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Progress in asymmetric heterogeneous catalysis: Design of novel chirally modified platinum metal catalysts [1]

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Abstract

Heterogeneous asymmetric catalysis on chirally modified supported platinum catalysts has undergone significant development recently. Based on the knowledge gained on the mechanism of the asymmetric hydrogenation of α-ketoesters, catalyzed by platinum modified with cinchona alkaloids, new efficient chiral auxiliaries have been developed and the scope of reactants has been extended. The research strategy which led to this progress and the results achieved are reviewed.

1. Introduction

The synthesis of optically pure chiral compounds has gained great importance, particularly in the areas of pharmaceuticals, agrochemicals, flavors and fragrances [1]. Research in this field has been fostered by the growing awareness that the 'wrong' enantiomer of a chiral product has to be considered at best as ballast and at worst as a 'pollutant', whose negative side effects can far outweigh the beneficial value of the 'right' enantiomer. The classical example in the pharmaceutical area is the drug thalidomide. The *R*-isomer of thalidomide is an effective sedative; tragically, the drug was sold as the racemate, and it was subsequently discovered that the *S*-enantiomer is a powerful teratogen. Birth defects caused by the 'wrong' enantiomer of this drug were one of the spurs towards today's emphasis on enantiomerically pure active ingredients. A less harmful example is chloramphenicol, of which only one enantiomer is active as an antibacterial agent. Other examples, demonstrating the role of optically pure substances are found in the production of agrochemicals [2], flavors and fragrances [3].

Several different strategies are applied to manufacture optically pure chiral substances [4,5]. Among these strategies, asymmetric catalysis provides powerful and unique advantages. Perhaps the foremost is the 'multiplication of chirality', a large quantity of chiral product can be produced using a catalytic amount of a chiral source.

There are several important selectivity problems, where asymmetric catalysis provides interesting opportunities. These include the reduction of functionalized C=O, C=C, and C=N groups, the oxidation (epoxidation, dehydroxylation) of C=C systems, and various C–C formations such as aldol reaction, Diels–Alder reaction, addition of carbenes, and hydroformylation. Although for many of these reactions

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there exist selective homogeneous catalysts [6] or biocatalysts [7], their activity and stability are frequently too low, and the technical handling too demanding for economic industrial application. From a technical point of view, heterogeneous asymmetric catalysis is mostly preferable to homogeneous catalysis, due to its definite process engineering advantages (handling, separation), rendering the development of heterogeneous catalysts a rewarding goal.

Various strategies have been applied to develop heterogeneous asymmetric catalysts [8,9], among which the modification of the catalytically active site by a chiral auxiliary (modifier) has been most successful. However, progress has been confined so far to two catalytic systems: nickel catalysts modified by tartaric acid [10] for the hydrogenation of β-ketoesters and 2-alkanones, and platinum modified by cinchona alkaloids [11] for the hydrogenation of α-ketoesters. Enantiomeric excesses as high as 90–95% have been achieved with these catalytic systems [12,13] and considerable effort has been undertaken to gain a better understanding of their functioning [14].

Intrigued by the remarkable properties of the platinum–cinchona system and by the fact that since its discovery in 1978 by Orito [11] no new chiral catalysts with similar efficiency have been reported, we started recently searching for new enantio-differentiating heterogeneous catalysts suitable for α-ketoester hydrogenation. As a result of this effort, novel efficient enantioselective platinum based catalysts were found. Here we elucidate the design strategy which led to the discovery of the new chiral catalysts and compare their catalytic behaviors to that of the classical Pt–cinchona system.

2. Basis for the design of new catalysts – the platinum–cinchona system

The design of the new chiral catalysts was mainly based on knowledge gathered on the platinum–cinchona system in the past decade. Several groups have contributed to a better understanding of this complex catalytic system. Information on relevant catalyst parameters and their control as well as some understanding of the reaction mechanism has been gained. Here we consider shortly the main characteristics of this reaction system, focusing on those findings which directly influenced the development of the new catalysts. For a more detailed overview, including work on the platinum–cinchona system published till 1995, the reader is referred to the most recent review [14].

The main features of the metal–cinchona alkaloid systems used for the enantioselective hydrogenation of α-ketoesters are illustrated in Fig. 1.

As catalysts, supported platinum [11,15–21] was found to be most suitable. Iridium is also applicable, but exhibits inferior catalytic behavior [22]. Palladium and rhodium show poor performance, and Ru and Ni are not effective [15]. Most frequently used supports are alumina, silica and carbon, but zeolites [23] have been applied as well. The use of zeolites may be disadvantageous in the case of bulky reactants due to possible intraparticle mass transfer limitations.

The cinchona alkaloids (Fig. 1) used most frequently are cinchonidine (**CD**) and its derivatives, such as 10,11-dihydrocinchonidine (**HCD**) [15] and 10,11-dihydro-*O*-methyl-cinchonidine [12], whereas quinine is less suitable [11]. The cinchona alkaloids shown in Fig. 1 differ structurally at three positions; a methoxy group is present or absent at C-6′ of the quinoline ring (R_2); a vinyl or ethyl group is present at C-3 of the quinuclidine ring (R_1); and different substituents may be introduced at C-9 (e.g. OCH_3 instead of OH yielding 10,11-dihydro-*O*-methyl-cinchonidine). Cinchona alkaloids contain five asymmetric atoms (C-3, C-4, C-8, C-9, and quinuclidine-N); however, they differ in configuration only at C-8 and C-9 [24]. Although cinchonidine and cinchonine (**CN**), and quinine and quinidine, respectively, are diastereomeric pairs, as illustrated in Fig. 1, their oppo-

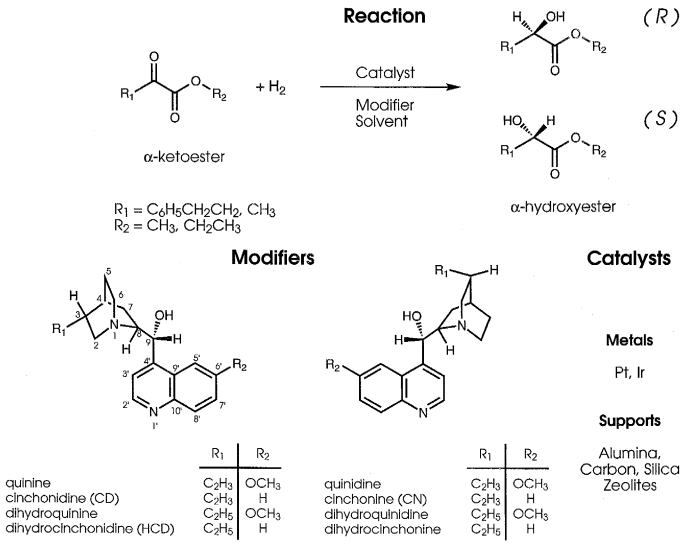


Fig. 1. Main features of platinum metal–cinchona alkaloid systems used for the asymmetric hydrogenation of α-ketoesters.

site stereochemistry at the crucial carbons C-8 and C-9 are more characteristic of enantiomers. As a result, they are sometimes called 'pseudo- or near-enantiomers'. It is not surprising that these pairs of near-enantiomers induce opposite chirality in the product, when used for stereochemical control [11].

