ELSEVIER

Catalysis Today 37 (1997) 441–463

CATALYSIS TODAY

Enantioselective hydrogenation of α-ketoesters using cinchona modified platinum catalysts and related systems: A review

Hans-Ulrich Blaser*, Hans-Peter Jalett, Manfred Müller, Martin Studer

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

---

Abstract

The state of the art for the heterogeneous enantioselective hydrogenation of α-ketoesters using cinchona modified Pt catalysts and related systems is reviewed. The effect of the following elements of the catalytic system are well known: *Catalyst.* Supported Pt catalysts with relatively low dispersion (particle diameter >2 nm) are preferred for the hydrogenation of α-ketoacid derivatives, Pd catalysts for functionalized olefins. Most support materials are suitable. *Substrate.* The reacting function is preferentially a ketone or a C=C bond, a carbonyl group in α-position is necessary for good optical yields. *Modifier.* The minimal requirements for an efficient modifier for the hydrogenation of α-ketoesters is the presence of a basic nitrogen atom close to one or more stereogenic centers and connected to an extended aromatic system (preferentially quinolyl or naphthyl). The presence of an alcohol or ether in β-position to the basic nitrogen often gives better enantioselectivities. *Solvent.* Solvents with a dielectric constant between 2 and 10 give best selectivities for α-ketoesters with best e.e.'s in acetic acid. For the hydrogenation of substrates with a free acid function aqueous polar solvents are preferred. The highest optical yields for the different substrate types: 95% e.e. for α-ketoesters, 85% for α-ketoacids and 70% for α,β-unsaturated acids. Practical problems for the use of the catalytic system are low e.e.'s at the start of the reaction, the instability of the modifier and some side reactions as well as the purity of the ethyl pyruvate. Mechanistic investigations have established interactions between substrate and modifier in solution and adsorption of the ethyl pyruvate and cinchonidine on the catalyst. The dependence of rate and e.e. on catalyst, cinchonidine, ethyl pyruvate and hydrogen concentration has been established for ethyl pyruvate hydrogenation using Pt/Al_2O_3–cinchona. A Langmuir–Hinshelwood scheme is well suited for explaining the observed kinetic results. Based on the kinetic results, the effect of modifier and substrate structure, and molecular modeling studies, the following mechanistic model has been developed: On the unmodified catalyst, the α-ketoester and hydrogen are reversibly adsorbed and the addition of the first hydrogen atom is rate determining. A modified active site is formed by adsorption of one cinchona molecule. It is postulated that a protonated adsorbed modifier interacts with the α-ketoester and forms a stabilized half hydrogenated intermediate. The rate determining step for the preferred enantiomer is the addition of the second hydrogen. The rate acceleration and the enantiodiscrimination is therefore due to the preferential stabilization of one of the two diastereomeric intermediates. Alternative mechanisms are discussed but considered to be less satisfying.

Keywords: α-Ketoester hydrogenation; Heterogenous enantioselective hydrogenation; Platinum–cinchona catalyst; Kinetics; Review

---

*Corresponding author. Tel.: (41-61) 697-3034; Fax: (41-61) 697-8453.

PII S0920-5861(97)00026-6

1. Introduction

Catalyst modification is a strategy that is applied widely in heterogeneous catalytic hydrogenation. Thereby the selectivity and activity of a catalyst are influenced by the addition of (organic) modifiers either to the catalyst or to the reaction mixture. When the modifier is chiral, the reaction can be carried out enantioselectively – at least in principle. In reality, this strategy has been successful only in a limited number of cases due to the high substrate specificity of such catalysts, i.e., a particular combination of a metal and a modifier is enantioselective only for a rather narrow class of starting materials. Historically, the hydrogenation of β-ketoesters was the first reaction catalyzed by a heterogeneous chiral catalyst with high and reproducible optical yields. Nickel modified with tartaric acid is certainly the best studied catalytic system of this type and has been reviewed extensively [1].

The enantioselective hydrogenation of α-ketoesters using Pt catalysts modified with cinchona alkaloids is the second reaction of industrial relevance. This fact as well as its outstanding properties have lead to a strong interest in the catalytic system. In the last years several research groups have started working in this area. Investigations were basically concentrated on two aspects: First, to understand how the original catalytic system as described by Orito et al. [2] really works, done mostly by studying the effect of the many system parameters and by kinetic and mechanistic investigations. Second, new type of reactants and transformation are sought that can extend the use of chirally modified catalysts. Therefore, the reference point for this review will always be the hydrogenation of α-ketoesters catalyzed by platinum catalysts that are modified with cinchona alkaloids as depicted in Fig. 1. Abbreviation that will be used throughout this manuscript are ***etpy*** for ethyl pyruvate, ***Cd*** for cinchonidine, ***HCd*** for 10,11-dihydrocinchonidine and e.e. for enantiomeric excess or optical yield.

Several reviews have already appeared [4]. The present report will therefore emphasize the progress and results obtained during the last few years. In addition, some new results obtained in our laboratory will be presented in more detail.

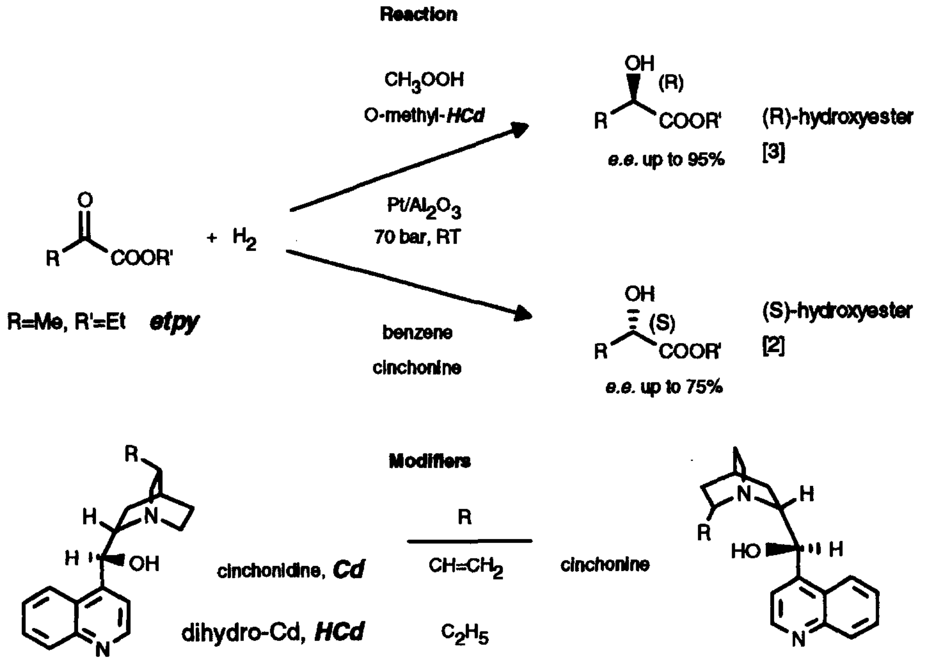


Fig. 1. Hydrogenation of α-ketoesters catalyzed by cinchona modified platinum catalysts. Modifier and substrate structure, best hydrogenation results [2,3].

2. The components of the catalytic system

2.1. Catalyst

For the hydrogenation of α-ketoacid derivatives in presence of cinchona alkaloids and related modifiers, supported Pt catalysts are preferred [2,4,5]. At the present time the best catalysts are commercially available 5% Pt/Al_2O_3 with low dispersion and a rather large pore volume [6]. Other inorganic carriers like SiO_2, TiO_2, $CaCO_3$ or various carbon supports are also suitable. Catalysts with metal particles <2 nm were reported to be less selective and they also showed lower turnover frequencies, see Webb et al. [4]. From the effect of dispersion and particle size it was concluded that flat surfaces are advantageous. Zeolites of different structure and acidity can give quite selective supported Pt catalysts as well [7–9]. Neither the acidity of the support nor the metal surface area had much effect on the enantioselectivity but the initial rates were reported to drop by a factor of three when the Pt surface area was varied between 2.5 and 4.1 m^2/g [7]. The view that the enantioselective reaction occurs on the flat surfaces was contested by Augustine et al. [10] who claimed that corner and ad-atoms form the active sites. Their conclusion was based on correlations of the rates of hydrogenation with the densities of particular sites obtained via a "single turnover" procedure. However, the measurements were carried out with very few catalyst samples and this issue remains to be clarified.

Interesting catalysts were described by Bhaduri et al. [11] who anchored anionic Pt and Ru carbonyl clusters on a 20% cross-linked polystyrene functionalized with cinchonidine and ephedrine. Best results were obtained for the hydrogenation of methyl pyruvate with a Pt-cinchonidine derived catalyst with e.e.'s up to 80%. These results are surprising for several reasons: all known supported small Pt crystallites are unselective; alkylation of the basic nitrogen leads to complete loss of selectivity; Ru/Al_2O_3 catalysts give racemic products; and ephedrine is not selective [5,6,12]. This means that these cluster catalysts must have a different mode of action.

Ir [13] as well Pd catalysts [5,14] were shown to be much less selective for the α-ketoester hydrogenation. Best optical yields for ***etpy*** were 39% and 14%, respectively. In both cases, no rate acceleration by the modifier was observed. Interestingly, Pd in presence of ***Cd*** gave an excess of the (*S*)-ethyl lactate, whereas all other metals lead to an excess of the *R*-enantiomer. This was explained by the preferential hydrogenation of the enol form [14]. Pd catalysts are preferred for C=C bonds and the C–Cl hydrogenolysis [14–16].

2.1.1. Immobilized modifier

Two catalyst types that were prepared and studied in our laboratory will be described in some more detail. The first one was obtained by immobilization of a the norcinchol ***M3*** derivative shown in Fig. 2 on the silica surface of a Pt/SiO_2 catalyst. The questions we wanted

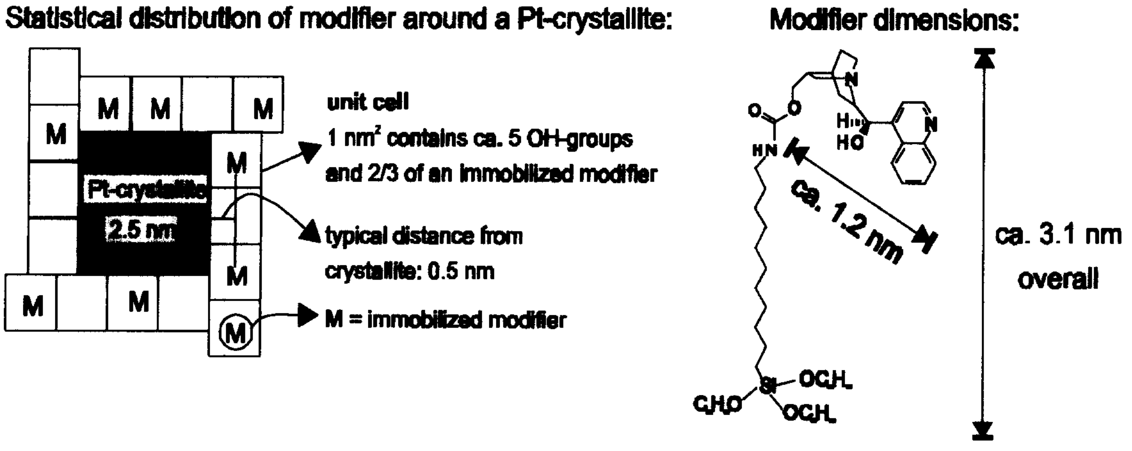


Fig. 2. Structure, dimensions and distribution model for the immobilized Pt/SiO_2–cinchona catalyst.

Table 1
Hydrogenation of ***etpy*** using the free and immobilized modifier

	Re-use	Reaction time (100%) (h)	e.e. (%)
Norinchol ***M3***	—	0.6	54
Immobilized ***M3***	—	0.5	50
	1	2.2	8
	2	6	0

to address were (i) the technical problem of improving the separation and productivity (re-use, stability) of the modifier; (ii) the scientific question of how the modifier adsorbs on the surface in order to form a modified active site. The modified catalyst was prepared as described in the experimental section. Calculation of the modifier content from elemental analysis indicated that approx. 30% of the surface OH groups had reacted (assuming 5 OH/nm^2 [17]), giving a modifier/Pt crystallites ratio of approx. 3000:1. This means that on the average, each crystallite (mean crystallite size=2.5 nm), can be reached by one to two cinchona moieties (see schematic diagram in Fig. 2).

