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Inversion of enantioselectivity in the 2,2,2-trifluoroacetophenone hydrogenation over Pt-alumina catalyst modified by cinchona alkaloids

Kornél Szőri [a], Katalin Balázsik [a], Szabolcs Cserényi [b], György Szőllősi [a,*], Mihály Bartók [a,b,*]

[a] Stereochemistry Research Group of the Hungarian Academy of Sciences, Dóm tér 8, H-6720 Szeged, Hungary
[b] Department of Organic Chemistry, University of Szeged, Dóm tér 8, H-6720 Szeged, Hungary

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ABSTRACT

The enantioselective hydrogenation of 2,2,2-trifluoroacetophenone (TFAP) was investigated over Pt-cinchonidine (CD) and Pt-cinchona alkaloid derivatives chiral catalysts not yet studied in this reaction, such as Pt-cinchonine (CN), Pt-quinine (QN), Pt-quinidine (QD), Pt-β-isocinchonine (β-ICN), Pt-cinchona-C9-methyl ethers, Pt-hydroquinine- and -hydroquinidine-4-chlorobenzoate. As a result of the studies in toluene, toluene + trifluoroacetic acid, 2-propanol, acetic acid and dichloromethane, relationships were established between the structure and concentrations of the chiral modifiers in different solvents and the reaction rates and enantioselectivities (ee). As compared with the enantioselective hydrogenation of other activated ketones low to medium ee values and low rate enhancements were obtained which is probably due to the structure of the adsorbed intermediate complexes responsible for enantioselection. It has been confirmed by NMR measurements that, under the conditions of the hydrogenations, TFAP is present in the form of H-bonded dimers and oligomers in the liquid phase, which accounts for the low hydrogenation rate. When CN, QD and their C9-ether and ester derivatives were used as modifiers inversion of the sense of the enantioselection was observed, which amounted up to ee 30% over the cinchonine methyl ether and β-ICN modified catalysts. The present study is the first to report inversion of the enantioselectivity over Pt-CN chiral catalyst in the hydrogenation of an activated ketone.

1. Introduction

One of the most important characteristics of the heterogeneous catalytic reactions of organic compounds is their selectivity [1–5]. Special attention is given to the enantioselectivities of the asymmetric heterogeneous catalytic reactions such as the hydrogenations of ketones over Raney-Ni catalysts modified with tartaric acid [6–8] and Pt catalysts modified by cinchona alkaloids. The latter reaction was discovered by Orito and co-workers in 1979 (Scheme 1) [9,10]. These two hydrogenations are the most intensively studied enantioselective heterogeneous catalytic reactions, also exploited on an industrial scale [11]. The increased significance of the latter reaction is in great part due to the high enantioselectivities (above 90%) observed [12–19], also underlined by numerous reviews (e.g. since 2006: [20–23]) discussing and evaluating the steady flow of novel results in the enantioselective hydrogenation of activated ketones.

As shown in Scheme 1 and Fig. 1, the presence of C8(*S*)-C9(*R*) cinchonas (CD, QN) promote the formation of (*R*)-α-hydroxy carboxylic acid esters in excess, whereas the use of C8(*R*)-C9(*S*) cinchonas (CN, QD) lead to excess of (*S*)-α-hydroxy carboxylic acid esters. The term "inversion of enantioselectivity" in the title of the manuscript implies the formation of products with opposite configurations, i.e. excess formation of (*S*)-products in the presence of CD or QN and that of (*R*)-products by using CN or QD as modifiers.

Out of various activated ketones (α-ketoesters, α-ketoacids, α-ketoamides, α-diketones, α-ketoacetals), the hydrogenation of those containing α-C–F bonds have also been studied in the Pt-cinchona alkaloid catalytic system. Results achieved to date in experiments on fluoroketones have been reported in refs. [14,15,24–34], among others. Since this manuscript describes new results observed in the hydrogenation of 2,2,2-trifluoroacetophenone (TFAP), it appears expedient to briefly review the results of the enantioselective hydrogenation of TFAP, including, naturally, the inversion of enantioselection in these reactions (Scheme 2).

The first model compound representing an activated ketone containing a C–F bond was TFAP [14,24,25,35–38]. Baiker and co-

* Corresponding authors.
E-mail addresses: szollosi@chem.u-szeged.hu (G. Szőllősi), bartok@chem.u-szeged.hu (M. Bartók).

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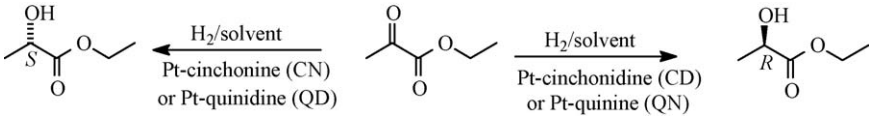


Scheme 1. Enantioselective hydrogenation of an α-keto ester over cinchona alkaloid modified Pt catalyst.

