Journal of Catalysis 278 (2011) 94-101

Contents lists available at ScienceDirect

Journal of Catalysis

journal homepage: www.elsevier.com/locate/jcat

Hydrogenation of acetophenone derivatives: Tuning the enantioselectivity via the metal-support interaction

Fatos Hoxha^a, Erik Schmidt^a, Tamas Mallat^a, Bjoern Schimmoeller^b, Sotiris E. Pratsinis^b, Alfons Baiker^{a,*}

^a Institute for Chemical and Bioengineering, Department of Chemistry and Applied Biosciences, ETH Zurich, Hönggerberg, HCI, CH-8093 Zurich, Switzerland ^b Particle Technology Laboratory, Department of Mechanical and Process Engineering, ETH Zurich, CH-8092 Zurich, Switzerland

ARTICLE INFO

Article history: Received 4 November 2010 Revised 25 November 2010 Accepted 29 November 2010 Available online 8 January 2011

Keywords: Metal-support interaction Acetophenone derivatives Asymmetric hydrogenation Platinum Cinchonidine

ABSTRACT

The influence of acidic and basic supports on the enantioselective hydrogenation of acetophenone and its aryl-substituted derivates was studied. The Pt/Al₂O₃, Pt/Al₂O₃–SiO₂, and Pt/Al₂O₃–Cs₂O catalysts were prepared by single-step flame spray pyrolysis, and cinchonidine (CD) was used as chiral modifier. For all five aromatic ketones, the acidic support improved the ee, while the basic support diminished it. Opposite tendencies were observed for the reaction rate: acidic support lowered and basic support enhanced the rate of ketone conversion. In situ investigation of the hydrogenation of the quinoline ring of CD revealed for the first time that degradation of the modifier leads to remarkable variation in the substrate/modifier ratio. This effect and a possible catalyst deactivation due to aldol condensation of the ketones may be the origin of the decrease in ee with conversion.

Following the diastereoselectivity during hydrogenation of the heteroaromatic ring of the quinoline unit of CD proved dominantly pro(S) adsorption mode on Pt/Al_2O_3 and Pt/Al_2O_3 -SiO₂, and pro(R) on Pt/Al_2O_3 -Cs₂O catalysts. Changes in the adsorption mode were minor during hydrogenation of aromatic ketones. This, together with the small effect of ketones on the hydrogenation rate of CD, is interpreted as an indication to weak substrate–modifier interactions, in contrast to the situation during the hydrogenation of α -ketoesters (methyl benzoylformate).

© 2010 Elsevier Inc. All rights reserved.

JOURNAL OF CATALYSIS

1. Introduction

Many facets of metal-support interactions and their critical influence on the activity and selectivity of metal nanoparticles have been clarified in the past decades [1–5]. The role of the acid/base properties (ionicity) of the support on the electronic properties of Pt particles has been extensively investigated by Koningsberger and co-workers, using a broad range of characterization techniques and DFT calculations [6–13]. They have shown that basic supports enhance the Pt electron density, resulting in higher H coverage on Pt and also higher Pt–H bond strength, with a direct impact on hydrogenation and hydrogenolysis reactions. The opposite effect of acidic supports has also been proven experimentally at high-temperature reaction conditions.

Transformation of larger polyfunctional organic compounds under very mild conditions is expected to be more complex, since the reactivity and (stereo)selectivity of bulky flexible molecules is influenced also by the adsorption geometry, which may be controlled by the electronic state of the active metal particles. Our aim was to understand the role of metal-support interaction in the stereoselective hydrogenation of complex molecules. At first,

* Corresponding author. Fax: +41 44 632 11 63.

E-mail address: baiker@chem.ethz.ch (A. Baiker).

we choose the Pt-catalyzed enantioselective hydrogenation of activated ketones—methyl benzoylformate and ketopantolactone—in the presence of cinchonidine (CD) as chiral modifier [14,15]. The acid–base properties of the support were tuned by doping Al_2O_3 with SiO₂ and Cs₂O, respectively. The catalysts were prepared by flame spray pyrolysis to minimize the disturbing effect of impurities originating from the catalyst synthesis [14,15]. The enantiose-lectivity decreased on basic and increased on acidic supports, and an outstanding ee of 94% could be achieved in the synthesis of (*R*)-pantolactone. The fundamental role of support ionicity was proven by the good correlation between the enantioselectivity of all catalysts and the ratio of CO adsorbed in bridged to linear ratio [12,15].

A practical limitation of this study is that the Pt–cinchona system is known to be the most efficient in the hydrogenation of activated ketones possessing an electron-withdrawing group in α -position to the carbonyl function (for recent reviews, see [16–23]). These reactions provide up to 98.5% ee using a commercial Pt/Al₂O₃ catalyst, and further improvement by tuning the metal-support interaction is barely possible. Hence, the aim of the present work is to test the concept in the hydrogenation of non-activated ketones such as acetophenone.

