Low metal loading Ru-MCM-41 stereocontrolled hydrogenation of prostaglandin intermediates

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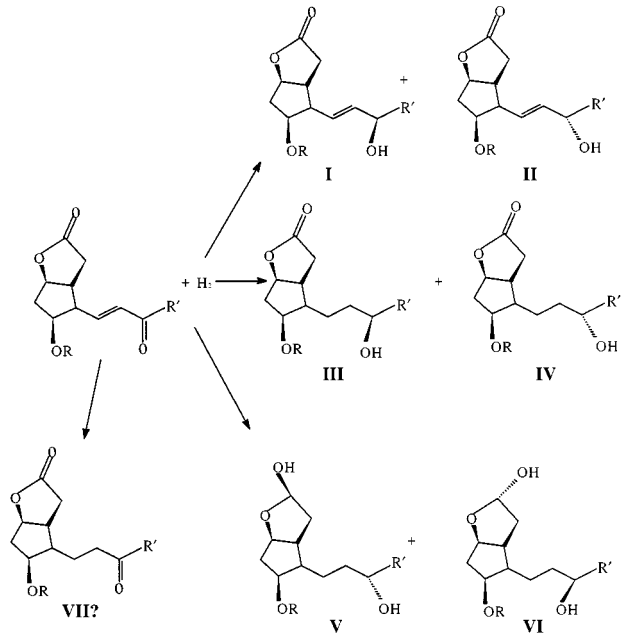
Low metal loading Ru-MCM-41 (0.134 and 0.667 wt% Ru) have been prepared by adsorption of ruthenocene from a diethyl ether solution, calcination and reduction under flowing hydrogen at 350 °C; the physical characteristion by a combination of several techniques has shown that Ru is homogeneously distributed inside the MCM pores, and that it is only partially reduced; these catalysts exhibit a very high diastereoselectivity in hydrogenation of an F prostaglandin intermediate leading only to the 11*S*,15*R* diastereomer.

Diastereoselective hydrogenation is generally considered to occur on high loading noble metal catalysts (min. 5 wt%) in the absence of any chiral modifiers.[1,2] Some beneficial effects of the latter[3] or of some chiral auxiliaries have even been reported.[4,5] In all these cases the diastereoselectivity is related to some specific features of the metallic species or to the choice of an adequate reaction solvent. Otherwise the reaction product is a racemic blend. In most cases the diastereomeric excess (de) is low. Diastereoselective hydrogenation of α,β-unsaturated carbonyl compounds such as prostaglandin intermediates (Scheme 1) raises some additional problems because the interesting compounds are the allylic alcohols and from the thermodynamic point of view it is easier to hydrogenate the C=C double bound than the carbonylic one. Some shape selectivity effects have already been reported in the case of cinnamaldehyde hydrogenation[6] but it is still not clear if, for high metal loading and microporous supports, the effect of some adjacent Lewis sites, which are well known to exert a positive influence in this reaction, is not responsible for the observed results.



Scheme 1 Possible routes in hydrogenation of the F prostaglandin intermediate.

Here, we report a first example of the positive influence exerted by the mesoporous texture in the diastereoselective hydrogenation of a F prostaglandin intermediate on Ru-MCM-41 catalysts with very low Ru content using hydrogen as the reducing agent. Hydrogenation of the 15-carbonylic bond with generation of the chiral allylic structure is of special interest for these molecules because of its pharmaceutical applications.

The MCM-41 silica catalyst support was synthesised using sodium silicate (Aldrich) as the source of silicon and hexadecyltrimethylammonium bromide as the template. The synthesis was conducted at 70 °C and pH 11 for 7 days. The MCM-41 material was then filtered off, washed, dried and calcined at 550 °C for 12 h. The calcined material had a BET surface area of 1127 $m^2\ g^{-1}$ and a BJH pore diameter of 27 Å.