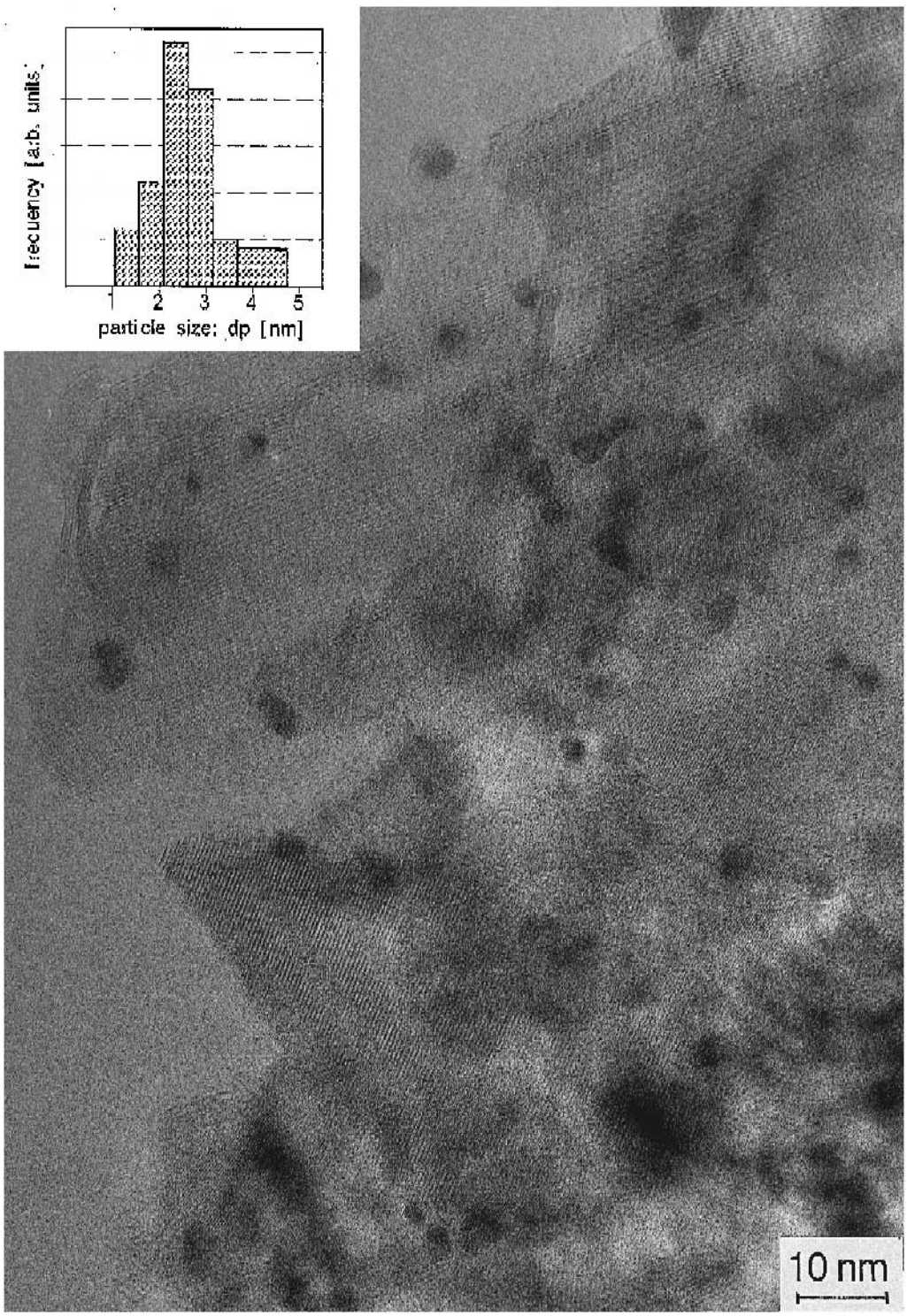
Most of the work reported in the literature has been performed using alumina- or silica-supported platinum catalysts. Although various substrates have been hydrogenated to chiral products using cinchona alkaloid-modified platinum or palladium catalysts [5,8,9,14], only the hydrogenation of α-ketoesters and their derivatives show high optical yields, reaching 95% under optimal conditions [12]. Most information about the cinchona-modified platinum system has been gained by studying the enantioselective hydrogenation of methyl or ethyl pyruvate to the corresponding lactates.

The alkaloid-modified catalyst can either be prepared by stirring the metal catalyst with a solution of the alkaloid in air and subsequent separation by decantation, as described by Orito et al. [11], or the alkaloid can be added in situ to the reactant mixture [15–19]. Good optical yields can be obtained with both methods. Reactions are generally carried out at ambient temperature or slightly above, and at hydrogen pressures ranging from 10–70 bar.

Provided that appropriate reaction conditions (temperature, pressure, mixing) are used, the catalytic performance of the platinum–cinchona system depends mainly on the properties of the supported platinum catalyst, the structure and concentration of the modifier, and the solvent.

2.1. Catalyst

A very decisive catalyst property is the platinum dispersion [16,17,19]. If the platinum dispersion is varied in the range between 4 to 50%, corresponding to a change in the mean platinum particle size from about 24 to 2 nm, optical yield changes significantly, indicating a strong structure sensitivity of the reaction [19]. Only catalysts containing platinum with a mean particle size larger than ca. 3 nm afford good optical yields. The reason for this structure sensitivity is not clear yet, but it seems that extended relatively flat low index planes (high coordination sites) of platinum are more suitable for cinchonidine adsorption than the rougher higher index planes (low coordination sites). This view


frecuency [a.b. units]
1
2
3
4
5
particle size: dp [nm]
10 nm

is supported by the fact that heat pretreatment, generally leading to growth of the low index planes at cost of the high index planes, results in higher enantioselectivity [15]. It is known that for an ideal crystallographic fcc particle, the number of surface atoms with a specific coordination and symmetry changes most drastically in the crystal size range up to about 4 nm [25]. However, with supported metal particles the anisotropy induced by the metal–support interaction may drastically change this behavior. This becomes evident when the catalytic behavior of differently prepared alumina supported platinum catalysts are compared [16,19]. Clearly not only the platinum particle size, but also its morphology and contaminants, stemming from the platinum precursor or the reduction agent applied, can affect enantio-differentiation [16,19]. Catalysts with relatively flat highly crystalline Pt particles, showing a preferential orientation, generally afford higher optical yields than spherical particles with poor contact with the support [16]. The morphology of the particles is, of course, strongly dependent on the preparation and reduction procedure applied [16].

Modifying platinum by deposition of tin alkyls [26] or palladium [27] results in lower activity and optical yield, in line with the structure sensitivity observed and the poor catalytic performance for α-ketoester hydrogenation of palladium compared to platinum.

Another catalyst property influencing the catalytic behavior is the texture, or more specifically, the pore size distribution. This was demonstrated by comparing two well characterized commercial catalysts with similar platinum dispersion but different texture [28]. Irrespective of the α-ketoester (ethyl pyruvate, ethyl 2-oxo-4-phenylbutyrate) and the solvent (toluene, ethanol) used, the catalyst with the larger pores showed better optical yields and higher turnover frequencies, indicating some limitation by intraparticle mass transfer.

The new chiral catalytic systems described in this report have been based on a commercial alumina-supported platinum catalyst (Engelhard 4759) which nearly meets the optimal structural and textural requirements pointed out above. Fig. 2 depicts the structure of this catalyst as investigated by high-resolution transmission electron microscopy. The characteristic properties of this catalyst are: platinum content, 5 wt%; platinum dispersion, 0.22; mean platinum particle size, 4.5 nm (determined by CO chemisorption); support, γ-alumina, BET surface area, 168 $m^2\ g^{-1}$; platinum surface area, 3.3 $m^2\ g^{-1}$; specific pore volume, 0.27 $cm^3\ g^{-1}$. Before use the catalyst is generally prereduced at 673 K for 1.5 h in a hydrogen flow and transferred into the autoclave under solvent with the exclusion of oxygen. This pretreatment results in a significant increase of the mean platinum particle size as compared to the untreated catalyst.

2.2. Modifier

Three functional parts of the cinchona alkaloid modifiers can be distinguished (Fig. 1): the quinoline ring, the asymmetric region embracing C-9 and C-8, and the bicyclic quinuclidine part with the double bond in 10,11-position. This double bond is relatively easily hydrogenated under reaction conditions [16,17]. A characteristic feature of the catalytic behavior of Pt–cinchona systems is that the enantio-differentiation induced by the presence of the chiral modifier is accompanied by a strong increase of the reaction rate [15,16,29–31]. This behavior is illustrated in Fig. 3, which depicts the dependence of the enantiomeric excess ee $(\%) = 100|[R]-[S]|/([R]+[S])$ and the reaction rate on the modifier concentration. Very small quan-

Fig. 2. High-resolution transmission electron micrograph of unpretreated alumina supported platinum catalyst (E4759) used for chiral modification. Inset depicts platinum particle size distribution as determined before reductive pretreatment.

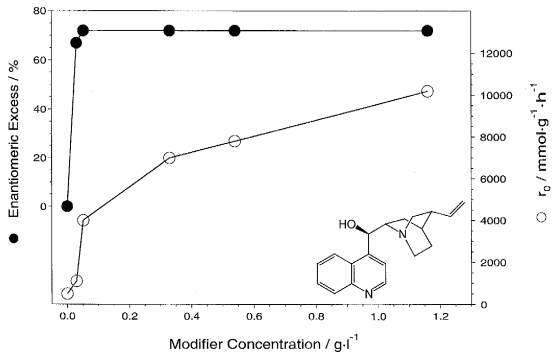


Fig. 3. Influence of modifier concentration on enantiomeric excess and reaction rate (r_o) for the hydrogenation of ethyl pyruvate (**EP**) over platinum modified with cinchonidine (**CD**). Experimental conditions: 100 mg catalyst, 6.22 μmol **CD**, 10 ml (0.09 mol) **EP**, 20 ml acetic acid, 25°C.

tities of the chiral modifier (modifier: Pt_{surf} = 0.1–1, depending on solvent) are sufficient to induce maximum enantio-differentiation [16,29,30]. Kinetic models for quantifying the marked increase in the reaction rate occurring upon modification have been described by Wehrli [16] and by Garland and Blaser [29]. Both models, which are essentially similar, are based on a two-cycle mechanism, as predicted for a ligand accelerated reaction [32], where a slow unselective (unmodified catalyst) and a fast enantioselective reaction cycle are assumed to occur simultaneously.

Although the observed rate acceleration effect is partly due to the base catalysis effect known for ketone hydrogenation [33], it cannot completely account for it. This has been revealed by hydrogenations carried out under standard conditions in the presence of N-bases of various strength [15,34]. With few exceptions the acceleration depends on the pK_a value of the base, but the effect of cinchonidine is much stronger than that of comparable N-bases.

