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Rhodium-catalyzed enantioselective hydrogenation of ketopantolactone

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Abstract

Hydrogenation of ketopantolactone was investigated on a 5 wt.% Rh/Al_2O_3 catalyst modified by cinchonidine (CD) and its *O*-methyl (MeOCD) and *O*-phenyl (PhOCD) derivatives. Weakly polar solvents, moderate pressure, and relatively high modifier/substrate ratios were advantageous for enantioselection. Chiral modification resulted in significant rate acceleration. The major enantiomer was (*R*)-pantolactone in the presence of CD and MeOCD, while an inversion was observed when using the bulky PhOCD. The similar ees measured with CD and MeOCD indicated that the OH function of CD is not involved in the enantioselection. The nonlinear behaviour of CD–PhOCD mixtures is probably due to the weaker adsorption of the latter modifier on rhodium. The highest ee achieved in this study with CD was 40%, less than half of that reported for CD-modified platinum. The lower efficiency of the rhodium–cinchona system is attributed partly to the weaker adsorption of the modifier and the faster hydrogenation of the quinoline ring of the alkaloid resulting in a gradual loss of enantioselectivity at high pressures.

Keywords: Ketopantolactone; Asymmetric; Hydrogenation; Rh/Al_2O_3; *O*-methyl-cinchonidine; *O*-phenyl-cinchonidine; Nonlinear phenomenon

1. Introduction

In the asymmetric hydrogenation of C=O and C=C bonds soluble chiral Ru and Rh complexes offer the highest enantioselectivities [1,2]. In contrast, in heterogeneous catalysis the most effective catalysts are the Ni–tartaric acid [3–5], the Pt–cinchona [6–10], and the Pd–cinchona systems [11–15]. Reports on the application of chirally modified Ir [16,17], Ru [18], and Rh are sporadic and these catalysts are in most cases inferior to Ni, Pt, or Pd. Recently, cinchona-modified Rh has been used in the hydrogenation of ethyl pyruvate [19–22], fluorinated ketones [23] and hydroxyketones [24], but good ees up to 80% were achieved only in the last case.

The synthesis of *R*-pantolactone, an intermediate in the production of pantothenic acid (Vitamin B family) and a constituent of coenzyme A, by asymmetric hydrogenation of ketopantolactone (Scheme 1) is a practically important process [25]. The reaction has been extensively studied using chiral Rh, Ru, Cr, and Ir complexes that afford at best close to 99% ee [26–31]. Chiral heterogeneous catalysts are less efficient so far. Nevertheless, under optimized conditions CD-modified Pt/Al_2O_3 affords better than 90% ee [32] and even the continuous operation mode is feasible [33]. Recently, the studies on platinum have been extended to synthetic chiral modifiers including various amines, amino alcohols, amino esters, amides, and diols but none of them are as good as CD [34,35]. Intrigued by the interesting properties of chirally modified Rh, observed recently in the hydrogenation of hydroxyketones [24], we explored here the enantioselective hydrogenation of ketopantolactone over a 5 wt.% Rh/Al_2O_3 modified by cinchonidine (CD) and its ether derivatives MeOCD and PhOCD (Scheme 1).

2. Experimental

2.1. Materials

Ketopantolactone (Roche, 99%), cinchonidine (CD, Fluka, 92%: 1% quinine, 7% quinidine as determined by HPLC at Fluka), toluene (Fluka, 99.7%), 1,4-dioxane (Merck, 99.5), tetrahydrofuran (Fluka, 99.5%), dichloromethane (J.T. Baker, 99.5%), *N*,*N*-dimethylformamide (Scharlau, 99%), 2-propanol (J.T. Baker, 99.5%), and acetic acid (Fluka, 99.8%) were used as received. *O*-methyl-cinchonidine (MeOCD) and *O*-phenyl-cinchonidine (PhOCD) [36] were synthesized as described before.

