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Heterogeneous asymmetric reactions Part 25. On the pretreatment and prehydrogenation of Pt-alumina catalyst in the hydrogenation of ethyl pyruvate☆

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Abstract

The effect of the prehydrogenation on the enantioselective hydrogenation of ethyl pyruvate on the Pt-alumina catalyst (Engelhard 4759) pretreated in hydrogen at 673 K was studied by ESI-MS. It was established that in the concentration range used the hydrogenation of the quinoline skeleton of cinchonidine and dihydrocinchonidine takes place under relatively mild conditions (room temperature, 1 bar H_2 pressure), leading to a decrease in the optical yield attained (90%). In order to avoid this, it is necessary to prehydrogenate the pretreated catalyst in the absence of modifier and hydrogenation of ethyl pyruvate must be stopped approximately at 70% conversion.

Keywords: Enantioselective; Hydrogenation; Platinum-alumina; Pretreatment; Prehydrogenation; Ethyl pyruvate; Cinchonidine

1. Introduction

Studies on heterogeneous asymmetric catalytic reactions have been greatly accelerated in the past few years [1–4]. One of the best known heterogeneous asymmetric catalytic reactions is the enantioselective hydrogenation of α-ketoesters [5,6]. A model compound of the most wide-ranging studies is ethyl pyruvate (EtPy) which can be converted to (*R*)- and (*S*)-ethyl lactate (EtLt) with an enantioselectivity of 90–97% [7,8] on alumina-supported platinum catalyst modified with suitable cinchona alkaloids (Scheme 1).

Even in these days numerous publications reporting on the determination of the optimal parameters of (*R*)-EtLt production and on the elucidation of the reaction mechanism are published; some of these are called special attention to, also referring to the research laboratories involved [9–16].

The selection and pretreatment of the catalyst have been basic problems ever since the initial period of these studies [17–19]. The use of alumina-supported Pt is the result of widespread research. Based on the data in the literature, from several catalysts the one most often used is Engelhard 4759 (E 4759). The properties of this contact catalyst are the following: Pt-content, 5% (w/w); Pt dispersion, 22%; mean Pt particle size, 4.5 nm; support, γ-Al_2O_3; specific surface area, 168 $m^2\ g^{-1}$; mean pore diameter, 2 nm; specific pore volume, 0.27 $cm^3\ g^{-1}$.

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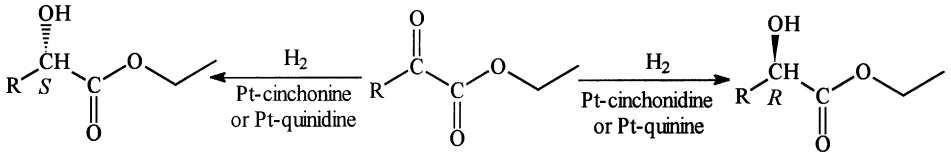


R = Me (ethyl pyruvate = EtPy), R = Ph (ethyl benzoylformate = EtBFT)

Scheme 1.

At the time of the discovery of the reaction, Orito et al. realized [20,21] that in order to achieve a favourable enantioselectivity, it is essential to pretreat the catalyst with hydrogen at 673 K. Based on later investigations, several possible explanations exist to give account for the positive effect of the reductive pretreatment (although experimental verification occasionally led to opposite conclusions): (i) pretreatment cleans up the surface of the catalyst by removing oxygen as well as impurities [5,18,20,21]; (ii) residual Pt-salts are converted to metallic Pt [22–24]; (iii) the average particle size of Pt increases [5,6,18,25]; (iv) the morphology of Pt particles, i.e. the distribution of exposed face, edge and corner atoms is also altered favourably [5,17,26,27]; (v) adsorbate-induced surface restructuring [27–29].

In the present paper our experiences regarding the pretreatment and prehydrogenation of E 4759 (to remove surface oxygen), obtained by electospray ionization mass spectrometry (ESI-MS) [30,31] are presented. These measurements made possible the selection of a method for catalyst pretreatment which ensures an enantioselectivity of 90% under mild conditions (room temperature; hydrogen pressure, 1 bar; cinchonidine concentration, 0.01 mM/l).