It was demonstrated that the immobilized modifier is indeed effective. The rates and e.e.'s are compared in Table 1. Re-use leads to loss of optical yield, probably due to hydrogenation of the quinoline ring. The effectiveness of the immobilized modifier supports the idea that only one cinchona molecule is necessary in order to form a modified site.

2.1.2. *Colloidal catalysts*

The presence of a support with a much larger surface area compared to that of platinum can interfere when studying catalyst properties. Therefore, we prepared a Pt colloid according to the method described by Duff et al. [18] using H_2PtCl_6 and polyvinylpyrrolidone as stabilizer in MeOH/H_2O. Two batches were made in order to test reproducibility. In both cases a stable colloid resulted which could be stored, concentrated or diluted without visible precipitation. A TEM investigation showed that we had obtained somewhat larger particles than described by Duff et al. and that in sample #2 some aggregation occurred (see Table 2). Both batches showed catalytic activity for the hydrogenation of ***etpy*** and, in presence of cinchona modifiers, optically active ethyl lactate was obtained. However, the activity and the optical yields of this colloid catalysts were generally lower than those reached with the best Pt/Al_2O_3 catalysts. The second batch was somewhat less active and enantioselective. The effect of the solvent on e.e. is quite different from that observed with the conventional catalysts (see Section 2.4). A similar acceleration effect by the modifier (factor of about 50) is observed as described for the Pt/Al_2O_3 catalysts (see Section 4.3.2, Fig. 10a).

Table 2
Rate and enantioselectivity for the hydrogenation of ***etpy*** using Pt colloids

Solvent	Toluene		EtOH		*i*-PrOH	
Modifier	e.e.	Rate	e.e.	Rate	e.e.	Rate
None			0	0.05		
HCd	15	0.1	45	0.3	50	0.2
MeO***HCd***			65	0.7	68 (45)	0.7 (0.3)
Norcinchol			35	0.1		

Conditions: Colloid #1, 5 mg Pt in 2.5 ml H_2O/MeOH 1/1 (values in parenthesis colloid #2), 20 ml solvent, 10 mg modifier, r.t. 100 bar.

Somewhat similar results were obtained with Pt colloids prepared by metal vapor deposition techniques [19]. With an optimized preparation procedure, optical yields up to 40% were obtained. Even higher selectivities for the hydrogenation of ***etpy*** were reported by Bönnemann et al. [20], who prepared stable colloids (average particle diameter approx. 1.5–3.5 nm) by reducing Pt salts with formic acid in presence of ***HCd***. With excess modifier in the reaction solution e.e.'s of approx. 80% were obtained.

2.1.3. *Catalyst: Summary*

Pt is the metal of choice for the hydrogenation of functionalized ketones. For the enantioselective hydrogenation of C=C bonds, Pd is superior. Many different supports are suited, Al_2O_3, SiO_2, TiO_2 and zeolites give the best results. In general, high metal dispersions are detrimental for high enantioselectivities. However, the notion that flat surfaces are required for effective catalysts has not really been established experimentally. The good results obtained with colloids show that the support only plays an indirect role.

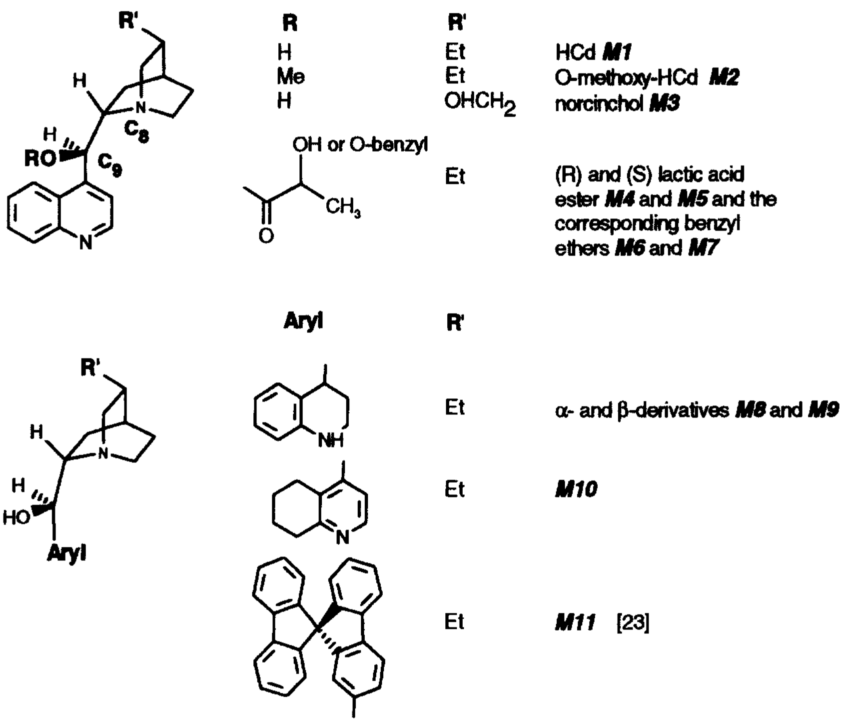


Fig. 3. Structures of cinchona modifiers.

2.2. *Modifier*

In preliminary screenings of various cinchona derivatives, ***HCd*** and O-methyl-***HCd*** were found to be the best modifiers [3,6]. The major conclusions were as follows: The absolute configuration at C_8 determines the sense of chiral induction (see Fig. 3); OH or OMe at C_9 lead to the highest optical yields; alkylation of the nitrogen atom in the quinuclidine ring to complete loss of enantioselectivity; and partial hydrogenation of the quinoline nucleus also lowers the selectivity.

These results were confirmed but had to be somewhat refined when a more elaborate screening was carried out in three solvents (toluene, acetic acid and ethanol) and at 1 and 10 mg modifier loading [21]. Additional new modifiers related to cinchona alkaloids [21,22,23] (see Fig. 3) were also tested; the results are shown in Table 3.

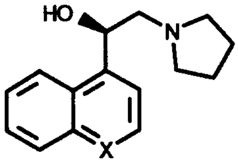
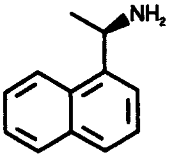
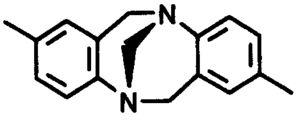
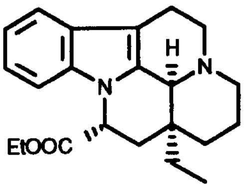
As described before [6], only small R-substituents like H, Me and Ac on the oxygen atom of C_9 give good e.e.'s. The optical yields obtained with the corresponding lactic acid derivatives ***M4–M7*** are significantly lower. It is interesting to note that with both (*R*)- and (*S*)-lactic acid esters ***M4*** and ***M5***, the same results are obtained. The corresponding benzyl ethers ***M6*** and ***M7*** behave again very similarly, but with even lower optical yields. With the sharpless ligands [22], carrying two dihydroquinidine (***DHQD***) or two dihydroquinine (***DHQ***) units connected through an aromatic linker via C_9–O, enantioselectivity is almost lost. To our surprise, a small excess of (*S*)-lactate was observed with ***(DHQ)$_2$PYR***. One possible explanation is that the ligand is adsorbed on the catalyst surface through the large aromatic system of the linker rather than through the quinoline-ring, thus acting very differently from the parent dihydroquinine.

Baiker and Pfaltz [25,26–29] described a number of rather efficient modifiers, that can be considered to be simple cinchona models. Particularly successful were 2-(1-pyridine)-aryl-ethanol ***M12*** and aryl-ethyl amine ***M13*** derivatives (see Table 4). It was shown that the amino group of ***M13*** underwent reductive alkylation with ***etpy*** and that the resulting secondary amines were the actual modifiers. Interestingly, the two diastereomers gave the same e.e. values, analogous to the results for ***M4–M7***. Vinca-type alkaloids ***M15*** also

Table 3
Hydrogenation of ***etpy*** with Pt/Al_2O_3 using new cinchona related modifiers (best optical yields and reaction conditions, 50–100 mg Pt/Al_2O_3, 10 ml ***etpy*** and 20 ml solvent, r.t., 100 bar)

Modifier	Amount (mg)	Solvent	e.e.	Ref.
HCd	1	AcOH	90% (*R*)	[6,21]
M2	1	AcOH	95% (*R*)	[3]
M3	1	AcOH	91% (*R*)	[21]
M4	1	AcOH	44% (*R*)	[21]
M5	1	AcOH	46% (*R*)	[21]
M6	1	EtOH	20% (*R*)	[21]
M7	10	EtOH	25% (*R*)	[21]
M8	2.4	AcOH	74% (*R*)	[21]
M9	2.6	AcOH	65% (*R*)	[21]
M10	10	AcOH	47% (*R*)	[21]
M11	1	Toluene	6% (*R*)	[21,23]
(DHQ)$_2$PHAL	1	AcOH	16% (*R*)	[21]
(DHQ)$_2$PYR	1	AcOH	6% (*S*)	[21]
(DHQD)$_2$PHAL	1	AcOH	4% (*S*)	[21]
(DHQD)$_2$PYR	10	EtOH	9% (*R*)	[21]

Table 4
Pt catalyzed hydrogenation of ***etpy*** using new modified types (best optical yields and reaction conditions)

Modifier	e.e.	Substrate	Catalyst	Solvent	Conditions	Ref.
	X=CH:75%, X=N:66%	***etpy***	Pt/Al_2O_3	Acetic acid	23°C, 10–75 bar	[26,28,29]
	82%	***etpy***	Pt/Al_2O_3	Acetic acid	9°C, 8 bar	[25]
 Tröger's base	65%	***etpy***	Pt/Al_2O_3	Acetic acid	r.t., 10–75 bar	[27]
	30%	***etpy***	Pt/Al_2O_3	MeOH/0.5% acetic acid	r.t., 6 bar	[30]

induced moderate enantioselectivity [30,31], whereas other alkaloids were hardly effective [12,31].

2.2.1. *Modifier: Summary*

One can conclude from these results that the minimal requirements for an efficient modifier for the hydrogenation of α-ketoesters is the presence of a basic nitrogen center, close to one or more stereogenic centers and connected to an aromatic system. The best results are obtained with interconnected, flat rings, e.g., quinolyl or naphthyl. A major problem is the competing hydrogenation of the aromatic rings, because even partially hydrogenated compounds are much less effective.

2.3. *Substrate*

One important limitation of modified hydrogenation catalysts is their rather high substrate specificity, i.e., only few types of substrates are transformed with good enantioselectivity, see Blaser et al. [4]. For the cinchona alkaloid-platinum catalysts, the preferred substrates are α-ketoesters and the model compound most studied is ***etpy***. Some recent publications slightly extended the use of the cinchona Pt system for the hydrogenation of functionalized ketones. Wells et al. [32] described the chemo- and enantioselective hydrogenation of α-diketones to the corresponding α-hydroxyketones with e.e.'s up to 38%. Ketopantolactone was hydrogenated with optical yields up to 79% using Pt/Al_2O_3 in water free toluene in presence of ***HCd*** [33]. α-Ketoacids were hydrogenated with enantioselectivities >80% by optimizing the solvent, the catalyst and the modifier [34]. In both cases, the absolute configuration of the hydroxy compounds was the same as the one observed for the α-ketoester for the same catalytic system and there is also a similar rate enhancement.

The hydrogenation of C=C bonds is more difficult. Up to now, the best result was described for (*E*)-α-phenylcinnamic acid that was hydrogenated with e.e.'s up to 72% with Pd/TiO_2, using ***Cd*** as modifier Nitta et al. [16]. The hydrogenation of a variety of α,β-unsaturated acids was also investigated by Baiker et al. [33] and Wells and co-workers [14] (see Table 5). The effect of solvent, support and catalyst preparation was investigated [16]. Tungler et al. [30,31,35] investigated the application of vinca-type alkaloids and could hydrogenate the C=C bond of isophorone with e.e.'s up to 40%. Several parameters were investigated in detail. It is interesting to note that in these cases, the modifier decreases the rate of reaction.

