

# Diastereoselective hydrogenation of *o*-toluic acid coupled with (*S*)-proline and (*S*)-pyroglutamic acid methyl esters on ruthenium catalysts

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## Abstract

The diastereoselective hydrogenation of two *o*-toluic acid derivatives, *N*-(2-methyl-benzoyl)-(*S*)-proline methyl ester here named substrate **1**, and *N*-(2-methyl-benzoyl)-(*S*)-pyroglutamic acid methyl ester abbreviated as substrate **1'**, was studied on metallic ruthenium particles deposited on two oxidic supports, Al<sub>2</sub>O<sub>3</sub> and SiO<sub>2</sub> and on different carbon materials, such as an activated carbon, a carbon molecular sieve and two high surface area graphites. The asymmetric induction was dependent on the chiral auxiliary employed: *cis* isomers were formed preferentially, with configuration (1*R*, 2*S*, 2'*S*) and (1*S*, 2*R*, 2'*S*) for substrates **1** and **1'**, respectively. The diastereoselectivity also depended on the nature of the support and higher values of diastereomeric excess (d.e.) were obtained on catalysts supported on metal oxides, 35% for substrate **1** and 82% for **1'**, than on catalyst supported on carbon materials, 23% for substrate **1** and 61% for **1'**. No relevant effects were found among the various allotropic forms of carbon. The introduction of an additive, ethyldicyclohexylamine (EDCA), in the hydrogenation solution of substrate **1** reduced the d.e. from 21 to 10% for high surface area graphite catalyst, while for alumina supported catalyst the d.e. was inverted from 35% (1*R*, 2*S*, 2'*S*) isomer to 2% in favour of isomer (1*S*, 2*R*, 2'*S*). All these findings confirm the importance of catalytic supports in modifying the adsorption properties of ruthenium particles deposited on them. © 2000 Elsevier Science B.V. All rights reserved.

**Keywords:** Stereoselective hydrogenation; Ruthenium catalysts; Proline auxiliary; Pyroglutamic acid auxiliary

## 1. Introduction

Asymmetric catalysis provides a powerful strategy for the synthesis of optically pure chiral compounds. Two approaches have been applied to the reduction of functionalised C=O, C=C and C=N groups using

heterogeneous catalysts. In the enantioselective hydrogenations, the catalyst is modified with a chiral auxiliary. However, only few catalytic systems have resulted efficient, i.e. platinum catalysts modified with cinchona alkaloids for the hydrogenation of  $\alpha$ -keto esters [1,2], nickel catalysts modified with tartaric acid for the reduction of  $\beta$ -keto esters [3,4] and supported palladium catalysts in the presence of cinchona alkaloids for the hydrogenation of alkenoic acids [5]. On the other hand, in the diastereoselective hydrogenation

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tion reactions, the auxiliary that contains the chirality inducing group is bonded to the substrate before reaction, and later removed to obtain the products. This latter method has been applied in recent years to the reduction of substituted aromatic compounds to the corresponding optically active cyclohexyl compounds, which are constituents of biologically active molecules [6–14]. The effect of several factors on the activity and on the asymmetric induction has been analysed in some recent reports, among them, nature of the active metal, structure of the chiral auxiliary, solvent, support or additives. Specifically, it has been shown that the selectivity of the diastereoselective hydrogenation of *o*-toluic acid was largely influenced by the nature of the chiral auxiliary, especially the steric hindrance induced on one face of the aromatic substrate.

In this paper, the study of the diastereoselective hydrogenation of *o*-toluic acid derivatives has been extended to supported ruthenium catalysts. The major aim of this work was to investigate the support effects in activity and diastereoselectivity, comparing two different chiral auxiliary, (*S*)-proline and (*S*)-pyroglutamic acid methyl esters. We have, therefore, studied the catalytic behaviour of ruthenium supported on metal oxides (alumina and silica) and several carbon materials (molecular sieve, activated carbon and high surface area graphites).

