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Enantiodifferentiation in asymmetric sonochemical hydrogenations

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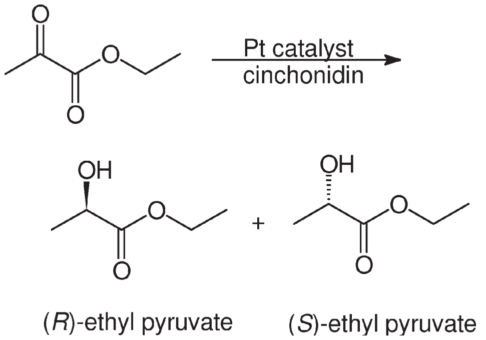
The effect of sonochemical pretreatment on the enantioselectivity of Pt/Al_2O_3–cinchonidine-catalyzed ethyl pyruvate hydrogenation was studied at different hydrogen pressures in various solvents, mainly in acetic acid. The sonochemical pretreatment of a commercial Pt/Al_2O_3–cinchonidine catalytic system in acetic acid resulted in enhanced enantioselectivity providing excellent ee values (97% ee) under mild and widely varied experimental conditions. Moreover, the application of ultrasonics provides a possibility of the catalyst recycling without regeneration. The catalyst was tested by transmission electron microscopy to determine the effect of the sonication on the metal particle size morphology.

Keywords: hydrogenation, enantioselective, Pt/Al_2O_3, cinchonidine, ethyl pyruvate, ultrasounds, particle size distribution

1. Introduction

The steadily increasing number of important chiral pharmaceuticals and agrochemicals provides significant actuality and potential for asymmetric synthesis including enantioselective hydrogenations [1]. Although the findings steps in the asymmetric hydrogenation of α-ketoesters over platinum catalysts were reported almost twenty years ago by Orito [2], the topic has still received significant attention in recent years [3]. The most popular model reaction in this field, the chiral hydrogenation of ethyl pyruvate (1), provides excellent enantioselectivity using cinchona alkaloids and supported platinum catalysts under hydrogen pressure [4a]; the highest ee obtained is 95% (dihydrocinchonidine, 5% Pt/Al_2O_3, AcOH, 100 bar) [4b]. The reaction also takes place in atmospheric systems, however, with moderate selectivity ($\sim$60% ee) [5]. Taking into account the importance of developing effective, chirally modified heterogeneous catalytic systems for enantioselective synthesis extensive efforts have been made and reviewed [6] to optimize the reaction conditions. Most experimental parameters were systematically studied such as the catalysts (metal, support, particle size, etc.) [6,7a], the structure and concentration of the modifier [6,7b,c], solvents [7d], mass-transfer limitations and hydrogen pressure [7e].



(1)

As one of the most promising techniques, the sonochemical activation was recently introduced among the tools of heterogeneous catalysis [8]. The method is highly efficient for the rate increase in the hydrogenation [8b,9a,b] and hydrosilylation of alkenes [9c]. Although Bönnemann and Braun [10a] recently described the enantioselective hydrogenation of ethyl pyruvate in quasi-homogeneous, sonochemically peptized platinum colloids (76–78% ee), the only report with respect to the application of ultrasounds in heterogeneous asymmetric hydrogenations has been published by Tai et al. [10b]. The hydrogenation of β-diketones and ketoesters catalyzed by tartrate-modified Raney-Ni resulted in increasing ee (up to 94%) [10b].

The major thrust of this work was to investigate the effect of ultrasonic irradiation on the enantioselective hydrogenation of ethyl pyruvate over Pt/Al_2O_3–cinchonidine catalyst. Here we report our unique observations concerning the effect of the sonochemical pretreatment on the enantioselectivity and the actual changes of the catalyst.

2. Experimental

Materials. Ethyl pyruvate used was of analytical grade and purchased from Fluka, while the solvents with minimum purity of 99.5% were Reanal and Fluka products. The cinchonidine used as modifier (minimum purity >98%) was purchased from Fluka. The organic compounds including the reactant and the solvents were freshly distilled before

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each run. The catalyst used in the hydrogenations was 5% Pt/Al_2O_3 (Engelhard, 40655).

