37
Industrial Applications

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37.1
Introduction and Scope of the Chapter

While hydrogenation is without doubt the most important catalytic methodology for the manufacture of fine chemicals, until now most reactions have been carried out with heterogeneous catalysts. Heterogeneous hydrogenation catalysts have an exceptionally broad applicability for the chemo- and diastereoselective reduction of various functional groups, are convenient to handle, and catalyst separation is usually straightforward [1]. Homogeneous catalysts have found application for a number of special selectivity problems, the most important of which is enantioselective hydrogenation. While this will be the dominant topic of this chapter, a few scattered reports have been made where achiral complexes such as the Wilkinson catalyst, $RhCl(Ph_3P)_3$, or Ru–phosphine complexes have been applied on an industrial scale. In this regard, we will mention three examples [2]: (i) the chemoselective hydrogenation of α,β-unsaturated aldehydes; (ii) the diastereoselective hydrogenation of a tetracycline antibiotic; and (iii) the chemoselective hydrogenation of avermectin derivatives.

As already mentioned, the most important industrial application of homogeneous hydrogenation catalysts is for the enantioselective synthesis of chiral compounds. Today, not only pharmaceuticals and vitamins [3], agrochemicals [4], flavors and fragrances [5] but also functional materials [6, 7] are increasingly produced as enantiomerically pure compounds. The reason for this development is the often superior performance of the pure enantiomers and/or that regulations demand the evaluation of both enantiomers of a biologically active compound before its approval. This trend has made the economical enantioselective synthesis of chiral performance chemicals a very important topic.

Industrial interest in the application of enantioselective catalysts began in earnest during the mid-1960s when the first reports of successful enantioselective transformations with homogeneous metal complexes were published. Within a surprisingly short period, production processes for two small-scale products, L-dopa (hydrogenation) and cilostatin (cyclopropanation) were developed and implemented by

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Monsanto and Sumitomo, respectively. For quite some time it was not really clear whether these applications were mere curiosities or whether this would be the beginning of a new area where chiral compounds would be produced predominantly by asymmetric catalysis. One reason for this state of affairs was that both companies were reluctant to disclose information on the new technology.

Very soon, other chemical and pharmaceutical companies entered the field with appreciable manpower, examples being Roche, Ciba-Geigy, Takasago, Enichem and VEB-Isis. Some companies worked in collaboration with academic laboratories, while others relied on strong in-house research efforts. During the past few years, a new type of player has appeared, however – smaller companies which are more or less dedicated exclusively to the development and application of enantioselective processes for the manufacture of chiral intermediates and products. Many of these enterprises are either start-ups, for example Chiral Quest or Chirotech (now part of the Dow Chemical Company), concentrating on a few promising technologies. Alternatively, they are spin-offs from large corporations, examples being our own company, Solvias (a spin-off from Ciba-Geigy/Novartis), NSC Technologies (a spin-off from Monsanto, now part of Great Lakes Chemicals) or Degussa Homogeneous Catalysts, and these usually have a broader technology base.

A very good overview on the scientific state of the art of enantioselective catalysis can be found in two recent monographs, *Comprehensive Asymmetric Catalysis* (edited by Jacobsen, Yamamoto and Pfaltz) [8], and *Catalytic Asymmetric Synthesis* (edited by Ojima) [9]. Progress in enantioselective hydrogenation has been summarized in several recent reviews [10–13]. For the compilation of industrial applications, we have relied on a recent study [14], a monograph on large-scale asymmetric catalysis [15], and several excellent up-to-date overviews [16–21] describing the applications of enantioselective hydrogenation technology, mainly in the pharmaceutical industry. Since it is notoriously difficult to obtain precise information on industrial processes, many references relate to rather informal sources such as *Chemical and Engineering News* reports, proceedings of commercial meetings, and personal communications. This chapter describes the state of the art for the application of homogeneous hydrogenation for the industrial production of enantiomerically enriched chiral compounds. Within the chapter, the subjects covered include the enantioselective hydrogenation processes that have been and/or are presently used for commercial manufacture, pilot- and bench-scale processes not (yet) used in actual production, as well as some feasibility studies and optimized hydrogenations of model substrates.

37.2
Requirements for Technical-Scale Applications

Pharmaceuticals or agrochemicals usually have complex, multifunctional structures and are produced via multistep syntheses. Compared to basic chemicals, they are relatively small-scale but high-value products with short product lives,

traditionally produced in multipurpose batch equipment. The time for development of the production process is often very short since the "time to market" affects the profitability of the product.

Despite dramatic progress in the scientific domain, relatively few enantioselective catalytic reactions are used on an industrial scale today [14, 15]. A major reason for this is that the application of enantioselective catalysts on a large scale presents some very special challenges and problems [22, 23]. Some of these problems are due to the special situation for manufacturing chiral products, while others are due to the nature of the (enantioselective) catalytic process. Whether a synthetic route containing an enantioselective catalytic step can be considered for a particular product is usually determined by the answer to two questions [23, 24]:

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

Several critical factors determine the technical feasibility of an enantioselective process step, but it must be stressed that even if all these criteria are met there is no guarantee that it is actually used!

37.2.1 Catalyst Performance

The *enantioselectivity*, expressed as enantiomeric excess (ee, %) of a catalyst should be >99% for pharmaceuticals if no purification is possible. This case is quite rare, and ee-values >90% are often acceptable. *Chemoselectivity* (or functional group tolerance) will be very important when multifunctional substrates are involved. The *catalyst productivity*, given as turnover number (TON: mol product per mol catalyst) or as substrate:catalyst ratio (SCR), determines catalyst costs. For hydrogenation reactions, TONs should be >1000 for high-value products and >50 000 for large-scale or less-expensive products (catalyst re-use increases the productivity).

The *catalyst activity*, given as average turnover frequency (TOF: mol product per mol catalyst per reaction time; units h^{-1}), affects the production capacity. For hydrogenations, TOFs should be $>200\,h^{-1}$ for small-scale products, and $>10\,000\,h^{-1}$ for large-scale products. Due to lower catalyst costs and often higher added values, lower TON and TOF values are acceptable for enantioselective oxidation and C–C bond-forming reactions.

37.2.2 Availability and Cost of the Catalyst

Chiral ligands and many metal precursors are expensive and/or not easily available. Typical costs for chiral diphosphines are 100 to 500 $ per gram for laboratory quantities, and 2000 to >100 000 $ per kg on a larger scale. Chiral ligands

such as salen or amino alcohols used for early transition metals are usually much cheaper. At this time, only relatively few chiral ligands are available commercially on a technical scale, and many of these are patent protected and therefore a license is need for their commercial application.

37.2.3 Development Time

The development time can be a hurdle, especially when the optimal catalyst has yet to 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, the time restraints can be severe (Fig. 37.1). 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 – for example, for chiral switches, generic pharmaceuticals or for 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. The increasing time pressure has led to the development and implementation of high-throughput systems (HTS) for catalyst testing with the help of robots and multi-parallel high-pressure equipment allowing the screening of up to 100 samples per day [25, 26].

In addition, many other aspects must be considered when developing a catalytic reaction for industrial use; these include catalyst separation, stability and poisoning, handling problems, space-time yield, process sensitivity and robustness, toxicity of metals and reagent, and safety aspects, as well as the need for high-pressure equipment.

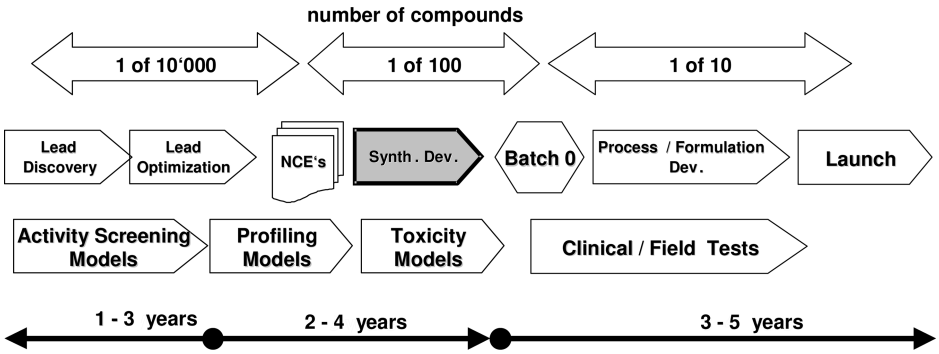


Fig. 37.1 Development process for a new chemical entity in the pharmaceutical industry.

37.3
Process Development and Equipment

The choice of a development strategy that promises the best answer in the shortest time is the first decision to be made at the start of every process development [27]. This strategy will depend on a number of considerations, including the goal of the development, the know-how of the investigators, the time frame, the available manpower and equipment, and so on. In process development, there is usually a hierarchy of goals (or criteria) to be met. It is simply not possible to reach all the requirements for a technically useful process in one step. The catalyst selectivity (combined of course with an acceptable activity) is the first criterion – just as in academic research. However, when a reasonable selectivity has been obtained, other criteria will become important: catalyst activity, productivity and stability, catalyst separation (and maybe recycling). Then, questions such as the effect of substrate quality and last but not least the cost and availability of the chiral catalyst and other materials must be addressed. The final process is a compromise, since quite often not all of these requirements can be fulfilled maximally. It is useful to divide the development of a manufacturing process into different phases, although it is rarely possible to proceed in a linear fashion and very often one has to go back to an earlier phase in order to answer additional question before it is possible to go on.

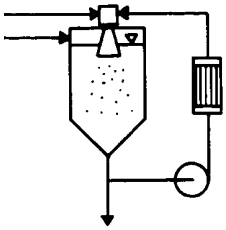
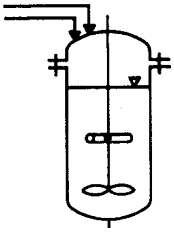
Most chiral chemicals are relatively small-scale products (1 to 1000 tonnes per year for pharmaceuticals, 500 to 10 000 tonnes per year for agrochemicals) that are usually produced in multipurpose batch equipment. This is probably the case for most catalytic reactions described in this chapter; however, as a rule very little information on process technology is provided by the manufacturers. Here, we will discuss only briefly the reactor choices for hydrogenation reaction typically carried out in the liquid phase. For a successful implementation the following demands must be met:

- Very good dispersion of the hydrogen gas (and a suspended catalyst for heterogeneous systems) in the reaction solution (efficient gas-liquid mixing and stirring).
- Very effective heat removal (reaction control), as well as safe handling of the sometimes pyrophoric and/or air-sensitive catalysts.

In practice, two reactor types have proven to be capable of meeting these requirements as well as the need for high reliability in operation and ease of control: the stirred autoclave and the loop reactor (see Table 37.1).

- The loop reactor provides very efficient hydrogen dispersion, with the heat exchanger surface being almost unlimited. It is especially useful when the space-time yield is very high (fast reaction, high substrate concentration) or when a low reaction temperature is required.
- The stirred autoclave is probably more versatile; it has an advantage when substrate slurries or viscous media are to be used, or when the starting material is added continuously. In addition, it is usually easier to clean and less space and lower investment costs are required.

Table 37.1 Comparison of the loop reactor and the stirred autoclave.

Reactor type	Loop reactor	Stirred autoclave
		
Gas-dispersion	Mixing nozzle (Venturi principle)	Mechanical agitator (hollow–shaft turbine)
Efficiency	High	Medium to high
Heat removal	>1300 W m^{-2} K, very high exchange area	~900 W m^{-2} K, limited exchange area
Problem areas	Circulating pump (viscous slurries) continuous feed addition	Heat exchange capacity
Recommended	High performance, dedicated plant	Multi-purpose plant

37.4 Industrial Processes: General Comments

In a recent study [14] we have collected and tabulated information on chemocatalytic asymmetric processes operated in regular production, as well as on those in the pilot- and bench-scale state; a statistical summary of this information is presented in Table 37.2. The following definitions were used:

- *Production processes* are operated on a more or less regular basis – that is, all relevant problems concerning catalyst performance and separation, supply of materials, product isolation and purification, noble metal recovery, etc. have been solved.
- *Pilot processes* are technically on a similar level especially with regard to catalyst performance; they have been carried out on multi kilogram to tonne scale, but have not (yet) been applied on a regular basis.
- *Bench-scale processes* have an optimized catalyst performance and have been carried out a few times on a small scale, but are for some reason not yet ready for production purposes.
- *Feasibility studies* very often demonstrate proof of principle without much optimization.

An analysis of the processes listed in Table 37.2 shows that asymmetric hydrogenation of C=C and C=O functions is by far the predominant transition metal-catalyzed transformation applied for industrial processes, followed by epoxidation and dihydroxylation reactions. On the one hand, this is due to the broad scope of catalytic hydrogenation, and on the other hand it could be attributed to

Table 37.2 Statistics for the industrial application of chemocatalytic enantioselective processes [14].

Transformation	Production		Pilot		Bench scale
	> 5 t y^{-1}	< 5 t y^{-1}	> 50 kg	< 50 kg	
Hydrogenation of enamides	1	1	2	6	4
Hydrogenation of C=C-COOR and C=C–CH–OH	2	0	3	4	6
Hydrogenation of other C=C systems	1	0	1	1	2
Hydrogenation of α and β functionalized ketones	2	3	3	2	4
Hydrogenation/reduction of other keto groups	0	0	2	2	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 sulfide	2	2	1	0	2
Isomerization, epoxide opening, addition reactions	2	4	2	0	1
Total	11	11	15	15	27

the early success of Knowles with the L-dopa process, because for many years, most academic and industrial research was focused on this transformation. The success with epoxidation and dihydroxylation can essentially be attributed to the efforts of Sharpless, Katsuki and Jacobsen. If one analyzes the structures of the starting materials, it is quite clear that many of these compounds are complex and multifunctional – that is, the successful catalytic systems are not only enantioselective but also tolerate many functional groups.

The most common chiral auxiliaries are diphosphines (biphep, binap and analogues, DuPhos, ferrocenyl-based ligands, etc.) and cinchona and tartaric acid-derived compounds. It is clear that the optimal chiral auxiliary is determined not only by the chiral backbone (type or family) but also by the substituents of the coordinating groups. Therefore, modular ligands with substituents that can easily be varied and tuned to the needs of a specific transformation have an inherent advantage (principle of modularity).

