Enantioselective Hydrogenation Using Heterogeneous Modified Catalysts: An Update

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Abstract: The state of the art for the enantioselective hydrogenation applying chirally modified heterogeneous catalysts is reviewed with emphasis on new developments between 1997 and 2002. Discussed are various combinations of metal–modifier–substrate which give enantioselectivities useful for synthetic applications. The three most important asymmetric catalysts types are nickel catalysts modified with tartaric acid, useful for β-functionalized ketones with ees up to 98.6%, platinum catalysts modified with cinchona alkaloids and related modifiers, successful for α-functionalized ketones with ees up to 98% and palladium catalysts modified with cinchona alkaloids which achieve ees up to 94% for selected activated C=C bonds. Mechanistic investigations comprising surface science and spectroscopic studies often combined with computational modeling as well as kinetic studies are summarized and the various mechanistic models are discussed.

Keywords: cinchona-alkaloid modified catalysts; enantioselective hydrogenation; heterogeneous modified catalysts; hydrogenation of functionalized ketones; tartrate-modified nickel catalysts

1 Introduction

Catalyst modification is a strategy that is applied widely in heterogeneous catalytic hydrogenation. Thereby 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., only a particular combination of a metal, a modifier and a substrate type leads to good enantioselectivity. Already quite small variations in one of the three components can lead to drastic changes in enantiodiscrimination. For this reason, our review will be structured according to successful catalyst–modifier–substrate systems. Historically, the hydrogenation of β-keto esters was the first reaction catalyzed by a heterogeneous chiral catalyst with high and reproducible enantioselectivities.[1] In recent years, catalysts modified with cinchona alkaloids originally described by Orito et al.[2] for α-keto esters have been the focus of over 100 papers whereas attempts to find new types of catalyst systems were less numerous and also less successful.

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From left to right: M. Studer, C. Exner, H.-U. Blaser.

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Christian Exner received his Diploma in 1998 from the University of Bielefeld, Germany under the supervision of Prof. Dr. Hans-Friedrich Grützmacher and PD Dr. Dietmar Kuck. During his dissertation (1998–2002) with Prof. Dr. Andreas Pfaltz at the Max-Planck-Institut für Kohlenforschung in Mülheim a. d. Ruhr, Germany and at the University of Basel, Switzerland he investigated the synthesis and screening of new chiral modifiers for the heterogeneous asymmetric hydrogenation of α-keto esters and related activated compounds.

Hans-Ulrich Blaser received the Diploma in Natural Sciences from the Federal Institute of Technology (ETH) Zürich in 1966. His doctoral research was carried out with A. Eschenmoser at the same institution, from which he received the PhD degree in 1971. Between 1971 and 1975 he held post-doctoral positions at the University of Chicago (J. Halpern), Harvard University (J. A. Osborn), and Monsanto (Zürich). During 20 years at Ciba-Geigy (1976–1996) he gained practical experience at R&D in the fine chemicals and pharmaceutical industry, which continued at Novartis (1996–1999) and at Solvias where he presently is chief technology officer. During his industrial carrier, he has developed and implemented numerous catalytic routes for agrochemicals, pharmaceuticals and fine chemicals (both as project leader and section head). His main interests are the development and the industrial application of selective catalysts.

The overview gives an update on recent progress achieved in the development and understanding of selected heterogeneous enantioselective catalyst systems. In the last few years several excellent reviews covering various aspects of enantioselective heterogeneous hydrogenation have appeared[3–6]. Where appropriate, we will refer our discussions to these reviews.

2 Nickel Catalysts Modified with Tartaric Acid and Related Catalysts

Two recent reviews by Tai and Sugimura[3a] and Osawa et al.[3b] give a historical account as well as an extensive description of the important parameters affecting catalyst performance and a thorough discussion of the mechanistic interpretations offered by the Japanese School.

2.1 Modifiers

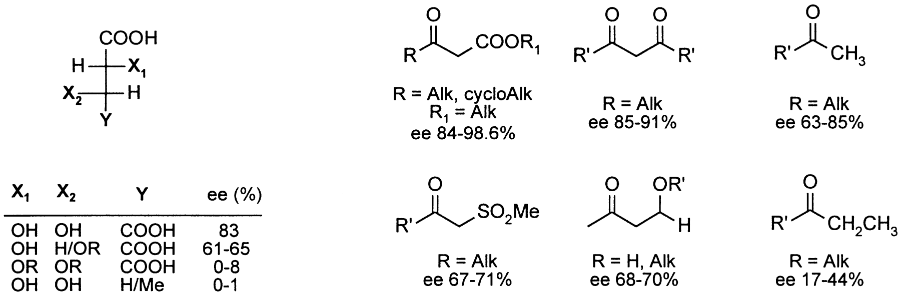
Tartaric acid is by far the best modifier for Ni-catalyzed reactions. Substituting more than one of the hydroxy groups or one of the acid groups leads to almost complete loss of enantiodifferentiation[3a] (see Figure 1). α-Amino acids have been reported to give low to medium enantioselectivities.[1] Especially for the hydrogenation of unfunctionalized methyl ketones, co-modifiers such as pivalic acid have been shown to have a significant effect on the enantioselectivity.[3]

2.2 Substrates

Careful optimization of the impregnation and reaction conditions have improved the enantioselectivity of the Raney nickel system for several β-functionalized ketones as well as for 2- and 3-alkanones (see Figure 1). Special note should be given to the very high ees for methyl 3-cyclopropyl-3-oxopropanoate (98.6%[7]) and of 85% for 3,3-dimethyl-2-propanone in the presence of an organic acid as co-modifier.

Recent results: The gas phase hydrogenation of 2-butanone was described with ees up to 31% using a tartrate-modified nickel on Y-zeolite catalyst.[8] Aromatic β-keto esters (R = Ar in Figure 1) give lower ees (46–77%) compared to the alkyl analogues.[9]

Synthetic applications for β-keto esters using Ni-tartrate catalysts have been described for sex pheromones of the pine sawfly,[10] for biologically active C_{10} to C_{16} 3-hydroxy acids[11] and for an intermediate of tetrahydrolipstatin, a pancreatic lipase inhibitor (ee 90–92%, 6–100 kg scale).[12] A β-diketone was also used as starting material for a diphosphine ligand.[13]



X_1	X_2	Y	ee (%)
OH	OH	COOH	83
OH	H/OR	COOH	61-65
OR	OR	COOH	0-8
OH	OH	H/Me	0-1

Figure 1. Effect of modifier and substrate structure on enantioselectivity for Raney Ni-catalyzed reactions of ketones.[3a] Standard reaction: Methyl acetoacetate with Ra-Ni/tartrate/NaBr. For 2- and 3-alkanones a bulky carboxylic acid was used as co-modifier.

2.3 Catalysts

The state of the art can be summarized as follows.[3] The preferred catalyst is freshly prepared Raney nickel; the only useful modifier is tartaric acid and sodium bromide is an obligatory co-modifier for high ee. The composition of the Ni-Al alloy, the impregnation procedure (tartaric acid and NaBr concentrations, pH, T, time, ultrasound[14]) as well as the reaction conditions (solvent, p, T, acid co-modifiers) are crucial for getting good results. Supported nickel catalysts or various nickel powders can also be modified, often with satisfactory results.[3a] In general, the preparation procedure is quite cumbersome and all these catalysts have relatively low activity; high catalyst loading as well as high pressures and temperatures are usually necessary for preparative applications. Some of these problems were addressed in recent publications by Osawa et al.[3b,15] who described active catalysts prepared by *in-situ* modification with tartaric acid/NaBr of a pre-hydrogenated metallic Ni powder. Methyl acetoacetate was hydrogenated with reasonable activity and, especially notable, the catalyst could be re-used at least 30 times with little loss of activity with ee values around 80–84%. At the moment, these catalysts are not commercially available, making synthetic applications difficult for organic chemists.

2.4 Summary: Ni-Based Catalysts

Suitable substrates are β-functionalized ketones and bulky methyl ketones in the presence of bulky carboxylic acids. Tartaric acid is the only useful modifier and Raney nickel is the catalyst of choice. Ordered domains with high crystallinity are thought to be modifiable leading to enantioselective hydrogenation whereas disordered domains are not modifiable and give a racemic reaction. High ees are only observed in the presence of NaBr; bromide ions are proposed to block racemic sites while Na^+ might influence the structure of the adsorbed tartrate.

3 Platinum Catalysts Modified with Alkaloids and Related Catalysts

3.1 Modifiers and Solvents

Several reviews describe the status between 1997 and 1999[4–6]. Minimal requirements for an efficient modifier for the hydrogenation of α-keto esters were described to be a basic nitrogen atom, close to one or more stereogenic centers and connected to an aromatic system. The best results were obtained with interconnected, flat rings, e.g., quinolyl or naphthyl. The main conclusions of a detailed study of the hydrogenation of ethyl pyruvate with a variety of different cinchona derivatives (structures and abbreviations see Figure 2) can be summarized as follows.[6]

- Best results were obtained with cinchonidine or slightly altered derivatives such as HCd or 9-methoxy-HCd (MeOHCd) to give ethyl (*R*)-lactate and with cinchonine derivatives to give the (*S*)-enantiomer, albeit with lower ees.
- Three structural elements in the cinchona molecule were identified to affect rate and ee of the enantioselective hydrogenation of α-keto acid derivatives: i) an extended aromatic moiety, ii) the substitution pattern of the quinuclidine (the absolute configuration at C-8 controls sense of induction, *N*-alkylation yields racemate), iii) the substituents at C-9 (OH or MeO are optimal, larger groups reduce enantioselectivity).
- The choice of the solvent had a significant effect on enantioselectivity and rate. MeOHCd in acetic acid

8(*R*), 9(*S*)		R′	R″	8(*S*), 9(*R*)	
Cinchonine	(Cn)	Vinyl	H	(Cd)	Cinchonidine
10,11-Dihydrocinchonine	(HCn)	Ethyl	H	(HCd)	10,11-Dihydrocinchonidine
Quinidine	(Qd)	Vinyl	OMe	(Qn)	Quinine
10,11-Dihydroquinidine	(HQd)	Ethyl	OMe	(HQn)	10,11-Dihydroquinine

Figure 2. Structures of the parent cinchona alkaloid families.

and HCd/toluene were the most effective modifier/solvent combinations.

