Enantioselective hydrogenation of α-ketoesters: comparison of homogeneous and heterogeneous catalysts

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Abstract

A case study concerning the development of enantioselective hydrogenation processes for aliphatic α-ketoesters, particularly ethyl 2-oxo-4-phenylbutyrate (1) and ethyl pyruvate (2), using homogeneous Rh–diphosphine and heterogeneous Pt/Al$_2$O$_3$–cinchona catalysts is presented. Important parameters to obtain high enantioselectivities using the *homogeneous system* were shown to be the ligand, the nature of the Rh complex and the solvent. Unfortunately, the best optical yields (ee 96%) were achieved only at a low substrate/catalyst ratio of s/c = 50. For the *heterogeneous system*, the structure and concentration of the modifier, the nature and pretreatment of the Pt/Al$_2$O$_3$ catalyst, the type of solvent and the hydrogen pressure were decisive for high enantioselectivity (ee's up to 95%). A major problem was the effect of the substrate quality on rate and optical yield. A comparison of catalyst costs showed a significant advantage for the heterogeneous catalyst, mainly due to its very high activity and catalyst productivity.

Keywords: Enantioselectivity; Hydrogenation; α-Ketoesters; (R)-α-Hydroxyesters; Rhodium diphosphine complexes; Cinchona modified catalysts; Platinum; Solvent effects; Process development

1. Introduction and background

The industrial application of enantioselective catalysts is still rather limited [1]. There are several reasons for this situation. Up to a few years ago, only very few catalytic systems were able to give the high optical yields necessary for a technical application. Today, this is no longer the case since hundreds of examples are now in the literature with optical yields > 95%. Still, there remain many obstacles before a chiral catalyst is applied on a technical level. Activity, productivity, handling, separation and cost are probably the most important additional factors that decide whether a

enantioselective catalyst is feasible for the commercial manufacture of fine chemicals.

Optically pure α-hydroxyacid derivatives are of interest as intermediates for the synthesis of a wide variety of products such as amino acids, angiotensin converting enzyme (ACE) inhibitors [2,3] or coenzyme A [4]. An elegant method for their synthesis is the enantioselective hydrogenation of the corresponding α-ketoacid derivative. In the last few years, considerable work was carried out at Ciba-Geigy in order to develop an enantioselective production method for ethyl (R)-2-hydroxy-4-phenylbutyrate, an important intermediate for the ACE inhibitor *Benazepril* (Fig. 1). Our results for the enantioselective reduction of 2-oxo-4-phenylbutyric acid by biocatalytic methods were already summarized ear-
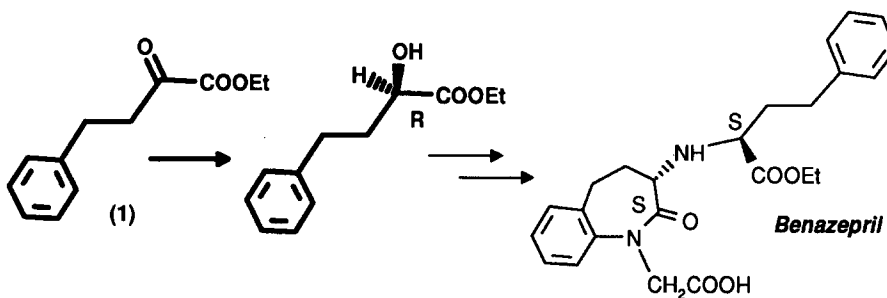
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Fig. 1. Key step in the synthesis of the ACE inhibitor *Benazepril*.

lier [5]. The present article describes the strategies and results for the development of the enantioselective hydrogenation of ethyl 2-oxo-4-phenylbutyrate (**1**) using homogeneous Rh–diphosphines complexes and cinchona modified heterogeneous Pt catalysts.

