Available online at www.sciencedirect.com
SCIENCE DIRECT®
Journal of Molecular Catalysis A: Chemical 231 (2005) 1–20
JOURNAL OF MOLECULAR CATALYSIS A: CHEMICAL
www.elsevier.com/locate/molcata

Review

Progress in enantioselective catalysis assessed from an industrial point of view

Hans-Ulrich Blaser*, Benoît Pugin, Felix Spindler

Solvias AG, WKL 127, P.O. Box, CH-4002 Basel, Switzerland

Received 25 November 2004; accepted 29 November 2004
Available online 15 January 2005

Abstract

In this overview, the opportunities and problems associated with the industrial application of chiral catalysts (restricted to homogeneous metal complexes and modified metallic catalysts) are being analyzed in detail. In a first chapter, critical factors affecting the industrial feasibility of an enantioselective catalyst are discussed. In the following chapters, chiral catalysts with synthetic relevance are described and about 40 types of catalytic transformations are discussed in some detail and characterized regarding enantioselectivity, catalyst activity and productivity. In addition, existing selected industrial applications for pharmaceuticals, agrochemicals and fragrances are reviewed. Finally the various transformations are assessed regarding their potential for future technical applications.

Keywords: Enantioselective catalysis; Industrial application; Chiral ligand; Catalyst performance; Catalytic technology

Contents

* Corresponding author. Tel.: +41 616866155; fax: +41 616866100.
E-mail address: hans-ulrich.blaser@solvias.com (H.-U. Blaser).

1381-1169/$ – see front matter © 2004 Elsevier B.V. All rights reserved.
doi:10.1016/j.molcata.2004.11.025

1. Introduction and background

For many applications of chiral compounds the racemic forms will no longer be accepted [1,2]. As a consequence, the importance of enantioselective synthesis in general and of enantioselective catalysis in particular has increased. Four general approaches for producing enantiopure (ee > 99%) or enantioenriched compounds have evolved (see Table 1 for a comparison of the different methodologies and an assessment concerning their suitability for industrial applications) [3].

Separation of enantiomers via classical resolution, i.e. crystallisation of diastereomeric adducts, still accounts for the production of more than 50% of enantioenriched drugs [4a]. An emerging technology is separation by chiral high-performance liquid chromatography (HPLC) using moving simulated bed technology [5]. While crystallisation of diastereomeric adducts can be applied on any scale, separation via HPLC is probably most important in the early phase of product development and is restricted to small-scale (100 kg to tonnes), high-value products. In both cases, large amounts of solvents have to be handled and of course at least 50% of the material with the wrong absolute configuration has to be either recycled or discarded.

The *chiral pool approach* uses chiral building blocks originating from natural products for the construction of the final molecule. This approach is very often chosen in the early phases of drug development but, depending on the commercial availability of the starting material, it can also be used for large-scale products. Because natural products very often (but not always!) have high enantiomeric purity, no further enrichment is usually necessary. An additional complication is the fact that products of human or animal origin must be declared for the manufacture of medicinal products in order to minimize the risk of transmitting animal spongiform encephalopathy.

Enantioselective syntheses are performed with the help of covalently bound chiral auxiliaries (often from the chiral pool). These are not incorporated in the target molecule but are removed after the stereogenic centres have been established and must be either recycled or discarded.

In many respects the most elegant approach is *enantioselective catalysis* where prochiral starting materials are transformed to enantioenriched products with the help of chiral catalysts. Effective catalysts are either synthetic (chemocatalysis) or can be of natural origin (biocatalysis). In this discussion we will focus on the application of chemical catalysts but the use of enzymatic and microbial transformations have in many respects similar opportunities and concerns [6]. An important issue is often the time needed to find and develop an efficient biocatalyst, especially when the starting material is not a very close analogue to the natural substrate. In addition, product isolation can be a serious problem since reactions are often carried out in a rather dilute aqueous solution. But as several recent publications convincingly show [6,7], these hurdle can be overcome.

Over the years, three types of enantioselective chemocatalysts have proven to be synthetically useful. The most versatile ones are *homogeneous metal complexes* containing bidentate ligands with a chiral backbone carrying two coordinating heteroatoms. For noble metals, especially Rh, Pd, Ru, Ir and Os these are tertiary P or N atoms, for metals such as Ti, B, Zn, Co, Mn or Cu ligands with coordinating O or N atoms are usually preferred. This methodology has just received its due recognition in the 2001 Nobel Prize to W.S. Knowles and R. Noyori for enantioselective hydrogenation and to K.B. Sharpless for enantioselective oxidation catalysis [8]. Also useful for synthetic application are *heterogeneous metallic catalysts*, modified with chiral auxiliaries [9] and finally organocatalysis, i.e. the use of chiral *soluble organic bases and acids* is at the moment a very hot research topic with quite a lot promise for future industrial applications [10]. Chiral polymeric and gel-type materials [11a], phase transfer catalysts [12] and immobilized complexes [13] are less common for synthetic purposes.

While most applications are in the field of *asymmetric synthesis* starting from a prochiral substrate, *kinetic resolution*, i.e., the preferential transformation of one enantiomer of a racemic substrate, is of growing synthetic importance [14]. Up to now, relatively few enantioselective catalysts are used on an industrial scale [6,15]. One reason is that enantioselective catalysis is a relatively young discipline, but there are many other reasons and these will be discussed below.

In this overview, the opportunities and problems associated with the industrial application of chiral catalysts (restricted to homogeneous metal complexes and modified metallic catalysts) will be analyzed in detail. The review is an amended and updated version of a chapter written in 2002 for the second edition of “Applied Homogeneous Catalysis by Organometallic Complexes” [16], supplemented with information on heterogeneous catalysts. In the first chapter, we discuss critical factors affecting the feasibility of an enantioselective catalyst. In the following chapters, chiral catalysts with synthetic relevance are listed and finally about 40 types of catalytic transformations are described and characterized regarding enantioselectivity, catalyst activity and productivity, and their potential for technical applications is assessed.

2. Critical factors for the technical application of homogeneous enantioselective catalysts

The application of homogeneous enantioselective catalysts on a technical scale presents some very special challenges and problems [3,4,6a,15,17]. Some of these problems are due to the special manufacturing situation of the products involved, others are due to the nature of the enantioselective catalytic processes.

Table 1
Scope and limitations of major production methods for enriched chiral molecules

	Chemocatalysis	Biocatalysis	Chiral pool	Crystallisation	HPLC
Enantioselectivity	1–2	1	1	1–2	1–2
Activity and productivity	1–2	2–3	–	–	–
Availability and diversity	1–2	2–3	2	1	1
Substrate specificity	2	2–3	1	1	2
Work-up and ecology	1–2	2–3	2	2	2
Development time and effort	2	3	1	1–2	1
Application in the lab	2	3	1	1–2	1
Application in development	1–2	2	1	2	2
Small-scale production	1–2	1–2	1	1–2	2
Large-scale production	1	2	2–3	1–2	3

Rating: 1: broad scope, 2: medium scope and/or some problems, 3: narrow scope and/or often problematic.

2.1. Characteristics of the manufacture of enantiomerically enriched products

Enantiomerically enriched compounds will be used above all as pharmaceuticals and vitamins [1], as agrochemicals [2] and as flavors and fragrances [18]. Other potential but at present less important applications are functional materials such as chiral polymers, materials with non-linear optical properties or ferroelectric liquid crystals [4b,19]. The manufacture of pharmaceuticals and agrochemicals can be characterized as follows (typical numbers are given in parenthesis):

- *Multifunctional molecules* produced via multistep syntheses (10–15 steps for pharmaceuticals and 3–7 for agrochemicals) with short product lives (often <20 years).
- *Relatively small scale products* (1–1000 t/year for pharmaceuticals, 500–10,000 t/year 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 tolerant to higher process costs (especially for very effective, small scale products).
- The *development time* can be a hurdle, especially when the optimal catalyst has to yet be developed or no commercial catalyst is available for a particular substrate (substrate specificity) and/or when not much is known on the desired catalytic transformation (technological maturity). When developing a process for a new chemical entity (NCE) in the pharmaceutical or agrochemical industry, time restraints can be severe (see Fig. 1). In these cases it is more important to find a competitive process on time than an optimal process too late. So-called second generation processes, e.g., for chiral switches, for generic pharmaceuticals or the manufacture of other fine chemicals have different requirements; here the time factor is usually not so important but a high performance process is necessary.

2.2. Characteristics of enantioselective catalytic processes

Enantioselective catalysis is a relatively young but rapidly expanding field. Up to 1985, only few catalysts affording enantioselectivities of more than 90% were known [20]. This has changed dramatically in recent years and there are now a large number of chiral catalysts able to catalyze a variety of transformation with ees >98% [11,21]. A major challenge which still remains is the transfer of the results obtained for a particular substrate to even a close analog due to the low tolerance for structure variation even within a class of substrates (substrate specificity). The industrial application of enantios-

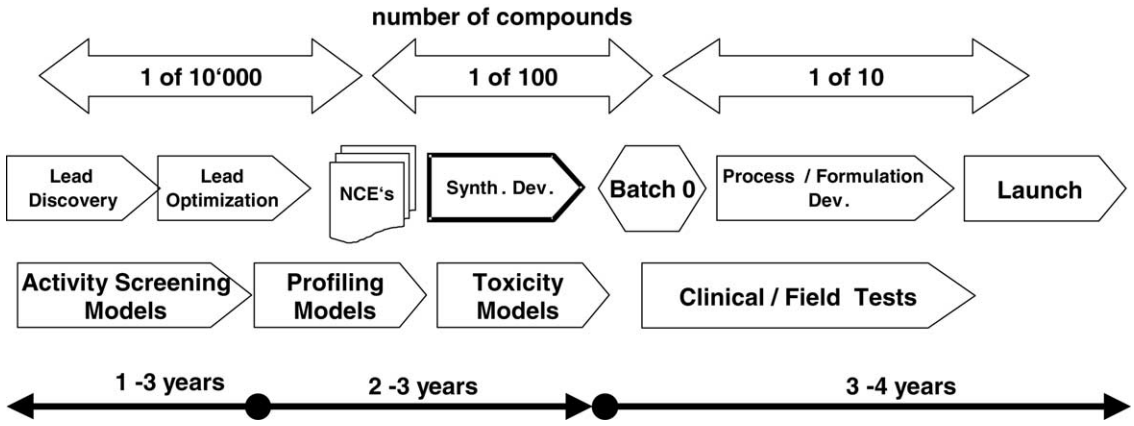

Fig. 1. Development process for a new chemical entity in the pharmaceutical industry.

elective catalysts is also hampered by a lack of information on their synthetic scope and limitations. In addition, catalyst activities or productivities are often not given for new catalysts (in the literature enantioselectivity is still the dominant criterion) and applications to the synthesis of "real" substrates are rather scarce (usually simple model reaction are studied). Finally, many chiral ligands and metal precursors are expensive and/or not easily available in technical quantities.

2.3. Critical factors for the application of enantioselective catalysts

In the final analysis, the choice of a specific catalytic step is usually determined by the answer to two questions:

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

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

- The *enantioselectivity*, expressed as enantiomeric excess (% ee), i.e., % desired − % undesired enantiomer. The ee of a catalyst should be >99% for pharmaceuticals if no purification is possible (via recrystallization or at a later stage via separation of diastereomeric intermediates). This case is quite rare and ees >90% are often acceptable; for agrochemicals ees >80% can be sufficient.
- The *chemoselectivity and/or functional group tolerance* will be very important when multifunctional substrates are involved.
- The *catalyst productivity*, given as turnover number (TON), determines catalyst costs. TONs ought to be >1000 for small scale, high value products and >50,000 for large scale or less expensive products (catalyst re-use increases the productivity).
- The *catalyst activity*, given as turnover frequency for >95% conversion (TOF, h^{-1}), determines the production capacity. For hydrogenations, TOFs ought to be >500 h^{-1} for small scale and >10,000 h^{-1} for large scale products.
- *Availability and cost of ligands*. In the majority of cases these are chiral diphosphines that need special synthetic know how and can be rather expensive. Typical prices are 100–500 $/g for laboratory quantities and 5000 to >20,000 $/kg on a larger scale. Chiral ligands such as diamines or amino alcohols used for early transition metals are usually cheaper.
- *Intellectual property*. Many chiral ligands and/or catalysts are patent protected. It is essential to obtain the right to use proprietary catalysts on a commercial basis at reasonable costs and conditions.
- *Availability and cost of starting materials*. Starting materials are often expensive and difficult to manufacture on a large scale with the high purity required for catalytic reactions.
- *Development time*. Can be crucial if an optimal ligand has to be developed for a particular substrate (substrate specificity) and when not much know-how is available on the catalytic process (technological maturity).

