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Stereocontrolled hydrogenation of prostaglandin intermediates over Ru–MCM-41 catalysts

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Abstract

Ru–MCM-41 catalysts were investigated in the diastereoselective hydrogenation of class F prostaglandin intermediates. The catalysts were prepared by deposition of Ru from different precursors (ruthenium acetylacetonate, ruthenium chloride or ruthenium hexaamine chloride). These catalysts were characterized using several techniques: atomic emission spectroscopy with inductively coupled plasma, N_2 adsorption–desorption curves at 77 K, H_2-chemisorption, temperature-programmed oxidation, temperature-programmed reduction, XPS, XRD and transmission electron microscopy (TEM). The measurements indicated that Ru is homogeneously distributed on the surface of MCM-41 and that using the hexamine chloride complex allows a better penetration of Ru inside the mesoporous tubes then the other two precursors. Hydrogenation of a prostaglandin F intermediate, namely the one with R = H and $-R' = CH_2–O–C_6H_4$ (m) Cl, showed that the catalysts prepared using ruthenium acetylacetonate and ruthenium chloride exhibit a higher selectivity to allylic alcohol than that prepared using ruthenium hexaamine chloride. In all the investigated catalysts the diastereomeric excess was in the (11*R*,15*S*) allyl alcohol and it varied in the same order as the chemoselectivity. A positive effect of pressure was found.

Keywords: Ru–MCM-41 catalysts; Diatereoselective hydrogenation; Prostaglandin intermediates; H_2-chemisorption; Temperature-programmed oxidation; Temperature-programmed reduction; XPS; XRD; Transmission electron microscopy

1. Introduction

In the last 40 years a large effort has been made to create more sophisticated and adequate drugs the structure of which mimics those of the natural-isolated compounds [1]. The research concerning the synthesis of prostaglandin natural-like compounds is in the same line [2,3]. These molecules which were found in mammals and marine corals, exhibit a remarkably broad range of physiological properties. Structurally they differ by the nature of the functional group and side chains attached to the five-membered ring, but all have a 15-OH group located in an

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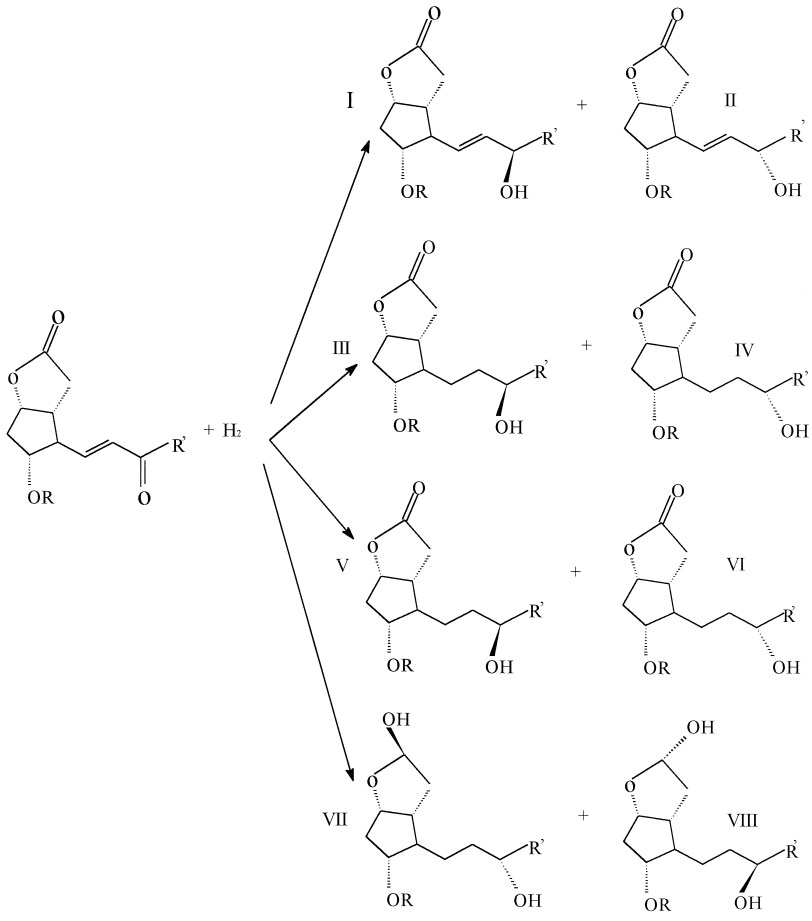
allylic position which must be in an epi-configuration [4]. The formation of this group is generally achieved by the diastereoselective hydrogenation of C=O bond [5]. In spite of the tremendous amount of work on the synthesis of these molecules, only homogeneous catalysts were used.