The most often cited *success factor* by industrial developers was the choice of the right ligand – that is, the desired transformation was possible because either a new ligand type was found (or claimed to be designed) or because an existing ligand could be optimized by adapting the coordinating groups to the needs of the reaction (electronic and/or steric tuning). However, the choice of the right metal precursor (especially for Ru-catalyzed reactions) and/or anion as well as the addition of promoters were also reported to be decisive for high catalyst activity and productivity. Careful optimization of the reaction conditions (temperature, pressure, solvent, concentrations, etc.) and the ability to crystallize the product directly from the reaction solution with very high ee were also mentioned several times to have been important for a successful commercial process.

The following *critical factors* often made process development difficult. The sensitivity of the catalyst towards impurities (byproducts in the starting material, oxygen, water, etc.) usually could be controlled with a strict purification protocol, but in some cases a change of the overall synthetic route of the substrate was necessary. Sometimes, the stability of the ligand or catalyst and its productivity (given as TON) or its activity (given as TOF) were critical; careful optimization was often successful to overcome this problem. Other critical issues mentioned included the need for high pressures or very low temperatures (expensive equipment), a lack of commercial availability, difficult preparation of the ligand or catalyst, and/or problems with a patented ligand system. Surprisingly, despite the fact that homogeneous catalysts were used in most applications, catalyst separation was mentioned only once to have been a major obstacle. More of an issue were residual metals in the product, especially for pharmaceutical applications and when the homogeneous catalyst was used late in the synthesis.

Besides the already cited study, we have relied on the overviews mentioned earlier [16–21] describing the application of enantioselective hydrogenation technology mainly in the pharma industry, and also on a literature search.

37.5
Chemo- and Diastereoselective Hydrogenations

Unsaturated alcohols are important intermediates for aroma chemicals and vitamins, with one interesting access being hydrogenation of the corresponding unsaturated aldehyde, which is very difficult to achieve with heterogeneous catalysts. Rhone-Poulenc has developed a water-soluble Ru catalyst with sulfonated triphenylphosphine ligands (TPPTS) for the hydrogenation of cinnamaldehyde (Fig. 37.2; $R_1 = H$, $R_2 = Ph$) to cinnamyl alcohol and of 3-methyl-2-buten-1-al (Fig. 37.2; R_1, $R_2 = Me$) to 3-methyl-2-buten-1-ol (prenol) with very high chemoselectivities at high conversion [2a]. The reaction was preformed in a two-phase aqueous organic system allowing easy recycle of the catalyst by phase separation, but it appears that the economics of the catalytic system was still insufficient for commercial application.

While diastereoselective reactions are well known with heterogeneous catalysts, in many cases a homogeneous catalyst will give a higher selectivity. For hydrogenation of the exocyclic C=C bond in methacycline, Hovione has developed a modified form of Wilkinson's catalyst which produces the desired 6-α epimer in >99% yield. According to De Vries [2a], the reaction is performed on a scale of several tens of tons per year. The catalyst is not recycled, but the Ph_3P is oxidized to $Ph_3P{=}O$ which is recovered as is the rhodium salt.

The final example shown in Figure 37.2 is the highly chemoselective hydrogenation of the C_{22}–C_{23} double bond in avermectin derivatives to give ivermectin, used against river blindness in many African countries. This drug, which originally was developed by Merck as an antiparasitic agent, was shown to be highly effective also for human treatment, and in 1987 Merck decided to donate the

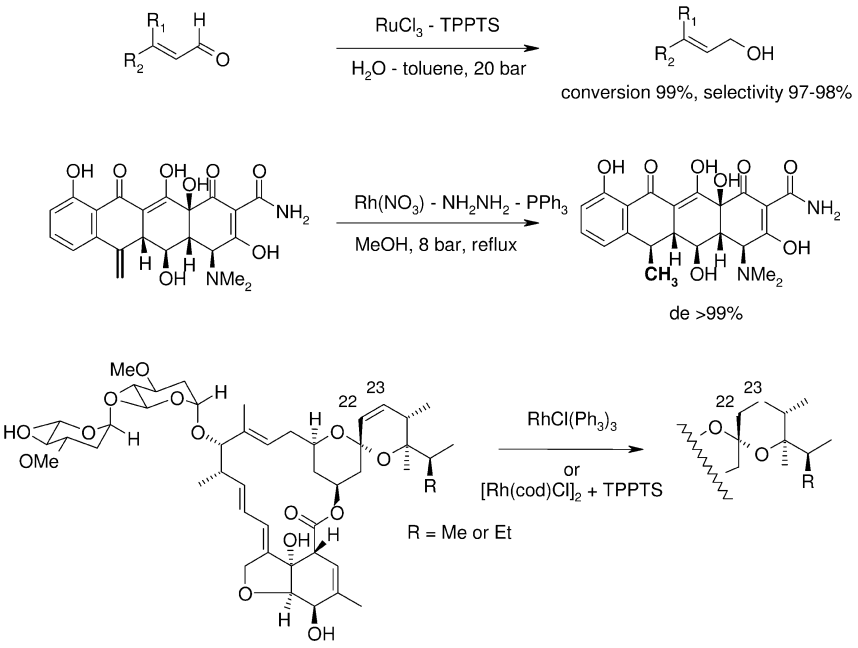


Fig. 37.2 Chemo- and diastereoselective hydrogenations of complex molecules with homogeneous catalysts.

drug to all affected persons [2b]. Avermectin is a fermentation product, and Merck chemists developed a very selective hydrogenation process using the classical Wilkinson catalyst in toluene at 3 bar hydrogen pressure which is probably still used for the manufacture of ivermectin [2c]. Since a major problem is the complete removal of Rh, Antibioticos developed a two-phase process (toluene/water/nBu$_4$NBr) using a catalyst formed *in situ* from [Rh(cod)Cl]$_2$ and TPPTS which gave yields of >98% with all the rhodium in the aqueous phase [2d].

37.6
Enantioselective Hydrogenation of C=C Bonds

37.6.1
Dehydro α-Amino Acid Derivatives

There is little doubt that the hydrogenation of dehydro α-amino acids is the best-studied enantioselective catalytic reaction. This was initiated by the successful development of the L-dopa process by Knowles (see below) and for many years, acetylated aminocinnamic acid derivatives were the model substrates to test most newly developed ligands. As can be seen below, this is the transformation most often used for the stereoselective synthesis of a variety of pharma and

agro targets, even though the difficult and expensive preparation of the dehydro amino acids derivatives precluded the manufacture of large-volume α-amino acids. Because of their importance for the development of industrial enantioselective catalysis, we will discuss several early applications in some detail, but will only summarize the results obtained in other cases.

37.6.1.1 L-Dopa (Monsanto, VEB Isis-Chemie)

According to Knowles [28], Monsanto has been producing L-dopa, a drug to relieve Parkinson's disease, on the scale of ca. 1 t y^{-1} for many years. A few years after Monsanto, the East-German company VEB Isis-Chemie also carried out this process on a similar scale but terminated the production after a few years [29]. The key step in the synthesis is the enantioselective hydrogenation of an enamide intermediate (Fig. 37.3).

Monsanto carried out the reaction in a water/isopropanol mixture at relatively low temperature and pressure. Because the free ligand racemizes slowly, an isolated $[Rh(dipamp)(diene)]^+BF_4^-$ complex was used as the catalyst, showing a very good performance: an ee of 95%, TON 10 000–20 000, TOF 1000 h^{-1}. Today, ee-values of 95% are no longer exceptional for the hydrogenation of enamides, but this was certainly not the case at the time the process was developed. It is therefore not surprising that for many years enamide hydrogenation was *the* standard test reaction for new ligands. One of the key factors for success was of course the dipamp ligand developed by Knowles and his team within an amazingly short time. Figure 37.4 shows the concept of the Monsanto scientists: (i) stereogenic phosphorus atom; and (ii) bidentate structure with C_2-symmetry. The VEB Isis team chose a different

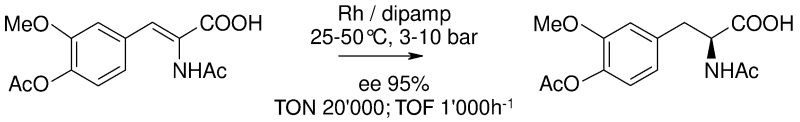


Fig. 37.3 Monsanto's L-dopa process.

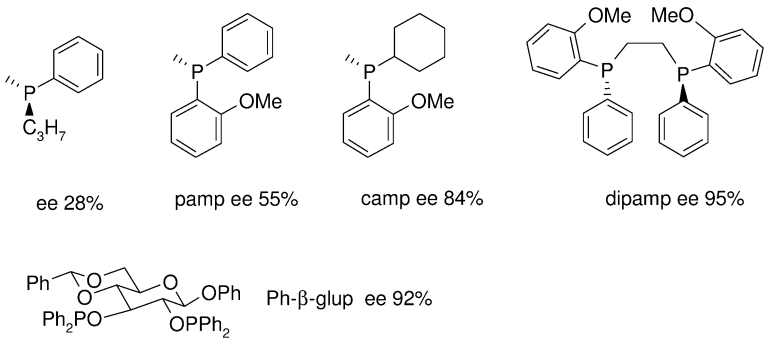


Fig. 37.4 Ligands developed for the manufacture of L-dopa.

approach by starting with a (cheap) chiral pool molecule for the construction of the Ph-*β*-glup ligand, also with two coordinating P atoms. The Rh/Ph-*β*-glup sulfate complex functioned at 40 °C/1 bar; however, with ee-values of 91–92%, TONs of 2000 and TOFs of ∼330 h^{-1} it did not quite reach the performance of Rh–dipamp.

One very important feature of the Monsanto process was the fact that the reaction was started with a slurry of reactants and ended with a slurry of the pure product with close to 100% ee, allowing easy separation of both the catalyst and the undesired racemate in one step. Critical issues for both the Monsanto and the VEB Isis processes were the quality of the starting material (enamide syntheses are often problematic) and especially the concentration of oxygen and peroxides in the reaction solution.

A Rh–dipamp complex was later applied by NSC Technologies for the manufacture of several unnatural amino acids with good catalyst performances (ee 95–98%, TON 5000–20 000) [30] and was also very selective but with low activity (ee 98%, TON 20) in a feasibility study for a synthesis of acromelobic acid by Abbott Laboratories [31].

37.6.1.2 **Aspartame (Enichem/Anic, Degussa)**

Phenylalanine is an intermediate for the aspartame sweetener and, for a short time, it was produced by Enichem/Anic [32] on a scale of ca. 15 t, using a variant of the L-dopa procedure as summarized in Figure 37.5. The Rh–eniphos catalyst was considerably less selective than Rh–dipamp, but easier to prepare and much cheaper. Traces of Rh were removed by treatment with a thiol-containing resin, and crystallization of the ammonium salt gave a product of >99% ee [33]. Due to the low stability of the ligand (P–N bond cleavage) reaction conditions had to be carefully controlled. A few years later, Degussa developed a pilot process with a Rh–deguphos catalyst which operated at 50 °C/15 bar and achieved ee-values up to 99% (TON 10 000, TOF 3000 h^{-1}) [34].

37.6.1.3 **Various Pilot- and Bench-Scale Processes for *α*-Amino Acid Derivatives**

Processes for several *α*-amino acid derivatives with a variety of structural elements were developed and carried out on a scale of up to multi hundred kilograms by

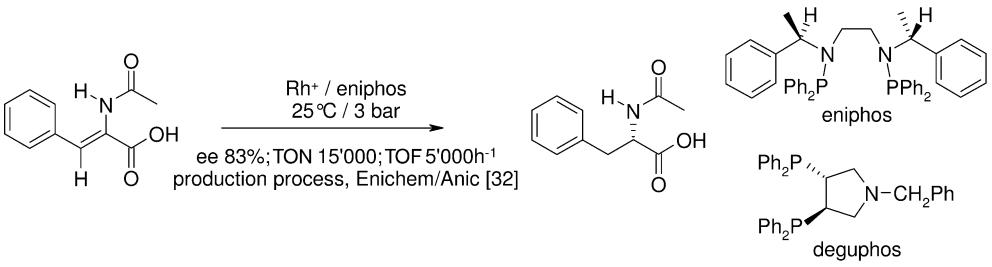


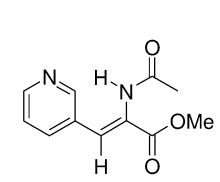
Fig. 37.5 The phenylalanine process.

Dow/Chirotech [35, 36], Topcro Pharma [37] as well as by Solvias [38] using Rh–DuPhos catalysts (Fig. 37.6). Besides these successful examples, a process using Rh–DuPhos was abandoned because of reproducibility problems due to impurities carried over from the preceding step, and because of concerns about the toxicity of 2-nitropropane, even though ee-values of 99% were achieved [39].

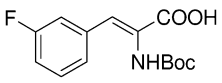
Tunable ferrocene-based diphosphines lead to effective catalysts for the production of α-amino acid derivatives with unusual structural elements. 2-Piperazinecarboxylic acid derivatives are interesting intermediates – for example, for Crixivan, the well-known HIV protease inhibitor produced by Merck. The hydrogenation of an unusually substituted cyclic enamide was used by Lonza [40–42] to produce >200 kg of the piperazine intermediate depicted in Figure 37.7 using an optimized Rh–Josiphos catalyst. Important for good catalyst performance were the choice of the ligand as well as the substituents at the tetrahydropyrazine. Surprisingly, the same catalyst was also able to hydrogenate a corresponding pyrazine amide with ee-values up to 77%, but much lower activity [43].

A Ru–Josiphos catalyst was highly selective for the hydrogenation of an intermediate for an anthrax lethal factor inhibitor with a tetra-substituted C=C bond, as depicted in Figure 37.8 (Merck [44]). Rh–Josiphos (Lonza [42]) and Rh–BoPhoz (Eastman [45]) catalysts were effective for the hydrogenation of an exocyclic and a cyclopropyl-substituted C=C bond.