The catalysts used in the present study were prepared by adsorption of ruthenocene from a diethyl ether solution. After Ru deposition the catalysts were dried and calcined for 6 h at 550 °C, after raising the temperature at 1 °C min^{-1}. The reduction of these catalysts was performed under flowing hydrogen for 3 h at 350 °C with a heating rate of 1 °C min^{-1}. The Ru loading was determined using ICP-AES. Catalysts containing 0.134 and 0.667 wt% Ru were respectively obtained. The catalysts were characterised using surface area measurements by standard N_2 adsorption at 77 K, H_2-TPR, Mossbauer spectroscopy, H_2-chemisorption and XRD. The parameters determined using the above measurements are reported in Table 1.

Hydrogenation of the substrate was carried out in a stainless steel stirred autoclave under 2–8 atm hydrogen pressure at 20 °C using a solution of prostaglandine intermediate in anhydrous

Table 1 Characteristics of the Ru-MCM-41 catalysts

	MCM-41 Catalyst	
Property	0.13 wt% Ru	0.67 wt% Ru
BET surface area/$m^2\ g^{-1}$	807	739
BJH pore diameter/nm	2.6	2.6
Ru $3p_{3/2}$/eV	462.7	462.2
Ru/Si (XPS)	3.4×10^{-3}	5.3×10^{-3}
Ru/Si (ICP-AES)	2.8×10^{-3}	10.4×10^{-3}
Reduction degree (%)	16.6	39.5
Ru^0/Ru^{IV},[a] (%)	17.2	41.3
Adsorbed $H_2/cm^3\ g^{-1}$	0.0601	0.2202
Dispersion[b] (%)	20.8	14.8
d_{Ru}[b]/nm	6.5	9.1

[a] Determined from Mossbauer spectroscopy. [b] Determined from H_2 chemisorption.

methanol, ethanol or isopropyl alcohol. Analysis of the reaction products was carried out by HPLC using a Nucleosil 5C18 column as well as by ^{13}C and ^{1}H NMR. The diastereoselective excess (de) was defined using eqn. (1):

$$de = \{[(15R) - (15S)]/[(15R) + (15S)]\} \times 100 \quad (1)$$

We defined 15*R* and 15*S* as the allylic chiral products from the reaction scheme.

Data presented in Table 1 show that at such low loadings, Ru is only partially reduced. The same conclusion was reached from the H_2-TPR measurements. In addition these determinations indicated only one reduction peak thus suggesting the presence of only one reducible Ru species. The good concordance beween the XPS and the analytical Ru/Si ratios suggests that Ru is homogeneously distributed inside the mesopores. However, H_2-chemisorption results indicate that even at such a low concentration Ru has a tendency to agglomeration. XRD indicates however (no diffraction peak of Ru or of a Ru compound), that these particles are rather small which is again in good concordance with chemisorption data.

The activity of the Ru-MCM-41 catalysts was found to increase with Ru content (Fig. 1). For each catalyst, increasing the pressure resulted in an increase of both the conversion and the selectivity to allylic alcohol. For the catalyst containing 0.13 wt% Ru the conversion increases by 15 times, and for that with 0.67 wt% Ru by 5 times, when the pressure is increased from 2 to 8 atm. At an Ru loading of 0.67 wt% a conversion of near 100% was reached. In all cases the formation of the allylic alcohol occurs with a total de in the 11*S*,15*R* form (product **II** in Scheme 1). Other studies using high Ru loading on zeolite Y,[6] showed that when the reaction occurs on the external surface of the catalysts, and in the absence of any chiral modifiers, only the racemic blend was obtained. Under these conditions an increase of the pressure led to a decrease of the selectivity to allylic alcohol.

