Heterogeneous asymmetric reactions. 29. Enantioselective hydrogenation of ethyl benzoylformate over dihydrocinchonidine-modified platinum–alumina catalyst in acetic acid

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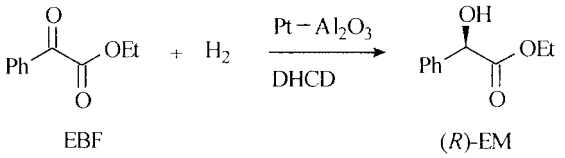
The enantioselective hydrogenation of ethyl benzoylformate to (*R*)-ethyl mandelate over dihydrocinchonidine (DHCD)-modified Pt/Al_2O_3 catalyst in acetic acid was studied as a function of modifier concentration, hydrogen pressure and reaction temperature. The maximum enantioselectivity obtained under optimized conditions (DHCD concentration 1 mmol dm^{-3}, 25 bar H_2, 0 °C, AcOH/toluene 1 : 1) was 98% ee. The difference between the rates of racemic and enantioselective hydrogenation was less significant than in the case of ethyl pyruvate. This indicates that the high reaction rate in the enantioselective heterogeneous hydrogenation of α-ketoesters is not a necessary condition of the chiral induction.

KEY WORDS: hydrogenation; enantioselective; Pt–alumina; dihydrocinchonidine; ethyl benzoylformate; ethyl mandelate.

1. Introduction

Utilization of chiral molecules in a variety of fields has lent exceptional significance to the research of asymmetric syntheses [1]. Owing to the well-known advantages of heterogeneous catalytic reactions, enantioselective catalytic hydrogenation has become a frequent choice of subject for such studies [2]. Chiral α-hydroxycarboxylic acids and their derivatives are important building blocks for organic syntheses and may be produced in outstandingly high ee under the conditions of heterogeneous catalysis [3–6]. Ever since the recognition of the reaction [7], studies on the hydrogenation of α-ketoesters have often contributed valuable new information to the understanding of the reaction mechanism. The most widely studied model compound has been ethyl pyruvate [3,4]. Although many details of the reaction mechanism of the hydrogenation of EtPy have not been elucidated, an important observation is that the modified reaction is faster than the unmodified one, and furthermore that reaction rate and enantioselectivity change in parallel (*i.e.* low reaction rates are associated with low ee and high reaction rates with high ee) [3,4,8].

In contrast to EtPy, the hydrogenation of ethyl benzoylformate (EBF) has been very little studied [7,9,10], in spite of the fact that the reaction was already described by Orito *et al.* [7] as an example for the enantioselective hydrogenation of α-ketoesters and an ee of 84% was achieved. Hydrogenation of EBF also yields a very valuable building block, ethyl-(*R*)- and (*S*)-mandelate (EM) (see scheme 1). It has to be noted that homogeneous catalytic procedures utilizing chiral boranes have also been developed for the enantioselective reduction of EBF [11,12].



EBF (*R*)-EM

Scheme 1.

The present work describes the results of our observations made during the optimization of the enantioselective hydrogenation of EBF to (*R*)-EM on Pt/Al_2O_3 catalyst modified with dihydrocinchonidine (DHCD).

2. Experimental

2.1. Materials

Cinchonidine (CD), AcOH, MeOH, EtOH and toluene were purchased from Fluka. EBF (Fluka) was distilled before use to attain 99.5% purity. DHCD was prepared by hydrogenation of CD (Pd/C, 1 N H_2SO_4/H_2O, 1 bar, 25 °C) and used after crystallization.

The catalyst used in the hydrogenations was a well-known reference catalyst 5% Pt/Al_2O_3 (Engelhard 4759: E 4759). It was subjected to a reductive heat

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treatment (400 °C, H_2 flow, cooling in flowing He) before reactions [13].

2.2. Hydrogenation

Hydrogenation was performed in an atmospheric glass batch reactor or in a Berghof Bar 45 autoclave. The catalytic system including the catalyst and 2 ml of solvent was purged three times with hydrogen, and after prehydrogenation (30 min), the calculated amount of modifier and 0.16 or 0.31 ml of EBF were introduced and stirred (1200 rpm) in the presence of hydrogen for the required reaction time. Standard conditions are: 25 mg E 4759, 2 ml AcOH, 0.1 mmole dm^{-3} DHCD, 1 bar H_2, 24 °C, 1200 rpm, 0.16 ml EBF. The quantification of conversion and ee are based on GC data. The product identification and the enantiomeric excess, $ee\% = ([R] - [S]) \times 100/([R] + [S])$, were monitored by gas chromatography (HP 5890 GC-FID, 30 m long Lipodex-A capillary column, uncertainty ±2%).