2. Strategies for process development

The choice of a development strategy that promises the best answer in the shortest time is the first decision at the start of a process development. This strategy will depend on a number of considerations: The goal of the development; the know how of the investigators; the time frame; the available manpower and equipment; and so on. As a general rule, the *parameters of the catalytic system* will be chosen first (metal, support or ligands, chiral auxiliary, solvent and maybe some additive). Naturally, the first choice will rely on experience and on analogies in the literature. Depending on the results of this preliminary phase, one then has to decide whether to find better catalysts by screening alternative structures or by optimizing the most promising catalytic system by small changes of the catalyst and the chiral auxiliary. When a definitive choice has been made, the *reaction conditions* (H_2 pressure, temperature and concentrations and ratios of reactants, catalyst and auxiliary) are optimized. If the minimal requirements are not reached, one has to go back to finding a more suitable catalyst/auxiliary. Then, the optimization has to be repeated. This means that very often, the development of a technical process does not proceed linearly.

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. Usually, the catalyst selectivity (combined of course with an acceptable activity) is the first criterion – just as in academic research. But when a reasonable selectivity has been obtained, other criteria will become important: catalyst activity, productivity and stability, catalyst separation (and maybe recycling). Then, questions like e.g., the effect of substrate quality and last but not least the cost of the chiral catalyst and other materials have to be addressed. The final process is usually a compromise since quite often not all of these requirements can be fulfilled maximally.

In the following sections we will discuss the approaches taken for the selection of the different components of both the homogeneous and the heterogeneous catalytic systems. The results obtained for the homogeneous and heterogeneous catalysts are compared and discussed.

3. Homogeneous system

3.1. Preliminary experiments

When we started our investigations ca. 1984, the best results for α-ketoesters were reported by Ojima [6] for the Rh–*bppm*–Cl catalyst. However, first experiments with ethyl 2-oxo-4-phenylbutyrate (**1**) gave optical yields (ee 50–65%) well below the published results for pyruvates (ee 76%). In order to get better enantioselectivities we could either vary and optimize the structure of

the *bppm* ligand or we could try to find another class of ligands. Because the synthesis of diphosphines requires special know how that we did not have at that time, we decided to screen the Rh complexes of commercially available diphosphines. Unfortunately, only about 10 different ones were then available to us and all of the tested ligands gave lower optical yields than *bppm* and the project was abandoned.

3.2. Random screening

When we re-started our work a few years later, we could choose from among many more commercially available diphosphines. Therefore, we decided to carry out a new screening program to find a more selective catalyst. All parameters that in our experience have an influence on the catalyst performance were varied: Rh complexes of 7 different classes of *diphosphines* (see Table 1), three *solvents* (methanol, toluene and a 1:1 mixture of methanol/toluene) and 4 different *reaction conditions* (25 and 50°C; 20 and 80 bar H_2 pressure). In order to get some insight into the effect of the substrate structure, we tested not only ethyl 2-oxo-4-phenylbutyrate (1) and ethyl pyruvate (2) but also ethyl benzoylformate and 2-oxo-4-phenylbutyric acid. Testing all possible 356 combinations was not feasible. Therefore, we performed about 30 experiments using *random combinations* of the variables under standard conditions. A few additional experiments were carried out in order to confirm some of the observed results. The optical yields obtained for substrates (1) and (2) are reported in Table 1 (for the complete results see [7]).

Effect of the ligand on enantioselectivity

Most of the enantioselectivities obtained in this screening program were in line with results reported for other Rh catalysts in the literature [8,9]. However, the high enantioselectivity of [Rh(*nbd*)Cl]$_2$/(2S; 3S)-*norphos* was unexpected because 1,2-diphosphines (5-membered metallocycle) were reported to give low rates and ee's [9]. For substrate (1) 91% ee (50°C; meth-

anol) and for (2) 89% ee (RT; MeOH/tol 1:1) were obtained. Also remarkable was the high substrate specificity: only *aliphatic* α-ketoesters were hydrogenated with good optical yields. Those observed for aromatic α-ketoesters and for α-ketoacids were low (not shown).

