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Journal of Catalysis 239 (2006) 255–262
JOURNAL OF CATALYSIS
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Steric and electronic effects in the enantioselective hydrogenation of activated ketones on platinum: Directing effect of ester group

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Received 19 December 2005; revised 1 February 2006; accepted 2 February 2006

Available online 6 March 2006

Abstract

Steric effects in the Pt-catalyzed asymmetric hydrogenation of nine different α-ketoesters were studied by variation of the bulkiness at the keto and ester side of the substrates, and by using cinchonidine (CD), its 6′-methoxy derivative quinine, and *o*-phenyl derivative PhOCD as chiral modifiers. In the presence of CD, the (*R*)-enantiomer always formed in good to high *ee* (up to 96%), independent of the steric bulkiness of the α-ketoester. None of the mechanistic models developed for ketone hydrogenation on Pt are conform to the observations. Only additional steric effects in the modifiers and replacement of toluene by acetic acid as a reaction medium enhanced the sensitivity of the catalyst system to steric effects in the substrates (*ee* = 0–94%). An important mechanistic consequence of the observations is that on CD-modified Pt preferred adsorption of the α-ketoester on the *si*-side is directed by the position of the ester group relative to the modifier, independent of the steric bulkiness on any side of the keto-carbonyl group. Ester, carboxyl, amido, carbonyl, acetal, and trifluoromethyl functions have similar directing effects, but when both trifluoromethyl and an ester or carbonyl groups are present in the molecule, the latter function is dominant. The directing effect of the electron-withdrawing (-activating) function on adsorption of the ketone is obviously related to the electronic environment provided by the chiral modifier. The critical role of electronic interactions is supported by the remarkable influence of aryl substituents in the hydrogenation of ethyl benzoylformates.
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Keywords: Enantioselective hydrogenation; α-Ketoester; α-Hydroxyester; Cinchonidine; Quinine; *o*-Phenyl-cinchonidine; Pt/Al_2O_3; Mechanism

1. Introduction

Optically active α-hydroxyesters and α-hydroxyacids are important building blocks for the synthesis of biologically active natural products and analogues thereof [1]. A viable option for this synthesis is the heterogeneous enantioselective hydrogenation of α-ketoesters on cinchona-modified Pt. Since the first description of the route by Orito et al. in 1979 [2,3], several research groups have been fascinated by the potential of this catalyst system (for recent reviews see Refs. [4–13]). Hydrogenation of ethyl pyruvate (**1**, Scheme 1) is the most studied heterogeneous enantioselective hydrogenation reaction and now serves as a standard model reaction for chirally modified Pt. After years of optimization, 97–98% *ee* has been achieved in the synthesis of α-hydroxyesters using CD [14–16] or QN [17] as chiral modifiers of supported and colloidal Pt.

The only systematic study of the structural effects in the hydrogenation of α-ketoesters revealed that an increase in the size of the alkyl group (from methyl to *t*-butyl) in the ester group of pyruvate barely decreased the *ee* [18]. Introduction of a *t*-butyl group in α-position to the keto group reduced the *ee* to 81%, probably due to hindered adsorption of the keto group. The electronic effects of substituents on the performance of chirally modified Pt have been studied in only two series of acetophenone and trifluoroacetophenone derivatives [19–21].

Several mechanistic models have been developed and refined to rationalize the stereochemical outcome of the hydrogenation of α-ketoesters (for a recent overview see Ref. [22]). Most models postulate a 1:1-type interaction between substrate and modifier, involving an N–H–O-type hydrogen bond interaction [23–27] or a nucleophilic attack of the basic N atom of the modifier on the keto C atom [28–33]. A common limitation of

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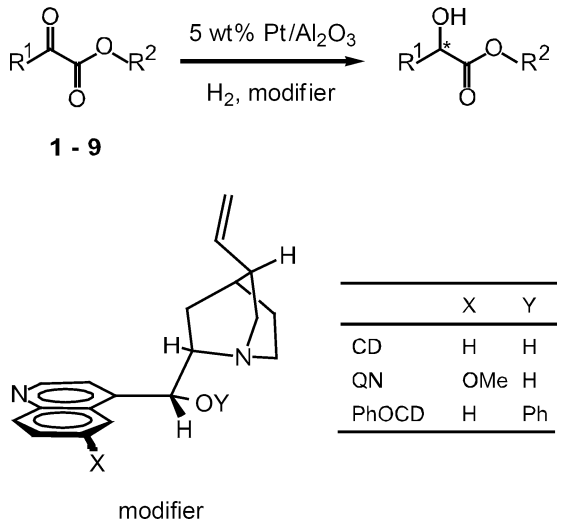
doi:10.1016/j.jcat.2006.02.001



Scheme 1. Enantioselective hydrogenation of α-ketoesters **1–9** over Pt/Al_2O_3 modified by CD, QN, and PhOCD.

these models is that only transformation of the simplest substrates, usually methyl or ethyl pyruvate, are described, and steric effects relevant in the hydrogenation of bulkier molecules have not been considered.

