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Diastereoselective hydrogenation of a prostaglandinic intermediate over chirally modified Pt/Al_2O_3

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Abstract

Liquid phase diastereoselective hydrogenation of a prostaglandin-F intermediate has been studied over two commercial 5% Pt/Al_2O_3 catalysts. More specifically, the effect of metal dispersion and pore diameter on the reaction, as well as the conditions which allow to improve the diastereoselectivity and eventually orient towards the synthesis of the natural-like compound have been examined. The catalysts were characterized by nitrogen sorption isotherms, XRD, H_2-chemisorption, and XPS. It has been found that the characteristics of the catalysts (especially the textural properties) and the nature of the solvent strongly influence the catalytic behavior. In the presence of acetic acid as a solvent, it is possible to direct the formation of allylic alcohol to the (11*S*,15*S*) configuration which corresponds to the natural-like diastereoisomer compound. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: Diastereoselective hydrogenation; Platinum supported catalysts; Prostaglandin-F intermediate; Texture; XRD; H_2-chemisorption; XPS

1. Introduction

There is a growing demand in the pharmaceutical and agrochemical industries for enantio- and diastereoisomerically pure products. One of the major problems in synthesis processes of fine chemicals is related to the selective reduction of organic molecules with different functional groups [1]. Heterogeneous catalysts play an important role in these reactions. For enantio- and diastereoselective hydrogenation, modified heterogeneous catalysts are of interest, both from theoretical and practical point of views [2]. Till now, only two efficient heterogeneous catalyst systems are known with enantio selectivities of 90% and higher: (i) tartrate-modified Raney nickel catalysts with enantiomeric excess (e.e.) to β-keto esters and β-diketones up to 98% [3] and (ii) the cinchonine-modified Pt catalysts for the hydrogenation of α-keto-esters with e.e. up to 98% [4].

Optically pure alcohols, particularly allylic alcohols, are excellent organic syntons for structural elaborations leading to various biologically active molecules. This chemical versatility constitutes the main reason for the increasing research efforts directed to the development of efficient routes to optically pure alcohols [5].

The diverse clinical applications of prostaglandins reflect their wide-ranging physiological and pharmaceutical properties. Synthetic analogues have been developed with the aim of obtaining more stable compounds, with a longer duration of action, and a more specific effect. Cloprostenol, a synthetic analogue of prostaglandin $F_{2\alpha}$, is used as a luteolytic agent in veterinary medicine. One of the steps of the synthesis

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process is the stereoselective hydrogenation of the carbonylic bond of the molecular framework. In addition, the main reaction compound must have the same configuration as natural prostaglandins. Thus, the challenge in this reaction is to have not only high activity but high chemoselectivity and diastereoselectivity.

Our previous studies on the hydrogenation of prostaglandin intermediates showed that Ru deposition on different molecular sieves constituted effective catalysts, providing prostaglandin structures with natural-like configuration [6,7]. Based on these results, the behavior of commercial supported Pt catalysts has been explored in the liquid phase hydrogenation of a prostaglandin-F intermediate. This study presents results showing the effect of metal dispersion and pore diameter of the catalysts on the catalytic behavior, and on the way the diastereoselectivity may be influenced by the reaction conditions.

2. Experimental

Two commercial Pt catalysts were used in the hydrogenation reaction: 5% Pt/Al_2O_3 from Johnson Matthey (JMC) and 5% Pt/Al_2O_3 from Engelhard (E). These were reduced in flowing hydrogen ($50\,ml\,min^{-1}$) at 300°C for 2 h and characterized by nitrogen adsorption–desorption isotherms, hydrogen chemisorption, X-ray diffraction (XRD), and X-ray photoelectron spectroscopy (XPS). The nitrogen sorption isotherms were established at 77 K with a Micromeritics ASAP 2000 sorptometer. H_2-chemisorption was carried out using a Micromeritics ASAP 2010C. XRD patterns of the samples were obtained with a SIEMENS D-5000 equipment. XPS spectra were recorded with a SSI X probe FISONS spectrometer (SSX-100/206) with monochromatic Al Kα radiation. The peaks assigned to the Pt 4d, Al 2s and O 1s levels were analyzed.

