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Fine tuning the "chiral sites" on solid enantioselective catalysts

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Abstract

A fundamental point in the mechanism of enantioselective hydrogenation over chirally modified metals is the nature of "chiral sites" developed by adsorption of the modifier on the metal surface. Despite considerable effort toward unraveling the adsorption mode of the modifier by surface science techniques, most of these spectroscopic measurements were done under conditions relatively far from those met under real reaction conditions. Here we applied a truly in situ "synthetic" approach, the systematic variation of the structure of the chiral modifier used for enantioselective hydrogenation over 5 wt% Pt/Al_2O_3. We have synthesized various *O*-alkyl, -aryl, and -silyl derivatives of cinchonidine (CD) and tested them in the enantioselective hydrogenation of ethyl pyruvate, ketopantolactone, 4,4,4-trifluoroacetoacetate, and 1,1,1-trifluoro-2,4-diketopentane. With increasing bulkiness of the ether group, the *ee* gradually decreased or even the opposite enantiomer formed in excess (up to 53% *ee*). We propose that the increasing bulkiness of the ether group prevents the strong, π-bonded adsorption of the quinoline ring of CD close to parallel to the Pt surface. In this tilted position the modifier adsorbs weaker via the quinoline N and also the position of the interacting function, the quinuclidine N, is shifted. This shift results in a different shape and size of the "chiral pocket" available for adsorption of the activated ketone substrate. The weaker adsorption of the bulky ether derivatives was proved by UV–vis spectroscopy and by the nonlinear behavior of modifier mixtures. The tilted adsorption mode was corroborated by the lower hydrogenation rate of the quinoline ring of the ether derivatives, relative to that of CD.

Keywords: Enantioselective hydrogenation; Adsorption mode of cinchonidine derivatives; Nonlinear effect (NLE); Activated ketones; Pt/alumina; Inversion of enantioselectivity; UV–vis spectroscopy

1. Introduction

A successful and commonly applied strategy in heterogeneous enantioselective catalysis is the modification of the active metal catalyst by a strongly adsorbing chiral organic compound termed as modifier [1–6]. Supported Pt and Pd modified by cinchona alkaloids provide the highest enantioselectivity in the hydrogenation of various activated ketones [7–13] and functionalized olefins and heteroaromatic compounds [14–19].

Although the number of applications is increasing, the fundamental understanding of the nature of enantiodifferentiation is still at an early stage of development, compared to the state of art in homogeneous enantioselective catalysis [20–22]. Presumably, the most important question to be answered is the nature of "chiral sites" developed by adsorption of the chiral modifier on the metal surface [23,24]. An example of the importance of adsorption geometry is Augustine's early model proposed for the hydrogenation of ethyl pyruvate on cinchona-modified Pt [25,26]. According to the authors' assumption, a change of the adsorption mode of the modifier should result in the inversion of enantioselectivity. Despite the impressive development in this field in the past years, the adsorption mode of substrate and modifier in the enantio-differentiating step is still the most speculative part of the mechanistic models.

Various surface science techniques, including near-edge absorption fine structure spectroscopy (NEXAFS) [27], scanning tunneling microscopy (STM) [28], X-ray photo-

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electron spectroscopy (XPS) [29,30], low-energy electron diffraction (LEED) [30], electrochemical polarization [31], reflection-absorption infrared spectroscopy (RAIRS) [32,33], and surface-enhanced Raman spectroscopy (SERS) [34,35] revealed some important details of the adsorption behavior of CD on Pt but the conditions were mostly far from those of catalytic hydrogenation. A recent ATR-IR spectroscopic study on Pt/Al_2O_3 in the presence of an organic solvent and hydrogen revealed three different adsorption modes of cinchonidine [36,37]. These species differ from each other by their adsorption strength and adsorption geometries: a π-bonded species, which adsorbs via the aromatic ring nearly parallel to the metal surface and two species, in which the aromatic ring is tilted relative to the Pt surface. Still, the method could not answer the key question, namely, which of these species interacts with the substrate in the enantiodifferentiating step as the substrate could generally not be involved in the investigation.

The aim of the present study is to explore how the adsorption mode of the modifier interacting on the metal surface with the coadsorbed substrate affects the enantiodifferentiation. The hydrogenation of some activated ketones on cinchona-modified Pt has been chosen as model reactions. Several mechanistic models have been developed in the past years for the hydrogenation of ethyl pyruvate, the most investigated reaction in heterogeneous enantioselective catalysis. Beside the template model of Wells that has been withdrawn [38], all other models postulate 1:1 type interactions between CD and ethyl pyruvate. Augustine and co-workers [25] and Bartók and co-workers [39,40] proposed that not only the quinuclidine N but also the OH function of CD would be involved in the interactions, but adsorption of the rigid structures on the metal surface is unlikely due to steric restrictions [17]. Four other groups have rationalized the stereochemical outcome of the reaction by assuming a single interaction between CD and ethyl pyruvate, as depicted in Fig. 1 [8,41–44]. Despite the striking differences in the details, all these models agree on one point: the critical role of the basic quinuclidine N atom of CD in the interaction with the substrate. The quinoline ring of the alkaloid is commonly considered as the "anchoring" moiety that provides fixed adsorption on the metal surface [41,45].

Our approach is the following: we tried to influence the adsorption mode of CD, and thus the properties of the "chiral site" available for the adsorption of the substrate, by replacing the OH group by *O*-alkyl, -aryl, and -silyl groups of increasing bulkiness. We assume that this modification does not influence directly the modifier–substrate interaction as the OH function is relatively far away from the quinuclidine N atom of CD. If the adsorption mode of the modifier is really important in the enantioselection, then the increasing bulkiness of the OR group in the close neighborhood of the quinoline moiety should have a strong effect on the *ee* of the hydrogenation reactions (or should not have any influence according to the model in Fig. 1b). The structure of the ketone substrates and those of CD derivatives used as modifiers are shown in Scheme 1. Note that a preliminary report of our work on the hydrogenation of ketopantolactone (**3**) in the presence of four ether derivatives of CD has already been published [46].