2.3.1. *Substrate: Summary*

α-Ketoacid derivatives are still the only substrates that give good results using Pt catalysts. First encouraging results were found for functionalized olefins. The dehalogenation of dichlorobenzazepinone remains a curiosity.

2.4. *Solvent*

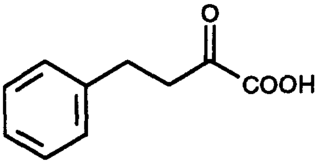
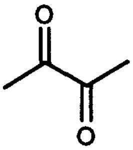
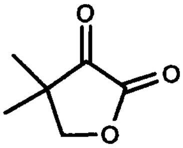
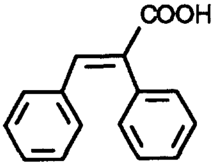
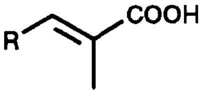
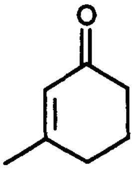
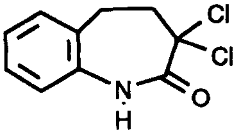
Not unexpectedly, the solvent has a decisive effect on the enantioselectivity of the cinchona modified catalysts. Nevertheless, quite a number of solvents are suitable. The first systematic investigations of the effect of the solvent on e.e. found an optimum selectivity for solvents with a dielectric constant between 2 and 10 with a clear maximum for acetic acid [3]. Rates varied less and showed no clear correlation with the polarity. Very similar dependencies for the hydrogenation of ***etpy*** were reported by Reschetilowski et al. [37] with Pt/zeolite–***Cd*** as well as by Baiker and Pfaltz et al. using Pt/Al_2O_3 modified by amino alcohol ***M12*** [26] (Fig. 4a and b). If e.e.'s for the hydrogenation of ***etpy*** are correlated with the empirical solvent parameter E_T^N, a linear dependence with a strong deviation for acetic acid is found [38]. The hydrogenation of ***etpy*** with Pt/Al_2O_3 and ***Cd*** in supercritical ethane was about three times faster than in toluene with about the same enantioselectivity [39].

For the hydrogenation of substrates with a free acid function, mixtures of water and polar solvents gave best results: α-ketoacids gave e.e.'s up to 80% in alcohol/water [34], phenylcinnamic acid was hydrogenated with 72% e.e. in dimethyl formamide/water [16] (see Table 5). On the other hand, cyclohexane gave the best results for aliphatic α,β-unsaturated acids [33].

2.4.1. *Solvent: Summary*

For the case of α-ketoesters, a clear trend is visible. The optimal solvent has a dielectric constant between 2 and 10 and acetic acid very often leads to the highest optical yields. For C=C hydrogenation the results are ambiguous (see Fig. 5).

Table 5
Hydrogenation of various substrates using cinchona modified catalysts (best optical yields and reaction conditions)

Substrate	e.e. (%)	Catalyst	Modifier	Solvent	Condition	Ref.
	85	Pt/Al_2O_3	O-methyl-***HCd***	$EtOH/H_2O$ 9:1	20–30°C, 100 bar	[34]
	38	Pt/SiO_2	***Cd***	CH_2Cl_2	−5°C, 9 bar	[32]
	79	Pt/Al_2O_3	***HCd***	Toluene	12°C, 70 bar	[33]
	72	Pd/TiO_2	***Cd***	DMF/H_2O 9:1	10°C, 1 bar	Nitta et al. [16]
	52	Pd/Al_2O_3	***HCd***	Cyclohexane	r.t., 50 bar	[33]
R = Et, Me	27	Pd/SiO_2	***Cd***	THF	20°C, 10 bar	[14]
	40	Pd black	Dihydrovinpocetine ***M15***	MeOH/0.5% acetic acid	r.t., 6 bar	[30]
	50	$Pd/BaSO_4$	Cinchonine	THF, $N(Bu)_3$	r.t., 4 bar	[15]

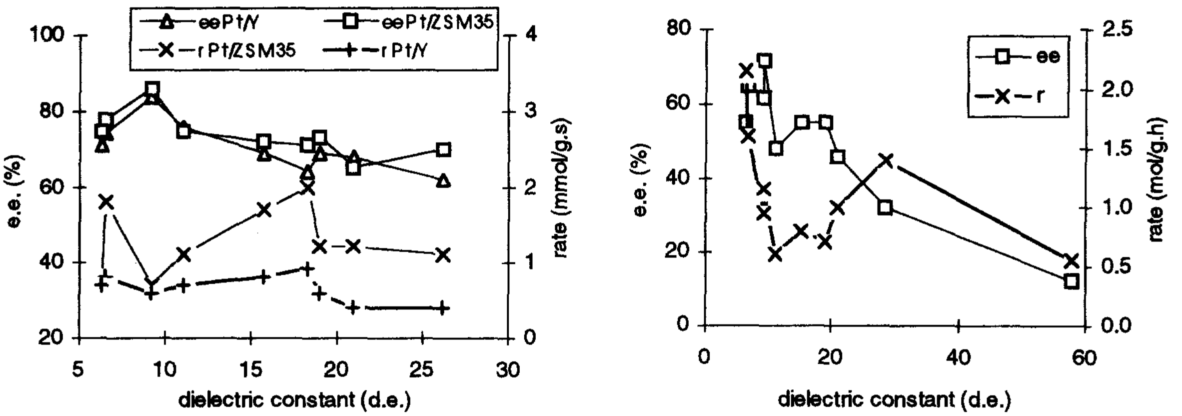


Fig. 4. Effect of the dielectric constant of the reaction mixture on e.e. and rate for the hydrogenation of ***etpy***. The dielectric constant of the reaction mixture was calculated by linear interpolation, assuming a value of 15 for d.e. of ***etpy***. (a) Pt/Zeolite Y and Pt/zsm-35-***CD*** [37]. (b) Pt/Al_2O_3, amino alcohol ***M12*** [26].

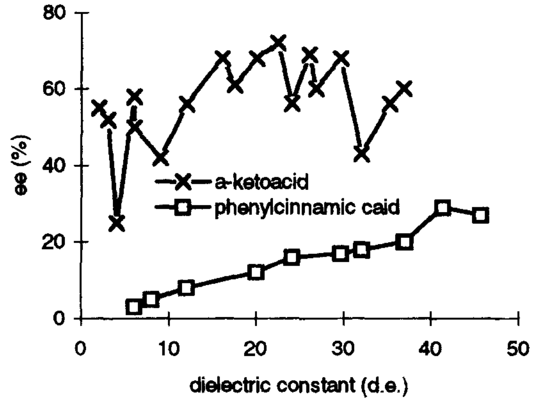


Fig. 5. Effect of solvent polarity on e.e. for the hydrogenation of 4-phenyl-2-oxobutyric acid with Pt/Al_2O_3–***HCd***. [34] and α-phenylcinnamic acid with Pd/Al_2O_3–*Cd*, Nitta et al. [16]. The dielectric constants of solvent mixtures were calculated by linear interpolation.

3. Practical problems and synthetic applications

Several practical problems can lead to very unsatisfactory results for the synthetic application of modified catalysts. It seems that these catalytic systems are somewhat more sensitive than "ordinary" hydrogenation catalysts.

3.1. Catalyst pretreatment and re-use

Orito [2] had already developed a very elaborate procedure in order to get highly enantioselective catalysts. First, the catalyst was pretreated in hydrogen at 300–400°C, then, the catalyst was impregnated in a modifier solution. Generally, the pre-reduction is still carried out by most groups. It is not well understood why this treatment gives improved optical yields. A TPR study indicated that residual Pt salts are converted to Pt metal and that carbonaceous impurities might be removed [40]. It is quite well established that the crystallite size does not change much but it is possible that smoother surfaces are produced. The pre-adsorption of the modifier was shown to be optional. The modifier can be added directly to the reaction solution with equal results [5]. For the EUROPT-1, Wells developed an elaborate aerobic modification procedure in ethanol that lead to much better enantioselectivity than the anaerobic variant Webb et al. [4]. Several explanations were offered for the role of the oxygen. Wells et al. [41,42] postulated that oxygen might keep Pt sites free for ***etpy*** adsorption. Baiker et al. [38] proposed that the oxidative treatment might remove traces of adsorbed CO on the catalyst and oxidation of ethanol gives traces of acetic acid that are known to improve optical yields. In most cases, however, the pre-modification is not mandatory for good optical yields.

It was shown that the catalyst can be re-used, thereby improving catalyst productivity [8,36]. However, the rates slowly decreased and it was necessary to freshly add ***Cd*** modifier for each re-use. These results are somewhat in contradiction to the results obtained by Wells and coworkers [43] with a pre-modified catalyst in a flow reactor. The e.e. decreased only slowly over several hours, even though substantial amounts of modifier was leached into the product solution.

3.2. *Rate and e.e. vs. conversion*

Early investigations both of ourselves [5] and of Wells et al. [43] seemed to indicate that the hydrogenation of ***etpy*** with ***Cd*** modified Pt catalyst were relatively "well behaved", i.e., e.e. values remained either relatively constant or there was a small decrease during the course of the reaction. The rates decreased as expected with decreasing ***etpy*** concentrations. More detailed investigations, especially at low conversions, revealed a much more complex situation.

Under certain conditions the maximum rate is only reached after some time [43,44,45]. Even more pronounced is the effect on the optical yield and this will be discussed in some more detail here. Several reports by Margitfalvi et al. [44,46–48] described rather bewildering effects for the change in e.e. when adding the modifier at various reaction times to the unmodified system. They postulated from these and other observations, that ***etpy*** is hydrogenated racemically at the start of the reaction even when ***Cd*** is present [46]. Blackmond and coworkers [45,49] investigated the course of the enantioselectivity at very low conversion in detail. They found in all cases that the first few percents of ***etpy*** are converted with low optical yields, which then gradually increases to the steady state value. There is a small technical problem involved here when trying to determine when the steady state is really reached. When withdrawing samples at various reaction times, an increase in the measured e.e. values does not necessarily indicate an increasing selectivity of the catalyst. When the incremental selectivity is higher than the cumulated optical yield of ethyl lactate produced up to that point, the e.e. will increase with each new measurement. We get the actual picture of the working state of the catalyst only when we calculate the incremental enantioselectivity $\mathrm{e.e.}_{(\mathrm{inc})}$, i.e., the real enantioselectivity between two points of measurements given as $\mathrm{e.e.}_{(\mathrm{inc})}=[c_2\times \mathrm{e.e.}_2-c_1\times \mathrm{e.e.}_1]/[c_2-c_1]$ where c is the actual concentration of ethyl lactate and e.e. is the measured optical yield. This is demonstrated in Fig. 6(a) where one of our own measurements is depicted but the same trends were found by Blackmond [45,49]. Fig. 6(b), gives another illustration of the incremental and measured e.e. The increase in e.e. is due to the change from a hydrogen starved to a hydrogen saturated situation [51].

At the moment it is not clear why the catalyst is less selective in the very beginning of the reaction. Blackmond [45] showed that neither the addition of ethyl lactate nor the in situ reduction of the catalyst in solution changes the situation. Under certain conditions the phenomenon is more pronounced, but under optimal conditions, specially at high pressure, only a few percent of e.e. are "lost".

3.3. *Stability of the modifier*

Margitfalvi and Baiker et al. carefully investigated the behavior of ***Cd*** in the reaction mixture [44] and the fate of the modifier during the reaction [52]. They found that ***Cd*** is hydrogenated very fast to ***HCd***, which

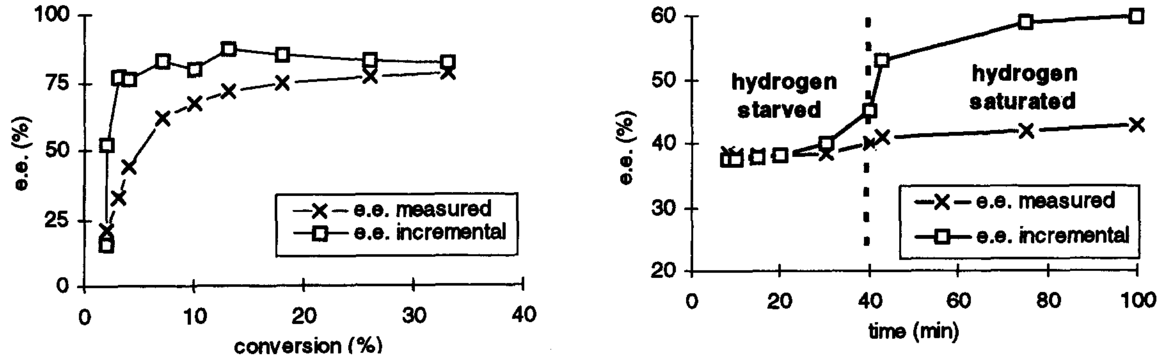


Fig. 6. Measured and incremental e.e. for the hydrogenation of ***etpy***. (a) Pt/Al$_2$O$_3$, ***HCd***; toluene, 100 bar e.e. vs. conversion [24]. (b) Pt/Al$_2$O$_3$, ***HCd***, *n*-propanol, 5.8 bar, hydrogen starved and hydrogen rich regime (adapted from Ref. [51]).

