Journal of the Chilean Chemical Society
ISSN 0717-9707 *versión on-line*

J. Chil. Chem. Soc. v.50 n.1 Concepción mar. 2005

J. Chil. Chem. Soc., 50, N 1 (2005)

Effect of the nature of the support on the enantioselective hydrogenation of 1-phenyl-1,2-propanedione over supported iridium catalysts.

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ABSTRACT

The enantioselective hydrogenation of 1-phenyl-1,2-propanedione at 298 K and 40 bar over modified supported iridium catalysts has been studied. Cinchonidine has been used as chiral inducer. The catalysts were obtained by impregnation of $Ir(acac)_3$ on three different supports: SiO_2, TiO_2 and MoO_3, followed by calcination in air and reduction under hydrogen at 773 K. All the solids were characterized by nitrogen adsorption-desorption isotherms at 77 K, H_2 chemisorption, XRD, TEM, TPR and XPS. It was found that Ir/SiO_2 and Ir/TiO_2 catalysts reduced at high temperatures, 773 K, possess similar metal particle size, close to 2.0 nm, eventhough the H/Ir ratio obtained from H_2 chemisorption showed larger differences, with the H/Ir ratio being lower for titania- and molybdenum-supported iridium catalysts. In these samples, migration of the partially reduced supports, TiO_x and MoO_x moieties, on the metal crystals induce the creation of $Ir\delta+$ species. TPR and XPS results confirmed that the metal component was not completely reduced.

The activity was influenced by the nature of the support, being more active those in the SMSI state such as Ir/TiO_2 and Ir/MoO_3 being more active. This has been attributed to the presence of electron deficient metal species, $Ir\delta+$, which are responsible for the polarization of the carbonyl bond of the substrates, thus favoring the activity and enantioselectivity of the reaction. The effect of different solvents on the activity and the enantioselectivity of the reaction was also studied. The highest enantiomeric excess (ee) of (R)-1-phenyl-1-hydroxy-2-propanone (20%) was obtained with the Ir/TiO_2 catalyst using acetic acid as solvent.

Keywords: Ir, 1-phenyl-1,2-propanedione, cinchonidine, hydrogenation, enantioselectivity.

1. INTRODUCTION

The enantioselective hydrogenation of α-ketoesters to the corresponding α-hydroxyesters and diketones is of great interest for obtaining fine chemicals. The use of metal-supported catalysts modified by the adsorption of some organic compounds onto their surface has provided an interesting way to synthesize certain enantioisomers. In 1979 Orito et al.[1] mentioned that during the hydrogenation of methyl pyruvate on Pt/carbon catalysts, the adsorption of the alkaloid cinchonidine onto the metal component led very selectively to R-methyl lactate. Since then, work has been done to explain this interesting system with different supports, solvents and chiral modifiers for different substrates. Thus, hydrogenation of pyruvate esters on Pt catalysts by using natural alkaloids as modifiers of reactions at room temperature and high hydrogen pressures may achieve important enantioselectivity (enantiomeric excess (ee) = 60 to 80%). For these kind of reactions it has been shown that the optical yield and activity decrease linearly with increase of dielectric constant of the solvent [2]. The role of the modifier is to guide the adsorption of the reagent in such a way that enantioselective hydrogenation is enabled. Enantioselective hydrogenation ofα-ketoesters with a Pt catalyst modified by alkaloids such as cinchonidine has been studied extensively [3]. Minimal requirements for an efficient modifier for the hydrogenation of a-ketoesters were said to be a basic nitrogen atom close to one or more stereogenic centers, and connection to an aromatic system. The best results were obtained with quinolyl or naphthyl groups.

The main conclusions dealing with a detailed study of the hydrogenation of ethyl pyruvate with a variety of different cinchona derivatives can be summarized as follows [4]: 1) The best results were obtained with cinchonidine (CD) or slightly modified derivatives such as HCD (10,11-dihydrocinchonidine) or 9-methoxy HCD (MeOHCD) to produce ethyl (R)-lactate, and with cinchonine derivatives to lead to the (S)-enantiomer, although with lower ee. 2) Three structural elements in the cinchona molecule were identified as affecting both the reaction rate and the enantioselective hydrogenation of α- keto acid derivatives: i) An extended aromatic moiety; ii) the substitution pattern of the quinuclidine (the absolute configuration at C-8 controls the sense of induction, N-alkylation yields racemate); iii) The substituents at C-9 (OH or MeO are optimal, larger groups reduce the enantioselectivity). 3) The choice of solvent has a significant effect on enantioselectivity and reaction rate. MeOHCD in acetic acid and HCD in toluene appear to be the most effective modifier/solvent combinations. In fact, CD has been widely used as a modifier, with Pt being usually the active component of the catalyst. Since cinchonidine is both a polar and an aromatic molecule, it is reasonable to assume that differences in solvatation of the modifier between polar and non-polar solvents will occur, which may affect the adsorption equilibrium between the modifier and the surface of the catalyst. The existence of this effect was pointed out by Blaser et al. [5] from the dependence of the optical yield on modifier concentration for a range of solvents. The common assumption is that adsorption of the modifier is necessary for enantioselectivity and rate acceleration [6], or alternatively that a pyruvate-modifier complex is

formed in solution prior to the adsorption and hydrogenation reaction [7]. However, it is clear that solvation of the modifier (or modifier-pyruvate complex) will differ significantly in solvents such as ethanol and toluene. A similar suggestion was advanced by Wehrli et al. [2] on the basis of optical yield and initial reaction rate. This difference in solvation may have consequences for the enantioselectivity of this reaction and contribute to the higher optical yield seen in toluene than in ethanol. Selection of the support has been relevant in the preparation of heterogeneous catalysts for the enantioselective hydrogenation of a-ketoesters, α-functionalized ketones, and α,β-diketones. Several groups have tried to improve the hydrogenation of ethyl pyruvate by preparing cinchonidine-modified Pt catalysts on various supports. Thus, Hall et al.[8] described the used of a Pt/MCM-41 catalyst which exhibits low reaction rate due to mass transfer limitation, and enantiomeric excess up to 64%. Zeolites of different structures and acidities can also display high enantioselective hydrogenation on supported Pt catalysts. In fact, Böhmer et al. [9] have reported the reuse of Pt/HNaY zeolite in the hydrogenation of ethyl pyruvate in acetic acid and cyclohexane, reaching an important ee (88%). Additionally, ee up to 75% was reported for Pt/clay catalysts (28% ee for Rh/K-10) [10], while ee below 35% was described for Pt/C catalysts despite improvement by oxidative treatment [11]. Nevertheless, two commercially available 5% Pt/Al_2O_3 catalysts have emerged as "standard" catalysts: E4759f from Engelhard and JMC 94 from Johnson Matthey [12].