Hydrogenation of aromatic ketones with the Pt-cinchona system is characterized by poor reaction rates and ees. In case of



^{0021-9517/\$ -} see front matter \odot 2010 Elsevier Inc. All rights reserved. doi:10.1016/j.jcat.2010.11.025

acetophenone, the enantioselectivity rarely exceeds 20% [24,25]. Basu et al. [26,27] achieved up to 49% ee on MCM-41-supported Pt, but the enantioselectivity dropped with the conversion irreversibly, probably due to agglomeration and deactivation. Note also that XPS analysis revealed the presence of PtCl₂ beside Pt in the catalyst; thus, the higher ee cannot simply be attributed to the support acidity, since reduction of PtCl₂ to Pt under reaction conditions produces HCl. Aryl-substitution of acetophenone in mor *p*-position with electron-withdrawing groups (F, CF₃, and ester functions) increased the reaction rate and ee, while electronreleasing groups (Me and MeO) had the opposite effect [28]. At best, 69.5 % ee was obtained in the hydrogenation of 3,5-di(trifluoromethyl)acetophenone by carefully optimizing the reaction conditions [29] and after redispersion of Pt by stirring the reaction mixture under nitrogen prior to hydrogenation [30]. Recent data indicate the Ru- and Ir-based chirally modified metal catalysts are better suited to the enantioselective hydrogenation of aromatic ketones [31–33], although leaching of Ru may be a critical issue.

A novel route to understand the metal–support interaction in complex reactions is the diastereoselective hydrogenation of CD. Hydrogenation of the quinoline unit of CD is the most important side reaction in enantioselective hydrogenations on Pt-group metals, since this part of the alkaloid "anchors" the chiral modifier to the metal surface (π -bound) [34–38]. The analysis of the chemoand diastereoselectivity of this reaction (Scheme 1) presents a unique tool to investigate in situ the orientation of the alkaloid on the metal surface [39–42].

In this study, we report the hydrogenation of acetophenone and some selected ring-substituted derivatives (Scheme 2). From the



Scheme 1. Chemo- and diastereoselective hydrogenation of dihydrocinchonidine CDH₂.



Scheme 2. Asymmetric hydrogenation of ring-substituted acetophenones on supported Pt catalysts in the presence of CD as chiral modifier.



Scheme 3. Hydrogenation of methyl benzoylformate on CD-modified Pt catalysts.

flame-made Pt/Al₂O₃–SiO₂ and Pt/Al₂O₃–Cs₂O catalyst series mentioned previously [15], we used the most acidic and basic catalysts (22.5 wt.% SiO₂ and 10 wt.% Cs₂O in the alumina support, respectively), as representative examples, and compared their performance with those of the unmodified and a commercial reference Pt/Al₂O₃ catalyst. For a better understanding of the variations in rate and enantioselectivity, we followed also the hydrogenation of CD during hydrogenation of the ketone substrates.

2. Experimental

2.1. Materials

All chemicals were used as received: acetophenone **1** (Acros, 98% extra pure), 3',5'-bis(trifluoromethyl)acetophenone **2** (ABCR-Chemicals, 99%), 4'-(trifluoromethyl)acetophenone **3** (ABCR-Chemicals, 98%), 2'-(trifluoromethyl)acetophenone **4** (ABCR-Chemicals, 98%), 3'-(trifluoromethyl)acetophenone **5** (Acros, 99%), bicy-clohexyl (Fluka, \geq 99%), cinchonidine (CD, Fluka, \geq 98% alkaloid), methyl benzoylformate **6** (Acros, 99%), toluene (Acros, extra dry, water <30 ppm), and 5 wt.% Pt/Al₂O₃ (Engelhard 4759) as reference catalyst (acronym: Pt/Al₂O₃ (ref.)).

The preparation of the flame-made supported Pt catalysts has been reported elsewhere [14]. Aluminum sec. butoxide (Aldrich, >98%), hexamethyldisiloxane (Fluka, >98%), and cesium acetylacetonate (Fluka) dissolved in 2-ethylhexanoic acid (Aldrich, >98%, 0.5 M) were used as aluminum, silicon, and cesium precursors, respectively. The chemical and textural properties of the catalysts applied in this study are collected in Table 1.

2.2. Catalytic hydrogenation

The catalysts were always reduced at elevated temperature prior to use. The standard procedure for the catalyst pretreatment

1	Table 1				
(Chemical and to	extural prope	rties of the i	flame-made I	Pt catalysts

Catalyst	Pt content (wt.%)	Promoter in the support (wt.%)	BET surface area (m ² g ⁻¹)	Average Pt particle size (nm)	Pt dispersion (%)
Pt/Al ₂ O ₃	4.7	0	138	1.9	60.3
Pt/ Al ₂ O ₃ -SiO ₂	4.7	22.5	136	5.5	20.6
$Pt/-Al_2O_3-Cs_2O$	4.7	10	227	1.8	61.5
Pt/Al ₂ O ₃ (ref.)	5	0	-	6.0	18.7

was as follows: the catalyst was heated under flowing nitrogen up to 400 °C in 30 min, followed by a reduction in flowing hydrogen for 60 min at the same temperature, and finally cooling down in hydrogen in 30 min. At the end, the freshly reduced catalyst was purged with nitrogen for 10 min at room temperature and then transferred immediately to the autoclave.