In previous papers we have reported about the possibility to achieve this hydrogenation with rather high diastereomeric excess using Ru supported on different molecular sieves and in the presence of cinchona, tartaric acid or pivalic acid as modifiers [6,7]. It was shown that these materials can be catalytically active for this reaction and that therefore heterogeneous catalysts may also be very effective.

In this paper we report the use of a new type of catalyst support, namely the mesoporous molecular sieve MCM-41. The aim of this research is to investigate if the size controlled diameters of the mesopores could exert a benefic effect upon the selectivity, and especially upon the diastereoselectivity, which would be designated as a 'shape diastereoselectivity'. Tests were performed for the diastereoselective hydrogenation of a class F prostaglandin intermediate having R = H and R′ = CH_2–O–C_6H_4 (m) Cl. The complexity of the reactions which could occur during this hydrogenation is depicted by Scheme 1. Two kinds of selectivities indeed control this hydrogenation, namely chemo- and diastereoselectivity.



Scheme 1. Reaction pathways in hydrogenation of prostaglandin F intermediates.

2. Experimental

Prostaglandin intermediates were prepared via stereocontrolled synthesis starting from norbornadiene using the well known procedure described by Bindra and Bindra [8]. The products were characterized by ^{1}H NMR and ^{13}C NMR on a Varian 300 NMR spectrometer.

Ru–MCM-41 catalysts were prepared by Ru deposition from a 0.4 M solution of a Ru containing salt. High purity $RuCl_3 \cdot 3HCl$, $[Ru(NH_3)_6]Cl_2$ and $Ru(acetylacetonate)_3$, all from Johnson Matthey were used. The MCM-41 silicate support was prepared in acidic medium using tetraethylorthosilicate as the source of silicon and CTAC as the template. The support was calcined in air at 500°C. Before its exposure to the Ru solution, the support was evacuated at room temperature. After Ru deposition, the catalysts were washed with distilled water, dried at room temperature in a vacuum oven overnight and then reduced in flowing hydrogen (30 ml min^{-1}) for 5 h at 400°C. The Ru loading was determined using atomic emission spectroscopy with inductively coupled plasma (ICP-AES). Following the above procedure, samples with ruthenium content of 5 wt.% were prepared. These are denoted Ru–HCl, Ru–NH, and Ru–Ac, respectively. The above catalysts were characterized using several techniques. Adsorption and desorption curves of N_2 at 77 K were obtained with a Micromeritics ASAP 2000 apparatus. H_2-chemisorption was carried out using a Micromeritics ASAP 2010C. In these experiments it was considered that the amount of reduced Ru species were those determined by temperature-programmed oxidation (TPO). A Micromeritics PulseChemisorb 2705 apparatus was used in TPO experiments in the presence of 50 ml min^{-1} O_2 (5%)—He flow. Reduced ruthenium was determined from the oxygen balance assuming that at 500°C Ru^0 is converted to RuO_2. This assumption was confirmed also by XPS. TPO results were used to determine the metal dispersion. Temperature-programmed reduction (TPR) was carried out in the same installation than TPO. XPS spectra were recorded using a SSI X probe FISONS spectrometer (SSX-100/206) with monochromatic Al Kα radiation. The bands assigned to Ru_{3p}, Si_{2p} and O_{1s} were recorded. XRD measurements of the samples were made using a SIEMENS D-5000 diffractometer. The diffractograms were recorded in the range 2θ: (0–80°) using CuKα radiation ($\lambda = 1.5418$ Å). For the transmission electron microscopy (TEM) investigations the catalytic material was placed on a specially produced structureless carbon support film with a thickness of only 4 nm. These thin support films are stable enough for covering copper grids with a mesh width of 60 μm without an additional holey organic film. The powder was suspended in ethanol by an ultrasonic method. A drop of this suspension was placed on the support film and after 1 min the remaining unabsorbed solution was removed. The electron microscopy investigation was carried out with a Siemens Elmiskop 102. A electron magnification of 50 000:1 was sufficient for the deduction of all significant structural specimen details.