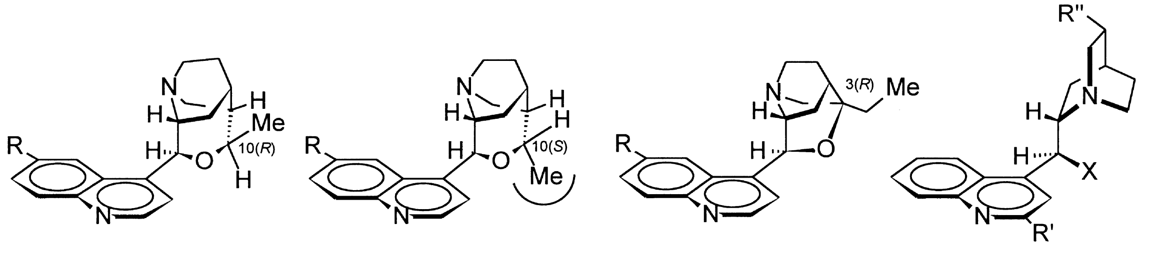
In order to get information on the productive conformation of the cinchona alkaloids, several derivatives with conformational constraints were tested by the group of Bartók[16] (see Figure 3). For α-IQd and α-ICn, comparable ees to the parent alkaloids were found, whereas the ee was much lower for γ-IQd. Bartók explained these differences with the sterical hindrance of methyl group on C-10 which hinders adsorption of the alkaloid on the metal surface. Since rotation around the C-8–C-9 bond is blocked, a closed conformation is not possible for these modifiers. The β-ICn derivative yielded lower ees (50% in toluene and 62% in AcOH) than the α-derivatives due to their higher rigidity.[16e] Really surprising was the finding that while in AcOH the expected excess of (*R*)-lactate was observed, in toluene the (*S*)-form was formed preferentially. Similar but weaker solvent effects were reported for some cinchona derivatives with bulky OR groups at the C-9 position, but only ees of < 20% were observed there.[6b] The cinchonidine derived modifier with a 2-phenyl group was synthesized to test the notion that the productive adsorption is *via* the π-face of the quinoline ring and not the lone pair; the resulting ees support the flat adsorption.[17]

3.1.1 Cinchona Mimics and Various Modifiers

The cinchona mimics developed by Pfaltz and Baiker[4,6] indicate that good enantioselectivities can be reached with relatively simple amino alcohols having just one stereogenic center (best modifiers see Figure 4). Recently it was shown that for amino alcohols with a second stereogenic center the *R,S*-stereoisomers (*erythro*) were the effective ones as observed for the natural alkaloids.[18] The importance of size of the aromatic group was confirmed: ees increase in the order phenyl (ineffective) ≪ naphthyl < anthryl[18] (Figure 4). Amino alcohols derived from L-tryptophane yielded ees up to 43%, while the corresponding acids or esters were not effective.[19] Morphine modifiers were reported to give 13% ee.[20]

3.2 Substrates

For the organic chemists who wants to apply a specific transformation, the substrate scope of a catalyst system is the most important information in synthesis design and planning. For this reason this section describes in some detail which substrate types can be transformed with good enantioselectivity and also what conditions are optimal.

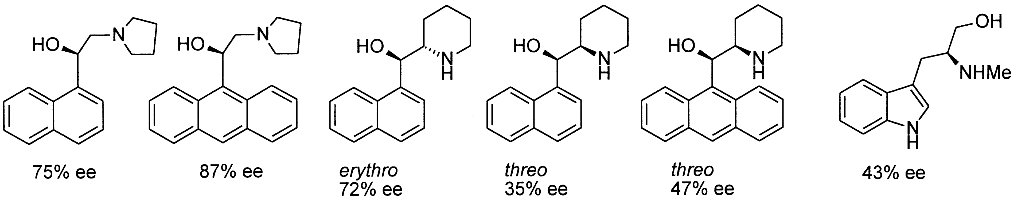


α-ICn R = H 88% ee
α-IQd R = MeO 85% ee
γ-IQd R = MeO 22% ee
β-ICn R = H 62% ee
X = OH R' = H R'' = Vinyl 83% ee
X = H R' = H R'' = Ethyl 57% ee
X = H R' = Ph R'' = Ethyl 48% ee

Figure 3. Cinchona derivatives with conformational constraints and a 2-phenyl substituent (ee for hydrogenation of ethyl pyruvate, Pt/Al_2O_3, AcOH).

Table 1. Best ee for various α-keto acid derivatives (substrate structures see Figure 5).

Substrate	ee	Catalyst, Modifier, Solvent, Reaction conditions, Remarks	Ref.
1 R = Me	98%	Pt colloids, Cd, AcOH, 40 bar, 25 °C	[23]
1 R = Et	97%	5% Pt/Al_2O_3 (E 4759), MeOHCd, AcOH, 10 bar, 25 °C, ultrasound	[24a]
2	96%	5% Pt/Al_2O_3 (E 4759), MeOHCd, AcOH, 10 bar, 25 °C, ultrasound	[24a]
2	94%	1% Pt/Al_2O_3 (Aldrich), HCd, AcOH, 5.8 bar, 17 °C, dosing of modifier	[25]
3	98%	5% Pt/Al_2O_3 (E 4759), HCd, AcOH/toluene mixture, 25 bar, 0 °C	[26]
4	96%	5% Pt/Al_2O_3 (JMC 94), MeOHCd, AcOH, 20 bar, 20 °C	[27]
5	86%	5% Pt/Al_2O_3 (JMC 94), HCd, toluene, 60 bar, 25 °C	[28]
6	60%	5% Pt/Al_2O_3 (E 4759), Cd, AcOH, 60 bar, r.t.	[29]
7	92%	5% Pt/Al_2O_3 (E 4759), Cd, toluene, 70 bar, − 13 °C	[30]
8	91%	5% Pt/Al_2O_3 (E 4759), Cd, toluene, 70 bar, 17 °C	[30]



75% ee 87% ee *erythro* 72% ee *threo* 35% ee *threo* 47% ee 43% ee

Figure 4. Amino alcohols as cinchona mimics (best ees for the hydrogenation of ethyl pyruvate, Pt/Al_2O_3).

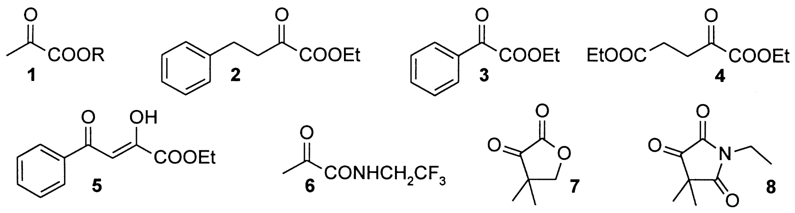


Figure 5. α-Keto acid derivatives listed in Table 1.

3.2.1 α-Keto Acid Derivatives

α-Keto esters like methyl and ethyl pyruvate and phenyl glyoxylic acid esters are still the substrates with the highest ees (Table 1). Various strategies were applied for increasing the ee (special colloids, use of ultrasound, solvent mixtures, acids and bases as additives) but, not surprisingly, the reaction conditions have to be optimized for every substrate. An analysis of the results shows that for most aliphatic keto ester derivatives, AcOH in combination with MeOHCd or HCd gave the best results. Both trifluoroacetic acid[21] and amines[22] as additive were reported to have an additional beneficial effect on enantioselectivity. For aromatic, conjugated and cyclic systems, the combination of HCd and toluene was optimal. Usually, the rate and productivity of the catalytic systems was not addressed.

Szöri et al.[31] found that bulky R and to a lower extent R' groups in a series of α-keto esters RCOCOOR' caused a significant decrease in ee as well as rate. Similar results were reported for various R' groups with Pt-colloids.[23] Good enantio- and very high chemoselectivity were achieved for α,γ-diketo esters (> 90% enol form)[28] (also see Section 3.4.2).

3.2.2 Other Activated Ketones

The trifluoromethyl group was identified as having a similar activating property as an ester group in 1997 and several papers by the group of Baiker[32] elaborate on this topic. Me, Et and *i*-Pr esters of 4,4,4-trifluoroacetoacetate gave ees of 90 – 93% in AcOH or trifluoroacetic acid/THF mixtures, MeOHCd was significantly more efficient than HCd (see Table 2). Various trifluoroacetophenone derivatives with additional CF_3 or $N(Et)_2$-substitutents on the aromatic ring gave ees between 36 and 92%, but ee and TOF were highest without any substituent. The same substrates showed significantly lower ees in *o*-dichlorobenzene/EtOH with Pt-PVP colloids,[33] or in *o*-dichlorobenzene using Pt/Al_2O_3.[24b,32b] Other CF_3-substituted ketones were tested, but except for 2-trifluoroacetylpyrrole (63% ee) none of them gave ees significantly above 20%.[24b,32d] In contrast to α-keto esters, trifluoroketones easily form hemiketals which can negatively affect ees during the course of the reaction.[32c]

Recently, it was shown that other groups can also activate ketones sufficiently and Table 2 shows results obtained with a variety of α-functionalized ketones. Very high ees (> 90%) were obtained with α-keto

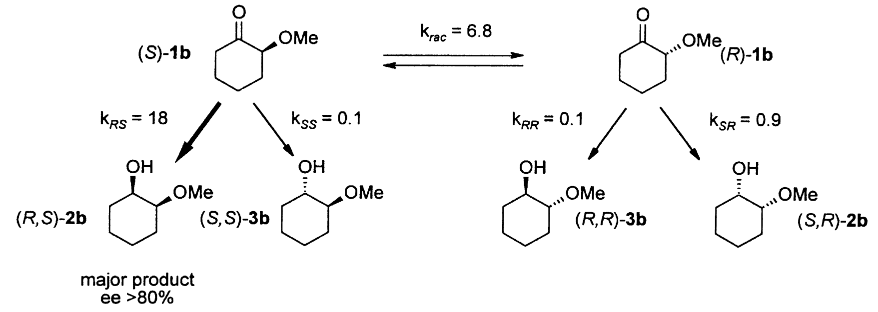


Figure 6. Reaction pathways, rates and product isomers for the hydrogenation of a cyclic α-keto ether [5% Pt/Al_2O_3 (JMC 94), MeOHCd, AcOH, solid base].[36]

Table 2. Best ee for various activated ketones (substrate structures, see Figure 7).