3. Results and discussion

Since ee for the chiral hydrogenation of EtPy could be significantly increased by optimizing the reaction conditions [3-6], it was expected that the ee value of 84%, achieved by Orito *et al.* [7] for EBF, could be similarly enhanced. We therefore initiated experiments to study the effects of DHCD concentration, hydrogen pressure and temperature on ee. Before describing the results it is important to note that reaction-rate measurements of the chiral hydrogenation of EBF proved to be much more difficult to reproduce than in the case of EtPy. In contrast, ee results were easily reproducible. Sound results could only be obtained when freshly pretreated catalyst and EBF purified by column chromatography were used. In the case of EBF, catalyst freshly activated on the day of the measurement had to be used, whereas in the case of EtPy, the pretreated catalyst retained its original activity even after storage for a week [13]. The best experimental data were selected for publication.

3.1. The effect of DHCD concentration

The pertinent experimental data on the reaction rates as the functions of the DHCD concentration are presented in table 1 and figure 1.

The experimental data in figure 1 reveal that the rate of hydrogen uptake in racemic hydrogenation is not significantly different from that of chiral hydrogenation as was the case with EtPy [3,4,14].

Another important difference relative to EtPy hydrogenation is that significantly longer reaction times and higher DHCD concentrations had to be employed in order to achieve high conversion and high ee values (figure 1). The difference is most probably accounted for by the adsorption tendencies of the two reactants and by the competition of EBF and DHCD adsorption [15]. The data in table 1 also confirm that an enantioselectivity of 93% can be achieved under very mild experimental conditions (hydrogen pressure: 1 bar, temperature: 0 °C) for preparation of (*R*)-EM. LeBlond *et al.* [15] achieved ee values over 92% in the case of ethyl pyruvate and 91% for ethyl 2-oxo-4-phenylbutyrate, under mild experimental conditions.

Table 1
Conversion and enantioselectivity as functions of DHCD concentration and temperature for hydrogenation of EBF to (*R*)-EM (25 mg E 4759, 1 bar H_2, 2 ml AcOH at 24 °C and 2 ml AcOH–toluene (1 : 1 in order to keep AcOH dissolved), 0.16 ml EBF, 1200 rpm)

DHCD (mmol dm^{-3})	Conversion (%)		ee of (*R*)-EM (%)	
	24 °C	0 °C	24 °C	0 °C
0	80	70	–	–
0.1	70	50	20	75
1	92	92	73	87
10	96	92	90	93

Note: Time of reaction 60 min, EBF = ethyl benzoylformate, EM = ethyl mandelate, DHCD = dihydrocinchonidine.

3.2. The effect of temperature and hydrogen pressure

The role of temperature [16,17] and hydrogen pressure [4,18] in the hydrogenation of α-ketoesters were first studied for EtPy and important conclusion were drawn. As far as we know, results obtained under the mild experimental conditions applied in this work (0 °C, 1 bar) have not been published before. Our experimental results are summarized in figures 2 and 3.

The experimental data clearly show that ee is favorably affected by decreasing temperature and increasing

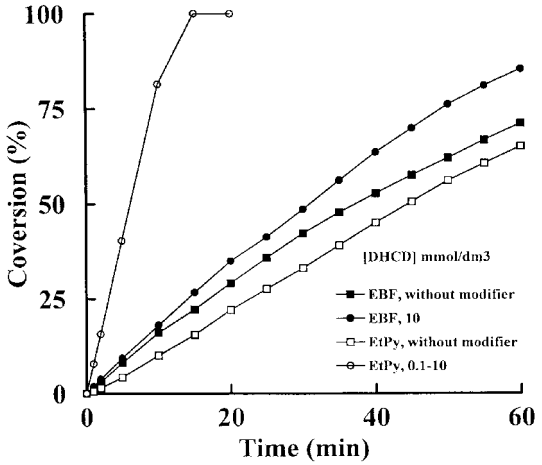

Figure 1. Enantioselective and racemic hydrogenations of ethyl pyruvate (EtPy) and ethyl benzoylformate (EBF) over a dihydrocinchonidine modified 5% Pt/Al_2O_3 catalyst (25 mg E 4759 catalyst, 1 bar hydrogen pressure, 24 °C, 0.1 ml EtPy, 0.16 ml EBF, 2 ml AcOH).