There are only few papers concerning the enatioselective hydrogenation of conjugated diketones [13,14,15]. With regard to this reaction, Blaser et al. [12] have reported the hydrogenation of butane-2,3-dione to (R)-3-Hydroxybutan-2-one, obtaining an ee in the range 85 - 90%, although with low yield, with the Pt/Al_2O_3-cinchona system; also, both butane-2,3-dione and hexane-3,4-dione can be hydrogenated enantioselectively over Pt/silica modified by cinchonidine, giving ee of up to 38% in favor of (R)-(-)-3-hydroxybutan-2-one and of up to 33% for (R)-(-)-4-hydroxyhexan-3-one [14]. In spite of the important applications of one of their partially hydrogenated products, the hydrogenation of 1-phenyl-1,2-propanedione has been rarely studied [16,17]. For this reaction the effect of cinchonidine concentration, reaction temperature, nature of the solvent (ethanol, ethyl acetate, and dichloromethane) and reduction temperature of the catalysts have been studied on Pt/Al_2O_3 catalysts [13,15]. The most effective catalyst in terms of activity and enantioselectivity was obtained by *in situ* modification in dichloromethane, yielding up to 67 mole% of (R)-1-hydroxy-1-phenylpropanone, corresponding to an ee of 64% regardless of reactant conversion. In the same report, the authors pointed out that the hydrogenation rate in a mixture of solvents, ethanol and acetic acid, was higher with the Pt/C catalyst than with Pt/Al_2O_3, but the ee was lower (17% and 33%, respectively). There was a beneficial effect on the ee when acetic acid was added to the reaction mixture in ethanol, the original ee of 24% increasing to 33% upon the addition of acetic acid. This reaction was also studied on Pt/SiO_2 fibers [15] and the results indicate that the hydrogenation rate was lower than with the alumina-supported Pt catalyst, displaying an ee of 50% for (R)-1-phenyl-1-hydroxy-2-propanone. Additionally, the use of Pt on mesoporous MCM-41 in the enantioselective hydrogenation of 1-phenyl-1,2-propanedione was successfully demonstrated. Toukoniitty et al. [18] have studied three different metal contents (5, 10 and 15 wt.%) of Pt on MCM-41 modified with (-)-cinchonidine (CD), obtaining a maximum ee of (R)-1-phenyl-1-hydroxy-2-propanone close to 44% using the 15 wt.% Pt/MCM-41 catalyst. This

behavior was attributed to the larger metal Pt particles in this catalyst. Similar results in terms of activity and enantioselectivity were obtained by Reyes et al. [19] in the same reaction using a 1 wt.% Pt/MCM-41 catalyst. The observed behaviour has been attributed to confinement effects produced in the hexagonal channel of the MCM-41.

The aim of the present work is to study the enantioselective hydrogenation of 1-phenyl-1,2-propanedione on Ir-supported catalysts in the presence of cinchonidine as chiral inducer. The effect of the nature of the support (SiO_2, TiO_2 and MoO_3) and of the solvent (acetic acid and chloroform) on activity and enantioselecivity to (R)-1-phenyl1-1-hydroxy-2-propanone is studied.

EXPERIMENTAL

2.1 Catalyst preparation

The catalysts were prepared by wet impregnation of the support (SiO_2 BASF D-11-11, MoO_3 MERCK and TiO_2 P 25 DEGUSSA). An acetone solution of iridium acetylacetonate in an appropriate amount to get 1 wt% of Ir was used to impregnate SiO_2 and MoO_3, whereas an aqueous solution of iridium (IV) chloride was used for TiO_2. The solids were calcined in air at 573 K and reduced in flowing H_2 at 773 K (HT), prior to the catalytic evaluation or characterization.

2.2 Characterization

Characterization of catalysts was carried out by the following techniques: The temperature-programmed reduction of the catalysts (TPR) was studied in a TPR/TPD 2900 Micromeritics system equipped with a thermal conductivity detector. The reductant gas was a 5% H_2/Ar (40 cm^3min^{-1}) mixture, at a heating rate of 10 °C min^{-1} from room temperature up to 600 °C. The specific surface area was evaluated from the adsorption of N_2 at 77 K in an automatic Micromeritics system Model ASAP 2010. The hydrogen chemisorption experiments at room temperature were performed in a pressure range of 1 to 300 mm Hg followed by a second adsorption isotherm of H_2 after outgassing at room temperature in the same equipment. The amount of hydrogen irreversibly adsorbed was obtained by subtraction of both isotherms. X-ray diffraction (XRD) patterns were obtained on a Rigaku diffractometer using a Ni filter and Cu $K\alpha_1$ radiation. Intensity was measured by scanning steps in the 2θ range between 3° and 70° at 1°/min^{-1}. TEM studies were carried out by using a Jeol Model JEM-1200 EXII System. XPS studies were recorded using an Escalab 200R spectrometer provided with a hemispherical analyser, operated in a constant pass energy mode and unmonochromatized Mg K_ X ray radiation (h_ = 1253.6 eV) operated at 10 mA and 12 kV. The system was provided with a reaction cell which allows pretreatment at high temperatures. The catalysts were reduced *in situ* in hydrogen at 773 K for 2 h and then transported to the analysis chamber without contact with air. The surface Ir/Si, Ir/Ti and Ir/Mo were estimated from the integrated intensities of the Ir $4f_{7/2}$, Si 2p, Ti 2p and Mo 3d lines after background subtraction, and corrected by the atomic sensitivity factors [20]. The lines of Si 2p at 103.4 eV and of C 1s at 284.9 eV were used as internal standards. Ir peaks were decomposed into several components assuming that the peaks had Gaussian-Lorentzian shapes.

2.3 Catalytic evaluation

Hydrogenation in the liquid phase of 1-phenyl-1,2-propanedione was carried out in a stainless steel batch reactor at 298 K and a hydrogen pressure of 40 bar. The hydrogen pressure was kept constant during the reaction. In the enantioselective hydrogenation reactions using cinchonidine as a modifier, the premixing method was used. The powdered catalyst was reduced in a H_2 stream at 773 K, and the catalyst imbibed in the solvent was then fed to the reactor and stabilized at the reaction temperature, 298 K, under nitrogen, and subsequently the modifier, substrate and remaining solvent were added to the reactor. Hydrogen was flashed into the reactor at atmospheric pressure to remove the inert gas and then pressurized up to 40 bar. The solvents used in this study were acetic acid (glacial GR-Merck, 100%) and chloroform (GR for analysis-Merck). In all experiments the volume of solvent in the pressured batch reactor was 50 ml, the cinchonidine and 1-phenyl-1,2-propanedione concentrations were 10^{-4} M and 0.0223 M respectively, and the weight of the catalyst was 50 mg.