The aim of the present study was to analyze the steric and electronic effects on the Pt-catalyzed enantioselective hydrogenation of α-ketoesters. Nine different substrates were hydrogenated in the presence of CD, its 6′-methoxy derivative QN, and *o*-phenyl derivative PhOCD (Scheme 1). That is, not only was the bulkiness of α-ketoesters at the keto and the ester side varied, but also additional steric effects were introduced in the modifier. The additional functions of CD influence the adsorption mode and strength of the modifier [17,31,34–36], and thus the shape of the chiral pocket available for adsorption of the α-ketoester, while interacting with the alkaloid during hydrogen uptake.

2. Experimental

2.1. Materials

Ethyl pyruvate **1** (Fluka) and ethyl benzoylformate **3** (Aldrich) were carefully distilled in vacuum before use. *t*-Butyl benzoylformate **4** was synthesized via α-oxo-benzeneacetyl chloride by treating the acid chloride with *t*-butanol in basic medium [37,38]. α-Oxo-benzeneacetyl chloride was synthesized from benzoylformic acid by chlorination with dichloromethyl methyl ether [37,38]. Ethyl *t*-butylglyoxylate **2**, ethyl 3,5-dimethylbenzoylformate **5**, ethyl 3,5-difluorobenzoylformate **6**, ethyl 3,5-di(trifluoromethyl)benzoylformate **7**, ethyl 3,5-dimethoxybenzoylformate **8**, and ethyl naphthylglyoxylate **9** were prepared by reaction of the corresponding Grignard reagents with diethyl oxalate according to a known method [39]. All synthesized substrates underwent flash chromatography and had their purity (>99%) confirmed by GC, HPLC, and NMR analysis. Acetic acid (AcOH, 99.8%, Fluka) was used as received, and toluene (99.5%, J.T. Baker) was dried and stored over activated molecular sieve. Cinchonidine (CD, 92%, Fluka; impurities: 1% quinine, 7% quinidine, determined by HPLC at Fluka) and quinine (QN, 99%, Fluka) were used without further purification. *o*-Phenyl-cinchonidine (PhOCD) was synthesized as described earlier [34]. The 5 wt% Pt/Al_2O_3 (E4759) catalyst was purchased from Engelhard.

2.2. Catalytic hydrogenation

The hydrogenation reactions were carried out in a mechanically stirred eight parallel pressure reactor system (Argonaut Technologies) or in a magnetically stirred stainless steel autoclave controlled by a computerized constant-volume, constant-pressure equipment (Büchi BPC 9901). Optimally, the 5-wt% Pt/Al_2O_3 catalyst was prereduced before use in a fixed-bed reactor by flushing with N_2 at 400 °C for 30 min, followed by reductive treatment in H_2 for 60 min at the same temperature. After cooling to room temperature in H_2 (30 min), the catalyst was used directly for hydrogenation. Under standard conditions, 42 mg of catalyst, 1.84 mmol of substrate, 6.8 μmol of modifier, and 5 ml of solvent were stirred (1000 rpm) at 10 bar and room temperature (23–25 °C) for 2 h. In the hydrogenation of **1–9** over Pt/Al_2O_3 modified by CD and QN, (almost) always the (*R*)-α-hydroxy ester was produced in excess, whereas the (*S*)-α-hydroxy ester was the major enantiomer in the presence of PhOCD.