Hydrogenation of ketones were carried out at 90 bar in a 25-ml stainless steel Parr autoclave equipped with a 16-ml glass liner, a PTFE cover, and a magnetic stirrer. The hydrogen pressure was held at a constant value with a pressure regulator valve. The autoclave was equipped also with a valve for sample collection or substrate addition. The treatment of the catalyst was carried out in a fixed-bed reactor following the standard procedure. The proper amount of catalyst containing 10.3 μ mol Pt (42 mg), 13.6 μ mol modifier (4 mg), 0.92 mmol substrate, and 5 ml solvent (toluene) were stirred magnetically (1000 rpm) at 20 °C for 4 h. The Pt/modifier/substrate molar ratios were kept constant at 1/1.3/89.7.

The conversion and enantioselectivity (ee) were determined by GC analysis, using an HP 6890 gas chromatograph and a Chirasil– DEX CB (Chrompack 7502 25 m × 0.25 mm × 0.25 µm) capillary column. All experiments were carried out at least twice, and the average values are shown in the figures. Always the (*S*)-enantiomer was formed in excess without any detectable side product. Bicyclohexyl was used as internal standard (0.1 mmol). The estimated standard deviation of ee was about $\pm 0.5\%$ ($\pm 1\%$ at less than 5% ee). The actual or incremental ee was calculated as $\Delta ee = (ee_1y_1 - ee_2y_2)/(y_1 - y_2)$, where *y* represents the yield to the hydrogenation product and index 2 refers to a sample subsequent to sample 1.

In the hydrogenation of CD [41], the very fast initial saturation of the vinyl-group to dihydrocinchonidine (CDH₂, Scheme 1) is unimportant for the enantioselection [43] and was not followed in detail. The subsequent chemo- and diastereoselective hydrogenation of the quinoline ring of CDH₂ to hexahydrocinchonidines (CDH₆, Scheme 1) is the key reaction step. Details on the preparation and characterization of the hydrogenated CD derivatives are reported elsewhere [39].

The TOF values were calculated based on the number of surface Pt atoms [14]; their reproducibility was in the range $\pm 10\%$.

3. Results and discussion

The preparation and structural characterization of the flamemade catalysts by N_2 -adsorption, CO chemisorption, X-ray diffraction, and electron microscopy have been reported elsewhere [14]. The important chemical and textural properties of the catalysts applied in this study are collected in Table 1.

In preliminary screening, several solvents such as tetrahydrofurane, cyclohexane, 1,2-dichlorobenzene, and toluene were tested in the hydrogenation of acetophenone over CD-modified Pt/ Al₂O₃–SiO₂ catalyst, where the amount of the modifier varied from 2 to 60 mg in 5 ml solvent, depending on the solubility of CD. The best performance (activity and enantioselectivity) was reached in toluene at high hydrogen pressure. Based on this screening, we have chosen this weakly polar medium for further investigations.

3.1. Enantioselective hydrogenation of acetophenones

The importance of support composition in the hydrogenation of acetophenone is illustrated in Fig. 1. An unusual feature of this transformation is the strong variation of enantioselectivity with the conversion. In the presence of Pt/Al_2O_3 and $Pt/Al_2O_3-Cs_2O$, the enantioselectivity dropped from the beginning of the reaction, and this trend was underlined by the even faster drop of the calculated incremental ee (Δee). Over the SiO₂-doped catalyst, the ee decreased only after a sharp initial transient period of about 10% conversion. The origin of this phenomenon will be discussed later. Despite of the strong variation of ee with conversion, a qualitative



Fig. 1. Conversion-dependent enantioselectivity in the hydrogenation of acetophenone **1** over CD-modified Pt catalysts. Open symbols refer to the calculated incremental enantioselectivity (Δee); standard conditions.

comparison is possible, when the best enantioselectivities achieved at 10–30% conversion are compared. Similarly to the hydrogenation of activated ketones [15], acidic support increased and basic support diminished the enantioselectivity of CD-modified Pt, compared to the performance of unmodified Pt/Al₂O₃.

The outcome of the hydrogenation of the aryl-substituted ketones **2** (Fig. 2a) and **3** (Fig. 2b) was similar to that of acetophenone: a clear positive effect of the acidic support on the enantioselectivity and significantly lower ees in the presence of the basic support. Unfortunately, also the drop of enantioselectivity with time (conversion) is similar. Another interesting feature is the opposite effect of the supports on the reaction rate compared to the enantioselectivity: acidic support lowered and basic support enhanced the rate of ketone conversion (Fig. 2).

The kinetics of the hydrogenation of **1** is shown in Fig. 3. Here, again, hydrogenation of the ketone was the slowest over the SiO_2 -doped catalyst and the fastest over the Cs_2O -doped catalyst. In the latter case, the reaction was almost complete within 1 h. Saturation of the aromatic ring of CD was also determined during reaction. The rate of this undesired side reaction followed the same reactivity pattern with the support acid–base properties, but in this transformation, the differences among the three catalysts were relatively small.