## 2. Experimental

### 2.1. Catalysts preparation

The supports used in the catalysts preparation were: Al<sub>2</sub>O<sub>3</sub> (Puralox Condea,  $S_{\text{BET}} = 192 \text{ m}^2 \text{ g}^{-1}$ ), SiO<sub>2</sub> (Aerosil Degussa,  $S_{\text{BET}} = 180 \text{ m}^2 \text{ g}^{-1}$ ), active carbon (ICASA, Spain,  $S_{\text{BET}} = 961 \text{ m}^2 \text{ g}^{-1}$ ), molecular sieve of carbon ( $S_{\text{BET}} = 970 \text{ m}^2 \text{ g}^{-1}$ ) and high surface area graphite ( $S_{\text{BET}} = 299 \text{ m}^2 \text{ g}^{-1}$ ). The carbon molecular sieve was prepared by calcination of the copolymer Saran (Aldrich) in N<sub>2</sub> flow at 1273 K [15]. The commercial high surface area graphite, here named H1, was supplied by Lonza. This graphite was treated under He at 1173 K resulting in graphite H3, which in contrast with H1 does not exhibit oxygen surface groups [16].

Catalysts supported on Al<sub>2</sub>O<sub>3</sub>, SiO<sub>2</sub> and active carbon, AC, were prepared by incipient wetness im-

pregnation with an aqueous solution of RuNO(NO<sub>3</sub>)<sub>3</sub> (Alfa). After impregnation, the catalysts were dried overnight at 383 K. Furthermore, catalysts Ru/Al<sub>2</sub>O<sub>3</sub> and Ru/SiO<sub>2</sub> were calcined in air at 723 K for 3 h.

Two catalysts were prepared over Saran derived carbon, S. Ru/S was prepared by impregnation of the outgassed support with an ethanol solution of RuNO(NO<sub>3</sub>)<sub>3</sub>. Catalyst RuCO/S was prepared by adsorption of Ru<sub>3</sub>(CO)<sub>12</sub> (Aldrich) in hexane solution. The latter method was also applied to the preparation of catalysts supported on graphite, RuCO/H1 and RuCO/H3 [17].

### 2.2. Characterisation of the catalysts

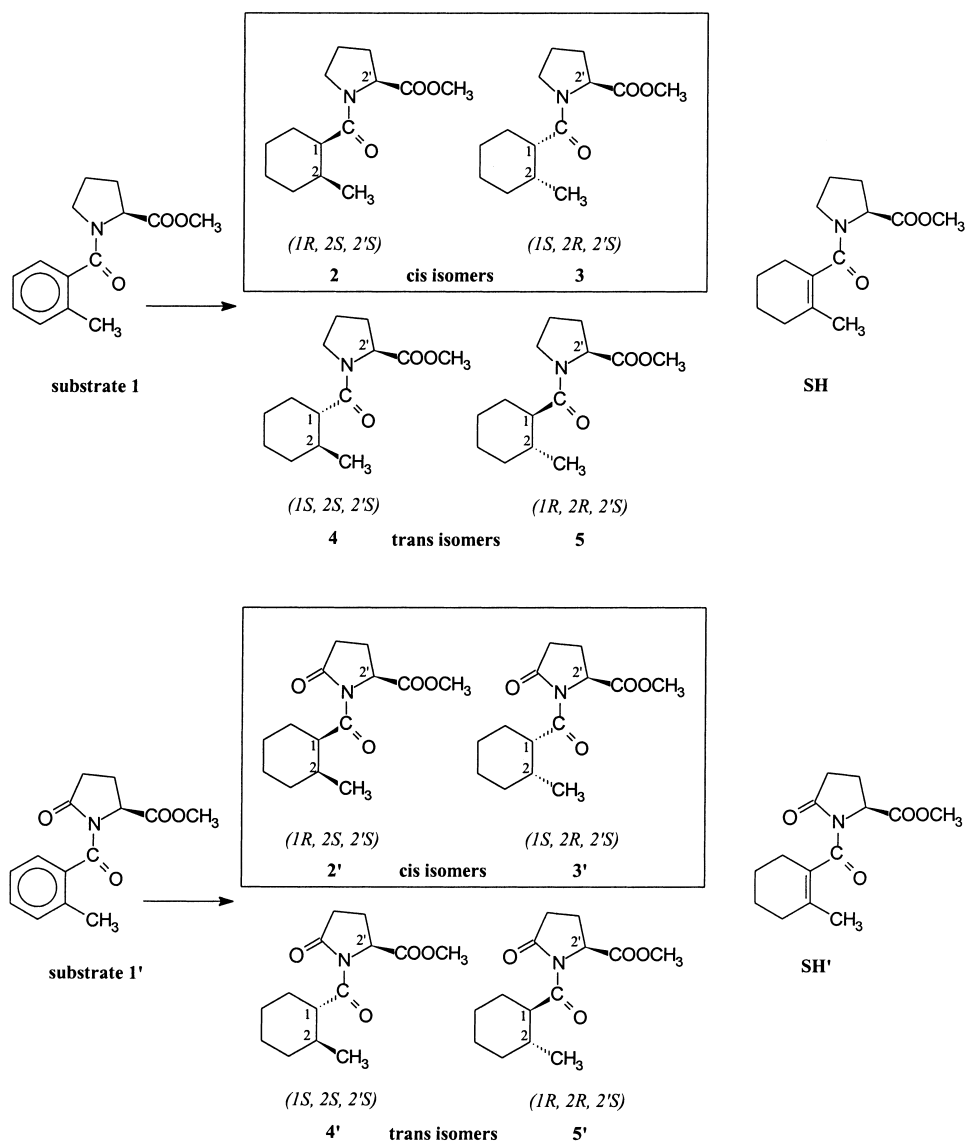
Ruthenium content of the catalysts prepared on carbon materials was determined by burning away the support in air at 1073 K and weighing the residue (RuO<sub>2</sub>, as verified by X-ray diffraction). Atomic absorption spectroscopy was also applied to obtain the metal loading of catalysts, after dissolution of the catalyst.