Samples were taken periodically from the reactor and analyzed in a gas chromatograph-mass spectrometer (GCMS-QP5050 Shimadzu) provided with a chiral β-dex 225 column (30 m; Supelco). A scheme of the reaction is shown in Fig.1.

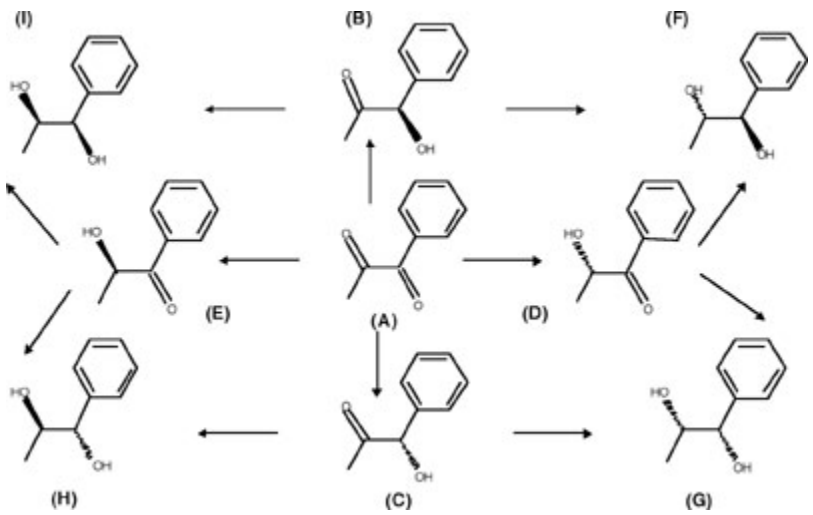


Fig. 1.- Reaction scheme of hydrogenation of (*A*) 1-phenyl-1,2-propanedione. (*B*) (R)-1-phenyl-1-hydroxy-2-propanone; (*C*) (S)-1-phenyl-1-hydroxy-2-propanone; (*D*) (R)-1-phenyl-1-keto-2-propanol; (*E*) (S)-1-phenyl-1-keto-2-propanol; (*F*) (1R,2S)-1-phenyl-1,2-propanediol; (*G*) (1R,2R)-1-phenyl-1,2-propanediol; (*H*) (1S,2R)-1-phenyl-1,2-propanediol; (*I*) (1S,2S)-1-phenyl-1,2-propanediol.

The ee of (R)-1-phenyl-1-hydroxy-2-propanone and regioselectivity (rs) are defined as:

$$ee = \frac{[B]-[C]}{[B]+[C]} \times 100\%$$

$$rs = \frac{[B]+[C]}{[D]+[E]} \times 100\%$$

where B = (R)-1-phenyl-1-hydroxy-2-propanone; C = (S)-1-phenyl-1-hydroxy-2-propanone; D = (R)-1-phenyl-1-keto-2-propanol, and E = (S)-1-phenyl-1-keto-2-propanol

2. RESULTS AND DISCUSSION

3.1 Characterization.

Table 1 summarizes the specific surface areas, H/Ir ratios obtained from chemisorption, and metal particle size evaluated from TEM micrographs. Significant differences can be seen in the surface area of the supports used, ranging from 3 to 150 m^2/g. The H/Ir ratio varies from 0.43 for the Ir/SiO_2 catalyst, down to extremely low values, lower than 0.10, in the samples supported on TiO_2, and even lower on MoO_3. The low Ir exposure for the Ir/TiO_2 catalyst is not a consequence of larger Ir particles size, but is the result of a partial surface coverage of Ir surface atoms by TiO_x species generated by the reduction of the solids at high temperature, due to the so called SMSI effect, leading to a surface coverage of the metal crystals. This behaviour is also supported by the TEM results. For Ir/MoO_3 the low H/Ir value is a consequence of both factors, large metal particle size (5 nm) which implies low dispersion, and coverage of the Ir crystals by mobile MoO_x species.

Table 1. Specific surface areas, H/Ir ratio and metal particle size of Ir catalysts:

Catalyst	Surface area, m^2g^{-1}	H/Ir (%)	d_{TEM} ,nm
Ir/SiO_2	148	43	1.7
Ir/TiO_2	54	10	2.1
Ir/MoO_3	3	3	5.0

Figure 2 shows the TPR profiles of the catalysts studied. The Ir/SiO_2 sample shows a single reduction peak centered at 357 K attributed to the reduction of iridium oxide. The reduction profile shown by the Ir/TiO_2 sample is more complex. At 384 K reduction of iridium species occurs, and at temperatures close to 450 K partial reduction of the support begins, showing a peak centered at 506 K. With regard to the Ir/MoO_3 sample, the profile shows some similarities with those previously described for Ir/TiO_2, but with higher H_2 consumption. This may be attributed to a greater extent of the reduction of the support induced by hydrogen spillover. This result is also supported by XPS studies. For comparison, the TPR of MoO_3 is also given. It is clearly seen that reduction of the pure MoO_3 takes place at higher temperatures and occurs to a smaller extent compared with the Ir/MoO_3 sample.