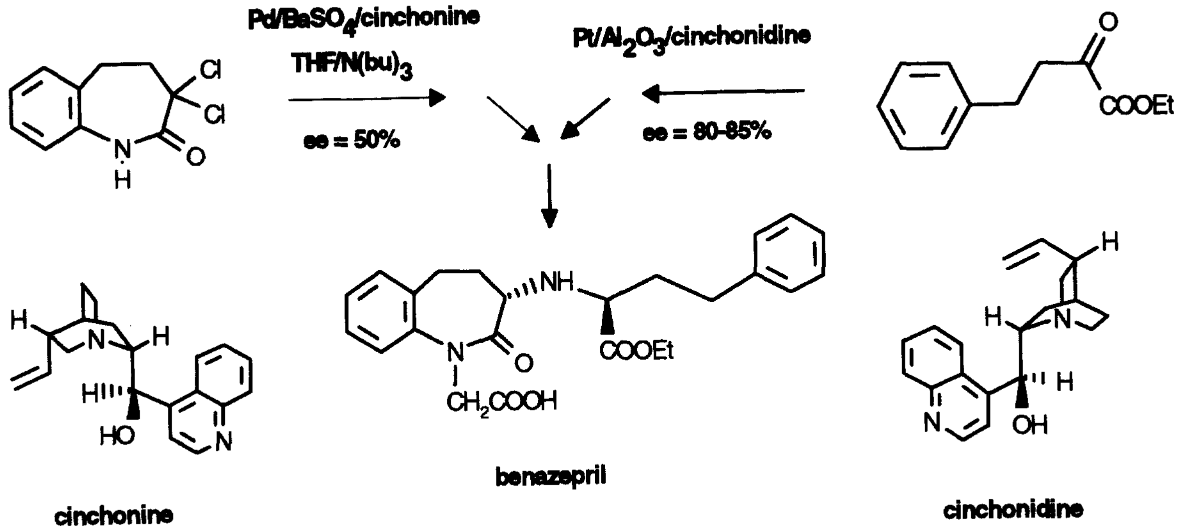


Fig. 7. Synthesis of benazepril.

is then hydrogenated further more slowly. This phenomenon is probably not problematic as long there is enough of the unchanged modifier in solution. However, at low modifier concentration [48,53] or when the modifier is easily hydrogenated as described by Baiker and Pfaltz et al. [26], e.e.'s can depend very much on the reaction time.

Besides hydrogenation, it was also proposed that the cinchona modifiers form a hemiketal with ***etpy*** [46,52]. Because O-methyl-cinchona derivatives are efficient modifiers, this hemiketal can be excluded as an important reaction intermediate.

3.4. Side reactions of ethyl pyruvate

Especially the group of Margitfalvi [46,47,54] has identified a number of side reactions of the rather reactive α-ketoesters that may lead to problems in the hydrogenation reaction. In alcoholic solvents, hemiketals can be formed with the solvent; this reaction is catalyzed by cinchona alkaloids. Some oligomers of ***etpy*** can, under certain conditions, poison the catalyst [46]. Especially for kinetic investigations, the purity and the provenance of the ***etpy*** is a major problem because the variations in e.e. and in reaction rate can be astonishing [54,55]. Augustine [10] recommends that ***etpy*** should be freshly distilled every day! The impurities that are responsible for these problems are not known.

3.5. Existing synthetic applications

In spite of all these practical problems, it was demonstrated quite early, that a technical application of chirally modified heterogeneous catalysts is feasible [55,56]. However, the application of cinchona modified Pt and Pd catalysts for the synthesis of two potential intermediates for the angiotensin-converting enzyme inhibitor benazepril still remains the only synthetic use known to us (Fig. 7). The hydrogenation of the α-ketoester was developed and scaled-up into a production process (10–200 kg scale, chemical yield >98%, e.e. 79–82%) [55,56]. The novel Pd catalyzed enantioselective hydrodechlorination reaction is a potential alternative to the established synthesis where the racemic α-bromobenzazepinone is used [15]. However, both selectivity and productivity of the Pd-cinchona catalyst are too low for an efficient synthesis.

4. Mechanistic investigations

Trying to understand the mode of action of a catalyst is fascinating but also very difficult endeavor. This is especially true for enantioselective catalysis. For the hydrogenation of α-ketoesters using Pt catalysts modified with cinchonidine derivatives, investigations are focused on explaining the very good enantiodiscrimination and on finding an explanation for the remarkable rate enhancement.

At the moment there is a lively discussion among several research groups concerning mechanistic models [42,54,57]. However, there seem to be different interpretations as to what the term reaction mechanism means. In our view, a reaction mechanism should postulate the structure of the controlling reaction intermediates as well as the kinetics of their transformations and it should do that for the main reaction in its steady state. This means that a "mechanism" cannot always (and does not need to) explain the pre-steady state behavior or all the side reactions that might occur (see also the comments by Wells in [42]).

From these arguments, it follows that we need information on structural and on dynamic aspects. Since the structure of most intermediates of the rate and product determining step cannot be determined directly, we have to deduce these from information on the effect of structural changes of the modifier and substrates and on the interactions of the species involved in the catalytic reaction (substrate (s), active site, modifier). The dynamic aspects can be determined directly via kinetic measurements.

4.1. Structural aspects and interactions between reacting species

4.1.1. Effect of substrate and modifier structure

As described above, the following components are important for high enantioselectivity:

- *Catalyst.* Pt with relatively low dispersion (particle diameter >2 nm) gives the best results.
- *Modifier.* The minimal requirements for an efficient modifier in the hydrogenation of α-ketoesters is the presence of a basic nitrogen atom close to one or more stereogenic centers, connected to an extended aromatic system (preferentially quinolyl or naphthyl). The presence of an alcohol or ether in β-position to the basic nitrogen often gives better optical yields.
- *Substrate.* The reacting function is preferentially a ketone or a C=C bond. In α-position there must be a C=O group. For ketones, this is either an ester or acid function, for olefins an acid function.

Using D_2, it has been shown that the keto group and not the enol form is hydrogenated [5,58].

4.1.2. Interactions between reacting species

4.1.2.1. Interactions between substrate and modifier in solution. Margitfalvi et al. [46] reported that the NMR spectrum of ***Cd*** changes in presence of ***etpy***, which they take as proof that an interaction takes place, thereby altering the conformation of ***Cd***. Tungler and coworkers [30] described that the circular dichroism spectrum of dihydrovinpocetine ***M15*** changes upon addition of both isophorone as well as ***etpy***, again indicating interactions between the two molecules.

4.1.2.2. Interactions between catalyst and substrate or modifier. Adsorption measurements in solution Webb et al. [4,5] using 5% Pt/Al_2O_3 catalysts have shown that both ***etpy*** as well as ***Cd*** adsorb quite strongly. However, adsorption on the metal surface cannot be distinguished from the one on the much larger support surface. This was also found by Margitfalvi [47], except when ***etpy*** was adsorbed first, adsorption of ***HCd*** was suppressed. Unfortunately no details on the results were given. Augustine [10] described the desorption of ***HCd*** when warming a solution of the modified Pt/Al_2O_3 catalyst to 50°C. That ***HCd*** indeed interacts with a Pt surface was demonstrated by Wells and co-workers [41] who reported the XPS spectra of ***HCd*** adsorbed on a Pt (1 1 1) single crystal. It was calculated that approximately a monolayer of the cinchona alkaloid was present. However they failed to find any ordered arrays of adsorbed ***HCd*** using LEED spectroscopy.

Indirect proof of adsorption of the modifier on the Pt surface was obtained by the observation that treatment of ***HCd*** solution with D_2 in presence Pt, Ru, Rh, and Pd catalysts lead not only to saturation of the quinoline ring but also to H/D exchange [59]. This finding is in agreement with parallel adsorption of the quinoline ring (as opposed to adsorption via the N atom of either quinoline or quinuclidine). Another indication of strong adsorption of ***HCd*** was recently reported by Tungler et al. [30] for the hydrogenation of both ***etpy*** and isophorone. They found that addition of even small amounts of ***HCd*** to a catalyst modified with dihydrovinpotecine ***M15*** lead to a reversal of the absolute configuration of the product.

4.1.3. *Interactions: Summary*

There is little doubt that rather strong interactions take place between the substrate, the modifier as well as the active metal surface. It must be pointed out that all these observations support the mechanistic models presented below but these are interactions in the ground state not in the transition state where the outcome of a catalytic reaction is determined.

4.2. *Molecular modeling*

There is hope that theoretical calculations might help to understand the mode of action of a catalyst by predicting the relative energies and structures of potential reaction intermediates. Several groups have tried to do this for the interactions of ***etpy*** and ***Cd***. The most advanced studies are those of Baiker and Weber et al. [28,57,60,61] who published molecular mechanics and quantum chemical studies of the interactions between ***etpy*** and protonated as well as non-protonated ***Cd*** and simple amino alcohols. Unfortunately, the interaction with the Pt surface could not be taken into account but the steric constraint of a flat metal surface was applied. From these calculations it was concluded that the most favorable activated complex is formed by the adsorbed N-protonated modifier in its open conformation interacting with the carbonyl oxygen of the adsorbed ***etpy***. This activated complex is transformed very easily into a stabilized half-hydrogenated species and then the second hydrogen atom is added to give ethyl lactate. For ***Cd*** as modifier, the calculations give a lower energy for the activated complex leading to (*R*)-ethyl lactate, in agreement with experimental results. Similar results and conclusions were reported by Wells et al. [41].

Margitfalvi and co-workers [46] come to the conclusion that the most important interactions take place between ***etpy*** and the quinuclidine nitrogen of ***Cd*** in its closed form. This places the reacting carbonyl group on top of the quinoline ring, allowing some π–π interactions resulting in what the authors call a "shielding effect". Without giving any details, it is claimed that the most stable of these complexes give (*R*)-ethyl lactate when hydrogen is added from the unshielded side, again in agreement with the observed results. A similar scheme was also proposed for Tröger's base ***M14*** as modifier [62].

There are several problems associated with these calculations. First, it is assumed that the energy differences of the calculated diastereomeric adducts determines the enantioselectivity. But this is not always the case as demonstrated very impressively by Halpern [63] for the Rh-diphosphine catalyzed hydrogenation of enamides. There, the more stable adduct of the substrate with the Rh-diphosphine complex leads to the minor enantiomer. Second, the interactions with the platinum surface are not considered. This is a major handicap for those models that assume that the activated complex includes the active Pt site. Another problem is that very little details are given on the underlying assumptions used for the calculations and that it is not clear how sensitive the claimed energy minima are towards changes that are known to strongly influence the selectivity (such as the presence or absence of functional groups).

4.2.1. *Comment*

Calculations will help to give some insight into the structural aspects of the mechanism of enantiodiscrimination. They provide a good basis to visualize the geometrical aspects of structural changes in the substrate or the modifier. However, at the moment we are still far from answering even the most basic questions.

4.3. *Kinetic investigations*

The dependencies of the rate of reaction and the e.e. on the concentrations of modifier, hydrogen and substrate gives information on feasible reaction schemes. In favorable cases, the rate and product determining step can be determined. This is especially important for understanding the acceleration effect of the modifier. If we do not know which step of the unmodified reaction is turnover limiting, it is difficult to say why the modified reaction is faster.

In addition to describing published results, the most significant findings of a recently completed study of our group are included [64].