3.3. Systematic variations

Next, the effects of solvent, additives, s/c ratio, pressure and temperature for the [Rh(*nbd*)Cl]$_2$/ *norphos* catalyst in the hydrogenation of (1) was studied in more detail. The goal of these investigations was not only to improve the enantioselectivity but also to get a first indication of how the *activity* was affected. Important results are summarized in Table 2.

Effect of the solvent on enantioselectivity and activity

For the Rh–*norphos* catalyst, the solvent had a rather unexpected and dramatic effect on both criteria. For substrate (1) we observed a large decrease in conversion and even a reversal of the absolute configuration when changing from toluene to methanol! The use of the cationic Rh/*norphos*–BF$_4$ catalyst in methanol caused a significant drop in both the activity and the enantioselectivity. While alcohols had a positive effect on both rate and ee, water or small amounts of an amine were detrimental. These results are quite different from those described for the hydrogenation of ketones where neutral Rh catalysts in aprotic solvents usually give the highest optical yields [8,10,11]. For acetophenone in methanol, neutral and cationic Rh catalysts gave comparable results [11].

The effect of other reaction parameters

The effect of other reaction parameters on the *enantioselectivity* of the hydrogenation of (1) by Rh–*norphos* can be summarized as follows: As expected, an increase in *temperature* led to higher conversions but lowered the optical yields. The *hydrogen pressure* did not significantly affect the enantioselectivity in the hydrogenation of (2)

Table 1
Effect of ligand structure and solvent on the optical yield of ethyl 2-hydroxy-4-phenylbutyrate (1) and ethyl lactate (2). Catalyst [Rh(*nbd*)Cl]$_2$/PP (*nbd* = norbornadiene). Substrate/catalyst ratio s/c = 50. Conditions: a: 25°C, 20 bar, b: 50°C, 20 bar, c: 25°C, 80 bar, d: 50°C, 80 bar, e: 25°C, 100 bar, f: [RuCl$_2$(S)-*binap*], g: s/c = 800.

		(2S; 3S)-*norphos*	(4S; 5S)-*diop*	(S)-*binap*	(2S; 4S)-*bppm*	(R)-(S)-*bppfoh*	(2S; 4S)-*bdpp*	(R)-*prophos*
(1)	Tol	b: 91 (S)			a: 68 (R)		d: 18 (R)	
(1)	M/T	d,g: 13 (S)		b: 21 (R)				
(1)	MeOH		c: 29 (S)				c: 28 (S)	c: 7 (R)
(2)	Tol	a: 89 (S)	a: 24 (S)		a: 71 (R)	a: 5 (S)		
(2)	M/T							
(2)	MeOH	d,g: 59 (S)		d,f: 43 (S)		b: 11 (S)		

Table 2

Effect of solvent, additives, temperature and the s/c ratio on conversion and optical yield of ethyl 2-hydroxy-4-phenylbutyrate. Conditions: 4 g (1), 20 ml solvent, 30°C, 100 bar. Catalyst $[Rh(nbd)Cl]_2/(2S; 3S)$-norphos. Conditions: (a) 60°C, (b) 90°C, (c) s/c = 50, 25°C, (d) $[Rh(nbd)_2]^+ BF_4^-/(2S; 3S)$-norphos

	Reaction time (h)		Conversion (%)		ee (%), S-configuration	
	s/c = 800	s/c = 200	s/c = 800	s/c = 200	s/c = 800	s/c = 200
Toluene	24	21	17	23	12 (R)	8 (R)
MeOH/toluene 1:1	21		25		73	
EtOH	21	18	27	98	82	87
EtOH (a)	21		92		70	
EtOH (b)	22		99		57	
MeOH	21	20	35	98	86	91
MeOH (d)	21		10		11	
MeOH		3 (c)		95 (c)		96 (c)
MeOH/5% H$_2$O	19		22		69	
MeOH/1 eq NEt$_3$ (a)	22		99		5	

(results not shown), consistent with the results reported by Mortreux et al. for more basic ligands [12]. Unfortunately, the *s/c ratio* (or the catalyst concentration) had an unusually strong effect on the enantioselectivity of the Rh–*norphos* catalyst. The best optical yields (ee 96%, MeOH, 25°C) were obtained with s/c = 50 but decreased to 86% with s/c = 800. Only a few studies have dealt with the effect of the s/c ratio on the optical yields [12,13] but usually the effect is not very strong. Also the *activity* of the neutral $[Rh(nbd)Cl]_2/(2S; 3S)$-*norphos* catalyst in alcoholic solvents was not quite satisfactory: at s/c ratios > 200 high pressures (> 50 bar H$_2$) and high temperatures were necessary in order to get a reasonable reaction time.

