

Cinchona-Modified Platinum Catalysts: From Ligand Acceleration to Technical Processes

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Received April 11, 2007

ABSTRACT

This Account records work carried out in our laboratories during the last 2 decades in the field of enantioselective heterogeneous hydrogenation. Of particular interest was Orito's catalytic system, platinum catalysts modified with cinchona alkaloids for the hydrogenation of activated ketones. Described are the development of the optimal platinum catalyst and modifier and the expansion of the scope of the catalyst. Kinetic studies aimed at understanding the mode of action of the catalyst revealed that the cinchona modifier not only renders the catalyst enantioselective but strongly accelerates the hydrogenation. This was the first case of ligand acceleration with a heterogeneous catalytic system. Finally, a number of industrial processes are summarized with the enantioselective hydrogenation of various α -keto esters as a key step.

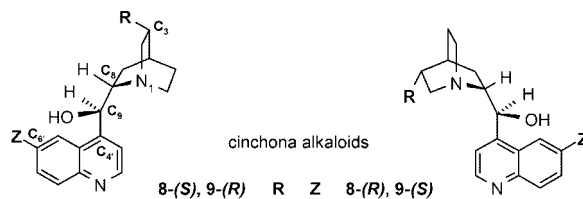
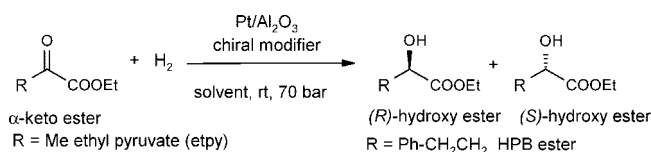
Introduction

Heterogeneous hydrogenation catalysis at Solvias¹ has its roots in the "Hydrierlabor" of Geigy, founded in the 1940s to support research chemists. This was a specialized laboratory equipped first with simple glass reactors and later also with steel autoclaves to carry out hydrogenations on a preparative scale. Over the years, a large know how for the hydrogenation of all kinds of substrates was accumulated, and at the moment, around 33 000 procedures are documented. In the 1970s, environmental protection legislature led to the gradual replacement of many classical stoichiometric reduction processes, such as the Béchamp reduction of nitro arenes by catalytic hydrogenation. The growing experience with technical hydrogenations and the availability of suitable commercial

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Martin Studer received his Ph.D. degree in 1988 under the supervision of T. Kaden from the University of Basel. Between 1988 and 1990, he held postdoctoral positions at the University Hospital in Basel (H. Mäcke) and the University of California, Davis (C. F. Meares). He started his industrial career at Ciba-Geigy (1991–1996) in the catalysis group, first in development and later in research. This continued at Novartis (1996–1999) and at Solvias, where was head of catalysis research until 2003. Presently, he is head of the environmental laboratories of the F. Hoffmann–La Roche Basel site.

Scheme 1



cinchonidine (Cd)	Vin	H	(Cn)	cinchonine
10,11-dihydrocinchonidine (HCd)	Et	H	(HCn)	10,11-dihydrocinchonine
quinine (Qn)	Vin	OMe	(Qd)	quinidine
10,11-dihydroquinine (HQn)	Et	OMe	(HQd)	10,11-dihydroquinidine

hydrogenation catalysts lowered true and perceived barriers facing the application of catalytic technologies in the company (then Ciba-Geigy, after the merger of Ciba and Geigy).

In the early 1980s, it became clear that racemic pharmaceuticals and agrochemicals would often be unacceptable to regulatory bodies and that enantioselective synthesis would become more and more important. With our background in heterogeneous hydrogenation, we noticed with interest the results on hydrogenation catalysts modified with chiral auxiliaries reported by several Japanese groups. Of particular significance to us were the tartrate-modified nickel catalysts² and the amazing results described by Orito³ for the enantioselective hydrogenation of α -keto esters using Pt catalysts modified with cinchona alkaloids (Scheme 1). Both catalytic systems achieved enantioselectivities of almost 90%, at the time very encouraging values, and we decided to start a small research program in this area. While we also tried to reproduce and improve on the modified nickel system, we quickly focused on the Pt–cinchona catalysts for two reasons: First, the catalysts could be modified *in situ*, i.e., did not require a difficult catalyst preparation as was the case for the Ni catalysts. Secondly, a few months after the start of the program, our colleagues of pharma development asked our help to find an enantioselective catalyst to make methyl (*R*)-2-hydroxy-4-phenyl butyrate (HPB ester, Scheme 1). In this Account, we will describe our efforts to adapt the Orito catalyst to industrial application as well as our attempts to unravel its mode of action. Pertinent reviews describing various aspects of the enantioselective hydrogenation of ketones have recently been published by various authors.⁴

Finding Suitable Catalysts

When we started our investigations and tried to reproduce some of Orito's results, we noticed immediately that this