Standard reaction experiments used 10 mg substrate dissolved in 10 ml methanol or THF. Hydrogenation of the prostaglandin F intermediate was carried out in a 50 ml stainless steel stirred autoclave under 2–10 atm hydrogen pressure at 20°C using the above described solution of prostaglandin intermediate in anhydrous methanol or THF and 50 mg catalyst. The agitation speed was of 1500 rpm. Analysis of the reaction products was carried out by HPLC using a Nucleosil 5C18 column as well as by $^{1.3}$C and ^{1}H NMR. The diastereoselective excess (d.e.) was defined using Eq. (1):

$$\text{d.e.} = \left[(11R,15S) - (11R,15R)/(11R,15S) + (11R,15R)\right] \times 100 \quad (1)$$

In this equation $(11R,15S)$ and $(11R,15R)$ designate the two allyl alcohol chiral products noted respectively I and II in Scheme 1. Similarly, the

two hydrogenated compounds noted III and IV in Scheme 1 will be referred as 13,14 dihydro-(11*R*,15*S*) and 13,14 dihydro-(11*R*,15*R*), respectively.

3. Results

3.1. Catalysts characterization

3.1.1. Textural characterization

Fig. 1 shows the N_2 adsorption isotherms (a) and the pore size distribution (b) of the investigated catalysts compared with the parent MCM-41. Fig. 1a indicates typical shape curves for the mesoporous texture. The parent MCM-41 as well as Ru-containing samples exhibits a bimodal pore distribution with a first maximum centered on 26 Å and a second one at about 36 Å. Careful analysis of these curves indicates a certain influence of the precursor nature. This is more evident for Ru–HCl and Ru–Ac catalysts. For these samples, the hysteresis in the desorption branch in the range of relative pressures 0.4–0.6 disappeared and the relative ratio of the peak areas in the pore distribution is altered. This behavior could be an indication that in these samples there is more Ru inside the mesopores. Another indication results from the decrease of the surface area (Table 1). For the same Ru content, Ru–HCl and merely Ru–Ac exhibit a higher decrease of both the internal and external surface area.

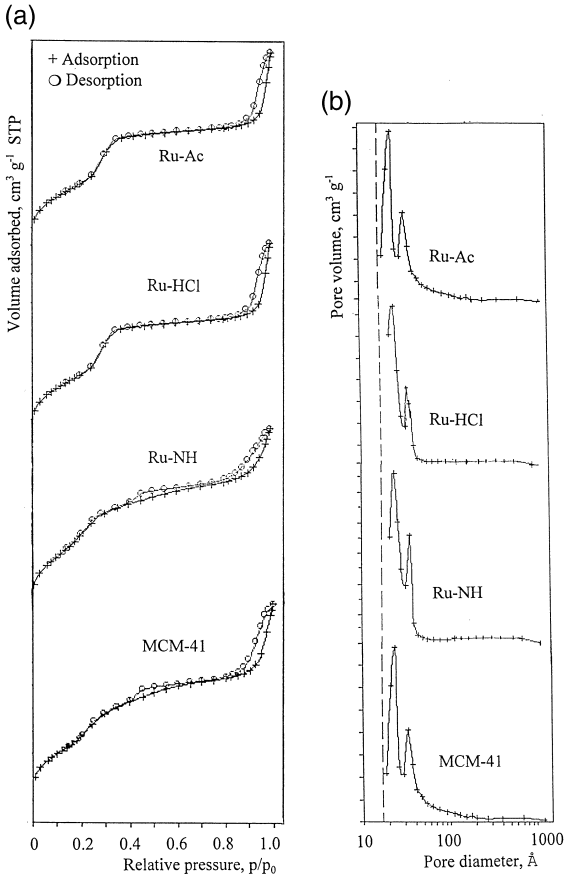


Fig. 1. Textural characterization of the investigated catalysts. (a) N_2 adsorption–desorption isotherms at 77 K. (b) Pore volume distribution as a function of pore diameter.