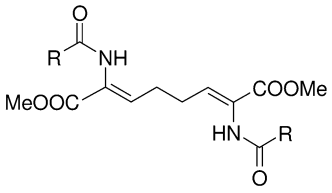
Earlier examples of pilot- and bench-scale processes are summarized in [14]. Several cases with high ee-values and medium activity using Rh–bpm ligands were reported by Hoechst (now Sanofi Aventis) [46]; Ru–binap and Ru–biphep



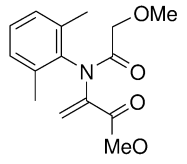
Rh / Et-DuPhos / 1 eq. HBF_4
30 °C, 4 bar
ee 98%,TON 20'000; TOF n.a.
pilot process, Chirotech [35]



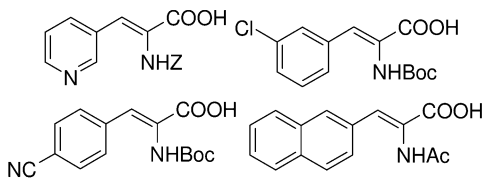
Rh / Me-DuPhos
40 °C, 6 bar
ee 86%,TON 1'400; TOF n.a.
pilot process, Dow/Chirotech [36]



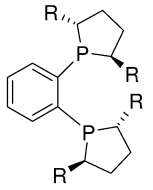
Rh / Et-DuPhos
20 °C, 4 bar
ee >99%,TON 1'000; TOF n.a.
pilot process, Topcro Pharma [37]



Rh / Me-DuPhos
60 °C, 10 bar
ee 96%,TON 50'000; TOF 5'200h^{-1}
pilot process, Solvias [38]



Rh / Me-DuPhos
no details available
pilot processes, Dow Chirotech [36]



R = Me, Et
Me-DuPhos / Et-DuPhos

Fig. 37.6 Substrates and ligands for the synthesis of various α-amino acid derivatives.

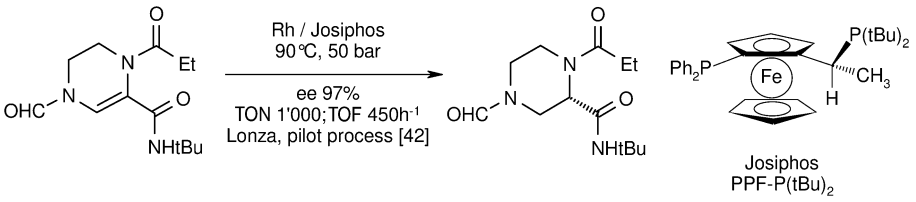


Fig. 37.7 Process for a 2-piperazinecarboxylic acid derivative.

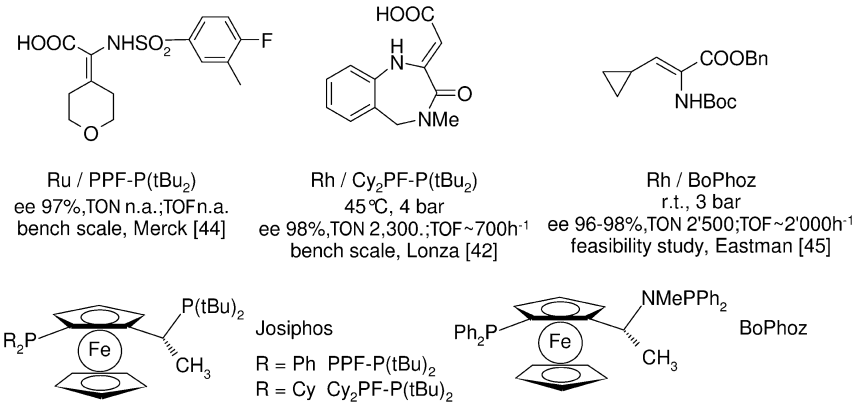


Fig. 37.8 Substrates and ligands for the synthesis of various α-amino acid derivatives.

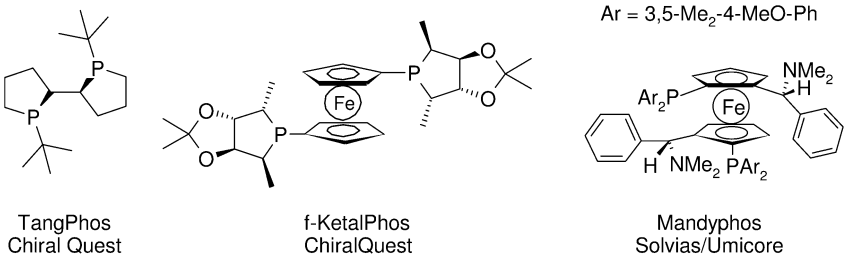


Fig. 37.9 Structures of TangPhos, f-KetalPhos and Mandyphos.

complexes were also effective catalysts for cyclic and exocyclic dehydro amino acid derivatives.

Recent results have shown that a number of other commercially available ligands can be expected to have industrial potential for the hydrogenation of dehydro α-amino acid derivatives. However, it must be pointed out that in most cases model substrates and not industrially relevant targets have been investigated until now. Chiral Quest has shown that Rh–TangPhos as well as Rh–f-KetalPhos (for structures, see Fig. 37.9) were able to hydrogenate a variety of α-dehydro amino acid derivatives with ee-values of 98–>99%, TONs of up to 10 000

and TOFs of $>100\ h^{-1}$ under mild conditions (r.t., 2–3 bar) [47]. A Rh–Mandyphos catalyst of Solvias/Umicore (see Fig. 37.9) achieved ee-values >98% with TONs >20 000 and TOF up to $7700\ h^{-1}$ (25 °C, 1 bar) for the model substrate MAC [48]. Finally, Eastman's Rh–BoPhoz also achieved ee-values of 97–>99% for a variety of α-dehydro amino acid derivatives, in some cases with TONs up to 10 000 and very high activities at r.t./~1 bar [49].

37.6.2
Dehydro β-Amino Acid Derivatives

In contrast to dehydro α-amino acids, the hydrogenation of acetylated β-dehydroamino acid derivatives has only recently been of industrial interest and, accordingly, no applications on a larger scale have yet been reported. Several ligands such as certain phospholanes or phosphoramidites might have industrial potential, but until now these have only been tested on model substrates under standard conditions [50]. Chiral Quest's TangPhos and Binapine (Fig. 37.10) have been shown to hydrogenate several acetylated dehydro β-amino acid derivatives with ee-values of 98–99% and TONs of 10 000 at r.t., 1 bar [3, 47].

With this background, the finding by Merck chemists [51] that unprotected dehydro β-amino acids are good substrates for the Rh-catalyzed hydrogenations was both very unexpected and very exciting. Interestingly, deuteration experiments indicate that it is not the enamine C=C bond which is reduced but the tautomeric imine! Not only simple derivatives but also the complex intermediate for MK-0431 (see Fig. 37.10) can be hydrogenated successfully, and the latter has been pro-

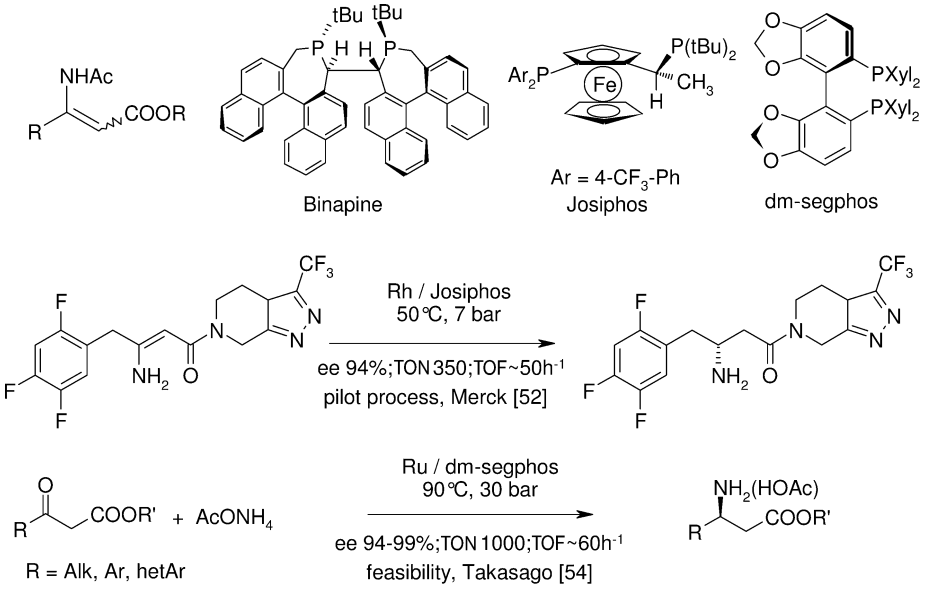


Fig. 37.10 Hydrogenation of β-dehydro amino acid derivatives; substrate and ligand structures.

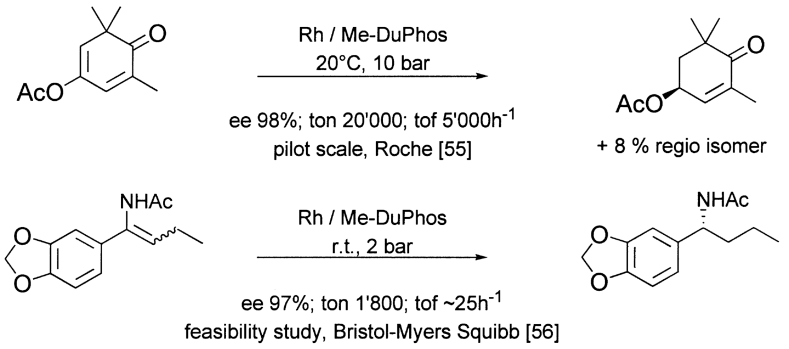


Fig. 37.11 Hydrogenation of enamides and enol acetates.

duced on a >50-kg scale with ee-values up to 98%, albeit with low to medium TONs and TOFs [52]. At almost the same time, Takasago [53, 54] reported that a Ru–segphos catalyst could hydrogenate unprotected dehydro β-amino esters with ee-values of 94–97%. Of special industrial relevance is the fact that the Ru–segphos catalysts also work very well for the reductive amination of a variety of β-keto esters to give the corresponding β-amino ester in one step, with ee-values up to 99% at an SCR of 1000 with TOFs of $\sim 60\ h^{-1}$ (Fig. 37.10 [53c, 54]).

37.6.3
Simple Enamides and Enol Acetates

The hydrogenation of enamides and enol acetates without acid function is often more demanding, and at present is not applied widely. Besides a bench-scale application by Roche with a Ru–biphep catalyst [55], two examples are of interest: a pilot process for a cyclic enol acetate by Roche [55], and a feasibility study by Bristol-Myers Squibb [56], both using Rh–DuPhos catalysts (Fig. 37.11). In the latter case, despite very good ee-values, a chiral pool route was finally chosen. Chiral Quest's Rh–f-KetalPhos (see Fig. 37.9) has been shown to hydrogenate a variety of substituted aryl enamide model substrates at r.t., 1 bar, with very promising catalyst performance (ee 98–99%, TON 10 000) [47].

37.6.4
Itaconic Acid Derivatives

Even though it was realized early on that, in analogy to enamides, itaconic acid derivatives are also preferred substrates due to the presence of a second coordinating group, industrial applications are still rare. Just as dehydro amino acids, substituted itaconic derivatives exist as *E* and *Z* isomers, but several phospholane type ligands are able to accept *E*/*Z* mixtures. Two early examples using a Rh–deguphos and Rh–bpm catalyst, respectively, were reported by Hoechst (now Sanofi Aventis) with good to high ee-values but low TONs (for details see [14, 46]).

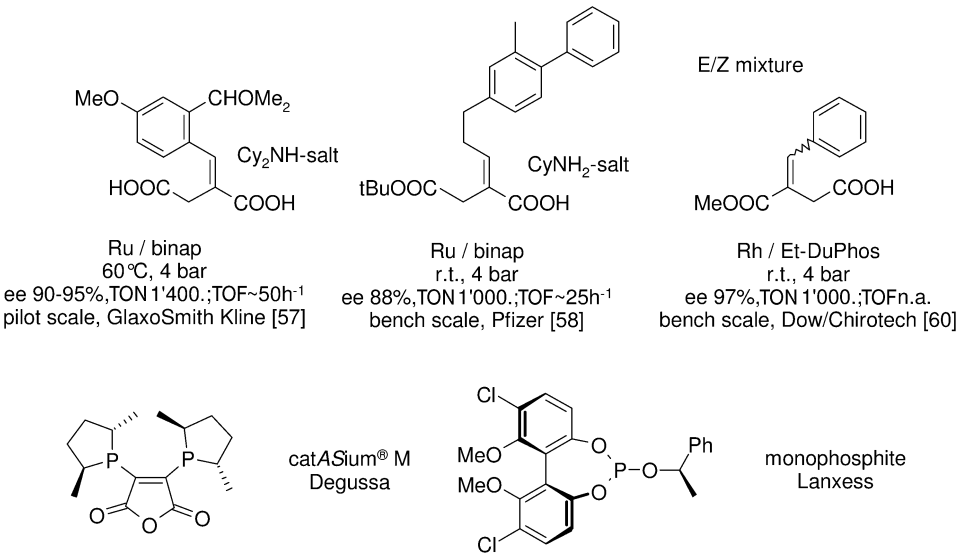


Fig. 37.12 Hydrogenation of itaconic acid derivatives; substrate and ligand structures.

During the past few years, several applications on the pilot and bench scale have been reported (Fig. 37.12). Interestingly, in two cases it was not the otherwise very effective Rh–phospholane complexes that was selected for preparative purposes but rather a Ru–binap catalyst. As described by GlaxoSmithKline, Rh–DuPhos actually gave higher ee-values in the ligand screening, but the results were not always reproducible and the Ru–binap catalyst was cheaper [57]. Pfizer obtained good results for the Rh–FerroTANE-catalyzed hydrogenation of the free acid (ee 94%, TON 1000), but ultimately chose a Ru–binap catalyst for scale-up [58].