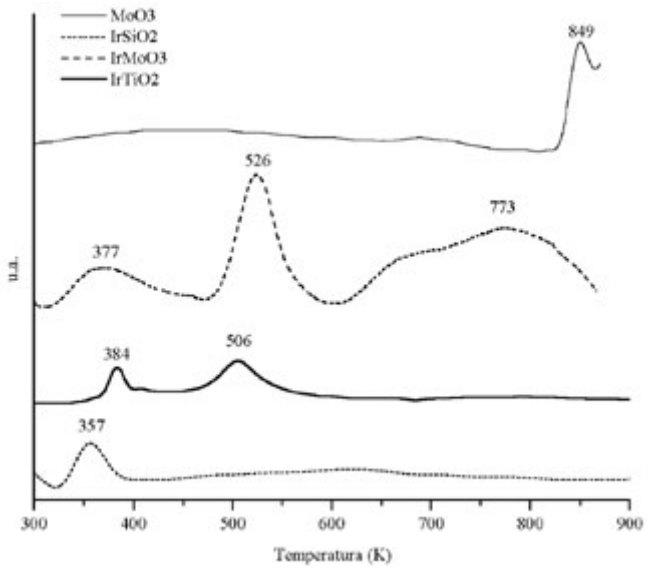
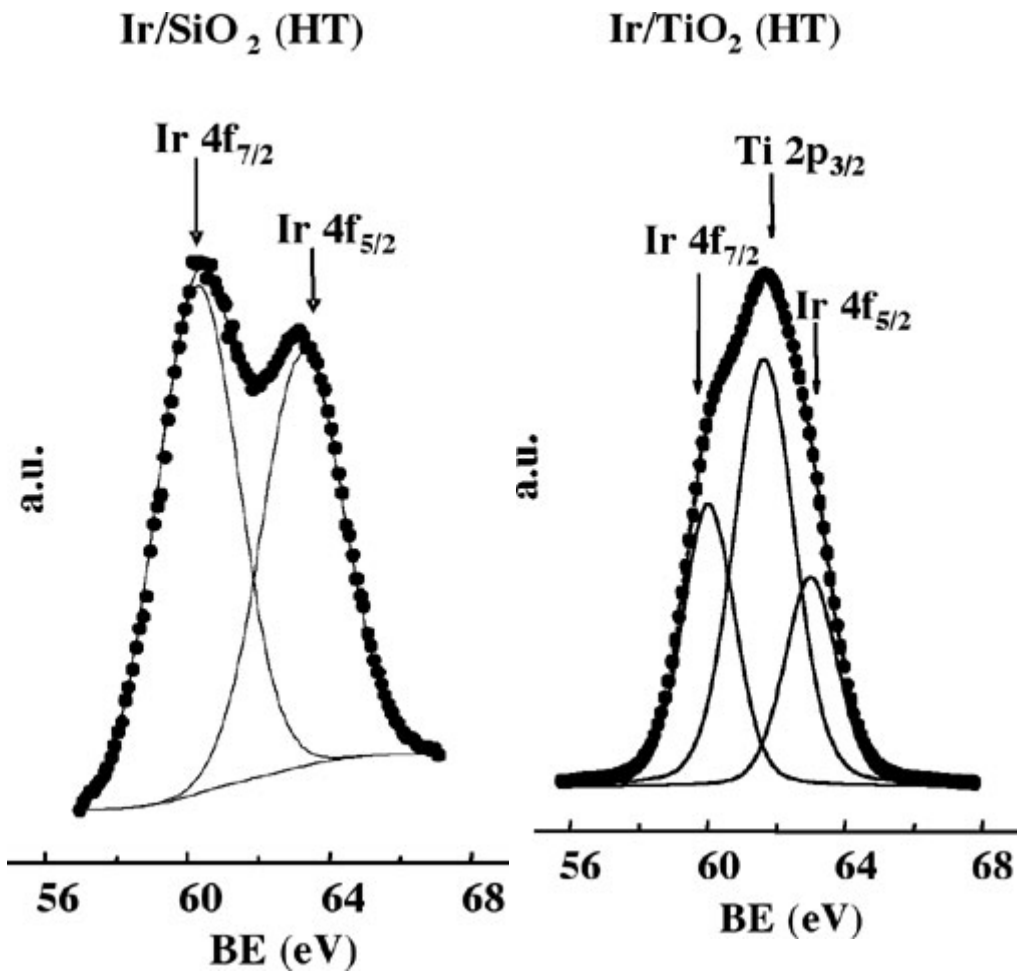


Fig. 2.- TPR profiles of Ir supported catalysts.

Figure 3a shows the Ir $4f_{7/2}$ core level for the reduced catalysts. It can be seen that Ir/SiO_2 has the expected spectrum, centered at 60.3 eV, corresponding to Ir° species. The spectrum of Ir/MoO_3 is more complex, and it is possible to detect a broadening due to Ir° and Irδ+ species. In the case of Ir/TiO_2, the spectrum in the recorded B.E. range involves, beside the Ir signal, that corresponding to Ti $2p_{3/2}$, making more difficult the deconvolution of the curve. Nevertheless, the presence of $Ir\delta^+$ in this catalyst may also be expected. The presence of partially reduced species of the supports (TiO_x and MoO_x) is responsible for the slight electron deficiency seen in the iridium species. Fig 3b shows the Mo 3d core level. It can be deconvoluted into two species, one with BE close to 230 eV, usually assigned to MoO_2, while the other one at 231.6 eV is attributed to MoO_3. Table 2 summarizes the B.E. of Ir $4f_{7/2}$, Ti $2p_{3/2,}$ Si 2p and Mo 3d and the Ir/M atomic surface ratios (M = Si, Ti or Mo) for the catalysts studied. As expected, significant differences in the Ir/M ratios were detected, with the lowest being that of the sample supported on SiO_2, the catalyst that has the largest surface area and metal dispersion.


Ir/SiO 2 (HT)
Ir 4f7/2
Ir 4f5/2
a.u.
56
60
64
68
BE (eV)
Ir/TiO2 (HT)
Ti 2p3/2
Ir 4f7/2
Ir 4f5/2
a.u.
56
60
64
68
BE (eV)