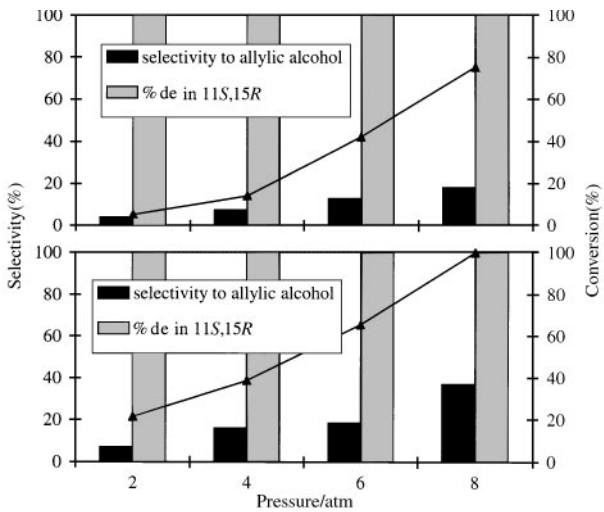


Fig. 1 Variation of the conversion, selectivity to allylic alcohol and de *vs.* pressure (a) 0.13 wt% Ru-MCM-41, (b) 0.67 wt% Ru-MCM-41; solvent methanol, room temp., 2h).

The variation of the same parameters as a function of the solvent (Fig. 2) shows that the solvent affects the total conversion and the selectivity to allylic alcohol. The best conversions were obtained using methanol and the best selectivities to allylic alcohol with isopropyl alcohol. The de was 100% in the 11*S*,15*R* form irrespective of the solvent nature.

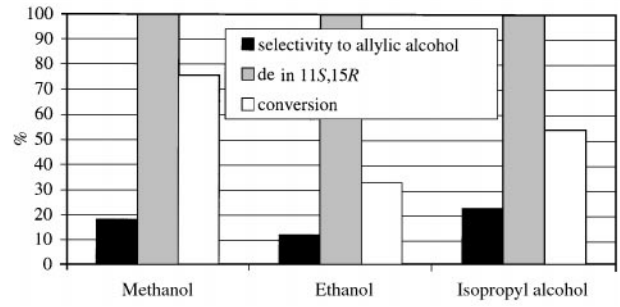


Fig. 2 Variation of the conversion, selectivity to allylic alcohol and de with solvent (0.67 wt% Ru-MCM-41, room temp. 2 h).

To explain these data one should accept that all the reaction parameters, namely the conversion, the selectivity to allylic alcohol and the diastereoselectivity are determined by the access of the prostaglandin intermediate to the MCM pores. The kinetic diameter of this molecule is rather high, and its penetration in the pores is diffusionally controlled. Ru is well distributed inside of these and even if it exhibits a tendency to agglomeration, the metal patches are smaller than those generally reported to have activity in such reactions. A deeper penetration of the reactant molecule leads to an increased number of molecules involved in a direct CO···Ru interaction. Under these conditions, because of the relatively small Ru size, the hydrogenation of the C=C double bond becomes less favoured and the selectivity to allylic alcohol increases. Other effects such as pore hindrance could be expected. The MCM-41 support is a pure silica, and therefore no Lewis acid sites are expected. The complete diastereoselective hydrogenation is very probably the consequence of the steric hindrance described below. As mentioned above the 11-OH group is in the *S* conformation. Owing to this conformation, an extended hydrogen bond interaction *via* the hydrogen of the alcohol group is possible. Because of this, hydrogen will attack the CO bond on the other side of the F prostaglandin intermediate molecule leading to the 15*R* isomer (compound **II** in Scheme 1). A cooperative contribution between the solvent and the pore hindrance is also sustained by the observed differences in conversion and selectivity in various solvents.

In conclusion, this data shows that the diastereoselective hydrogenation of large enones such as the F prostaglandin intermediate can be improved by using pore size controlled mesoporous materials as support for the ruthenium. It is also shown that in such a surrounding these reactions could also be carried out at very low metal loading, namely < 1 wt%, which is rather unusual for such large molecules.

Notes and references

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