Systematic studies [28] on the interrelationship between modifier structure and enantio-differentiation provided information on the structural requirements of modifiers. Changing the absolute configuration at C-8 and C-9 of cinchonidine, i.e. substituting cinchonidine by its near-enantiomer cinchonine, alters the chirality of the product lactate [11,28,35]. Alkylation of the quinuclidine-N results in a complete loss of ee, which indicates that this center plays a crucial role in the mechanism of enantio-differentiation. Partial hydrogenation of the quinoline ring causes a strong drop in ee. The selectivity is influenced by the substituents at C-9, substituting OH by OCH_3 (*O*-methylation) has a marginal, but positive effect on ee, whereas substitution of OH by H or OAc greatly lower ee. The influence of the substituents at C-9 can be attributed to their role in determining the stable conformation of the cinchona alkaloid, as will be discussed later on Section 2.4. The influence of the double bond in 10,11-position on the enantioselectivity cannot be judged unambiguously, because it is rapidly hydrogenated under reaction conditions.

Studies of the interrelationship between modifier structure and enantio-differentiation indicated that the three crucial structural elements for the functioning of cinchona alkaloids as chiral modifiers are: (i) the *anchoring part*, represented by the flat aromatic ring system (quinoline), which is assumed to be adsorbed on the platinum surface via the π-bonding system, (ii) the *stereogenic region*, embracing C-9 and C-8, which determines the chirality of the product; and (iii) the *tertiary quinuclidine-N* which is directly involved in the interaction with the reactant α-ketoester.

2.3. Solvent

The solvent can influence the enantioselective hydrogenation in different ways. Possible effects originate from hydrogen and α-ketoester solubility, and interactions with reactant, modifier and platinum surface. Little is known so far about these interactions on a fundamental level, rendering it often difficult to explain the different solvent effects observed. Most studies reported in the literature were carried out with either toluene or ethanol as solvent. In the hydrogenation of ethyl pyruvate both enantioselectivity and reaction rate were found to decrease

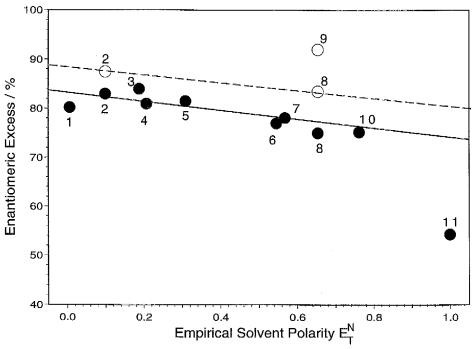


Fig. 4. Effect of solvent on enantio-differentiation of Pt–cinchonidine [36] and Pt–dihydrocinchonidine [12] in ethyl pyruvate hydrogenation. Dependence of enantiomeric excess on empirical solvent parameter E_T^N [37]. Solvents: (1) cyclohexane, (2) toluene, (3) chlorobenzene, (4) tetrahydrofuran, (5) dichloromethane, (6) 2-propanol, (7) 1-pentanol, (8) ethanol, (9) acetic acid, (10) methanol, and (11) water.

with increasing polarity of the solvent [16,18]. Fig. 4 depicts the dependence of ee on the empirical solvent parameter E_T [36]. Good enantioselectivities are obtained in moderately apolar solvents, in which the reactant and modifier dissolve. Interestingly, primary alcohols are also good solvents, although they react rapidly with the reactant ethyl pyruvate to the corresponding hemiketals [36]. The highest optical yields reported so far, namely 95% [12], was achieved in acetic acid. NMR studies indicated that in the presence of acetic acid the quinuclidine-N of cinchonidine is protonated [36], favoring the interaction between modifier and reactant, which is crucial for the enantio-differentiation (Section 2.4). Acetic acid can also be formed during oxidative treatment of supported Pt catalysts in ethanol, which partly explains why higher optical yields have been observed in ethanol after oxidative treatment [36].

Recently, supercritical CO_2 and ethane have been used as solvents [38]. A comparison between supercritical ethane and the two most frequently used solvents, ethanol and toluene, showed that, under otherwise identical conditions, the hydrogenation is accelerated by a factor of 3.5 in supercritical ethane, without any loss in enantioselectivity. A further advantage of supercritical ethane is that ee remains high, even at high catalyst/reactant mass ratio, which is interesting in view of a possible application of a continuous fixed-bed reactor for this hydrogenation. Carbon dioxide, the most widely applied solvent under supercritical conditions, is not suitable for α-ketoester hydrogenation due to strong catalyst deactivation originating from CO formed by reduction of CO_2 under reaction conditions [38].

2.4. Stereochemical control – interaction between chiral modifier and reactant

An important requirement for developing new enantio-differentiating platinum metal catalysts was to gain some understanding on the mechanism of the asymmetric hydrogenation over the platinum–cinchona system. A feasible mechanism has to account for the sense of the observed enantioselectivity and the rate enhancement.

The first attempt to interpret the sense of enantio-differentiation was made by Wells and co-workers [20]. These authors developed a ‘template model’, which provided an interpretation of the enantio-differentiation on purely geometrical arguments, assuming that the alkaloid modifier is adsorbed by its quinoline ring and forms non close-packed arrays on the platinum surface in such a manner that shaped ensembles of Pt atoms were left exposed, onto which a methyl pyruvate molecule could only adsorb in a manner to afford (*R*)-methyl lactate ((*S*)-methyl lactate in case of cinchonine) on hydrogenation. Although this model suffered from several inconsistencies with experimental findings, it was the origin of all further developments [39] towards a mechanistic understanding of enantio-differentiation. Later the authors re-examined their model [40], based on the results of LEED studies which revealed that quinoline and 10,11-dihydrocinchonidine adsorb in a disordered state on Pt(111) [41], and postulated that a hydrogen bond interaction is established between the quinuclidine-N of the adsorbed al-

kaloid and the half-hydrogenated state derived from pyruvate. This interaction was suggested to stabilize the half-hydrogenated state against H-atom loss, thus increasing its steady-state concentration and thereby rate of conversion to product in the rate determining step [34].

In contrast to Wells and co-workers, we developed our model assuming a 1:1 interaction between reactant and modifier. Intrigued by the experimental observation that alkylation of the quinuclidine nitrogen results in a complete loss of enantio-differentiation of cinchonidine [28], we first studied the interaction of this center with the reactant pyruvate. Theoretical studies aimed at rationalizing this interaction were undertaken using quantum chemistry techniques at both ab initio and semi-empirical levels and molecular mechanics.

The quinuclidine-N can either act as a nucleophile or after protonation as an electrophile. In a first step, NH_3 and NH_4^+ have been used as models of these reaction centers and the minimum energy conformations and complexation energies of the complex formed between methyl pyruvate and NH_3 as well as NH_4^+ were calculated [42]. The pyruvate–NH_4^+ complex was found to be much more stable (by 25 kcal/mol) due to favorable electrostatic interaction, indicating that in protic solvents, this species will interact with pyruvate. This findings clearly indicated the important role of the hydrogen bond interaction for stabilizing the complex formed between the pyruvate and the alkaloid. Based on this result and the experimental finding that the quinuclidine-N is protonated in acetic acid — the best solvent known for this reaction — the calculation of the energetically most favorable structure of the complex were made using protonated cinchona alkaloids.

The next step was to gain detailed knowledge of the conformational behavior of the cinchona alkaloids and their protonated form. Cinchona alkaloids (Fig. 1) are composed of two relatively rigid entities, an aromatic quinoline ring and an aliphatic bicyclic quinuclidine ring, both connected to a hydroxyl-bearing carbon atom. Hindered rotation is possible around these two bonds. The three other bonds around which some rotational freedom is possible are those with the vinyl, the hydroxyl and methoxy groups (quinine). The conformation of cinchona alkaloids has been addressed in several studies [43–46], the general result being that only rotation around C-4′–C-9 and C-9–C-8 (Fig. 1) are important to a first approximation for the major conformational changes in the molecules. The minimum energy conformations of the cinchona alkaloids can be influenced in different ways, by varying the substituent at the benzylic position (C-9), or interaction with reactant and/or solvent. Calculations of the molecular mechanical energy as a function of the two dihedral angles C-3′–C-4′–C-9–C-8 and C-4′–C-9–C-8–N-1 (Fig. 1), indicated that cinchonidine and cinchonine, in unprotonated and N-protonated form, can adopt six minimum energy conformations [47]. Among these, two are ‘closed’ conformations, in which the quinuclidine nitrogen points toward the quinoline ring, whereas the others are ‘open’ conformations in which the quinuclidine-N points away from the quinoline ring. Fig. 5 depicts the most stable ‘closed’ and ‘open ’ conformers of protonated cinchonidine and cinchonine, respectively, as suggested by molecular mechanics and ab initio calculations [47].

Changing the substituent at C-9 of cinchonidine from OH to OAc results in an increasing destabilization of the ‘open’ conformer. This may explain the poor enantio-differentiation observed with the cinchonidine derivative, in which OH was substituted by OAc [28]. Dijkstra et al. [45,46] concluded from their NMR, molecular mechanics and X-ray studies that if a hydroxyl group is present at the benzylic position of the cinchona alkaloid, the ‘open’ conformation is preferred, particularly, when the alkaloids are protonated, irrespective of their starting conformation and extra stabilization by the solvent.