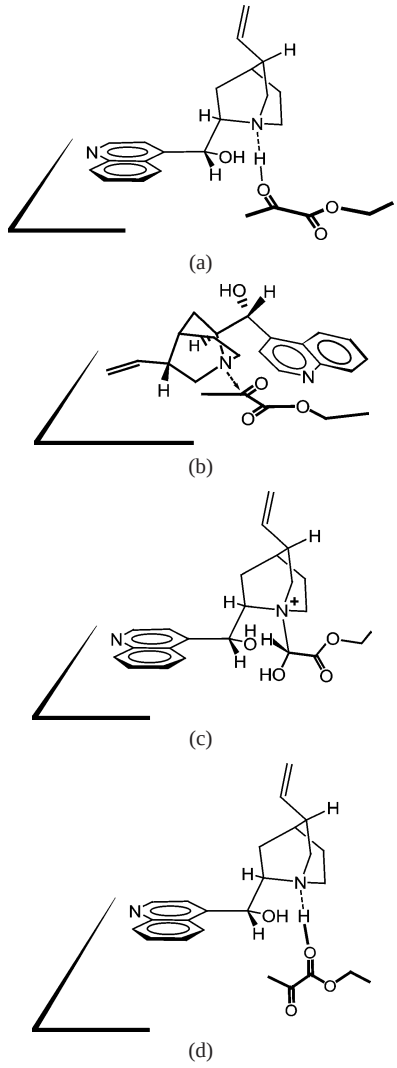
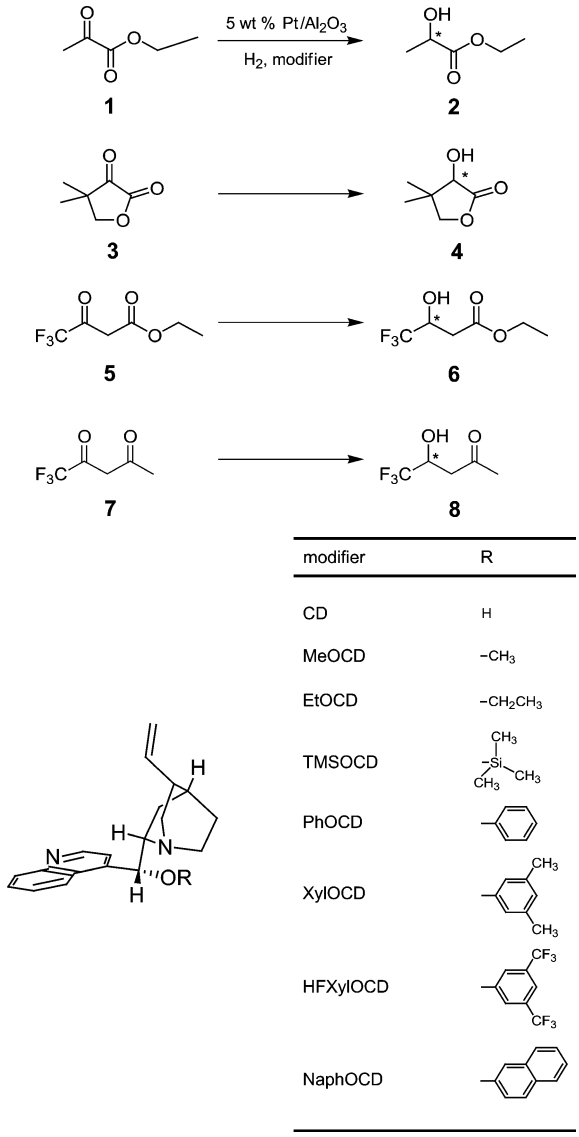


Fig. 1. Schematic representation of the mechanistic models published by Baiker and co-workers (a) [41], Margitfalvi and co-workers (b) [42], Sun co-workers (c) [43], and McBreen co-workers (d) [44] to explain the enantioselection in the hydrogenation of ethyl pyruvate on cinchona-modified Pt. The drawings represent top-side views over the Pt surface.

2. Experimental

2.1. Materials

Tetrahydrofuran (THF, 99.5%, J.T. Baker) was dried over Na before use. Toluene (99.5%, J.T. Baker), acetic acid (AcOH, 99.8%, Fluka), trifluoroacetic acid (TFA, 99%, Fluka), α,α,α-trifluorotoluene (99%, Sigma–Aldrich), anisole (99%, Fluka), quinine (QN) (Fluka), CD (92%, Fluka; impurities: 1% quinine, 7% quinidine, determined by HPLC at Fluka), and ketopantolactone (**3**, Roche) were used



Scheme 1. Enantioselective hydrogenation of activated ketones over Pt/Al_2O_3 chirally modified by ether derivatives of cinchonidine.

as received. Ethyl pyruvate (**1**, Fluka), 4,4,4-trifluoroacetoacetate (**5**, ABCR) and 1,1,1-trifluoro-2,4-diketopentane (**7**, Acros) were carefully distilled in vacuum before use.

2.2. Synthesis of ether derivatives of CD

Melting points were determined using a Büchi-545 automatic melting point apparatus. ^{1}H NMR spectra were recorded by Varian Unity Inova at 400 MHz in $CDCl_3$. All reactions were carried out under an Ar atmosphere. Starting materials were purchased from Aldrich and used without further purification. DMSO, DMF, and THF were dried over molecular sieves before use. The synthesis of MeOCD, EtOCD, PhOCD, and TMSOCD has been described elsewhere [46]. TMSOCD was prepared using the literature procedure of silylation of CD with chlorotrimethylsilane in anhydrous THF in the presence of triethylamine [47].

2.2.1. (1-Naphthyl)cinchonidine (NaphOCD)

The general arylation procedure described in an earlier paper [46] was used starting from CD and the corresponding aryl iodide.

Yield: 29%; ^{1}H NMR 8.74 (*d*, 1H), 8.57 (*d*, 1H), 8.28–8.17 (*m*, 2H), 7.83–7.54 (*m*, 5H), 7.45 (*d*, 1H), 7.35 (*d*, 1H), 7.07 (*t*, 1H), 6.44–6.36 (*m*, 2H), 5.86–5.68 (*m*, 1H), 5.03–4.91 (*m*, 2H), 3.40–3.30 (*m*, 1H), 3.28 (*s*, 2H), 2.75–2.55 (*m*, 2H), 2.13–2.10 (*m*, 1H), 1.80–1.70 (*m*, 3H), 1.60–1.50 (*m*, 2H).

2.2.2. (3,5-Dimethylphenyl)cinchonidine (XylOCD)

The general arylation procedure described in our earlier paper [46] was used starting from cinchonidine and the corresponding aryl iodides.

Yield: 25%; ^{1}H NMR 8.82 (*d*, 1H), 8.17 (*d*, 2H), 7.81–7.62 (*m*, 2H), 7.46 (*d*, 1H), 6.54 (*s*, 1H), 6.42 (*s*, 2H), 6.03 (*d*, 1H), 5.78–5.64 (*m*, 1H), 4.99–4.88 (*m*, 2H), 3.40–3.30 (*m*, 1H), 3.28 (*s*, 2H), 2.75–2.55 (*m*, 2H), 2.15 (*s*, 6H), 2.13–2.10 (*m*, 1H), 1.80–1.70 (*m*, 3H), 1.60–1.50 (*m*, 2H).

2.2.3. O-[3,5-Bis(trifluoromethyl)phenyl]cinchonidine (HFXylOCD)

The general arylation procedure described in our earlier paper [46] was used starting from CD and the corresponding aryl iodide.

Yield: 22%; ^{1}H NMR 8.86 (*d*, 1H), 8.20 (*d*, 2H), 7.86–7.69 (*m*, 1H), 7.65 (*m*, 1H), 7.46 (*d*, 1H), 7.39 (*s*, 1H), 7.24 (*s*, 2H), 6.03 (*d*, 1H), 5.82–5.64 (*m*, 1H), 5.05–4.95 (*m*, 2H), 3.40–3.30 (*m*, 1H), 3.28 (*s*, 2H), 2.75–2.55 (*m*, 2H), 2.13–2.10 (*m*, 1H), 1.80–1.70 (*m*, 3H), 1.60–1.50 (*m*, 2H).

2.3. Catalytic hydrogenation

The 5 wt% Pt/Al_2O_3 catalyst (Engelhard 4759; BET surface area: 100 $m^2\ g^{-1}$; metal dispersion after reductive heat treatment: 0.27, determined by TEM) and Al_2O_3 (support of the catalyst Engelhard 4759) were treated with flowing H_2 for 60 min at 400 °C and cooled to room temperature in H_2 in 30 min. After flushing with N_2, the catalyst was transferred to the reactor within 10 min.