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might become more cumbersome than anticipated. We were of course familiar with the problem that heterogeneous catalysts can not be characterized on a molecular level and that reproducibility is often an issue for catalytic processes. For this reason, we have learned to rely on the expertise and quality control of the major suppliers of hydrogenation catalysts. In this case, two facts made the situation more difficult. First, most of Orito's publications were in Japanese; therefore, it took some time to understand them, and secondly, the catalysts he used were neither available in Europe nor well-characterized. In this situation, we decided to turn to a catalyst expert and started a joint project with Alfons Baiker (ETH Zürich). Under the guidance of Daniel Monti (a former Baiker student), Jürg Wehrli⁵ prepared and characterized around 100 different Pt/alumina catalysts and tested them for the hydrogenation of ethyl pyruvate (Scheme 1). The results can be summarized as follows:⁶ (i) We could reproduce and in some cases surpass the results described by Orito achieving ee values up to 91%. (ii) The platinum dispersion and the method of catalyst preparation had a decisive influence on the catalytic performance. To get high enantioselectivities, the platinum dispersion should be lower than 0.2–0.3. There also were some indications that flat surfaces are favorable. (iii) Two commercial 5% Pt/Al₂O₃ catalysts showed superior performance: E 4759 from Engelhard and JMC 94 from Johnson Matthey. While both catalysts have dispersions around 0.2–0.3, E 4759 has rather small pores and a low pore volume, while JMC 94 is a wide-pore catalyst with a large pore volume. E 4759 from Engelhard has emerged as “standard” catalysts for many groups working with the Pt–cinchona system and was used in process development of the HPB ester (see below).

Monti's own investigations also confirmed that a reductive pretreatment in flowing hydrogen at 400 °C just before catalyst use significantly increases enantioselectivity and the reaction rate.⁷ While this was not much of a problem on a small scale, it complicated process applications and, many years later, an alternative catalyst, catASium F214, which does not need a pretreatment for optimal performance, was developed in collaboration with Degussa.⁸ The reason for the better performance of the catASium F214 catalyst was attributed to a lower reducible residue level and a narrower Pt crystal size distribution.

As summarized in a recent review,^{4a} several groups tried to improve catalyst performance by using different supports or catalyst pretreatments but with limited success. In many cases, measures that had a positive effect did not work under slightly different conditions or were not reproducible by other groups. Special mention is due to colloidal catalysts, which are of interest for two reasons: First, support effects can be eliminated, and secondly, there is hope that the morphology (size and shape) of the metal particles can be controlled better than for classical supported catalysts. Our own attempts confirmed that colloids behave in many respects similar to supported Pt catalysts, but because of our inexperience, we failed to get reproducible results.⁹ Other groups were more suc-

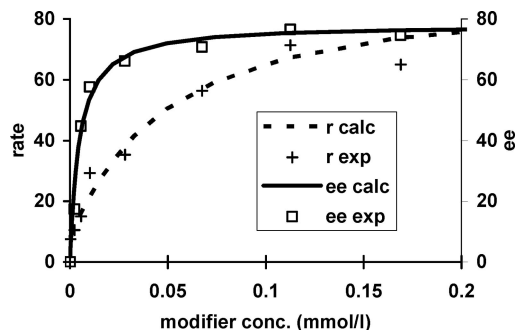


FIGURE 1. Hydrogenation of ethyl pyruvate. Rate and ee versus the modifier concentration (Pt/Al₂O₃, dihydrocinchonidine, 20 bar in EtOH).

cessful and, especially the work by Liu and co-workers,¹⁰ showed that clusters with diameters as low as 1 nm can give very high enantioselectivities. Indeed, a Pt colloid stabilized with polyvinyl pyrrolidone and modified with cinchonidine hydrogenated methyl pyruvate with up to 98% enantiomeric excess (ee). Even though colloids are not well-suited for technical applications, these results of course reopen the debate about the optimal size of the Pt crystallites.

Kinetic Studies and the Ligand Acceleration Hypothesis

As already mentioned, we had great difficulties in getting reproducible results, not only concerning enantioselectivity but also the reaction rates (easily measured via hydrogen uptake) varied more than usual. Nevertheless, we had the impression that a fast reaction often indicated good enantioselectivity. This was a bit surprising, because it is quite common that a modified heterogeneous catalyst is less active; i.e., an increase in selectivity has to be “paid for” with a decrease in activity. For this reason, we decided to have a closer look at the kinetics of the modified catalyst. We were lucky that at this point Marc Garland, a chemical engineer, joined our group as a postdoc and got interested in the problem. He started a systematic investigation of the effect of various reaction parameters, especially the modifier concentration. He very quickly found that already rather small modifier concentrations are effective and that ee *and* rate increased with an increasing cinchona concentration and that the two effects are somehow linked to each other as illustrated by Figure 1. However, the different shape of the ee and rate curves was puzzling. By an interesting coincidence, Sharpless and co-workers¹¹ reported similar behavior for the Os-catalyzed dihydroxylation of olefins with a cinchona alkaloid as a chiral ligand just at this time. They coined the term “ligand acceleration” for this phenomenon, where a nonchiral but catalytically active catalytic species can be rendered enantioselective *and* faster by reversible coordination of a chiral ligand. Marc very quickly developed the appropriate kinetic models for the Pt–cinchona system, assuming that the cinchona modifier reversibly adsorbs on the surface of the Pt catalyst, thereby creating highly active chiral sites.¹² In this model, the resulting ee