As concerns conformational effects caused by the interaction with the reactant pyruvate or solvent molecules, these effects seem to be able

to dictate the conformation of the cinchona alkaloid only in certain circumstances. The experimental and theoretical results collected so far indicate that it is mainly the quinuclidine-N which is responsible for these interactions. Interactions with the benzylic (C-9) OH (e.g. half-ketal formation [36]) may be possible, however, their influence seems to be of minor importance. In the 'closed' conformation of the cinchona alkaloids, there exists significant steric hindrance for the quinuclidine-N lone pair to participate in alkaloid-reactant or alkaloid solvent interactions, whereas in the case of the 'open' conformation, the nitrogen lone pair is better accessible to reactant or solvent molecules. The steric constraints of the 'closed' conformer become particularly evident when the interaction between coadsorbed cinchona alkaloid and the reactant pyruvate is rationalized by molecular modeling.

Based on the available information on the conformation of cinchona alkaloids discussed above, we decided to use the 'open' conformers of cinchonidine (**CD**) and cinchonine (**CN**), shown in Fig. 5, for the calculation of the structure of the complex formed upon interaction of the cinchona alkaloids (cinchonidine and cinchonine) with the reactant methyl pyruvate.

The adsorption behavior of the cinchona alkaloids and the reactant pyruvate on the active platinum surface is another crucial aspect to be considered when rationalizing the structure of a

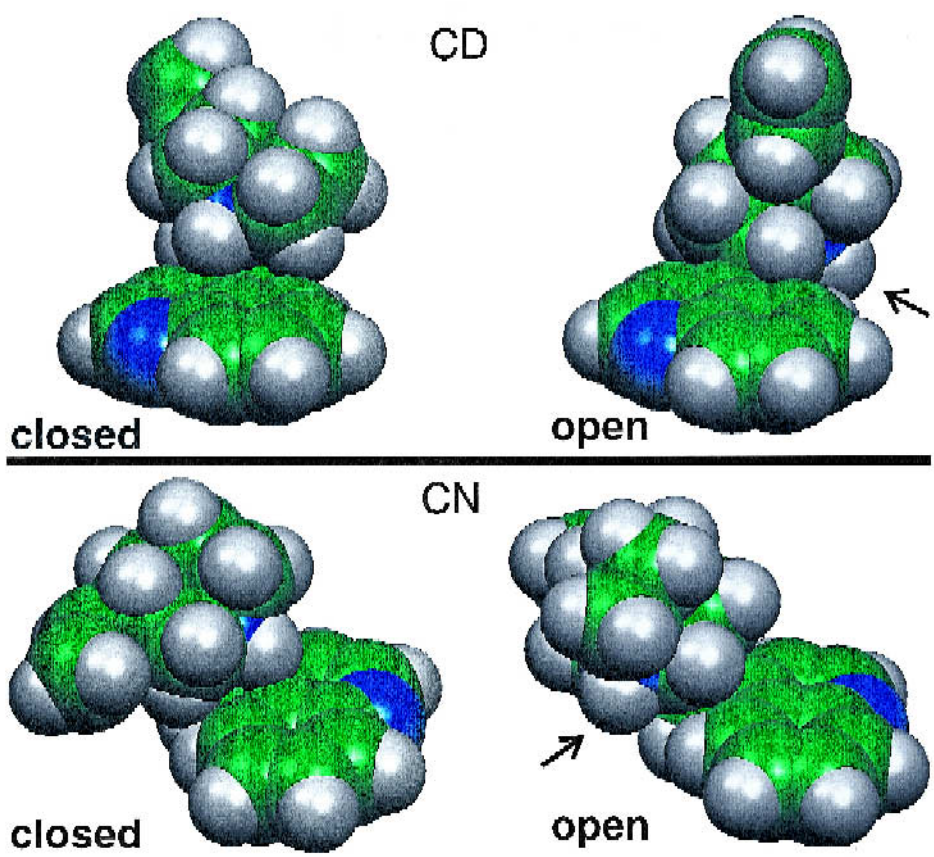


Fig. 5. Most stable 'open' and 'closed' conformers of cinchonidine (**CD**) and cinchonine (**CN**), calculated using molecular mechanics and ab in initio methods [47]. C is green, N is blue and H is grey. Arrow points towards quinuclidine-N.

possible transition complex. However, virtually no studies on the adsorption of cinchona alkaloids and α-ketoesters are available in the literature. Thus, valuable information only originates from indirect studies of reactivity (isotope exchange) or from adsorption studies of structurally related compounds.

As concerns the cinchona alkaloids, they are expected to be adsorbed on Pt in a similar way as quinoline and other N-containing extended aromatic ring systems. Indirect evidence for this has been provided by the hydrogen isotope (H/D) exchange studies carried out by Bond and Wells [48]. They found that in 10,11-dihydrocinchonidine, when adsorbed on Pt/silica at 293 K, fast exchange occurs in the hydroxyl group at C-9 followed by multiple exchange in the quinoline ring system, whereas no exchange takes place in the quinuclidine ring system. Based on these results and similar findings for quinoline exchange and hydrogenation, the authors concluded that 10,11-dihydrocinchonidine is adsorbed on Pt via the quinoline ring system and that the quinoline moiety is adsorbed approximately parallel to the platinum surface by multicenter π-bonding. However, depending on various factors such as structure of the exposed Pt face, surface coverage, interaction with coadsorbed species, and temperature, other adsorption modes (e.g. adsorption via quinoline-N) are conceivable. LEED, AES HREELS and electrochemical studies of bipyridyls and related compounds showed that pyridyl rings, unhindered at positions ortho to the ring nitrogen atom, adopt tilted vertical orientations with surface attachment mainly through the nitrogen atom, whereas pyridyl rings hindered by bulky groups *ortho* to nitrogen favor the horizontal orientation [49]. The important effect of temperature on the adsorption mode has been demonstrated by NEXAFS measurements of pyridine chemisorption on Pt(111), which revealed a strong increase in the angle between the aromatic ring plane and the surface plane, when the temperature was raised above 200 K [50]. A similar change could lead to a tilted adsorption of the cinchona alkaloid at higher temperature, which would explain the observed collapse in ee above ca. 320 K [15,16,21].

As to the adsorption of α-ketoesters, some information on the adsorption mode can be extracted from adsorption studies of other compounds containing carbonyl moieties [51,52]. These studies indicate significant differences in the adsorption of carbonyl compounds depending not only on the metal, but also on the exposed crystal face. Methyl pyruvate, in its lowest energy state, has the two carbonyl groups in *trans* configuration and it is assumed that this configuration is retained on adsorption [40]. Interaction of both carbonyls with the platinum surface is expected, in analogy to buta-1,3-diene adsorption [53], so that the adsorbed molecule shows a parallel orientation to the platinum surface.

It is clear that a global minimization of the energy of the adsorbed transition complex has to account for the relatively strong adsorption bonds established between the platinum surface and the cinchona alkaloid and reactant pyruvate. These interactions are proposed to be considerably stronger than the relatively weak interaction between the alkaloid and the pyruvate. Consequently, in rationalizing the diastereomeric transition complex, we assumed that the alkaloid as well as the pyruvate are adsorbed in a form parallel to the platinum surface, which allows optimal interaction of the platinum with both the aromatic quinoline ring and the two carbonyl moieties of the α-ketoester.

The possible structure of the diastereomeric transition complex formed between the protonated cinchona alkaloids (**CD** and **CN**) and methyl pyruvate were investigated using molecular mechanics methods [54–56]. Fig. 6 shows the structures of the most stable complexes formed by interaction of protonated cinchonidine and methyl pyruvate, which upon hydrogenation would yield (*R*)-(+)-methyl lactate and (*S*)-(−)-methyl lactate, respectively. The complexes are accommodated on a Pt(111) surface in order to illustrate the space requirements

of the adsorbed complexes. Note that the precursor to (*R*)-(+)-methyl lactate, can be adsorbed in a planar π-bonding mode on the Pt surface via the aromatic quinoline ring, without hindering the interaction of the carbonyl groups of methyl pyruvate with the Pt surface. This adsorption mode is sterically hindered for the complex suggested to be the precursor to (*S*)-(−)-methyl lactate.

The opposite behavior (Fig. 7) is found when the complexes, formed upon interaction of protonated cinchonine (the near-enantiomer of cinchonidine) with methyl pyruvate, are optimized. The transition complex resulting in (*S*)-(−)-methyl lactate upon hydrogenation can be adsorbed without significant steric hindrance, while the one affording (*R*)-(+)-methyl lactate is sterically hindered.