Table 1
Surface areas of Ru–MCM-41 and MCM-41 samples

Surface area	Sample			
	MCM-41	Ru–Ac	Ru–HCl	Ru–NH
BET surface area ($m^2\ g^{-1}$)	1264	702	865	940
Langmuir surface area ($m^2\ g^{-1}$)	1415	992	1235	1324
t-plot surface area ($m^2\ g^{-1}$)	1298	1015	1209	1193

3.1.2. XRD

XRD patterns showed the typical structure of MCM-41 materials (Fig. 2). Irrespective of the precursor nature, no lines corresponding to Ru species were evidenced. XRD patterns of the catalysts as well as the shape of the N_2 adsorption–desorption curves indicated that no damage of the MCM-41 occurred during the deposition of Ru or during the activation of the catalysts.

3.1.3. H_2–TPR

H_2–TPR curves corresponding to the investigated samples are given in the Fig. 3. These spectra show only one symmetrical peak irrespective of the precursor nature. However, the temperature at the maximum is different, increasing from acetylacetonate (319°C) to the

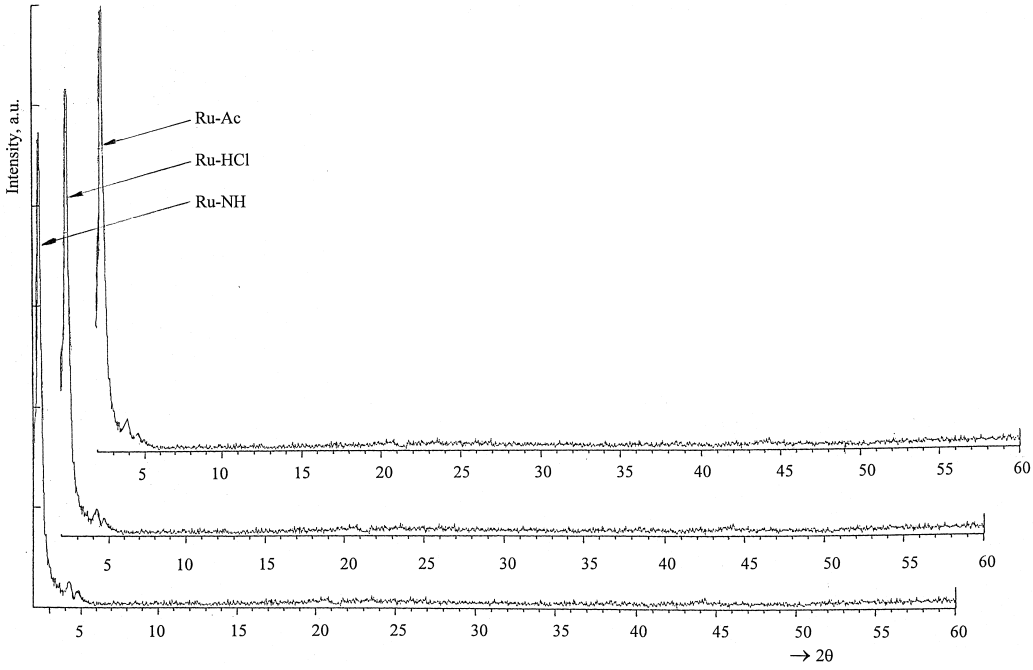


Fig. 2. XRD patterns of the investigated catalysts.

amino complex precursor (339°C). This data seems to indicate that indeed acetylacetonate leads to more superficial and agglomerated species than the other two precursors and these species are more easily reducible. One also should notice that the maximum recorded for Ru–Ac was lower than those reported in the literature for catalysts obtained from $Cu(acac)_2$ [9] or $Ni(acac)_2$ [10] supported on silica. The shape of the peaks suggests that the active Ru species are homogeneously distributed on the mesoporous catalysts surface, on each sample only one type of Ru being predominant.

The degree of reduction determined from combined TPO–H_2–TPR experiments indicated small differences between the investigated catalysts, Ru–Ac being the more reduced one (Table 2).

