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Journal of Catalysis 222 (2004) 117–128
JOURNAL OF CATALYSIS
www.elsevier.com/locate/jcat

Inversion of enantioselectivity in the platinum-catalyzed hydrogenation of substituted acetophenones

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Received 7 July 2003; revised 22 October 2003; accepted 22 October 2003

Abstract

The enantioselective hydrogenation of ring-substituted acetophenones that possess no functional group in the α-position to the keto group represents the latest extension of the application range of the Pt–cinchona system. The influence of the type of solvent, pressure, temperature, and modifier/substrate/Pt molar ratios was investigated in the hydrogenation of 3,5-di(trifluoromethyl)acetophenone. Modification of a 5 wt% Pt/Al_2O_3 catalyst by cinchonidine (CD) afforded the corresponding (*S*)-1-phenylethanol (69.5% ee). Working in strongly polar solvents, addition of trifluoroacetic acid in a weakly polar solvent, and replacing CD by its ether derivatives resulted in the inversion of enantioselectivity. Addition of CD or any of its derivatives always led to a lower reaction rate, contrary to the generally observed rate acceleration in the hydrogenation of α-functionalized activated ketones over the same catalyst system. Another fundamental difference to the hydrogenation of α-functionalized activated ketones is that both the quinuclidine N and the OH functions of CD influence the stereochemical outcome of the reaction, as clarified by using O- and N-substituted derivatives of CD. Ab initio calculations confirmed these remarkable mechanistic differences. Inversion of enantioselectivity in the presence of strongly polar and acidic solvents is attributed to special interactions with the OH function of CD, and to the formation of a CD–acid ion pair, respectively. A possible explanation for the moderate ee's in the hydrogenation of ring-substituted acetophenones is that a reaction pathway without involvement of the OH function of CD is also feasible. This competing pathway is even faster and provides low ee to the opposite enantiomer.

Keywords: Asymmetric hydrogenation; Ring-substituted acetophenones; Ethers of cinchonidine; Inversion of enantioselectivity; 3,5-Di(trifluoromethyl)acetophenone

1. Introduction

In heterogeneous catalysis, cinchona-modified Pt is the best choice for the enantioselective hydrogenation of ketones that are activated by a functional group in the α-position [1–4]. Thoroughly investigated reactions are the hydrogenation of α-ketoesters and α-ketolactones [3,5–8], α-diketones [9–13], α,α,α-trifluoroketones [14–17], and linear and cyclic α-ketoamides [18–20]. In these reactions over 90% ee could be achieved after optimization of catalyst pretreatment and reaction conditions. In contrast, hydrogenation of aromatic (deactivated) ketones over the Pt–cinchona system is characterized by poor enantioselectivity. A representative example is the hydrogenation of acetophenone with enantioselectivities in the range 3–20% [21–23]. The poor efficiency of the Pt–cinchona system is indicated also by the unusually low substrate/CD molar ratio of 6.7 that is necessary to achieve 20% ee to (*S*)-1-phenylethanol [23]. For comparison, this ratio is 237,000 in the hydrogenation of ketopantolactone [7].

Another heterogeneous catalyst, proline-modified Pd/C afforded 22% ee in the hydrogenation of acetophenone [24]. Later it was revealed, however, that 1-phenylethanol was produced in a diastereoselective reaction via hydrogenolysis of the C–N bond of the proline–acetophenone adduct [25].

We have found recently that several acetophenone derivatives possessing an electron-withdrawing functional group (F, CF_3, COOEt) in different positions at the aromatic ring can be reduced selectively over cinchona-modified Pt/Al_2O_3 [26]. The highest ee of 60% was obtained in the hydrogenation of 3,5-di(trifluoromethyl)acetophenone. Interestingly, addition of CD slowed down all hydrogenation reactions, independent of the nature or position of the functional group. This behavior contrasts to the gen-

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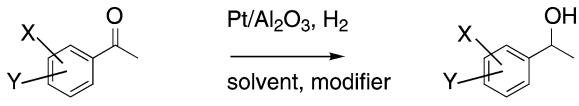
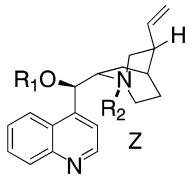
0021-9517/$ – see front matter
doi:10.1016/j.jcat.2003.10.021



X, Y = H, F, CF_3, COOEt, OCH_3, $OCOCH_3$



Modifier	R_1	R_2	Z
CD	H	-	-
MeOCD	methyl	-	-
EtOCD	ethyl	-	-
PhOCD	phenyl	-	-
TmsOCD	trimethylsilyl	-	-
CD•HCl	H	-	HCl
N-MeCDCl	H	methyl	Cl^-
N-BzCDCl	H	benzyl	Cl^-

Scheme 1. Hydrogenation of substituted acetophenones to phenylethanols over cinchona-modified Pt/Al_2O_3 and the structure of modifiers.

erally observed rate acceleration in the hydrogenation of α-functionalized activated ketones [27].

From a broader perspective, a variety of chiral homogeneous catalysts have been developed in the past years for the hydrogenation of aromatic ketones [28–31]. For example, Ru(II)–BINAP complexes of the empirical formula $RuX_2(binap)L_2$ (X = Cl, Br, or I) and derivatives thereof offer up to 99% ee's and very high turnover frequencies (TOF; up to 259,000 h^{-1}) [32].

Here we report a detailed study of the hydrogenation of acetophenone derivatives over cinchona-modified Pt/Al_2O_3 (Scheme 1). The general aim of the study was to gain a deeper understanding of the enantioselective hydrogenation of aromatic ketones over cinchona-modified Pt, and to clarify the similarities and differences of these reactions compared to the well-studied hydrogenation of α-functionalized activated ketones.

2. Experimental

2.1. Materials

All acetophenone derivatives and cinchonidine (CD, Fluka), *N*-benzylcinchonidinium chloride (*N*-BzCDCl, Fluka) and cinchonidine hydrochloride (CD•HCl, Sigma) were used as received. Ethoxycinchonidine (EtOCD), phenoxycinchonidine (PhOCD), and trimethylsiloxycinchonidine (TmsOCD) were prepared by Ubichem. Methoxycinchonidine (MeOCD) and *N*-methylcinchonidinium chloride (*N*-MeCDCl) were prepared according to a known method [33]. Elementary analysis and NMR spectroscopic data were in good agreement with the structure of the modifiers. ^1H and ^{13}C NMR spectra were measured using a DPX 300 spectrometer.

2.2. Catalytic hydrogenation

The 5 wt% Pt/Al_2O_3 catalyst (Engelhard 4759) was prereduced before use in a fixed-bed reactor by flushing with N_2 at 400 °C for 30 min, followed by a reductive treatment in H_2 for 90 min at the same temperature. After cooling to room temperature in hydrogen, the catalyst was immediately transferred to the reactor. Platinum dispersion after heat treatment was 0.27 (determined by TEM [34]).

Hydrogenations were carried out in a parallel pressure reactor system Endeavor, with eight mechanically stirred 15-ml stainless-steel reactors equipped with glass liners. Control experiments using different amounts of catalyst and varying the stirring frequency did not indicate significant external mass-transport limitations for the reactions studied. Intraparticle diffusion effects cannot be ruled out completely, but are unlikely due to the small catalyst particle size (50–100 μm) and the relatively low reaction rates compared to the corresponding racemic hydrogenations. Under standard conditions 42 ± 2 mg catalyst, 1.84 mmol substrate, 6.8 μmol modifier, and 5 ml solvent were stirred (500 rpm) at 10 bar and room temperature (23–25 °C) for 2 h.