Substrate	ee	Catalyst, Modifier, Solvent, Reaction Conditions, Remarks	Ref.
9 R = CH_2COOEt	93%	5% Pt/Al_2O_3 (E 4759), MeOHCd, THF/TFA mixture, 10 bar, 20 °C	[32a]
9 R = Ph	92%	5% Pt/Al_2O_3 (E 4759), toluene, Cd, 10 bar, 0 °C	[32a]
10	98%	5% Pt/Al_2O_3 (JMC 94), MeOHCd, AcOH, 60 bar, 25 °C, kinetic resolution; conversion 22%.	[36]
11 R = Me	97%	5% Pt/Al_2O_3 (E 40655), Cd, AcOH, 1 bar, 25 °C	[35]
11 R = $(CH_2)_3$	97%	5% Pt/Al_2O_3 (JMC 94), MeOHCd, AcOH, 60 bar, 25 °C	[34]
12 R = Ph	65% (> 90%)	5% Pt/Al_2O_3 (Strem), Cd, CH_2Cl_2, 5 bar, 25°C. Main product 1-hydroxy-1-phenylpropanone. Value in brackets obtained by kinetic resolution in EtOAc from enriched hydroxy ketone	[39]
12 R = Me	50% (90%)	5% Pt/Al_2O_3 (JMC 94), HCd, toluene, 107 bar, 25 °C. Value in brackets obtained by kinetic resolution	[37,38]

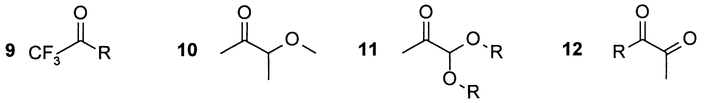


Figure 7. Activated ketones listed in Table 2.

acetals[34,35] and α-keto ethers,[36] where dynamic kinetic resolution yielded high ees and des with racemic starting materials (see Figure 6). As observed for α-keto esters,[31] bulky substituents on both parts of the molecule had a negative effect on rate and ee in the case of α-keto acetals.[34] The hydrogenation of 1,2-butanedione[37,38] and 1-phenyl-1,2-propanedione[39] gave significantly lower ees. In both cases, the ees for the hydroxy ketones increased during the reaction, because the minor enantiomer reacted significantly faster to the corresponding diol (kinetic resolution).[37–39] Other ketones like acetophenone,[40] ketoisophorone[41] and various β-keto esters[42] all gave ees of ≤ 20%.

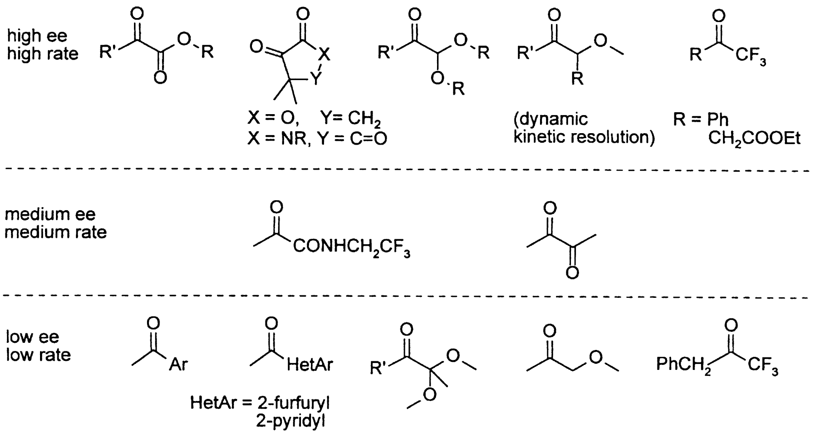


Figure 8. Structures of "good", "medium" and "bad" substrates for cinchona-modified Pt catalysts.

Significant progress in the substrate scope of the Pt-cinchona systems was made in the last five years. Besides α-keto acids and esters, some trifluoromethyl ketones and α-keto acetals and α-keto ethers have been to shown to give high ees (see Figure 8). Nevertheless, for the synthetic chemist, the substrate scope is still relatively narrow, and it is not expected that new important substrate classes will be found quickly. On the other hand, the chemoselectivity of the this system has not yet been exploited to its full value, and this might be a potential for future synthetically useful applications.

3.3 Catalysts

The status up to 1997 was summarized as follows.[5a]

- Pt is the metal of choice for the hydrogenation of functionalized ketones; for the enantioselective hydrogenation of C=C bonds, Pd is superior.
- Different supports are suitable, Al_2O_3, SiO_2, TiO_2 and zeolites give the best results, the results obtained with colloids show that the support only plays an indirect role.
- 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.

Two commercially available 5% Pt/Al_2O_3 have emerged as “standard” catalysts: E 4759 from Engelhard and JMC 94 from Johnson Matthey.[43] While both catalysts have dispersions of *ca.* 0.2 – 0.3, E 4759 has rather small pores and a low pore volume while JMC 94 is a wide-pore catalyst with a large pore volume. The support of E 4759 consists of γ-alumina and has a well-ordered, layered structure while 5 R 94 is a of γ- and θ-alumina with alumina crystallites of irregular shape with larger interstices. Despite of these differences, both catalysts achieve high ees and also satisfactory rates for a variety of α-functionalized ketones.

3.3.1 New Supports

Bartók[44] addressed the question, why Al_2O_3 is often better than other supports. In acetic acid, Al oxonium ions as well as their adducts with the alkaloid modifiers were detected in MS investigations. Since the addition of such Al-species to Pt-black led to a significantly higher ee and rate, Bartók interpreted this effect to be due to “electrostatic acceleration”. Several groups tried to improve the hydrogenation of ethyl pyruvate by preparing cinchonidine-modified Pt catalysts on various supports. Hall et al.[45] described Pt/MCM-41 (ees up to 64%, low rates due to mass transfer problems). Böhmer et al.[46] studied the re-use Pt/HNaY zeolite in AcOH and cyclohexane (88% ee). Also, ees up to 75% were reported for Pt/clay catalysts (28% ee for Rh/K-10),[47], while ees below 35% were described for Pt/C catalysts despite improvement by oxidative treatment.[48] Fodor et al.[49] tried to improve enantioselectivity by blocking unmodified sites with additives such as metals or sulfur compounds but only a decrease in rate but no change in ee were observed. Unorthodox catalysts were described by Yuan et al.[50] who deposited Pd and Pt on chiral supports like chitosan and wool. They claimed ees up to 100% for the hydrogenation of various ketones as well as other substrates. However, the validity of these results was challenged[51] and they have yet to be confirmed.

3.3.2 Catalyst Pretreatment

Various catalyst treatment procedures have been developed by different groups, the most important being a reduction of the Pt catalysts in hydrogen at 300 – 400 °C.[5a] An additional effect was claimed by pre-reduction in solution[52] and restructuring of the Pt/Al_2O_3 catalyst on account of these pretreatments was offered as potential explanation of the observed improvement.[53] Contact of the catalyst with air was also reported to give higher ees and rates for the hydrogenation of ethyl pyruvate in methyl acetate,[54] for trifluoroacetophenone in toluene,[55] and for 1-phenyl-1,2-propanedione in CH_2Cl_2,[39c] in all cases with Cd- or HCd-modified Pt/Al_2O_3. Wells et al.[56] studied the effect of air, N_2O, acetylene and other ‘adsorbates’ and claimed similar effects for the hydrogenation of ethyl pyruvate using Pt/SiO_2 modified by various alkaloids. Ru/SiO_2 modified by the same method was reported to reproducibly give 10 – 12% ee.[56b] Relatively small amounts of air seemed to be sufficient for the desired effects, larger amounts seemed to poison the system.[39c]

Another way to improve the catalyst performance was an ultrasound treatment of various Pt catalysts in the presence of cinchonidine as reported by the group of Bartók.[24c, d] For the hydrogenation of ethyl pyruvate on Pt/Al_2O_3 modified with HCd, 97% ee and the possibility to re-use the catalyst was claimed.[24d] Similar ee improvements were described for various α-keto esters,[24a,42] trifluoroacetophenone,[24b] and 1-phenyl-1,2-propanedione[39d] (anaerobic and aerobic pre-sonication). The positive effect was attributed to a restructuring of catalyst to obtain Pt-particles of the optimal size,[24a] ‘a more effective surface modification’[42] and ‘an increased surface density of the modifier’.[24a] The practical value of this pretreatment is not clear at the present time because all these experiments were only carried out on a small scale and high catalyst loading, and scale-up was reported to be difficult.[24d]

3.3.3 Colloidal Catalysts

Colloidal catalysts are of interest for two reasons. Firstly, support effects can be eliminated and secondly, there is hope to better control the morphology (size and shape) of the metal particles compared to classical supported catalysts.[5a] Pt and other colloids were investigated by a number of groups,[23,33,57–62] mostly for the cinchonidine-modified hydrogenation of pyruvates[23,33], but diketones[33b,59] and trifluoroacetophenone[33a] were also used as substrates. In most cases, polyvinylpyrrolidine (PVP) was used as stabilizer; HCd[57,60] was also an effective stabilizer and ees up to 80% were reported. Entrapment of this colloid in pectinate gave a more stable but less selective catalyst.[60] A Cd-Pt-PVP catalyst hydrogenated methyl pyruvate with ees up to 98%, the highest value ever reported. Interestingly, very small clusters of <2.0 nm gave the best results, opposite to what was reported for Pt/Al_2O_3.[5a] Pt colloids stabilized with KD1 (proprietary stabilizer of ICI) showed ees $<30\%$.[62] The performance and reproducibility of the colloids depended strongly on the preparation procedure, and the removal of HCl was shown to be essential.[58a] Similar rate acceleration[58b] and solvent effects[23] as with Pt/Al_2O_3 were observed. Promotion with rare earth metals[33d] led to a small increase in ee but no additional acceleration for methyl pyruvate, while addition of Sn^{2+} lead to higher rates for diketones, while the ee remained unaffected.[33b] A Rh-PVP colloid afforded ees up to 42% for ethyl pyruvate and similar rate acceleration as with Pt colloids,[61] the best value for a non-Pt catalyst for the hydrogenation of a ketone. A Pd-KD1 colloid gave 29% ee[62] for ethyl pyruvate and Ir-PVP 34% ee for methyl pyruvate.[33c]

In conclusion, not much progress has occurred concerning supports and Pt/Al_2O_3 pre-reduced with hydrogen at high temperature is usually the catalyst of choice. Ultrasound treatment improves catalyst performance but seems unpractical at larger scale. Considerable progress has been made with colloids where very high ees were reported. Since very small colloidal particles have afforded the highest ees, the debate about the optimal size of the Pt-crystallites is reopened. While the possibility to tailor them to a specific problem looks attractive, colloids are not suitable catalysts for technical applications.