2. Experimental

2.1. Materials

Cinchonidine (CD), AcOH, MeOH and EtOH were purchased from Fluka. EtPy (Fluka) was distilled before use to attain 99.5% purity. 5% (w/w) Engelhard 4759 was pretreated before use in a fixed bed reactor by flushing with 30 ml min^{-1} helium at 300–673 K for 30 min and 30 ml min^{-1} hydrogen at 673 K for 100 min. After cooling to room temperature in hydrogen, the catalyst was flushed with helium for 30 min and was stored before use. Dihydrocinchonidine (DHCD) was prepared by hydrogenation of CD (Pd/C, 1 N H_2SO_4/H_2O, 1 bar, 298 K) and used after crystallisation.

2.2. Hydrogenation

Hydrogenation was performed in an atmospheric bath reactor or in a Berghof Bar 45 autoclave at room temperature (298 K). The catalytic system including catalyst and 2 ml of AcOH was purged three times with hydrogen and after prehydrogenation (30 min), the calculated amount of modifier and 0.2–2 ml of EtPy were introduced and stirred (1200 rpm) in the presence of hydrogen for the required reaction time (usually 20–50 min). The product identification and the enantiomeric excess [ee% $= ([S]-[R]) \times 100/([R]+[S])$] were monitored by gas chromatography (HP 5890 GC-FID, 30 m long Cyclodex-B capillary column, uncertainty $\pm 2\%$).

2.3. ESI-MS measurements

A Hewlett-Packard HP 5989 B MS Engine quadrupole mass spectrometer equipped with a high energy dinode detector and an atmospheric pressure ionization electrospray (API-ES) interface (HP 59987 A) was used. To perform ES experiments, samples were dissolved separately in a mixture of MeOH/AcOH (98/2 v/v) and were introduced into the ES ion source by using a Harward Type 22 syringe pump at a flow rate of 20 μl min^{-1}. A fine spray was formed by applying nitrogen as nebulizer gas at a pressure of 135 kPa. Nitrogen drying gas (heated to 563 K) was used at a flow rate of 8 l min^{-1} to

facilitate solvent evaporation from the droplets. After tuning, the fragmentation patterns of cinchonas were studied by in-source collision-induced dissociation (CID). During the CID experiment capillary exit voltage (CapEx) was changed from 100 to 200 V in 50 V steps, and spectra were acquired for 0.5 min at each CapEx setting.

3. Results and discussion

Enantioselective hydrogenation with catalyst pretreated in hydrogen at 673 K is usually carried out using two different methods. One of these procedures involves separate modification of the supported platinum catalyst with the selected cinchona alkaloid according to Orito's original method [20,21] or a somewhat modified version thereof. According to the second, so-called in situ method recently favoured, modification is carried out in situ, within the solvent and catalyst containing hydrogenating reactor by adding the cinchona alkaloid prior to the addition of EtPy [5,6].

First it was necessary to examine how the selectivity of the catalyst pretreated at 673 K and stored in air changed in time. The data obtained are collected in Table 1.

In agreement with other data [32], the results obtained allowed the conclusion that E 4759 pretreated in hydrogen at 673 K could be stored for a week under air without a significant loss in enantioselectivity.

Table 1
Effect of storage time on the enantioselective hydrogenation of ethyl pyruvate[a]

	Storage time (days)				
	0	2	7	14	30
Conversion (%)	99	99	92	94	93
ee (%)	90	89	87	82	78

[a] Experimental conditions: 25 mg E 4759, 2 ml AcOH, 298 K, 1 bar H_2, prehydrogenation for 30 min, 1 mg DHCD and 0.2 ml EtPy.

3.1. Results obtained with Orito's modified method

The results obtained are summarized in Table 2. To 50 mg of E 4759 pretreated in hydrogen at 673 K as described in the experimental section and suspended in 5 ml of AcOH, 5 mg of DHCD was added and after stirring for 30 min in hydrogen atmosphere, the relative abundance of hydrogenated cinchonas (Scheme 2) were determined in the solution by ESI-MS m/z (%) = 297 (14), 299 (9), 301 (100), 307 (41).