Thus calculations showed that — in agreement with the experimental observations — a change in the chirality of the stereogenic region (C-8, C-9) of the cinchona alkaloid modifier results in a corresponding change in the chirality of the product lactate. In the transition complex the substrate is bound to the modifier via stabilizing hydrogen bond interaction (N–

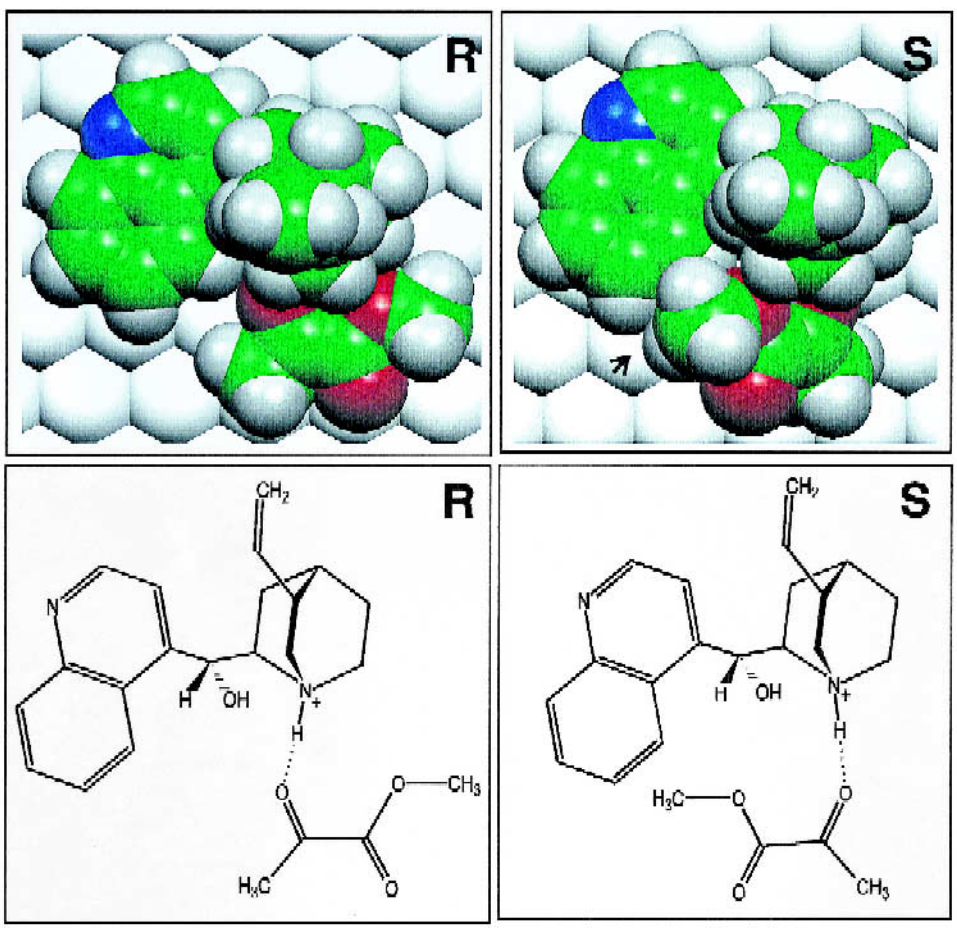


Fig. 6. Transition complexes, as proposed by molecular modeling, formed between protonated **CD** and methyl pyruvate (**MP**) which yield (*R*)-(+)-methyl lactate and (*S*)-(−)-methyl lactate, respectively, upon hydrogenation. **CD** is assumed to be adsorbed via π-bonding of the quinoline ring on the Pt surface. A Pt(111) surface is used for illustration. The adsorption of complex (*R*) is energetically more favorable due to the strong steric hindrance (indicated by the arrow) in the complex leading to the (*S*)-lactate. C is green, O is red, N is blue, H is grey and Pt is white.

H · · · O) between the protonated quinuclidine-N and oxygen atom of the α-carbonyl of the pyruvate. Although these theoretical studies were made for conditions, where the quinuclidine-N is protonated (e.g. acetic acid as solvent) similar transition complexes are also calculated starting from unprotonated cinchona alkaloid and a half-hydrogenated state of the reactant, as recently shown for the enantioselective hydrogenation of ketopantolactone over platinum–cinchonidine in toluene [57]. Fig. 8 depicts the calculated diastereomeric transition complexes leading to (*R*)-pantolactone and (*S*)-pantolactone, respectively. The transition complex affording (*R*)-pantolactone was calculated to be ca. 2 kcal/mol more stable than the corresponding complex leading to (*S*)-pantolactone. Based on this energy difference in the diastereomeric transition complexes one would expect at room temperature an ee-value of about 90% compared to 79% which were reached experimentally [57]. Most important, these studies clearly indicated that, in agreement with the experimental observations, protonation of the quinuclidine-N is not a requirement for the formation of the hydrogen bonding between the α-carbonyl of the α-ketoester and the cinchona alkaloid. When the enantioselective hydrogenation is carried out in an aprotic solvent (e.g. toluene, which was found to be most favorable for ketopantolactone hy-

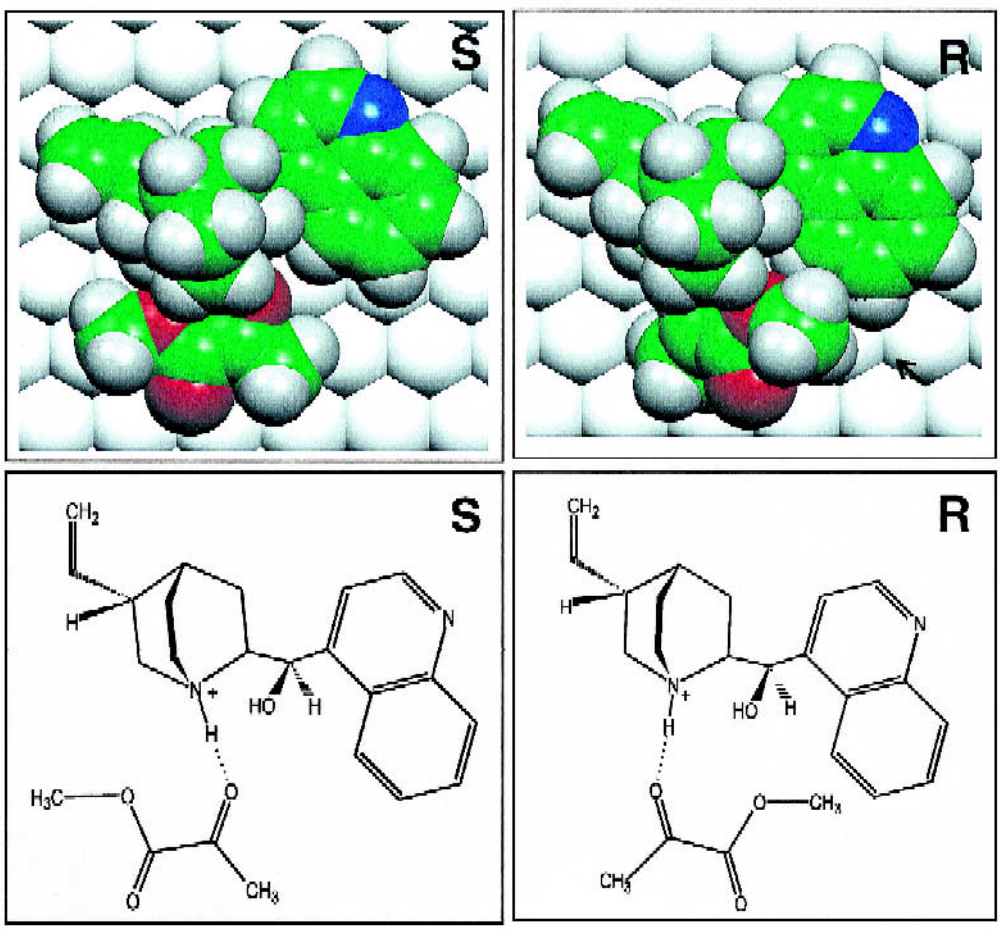


Fig. 7. Transition complexes formed between protonated **CN** and **MP** which yield (*S*)-(−)-methyl lactate and (*R*)-(+)-methyl lactate, respectively, upon hydrogenation. The adsorption of complex (*S*) is energetically more favorable due to the strong steric hindrance (indicated by the arrow) in the complex leading to the (*R*)-lactate. C is green, O is red, N is blue, H is grey and Pt is white.