4.3.1. *Effect of catalyst concentration*

In all studies, the rate of reaction was shown to be first order in catalyst [10,26,37,64]. In some cases diffusion limitation occurred at too high catalyst loading. Sometimes the specific rate at small catalyst concentration was lower than expected, probably due to poisoning effects.

4.3.2. *Effect of modifier concentration*

The addition of the modifier to the reaction system (either pre-adsorbed on the catalyst or added to the reaction solution) not only leads to enantiodiscrimination but also gives in many cases a notable rate enhancement. The analysis of the type of dependence allows to deduce possible mode of actions of the modifier. Indeed, several studies have addressed this point [24,26,39,41,43,53,65]. Probably the most thorough discussion has appeared in Ref. [53] and Fig. 8a depicts how rate and e.e. typically depend on modifier concentration. Instead of plotting e.e. and rate, an equivalent description uses the rate to (*R*)- and (*S*)-ethyl lactate (Fig. 9b). For the hydrogenation of ketones, such typical dependencies have been observed with the systems described in Table 5. The most plausible assumption is that the modifier reversibly adsorbs on suitable sites on the platinum surface and that these modified sites are not only enantioselective but also more active. The fact that at higher modifier concentration optical yields as well

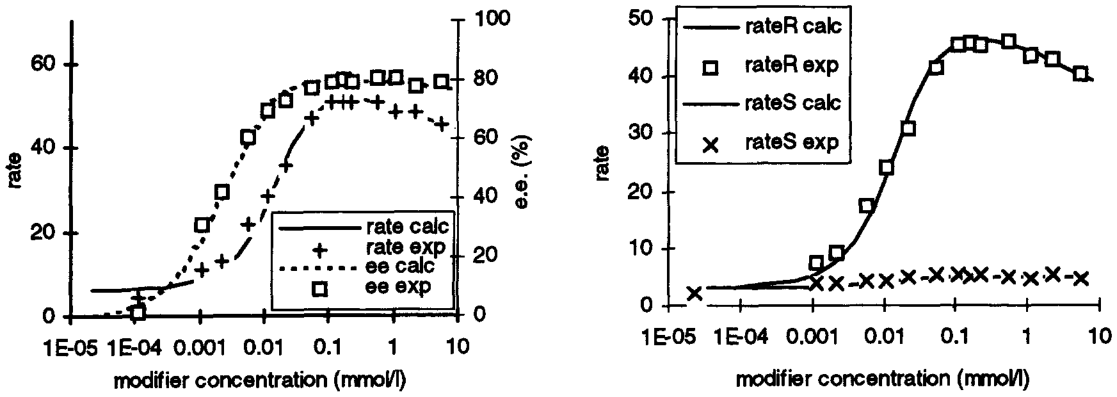


Fig. 8. Effect of the modifier concentration for the hydrogenation of ***etpy*** (Pt/Al_2O_3; ***HCd***; toluene; 20 bar) [53]. (a) On rate and optical yield; (b) On the rate of formation of *R*- and *S*-lactate.

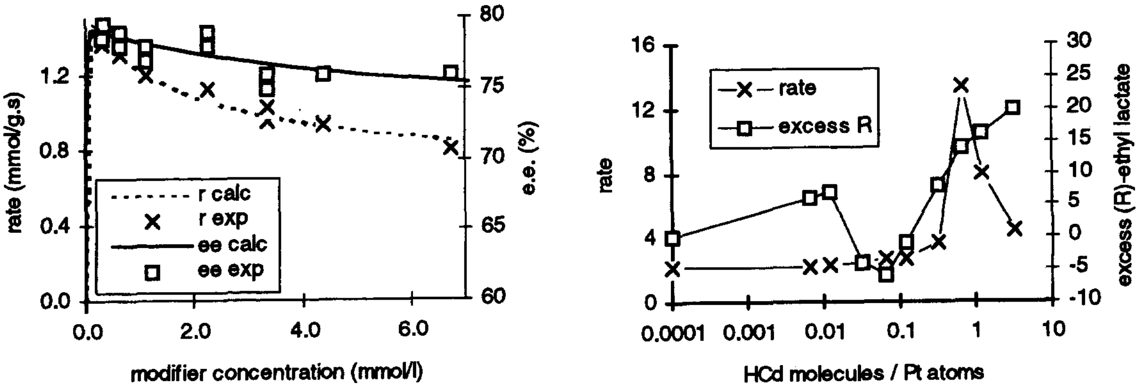


Fig. 9. (a) Effect of modifier concentration on rate and optical yield for the hydrogenation of ***etpy*** (5% Pt/ZSM-35, ***Cd***; dichloromethane; 20°C, 70 bar). Adapted from [8]. (b) Effect of modifier concentration on rate and e.e. for the hydrogenation of ***etpy*** (Pt/Al_2O_3; ***HCd***; methyl acetate; 1 bar), adapted from [10].

Table 6
Systems were the dependence of e.e. and rate can be explained with a reversible adsorption of the modifier on the active Pt sites

Ketone	Catalyst	Modifier	Solvent	Reaction conditions	Ref.
etpy	Pt/SiO_2 (EUROPT-1)	***Cd***	EtOH	r.t., 10 bar	[41,58]
etpy	Pt/SiO_2, Pt/$CaCO_3$, Pt/Al_2O_3	***Cd***, ***HCd***, OMe***HCd***, partially hydrogenated ***Cd*** derivatives	EtOH, $(i\text{-Pr})_2O$, acetic acid, toluene, acetone, acetonitrile	r.t., 70, 100 bar	[24,53]
etpy	Pt/Al_2O_3	Amino alcohol ***M12***	Acetic acid	25°C, 10 bar	[26]
etpy	Pt/Al_2O_3, Pt/C	dihydrovinpotecine ***M15***	MeOH/AcOH 1%	25°C, 10 bar	[65]
etpy	Pt colloid	***HCd***	*i*-PrOH	r.t., 100 bar	Fig. 10(a)
Ketoacid	Pt/Al_2O_3	OMe***HCd***	EtOH/H_2O 9:1	r.t., 100 bar	[34]

as rates sometimes decrease can be explained (and modeled) with a second modifier being adsorbed. Other models such as array formation have also been discussed but have finally been abandoned because a different type of e.e. and rate dependence would result [41] (see Table 6).

For the hydrogenation of ***etpy*** using Pt/Al_2O_3–***Cd*** in methyl acetate at 1 bar, Augustine [10] observed a change from (*S*)- to (*R*)-ethyl lactate by starting with extremely low modifier concentration. This behavior can at the moment not be explained with a simple model. Reschetilowski et al. also described a dependence of e.e. and rate on ***Cd*** concentration that looks very different from the cases described above (see Fig. 9). However, the ***Cd*** concentrations were so high that probably only the second adsorption was observed – and indeed, at least the general shape of the curves can be modeled with this assumption.

The situation is clearly different for the hydrogenation of C=C double bonds with alkaloid modified catalysts. The hydrogenation of α,β-unsaturated acids was reported to be slowed down by the presence of ***Cd*** by a factor of about 4–10 [14], Nitta et al. (1994) and Nitta and Kobiro (1996) in [16]. For the hydrogenation of isophorone, a similar rate decrease was observed with dihydrovinpotecine ***M15*** (Fig. 10b) [35].

4.3.2.1. Summary. Up to now, all reported investigations with ***etpy*** have revealed basically a similar dependence of rate and e.e. on modifier concentration. Because the saturation in both parameters is reached at modifier concentrations that are in the region of the available active sites on the catalyst surface, it is plausible to assume that these modifiers are adsorbed stronger than either the solvent

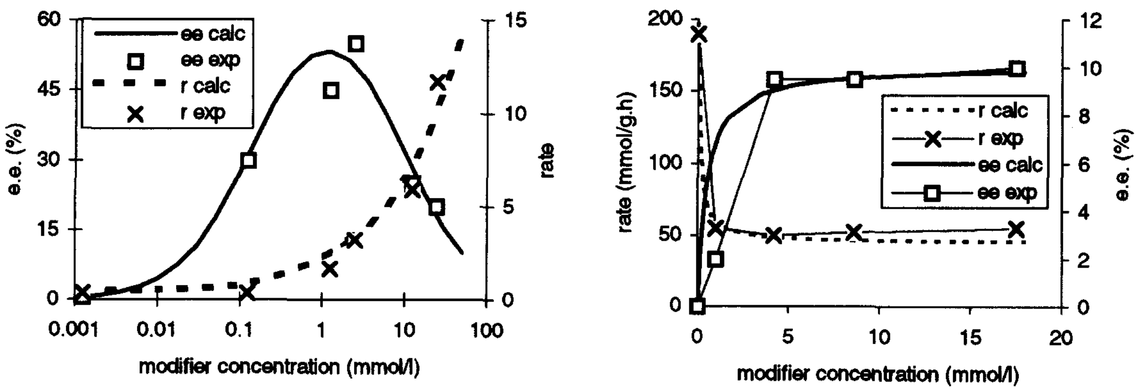


Fig. 10. (a) Effect of modifier concentration on rate and e.e. for the hydrogenation of ***etpy*** (colloid #1, ***HCd***; *i*-PrOH; r.t., 100 bar). (b) Effect of modifier concentration on rate and e.e. for the hydrogenation of isophorone (10% Pd/C; dihydrovinpotecine ***M15***; MeOH; 25°C, 1 bar). Adapted from [35].

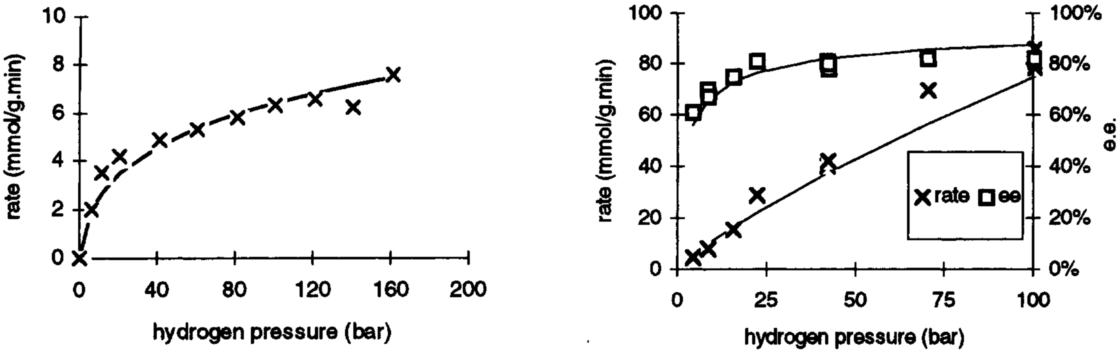


Fig. 11. Effect of hydrogen pressure for the hydrogenation of ***etpy*** (Pt/Al_2O_3; ***HCd***; toluene) [64]. (a) On the rate of the unmodified system; (b) On rate and e.e. of the modified system.

or the substrate. The term modified catalyst is therefore justified.

4.3.3. Effect of hydrogen pressure

Several recent papers describe the dependence of rate and e.e. on pressure for the hydrogenation of ***etpy*** with Pt–cinchona catalysts. The most important results of our own kinetic investigation [64] are depicted in Fig. 11a and b for the unmodified and the modified system, respectively. Wells and co-workers and Webb et al. [4,43] reported only a slight and unsystematic variation of e.e. and a first order dependence of the rate for hydrogen pressures between 10 and 100 bar (EUROPT-1, ***Cd***, ethanol, 25°C). Augustine et al. [10] found that e.e.'s increased from 1% to 15% between 200 and 400 torr, and then stayed constant until 800 torr, while the rate was approximately first order in hydrogen pressure (Pt/Al_2O_3, ***HCd***, methyl acetate, 25°C). Blackmond and co-workers [51,66] controlled the hydrogen concentration by changing the gas–liquid mass transfer coefficient. In this way they obtained a continuous increase in e.e. from 20% to 55% by increasing the hydrogen concentration from >0.01 to 10 mmol/l (Pt/Al_2O_3, ***HCd***, *n*-propanol, 30°C). The e.e.–[H_2] curve that looks very similar to the one in Fig. 11b. The results with Pt/zeolite modified with ***Cd*** are depicted in Fig. 12. A different result was observed when pyrrolidine-naphthyl-ethanol ***M12*** was used as modifier (Pt/Al_2O_3, acetic acid) [26]. E.e.'s drop from 71% to approx. 55% when the pressure is increased from 10 to 40 bar, whereas the rate increases linearly up to 20 bar and then remains constant up to 70 bar. This behavior was plausibly explained by a fast hydrogenation of the naphthyl ring at higher pressures.

