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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*

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ABSTRACT

The influence of acidic and basic supports on the enantioselective hydrogenation of acetophenone and its aryl-substituted derivates was studied. The Pt/Al_2O_3, $Pt/Al_2O_3–SiO_2$, and $Pt/Al_2O_3–Cs_2O$ 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 $Pt/Al_2O_3–SiO_2$, and pro(*R*) on $Pt/Al_2O_3–Cs_2O$ 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).

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, 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 SiO_2 and Cs_2O, respectively. The catalysts were prepared by flame spray pyrolysis to minimize the disturbing effect of impurities originating from the catalyst synthesis [14,15]. The enantioselectivity 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/Al_2O_3 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

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* Corresponding author. Fax: +41 44 632 11 63.
E-mail address: baiker@chem.ethz.ch (A. Baiker).

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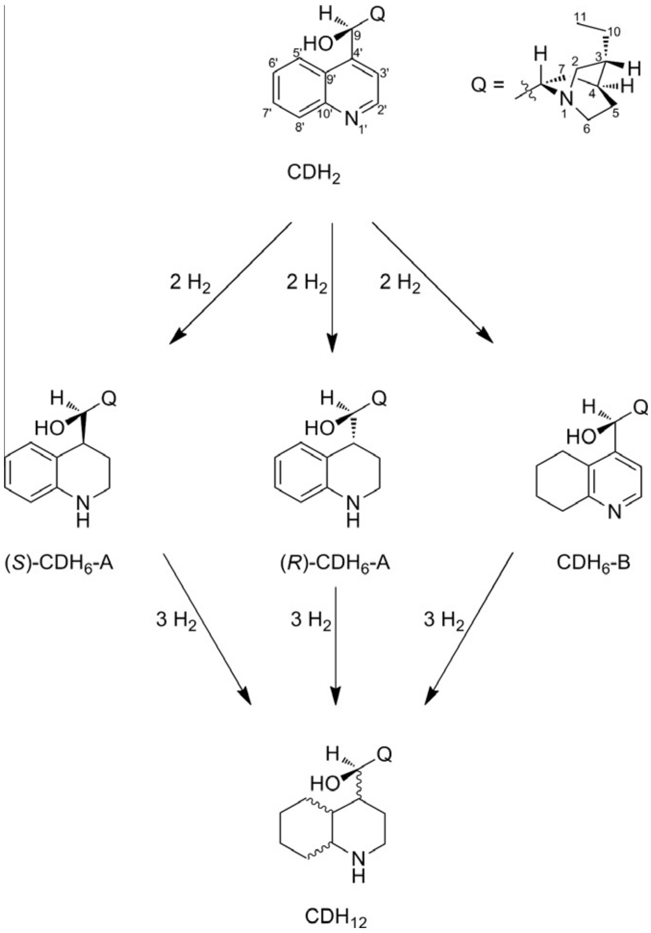
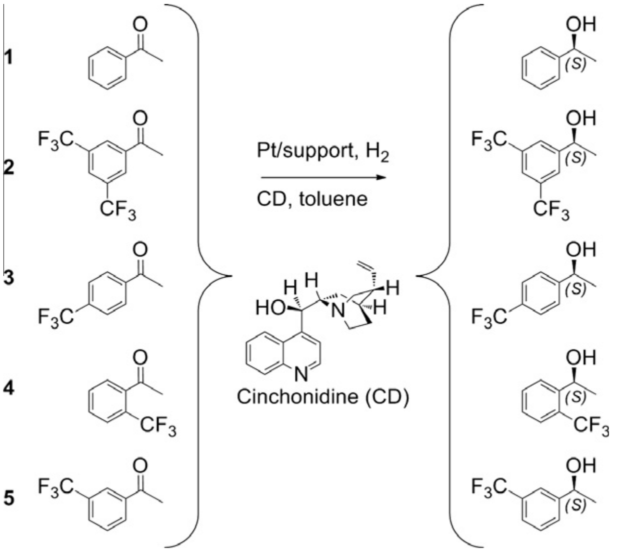
acetophenone, the enantioselectivity rarely exceeds 20% [24,25]. Basu et al. [26,27] achieved up to 49% ee on MCM-41-supported Pt, but the enantioselectivity dropped with the conversion irreversibly, probably due to agglomeration and deactivation. Note also that XPS analysis revealed the presence of $PtCl_2$ beside Pt in the catalyst; thus, the higher ee cannot simply be attributed to the support acidity, since reduction of $PtCl_2$ to Pt under reaction conditions produces HCl. Aryl-substitution of acetophenone in *m*- or *p*-position with electron-withdrawing groups (F, CF_3, and ester functions) increased the reaction rate and ee, while electron-releasing 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 chemo- and 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].

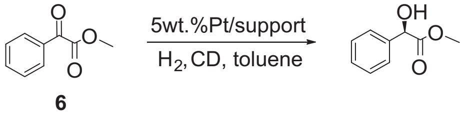
In this study, we report the hydrogenation of acetophenone and some selected ring-substituted derivatives (Scheme 2). From the flame-made $Pt/Al_2O_3–SiO_2$ and $Pt/Al_2O_3–Cs_2O$ catalyst series mentioned previously [15], we used the most acidic and basic catalysts (22.5 wt.% SiO_2 and 10 wt.% Cs_2O in the alumina support, respectively), as representative examples, and compared their performance with those of the unmodified and a commercial reference Pt/Al_2O_3 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.



Scheme 1. Chemo- and diastereoselective hydrogenation of dihydrocinchonidine CDH_2.



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.

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%), bicyclohexyl (Fluka, ⩾99%), cinchonidine (CD, Fluka, ⩾98% alkaloid), methyl benzoylformate **6** (Acros, 99%), toluene (Acros, extra dry, water <30 ppm), and 5 wt.% Pt/Al_2O_3 (Engelhard 4759) as reference catalyst (acronym: Pt/Al_2O_3 (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