Izumi, *Chem. Lett.*, 1984, 2083.

62 F. Spindler, U. Pittelkow and H.U. Blaser, *Chirality*, 1991, in print, and references cited therein.

63 H.C. Brown, G.G. Pai and P.K. Jadhav, *J. Amer. Chem. Soc.* 1984, **106**, 1531.

64 H. Simon, J. Bader, H. Günther, S. Neumann and J. Thanos, *Angew. Chem. Int. Ed.* 1985, **24**, 539.

65 G. Wittmann, G. Göndös, and M. Bartok, *Helv. Chim. Acta*, 1990, **73**, 635.

66 Sugimura, T,; Yoshikawa, M.; Yoneda, T.; Tai, A., *Bull. Chem. Soc. Jpn.*; 1990, **63**, 1080.

67 A. Tai, K. Ito and T. Harada, *Bull. Chem. Soc. Jpn.*, 1981, **54**, 223.

68 K. Ito, T. Harada and A. Tai, *Bull. Chem. Soc. Jpn.*, 1980, **53**, 3367.

69 T. Osawa, T. Harada,and A. Tai, *J. Catal.*, 1990, **121**, 7.

70 H. Sakuraba, N. Inomata and Y. Tanaka, *J. Org. Chem.*, 1989, **54**, 3482.

71 F. Toda and K. Mori, *J. Chem. Soc., Chem. Commun.*, 1989, 1245

72 Y. Kawajiri and N. Motohashi, *J. Chem. Soc., Chem. Commun.*, 1989, 1336.

73 A. Tai, M. Imaida, T. Oda and H. Watanabe, *Chem. Lett.*, 1978, 61.

74 A. Tai, M. N. Morimoto, M. Yoshikawa, K. Uehara, T. Sugimura, T. Kikukawa., *Agric. Biol. Chem.*, 1990, **54**, 1753.

75 M. Nakahata, M. Imaida, H. Ozaki, T. Harada and A. Tai, *Bull. Chem. Soc. Jpn.*, 1982, **55**, 2186.

76 J. Bakos, I. Toth and L. Marko, *J. Org. Chem.*, 1981, **46**, 5427.

77 Catalogue of Wako Pure Chemicals Industries (Osaka), 22. Edition, p. 471 and 547 (cited in ref. 3).

78 M. Ishii, Kawaken Fine Chemicals Co., personal communication.

79 E. Broger, Hoffmann-LaRoche, Basel, personal communication.

80 a) R. Noyori and M. Kitamura, in *Modern Synthetic Methods*, R. Scheffold (Ed.), Springer Verlag, Berlin, 1989, 115. b) A. Pfaltz, ibid, 199.

81 F. Toda and H. Akai, *J. Org. Chem.*, 1990, **55**, 3482.

82 F. Spindler, B. Pugin and H.U. Blaser, *Angew. Chem. Int. Ed. Engl.*, 1990, **29**, 558 and references cited therein. Y. Ng Cheong Chan and J.A. Osborn, *J. Amer. Chem. Soc.*, 1990, **112**, 9400.

83 K. Harada, in ref. 4, p. 345.

84 J.A.N. Augustyn, B.C.B. Bezuidenhoudt and D. Ferreira. *Tetrahedron*, 1990, **46**, 2651.

85 Y. Gao, R.M. Hanson, J.M. Klunder, S.Y. Ko, H. Masamune and K.B. Sharpless, *J. Amer. Chem. Soc.*, 1987, **109**, 5765.

86 A.R. Daniewski and T. Kowalczyk-Przewloka, *J. Org. Chem.*, 1985, **50**, 2976.

87 For reviews see: A.R. Pinder, *Synthesis*, 1980, 425; Houben-Weyl, *Methoden der organischen Chemie*, IV/1c, Georg Thieme Verlag, Stuttgart, 1980, p. 364.

88 S.K. Boyer, R.A. Pfund, R.E. Portmann, G.H. Sedelmeier and Hj. Wetter, *Helv. Chim. Acta*, 1988, **71**, 337.
G.H. Sedelmeier, H.U. Blaser and H.P. Jalett, EP 206993, 1986.