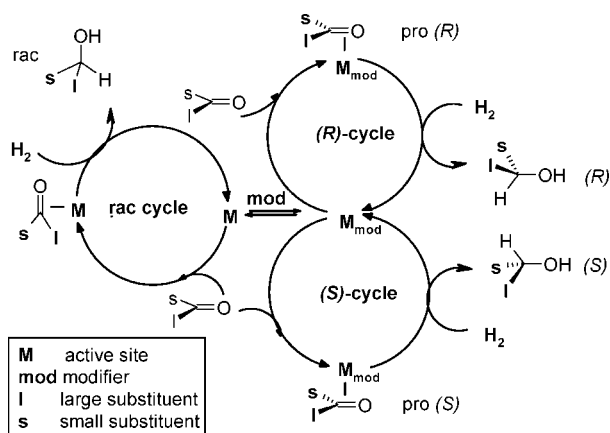


FIGURE 2. Schematic catalytic cycles for the hydrogenation of ketones on a partially modified catalyst (for clarity, the hydrogen activation and addition steps and the corresponding intermediates as discussed below are omitted).

will depend upon the ratio of modified/unmodified sites and the relative turnover frequencies of the three cycles schematically depicted in Figure 2. This simple kinetic model with a slow, racemic reaction on the unmodified catalyst and an about 10 times faster reaction with an ee around 80% on the modified sites gave a very good fit to the measured data in ethanol. In contrast to a homogeneous catalyst, neither the exact nature nor the number of active sites on a metal surface can be determined. This could be a single Pt atom or (more likely) ensembles of atoms. Furthermore, it is not sure that all catalytically active sites can be modified by the relative large cinchona molecule, and as a consequence, it is not possible to determine the *absolute* values of the rate and adsorption constants. Interestingly, many years later Jenkins et al.¹³ came to the conclusion that the rate acceleration might be due to the creation of additional active sites and not to enhanced activity because of the modification of existing sites.

In toluene and AcOH, the situation was even more complicated. In toluene, the maximum ee was reached at a lower HCd concentration than in EtOH, and both the ee and rate decreased when the modifier concentration was increased further. This dependence on the rate and ee can also be modeled assuming that, at a higher modifier concentration, a third type of active site with lower enantioselectivity and lower activity replaces M_{mod} , and an example of such a rate versus ee curve is depicted in Figure 3.¹⁴ Later, we found that this phenomenon is quite general and can be observed with a variety of different substrates, solvents, modifiers, and catalyst types.¹⁵

Encouraged by these results, we decided to carry out a full kinetic investigation for the hydrogenation of methyl pyruvate with and without dihydrocinchonidine.¹⁶ The effects of catalyst loading, modifier and substrate concentrations, hydrogen pressure, and temperature on the rate of the unmodified and rate and ee of the modified systems were studied. All results were compatible with a Langmuir–Hinshelwood (LH) description, where the basic catalytic cycle consists of a fast adsorption of ketone and

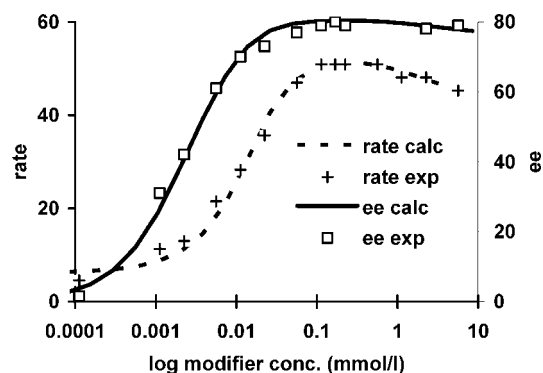


FIGURE 3. Hydrogenation of ethyl pyruvate. Rate and ee versus the modifier concentration ($\text{Pt}/\text{Al}_2\text{O}_3$, dihydrocinchonidine, 20 bar in toluene). Note that the log of the modifier concentration is used here.