Standard hydrogenation experiments used 10 mg substrate dissolved in 10 ml solvent (methanol, ethanol, isopropyl alcohol, acetic acid, toluene). Hydrogenation of the substrate was carried out in a stirred stainless steel autoclave under 2–8 atm hydrogen pressure, at 20°C and 1300 rpm. Prior to the reaction, the catalyst (50 mg) was pretreated in hydrogen in the autoclave, and the vessel was purged three times with hydrogen. Experiments were also carried out in the presence of alkaloid modifiers, cinchonine ((+)-CD) or cinchonidine ((−)-CD). The modifier was added in the reaction mixture in amounts in the range 3–24 mg. The reaction products were analyzed by HPLC, using a Nucleosil 5C18 column, as well as by ^{13}C and ^{1}H NMR. The diastereoselective excess (d.e.) was defined using Eq. (1):

$$\text{d.e.} = \left[\frac{(15R) - (15S)}{(15R) + (15S)}\right] \tag{1}$$

where 15*S* and 15*R* are allylic alcohol chiral products (noted with I and II, respectively, in Scheme 1).

3. Results

3.1. Catalysts characterization

The textural properties of the two catalysts are given in Table 1. Pt-E exhibited a higher surface area than Pt-JMC. Both catalysts showed a bimodal pore distribution, but the maximum of BJH diameter was centered at 70 Å for Pt-JMC, and 20 Å for Pt-E, thus with larger pores for the former catalyst.

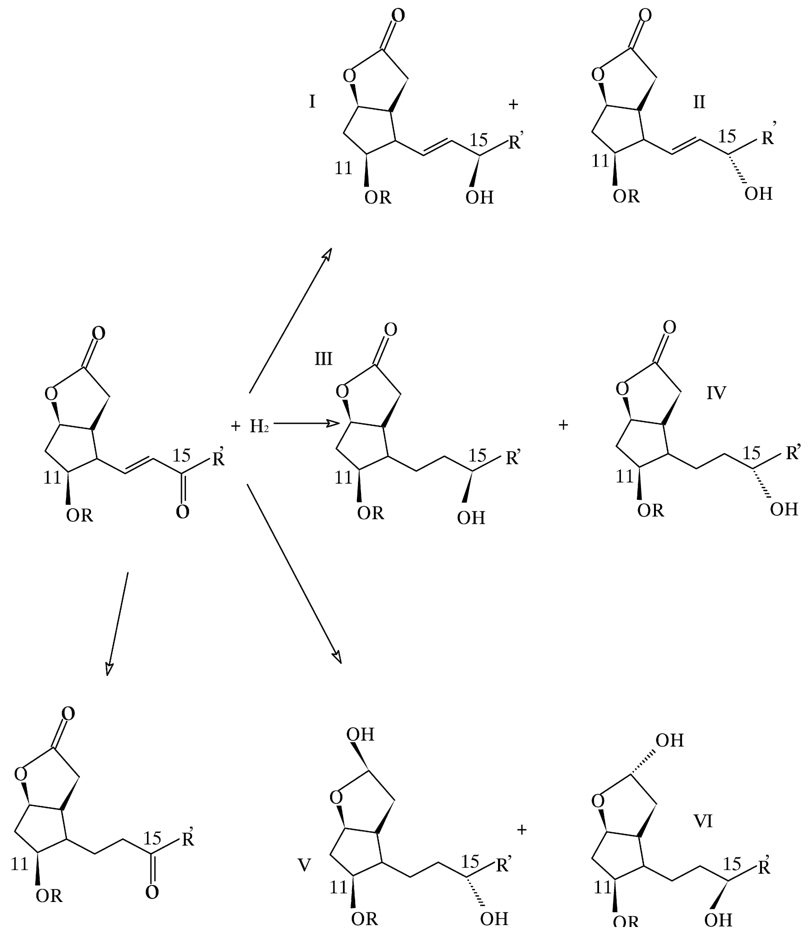
Data concerning H_2-chemisorption, namely, the hydrogen uptake and the platinum dispersion are compared in Table 1. A higher dispersion of Pt was achieved in Pt-JMC than in Pt-E.

