Available online at www.sciencedirect.com
SCIENCE DIRECT
Journal of Catalysis 239 (2006) 255–262
JOURNAL OF CATALYSIS
www.elsevier.com/locate/jcat

Steric and electronic effects in the enantioselective hydrogenation of activated ketones on platinum: Directing effect of ester group

Simon Diezi, Sven Reimann, N. Bonalumi, Tamas Mallat, Alfons Baiker *

Institute of Chemical and Bioengineering, Department of Chemistry and Applied Biosciences, ETH Zurich, Hönggerberg, HCI, CH-8093 Zurich, Switzerland

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

Available online 6 March 2006

Abstract

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

Keywords: Enantioselective hydrogenation; α-Ketoester; α-Hydroxyester; Cinchonidine; Quinine; *o*-Phenyl-cinchonidine; Pt/Al_2O_3; Mechanism

1. Introduction

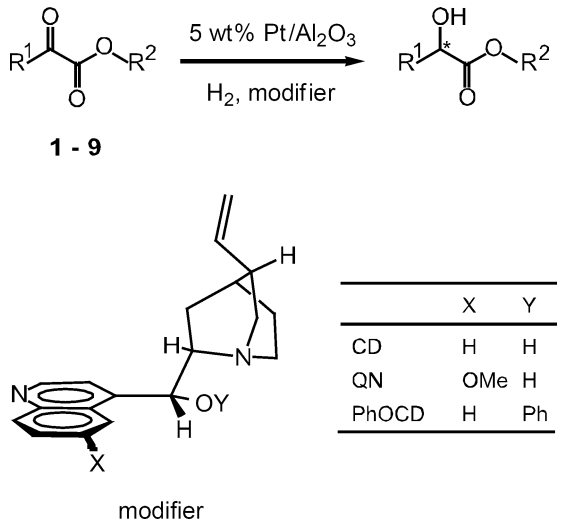
Optically active α-hydroxyesters and α-hydroxyacids are important building blocks for the synthesis of biologically active natural products and analogues thereof [1]. A viable option for this synthesis is the heterogeneous enantioselective hydrogenation of α-ketoesters on cinchona-modified Pt. Since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

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

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

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

0021-9517/$ – see front matter
doi:10.1016/j.jcat.2006.02.001



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

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

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

2. Experimental

2.1. Materials

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

2.2. Catalytic hydrogenation

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

2.3. Analyses

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

2.4. Vibrational circular dichroism spectroscopy

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