3.4 Practical Problems, Synthetic Applications and Technical Developments

3.4.1. Practical Problems

Several practical problems have been discussed in detail which can lead to very unsatisfactory results for the synthetic application of cinchona-modified Pt catalysts. The following factors where identified.[74a]

i) *Change of ee with conversion:* Under particular conditions maximum enantioselectivity and rate are reached only after a certain period of time. Despite a spirited debate,[63] the reasons for this effect are still controversial.

ii) *Stability of the modifier:* Depending on modifier structure and reaction conditions, ring hydrogenation occurs and leads to decreased enantioselectivity. Not surprisingly, this effect which has been confirmed[64,65] is stronger when low modifier concentrations are used, which on the other hand has been shown to be beneficial for obtaining high ees.[25,64] Electron-spray mass spectrometry has shown to be useful for identifying cinchona alkaloids and derivatives thereof.[64d]

iii) *Side reactions of ethyl pyruvate:*[5d] Important side reactions are the formation of hemiketals in alcoholic solvents and formation of oligomers; impurities can cause catalyst poisoning. It has been shown that not only bases but also Al_2O_3 can catalyze hemiketal formation.[66] While hemiketal formation is not critical for most α-functionalized ketones, enantioselectivities for trifluoroketones decrease during the reaction due to hemiketal formation and hydrogenolysis.[32c] Polymer formation of ethyl pyruvate has been observed on Pt surfaces under UHV conditions[67] and aldol condensation reactions can occur in non-acidic solvents.[68] Since the aldol products are slightly acid this can lead to an increased ees, a similar effect has been described when trace amounts of water hydrolyze ethyl pyruvate.[69]

Our own experience has shown that most of these problems are due to non-optimal conditions and can be easily avoided by the proper choice of solvent, catalyst handling and reaction conditions.

3.4.2 Synthetic Applications

The first technical application of a cinchona-modified Pt catalyst was reported already in 1986 for the synthesis of an intermediate for the ACE inhibitor benazepril. The hydrogenation of the corresponding α-keto ester to ethyl (*R*)-2-hydroxy-4-phenylbutanoate (HPB ester, Figure 9 upper part) was developed and scaled-up into a production process (10–200 kg scale, chemical yield $>98\%$, ee 79–82%).[28c] Even though this route was competitive at the time, it suffered from several problems such as stability of starting ester, or non-crystallinity of the HPB ester. Recently, an improved new synthetic route to HPB ester (Figure 9 lower part) which is feasible on a large scale has been developed.[28a, b] The following aspects were the keys for success: i) the low price of the diketo ester prepared *via* Claisen condensation of acetophenone and diethyl oxalate; ii) the high

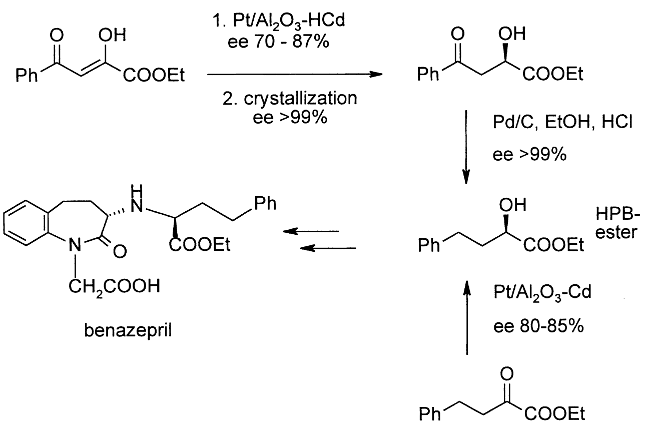


Figure 9. Two routes to HPB ester *via* Pt-cinchona-catalyzed hydrogenation.

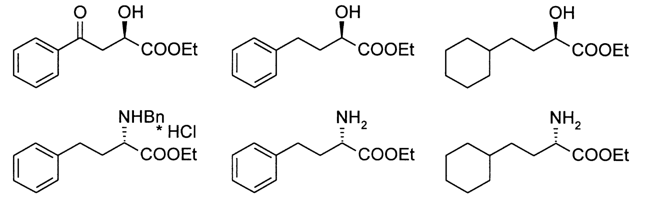


Figure 10. HPB ester-related compounds available from Fluka.[28c]

chemoselectivity in the Pt-cinchona hydrogenation, and iii) the possibility to enrich the hydroxy ketone intermediate with ees as low as 70% to >99% ee in a single crystallization step. The removal of the second keto group *via* Pd catalyzed hydrogenolysis did not lead to any racemization. Derived from the keto hydroxy intermediate, a whole range of chiral building blocks is now available in laboratory quantities from Fluka both in the (*R*)- and in the (*S*)-form (see Figure 10).

3.4.3 Technical Developments

As pointed out in several papers,[5a] high pressure (20–100 bar) is usually necessary for good ees and rates. Recently it was reported that pressures can be lowered to 1–5 bar when only minimal modifier concentrations are applied.[25,64] However, for high conversions it is necessary to add cinchona modifier to the reaction mixture.[25] Several groups have addressed the problem of catalyst re-use as well as reaction in the continuos mode. Catalyst re-use is only possible if new modifier is added.[5a] This has been confirmed[70a,71a] except when the hydrogenation is stopped at 70% conversion.[65] Several papers describe the continuous hydrogenation of ethyl pyruvate,[70,71] ethyl 2-oxo-4-phenylbutyrate[70b] and ketopantolactone.[71a, c] To maintain high ee, modifier had to be added to the feed.[70] Generally, the ees were lower than in batch hydrogenations and it is debatable whether these relatively small-volume products will ever be produced in this way. The use of supercritical solvents has also been tried for the hydrogenation of ethyl pyruvate; rate and ee were found to be considerably higher in CH_3CH_3 than in CO_2.[71b]

3.5 Summary: Pt-Based Catalysts

Several types of modifiers have been shown to be successful. Common features are a basic nitrogen atom close to one or more stereogenic centers connected to an extended aromatic system. By far the best over-all results are obtained with cinchonidine, Cd, derivatives for an excess of (*R*)-enantiomer and cinchonine derivatives for (*S*)-products, respectively. Suitable substrates are α-functionalized, activated ketones such as α-keto acid derivatives, α-keto ethers and acetals or trifluoromethyl ketones. Preferred solvents are acetic acid or toluene, base and acid additives can be effective. Pt/Al_2O_3 catalyst with moderate to low dispersion or Pt colloids with 1–2 nm particle size give best enantioselectivities.

4 Palladium Catalysts Modified with Alkaloids and Related Catalysts

Even though the first report on Pd-cinchona-catalyzed hydrogenation of a C=C bond was published in 1985,[72] systematic investigations started only in the mid-1990s and focused on α,β-unsaturated acids and ketones.[50,73] We will restrict this section to a short summary of important system parameters because despite considerable efforts, ees are usually low to moderate (see Figure 11), mechanistic aspects are discussed below. With the possible exception of a recently published Pd-cinchonidine-catalyzed hydrogenation of a hydroxymethylpyrone derivative (ee up to 94%),[74] no application with real synthetic potential has been reported up to now.

4.1 Modifiers and Substrates

For α,β-unsaturated acids (ees up to 72%) and hydroxymethylpyrone (ees up to 94%) cinchonidine is the preferred modifier (see Figure 11); substituting cinchonidine ($R_1 \neq H$, alkylation of N-1) leads to almost complete loss of enantioselectivity.[73,74,75b,76] Best enantioselectivities have been obtained for α,β-unsaturated acids with aryl and alkyl substituents whereas amido groups lead to low ees.[77] For isophorone, somewhat higher ees (up to 55%) are obtained with (−)-dihydrovinpocetine[78] (see Figure 12). Attempts to find conceptually different modifiers failed up to now, even though amino-substituted naphthalenes led to ees of 8%[79] and 21%[80] for the hydrogenation of α,β-unsatu-

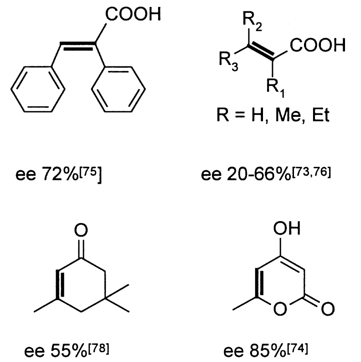
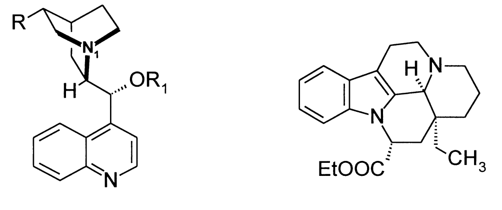


Figure 11. Structures of suitable substrates (best ees).