For most other aspects such as catalyst stability and sensitivity, handling problems, catalyst separation, space time yield, poisoning, process sensitivity, toxicity, safety, special equipment, etc., enantioselective catalysts have similar problems and requirements as nonchiral homogeneous catalysts.

Which of these criteria will be critical for the development of a specific process depends on the specific catalyst and transformation. The following factors have to be considered: the field of application and the price of the active compound (added value of the catalytic step); the scale of the process; the technical experience and the production facilities of a company; the maturity of the catalytic process; and last but not least, the chemist who plans the synthesis must be aware of the catalytic route!

Table 2
Statistics for the industrial application of enantioselective catalytic reactions [15]

Transformation	Production		Pilot		Bench scale
	>5 t/year	<5 t/year	>50 kg	<50 kg	
Hydrogenation of enamides	1	1	2	6	4
Hydrogenation of C=C–COOR and C=C–CH–OH	1	0	3	4	6
Hydrogenation of other C=C	1	0	1	2	2
Hydrogenation of α and β functionalized C=O	2	2	3	6	4
Hydrogenation/reduction of other C=O	0	0	0	1	4
Hydrogenation of C=N	1	0	1	0	0
Dihydroxylation of C=C	0	1	0	0	4
Epoxidation of C=C, oxidation of sulfides	2	1	2	0	2
Isomerization, epoxide opening, addition	2	0	3	0	1
Total	10	5	15	19	27

Definitions: production processes are operated on a regular basis; pilot processes are technically on a similar level but are not (yet) applied on a regular basis; bench scale processes have an optimized catalyst system and have been carried out on a kg scale.

3. State of the art and evaluation of catalytic systems and transformations

3.1. General comments

3.1.1. Transformations

In the last few years, information on industrial applications has increased both in quantity and in quality because especially smaller technology based companies are ready to publish relevant results. In a recent review we have collected and commented information on technical processes [15]; a statistical summary of this compilation is presented in Table 2. Even though some new applications have been published since the review was written [6], the general trend has not changed. From these numbers it is evident that hydrogenation is the transformation with the highest industrial impact, followed by epoxidation and dihydroxylation reactions. On the one hand, this is due to the broad scope of catalytic hydrogenation. On the other hand, it could be attributed to the early success of the L-dopa process, because for many years most academic and industrial research was focused on this reaction type. The success with epoxidation and dihydroxylation can essentially be attributed to the efforts of Sharpless, Katsuki and Jacobsen. Nevertheless, as will be shown in the following chapters, other catalytic transformations have the potential for industrial use—but this potential has to be translated into applications by the persons responsible for the actual choice of the technology: the development chemists.

In the Sections 3.2–3.5 synthetically useful enantioselective reactions and the corresponding catalysts are reviewed and tabulated in Tables 3–9. In addition, illustrative examples of processes in various stages of industrial development are shown. Critical issues will be discussed and an overall assessment of the technical maturity will be given. It has to be stressed that such an assessment, even though made on the basis of the criteria defined above, can not be completely objective and that it reflects the experiences (and of course also the prejudice) of the authors.

3.1.2. Chiral catalysts, ligands and modifiers

As already pointed out, there are two classes of synthetically versatile enantioselective catalysts, namely *homogeneous metal complexes* containing chiral ligands and *heterogeneous metallic catalysts* in presence of chiral modifiers (Fig. 2). Generally speaking, the metal component is the activating function while the chiral ligand/modifier is responsible for enantiocontrol. However, it has to be stressed that all components of a given catalytic system (metal, ligand/modifier, additives, solvents etc.) are needed to reach the desired catalytic effect and that in many cases the ligands/modifiers affect the catalytic activity as well. In each case, these parameters as well as the reaction conditions have to be carefully optimized in order to arrive at the best over-all catalyst performance.

Today, an impressively large number of chiral ligands and modifiers is recorded in the literature to achieve very high enantioselectivity for a variety of catalytic reactions [11,21]. This was not always so and for many of the early industrial processes, the search for and the preparation of the chiral ligand was the most time consuming problem. Most classes of chiral catalysts have a preferred application spectrum which is sometimes quite broad as, e.g., for diphosphine complexes and sometimes very narrow as, e.g., for metal porphyrins. Even today only few chiral ligands and modifiers are used on a regular bases for the synthesis of target molecules and Jacobsen has coined the term “privileged ligands” for these selected few [22]. The usefulness of a ligand can be negatively affected if it is extremely air and/or moisture sensitive. In addition, catalysts are often rather substrate specific, i.e., ligands have sometimes to be “tailored” for each individual substrate because even small changes can strongly affect the catalyst performance. In this respect, modular ligands are preferred since the effort required to adapt the ligand to the reaction are much smaller than for ligands with little structural variability [23]. Finally, a scarcely addressed point is the functional group tolerance and/or chemoselectivity of a catalysts which will get very important when more complex substrates must be transformed selectively. Needless to say that ligands with a wide scope (and well defined and known limitations), low substrate specificity and with good functional group tolerance and stability have a much better chance for being applied by the synthetic organic chemist than others.

As already pointed out above, the enantioselective hydrogenation of unsaturated functions is the most important industrial application of chiral catalysts. In the last few years a number of ligand classes have been shown to be especially versatile [24] and a sizeable number is now commercially available also on large scale. In the text we have chosen the following generic abbreviations: BIAR for atropisomeric diphosphines (Fig. 3), FERRO for ferrocene based diphosphines (Fig. 4), PCYCL for phospholane type ligands (Fig. 5.), MONO for monodentate and PCHIRAL for phosphines with a stereogenic P atom (Fig. 6). Structures and names (in capital letters) of commercially relevant ligands used for hydrogenation reactions and mentioned in the following sections are also given in Figs. 3–6, the structure of other ligands can be found in the cited references. Most of these ligands (and of course many more) can be purchased on a laboratory scale from Strem or Fluka-Aldrich. If appropriate, we have also indicated the company which markets or applies the ligands on a technical scale.

Besides these ligands which have been mainly developed for hydrogenation applications but which are effective for many other transformations as well, there are a few more chiral auxiliaries available commercially on a large scale and these are depicted in Fig. 7.

3.2. Reduction of C=C, C=O and C=N bonds

3.2.1. Hydrogenation of olefins

The enantioselective hydrogenation of olefins is the best studied reaction with the most industrial applications

Table 3
State-of-the-art for the hydrogenation of olefins

Substrates	ee (%)[a]	TON[a]	TOF (h^{-1})[a]	Preferred catalyst types[b]
Enamides, enol acetates, itaconates	90–99	1000–50000	200–5000	Rh/PCYCL, Rh/FERRO, Rh/MONO, Rh/PCHIRAL, Ru/BIAR, Rh/VARIOUS
Allylic alcohols	80–95	10000–50000	1000–5000	Ru/BIAR
α,β-Unsaturated acids	85–95	2000–20000	500–3000	Ru/BIAR (Rh/PCYCL, Rh/FERRO)
Tetrasubstituted C=C	85–95	500–2000	200–500	Ru/BIAR, Ru/PCYCL, Rh/FERRO, Rh/PCHIRAL
C=C without privileged function	80–95	20–100	2–5	Ir/PˆOXAZ (Ru/BIAR, Rh/PCYCL)

[a] Typical range for suitable substrate and optimized catalyst.
[b] Structures see Figs. 3–6; catalysts in parenthesis have narrow scope.

Table 4
State-of-the-art for the reduction of functionalized ketones

Substrate/Reducing agent	ee (%)[a]	TON[a]	TOF (h^{-1})[a]	Preferred catalyst types[b]
RCOCHRCOOR/H_2	90–98	5000–50000	2000–10000	Ru/BIAR, Ru/FERRO, Ni/TARTRATE
RCOCOOR/H_2	90–95	1000–5000	100–500	Rh/AMPP, Ru/BIAR, Pt/CINCHONA
RCOCHRX/H_2 X = NHR, OR	90–95	1000–5000	100–500	Ru/BIAR, Rh/FERRO, Rh/AMPP, Pt/CINCHONA
ArCOR/H_2	90–95	5000–20000	500–10000	Ru/BIAR-diamine
ArCOR/*i*-PrOH or HCOOH/NEt_3	85–95	1000–5000	100–500	Ru, Rh, or Ir/OˆN, NˆN, PˆN
Various ketones/BH_3	85–95	20–50	5–10	OXABOR

[a] Typical range for suitable substrate and optimized catalyst.
[b] Structures see Figs. 3–7; AMPP amidophosphine-phosphinite; XŶ bidentate ligand with O, N or P as coordinating atoms.

Table 5
State-of-the-art for the reduction of C=N groups

Reaction	ee (%)[a]	TON[a]	TOF (h^{-1})[a]	Preferred catalyst types[b]
N-Aryl imines	80–90	500–10000	50–100	Ir/FERRO, Rh/BDPP, Ir/PˆOXAZ, Ru/PˆP/NˆN
Alkyl imines	80–90	50–500	5–50	Rh/BDPP (Ir/PˆOXAZ)
Cyclic imines	90–98	50–1000	1–50	Ti/EBTHI, Ir/FERRO, Ir/BIAR
Various C=N–X	80–95	100–500	5–100	Rh/PCYCL, Ru/BIAR, Rh/FERRO

[a] Typical range for suitable substrate and optimized catalyst.
[b] Structures see Figs. 3–6.

Table 6
State-of-the-art for the oxidation of olefins and sulfides

Reaction	ee (%)[a]	TON[a]	TOF (h^{-1})[a]	Preferred catalyst types[b]
Epoxidation of allylic alcohols	85–95	10–40	Up to 20	Ti/TART
Epoxidation of C=C	80–95	50–2000	50–200	Mn/SALEN
Dihydroxylation of C=C	85–95	100–500	50–100	Os/CINCH
Aminohydroxylation of C=C	85–95	20–100	5–20	Os/CINCH
Sulfide oxidation	80–95	2–20	1–5	Ti/TART

[a] Typical range for suitable substrate and optimized catalyst.
[b] Structures see Fig. 7.

Table 7
State-of-the-art for miscellaneous addition reactions to olefins

Reaction	ee (%)[a]	TON[a]	TOF (h^{-1})[a]	Preferred catalyst types[b]
Hydrocarbonylation	85–95	100–1000	300–500	Rh/BIAR, Pd/BINO, various
Hydrosilylation	85–95	200–1000	20–100	Pd/MOP
Hydroboration	85–95	50–100	5–200	Rh/QUINAP, Rh/FERRO
Michael addition	85–95	50–200	5–100	var/BINO, Cu/PAMID
Cyclopropanation	85–95	50–1000	20–100	Cu/OXAZ, Rh/CARB[c]
Diels-Alder reaction	85–95	10–100	1–10	Cu/OXAZ, M/OˆO, M/OˆN, M/NˆN

[a] Typical range for suitable substrate and optimized catalyst.
[b] Selected structures see Figs. 3 and 7; OXAZ various bisoxazolidines, BINO various bisphenols.
[c] Chiral carboxylate or carboxamidate.

Table 8
State-of-the-art for addition reactions to C=O groups

Reaction	ee (%)[a]	TON[a]	TOF (h^{-1})[a]	Preferred catalyst types
Aldol reaction	90–95	5–20	1–10	Ln/BINOL, Ag/BIAR, Cu/OXAZ
Ene reaction	90–95	5–20	1–10	Ti/BINOL
Addition of MR to RCHO	90–95	5–100	1–20	M/N^O, M/O^O, M/N^N
Hetero Diels-Alder	85–95	10–50	2–10	Cu/OXAZ, M/O^O, M/N^O, M/N^N
Addition of CN^- to C=O	90–95	10–100	Low	Ti/BINOL, M/N^N, M/SALEN

[a] Typical range for suitable substrate and optimized catalyst.

Table 9
State-of-the-art for miscellaneous transformations

Reaction	ee (%)[a]	TON[a]	TOF (h^{-1})[a]	Preferred catalyst types[b]
Allylic substitution	85–95	50–1000	20–100	Pd, Mo/Trost lig, Pd/P^OXAZ, Pd/OXAZ, various
Cross coupling	80–90	500–200	2–20	Ni/P^N
Heck reaction	80–95	10–100	1–10	Pd/BIAR, Pd/P^OXAZ
Metathesis	90–95	20–100	10–100	Ru/carbene, Mo/O^O
Kinetic resolution of epoxides	98–99	500–1000	20–40	Co or Cr/SALEN

[a] Typical range for suitable substrate and optimized catalyst.
[b] Selected structures see Figs. 3 and 7; OXAZ: various bisoxazolidines.