Hydrogenation reactions were carried out in three different reactors. Reactions at 1 bar were carried out in a magnetically stirred 100-ml glass reactor. For higher pressure reactions a stainless-steel autoclave equipped with a 50-ml glass liner and a PTFE cover and magnetic stirring (1000 rpm) was used. Total pressure and hydrogen uptake were controlled by computerized constant-volume constant pressure equipment (Büchi BPC 9901). For screening of reaction conditions or testing different modifiers a parallel pressure reactor system Endeavor (Argonaut Technologies) was used. This multiple reactor system contains eight mechanically stirred, 15-ml stainless-steel pressure reactors equipped with glass liners. Under standard conditions 42 mg catalyst, 1.84 mmol substrate, 6.8 μmol modifier, and 5 ml solvent were stirred

(1000 rpm) at room temperature. Deviations from these conditions are indicated in the text.

The conversion and enantioselectivity were determined by gas chromatography using a Chirasil-DEX CB column (Chrompack). The actual or incremental *ee* was calculated as $\Delta ee = (ee_1 y_1 - ee_2 y_2)/(y_1 - y_2)$, where y represents the yield to the hydrogenation product, and index 2 refers to a sample subsequent to sample 1.

2.4. Spectroscopic methods

^{1}H NMR spectra for the modifier stability in Scheme 3 were measured at 500 MHz using a DPX 500 spectrometer from Bruker.

UV–vis measurements were performed in transmission mode on a CARY 400 spectrophotometer using a 1-cm path length quartz cuvette. For the UV–vis study the catalyst and support were pretreated as described for the hydrogenation experiments.

3. Results and discussion

3.1. Inversion of enantioselectivity

The ether derivatives of CD as chiral modifiers of a 5 wt% Pt/Al_2O_3 catalyst have been tested in the hydrogenation of activated ketones under various reaction conditions. Illustrative examples on the influence of the *O*-alkyl, -silyl, and -aryl substituents are shown in Figs. 2–5. A general tendency is observable in all four test reactions, independent of the reaction conditions: with increasing bulkiness of the ether groups the enantioselectivities decreased close to zero or even the opposite enantiomer formed in excess. The steric effects are particularly striking in the hydrogenation of ketopantolactone (**3**) in trifluorotoluene (Fig. 3): Unmodified CD afforded 73% *ee* to (*R*)-**4** and the bulky ether derivatives

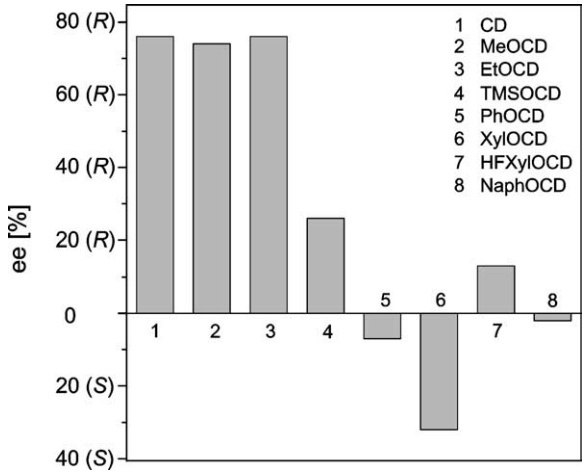


Fig. 2. Diminished enantioselectivity with increasing bulkiness of the ether function of the modifiers in the hydrogenation of **1** over Pt/Al_2O_3 (standard conditions, toluene, 1 bar).

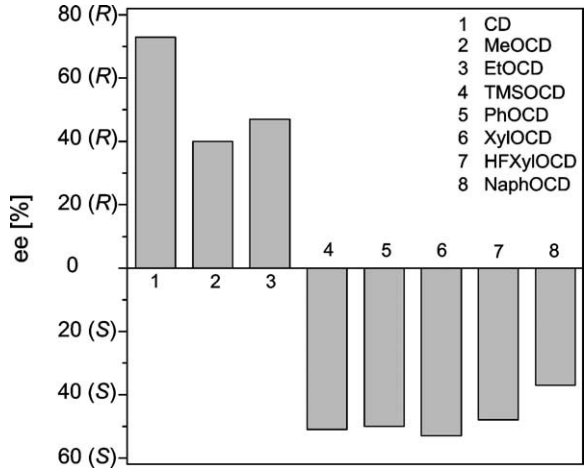


Fig. 3. Inversion of enantioselectivity in the hydrogenation of **3** over Pt/Al_2O_3 chirally modified by the ether derivatives of CD (standard conditions, α,α,α-trifluorotoluene, 40 bar).

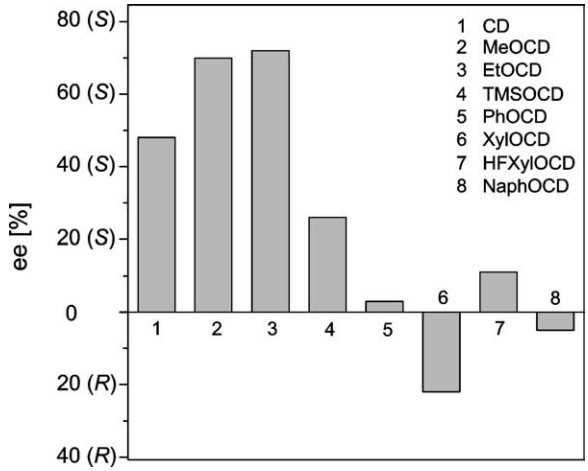


Fig. 4. Gradual loss of *ee* and the subsequent inversion of the sense of enantioselection by increasing bulkiness of the ether groups of the modifiers in the hydrogenation of **5** over Pt/Al_2O_3 (standard conditions, THF, 40 bar).

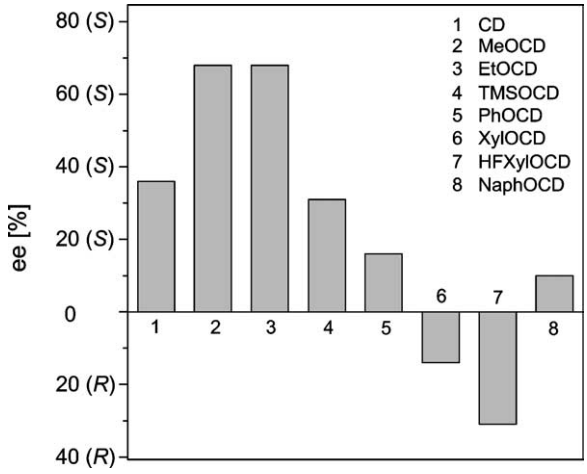
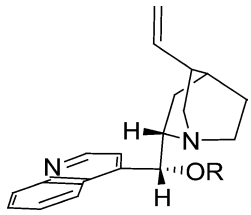
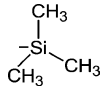
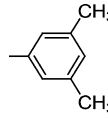
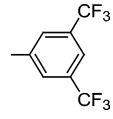
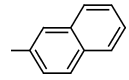
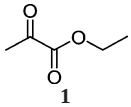
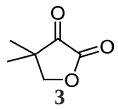
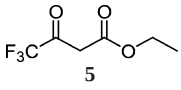
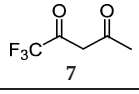


Fig. 5. Gradual loss of enantioselectivity by increasing bulkiness of the ether groups of the modifiers in the hydrogenation of **7** over Pt/Al_2O_3 (standard conditions, toluene, 10 bar).