Since the catalysts have different Pt particle sizes (dispersion, see Table 1), the initial hydrogenation rates related to the fraction of surface Pt atoms (TOFs) offer a better comparison. The data for



Fig. 2. Hydrogenation of 3',5'-bis(trifluoromethyl)acetophenone **2** (a) and 4'-(trifluoro-methyl)acetophenone **3** (b) over CD-modified Pt catalysts. Enantioselectivity is plotted as a function of reaction time and substrate conversion. The symbols triangle, circle, and square refer to the Pt/SiO₂-Al₂O₃, Pt/Al₂O₃, and Pt/Cs₂O-Al₂O₃ catalysts, respectively. Standard conditions.



Fig. 3. Time-dependent concentration of acetophenone **1** (closed symbols) and CD (open symbols) over supported Pt catalysts, under standard reaction conditions.

the substrates **1–3** are compared in Fig. 4, involving the three flame-made and the reference Pt/Al_2O_3 catalysts. The values were determined from the slope of the initial linear part of the conversion vs. time plots. Despite of the significant differences in the reactivity of **1–3**, basic support increased and acidic support decreased the activity of the flame-made Pt/Al_2O_3 catalysts in all three transformations. In addition, all flame-synthesized catalysts were more active in the test reactions than the widely used Pt/Al_2O_3 (ref.) catalyst.

A well-known limitation of the Pt–cinchona system is that not only the substrate but also the alkaloid is hydrogenated. Saturation of the aromatic ring results in lower enantioselectivity [44] and also weaker adsorption on Pt [39,45]. The impact of this side reaction is usually minor in case of the highly reactive activated ketones, but it has important consequences in the slow transformation of aromatic ketones, as shown below.

Under standard reaction conditions, the rates (TOFs) of the hydrogenation of the quinoline ring of CD were determined either



Fig. 4. Influence of acid-base properties of the Pt catalysts on the initial hydrogenation rates of acetophenone **1**, 3',5'-bis(trifluoromethyl)acetophenone **2** and 4'-(trifluoro-methyl) acetophenone **3** in the presence of CD. Standard conditions.

Table 2

Initial reaction rates of the hydrogenation of the quinoline ring of CD (alone or in the presence of substrate **1–3**) over supported Pt catalysts. Standard conditions; the TOFs were calculated at 21 ± 7% conversion of CDH₂.

Catalyst TO		h ⁻¹)			
	CD CD with 1		CD with 2	CD with 3	
$\begin{array}{l} Pt/Al_2O_3\\ Pt/Al_2O_3-SiO_2\\ Pt/Al_2O_3-Cs_2O\\ Pt/Al_2O_3\ (ref.) \end{array}$	5.2 7.1 6.3 3.1	3.7 5.8 6.4 3.0	3.8 6.1 5.9 2.0	5.1 7.3 6.7 2.0	

alone or in the presence of the substrates 1-3 (Table 2). Considering the estimated error of determination (about ±10%), the TOF values are astonishingly similar over the acidic and basic catalysts and higher than on the undoped Pt/Al₂O₃. The consumption of CD over the reference Pt/Al₂O₃ is the slowest, in line with the generally lower activity of this catalyst in the hydrogenation of 1-3 (Fig. 4).

The substrate/modifier ratio is a key parameter that controls the rate and enantioselectivity of ketone hydrogenations. Until now only the initial values set before starting the reaction have been given in the literature. Here, for the first time, we made a complete analysis of the reaction mixture including the transformation of the modifier, which analysis revealed some novel features of enantioselective hydrogenations.

The dramatic role of the different rates of hydrogenation of the ketone and the modifier is illustrated in Fig. 5, where the 1/CD molar ratio is plotted as a function of reaction time and conversion of 1. Please note that the experiments under standard conditions are performed with the saturated solution of CD in toluene (4 mg CD in 5 ml toluene), although the actual solubility in the presence of substrate and product is usually much higher. The 1/CD molar ratio changed dramatically with time and conversion, depending on the catalyst support. The initial value of 68 increased or decreased, depending on the relative reactivity of 1 and CD, and after 1 h reaction time, there was a 15-fold difference between the acidic and basic catalysts. Based on these results, it is probable that the remarkable variation of enantioselectivity with conversion shown in Fig. 1 is mainly due to the variation of the actual 1/CD molar ratio at the catalyst surface.

To confirm the importance of this parameter, the hydrogenation of **1** was carried out in the presence of different amounts of CD. The results in Fig. 6 show that higher amounts of CD (lower **1**/CD molar ratio) indeed have a positive impact on the ee, especially over the



Fig. 5. Variation of the acetophenone **1**/CD molar ratio during hydrogenation over Pt catalysts as a function of reaction time and substrate conversion. The symbols square, circle, and triangle refers the $Pt/SiO_2-Al_2O_3$, Pt/Al_2O_3 , and $Pt/Cs_2O-Al_2O_3$ catalysts, respectively. Standard conditions.