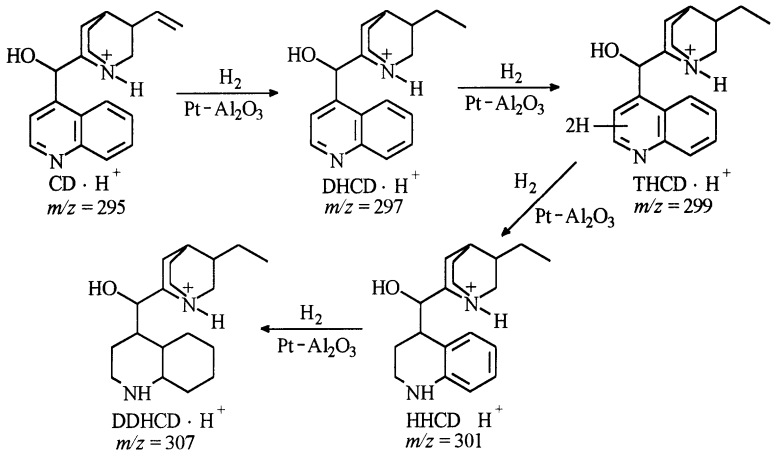
After removing the modified catalyst by filtration and washing it with 5 ml of AcOH, the distribution of various cinchonas in the AcOH solution was found to be m/z (%) = 297 (0), 299 (0), 301 (34), 307 (100).

To the catalyst washed with AcOH, 5 ml of AcOH and 0.25 ml of EtPy were added, the hydrogenation was carried out again and an ee of 71% was obtained. Only minimal amounts of material with $m/z = 301$

Table 2
Hydrogenation of ethyl pyruvate over cinchonidine modified Pt-alumina

Method	Conditions	Relative abundance of cinchona derivatives (%)[a]				Conversion (%)	ee (%)
		DHCD	THCD	HHCD	DDHCD		
Orito's	50 mg E 4759, 5 ml AcOH 5 mg DHCD, 1 bar H_2	14	9	100	41		
	Washed with AcOH	–	–	34	100		
	5 ml AcOH, 0.25 ml EtPy 1 bar H_2	–	–	<	<	99	71
	Reflux in AcOH	No cinchona derivatives detected					
In situ	100 mg E 4759, 10 ml AcOH, 3 mM/l CD, 1 bar H_2, prehydrogenation	93	44	100	37		
	0.5 ml Etpy					60	90
		14	45	32	100	98	85
Blaser's	25 mg E 4759, 5 ml AcOH, 0.5 mM/l CD, 100 bar H_2	100	90	n.d.	60	100	92

[a] Determined in the liquid phase by ESI-MS.



Scheme 2.

and 307 were detected in this solution by ESI-MS. After filtering the catalyst was refluxed for 30 min in 5 ml of AcOH. Cinchonas were undetectable by ESI-MS in the AcOH solution, indicating that they are bound to E 4759 very strongly.

3.2. Results obtained with the in situ method

In the second type of experiment, 10 mg of CD was added to 100 mg of E 4759 pretreated at 673 K and suspended in 10 ml of AcOH and the ratio of hydrogenated cinchonas was monitored in the solution for 60 min with constant stirring. After 60 min, the relative abundance of cinchonas continued to be followed by ESI-MS in the course of the hydrogenation of 0.5 ml of EtPy. The experimental data are summarized in Fig. 1 and Table 2. The optical purity of (*R*)-EtLt obtained by hydrogenation was 85% at 98% conversion level, while it was 90% ee at 60% conversion. This finding is in agreement with other experimental results [12,13].

As shown in Fig. 1, the hydrogenation of CD to DHCD is quite fast even under these mild reaction conditions and, with the progress of hydrogenation time, the amount of hydrogenated cinchonas shown