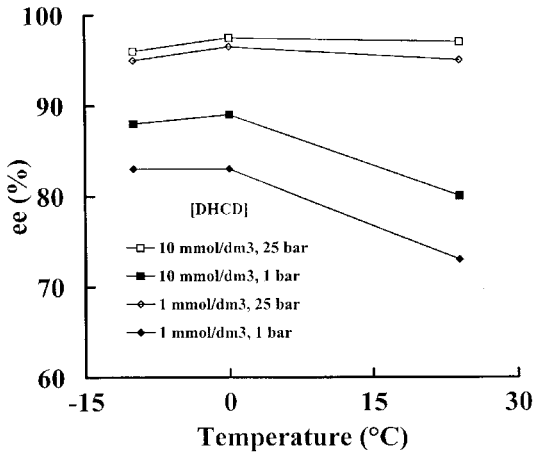

Figure 2. Effect of the DHCD concentration, temperature and H_2 pressure for the hydrogenation of EBF on optical yield (50 mg E 4759, 2 ml AcOH + 2 ml toluene, 0.31 ml EBF. For abbreviations, see table 1.

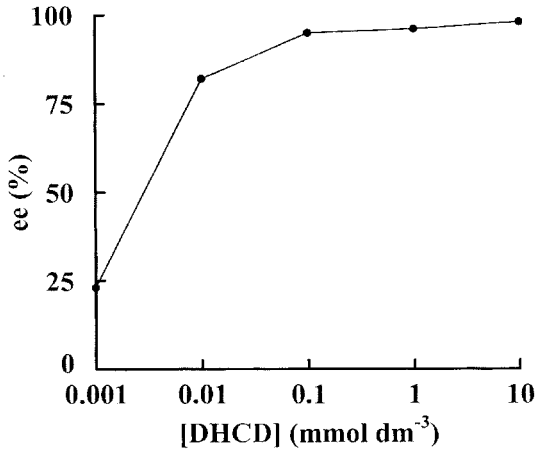

Figure 3. Effect of the DHCD concentration for the hydrogenation of EBF on optical yield at 0 °C and 25 bar H_2 pressure (50 mg E 4759, 2 ml AcOH + 2 ml toluene, 0.31 ml EBF. For abbreviations, see table 1.

hydrogen pressure; as a consequence, (*R*)-EM can be produced in an extremely high ee (98%). Accordingly, optimized conditions for preparation of (*R*)-EM are: DHCD concentration 1 mmol dm^{-3}, 25 bar H_2, 0 °C, AcOH/toluene 1:1, catalyst: E 4759 Pt-alumina (pretreated at 400 °C).

The favorable effect of temperatures below room temperature can be explained by a decrease in the hydrogenation rate of the quinoline skeleton of the DHCD. The favorable effect of higher hydrogen pressures is accounted for by the higher surface concentration of hydrogen.

4. Conclusions

According to our experiments on EBF, there is strong competition between DHCD and EBF in the course of adsorption, as a consequence of which higher DHCD concentrations are needed in order to achieve high ee. This is also clearly shown by the comparison of the reactant/DHCD ratio with that of EtPy. This ratio is 40 000 in the case of EtPy but only 2000 in the case of EBF. The rate-limiting step determining the reaction rate is presumably product desorption, since—due to the presence of the phenyl group—the (*R*)-ethyl-mandelate formed is strongly adsorbed on the surface of Pt. It is to be hoped that the basic mechanistic model developed by Baiker, Pfalz and Wells [3] for the interpretation of the enantioselective hydrogenation of EtPy will also be verified in the case of the chiral hydrogenation of EBF.

The case of EBF is a good example of the absence of a close correlation between the rate of enantioselective hydrogenation and high ee; in other words, ligand acceleration (heterogeneous ligand accelerated reaction) [19] does not play a special role in the realization of high enantioselectivity.

Acknowledgments

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