The XRD patterns of the catalysts showed different features. Only the diffractogram of the Pt-E catalyst contained the reflections of both Pt and Al_2O_3. The pattern of Pt-JMC was completely silent.

The XPS spectra of the Pt 4d peak are shown in Fig. 1. The surface Pt/Al atomic ratios of the two catalysts and those established by chemical analysis are compared in Table 1. The closer values for Pt-JMC suggest that, for this catalyst, Pt is more homogeneously distributed both on the external surface and inside the pores. For Pt-E catalyst, the same measurements show that the external surface is enriched in Pt, thus indicating a less homogeneous distribution.

3.2. Catalytic results

Hydrogenation of the prostaglandin-F intermediate occurs both at the carbonyl and C=C double bonds (Scheme 1). Therefore, the investigation of this reaction implies two selectivity aspects, one related to chemoselectivity and the other to stereoselectivity.



Scheme 1. Reaction routes in diastereoselective hydrogenation of a prostaglandin-F intermediate.

Several factors were considered in order to determine the way the selectivity could be controlled. These factors will be discussed separately. However, it is worth to note that among the possibilities illustrated in Scheme 1, the enols I and II, and the saturated alcohols III and IV constituted the only reaction products.

Table 1
Textural characteristics and Pt dispersion of the catalysts

Property	Catalyst	
	Pt-JMC	Pt-E
BET surface area ($m^2\,g^{-1}$)	131	168
Pore size (Å)	70	20
H_2 chemisorbed ($cm^3\,g^{-1}$)	0.5549	0.2037
Pt dispersion (%)	19.3	11.1
Pt/Al ratio (XPS)	7.24×10^{-3}	2.23×10^{-2}
Pt/Al ratio (chemical analysis)	14.58×10^{-3}	14.58×10^{-3}

3.2.1. *Influence of the hydrogen pressure*

The dependence of the reaction rate and the chemoselectivity on hydrogen pressure was studied in the range 2–8 atm (Fig. 2). The reaction rate slightly increased with the hydrogen pressure, whereas the chemoselectivity was only little influenced by the increase of pressure. It is important to note that in all the cases, the d.e. was 100% in the (11*S*, 15*R*) diastereoisomer.

It emerges from Fig. 2a and b that the two catalysts have a different behavior. The reaction rates are

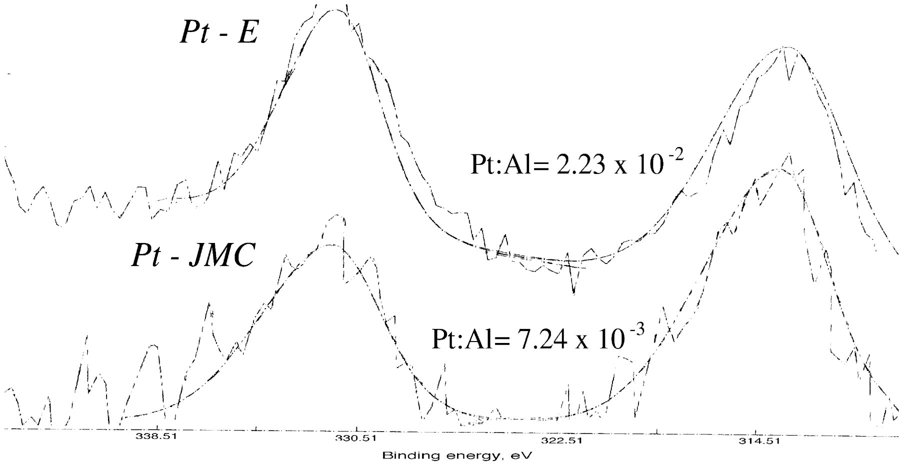


Fig. 1. Pt 4d XPS spectra.

essentially similar but the chemoselectivity of the two catalysts to enol is quite different. Under similar experimental conditions, the selectivity to enol is very high over Pt-E compared with Pt-JMC. For pressures in the range 2–4 atm, it exceeds 80%.