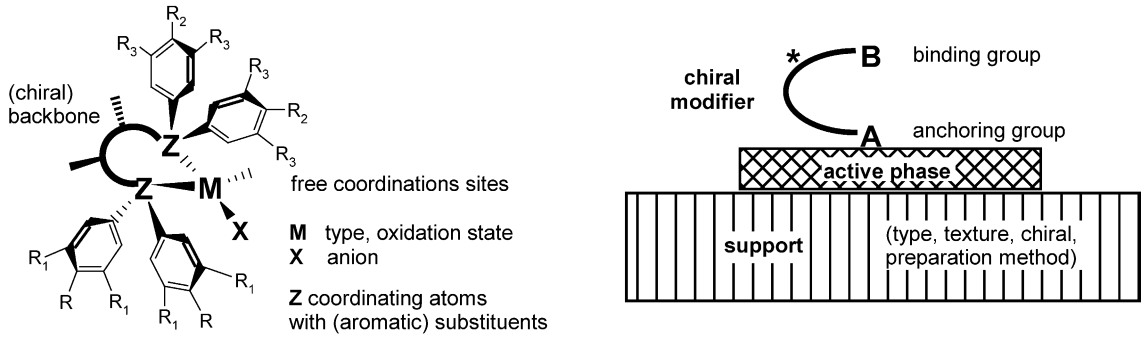

Fig. 2. Generic structural elements of chiral metal complexes (left) and chirally modified heterogeneous catalysts (right).

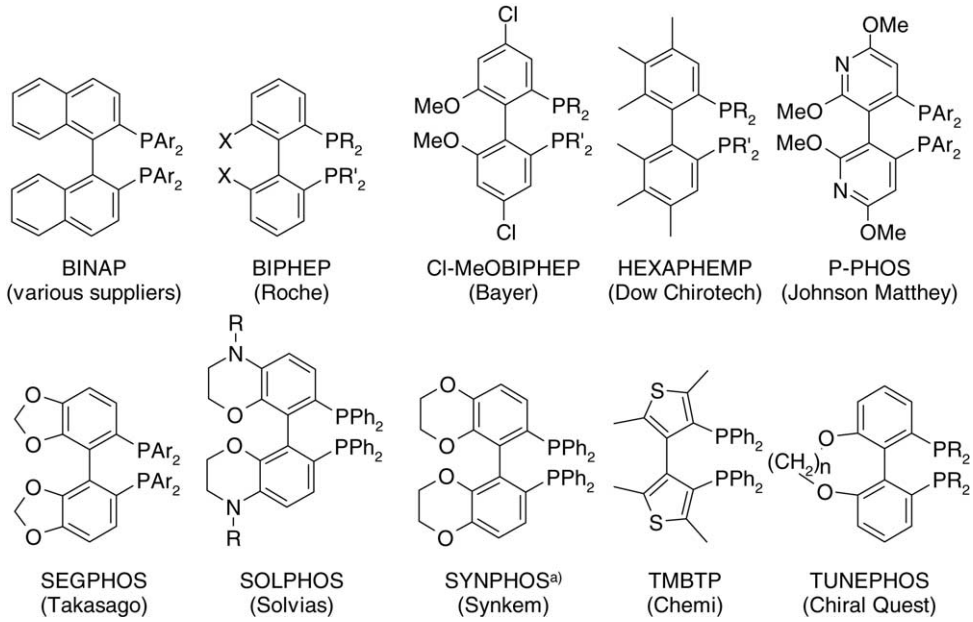

Fig. 3. Structure, name and company of commercially relevant atropisomeric biaryl ligands, generic abbreviation BIAR. [a)]Also known as BISBENZODIOXANPHOS.

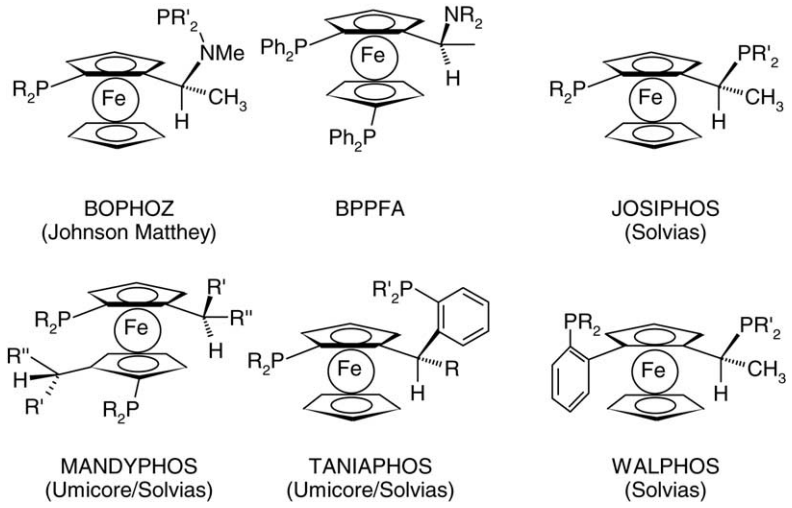

Fig. 4. Structure, name and company of commercially relevant ferrocene based ligands (generic abbreviation FERRO).

[11c,15,21a,24]. Over the last decades, a few privileged substitution patterns have evolved that almost guarantee high ees. These structures are depicted in Fig. 8 and the state-of-the-art is summarized in Table 3. With few exceptions, Rh and Ru complexes of a limited number of chiral diphosphine families are the preferred catalysts but in any case, the optimal complex (metal, ligand, anion, etc.) has to be determined for each substrate.

Hydrogenation of enamides (type **1** in Fig. 8 X = NR, Y = C, W = R), especially of α-dehydroamino acid derivatives (R_1 = COOR), is not only the best known test reaction but has also a very high potential for the production of pesticides or pharmaceuticals. The original motivation for developing this reaction type was the manufacture of α-amino acids but except for small scale applications or more complex structures, the preparation of the enamide substrates was too expensive and most large scale amino acids are now produced via biocatalytic methods [6b,25]. Many different substrates of type **1** such as α-dehydroamino and itaconic acid derivatives can now be hydrogenated with ees between 95 and 99% with moderate to very high catalyst activity and productivity even though model reactions are usually carried out with substrate/catalyst ratios of 100–1000. In general, more and larger substituents lead to a decrease in catalyst activity both when directly attached to C=C or when bound to X or W.

Selected examples depicted in Fig. 9 show what level of catalyst performance can be achieved by process development. The most prevalent catalysts are Rh complexes with various diphosphines but in some cases also Ru/BIAR catalysts are suitable. In addition, the selection demonstrates the variety of structural motives found in biologically active com-

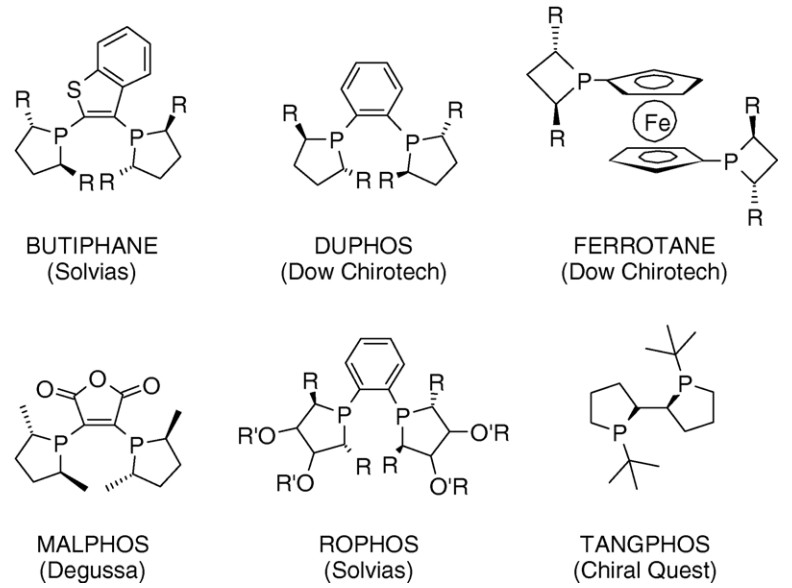

Fig. 5. Structure, name and company of commercially relevant phospholane type ligands (generic abbreviation PCYCL).

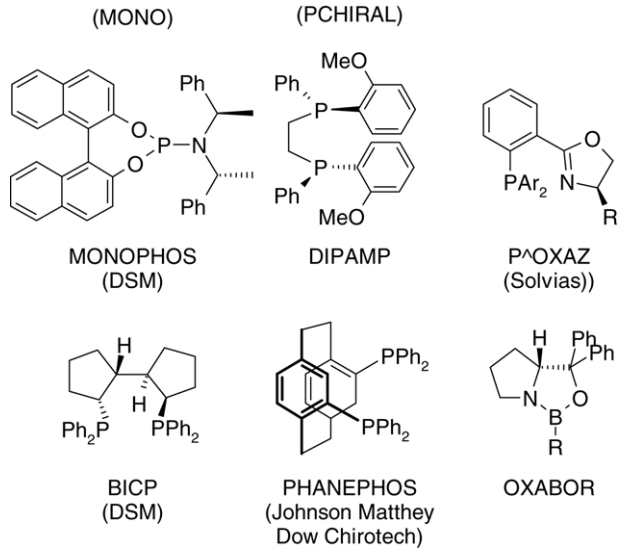

Fig. 6. Structure, name, company and generic abbreviation of miscellaneous commercially relevant ligands.

pounds and the need for tolerating functional groups such as pyridyl, cyano, thienyl or other C=C or C=O moieties.

The hydrogenation of allylic alcohols and α,β-unsaturated acids (**2** in Fig. 8) is another class of transformations with high industrial success rate. Also here some illustrative examples are depicted in Fig. 10; with few exceptions the catalysts of choice are Ru/BIAR complexes. While very high TONs and TOFs have been achieved for simple allylic alcohols, more complex substrates and especially α,β-unsaturated acids are reduced with lower efficiency.

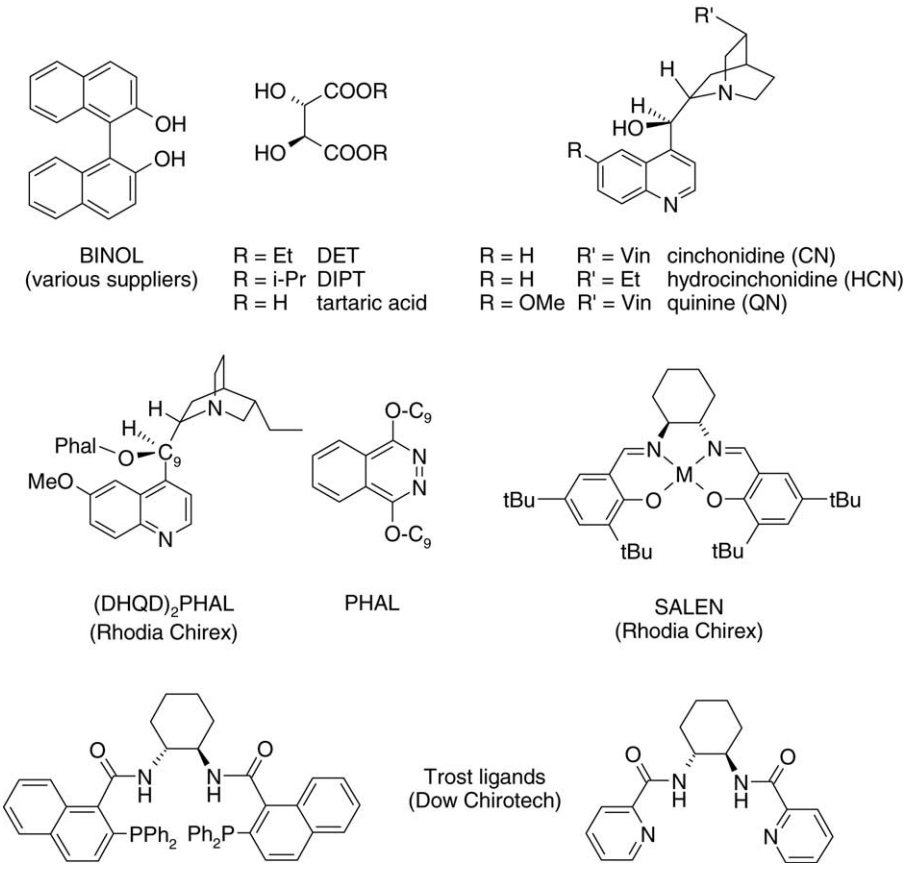

Fig. 7. Structure, name, company and generic abbreviation of miscellaneous commercially relevant chiral ligands and modifiers.