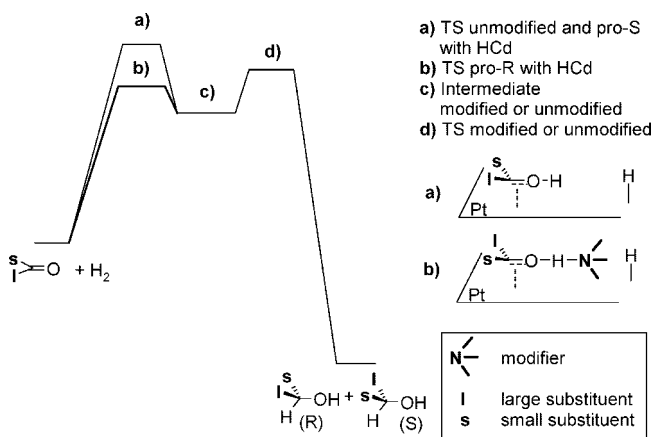


FIGURE 4. Schematic energy diagram for the hydrogenation of an α -keto ester with and without a cinchona modifier.

hydrogen on the Pt surface, the stepwise addition of the two adsorbed hydrogen atoms to the C=O bond with a half-hydrogenated intermediate, and finally, the fast desorption of the alcohol. Our results indicated that the observed rate acceleration can be explained by a shift of the rate-determining step for one of the two possible adsorbed forms of ethyl pyruvate as depicted schematically in Figure 4.

We can summarize our major conclusions from these investigations as follows: (i) We had observed the first case of ligand acceleration for a heterogeneous catalyst; i.e., the modified catalyst is not only enantioselective but also much more active than the unmodified one. However, there exists no correlation between the size of the acceleration and the enantioselectivity, and the groups of Bartók¹⁷ as well as of Murzin¹⁸ have shown that even negligible acceleration can lead to high ee values. (ii) The shape of the curves of ee and rate versus the modifier concentration show that the reversible adsorption of one modifier molecule forms a modified active site. Maximum ee and rate, i.e., complete modification, are reached at rather low modifier concentrations. This means that the product-determining interactions between the modifier and substrate for enantiodifferentiation must occur *on the surface* and not in solution. (iii) The optimal modifier concentration depends upon the type of catalyst, solvent,

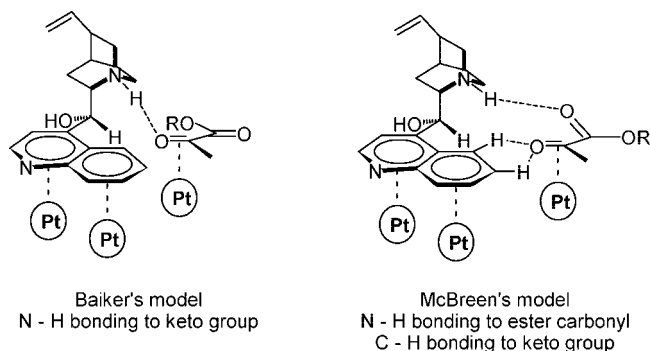


FIGURE 5. Schematic presentation of the activated surface complex.

and modifier. At higher modifier concentrations, both ee and rate decrease. Recently, Kubota and Zaera¹⁹ have shown that this decrease correlates with a change from a flat to a tilted adsorption of the cinchona molecule. (iv) The kinetic results are in agreement with a classical two-step addition of the adsorbed hydrogen to the adsorbed C=O bond, where the addition of the first hydrogen is facilitated by the modifier.

A first qualitative model involving a cinchona modifier π -bound to the Pt surface via the quinoline ring and attractive interactions between the quinuclidine nitrogen and the adsorbed ketone was put forward after modified cinchona molecules were prepared and tested (see the next section).⁶ This basic model was able to explain many of the most important experimental facts. It was refined and supported by a variety of very elegant and sophisticated surface science, spectroscopic, as well as computational investigations, especially by the groups of Baiker,²⁰ Bartók,^{4d} and McBreen.²¹ Nevertheless, the specific (attractive and repulsive) interactions between the adsorbed substrate and modifier, which lead to the observed stereo differentiation, is still under hot debate, and two competing but plausible models are depicted in Figure 5. It has to be pointed out that fundamentally different models have been put forward, such as the “shielding hypothesis” by Margitfalvi^{4a} or the formation of a zwitterionic adduct by Vayner et al.,²² which are also able to explain many of the experimentally observed effects.

The Quest for the Perfect Modifier

There is no doubt that the cinchona alkaloids selected by Orito are very effective modifiers for the Pt-catalyzed hydrogenation of α -keto esters. Nevertheless, there were a few drawbacks, and we had a lot of questions concerning their mode of action. As a consequence, we started a screening program to find alternative modifiers, and we synthetically altered the parent alkaloids depicted in Scheme 1. The screening for alternative modifiers failed miserably; even though we tested about 100 different chiral auxiliaries, we never found any meaningful enantioselectivity. The modification of the cinchona derivatives was carried out by Willi Lottenbach and was much more fruitful. After a detailed study of the hydrogenation of ethyl pyruvate with a variety of different cinchona derivatives, we concluded^{16,23} that three structural elements in the