Optimized procedures were developed for the hydrogenation of several model substrates, with very promising results for future industrial applications. Rh–DuPhos was used for itaconic amides by Dow/Chirotech [59, 60] and gave ee-values of 96–97%, TON 100 000, TOF 13 000 h^{-1} at 45 °C, 10 bar. For dimethyl itaconates, Chiral Quest reported ee-values up to 99%, TON 5000, at r.t./1.5 bar using TangPhos [47], while Rh–cat*AS*ium® M (Degussa [61]) achieved ee-values up to 99%, TON 10 000, TOFs up to 40 000 h^{-1} at 25 °C/4 bar, and Rh–monophosphite (Lanxess [62]) gave ee-values up to 99%, TON 10 000, TOFs up to 5 000 h^{-1} at 0 °C/0.5 bar (ligand structures see Fig. 37.12).

37.6.5
Allylic Alcohols and α,β-Unsaturated Acids

The hydrogenation of allylic alcohols and α,β-unsaturated acids leads to products with a very high synthetic potential, and both transformations were used quite early for industrial applications. In both cases Ru complexes with axially chiral biaryl ligands (binap analogues) are the catalysts of choice. Here, we will dis-

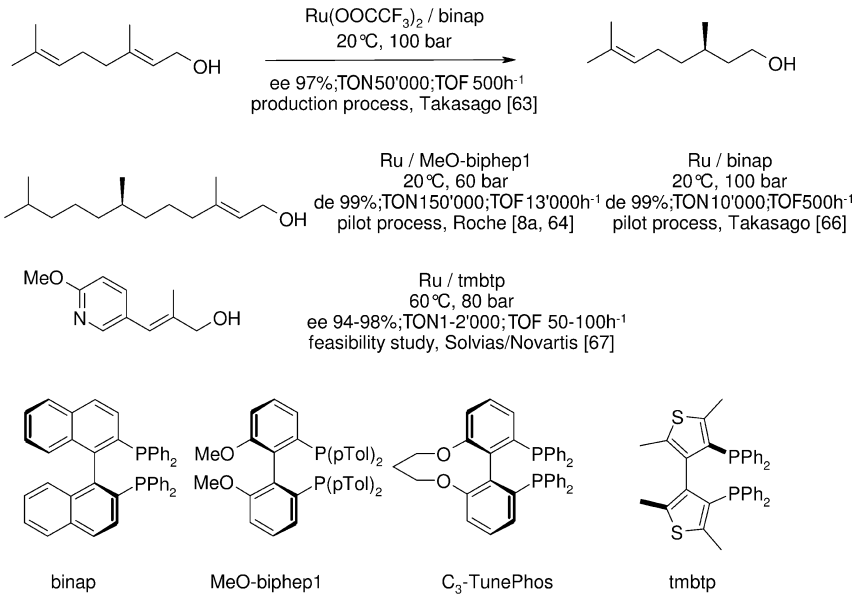


Fig. 37.13 Hydrogenation of various allylic alcohols.

cuss two examples in some detail and summarize the results for other processes.

37.6.5.1 **Allylic Alcohols** (Fig. 37.13)

Citronellol, a fragrance as well as an intermediate for vitamin E, can be prepared starting with geraniol. This transformation requires a specific Ru precursor and is highly chemoselective. It is carried out by Takasago on a 300 t y^{-1} scale [63]. Roche has reported a similar pilot process which works at 20 °C and 60 bar using the same Ru precursor with MeO-biphep as ligand; the ee is 99%, TON 30 000, and TOF 1500 h^{-1} [8a, 64]. In a recent feasibility study, Chiral Quest [65] has reached 98% ee and 100 000 turnovers with a Ru–TunePhos catalyst. Pilot processes with similar catalyst performances were developed by Roche [8a, 64] as well as by Takasago [66] for the longer-chain vitamin E intermediate. Clearly, the existing stereogenic center does not affect the enantioselectivity of the catalysts. Bench-scale processes for the hydrogenation of allylic alcohols using a Ru–binap and Ru–biphep catalyst, respectively, were reported by Roche earlier (summarized in [14]), and a recent feasibility study showed that heterobiaryl ligands can also be effective ligands for this transformation [67].

The hydrogenation of a racemic homoallylic alcohol is the key reaction for a new synthetic route for producing paroxetine, and recently reported by Ricordati [68] (Fig. 37.14). The best results (>99% ee for both *cis* and *trans* products) were

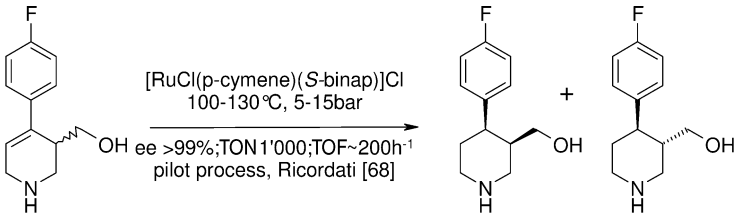


Fig. 37.14 Hydrogenation of a homoallylic alcohol.

obtained with a recrystallized [RuCl(*p*-cymene)(binap)]Cl complex in isopropanol. The reaction was carried out on a 100-kg batch size.

37.6.5.2 *α,β*-Unsaturated Acids

One of the first applications of the then newly developed Ru–binap catalysts for *α,β*-unsaturated acids was an alternative process to produce (*S*)-naproxen. (*S*)-Naproxen is a large-scale anti-inflammatory drug and is actually produced via the resolution of a racemate. For some time it was considered to be one of the most attractive goals for asymmetric catalysis. Indeed, several catalytic syntheses have been developed for the synthesis of (*S*)-naproxen intermediates in recent years (for a summary see [14]). The best results for the hydrogenation route were obtained by Takasago [69] (Fig. 37.15), who recently reported that a Ru–H_8-binap catalyst achieved even higher activities (TON 5000, TOF 600 h^{-1} at 15 °C, 50 bar) [16].

However, despite some quite good catalytic results it has become clear that the original resolution variant will be the optimal process for quite some time [70]. Several reasons are responsible for this situation, illustrating some of the issues when developing industrial processes as discussed earlier:

- The resolution process developed by Syntex is almost ideal (Pope Peachy resolution), with an efficient racemization and recycling of the unwanted (*R*)-enantiomer (yield >95% of (*S*)-naproxen from the racemate) and the chiral auxiliary (recovery >98%).
- The starting materials used for the catalytic versions are much more expensive; US$ 20–25 kg^{-1} for the vinyl and >>US$ 50 kg^{-1} for the acrylic acid derivative, compared to ca. US$ 10 kg^{-1} for methoxybromonaphthalene used in the Syntex process.

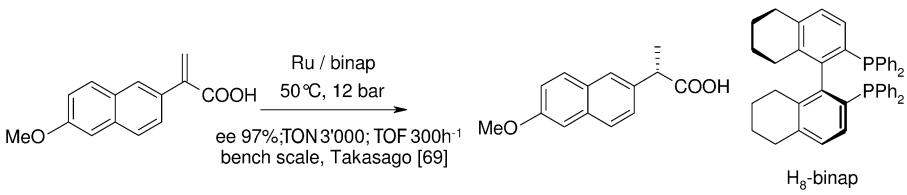


Fig. 37.15 Naproxen via enantioselective hydrogenation.

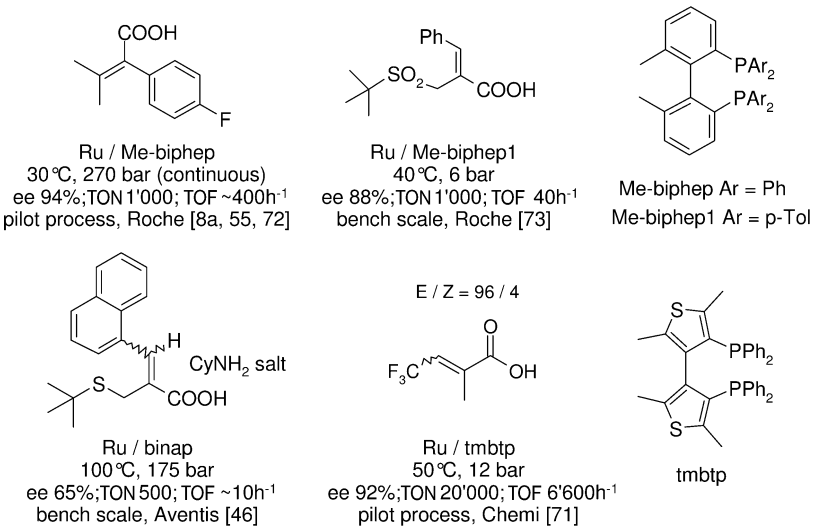


Fig. 37.16 Ru-catalyzed hydrogenation of *α,β*-unsaturated acids.

- Some of the developed catalytic transformations are not (yet) very effective, and in all cases further enrichment would be necessary, which can only be done by making a salt derivative.

Ru complexes containing biaryl-type ligands are the catalysts of choice for most *α,β*-unsaturated acids, and pertinent examples are depicted in Figure 37.16. The substrate range from tetrasubstituted C=C bonds to substrates with sulfur-containing substituents, even though in the latter case catalyst performance is as yet insufficient for technical application. A trifluoromethyl-substituted unsaturated acid (*E*/*Z* mixture) was hydrogenated by Chemi in a 4000-L reactor on a 340-kg scale with tmbtp, a hetero binap analogue [33, 71].

Interestingly, Rh complexes can also be used effectively for sterically hindered *α,β*-unsaturated acids or salts, as evidenced by the processes depicted in Figure 37.17. Few details have been released for the pilot process developed by Solvias for Speedel/Novartis [74, 75], but the hydrogenation has been carried out on a multi-hundred-kilogram scale. Recently, DSM has divulged bench-scale results for the same transformation with a novel Rh–phosphoramidite–PPh_3 catalyst with somewhat lower enantioselectivity [76], and seemingly has applied the process on a production scale. While the catalytic performance of these two catalysts is adequate for manufacture, this is not (yet) the case for the examples of SmithKline Beecham [77] and Takeda Chemical Industries [78]; indeed, Takeda has developed an alternative technical process for the active ingredient.

The *α,β*-unsaturated ester shown in Figure 37.18, with a rather unusual substitution pattern, was hydrogenated successfully for the synthesis of candoxatril.

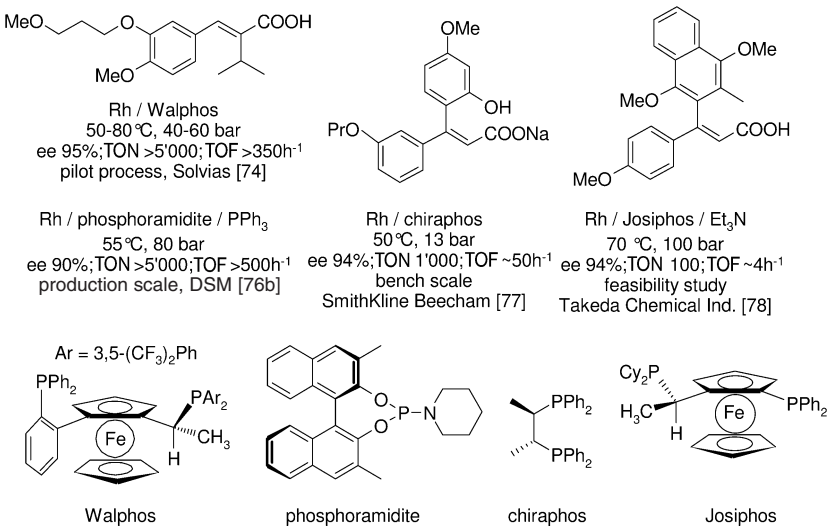


Fig. 37.17 Rh-catalyzed hydrogenation of α,β-unsaturated acids.

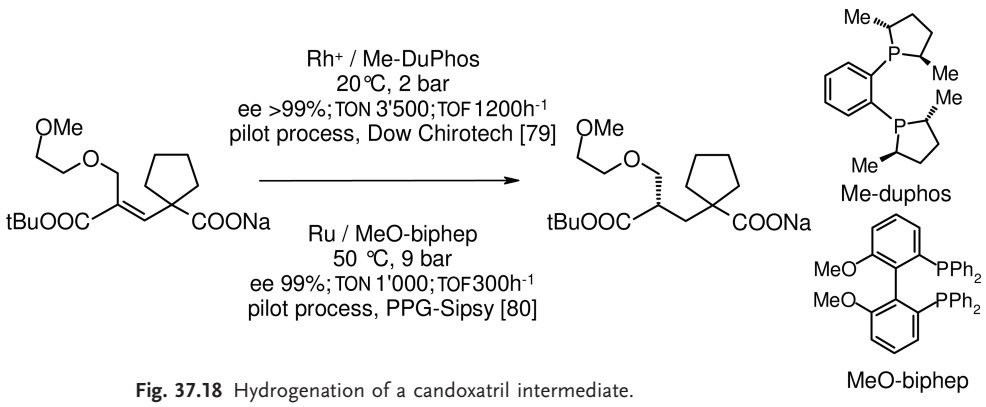


Fig. 37.18 Hydrogenation of a candoxatril intermediate.

The hydrogenation was carried out on 12-kg scale for Pfizer by Dow/Chirotech, using a cationic Rh–DuPhos catalyst [79] and on 250-kg scale by PPG-Sipsy with a Ru–biphep complex [80]. Both catalysts achieved very high enantioselectivities and medium activities.

37.6.6
Miscellaneous C=C Systems

Besides the olefins with privileged substitution patterns, several complex C=C substrates were hydrogenated on a production scale with good to excellent suc-

cess. Here, we describe several processes in some detail and summarize others, with minimal comment.

37.6.6.1 **Hydrogenation of a Biotin Intermediate (Lonza)**

During the course of the development of a new technical synthesis at Lonza for biotin (a water-soluble vitamin), the Rh–Josiphos-catalyzed diastereoselective hydrogenation of a tetrasubstituted C=C bond turned out to be a key step [40, 42, 81] (Fig. 37.19).

Selected results of the process development are summarized in Table 37.3. It is remarkable that homogeneous catalysts with most ligand classes gave even lower diastereomeric excess (de)-values than the achiral heterogeneous Rh–Al_2O_3 catalyst, and Rh–Josiphos complexes with aromatic R′ groups were inactive. The high effectiveness of catalysts with PPF-PtBu_2 as ligand was therefore even more surprising. While the feasibility study was carried out with SCR of 50 to 100, optimization of the reaction resulted in TONs of 2000. The enantioselective hydrogenation (*N*-benzyl instead of *N*-(*R*)-phenethyl) with Rh–PPF-PtBu_2 afforded the desired enantiomer with up to 90% *ee*. For the production process the diastereoselective variant was chosen and for a few years several tons were manufactured annually.