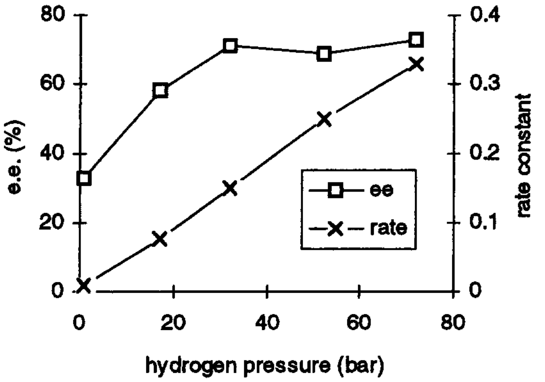


Fig. 12. Effect of hydrogen pressure on rate and e.e. for the hydrogenation of ***etpy*** (5% Pt/MgNaY; ***Cd***; cyclohexane; 20°C). Adapted from [7].

4.3.3.1. Summary. There is little doubt that for all systems studied so far, there is a pronounced dependence of e.e. on the hydrogen concentration. This can be controlled either by changing the hydrogen pressure and keeping the mass transfer coefficient constant (the classical way) or vice versa. The rate in all cases reported is first order in hydrogen for the modified system (as long it is stable). This is not the case for the unmodified catalyst where the rate approaches a constant value at higher pressures.

4.3.4. *Effect of substrate concentration*

The results of our own investigation is depicted in Fig. 13. The rate dependencies for both the unmodified and the modified catalyst show a maximum between an ***etpy*** concentration of 2 and 4 mol/l. In earlier experiments, Wells [4] observed a zero order dependence for ***etpy*** concentrations of 1.9–7.5 mol/l. The optical yields were quite insensitive for a wide range of ***etpy*** concentrations. Similar dependencies were found for Pt/Al_2O_3 modified with pyrrolidine-naphthyl-ethanol ***M12*** (Fig. 14(a)) and for Pt/MgNaY with ***Cd*** as modifier (Fig. 14(b)). When changing the ***etpy*** concentration from 0.25 to 1.0 mol/l, Blackmond et al. [45] found a small increase in maximum rates (Pt/Al_2O_3, ***Cd***, *n*-propanol, 10°C, 5.8 bar). For the same range, Margitfalvi [44,46] described almost constant rates but an increase of e.e. from 20–30% to >60% (Pt/Al_2O_3, ***Cd***, EtOH, r.t., 70 bar). At 1 bar, strong inhibition was observed even at very low ***etpy*** concentrations for the modified catalyst as depicted in Fig. 15. Interestingly, the rate for the unmodified catalyst was almost constant for ***etpy*** concentrations of 0.05 to 0.35 ml/15 ml solvent [10].

The addition of the product ethyl lactate to the reaction solution had only small effects on both rates and e.e.'s [45,48]. That (*R*)-ethyl lactate does not affect the reaction very much is also confirmed because the optical yields are usually constant at high conversions. At low pressures, however, Augustine [71] reported a marked effect of the addition of (*S*)-methyl lactate on the rate of formation of (*R*)-ethyl lactate.

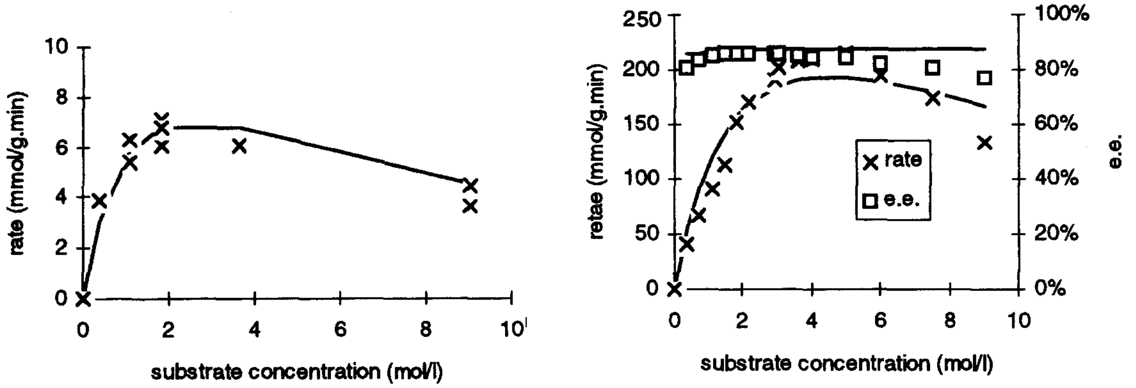


Fig. 13. Effect of ***etpy*** concentration for the hydrogenation of ***etpy*** (Pt/Al_2O_3; ***HCd***; toluene) [64]. (a) On the rate of the unmodified system; (b) On rate and e.e. of the modified system.

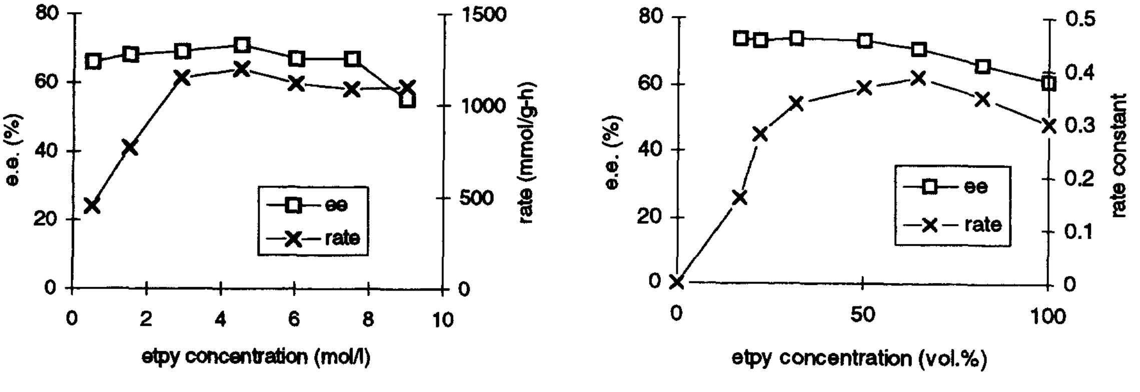


Fig. 14. Effect of ***etpy*** concentration on rate and optical yield for the hydrogenation of ***etpy***. (a) Pt/Al_2O_3, pyrrolidine–naphthyl–ethanol ***M12***, acetic acid, 25°C (adapted from [26]); (b) Pt/MgNaY; ***Cd***; cyclohexane; 20°C (adapted from [7]).

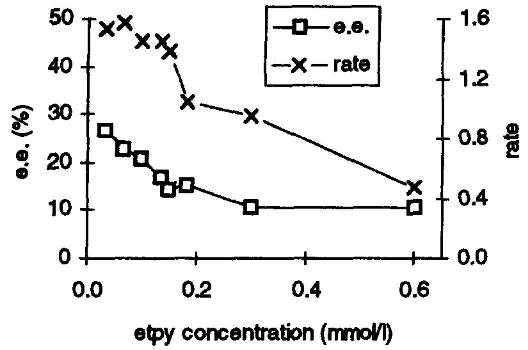


Fig. 15. Effect of *etpy* concentration on rate and optical yield for the hydrogenation of *etpy*. Pt/Al_2O_3, *Cd*, methyl acetate, 25°C, 1 bar (adapted from [10]).

4.3.4.1. Comment. The results for the dependence of rate of reaction on the concentration of the starting material both for the unmodified and modified catalyst are very similar. In principle, the decrease in rate at high ***etpy*** concentrations could be due to mass transfer problems or due to change in the polarity of the reaction solution. However, the fact that the rate maximum with the different systems occurs at different concentration suggests that the effect is of kinetic origin. The most plausible explanation is a competitive adsorption of hydrogen and ***etpy***. The small change in e.e. could be due to the change in polarity of the solution. Ethyl lactate does not seem to compete for adsorption.

4.3.5. Effect of temperature

The effect of the reaction temperature has been investigated both for the unmodified as well as the modified system. For the unmodified catalyst, the Arrhenius plot shows a rather good linear behavior between r.t. to 70°C [43] and Fig. 16a [64]. The situation for modified systems is more complex. A drop in the rate of reaction is observed above temperatures of 50°C for the hydrogenation of ***etpy*** using EUROPT-1, ***Cd*** or ***HCd*** in ethanol (Fig. 16b) [43] as well as with Pt/MgNaY, ***Cd*** in cyclohexane [7]. As suggested by Augustine [10], this is probably due to desorption of the modifier. In both cases, e.e.'s decrease gradually with higher temperatures. For conditions used in our own investigations, rates increase up to 70°C and a small decrease in e.e. is observed [64]. Apparent activation energies between 5 (Fig. 16a) and 10 kcal/mol [43] were determined.

4.4. Kinetic schemes

Any valid kinetic scheme has to accommodate the data presented above. There is no doubt that the rate determining step for the modified catalytic system must involve all four components: the catalyst, the modifier, ***etpy*** and hydrogen. Except for the hydrogen pressure dependence in the modified system, there are strong saturation effects, i.e., the rates reach a maximum value and in some cases decrease when the concentration of a given component is increased. The

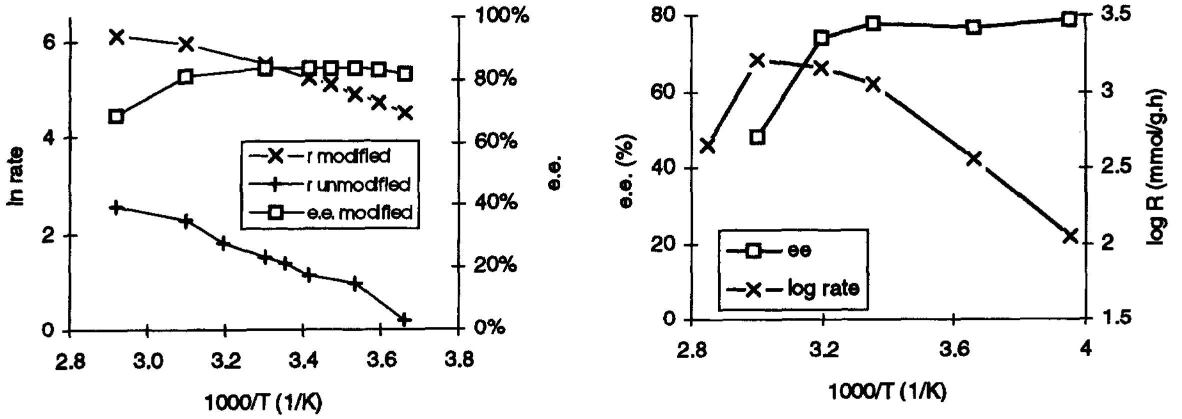


Fig. 16. Effect of temperature on e.e. and rate for the hydrogenation of *etpy*. (a) Pt/Al_2O_3 with and without HCd; toluene, 70 bar [64]. (b) EUROPT-1, HCd, ethanol, 10 bar (adapted from Ref. [43]).

optical yield is only affected by modifier concentration and the hydrogen pressure, and it varies only very little with amount of catalyst and ***etpy***.

To explain kinetic data for the hydrogenation of ketones, Langmuir–Hinshelwood (LH) treatments often give satisfactory answers [67,68]. Therefore, we combined the model developed for the modifier dependencies [53] with LH-models used for ketones. In this treatment, the free modifier, ***etpy*** and hydrogen are in equilibrium with an adsorbed form on the catalyst surface. These adsorbed species react with each other and the product(s) of the reaction(s) are finally desorbed from the catalyst surface. Up to the irreversible rate determining step, all species are assumed to be in fast equilibrium. The reaction sequence below presents the simplest model which can explain all the kinetic data. It is clear, however, that variants with same basic assumptions cannot be excluded. Another approach could be the steady state assumption as for example used by Halpern [63,69].

The following reactions with the indicated rate (k, k') and equilibrium constants (K, K') were used for calculating the fitted curves in Figs. 11 and 13.