Table 1
The efficiency of ether derivatives of cinchonidine (CD) used as chiral modifiers of Pt/Al_2O_3 in the hydrogenation of activated ketones[a]



Substrate	Solvent	Pressure [bar]	*ee*% [conv.]							
			CD	MeOCD	EtOCD	TMSOCD	PhOCD	XylOCD	HFXylOCD	NaphOCD
							R			
			H	$-CH_3$	$-CH_2CH_3$					
 **1**	THF	1	80 (*R*) [100]	79 (*R*) [100]	80 (*R*) [100]	5 (*R*) [100]	21 (*S*) [100]	26 (*S*) [100]	25 (*R*) [100]	1 (*S*) [100]
	$PhCH_3$	1	74 (*R*) [100]	74 (*R*) [100]	76 (*R*) [100]	26 (*R*) [100]	7 (*S*) [100]	32 (*S*) [100]	13 (*R*) [100]	2 (*S*) [100]
 **3**	THF	1	50 (*R*) [100]	40 (*R*) [100]	31 (*R*) [100]	26 (*S*) [100]	21 (*S*) [100]	36 (*S*) [100]	16 (*R*) [100]	–
	$PhCH_3$[b]	1	51 (*R*) [100]	48 (*R*) [100]	43 (*R*) [100]	18 (*S*) [100]	21 (*S*) [100]	38 (*S*) [100]	2 (*R*) [100]	16 (*S*) [100]
	$PhCF_3$[b]	40	73 (*R*) [100]	40 (*R*) [100]	47 (*R*) [100]	51 (*S*) [100]	50 (*S*) [100]	53 (*S*) [100]	48 (*S*) [100]	37 (*S*) [100]
 **5**	THF	1	55 (*S*) [77]	76 (*S*) [91]	79 (*S*) [94]	37 (*S*) [70]	9 (*S*) [42]	–	–	–
	THF	40	48 (*S*) [99]	70 (*S*) [99]	72 (*S*) [99]	26 (*S*) [96]	3 (*S*) [95]	22 (*R*) [94]	11 (*S*) [96]	5 (*R*) [90]
	$PhCH_3$	10	48 (*S*) [100]	43 (*S*) [100]	45 (*S*) [100]	27 (*S*) [100]	1 (*R*) [100]	26 (*R*) [100]	15 (*R*) [100]	4 (*R*) [100]
	$PhCF_3$	10	19 (*S*) [100]	42 (*S*) [100]	45 (*S*) [100]	27 (*S*) [100]	5(*R*) [100]	36 (*R*) [100]	16 (*S*) [100]	14 (*R*) [100]
 **7**	$PhCH_3$	10	36 (*S*) [37]	68 (*S*) [68]	68 (*S*) [74]	31 (*S*) [44]	16 (*S*) [34]	14 (*R*) [25]	31 (*R*) [23]	10 (*S*) [32]

[a] Standard conditions: 42 mg prereduced 5 wt% Pt/Al_2O_3, 6.8 μmol modifer, 1.84 mmol substrate, 5 ml solvent, rt, 2 h.
[b] Full conversion after 30 min.

gave 37–53% *ee* to (*S*)-**4**. More details of the reactions including kinetic data (conversions) are collected in Table 1. In most cases the *ee* was determined at full conversion of the ketone. Hydrogenation of the trifluoromethylketones **5** and **7** was somewhat slower and after 2 h the conversion varied between 20 and 100%.

In the hydrogenation of **1** the influence of the small *O*-alkyl groups in MeOCD and EtOCD was minor, in agreement with the former proposal that the OH function of CD is not involved in the enantiodifferentiating step [48,49]. In case of **3** a small decrease for MeOCD and EtOCD compared to CD was measured (Table 1). In the hydrogenation of **5** and **7** MeOCD [50] and EtOCD are even more effective modifiers than CD, likely due to a competing interaction of the free OH function of CD with the substrate.

The bulky trimethylsilyl and aryl substituents have a more pronounced effect on the enantioselection though no clear correlation could be found between the (estimated) bulkiness of these groups and the *ee*s. Obviously, special interactions among the reaction partners including the solvent and the competing adsorbent hydrogen (see pressure effects) are also important. For example, in the hydrogenation of **1** TMSOCD gave (*R*)-**2** and PhOCD (*S*)-**2**, independent of the reaction conditions. In contrast, in the hydrogenation of **3** both modifiers afforded the (*S*)-product and in α,α,α-trifluorotoluene even the extent of enantioselection was practically the same.

Another interesting example is the efficiency of XylOCD and the hexafluorinated derivative HFXylOCD. In most cases they afford the opposite enantiomers in excess. This difference is attributed to steric and electronic effects of

the methyl and trifluoromethyl groups [51,52]. Note also the remarkably different enantioselectivities in toluene and α,α,α-trifluorotoluene (Table 1). We assume that the bulky trifluoromethyl group prevents the adsorption of the aromatic ring of the solvent molecule parallel to the Pt surface via π-bonding and thus weakens its adsorption.

The bulkiest modifier NaphOCD gave for all substrates low selectivities, independent of the conditions (with only one exception, see Table 1). The poor efficiency of this modifier in the hydrogenation of **1** has been reported recently [48]. The naphthyl ring of NaphOCD has about the same size as the "anchoring" moiety of CD, the quinoline ring. Interaction of the naphthyl group with the metal surface may be significantly different from those of the other bulky groups. Among the possible interpretations, a feasible explanation for the low *ee*s is that adsorption of NaphOCD requires too big ensembles of surface Pt atoms. The smaller ensembles of surface sites, which cannot accommodate the modifier, afford a racemic mixture and diminish the *ee*.

We propose the following general interpretation of the results. Replacement of the OH function of CD by alkoxy, silyloxy, and aryloxy groups of increasing bulkiness results in increasing steric hindrance against the adsorption of the modifier close to parallel to the Pt surface via the quinoline ring. This gradual shift of the position of the quinoline ring repositions the quinuclidine N atom, and thus the substrate that is adsorbed on the neighboring Pt sites and interacts with the modifier during hydrogenation. In this new position of the substrate the steric hindrance against the formation of the minor enantiomer may be lost or even the formation of the opposite enantiomer is favored. Formally, we can describe this situation as shifting and reshaping the "chiral pocket" available for adsorption of the ketone substrate. In the following, we shall present some additional observations that support our proposal.

3.2. Stability of ether derivatives of cinchonidine under reaction conditions

A fundamental question in the interpretation of the results in Table 1 is the possible distortion of enantioselectivity by transformation of the modifier during the hydrogenation of ketone substrates. It has been shown earlier that even under mild conditions CD is hydrogenated on Pt resulting in less efficient modifiers [45,53]. Transformation of CD includes hydrogenation of the C=C bond and (partial) hydrogenation of the quinoline ring. The former side reaction has barely any effect on *ee* but the (partially) hydrogenated quinoline moiety adsorbs much weaker on Pt [54]. Here, a further possibility is the hydrogenolytic removal of the bulky ether groups [55].