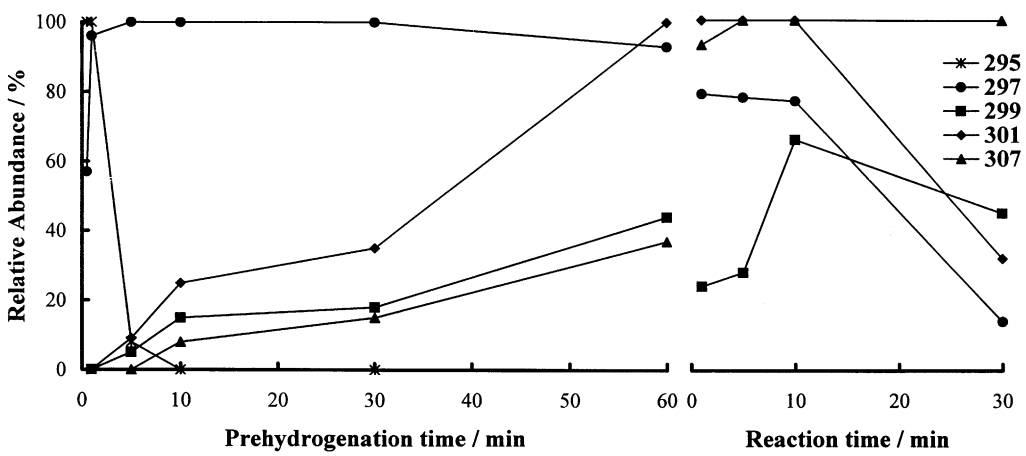


Fig. 1. Changes in the relative abundance of cinchonidine and hydrogenated cinchonidines in the course of prehydrogenation and the hydrogenation reaction (for abbreviations, see Scheme 2).

in Scheme 2 gradually increases in the solution. In the course of the prehydrogenation DHCD, the compound responsible for enantioselectivity is dominant for about 30 min. The most important conclusion drawn from these studies is that it is advisable to start the hydrogenation of EtPy no latter than after a prehydrogenation of 10–15 min. By the end of the 90 min hydrogenation reaction, DDHCD becomes dominant in the solution. Owing to its 10π electrons, DHCD has a significantly higher adsorption capability than hydrogenated cinchonas, therefore the surface of the catalyst is covered mostly by DHCD. It is also shown by the 85% ee obtained that at relatively high CD concentrations (in the present case, 3 mM/l) the optical purity is not affected significantly by the formation of hydrogenated cinchonas. According to our calculations—in agreement with experimental results from other laboratories [5,6]—DHCD concentration of 0.01 mM/l is more than enough for complete surface coverage of the catalyst E 4759.

Under the conditions applied by Blaser et al. (see [6] and references therein), (25 mg E 4759, 5 ml AcOH, 100 bar hydrogen, 2 ml EtPy, 0.5 mM/l CD, see Table 2) the relative abundance of the hydrogenated cinchonas at the end of hydrogenation are the following: $m/z(\%) = 295\ (0), 297\ (100), 299\ (90), 307\ (60)$. [HHCD ($m/z = 301$) was not detectable, because the m/z value of the adduct $[2\text{EtPy} + \text{EtOH} + \text{Na}]^+$ is also 301 [15] and this measurement was carried out in EtOH]. An ee of 92% was achieved. There appears to be no significant difference between the latter two methods (as Blaser et al. also used CD at a concentration more than 50-fold in excess over the one theoretically necessary) in spite of the fact that in the latter case hydrogenation was carried out at a hydrogen pressure of 100 bar.

The measurements presented above suggest that, in order to prevent further hydrogenation of the modifier DHCD, the time spent in the system by the modifier in the absence of EtPy must be kept at a minimum. Since enantioselective hydrogenation is considerably faster than racemic hydrogenation [33], prehydrogenation of the pretreated and stored catalyst must be performed in the absence of DHCD. This conclusion is supported by the following experimental data: 0.5 ml of EtPy was hydrogenated in 10 ml of AcOH, in the presence of 100 mg of E 4759 catalyst, at a DHCD concentration of 3 mM/l, prehydrogenation of the catalyst in the presence of DHCD (a) m/z (%) = 297 (65), 299 (100), 301 (73), 307 (49) or in the absence of DHCD (b) m/z (%) = 297 (100), 299 (38), 301 (45), 307 (17).

Reduction of the E 4759 catalyst at 673 K in flowing H_2 was proved to be necessary as even after this pretreatment procedure Pt^{n+} surface species could be detected by ESI-MS (Fig. 2).