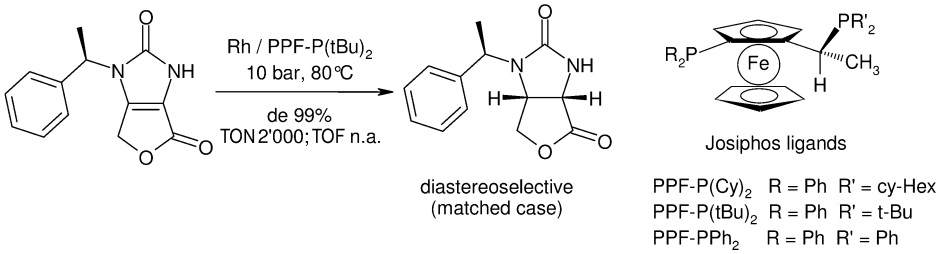
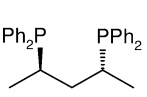
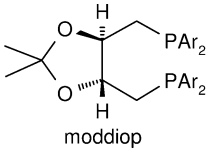


Fig. 37.19 Hydrogenation of a biotin intermediate.

Table 37.3 Selected results for the hydrogenation of the biotin intermediate.

Catalyst	de [%]	Comments/ligand structures
Rh–Al_2O_3	40	Heterogeneous
Rh–bdpp	50	 bdpp
Rh–moddiop	66	 moddiop Ar = 3,5-Me_2-4-(OMe)Ph
Rh–PPF-PPh_2	No reaction	
Rh–PPF-PCy_2	88	
Rh–PPF-P(tBu)$_2$	99	

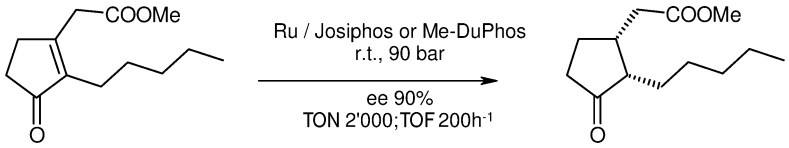
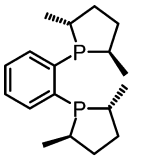


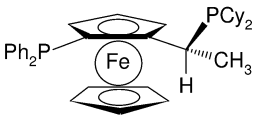
Fig. 37.20 Hydrogenation of a dihydrojasmonate intermediate.

Table 37.4 Ligand effect on activity and selectivity.

Ligand	SCR	TOF [h^{-1}]	*cis/trans*	ee *cis* [%]
Me-DuPhos	300	5	99/1	69
Josiphos	500	250	98/2	86
Me–DuPhos	2000	120	>97/3	60
Josiphos	2000	200	>97/3	90



Me-DuPhos



Josiphos

Catalyst: [Ru(H)(cyclooctatriene)(ligand)]BF_4.
SCR: Substrate : catalyst ratio.

37.6.6.2 Synthesis of (+)-Methyl *cis*-Dihydrojasmonate (Firmenich)

Dihydrojasmonates are ubiquitous and cheap perfume ingredients. Firmenich established that (+)-*cis*-methyl dihydrojasmonate (Fig. 37.20) is the preferred stereoisomer, and subsequently developed an enantioselective process and began production on a multi-ton per year scale [82, 83].

A novel Ru precursor and a new reaction system had to be found because the classical Ru complexes and conditions for the hydrogenation of C=C bonds did not work. Besides the enantioselectivity, chemo- and *cis*-selectivity and activity problems (tetrasubstituted C=C) were solved on a very good level. A broad screening of Ru catalysts (partly in collaboration with Solvias) showed that selected Josiphos ligands and DuPhos satisfied the prerequisites (see Table 37.4).

37.6.6.3 Intermediate for Tipranavir (Chirotech)

The diastereoselective process depicted in Figure 37.21 was developed by Chirotech [18, 36, 84] for Pharmacia and Upjohn [85], and is being carried out on a "production" scale. Essential was the addition of Na_2CO_3 as co-catalyst. The catalyst tolerates an *E*/*Z* mixture of substrate, and shows high chemoselectivity with respect to reduction of the nitro group, which can be a problem. An alternative pilot process was recently described by Boehringer-Ingelheim using a Rh–cat*A*-*S*ium® M catalyst which achieved selectivities of >98% de and a TOF of ca. 40 h^{-1} with an SCR of 1000 at 60 °C/10 bar [86].

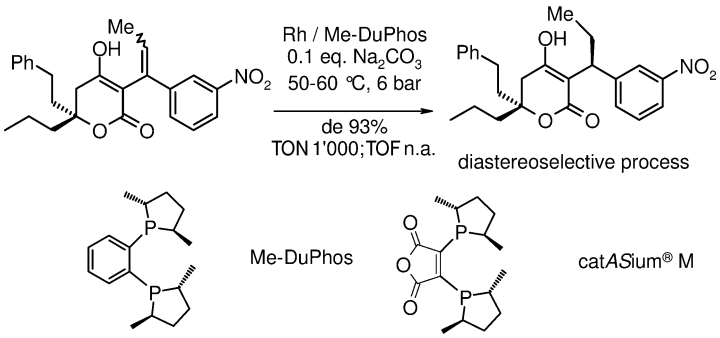


Fig. 37.21 Hydrogenation of a tipranavir intermediate.

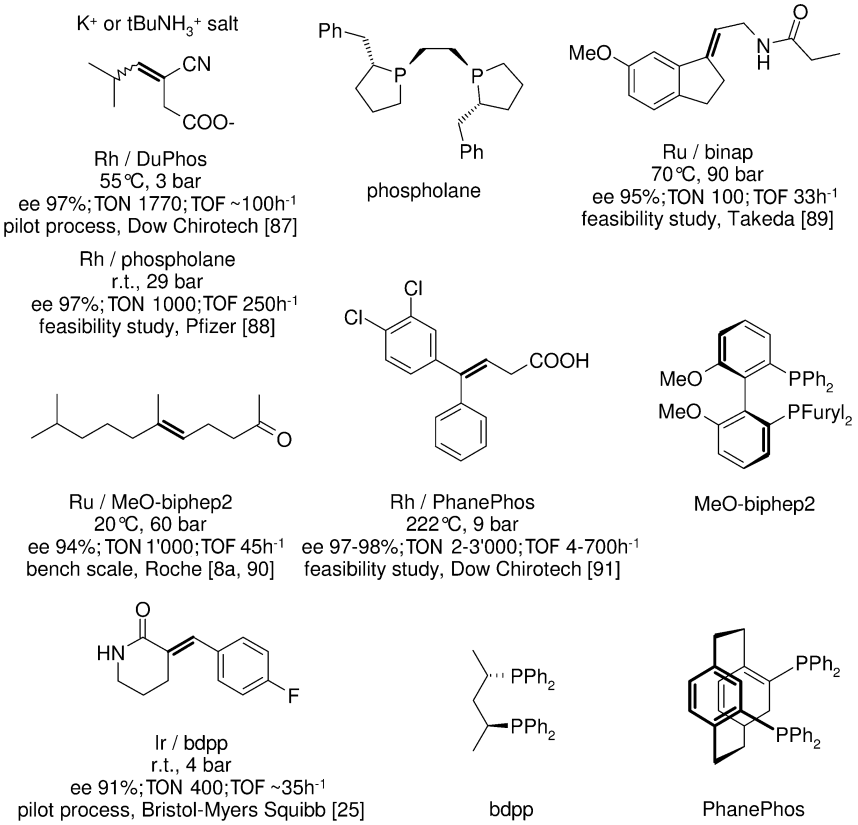


Fig. 37.22 Hydrogenation of various functionalized alkenes.

37.6.6.4 Various C=C Substrates

Further hydrogenations of a variety of C=C substrates depicted in Figure 37.22 range from a pilot process to several feasibility studies. Of special interest are PhanePhos, originally reported by Merck, an unsymmetrically substituted phospholane developed by Pfizer, and the rare case of an Ir–diphosphine complex active for the hydrogenation of a C=C bond. Nevertheless, the catalyst performances of most processes summarized in Figure 37.22 are probably not (yet) sufficient for manufacturing purposes. Indeed, several of the reports explicitly mention that further development was stopped, either because another route proved to be superior or because the compound was abandoned.

37.7 Enantioselective Hydrogenation of C=O Bonds

Most catalysts originally developed for C=C bonds show a rather poor performance for the hydrogenation of many ketones. However, this situation changed dramatically when it was found that selected Ru–binap and later Ru–binap–diamine complexes achieve excellent enantioselectivities, as well as very high TONs and TOFs, for a variety of ketones [92]. Since then, it has been demonstrated that many α- and β-functionalized, as well as aromatic ketones, are suitable substrates for hydrogenation with industrially viable catalytic results. For the reduction of various ketones biocatalytic methods are an industrially viable alternative to chemocatalysts [15].

37.7.1 α-Functionalized Ketones

(*R*)-1,2-Propanediol is an intermediate for (*S*)-oxafloxazin, a bactericide which until recently was sold as a racemate. The (*R*)-diol is now produced by Takasago via hydrogenation of hydroxyacetone (see Fig. 37.23) using a Ru–Tol–binap catalyst on a 50 t y^{-1} scale [92b]. Recently, it was reported that segphos – a newly developed biaryl diphosphine – shows even better results, achieving >98% ee and TON and TOF of 10 000 and $\sim$1400 h^{-1}, respectively [16, 93].

The two production processes using α-amino ketone substrates depicted in Figure 37.24 were developed by Boehringer-Ingelheim to improve on existing resolution syntheses for adrenaline and phenylephrine [94]. Unfortunately, few details are available but both processes are carried out with a Rh–mccpm catalyst with very high TONs and TOFs, albeit with medium ee-values of 88% which increase to >99% after precipitation of the free base.

The hydrogenation of α-amino ketones was also a key step for the synthesis of three more pharma actives (Fig. 37.25). Roche [95] divulged a pilot process involving the hydrogenation/dynamic kinetic resolution of a cyclic α-amino ketone using an optimized MeO–biphep ligand. The Ru-catalyzed reaction was carried out on a 9-kg scale with excellent enantio- and diastereoselectivities, and very

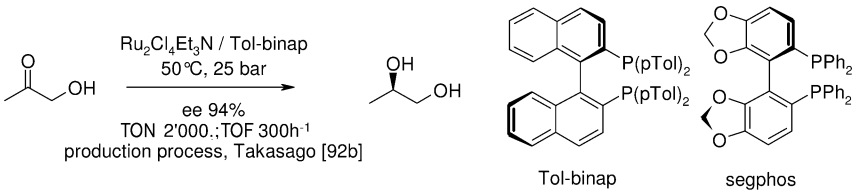


Fig. 37.23 Hydrogenation of hydroxyacetone.

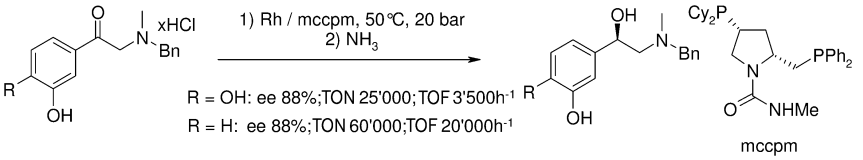


Fig. 37.24 Production processes for adrenaline (R=OH) and phenylephrine (R=H) intermediates.

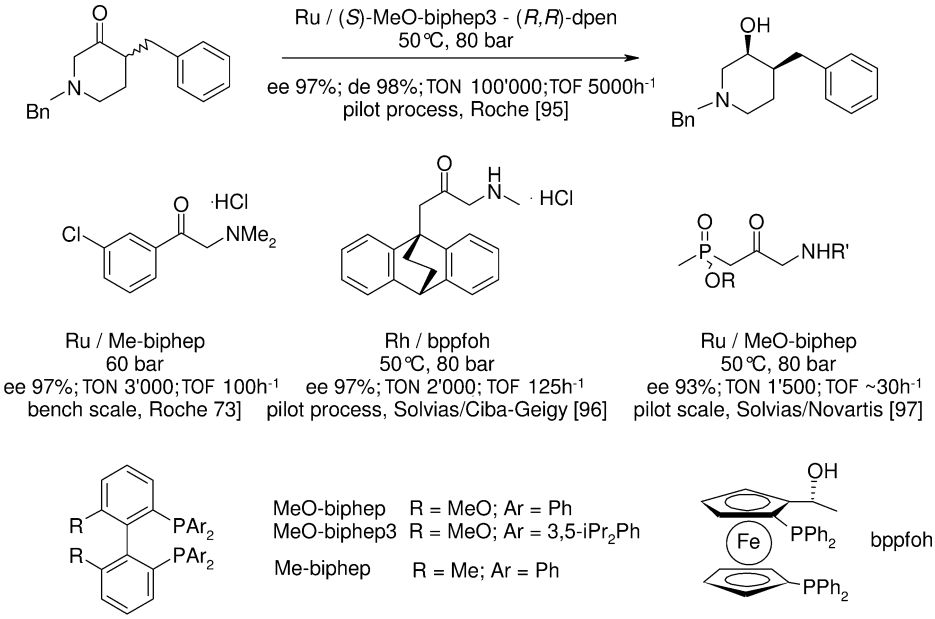


Fig. 37.25 Hydrogenation of various α-amino ketones.

high TON and TOF. A bench-scale process for the reduction of an aromatic ketone reported earlier relied on a Ru–Me-biphep catalyst [73]. A pilot process was reported by Solvias/Ciba-Geigy which was operated on a multi-10-kg scale involving a Rh–bppfoh-catalyzed hydrogenation of an intermediate for the antide-

pressant levoprotiline [96]. Important for success was the fact that crystallization of the product both enhanced ee-values and allowed separation of the catalyst from the product. A pilot process was developed by Solvias for Novartis for the hydrogenation of an α-amino-α'-phosphinate ester with moderate catalyst performance using a Ru–MeO–biphep catalyst [97]. Clearly, this substrate could also be considered to be an analogue of a β-keto ester (see below). Recently, the application of Ru/C_3-TunePhos to the hydrogenation of aromatic α-phthalimide ketones was reported as having excellent catalyst performance but requiring relatively high temperatures and pressures (60–80 °C, 100 bar, ee up to >99%, TON up to 10 000, TOF 140 h^{-1}), thus opening up a viable route for the synthesis of a variety of amino alcohols [98].