We have examined the stability of the ether derivatives of CD under reaction conditions in various solvents. The effect of acidic medium is shown in Fig. 6 by the example of the hydrogenation of **1** over Pt/Al_2O_3 modified by PhOCD. In THF this modifier gave a small excess to (*S*)-**2** but in AcOH

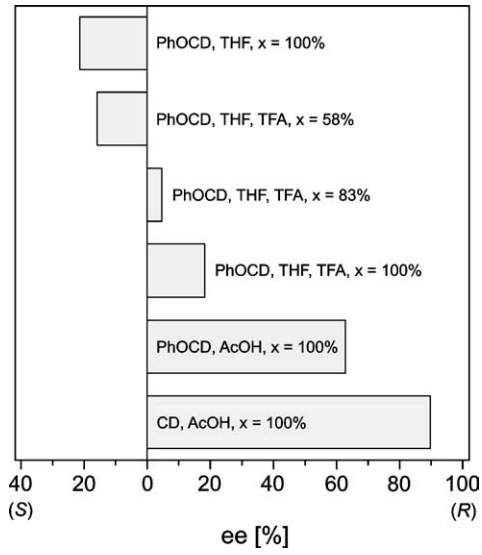
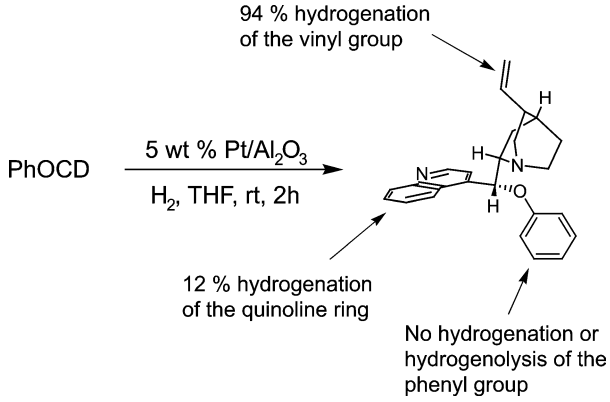


Fig. 6. Stability of PhOCD in the presence of acids, as illustrated by the hydrogenation of **1** over Pt/Al_2O_3 modified by PhOCD or CD (standard conditions, 1 bar, TFA:PhOCD = 5 M eq; x, conversion).

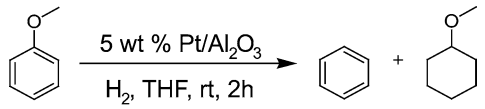
($pK_a = 4.75$ [56]) (*R*)-**2** formed in higher than 60% *ee*. The latter value is close to that achieved with CD under the same conditions. The likely explanation is that hydrogenolysis of the ether C–O–C bond is catalyzed by acids and some CD forms in the early stage of ketone hydrogenation and CD is the actual modifier of Pt. To prove this assumption we repeated the experiment in THF in the presence of the strong acid TFA ($pK_a = 0.3$ [56]). The gradual shift of the major enantiomer from (*S*)-**2** to (*R*)-**2** indicates the formation of an increasing amount of CD. We have shown in a preliminary report [46] that CD adsorbs much stronger on the Pt surface than PhOCD and as soon as a sufficient amount of CD formed, this modifier controls the enantioselection. Note that hydrogenolysis of TMSOCD in acidic medium was even faster than that of PhOCD. Accordingly, no acidic solvents were used in testing of the modifiers (Table 1).

Next, the resistance of PhOCD against hydrogenation was examined in nonacidic medium. The reactions were carried out under standard reaction conditions but in the absence of any substrate and the modifier concentration was increased by a factor of 10 (Scheme 2). No hydrogenation of the phenyl group or hydrogenolysis of the ether C–O–C bond could be detected by ^1H NMR. Hydrogenation took place at the vinyl group and to a smaller extent at the quinoline ring. Hydrogenation of the anchoring part of the modifier (quinoline ring) leads to a weaker adsorption of the modifier [54]. The destructed modifier molecule desorbs from the Pt surface and is replaced by an intact modifier molecule from solution or from the alumina support. Hence, the transformation shown in Scheme 2 should not distort the output of the ketone hydrogenation reaction until there is sufficient amount of intact modifier present in the system.

The good stability of the ether connectivity of PhOCD in nonacidic medium can be explained by the hydrogenation



Scheme 2. Transformation of PhOCD on Pt/Al_2O_3.



1 bar:	< 1%	16%
10 bar:	0	7%
30 bar:	0	3%

Scheme 3. Hydrogenation of anisole on Pt/Al_2O_3 (6.8 μmol in 5 ml solvent, otherwise standard conditions).

of anisole, the simplest phenyl ether. Under ambient conditions in THF, hydrogenolysis of the C–O bond was very slow, affording less than 1% benzene in 2 h (Scheme 3). Saturation of the phenyl ring was about 20-fold faster but the yield to methyl cyclohexyl ether dropped rapidly with increasing pressure. Parallel to this change, benzene formation was not detectable at 10 bar or above. The probable explanation to this unusual reactivity is that at high surface hydrogen concentration (at high pressure) the increased competition between hydrogen and anisole hinders the π-bonded adsorption of the latter parallel to the metal surface and thus slows down the saturation of the phenyl ring. Using this observation as an analogy we can deduce that the absence of saturation of the phenyl ring in PhOCD is a strong indication of the tilted adsorption of the phenyl ring of PhOCD relative to the Pt surface. In this position the C–O–C fragment (ether bond) of the modifier is far from the Pt surface and its hydrogenolysis is improbable.

In order to prove that transformation of the chiral modifiers is unimportant compared to the rate of hydrogenation of the ketone substrates, we did some comparative study under standard conditions (Table 2). Three modifiers have been chosen for this comparison: CD and its ether derivatives with a small alkyl (MeOCD) and a bulky aryl (PhOCD) group. The rate of saturation of the quinoline ring of the modifiers was determined by UV–vis analysis in the absence of substrate (for details see later). The reactivity order of modifiers (CD > MeOCD > PhOCD) is the opposite to that of increasing bulkiness of the OH < OMe < OPh groups. That is, increasing bulkiness of the OR groups decreases the hydrogenation rate of the quinoline moiety of the chiral modifiers. This observation is in agreement with our preliminary assumption that increasing bulkiness of the ether group should prevent the adsorption of the quinoline ring parallel to the Pt surface. It is expected that the more tilted the position of the quinoline ring on the surface, the slower the rate of its hydrogenation.

Table 2
Initial rate of conversion of substrates and modifiers followed by GC and UV–vis, respectively (standard conditions, THF, 1 bar)

Substrate	Modifier	Initial rate (μmol/h)	
		Substrate	Modifier
1	CD	3680	–
3	CD	6450	–
3	MeOCD	9120	–
5	CD	710	–
5	MeOCD	840	–
5	PhOCD	780	–
7	MeOCD	450	–
–	CD	–	0.47
–	MeOCD	–	0.32
–	PhOCD	–	0.11

The initial rates of hydrogenation of the ketone substrates (determined by GC analysis) depended on the modifier but in all cases it was faster than that of the corresponding modifier by a factor of 1400–28,500 (Table 2). Under standard conditions the substrate/modifier ratio was 270. It can be deduced that even in the worst case there was a sufficient amount of chiral modifier present in the reaction mixture to replace the hydrogenated, weakly adsorbing modifier molecules on the Pt surface.