89 H.B. Kagan and F. Rebiere, *Synlett* 1990, 643.

90 J.M. Brown and S.G. Davies, *Nature*, 1989, **342**, 631.

91 H.B. Kagan and J.C. Fiaud, *Topics in Stereochemistry*, 1978, **10**, 175.

92 B. Bosnich (Ed.), *Asymmetric Catalysis*, Martinus Nijhoff Publishers, Dordrecht, 1986, p. 4.

93 J. Rebek, Jr., *Science* 1987, **235**, 1478.

94 T.D. Stewart and D. Lipkin, *J. Amer. Chem. Soc.*, 1939, **61**, 3297.

95 M. Nakazaki, *J. Chem. Soc. Jpn, Pure Chem. Sect.*, 1954, **75**, 831.

96 R.M. Laine, G. Hum, B.J. Wood and M. Dawson, *Stud. Surf. Sci. Catal.*, 1981, **7**, 1478.

97 T. Yoshida and K. Harada, *Bull. Chem. Soc. Jpn.*, 1971, **44**, 1062.

98 E.S. Neupokoeva, E.I. Karpeiskaya, L.F. Godunova and E.I. Klabunovskii, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1975, 2354 (engl. 2241).

99 Asahi Chem. Ind. Co., JP 13307, 1963, *C.A.*, 1966, **60**, 3092.
100 H. Hirai and T. Furuta, *J. Polymer. Sci. B (Polymer Letters)*, 1971, **9**, 459.
101 R.L. Beamer, R.H. Belding and C.S. Fickling, *J. Pharm. Sci.*, 1967, **58**, 1419.
102 R.M. Dessau, Mobil Oil Co., US 4,554,262, 1985.
103 R. Fornasier, F. Marcuzzi and D. Zorzi, *J. Mol. Catal.*, 1987, **43**, 21.
104 A.P. Teren'tev and E.I. Klabunovskii, *C.A.*, 1955, **49**, 5263.
105 T.L. Jacobs and D. Danker, *J. Org. Chem.*, 1957, **22**, 1424.
106 A.G. Osinovskii and B.V. Erofeev, *Dokl. Akad. Nauk. BSSR*, 1984, **28**, 1006. *C.A.* 1985, **102**, 95926.
107 M. Lahav, F. Laub, E. Gati, L. Leiserowitz and Z. Ludmer, *J. Amer. Chem. Soc.*, 1976, **98**, 1620.
108 S. Inoue, S. Ohashi, A. Tabata and T. Tsuruta, *Makromol. Chem.*, 1968, **112**, 66.
109 Y. Tanaka, H. Sakuraba and H. Nakanishi, *J. Org. Chem.*, 1990, **55**, 564.
110 S. Itsuno, M. Sakakura and K. Ito, *J. Org. Chem.*, 1990, **55**, 6047.
111 S. Kwee and H. Lund, *J. Electroanal. Chem.*, 1980, **116**, 693.
112 M. Bartok, G. Wittmann, G.B. Bartok and G. Göndös, *J. Organomet. Chem.*, 1990, **384**, 385.
113 H. Sakuraba, H. Ishizaki, Y. Tanaka and T. Shimizu, *J. Incl. Phenom.* 1987, **5**, 449.
114 Y. Tanaka, H. Sakuraba, Y. Oka and H. Nakanishi, *J. Incl. Phenom.* 1984, **2**, 841.
115 H. Sakuraba, T. Nakai and Y. Tanaka, *J. Incl. Phenom.* 1984, **2**, 829.
116 A. Tallec, R. Hazard, A. Le Bouc and J. Grimshaw, *J. Chem. Research (S)*, 1986, 342.
117 R. Hazard, S. Jaouannet and A. Tallec, *Tetrahedron*, 1982, **38**, 93.
118 Agency of Ind. Sci. Technol., JP 2158-168-A, 1986.
119 C. Carlini and F. Ciardelli, in *Homogeneous and Heterogeneous Catalysis*, Y. Yermakov and V. Likholobov (Eds.), VNU Science Press, Utrecht, 1986, 471.