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Influence of achiral amine additives on the Orito's reaction

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ABSTRACT

In enantioselective hydrogenation of ethyl pyruvate and methylbenzoyl formate over Pt/Al_2O_3 catalyst achiral tertiary and secondary amine additives increased both the reaction rate and the enantiomeric excess using low cinchonidine concentration and toluene as a solvent. However, no beneficial effect of primary amine was observed. Results of circular dichroism spectroscopic measurements proved that in the presence of both secondary and tertiary amines the virtual concentration of chiral modifier increased in accordance with the shift of dimer–monomer equilibrium of cinchonidine. The effect of achiral amines was more pronounced at ethyl pyruvate than at methylbenzoyl formate substrate.

1. Introduction

The Orito's reaction [1], *i.e.* the heterogeneous catalytic asymmetric hydrogenation of activated ketones over cinchona alkaloid-supported Pt catalyst system has both theoretical [2–5] and practical importance [6–8] in the preparation of various enantiopure alcohols. This reaction has been reviewed by different authors [2–5,9]. Heterogeneous catalytic reactions provide several economic and technical advantages, namely the easy separation of catalyst and the possibility of continuous operating methods [10]. Furthermore cinchona alkaloids such as quinine, quinidine, cinchonidine, cinchonine are low cost natural products and are available in sufficient quantities. Under optimized reaction conditions, large scale of α-ketoesters can be successfully hydrogenated achieving enantiomeric excess (ee) over 90% [11,12]. High ee values (75–85%) can be obtained even at very low alkaloid concentration ($\sim 10^{-5}$ M) [13,14].

Due to the complexity of this catalyst system in spite of the tremendous efforts done in the past three decades there are still many open questions. Characteristic feature of this reaction is that due to the intrinsic reactivity of activated ketones, besides their hydrogenation different side reactions take place both in the liquid phase and on the catalyst surface. In this respect semiketal formation, oligomerization (condensation, polymerization), hydrolysis, transesterification, decarboxylation [9] can be mentioned. The negative effect of side reactions is very pronounced at low concentration of chiral modifier ($\sim 10^{-5}$ M). All these facts significantly influence and partly obscure the main reaction and make difficult to understand the mechanism of the Orito's reaction.

It has been documented, that cinchonidine and its derivatives undergo hydrogenation over platinum catalyst forming dihydro-, tetrahydro- hexahydro- and further hydrogenated derivatives [15–17]. Among the hydrogenation products 10,11-dihydrocinchonidine is the most active chiral modifier, however hexahydro and dodecahydro derivatives show much less activity or they are practically inactive in asymmetric induction [18,19]. Recently it has been found that the hydrogenation of cinchonidine is influenced by the substrate itself. [20].

Amine additives can influence the heterogeneous catalytic hydrogenation reactions in different ways. Upon hydrogenation of acetophenone to 1-phenyl-ethanol over supported palladium catalyst, basic additives can suppress the ethylbenzene formation [21,22]. In the hydrogenation of unsaturated carboxylic acids over cinchona modified palladium catalysts in wet dioxane or methanol, the use of benzylamine has led pronounced increase in the ee and the reaction rate [23–25]. These results have been explained with the promotion of desorption of saturated products from the modified sites. However, in toluene the addition of amine was not required due to the weaker acidity of the product in this solvent resulting in smooth desorption [26].

Cinchona alkaloids have two main structural units, the quinoline ring and the quinuclidine part. These amines as additives were used as a tool in modeling the behavior of the chiral modifier [27].

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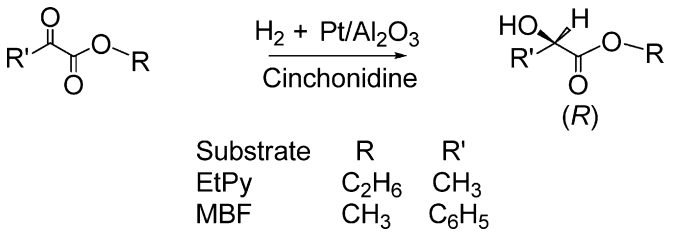

Scheme 1. Hydrogenation of activated ketones (EtPy = ethyl pyruvate, MBF = methylbenzoyl formate).

In the racemic hydrogenation of ethyl pyruvate (EtPy), achiral amine additives have resulted in significant rate increase [28]. The magnitude of the rate enhancement increased with the pK_a of the additive. Quinuclidine and quinuclidinol increased the rate of racemic hydrogenation of methyl pyruvate in ethanolic solution 6.5-fold, while quinoline led only to slight increase [27]. Rate enhancement by tertiary amines, especially quinuclidine, was attributed to the interaction with the half-hydrogenated form of the α-ketoester [27]. However, at very low initial concentration of EtPy (0.025 M) and relative high amount of quinuclidine (3.4×10^{-4} M) the reaction rate dropped by 50% what was attributed to the competitive adsorption [29].