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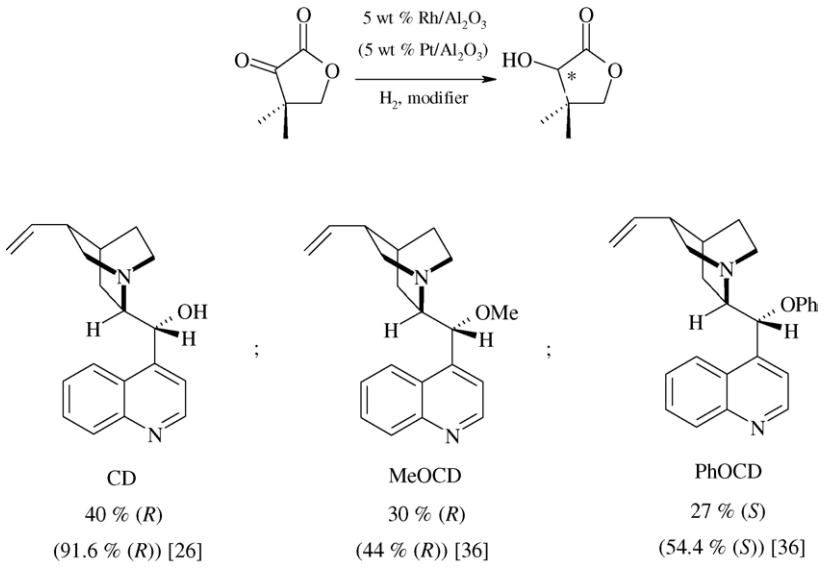

Scheme 1. Enantioselective hydrogenation of ketopantolactone in the presence of cinchonidine and its ether derivatives and the highest ees achieved with Rh/Al_2O_3 and Pt/Al_2O_3 (in brackets).

2.2. Catalytic hydrogenation

According to the standard procedure, the 5 wt.% Rh/Al_2O_3 catalyst (Engelhard 8001 ESCAT 34) was pre-treated before use in a fixed-bed reactor in flowing nitrogen at 400 °C for 30 min, followed by a reductive treatment in hydrogen for 1 h at the same temperature. After cooling to room temperature in hydrogen, the catalyst was immediately transferred to the reactor. Scanning transmission electron microscopy combined with energy-dispersive X-ray analysis revealed that during the pre-treatment big rhodium agglomerates of irregular shape were formed that hindered a reliable determination of the average particle size [23]. The catalyst was first contacted with the solvent, containing the modifier(s).

Hydrogenations were carried out in two different reactors. For screening the reaction conditions or testing different modifiers, a parallel pressure reactor system Endeavor™ (Argonaut Technologies) with eight 15 mL mechanically stirred stainless steel reactors, equipped with glass liners and PTFE covers, were used. The hydrogenations at 50 bar were performed in a 100 mL autoclave, equipped with a 50 mL glass liner and a PTFE cover, and a magnetic stirrer. Total pressure and hydrogen uptake were controlled by computerized constant volume–constant pressure equipment (Büchi BPC 9901).

Under standard conditions 20 mg pre-treated catalyst was added to 5 mL solvent containing 6.8 μmol modifier. After 5 min preadsorption period the reaction was started by introducing 236 mg (1.84 mmol) ketopantolactone. The reaction mixture was stirred (1000 rpm) under hydrogen at 10 bar and room temperature (23–25 °C), if not stated otherwise.

Conversion and enantioselectivity were determined by an HP 6890 gas chromatograph, using a Chirasil-DEX CB (Chrompack 7502, 25 m × 0.25 mm × 250 nm) capillary column. Conditions: split injection (250 °C, 20:1), He carrier gas (42 cm s^{-1}), FID detector (250 °C), 80–180 °C column temperature. Enantioselectivity is expressed as enantiomeric excess, ee (%) = 100 × (|$R - S$|)/($R + S$). Reproducibility of ee was within ±0.5%.