Conversion and ee were determined by an HP 6890 gas chromatograph equipped with a chiral capillary column (WCOT fused silica 25 m × 0.25 mm, coating CP-Chirasil-Dex CB, Chrompack). Enantioselectivity is expressed as ee (%) $= 100 \times |(R - S)|/(R + S)$. The products were identified by GC/MS. Reproducibility of ee was within ±0.5%. The individual optical isomers were identified by GC analysis using authentic samples, or by comparison of their optical rotation (Perkin-Elmer 241 Polarimeter) with literature data [35,36]. The assignment of the absolute configuration based on GC retention times as done in [26] gives false results.

The average reaction rate is expressed as turnover frequency (TOF, h^{-1}), i.e., the molar amount of reactant converted by 1 mol of surface Pt atoms (Pt_{surf}) in 1 h. The rate is always calculated in the conversion range specified for each series of experiments in the captions.

2.3. UV–vis analysis

UV–vis measurements were used to determine the actual amount of CD remaining in the reaction solution after removal of the catalyst [37]. Measurements were performed in transmission mode on a CARY 400 spectrophotometer using a 1-cm path length quartz cuvette. Spectra are given in absorbance units with neat toluene serving as the reference. Pretreatment of the catalyst was performed as described for the catalytic experiments (see above).

2.4. Theoretical calculations

All electronic structure calculations were carried out using GAUSSIAN 98 [38]. The level of theory chosen was Hartree–Fock with 6-31G(d) basis set [39,40]. All structures were optimized using the default cutoff values. In some calculations the effect of the surface was implicitly considered. For this, planar constraints were set in order to keep the quinoline moiety of cinchonidine and the π-system of the

3,5-di(trifluoromethyl)acetophenone on the same plane, as has been described elsewhere [2,41–44]. All internal coordinates were optimized where no planar constraints were set. Molden [45] was used as graphical interface.

3. Results and discussion

Preliminary screening of conditions revealed that the most influential parameters are the chemical nature of solvent, the pressure and temperature, and the modifier/substrate/Pt molar ratios. The effect of these parameters will be presented in the hydrogenation of 3,5-di(trifluoromethyl)-acetophenone. In this reaction CD afforded the (*S*)- and CN the (*R*)-enantiomers in excess. Though there are other acetophenone derivatives that could be hydrogenated with higher selectivity (2- and 3-trifluoromethylacetophenone [26]), those reactions were significantly slower. For the study of the role of reaction conditions, the two best solvents, toluene and ethyl acetate, were chosen. The preliminary screening experiments indicated that in the early stage of the reactions the ee varied strongly with conversion. To minimize this distortion effect, the reaction rates and enantioselectivities are compared in a narrow conversion range.

3.1. Influence of pressure and temperature

The influence of pressure on the enantioselectivity and reaction rate (TOF) in toluene and ethyl acetate is shown in Fig. 1. The rate increases with increasing pressure as expected though the reaction order to hydrogen is very low in ethyl acetate. Interestingly, low pressure corresponding to low hydrogen availability at the Pt surface is favorable for enantioselection. A similar effect of surface hydrogen concentration has been found in the enantioselective hydrogenation of acetophenone [23] and 2,2,2-trifluoroacetophenone [14,46]. This correlation is, however, opposite to the typical behavior of the Pt–cinchona system in the hydrogenation of α-ketoesters and other activated ketones [27].

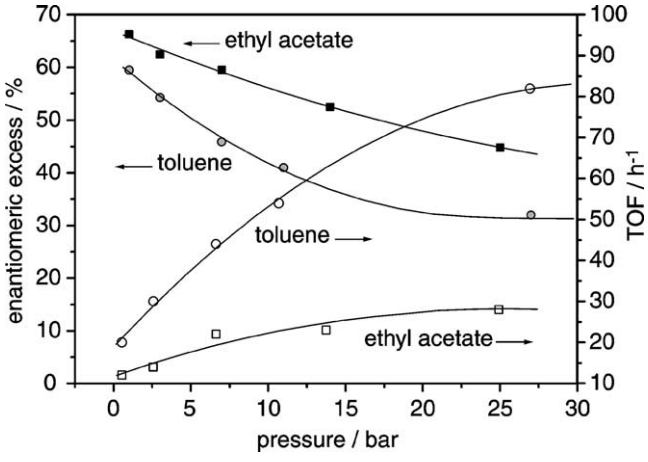


Fig. 1. Influence of hydrogen pressure on the reaction rate (TOF) and enantioselectivity in the hydrogenation of 3,5-bis(trifluoromethyl)acetophenone with 5 wt% Pt/Al_2O_3 (standard conditions, toluene or ethyl acetate). The conversion was always in the range 21–23%, corresponding to 90–720 min of reaction time.

The surface hydrogen concentration may directly influence the adsorption of reactant or modifier and thus the enantioselection. It has been shown recently [47] that the adsorption geometry of ethyl pyruvate on Pt changes from perpendicular to a tilted position due to coadsorption of hydrogen. Furthermore, this competition of hydrogen with substrate and modifier for surface Pt sites could be an explanation for the negative pressure effect shown in Fig. 1.

In addition, high surface hydrogen concentration may have an indirect effect on the enantioselectivity by accelerating the hydrogenation of CD. Competing hydrogenation of the quinoline ring of CD during hydrogenation of ethyl pyruvate [48] and 2-pyrones [49] diminished the enantioselectivity, presumably due to weaker adsorption of the partially saturated modifier. This effect is important also here during the slow hydrogenation of acetophenone derivatives, as illustrated in Figs. 2 and 3. The concentration of CD was followed by UV–vis measurements; details of the method have been published elsewhere [37]. Fig. 2a shows the characteristic peak of the unhydrogenated quinoline moiety of CD at 315 nm and how it disappears over time due to saturation of the aromatic and/or heteroaromatic ring. The UV spectrum of quinoline resembles very much that of CD, con-

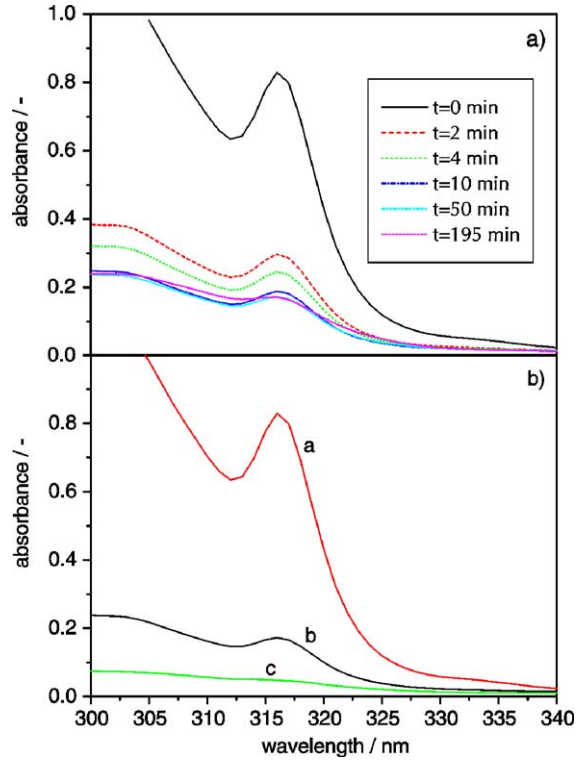


Fig. 2. UV–vis analysis of CD concentration in solution: (a) spectra taken during hydrogenation of 3,5-bis(trifluoromethyl)acetophenone (standard conditions, 1 bar, toluene); (b) an example of the calculation of the actual CD concentration (for details see the text).