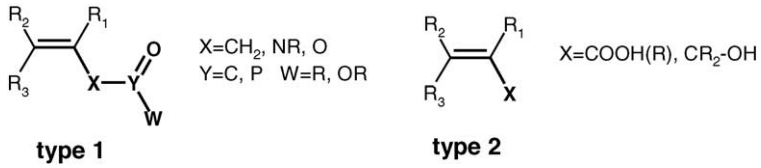

Fig. 8. Olefins with privileged substitution patterns.

Homogeneous hydrogenations of tetra substituted olefins are still rare, even though high ees and reasonable activities can now be achieved. Three industrial examples are depicted in Fig. 11; favored catalysts are Rh and Ru/JOSIPHOS and Ru/DUPHOS complexes, also effective catalysts are Ru/BIPHEP and Rh/TRAP.

Even though the hydrogenation of alkenes without "privileged" functional groups is much more difficult and requires much more effort to achieve good enantioselectivity there are some successful examples as depicted in Fig. 12. Of special interest are the Ir-phosphine dihydrooxazol catalysts (Ir/PˆOXAZ) recently reported be Pfaltz et al. [37] even though their functional group tolerance is relatively low.

For the enantioselective reduction of olefins, there are few alternatives to homogenous hydrogenation because neither transfer hydrogenations with hydrogen donors such as HCOOH/NEt3 [24,38] nor chiral heterogeneous catalysts [9,11a] have the required catalyst performance for synthetic applications

3.2.2. Reduction of ketones

The hydrogenation of ketones using Rh and Ru diphosphine catalysts is the most versatile and efficient method for the synthesis of a large variety of chiral alcohols (see Table 4) [11e,21a]. While Rh diphosphine catalysts are often substrate specific, several Ru/BIAR type catalysts have a rather broad scope. These catalysts are effective for the hydrogenation of functionalized ketones such as β-keto esters, 2-amino and 2-hydroxyketones with high ees and often reasonable TONs and TOFs. An alternative for β-functionalized ketones is the heterogeneous Raney nickel modified with tartaric acid and bromide [9]. Due to the low activity of homogeneous catalysts, α-keto esters, acetals and ethers are preferentially hydrogenated with heterogeneous cinchona modi-

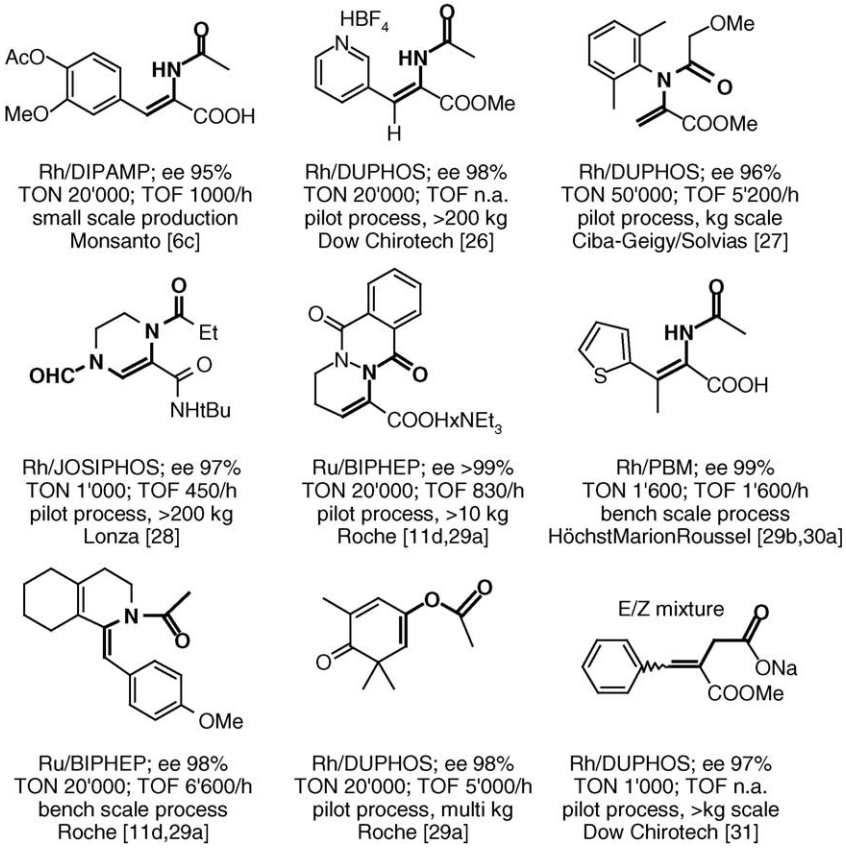

Fig. 9. Selected applications with type **1** substrates: catalyst type and performance, development stage and company [6c,11d,26–28,29a,b,30a,31].

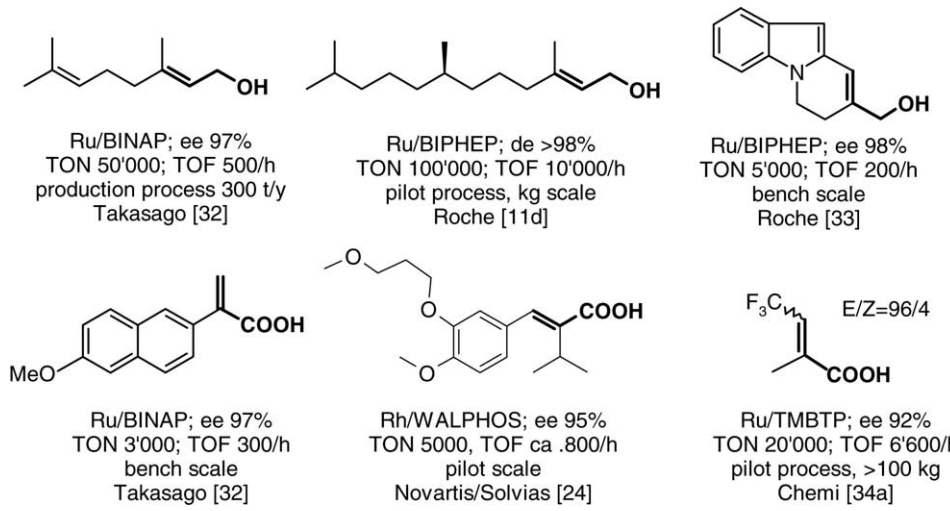

Fig. 10. Selected applications with type **2** substrates: Catalyst type and performance, development stage and company [11d,24,32–34].

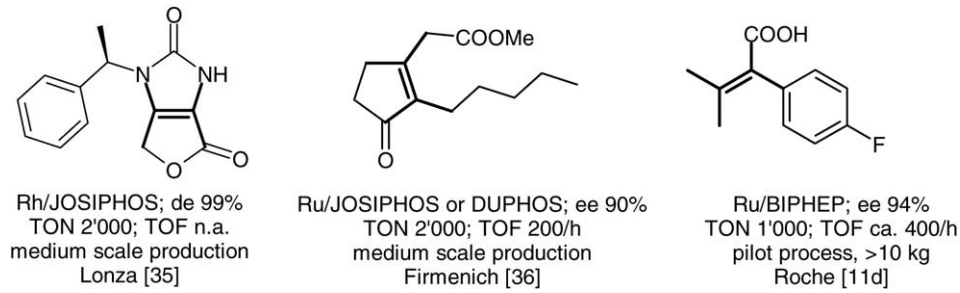

Fig. 11. Hydrogenation of tetrasubstituted olefins: catalyst type and performance, development stage and company [11d,35,36].

fied Pt catalysts [9,11a]. At the moment there exist two commercial applications of such catalyst systems (see Fig. 13). The Ru/BINAP/chiral diamine catalysts developed by Noyori [21a] are very effective for the hydrogenation of aryl ketones (TOF up to 2,400,000!) and are also suitable for α,β-unsaturated ketones. The technology has been licensed by companies like DSM, Dow Chirotech and Johnson Matthey Synetix who have developed analogous systems with their own chiral diphosphines. Unfunctionalized alkyl ketones are still a problem, ees >90% have only been reported for a few rare cases [21a]. Fig. 13 shows a selection of ketones where industrial processes have been developed. Also here, tolerance against functional groups such as pyridines, C–Cl and C=C bonds is important.

Other reducing agents are of interest especially for small scale reductions and/or when no hydrogenation facilities are available. Transfer hydrogenation [21a,24] using *i*-PrOH/base or HCOOH/NEt_3 as reducing systems shows some promise for the reduction of aryl ketones due to the recent development of efficient Rh and Ru transfer hydrogenation catalysts with new bidentate N^N, N^O and P^N ligands. For several model aryl ketones ees up to 99% were obtained, however activities and productivities are usually relatively low even though in a few cases TONs up to 5000 and TOFs of 3000–6000 h^{-1} were described. Avecia has developed the so-called CATHy technology for technical applications and has carried out the reduction of the model ketones depicted in Fig. 14 on a 50–200 l scale [6d].

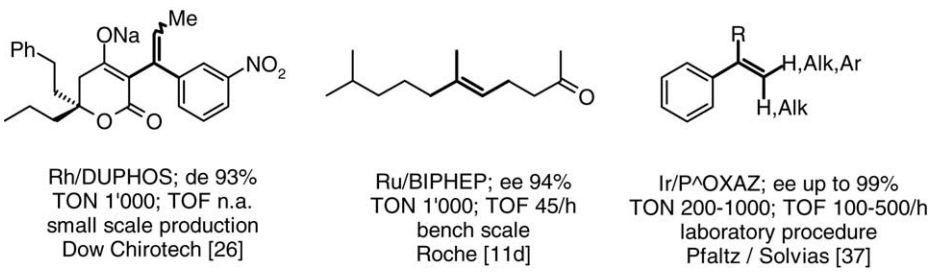

Fig. 12. Hydrogenation of olefins without privileged substitution: catalyst type and performance, development stage and company [11d,26,37].

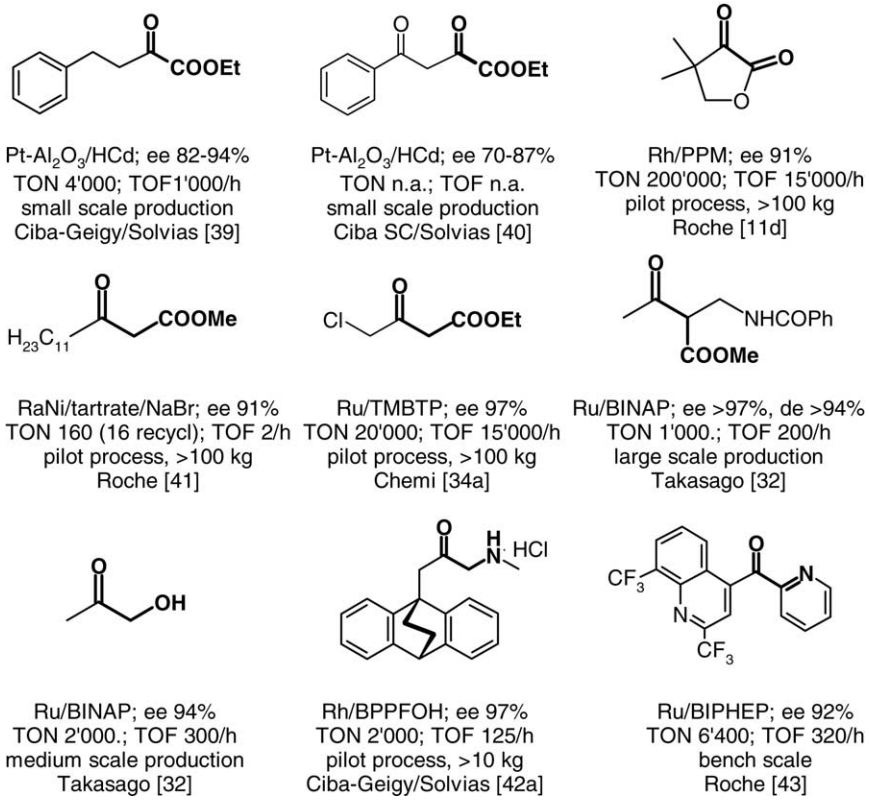

Fig. 13. Hydrogenation of functionalized ketones: catalyst performance, development stage and company [11d,32,34a,39–41,42a,43].

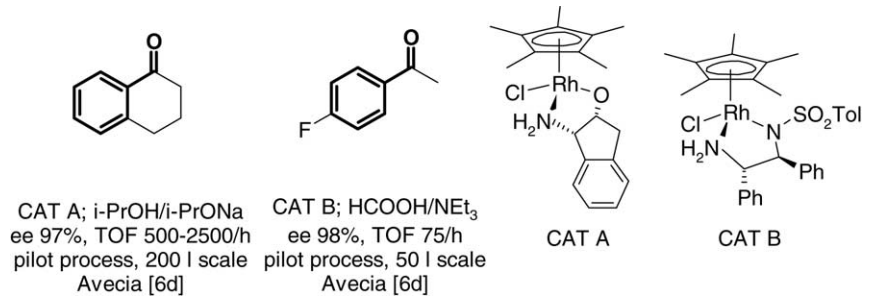

Fig. 14. Transfer hydrogenation of aryl ketones using CATHy technology, substrate and catalyst structures [6d].