3.1.4. H_2-chemisorption

Hydrogen chemisorption data are given in Table 2. The metal dispersion varies as a function of the ligand in the order Ru–Ac < Ru–HCl ≪ Ru–NH. This corresponds to an inverse order of the average particle diameter. One should notice that the average particle diameter determined from H_2-chemisorption data ($d = 134/\text{Dispersion}$) shows, especially for the samples prepared using $Ru(NH_3)_6Cl_2$, as precur-

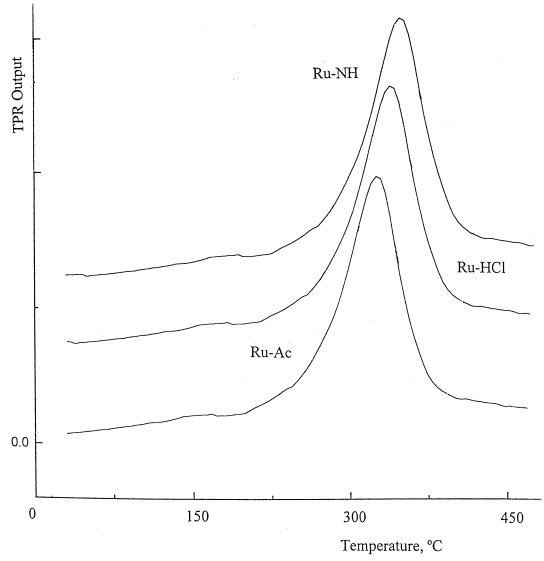


Fig. 3. H_2–TPR profiles of the Ru–MCM-41 zeolites.

Table 2
H_2-chemisorption data

Catalyst	H_2 uptake ($cm^3\ g^{-1}$)	Degree of reduction (%)	Dispersion	Particle diameter (chemisorption) (nm)
Ru–Ac	0.16	91.2	1.4	9.7
Ru–HCl	0.20	89.8	1.8	7.6
Ru–NH	5.17	87.2	53.5	0.3

sors, the existence of rather small Ru particles for such high metal concentrations. Nevertheless, this concords very well with the results already published by Bhat and Sachtler [11] who indicate also very high dispersions on Y zeolite using $Rh(NH_3)_5Cl_3$ as the precursor.

3.1.5. XPS

XPS parameters of the air exposed H_2 reduced samples are given in Table 3. Binding energies of Ru correspond to the reduced species irrespective of the precursor nature [12]. But the data given in Table 1 show important modification of the Ru-to-Si XPS ratio with the precursor nature. Silicon was considered as etalon because it exhibits a well located 104 eV symmetric peak. If one compare this ratio with those determined from ICP-AES, one can conclude that Ru is indeed distributed inside of the mesoporous tubes and that its penetration varies in the order Ru–Ac < Ru–HCl < Ru–NH. However, these data clearly show that there are no Ru local concentrations on the external surface and at least in the limits of XPS depth of analysis.

3.1.6. Electron microscopy

Fig. 4 shows an image corresponding to the Ru–Ac sample. A rather sharp distribution of the dimensions of Ru particles was determined. The mean size corresponding to these particles is about 10 nm in good agreement with the value found from H_2-chemisorption (Table 2). One should also notice that most part of the metal particles seem to be inside of the mesopores and only a small fraction outside of these. A good concordance was also found for Ru–HCl. The mean size corresponding to Ru particles for this catalyst is about 7 nm. For Ru–NH the Ru particles were not visible which is also in good agreement with the small particle sizes determined by H_2-chemisorption.

3.2. Diastereoselective hydrogenation

Fig. 5 shows the variation of the total conversion of the prostaglandin F intermediate on the investigated catalysts at 25°C. Irrespective of the pressure conditions the best conversions were obtained on the Ru–Ac catalyst. However, one should notice that at 8 atm, Ru–HCl gave nearly similar conversions.

Separate experiments were carried out to check the contribution of the mass transfer phenomena. The very high agitation speed excludes the effect of the external diffusion in these reactions and, as Sun et al. [13] have demonstrated, affords the ‘saturation’ of the reactant mixture with hydrogen. But the verification of the Koros–Nowak criterion [14,15] shows that indeed there is an effect of the internal diffusion [16]. Except the Ru–NH catalyst for which the slope of the dependence was about 0.95, for the other two this parameter was less than 0.8 showing the existence of the internal mass transfer limitations. The dependence presented in Fig. 5 is in the same sense. The conversion on Ru–NH is less sensible to pressure than the conversion over Ru–Ac or Ru–HCl.