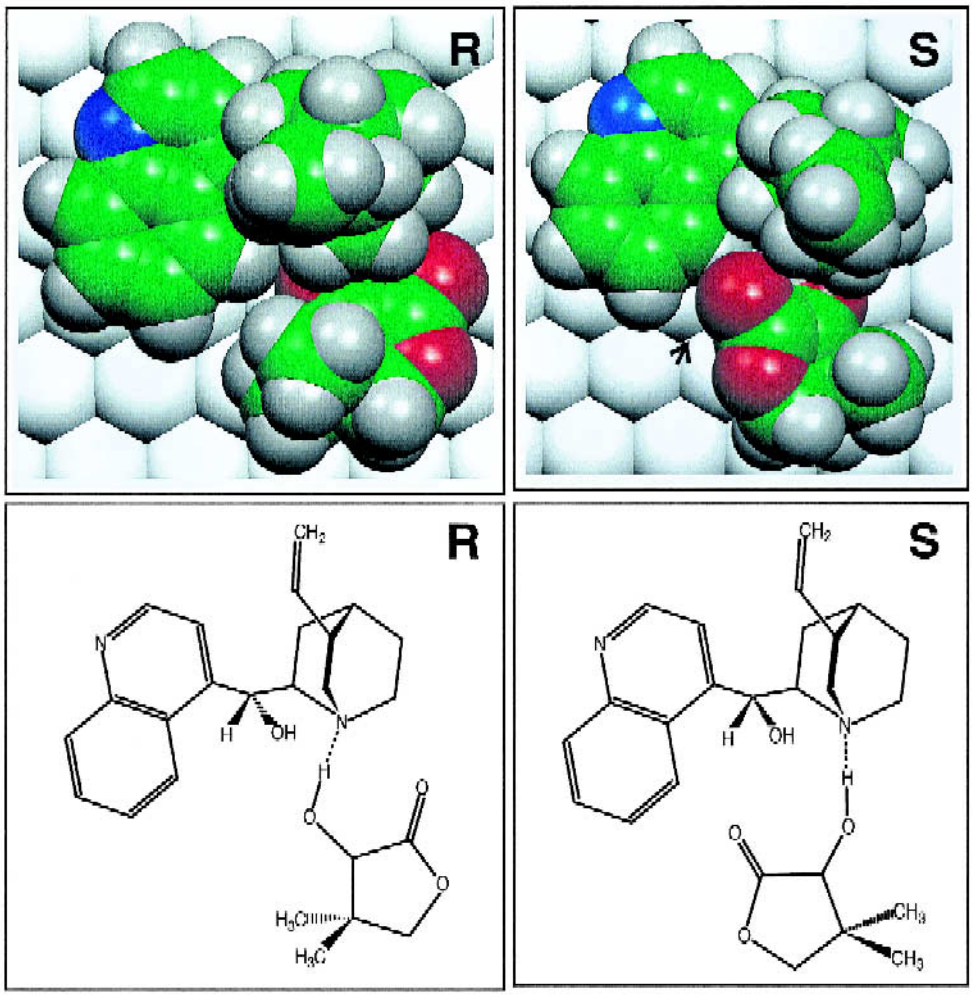


Fig. 8. Transition complex formed between **CD** and half-hydrogenated state of ketopantolactone resulting in (*R*)-pantolactone upon hydrogenation [57]. C is green, O is red, N is blue, H is grey and Pt is white.

drogenation), the hydrogen bond is proposed to be established by a half-hydrogenated state of the reactant (O–H · · · N). The origin of the hydrogen responsible for the stabilizing interaction between the cinchona modifier and the reactant α-keto ester may change depending on the solvent. The proton could either come from the solution (acetic acid) or from dissociatively adsorbed hydrogen. In this scenario, the second H-atom would be added as hydride.

The molecular modeling approach, taking into account the pyruvate and cinchona alkaloid interaction, and the steric constraints imposed by the adsorption of these species on the platinum surface, leads to a reasonable explanation for the enantio-differentiation of this system. Although the prediction of the complex formed between the methyl pyruvate and the cinchona modifiers have been made for an ideal case (solvent effects and a quantum chemical description of the interaction with the platinum surface atoms were not considered), this approach provided a reasonable explanation for the enantioselectivity and proved to be very helpful in the search of new modifiers, which will be discussed next.

3. Novel chirally modified platinum catalysts

The search strategy, which included a systematic reduction of the cinchona alkaloid structure to the essential functional parts and validation of the steric constraints imposed to the transition complex between modifier and methyl pyruvate by means of molecular modeling, indicated that simple chiral amino alcohols should be promising substitutes for cinchona alkaloid modifiers. Using the Sharpless asymmetric dihydroxylation [58] as a key step, a series of enantiomerically pure 2-hydroxy-2-aryl-ethylamines (Fig. 9) were synthesized and tested as modifiers in the hydrogenation of ethyl pyruvate over Pt/alumina [59–61]. The napthylene derivative (*R*)-2-(1-pyrrolidinyl)-1-(1-naphthyl)ethanol (**1a**, Fig. 9) proved to be a remarkably efficient modifier inducing at low hydrogen pressures (1–10 bar) enantiomeric excesses as high as 75%, which is comparable to that obtained with dihydrocinchonidine (**HCD**) in this pressure range [60]. In contrast to **HCD** which is more effective at higher pressures (10–100 bar) [62], the enantioselectivity of **1a** decreases at higher hydrogen pressures due to partial hydrogenation of the naphthalene ring and concomitant loss of the π-bonding [60]. The importance of the extended aromatic ring system for anchoring is confirmed by the fact that corresponding benzene and pyridine derivatives (modifiers **2a** and **2b**) are ineffective [59]. Modifier **1b** which is structurally identical to **1a** but possesses a quinoline anchoring moiety, affords an ee similar to that of **1a** under identical conditions (note that the ee of 75% for **1a** was obtained under optimized conditions, whereas the conditions for **1b** were not optimized). These experimental observation indicates that the N heteroatom in the quinoline ring has no importance in the adsorption of modifier **1b**. Naphthalene-derived modifiers containing more bulky amino groups (modifiers **3b**–**3e**) induce markedly lower enantioselectivity. The structurally related diols of modifiers **1a** and **1b** do not provide enantio-differentiation, indicating

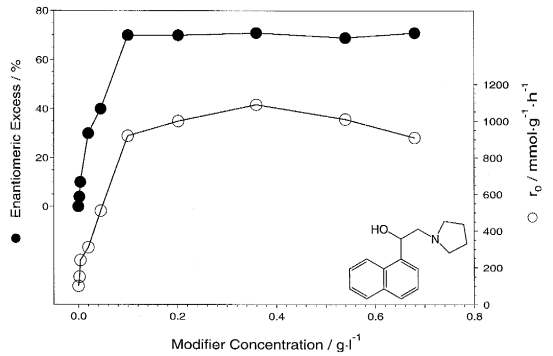


Fig. 10. Influence of modifier concentration on enantiomeric excess and reaction rate (r_0) for the hydrogenation of **EP** over platinum modified with (2-(1-pyrrolidinyl)-1-(1-naphthyl) ethanol (**1a**, Fig. 9). Experimental conditions: 100 mg catalyst, 6.22 μmol **1a**, 10 ml (0.09 mol) **EP**, 20 ml acetic acid, 25°C.

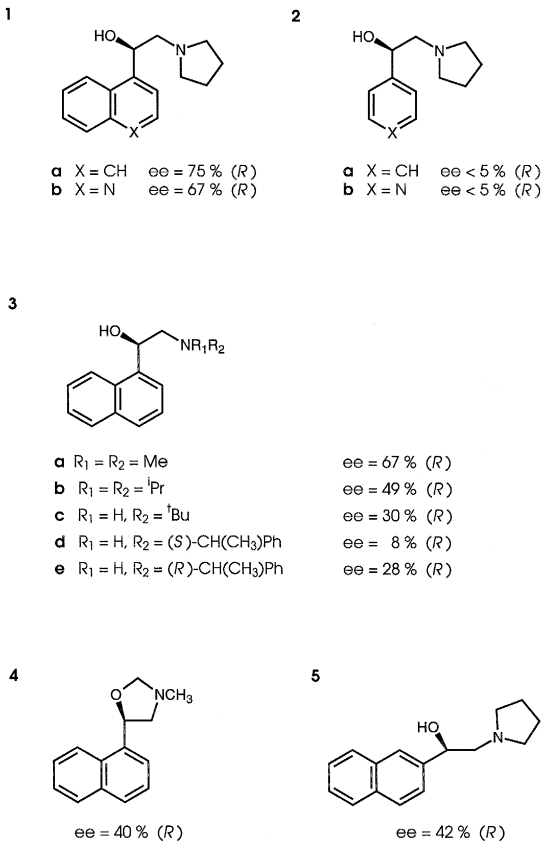


Fig. 9. 1,2-aminoalcohols as structurally simple substitutes of cinchona alkaloid modifiers. Enantiomeric excesses indicated were measured for **EP** hydrogenation at 25 bar hydrogen pressure.

the importance of the N-H-O interaction [59]. The 1-naphthyl-substituted amino alcohol (**1a**) is superior concerning enantio-differentiation compared to the corresponding 2-naphthyl-substituted amino alcohol (modifier **5**).

Interestingly, the Pt–**1a** system shows qualitatively the same dependence of ee and reaction rate on the modifier concentration (Fig. 10) as observed with the classical Pt–**CD** system (Fig. 13), suggesting that both systems function in a similar way. The initial rate is accelerated by a factor of 7–8 compared to the unmodified hydrogenation of ethyl pyruvate (**EP**). The optimal modifier concentration at which the Pt–**1a** system shows maximum performance is around 10^{-4} M, corresponding to a modifier: reactant molar ratio of 1:30000. Note that for the Pt–**CD** system the generally used ratios are around 1:1000 [12,17–21], which lends further support for the efficiency of the Pt–**1a** system. The lowest modifier reactant ratio reported so far is that used under optimized conditions for the 10,11-dihydro-*O*-methylcinchonidine which amounts to 1:130000 [62]. The structurally simple modifier **1a** was the first which provided enantiomeric excesses comparable to that obtained with the traditional cinchona alkaloids. However, in contrast to the cinchona alkaloids its structure can be easily modified in various ways.

The structural similarity of the transition complexes formed between the reactant methyl pyruvate (**MP**), cinchonidine (**CD**) and (*R*)-2-(1-pyrrolidinyl)-1-(1-naphthyl)ethanol (**1a**, Fig.