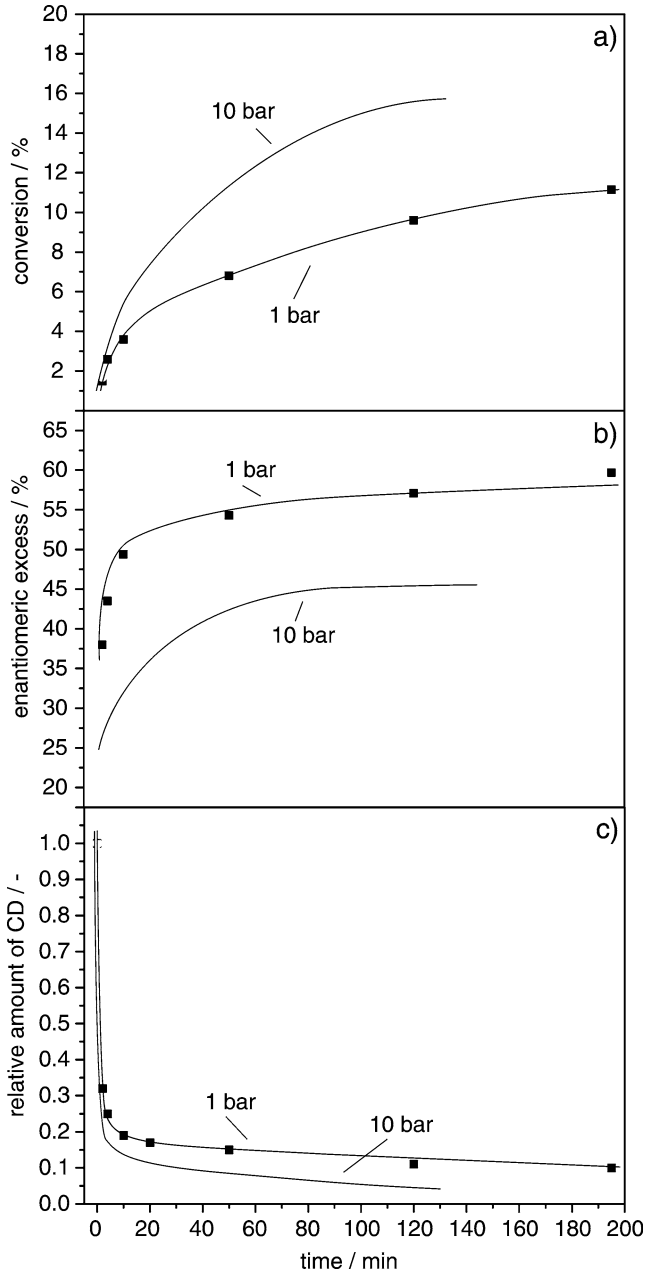


Fig. 3. Time-dependent changes of conversion, enantioselectivity, and the relative amount of CD in solution during hydrogenation of 3,5-bis(trifluoromethyl)acetophenone (standard conditions, 1 and 10 bar, in toluene).

firming that the UV spectrum of CD is determined by the quinoline chromophore [37]. Fig. 2b illustrates the determination of the actual CD concentration in solution after filtering off the catalyst. Curve (a) represents the reference spectrum of CD before reaction (zero time, before interacting with the catalyst). Curve (b) represents the spectrum of CD after a certain reaction time. Curve (c) was generated in the following way:

$$\text{curve (c)} = \text{curve (b)} - f * \text{curve (a)},$$

where f represents the factor that has to be chosen to eliminate from curve (c) the characteristic peak of the unhydrogenated quinoline moiety at 315 nm. Multiplying the initial CD concentration with f gives the actual CD concentration at the sampling time. The reliability of the method was confirmed by measuring the spectra of solutions containing the calculated amount of CD.

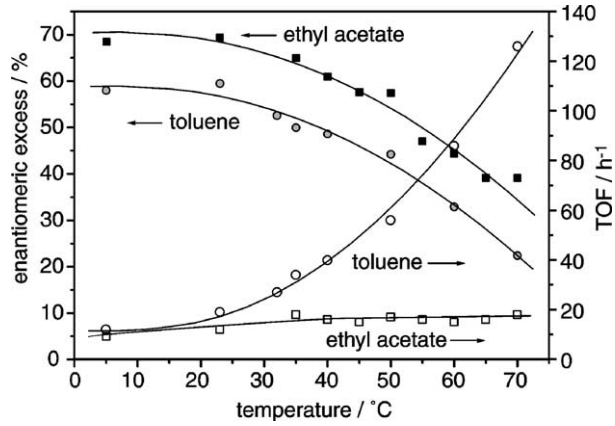


Fig. 4. Influence of temperature on the enantioselectivity and TOF in the hydrogenation of 3,5-bis(trifluoromethyl)acetophenone (standard conditions, 1 bar, in toluene or ethyl acetate). Conversion: 29–31% (corresponding to 105–1140 min of reaction time) in toluene and 9–10% (corresponding to 120–240 min of reaction time) in ethyl acetate.

Fig. 3 shows the time-dependent changes of conversion, ee, and the actual amount of CD in solution when carrying out the hydrogenation of 3,5-di(trifluoromethyl)acetophenone at 1 and 10 bar. The results illustrate why it is necessary to compare the selectivities in a narrow conversion range, preferentially at above 10% conversion. The sharp drop in CD concentration in the first period cannot be interpreted unambiguously as the disappearance of CD from solution may be attributed to its hydrogenation and also to its adsorption on the catalyst, particularly on the relatively high surface area of alumina support. After 2–3 min the rate of disappearance of CD strongly depends on the pressure and this effect is clearly due to the different rates of hydrogenation of the quinoline moiety.

Increasing reaction temperature (above room temperature) diminished the ee in both weakly polar solvents (Fig. 4). The selectivity could not be improved by working below room temperature, as it was observed in several other reactions catalyzed by the Pt–cinchona system [7,9,11,20,50]. The negative effect of increasing temperature above room temperature on the ee is a general feature of hydrogenations over cinchona-modified Pt. No unambiguous explanation has yet been provided for this effect. A feasible interpretation could be the change of adsorption mode of substrate and modifier, though recent NEXAFS studies with dihydrocinchonidine and quinoline do not support this assumption [51,52]. Another likely explanation is that the quinoline ring of CD is hydrogenated faster at higher temperature leading to a successive loss of ee.

The minor rate enhancement in ethyl acetate with increasing temperature, compared to the behavior in toluene, is partly due to the increasing partial pressure of the volatile

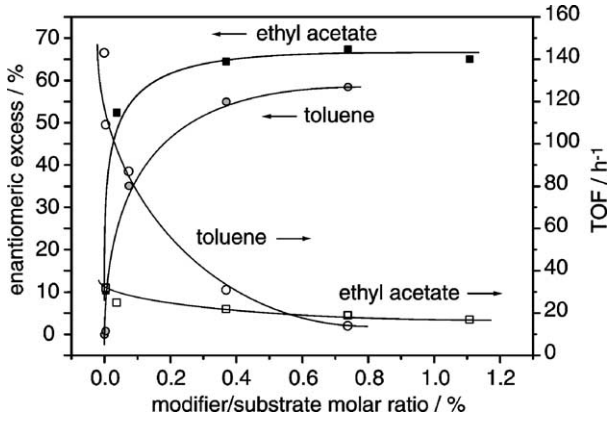


Fig. 5. Influence of modifier/substrate molar ratio on the enantioselectivity and TOF in the hydrogenation of 3,5-bis(trifluoromethyl)acetophenone (standard conditions, 1 bar, in toluene or ethyl acetate). Conversion: 24–26% (corresponding to 75–580 min of reaction time) in toluene and 20–21% (corresponding to 260–435 min of reaction time) in ethyl acetate.