3. Results and discussion

3.1. Comparison of modifiers in different solvents

The enantioselectivities achieved with CD, MeOCD, and PhOCD at full conversion of ketopantolactone are presented Fig. 1 as a function of the empirical solvent parameter E_T^N [37]. The enantioselectivities were the highest in the weakly polar solvents tetrahydrofuran, dioxane, and toluene, and the lowest in acetic acid; in the latter solvent racemic product was formed in the presence of MeOCD. Generally, polar aprotic and protic solvents were detrimental to the enantioselection. A similar

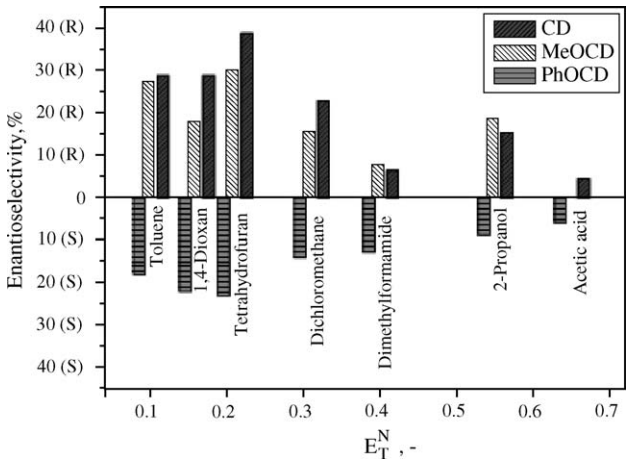

Fig. 1. Solvent effect on the enantioselectivity in the hydrogenation of ketopantolactone; standard conditions, ee at full conversion.

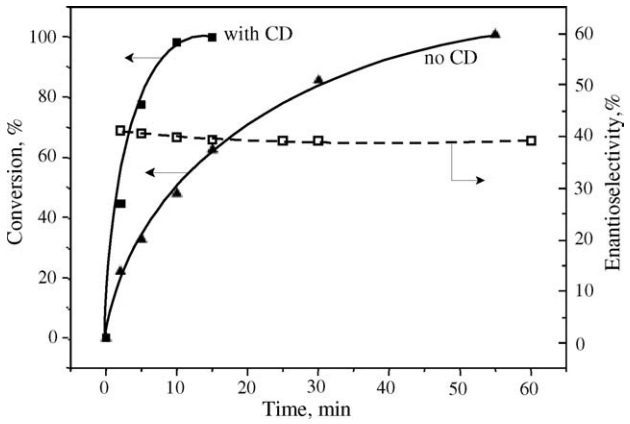

Fig. 2. Time-dependent changes of conversion and enantioselectivity during hydrogenation of ketopantolactone over Rh/Al_2O_3 in the presence and absence of CD; standard conditions, in tetrahydrofuran.

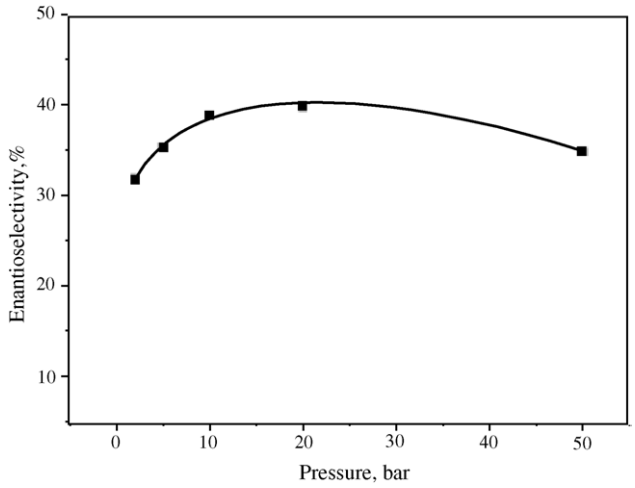

Fig. 3. Influence of hydrogen pressure on the enantioselectivity in the hydrogenation of ketopantolactone over Rh/Al_2O_3; standard conditions, in tetrahydrofuran, ee at full conversion.

negative effect of polar solvents on the enantioselectivity was observed in ketopantolactone hydrogenation on Pt [38], and ab initio calculations could not explain this behavior [39]. The probable reason is the complex effect of solvent on the conformation and adsorption of substrate and modifier [40] on the metal surface.