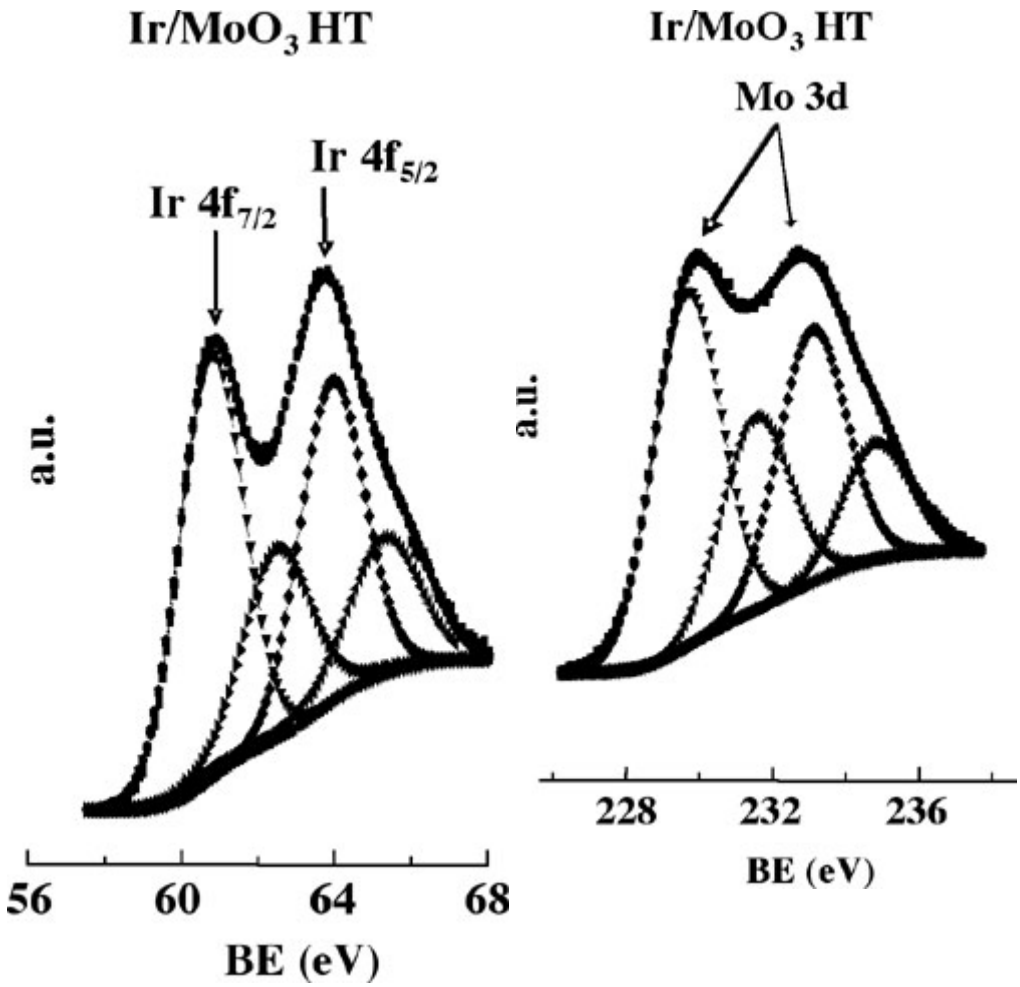


Fig.3.- Ir 4f core level spectra of reduced Ir catalysts. a), b) and c), and Mo 3d of Ir/MoO_3 catalyst

XRD studies of the different samples detected only the lines attributed to the supports, MoO_3 (and MoO_2 generated by the reduction treatment) and TiO_2 (anatase and rutile, the former in higher proportion), whereas no lines were observed in SiO_2, an amorphous support.

Table 2. Binding energies (eV) and Ir/M (M = Si, Ti or Mo) of reduced supported Ir catalysts.

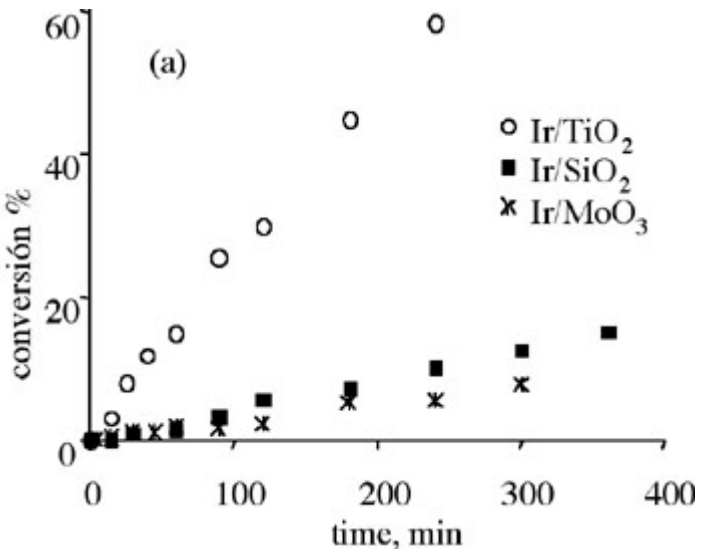
Catalyst	Ir $4f_{7/2}$	Ti $2p_{3/2}$	Si 2p	Mo $3d_{5/2}$	Ir/M (Si,Ti or Mo)
Ir/SiO_2	60.3	—	103.4	—	0.0042
Ir/TiO_2	60.6	458.5	—	—	0.027
Ir/MoO_3	60.8(70)	—	—	229.9 (65)	0.115
	63.0(30)			231.6 (35)	

Catalytic activity

The enantioselective hydrogenation of 1-phenyl-1,2-propanedione was

carried out at 25 C and 40 bar of H_2 in acetic acid or chloroform over modified supported Ir catalysts. Typical kinetics curves of the hydrogenation of 1-phenyl-1,2-propanedione on the three different supports, Ir/TiO_2, Ir/SiO_2 and Ir/MoO_3, are shown in Fig. 4a and 4b for two different solvents, acetic acid and chloroform, respectively. The reaction is usually assumed to be first order with respect to the reactant, in agreement with the kinetic studies of Margitfalvi et al.[7] for the enantioselective hydrogenation of ethyl pyruvate, and generally the log (1-X) *vs.* t plots have two segments. The first is used as representative of the first order reaction, while the second also includes interactions of the solvent with the modifier and the substrate as well as the presence of the other products of side reactions, such as cinchonidine dimerization. The first-order rate constants obtained in acetic acid for the three catalysts, calculated from the first 60 min of reaction, are shown in Table 3.

The hydrogenation rate was greater with Ir/TiO_2 than with the other catalysts in the presence of both acetic acid and chloroform as solvents. The conversion of the diketone with the three systems studied increases with reaction time, even though the Ir/MoO_3 catalyst showed a much lower increase, reaching 5.5% conversion at 240 min, while for the same reaction time the conversions with Ir/TiO_2 and Ir/SiO_2 were 45% and 8%, respectively. The low conversion level achieved by the Ir/MoO_3 catalyst may be attributed to the small amount of superficial metallic Ir shown by this catalyst. The reaction studied in chloroform as solvent (see Fig. 4b.) shows that the observed trends are similar to that previously discussed for the Ir/TiO_2 HT catalyst, but they reach a rather constant conversión value (2% conversion) in the Ir/SiO_2 HT catalyst. Activity in chloroform is lower compared to that shown by the same catalysts in acetic acid, and the induction time present in these curves, attributed to the interaction between cinchonidine and substrate in the solvent (by solvation), is striking. The above results showed that the first order reaction rate is affected by the dielectric constant of the solvent.



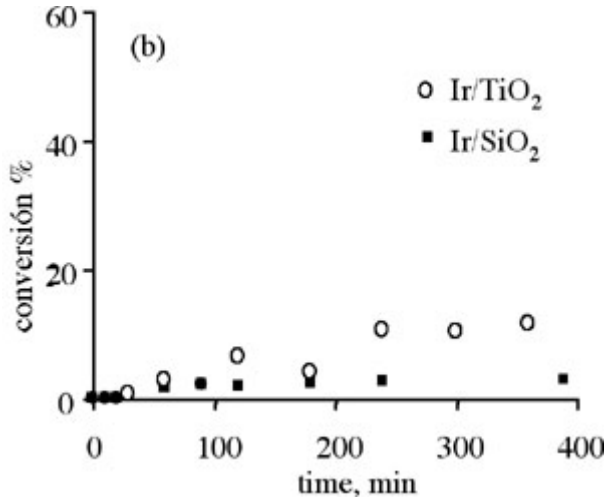


Fig. 4.- Hydrogenation of 1-phenyl-1,2-propanedione over Ir catalysts at 40 bar and 298 K. Effect of the solvent on the evolution of the conversion level over time. a) acetic acid; b) chloroform.