The hydrogenation of α-keto acid derivatives is a promising route to a variety of α-hydroxy and α-amino acids. Until now, homogeneous catalysts have achieved good ee-values but only insufficient TONs and TOFs and, indeed, heterogeneous cinchona-modified Pt catalysts are a viable alternative [10, 99, 100]. The hydrogenation of an α-ketolactone (Fig. 37.26) was the key step for the enantioselective synthesis of pantothenic acid. A pilot process was developed by Roche [8a], and (*R*)-pantolactone was produced in multi-100-kg quantities. A Rh–bpm catalyst proved to be highly active with satisfactory selectivity. Important were the fine tuning of the ligand and the choice of anion; critical for the very good catalyst performance were the purity of substrate and solvent, as well as of hydrogen. For the production of kilogram quantities of (*S*)-*p*-chloro mandelic acid, a Ru–MeO–biphep catalyst achieved 90–93% ee with acceptable TONs and TOFs, indicating that this hydrogenation might be feasible for the production of an agrochemical intermediate, both from a technical and an economical point of view [100]. The hydrogenation of two other α-keto esters was less successful as the catalyst activities were relatively low [73].

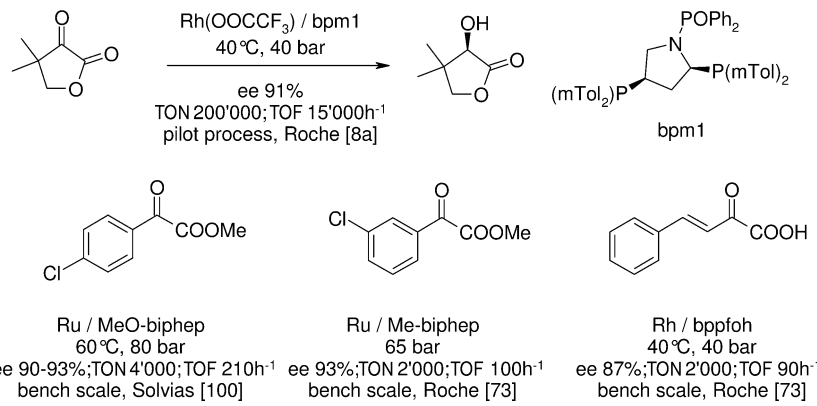


Fig. 37.26 Hydrogenation of α-keto acid derivatives.

37.7.2
β-Functionalized Ketones

β-Ketone esters are certainly privileged substrates, and several industrial processes rely on their enantioselective hydrogenation. The most important is the hydrogenation/dynamic kinetic resolution shown in Figure 37.27 for the production of an intermediate for carbapenem antibiotics carried out by Takasago on a scale of 50 to 120 t y^{-1} [66, 92b, 101]. Similar results (ee 98–99%, de 94%, TON 200, TOF ~600 h^{-1} at 50 °C/100 bar) were obtained by Chemi with a Ru–tmbtp catalyst [33, 102]. It was also recently reported that an optimized segphos ligand can achieve even higher stereoselectivities with >99% ee and 99% de (TON and TOF not specified) [16, 93].

Several processes using simple *β*-keto ester substrates were developed to various stages. Some early examples of bench-scale processes using Ru–binap were described by Takasago and Aventis (for more information, see [14]). NSC Technologies [103] manufactures three *β*-hydroxy esters building blocks; one of these is produced on the scale of 100s of kilograms, while two other are in the pilot stage. Lanxess has developed similar technology for the hydrogenation of several substrates on the basis of its ClMeO–biphep ligand which is applied on technical scale [3, 104] (Fig. 37.28). Also depicted in Figure 37.28 is the hydrogenation of a chlorinated *β*-keto ester developed to the pilot stage and applied on a multi-100-kg scale by Chemi, using its proprietary tmbtp ligand [71]. Chiral Quest has claimed a technical process for this substrate as well as for other keto esters using Ru–TunePhos catalysts [3, 47]. Acetyl acetone can be reduced to 2,4-pentane diol with >99% ee and >98% de using Ru–ClMeO–biphep, the reaction having been carried out by Lanxess on a scale of several kilograms, though few details are available [3, 104, 105] and Roche has described a pilot process for a long-chain *β*-keto ester, an intermediate for Orlistat (see Fig. 37.28) [8a, 73]. More complex substrates can also be hydrogenated successfully, as demonstrated by the two last examples shown in Figure 37.28. A bench-scale process

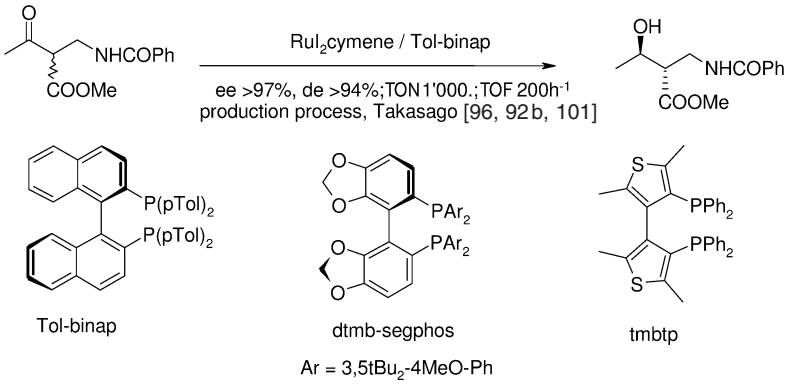


Fig. 37.27 Hydrogenation/dynamic kinetic resolution of a penem intermediate.

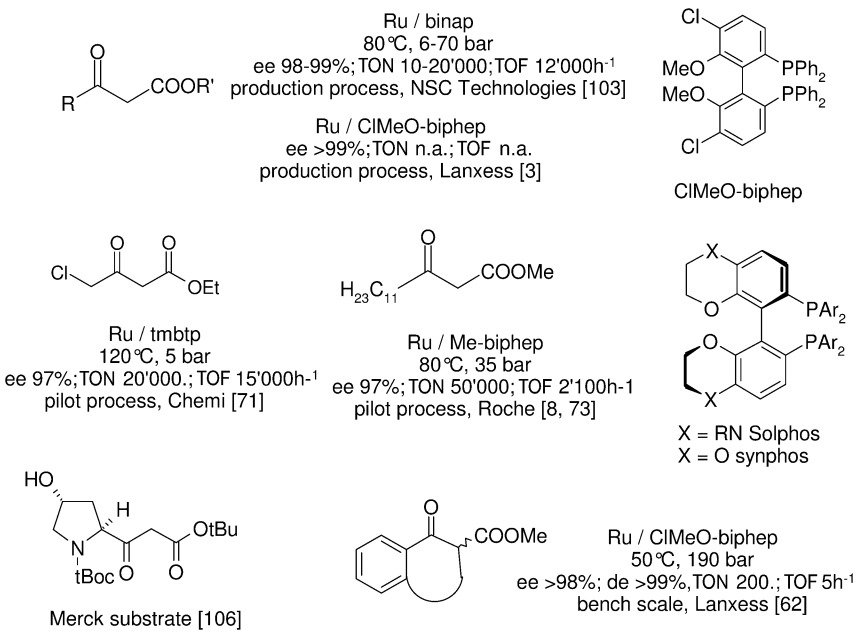


Fig. 37.28 Hydrogenation of β-keto acid derivatives.

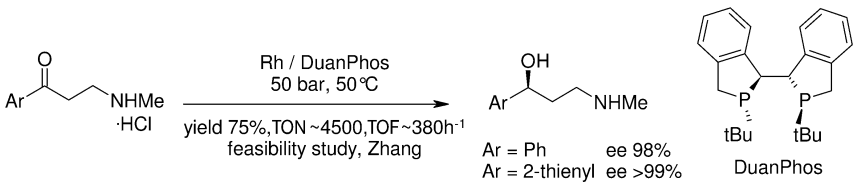


Fig. 37.29 Hydrogenation of γ-amino ketones.

has been reported by Lanxess for a cyclic keto ester (exact structure unknown) with high stereoselectivities but low catalyst activity [62], and Ru–Tol–binap was used by Merck to hydrogenate a hydroxyproline derivative, albeit with modest stereoselectivity of 76% de on a kilogram scale [106].

Based on hydrogenations of model substrates, several new ligands promise to have a similar potential as those described above. For example, Ru–Solphos (Solvias) catalysts have been shown to hydrogenate various β-keto esters and β-diketones with ee-values up to >99% and TONs of up to 100 000 (for ethyl-3-oxobutanoate) [75], while Ru–Synphos (Synkem) [107] catalysts achieved 99.4% ee at an SCR of 7000 for the hydrogenation of ethyl acetoacetate (for ligand structures, see Fig. 37.28).

Recently, Zhang and coworkers [108] showed Rh–DuanPhos to be a very effective catalyst for the hydrogenation of a variety of aromatic γ-amino ketones. In a

feasibility study, the hydrogenation of the intermediates of (*S*)-fluoxetine and (*S*)-duloxetine was achieved with ee-values of 89% and >99%, respectively, at an impressive SCR of 6000, albeit with a relatively low chemical yield of 75% (Fig. 37.29).

37.7.3
Aromatic Ketones

The effective hydrogenation of ketones without *α*- or *β*-functionality has only recently developed to be an important methodology with Noyori's discovery of the Ru-based transfer hydrogenation catalysts on the one hand, and the very active Ru–diphosphine–diamine systems on the other hand [92a]. Both methodologies rely on the presence of an N–H bond allowing an effective outer sphere reduction mechanism. The technology has been licensed by several companies using various diphosphines [16, 109–112], but it is not clear whether it is already used for specific manufacturing purposes.

The hydrogenation of a number of aromatic ketones is shown in Figure 37.30. Noyori's very effective Ru–diphosphine–diamine technology was developed by several companies. It is not clear on which scale the processes developed by Takasago (dm-binap = 3,5-xylyl-binap) [16] and Dow/Chirotech [109–111] for the reduction of substituted acetophenones are actually applied commercially. Using the Xyl-PhanePhos–dpen catalyst, a highly efficient bench-scale process was developed for the hydrogenation of *p*-fluoroacetophenone (ee 98%, TON 100 000, TOF 50 000 h^{-1} at r.t., 8 bar) [109]. Ru–P-Phos (licensed to Johnson Matthey [112]) achieved ee-values >99.9% and TON up to 100 000 for sev-

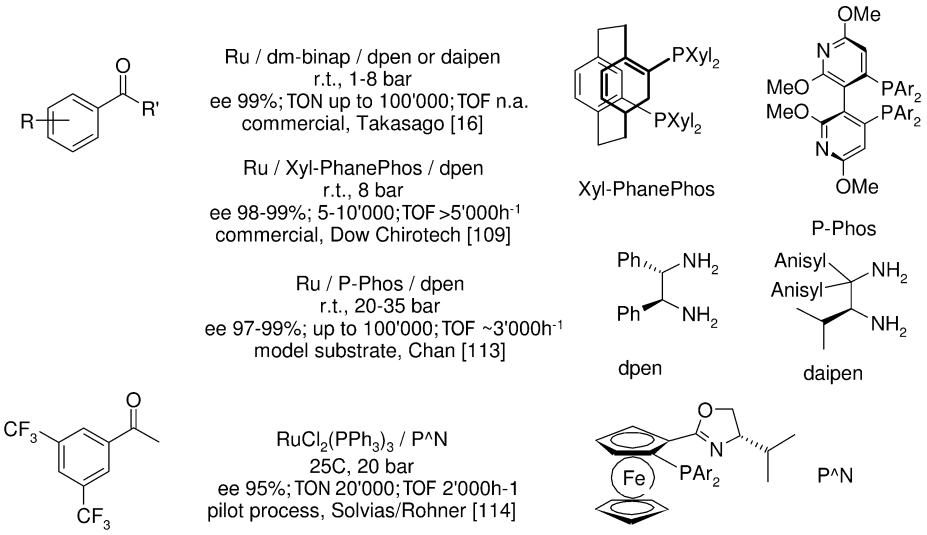


Fig. 37.30 Hydrogenation of aromatic ketones.

eral model substrates [113]. A pilot process was developed by Solvias for the production of 3,5-$(CF_3)_2$-phenyl ethanol using a newly developed Ru–(phosphinoferrocenyl)oxazoline complex [114] which, though not containing an N–H bond, showed very high activity for the hydrogenation of a variety of aryl ketones.

Several Ru-catalyzed transfer hydrogenations have been developed and applied up to the multi-10-kg scale. Two variants are applied, one based on Ru–amino alcohol complexes with *i*PrOH/base, and the other based on Ru–Ts–dpen complexes with HCOOH/NEt_3 as reducing system, respectively. As shown in Figure 37.31, excellent enantioselectivities have been obtained for several aryl ketones, but with lower activities than for comparable hydrogenation reactions described above (see, for example, the results for *bis*-trifluoromethyl-acetophenone in Fig. 37.30). Avecia has developed transfer hydrogenation technology under the term CATHy using Me_5cp–Ru catalysts, and claims several applications on the multi-100-kg scale [3, 115], while Lanxess has applied Noyori's Ru–Ts–dpen system to the reduction of aryl keto esters on a scale of >2 tons [62, 104]. Of special interest are the chemoselectivity in the case of nitro-acetophenone [3] and the ability to reduce rather complex molecules, as illustrated by the Otsuka feasibility study [116].

Finally, hydride reduction using BH_3 in presence of 1,2-amino alcohols (CBS reduction) can be run catalytically, albeit with very low TONs and TOFs. Nevertheless, several processes based on this technology have been developed and run on a scale of up to 50 kg. Three such cases are shown in Figure 37.32 (more can be found in [14]). Lonza used a proline-derived catalyst to manufacture 50 kg of an intermediate for Josiphos ligands [119]. Merck used the same catalyst to reduce bistrifluoro-acetophenone on kilogram scale but, compared to the results for the (transfer) hydrogenation processes described above, the TON (20–50) and TOF ($\sim 20\ h^{-1}$) were much lower [117, 120]. Sepracor also developed this technology for an aryl-γ-keto ester with respectable ee-values but, again, low activity [121], while Merck reported a pilot process for the reduction of a more complex intermediate using the aminoindanol ligand N^O (see Fig. 37.31) [122]. Finally, a Co-salen-catalyzed borohydride reduction was developed by Mitsui for a heteroaryl ketone, albeit with relatively low ee-values [123].