3.4. Conclusions for the homogeneous system

The investigation was stopped at this point. The main reason for this decision was that the s/c ratio of the Rh/*norphos* catalysts could not be increased without detrimental effect on the enantioselectivity making this catalytic system too expensive for commercial application (see below). On the positive side, the complex generated in situ from $[Rh(nbd)Cl]_2$ and *norphos* is among the most selective catalysts for the hydrogenation of aliphatic α-ketoesters [14]. Since both enantiomers of *norphos* are available, this represents an efficient small scale synthesis for aliphatic (R)- and (S)-α-hydroxyesters.

4. Heterogeneous system

The situation for chiral heterogeneous catalysts was very different when we started in 1983. Only two catalytic systems with useful enantioselectivities were described in the literature: Pt-catalysts, modified with cinchona alkaloids for α-ketoesters [15] and Raney nickel, modified with tartaric acid/NaBr for β-ketoesters [16]. In the case of the Pt system, only two modifiers were described to give the desired (R)-α-hydroxyesters preferentially: cinchonidine and quinine, fortunately both are available commercially.

We learnt very early that the nature of the supported Pt catalyst was a decisive factor in reproducing the good results reported by Orito et al. [15]. In contrast to well defined soluble metal complexes, a heterogeneous hydrogenation catalyst cannot be characterized on a molecular level. Rather, its properties have to be controlled by the type of support and the details of its preparation. Indeed, it took us years to find commercially available catalysts, the proper activating protocols and reaction conditions that enabled us to hydrogenate ethyl pyruvate with the same or better optical yields as Orito. Some of this work using ethyl
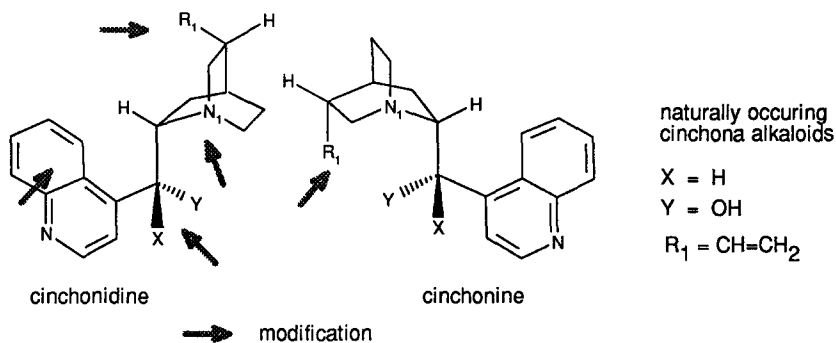
Fig. 2. Relative and absolute configuration of the modified cinchona alkaloid derivatives.

pyruvate as model substrate has been summarized [17].

In the following paragraphs, certain aspects of the development of a heterogeneous technical process will briefly be discussed. Proprietary interests preclude a more detailed discussion of the results obtained for ethyl (R)-2-hydroxy-4-phenylbutyrate (1). Instead, important effects are described for ethyl pyruvate (2) as substrate that shows a similar behavior.

4.1. Effect of individual elements of the catalytic system

Pt catalysts

Several investigations [15,18,19] showed that only Pt catalysts (on supports such as alumina, carbon or silica) gave good enantioselectivities for the hydrogenation of α-ketoesters. Rh and Ir [20] gave moderate ee's, Pd, Ru and Ni were not effective.