Ultrasonic pretreatment. The presonication of the 5% Pt/Al_2O_3 (Engelhard) catalyst was carried out at 25 °C in a 20 ml glass reactor equipped with a hydrogen inlet and a rubber septum. Before sonication, acetic acid was added to the catalyst–cinchonidine system and flushed with high-purity oxygen-free hydrogen (Whatman model 75-34 hydrogen generator) for 15 min, then the irradiation was proceeded for the required time (usually 30 min) in a closed hydrogen atmosphere. A Realsonic 40SF ultrasonic bath (20 kHz, 30 W) was used for the presonication. The reactor used for pretreatment was immersed in a center position in the ultrasonic bath, and the solvent level was under the water bath level with 2 cm.

Enantioselective hydrogenation of ethyl pyruvate. The hydrogenation was performed in an atmospheric batch reactor or in a Berghof Bar 45 autoclave at room temperature (25 °C). The catalytic system including the catalyst, solvent and modifier (50 mg of 5% Pt/Al_2O_3 (Engelhard), 5 mg of cinchonidine and 5 ml of solvent) was activated (1 bar or the reaction hydrogen pressure), and the reactant (0.250 ml of ethyl pyruvate) was introduced. The sonochemically activated catalysts were prepared as described above and transferred into the autoclave in hydrogen atmosphere and then the reactant introduced. After that, the autoclave was flushed with hydrogen several times and filled to the desired pressure and stirred (1300 rpm) for the required reaction time (usually 1.5 h).

The product identification and the enantiomeric excess (ee% $= \{([R]-[S])/([R]+[S])\} \times 100$) were monitored by gas chromatography (HP 5890 GC-FID, 30 m long Cyclodex-B capillary column). The ee values were reproducible within 1%.

Transmission electron microscopy (TEM). Measurements were performed with a Philips CM10 electron microscope at 90 kV at a magnification of 300,000. Catalysts were tested before and after various sonication periods. Samples were dispersed in toluene and mounted and air-dried on a plastic film supported by a Formvar grid. The metal particle size distribution was determined, and the mean metal particle diameters were calculated as average of individual diameters ($\sum n_i d_i / \sum n_i$, $n = 10^3$) from the magnified TEM images.

3. Results and discussion

First, the reaction was run in different solvents in order to find nearly-optimized conditions for a systematic study with ultrasounds. In accordance with the literature [7d], acetic acid was found to be the best medium producing the highest ee value in atmospheric system (ee for (R)-ethyl lactate: AcOH – 80.2, toluene – 58.1, EtOH – 57.5) without sonication. The same preference was obtained under 10 bar hydrogen pressure, with higher difference between toluene and EtOH. As a result, the systematic investigations to describe the effect of sonochemical activation on the enantioselectivity of asymmetric pyruvate hydrogenation were carried out in acetic acid. In addition, to get better insight into the nature of the sonochemical activation, the ee values were determined at different hydrogen pressures as a function of insonation time. The collected results including the simple stirred reactions are shown in figure 1.

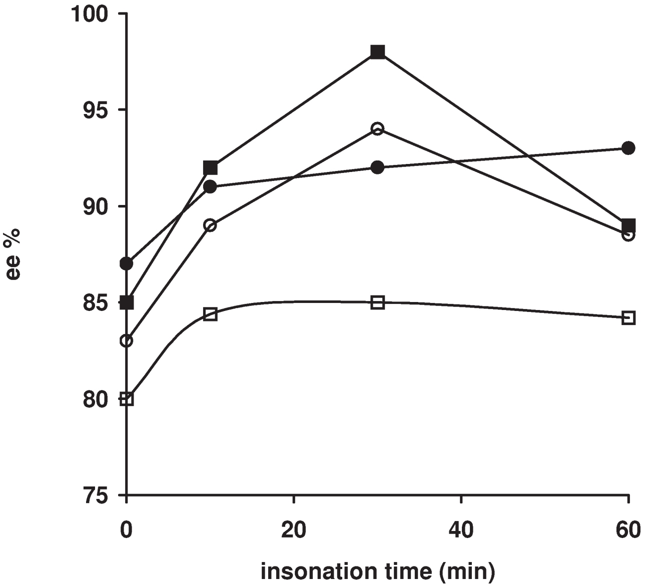

Figure 1. Enantiomeric excess versus insonation time functions at different hydrogen pressures for the enantioselective hydrogenation of ethyl pyruvate over a 5% Pt/Al_2O_3–cinchonidine catalyst system in acetic acid at 25 °C ((☐) 1 bar, (■) 10 bar, (○) 20 bar, (●) 25 bar).