(1) Modification of an active sites ($*$) by adsorption of the modifier to give a chiral active site ($\star$) [53]. Doubly modified sites ($\star$mod) are assumed to be inactive for hydrogenation reaction in all solvents except acetic acid [24]. Adsorption of reactants on unmodified and modified sites is assumed to be fast [67].

$$\begin{array}{lll} * + \text{mod} & \rightleftarrows \ \star & K_{\text{m1}} \\ \star + \text{mod} & \rightleftarrows \ \star\text{mod} & K_{\text{m2}},\ \text{inactive} \end{array}$$

(2) Competitive adsorption of hydrogen and ***etpy*** (E) on unmodified sites. Formation of $\star$-H is postulated to be an exchange reaction. If the keto group is adsorbed on the Pt surface via the π-electrons, two diastereomeric modes are possible: adsorption via the *si* (see Fig. 17) or the *re* face. For the unmodified catalyst, these enantiomeric adsorbed forms are energetically equal. For a chiral site, the two forms are distereomeric. Assuming addition of the H atom from the side of the metal, the *si* form leads to (*R*) the *re* form to (*S*)-ethyl lactate, respectively. $\star$-*si/re*-E is assumed to be inactive in the hydrogenation reaction.

$$\begin{array}{lll} 2* + \text{H}_2 & \rightleftarrows \ 2*\text{-H} & K_{\text{H}} \\ * + \text{E} & \rightleftarrows \ *\text{-}si/re\text{-E} & K_{\text{E}},\ \text{same for } re \text{ and } si \text{ form} \\ *\text{-H} + \star & \rightleftarrows \ \star\text{-H} + * & K'_H \\ \star + \text{E} & \rightleftarrows \ \star\text{-}si/re\text{-E} & \text{K}'_{\text{E}},\ \text{unproductive} \end{array}$$

(3) Addition of the first H to E can take place either on a modified or an unmodified site. For the reaction of the unmodified sites and for the formation of $\star$-*re*-EH leading to (*S*)-lactate, this step is postulated to be rate determining.

$$\begin{array}{lll} *\text{-H} + \text{E-}* & \rightarrow \ *\text{-}si/re\text{-EH} + * & k_{\text{EH}} \\ \star\text{-H} + \text{E-}* & \rightleftarrows \ \star\text{-}si/\text{-EH} + *\text{-H} & K'_{\text{siEH}}(K'_{\text{siEH},}k'_{-\text{siEH}}) \\ \star\text{-H} + \text{E-}* & \rightarrow \ \star\text{-}re\text{-EH} + * & K'_{\text{reEH}} \end{array}$$

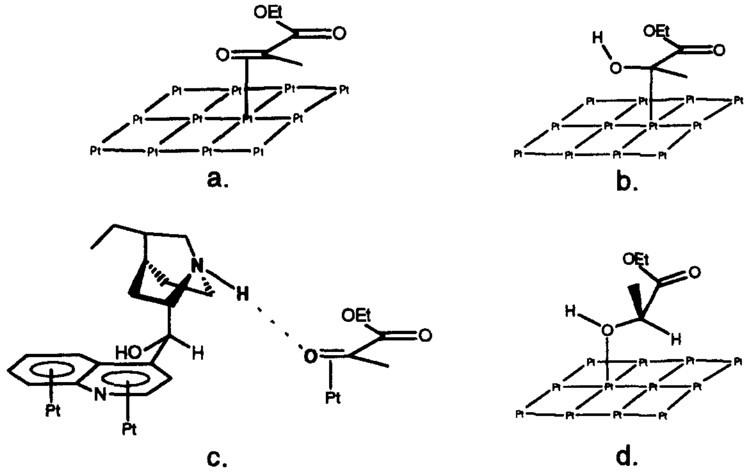


Fig. 17. An artist's view of the structure of adsorbed reaction intermediates: (a) adsorbed ***etpy*** *si*-face; (b) half hydrogenated ketone (*re*-form); (c) interaction of protonated ***HCd*** with *si*-form; (d) weakly adsorbed (*R*)-lactate.

(4) Addition of the second H is assumed to be the rate determining step for the reaction of $\star$-*si*-EH to (*R*)-lactate. For the unmodified sites and the formation of (*S*)-lactate, these steps are fast compared to the first addition.

$$\begin{array}{lcll} \ast\text{-H} + \ast\text{-}si/re\text{-EH} & \rightarrow & \ast\text{-}(R,S)\text{-EH}_2 + \ast & \text{Fast} \\ \ast\text{-H} + \star\text{-}si\text{-EH} & \rightarrow & \star\text{-}(R)\text{-DH}_2 + \ast & K'_{\text{REH}_2} \\ \ast\text{-H} + \star\text{-}re\text{-EH} & \rightarrow & \star\text{-}(S)\text{-EH}_2 + \ast & \text{Fast} \end{array}$$

(5) Desorption of ethyl lactate EH_2 is assumed to be fast in all cases, with a small adsorption constant.

$$\begin{array}{lcll} \ast\text{-}(R,S)\text{-EH}_2 & \rightarrow & \ast + (R,S)\text{-EH}_2 & \text{Fast} \\ \star\text{-}(R)\text{-EH}_2 & \rightarrow & \star + (R)\text{-EH}_2 & \text{Fast} \\ \star\text{-}(S)\text{-EH}_2 & \rightarrow & \star + (S)\text{-EH}_2 & \text{Fast} \end{array}$$

The calculated curves for the unmodified catalyst (Fig. 11(a), Fig. 13(a)) were fitted with the following three variables: k_{EH}, K_{H}, K_{E}. For the modified system (Fig. 11(b), Fig. 13(b)) it was assumed that only 50% of the surface Pt atoms can be modified and that the unmodifiable sites react with same rate and adsorption constants as determined for the unmodified system. For the modified catalyst the following five variables were fitted: k'_{reEH}, k'_{siEH_2}, K'_{siEH}, K'_{H}, K'_{E}.

4.5. *Proposed mechanisms*

An extended discussion of the different reaction mechanisms was presented in [57]. Most investigators probably agree that rate enhancement and enantiocontrol are closely connected effects and should be discussed together. There is also agreement that very specific interactions between modifier and substrate are necessary in order to give such high enantioselectivities. There is less agreement as to whether interactions with platinum surface are important: Two types of mechanisms have been proposed. Most groups working with the Pt–cinchona catalysts think that a *modified catalyst* is involved, i.e., that the modifier adsorbs on Pt sites and that the product determining step involves adsorbed modifier, ***etpy*** and hydrogen [10,41,53,57]. Margitfalvi [46,54] argues that substrate–modifier interactions in solution are decisive, i.e., he proposes a modified substrate as key species. These two ideas are commented below.

4.5.1. *Proposals involving a "modified catalyst"*

Several proposal were made as to the composition and structure of a modified catalytic site. Blaser and Garland [53] deduced from kinetic results that approx. 15 platinum surface atoms and one cinchona molecule constitute a selective site. From the effect of catalyst dispersion it was speculated that a flat arrangement of the Pt atoms should be favorable. Adsorption of the modifier was thought to be with the quinoline part, probably parallel to the surface (via the π system).

Wells and co-workers [50,58] suggested at first that an array of adsorbed cinchona molecules might be responsible for enantiocontrol. They explained the observed rate enhancement with three effects [50]: (i) the activation of the substrate by the quinuclidine nitrogen (from the effect of quinuclidine addition); (ii) a higher hydrogen coverage of the modified catalyst (enhanced H_2/D_2 exchange); (iii) the electronic effect of the adsorbed quinoline part (from the effect of quinoline addition). This interesting idea of ordered adsorption had to be abandoned for several reasons. The most important one was that the observed dependence of e.e. and rate on the modifier concentration was not in agreement with the formation of an array of modifier molecules [41]. Instead, the active site model described above was used with the suggestion, that the adsorbed cinchonidine would stabilize the half-hydrogenated ***etpy*** via the quinuclidine nitrogen, thereby leading to the observed rate enhancement.

Augustine [10] proposed that the cinchona molecule is adsorbed via the N of the quinoline (edge on) close to an Pt ad-atom where H and ***etpy*** were adsorbed. In this proposal the N of the quinuclidine was thought to interact with one of the carbonyl groups of ***etpy***.

From the molecular modeling studies described above, Baiker and Weber et al. [28,57,60,61] proposed that it is the protonated cinchona modifier that interacts with the oxygen of the carbonyl bond, thereby activating ***etpy*** for hydrogenation.

Comment. With the exception of the array model, all of these proposals are basically in agreement with the kinetic results discussed above. The suggestion made by Augustine seems to imply that both ***etpy*** and hydrogen can adsorb on the same Pt atom. This is not likely and is not in agreement with the rate decrease at high ***etpy*** (competitive adsorption). The two suggestions by Wells and by Baiker concerning the hydrogen bridged species are almost identical. We get a good fit in kinetic modeling assuming a reaction between ⋆-H and an adsorbed ***etpy*** to give the stabilized half-hydrogenated ketone. ⋆-H can be interpreted as a protonated adsorbed cinchona modifier. The proton could either come from the solution (e.g. from acetic acid) or from dissociatively adsorbed hydrogen. In this scenario, the second H-atom would be added as hydride.

4.5.2. *Proposals involving a "modified substrate" (shielding effect)*

The main ideas of Margitfalvi and co-workers [46,62] have already been described above. It is proposed that ***etpy*** forms a complex with the aromatic part of the effective modifiers and that this activated complex is hydrogenated. The authors have described two different scenarios of how this might happen. In the first [54,62], the role of the metal is described as "to provide adsorbed hydrogen for the hydrogenation", implying some sort of Eley–Rideal mechanism. In the second [46], the substrate-modifier complex was proposed to adsorb on the metal surface where it is then hydrogenated.

Comment. The first proposal (Eley–Rideal mechanism) can strictly be excluded because the observed saturation effects are not compatible with such a course of reaction. The present results do not allow to completely rule out the hydrogenation of a modifier-substrate complex. In principle, similar dependencies of rate and e.e. could be assuming that the ***etpy-Cd*** complex adsorbs much stronger than both ***etpy*** and ***Cd*** alone. In order to explain the rate and e.e. dependence at low ***Cd*** concentration, a very strong adsorption of the ***etpy-Cd*** complex is necessary. If ***Cd*** is adsorbed stronger than the modifier-substrate complex, there would be no difference to a modified catalyst as described above.

4.5.3. *Mechanism: Conclusions*

With the information summarized above and the at this stage of knowledge, the most convincing explanation for both the enantiodiscrimination and the rate acceleration is the preferential stabilization of one of the two possible diastereomeric intermediates (or transition states). As to the precise structure of these intermediates, no hard information is available. These will probably be the subject of future controversial speculation and discussion.

5. Experimental

5.1. *Immobilized cinchona modifier*

The Pt/SiO_2 catalyst was prepared by an ion exchange method with silica Grace 952W (BET 270 m^2/g, pore diameter 11 nm), $[Pt(NH_3)_4]Cl_2$ and $[Pt(NH_3)_4](OH)_2$ [70]: $D=0.67$, mean crystallite size=2.5 nm, Pt content: 1.65%. The functionalized cinchol derivative was grafted onto the silica surface by reaction of surface Si–OH groups with the Si(OEt)-groups of the spacer in boiling toluene under formation of Si–O–Si bonds, for a review on the modification of silica surface see [17]. Blocking the Pt surface with CO during immobilization proved to be essential for getting an active and selective catalyst. Elemental analysis of the modified catalyst: C=9.8%, H=1.7%, N=1.2%. The catalyst was activated by mild air oxidation to remove CO.

5.2. *Experimental details for the preparation and characterization of Pt colloids*

The colloid was prepared according to Duff et al. [18] using H_2PtCl_6, polyvinylpyrrolidone (medium MW 10.000) in $MeOH/H_2O$. The hydrogenation tests were carried out in a 50 ml stainless steel autoclave with a magnetic stirring bar. Standard conditions: 5 ml ***etpy*** (Boeringer, freshly distilled); 20 ml solvent; 5 mg Pt (added as $MeOH/H_2O$ 1:1 solution with 2 mg Pt/ml), 10 mg modifier; r.t.; 100 bar. Conversion (glc on OV 101) and optical yield (derivatization with isopropylisocyanate; glc on CHIRASIL-L-VAL) were determined at the end of each experiment (usually after 1–2 h). Activity is expressed as average conversion per min.