3.3. Nonlinear behavior of modifier mixtures

The nonlinear effect of enantiomerically impure ligands has been a topic of great interest in homogeneous catalysis [57,58]. The concept can be extended to two different ligands giving products of opposite configuration [59,60], and also to chiral modifiers in heterogeneous asymmetric catalysis [61,62]. Studying the nonlinear behavior of mixtures of two modifiers is a powerful tool in heterogeneous catalysis for characterizing the relative adsorption strength of modifiers under truly in situ conditions [54]. The nonlinear behavior is considered as a deviation from the expected ideal behavior assuming that the molar ratios of the modifiers in solution and on the metal surface are identical, and the reaction rates and *ee*s are linear combinations of those measured by the two modifiers alone.

The simplest method for clarifying the relative adsorption strength of modifiers is to carry out the reaction in the presence of 1:1 mixtures of two modifiers that give the opposite enantiomers in excess. Hydrogenation of **1** over Pt/Al_2O_3 modified by MeOCD and PhOCD is shown in Fig. 7 as a typical example. The first two columns represent the result of the reaction with the modifiers alone and the last column shows the enantioselectivity provided by the 1:1 mixture.

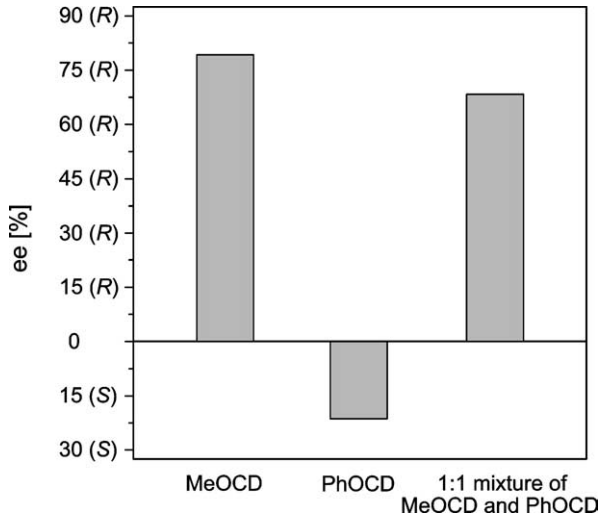


Fig. 7. Enantioselectivities in the hydrogenation of **1** over Pt/Al_2O_3 modified by MeOCD or PhOCD, or by an equimolar mixture of the two modifiers (standard conditions, THF, 1 bar).

The calculated *ee* based on a linear combination is 5% to (*R*)-**2** but the measured *ee* was 68%, a value close to that given by MeOCD alone (79%). It indicates that PhOCD adsorbs weaker on Pt and has only a minor influence on the enantioselection when mixtures of the two modifiers are used.

In order to obtain a more general correlation, the experiments have been extended to the hydrogenation of **3** and more cinchona derivatives have been involved. On the basis of these experiments we propose the following order of adsorption strength on Pt: CD > MeOCD > EtOCD > PhOCD ≈ TMSOCD. Apparently, the bulkier the ether group of the cinchona derivative, the weaker the adsorption on Pt/Al_2O_3. It has to be emphasized that this conclusion is related to real in situ conditions, during transformation of **1** or **3**. None of the known physicochemical methods offers this possibility as we stated it in the Introduction.

We applied also a transient method [54,62] to visualize the competition between the various CD derivatives (Fig. 8). Hydrogenation of **3** in THF over Pt/Al_2O_3 afforded 50% *ee* to (*R*)-**4** in the presence of CD and 26% *ee* to (*S*)-**4** when TMSOCD was applied alone as modifier; both values were measured at full conversion. In a transient experiment the reaction was started with Pt/Al_2O_3 modified by CD and after 20 min 1 M equivalent TMSOCD related to CD was injected into the slurry. The enantioselectivity was not affected by the addition of TMSOCD; the *ee*–time correlation remained practically the same as measured with CD alone. In the control experiment the reaction was started with Pt/Al_2O_3 modified by TMSOCD and after 20 min 1 M equivalent CD was added. The rapid shift of *ee* and particularly that of the calculated differential *ee* (Δ*ee*) demonstrate that within a few minutes CD replaced TMSOCD on the Pt surface, resulting in the inversion of enantioselectivity. Obviously, CD adsorbs much stronger on Pt than the bulky ether derivative TMSOCD.

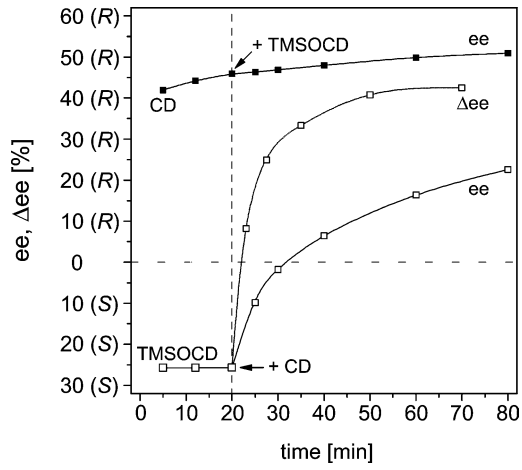


Fig. 8. Transient behavior of the hydrogenation of **3** over Pt/Al_2O_3 induced by addition of 1 M equivalent of TMSOCD or CD to the reaction mixture containing CD or TMSOCD, respectively. Standard conditions, THF, 1 bar; second modifier added in 1 mL THF; Δ*ee*: differential *ee*.

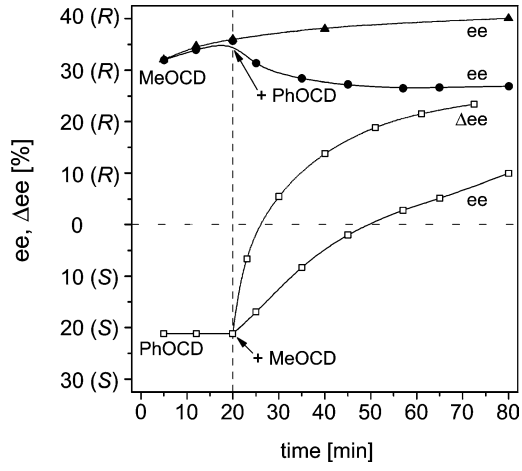


Fig. 9. Transient behavior in the hydrogenation of **3** on Pt/Al_2O_3 induced by addition of 1 M eq of MeOCD or PhOCD to the reaction mixture containing PhOCD or MeOCD, respectively. Standard conditions, THF, 1 bar; second modifier added in 1 mL THF; Δ*ee*: differential *ee*.

Stronger adsorption of the less bulky ether derivative is shown in Fig. 9 by the competition of MeOCD and PhOCD. Hydrogenation of **3** on Pt/Al_2O_3 modified by MeOCD afforded 40% *ee* to (*R*)-**4** at full conversion, and 21% *ee* to (*S*)-**4** when PhOCD was applied. When the reaction was started with MeOCD-modified Pt/Al_2O_3, addition of PhOCD after 20 min led to a small decrease in enantioselectivity. In the reverse case, addition of MeOCD to the reaction mixture containing PhOCD resulted in a bigger shift and even inversion of the sense of enantioselection. The time-dependent changes of the differential *ee* show that MeOCD controlled the enantioselection on the Pt surface modified by the equimolar mixture, and the actual *ee* at full conversion was about the same, independent of the order of addition of the two modifiers. A comparison of Figs. 8 and 9 indicates that the difference in adsorption strength between MeOCD and PhOCD is smaller than that between CD and TMSOCD.