The reduction with BH_3 [11f] adducts in presence of catalytic amounts of amino alcohols has already found some industrial applications, especially by PPG-Sipsy and Rhodia Chirex (see Fig. 15). Hydrosilylation [21b] is of less preparative interest since most silanes are quite expensive. Activities and productivities for both methods are often low and for large scale processes, the disposal of wastes from the stoichiometric reducing agent

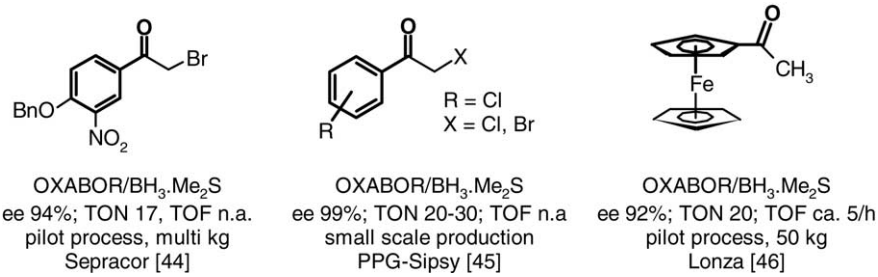

Fig. 15. Reduction of aryl ketones: catalyst performance, development stage and company [44–46].

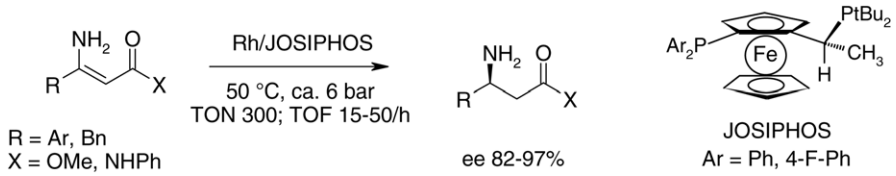

Fig. 16. Hydrogenation of unprotected β-enamine esters.

could be problematic (borate or silane hydrolysis products).

3.2.3. Reduction of C=N bonds

Even though chiral amines are important intermediates for biologically active compounds, the asymmetric hydrogenation of C=N has been investigated less systematically than that of C=C and C=O groups. In recent years this has begun to change and now, various Rh, Ir and Ru complexes are known with reasonable enantioselectivities (see Table 5) [11g,21a,47a]. With few exceptions, Rh complexes often have relatively low catalyst activities and productivities while some Ir complexes have high initial rates but often tend to deactivate [48]. Recently it was shown that Noyori's Ru diphosphine diamine catalyst also is useful for selected C=N groups [49].

Very recently, the hydrogenation of an unprotected β-enamine esters depicted in Fig. 16 was described representing an important breakthrough for the catalytic synthesis of chiral β-amino acids [50]. Mechanistic studies indicate that the reaction occurs via the hydrogenation of the corresponding C=N tautomer. Up to now, only few industrial applications have been reported. The metolachlor process carried out by Ciba-Geigy/Syngenta with a volume of >10,000 t/year is the largest known enantioselective catalytic production process [51,52]. In addition, pilot processes developed by Imwinkelried [35] for a dextromethorphan intermediate and by Avecia [6d] for a transfer hydrogenation of phosphinyl imine were reported (see Fig. 17).

The hydrogenation of acyl hydrazones with Rh/DUPHOS with ees up to 95%, of N-diphenylphosphinyl ketimines with Rh/JOSIPHOS and a Ti/EBTHI catalyst for cyclic imines (>98% ee) have some synthetic potential, however, the Ti catalysts unfortunately have a low functional group tolerance and very poor catalytic activity. Good to high enantioselectivities can be achieved with transfer hydrogenation and BH_3 reduction with medium to very low catalyst activities. Recently, the first example of a reductive alkylation of an aniline derivative with high TON and TOF values has been described, an interesting variant from an industrial point of view [53].

3.3. Oxidation reactions

The catalytic oxidations with industrial potential are epoxidation, dihydroxylation and aminohydroxylation of olefins and with a more narrow potential sulfide oxidation(Table 6).

3.3.1. Oxidation of olefins

Enantioselective oxidation of olefins is a very elegant way of introducing oxygen and in some cases also nitrogen functions into a molecule. The epoxidation of allylic alcohols using Ti/diisopropyl tartrate (Ti/DIPT) or Ti/diethyl tartrate (Ti/DET) catalysts has been applied in numerous multistep syntheses of bioactive compounds [11h,21c]. In presence of molecular sieves, the catalyst is effective for a variety of substituents at the C=C bond and tolerates most functional groups with good to high ees but rather low activity. However, applications on a larger scale are still restricted to a few examples [15] and selected ones are depicted in Fig. 18. The most important is the manufacture of glycidol developed by Arco and later operated by PPG-Sipsy [4c]. The reaction has been carefully optimized and is run with cumyl hydroperoxide as oxidant. Potential problems are the stereoselective preparation of certain allylic alcohols, the handling of organic peroxides (*t*-butyl or cumyl hydroperoxide) on a large scale, the rather low catalytic activity and productivity and sometimes the isolation and purification of the epoxy alcohols. An interesting new development is a Ta/DIPT attached to silica (ees up to 97%, TON up to 25 and TOF <1) [54] but its synthetic potential has not yet been explored.

In the last few years, the epoxidation of unfunctionalized olefins using cheap NaOCl as oxidizing agent has been developed industrially by Rhodia Chirex in collaboration with Jacobsen [42b,56] and an example is depicted in Fig. 19. Mn/SALEN type catalyst give good results for terminal and cis substituted olefins results with ees up to >97% with moderate to good catalytic activity [11i,21d]. New developments are the discovery of the beneficial effect of pyridine N-oxides [42b] and of new types of SALEN ligands by Katsuki with TONs up to 9000 [11c]. Of potential interest is the use of ionic liquids which allow recycling of the catalyst [57]. α,β-Unsaturated ketones can be epoxidized with hydrogen peroxide in presence of a polypeptide catalyst with ees up to >98%, albeit with usually very low activity [58]. Recently it was described that addition of phase transfer catalysts significantly enhance catalytic activity [59].

The asymmetric dihydroxylation (AD) of olefins leads to cis-diols with high to very high ees using Os/CINCH complexes (for a representative structure see Fig. 7) [11k,21e,21f]). This reaction has been applied in numerous lab scale syntheses and a catalyst/oxidant mixture (AD-mix) is available from Strem. However, even though it has been developed by Rhodia Chirex [56] (for an example see Fig. 19)

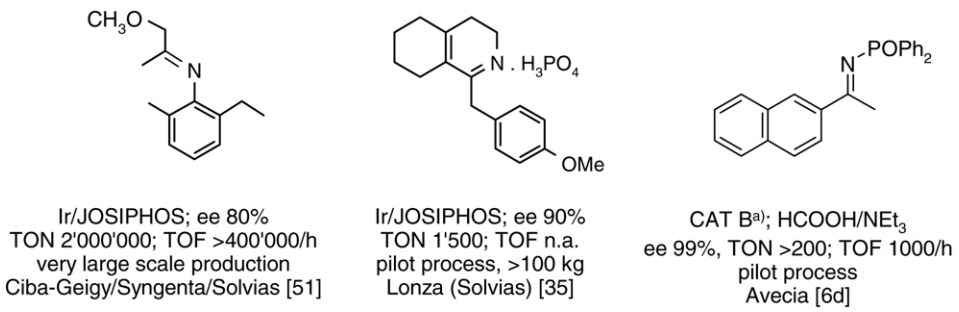

Fig. 17. Hydrogenation of C=N groups: catalyst performance, development stage and company. [a]See Fig. 14 [6d,35,51].

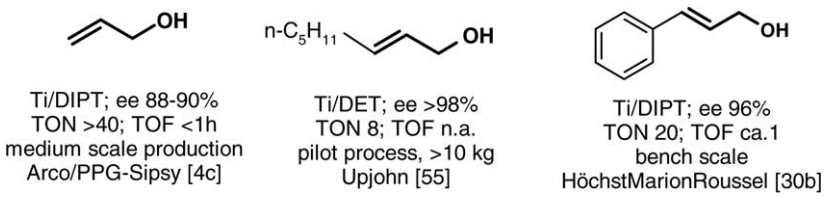

Fig. 18. Epoxidation of allylic alcohols: catalyst performance, development stage and company [4c,30b,55].

its application on a commercial scale seems to be challenging. $K_3Fe(CN)_6$-K_2CO_3, the oxidant used in the commercially available AD-mixes is problematic on larger scale. Recently, Beller has shown that oxygen can be used instead which is more promising for industrial applications [47b,60]. The analogous aminohydroxylation reaction [21f,47c] leading directly from olefins to 1,2-aminoalcohols has a similar synthetic potential but the additional problems of chemo- and regioselectivity make synthetic and particularly industrial applications more difficult.

Allylic oxidation [11l,61], aziridination [11m] as well as chiral variants of the Baeyer Villiger oxidation [62] are not yet mature for technical use, even though in specific cases high ees have been achieved.

3.3.2. Miscellaneous oxidation reactions

The oxidation of aromatic or hetero aromatic sulfides [21g] using Ti/TART catalysts exhibits good enantioselectivities but usually very low TONs (2–20) and TOFs (1–5/h); nevertheless two industrial applications are on record (Fig. 20), one of them for the chiral switch of one of the largest anti ulcer drugs [6e,63].

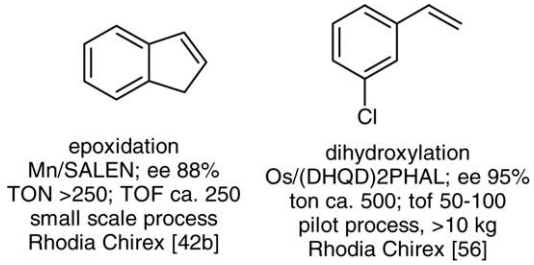

Fig. 19. Epoxidation and dihydroxylation of C=C groups. Catalyst performance, development stage and company [42b,56].

A very recent development is the Ti and Cu catalyzed enantioselective halogenation of 1,3-dicarbonyl compounds using electrophilic reagents, usually with an N–X function (X = F, Cl, Br) [64]. While in several cases ees up to 95% were reached, catalyst activities are too low for industrial use and the synthetic scope remains narrow.

3.4. Addition reactions to C=C, C=O and C=N bonds

3.4.1. Addition reactions to C=C bonds

Addition reactions to olefins can be used both for the construction and the functionalization of molecules. Accordingly, chiral catalysts have been developed for many different types of reactions with often very high enantioselectivity. Unfortunately, most have either a narrow synthetic scope or are not yet developed for immediate industrial application due to insufficient activities and/or productivities and most of the ligands are not available on technical scale. For this reason, these transformations will be discussed only summarily; the synthetically most versatile ones are listed in Table 7.

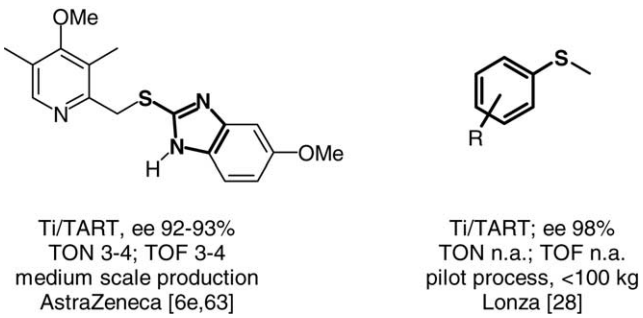

Fig. 20. Oxidation of sulfides: catalyst performance, development stage, company [6e,28,63].

