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Effect of modifier structure in asymmetric 1-phenylpropane-1,2-dione hydrogenation

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Abstract

Sixteen chiral catalyst modifiers including the natural cinchona alkaloids cinchonidine, cinchonine and quinine together with their several analogues were studied in the hydrogenation of 1-phenylpropane-1,2-dione over a 5% Pt/Al_2O_3 catalyst at 10 bar H_2 and 15 °C. The influence of the different functional parts of the cinchona alkaloid on the reaction rate, enantio and regioselectivity and diol distribution was investigated. The modifier hydroxyl group in C-9 position is crucial for achieving high enantioselectivity. Replacement of the 9-OH group with a methyl ether results in a complete loss of enantioselectivity for cinchonidine and quinine, whereas an inversion of enantioselectivity was observed for the cinchonine-based modifiers. The role of the absolute configuration at C-8 and -9, the bicyclic quinuclidine part and aromatic system of the cinchona alkaloid on the reaction kinetics was studied as well. Acetic acid is detrimental for enantioselectivity in the hydrogenation of 1-phenylpropane-1,2-dione to the corresponding hydroxyketones whereas in the second hydrogenation step from hydroxyketones to diols, high enantiomeric excesses are observed. The results obtained demonstrate the principal dissimilarity in the enantiodifferentiating mechanism between the well-investigated α-keto esters and vicinal diketones.

Keywords: Enantioselective hydrogenation; Chiral modifiers; Cinchonidine; 1-Phenylpropane-1,2-dione; Platinum catalyst

1. Introduction

The mechanism of asymmetric induction over chirally modified metal surfaces has been extensively studied. Most of the hitherto-reported investigations have focused on supported Pt and Pd catalysts modified by cinchona alkaloids [1–6]. Despite the recent progress in the field, the nature of the chiral site and the enantiodifferentiating reactant–modifier–metal interactions remain largely unknown and speculative. Suitable experimental techniques and theoretical methods for in situ monitoring and description of asymmetric hydrogenation over a real chirally modified supported metal catalyst under actual operating conditions do not yet exist. Thus, empirical determination of modifier structure–selectivity correlations is still the most frequently pursued approach for investigating the mechanism of heterogeneous enantioselective hydrogenation [7–10]. Studies on the influence of modifier structure on reaction rate and enantioselectivity provide valuable information for understanding and construction of experimentally feasible reaction mechanisms. Hydrogenation of vicinal diketones including butane-2,3-dione [11–13], hexane-3,4-dione [11], cyclohexane-1,2-dione [14], 1,2-diphenyl-1,2-dione [15], hexane-2,3-dione [11], and 1-phenylpropane-1,2-dione (A) [16,17] over chirally modified Pt catalysts represents an extension to the Orito et al. reaction [18] providing in some cases high enantiomeric excesses (ee) of the corresponding chiral alcohols. For asymmetrically substituted vicinal diketones, such as A, the reaction is inherently complex as the presence of two reactive keto groups raises issues of both regio and enantioselectivity. At high conversions, a product mixture consisting of four

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different hydroxyketones and four diols may be obtained, as illustrated in Scheme 1. Some of the products obtained in the hydrogenation of A, are important as chiral building blocks for the synthesis of pharmaceutically active substances, e.g. the main product (*R*)-1 (phenylacetylcarbinol, PAC) (Scheme 1) is utilized in the synthesis of ephedrine [19].

Some evident mechanistic analogies exist between the hydrogenations of vicinal diketones and α-keto esters [1–6] over chirally modified catalysts. In both cases, the dependence of rate and enantioselectivity on the catalyst properties (pretreatment, activation, structure) and modifier concentration are similar. However, there are also significant differences, e.g. the lack of overall rate acceleration in the enantioselective hydrogenation, the detrimental role of acetic acid and the influence of C-9 OH group of cinchonidine are characteristic for the diketone hydrogenation while not observed in the hydrogenation of keto esters.