Overall, the transient experiments and the reactions using equimolar mixtures of modifiers indicated the same order of adsorption strength of CD derivatives: CD adsorbs stronger on Pt than any of its ether derivatives, and the ether derivatives with small alkyl groups adsorb stronger than the bulky trimethylsilyl or phenyl ethers (CD > MeOCD > EtOCD > PhOCD ≈ TMSOCD). These results are in line with the adsorption model we propose for the ether derivatives of CD: the bulky ether groups prevent the adsorption of the quinoline ring parallel to the Pt surface. As it was shown by ATR-IR measurements [36,37], in a tilted position of the quinoline ring relative to the Pt surface the modifier adsorbs weaker (via the quinoline N atom) than in a close to parallel position via the strong π-bonding between the quinoline ring and the Pt surface.

3.4. UV–vis study of modifier adsorption and hydrogenation

The interaction of the ether derivatives of CD with Pt/Al_2O_3 in the presence of hydrogen but in the absence of ketone substrate was analyzed by an indirect UV–vis spectroscopic method (Fig. 10). The disappearance of modifiers from the THF solution was followed by the quinoline chromophore at 315 nm [54]. A decrease of the modifier concentration detected by UV–vis is attributed to adsorption on Pt and on the Al_2O_3 support, and to partial or complete saturation of the quinoline ring (Scheme 2). It is commonly accepted that saturation of the quinoline ring of the modifier leads to weaker adsorption on Pt and the hydrogenated modifier is replaced by an intact modifier from solution [12,53,54,63]. Adsorption on the support was taken into consideration by repeating the analysis with the support alone. From the difference of the two curves (Fig. 10a) the consumption of each modifier due to adsorption and hydrogenation on Pt was calculated (Fig. 10b). The initial amounts extrapolated to zero time represent the fraction of modifiers adsorbed on Pt and the rate of hydrogenation of the quinoline ring is estimated from the slopes of the lines. Clearly, under identical conditions remarkably more CD adsorbed on the Pt surface than MeOCD or PhOCD, and the rate of their hydrogenation followed the same order (CD > MeOCD > PhOCD). The order of the adsorption strength of modifiers is the same as that concluded from the nonlinear behavior of modifier mixtures in the presence of substrates. Note that the stronger adsorption of CD relative to the ether derivatives on Al_2O_3 is likely due to interaction between the OH function of CD and the basic O atoms of Al_2O_3.

In the former section the nonlinear behavior of modifier mixtures in the hydrogenation of **1** and **3** was attributed to the different adsorption strength of the modifiers that results in considerably different concentrations on the Pt surface. To prove this interpretation, we investigated the relative rate of the hydrogenation of modifiers in equimolar mixtures by UV–vis spectroscopy, in the absence of ketone substrate. Since the UV–vis spectra of CD and its ether derivatives are

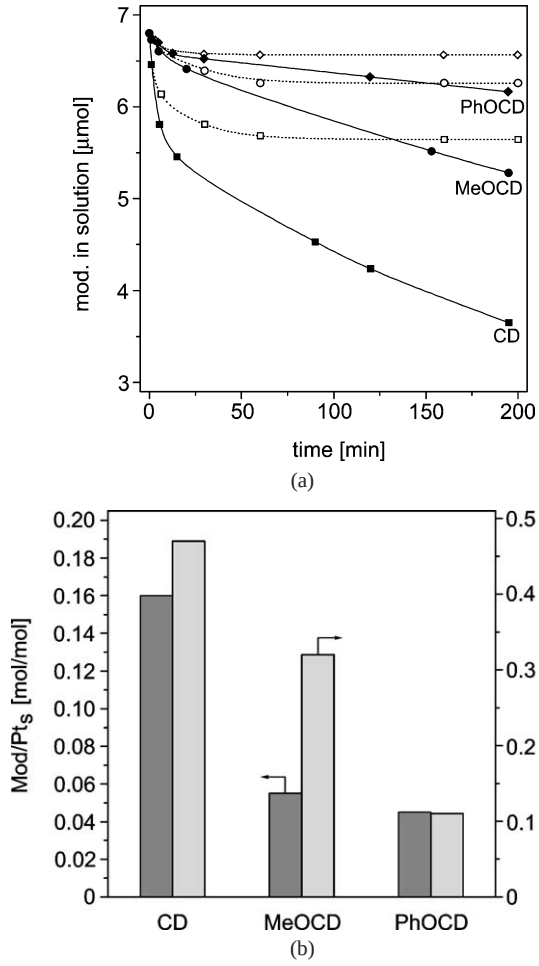


Fig. 10. Kinetic analysis of the adsorption and hydrogenation of CD, MeOCD, and PhOCD (standard conditions but in the absence of substrate, 1 bar, THF). (a) Filled symbols represent adsorption and hydrogenation on Pt/Al_2O_3, open symbols show adsorption on the catalyst support (Al_2O_3). The actual modifier concentration in solution was determined by UV–vis spectroscopy from the absorbance at 315 nm. (b) The dark columns represent the calculated ratio between the modifier molecules and surface Pt atoms (Pt_s). The light columns show the estimated initial rates of conversion of the modifiers.

the same, quinine (QN) was used as a reference modifier. In the latter molecule the presence of the 6′-methoxy group at the quinoline ring shifts the adsorption band from 315 to 338 nm [54].

At first the competitive hydrogenation of CD and QN was investigated (Fig. 11a). When the two alkaloids were hydrogenated alone, CD disappeared from the solution somewhat faster than QN. When the 1:1 mixture of CD and QN was hydrogenated, the difference in their reactivity was much bigger. This change is attributed to the stronger adsorption of CD on Pt, i.e., in the equimolar mixture the much faster consumption of CD is mainly due to its higher surface concentration and partly to its higher reactivity. Next, the reactivity and the adsorption strength of MeOCD (Fig. 11b) and TMSOCD (Fig. 11c) were determined using QN as a reference. It is clear from the very slow consumption of TMSOD that this modifier adsorbs much weaker than QN and