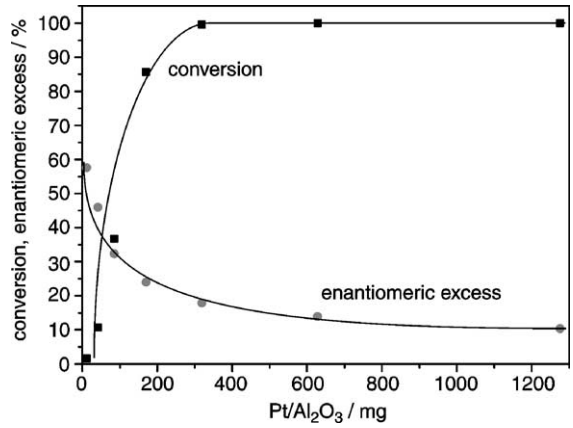


Fig. 6. Influence of the amount of catalyst (5 wt% Pt/Al_2O_3) on the enantioselectivity and conversion in the hydrogenation of 3,5-bis(trifluoromethyl)acetophenone (standard conditions, toluene).

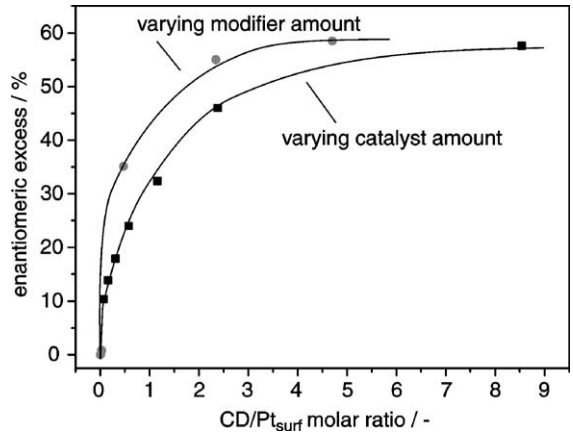


Fig. 7. Influence of the modifier/Pt_{surf} molar ratio on the enantioselectivity in the hydrogenation of 3,5-bis(trifluoromethyl)acetophenone in toluene. The modifier/Pt_{surf} molar ratio was calculated from the experiments where either the amount of modifier (at 1 bar, Fig. 5) or the amount of catalyst was varied (at 10 bar, Fig. 6).

solvent, leading to a decrease in hydrogen partial pressure at the fixed total pressure of 1 bar.

3.2. Influence of substrate/modifier/platinum ratios

The effect of varying the modifier/substrate molar ratio is shown in Fig. 5. The concentration range investigated was limited by the solubility of modifier in the weakly polar solvents. Increasing the modifier concentration at constant substrate and catalyst concentrations improved the enantioselection, as expected. In both solvents the highest ee's were achieved at a modifier/substrate ratio of 0.74 mol%, corresponding to a substrate/modifier molar ratio of 135. At this concentration the modifier/Pt_{surf} molar ratio was 4.7. Note that this is only a nominal value related to the total amounts of CD and surface Pt atoms present in the reactor and no conclusion can be drawn concerning the actual surface modifier/Pt molar ratio or the reaction mechanism.

Addition of modifier to the reaction mixture diminished the reaction rate as reported earlier for several acetophenone derivatives, including 3,5-di(trifluoromethyl)acetophenone [26]. For example, in toluene under standard conditions the TOF was 14 h^{-1} at 0.74 mol% CD/substrate ratio, as compared to 143 h^{-1} measured in the unmodified reaction leading to racemic product. In the hydrogenation of α-functionalized activated ketones addition of CD usually induces significant rate acceleration compared to the unmodified reaction [27]. There is a general agreement in the literature that enantioselection and rate acceleration are coupled phenomena over cinchona-modified Pt [3,4,53]. Clearly, hydrogenation of acetophenone derivatives does not follow this correlation.

The influence of substrate/modifier/Pt ratios has also been investigated by varying the amount of catalyst (Fig. 6). An increase in the amount of catalyst (the number of active sites) led to a rapid increase in conversion but also to an almost sixfold drop of ee. This correlation illustrates the difficulties of performing the reaction in a continuous-flow fixed-bed reactor where the modifier is fed to the reactor together with the reactant and hydrogen, and the actual modifier/catalyst ratio is low [54]. Another important conclusion is that it is not the cinchonidine/substrate ratio that is crucial for enantioselection but the cinchonidine/Pt ratio. To prove this conclusion, both series of experiments, carried out in toluene and presented in Figs. 5 and 6, are replotted in Fig. 7. Here the ee as a function of the CD/Pt_{surf} molar ratio is presented. Despite of the different pressures (1 and 10 bar) the two curves are very similar. Clearly, good ee can be achieved only at high CD/Pt_{surf} molar ratios.

The best ee measured during this parameter study was 69.5% in the hydrogenation of 3,5-di(trifluoromethyl)acetophenone under standard conditions at 1 bar in ethyl acetate. Under these conditions the conversion was only 10% after 2 h. After a prolonged reaction time (19 h) 58% ee at 63% conversion was obtained. The lower enantioselectivity is likely due to partial hydrogenation of the quinoline ring

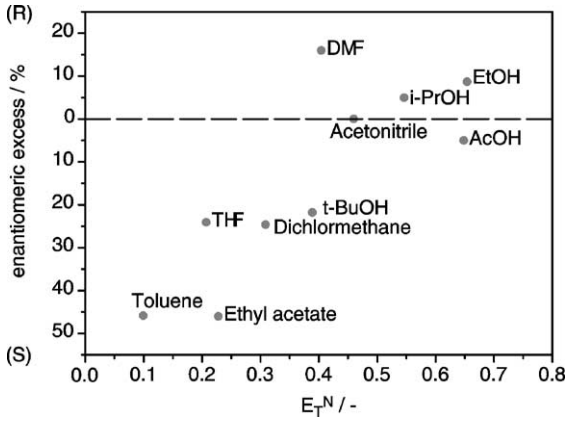


Fig. 8. Influence of solvent polarity characterized by the empirical solvent parameter E_T^N in the hydrogenation of 3,5-bis(trifluoromethyl)-acetophenone (standard conditions).

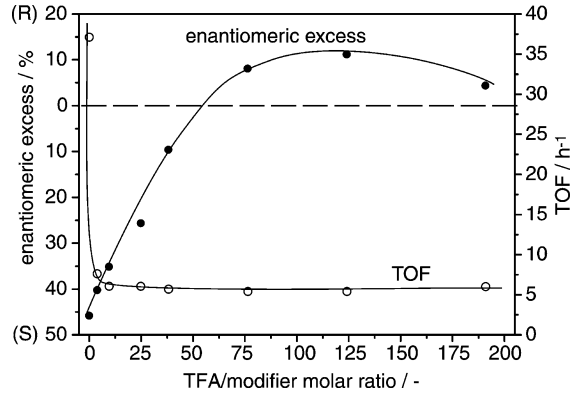


Fig. 9. Enantioselective hydrogenation of 3,5-bis(trifluoromethyl)acetophenone in the presence of trifluoroacetic acid (TFA) (standard conditions, toluene).

of CD. Note that optimization of the reaction conditions to achieve the highest yield and ee has not been attempted.