37.8
Enantioselective Hydrogenation of C=N Bonds

The enantioselective hydrogenation of C=N bonds is the least-developed hydrogenation reaction, even though many active ingredients contain chiral amine moieties. The main reason for this situation is that effective catalysts – mainly Ir–diphosphine complexes – have been developed only during the past 10 years [124]. A major incentive for the development of more active catalysts was the chiral switch of metolachlor made in 1997 by Ciba-Geigy [125, 126].

Metolachlor is the active ingredient of Dual, one of the most important grass herbicides for use in maize and a number of other crops. In 1996, after years of intensive research, Dual Magnum with a content of approximately 90% (*S*)-diaste-

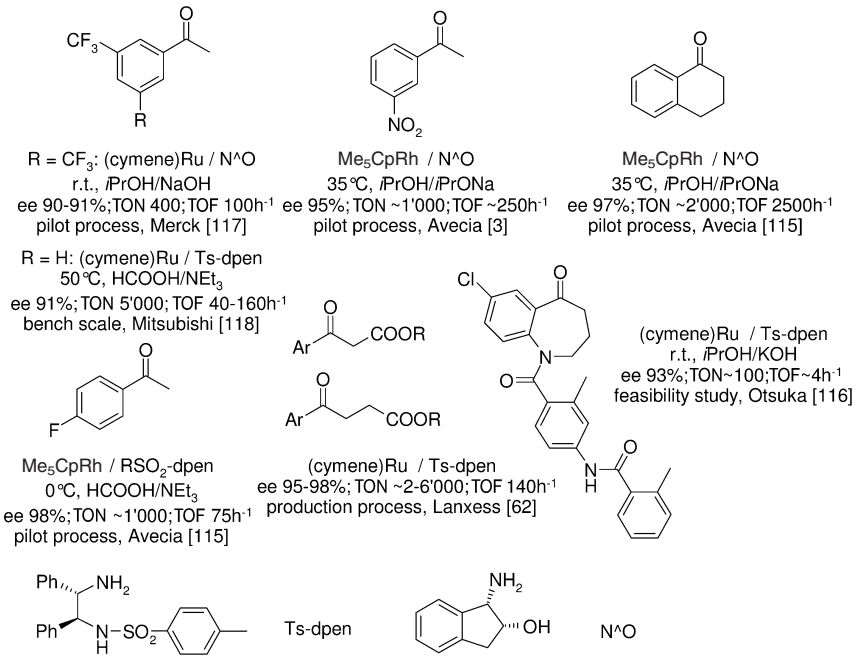


Fig. 37.31 Transfer hydrogenation of aromatic ketones.

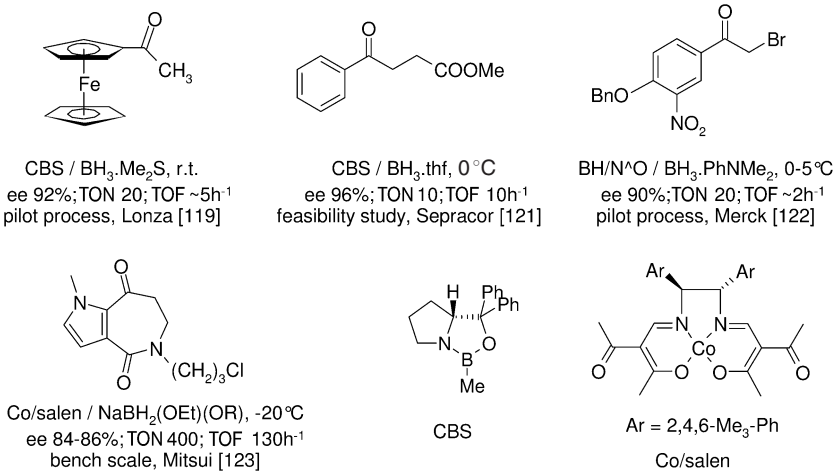


Fig. 37.32 Hydride reductions of aromatic ketones.

reomers and with the same biological effect at about 65% of the use rate, was introduced onto the market. This "chiral switch" was made possible by the new technical process that is briefly described below. The key step of this new synthesis is the enantioselective hydrogenation of the isolated MEA imine (Fig. 37.33).

The search for a commercially viable process took many years [126]. Several approaches with Rh or Ir complexes using commercially available diphosphine ligands were not successful. A critical breakthrough was achieved when Ir complexes with a new class of ferrocenyl-based ligands (now called Solvias Josiphos) were used. Extremely active and productive catalysts were obtained, especially in the presence of acid and iodide ions. Different Josiphos ligands were tested and a selection of the best results obtained is shown in Table 37.5.

The optimized process operates at 80 bar hydrogen and 50 °C with a catalyst generated *in situ* from $[Ir(cod)Cl]_2$ and the Josiphos ligand PPF-$PXyl_2$ (short name Xyliphos) at a SCR of >1 000 000. Complete conversion is reached within 3–4 h, the initial TOFs exceed 1 800 000 h^{-1}, and the ee is about 80%. This process is now operated by Syngenta on a scale of >10 000 t y^{-1} [127].

Following this success, a number of technical C=N hydrogenation processes were developed (Fig. 37.34). While enantioselectivities are good to excellent, catalytic activities and productivities are far behind the metolachlor process. An Ir-catalyzed hydrogenation developed by Lonza for an intermediate of dextromethorphan was carried out on a >100-kg scale [41, 42, 81]. Important success factors were the ligand fine tuning and use of a biphasic system. Chemoselectivity is high, but catalyst productivity rather low, for an economical technical application. Satoh et al. reported up to 90% ee for the hydrogenation of an intermediate of the antibiotic levofloxacin using Ir–diphosphine complexes. The best

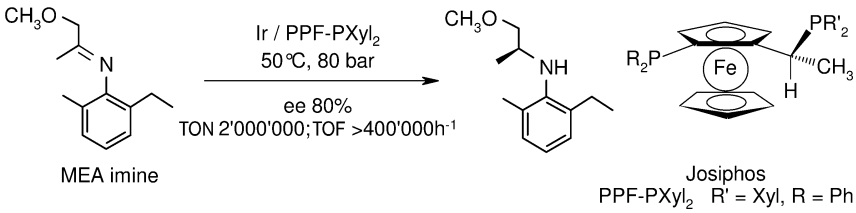


Fig. 37.33 Metolachlor hydrogenation process.

Table 37.5 Most successful ligands for the hydrogenation of MEA imine (for ligand structures, see Fig. 37.33).

R	R′	TON	TOF [h^{-1}]	ee [%]	Comments
Ph	3,5-xylyl	1 000 000	> 300 000	79	Production process
p-CF_3Ph	3,5-xylyl	800	400	82	Ligand screening
Ph	4-*t*Bu-C_6H_4	5000	80	87	Low temperature
Ph	4-(^{n}Pr)$_2$N-3,5-xyl	100 000	28 000	83	Optimized conditions

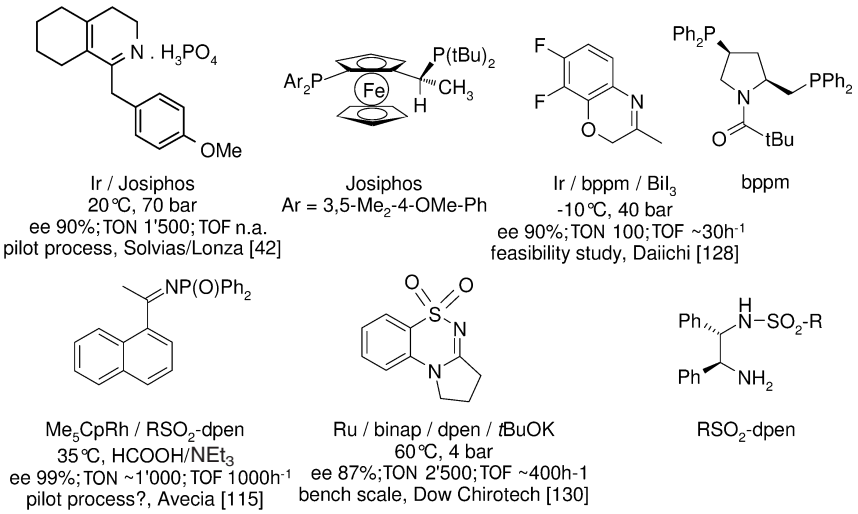


Fig. 37.34 Hydrogenation of a various C=N bonds.

results were obtained with bppm and modified diop ligands in the presence of bismuth iodide at low temperature [128].

Besides Ir–diphosphines, two more catalyst systems have shown promise for industrial application. As mentioned in Section 37.5.2, the Rh–Josiphos-catalyzed hydrogenation of unprotected β-dehydro amino acid derivatives by Merck actually involves the hydrogenation of a C=N and not a C=C bond (see Fig. 37.10) [3, 51]. Noyori's Ru–PP–NN catalyst system seems also suitable for C=N hydrogenation [129], and was successfully applied in a feasibility study by Dow/Chirotech for the hydrogenation of a sulfonyl amidine [130]. Avecia also showed the viability of its CATHy catalyst for the transfer hydrogenation of phosphinyl imines [115] (see Fig. 37.34).

37.9
Ligands and Metal Complexes for Large-Scale Applications

There is no doubt that the chiral ligand is at the heart of any enantioselective homogeneous process. As explained above, it is of course crucial to apply the correct metal (the correct choice of metal precursor or anion can be decisive), as well as a suitable solvent and reaction conditions. However, since there are much fewer metal precursors, anions or solvents than there are potential ligands, process research and development (R&D) is very much centered around finding the optimal ligand. Accordingly, most patents of hydrogenation processes are focused on the structure, the synthesis and/or the application of chiral ligands and the availability of the ligands in the required quantity at the right time is one of the central issues of process development.

In the past, when an enantioselective catalytic process was developed and scaled up for the production of a chiral intermediate, the preparation of the chiral ligand in the amounts required for each phase was very much part of process development. This is well described in Knowles' Nobel Lecture for the L-dopa process [28a]. While the design of the dipamp ligand was an extraordinary achievement, without a technical synthesis the manufacture of L-dopa would still not have been possible. The same was also true for the Josiphos ligands developed by the former Ciba-Geigy (now Solvias/Syngenta) for the manufacture of (*S*)-metolachlor which, with an annual volume of >10 000 tonnes is today's largest catalytic process for a chiral intermediate [127]. The need to develop the actual manufacturing process not only for the intermediate but also for the chiral ligand places additional pressure on the application of chiral catalysts which had (and will have even more) to compete with alternative technologies such as resolution processes (simulated moving bed, crystallization, etc.), chiral pool approaches or biocatalysis.

During the past few years the situation has changed considerably as several companies have developed technology and ligand portfolios which are available for applications on a technical scale [47, 111, 112, 131–135, 141]. In the following sections we have compiled: (i) a list of companies offering technology and various services in the field of homogeneous hydrogenation; (ii) ligands which have been used on a technical scale as described in Sections 37.6 to 37.8, and/or which are available on scale and have a confirmed potential for technical applications; (iii) information on metal complexes; and (iv) information on intellectual property (IP) issues.

37.9.1 Companies Offering Services, Technology, Ligands and Catalysts

- *Chemi:* Proprietary diphosphine ligands, process R&D, custom manufacturing. Some pilot and bench scale processes.
- *Chiral Quest Inc.*: Proprietary chiral ligands, process R&D [47].
- *Degussa Homogeneous Catalysts*: Proprietary chiral ligands, process R&D, custom manufacturing. Various bench-scale and pilot applications [135].
- *Digital Specialty Chemicals*: Supply of phosphine ligands on kilogram scale, especially patent-free ligands [136].
- *Dow/Chirotech*: Proprietary chiral ligands, process R&D, custom manufacturing. Several production processes, many pilot- and bench-scale processes [111].
- *DSM Pharma Chemicals*: Proprietary technology, process R&D, custom manufacturing. Production process [137].
- *Great Lakes Fine Chemicals*: Know-how from NSC Technologies/Monsanto, several production and pilot processes [30].
- *Japan Science and Technology Corporation:* Licensing Noyori technology.

- *Johnson Matthey, Catalysis and Chiral Technologies (Synetix)*: In licensed chiral ligands, process R&D. Metal precursors and M-L complexes in technical quantities; recovery of noble metals [112].
- *Lanxess (Bayer)*: Proprietary ligands, process R&D, custom manufacturing [62].
- *Lonza*: Process R&D, custom manufacturing. One production process, several pilot- and bench-scale processes [42].
- *NPIL Pharma (Avecia)*: Proprietary technology, process R&D, custom manufacturing. Some pilot and bench scale processes [115].
- *Rhodia*: Expertise in phosphorus chemistry, manufacture of binap [138].
- *PPG-Sipsy*: License for selected catalyst systems, process R&D, custom manufacturing. Several processes [139].
- *Synkem*: Proprietary ligands, process R&D, custom manufacturing [140].
- *Solvias* (spin-off from Ciba-Geigy/Novartis): Proprietary chiral ligands, process R&D. Several production processes, many pilot- and bench-scale applications [141].
- *Takasago*: Early and strong efforts in developing the potential of the binap ligand for isomerization and hydrogenation. Proprietary ligand families, process R&D, custom manufacturing. Several production and pilot processes [142].
- *Umicore AG* (formerly OMG, dmc^2, Degussa): Proprietary chiral ligands (collaboration with Solvias). Metal precursors and M-L complexes in technical quantities; recovery of noble metals [143].

37.9.2
Chiral Ligands with Established Industrial Performance

Here, we list only those ligands which have either been used successfully on industrially relevant target substrates or have demonstrated excellent overall catalyst performance (ee >98%, TON >5000, TOF >1000 h^{-1}) for the hydrogenation of model substrates. Comments and references can be found in the preceding sections. It must be stressed that, in addition to the ligands compiled in Figures 37.35 to 37.38, the ligand suppliers listed above offer many more ligands with industrial potential which, however, has not (yet) been documented adequately.