Two negative-ion electrospray mass spectra are presented for comparison. 25 mg of E 4759 catalyst, pretreated in hydrogen for 2 h at 673 K was kept in

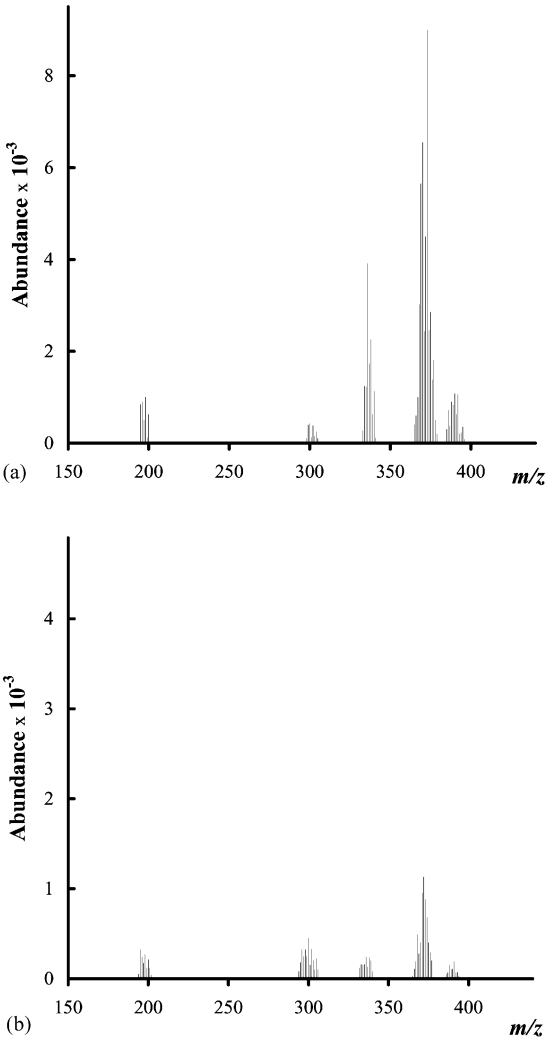


Fig. 2. Negative-ion electrospray mass spectra (capillary exit voltage 100 V) of a H_2PtCl_6/AcOH solution (a) and of the product mixture (b) (25 mg pretreated E 4759, 2 ml AcOH, 343 K, 24 h).

2 ml of AcOH at 343 K for 24 h with constant stirring. On comparison of the spectrum of the above solution (Fig. 2b) with that of the AcOH suspension of H_2PtCl_6 (Fig. 2a), it may be verified on the basis of the characteristic abundance that after a pretreatment of 2 h the reduction of Pt^{n+} is incomplete ($m/z = 373$ can be identified as $HPtCl_5^-$, whereas $m/z = 336$ and 300 represent species with four and three chlorine atoms, respectively). These experimental data are in agreement with data obtained by other methods [34], also demonstrating the presence of chlorine-containing platinum compounds after pretreatment, i.e. "the metal retains a significant δ+ character in the postreduction state". However, until now no experimental results have been published regarding the possible role of Pt^{n+} species in the enantioselective hydrogenation of EtPy. Determination of their possible role in this reaction needs further studies. It is to be noted that Pt^{n+} species were not shown to play a significant role in the enantioselective hydrogenation of ketopantolactone [27].

4. Conclusion

We utilized the fast and sensitive ESI-MS method for the determination of the optimal parameters of the prehydrogenation in the enantioselective hydrogenation of α-ketoesters. Based on the experimental results it can be established that high enantioselectivities may be achieved by pretreatment of the Pt-Al_2O_3 catalyst E 4759 in hydrogen at 673 K. The pretreated catalyst was stored for less than one week and was prehydrogenated at 298 K in the hydrogenating reactor, in AcOH, in the absence of DHCD. The use of such a catalyst ensures an enantioselectivity of about 90% for the production of (*R*)-ethyl lactate at room temperature and at a hydrogen pressure of 1 bar (i.e. under mild experimental conditions) at 70% conversion level. In conclusion and in accordance with the results published so far, the hydrogenation of the quinoline skeleton of DHCD is a significant factor in decreasing the enantioselectivity [16,31, 35].

In order to produce a catalyst with optimal activity and selectivity for the enantioselective hydrogenation of α-ketoesters, subsequent research should be focused on the development (possibly with the help of selective catalyst poisons) of a special surface structure which inhibits further hydrogenation of DHCD.

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