CD and MeOCD gave (*R*)-pantolactone in excess, and the comparable ees indicate that the OH function of CD is not involved in the substrate–modifier interaction leading to enantioselection. The enantioselectivity was inverted when MeOCD was replaced by PhOCD. The increasing bulkiness of the ether group had a similar effect on the hydrogenation of ketopantolactone and other activated ketones [36,41], α-hydroxyketons [42] and fluorinated acetophenones [43] on Pt/Al_2O_3, and also on Rh/Al_2O_3 [23,24]. ATR-IR spectroscopy and theoretical calculations indicated that introduction of the bulky phenoxy group changes the adsorption mode of the modifier and the size and shape of the chiral pocket available for the adsorption of the substrate [44].

3.2. Rate acceleration induced by CD

Addition of CD to the reaction mixture resulted in a significant rate acceleration compared to the unmodified reaction. The time-dependent changes of ketopantolactone conversion in the presence and absence of modifier and the ees are shown in Fig. 2. Addition of CD reduced the reaction time required for full conversion from 55 to 15 min. Since CD adsorbs strongly on the metal surface and occupies a large fraction of surface rhodium atoms, the real difference related to the actual number of available surface cites is expected to be much higher. With increasing conversion the enantioselectivity decreased only slightly (by 2%).

3.3. Catalyst pre-treatment

A reductive treatment at elevated temperature increases remarkably the enantioselectivity of the Pt–CD system [45] and the reversibility of this change by repeating the reductive and oxidative cycles indicates a surface restructuring favoring the enantioselection [46]. Under the standard conditions applied here, the Rh/Al_2O_3 catalyst was pre-treated at 400 °C in flowing hydrogen before hydrogenation of ketopantolactone. The control experiments revealed that in case of rhodium the reductive heat treatment has only a minor influence on the catalyst performance. In tetrahydrofuran the ee at full conversion increased from 37 to 39% and the conversion after 5 min reaction time increased from 73 to 78%.

3.4. Effect of pressure

The enantioselectivity increased with increasing pressure corresponding to higher surface hydrogen concentration, but reached a maximum at 20 bar (Fig. 3). The lower ee at high pressures is attributed to the rapid hydrogenation of the quinoline moiety of CD [24] that weakens the adsorption of the modifier on the metal surface. This behaviour is similar to that typical for the Pt–cinchona system in the hydrogenation of activated ketones [47], though the optimum is usually located at higher pressures due to the lower activity of Pt in the hydrogenation of the aromatic ring [48].

3.5. Role of modifier/substrate ratio

The influence of the modifier/substrate ratio on the catalytic performance is illustrated in Fig. 4. The ketopantolactone concentration was kept constant and the amount of CD was varied that results in a change also in the CD/Rh ratio. The maximum enantioselectivity (39–40%) was reached by using at least 2 mg CD, corresponding to a 3.7×10^{-3} modifier/substrate ratio. For comparison, a modifier/substrate ratio of only a few ppm was sufficient to induce the maximum enantioselectivity of the Pt/Al_2O_3–CD system [32,33]. The probable explanation for the huge difference is the weaker adsorption and faster destruction of CD on Rh, compared to Pt.

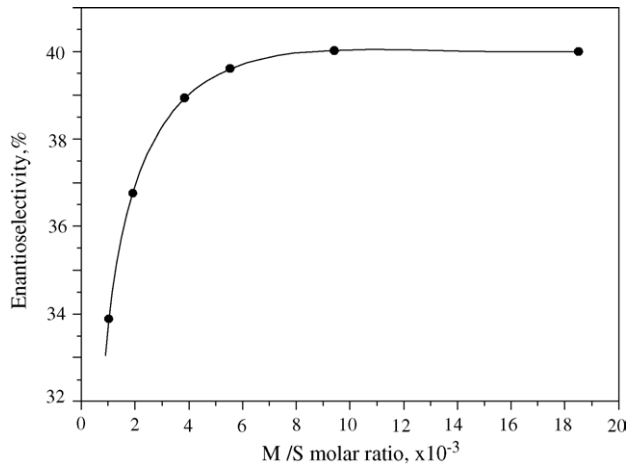

Fig. 4. Influence of modifier/substrate molar ratio (M/S) on the enantioselectivity; standard conditions, in tetrahydrofuran, ee at full conversion.