According to Scheme 1 one can discuss two types of selectivities: chemo- and diastereoselectivity, respectively. Fig. 6 illustrates the evo-

Table 3
XPS parameters of the investigated catalysts

Property	Catalyst		
	Ru–Ac	Ru–HCl	Ru–NH
Binding energy Ru 3d5 (eV)	280.7	280.7	280.8
Binding energy Ru 3d5 (eV)	462.9	462.8	463.0
Binding energy Ru 3d5 (eV)	104.0	104.0	104.0
Binding energy Ru 3d5 (eV)	533.3	533.0	532.9
XPS Ru/Si ratio	0.101	0.086	0.014
ICP-AES Ru/Si ratio	0.13	0.13	0.13

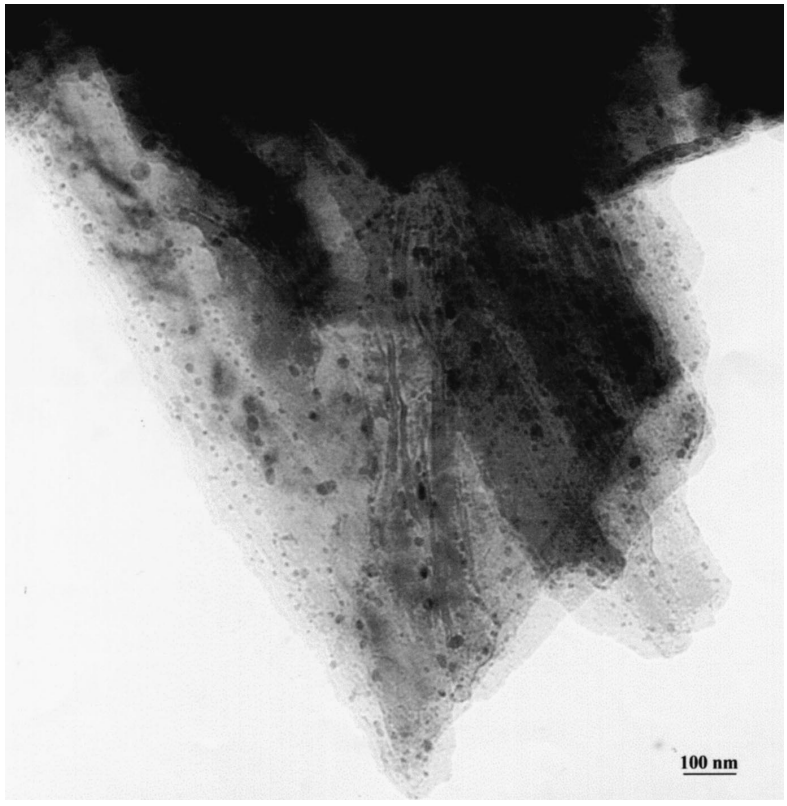


Fig. 4. TEM micrograph of Ru–Ac zeolite.

lution of the chemoselectivity recorded on these catalysts for nearly the same conversion. One can observe that for the same conversion, namely 60%, on Ru–Ac and Ru–HCl the reaction occurs with higher selectivity to allyl alcohol than on Ru–NH on which high amounts of saturated alcohol also result.

Fig. 7a–c shows the relation between the conversion and selectivity to allyl alcohol and saturated alcohol on the investigated catalysts. Similar dependencies were found for all the investigated systems.

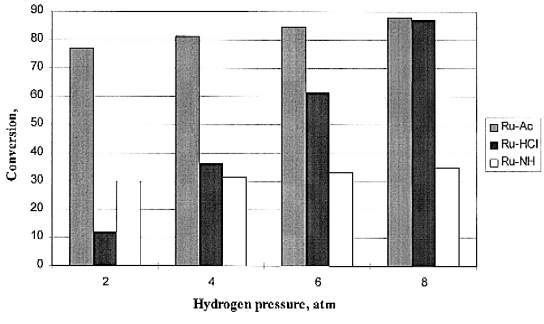


Fig. 5. Variation of the conversion of the prostaglandin F intermediate with the pressure (room temperature, 4 h).

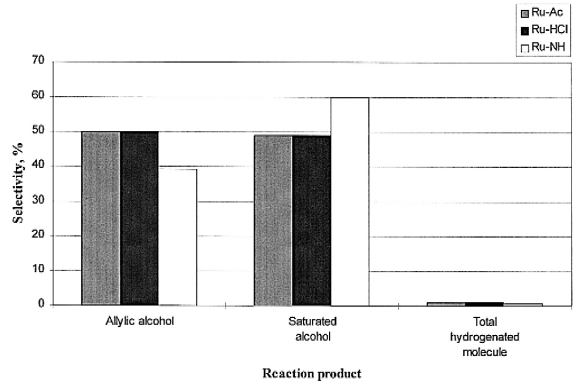


Fig. 6. Variation of the chemoselectivity on Ru–MCM-41 zeolites (room temperature, conversion 60%).