3.2.2. *Influence of chiral modifier*

It has been shown in the hydrogenation of ethyl pyruvate that the presence of various chiral modifiers in the reaction medium produced a change of the stereoselectivity [8]. The results presented in Fig. 3 show that both reaction rate and diastereoselectivity are influenced by the alkaloid configuration. The differences of the configuration of these alkaloids are illustrated in Scheme 2. Compared with the experiments done in the absence of modifier, both (+)-CD and (−)-CD produce an increase of the reaction rate for both catalysts. But more specific is the effect of the alkaloid configuration on the chemoselectivity. Over the Pt-JMC catalyst, (+)-CD has almost no effect, whereas (−)-CD orientes the reaction only to the saturated alcohol (Fig. 3a). On the contrary, over the Pt-E catalyst, the presence of the (−)-CD leads to an important increase of the selectivity to enol. Under similar experimental conditions, the saturated alcohol is the main reaction product (Fig. 3b) in the presence of (+)-CD.

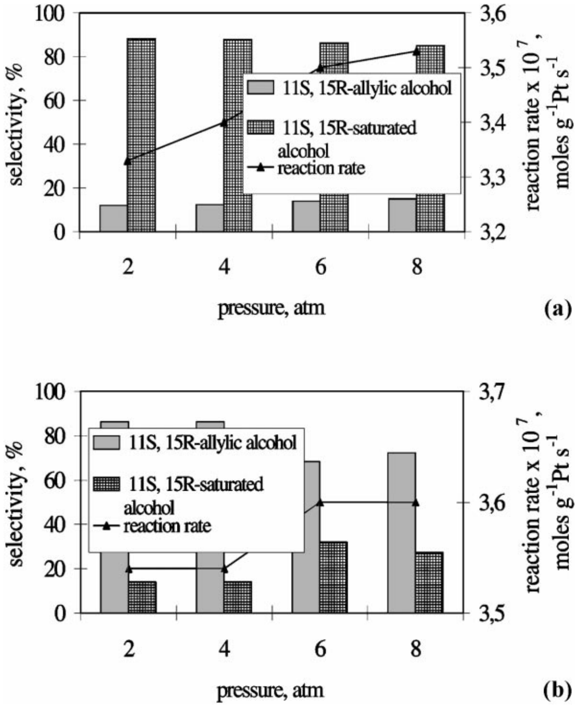


Fig. 2. Influence of hydrogen pressure on the selectivity to enol and saturated alcohol, and on the reaction rate. Catalyst: (a) Pt-JMC, (b) Pt-E; room temperature; solvent: ethanol; 3 mg (+)-CD; conversion 18%; 1300 rpm.

In order to examine the influence of the amount of the chiral modifier, the alkaloid concentration was deliberately changed during the reaction. Fig. 4a and b show, the modification of the reaction rate and the chemoselectivity to enol as a function of the amount of the (+)-CD modifier.