H<sub>2</sub> or CO chemisorption measurements were performed in a conventional volumetric system at 298 K. The samples were first reduced in H<sub>2</sub> at 673 or 723 K for 2 h. Hydrogen uptake was determined by extrapolation of the linear part of the isotherm to zero pressure. CO uptake was determined following the dual isotherm method. Complementary information of particle size was obtained from X-ray diffraction patterns of the reduced samples measured in a Philips PW 1050/81 apparatus using a filtered Cu K $\alpha$  radiation and a graphite monochromator. Also direct observation of samples by transmission electron microscopy (TEM) was performed with a JEOL 2010 microscope.

### 2.3. Activity measurements

The experimental procedure for the synthesis of substrates **1**, *N*-(2-methyl-benzoyl)-(*S*)-proline methyl ester, and **1'**, the *N*-(2-methyl-benzoyl)-(*S*)-pyroglutamic acid methyl ester, was described in [7,11]. In short, the substrates **1** and **1'** were prepared by coupling (*S*)-proline or pyroglutamic acid methyl ester with *o*-toluoyl chloride.

The hydrogenation was carried out in a 250 ml stirred autoclave (1200 rpm) at a hydrogen pressure of 5 MPa at room temperature. The substrate (2.2 mmol)



Scheme 1. Diastereoselective hydrogenation of substrate **1** *N*-(2-methyl-benzoyl)-(*S*)-proline methyl ester and substrate **1'** *N*-(2-methyl-benzoyl)-(*S*)-pyroglutamic acid methyl ester.

was dissolved in ethanol (130 ml) and the supported ruthenium catalyst (molar ratio substrate/Ru = 30) was transferred into the autoclave without contact with air, after reduction in the gas phase at 673 K for 2 h. In the experiments with addition of EDCA (ethyldicyclohexylamine), the molar ratio EDCA/Ru was 3.5. The distribution of products was followed by

repetitive sampling through a special valve. Samples were analysed by gas chromatography using a J&W DB 1701 column and a FID detector.

Scheme 1 shows the products and reaction intermediates identified by GC-MS and by  $^1\text{H-NMR}$  for substrates **1** and **1'** as described elsewhere [8,11]. The two *cis* hydrogenated isomers were predominantly formed

and the diastereomeric excess (d.e.) of *cis* isomers **2** and **3**, or **2'** and **3'** was defined as

$$\text{d.e.(\%)} = \left| \frac{[\% (1S, 2R, 2'S) - \% (1R, 2S, 2'S)]}{[\% (1S, 2R, 2'S) + \% (1R, 2S, 2'S)]} \right| \times 100$$

### 3. Results and discussion

#### 3.1. Characterisation of ruthenium catalysts

Table 1 lists the results of characterisation of the ruthenium catalysts (nominal content, particle size estimated from chemisorption, X-ray diffraction and TEM measurements). Catalysts supported on oxides, SiO<sub>2</sub> and Al<sub>2</sub>O<sub>3</sub>, present low dispersion values. This fact is probably due to the sintering and migration of RuO<sub>2</sub> species during the calcination process. The particle size determined from X-ray diffraction and TEM follows the same trend as the values obtained from chemisorption data.