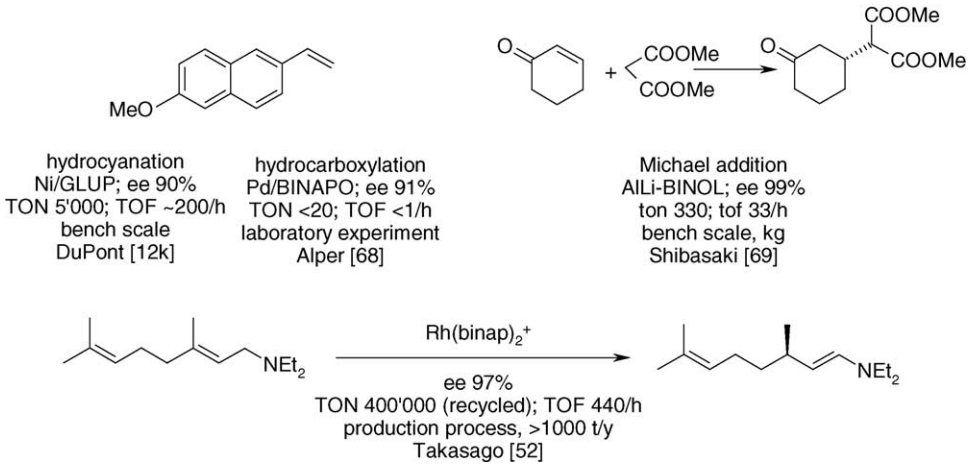

Fig. 21. Hydrocyanation, hydrocarboxylation, Michael addition, allylamine isomerization: catalyst performance, development stage and company [12k,52,68,69].

The most common classes of substrates for the addition of various H–X fragments are styrenes and other functionalized olefins; very often regioselectivity is an issue. Hydrocarbonylations [21h] are possible with good ees, especially with the Rh/phosphine-phosphite catalysts, but only few applications for industrially relevant targets have been reported (Fig. 21). Hydrosilylation [11n] and hydroboration [11o] of olefins followed by oxidation are attractive alternative methods for preparing chiral alcohols or amines. High catalyst activities (TOF up to 100,000/h) have been reported for the Pd catalyzed hydrosilylation of styrene in presence of arylphosphine ferrocene ligands with planar chirality [65]. The Ni catalyzed hydrocyanation reaction [11p] occurs with lower ees and requires the handling of HCN (Fig. 21). All four methods have an interesting synthetic potential but also some obvious draw backs. For the foreseeable future, they will be used industrially at best in niche applications.

Both the Michael addition [11q,11r,21s,66] and the Diels-Alder reaction [11s,21i,67] have a broad synthetic scope, however, with the exception depicted in Fig. 21, most investigations were carried out using model substrates or for proof-of-concept syntheses of natural products. The cyclopropanation with Cu and Rh complexes [11t,11u, 21k] and the Rh/BINAP catalyzed isomerization of allylamines [11v] are already used commercially for the manufacture of Cilastatin (one of the first industrial processes) [11w] and citronellol and menthol (presently the second largest catalytic process, Fig. 21) [11b], respectively. However, both transformations have a rather narrow scope for industrial applications. The insertion of carbenes in C-H bonds [11t,11u,21k] has a somewhat broader synthetic potential but involves the handling of diazo compounds.

3.4.2. *Addition reactions to C=O bonds*

Addition reactions to carbonyl groups are very important in synthetic methodology. Even though a wealth of catalysts with high enantioselectivity have been developed in the last years (Table 8), there are only few industrial applications. Most catalysts have low to medium catalytic activity and TONs of 5–100.

The aldol reaction [11x,21l,21m], ene reaction [11y,21n] and hetero Diels-Alder reaction [11z,21i,70] are catalyzed

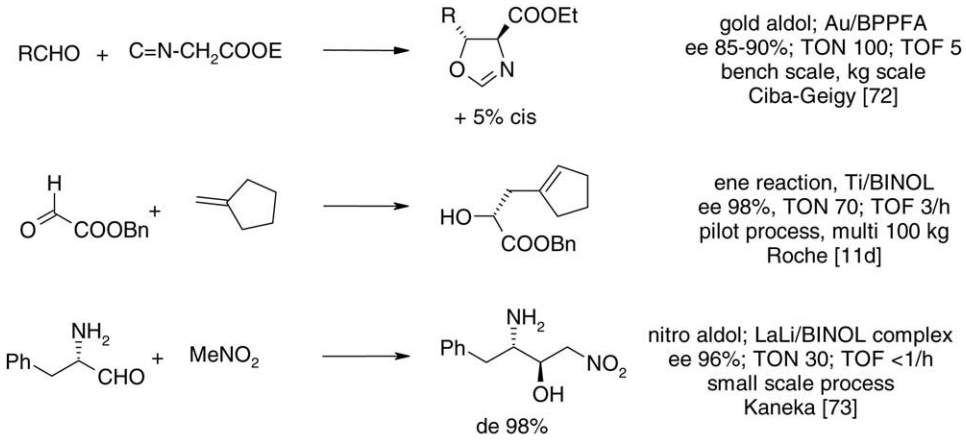

Fig. 22. Various addition reaction to C=O bonds: catalyst performance, development stage and company [11d,72,73].

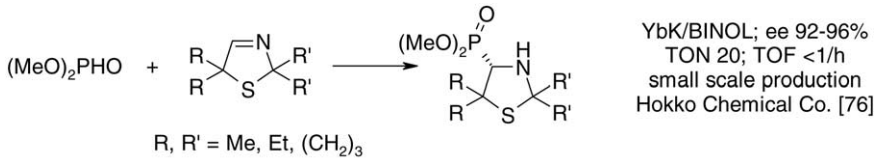

Fig. 23. Hydrophosphonylation of a C=N group: catalyst performance, development stage and company [76].

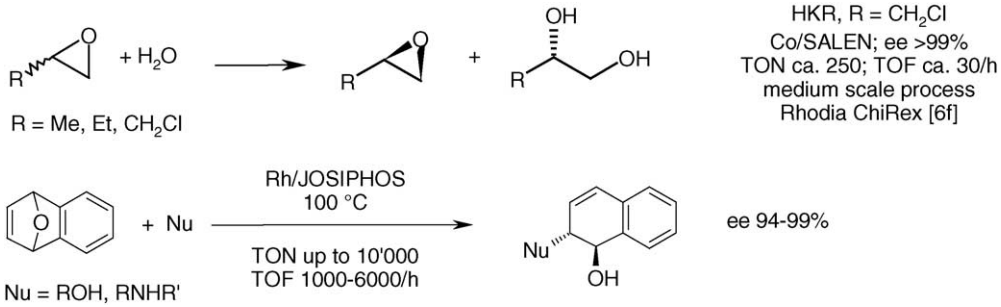

Fig. 24. Hydrolytic kinetic resolution of epoxides (catalyst performance, development stage and company), opening of oxabicycles [6f].

most effectively by early transition metal and lanthanide complexes. The addition reactions of ZnR_2 and similar reagents to aldehydes [11za] in presence of catalytic amounts of amino alcohols or early transition metal complexes is one of the classical model reactions but with few synthetic applications. The synthesis of chiral cyanohydrins as versatile building blocks via catalytic addition of cyanide to C=O groups has seen much progress in the last few years [71]. The most effective catalysts are early transition complexes with O and N ligands which achieve ees up 90–95% albeit with modest TON and TOF. Somewhat of a draw back is the need for trimethylsilylcyanide as cyanation reagent since there are few cases where HCN or KCN works well. Industrial applications have been reported for the gold-aldol reaction [21l,72] as an interesting approach to β-hydroxy amino acids, an ene reaction for an intermediate for Trocade, a collagenase inhibitor [11d], and the nitro-aldol reaction [11zb,73] (Fig. 22).

3.4.3. Additions to C=N bonds

Several addition reactions to C=N groups have been developed in recent years with a high synthetic potential but with few exceptions, industrial use is not yet feasible [11zc]. A notable exception is the Strecker reaction where in parallel to cyanohydrin synthesis progress has been impressive in recent years [74]. Avecia has developed a catalyst system based on V and Ti/salen catalysts [75]. Feasible catalysts are Al, Ti, Zr and Sc/BINOL, Ti/tripeptide and Al/SALEN catalysts, typical ees are 85–95%, TONs 10–50 but TOFs are often <1/h. The addition reaction of $(MeO)_2PHO$ to cyclic imines (Fig. 23), an interesting method for the preparation of α-amino phosphonic acids, seems to be an exception [76]. While ees of the heterobimetallic catalyst are very high, TON and TOF values are relatively low.

3.5. Miscellaneous transformations

Even though most of the reactions in Table 9 form new C–C bonds asymmetrically, none has really been developed to technical maturity, major issues being in many cases catalyst activity and productivity, and especially for the very versatile Heck and metathesis reactions also the relatively narrow synthetic scope for making chiral molecules.

Nucleophilic allylic substitution reactions [21q] with C- and N-nucleophiles catalyzed by Pd/P^P, Pd/P^N and Pd/N^N complexes have recently been applied not just in model studies but also in for the synthesis of natural products and pharma relevant molecules [77]. Indeed, Dow Chirotech has commercialized two ligands developed by Trost (see Fig. 7) [78] but to our knowledge no large scale application has been reported. The Ni/P^N catalyzed cross coupling reactions [21r] tolerate only few functional groups. The asymmetric Heck reaction is still in an exploratory phase even though some syntheses of natural products have been reported [21o]. In the last few years, the Ru and Mo catalyzed metathesis of olefins has been on of the hottest research topics in organic synthesis. Several chiral catalysts have been developed with an interesting but narrow synthetic scope since only rather special substrate structures are feasible [79]. With the exception of allylic substitution, all these methodologies will find at best industrial niche applications.

Finally, two ring opening reaction have an interesting potential. The first is the Co/SALEN catalyzed hydrolytic kinetic resolution of epoxides (Fig. 24) [11zd,80], a reaction which is in many cases more economical than asymmetric epoxidation and often competitive with biocatalytic methods. Rhodia Chirex has developed the catalytic system and manufactures several epoxides with this technology [6f,81]. The

Table 10
Classification of industrial potential of selected transformations

Existing applications, broad scope	• Hydrogenation of enamides and itaconates • Hydrogenation of β functionalized C=O
Existing applications, medium scope	• Hydrogenation of C=C–COOR and C=C–CH–OH • Hydrogenation of α functionalized and aryl C=O • Hydrogenation of C=N–Ar
Existing applications, narrow scope, niche applications	• Hydrogenation/reduction of other C=C and C=O • Hydrogenation of and addition to various C=N • Dihydroxylation and epoxidation of C=C • Oxidation of aryl sulfides • Epoxide opening (kinetic resolution) • Isomerization, cyclopropanation, hydrocyanation of C=C
Broad substrate scope, good chance for selected application	• (Hetero) Diels Alder • Michael additions, allylic alkylation • Aldol and ene reactions • Various addition reactions to C=O and C=N
Narrow substrate scope, niche applications only	• Aminohydroxylation of C=C • Hydrocarbonylation, hydroboration, hydrosilylation of C=C • Cross coupling, metathesis and Heck reactions

second transformation, the Rh/JOSIPHOS catalyzed opening of oxabicyclic alkenes has not yet been applied on an industrial level but is a very promising method for the synthesis of substituted dihydronaphthalenes, important building blocks in medicinal chemistry [82].

4. Conclusions and prospects

In the last few years, the industrial application of enantioselective homogeneous catalysts has made slow but significant progress. Even though the list of processes compiled in [6,15] which are applied or have been shown to be suitable for manufacture of chiral fine chemicals is certainly not comprehensive, an impressive number has been documented. At this time, relatively few are (or have been) really implemented as production processes run on a regular basis but there is every reason to assume that this technology is here to stay.

On the basis of the results presented in Sections 3.2–3.5 we have classified the transformations according to their industrial potential and the conclusions are summarized in Table 10.

Concerning the technical feasibility of the various catalytic systems it is obvious that homogeneous diphosphine complexes of Rh, Ru and to some extent Ir are the most versatile for industrial applications. Also a certain industrial potential is expected for selected Pd, Ti, B, Zn, Co, Mn or Cu complexes. Chirally modified heterogeneous catalysts are relatively easy to handle but for the time being there use is restricted to the hydrogenation of α- and β-activated ketones, even though recently a phosphites modified Pd colloid gave high ee's in an allylic alkylation reaction [83].

We are convinced that the number of industrial applications will increase significantly in the near future for several reasons. First, after more than 20 years of successful academic and industrial research it is highly probable that we are now in the steeper part of the usual S-shaped learning curve for technical applications. Second, there are many indications that development chemists in large pharma and chemical companies who are responsible for the choice of process technology have a greater awareness for the potential of enantioselective catalysis. Thirdly, many specialized technology companies such as Solvias, Rhodia Chirex or Dow Chirotech have evolved offering know-how and experience in catalytic process development and producing technical quantities of the chiral ligands. This gives smaller companies who are not able to develop technology on their own access to catalytic processes and ligands.