SiO₂-doped catalyst. Another interesting observation is that when using high amounts of CD (higher than the solubility limit in pure toluene), the initial transient phenomenon is not observed anymore with the Pt/Al₂O₃–SiO₂ catalyst. The initial increase in the ee with the conversion was not observed as well, if the reaction mixture was stirred under nitrogen for 1 h before the hydrogenation reaction under standard conditions (see "+" symbols in Fig. 6). Our explanation is that a restructuring of the catalyst may occur in the presence of CD. A considerable restructuring of Pt has already been reported in the hydrogenation of **3** over the Pt/ Al₂O₃ (ref.) catalyst [**30**], which resulted in the disappearance of a remarkable initial transient period. It was also shown that in the redispersion of Pt, the quinoline ring of CD played a critical, catalytic role.

Independent of the support acid–base properties, in all cases the enantioselectivity decreased monotonously even at high **1**/CD molar ratios. A feasible explanation may be that hydrogenation of CD provides significant amounts of alkaloid molecules possessing partially saturated aromatic rings that disturb the enantioselection. These partially degraded molecules are less efficient modifiers [44] and may compete with the intact alkaloid molecules and diminish the enantioselectivity. In the fast hydrogenation of activated ketones, the similar but much less extensive side reaction is usually neglected, assuming that the intact modifier present in the reaction mixture will replace the degraded modifier at the Pt surface, and thus the ee barely changes with time or conversion. According to Fig. 5, the fraction of intact CD may decrease rapidly, and this common assumption is probably not valid for the slow hydrogenation of aromatic ketones.

There are some possible side reactions during acetophenone hydrogenation, which should also be considered. Hydrogenation of acetophenone to the corresponding alcohol is frequently accompanied by some hydrogenation of the aromatic ring and by C–O bond hydrogenolysis [14,46–49]. A special feature of cinchona-modified Pt is that the strongly basic quinuclidine N of the alkaloid suppresses hydrogenolysis and provides always the alcohol. On the other hand, acetophenones may take part in aldol condensation due to the presence of an H atom in α -position to the keto-carbonyl group, and the high molecular weight products may poison the catalyst [22,50–52]. The possibility of this transformation has been proven experimentally in the presence of acidic and basic supports, e.g. with alumina under mild conditions, at room temperature [53] and with acidic zeolites at elevated temperature [54]. Strong Brønsted acid sites were recognized as the most active and



Fig. 6. The influence of CD concentration on the ee in the hydrogenation of acetophenone **1** over Pt/SiO₂-Al₂O₃, Pt/Al₂O₃ and Pt/Cs₂O-Al₂O₃ catalysts. Marker "+" indicates the hydrogenation over Pt/SiO₂-Al₂O₃ catalyst after the reaction mixture was stirred in the autoclave for 1 h under N₂ (4 mg CD). Standard conditions.

effective catalyst for the aldol condensation of acetophenone over aluminosilicate zeolites, while the basic zeolites exchanged with potassium or cesium exhibited very low activity.

In the present study, aldol condensation of acetophenones is a feasible side reaction, particularly over the most acidic Pt/Al_2O_3 -SiO₂ catalyst. In control experiments, the aldol condensation products were not detectable in solution and the mass balance was better than 99%, which is about the expected error range based on the gas-chromatographic analysis (±1%). Our interpretation is that CD present in large excess probably blocks the most acidic sites on the support and thus suppresses the aldol reaction. In this respect, the hydrogenated products of CD act the same way as the intact alkaloid. Nevertheless, this side reaction could not be completely excluded.

Considering all these points, it seems that only a qualitative analysis of the support effect is possible for the hydrogenation of acetophenones 1–5. To illustrate the effect of support acid-base properties on the enantioselection, the best choice is to compare the highest enantioselectivities achieved after a relatively short reaction time. At these conditions, the possible catalyst restructuring has already been finished and the degradation of the modifier is yet not too extensive. Examples are shown in Figs. 1 and 2 for substrates 1-3, and Table 3 presents the data selected accordingly for all five substrates. Table 3 includes also the data obtained with the widely used Pt/Al₂O₃ (ref.) catalyst, which is compared to the flame-made catalysts under the same conditions. Note that the flame-synthesized Pt/Al₂O₃ showed for substrates 1-3 remarkably better enantioselectivity, indicating the potential of flame-derived catalytic materials. It is clear from Table 3 that Pt/Al₂O₃-SiO₂ offers the highest enantioselectivity for all substrates. For example, in case of acetophenone (1), the effect of acid doping of alumina is more than threefold. The 63% ee is so far the best result published over the Pt-CD system. On the other hand, doping the support with cesium oxide diminished the enantioselectivity in all investigated reactions.