Among the catalysts supported on carbonaceous materials, all the techniques point to Ru/AC catalyst as the highest dispersed, with ruthenium particles around 2–3 nm homogeneously dispersed on the activated carbon. Catalyst supported on Saran, Ru/S, was prepared by impregnation with an ethanolic solution of Ru(NO)(NO<sub>3</sub>)<sub>3</sub> after evacuation of the support in vacuum, to force the salt precursor entering into the pores (1.1 nm). XRD and TEM measurements indicate that the particles are well distributed all over the support with some concentration of particles at the edges

of the grains. The small particle size determined by these two techniques and the good distribution seem to indicate that the majority of the particles are inside the pores of the molecular sieve of carbon, Saran. The discrepancy with the mean particle size determined by hydrogen chemisorption is consequence of the well-established character of activated process that exhibits the hydrogen adsorption on ruthenium, more pronounced when the particle is smaller, as in the present situation [18]. On the other hand, XRD and TEM studies of catalyst RuCO/S show very large particles in concordance with the dispersion values determined by hydrogen chemisorption.

Catalysts prepared on graphite are rather regularly dispersed and both catalysts, RuCO/H1 and RuCO/H3, present a mean particle size of less than 4 nm. It has been proposed that this high dispersion is due to the specific interaction of the ruthenium carbonyl with the edges of the graphitic layers [17].

Results of the hydrogenation reaction of the two substrates **1** and **1'** over the different catalysts are summarised in Table 2. These results will be analysed in detail hereafter.

#### 3.2. Hydrogenation of substrate **1**

Reduction of substrate **1** led to the formation of the two *cis* isomers, **2** and **3**, and the semihydrogenated compound, SH, which went through a maximum and was hydrogenated subsequently once the substrate has been completely consumed or when its concentration was very low. The hydrogenation of this cyclohexene intermediate proceeded slower than that of the substrate. The *trans* isomers were obtained in small amounts (<5%). To illustrate this behaviour and as an example, the evolution of the product distribution with reaction time for Ru/Al<sub>2</sub>O<sub>3</sub> catalyst is shown in Fig. 1.

The initial reaction rates of the different ruthenium catalysts (Table 2), which were calculated from the slope of the curves conversion versus time (*t*) at *t* = 0, are in the same order as those previously reported for Rh and Ru catalysts in the same reaction [7–9]. Comparison of the catalysts reveals that the highest values are obtained for Ru/Al<sub>2</sub>O<sub>3</sub>, and for RuCO/H1 and RuCO/H3 catalysts, with very different particle sizes. Also it is observed that catalysts Ru/Al<sub>2</sub>O<sub>3</sub> and RuCO/S presenting similar ruthenium particle size show a great difference in the activity values.

Table 1  
Main characteristics of ruthenium catalysts reduced at 673 for 2 h

Catalyst	% Ru	Hydrogen chemisorption		<i>d</i> <sub>XRD</sub> (nm)	<i>d</i> <sub>TEM</sub> (nm)
		<i>D</i> (%)	<i>d</i> <sub>H</sub> (nm)		
Ru/Al <sub>2</sub> O <sub>3</sub>	2 <sup>a</sup>	7	18.8	14.1	10–20
Ru/SiO <sub>2</sub>	1.42	4	33.0	15.6	20–35
Ru/AC	1.60	51	2.6	n.d. <sup>b</sup>	2–5
Ru/S	1.23	5	26.4	n.d.	2–5
RuCO/S	0.60	6	22.0	16.4	10–20
RuCO/H1	0.80	33 <sup>c</sup>	4.0 <sup>c</sup>	–	–
RuCO/H3	1.00	–	–	–	2–4

<sup>a</sup> Nominal content.

<sup>b</sup> n.d.: indicates that the peaks assigned to metallic ruthenium were not detected.

<sup>c</sup> Determined by CO chemisorption after reduction at 723 K.