3.6. Nonlinear phenomenon with modifier mixtures

The nonlinear behaviour of mixtures of two modifiers is a powerful tool in heterogeneous catalysis for characterizing the relative adsorption strength of modifiers under in situ conditions [34,41,49,50]. The nonlinear phenomenon is considered as a deviation from the ideal behaviour assuming that the molar ratios of the modifiers in solution and on the metal surface are identical, they do not interact with each other, and the hydrogenation rates and ees are linear combination of those measured by the two modifiers alone.

For the hydrogenation of ketopantolactone on Rh/Al_2O_3 a significant deviation from the ideal behaviour was obtained when mixtures of CD and PhOCD were applied (Fig. 5). The two modifiers alone gave the opposite enantiomers of pantolactone in excess, though the average hydrogenation rates were similar: 30.1 and 30.7 mmol/h for CD and PhOCD, respectively. Nevertheless, when a modifier mixture containing 12% CD was applied, already (*R*)-pantolactone was formed in 3% excess (instead of the calculated 11.5% excess to (*S*)-pantolactone). A similar study on Pt/Al_2O_3 modified by mixtures of CD and PhOCD revealed remarkably bigger nonlinear behaviour: only 0.7% CD was enough to afford 33% (*R*)-pantolactone [36]. The probable explanation is that introduction of the bulky phenoxy group in PhOCD weakens the adsorption on both metals but the difference between the adsorption behaviour of CD and PhOCD is smaller on rhodium than on platinum.

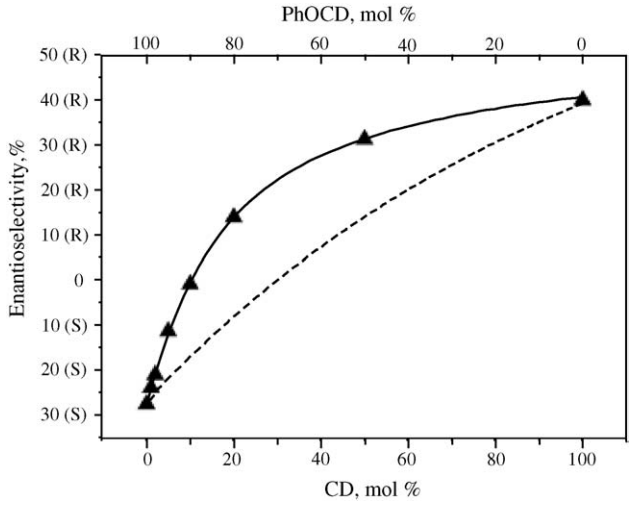

Fig. 5. Hydrogenation of ketopantolactone in tetrahydrofuran over Rh/Al_2O_3 modified by mixtures of CD and PhOCD; standard conditions, 20 bar, in tetrahydrofuran. The dashed line represents the ideal behaviour (calculated ee).

4. Conclusions

The study revealed that in the hydrogenation of ketopantolactone cinchona-modified Rh/Al_2O_3 and Pt/Al_2O_3 behave similarly but the latter is a more effective catalyst system (Scheme 1). Both catalysts afford (*R*)-pantolactone in excess in the presence of CD and MeOCD and an inversion is observed when MeOCD is replaced by the bulkier ether derivative PhOCD. The results indicate that the OH group of CD is not involved in the enantioselection. The lower enantioselectivity on rhodium is partly attributed to the faster hydrogenation of the quinoline ring of the modifiers that side reaction prevents the application of high pressures. For comparison, cinchona-modified platinum afforded only about 50% ee at low pressures and the optimized value above 90% ee was achieved at 70 bar [32]. A possible solution to this complication is the development of new synthetic modifiers that do not contain a reducible “anchoring” moiety.

Acknowledgement

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