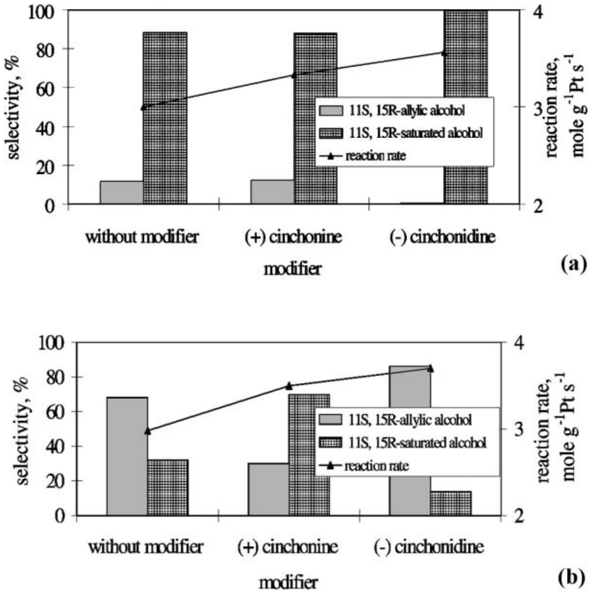
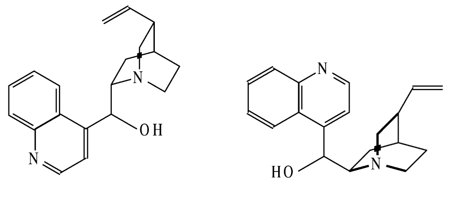


Fig. 3. Influence of the configuration of the modifier. Catalyst: (a) Pt-JMC, (b) Pt-E; room temperature; solvent: ethanol; 2 atm; conversion 18%; 3 mg modifier; modifier/substrate ratio: 0.28; 1300 rpm.

The addition of (+)-CD to the reaction medium, as previously mentioned, slightly increases the reaction rate. However, the data presented in Fig. 4 show that, at least in the range of the (+)-CD/substrate ratios used, the reaction rate is almost insensitive to this ratio.

More important is the influence exhibited by the change of this ratio on the chemoselectivity. The results presented in Fig. 4 show that using (+)-CD, the selectivity to enol is slightly increased over Pt-JMC, for modifier/substrate ratios up to about 1, whereas over Pt-E, increasing this ratio leads to the saturated alcohol.



Scheme 2. Configuration of cinchonidine (left) and cinchonine (right).

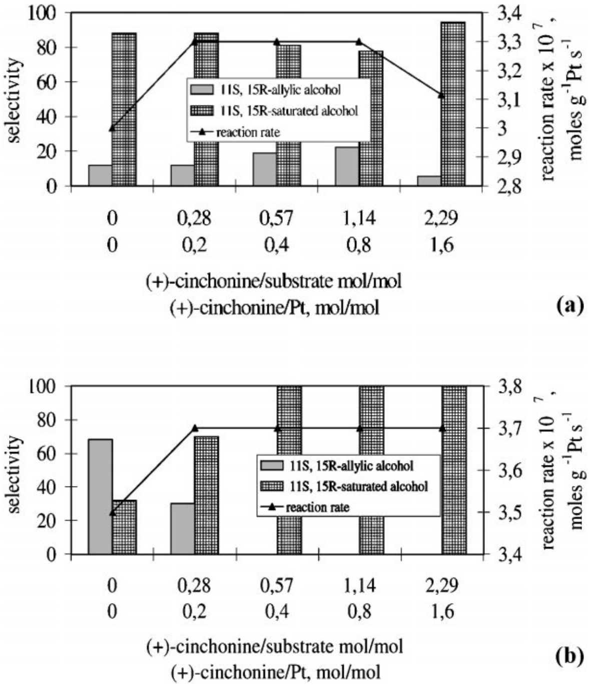


Fig. 4. Influence of the amount of the modifier on the selectivity and reaction rate. Catalyst: (a) Pt-JMC, (b) Pt-E; room temperature; solvent: ethanol; 2 atm; conversion 18%; 1300 rpm.

3.2.3. *Effect of solvent*

The solvent in which the chemical processes take place, far from being indifferent, plays a predominant role in solution chemistry. The complex interaction between solvent and substrate molecules results in a modification of their free energy and, consequently, of the reactivity and stereoselectivity [9].

Fig. 5a and b show the change of the reaction rate and the chemoselectivity as a function of the solvent nature. It is obvious from Fig. 5a that the ability of the solvent to enhance the selectivity to enol, over Pt-JMC, increases in the following order: methanol <ethanol<2-propanol<acetic acid. In the presence of Pt-E, the allyl alcohol is the main reaction product, irrespective of the solvent (Fig. 5b). An effect of the solvent is also observed for this catalyst. The best selectivities to enol are obtained in ethanol and toluene. It should also be noted that the solvent influences not only the selectivity, but also the reaction rate, as seen in Fig. 5.