Table 2

Catalytic properties of the catalysts in the diastereoselective hydrogenation of substrates **1** and **1'** after reduction at 673 K

Catalyst	Substrate <b>1</b>			Substrate <b>1'</b>		
	Initial activity (mol h <sup>-1</sup> mol <sub>Ru</sub> <sup>-1</sup> )	SH (%)	d.e. (%) <sup>a</sup> (isomer <b>2</b> )	Initial activity (mol h <sup>-1</sup> mol <sub>Ru</sub> <sup>-1</sup> )	SH' (%)	d.e. (%) (isomer <b>3'</b> )
Ru/Al <sub>2</sub> O <sub>3</sub>	5.3	42	29 (36)	4.1	35	83
+ EDCA	1.3	25	2 <sup>c</sup>			
Ru/SiO <sub>2</sub> <sup>b</sup>	1.7	32	35	1.7	15 <sup>d</sup>	82 <sup>d</sup>
Ru/AC <sup>b</sup>	1.9	22	23			
Ru/S <sup>b</sup>	0.8	15	13			
RuCO/S	2.8	38	21 (34)			
RuCO/H1	4.2	42	21 (34)			
RuCO/H3	4.8	46	22 (36)	3.2	30	61
+ EDCA	4.5	36	10			

<sup>a</sup> Diastereomeric excess at 100% conversion of **1** or **1'**. Values in parentheses given at total conversion of SH.<sup>b</sup> Data measured at conversion lower than 60%.<sup>c</sup> Diastereomeric excess in favour of isomer **3**.<sup>d</sup> Data measured at 40% conversion.

The latter results indicate that the initial reaction rate depends not only on the metal active area. These findings may be compared to results reported previously for Rh catalysts [9]. In that case, active carbon supported catalysts were slightly more active than those supported on alumina, while graphite supported catalysts provided reaction rates 3–4 times lower

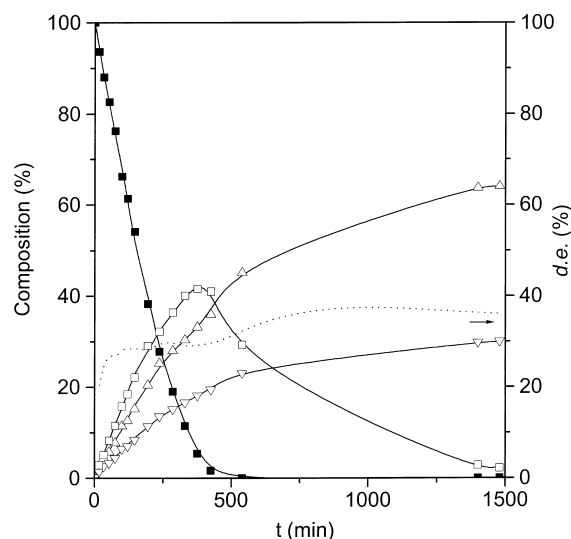


Fig. 1. Evolution of products distribution and d.e. with time in the hydrogenation of substrate **1**, *N*-(2-methyl-benzoyl)-(*S*)-proline methyl ester, over Ru/Al<sub>2</sub>O<sub>3</sub> catalyst, (■) substrate **1**, (△) isomer **2**, (▽) isomer **3**, (□) SH, (...) d.e.

than those supported on alumina or active carbon. This was attributed to steric constraints hampering the approach of the aromatic ring to the Rh particles located along the graphite steps [9]. From the present results, it could be inferred that the metal particles on RuCO/H1 and on RuCO/H3 are located on the basal planes of the graphite layers, which would facilitate the approach of the substrate molecule. However, calorimetric experiments of CO adsorption over these catalysts indicate that the metal particles are located on the edges of the graphite layers [17]. So that, additional factors such as electronic effects must control the adsorption of the molecule on the graphite supported catalysts.

For all the catalysts the diastereomer obtained in excess was the isomer **2**, as it has been earlier reported for carbon supported Ru and Rh catalysts [8]. Compound SH was produced in great amounts (40%) during the hydrogenation of **1** and was subsequently hydrogenated preferentially to the isomer **2**. The diastereomeric excess between the two *cis* isomers remained relatively constant with conversion of substrate **1**. At total conversion of the substrate, catalysts supported on metal oxides, SiO<sub>2</sub> or Al<sub>2</sub>O<sub>3</sub>, showed higher diastereoselectivity (35 and 29%, respectively) than the catalysts supported on carbon materials (13–23%). Similar support effects on the diastereoselectivity have been observed in the hydrogenation of (*S*)-proline modified anthranilic acid or *o*-toluidine with Rh and Ru catalysts, i.e. higher

d.e. for the catalysts supported on alumina [13,14]. However, the d.e. values increased independent of the support up to 35% at the end of the experiment, due to the nearly total hydrogenation of SH to yield isomer **2**, once the total conversion of **1** was achieved. It is interesting to note that all the catalysts supported on carbon materials, except Ru/S catalyst, reach similar d.e. values at 100% conversion of **1** (21–23%), these latter being therefore not dependent on the method of preparation, the particle size and the support structure or surface chemistry.