Cichonidine derivatives (–)-Dihydrovinpocetine

Figure 12. Structure of effective modifiers.

rated acids. The nature of the solvent as well as the presence of water, acids or bases can have strong effects on activity and enantioselectivity of these catalysts.[73–75] Hydrogen pressure has been shown to affect enantioselectivity differently for different α,β-unsaturated acids[75e] and isomerization of the alkanoic acid can give a significant loss of ee.[73c]

4.2 Catalysts

Preferred catalysts are Pd supported on TiO_2, Al_2O_3 or SiO_2 for α,β-unsaturated acids[73,75a,76] and hydroxymethylpyrone,[74] and Pd black for α,β-unsaturated ketones.[78] Several reports show that the Pd dispersion, the nature and texture of the support as well as the catalyst preparation and pre-treatment can have significant effects on the enantioselectivity of the Pd catalysts.[73,75,76,78]

4.3 Summary: Pd-Based Catalysts

Unsubstituted cinchona derivatives (and some vinca-type alkaloids) are the preferred modifiers. Best substrates are α,β-unsaturated acids and hydroxymethylpyrone. Pronounced acid and base effects are observed. Supported Pd catalysts with relatively low dispersion on wide pore supports give the best results.

5 Miscellaneous Catalytic Systems

Miscellaneous attempts to find new modified catalysts have met with little success up to now.[5a] Pd-ephedrine gave 26% ee for pyruvic acid oxime and 36% ee for an α,β-unsaturated ketone; Pd-camphor-10-sulfonic acid afforded 50% ee for a pyrazine derivative. Recently Fogassy et al.[81] described the Pd-catalyzed hydrogenation of an α,β-unsaturated exocyclic ketone in the presence of proline (ee up to 20%). However, in all cases very high modifier-substrate ratios were necessary for good results. It is possible that, in these cases, modifier-substrate adducts were the reactive species. A different approach was chosen by Smith et al.[82] who described the preparation of chiral catalysts by partial decomposition of chiral silyl ethers on Pd/SiO_2 catalysts. Here, ees up to 22% were reported for some α,β-unsaturated acids, but it is very doubtful that this procedure can ever yield catalysts with controllable properties. Margitfalvi's group[83] reported Pd/SiO_2 catalysts modified with chiral amino alcohols covalently bound to the silica surface and Pd/C catalysts modified with various chiral amino acid derivatives. Both catalyst systems were active for the reductive amination of methoxyacetone with benzylamine affording ees of up to 21%.

6 Mechanistic Investigations of Heterogeneous Catalytic Reactions

Trying to understand the mode of action of a catalyst is a fascinating but also very difficult endeavor. This is particularly true for enantioselective and even more so for heterogeneous catalysts. In our view, a reaction mechanism should postulate the structure of the controlling reaction intermediates as well as the kinetics of their transformations. From this it follows that information on both structural and dynamic aspects is required. Since the structure of most reaction intermediates cannot be determined directly, it is usually deduced from the observed effects 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 inferred directly *via* kinetic measurements.

For the hydrogenation of ketones on Ni/tartrate catalysts the group of Tai proposed a basic model around 1980 which was significantly refined in the last few years.[3a] Mechanistic investigations of the hydrogenation using Pt and Pd catalysts modified with cinchona derivatives started much later. We will summarize the literature for three catalytic systems (combination of catalyst – modifier – substrate) that have been investigated in some depth:

- Ni-tartaric acid/(NaBr) – β-keto esters,
- Pt-cinchona modifiers – α-functionalized ketones,

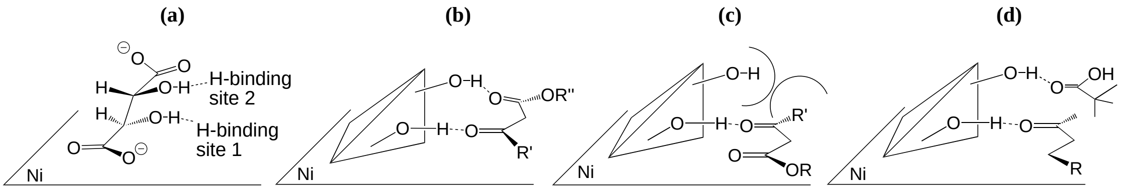


Figure 13. Ni-tartrate-catalyzed hydrogenation: (**a**) Modified active site, monotartrate form. (**b**) 2-point interaction with β-keto ester, major diastereomer. (**c**) 2-point interaction with β-keto ester, minor diastereomer with repulsive interaction. (**d**) 1-point interaction with 2-alkanone, site 2 blocked by bulky carboxylic acid.[3]

– Pd-cinchona modifiers – activated C=C bonds.

We will group the discussion for the three systems along the following lines:

- Structural models of activated complexes,
- Surface science and spectroscopic studies,
- Computational modeling,
- Kinetic investigations,
- Assessment of the mechanistic proposals.

6.1 Structural Models of Activated Complexes

In order to facilitate our discussions, we first give an overview over the structures proposed for the product-determining reaction intermediates for the three catalytic systems. We will try to do this using simple "artist's view" sketches because the more elaborate stick-and-ball or space-filling models used in the original papers are not easy to interpret. These structures are based on the evidence described above (structure-activity data) and the spectroscopic and theoretical studies summarized in the following two sections.

As a basic reaction model, the stepwise addition of dissociatively adsorbed hydrogen to the adsorbed C=O and C=C group, respectively, is the most plausible (Langmuir–Hinshelwood kinetics, see Figure 21). Reaction on an unmodified metal site leads to racemic product. A chiral active site is formed by strong adsorption of a modifier molecule on the metal surface. Hydrogen bonds between modifier and selected functional groups of the substrate molecule not only control the adsorption mode (*via re-* or *si*-face) of the reacting molecule but also facilitate and control the addition of hydrogen. It is assumed that the energy difference between the *pro-S* and *pro-R* activated complex determines the sense of induction and the enantioselectivity, i.e., that there is no kinetic preference for the less stable complex as found by Halpern for Rh-catalyzed homogeneous hydrogenation reactions.[84]

6.1.1 Ni-Tartaric Acid/(NaBr) – Ketones

According to the Japanese teams, the relatively simple model for the Ni catalysts depicted in Figure 13 is able to explain the preference for β-keto esters (distance between OH groups in tartaric acid), the observed absolute configuration of the product (site 1 gives activated binding, OH of site 2 is too far from the Ni surface to give a productive complex with the keto group) as well also the steric effect of substituents in β-keto esters (repulsion in the minor isomer). For methyl ketones both the observed effect of the substitution pattern as well as the blocking effect of bulky organic acids can be explained. There is a discrepancy concerning the binding mode of tartrate on the Ni surface. While Osawa et al.[3b] assume that only one carboxylate group is bound to Ni as depicted in Figure 13, Tai and Sugimura[3a] propose binding of both carboxylate groups. It is conceivable that Na^+ ions introduced *via* NaBr could play a role in determining the adsorption geometry of the tartrate molecule.

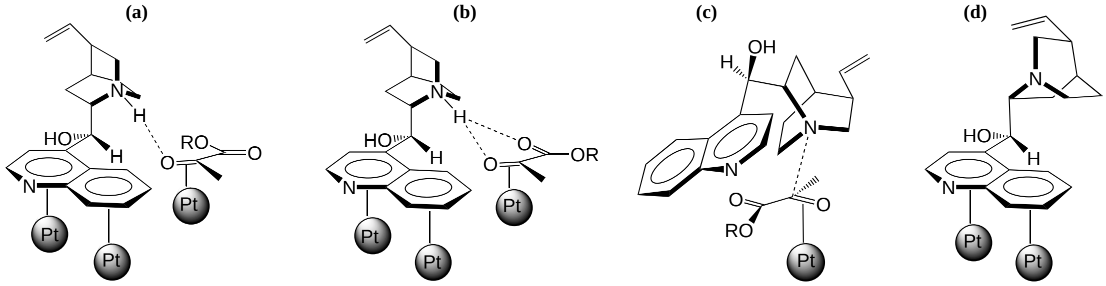


Figure 14. Stable conformers of cinchonidine and proposed activated complexes adsorbed on the Pt surface, (**a**) open(3) with *trans* α-keto ester,[4a,5a] (**b**) open(3) with *cis* α-keto ester,[86] (c) shielded complex with closed(1),[85] (**d**) closed(2) conformation.

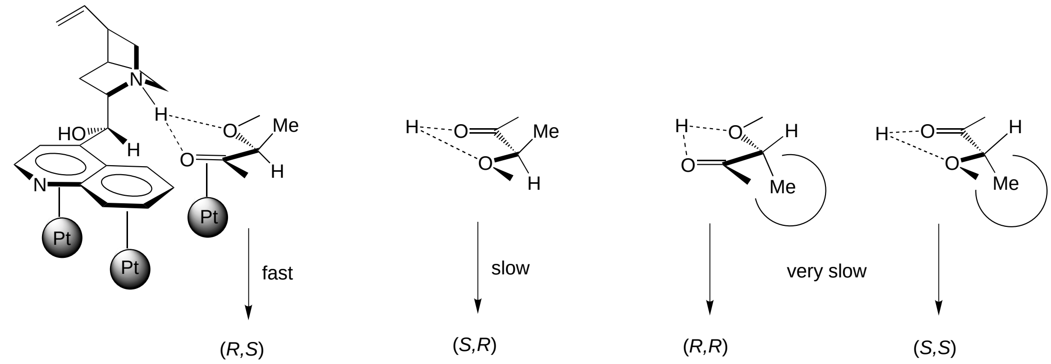


Figure 15. Kinetic resolution of α-keto ethers: Proposed structures of adsorbed substrate-modifier complexes.[36]

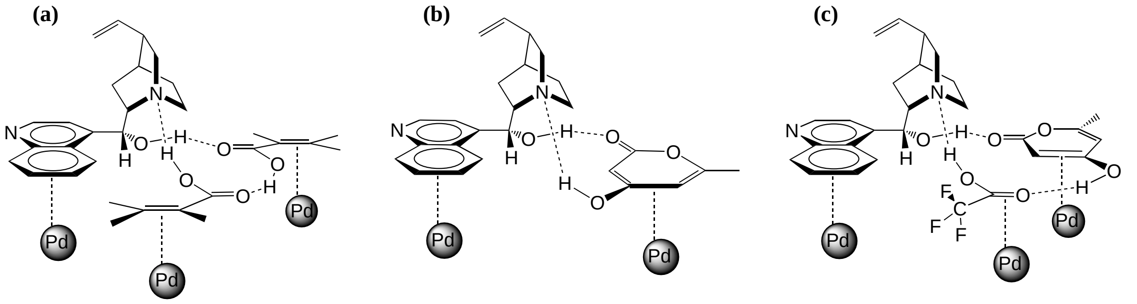


Figure 16. Proposed activated complexes of cinchonidine in open(3) conformation adsorbed on the Pd surface, (**a**) with an α,β-unsaturated acids dimer, (**b**) with hydroxymethylpyrone, (**c**) with a pyrone-trifluoroacetic acid adduct.[73b,74b]

6.1.2 Pt-Cinchona Modifiers – α-Functionalized Ketones

As described in the cited reviews[4,5,85] the mode of action of this catalytic system has been investigated and discussed extensively in the last few years. In the following Figures, the most important intermediates are sketched of stable conformers of cinchonidine and proposed activated complexes with α-keto esters adsorbed on the Pt surface (Figure 14) and for structures proposed for adsorbed substrate-modifier complexes for the kinetic resolution of α-keto ethers (Figure 15). While calculations seem to be able to predict the preferred adsorption mode of the C=O bond, it is not clear which specific (repulsive) interactions are responsible for the discrimination. For the α-keto ethers, the favored formation of the (*R,S*)-isomers was proposed to be due to the steric effect of the methyl group in the adsorbed state.