3.2. Diastereoselective hydrogenation of cinchonidine

We have shown recently [41] that the adsorption mode of CD on the Pt surface is directly guided by the acid–base properties of the support. The orientation of CD over the Pt surface was determined by following the diastereoselectivity (d.e.) during the hydrogenation of the heteroaromatic ring of the quinoline unit (Scheme 1). Here, we used this method to understand the origin of support effect in the hydrogenation of aromatic ketones. Hydrogenation of

Table 3

Best ees achieved in the enantioselective hydrogenation of acetophenone and its ringsubstituted derivatives in the presence of CD. Standard conditions; always the (S)enantiomer was formed in excess. Values of corresponding conversions are given in italics.

Substrate	ee (%) conversion %			
	Pt/Al ₂ O ₃ -SiO ₂	Pt/Al_2O_3	$Pt/Al_2O_3-Cs_2O$	Pt/Al ₂ O ₃ (ref.)
1	63 ^a	33 ^a	11 ^a	20
	2	55	34	3
2	67 ^a	54	20	34
	12	45	55	30
3	52 ^a	38 ^a	18	22
	21	18	46	11
4	52 ^a	_ ^b	_b	30
	2			55
5	70 ^a	_ ^b	_b	40
	23			12

^a The amount of CD in the reaction mixture was 8 mg (instead of 4 mg under standard conditions).

^b Not determined.

CD was performed under the same conditions as in the previous study [41]. Table 4 presents the diastereoselectivities in CD hydrogenation, either alone or in the presence of substrates **1–3**, i.e., under truly in situ conditions. As reported previously [41], in the absence of substrate, the (*S*) diastereomer formed in excess over Pt/Al_2O_3 and Pt/Al_2O_3 –SiO₂ catalysts and addition of Cs₂O inverted the major diastereomer to (*R*). Note that in the former study, at low temperature, the diastereoselectivities were significantly higher [41].

The presence of the aromatic ketones changed the diastereoselectivity only to a small extent (Table 4). The biggest deviation was observed in the hydrogenation of **2** and **3** on Pt/Al₂O₃ where even an inversion of the major product occurred, but the diastereoselectivities were very small and the error of analysis for such low values is rather high (\pm 1%). The probable interpretation of the relatively small changes by the addition of the substrates is that interaction of the alkaloid with the aromatic ketones is very weak. This conclusion is supported by the kinetic data in Table 2, showing that addition of the aromatic ketone has only a small effect on the rate of CD hydrogenation.

This behavior is in contrast to the intense interaction found previously in the hydrogenation of activated ketones [40]. In the presence of α -ketoesters, both the rate and the adsorption geometry of CD on Pt/Al₂O₃ (ref.) were strongly affected. That study provided the first evidence to a so-called "inverse ligand acceleration" effect, that is, the strong ketone–modifier interaction influences the rate and stereoselectivity of their hydrogenation. In other words, the interacting partners symbiotically guide each other's adsorption mode and enhance their reactivity toward hydrogenation.

To obtain a complete picture, we extended the study with the CD-activated ketone interaction on acid- and base-promoted catalysts. Methyl benzoylformate 6 (Scheme 1) was selected as a model substrate to avoid aldol-type side reactions. Since the hydrogenation of α -ketoesters under standard conditions is very fast, the amount of 6 was increased tenfold, compared to the standard conditions. As expected, the enantioselectivity to the (R) alcohol decreased with the support basicity by up to 30% at (close to) full conversion of the ketone (see Table 5). Hydrogenation of CD always provided the (R) diastereomer on all catalysts, but the d.e. decreased remarkably from acidic to basic support. A comparison of the data in Tables 4 and 5 reveals that in case of Pt/Al₂O₃ and Pt/ Al_2O_3 -SiO₂ catalysts, the d.e. inverted from (S) to (R) in the presence of **6** and in this case, the differences are high. Interestingly, on Pt/Al₂O₃-Cs₂O, the adsorption mode of CD is barely influenced by any of the substrates **1–6**, as indicated by the similar

Table 4

The role of acid-base properties of the support on the diastereoselective hydrogenation of CD; d.e. was calculated at $21 \pm 7\%$ conversion of CDH₂.

Catalyst	Diastereo	Diastereomeric excess (%)				
	CD	CD with 1	CD with 2	CD with 3		
$\begin{array}{c} Pt/Al_2O_3\\ Pt/Al_2O_3-SiO_2\\ Pt/Al_2O_3-Cs_2O\\ Pt/Al_2O_3\ (ref.) \end{array}$	11 (S) 21 (S) 14 (R) 24 (S)	14 (S) 13 (S) 19 (R) 23 (S)	2 (S) 9 (S) 13 (R) 29 (S)	5 (<i>R</i>) 9 (<i>S</i>) 11 (<i>R</i>) 24 (<i>S</i>)		

Table 5

Reaction rates and selectivities in the hydrogenation of methyl benzoylformate (**6**) and CD (see Scheme 3). Standard conditions, 9.2 mmol **6**, 5-min reaction time.