2.3. Analyses

Conversion and *ee* were determined by a Thermo Finigan trace gas chromatograph using a Chirasil-DEX CB (25 m × 0.25 mm × 0.25 μm) capillary column for the hydrogenation products of **1**, **2**, **4**, **6**, and **7**, or by HPLC using a Merck LaChrom system with a CHIRACEL OD (4.6 mm i.d., 240 mm length, 10 μm particle size) chiral column for the hydrogenation products of **3**, **5**, **8**, and **9**. The HPLC analysis was carried out at 10 °C with a liquid flow rate of 0.5 ml/min. The UV detector was set at 210 nm. For all substrates, a *n*-hexane/isopropanol (90%/10%) mixture was used as eluent. Products were identified by GC/MS (HP-6890 coupled with a HP-5973 mass spectrometer) and by ^1H and ^{13}C NMR. All NMR data were recorded on a Bruker Avance 500 with TMS as an internal standard. The enantiomers of **1** was verified by GC analysis of the commercially available product, and those of **3** [2] and **4** [40] were verified by comparing the sign of their optical rotation (Jasco DIP-1000 polarimeter) with literature data. In the hydrogenation of **2** and **5–9**, the products were identified by assuming the analogous chromatographic separation of the products. The conversion values could be reproduced within ±1% by repeating the experiments. The reproducibility of ee was at best ±0.5% in GC analysis, but the error increased with HPLC analysis (to ±1%) and particularly at ee values <5% *ee*, as expected.

2.4. Vibrational circular dichroism spectroscopy

Vibrational circular dichroism (VCD) spectra were measured using a Bruker PMA 37 accessory coupled to a VEC-

TOR 33 Fourier transform infrared spectrometer. A photoelastic modulator (Hinds PEM 90) set at $\lambda/4$ retardation was used to modulate from right to left circular polarized light at a frequency of 50 kHz. The demodulation was performed by a lock-in amplifier (Stanford Research Systems SR830 DSP). The sensitivity of the lock-in amplifier was set at 1 mV for the samples, with a dynamic reserve of 40 dB. To enhance the signal-to-noise ratio, an optical low-pass filter (<1800 cm^{-1}) was set before the photoelastic modulator. The samples were analyzed in a transmission cell equipped with KBr windows and a 0.2-mm Teflon spacer. A single-beam spectrum of the neat solvent served as the reference for the absorption spectrum, and a spectrum of the neat solvent recorded in VCD mode was subtracted from the VCD spectrum of the dissolved molecules.

Calculations were performed using the Gaussian 98 program package [41]. All internal coordinates of the molecules were optimized at the density-functional B3LYP level of theory, using a 6-31G (dp) basis set. For the minimized structures, a normal coordinate analysis was performed. Rotational and dipole strengths associated with the normal modes were calculated to simulate adsorption and VCD spectra [42].

3. Results

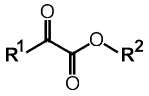
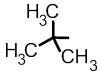
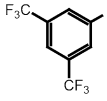
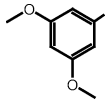
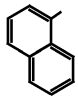
Hydrogenation of **1**–**3** on CD-modified Pt has been reported previously [2,3,18,35,43]. In this study, slightly modified reaction conditions and a broader range of modifiers were applied, and these substrates are used for comparison.

Although a detailed kinetic analysis was beyond the scope of this study, a comparison of the conversions achieved in toluene in 2 h in the high-throughput screening enables a qualitative assessment of the reactivity of α-ketoesters **1**–**9** in the presence and absence of the modifiers CD, QN, and PhOCD (Table 1). Hydrogenation of **2**, **4**, and **9** indicates that rate acceleration due to the presence of a cinchona alkaloid (CD or QN) is not a general feature of α-ketoester hydrogenation, in agreement with recent observations also in pyruvate hydrogenation [43–45]. Note, however, that a reliable kinetic analysis of α-ketoester hydrogenation is complicated by numerous side reactions catalyzed by the amine-type modifier and the Pt surface [8,46–49].

3.1. VCD spectroscopy

In the hydrogenation of **2** and **5**–**9**, the products were identified by assuming the analogous chromatographic separation of the products. This assumption was confirmed by VCD spectroscopy for the most critical substrates **2**, **7**, and **8**, because the greatest effect of the functional groups on adsorption on the chiral chromatographic column was expected in these cases. The absolute configuration of the major enantiomers was determined by comparing the calculated VCD spectrum of one enantiomer with the experimental VCD spectrum of the product of the hydrogenation reaction on CD-modified Pt/Al_2O_3. As a representative example, Fig. 1a shows the theoretical VCD spectrum and Fig. 1b shows the experimental VCD spectrum of the product for substrate **8**. Matching of the spectra allows as-

Table 1
Enantioselective hydrogenation of **1**–**9** in toluene (standard conditions) (as an example: entry 1, R^1–CH_3, R^2–CH_2CH_3)