More important is the effect of the solvent on the diastereoselectivity. Using the alcohols (methanol,

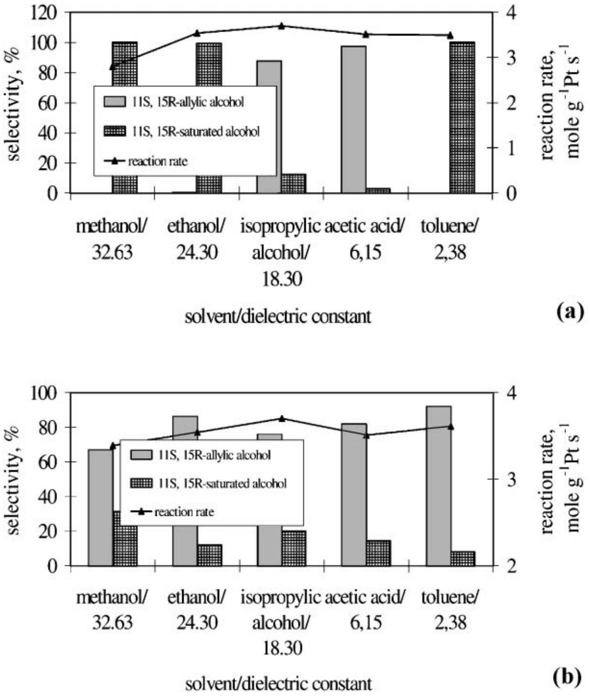


Fig. 5. Influence of the solvent nature on the selectivity and reaction rate. Catalyst: (a) Pt-JMC, (b) Pt-E; room temperature, 3 mg (−)-CD, 2 atm, conversion 18%, 1300 rpm.

ethanol or 2-propanol) or toluene, d.e. was 100% in the (11*S*, 15*R*) conformer, irrespective of the reaction conditions. The use of acetic acid as solvent changed the diastereoselectivity, the reaction product being the (11*S*, 15*S*) conformer (d.e. 76% in the presence of (−)-CD and for 2 atm hydrogen pressure). This allylic alcohol is the one with natural-like configuration.

4. Discussion

The data of Table 1 show that the two investigated catalysts have different textural characteristics and metal dispersions. Pt-JMC exhibits larger pores and higher Pt dispersion than Pt-E. In addition, the crystallinity of the support is different in the two samples. XRD pattern of Pt-JMC showed no reflections corresponding to alumina.

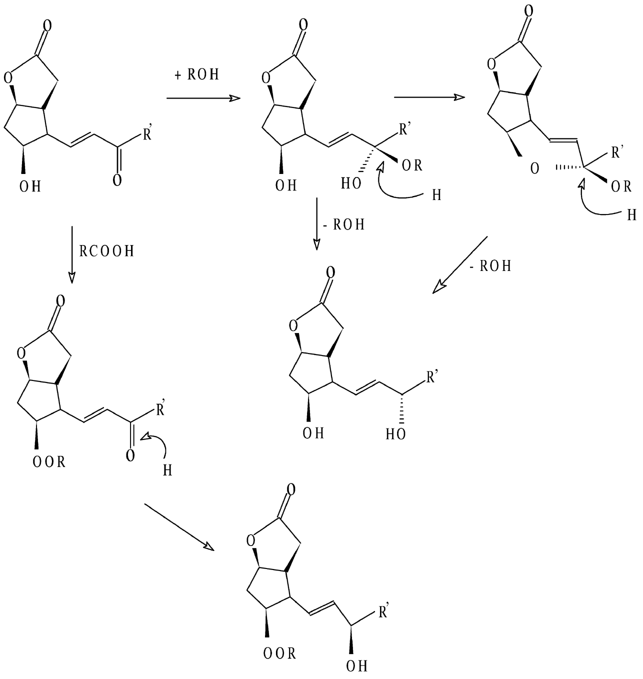
The catalytic results reflected those differences. Over Pt-JMC, the hydrogenation takes place to a larger extent in methanol, ethanol or toluene, the saturated alcohol being the predominant product, regardless of the reaction conditions. Larger pores allow an easier penetration of the molecules and a more advanced hydrogenation. The addition of the modifier brings about a slight increase of the reaction rate. The chemoselectivity is also influenced. Using (+)-CD, the increase of the modifier-to-substrate ratio up to about 1 leads to a slight increase of the selectivity to allylic alcohol. Using (−)-CD, a nearly total selectivity to the saturated alcohol is achieved. These data suggest a competition between the substrate and modifier. For Pt-JMC, the diameter of the metal particles is not sufficient to allow the chemisorption of a substrate-modifier complex. The increase of the amount of the modifier in the reaction medium beyond a certain level could result in a partial poisoning of the catalyst by the adsorbed modifier, which may account for the changes of the chemoselectivity.