6.1.3 Pd-Cinchona Modifiers – Activated C=C Bonds

Baiker's group has studied several systems in much detail both experimentally and theoretically and has proposed rather elaborate models comprising adsorbed activated complexes consisting of one modifier molecule and one or two substrate or additive molecules (Figure 16). As for the Pt-cinchona systems, specific interactions have not been identified.

6.2 Surface Science and Spectroscopic Studies

Until very recently, only limited experimental data were available for any of the proposed adsorbed species. This is slowly beginning to change with the application of sophisticated spectroscopic techniques such as RAIRS, STM or XANES to chiral molecules adsorbed on metal Ni and Pt surfaces as well as to intrinsically chiral metal surfaces.[87]

The adsorption of tartaric acid was investigated by the group of Raval[88] both on Cu and Ni surfaces. Of special interest are the results obtained for tartaric acid adsorbed on Ni(110) with a combined approach using periodic density functional calculations and spectroscopic investigations.[88b] At low coverage, the modifier is adsorbed *via* both carboxylate groups in what the authors call the bitartrate form. Interestingly, the very strong interactions between the Ni surface and the tartrate lead to a significant surface reconstruction and the creation of a chiral arrangement of the Ni surface atoms. Raval uses the term "chiral footprint" and proposes that such a chiral metal surface might be an

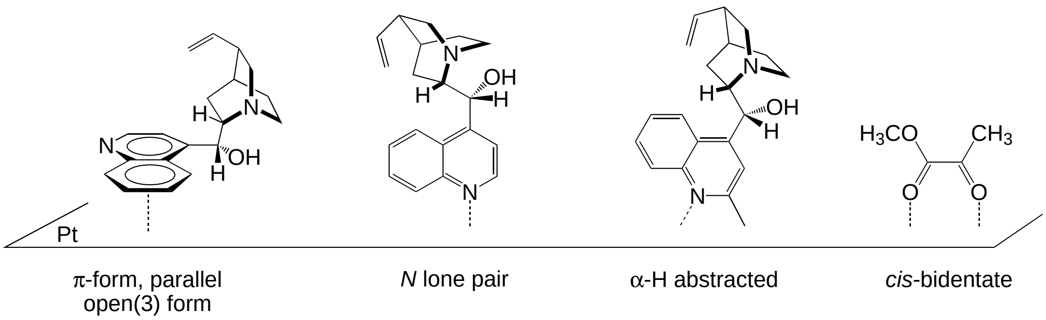


Figure 17. Adsorbed forms of cinchonidine and methyl pyruvate on a schematic metal surface.

important feature for enantiodiscrimination. On the Cu surface, the tartaric acid changes the binding mode with coverage: from monotartrate at low coverage and temperature to bitartrate at higher coverage and or temperature. Ordered surfaces with extended chirality were also observed under certain conditions.[88a] While these are interesting from a theoretical view point, they are unlikely to play any role in enantioselective reactions.

The adsorption of cinchona derivatives on Pt was studied by several groups. Evans et al.[89] applied NEXAFS to HCd on Pt(111) under high vacuum conditions and postulated parallel adsorption of the quinoline ring at 25 °C and tilted adsorption at 50 °C; similar results were found for the adsorption of quinoline derivatives.[90] Two recent reports described adsorption studies of cinchona alkaloids using *in-situ* ATR-IR[91] with a Pt/Al_2O_3 model catalyst and RAIRS[92a] with a Pt foil. In both cases, parallel adsorption *via* the quinoline ring was observed, while at higher cinchonidine concentrations tilted species were observed as well. Ferri and Bürgi[91] postulated two such species, one bound *via* the lone pair, one *via* a C-Pt bond resulting from H-abstraction (see Figure 17). Kubota and Zaera[92a] correlated the appearance of tilted species with a decrease in enantioselectivity often observed at high modifier concentrations for the hydrogenation of ethyl pyruvate.[5a,92b,93] Recent electrochemical studies using chiral single crystal Pt surfaces (Pt{531}) yielded the following information on the adsorption of cinchonidine.[94] There was no difference between HCd and its pseudo-enantiomer HCn, both are adsorbed equally *via* the quinoline ring on steps, terraces as well as kinks (random distribution, no chiral discrimination). This is in contrast to the adsorption of pyranoses where discrimination was observed. In addition, about 30–40% of the Pt surface was estimated to be not covered under these conditions and it was also found that the cinchona molecule is easily removed by the presence of hydrogen.

Finally, the adsorption under vacuum conditions of methyl pyruvate on Ni(111) with RAIRS[95] and of ethyl pyruvate on Pt(111) with XANES[96a] as well as XPS and UPS[96b] was investigated. While methyl pyruvate is bound to the Ni surface exclusively in its *cis*-bidentate form, there are indications that on the Pt surface in presence of hydrogen a tilted species exists besides the more prevalent species bound *via* the lone pair (see Figure 17). The question remains whether perpendicular adsorption *via* lone pairs really enables reaction with hydrogen or – and that seems more plausible – whether a rearrangement to a ketone adsorbed parallel to the surface is necessary.

6.3 Computational Modeling

Computational modeling both on the semiempirical or *ab-initio* level might help us to understand the mode of action of a modifier by predicting the relative energies and structures of potential intermediates not observable experimentally. Earlier results can be summarized as follows.[4,5a] The group of Baiker[4] concluded that, while cinchonidine and ethyl pyruvate can interact, the more favorable activated complex is formed by the adsorbed N-protonated modifier in its open(3) conformation (see, e.g. Figure 11) which forms an H bond with the carbonyl oxygen of the adsorbed ethyl pyruvate. Similar results and conclusions were reported by Wells et al.[5] albeit with unrealistically high energy differences between the *pro(R)* and *pro(S)* activated complex. Margitfalvi's calculations[85c] on the other hand yielded a preferred activated complex between the carbonyl group of ethyl pyruvate and the quinuclidine nitrogen of Cd in its closed form with $\pi - \pi$ interactions with the quinoline, resulting in the shielding of one enantioface of ethyl pyruvate (shielding model). These calculations of activated complexes were carried out without taking binding to the Pt surface into account except as a steric constraint.

First attempts to model adsorbed species including the binding to the metal surface were recently published by Humblot et al.[88b] who carried out periodic density functional calculations combined with spectroscopic investigations for adsorbed tartaric acid. For this purpose a (3×3) Ni(110) surface with four Ni layers

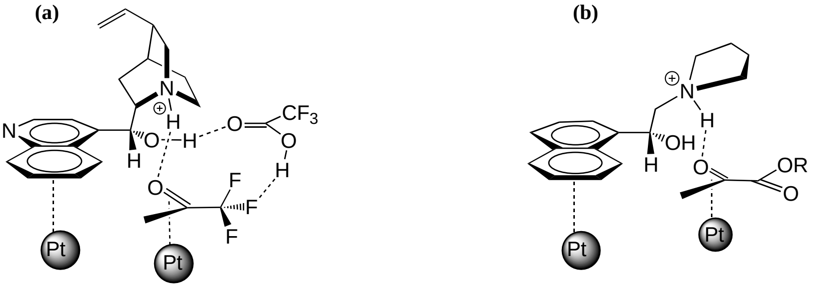


Figure 18. Activated complexes adsorbed on the Pt surface (**a**) one of several possible adducts of cinchonidine in open(3) conformation with a trifluoroketone and trifluoroacetic acid,[32a] (**b**) of a cinchona mimic with *trans* ethyl pyruvate.[98d]

was used. From these calculations, both a strong distortion of the adsorbed tartrate molecule as well as a chiral arrangement of the underlying Ni atoms were deduced (chiral footprint). For the Pt-cinchona – α-keto ester, interactions with small Pt clusters were also calculated using an universal force field[23,97] (see also below).