In the enantioselective hydrogenation of EtPy over 9,10-dihydrocinchonidine-Pt/Al_2O_3 catalyst system upon using toluene as a solvent, the *achiral* quinoline additive has resulted in a small increase in ee [30], while in another study it has increased both the rate and ee values [31]. However, the effect of quinoline was observed only at low concentration of cinchonidine. It has been concluded that quinoline replaces cinchonidine from the Pt surface and this replacement reduces the chance of cinchonidine to be hydrogenated by its quinoline ring [30]. In the enantioselective hydrogenation of EtPy over cinchonidine-Pt/graphite system in dichloromethane the presence of *achiral* quinuclidine additive has resulted in an increase in the rate of the formation of chiral product with only slight depression of ee [32]. It was supposed that cinchonidine and quinuclidine acted cooperatively in decoupling the pyruvate ester polymer and increased the fraction of productive surface. In contrast, at very low initial concentration of EtPy the reaction rate dropped significantly upon addition of *achiral* quinuclidine to cinchonidine [29]. At low cinchonidine concentration (~10^{-5} M) in aprotic solvent *achiral* tertiary amine additives (ATAs) such as triethylamine, DABCO (1,4-diazabicyclo[2.2.2]octane), quinuclidine, 1-methyl piperidine increased significantly both reaction rate and ee [14,33,35]. The so-called "ATA effect" was attributed to the virtual increase of the cinchonidine concentration [33]. Nevertheless, this beneficial effect disappeared upon using high cinchonidine concentration (10^{-4} M) or 9-methoxy cinchonidine as chiral modifier and alcohols as solvent. Earlier results suggested that cinchonidine could exist in its dimer form in the liquid phase [36–39]. Circular dichroism spectroscopic measurements provided evidences for the suppression of dimer formation in the presence of ATAs in aprotic solvents [14,35]. However, upon using ethanol as a solvent or 9-methoxy-cinchonidine as chiral modifier the circular dichroism signal characteristic for the formation of dimer was not observed [14,35,38]. Consequently, the "ATA" effect can be attributed to shifting the dimer–monomer equilibrium, *i.e.* to the virtual increase of the cinchonidine concentration.

The aim of this work was to extend the study using other types of amine additives (such as secondary and primary amines), other substrates and to get further information about the achiral amine effect in the Orito's reaction. The investigated systems are described in Scheme 1.

2. Experimental

2.1. Materials

The achiral amines such as *n*-butylamine, ethylmethylamine, diisobutylamine, triethylamine were purchased from Aldrich and used as received. Piperidine (Reanal, Hungary) was distilled prior to use. The hydrogenation reactions were performed in toluene (Carlo Erba) solvent treated with Na_2CO_3. Water content of toluene measured by Metrhom 684 KF Coulometer was 190 ppm. EtPy substrate (Fluka) was distilled under vacuum prior to use. Methylbenzoyl formate (MBF) substrate and cinchonidine chiral modifier were purchased from Fluka and used as received. Alumina supported Pt catalyst CatASium F214 (Degussa) of 5 wt.% Pt content (CO chemisorption = 1.5 cm^3 CO/g catalyst, Pt dispersion: 26.3%, low-pressure activity test: 192 cm^3 H_2/(min g_{cat}) [40]) was used as received. This catalyst does no need high temperature hydrogen treatment prior to its use.

2.2. Kinetic investigations

Hydrogenation of EtPy and MBF was carried out in a 300 cm^3 SS-autoclave at 20 °C. The pressure of H_2 and the rate of agitation were 50 bar and 1000 rpm, respectively. The concentration of cinchonidine was varied in the range of 6×10^{-6}–1.0×10^{-4} M. The initial concentration of the substrates was 0.25–0.85 M. Concentration of achiral amine additives was 1×10^{-4} M. Both injection and premixing techniques were used to introduce the chiral modifier and the amine additives. Further details can be found elsewhere [34,35]. Samples were taken at different reaction time and analyzed by a GC using a capillary column (Supelco BETA DEX 225) and flame ionization detector. The enantioselectivity is expressed as ee = ([R] – [S])/([R] + [S]). The ee_{max} means the highest enantiomeric excess value measured in a given reaction. The ee_{end} values were measured at the termination of the reaction. First order rate constant k_1 were calculated from experimental points measured in the first 3–10 min described earlier [41,42]. The k_1 values were reproducible within 10% providing the use of the same batch of substrates. The ee values in the conversion-ee dependencies had a relative error in the range of 5%, but the shapes of these dependencies were completely reproduced. The slope of dependencies in the [R] – [S] *vs.* 2[S] coordinates gives the rate enhancement as the k_e/k_r ratio where k_e and k_r are rate constants for the enantioselective and racemic hydrogenation reactions running parallel in the same experiment [43].

2.3. MS measurements

An AB Sciex API 2000 (AB Sciex, Toronto, Canada) triple-quadrupole mass spectrometer equipped with Turbo Ion Spray source was used. The probe was operated at a sprayer voltage of 5 kV. The electrospray source temperature was set to 300 °C. Curtain gas of 0.14 MPa (20 psi), nebuliser gas of 0.28 MPa (40 psi), turbo gas of 0.14 MPa (20 psi) were applied. A 10 μl sampling loop was fitted to the injector; and the flow rate was 200 μl/min using acetonitrile solvent. The mass spectrometer was operated in positive MRM scan mode with a declustering potential (cone voltage) of 30 V. Two MRM transitions were monitored: 186/112 for EtPy and 86/30 for piperidine. The collision energy was 40 eV and the dwell time was 300 ms for each transitions.

Samples for MS measurements were prepared by using similar reactor set up and reaction conditions as applied for kinetic investigation. Substrate concentrations 0.25 M of MBF and 0.85 M of EtPy were used. The concentration of achiral amine was 10^{-2} M. Sample preparation was carried out both in the absence and in the presence of cinchonidine. The duration of the reaction was 90 and 180 min