	Substrate		No modifier	CD	QN	PhOCD
				*ee* (%) [conv.]	*ee* (%) [conv.]	*ee* (%) [conv.]
1	$-CH_3$	$-CH_2H_3$	– [100]	80 (*R*) [100]	21 (*R*) [100]	21 (*S*) [100]
2		$-CH_2CH_3$	– [100]	56 (*R*) [91]	12 (*R*) [61]	41 (*S*) [98]
3		$-CH_2CH_3$	– [100]	86 (*R*) [100]	79 (*R*) [100]	57 (*S*) [100]
4			– [61]	95 (*R*) [94]	89 (*R*) [43]	78 (*S*) [52]
5		$-CH_2CH_3$	– [100]	92 (*R*) [100]	75 (*R*) [97]	52 (*S*) [100]
6		$-CH_2CH_3$	– [93]	87 (*R*) [100]	76 (*R*) [99]	68 (*S*) [99]
7		$-CH_2CH_3$	– [38]	66 (*R*) [94]	47 (*R*) [90]	48 (*S*) [94]
8		$-CH_2CH_3$	– [100]	94 (*R*) [95]	84 (*R*) [100]	73 (*S*) [100]
9		$-CH_2CH_3$	– [48]	86 (*R*) [100]	60 (*R*) [32]	31 (*S*) [31]

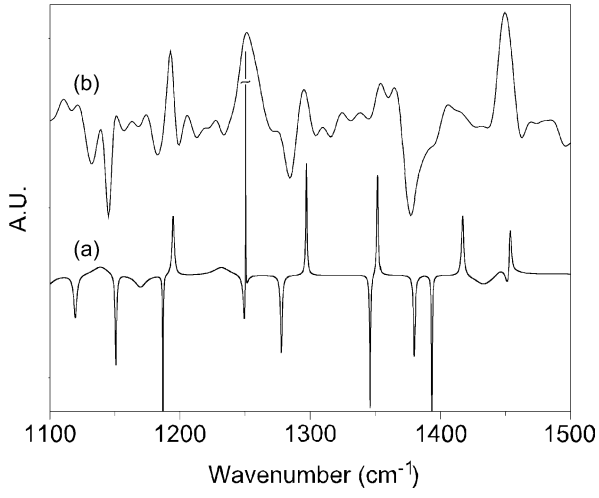


Fig. 1. (a) Theoretical VCD spectra; (b) experimental VCD spectra of the mixture of enantiomers obtained by the hydrogenation of **8** in the presence of CD (0.2 M in methylene chloride-d_2).

signment of the absolute configuration of the main product of hydrogenation as *R*.

3.2. Steric effects of substrates and modifiers

Variations in the rate and *ee* in the hydrogenation of **1**–**9** in toluene (Table 1) may be attributed to steric and electronic effects of R^1 and R^2 (Scheme 1). In some cases the steric effects are dominant. For example, the lower reactivity of the α-ketoester due to bulkiness of the ester group is shown by the replacement of the ethyl group (**3**) by a *tert*-butyl group (**4**). Interestingly, the bulky ester group had a negative effect only on the reactivity of **4**; the enantioselectivities were highest in this series with all three modifiers. In contrast, replacement of the methyl group at the keto-carbonyl function in **1** by a *t*-butyl group in **2** decreased both the rate and the enantioselectivity (except with PhOCD). Another example of the steric effects is the lower rate and *ee* in the hydrogenation of **9** compared with **3**, due to replacement of the phenyl group by a naphthalene ring next to the keto-carbonyl group.

The data in Table 1 demonstrate that even stronger steric effects can be induced by variations in the modifier structure. Replacement of CD by its 6′-methoxy derivative QN caused a general negative effect on the *ee*. The probable explanation for this is that the aromatic methoxy function occupies a part of the chiral pocket available for adsorption of the substrate. This observation is in line with the mechanistic models assuming that in the enantiodifferentiating complex, the quinoline ring of the alkaloid, being in the so-called "open-3" conformation [50], is "flipped" toward the α-ketoester adsorbed in the neighborhood of the modifier [22,51]. Replacing the OH function of CD by a phenoxy group in PhOCD inverted the major enantiomer, in agreement with earlier reports on the hydrogenation of some other ketones [34–36]. The inversion is probably due to the steric bulkiness of the phenoxy group relative to that of OH function, and also to a change in the adsorption geometry of the alkaloid, resulting in a shift in the position of the interacting function, the quinuclidine N atom.