References

[1] For a recent update on chiral pharmaceuticals see A.M. Rouhi, C&EN, June 14, 2004, p. 47.
[2] G.M. Ramos Tombo, H.U. Blaser, in: G.T. Brooks, T.R. Roberts (Eds.), Pesticide Chemistry and Bioscience, Royal Society of Chemistry, Cambridge, 1999, p. 33, and references cited therein.
[3] J. Crosby, in: A.N. Collins, G.N. Sheldrake, J. Crosby (Eds.), Chirality in Industry I, John Wiley, Chichester, 1992, p. 1.
[4] (a) A. Bruggink, Chirality, in: A.N. Collins, G.N. Sheldrake, J. Crosby (Eds.), Chirality in Industry II, John Wiley, Chichester, 1997, p. 81;
(b) D. Pauluth, A.E.F. Wächter, Chirality, in: A.N. Collins, G.N. Sheldrake, J. Crosby (Eds.), Chirality in Industry II, John Wiley, Chichester, 1997, p. 263;
(c) W.P. Shum, M.J. Cannarsa, Chirality, in: A.N. Collins, G.N. Sheldrake, J. Crosby (Eds.), Chirality in Industry II, John Wiley, Chichester, 1997, p. 363.
[5] P. Franco, M. Schaeffer, T. Zhang, D. Heckmann, Chim. Oggi 22 (2004) 28;
J.R. Bruno, Chim. Oggi 22 (2004) 32.
[6] (a) H.U. Blaser, E. Schmidt, in: H.U. Blaser, E. Schmidt (Eds.), Large Scale Asymmetric Catalysis, Wiley-VCH, Weinheim, 2003, p. 1;

(b) H. Gröger, K. Drautz, in: H.U. Blaser, E. Schmidt (Eds.), Large Scale Asymmetric Catalysis, Wiley-VCH, Weinheim, 2003, p. 131;
(c) W.S. Knowles, in: H.U. Blaser, E. Schmidt (Eds.), Large Scale Asymmetric Catalysis, Wiley-VCH, Weinheim, 2003, p. 23;
(d) J. Blacker, J. Martin, in: H.U. Blaser, E. Schmidt (Eds.), Large Scale Asymmetric Catalysis, Wiley-VCH, Weinheim, 2003, p. 201;
(e) H.J. Federsel, M. Larsson, in: H.U. Blaser, E. Schmidt (Eds.), Large Scale Asymmetric Catalysis, Wiley-VCH, Weinheim, 2003, p. 413;
(f) L. Aouni, K.E. Hemberger, S. Jasmin, H. Kabir, J.F. Larrow, I. Le-Fur, P. Morel, T. Schlama, in: H.U. Blaser, E. Schmidt (Eds.), Large Scale Asymmetric Catalysis, Wiley-VCH, Weinheim, 2003, p. 165.

[7] A.J.J. Straathof, S. Panke, A. Schmid, Curr. Opinion Biotechnol. 13 (2002) 548.

[8] For details see Nobel Lectures, Angew. Chem. Int. Ed. 41 (2002) 1998–2022.

[9] M. Studer, H.U. Blaser, C. Exner, Adv. Synth. Catal. 345 (2003) 45.

[10] For a recent account see K.N. Houk, B. List, Acc. Chem. Res. 37 (2004) 487.

[11] (a) H.U. Blaser, M. Studer, in: E.N. Jacobsen, A. Yamamoto, A. Pfaltz (Eds.), Comprehensive Asymmetric Catalysis, Springer, Berlin, 1999, p. 1353;
(b) S. Akutagawa, in: E.N. Jacobsen, A. Yamamoto, A. Pfaltz (Eds.), Comprehensive Asymmetric Catalysis, Springer, Berlin, 1999, p. 1461;
(c) J.M Brown, in: E.N. Jacobsen, A. Yamamoto, A. Pfaltz (Eds.), Comprehensive Asymmetric Catalysis, Springer, Berlin, 1999, p. 121;
(d) R. Schmid, M. Scalone, in: E.N. Jacobsen, A. Yamamoto, A. Pfaltz (Eds.), Comprehensive Asymmetric Catalysis, Springer, Berlin, 1999, p. 1439;
(e) T. Ohkuma, R. Noyori, in: E.N. Jacobsen, A. Yamamoto, A. Pfaltz (Eds.), Comprehensive Asymmetric Catalysis, Springer, Berlin, 1999, p. 199;
(f) S. Itsuno, in: E.N. Jacobsen, A. Yamamoto, A. Pfaltz (Eds.), Comprehensive Asymmetric Catalysis, Springer, Berlin, 1999, p. 289;
(g) H.U. Blaser, F. Spindler, in: E.N. Jacobsen, A. Yamamoto, A. Pfaltz (Eds.), Comprehensive Asymmetric Catalysis, Springer, Berlin, 1999, p. 247;
(h) T. Katsuki, in: E.N. Jacobsen, A. Yamamoto, A. Pfaltz (Eds.), Comprehensive Asymmetric Catalysis, Springer, Berlin, 1999, p. 621;
(i) E.N. Jacobsen, M.H. Wu, in: E.N. Jacobsen, A. Yamamoto, A. Pfaltz (Eds.), Comprehensive Asymmetric Catalysis, Springer, Berlin, 1999, p. 649;
(j) I.E. Marko, J.S. Svendsen, in: E.N. Jacobsen, A. Yamamoto, A. Pfaltz (Eds.), Comprehensive Asymmetric Catalysis, Springer, Berlin, 1999, p. 713;
(k) T. Katsuki, in: E.N. Jacobsen, A. Yamamoto, A. Pfaltz (Eds.), Comprehensive Asymmetric Catalysis, Springer, Berlin, 1999, p. 791;
(l) E.N. Jacobsen, in: E.N. Jacobsen, A. Yamamoto, A. Pfaltz (Eds.), Comprehensive Asymmetric Catalysis, Springer, Berlin, 1999, p. 607;
(m) T. Hayashi, in: E.N. Jacobsen, A. Yamamoto, A. Pfaltz (Eds.), Comprehensive Asymmetric Catalysis, Springer, Berlin, 1999, p. 319;
(n) T. Hayashi, in: E.N. Jacobsen, A. Yamamoto, A. Pfaltz (Eds.), Comprehensive Asymmetric Catalysis, Springer, Berlin, 1999, p. 351;
(o) T.V. RajanBabu, A.L. Casalnuovo, in: E.N. Jacobsen, A. Yamamoto, A. Pfaltz (Eds.), Comprehensive Asymmetric Catalysis, Springer, Berlin, 1999, p. 367;
(p) K. Tomioka, Y. Nagaoka, in: E.N. Jacobsen, A. Yamamoto, A. Pfaltz (Eds.), Comprehensive Asymmetric Catalysis, Springer, Berlin, 1999, p. 1105;
(q) M. Yamaguchi, in: E.N. Jacobsen, A. Yamamoto, A. Pfaltz (Eds.), Comprehensive Asymmetric Catalysis, Springer, Berlin, 1999, p. 1121;
(r) D.A. Evans, J.S. Johnson, in: E.N. Jacobsen, A. Yamamoto, A. Pfaltz (Eds.), Comprehensive Asymmetric Catalysis, Springer, Berlin, 1999, p. 1177;
(s) A. Pfaltz, in: E.N. Jacobsen, A. Yamamoto, A. Pfaltz (Eds.), Comprehensive Asymmetric Catalysis, Springer, Berlin, 1999, p. 513;
(t) K.M. Lydon, M.A. McKervey, in: E.N. Jacobsen, A. Yamamoto, A. Pfaltz (Eds.), Comprehensive Asymmetric Catalysis, Springer, Berlin, 1999, p. 539;
(u) S. Akutagawa, in: E.N. Jacobsen, A. Yamamoto, A. Pfaltz (Eds.), Comprehensive Asymmetric Catalysis, Springer, Berlin, 1999, p. 813;
(v) T. Aratani, in: E.N. Jacobsen, A. Yamamoto, A. Pfaltz (Eds.), Comprehensive Asymmetric Catalysis, Springer, Berlin, 1999, p. 1451;
(w) E.M. Carreira, in: E.N. Jacobsen, A. Yamamoto, A. Pfaltz (Eds.), Comprehensive Asymmetric Catalysis, Springer, Berlin, 1999, p. 997;
(x) K. Mikami, M. Terada, in: E.N. Jacobsen, A. Yamamoto, A. Pfaltz (Eds.), Comprehensive Asymmetric Catalysis, Springer, Berlin, 1999, p. 1143;
(y) T. Ooi, K. Maruoka, in: E.N. Jacobsen, A. Yamamoto, A. Pfaltz (Eds.), Comprehensive Asymmetric Catalysis, Springer, Berlin, 1999, p. 1237;
(z) K. Soai, T. Shibata, in: E.N. Jacobsen, A. Yamamoto, A. Pfaltz (Eds.), Comprehensive Asymmetric Catalysis, Springer, Berlin, 1999, p. 911;
(za) M. Shibasaki, H. Gröger, in: E.N. Jacobsen, A. Yamamoto, A. Pfaltz (Eds.), Comprehensive Asymmetric Catalysis, Springer, Berlin, 1999, p. 1075;
(zb) S.E. Denmark, O.J.-C. Nicaise, in: E.N. Jacobsen, A. Yamamoto, A. Pfaltz (Eds.), Comprehensive Asymmetric Catalysis, Springer, Berlin, 1999, p. 923;
(zc) E. Jacobsen, M.H. Wu, in: E.N. Jacobsen, A. Yamamoto, A. Pfaltz (Eds.), Comprehensive Asymmetric Catalysis, Springer, Berlin, 1999, p. 1309, and references cited in the reviews.

[12] K. Maruoka, T. Ooi, Chem. Rev. 103 (2003) 3013.

[13] P. McMorn, G.J. Hutchings, Chem. Soc. Rev. 33 (2004) 108.

[14] J.M. Keith, J.F. Larrow, E.N. Jacobsen, Adv. Synth. Catal. 343 (2001) 5;
D.E.J.E. Robinson, S.D. Bull, Tetrahedron: Asymmetry 14 (2003) 1407.

[15] For a recent compilation of known industrial processes see H.U. Blaser, F. Spindler, M. Studer, Appl. Catal A: General 221 (2001) 119.

[16] H.U. Blaser, B. Pugin, F. Spindler in, B. Cornils, W.A. Herrmann (Eds.), Applied Homogeneous Catalysis by Organometallic Complexes, second ed., Wiley-VCH, Weinheim, 2002, p. 1131.

[17] R.A. Sheldon, Chirotechnology, Marcel Decker, Inc., New York, 1993.

[18] R. Noyori, Chemtech 22 (1992) 366.

[19] E. Polastro, in: G. Jannes, V. Dubois (Eds.), Chiral Reaction in Heterogeneous Catalysis, Plenum Press, New York, 1995, p. 5.

[20] J.D. Morrison (Ed.), Asymmetric Synthesis, vol. 5, Academic Press, New York, 1985.

[21] (a) T. Ohkuma, M. Kitamura, R. Noyori, in: I. Ojima (Ed.), Catalytic Asymmetric Synthesis, second ed., Wiley-VCH, Weinheim, 2000, p. 1;
(b) K. Mikami, T. Nakai, in: I. Ojima (Ed.), Catalytic Asymmetric Synthesis, second ed., Wiley-VCH, Weinheim, 2000, p. 543;
(c) R.A Johnson, K.B. Sharpless, in: I. Ojima (Ed.), Catalytic Asymmetric Synthesis, second ed., Wiley-VCH, Weinheim, 2000, p. 231;
(d) T. Katsuki, in: I. Ojima (Ed.), Catalytic Asymmetric Synthesis, second ed., Wiley-VCH, Weinheim, 2000, p. 287;

(e) R.A. Johnson, K.B. Shrpless, in: I. Ojima (Ed.), Catalytic Asymmetric Synthesis, second ed., Wiley-VCH, Weinheim, 2000, p. 357;
(f) C. Bolm, J.P. Hildebrand, K. Muniz, in: I. Ojima (Ed.), Catalytic Asymmetric Synthesis, second ed., Wiley-VCH, Weinheim, 2000, p. 399;
(g) H.B. Kagan, in: I. Ojima (Ed.), Catalytic Asymmetric Synthesis, second ed., Wiley-VCH, Weinheim, 2000, p. 327;
(h) K. Nozaki, I. Ojima, in: I. Ojima (Ed.), Catalytic Asymmetric Synthesis, second ed., Wiley-VCH, Weinheim, 2000, p. 429;
(i) K. Maruoka, in: I. Ojima (Ed.), Catalytic Asymmetric Synthesis, second ed., Wiley-VCH, Weinheim, 2000, p. 467;
(j) M.P. Doyle, in: I. Ojima (Ed.), Catalytic Asymmetric Synthesis, second ed., Wiley-VCH, Weinheim, 2000, p. 191;
(k) M. Sawamura, Y. Ito, in: I. Ojima (Ed.), Catalytic Asymmetric Synthesis, second ed., Wiley-VCH, Weinheim, 2000, p. 493;
(l) E.M. Carreira, in: I. Ojima (Ed.), Catalytic Asymmetric Synthesis, second ed., Wiley-VCH, Weinheim, 2000, p. 513;
(m) M. Ogasawara, T. Hayashi, in: I. Ojima (Ed.), Catalytic Asymmetric Synthesis, second ed., Wiley-VCH, Weinheim, 2000, p. 651;
(n) Y. Donde, L.E. Overmann, in: I. Ojima (Ed.), Catalytic Asymmetric Synthesis, second ed., Wiley-VCH, Weinheim, 2000, p. 675;
(o) B.M. Trost, C. Lee, in: I. Ojima (Ed.), Catalytic Asymmetric Synthesis, second ed., Wiley-VCH, Weinheim, 2000, p. 593;
(p) H. Nishiyama, K. Itoh, in: I. Ojima (Ed.), Catalytic Asymmetric Synthesis, second ed., Wiley-VCH, Weinheim, 2000, p. 111;
(q) M. Kanai, M. Shibasaki, in: I. Ojima (Ed.), Catalytic Asymmetric Synthesis, second ed., Wiley-VCH, Weinheim, 2000, p. 569, and references cited in these reviews.