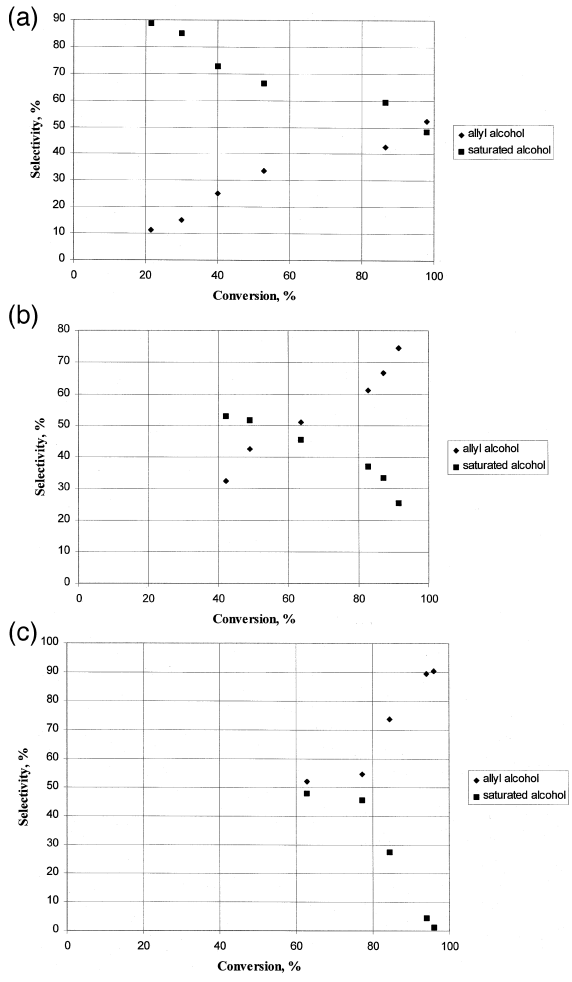


Fig. 7. Variation of the selectivity with the conversion. (a) Ru–NH, (b) Ru–HCl, (c) Ru–Ac.

Diastereoselectivity, according to Scheme 1, can result not only in relation with the hydrogenation to allyl alcohol (products I and II) but also in relation with the hydrogenation of both C=O and C=C bonds (products III and IV). Fig. 8 presents the variation of the diastereoselectivity to allyl alcohol as a function of pressure and of the catalyst nature. One should again notice Ru–Ac catalysts on which, irrespective of the pressure, only one diastereoisomer was obtained, (11*R*,15*S*). Very good diastereoselectivities to (11*R*,15*S*) allyl alcohol were also obtained on Ru–HCl. The variation presented in Fig. 8 indicates a positive effect of pressure. Thus, for pressures higher than 6 atm only the R form resulted irrespective of the catalyst nature.

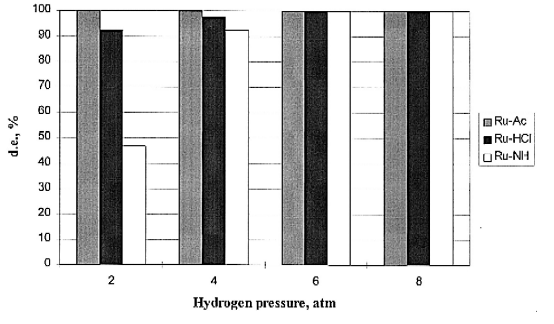


Fig. 8. Variation of the d.e. in (11*R*,15*S*) allyl alcohol.

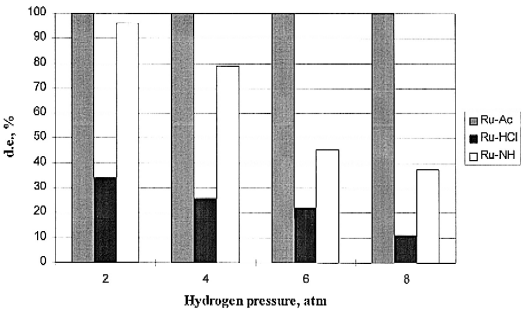


Fig. 9. Variation of the d.e. in (11*R*,15*S*) hydrogenated alcohol.