The substrate **1** exists as two probable conformations, with the proline moiety external with respect to the aromatic ring, in a ratio 80:20 [6,8]. The two faces of the conformers are not equivalent because of the bulkiness of the proline group on one of the faces. Therefore, the diastereoselectivity is controlled by the preferential adsorption of the conformers on the catalyst through one of the two faces of the aromatic ring, which is finally determined by electronic or steric effects. In the absence of these effects the reaction is unselective, because the hydrogenation can take place via both faces of the conformers without significant hindrance. Steric constraints may be imposed by the morphology of the metal particle [6], i.e. a flat surface favours the adsorption of the conformer via the less bulky side. In the present case, the range of particle size studied in the ruthenium supported catalyst is very wide, and there were not observed differences in the d.e. values for the catalysts supported on carbon materials. Then, the steric constraints that a more flat surface could impose to the approach of the molecule conformers seem not to be decisive. So that, the d.e. values obtained with Ru catalysts should be explained in terms of electronic interactions. The behaviour found for Ru catalysts has been ascribed to the anchoring (or haptophilic) effect of Ru that interacts strongly with the oxygen atoms of the carbonyl and carboxylic groups of the substrate due to its higher electropositive character in comparison with other metals. This fact orientates the adsorption of the conformers of the molecule in such a way that the conformer in higher proportion yields isomer **2** and the conformer in lower proportion gives isomer **3**, the final diastereoselectivity being in favour of isomer **2** [8]. Therefore, any modification in the electronic properties of the metal particles may influence these interactions and consequently the diastereose-

lectivity of the reaction. Then, the higher d.e. obtained with Ru/Al<sub>2</sub>O<sub>3</sub> and Ru/SiO<sub>2</sub> could be a consequence of a higher affinity of the Ru particles for the oxygen atoms due to the presence of non totally reduced species that are stabilised by interaction with the support. Earlier studies have pointed out the influence of these species on the catalysts reactivity. It has been suggested that a partly reduced catalyst is more active than a fully reduced one [8,14], and that during the hydrogenation reaction the catalyst becomes reduced inducing its progressive deactivation [14]. Also, the presence of oxidised species in the Rh/Al<sub>2</sub>O<sub>3</sub> catalyst has been claimed to explain the different behaviour of Rh catalysts supported on alumina and on carbon in the present reaction. Thus, oxidised species can interact more strongly with the aromatic ring and the oxygen atoms of the carbonyl and carboxyl groups [7].

Ru/S catalyst as mentioned before, did not show the same tendency as the rest of the catalysts supported on carbon materials. This catalyst presented lower activity and diastereoselectivity. The results could be indicative of steric constraints due to the control of the molecule diffusion into the small pores (1.1 nm), where the major part of the metal particles are located, as it was described above.

The addition of various amines was shown to influence the diastereoselectivity of the reaction [6,8]. Consequently, some experiments in presence of EDCA were carried out with catalysts Ru/Al<sub>2</sub>O<sub>3</sub> and RuCO/H<sub>3</sub>. These catalysts were selected because they are representative of the two types of supports used, an oxidic and a carbonaceous material. It can be seen in Table 2 that the activity is four times diminished for Ru/Al<sub>2</sub>O<sub>3</sub>, while for RuCO/H<sub>3</sub> it is almost the same. Similar drops in the reaction rates have been reported for Rh and Ru catalysts in the diastereoselective hydrogenation of some aromatic derivatives in the presence of amines as additives [9,13,14], which were attributed to the covering of the metal surface by the amine. Moreover, both catalysts show higher deactivation with time on reaction and the product distribution varies slightly, as it is shown in Fig. 2. The amount of SH is reduced from 42 to 25% for Ru/Al<sub>2</sub>O<sub>3</sub> and from 46 to 36% for RuCO/H<sub>3</sub>, and its subsequent hydrogenation is inhibited. The selectivities for the diastereoisomers **2** and **3** are also lower than that obtained in the experiments without amine, 2% for Ru/Al<sub>2</sub>O<sub>3</sub> and 10% for RuCO/H<sub>3</sub>. It should