Tabla 3. First-order rate constant in the hydrogenation of 1-phenyl-1,2-propanodione at 298 K obtained in acetic acid and chloroform as solvents

Catalyst	Acetic acid	Chloroform
	k_1 min^{-1}	k_1 min^{-1}
Ir/TiO_2	0.0419	0.0146
Ir/SiO_2	0.0076	0.0044
Ir/MoO_3	0.0045	0.0025

Figure 5 shows the evolution of the enantiomeric excess during the reaction for the three catalysts in both solvents. The ee has a maximum value of 20% at 120 min with Ir/TiO_2 HT catalysts, then its decreases to 16% as conversion increases. The same effect occurs with the Ir/MoO_3 HT catalysts, but this value is slightly lower than that of the Ir/TiO_2 HT catalysts (see Table 4). In the case of Ir/SiO_2 HT, the ee remained constant (11%) with increasing conversion. Although these values are lower, they are not unusual and they are in agreement with previous results that have shown low activity and ee for the hydrogenation of diketones. In fact, the hydrogenation 1-phenyl-1,2-propanedione is considered a very difficult reaction for inducing enantioselectivity. Blaser et al. [21] have summarized the activity and ee of different activated ketones and they have shown that the hydrogenation of 1,2-butanedione and 1-phenyl-1,2-propanedione lead to lower ee. They have explained this behavior considering that the hydrogenation of the desired hydroxy ketones is faster compared to the substrate, thus the reaction leads to a greater extent to the corresponding diol (kinetic resolution).

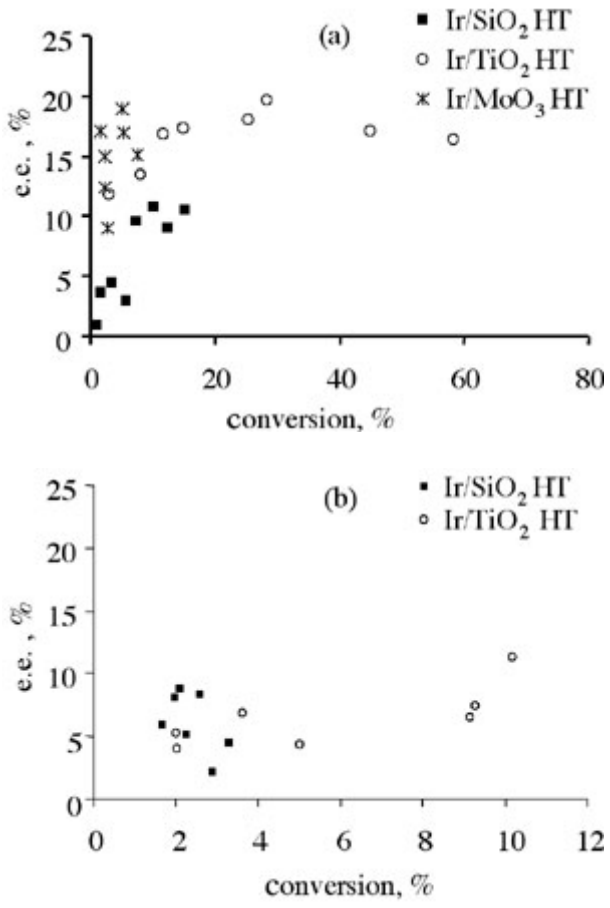


Fig. 5.- Hydrogenation of 1-phenyl-1,2-propanedione over Ir catalysts at 40 bar and 298 K. Enantiomeric excess as a function of conversion level. Solvent a) acetic acid; b) chloroform.

Tabla 4. Support and solvent effect on enantioselectivity in the hydrogenation of 1-phenyl-1,2-propanodione.

Catalyst	Solvent	Conversion	ee_{max} (%)	rs_{max} (max)
Ir/SiO_2	Acetic acid	15	11	660
	Chloroform	3	9	280
Ir/TiO_2	Acetic acid	58	20	630
	Chlorform	10	11	400
Ir/MoO_3	Acetic acid	8	19	(a)
	Chlorform	—	—	—

Reaction conditions: T=25 °C, P = 40 bar, [1-phenyl-1,2-propanedione] = 0.0223M, [CD] = 1.02×10^{-4} M, catalyst = 0.05 g, reaction time = 240 min.

(a) No 2-hydroxyketone formation was detected.

Nevertheless, high values for the regioselectivity (Fig. 6) were achieved with both Ir/TiO_2 HT and Ir/SiO_2 HT catalysts (Table 4), but these values were lower in chloroform as the solvent. These values are much higher than those reported previously [13] for the same kind of reaction conducted on Pt catalysts, and this is because Ir catalysts display low activity for the hydrogenation of 2-hydroxy ketones. Additionally, under the conditions studied, the hydrogenation of both C=O groups to produce diols was not detected, in contrast to Toukoniitty's results obtained on Pt catalysts. This is one of the main characteristics of the modified supported Ir catalyst because the separation of the products is difficult and expensive.

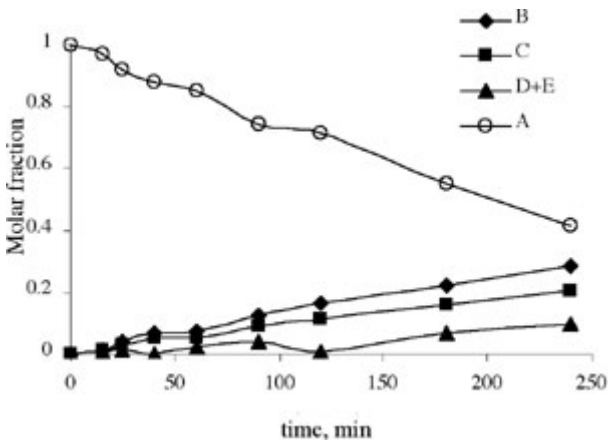


Fig. 6.- Kinetics of the hydrogenation of 1-phenyl-1,2-propanedione in acetic acid over Ir/TiO_2 HT at 298 K and 40 bar: (o) A: 1-phenyl-1,2-propanedione; (®) B: (R)-1-phenyl-1-hydroxy-2-propanone; ( ) C: (S)-1-phenyl-1-hydroxy-2-propanone; (D) D: (R)-1-phenyl-1-keto-2-propanol + E: (S)-1-phenyl-1-keto-2-propanol