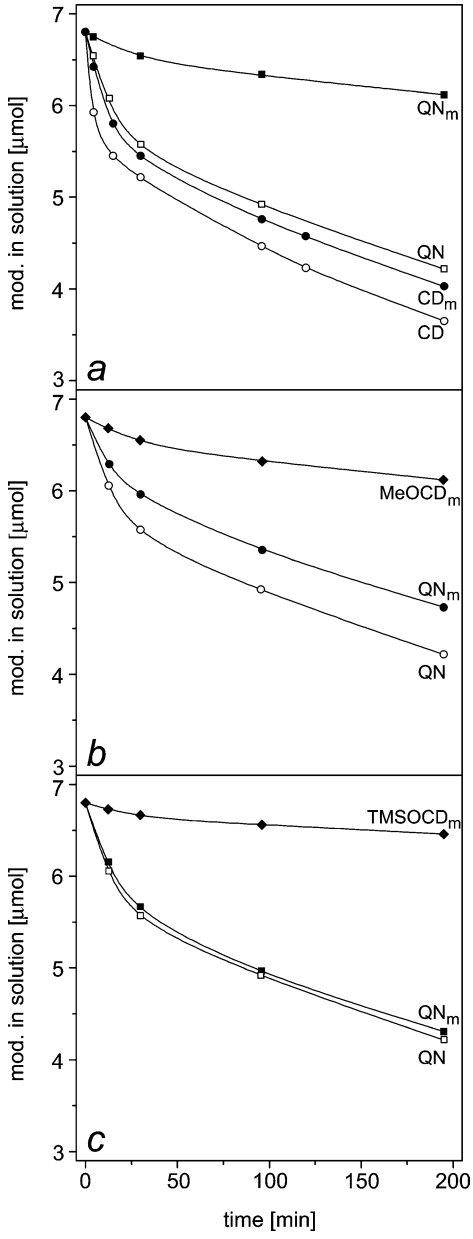


Fig. 11. Kinetic analysis of the hydrogenation of modifier mixtures (standard conditions but in the absence of ketone substrate, THF, 1 bar). (a) Hydrogenation of CD and QN alone and in a 1:1 mixture (index m). (b) Hydrogenation of QN alone and a 1:1 mixture of QN and MeOCD (index m). (c) Hydrogenation of QN alone and a 1:1 mixture of QN and TMSOCD (index m).

cannot efficiently compete for the Pt surface sites. The difference between MeOCD and QN is smaller, as expected. The order of adsorption strength obtained from these experiments (CD > MeOCD > TMSOCD) confirms that the bigger the ether group of the modifier, the weaker the adsorption and slower the hydrogenation on Pt. This conclusion supports the interpretation of the nonlinear behavior of modifier mixtures measured in the hydrogenation of ketone substrates (Figs. 7–9).

3.5. Mechanistic considerations

Various models have been proposed for the enantioselective hydrogenation of activated ketones on cinchona-modified Pt [8,25,40–44]. These models assume that in the enantio-differentiating step the quinoline ring of CD is adsorbed either close to parallel or perpendicular to the Pt surface, or the modifier is in an "upside down" position above the ketone substrate ("shielding" model). The present study provides an interesting set of experimental data to test the feasibility of these mechanistic ideas.

Our primary observation here is that replacement of the OH group of CD by a relatively small methoxy or ethoxy group has only a moderate effect on the enantioselectivity but introduction of bulky silyloxy and aryloxy groups diminishes the *ee* close to zero or even the opposite enantiomer is formed in a reasonable excess. Obviously, the "shielding" model depicted in Fig. 2b cannot explain this dramatic shift in enantioselection. We noted in the Introduction that two other models (by Augustine's [25] and Bartók's [39,40] groups) that assume involvement of the O atom of CD in an electron-pair donor interaction are unlikely due to steric restrictions. The better than 50% *ee* achieved with the bulky ether derivatives of CD (Table 1) provides further experimental evidence against the probability of these models. Involvement of the sterically "hidden" ether O of the modifier in the enantiodifferentiating complex can be excluded.

The second major result of the present study is that increasing bulkiness of the ether groups of CD derivatives decreases the adsorption strength of the modifier and diminishes also the rate of hydrogenation of the quinoline ring, a well-known disturbing side reaction on cinchona-modified Pt and Pd. A feasible interpretation of these observations is based on a recent ATR-IR spectroscopic study of CD adsorption under close to in situ conditions [36,37]. It has been proved that in the strongest adsorption mode CD adopts a position in which the π-bonded quinoline ring is close to parallel to the Pt surface, and a change of the adsorption mode to a tilted position of the quinoline ring (anchored to Pt via the N atom) results in a considerable weakening of the modifier–Pt interaction. The suggested adsorption geometries of CD and PhOCD as examples are visualized in Fig. 12. The bulky phenoxy group hinders the strong π-bonded adsorption of the quinoline ring. In the suggested tilted adsorption mode the hydrogenation of the quinoline ring is slow and hydrogenolysis of the ether C–O–C connectivity is not detectable (in nonacidic medium, in which the modifiers were tested). Weaker adsorption of the bulky ether derivatives of CD explains the strong nonlinear effect observed in the hydrogenation of **1** and **3** when mixtures of two modifiers were applied (Figs. 7–9). The tilted position of the phenyl ring is in agreement with its high stability against hydrogenation in nonacidic media. For comparison the aromatic ring of the model compound anisole is slowly saturated at low pressures (Scheme 3).

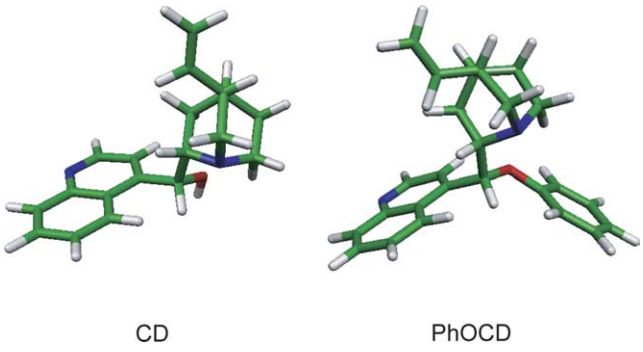


Fig. 12. Schematic illustration of the adsorption of CD and PhOCD on an idealized flat Pt surface via the aromatic rings (top-side views; the metal surface is not shown). The structures of the molecules are optimized by HyperChem's MM+ force field without any involvement of the solvent or Pt surface.

Two mechanistic models in Figs. 1a and d assume that in the enantio-differentiating step the quinoline ring is adsorbed close to parallel to the Pt surface; thus, they are in agreement with the present results. The model depicted in Fig. 1c is similar to the above two structures concerning the adsorption geometry of CD. This model, however, predicts that the enantioselection is due to formation of a zwitterionic intermediate with a tetrahedral C atom (from the ketocarbonyl group of the substrate) [43]. This structure is sterically impossible with the cyclic ketone **3**, in contrast to the good enantioselectivities achieved in the hydrogenation of **3** using CD and some of its ether derivatives as chiral modifiers of Pt (Table 1). Obviously, this model cannot be generally valid for the hydrogenation of activated ketones as suggested by the authors. It is also unlikely that the structurally related **1** and **3** (acyclic and cyclic α-ketoesters, respectively) would follow different reaction mechanisms.

4. Conclusions

Understanding the nature of substrate–modifier interaction and elimination of the most speculative element of the available mechanistic models necessitates clarification of the adsorption mode of the interacting molecules on the metal surface under real in situ conditions. Since none of the spectroscopic or surface science techniques could completely fulfill this requirement so far, we choose another approach: the systematic variation of the structure of chiral modifier, a proven strategy in homogeneous enantioselective catalysis.

In heterogeneous catalysis several surface metal atoms, which are located at a certain distance to each other, interact with the substrate and the chiral modifier. Due to adsorption on the metal surface, relatively small changes in the structure of the chiral modifier far from the interacting function may result in dramatic shifts in the enantioselectivity. Systematic variation of the modifier structure confirmed that in the enantio-differentiating step during the hydrogenation of activated ketones on cinchona-modified Pt the alkaloid adsorbs via the quinoline ring being close to parallel to the Pt surface. A forced deviation from this adsorption geometry diminishes the adsorption strength and the enantioselectivity, and even the opposite enantiomer can form in excess.

The results illustrate also the efficiency of developing new catalyst systems by fine tuning the structure of the chiral modifier.

Acknowledgment

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