A general observation is that additional steric effects in the chiral modifiers increase the "sensitivity" of the catalyst system to steric effects in the substrates, as indicated by the greater differences in enantioselectivities when CD was replaced by QN or PhOCD in the hydrogenation of **1**–**9**.

3.3. Electronic effects of aryl substituents

The α-ketoesters **3** and **5**–**8** have the same ester group but different aryl substituents on the keto side. The electron-withdrawing and -releasing properties of the functional groups at the phenyl ring, characterized by the Hammett σ-constants [52], correlate reasonably well with the enantioselectivities achieved in toluene. To provide a better visualization of this relationship, the important data in Table 1 are plotted in Fig. 2. In all reactions the conversion was >90%; hence the *ee*'s represent the final, integral values. The advantage of this modification is that the electron density at the carbonyl group can

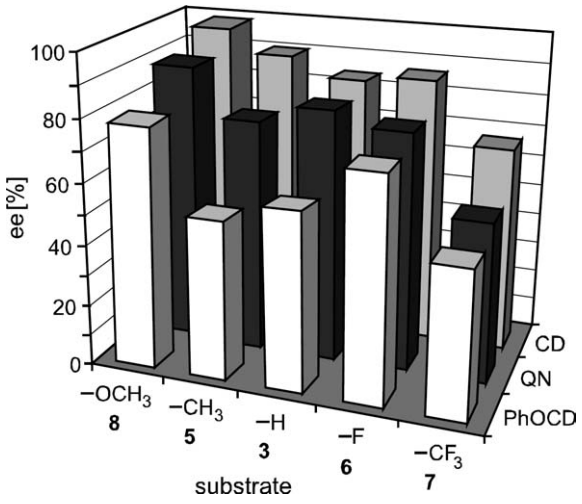


Fig. 2. The influence of electron withdrawing and releasing aryl substituents of ethyl benzoylformate (**3**) on the enantiomeric excess (standard conditions, in toluene). The (*R*)-enantiomer is formed with CD and QN, and the (*S*)-enantiomer with PhOCD.

be tuned by aryl substitution without significantly changing the environment in the close neighborhood of the carbonyl group. Moreover, in the weakly polar toluene, the distorting effect of solvent–substrate interactions is expected to be minor.

For all three modifiers, the highest *ee* was achieved in the hydrogenation of **8**, the substrate of which contains the strongest electron-releasing substituents, two methoxy groups (Scheme 1). In contrast, *ee* was lowest in the hydrogenation of **7**, the substrate of which contains the strongest electron-withdrawing substituents, two CF_3 groups. The enantioselectivity is between the two extremes in the hydrogenation of ethyl benzoylformate **3**, the substrate of which has an unsubstituted aromatic ring. Considering all five α-ketoesters, the correlation between the electron-releasing or -withdrawing effects of the substitutents and the *ee* is the best for CD-modified Pt, and deviations become more significant with increasing steric effects in the modifiers.

3.4. Influence of acidic medium

In the commonly used model reaction, the hydrogenation of ethyl pyruvate (**1**), the enantioselectivities in toluene and acetic acid are similar [53]. Extending the study to structurally more demanding substrates reveals significant differences between weakly polar and acidic medium (Tables 1 and 2). Because hydrogenolysis of the C–O–C (ether) bond of PhOCD is catalyzed by acids [35], only CD and QN could be used in acidic medium.

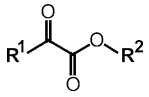
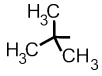
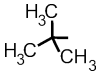
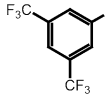
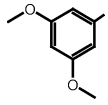
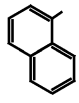
The hydrogenation rates in toluene and acetic acid are rather similar. The greatest drop in conversion was measured for the hydrogenation of **9** on CD-modified Pt when changing to acidic medium. This behavior may be traced to the strong, competing adsorption of acetic acid.

In acetic acid, the highest *ee* of 94% was achieved with CD-modified Pt in the hydrogenation of **8**. Introduction of the 6′-methoxy group in QN mostly diminished the *ee* in this medium, with the important exception of the hydrogenation of

ethyl pyruvate (**1**), in which reactions up to 98% *ee* were obtained [17].