Catalyst	CD with 6			6	
	Conv. (%)	TOF (h^{-1})	d.e. (%)	Conv. (%)	ee (%)
Pt/Al ₂ O ₃ Pt/Al ₂ O ₃ –SiO ₂ Pt/Al ₂ O ₃ –Cs ₂ O	59 67 27	16.2 57.3 7.8	43 (R) 69 (R) 21 (R)	100 97 100	86 (<i>R</i>) 92 (<i>R</i>) 62 (<i>R</i>)

diastereoselectivities $\{11-21\% (R)\}$. Another important point is that the TOF of CD hydrogenation in the presence of **6** increased dramatically on Pt/Al₂O₃-SiO₂.

All these observations derived from the diastereoselective hydrogenation of CD indicate a weak interaction between the aromatic ketone substrates and the alkaloid modifier.

4. Conclusions

In a series of recent papers, we addressed the role of metal–support interaction in the chemo- and enantioselective hydrogenation of ketones on Pt [14,15,41]. The present work extends this study from activated ketones to acetophenone and its aryl-substituted derivatives. Hydrogenation of this reactant class on the Pt–cinchona system is sluggish and characterized by poor enantioselectivities. Our study revealed that the enantioselectivities can be improved remarkably by replacing the widely used Pt/Al₂O₃ with Pt on an acidic support, such as Pt/Al₂O₃–SiO₂. A drawback of the acidic support is the lower reaction rate. Basic support exerts the opposite effect, decreases the ee, and enhances the hydrogenation rate. Although the results are promising, further effort is necessary to go beyond the mechanistic importance and explore the synthetic potential of acidic supports in enantioselective hydrogenations.

Analysis of the competing hydrogenation of the quinoline unit of CD during ketone hydrogenation provided another, mechanistically important result, namely the weak interaction between the chiral modifier and the aromatic ketone substrates. This observation has been made under truly in situ conditions that cannot yet be achieved with any theoretical or spectroscopic method. Seeing the present observations from a more general point of view, diastereoselective hydrogenation of CD appears to be a general and extremely useful new tool for studying the reaction mechanism of enantioselective hydrogenations under truly in situ conditions.

Acknowledgments

Financial support of this work by the Swiss National Science Foundation and ETH Research Grants TH-09 06-2 is kindly acknowledged.

References

- [1] B. Coq, Metal-ligand interactions in chemistry, Phys. Biol. 546 (1999) 49.
- [2] B. Coq, F. Figueras, Coord. Chem. Rev. 180 (1998) 1753.
- [3] G. Haller, D.E. Resasco, Adv. Catal. 36 (1989) 173.
- [4] K. Hayek, R. Kramer, Z. Paal, Appl. Catal., A 162 (1997) 1.
- [5] A.Y. Stakheev, L.M. Kustov, Appl. Catal., A 188 (1999) 3.
- [6] D.C. Koningsberger, M.K. Oudenhuijzen, J. de Graaf, J.A. van Bokhoven, D.E. Ramaker, J. Catal. 216 (2003) 178.
- [7] M.K. Oudenhuijzen, J.A. van Bokhoven, D.E. Ramaker, D.C. Koningsberger, J. Phys. Chem. B 108 (2004) 20247.
- [8] Y.Y. Ji, A.M.J. van der Éerden, V. Koot, P.J. Kooyman, J.D. Meeldijk, B.M. Weckhuysen, D.C. Koningsberger, J. Catal. 234 (2005) 376.
- [9] M.K. Oudenhuijzen, J.A. van Bokhoven, J.T. Miller, D.E. Ramaker, D.C. Koningsberger, J. Am. Chem. Soc. 127 (2005) 1530.
- [10] D.E. Ramaker, M.K. Oudenhuijzen, D.C. Koningsberger, J. Phys. Chem. B 109 (2005) 5608.
- [11] Y.Y. Ji, V. Koot, A.M.J. van der Eeirden, B.M. Weckhuysen, D.C. Koningsberger, D.E. Ramaker, J. Catal. 245 (2007) 415.
- [12] A.Y. Stakheev, Y. Zhang, A.V. Ivanov, G.N. Baeva, D.E. Ramaker, D.C. Koningsberger, J. Phys. Chem. C 111 (2007) 3938.
- [13] D.E. Ramaker, M. Teliska, Y. Zhang, A.Y. Stakheev, D.C. Koningsberger, Phys. Chem. Chem. Phys. 5 (2003) 4492.
- [14] B. Schimmoeller, F. Hoxha, T. Mallat, F. Krumeich, S.E. Pratsinis, A. Baiker, Appl. Catal., A 374 (2010) 48.
- [15] F. Hoxha, B. Schimmoeller, Z. Cakl, A. Urakawa, T. Mallat, S.E. Pratsinis, A. Baiker, J. Catal. 271 (2010) 115.
- [16] T. Mallat, E. Orglmeister, A. Baiker, Chem. Rev. 107 (2007) 4863.
- [17] M. Bartók, Curr. Org. Chem. 10 (2006) 1533.
- [18] D.Y. Murzin, P. Maki-Arvela, E. Toukoniitty, T. Salmi, Catal. Rev. Sci. Eng. 47 (2005) 175.
- [19] F. Zaera, J. Phys. Chem. C 112 (2008) 16196.