The behavior of the Pt-E catalyst differs from that of Pt-JMC. Except for the high concentrations of the modifier, the reaction is oriented towards the allylic alcohol. This behavior could be associated with the characteristic of catalyst, namely, lower metal dispersion and smaller pores. As for Pt-JMC, the addition of the modifier is accompanied by a slight increase of the reaction rate.

The effect of the modifier configuration is more evident for this catalyst. The use of (−)-CD leads to allylic alcohol in a larger extent than (+)-CD. The existence of a competition between the modifier and substrate is also illustrated by the effect of the amount of the modifier. Indeed, Fig. 4 shows that the increase of the (+)-CD to substrate ratio leads to the complete hydrogenation of the substrate.

Summarizing the effect of the catalyst and the modifier, it seems that large metal particles are beneficial to this reaction. The substrate-modifier interaction is manifested by a slight change of the reaction rate and a modification of the chemoselectivity, (−)-CD appearing to be more adequate for that purpose.

The solvent brings an important contribution in these reactions. The results presented in Fig. 5 show substantial modifications of the selectivity according to the nature of the solvent (both the dielectric constant and the chemical nature may influence the reaction). These changes are more evident for Pt-JMC, where the access to the metal species is controlled by the metal particle size. In the literature, there are also



Scheme 3. The influence of the solvent on the reaction mechanism.

several examples of solvent effects on face-selectivity. More particularly, in many diastereoselective reactions, a variation of the d.e. with the nature of the solvent has been observed [10,11]. Other examples reported on the complete reversal of the diastereoselectivity when the solvent was changed [12].

A similar phenomenon was observed when acetic acid was added to the reaction medium. Only in that case, the diastereoisomer with the natural-like configuration was produced. In order to explain these results, it has to be admitted that in alcohol solvent, a ketalyzation could occur. This will form a hemi-ketalic intermediate which, finally, can be etherified in the alcohol solvent. The attack of hydrogen will be made on COR bond, leading to the (11*S*, 15*R*) diastereoisomer (Scheme 3). The presence of the acid avoids the formation of the cycle, making possible the attack of hydrogen on the same side of the OH group, leading to the natural-like configuration.

5. Conclusions

Diastereoselective hydrogenation of a prostaglandin-F intermediate over Pt–Al_2O_3 catalysts with different pore diameter and metal particle size has shown this latter property to be a very important factor in such reactions. Large pores also exert a beneficial effect. Alkaloid modifiers influence the chemoselectivity and the reaction rate, but have no influence on the diastereoselectivity. On the contrary, the solvent plays an important role. In alcoholic media, a ketalization may possibly occur. This orient the chemisorption of the substrate in a way which allows an attack of hydrogen on the side leading to the (11*S*, 15*R*) diastereoisomer. In the presence of acetic acid, this process is limited, and the hydrogen attack occurs on the same side of the 11OH group, giving the isomer a natural-like configuration.

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