The effect of the solvent on the enantioselective hydrogenation of 1-phenyl-1,2-propanedione was evidenced in the previous results. It has already been reported that the solvent has an important effect on the enantioselectivity of the cinchona modified catalysts. Nevertheless, only a few solvents have been tested. The first systematic research of the effect of the solvent on the ee reported an optimum selectivity for solvents with a dielectric constant between 2 and 10 [5]. The effect of several organic acids and bases used as solvents and additives for the enantioselective hydrogenation ofa-ketoesters with cinchona-modified platinum catalyst was studied. Carboxylic acids have a positive influence on the enantioselectivity of the reaction, both as solvents and as additives. The best results were observed in acetic acid, where the optical yields increase between 8 and 12% compared to toluene or ethanol as solvents. In addition, extremely low modifier concentrations are necessary. For the hydrogenation of ethyl pyruvate, using a special wide pore Pt/Al_2O_3 catalyst and 10,11-dihydro-O-methylcinchonidine as modifier, the highest value ever reported for any chiral heterogeneous catalyst is 95% enantioselectivity. Even though bases are not suitable as solvents, in some cases they have a beneficial effect as additives at low concentration. With regard to the reaction rates, it has been found that only slight changes are produced without showing a clear correlation with polarity. Murzin et al. [13,18] have studied the solvent effect in the hydrogenation of 1-phenyl-1,2 propanedione on Pt/Al_2O_3 in the presence of cinchonidine as modifier, giving a higher ee (65%) of (R)-1-hydroxy-1-phenyl-2-propanone when the reaction was carried out in dichloromethane, and a lower ee when ethyl acetate or methanol were used as solvent.

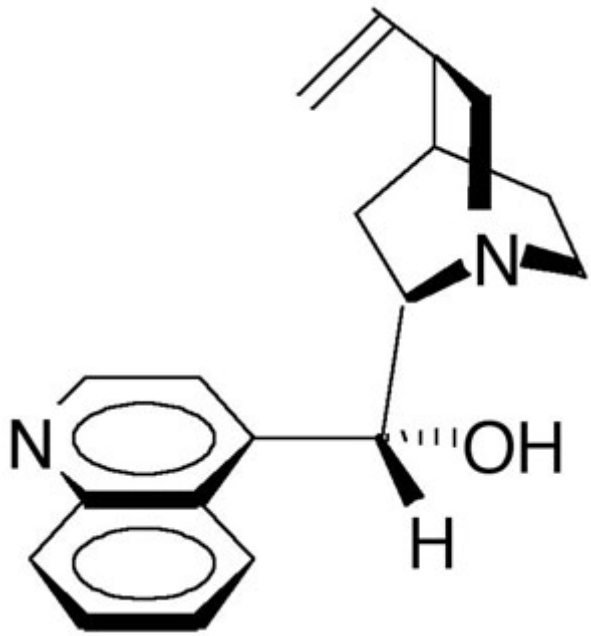


Fig. 7.- Cinchonidine structure, Open(3) conformer.

In the present work the differences displayed in the catalytic activity when acetic acid and chloroform are used as solvents with the three catalysts studied may be explained on the basis of two main effects: (i) the

concentration of cinchonidine Open(3) conformer (see Fig. 7) and (ii) the activating effect on the C=O bond of the substrate induced by a protic solvent.

Bürgi and Baiker [22] have studied the importance of the solvent-dependent cinchonidine conformation in the hydrogenation of activated carbonyl compounds over cinchonidine-modified Pt catalysts. The achieved enantiomeric excess shows the same solvent dependence as the fraction of Open(3) conformer in solution, suggesting that this conformer plays a crucial role in the enantiodifferentiation. Both NMR experiments and *ab initio* calculations show that the Open(3) conformer of cinchonidine is the most stable conformer in nonpolar solvents. The stabilization of the closed conformers is mainly due to their larger dipole moment as compared to Open(3). In polar solvents the fraction of cinchonidine adopting a closed conformation is more than 50% at room temperature. Agreement between the experiment and the calculations is within about 0.3 kcal/mol.

On the other hand, different authors have pointed out that modifier concentration plays an important role on selectivity. Margitfalvi et al. [23] reported that during pyruvate hydrogenation the dependence on modifier concentration shows a bell type curve. At lower CD concentrations only a slight fraction of the metallic phase is covered by the modifier, and low enantioselectivity can be achieved. Conversely, at higher CD concentration the formation of dimers $(CD)_2$, which are inactive species, is likely, thus limiting the amount of the desired enantiomer. Therefore, since in the present study the same CD concentration was used in all experiments, and the catalysts had the same metal load but different metal dispersion, the CD concentration was not optimized for the system studied. The low cinchonidine concentration can be the reason for the ee value observed with both the Ir/TiO_2 HT and Ir/MoO_3 HT catalysts. These results are in agreement with different authors [5, 24, 25] who have studied hydrogenation rate and ee as a function of modifier concentration in the hydrogenation of ethyl pyruvate to (R)-ethyl lactate. Further improvements in the experimental conditions have led to significant increases in reaction rate and enantioselectivity [26].

There is much evidence that the choice of support is important because it affects activity and enantioselectivity in the hydrogenation of many substrates. As a matter of fact, the effect of the support on catalytic performance in the hydrogenation of ethyl pyruvate over silica, alumina, active charcoal and zeolite-supported Pt catalysts using cinchonidine as modifier has been studied [27, 28]. The support itself may display not only a slight effect on the reaction, but it can also affect strongly the metal dispersion. It is well known that metal particle size affects not only the activity but also the selectivity. Thus, for Pt catalysts used in the hydrogenation of ethyl pyruvate, relatively large Pt particles with dispersions lower than 50% have yielded the best results [3]. Similar studies on other reactions have also been made. In the hydrogenation of 1-phenyl-1,2-propanedione, Toukoniitty et al. [29] have studied two different commercial catalysts, 5%-Pt/C and 5%-Pt/Al_2O_3, with mean metal particle sizes of 1.5 and 8.3 nm, respectively. The hydrogenation rate was higher with the Pt/C catalysts than with Pt/Al_2O_3, but the ee of (R)-1-phenyl-1-hydroxy-2-propanone was lower with the Pt/C catalysts than with Pt/Al_2O_3. The low ee obtained over Pt/C catalysts was attributed to the smaller mean Pt particle size. According to the literature [29], these results are due to the fact that catalysts with larger mean Pt particle size give higher

enantioselectivities.