Interestingly, in the hydrogenation of **2**, a low *ee* to the opposite enantiomer was observed. Considering the estimated error of the analytical method at low *ee*, it is better to evaluate the result as a loss of enantioselection. Nonetheless, the effect of replacement of the methyl group at the keto side in **1** by a *t*-butyl group in **2** is dramatic. Hydrogenation of **3** and **9** was also nonselective.

Table 2
Enantioselective hydrogenation of **1–9** in acetic acid (standard conditions)

	Substrate 		CD *ee* (%) [conv.]	QN *ee* (%) [conv.]
1	–CH_3	–CH_2CH_3	88 (*R*) [100]	92 (*R*) [100]
2		–CH_2CH_3	27 (*R*) [99]	2 (*S*) [99]
3		–CH_2CH_3	86 (*R*) [100]	4 (*R*) [100]
4			70 (*R*) [73]	24 (*R*) [64]
5		–CH_2CH_3	80 (*R*) [100]	31 (*R*) [100]
6		–CH_2CH_3	86 (*R*) [100]	76 (*R*) [100]
7		–CH_2CH_3	72 (*R*) [98]	72 (*R*) [98]
8		–CH_2CH_3	94 (*R*) [94]	80 (*R*) [91]
9		–CH_2CH_3	46 (*R*) [31]	0 (*R*) [7]

Clearly, the negligible difference between acidic and nonacidic solvents in the hydrogenation of pyruvates is the exception rather than the rule.

3.5. The role of reaction conditions

The influence of some reaction parameters was further investigated for the two most selective reactions, the hydrogenation of **4** and **8** in toluene, in the presence of CD (Table 3). Working at higher pressure (i.e., at higher surface hydrogen concentration) either had no influence (**4**) or even diminished the *ee* (**8**). A similar negative effect of high surface hydrogen concentration was found in the Pt-catalyzed enantioselective hydrogenation of some other ketones, including acetophenone [54], 2,2,2-trifluoroacetophenone [19], ring-substituted acetophenones [21], and fluorinated β-diketones [55]. This correlation is opposite to the typical behavior of the Pt-cinchona system in the hydrogenation of α-ketoesters [56].

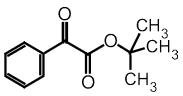
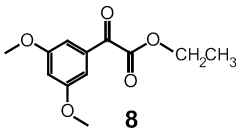
Reaction temperatures below room temperature increased *ee* at the expense of conversion. Changes in the amounts of catalyst and solvent did not significantly improve enantioselectivity. Applying a mixture of toluene and acetic acid (1:1), a favorable medium in the hydrogenation of **3** over CD-modified Pt [43], diminished the *ee* in the hydrogenation of **4** and **8**. Ultrasonication of the catalyst slurry in the presence of CD likewise had no positive effect. Finally, the best ee's in the hydrogenation of **4** (96%) and **8** (95%) were only marginally better than those achieved in the preliminary screening.

4. Mechanistic considerations

Hydrogenation of α-ketoesters **1–9** on CD-modified Pt/Al_2O_3 demonstrates that the (*R*)-enantiomer always forms in good to excellent *ee*, independent of the steric bulkiness of the ester group and the size and electronic structure of the alkyl and functionalized aryl group on the other side of the keto function (Table 1). The lowest *ee*, 56% in the hydrogenation of **2**, is probably due to sterically hindered adsorption and hydrogenation of the keto-carbonyl group by the neighboring *t*-butyl group, as suggested previously [18]. Note also that a limited optimization of the reaction conditions resulted in an improvement to 81% *ee* in the same reaction [18].

The steric effects in the substrates are more pronounced when additional steric effects in the alkaloid are introduced: the

Table 3
Influence of temperature, pressure and acid additive on the hydrogenation of **4** and **8** over CD-modified Pt/Al_2O_3 (standard conditions)

Substrate	Pressure (bar)	Temperature (°C)	Solvent (ml)	Conversion (%)	*ee* [(*R*), %]
 **4**	10	25	Toluene (5)	94	95
	25	25	Toluene (5)	99	95
	25	10	Toluene (5)	40	**96**
	25	0	Toluene (5)	25	95
	25	10	Toluene (2.5) + AcOH (2.5)	100	93
 **8**	10	25	Toluene (5)	95	94
	25	25	Toluene (5)	95	91
	10	10	Toluene (5)	37	94
	10	0	Toluene (5)	23	**95**
	10	10	Toluene (2.5) + AcOH (2.5)	100	93

methoxy group in QN and the phenoxy group in PhOCD (Table 1). We assume that both modifications change the "chiral pocket" available for adsorption of the ketone while interacting with the modifier during hydrogen uptake and thus modify the efficiency of Pt. Even though we expect these results to be valuable in refining the mechanistic concepts, we limit the following discussion to the commonly used and most understood catalyst, CD-modified Pt.