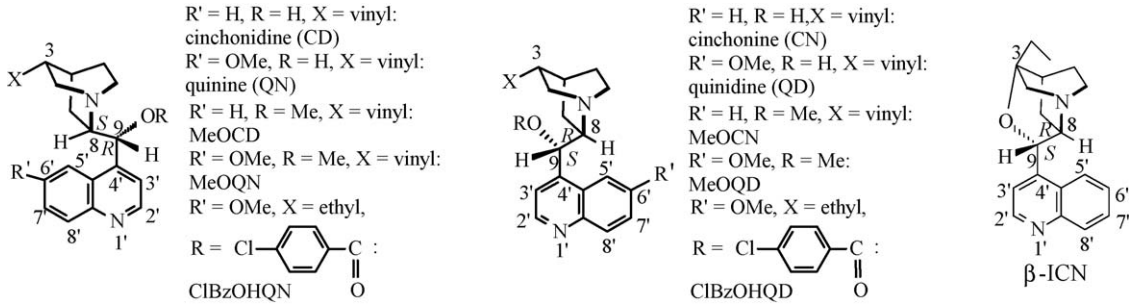


Fig. 1. The structure of the chiral modifiers (parent cinchona alkaloids and derivatives).

workers extensively investigated and reported in the literature the hydrogenation of TFAP, including the effect of solvent, H_2 pressure, water and acid additives, mass transport, modifier structure and the initial transient period [14,24,35,36]. During the optimization of TFAP hydrogenation, outstandingly high enantiomeric excess (ee) was achieved at 273 K, under 10 bar H_2 pressure, in the presence of CD modifier and trifluoroacetic acid (TFA) additive in toluene [14]. These studies employed CD and two of its derivatives (CD × HCl, MeOCD) as chiral modifiers. To the best of our knowledge no experimental observations have been made on the use of other cinchonas such as CN, QN, QD or other derivatives. In Ref. [14] the authors have mentioned that in the hydrogenation of TFAP in toluene inversion of the sense of the enantioselectivity was observed: ... the use of MeOCD as the chiral modifier led to an almost complete loss of ee and even to a small ee in favour of the opposite (*S*)-enantiomeric product [14].

Inversion of the enantioselectivity in the hydrogenation over cinchona modified catalysts had already been reported from 1993 [14,39–42], but due to the low ee values involved – these results aroused little attention. Since the publication of Refs. [26,43], however, the inversion of enantioselection has become a preferred research objective, as evidenced by the works published for example in 2004 [27–30,44,45]. These results yielded important new information regarding the reaction mechanism. The inversion was the first significant experimental observation indicating that in enantioselective hydrogenations over cinchona alkaloids modified catalysts, it is not the C8 chiral centre of the alkaloid that controls the sense of the chiral induction [43]. The experimental data obtained using α-isocinchonine (α-ICN), β-isocinchonine (β-ICN) [46–48] and *O*-phenyl-cinchonidine [28,31] demonstrated the decisive role of the conformation and adsorption mode of modifier molecules in directing the chiral induction.

In view of the preliminaries briefly described above, it was evident that, in addition to the Pt-CD catalyst, experiments should also be performed on the enantioselective hydrogenation of TFAP using catalyst systems not yet studied, i.e. Pt-CN, Pt-QN, Pt-QD and Pt-ether and ester derivatives of cinchona alkaloids.

2. Experimental

2.1. Materials

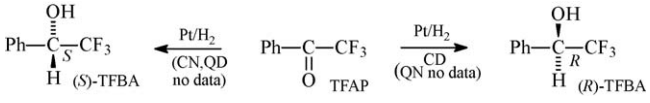
TFAP, cinchona alkaloids (CD, CN, QN, QD and ClBzOHQN, ClBzOHQD derivatives), solvents (toluene = T, acetic acid = AcOH, 2-propanol = 2P, dichloromethane = DCM) and TFA were purchased from Fluka and Aldrich and used as received. TFAP was distilled under vacuum before use. The C9-OMe cinchonas (MeOCD, MeOCN, MeOQN) were synthesized as in Ref. [16]. β-ICN was synthesized according to the method described in Ref. [46]. 5% Pt-alumina catalyst (Engelhard 4759) was used after pretreatment. From the efficient pretreatment methods of this catalyst (high temperature [49,50], ultrasound [25,51]) we have used the former method. The catalyst was pretreated in a fixed-bed reactor by flushing with 30 cm^3 min^{-1} He at 300–673 K for 30 min then hold in 30 cm^3 min^{-1} H_2 flow at 673 K for 100 min. After cooling to room temperature in H_2, the catalyst was flushed with He for 30 min and was stored under air until use.

2.2. NMR measurements

The ^1H and ^{13}C NMR spectra of 0.5 cm^3 total volume samples containing different amounts (vol.%) of TFAP were recorded on an Bruker Avance DRX 500 NMR instrument (^1H at 500 MHz, ^{13}C at 125 MHz) in d_6-benzene solution using $(CH_3)_4Si$ or the solvent signals as internal standard.

2.3. Hydrogenation measurements

The hydrogenations were carried out either under atmospheric pressure in a conventional glass hydrogenation apparatus or under elevated pressure using stainless steel autoclave and glass liner. In



Scheme 2. Enantioselective hydrogenation of TFAP (TFBA = α-trifluoromethyl-benzylalcohol).