[22] T.P. Yoon, E.N. Jacobsen, Science 299 (2003) 1691.

[23] Josiphos ligands illustrate this principle very well H.U. Blaser, W. Brieden, B. Pugin, F. Spindler, M. Studer, A. Togni, Top. Catal. 19 (2002) 3.

[24] H.U. Blaser, Ch. Malan, B. Pugin, F. Spindler, H. Steiner, M. Studer, Adv. Synth. Catal. 345 (2003) 103.

[25] A.S. Bommarius, M. Schwarm, K. Drauz, Chimia 55 (2001) 50.

[26] M.J. Burk, Dow Chirotech, Personal communication.

[27] H.U. Blaser, F. Spindler, Top. Catal. 4 (1997) 275.

[28] W. Brieden, Proceedings of the ChiraSource'99 Symposium, The Catalyst Group, Spring House, USA, 1999;
W. Brieden, A.G. Lonza, Personal communication.

[29] (a) M. Scalone, R. Schmid, E.A. Broger, W. Burkart, M. Cereghetti, Y. Crameri, J. Foricher, M. Henning, F. Kienzle, F. Montavon, G. Schoettel, D. Tesauro, S. Wang, R. Zell, U. Zutter, in: Proceedings of the ChiraTech'97 Symposium 1997, The Catalyst Group, Spring House, USA.;
(b) H. Jendralla, in: Proceedings of the ChiraTech'97 Symposium 1997, The Catalyst Group, Spring House, USA.

[30] (a) G. Beck, Synlett (2002) 837;
(b) G. Beck, Proceedings of the ChiraTech'96 Symposium, The Catalyst Group, Spring House, USA, 1996.

[31] M.J. Burk, F. Bienewald, M. Harris, A. Zanotti-Gerosa, Angew. Chem. Int. Ed. 37 (1998) 1931.

[32] S. Akutagawa, Appl. Catal. 128 (1995) 171;
H. Kumobayashi, Recl. Trav. Chim. Pays-Bas 115 (1996) 201.

[33] E.A. Broger, Roche, Book of Abstracts of EuropaCat. I 1993 and Personal communication.

[34] T. Benincori, S. Rizzo, F. Sannicolo, O. Piccolo, in: Proceedings of the ChiraSource2000 Symposium 2000, The Catalyst Group, Spring House, USA.

[35] R. Imwinkelried, Chimia 51 (1997) 300.

[36] V. Rautenstrauch, Proceedings of the International Symposium on Chirality, Spring Innovation, Stockport, UK, 1999, p. 204.

[37] A. Pfaltz, J. Blankenstein, R. Hilgraf, E. Hörmann, S. McIntyre, F. Menges, M. Schönleber, S.P. Smidt, B. Wüstenberg, N. Zimmermann, Adv. Synth. Catal. 345 (2003) 33.

[38] W. Leitner, J.M. Brown, H. Brunner, J. Am. Chem. Soc. 115 (1993) 152;
M. Saburi, M. Ogasawara, T. Takahashi, Y. Uchida, Tetrahedron Lett. 33 (1992) 5783, and references therein.

[39] H.U. Blaser, M. Studer, Chirality 11 (1999) 459.

[40] (a) M. Studer, S. Burkhardt, A.F. Indolese, H.U. Blaser, Chem. Commun. (2000) 1327;
(b) P. Herold, A.F. Indolese, M. Studer, H.P. Jalett, H.U. Blaser, Tetrahedron 56 (2000) 6497.

[41] R. Schmid, E.A. Broger, Proceedings of the ChiralEurope'94 Symposium, Spring Innovation, Stockport, UK, 1994, p. 79.

[42] (a) H.U. Blaser, R. Gamboni, G. Rihs, G. Sedelmeier, E. Schaub, E. Schmidt, B. Schmitz, F. Spindler, Hj. Wetter, in: K.G. Gadamasetti (Ed.), Process Chemistry in the Pharmaceutical Industry, Marcel Dekker Inc., New York, 1999, p. 189;
(b) C.H. Senanayake, E.N. Jacobsen, Process Chemistry in the Pharmaceutical Industry, Marcel Dekker Inc., New York, 1999, p. 347.

[43] R. Schmid, E.A. Broger, Proceedings of Chiral Europe '94 Symposium, Spring Innovations, Stockport, UK, 1994, p. 79.

[44] R. Hett, Q.K. Fang, Y. Gao, S.A. Wald, C.H. Senanayake, Org. Proc. Res. Dev. 2 (1998) 96;
A.K. Ghosh, S. Fidanze, C.H. Senanayake, Synthesis (1998) 937.

[45] J.C. Caille, PPG-Sipsy, Personal communication.

[46] W. Brieden, WO 9616971, 1994 (assigned to Lonza AG) and W. Brieden, Lonza, Personal communication.

[47] (a) F. Spindler, H.U. Blaser, in: C. Bolm, M. Beller (Eds.), Transition Metals for Organic Synthesis, vol. 2, second ed., Wiley-VCH, Weinheim, 2004, p. 113;
(b) K. Muñiz, in: C. Bolm, M. Beller (Eds.), Transition Metals for Organic Synthesis, vol. 2, second ed., Wiley-VCH, Weinheim, 2004, p. 298;
(c) H.C. Kolb, K.B. Sharpless, in: C. Bolm, M. Beller (Eds.), Transition Metals for Organic Synthesis, vol. 2, second ed., Wiley-VCH, Weinheim, 2004, p. 309.

[48] H.U. Blaser, H.P. Buser, R. Häusel, H.P. Jalett, F. Spindler, J. Organomet. Chem. 621 (2001) 34;
H.U. Blaser, B. Pugin, F. Spindler, A. Togni, C.R. Chim. 5 (2002) 1.

[49] C.J. Cobley, J.P. Henschke, Adv. Synth. Catal. 345 (2003) 195.

[50] Y. Hsiao, N.L. Rivera, T. Rosner, S.N. Krska, E. Njolito, F. Wang, Y. Sun, J.D. Armstrong, E.J.J. Grabowski, R.D. Tillyer, F. Spindler, C. Malan, J. Am. Chem. Soc. 126 (2004) 9918.

[51] H.U. Blaser, H.P. Buser, K. Coers, R. Hanreich, H.P. Jalett, E. Jelsch, B. Pugin, H.D. Schneider, F. Spindler, A. Wegmann, Chimia 53 (1999) 275.

[52] H.U. Blaser, Adv. Synth. Catal. 344 (2002) 17.

[53] H.U. Blaser, H.P. Buser, H.P. Jalett, B. Pugin, F. Spindler, Synlett (1999) 867.

[54] D. Meunier, A. Piechaczyk, A. de Mallmann, J.-M. Basset, Angew. Chem. Int. Ed. 38 (1999) 3540.

[55] B.K. Sharpless, Janssen Chem. Acta 6 (1988) 3.

[56] A.A. Smith, Proceedings of the ChiraTech'96 Symposium, The Catalyst Group, Spring House, USA, 1996.

[57] C.E. Song, E.J. Roh, Chem. Commun. (2000) 837.

[58] M. Porter, J. Skidmore, Chem. Commun. (2000) 1215, and references cited ;
C. Lauret, S.M. Roberts, Aldrichim. Acta 35 (2002) 47.

[59] T. Geller, A. Gerlach, C.M. Krüger, H.-C. Militzer, Tetrahedron Lett. 45 (2004) 5065.

[60] C. Döbler, G.M. Mehltretter, U. Sundermeier, M. Beller, J. Am. Chem. Soc. 122 (2000) 10289.

[61] J. Eames, M. Watkinson, Angew. Chem. Int. Ed. 40 (2001) 3567.

[62] M.D. Mihovilovic, F. Rudroff, B. Grötzl, Curr. Org. Chem. 8 (2004) 1057;
T. Uchida, T. Katsuki, K. Ito, A. Ishii, T. Kuroda, Helv. Chim. Acta 85 (2002) 3078.

[63] H. Cotton, T. Elebring, M. Larsson, L. Li, H. Sörensen, S. von Unge, Tetrahedron: Asymmetry 11 (2000) 8319.

[64] H. Ibrahim, A. Togni, Chem. Commun. (2004) 1147.
[65] H.L. Pedersen, M. Johannsson, J. Org. Chem. 67 (2002) 7982.
[66] J. Christoffers, A. Baro, Angew. Chem. Int. Ed. 42 (2003) 1688; N. Krause, A. Hoffmann-Röder, Synthesis (2001) 171.
[67] Y. Hayashi, in: S. Kobayashi, K.A. Jorgensen (Eds.), Cycloaddition Reactions in Organic Synthesis, Wiley-VCH, Weinheim, 2002, p. 5.
[68] H. Alper, N. Hamel, J. Am. Chem. Soc. 112 (1990) 2803.
[69] S. Shimizu, K. Ohri, T. Arai, H. Sasai, M. Shibasaki, J. Org. Chem. 63 (1998) 7547;
Y. Xu, K. Ohori, T. Ohshima, M. Shibasaki, Tetrahedron 58 (2002) 2585.
[70] K.A. Jorgensen, Eur. J. Org. Chem. (2004) 2093.
[71] M. North, Tetrahedron: Asymmetry 14 (2003) 147.
[72] A. Togni, S.D. Pastor, G. Rihs, Helv. Chim. Acta 72 (1989) 1471.
[73] H. Sasai, W-S. Kim, T. Suzuki, M. Shibasaki, Tetrahedron Lett. 35 (1994) 6123;
Y. Xu, K. Ohori, T. Ohshima, M. Shibasaki, Tetrahedron 58 (2002) 2585.
[74] H. Gröger, Chem. Rev. 103 (2003) 2795.
[75] Y.N. Belokon, A.V. Gutnov, M.A. Moskalenko, L.V. Yashkina, D.E. Lesovoy, N.S. Ikonnikov, V.S. Larichev, M. North, Chem. Commun. 244 (2002), and references cited http://www.avecia.com/pharms/coretech/technologies/cachy.htm.
[76] H. Gröger, Y. Saida, H. Sasai, K. Yamaguchi, J. Martens, M. Shibasaki, J. Am. Chem. Soc. 120 (1998) 3089;
Prof. M. Shibasaki, University of Tokyo, Personal communication.
[77] B.M. Trost, J. Org. Chem. 69 (2004) 5813.
[78] D. Chaplin, I.C. Lennon, M. Jackson, J.A. Ramsden, S. Winter, Proceedings of the ChiraTech'98 Symposium, The Catalyst Group, Spring House, USA, 1998, also see http://www.dow.com/pharma/cap/chemocat.htm.
[79] For a review see A.H. Hoveyda, R.R. Schrock, Organ. Synth. Highl. V (2003) 210;
For a recent application G.S. Weatherhead, G.A. Cortez, R.R. Schrock, A.H. Hoveyda, Proc. Nat. Acad. Sci. 101 (2004) 5805.
[80] J.M. Keith, J.F. Larrow, E.N. Jacobsen, Adv. Synth. Catal. 343 (2001) 5.
[81] www.rhodia-pharmasolutions.com/page_71.html.
[82] M. Lautens, K. Fagnou, S. Hiebert, Acc. Chem. Res. 36 (2003) 48.
[83] S. Jansat, M. Gomez, K. Philippot, G. Muller, E. Guiu, C. Claver, S. Castillon, B. Chaudret, J. Am. Chem. Chem. 126 (2004) 1592.