Fig. 9 shows the variation of diastereoselectivity to the hydrogenated alcohol. Again on Ru–Ac a complete diastereoselectivity to (11*R*,15*S*) hydrogenated alcohol was recorded. An increase in pressure was found in this case to induce a decrease in diastereoselectivity and this behavior is very well illustrated for Ru–HCl and Ru–NH. For low pressures such as 2 atm, Ru–NH also leads to a high d.e. in saturated alcohol.

4. Discussion

Deposition of Ru using different precursors was found to lead to different dispersions. The use of the hexaamine precursor allows the docking of the precursor presumably via an ion-exchange mechanism leading to electrostatic interactions. At high temperature, during reduction,

these interactions could favor the migration of Ru species and their penetration inside the mesopores leading to small metal particles. This behavior is in total concordance with the model proposed by Bonneviot et al. [17] for a similar precursor containing Ni as active species and using SiO_2 as the support. Contrary to hexaamine, acetylacetonate species form rather strongly bonded Ru–(acac)–OSi-species which loose the second acac ligand only at high temperatures. Such a behavior was already stressed by several authors for Cu [9] and Ni [10]. Under such conditions, the migration of these species becomes more difficult and larger agglomerates are formed. However, one should notice that even for Ru–Ac, XPS Ru-to-Si atomic ratio indicated a value close from the value given by the chemical analysis and electron microscopy, showing that an important part of the metal is inside the channels.

Other evidences concerning the presence of Ru inside the mesopores were given by the textural characterization of these materials and by electron microscopy. H_2-TPR curves also indicated that only one type of Ru was obtained irrespective of the precursor nature. However, one should notice that from the same measurements it was found that for Ru–Ac the size of the metallic particles was much higher than for Ru–NH.

Catalytic data confirmed these differences. Ru–Ac was the best catalyst irrespective of the reaction conditions. On this catalyst not only very good selectivities to allyl alcohol were obtained but also a complete diastereoselectivity to (11*R*,15*S*) and to 13,14 dihydro-(11*R*,15*S*).

An intriguing question resulting from this data is to explain why on the catalysts containing rather large metal particle (Ru–Ac and Ru–HCl) an increased amount of allyl alcohol results while on those containing small metal particles (Ru–NH) important amount of saturated alcohol were obtained. One of the keys in this behavior could be the mechanism suggested for hydrogenation of unsaturated aldehydes on $Rh/AlPO_4$ by Campello et al. [18]. They suggested that unsaturated alcohols may isomerize into saturated aldehydes which can be then more hydrogenated to saturated alcohols. High metal size particles existent in Ru–Ac determine a different chemisorption of the organic molecule, involving either chemisorption of C=O or of unsaturated C=C one.

Diastereoselectivity is generally related to the formation of rather stable reaction intermediates [19]. Therefore, the high diastereoselectivities on Ru–Ac both to (11*R*,15*S*) (I) and to 13,14 dihydro-(11*R*,15*S*) species could again be related with the size of the metal particles in these catalysts. Large metal particles could induce some hindrances in the chemisorbed species and in such a way could improve the reaction intermediate stability and at the end, the diastereoselectivity. However, one should notice that the reaction should occur inside of the mesopores because experiments carried out using X or ZSM-5 zeolites as support showed that in the absence of the chiral modifiers only the racemic mixture was obtained irrespective of the reaction conditions. Furthermore, the variation of the d.e. with the pressure also indicates that the reaction should occur in the mesopores. The reaction, at least for Ru–Ac and Ru–HCl, is affected by the internal diffusion. It is therefore expected that an increased amount of species inside of the mesopores will correspond to an increased diastereoselectivity.

5. Conclusions

The deposition of Ru from different salts: ruthenium acetylacetonate, ruthenium chloride or ruthenium hexaamine chloride on mesoporous MCM-41 occurs with the formation of homogeneous particles which are merely disposed inside of the mesoporous tubes. Hydrogenation of a prostaglandin F intermediate on these catalysts has been found to occur diastereoselectively even in the absence of chiral modifiers. The selectivity to allyl alcohol, which is

the interesting product, seems to be governed by a geometrical factor, related to the size of the metal particles.

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