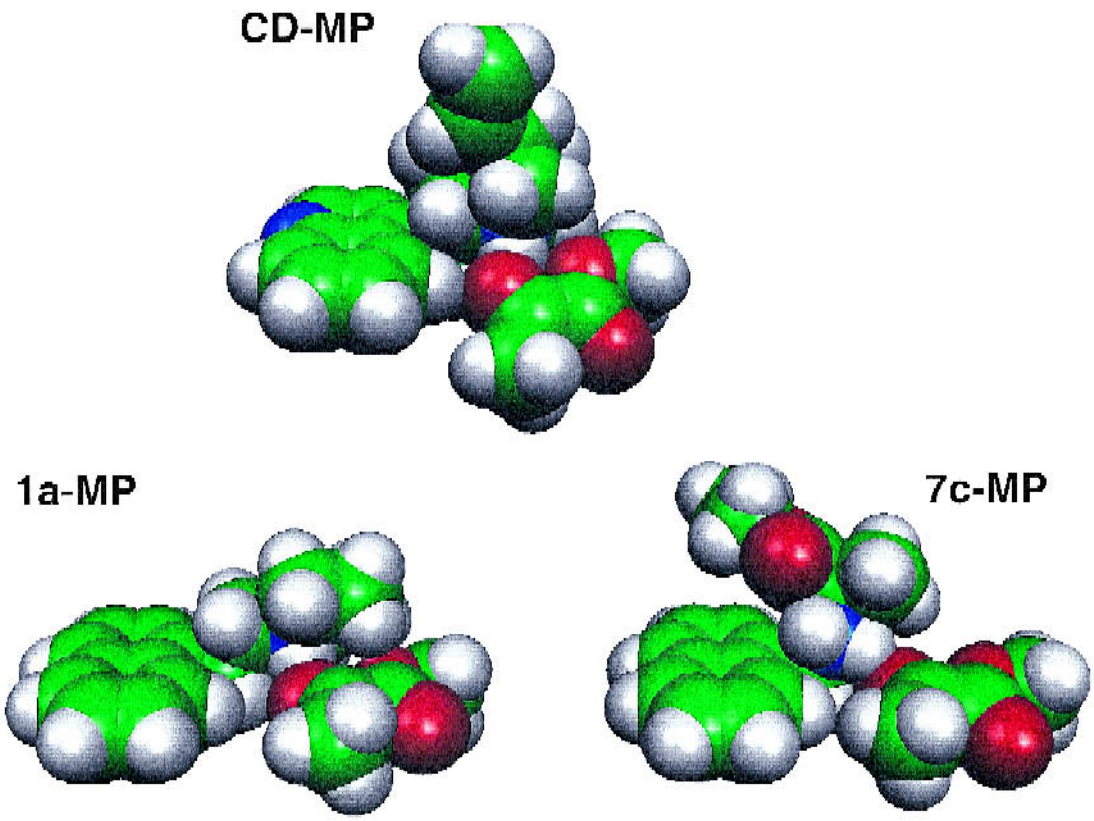


Fig. 11. Proposed structures of diastereomeric transition complexes formed by interaction of methyl pyruvate (**MP**) with different modifiers, all leading to (*R*)-methyl lactate. Protonated cinchonidine-methyl pyruvate (**CD**–**MP**), protonated (2-(1-pyrrolidinyl)-1-(1-naphthyl) ethanol-methyl pyruvate (**1a**–**MP**), and (2*R*, 1′*R*)-*N*-[1′-(1-naphthyl)ethyl]-2-amino propionic acid methylester (**7c**, Fig. 13) formed by reductive alkylation of **6a** (Fig. 12) with **MP** (**7c**–**MP**). C is green, O is red, N is blue and H is grey.

9), respectively, becomes apparent if one compares the energetically optimized structure of these complexes, which are depicted in Fig. 11.

An interesting alternative to the amino alcohols are the recently discovered modifiers derived from 1-(1-naphthyl)ethylamine (**6a** and **6b**, Fig. 12) [63–65]. Catalytic quantities of (*R*)- or (*S*)-1-(1-naphthyl)ethylamine induce up to 82% ee in the hydrogenation of ethyl pyruvate over Pt/alumina [65]. **6a** and **6b** are only the precursors of the actual modifiers, which are secondary amines formed in situ by reductive alkylation with the reactant pyruvate. This transformation, shown for **6b** in Fig. 12, proceeds via imine formation and subsequent reduction of the C=N bond, and is highly diastereoselective (de > 95%). Further reductive alkylation with **EP** to a tertiary amine does not occur under the conditions used for hydrogenation of **EP**. Interestingly, the two diastereomers **7a** (*S,S*) and **7b** (*S,R*) induce the same enantioselectivity in the hydrogenation of **EP**. This demonstrates that the configuration at the stereogenic center in α-position to the ester group has no influence on the enantioselection of modifiers **7a** and **7b**. Isomerization of **7b** to **7a**

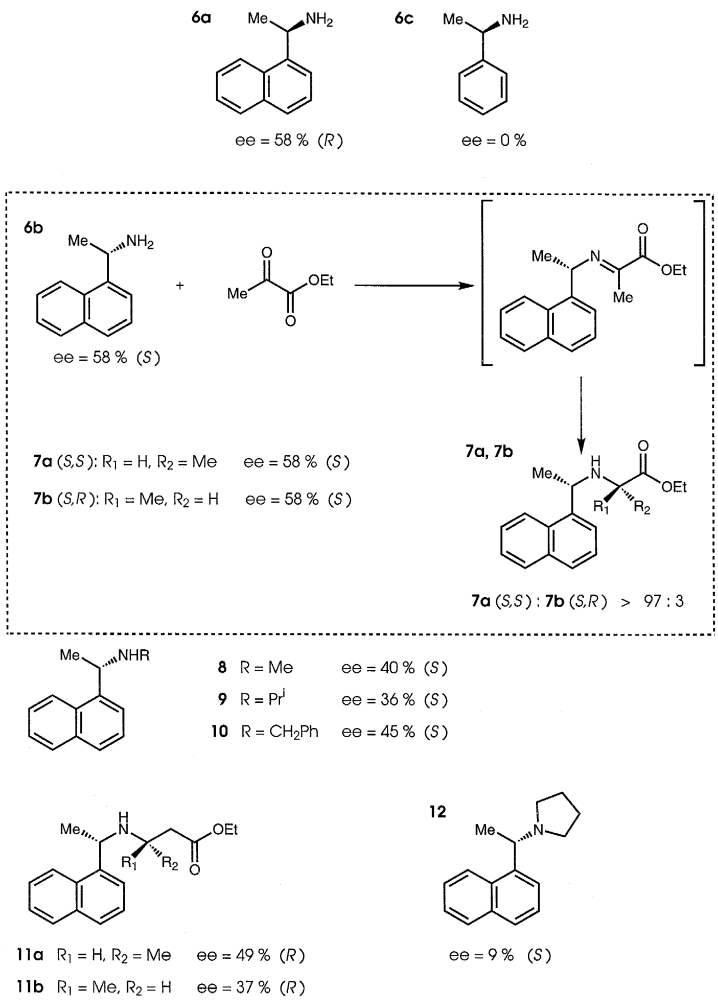


Fig. 12. (*R*)-1-(1-naphthyl)ethylamine (**6a**) and derivatives as simple substitutes of cinchona alkaloid modifiers. Note that reductive alkylation resulting in the 'real' modifier occurs in situ in the reaction solution. Stereogenic center at α-carbon determines chiral induction, as revealed by the fact that modifiers **7a** and **7b** both favor (*R*)-ethyl lactate formation.

occurs to less than 3% during hydrogenation of **EP**. Reductive alkylation of **6a** with different aldehydes or ketones provides easy access to a variety of related modifiers, such as **11a** and **11b** (Fig. 12). Note that **11a** and **11b** both favor the formation of *R*-lactate, although the relative configuration at the α-C to the ester group is changed, corroborating the behavior of modifiers **7a** and **7b**.

The enantioselection occurring with the modifiers derived from **6a** could be rationalized with the same strategy of molecular modeling as demonstrated for the Pt–cinchona system. Fig. 11 depicts the structure of the complex formed between (2*R*, 1′*R*)-*N*-[1′-(1-naphthyl)ethyl]-2-amino propionic acid methylester (formed by reductive alkylation of **6a** with **MP**) and the reactant methyl pyruvate as predicted by the theoretical calculations. Note the striking similarity in the interaction of this complex and that of **CD**–**MP** and **1a**–**MP**, respectively.

The similarity in the interaction affording the stereochemical control is further substantiated by the behavior of the platinum catalyst modified with this chiral auxiliary. Again we find a similar dependence of ee and reaction rate on the modifier concentration (Fig. 13). Both rate and ee increase with higher modifier concentration and reach a broad maximum between 0.2

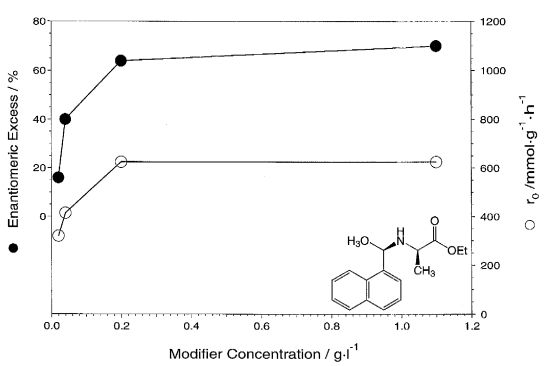


Fig. 13. Influence of modifier concentration on enantiomeric excess and reaction rate (r_o) for the hydrogenation of ethyl pyruvate over platinum modified with (*R*)-1-(1-naphthyl)ethylamine (**6a**). Experimental conditions: Experimental conditions: 100 mg catalyst, 6.22 μmol **6a**, 10 ml (0.09 mol) **EP**, 20 ml acetic acid, 25°C.