The mechanistic models developed mainly for pyruvate hydrogenation assume two interactions between the amine-type modifier and the ketone: an N–H–O- or N–C-type attractive interaction (as discussed in the Introduction), and a second attractive [26] or repulsive [22] interaction to direct the adsorption of the ketone on Pt. (Note that some models describe only the nature of the attractive interaction and do not explain the origin of enantioselection.) Careful scrutiny of the data in Table 1 reveals that none of the models can account for the observed enantioselectivities. For example, in case of ethyl pyruvate (**1**), the ester group is the bulky and electron-rich substituent. The situation is different for **8** or **9**; the ester group is less bulky than the aromatic function, but the (*R*)-enantiomer still forms with excellent *ee*. Obviously, the model operating with a second, repulsive interaction [22] based on the different bulkiness on the two sides of the keto group needs to be refined. Similarly, the proposed second attractive interaction [26] involving a H bond between the small methyl group of ethyl pyruvate (R_1 in **1**) and the quinoline ring of CD cannot be valid with substrates **3**–**9**.

It seems to be more likely that the ester group serves not only as an activating group for carbonyl hydrogenation, but also as a directing group that is mainly responsible for favoring the adsorption on one side of the substrate. In this respect, it is interesting to compare the dominant adsorption mode of various activated ketones on CD-modified Pt. The drawings in Fig. 3 are based on the stereochemical outcomes of the hydrogenation reactions. The model for the CD-α-ketoester interaction (Fig. 3a) was published a few years ago [57], and the feasibility of the uptake of a proton by CD from the Pt surface in aprotic medium was demonstrated recently [58]. Assuming H uptake from the Pt surface (from "below"), a similar adsorption on the *si*-side would be expected for α-ketoacids [59], α-ketoamides [60], ketopantolactone [61], pyrrolidine-2,3-5-triones [62], α-ketoacetals [63,64], and α-diketones [65–67].

Besides α-ketoesters, α,α,α-trifluoromethyl ketones are the most studied substrates on cinchona-modified Pt. A probable model for their hydrogenation – interaction of the quinuclidine N atom of CD with the O atom of the ketones – is depicted in Fig. 3b. (Note that a bifurcated H bond also involving one F atom is also feasible.) In the hydrogenation of simple alkyl and aryl trifluoromethyl ketones, CD favors the formation of (*R*)-alcohol in a weakly polar reaction medium, in which solvent effects are less important [68–72].

An interesting case is the hydrogenation of a trifluoromethyl β-ketoester (Fig. 3c), where (*S*)-alcohol is the major enantiomer on CD-modified Pt, indicating adsorption on the *re*-side of the activated carbonyl [73]. The trifluoromethyl group in α-position activates the carbonyl, whereas the ester group in