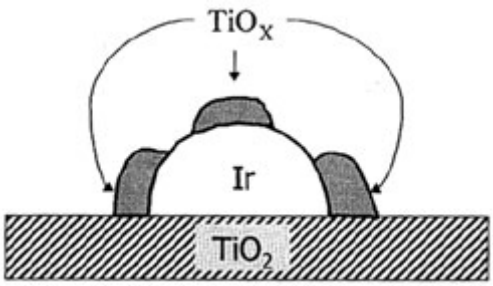


Fig. 8.- Scheme of surface coverage of Ir/TiO_2 catalyst.

The observed differences in the behavior of the catalysts studied in this work, Ir/SiO_2, Ir/TiO_2 and Ir/MoO_3, can be attributed mainly to differences in the performance of the support. Thus, the Ir/SiO_2 catalyst has iridium crystallites with particle size close to 1.7 nm, and the metal is essentially Ir°. Although in the Ir/TiO_2 catalyst the metal particles have similar size, 2.1 nm, the metal is not fully reduced because of a partial migration of TiO_x species over the Ir species, leading to a partial coverage of Ir crystals. This feature is even more significant in the Ir/MoO_3 catalyst, in which a reduction of the MoO_3 takes place to a large extent, and the partially reduced MoO_x species migrate over the Ir crystals producing a significant coverage of the Ir particles, and by electronic transfer generate Ird+ species. Additionally, in this sample, due to the small surface area of the support, the metal particle size is larger (5.0 nm) than that of the other catalysts studied. These two facts are of great importance because the presence of electron deficient metal particles favors the polarization of the carbonyl group of the ketones and aldehydes [30, 31, 32], leading to an enhancement of the catalytic activity [33] which occurs essentially in titania- and molybdena-supported Ir catalysts. The better performance of the former catalyst can be attributed to its particle size. As already mentioned, different authors have pointed out that the hydrogenation of diketones requires a metal particle size of around 3 nm, which is closer to that shown by Ir/TiO_2 than by Ir/MoO_3.

To understand the rather low enantiomeric excess obtained under the experimental conditions used, it should be kept in mind that it is necessary to create a chiral site, otherwise the reaction leads to the racemic mixture, as occurs on unmodified metal sites. A chiral site is formed by the adsorption of a modifier molecule on the metal surface. There is no doubt that the chiral modification step is the key to enabling the catalyst to behave enantioselectively. To explain the mechanism of enantioselective promotion, specifically the mode of action of Pt-cinchona modifiers on the a-functionalized ketone system, several studies have been made [33, 34c, 6a, 35]. The most widely accepted model, which has been proposed by various groups (Blaser, Baiker and Wells), is the so-called "*active chiral site model*". In this model there is no requirement for the formation of an ordered arrangement of modifiers. Instead, the chiral-directing interaction is proposed to occur between a single adsorbed modifier and a reactant molecule. If the chiral modifier is adsorbed parallel to the surface via its aromatic ring system, steric constraints imply that the N atom of the quinuclidine moiety would be unable to interact with the surface and hence

would be available to interact with the reactant molecule. It is proposed that, during the hydrogenation reaction, the protonation of either the N atom or the ketone O atom results in the ability to form a H-bonding interaction between the N atom of the quinuclidine moiety and the ketone group of the reactant. If the geometry of the α-ketoester is sterically constrained so that the intermediate to the R-product is favoured over the intermediate to the S-product, enantioselective hydrogenation would ensue. The stabilization of this partially hydrogenated intermediate by the modifier was also thought to be hydrogenated more rapidly than an isolated a-ketoester molecule, accounting for the rate enhancement observed on chirally modified surfaces [36].

The second model, proposed by Margitfalvi et al. [37], the *"shielding effect model,"* suggests the formation of a weak complex between the modifier and the substrate in the liquid phase. In that complex the modifier provides a specific shielding effect (SE). Due to the particular character of the shielding, the α-ketoester can interact with the metal surface only by its unshielded side. If the reactivity of the substrate in the shielded substrate-modifier complex is higher than that of the free substrate, significant enantiodifferentiation should be observed. In one of the shielded forms, the proper directionality of the quinuclidine nitrogen towards the carbonyl group provides the increased reactivity of the carbonyl group. Even though calculations seem to be able to predict the preferred adsorption mode of the C=O bond, it is not clear which specific (repulsive) interactions are responsible for the discrimination. For the α-ketoethers, the favored formation of the (R,S)-isomers was proposed to be due to the steric effect of the methyl group in the adsorbed state. However, it is necessary to carry out the study of different interactions by others techniques such as NMR [37], FTIR spectroscopy [38], near-edge X-ray absorption fine structure (NEXAFS) [39, 40, 41] to develop the model of each of the specific systems.

Whatever the model, competition between the substrate and the modifier, or substrate and supramolecule to be adsorbed on the metal surface, may also be important to understand the ee obtained. Thus, if the modifier (or the supramolecule) is preferentially adsorbed, an important ee may be expected. Conversely, if the substrate is preferentially adsorbed, almost no chiral induction takes place and consequently a low ee should be obtained.

CONCLUSIONS

The hydrogenation of 1-phenyl-1,2-propanedione at 40 bar and 298 K was studied on different cinchona-modified supported Ir catalysts. It was found that Ir/SiO_2 and Ir/TiO_2 catalysts reduced at high temperatures, 773 K, have similar metal particle size, close to 2.0 nm, even though the H/Ir ratio obtained from H_2 chemisorption showed greater differences (high for the former and low for iridium catalysts supported on titania and molybdenum,supported iridium catalysts). In these samples, the migration of the partially reduced supports, TiO_x and MoO_x moieties, on the metal crystals induce the creation of Ird+ species. TPR and XPS results are in line with these findings.

It was found that the nature of the support affects the catalytic performance of the solids during the hydrogenation of 1-phenyl-1,2-propanedione, especially in catalysts in the SMSI state such as Ir/TiO_2 and

Ir/MoO_3. This has been attributed to the present of electron deficient metal species, $Ir\delta+$, which are responsible for the polarization of the carbonyl bond of the substrates, thus favoring the activity and the enantioselectivity of the reaction. It should be emphasized that high regioselectivity values were obtained with all the catalysts.

The effect of the solvent was also studied. Experiments carried out in acetic acid as solvent led to better results. This behaviour was attributed to two main effects: the activation effect of the C=O bond of the substrate induced by a protic solvent, and the fact that polar solvents increase the extent of the active conformer of the cinchonidine (Open(3) conformer), which increases selectivity to the desired enantiomer.

ACKNOWLEDGMENTS

The authors thank the support of Núcleo Científico Milenio ICM P99-92, and FONDECYT Grant 1030670.

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