In our experience 5% Pt/Al$_2$O$_3$ catalysts showed the best overall performance. Since many different types are available commercially, we decided to identify important catalyst parameters for the enantioselectivity of the Pt–*cinchona* system. These investigations resulted in the following conclusions [21]: The *platinum dispersion* should be <0.2 in order to obtain high optical yields. The *texture of the support* generally had a limited influence but aluminas with relatively low S_{BET}, high pore volume and rather large pores were preferred. The *method of catalyst preparation* (impregnation, reduction) had a strong influence on both activity and enantioselectivity.

We had already chosen the commercial catalyst E 4759 (Engelhard) as our standard reference catalyst (as a matter of fact, we still use this type for our ongoing mechanistic investigations). From the results summarized above, a second type was developed in collaboration with Johnson Matthey: the type 5 R 94. A comparison showed that 5 R 94 had about the same dispersion as the E 4759 but a larger pore volume and larger average pore diameters. 5 R 94 showed a consistently higher enantioselectivity and turnover frequency for the hydrogenation of both ethyl pyruvate (2) and ethyl 2-oxo-4-phenylbutyrate (1) [22]. This type was finally the catalyst of choice for a technical hydrogenation process.

Influence of the modifier structure

We tried to find other types of modifiers such as different alkaloids [23] and simple chiral amines [24] but the results were so disappointing that we turned to modifying the cinchona molecules (see Fig. 2).

The following results were important [22]: If N$_1$ was alkylated, optical induction was lost completely. Changes of X and Y (H, OH, Cl, Br, OAc) resulted in most cases in lower optical yields, but modifiers derived from cinchonidine always gave excess of ethyl (R)-lactate, whereas modifiers derived from cinchonine always gave excess of ethyl (S)-lactate. The best results were obtained with HCd and MeOHCd were X = H, Y = OH and OCH$_3$, respectively. Hydrogenation of the quinoline nucleus led to lower enantioselectivities. We have found that some ring hydrogenation does indeed occur under our reaction conditions, but it
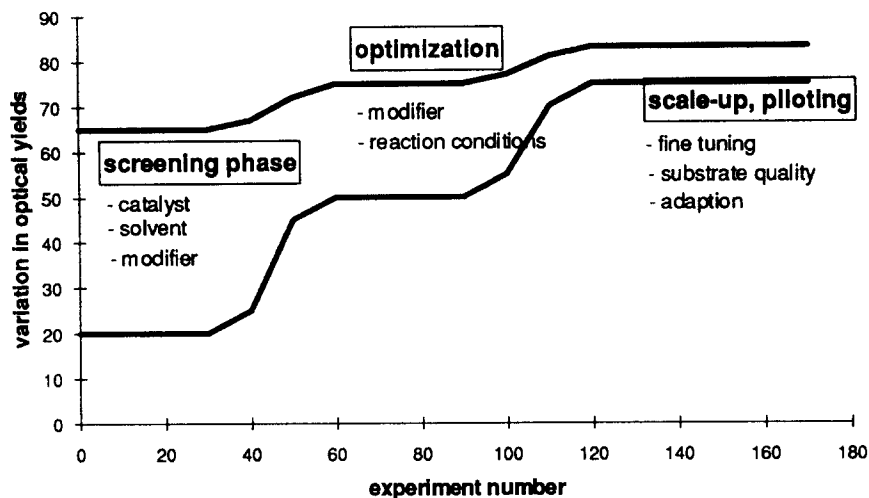
Fig. 3. Schematic representation of the variations in optical yields during the different phases of process development.

is usually too slow to influence the optical yields under preparative conditions. The nature of R_1 had little effect on the optical yield but we showed that the double bond of cinchonidine is hydrogenated very fast.

For the process development, 10,11-*dihydrocinchonidine* (*HCd*) and *O-methyl*-10,11-*dihydrocinchonidine* (*MeOHCd*) were chosen as modifiers.