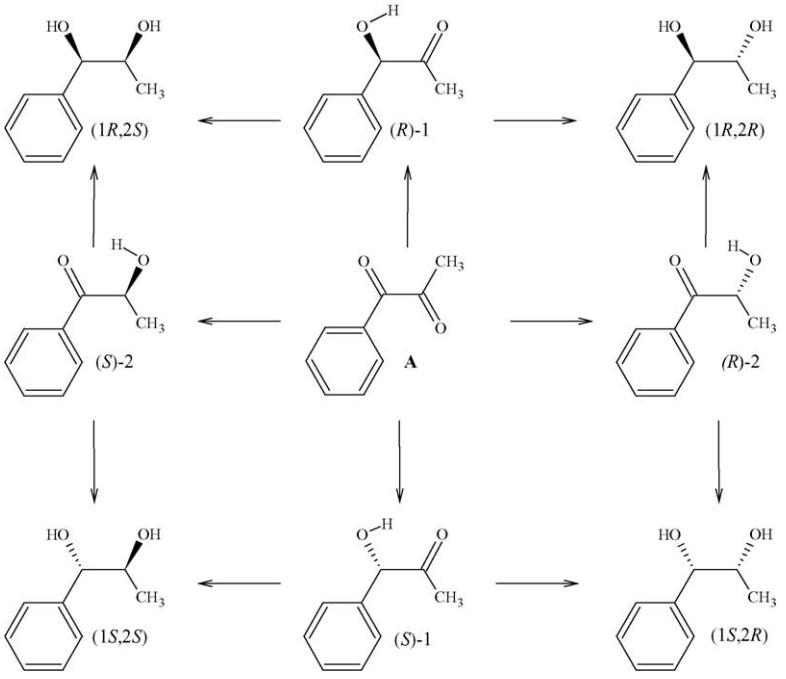
In previous work, we observed slightly improved enantiocontrol in the hydrogenation of A to (*R*)-1 by use of a cinchonidine derivative with sterically demanding substitution in the 11-position of the modifier [20]. In ethyl acetate, the hydrogenation of A over Pt/Al_2O_3 modified by 11-(triethoxysilyl)-10,11-dihydrocinchonidine resulted in an increase of ee from 56 to 70% in comparison to cinchonidine, indicating that distal modifier substitution in the C10–11 region may influence both the enantioselectivity and hydrogenation rate. Also, we were able to obtain higher enantioselectivities than observed for the parent modifier Cd. In α-keto ester hydrogenation, the influence of modifier structure has recently been elucidated in detail by Blaser and coworkers by use of several structurally modified cinchona alkaloid derivatives [9,10].

The aim of the present study was to investigate the effect of chiral modifier structure on the enantiodifferentiation in 1-phenylpropane-1,2-dione (A) hydrogenation over chirally modified Pt. Sixteen different chiral modifiers including Cd, Cn, quinine (Qn) and their closely related analogues or derivatives (Scheme 2), many of which were recently evaluated in α-keto ester hydrogenations [9] were employed in order to clarify the modifier structure–selectivity-activity relationships in toluene and/or acetic acid.

2. Experimental

2.1. Catalyst and chemicals

A commercial 5 wt.% Pt/Al_2O_3 catalyst (Strem Chemicals, 78–1660) was used in the hydrogenations (BET specific surface area 95 $m^2\,g^{-1}$, the mean metal particle size 8.3 nm (XRD), dispersion 40% (H_2 chemisorption), the mean catalyst particle size 18.2 μm (Malvern)). Catalyst characterization has been described in detail previously [16]. 1-Phenylpropane-1,2-dione (Aldrich, 22303-4, 99%) was vacuum-distilled before using. Toluene (J.T. Baker, 8077, >99.5%), acetic acid (J.T. Baker, 6052, 99.9%), cinchonidine (Fluka, 27350, 98%), quinine (Aldrich, 14,590-4, 90%, remainder hydroquinine), hydroquinine (Aldrich, 337714-1G, 98%), cinchonidine hydrochloride (C-0894), cinchonine (Fluka, 27370, 85%, remainder 15% dihydrocinchonine) were used as received. The synthesis and characterization of



Scheme 1. Reaction scheme of 1-phenylpropane-1,2-dione (A) hydrogenation.