3.3. Solvent effect: Inversion of enantioselectivity

The effect of solvents on the enantioselectivity in the hydrogenation of 3,5-di(trifluoromethyl)acetophenone is plotted in Fig. 8 as a function of the empirical solvent parameter E_T^N [55]. The correlation between the two parameters is not really good and replacing the empirical solvent parameter by the relative permittivity (dielectric constant) or considering the Taft constants α or β did not improve the correlation. Still, the striking effect of solvent properties is obvious. The highest ee to (*S*)-3,5-di(trifluoromethyl)phenylethanol was obtained in the weakly polar solvents toluene and ethyl acetate (46%). The ee decreased in polar solvents, and in dimethylformamide, isopropanol, and ethanol the ee inverted from the (*S*) to the (*R*) enantiomer. This behavior may be an indication for a significant change in the reaction mechanism. Note that (hemi)ketal formation could not be detected in ethanol or 2-propanol.

The conversion achieved in 2 h varied in the range of 1–71%. There is no correlation between the average reaction rate and the empirical solvent parameter or the dielectric constant.

In the hydrogenation of some activated ketones over the Pt–cinchona system increasing solvent polarity reduces the enantioselectivity. Examples include α-ketoesters [27,56], α-ketolactones [34], pyrrolidine-triones [19], and α-diketones [12]. The strong effect of solvent polarity may be attributed to unfavorable interactions of the solvent with the substrate–modifier complex. In the hydrogenation of ethyl-4,4,4-trifluoroacetoacetate a clear positive correlation between solvent polarity and enantioselectivity was found, which indicates that in this reaction the substrate–CD interaction is different from that proposed for α-ketoester hydrogenation [17].

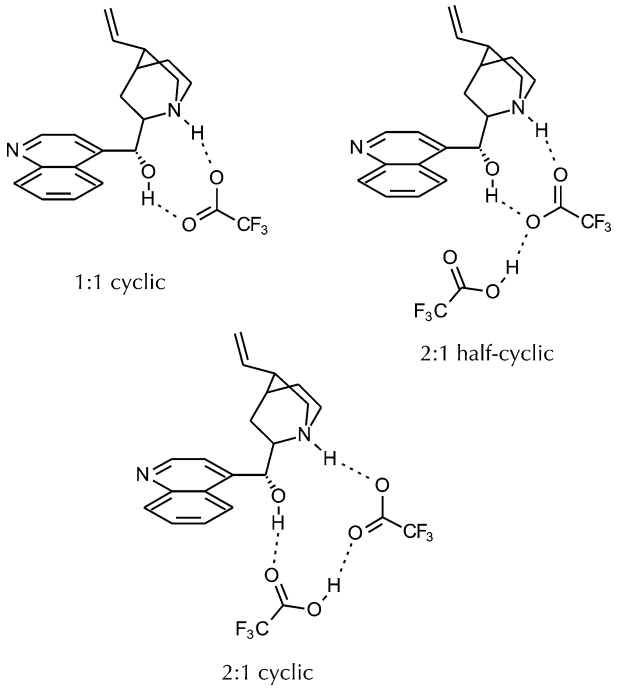
Furthermore, it was shown that solvent polarity influences the conformation of CD [57,58]. The most favorable conformation for α-ketoester hydrogenation—open(3)—is dominant in apolar and acidic solvents [43,59,60].

Inversion of enantioselectivity by changing the solvent composition is not unusual in asymmetric hydrogenation reactions. Examples from homogeneous catalysis include the hydrogenation of dehydroamino acid derivatives with rhodium(I) complexes [61,62] and the hydrogenation of imines in the presence of reverse micelles [63]. There are only a few reports on heterogeneously catalyzed reactions, such as the hydrogenation of ethyl-4,4,4-trifluoroacetate over the Pt/Al_2O_3–MeOCD system [64], and the hydrogenation of pyruvate esters on Pd and Pt modified by a cinchona alkaloid [65]. The inversion of ee is usually attributed to changes in the reaction mechanism. A special case is the hydrogenation of a pyruvate ester on Pt/Al_2O_3 modified by 3-(1-methyl-indol-3-yl)-2-methylamino-propan-1-ol [66], where the inversion of ee in acetic acid was attributed to extensive transformation of the modifier.

3.4. Inversion of enantioselectivity by addition of TFA

The influence of a strong acid additive on the enantiodifferentiation has been investigated using trifluoroacetic acid (TFA, $pK_a = 0.3$ [67]) that is well miscible with organic solvents (Fig. 9). Note that no (hemi)ketal formation with the alcohol product in the presence of TFA could be detected by GC analysis. Addition of TFA had a strong effect on the reaction rate. The TOF dropped by a factor of about 6 already at low TFA concentration and then barely changed. The selectivity to (*S*)-3,5-di(trifluoromethyl)phenylethanol decreased monotonously with increasing TFA/CD ratio and an ee of 11% to (*R*)-3,5-di(trifluoromethyl)phenylethanol was obtained in the presence of 0.07 ml TFA (TFA/CD = 124 mol/mol, or 1.4 vol% TFA in toluene). The dramatic change in ee is similar to the effect of strongly polar solvents (Fig. 8).

According to NMR analysis, protonation of the quinuclidine N of CD ($pK_a = 10.0$) requires only one equivalent of TFA [67]. Even if the adsorption of TFA on the alumina support is taken into account, inversion of enantioselectiv-



Scheme 2. Structure of TFA–CD complexes in solution (see Ref. [69]).

ity cannot simply be attributed to protonation of the modifier. For example, addition of 0.002 ml TFA (TFA/CD = 3.8 mol/mol) reduced the ee from 46 to 40% and the (*R*)-product formed in excess only at above a TFA/CD molar ratio of ca. 50.

A probable explanation for the striking effect of TFA is the formation of cyclic TFA–CD ion pairs [68]. The possible structures of these ion pairs identified by IR spectroscopy [69] are shown in Scheme 2. According to a new three-step reaction pathway [69], not CD but the TFA–CD ion pair is the real modifier that interacts with the reactant in the enantiodifferentiating step. The decrease of ee with increasing acid concentration may be interpreted by the increasing dominance of this three-step reaction pathway.

The equilibrium of formation of the complexes shown in Scheme 2 depends on the acid strength. This is the likely explanation for the smaller effect of AcOH ($pK_a = 4.75$) on the enantioselectivity compared to that of TFA ($pK_a = 0.3$) (compare Figs. 8 and 9).

The existence of this three-step reaction pathway has been demonstrated for the enantioselective hydrogenation of 4-hydroxy-6-methyl-2-pyrone over cinchona-modified Pd/TiO_2 [68] and ethyl-4,4,4-trifluoroacetoacetate over cinchona-modified Pt/Al_2O_3 [69]. In contrast, no evidence for the importance of this model could be found yet for the Pt-catalyzed hydrogenation of α-ketoesters or other activated ketones [69].