Solvent effects

It was well known that the solvent has very strong effects both for the nickel–tartrate [16] as well as the Pt–*cinchona* system [15]. This was confirmed in a solvent screening for the hydrogenation of α-ketoesters (**1**) and (**2**) [25]. The best optical yields were found for aromatic solvents like benzene or toluene. For toxicological reasons we chose toluene as solvent for the production process. Due to new information, we looked at solvents and additives once more a few years later and found that acetic acid was by far the best solvent, giving optical yields of 92% for (**1**) and of 95% for (**2**) (catalyst 5 R 94, modifier MeOHCd) [26].

4.2. Optimization and final production process

In about two years the production process was developed and scaled up. 1987 a few hundred kil-

ograms were produced in a 500 l autoclave. The progress of the optimization can best be demonstrated by a plot of the optical yields versus the experiment number in the different development phases (see Fig. 3). From this plot, the effect of various measures can be seen that improved the ee's and – just as important – that led to a stable selectivity. This means that the process was no longer very sensitive to the variations.

4.3. Effect of substrate quality

This is the last topic that will be addressed in some detail. It is a very sensitive topic and very seldom documented in the literature even though it is well known that small quantities of impurities can affect a catalytic process dramatically. In most cases, the analytical identification of the 'culprit' is not possible and quality control is extremely difficult. The enantioselective hydrogenation of α-ketoesters proved to be rather sensitive to the origin of the substrate. Table 3 lists initial rates and optical yields obtained for individual batches of ethyl pyruvate from *different suppliers* tested as received and distilled. The results for individual batches can be compared using the average for rate and ee – and the differences are remarkable: $rate_{av}$ ranged from 0.02 to 0.78 moles/g cat/min and ee_{av} from 73 to 87%! The variations in rate (ratio of fastest to slowest reaction) and optical

Table 3
Effect of substrate origin and quality on initial rate (mol/g catalyst/min) and optical yield (%) of ethyl lactate under different conditions (catalyst, solvent, pressure in bar). Variation in rate is given as the ratio of the highest and lowest rate (bold numbers), variation in optical yield is expressed as the difference between highest and lowest ee (bold numbers)

| | Undistilled | | Distilled | | | | | | | | | | | | Average | |
| | JMC, tol, 20 | | JMC, tol, 20 | | E, tol, 20 | | JMC, AcOH, 20 | | E, EtOH, 20 | | JMC, tol, 100 | | | | | |
	rate	ee	rate	ee	rate	ee	rate	ee	rate	ee	rate	ee			*rate*	*ee*
Fluka 91	**0.003**	**63**	**0.012**	**69**	**0.010**	69	**0.012**	**83**	**0.025**	74	0.056	**82**			*0.020*	*73*
Fluka 92	0.004	78	0.044	80	0.050	80	0.064	88	**0.090**	74	0.096	83			*0.058*	*81*
Lancaster	0.007	71	0.014	78	0.014	77	0.026	87	0.036	77	**0.048**	85			*0.024*	*79*
ICN, Ohio	0.009	77	0.015	79	0.015	79	0.038	89	0.040	78	0.064	86			*0.030*	*81*
Sigma	0.009	76	0.024	80	0.020	80	0.046	87	0.040	78	0.114	87			*0.042*	*81*
Jansen	0.018	80	0.024	83	0.018	83	0.046	90	0.050	80	0.102	89			*0.043*	*84*
R. de Haen	0.005	73	0.030	81	0.021	79	0.046	87	0.050	78	0.148	87			*0.050*	*81*
Aldrich	**0.050**	**84**	**0.070**	**85**	0.036	**85**	0.076	**91**	0.070	**84**	0.132	**90**			*0.072*	*87*
TCI, Tokyo	**0.050**	82	0.048	83	**0.062**	83	**0.078**	90	0.068	**70**	**0.164**	80			*0.078*	*81*
Variation	*14.71*	*21*	*6.03*	*16*	*6.20*	*16*	*6.50*	*8*	*3.60*	*14*	*3.42*	*10*				

Table 4
Costs of catalyst ($/kg Pt and Rh metal) and auxiliary ($/kg). The metal price for Rh was assumed at 30 000 $/kg and for Pt at 20 000 $/kg