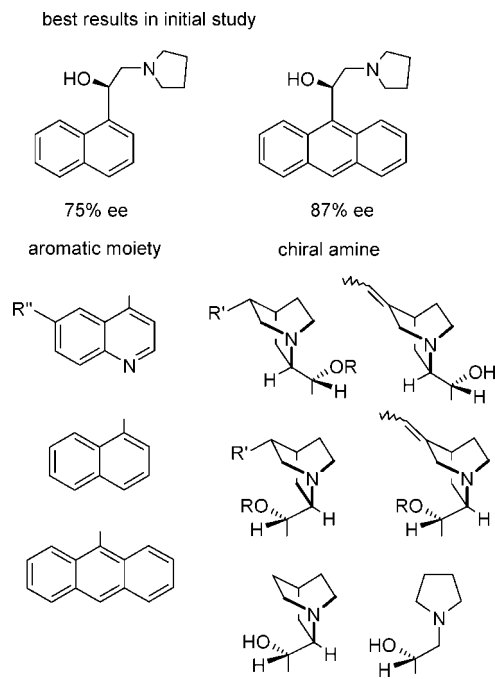


FIGURE 6. Structures of cinchona derivatives and mimics.

cinchona molecule were crucial: (i) an extended aromatic moiety, (ii) the substitution pattern of the quinuclidine (the absolute configuration at C₈ controls the sense of induction), and (iii) the substituents at C₉ (OH or MeO is optimal; larger groups reduce enantioselectivity and, in some cases, even lead to inversed induction).

The groups of Bartók^{4d} and Baiker²⁴ also investigated modified cinchona derivatives. While Bartók tested a series of derivatives with conformational constraints, Baiker concentrated on modifiers with large groups at C₉. While the general conclusions were confirmed, these studies give a much more detailed picture of the stereochemical requirements for good enantioselectivity. Interestingly, both modifications led to instances where the “wrong” product enantiomer was formed preferentially; i.e., the absolute configuration at C₈ no longer controlled the sense of induction. These effects are very sensitive to the nature of the solvent and were explained with different adsorption geometries.

A different approach to understand the importance of various structural elements was the synthesis of cinchona mimics. First studies by Pfaltz and Baiker indicated that good enantioselectivities can be reached with relatively simple amino alcohols having just one stereogenic center (for the best modifiers, see Figure 6).²⁵ Because synthetic modifiers would allow for the preparation of both product enantiomers with equal enantioselectivity, we undertook a joint research project with Andreas Pfaltz (University of Basel). In an in-depth study, Christian Exner²⁶ synthesized various cinchona analogues with a systematic variation of the aromatic part and the chiral amino group as depicted in Figure 6 and carried out tests with a set of different substrates.

From his data, the following conclusions were drawn:²⁷ (i) It was confirmed that the presence of an

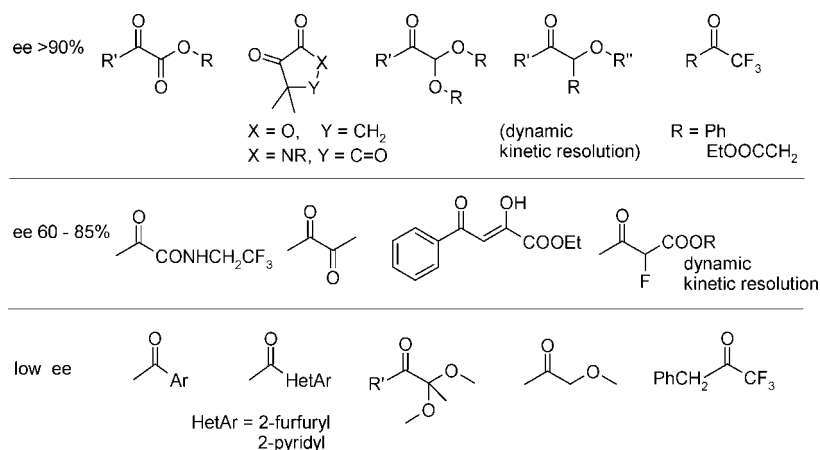


FIGURE 7. Structures of “good”, “medium”, and “bad” ketone substrates for cinchona-modified Pt catalysts.

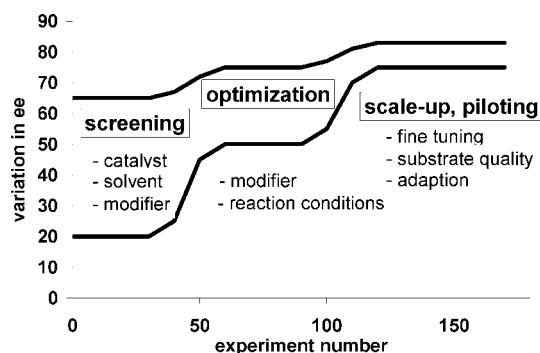
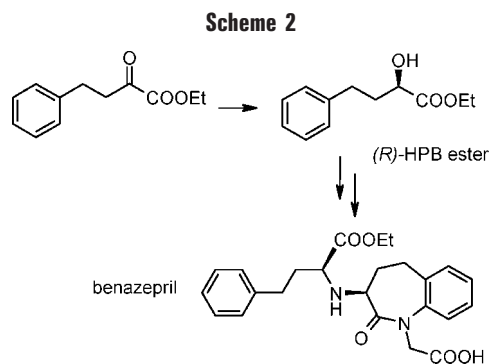


FIGURE 8. Different phases of HPB ester process development.