6.3.1 Conformation of Cinchona Modifiers

The results summarized above for the Pt-cinchona system point to the importance of the conformation of cinchona derivatives. Several investigations addressed this questions both *via* calculation[85,98a, b] as well as NMR, IR and vibrational circular dichroism spectroscopic studies.[69,98a–c] There is agreement that the open(3) conformation generally is the preferred one. It is more prevalent in solvents with low dielectric constant and indeed a correlation was found between the population of open(3) and the ee for the hydrogenation of ketopantolactone[98b] and for ethyl pyruvate in the presence of small amounts of water.[69] Adducts with acetic and trifluoroacetic acid involving interactions with both the N-H$^+$ and OH group of Cd were also shown to be formed with the open(3) conformation.[32a,98a]

6.3.2 Modeling of Activated Complexes: Pt-Cinchona – Ketones

A number of new calculations of activated complexes was published for the α-keto ester hydrogenation with Pt-cinchona catalysts [23,85,86,97–99] and also for Pt modified with cinchona mimics[98d] or other alkaloids[56a] and for Pt-cinchona-trifluoroketone.[32a]

New results for Pt-cinchona-alkyl pyruvate have not changed the picture very much. While Margitfalvi[85] finds additional arguments for his "shielded" complex between Cd and ethyl pyruvate, all other models identify the most stable activated complexes consisting of the open(3) conformation forming one or two hydrogen bonds between the quinuclidine N atom and the substrate molecule. These different predictions for the optimal structure of the Cd-ethyl pyruvate complex are puzzling and not easy to rationalize, unfortunately the publications usually give too few details on assumptions and restrictions of the calculations to make a reasonable comparison. Some additional points however do emerge. Calculations by the group of Baiker[4b,86] have shown that the situation is probably more complicated since the conformation of ethyl pyruvate significantly modifies the outcome of the calculations. Since the *trans* form of ethyl pyruvate is more stable in the gas phase, it was chosen to model interactions with the cinchona alkaloid. New calculations show that adduct with the *cis* form is better stabilized due to a "bifurcated" hydrogen bond between N$^+$-H and both C=O groups (see Figure 14). On the other hand calculated energy differences between the *pro-R* and the *pro-S* form are in better agreement with experimental results for the *trans* than for the *cis* isomer – clearly a question to be addressed in the future. Since quite small Pt colloids (1 – 2 nm) give very high ees for methyl pyruvate, the Chinese group of Liu[23] has modeled both the adsorption of Cd as well as Cd-methyl pyruvate on small Pt clusters. This is the only modeling study which claims to include the binding to the Pt surface atoms. It is shown that the stereochemical outcome of the hydrogenation [i.e., Cd induces excess of (*R*) lactate] does not significantly depend on the face of the Pt crystallite, i.e., the size of the Pt ensemble. Both large flat arrangements where the Cd-methyl pyruvate complex can be adsorbed on the same plane as well as smaller faces, where the two molecules are adsorbed on adjacent planes give similar energy differences between the *pro-R* and *pro-S* complex. It is not discussed whether taking the interaction with the Pt into account gives significant differences to the approach used by the Baiker group. To make the picture even more puzzling, a recently published study by Carneiro et al.[99] using *ab initio* calculations both on model systems as well as Cd-methyl pyruvate predicts the same structure for the best activated complex, however comes to the conclusion that the energy difference between the *pro-R* and *pro-S* cannot explain the observed enantiodifferentiation.

Comparable results as for the parent cinchona derivatives were obtained for interactions of cinchona mimics with ethyl pyruvate as depicted in Figure 18.[98d] However, a somewhat different result was obtained for the Pt-cinchona-trifluoroketone system[32a] where an activated complex was proposed consisting of one Cd in the open(3) form, one ketone and one trifluoroacetic acid molecule (see Figure 18). Calculations were also reported for the interaction of methyl pyruvate with other alkaloids adsorbed on Pt predicting some sort of chiral cavity.[56a]

6.3.3 *Pd-Cinchona Systems*

Calculations were also done for the Pd-cinchona-catalyzed hydrogenation of activated C=C bonds.[73b,74b] From spectroscopic studies an activated complex consisting of one Cd and two substrate molecules was deduced for α,β-unsaturated acids[73a, d] and confirmed by molecular modeling.[73b] For the interaction between pyrone and cinchona alkaloids, a comparable complex incorporating a Cd, one substrate and one trifluoroacetate was proposed again based on experimental as well as theoretical studies.[74] In both cases, an additional hydrogen bond to the OH group of the cinchonidine was considered to be essential for good enantioselectivity (compare Figure 18a).

6.4 Kinetic Studies

The dependencies of the rate of reaction and the ee 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 explain the higher (or lower) activity of the modified catalyst.

6.4.1 *Ni-Tartaric Acid/(NaBr) – β-Keto Esters*

A synopsis of earlier investigations using Raney-nickel catalysts can be found in Tai and Sugimura[3a] and Keane.[100a] The Ni/SiO_2-tartrate system has recently been investigated in great detail (effect of impregnation and reaction parameters, catalyst characterization) by Keane.[100] Since the modification of the Ni catalysts with tartaric acid is a corrosive process, quantitative concentration-rate relations are very difficult to obtain. Major effects are summarized in Table 3.

6.4.2 *Pt-Cinchona Modifiers – α-Functionalized Ketones*

An extensive kinetic investigation was carried out by Blaser et al.[101] for the hydrogenation of methyl pyruvate with a Pt/Al_2O_3 catalyst with and without dihydrocinchonidine. In this publication results of several teams up to 1998 are summarized as well. The effects of catalyst loading, modifier and substrate concentrations, hydrogen pressure, and temperature on the rate of the unmodified and on rate and ee of the modified system were studied. The modified reaction was approximately 20 – 30 times faster than the unmodified one. A significant increase of the ee from 1 to 40 bar was noticed and apparent activation energies were estimated to be 4 – 6 kcal/mol (compare Table 4). Toukoniitty et al.[39d] carried out a kinetic study for the hydrogenation of 1-phenyl-1,2-propanedione with a Pt/Al_2O_3 catalyst modified with cinchonidine. These results allow no mechanistic interpretation but rather serve for process engineering purposes.

The coupled effects of the modifier concentration on ee and rate are arguably the most significant correlation for mechanistic interpretations. Such dependencies have been described for several α-functionalized ketones (keto esters, keto acids, trifluoroketones[33a], keto acetals[34]) using Pt catalysts such as Pt/SiO_2, Pt/$CaCO_3$, Pt/Al_2O_3 and colloids and various modifiers in different solvents (for an overview see Blaser et al.[5a]). As illustration we depict two recently published examples in Figure 19. It is interesting to note that despite the

Table 3. Effect of various system parameters on rate and ee for the hydrogenation of methyl acetoacetate on Ni-tartrate catalysts.

Parameter	Effect on Specific Rate	Effect on ee
Catalyst concentration	First order[100]	Small or no effect (few results)
Tartrate concentration (adsorbed tartaric acid)	Few results[3a]; modified catalyst slightly more active[100]	Linear increase with saturation[3] maximum at moderate loading[100]
NaBr concentration in modifying solution	Slight decrease (qualitative results)	Strong increase with saturation[3a]
Temperature	Increase (E_A 44 – 57 kJ/mol)	Slight decrease with T (few results)
Methyl acetoacetate concentration	1 → 0 (saturation)	Invariant or slight increase, then plateau[100]

Table 4. Effect of various system parameters on rate and ee for the hydrogenation of ethyl pyruvate on Pt-cinchona catalysts.[5a,101]

Parameter	Effect on Specific Rate	Effect on ee
Catalyst concentration	First order	Small or no effect (few results)
Modifier concentration	strong increase with plateau or maximum (see text)	strong increase with plateau or maximum (see text)
Pressure (1 – 100 bar)	first order	increase with plateau
Temperature (20 – 70 °C)	Increase (E_A 5 – 10 kJ/mol)	slight decrease
Ethyl pyruvate concentration	1 → 0 (saturation), sometimes maximum	Invariant or slight increase, then plateau or maximum

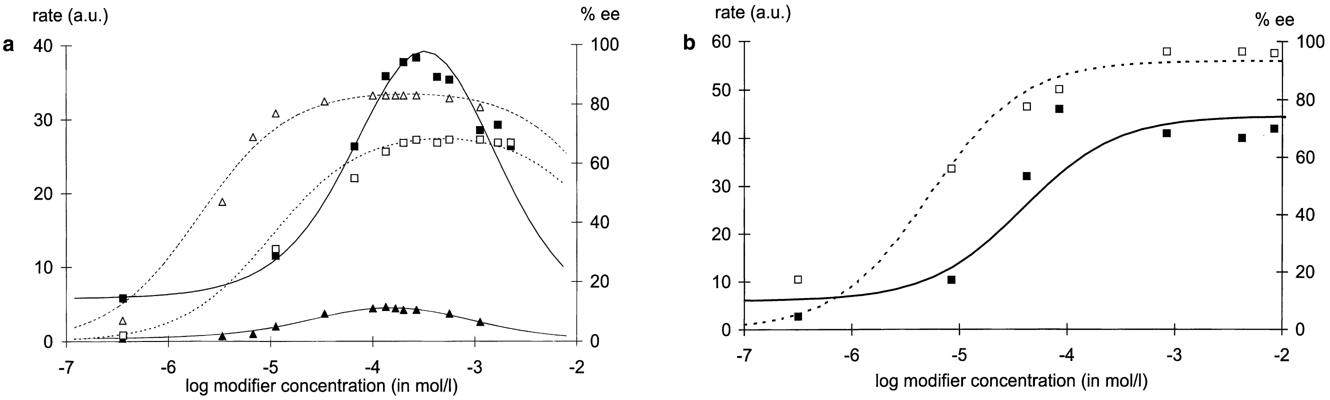


Figure 19. Dependence of ee (open symbols) and rate (solid symbols) on modifier concentration. **a:** Hydrogenation of ethyl pyruvate with different Pt/support catalysts (HCd, toluene, r.t., 100 bar): △ $CaCO_3$, □ SiO_2.[102] **b:** Hydrogenation of methyl glyoxal dimethyl acetal (MeOHCd, AcOH, Pt/Al_2O_3, 25 °C; 60 bar).[34]

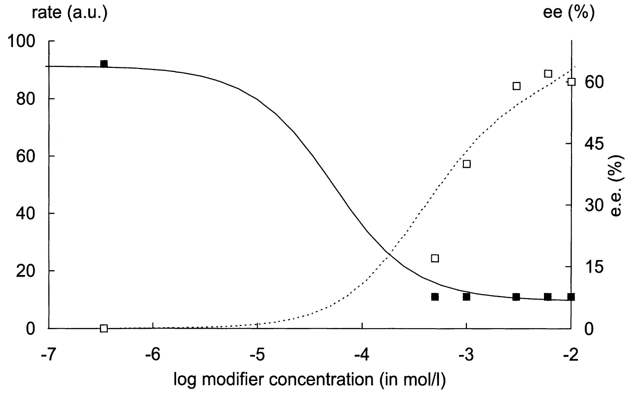


Figure 20. Effect of modifier concentration on rate and ee for the hydrogenation of 1-phenyl cinnamic acid with Pd/TiO_2, Cd in DMF/H_2O 9:1 (adapted from Nitta and Kobiro[75b]).

very different rates of the two catalysts, similar ees are obtained.