As shown, the sonochemical treatment increased the ee values and resulted in excellent enantioselectivities. The best selectivity was obtained under 10 bar after 30 min insonation (97.1±1% ee), although the ee observed in 20 bar reaction is just slightly lower (94%). The influence of the presonication does not depend significantly on the pretreatment time at 1 and 25 bar, however, the insonated catalysts produced higher ee by 5–6%. In contrast, the ee% versus insonation time functions show a maximum character under 10 and 20 bar, the maxima were observed after 30 min insonation time. The ee data and the TEM results (*vide supra*) are tabulated in table 1.

In the light of the usual industrial requirements, the reuse of catalyst was also tested under 10 bar. Before the first reaction, the usual pretreatment was applied as described in section 2 (30 min sonication and subsequent activation), however, no further ultrasonic treatment was carried out between the following reactions. The reaction mixture was removed, and the catalyst was washed three times with acetic acid. Fresh solvent and modifier was then introduced, and the system was activated in hydrogen. The originally insonated sample (30 min) produced quite high enantioselectivity during the first three runs, satisfactory in the fourth experiment, and significant ee decrease only after the fifth reaction was observed. It should be noted that the

Table 1
The mean particle diameters of the 5% Pt/Al_2O_3 catalyst as received and after ultrasonic irradiation as well as the corresponding enantioselectivity data for enantioselective hydrogenation of ethyl pyruvate at 10 bar and 25 °C, and the results obtained after cinchonidine-free sonication (the values are the average of three experiments).[a]

Entry	Insonated catalyst	Sonication (min)	d_{TEM} (nm)	Hydrogen pressure (bar)	ee (%)
1	5% Pt/Al_2O_3–CN[b]	0	13.7	10	85.2
2	5% Pt/Al_2O_3–CN	10	6.6	10	92.0
3	5% Pt/Al_2O_3–CN	30	3.9	10	97.1
4	5% Pt/Al_2O_3–CN	60	4.6	10	89.2
5	5% Pt/Al_2O_3[c]	30	–	1	81.4
6	5% Pt/Al_2O_3–CN	30	–	1	85.0
7	5% Pt/Al_2O_3[c]	30	–	10	85.0

[a] ee values were determined at 100% conversion.
[b] CN, cinchonidine.
[c] Cinchonidine was added after sonication.