Expanding the Substrate Scope

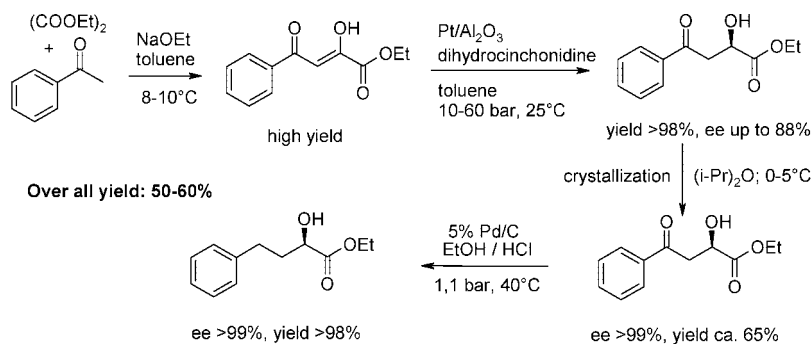
extended aromatic system with a chiral group carrying an amino function is necessary but not a sufficient prerequisite for high enantioselectivity. (ii) For every substrate, the highest ee values were obtained with quinuclidine-derived modifiers in combination with naphthalene or quinoline rings. (iii) The substituent R' at the quinuclidine system has a more important influence than previously thought and can significantly affect the ee compared to the unsubstituted derivatives (positive and negative effects). (iv) Both bi- and tricyclic aromatic system rings can lead to high enantioselectivity. The sterically more demanding and more rigid quinuclidine, quinoline, and to some lesser extent naphthalene were a better match, while the smaller pyrrolidinylmethyl group anthracene was superior. (v) HCd and Hcn derivatives usually gave higher ee values than the corresponding Qn and Qd, which carry a methoxy substituent at the quinoline system. (vi) Methylation of the OH group often had a positive effect for hydrogenations in AcOH but not in toluene.

Some of the new modifier–substrate combinations give significantly higher enantioselectivity than previously reported, especially for the (S) products. These results will be a useful basis for further optimization of the modifier structure as well as the development of modifiers for other substrates. Indeed, Baiker et al.²⁸ recently reported that a naphthylethylamine derivative gave higher ee values for the hydrogenation of fluorinated ketones than cinchona derivatives.

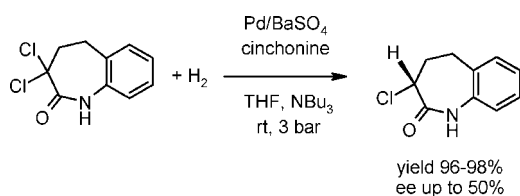
It is well-recognized that most enantioselective catalysts are rather substrate-specific. Once we had found an effective catalyst for the hydrogenation of α -keto esters, we wanted to find other suitable substrates with broad applicability. Because α -keto esters tend toward side reactions, Hans-Peter Jalett²⁹ prepared and reduced a number of the more stable α -keto acids. However, even this small variation led to decreased enantioselectivities (usually below 80% ee), despite an extensive optimization of the reaction parameters. The corresponding Na or K salts even gave racemic products! On the other hand, satisfactory enantio- and very high chemoselectivities were achieved for the hydrogenation of α,γ -diketo esters³⁰ (also see industrial applications below). As already described by Niwa et al.,³¹ α -keto lactones are also suitable substrates. This was confirmed by the Baiker group,³² who developed a process for the hydrogenation of keto pantolactone and expanded the substrate range to α -keto imides.

Because α -hydroxy acetals and ethers are valuable building blocks, we started to investigate the hydrogenation of the corresponding ketones. To our delight, enantioselectivities >90% were obtained for α -keto acetals³³ as well as α -keto ethers,³⁴ where dynamic kinetic resolution yielded high ee and diastereomeric excess (de) values with racemic starting materials. Independently, Bartók³⁵ reported similar results for α -keto acetals. As observed for α -keto esters, bulky substituents on both parts of the molecule had a negative effect on the rate and ee in the

Scheme 3



Scheme 4



case of α -keto acetals. The hydrogenation of 1,2-butane-dione³⁶ to the hydroxy ketone occurred with significantly lower enantioselectivities, which increased during the reaction because the minor enantiomer reacted significantly faster to the corresponding diol (kinetic resolution). Independently, Wells³⁷ and Salmi and co-workers³⁸ reported similar results for α -diketones. Baiker³⁹ and later also Bartók⁴⁰ showed that α -fluorination, especially the trifluoromethyl group, has an activating effect comparable to an ester group. Indeed, the hydrogenation of trifluoro acetoacetate as well as of various trifluoro acetophenones was reported with up to 93% ee.