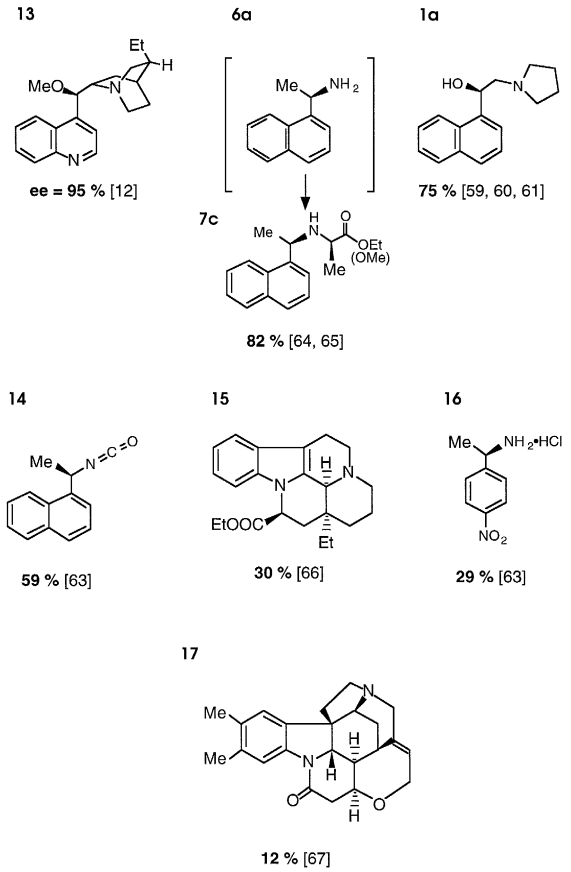


Fig. 14. Different types of modifiers used for chiral modification of Pt and highest enantiomeric excesses measured with them in **EP** hydrogenation. **13** 10-11-dihydro-*O*-methyl-cinchonidine, **6a** (*R*)-1-(1-naphthyl)ethylamine and **7c** (2*S*,1′*R*)-*N*-[1′-(1-naphthyl)ethyl]-2-amino propionic acid ethyl ester formed in situ during **EP** hydrogenation, **1a** 2-(1-pyrrolidinyl)-1-(1-naphthyl)ethanol, **14** (*R*)-1-(1-naphthyl)ethyl isocyanate, **15** dihydro-vinpocetine (dihydro-apovincamic acid ethyl ester), **16** (*R*)-1-(4-nitrophenyl)ethylamine hydrochloride, **17** brucine. (See also [12,59–61,63–67]).

and 20 mM. The required modifier: reactant molar ratio is 1:15000 and the modifier: Pt (surface) molar ratio 1:1 under the conditions applied. The hydrogenation rate of **EP** is accelerated in the presence of **6a** by a factor of up to 6 compared to the hydrogenation performed with unmodified Pt.

Finally, it is interesting to summarize the most important types of auxiliaries which are known today for modifying Pt catalysts for the enantioselective hydrogenation of α-ketoesters (Fig. 14). Although the ee values achieved in

EP hydrogenation allow a certain ranking, it should be emphasized that these enantiomeric excesses represent the best values achieved. The 10,11-dihydro-*O*-methyl-cinchonidine (**13**, Fig. 14), as a representative of the cinchona alkaloid derivatives, is the most efficient modifier known for high pressure hydrogenation of **EP**. At low hydrogen pressures **6a** is a superior modifier to the cinchona alkaloids and their derivatives, whereas **1a** shows about similar performance.(*R*)-1-(1-naphthyl)ethylisocyanate (**14**) is probably transformed to **6a** under hydrogenation conditions, either by reduction or by hydrolysis, and does not really represent a new modifier [63]. (*R*)-1-(4-nitrophenyl)ethylamine hydrochloride (**16**) also undergoes reductive alkylation under hydrogenation conditions. However, in contrast to modifier **6c** (Fig. 12) it shows significant enantio-differentiation, indicating that the presence of the amino group at the phenyl ring results in more favorable adsorption. Whereas, the enantio-differentiation induced by modifiers **1a**, **6a**, **13** and **16** can be rationalized in the framework of the knowledge gathered for the Pt–cinchona system, nothing is known so far about the functioning of the complex natural modifiers **15** [66] and **17** [67].

4. Broadening of scope of reactions

Progress has also been made by extending the scope of reactions for which platinum metal catalysts modified with cinchona alkaloids can be applied. Fig. 15 summarizes the compounds which have been hydrogenated over chirally modified Pt. New reactions include the enantioselective hydrogenations of ketoacids [68], trifluoracetophenone [69], and conjugated diketones [70]. Major improvement in enantiomeric excess from ee = 52% [71] to 79% [57] has been achieved in the hydrogenation of ketopantolactone due to special pre-conditioning of the catalyst, removal of oxygen and water, and adjustment of the solvent. The results achieved with the new reactants indicate that the application range of the Pt–cinchona systems may be considerably broader than expected from the work reported so far. Further extension of the scope of reactions, including the reduction of functionalized C=C [73–75] and C=N [76] bonds, has recently been achieved with chirally modified Pd catalysts. The opportunities for extension of the range of reactions with the new modifiers (**1a** and **6a** and derivatives thereof) cannot be judged yet, because they have been

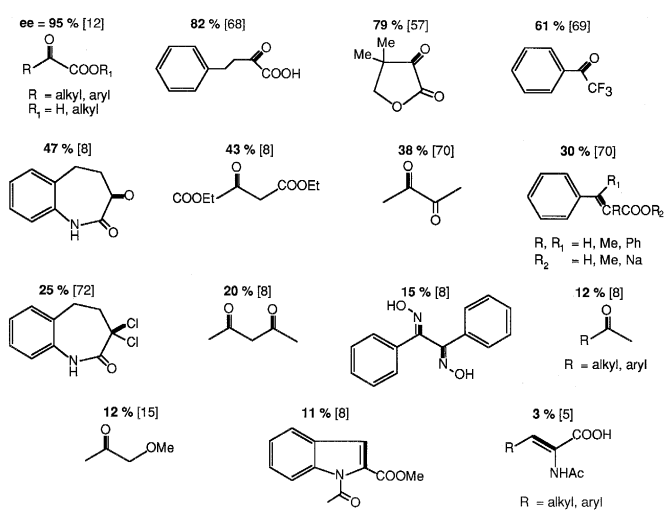


Fig. 15. Compounds enantioselectively hydrogenated using platinum modified with cinchonidine. Enantiomeric excesses (ee) quoted correspond to highest values achieved for the specific reaction. (See also [5,8,12,15,57,68–70,72]).

applied only to pyruvate hydrogenation so far. However, the fact that these structurally simple modifiers are more amenable to structural tailoring lends some hope that a significant broadening of the scope of reaction is possible in the near future.

5. Conclusions

Not so long ago, it seemed that only natural, structurally unique complex auxiliaries, such as cinchona alkaloids are suitable for chirally modifying platinum metal catalysts. However, recent results obtained with simple chiral amino alcohols and amines demonstrate the contrary. With enantiomeric excesses exceeding 80%, commercially available 1-(1-naphthyl)ethylamine is the most effective chiral modifier for low pressure hydrogenation of ethyl pyruvate reported to date. The development of the novel modifiers has been based on the mechanistic understanding gained for the enantioselective hydrogenation of α-ketoesters over platinum modified with cinchona alkaloids. At the origin of this development were experimental findings concerning the interrelationship between modifier structure and its enantio-differentiation capability. Theoretical consideration using quantum chemical techniques brought further insight and let finally to an explanation of the enantio-differentiation. The crucial interactions for the functioning of the modifier are its adsorption (anchoring) on the platinum metal surface and the hydrogen bonding between the tertiary nitrogen and the oxygen at the α-carbonyl group of the reactant pyruvate. The hydrogen responsible for the hydrogen bond interaction between the modifier and the reactant pyruvate can be provided either by protonation of the tertiary nitrogen or by a half-hydrogenated state of the α-ketoester (α-C–OH), depending on the solvent used. In acetic acid, protonation of the tertiary nitrogen will occur, whereas in apolar solvents, such as toluene, the hydrogen bonding is proposed to be established via the half-hydrogenated state. The hydrogen bonding interaction is considered to be relatively weak compared to the adsorption bond strength of the modifier and the reactant, suggesting that the formation of the enantio-differentiating complex will be greatly influenced by the latter. This may explain why the rigorous assumption concerning the adsorption of modifier and reactant, imposed to the model, proved to be successful in the search of new modifiers.

The search strategy, which included a systematic reduction of the cinchona alkaloid structure to the essential functional parts and validation of the steric constraints imposed to the transition complex between modifier and methyl pyruvate by means of molecular modeling, proved to be powerful. It is hoped that the combined use of experimental and theoretical methods will also be gratifying in extending the scope of reactions, which seems more promising than it was before the new modifier were found. In any case, we can be confident that further research will lead to other even more effective modifiers which are designed specifically for a particular reaction. The first steps towards extending the scope of enantioselective heterogeneous hydrogenation seem to have been made. The concept of coadsorbed auxiliaries for stereo- or chemocontrol [77–79] of reactions provides a potential tool which can pave the way to several novel catalytic systems.

Acknowledgements

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