The following classes of ligands with often similar performance profiles are distinguished: biaryl diphosphines, phospholanes, ferrocenyl-based diphosphines and miscellaneous phosphorus-based ligands. Only one enantiomer of each ligand is depicted, but in general both enantiomers are available, even though in a few cases the prices might vary if the ligand is prepared from chiral pool material.

37.9.3
Metal Complexes and Anions

Once the optimal metal/ligand/anion combination has been determined, the choice of the metal complex which is actually put into the reaction solution will become of importance. Active hydrogenation catalysts are metal–ligand complexes which can either be prepared *in situ* simply by mixing a suitable precur-

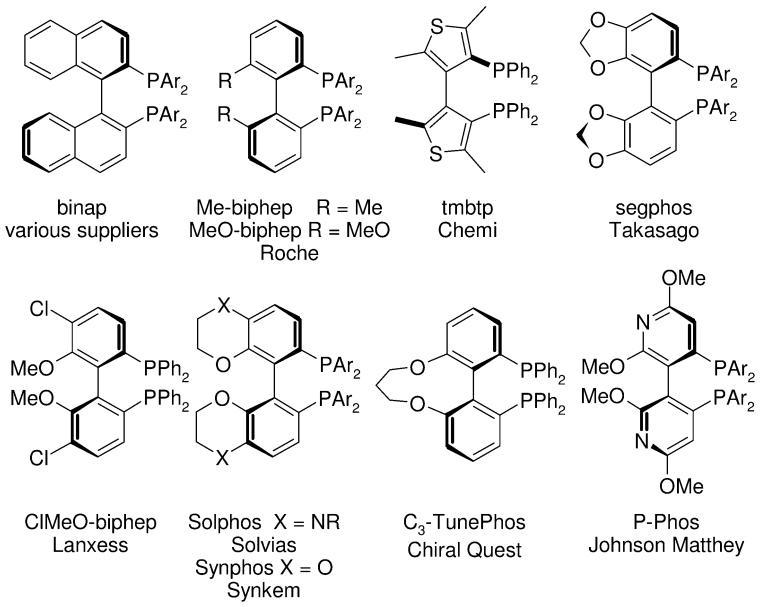


Fig. 37.35 Biaryl diphosphines; (*R*)-enantiomers are shown.

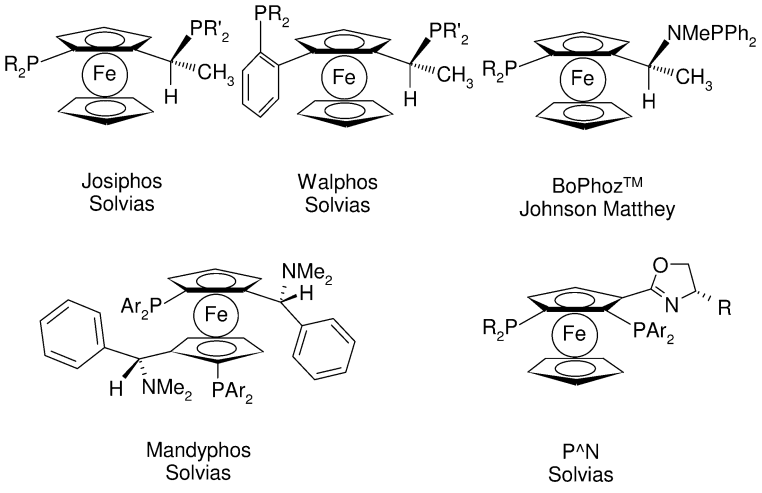


Fig. 37.36 Ferrocenyl phosphines.

sor and the ligand, or by using a single component, "ready-to-use" metal–ligand (M–L) system which is prepared in an extra step and isolated before use (selected examples are depicted in Fig. 37.39) [143, 144].

While there are cases where only one of the two methods works, very often both approaches give a similar catalyst performance, and consequently the de-

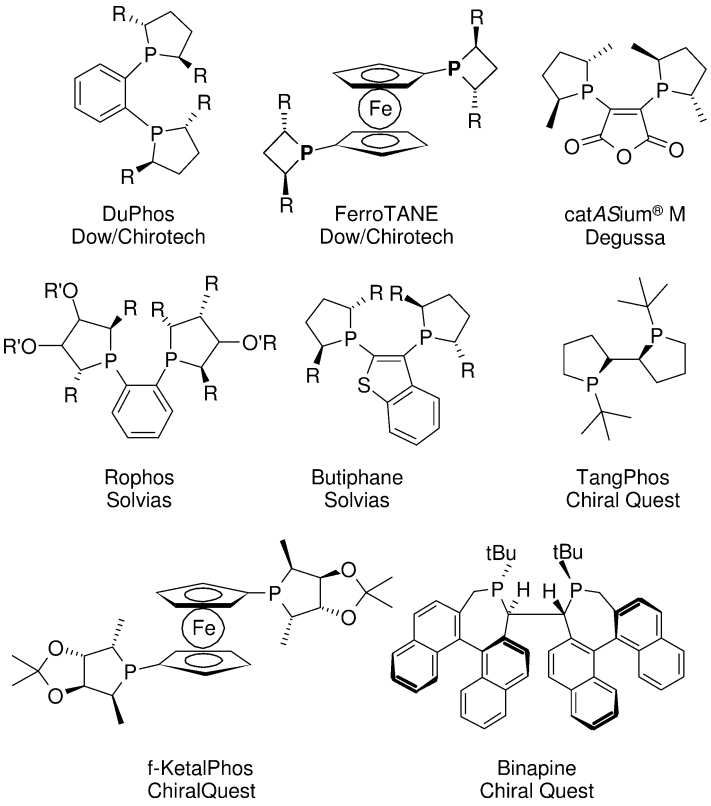


Fig. 37.37 Phospholane-type ligands and analogues.

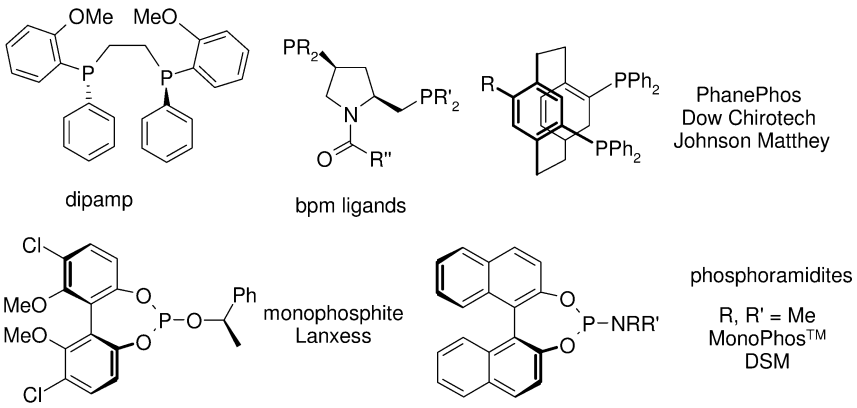
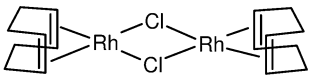
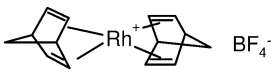


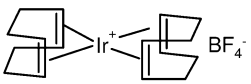
Fig. 37.38 Miscellaneous ligands.



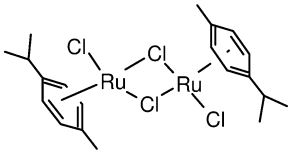
[Rh(cod)Cl]$_2$
bis-chloro-cyclooctadienerhodium(I)



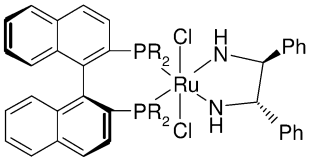
[Rh(nbd)$_2$]BF$_4$
bis-norbornadienerhodium(I)-tetrafluoroborat



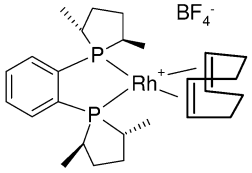
[Ir(cod)$_2$]BF$_4$
bis-cyclooctadieneiridium(I)-tetrafluoroborat



[Ru(p-cymene)Cl$_2$]$_2$
dichloro(p-cymene)ruthenium(II)-dimer



(*S*)-binapRuCl$_2$(*S,S*)-dpen



[(*R,R*)-Me-DuPhosRh(COD)]BF$_4$

Fig. 37.39 Important metal precursors and selected M-L-complexes.

velopment chemist has a choice. The *in-situ* method is very flexible and allows the use of standard metal precursor complexes which are offered by all major catalyst suppliers. Since several of the most effective ligands are air-sensitive, handling and ligand stability can be a problem. Single-component catalysts require an additional preparation step, but in many cases, the metal–phosphine complexes are more stable, less air-sensitive and therefore easier to handle than the free ligands. Furthermore, the reaction set-up is simplified because the initial step of premixing the precursor and the ligand is no longer required. As a drawback, the preparation of M–L complexes on a technical scale requires specific know-how for each individual complex and might therefore restrict the choice of the metal supplier.

As a general rule, most phospholanes are relatively air-sensitive and usually sold as rhodium–diene complexes. The ferrocene-based ligands, as well as phosphoramidites and phosphites, are relatively easy to handle, and the corresponding Rh, Ir and Ru complexes are usually prepared *in situ*. Even though most biaryl type ligands are quite insensitive, most of them are applied as preformed Ru complexes.

37.9.4
Intellectual Property Aspects

Not surprisingly, most of the versatile privileged ligands are patent-protected. If the licensing policy of the patent owner is very restrictive, or if the royalties are too high, many potential users will not use a patented technology [24]. On the other hand, a technology-providing company must finance its R&D efforts, and licensing fees are an important consideration in this context. In the chiral ligand business, two basic IP models are being used and most companies providing chiral ligands have adopted some variation thereof [132, 133, 145]:

- The classical royalty model, where the license fee is based on the added value of the new technology for the customer. As a rule, the royalties depend on the production volume and/or value of the chiral compound produced with the proprietary ligand, and are usually a percentage of product sales or a similar reference number. Also accepted are volume-independent royalties such as up-front or milestone payments.
- The "all-inclusive" model, where the price of the chiral ligand includes not only the manufacturing but also the IP license costs.

The classical royalty model has long been the norm, and is still well accepted for the manufacture of fine chemicals or commodities where the production costs are a very significant part of the final price of the product. However, our experience is that this model is not well accepted in the Life Science Industry and often presents a real hurdle for the application of proprietary technology for the production of new chemical entities. The "all-inclusive" model takes care of these concerns, and allows the customer to compare competing solutions on the basis of actual costs as well as of their potential for improvement. The same is true for volume-independent payments, and for both methods all process improvements totally benefit the customer's bottom line and are not reduced by increasing royalty fees.

37.10
Conclusions and Future Developments

Is homogeneous asymmetric hydrogenation a mature manufacturing technology? The answer is clearly "NOT YET" – with, perhaps, the exception of a few privileged substrate types. Our definition of a mature manufacturing technology can be summarized as follows:

- Well-defined and widely known scope and limitations (selectivity, activity, productivity, functional group tolerance).
- Many existing technical applications; required equipment widely available.
- Routinely considered in route design during process R&D.

- Relevant catalysts and auxiliaries are commercially available (including well-defined handling of IP issues), both in large numbers for screening as well as in technical quantities for production.

The results summarized in the preceding sections show, even for asymmetric hydrogenation, the most advanced catalytic methodology, that some of these points must be answered by "not quite" or "not yet satisfactory". However, we have the impression that during the past few years technical progress has accelerated, with one of the most significant signs of this development being the growing number of companies active in this exciting area of chemical technology. The visibility of enantioselective hydrogenation as a superb manufacturing tool for chiral intermediates and active products will certainly be enhanced not only by these companies scientific/technical publications but also by their considerable marketing efforts.

Since the first production processes were implemented by Monsanto and Sumitomo in the early 1970s, the number of production processes has grown rather slowly and comprises today (only) about 15 to 20 entries. Of these, 11 are medium to large scale, while all of the others are applied on a scale of 1 t y^{-1} or less, and several of them are no longer in operation. On the positive side, many more processes developed to the pilot or bench scale are, in principle, ready for technical application.

There are several reasons for this rather slow progress. Perhaps the most important reason is the fact that many development chemists are not familiar with the progress made in enantioselective catalysis. In many cases, catalytic methods would be competitive or even superior to classical methods, but they are not considered during synthesis planning. Because it takes more time (and money!) to identify and develop a suitable catalyst, the very tight time schedule and the very high attrition rate for new chemical entities in the pharmaceutical industry also is an obstacle. Another reason is the unfortunate fact that many reports on catalytic chemistry deal only with monofunctional model substrates, and often do not provide information on TON and TOF values. And last but not least, with the exception of the monodentate ligands based on binol and analogues thereof, many of the chiral ligands are not trivial to prepare. Furthermore, several very effective ligands have not been readily available in large quantities.

We are convinced that in the near future the industrial application of enantioselective hydrogenation technology will accelerate further, and there are several points to strengthen this view. There is the usual time lag for any new technology to be used in actual production – we think (or hope!) that we are at present on the flat part of the classical S-shaped curve. As the compilation in Section 37.9.1 shows, an increasing number of medium- and small-sized companies now have expertise in developing catalytic syntheses and offer their services to those companies which cannot – or do not want to – develop such processes in-house. In addition, several companies now offer chiral ligands or catalysts in the quantities required for large-scale processes.

On the chemical side, there is no doubt that new and more selective and active catalysts will be developed for ever-more types of transformations. Hopefully, some

of these will belong to the small elite group of privileged catalysts, able to tolerate significant structural variations without loss in catalyst performance. In addition, high-throughput experimentation will in many cases allow more tests to be carried out, thereby shortening the time needed to identify the correct catalyst.

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Abbreviations

de	diastereomeric excess
ee	enantiomeric excess
HTS	high-throughput system
NCE	new chemical entity
r.t.	room temperature
SCR	substrate : catalyst ratio
TOF	turnover frequency
TON	turnover number
TPPTS	sulfonated triphenylphosphine

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