Another possible explanation to be considered is the protonation of the weakly basic quinoline N of CD. On platinum and palladium two different adsorption modes of CD have been detected by ATR-IR spectroscopy [70]: a π-bonding

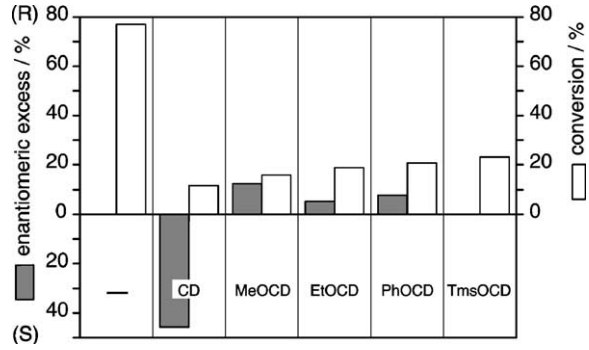


Fig. 10. Hydrogenation of 3,5-bis(trifluoromethyl)acetophenone over 5 wt% Pt/Al_2O_3 modified by ether derivatives of CD (standard conditions, toluene).

adsorption via the quinoline moiety being approximately parallel to the metal surface and a N-bonded species that is adsorbed via the quinoline moiety being in a tilted position. Protonation of the quinoline moiety of CD is expected to influence mainly the latter adsorption mode, while enantiodifferentiation is attributed to the π-bonded species. Hence, protonation of the quinoline moiety is expected to have only a minor influence on the enantioselection.

3.5. Hydrogenation of acetophenones with cinchonidine derivatives

In order to clarify the role of OH and quinuclidine N functions of the modifier, various CD derivatives (Scheme 1) have been tested in the hydrogenation of ring-substituted acetophenones. In the hydrogenation of 3,5-di(trifluoromethyl)acetophenone, replacement of CD by its ether derivatives MeOCD, EtOCD, PhOCD, or TmsOCD inverted the enantioselectivity from an excess of the (*S*)-alcohol to a small but significant excess to the (*R*)-alcohol (Fig. 10). Interestingly, the steric effects due to the different size of the *O*-alkyl or *O*-aryl group were small. In all reactions the rate was lower than in the unmodified ("racemic") reaction (not shown).

Due to the importance of these results in identifying the nature of reactant–modifier interaction(s), the experiments with CD, MeOCD, and EtOCD were repeated with acetophenone and 11 other acetophenone derivatives (for their structure see a former publication [26]). Some representative examples are shown in Fig. 11. The results are similar to those shown in Fig. 10: in all reactions inversion of configuration of the major product was observed when CD was substituted by one of its ether derivatives. Addition of any CD derivative resulted in a rate deceleration compared to the unmodified reaction. Importantly, the rates were higher with the ether derivatives of CD than in the presence of CD. Obvious conclusions which can be drawn from these experiments are that:

(i) the OH group of CD plays a critical role in the enantioselection, and

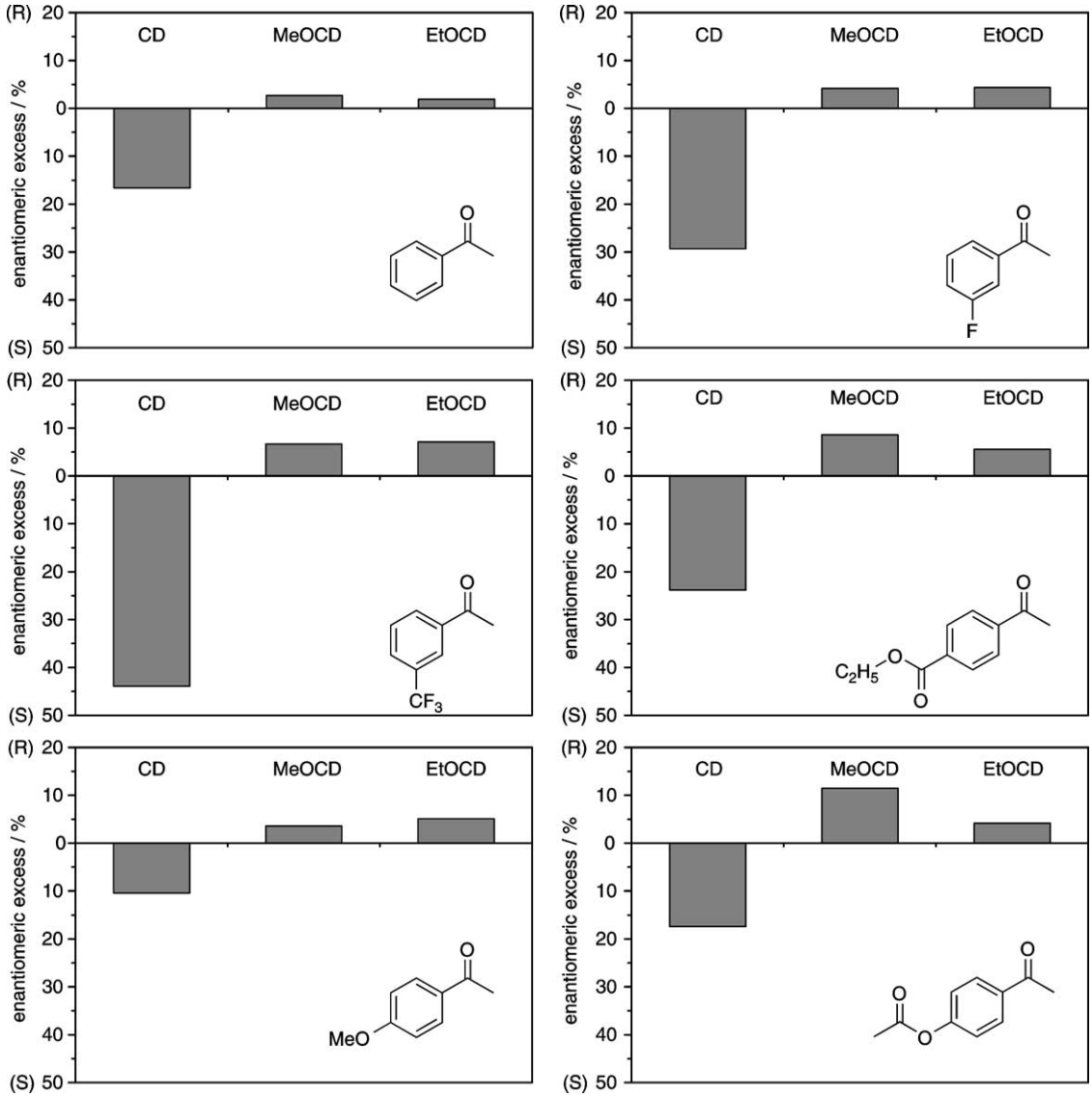


Fig. 11. Hydrogenation of acetophenone and some of its ring-substituted derivatives over 5 wt% Pt/Al_2O_3 modified by CD, MeOCD, and EtOCD (standard conditions, toluene).

(ii) a reaction pathway without involvement of the OH group is also feasible; this pathway is even faster and affords low ee to the opposite enantiomer.

There are numerous examples of the inversion of ee in asymmetric hydrogenations induced by (small) variation of the structure of the ligand in homogeneous catalysis [71,72], and that of the chiral modifier in heterogeneous catalysis [66, 73–75]. These striking changes in the sense of enantioselection provide valuable information on the reaction mechanism.