	$[Rh(nbd)Cl]_2$	5% Pt/Al_2O_3	Diphosphine	Cinchona alkaloid
Preparation	10 000–12 000	1600–2400		
Metal recovery	ca. 2000	700–900		
Metal loss	3000	1000		
Capital costs	750	500		
Auxiliary (lab. suppl.)			50 000–600 000	1000–2000
Auxiliary (est.)			1000–6000	300

yield (difference of best and worst ee) are most pronounced for the undistilled material. This is no surprise, but for some batches the improvement achieved by distillation is very small. The variations are diminished at higher pressure and less pronounced in EtOH and in acetic acid. These results are not very encouraging for a stable production process and indeed similar problems had to be solved for substrate (**2**).

5. Comparison of the two catalytic systems

5.1. Catalyst costs

For a batch process using chiral noble metal catalysts the *catalyst costs* are a decisive factor for the process economy. These consist of the follow-

ing cost elements: (1) *Metal*. This is usually treated as an investment, i.e., only the *interest costs* are taken into account and these depend on the recovery time cycle. The prices for the noble metals vary strongly. (2) *Metal losses*. Losses occur both in the process (including handling, chemical and filtration losses) and during recovery by the catalyst supplier. Process and handling losses in the range of 1 to 10% are considered normal. Recovery losses for Pt are 1–2%, for Rh ca. 10%. (3) *Catalyst preparation*. This includes the costs for the support or ligands etc. and are prices for technical quantities. (4) *Metal recovery*. The Pt or Rh in the filtration or distillation residue has to be extracted, purified and transformed to the noble metal. Costs vary strongly with the nature of the residue and the metal concentration. (5) *Chiral auxiliary*. These costs

Table 5
Comparison of various performance criteria for the enantioselective hydrogenation of α-ketoesters with Rh-*norphos* and Pt-*cinchona* catalysts. Catalyst costs were calculated per kg hydroxyester

	Homogeneous catalyst	Heterogeneous catalyst
Enantioselectivity	96%	80% (92%)
Solvent	EtOH, MeOH	toluene (acetic acid)
Catalyst loading	s/c 100	0.5% w/w 5% Pt/ Al$_2$O$_3$
Chiral auxiliary	Rh:PP 1:1	0.03% w/w HCd (MeOHCd)
Reaction time	20 h	3–5 h
p, T	20–100 bar, RT	70 bar, RT
Catalyst separation	not developed (distillation?)	filtration (HCd not removed)
Handling	oxygen sensitive	no special precaution
Process stability	not known	substrate quality crucial
Catalyst costs ($/kg)	140–400	1–2

depend very much on the scale of its preparation. The costs given in Table 4 are for commercially available gram amounts (e.g., Fluka, Strem, TCI etc.) and an estimate for the production of a few hundred kilograms.

5.2. Performance

Table 5 gives some important criteria to compare the performance of the two catalytic systems. In terms of selectivity, the homogeneous Rh–*norphos* is clearly superior to the heterogeneous Pt–*cinchona* catalyst. Because enrichment to >99% ee is relatively easy in a later stage of the synthesis of benazepril, this deficiency is not so important. The decisive factor for preferring the heterogeneous catalyst in this particular case was of course the catalyst costs. Other problems that often arise with homogeneous catalysts such as handling and separation were not investigated in this case.

6. Experimental

Materials and methods used for the homogeneous catalysts are described in detail in [7], those for the Pt–*cinchona* systems in [18,21,26]. The experiments with the different batches of ethyl pyruvate were carried out in a 50 ml autoclave loaded with 50 mg 5% Pt/Al$_2$O$_3$ (pretreated for 4h at 400°C under H$_2$), 10 mg HCd, 10 ml ethyl pyruvate and 20 ml solvent (puriss). The ethyl pyruvate was used as received or freshly distilled over a 20 cm Vigreux column at 8 mbar, bath temperature 40–50°C, the fraction boiling between 26 and 28°C was collected.

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