Despite significant progress in the last years, the synthetically useful substrate scope of the cinchona-modified platinum catalysts is still relatively narrow (see Figure 7). As reviewed by Studer et al.,^{4a} various attempts were made to modify other metals with cinchona alkaloids and to extend the scope to the hydrogenation of C=C bonds. However, with few exceptions, enantioselectivities and often catalytic activities were too low to be of practical interest.

Technical Processes

As described in the Introduction, a few month after we started to investigate the Orito system, our colleagues of pharma development asked for our help to find an enantioselective catalyst to make methyl (*R*)-2-hydroxy-4-phenyl butyrate (HPB ester), a key intermediate for the synthesis of benazepril, an angiotensin-converting enzyme (ACE) inhibitor then under development (Scheme 2). Because at the time homogeneous hydrogenation as well as biocatalytic reductions were not established for α -keto acid derivatives, the results described by Orito looked very promising.

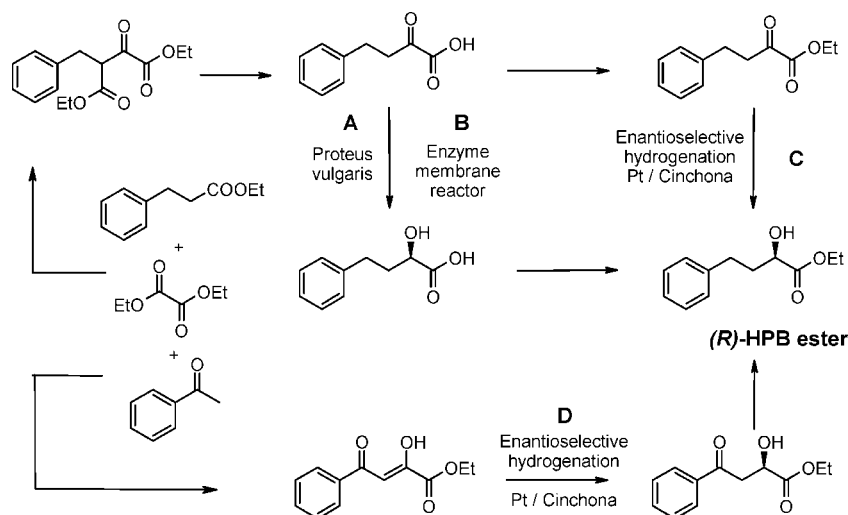
Because the reproduction of Orito's results turned out to be more difficult than expected, the development of a viable process for the HPB ester took more than a year, even though Hans-Peter Jalett, a very experienced chief

technician, took care of the experiments. Even before the age of high-throughput screening, the obvious strategy was first, to screen for the best catalyst, modifier, and solvent, secondly, to optimize relevant reaction parameters (*p*, *T*, concentrations, etc.), and finally, to scale up and solve relevant technical questions. Indeed, in the course of process development, Jalett carried out more than 200 hydrogenation reactions. The most important results of this development work can be summarized as follows: (i) Catalyst: 5% Pt/Al₂O₃ catalysts gave the best overall performance, and the E 4759 from Engelhard was the final choice. (ii) Modifier: About 20 modifiers were tested; Hcd (in toluene) and MeOHcd (in AcOH) gave the best results and were chosen for further development. (iii) Solvent: Jalett found that acetic acid was far superior to all classical solvents, allowing up to 92% ee for the HPB ester and 95% ee for ethyl pyruvate (then a new world record).⁴¹ For technical reasons, toluene was chosen as a solvent for the production process. (iv) Reaction conditions: Best results (full conversion after 3–5 h, high yield, 80% ee) were obtained at 70 bar and room temperature with 0.5% (w/w) 5% Pt/Al₂O₃ (pretreated in H₂ at 400 °C) and 0.03% (w/w) modifier. (v) Substrate quality: Enantioselective hydrogenation of α -keto esters proved to be exceptionally sensitive to the origin of the substrate.⁴²

After about 2 years, the production process was developed, patented,⁴³ and scaled up, and in 1987, a few hundred kilograms were successfully produced in a 500 L autoclave. The progress of the optimization can best be demonstrated by the variations in ee versus the experiment number in the different development phases (Figure 8). The effect of various measures can be seen that led to improved enantioselectivities and a stabile process. Despite this success, pharma production eventually decided to buy (*R*)-HPB ester from an external supplier.