Next, the role of the basic quinuclidine N in the substrate–modifier interaction was tested in the hydrogenation of 3,5-bis(trifluoromethyl)acetophenone (Fig. 12). When replacing CD by *N*-MeCDCl or *N*-BzCDCl, the ee dropped close to zero. A possible side reaction, the hydrogenolysis of the N–C bond in *N*-MeCDCl or *N*-BzCDCl would result in

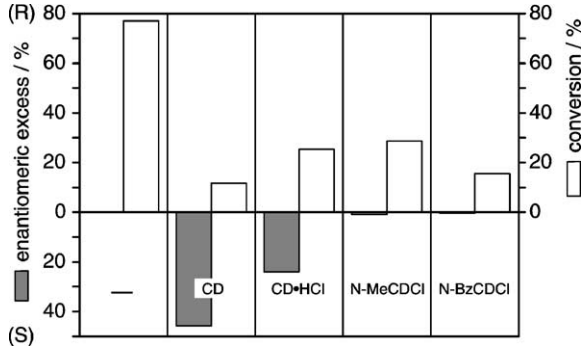


Fig. 12. Hydrogenation of 3,5-bis(trifluoromethyl)acetophenone over 5 wt% Pt/Al_2O_3, modified by N-substituted cinchona alkaloids (standard conditions, toluene).

CD•HCl. Fig. 12 shows that this possibility can be excluded as CD•HCl affords 24% ee to the (*S*)-product. These ex-

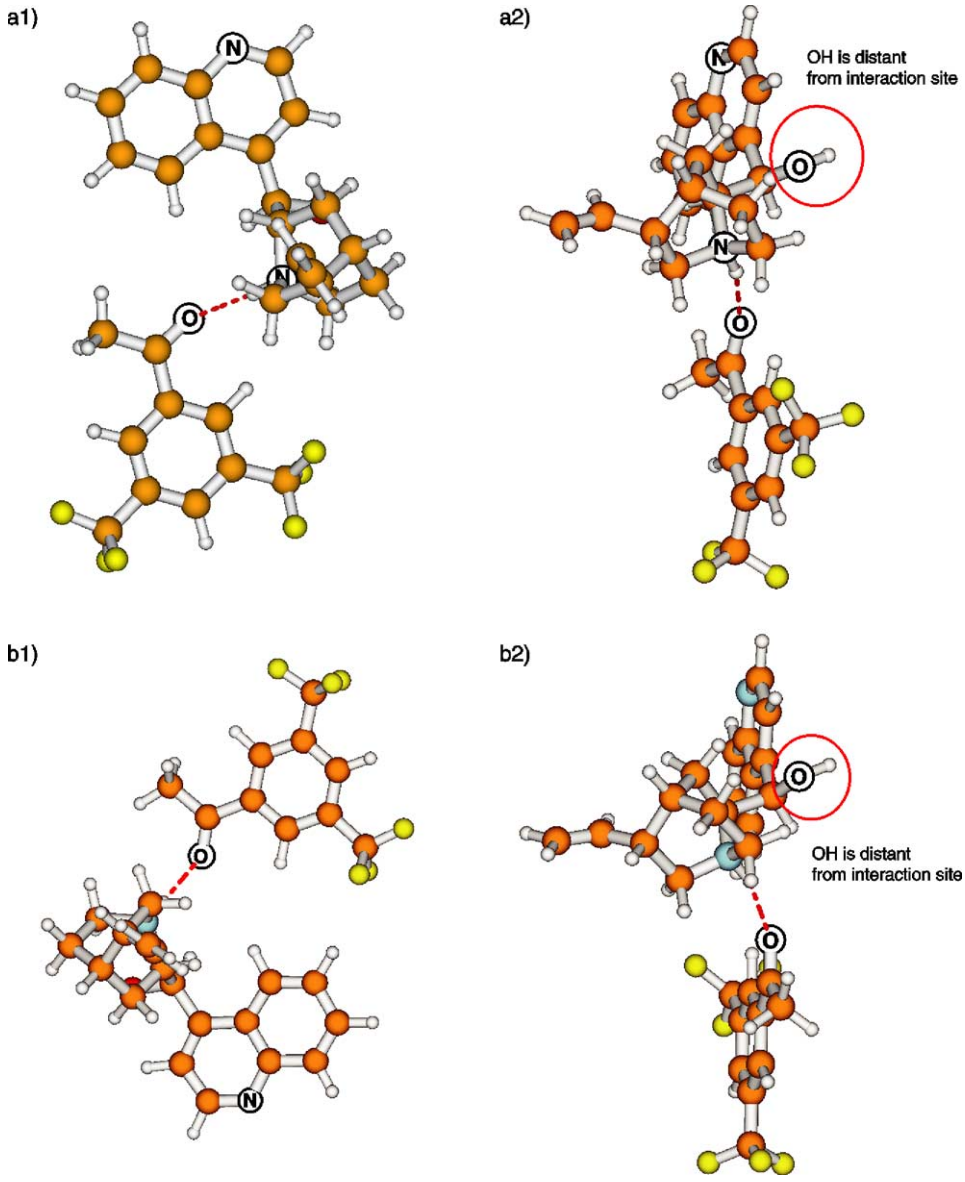


Fig. 13. Interaction of CD with 3,5-bis(trifluoromethyl)acetophenone with surface constraints. (a1) *pro*-(*R*) top view; (a2) *pro*-(*R*) side view; (b1) *pro*-(*S*) top view; (b2) *pro*-(*S*) side view.

periments demonstrate that the quinuclidine N of CD is essential for the substrate–modifier interaction leading to enantiodiscrimination—a crucial feature of reactions catalyzed by the Pt–cinchona system [5].

3.6. Theoretical calculations

The structure of the diastereomeric complex formed upon interaction between 3,5-di(trifluoromethyl)acetophenone and CD has been calculated within the frame of a previously proposed interaction model [2,41–44], that is in vacuum, with surface constraints simulating flat adsorption of both reactant and modifier and with the modifier adopting an "open(3)" conformation. The results are shown in Fig. 13. The geometry of the interaction complex is similar to that found for the acetophenones within the same interaction model [76]. The calculated energy difference between the pro-(*R*) and the pro-(*S*) complexes shown in Fig. 13 is 0.1 kcal/mol and does not imply significant enantiodifferentiation. The uncertainty of the calculated energy differences is in fact estimated to be considerably larger (circa 0.5 kcal/mol). The influence of the substitution at the hydroxyl oxygen of CD (O-alkylation) is not evident from these complexes. It is in fact clear from Fig. 13 that the hydroxyl group of CD is too distant from the interaction site to have a significant influence on the interaction with the reactant.

We attempted to find other CD conformations where the hydroxyl group of the alkaloid could be in proximity of the interaction site (N–H–O bond), therefore influencing enantioselectivity. In order to do so, the planar surface constraints were abandoned and the conformation of CD was