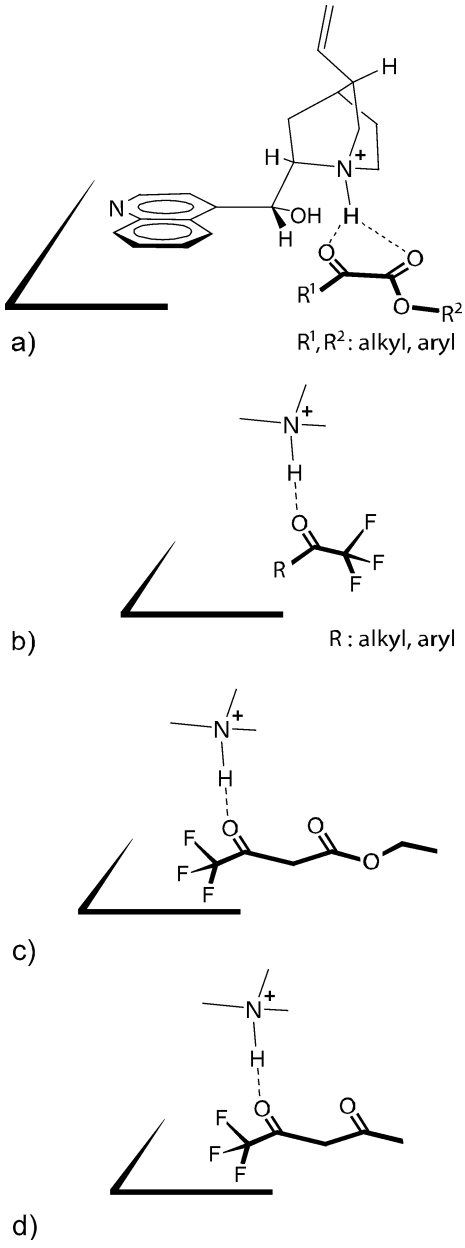


Fig. 3. Schematic illustration of the adsorption of α-ketoesters (a), trifluoromethyl ketones (b), a trifluoromethyl-β-ketoester (c), and a trifluoromethyl-β-diketone (d) on Pt during interaction with CD. These adsorption modes lead to the formation of the major enantiomers, assuming hydrogen-uptake from the metal surface.

β-position seems to be responsible for adsorption on the *re*-side of the substrate (Fig. 3a). Apparently, the ester group is a stronger directing function than the trifluoromethyl group and inverts the adsorption mode of the substrate relative to that of simple α,α,α-trifluoromethyl ketones. A similar case – the hydrogenation of a trifluoromethyl β-diketone that affords the (*S*)-enantiomer in excess in weakly polar solvents [55] – is shown in Fig. 3d, although in the absence of the directing effect of the second carbonyl group, the (*R*)-trifluoromethyl alcohol is expected to be the major enantiomer.

Analysis of the hydrogenation of aryl-substituted α-ketoesters **3** and **5**–**8** (Fig. 2) on CD-modified Pt provides fur-

ther information on the directing effect of the ester group. In these reactions, electron-withdrawing substituents (F, CF_3) decreases the *ee*, whereas electron-releasing substituents (CH_3, OCH_3) have a minor positive effect. Because the nature of the substrate–modifier interaction is expected to be the same for all substrates, the observed differences in *ee* are (mainly) attributed to variations in the electron density at the carbonyl group. In α-ketoesters, the carbonyl group is already activated by the ester group. The results illustrated in Fig. 2 show that additional activation on the other side of the keto group via the phenyl ring (**6**, **7**) is disadvantageous to enantioselectivity. It seems that activation should come from only one side of the carbonyl group, indicating the critical role of the electronic effect in enantiodifferentiation.

Aryl substituents have an opposite effect on the hydrogenation of acetophenone derivatives [21]. Electron-withdrawing substituents on the phenyl ring (CF_3, F, ester group) increase the hydrogenation rate and the *ee* (from 17 to 60%), whereas the electron-releasing methoxy function diminishes both the rate and the *ee*. The inverse effect of aryl substituents is probably connected to the absence of activating function on the other side of the keto group of acetophenones. In other words, in the hydrogenation of ketones on cinchona-modified Pt, the highest enantioselectivity may be expected for substrates in which the electronic effects of functional groups point in the same direction.

5. Conclusion

The unexpected steric and electronic effects observed in the hydrogenation of α-ketoesters over Pt/Al_2O_3 modified by CD, QN, and PhOCD cannot be explained by the existing mechanistic models. We propose that the position of the ester group determines the direction and extent of enantioselection, and the steric bulkiness on any side of the keto group and additional electronic effects of substituents play only secondary roles. Qualitatively, the directing effects of other activating functions, including carboxyl, amido, carbonyl, acetal, and trifluoromethyl groups, are the same as that of the ester function.

Hydrogenation of α-ketoesters **1**–**9** on Pt/Al_2O_3 modified by CD, QN, and PhOCD has revealed that the development of a concept for the hydrogenation of ethyl or methyl pyruvate is not sufficient to understand the complex steric and electronic effects in ketone hydrogenation exerted by structural variations in the substrate and the modifier. We hope that the present results will provide a useful database for testing the feasibility of future mechanistic models developed for the hydrogenation of α-ketoesters and other related ketones.

Some years ago we suggested – in opposition to the general opinion at the time – that the application range of chirally modified Pt covers all those ketones activated by an electron-withdrawing group in α-position to the keto-carbonyl group [68]. The present study may bring us closer to understanding the critical role of the electron-withdrawing group and thus the potential and limitations of Pt modified by chiral amines and amino alcohols.

Acknowledgment

Financial support from the Swiss National Science Foundation is gratefully acknowledged.

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