Acknowledgements

We would like to thank R.L. Augustine, A. Baiker, H. Bönnemann, D.G. Blackmond, P. Johnston, J.L. Margitfalvi, Y. Nitta, W. Reschetilowski, A. Tungler and P.B. Wells for providing information on recent publications as well as for informative discussions. The experimental part of our own unpublished contributions was carried out by D. Imhof and J. Salathin.

References

[1] Y. Izumi, Adv. Cat. 32 (1983) 2151; A. Tai, T. Harada, in: Y. Iwasawa (Ed.), Tailored Metal Catalysts, D. Reidel, Dordrecht, 1986, p. 265; A. Tai, Shokubai 37 (1995) 522.

[2] Y. Orito, S. Imai, S. Niwa, J. Chem. Soc. Jpn. (1979) 1118; (1980) 670; (1982) 137; Y. Orito, S. Imai, S. Niwa, G-H Nguyen, J. Synth. Org. Chem. Jpn. 37 (1979) 173; Y. Orito, S. Imai, S. Niwa, J. Chem. Soc. Jpn. (1980) 670.

[3] H.U. Blaser, H.P. Jalett and J. Wiehl, J. Mol. Catal., 68 (1991) 215.

[4] H.U. Blaser, M. Müller, Stud. Surf. Sci. Catal. 59 (1991) 73; H.U. Blaser, Tetrahedron: Asymmetry 2 (1991) 843; G. Webb, P.B. Wells, Catal. Today 12 (1992) 319; A. Baiker, H.U. Blaser Enantioselective Catalysts and Reactions, accepted for Handbook of Heterogeneous Catalysis, G. Ertl, H. Knötzinger, J. Weitkamp (Eds.), to appear in 1997.

[5] H.U. Blaser, H.P. Jalett, D.M. Monti, J.F. Reber and J.T. Wehrli, Stud. Surf. Sci. Catal., 41 (1988) 153.

[6] H.U. Blaser, H.P. Jalett, D.M. Monti, A. Baiker and J.T. Wehrli, Stud. Surf. Sci. Catal., 67 (1991) 147.

[7] U. Böhmer, K. Morgenschweis and W. Reschetilowski, Catal. Today, 24 (1995) 195.

[8] W. Reschetilowski, U. Böhmer and K. Morgenschweis, Chem. Ing. Tech., 67 (1995) 205.

[9] W. Reschetilowski, U. Böhmer, J. Wiehl, in: G. Jannes, V. Dubois (Eds.), Chiral Reactions in Heterogeneous Catalysis, Plenum Press, New York, NY, 1995, p. 111.

[10] R.L. Augustine, S.K. Tanielyan and L.K. Doyle, Tetrahedron: Asymmetry, 4 (1993) 1803.

[11] S. Bhaduri, V.S. Darshane, K. Sharma and D. Mukesh, J. Chem. Soc., Chem. Commun., (1992) 1738.

[12] S.P. Griffiths, P. Johnston, W.A.H. Vermeer and P.B. Wells, J. Chem. Soc., Chem. Commun., (1994) 2431.

[13] K.E. Simons, A. Ibbotson, P. Johnston, H. Plum and P.B. Wells, J. Catal., 150 (1994) 321.

[14] T.J. Hall, P. Johnston, W.A.H. Vermeer, S.R. Watson, P.B. Wells, Proceedings 11th International Congress on Catalysis, Baltimore 1996, Stud. Surf. Sci. Catal. 101 (1996) 221.

[15] H.U. Blaser, S.K. Boyer and U. Pittelkow, Tetrahedron: Asymmetry, 2 (1991) 721.

[16] Y. Nitta, Y. Ueda, T. Imanaka, Chem. Lett. (1994) 1095; Y. Nitta, K. Kobiro, Chem. Lett. (1995) 165; Y. Nitta, K. Kobiro, Chem. Lett. (1996) 897.

[17] H. Engelhardt, P. Orth, J. Liqu. Chrom. 10 (1987) 1999.

[18] D.G. Duff, P.P. Edwards, J. Evans, J.T. Gauntlett, D.A. Jefferson, B.F.G. Johnson, A.I. Kirkland and D.J. Smith, Angew. Chem., 101 (1989) 610.

[19] P.J. Collier, T. Goulding, J.A. Iggo, R. Whyman, in: G. Jannes, V. Dubois (Eds.), Chiral Reactions in Heterogeneous Catalysis, Plenum Press, New York, NY, 1995, p. 105.

[20] H. Bönnemann and G. Braun, Angew. Chem., 108 (1996) 2120.

[21] W. Lottenbach, H.P. Jalett, M. Studer, H.U. Blaser, manuscript in preparation.

[22] D.J. Berrisford, C. Bolm and K.B. Sharpless, Angew. Chem., 107 (1995) 1159.

[23] B. Winter-Werner, Dissertation ETHZ, 1996; we thank for the provided sample.

[24] H.U. Blaser, D. Imhof, M. Studer, manuscript accepted for the 4th International Symposium on Heterogeneous Catalysis and Fine Chemicals, Basel, September 1996.

[25] T. Heinz, G. Wang, A. Pfaltz, B. Minder, M. Schürch, T. Mallat and A. Baiker, J. Chem. Soc., Chem. Commun., (1995) 1421.

[26] B. Minder, T. Mallat, A. Baiker, G. Wang, T. Heinz and A. Pfaltz, J. Catal., 154 (1995) 371.

[27] B. Minder, M. Schürch, T. Mallat and A. Baiker, Catal. Lett., 31 (1995) 143.

[28] K.E. Simons, G. Wang, T. Heinz, T. Giger, T. Mallat, A. Pfaltz and A. Baiker, Tetrahedron: Asymmetry, 6 (1995) 505.

[29] G. Wang, T. Heinz, A. Pfaltz, B. Minder, T. Mallat and A. Baiker, J. Chem. Soc., Chem. Commun., (1994) 2047.

[30] A. Tungler, T. Mathe, T. Tamai, K. Fodor, J. Kajtar, I. Kolossvary, B. Herenyi and R.A. Sheldon, Tetrahedron: Asymmetry, 6 (1995) 2395.

[31] A. Tungler, T. Tarnai, T. Mathe, G. Vidra, J. Petro, R.A. Sheldon, in: G. Jannes, V. Dubois (Eds.), Chiral Reactions in Heterogeneous Catalysis, Plenum Press, New York, NY, 1995, p. 201.

[32] W.A.H. Vermeer, A. Fulford, P. Johnston and P.B. Wells, J. Chem. Soc., Chem. Commun., (1993) 1053.

[33] A. Baiker, K. Borzeky, T. Mallat, M. Schürch, O. Schwalm, Posters presented at the 4th International Symposium on Heterogeneous Catalysis and Fine Chemicals, Basel, September 1996.

[34] H.U. Blaser and H.P. Jalett, Stud. Surf. Sci. Catal., 78 (1993) 139.

[35] T. Tarnai, A. Tungler, T. Mathe, J. Petro, R.A. Sheldon and G. Toth, J. Mol. Catal., 102 (1995) 41.

[36] J.T. Wehrli, A. Baiker, D.M. Monti, H.U. Blaser and H.P. Jalett, J. Mol. Catal., 57 (1989) 245.

[37] W. Reschetilowski, U. Böhmer and J. Wiehl, Stud. Surf. Sci. Catal., 84C (1994) 2021.

[38] B. Minder, T. Mallat, P. Scrabble and A. Baiker, Catal. Lett., 29 (1994) 115.

[39] B. Minder, T. Mallat, K.H. Pickel, K. Steiner and A. Baiker, Catal. Lett., 34 (1995) 1.

[40] H.U. Blaser, H.P. Jalett, D.M. Monti and J.T. Wehrli, J. Appl. Catal., 52 (1989) 19.

[41] K.E. Simons, P.A. Meheux, S.P. Griffiths, I.M. Sutherland, P. Johnston, P.B. Wells, A.F. Carley, M.K. Rajumon, M.W. Roberts and A. Ibbotson, Recl. Trav. Chim. Pays-Bas., 113 (1994) 465.

[42] P. Johnston and P.B. Wells, J. Catal., 156 (1995) 180.

[43] P.A. Meheux, A. Ibbotson and P.B. Wells, J. Catal., 128 (1991) 387.

[44] J.L. Margitfalvi, B. Minder, E. Talas, L. Botz, A. Baiker, in: New Frontiers in Catalysis. Proceedings 10th International Congress on Catalysis, Budapest, 1992, L. Guczi, F. Solymosi, P. Tetenyi (Eds.), Akademiai Kiado, Budapest, 1993, p. 2471.
[45] J. Wang, Y. Sun, C. LeBlond, R.N. Landau and D.G. Blackmond, J. Catal., 161 (1996) 752.
[46] J.L. Margitfalvi, M. Hegedüs and E. Tfirst, Tetrahedron: Asymmetry, 7 (1996) 571.
[47] J.L. Margitfalvi, Chem. Ind., 62 (1995) 189.
[48] J.L. Margitfalvi and M. Hegedüs, J. Mol. Catal., 107 (1996) 281.
[49] U.K. Singh, R.N. Landau, Y. Sun, C. LeBlond, D.G. Blackmond, S.K. Tanielyan and R.L. Augustine, J. Catal., 154 (1995) 91.
[50] G. Bond, P.A. Meheux, A. Ibbotson and P.B. Wells, Catal. Today, 10 (1991) 371.
[51] Y. Sun, J. Wang, C. LeBlond, R.N. Landau and D.G. Blackmond, J. Catal., 161 (1996) 759.
[52] E. Talas, L. Botz, J.L. Margitfalvi, O. Sticher and A. Baiker, J. Planar Chromatogr., 5 (1992) 28.
[53] H.U. Blaser, M. Garland and H.P. Jalett, J. Catal., 144 (1993) 569.
[54] J.L. Margitfalvi, J. Catal., 156 (1995) 175.
[55] H.U. Blaser, H.P. Jalett, F. Spindler, J. Mol. Catal. A: Chemical 107 (1996) 85.
[56] G.H. Sedelmeier, H.U. Blaser, H.P. Jalett; 1986; EP 206 993, assigned to Ciba–Geigy AG.
[57] A. Baiker, T. Mallat, B. Minder, O. Schwalm, K.E. Simons, J. Weber in: G. Jannes, V. Dubois (Eds.), Chiral Reactions in Heterogeneous Catalysis, Plenum Press, New York, NY, 1995, p. 95.
[58] I.M. Sutherland, A. Ibbotson, R.B. Moyes and P.B. Wells, J. Catal., 125 (1990) 77.
[59] G. Bond and P.B. Wells, J. Catal., 150 (1994) 329.
[60] O. Schwalm, B. Minder, J. Weber and A. Baiker, Catal. Lett., 23 (1994) 271.
[61] O. Schwalm, J. Weber, B. Minder and A. Baiker, J. Mol. Struct. (Theochem)., 330 (1995) 353.
[62] J.L. Margitfalvi, M. Hegedüs, E. Tfirst, Proceedings 11th International Congress on Catalysis, Baltimore 1996, Stud. Surf. Sci. Catal. 101A (1996) 241; J.L. Margitfalvi, M. Hegedüs, J. Mol. Catal. A: Chemical 107 (1996) 281.
[63] C.R. Landis and J. Halpern, J. Am. Chem. Soc., 109 (1987) 1746.
[64] H.U. Blaser, H.P. Jalett, M. Garland, M. Studer, H. Thies and A. Wirth-Tijani, manuscript in preparation.
[65] A. Tungler, T. Mathe, K. Fodor, R.A. Sheldon, P. Gallezot, J. Mol. Catal. (1996).
[66] Y. Sun, R.N. Landau, J. Wang, C. LeBlond and D.G. Blackmond, J. Am. Chem. Soc., 118 (1996) 1348.
[67] J. Simonikokova, L. Hillaire, J. Panek and K. Kochloefl, Z. Phys. Chem., 83 (1973) 287.
[68] Y. Nitta, T. Imanaka and S. Teranishi, J. Catal., 80 (1983) 31.
[69] D.G. Blackmond, Private communication.
[70] H.A. Benesi, R.M. Curtis and H.P. Studer, J. Catal., 10 (1968) 328.
[71] R.L. Augustine and S.K. Tanielyan, J. Mol. Catal. A, 112 (1996) 93.