A few years later, a new process for the (*R*)-HPB ester was developed in collaboration with Ciba SC Life Science Molecules. After assessing a variety of synthetic routes, we focused on the one depicted in Scheme 3: Claisen condensation of cheap acetophenone and diethyl oxalate, followed by chemo- and enantioselective hydrogenation of the resulting diketo ester and hydrogenolysis to the HPB ester.⁴⁴ Even though the 2,4-dioxo ester was a new substrate type, it took only a few months to develop, scale up, and implement the new process. Key steps in the new process are undoubtedly the hydrogenation of the 2,4-

Scheme 5



dioxo ester with excellent chemo- and satisfactory enantioselectivities and the successful enrichment to >99% ee via crystallization.

We also tried to develop an enantioselective process for the benzazepinone building block of benazepril by selective dehalogenation of the dichloro precursor depicted in Scheme 4. However, despite an extensive screening of various modifiers, catalysts, and bases, we never achieved more than 50% ee, and therefore, the project was stopped.⁴⁵

In parallel to our work, two biocatalytic routes were developed to the pilot stage by colleagues at Ciba-Geigy, namely, the enantioselective reduction of the corresponding α -keto acid with immobilized *Proteus vulgaris* (route A in Scheme 5) and with D-lactate dehydrogenase (LDH) in a membrane reactor (route B), respectively. It was therefore of interest to compare the four approaches. In a collaboration with Konrad Hungerbühler (ETH Zürich), we used the Environmental Assessment Tool for Organic Syntheses (EATOS) program to compare the mass consumption (kilogram input of raw materials for 1 kg of product) as well as other parameters.⁴⁶

As shown in Figure 9, the new route D has the lowest overall mass consumption, even though the ee and yield for the reduction step are the lowest. This is compensated by fewer steps, higher atom efficiency, and lower solvent consumption for synthesis and extraction.

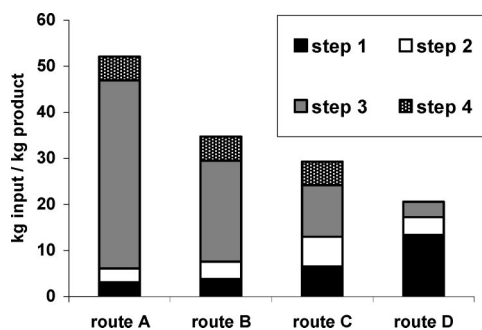
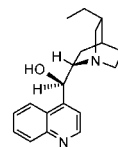
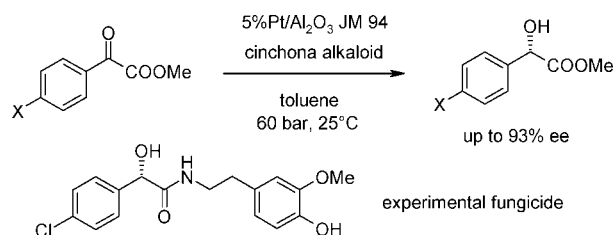
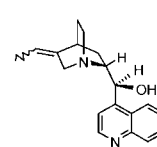


FIGURE 9. Pilot processes for (R)-HPB ester: mass consumption (without water) for routes A–D.

Scheme 6



10,11-dihydrocinchonidine (HCd)



iso-cinchonine (iso-Cn)

Finally, in a collaboration with Syngenta, a bench-scale process was developed for the enantioselective hydrogenation *p*-chlorophenylglyoxylic acid derivatives (Scheme 6).⁴⁷ A modified Pt catalyst achieved 93% ee for the (R)- and 86% ee for the (S)-methyl *p*-chloromandelate using HCd and iso-Cn as the modifier, respectively. For the HCd–Pt system, a scale-up from 100 mg to 15 g presented no problems, indicating that the Pt–cinchona system might be a viable alternative for the production of the (R) enantiomer.

Conclusions and Outlook

In the last 2 decades, significant progress has been made in the area of enantioselective hydrogenation using chiral modified heterogeneous catalysts. This is true with respect to understanding the mode of action of the catalytic systems as well as from a synthetic and industrial point of view. Obviously, our focus was more on synthetic applications, but to develop reproducible processes, we also benefited from kinetic studies. Our work has shown that selected modified catalysts are indeed industrially viable and that, in favorable cases, they can compete with homogeneous as well as biocatalytic alternatives. However, the scope of this technology is still restricted to the

hydrogenation of ketones activated in the α or β position, and furthermore, the mechanistic understanding of even the best characterized catalysts is still relatively poor compared to homogeneous catalysts. For this reason, we do not expect a fast progress or a breakthrough in the near future.

We are indebted to all of our colleagues mentioned in the references but in particular to Marc Garland, Hans-Peter Jalett, Willi Lottenbach, and Daniel Monti for their invaluable experimental and intellectual contributions and to Andreas Pfaltz for an outstanding collaboration.

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AR700088F