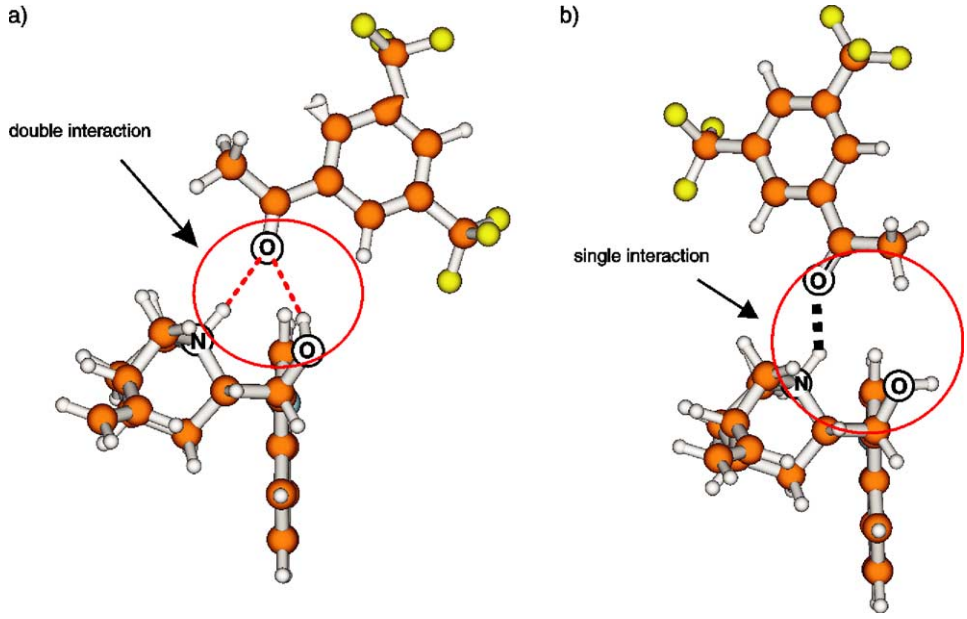
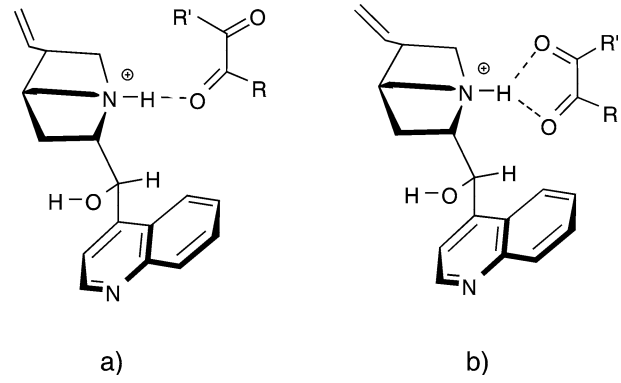


Fig. 14. Interaction of CD with 3,5-bis(trifluoromethyl)acetophenone without surface constraints. (a) Interaction mode (1); (b) interaction mode (2).

changed to open 5. Fig. 14a shows that this conformation allows a double interaction between the keto-carbonyl moiety of the substituted acetophenone and the alkaloid. Both the quinuclidine N and the OH groups of the modifier are involved in the interaction with the reactant through hydrogen bonding. Fig. 14b shows a similar complex, which, however, only exhibits a single hydrogen bond, not involving the O–H group of the modifier. Comparing the two complexes it turns out that the second hydrogen bond involving the O–H group does not stabilize the complex, it rather forces it in a high-energy geometry, resulting in an energy difference of 7.0 kcal/mol in favor of the singly hydrogen-bonded complex shown in Fig. 14b. Both these complexes exhibit higher energies than the ones with planar constraints shown in Fig. 13. The likely explanation is the higher stability of the open(3) conformation of CD compared to that of open(5).



Scheme 3. Schematic representation of the interaction of cinchonidine (CD) and an α-ketoester or ketopantolactone in the enantiodifferentiating step. (a) N–H–O interaction with the keto carbonyl of the substrate adsorbed on Pt in a *trans* position; (b) bifurcated H bond with the keto and ester carbonyls of the substrate adsorbed on Pt in *cis* position (see Ref. [41]).

3.7. Mechanistic considerations

The present study of the hydrogenation of ring-substituted acetophenones (Scheme 1) revealed that the reaction mechanism is different from that proposed for the hydrogenation of α-ketoesters [5,43,59] and extended later to ketopantolactone [77]. According to this model there is an attractive and a repulsive interaction between the substrate and CD, both adsorbed on the Pt surface via π-bonding of the quinoline ring of CD and the C=O groups of the substrate. The attractive interaction is a single or a bifurcated H bond involving the basic quinuclidine N and the carbonyl O atoms (Scheme 3) [41]. The OH function of CD is not involved directly in the substrate–modifier interaction, in agreement with the early observation that CD and MeOCD affords comparable enantioselectivities [78].

In contrast, in the hydrogenation of ring-substituted trifluoroacetophenones replacement of CD by MeOCD led to a loss of enantioselectivity or to a small ee to the opposite enantiomer [16]. The present study of ring-substituted acetophenones, not functionalized in α-position, indicates that this behavior is a general feature of aromatic ketones: replacement of CD by its ether derivatives MeOCD, EtOCD, PhOCD, or TmsOCD resulted in a drop in enantioselectivity and inversion of ee (Figs. 10 and 11). On the other hand, the loss of enantioselectivity by methylation or benzylation of the quinuclidine N supports the crucial importance of the N–H–O-type interaction between substrate and modifier (Fig. 12).

The ab initio calculations carried out to clarify the role of the OH function of CD were not conclusive. The model that has been successfully used in the past to explain enantiod-

ifferentiation in the hydrogenation of activated ketones on Pt modified by cinchonidine and a series of synthetic modifiers [43,59,76] failed to predict a considerable enantiodifferentiation in the case of 3,5-di(trifluoromethyl)acetophenone. This model does, furthermore, not offer an obvious explanation for the inversion of the sense of enantiodifferentiation upon alkylation of the OH group of the modifier. When assuming open(3) conformation for the modifier and parallel adsorption of both the quinoline ring of the modifier and reactant on a flat (ideal) Pt surface, then the OH group of the modifier is too far away from the binding site to have a significant influence on the interaction with the reactant. Furthermore, when changing to the conformation open(5), where the OH group is closer to the binding site, the energy increases. In this conformation a double interaction involving N–H–O and O–H–O hydrogen bonds is possible, when the constraint of coplanarity of modifier and reactant is released. However, the interaction involving only the N–H bond is considerably more stable.

The special (and yet unknown) role of the OH function of CD is indicated by the remarkable loss of enantioselectivity, or even inversion of ee, in strongly polar solvents including the toluene–TFA mixture. We assume that these solvents interact with the OH function of CD and thus disturb the substrate–modifier interaction and diminish the ee (Fig. 8). In case of acidic solvents, such as AcOH and TFA, a CD–acid ion pair has been suggested to be the real modifier of Pt [69] and Pd [68]. The consequence of the formation of this ion pair is the same as that of polar solvents or O-alkylation of CD: it blocks the OH function of CD and decreases the selectivity, or even inverts the ee to the opposite enantiomer at sufficiently high TFA/CD ratios (Fig. 9).

The considerable loss of enantioselectivity or even inversion of the sense of enantioselection observed in the presence of strongly polar solvents or acids, and when blocking the OH function of CD, has presumably the same origin. The likely explanation is that the OH function of CD is critical in the substrate–modifier interaction and blocking of this functional group diminishes or inverts the ee. This behavior of ring-substituted acetophenones contrasts to the mechanistic models developed for the hydrogenation of α-ketoesters and ketopantolactone over cinchona-modified Pt.

4. Conclusions

The successful enantioselective hydrogenation of ring-substituted acetophenones is the latest extension of the application range of the Pt–cinchona system and indicates the potential for further, yet unknown applications. These ring-substituted acetophenones do not contain any functional group in the α-position, a general feature of all other activated ketones that have been hydrogenated efficiently until now by the Pt/cinchona system [4].

A study of some important parameters including pressure, temperature, substrate/modifier/Pt ratios, and the nature of solvent afforded 69.5% ee, though optimization of the reaction conditions has not been attempted.

The present mechanistic investigations revealed some important features that are strikingly different from those observed in the hydrogenation of α-ketoesters and other activated ketones [5]. Further deepening of the understanding of the reaction mechanism would necessitate the in situ study of the adsorption of acetophenones and their interaction with CD on the Pt surface.

Acknowledgments

Financial support by the Swiss National Science Foundation is kindly acknowledged. The authors also thank Argonaut Technologies for technical support for the parallel pressure reactor system.

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