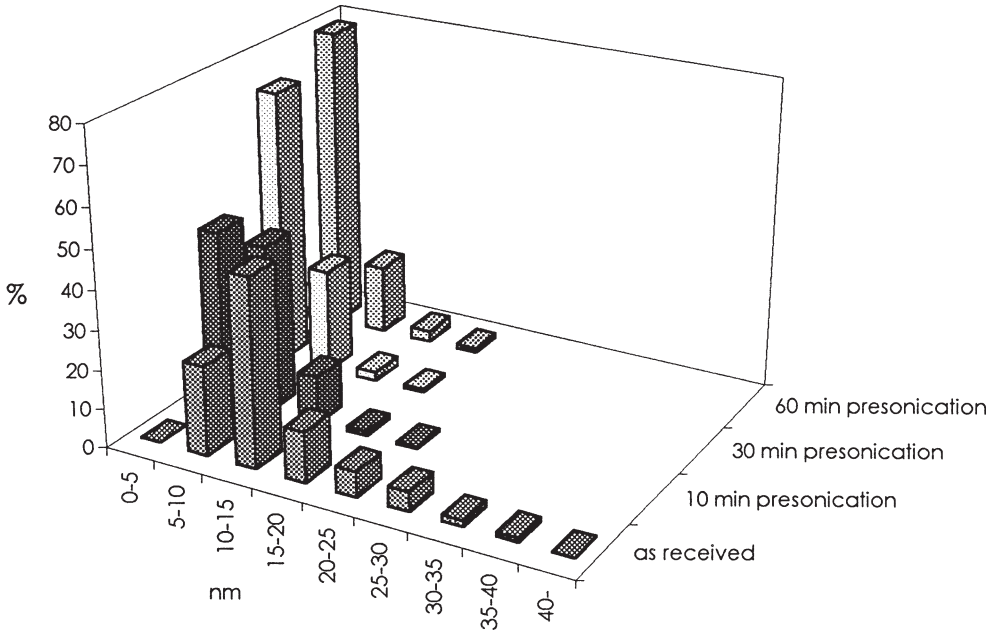

Figure 2. Metal particle size distribution of the 5% Pt/Al_2O_3 catalyst as received and after ultrasonic irradiation.

application of the sonication after the fifth reaction cannot regenerate the catalyst completely. The results are collected in table 2.

These results suggested an important contribution of ultrasounds to the formation of an effective Pt–cinchonidine catalytic system. Since ultrasonics strongly affect the particle size of solids [8], it was an obvious necessity to study the catalyst as well. The metal particle size of the catalysts was determined by transmission electron microscopy (TEM). On the basis of TEM images, the summarized metal particle size distributions of the Pt/Al_2O_3 catalysts as received and after ultrasonic irradiation are displayed in figure 2.

As additional representative data, the mean metal particle diameters obtained after different presonication time as well as the corresponding ee values (at 10 bar) for numeric comparison are collected in table 1.

Table 2
Enantioselectivity data for enantioselective hydrogenation of ethyl pyruvate over 5% Pt/Al_2O_3–cinchonidine catalyst system in acetic acid at 10 bar and 25 °C obtained in catalyst-recycling experiments.

Reaction	Sonication (min)	Activation[a] (min)	Conversion	ee (%)
1	30	60	100	97.4
2	–	60	100	93.8
3	–	60	100	93.4
4	–	60	100	89.2
5	–	60	95	83.6
6	30	60	100	84.1

[a] 10 bar hydrogen at 25 °C.

Although the exact theoretical basis of the beneficial effect of ultrasonic irradiation on the enantioselectivity is not clearly understood yet, two major points should be emphasized. First, as a rule, ultrasonics decrease the particle size in systems containing solid particles [11a] independently from the material applied. This phenomenon has been described recently [11b] in the case of supported metal catalysts as well. This is exactly what we observed: the metal particle size of the catalysts monotonically decreased as a function of the insonation time until 30 min (table 1). Furthermore, the size distribution (figure 2) became more homogeneous to provide quasi-uniform metal surface for the catalyst.

This effect of the decreasing metal particle size has already been studied in conventional systems on the ethyl pyruvate hydrogenation [7b]. Blaser and coworkers prepared supported platinum catalysts of various dispersions and found that smaller metal crystallites result in higher enantioselectivity [7b] up to ∼25% dispersion. Working under sonochemical conditions, the same tendency was observed, the ee increased with metal particle size decrease. However, this increase stops at 3.9 nm metal particle diameter. This suggests that the metal particle size plays an important role in the enantiodifferentiation. The sonication through particle size decrease may optimize catalyst dispersion and morphology. On the other hand, as an important secondary effect it should be noted that the modifier–catalyst interaction is more effective as the lower ee obtained after cinchonidine-free presonication indicates (table 1, entries 3–7 and 5,6). As a consequence, the presence of cinchonidine during the insonation process is crucial. As an additional contribution of the ultrasounds to the selectivity enhancement, the removal of the *in situ* formed blocking surface moieties should also be considered.

4. Conclusions

In conclusion, the sonochemical pretreatment of a commercial Pt/Al_2O_3–cinchonidine catalytic system in acetic acid resulted in enhanced enantioselectivity in ethyl pyruvate hydrogenation providing excellent ee values (97% ee) under mild and widely varied experimental conditions. This improved enantiodifferentiation indicates that sonochemical methods may open new intriguing possibilities in asymmetric heterogeneous hydrogenations.

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