6.4.3 Pd-Cinchona Modifiers – Activated C=C Bonds

With the exception of some data on the effect of the modifier concentration for α,β-unsaturated acids and isophorone[5a], no kinetic data are available. While ees increased with increasing modifier concentration, rates decreased in all reported cases[5a,74c,76] (see Figure 20). This means that in contrast to the Pt-cinchona-catalyzed hydrogenation of ketones, we observe rate deceleration by the modifiers. Nevertheless, the behavior can be modeled assuming an equilibrium between unmodified and modified sites (calcd. lines in Figure 20).

6.5 Kinetic Schemes

Any valid kinetic scheme has to accommodate the data presented above. Both the limited data for the nickel-tartrate-β-keto ester system[3a] as well as the full kinetic study for the Pt-cinchona-α-keto ester[101] are compatible with a Langmuir–Hinshelwood (LH) description. The basic catalytic cycle consists of a fast adsorption of ketone and hydrogen on an active site, the stepwise addition of the two hydrogen atoms to the C=O bond with a half-hydrogenated intermediate and finally the fast desorption of the alcohol. If the active site is modified either with tartaric acid (probably irreversible) or a cinchona molecule (probably reversible), the reaction occurs with a certain intrinsic enantioselectivity due to the difference in reactivities of the ketone adsorbed *via* the *re* and *si* faces, respectively. Another reaction pathway involving the enol instead of the keto form is unlikely for the Ni catalysts (non-enolizable

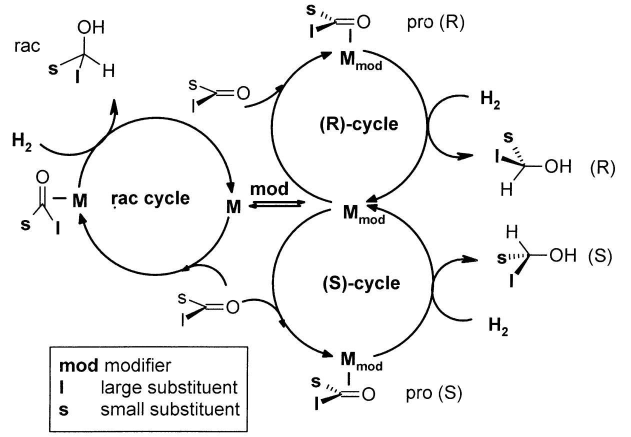


Figure 21. Catalytic cycles for the hydrogenation of ketones on a partially modified catalyst.

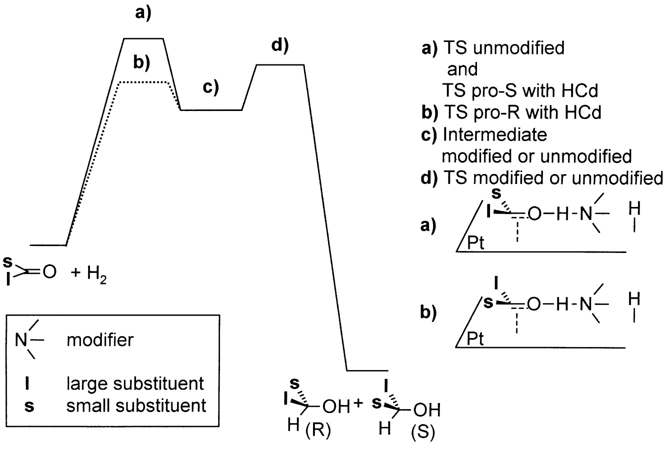


Figure 22. Schematic energy diagram for the hydrogenation of an α-keto ester with and without cinchona modifier. For conceivable structures of the adsorbed intermediates, see Figure 14.

ketones give the same ee[3a]) and excluded for the Pt catalysts using D_2: while several hydrogen atoms in the cinchonidine are exchanged, no D is incorporated in the methyl group of the pyruvate, i.e., that the keto group and not the enol form is hydrogenated.[103,104] These results were recently confirmed.[18c]

Since it is not possible to modify all active sites, there will be three competing catalytic cycles (see Figure 21): one for the unmodified catalyst leading to racemic product, two cycles for the modified site, yielding (*R*)- and (*S*)-product, respectively. The resulting enantiomeric excess will depend on the ratio of modified to unmodified sites and on the relative turnover frequencies of the three cycles.[93]

For the hydrogenation of ethyl pyruvate, a comprehensive kinetic scheme was proposed assuming competitive adsorption of an α-keto ester and hydrogen on a Pt site followed by step wise addition of the hydrogen atoms to the C=O bond.[101] For the unmodified catalyst, the addition of the first hydrogen atom was assumed to be rate-determining (Figure 22, solid line). On a chiral site, formed by reversible adsorption of one cinchona molecule, the rate-determining step to the major enantiomer was taken to be the addition of the second hydrogen (Figure 22, dotted line), whereas the first H addition remained rate determining for the minor enantiomer (Figure 22, solid line). This means that the observed rate acceleration was explained by a shift of the rate-determining step for one of the two possible adsorbed forms of ethyl pyruvate. A plausible explanation of this shift is the preferred formation of a hydrogen bridge between the ketone adsorbed *via* the *si*-face (*pro-R* adduct) and the modifier preferentially leading to (*R*)-ethyl lactate. A different kinetic framework was proposed by Murzin,[105] involving significant modifier-product interactions, but without much corroborating experimental evidence.

6.6 Assessment of the Mechanistic Proposals

There is ample evidence and general agreement that significant interactions between substrate, modifier and active metal surface are required for achieving high enantioselectivity. On the one hand, these interactions serve to activate the reactants to achieve catalysis while on the other hand these interactions control the stereochemical outcome of the reaction. In the overviews published on this topic two basic models have been defined, the concept of the modified catalyst[3–5] and that of the modified substrate.[18d,85] The information summarized in this update strongly supports the modified catalyst model for all three types of catalytic systems.

For the Ni-tartrate-β-functionalized ketone system, some proposed adsorption modes of the tartrate molecule have been confirmed spectroscopically. Otherwise, the model developed over the years by the Japanese groups which is able to rationalize all major effects is still mostly based on indirect evidence and intuition.

For the Pt-cinchona-α-functionalized ketone system, the qualitative model involving a cinchona (or analogue) modifier π-bound to the Pt surface *via* the quinoline ring with a hydrogen bridge to the adsorbed ketone (see Figures 11a and 14) is able to explain many of the most important experimental facts. Whether the activated complex is between a protonated cinchonidine and the ketone (originally proposed by Baiker[4,5d] and enlarged by Pfaltz[6a] for synthetic modifiers) or between the cinchonidine and the half-hydrogenated ketone (Wells[5b, c]) is still an open question. Other open questions relate to the conformation of the ketone and the number of hydrogen bridges. It should be checked whether a bifurcated hydrogen bridge would not also be possible for the *trans* form as invoked for the α-keto ethers (compare Figures 14a, b, 15). Also an important issue for future investigations is the identification of specific (repulsive) interactions of the substrate molecule with the modifier which directly affect enantioselectivity. Without understanding these aspects, predictions or rational optimizations are not possible. The modified substrate model of Margitfalvi can now be ruled out with some confidence. Neither the observed dependence of rate and ee on modifier concentration[5a,93,101] nor the fact that α-IQd or α-ICn (see Figure 3) which cannot attain a closed conformation achieve comparable ees to the parent alkaloids[16] are compatible with the proposed formation of an activated complex of the substrate with the closed form of cinchonidine which is then hydrogenated as depicted in Figure 14c.

For the Pd-cinchona-activated C=C system, an analogous model emerges with some indication that 1:2 adducts and an additional hydrogen bond to the OH group of the cinchona modifier might play important roles.

If one compares these structural models with those developed for homogeneous asymmetric catalysis[106] it is noticeable that both binding and repulsive interactions are much less directed and defined. Despite the claims that molecular modeling without including interactions with the metal produces adequate predictions of both the sense and the extent of the chiral induction, it is obvious that the metal surface is a significant factor. Otherwise the specificity of Ni or Pt for certain substrate-modifier combinations could not be explained. In this context it is amazing that such different surfaces as provided by Raney-type catalysts, metal powders, colloids and supported catalysts can all lead to very high ees. Obviously, the adsorbed modifier is somehow able either to find ideal active sites or – and that is a new idea in the context of enantioselective catalysis in solution – the adsorption of the modifier might induce a local reorganization of the surface metal atoms. Indeed first ideas in this direction have been described using expressions like "chiral footprint" by Raval[88] or "chiral surface sites" by Tungler[107], or in a somewhat different way, when Bartók[44] speaks of an "electrostatic potential". These notions are supported by growing experimental evidence that intrinsically chiral metal surfaces can indeed discriminate between enantiomers albeit with very low efficiency. However, at the moment these are simply catch words and the major issue is the "translation" into the design of experiments in order to be of any significance for further progress.

7 Conclusions

In the last five years, the area of heterogeneous enantioselective hydrogenation has seen a enormous activity in the directions of new synthetic applications, the development of new catalysts and modifiers as well as concerning the mode of action of these catalysts. On the positive side, the scope of the cinchona-modified Pt and Pd catalysts has expanded considerably but still remains relatively narrow. We have now a clearer picture of how chiral modification might work, which could lead to more effective catalysts. In addition, several of the catalytic systems are ready for synthetic application and some have indeed already been applied, even on a technical level.

On the other hand, the results of these over 150 papers look a bit discouraging: No conceptionally new catalyst has been discovered, there are still only three major catalytic systems and we still have at best a qualitative understanding of their mode of action. This is probably not so surprising considering the complexity of the task at hand and the difficulties involved in understanding any catalytic reaction, much less an enantioselective one on a heterogeneous catalyst! Still, there are plenty of interesting open questions waiting to be addressed and personally we are convinced that working in this fascinating area is still a rewarding endeavor, both from the academic as well as from an industrial point of view.

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