- [20] T. Bürgi, A. Baiker, Acc. Chem. Res. 37 (2004) 909.
- [21] M. Studer, H.U. Blaser, C. Exner, Adv. Synthesis Catal. 345 (2003) 45.
- [22] M. von Arx, T. Mallat, A. Baiker, Topics Catal. 19 (2002) 75.
- [23] P.B. Wells, A.G. Wilkinson, Top. Catal. 5 (1998) 39.
- [24] B. Török, K. Balàzsik, G. Szöllösi, K. Felföldi, M. Bartók, Chirality 11 (1999) 470.
- [25] A. Perosa, P. Tundo, M. Selva, J. Mol. Catal. A: Chem. 180 (2002) 169.
- [26] S. Basu, H. Paul, C.S. Gopinath, S. Bhaduri, G.K. Lahiri, J. Catal. 229 (2005) 298.
- [27] S. Basu, M. Mapa, C.S. Gopinath, M. Doble, S. Bhaduri, G.K. Lahiri, J. Catal. 239 (2006) 154.
- [28] R. Hess, T. Mallat, A. Baiker, J. Catal. 218 (2003) 453.
- [29] R. Hess, A. Vargas, T. Mallat, T. Bürgi, A. Baiker, J. Catal. 222 (2004) 117.
- [30] R. Hess, F. Krumeich, T. Mallat, A. Baiker, Catal. Lett. 92 (2004) 141.
- [31] H.Y. Cheng, J.M. Hao, H.J. Wang, C.Y. Xi, X.C. Meng, S.X. Cai, F.Y. Zhao, J. Mol.
- Catal. A: Chem. 278 (2007) 6. [32] C.F. Yang, H.Y. Jiang, J. Feng, H.Y. Fu, R.X. Li, H. Chen, X.J. Li, J. Mol. Catal. A: Chem. 300 (2009) 98.
- [33] H.Y. Jiang, C.F. Yang, C. Li, H.Y. Fu, H. Chen, R.X. Li, X.J. Li, Angew. Chem., Int. Ed. 47 (2008) 9240.
- [34] D. Ferri, T. Bürgi, J. Am. Chem. Soc. 123 (2001) 12074.
- [35] K.A. Avery, R. Mann, M. Norton, D.J. Willock, Top. Catal. 25 (2003) 89.
- [36] R.J. LeBlanc, W. Chu, C.T. Williams, J. Mol. Catal. A: Chem. 212 (2004) 277.
- [37] F. Zaera, Acc. Chem. Res. 42 (2009) 1152.
- [38] S. Lavoie, M.A. Laliberté, P.H. McBreen, J. Am. Chem. Soc. 125 (2003) 15756.

- [39] E. Schmidt, W. Kleist, F. Krumeich, T. Mallat, A. Baiker, Chem. Eur. J. 16 (2010) 2181.
- [40] E. Schmidt, T. Mallat, A. Baiker, J. Catal. 272 (2010) 140.
- [41] E. Schmidt, F. Hoxha, T. Mallat, A. Baiker, J. Catal. 274 (2010) 117.
- [42] G. Szöllösi, P. Forgó, M. Bartók, Chirality 15 (2003) S82.
- [43] H.U. Blaser, H.P. Jalett, D.M. Monti, A. Baiker, J.T. Wehrli, Stud. Surf. Sci. Catal. 67 (1991) 147.
- [44] H.U. Blaser, H.P. Jalett, W. Lottenbach, M. Studer, J. Am. Chem. Soc. 122 (2000) 12675.
- [45] E. Schmidt, D. Ferri, A. Baiker, Langmuir 23 (2007) 8087.
- [46] M. Bejblova, P. Zamostny, L. Cerveny, J. Cejka, Collect. Czech. Chem. Commun. 68 (2003) 1969.
- [47] C.S. Chen, H.W. Chen, W.H. Cheng, Appl. Catal. A Gen. 248 (2003) 117.
- [48] S.D. Lin, D.K. Sanders, M.A. Vannice, Appl. Catal., A 113 (1994) 59.
- [49] R.V. Malyala, C.V. Rode, M. Arai, S.G. Hegde, R.V. Chaudhari, Appl. Catal., A 193 (2000) 71.
- [50] F. Hoxha, N. van Vegten, A. Urakawa, F. Krumeich, T. Mallat, A. Baiker, J. Catal. 261 (2009) 224.
- [51] E. Talas, L. Botz, J. Margitfalvi, O. Sticher, A. Baiker, J. Planar Chrom. 5 (1992) 28.
- [52] D. Ferri, S. Diezi, M. Maciejewski, A. Baiker, Appl. Catal., A 297 (2006) 165.
- [53] J. Muzart, Synthesis Stuttgart (1982) 60.
- [54] T. Komatsu, M. Mitsuhashi, T. Yashima, Impact of Zeolites and Other Porous Materials on the New Technologies at the Beginning of the New Millennium, Pts a and B, vol. 142, 2002, p. 667.