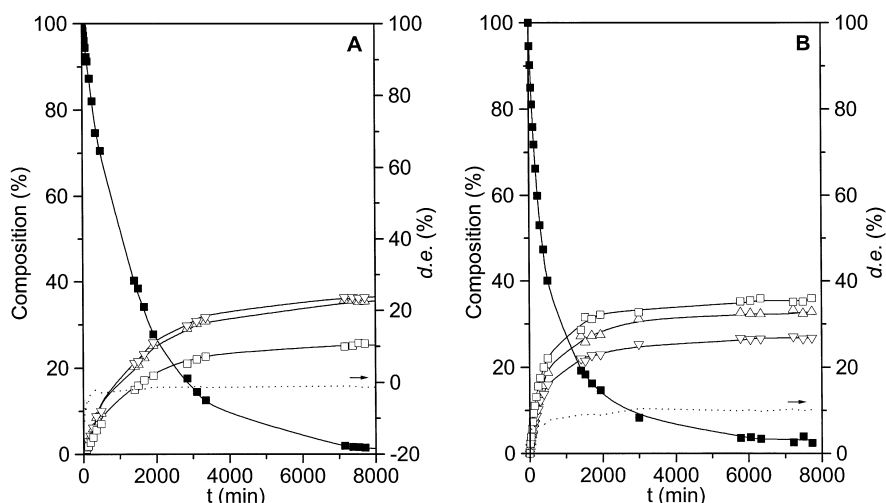


Fig. 2. Evolution of products distribution and d.e. with time in the hydrogenation of substrate **1**, *N*-(2-methyl-benzoyl)-(*S*)-proline methyl ester, in presence of EDCA over: (A) Ru/Al<sub>2</sub>O<sub>3</sub> and (B) RuCO/H<sub>3</sub> catalysts, (■) substrate **1**, (△) isomer **2**, (▽) isomer **3**, (□) SH, (...) d.e.

be noted that for the former catalyst the diastereoselectivity has suffered an inversion and the induction is in favour of isomer **3** instead of the isomer **2**, which was still the main isomer in catalyst RuCO/H<sub>3</sub>.

To account for the extent of the effect that the addition of an amine has on the initial rate of ruthenium catalysts depending on the support, the electronic properties have to be considered. They can influence the strength of the bonding between the metal and the amine, as above described for the interaction between the substrate and the metal. The great reduction of the initial rates for Ru/Al<sub>2</sub>O<sub>3</sub> catalyst linked to the inversion in the diastereoselectivity evidences the partial covering of the metal surface by the amine, in agreement with early reports on alumina supported rhodium catalysts [9]. Moreover, the bonding of the amine on the ruthenium particle supported on alumina (Ru/Al<sub>2</sub>O<sub>3</sub>) is stronger than that supported on carbon (RuCO/H<sub>3</sub>), due to the existence of non totally reduced species of ruthenium, giving rise to a higher surface coverage. This more important covering of ruthenium results in a greater difference in the activity values for the alumina supported catalysts.

Concerning the diastereoselectivity, the adsorption of EDCA molecules on the ruthenium surface led to some steric constraints that directs the approach of the substrate via the face of the molecule which occupies the smallest surface catalysts, as previously shown [7].

This effect balances the probability of adsorption of the two stable conformers by the two faces of the aromatic ring, which lead to a decrease of the d.e. values. The higher EDCA coverage of the metal surface evidenced for Ru/Al<sub>2</sub>O<sub>3</sub> would favour this fact, and then the reduction of the d.e. would be stressed, as it was observed, even causing an inversion in the selectivity.

### 3.3. Hydrogenation of substrate **1'**

In Table 2 are included some results of the hydrogenation of substrate **1'** prepared by coupling *o*-toluic acid with (*S*)-pyroglutamic acid methyl ester which presents an additional C=O bond with respect to the (*S*)-proline methyl ester in substrate **1** [10,11]. Comparing with the initial rates obtained in the hydrogenation of substrate **1**, although the same order is maintained (Ru/SiO<sub>2</sub> < RuCO/H<sub>3</sub> < Ru/Al<sub>2</sub>O<sub>3</sub>), the values are slightly lower. In addition to this, the deactivation of the catalysts with time in reaction is higher.

The evolution of the products distribution is presented in Fig. 3 for Ru/Al<sub>2</sub>O<sub>3</sub> catalyst, and similar profiles were obtained for the other catalysts. The main products are isomers **2'** and **3'**, and the compound SH' (up to 30%) which is subsequently reduced when the conversion of **1'** is completed. The hydrogenation of this intermediate takes place again with a lower rate

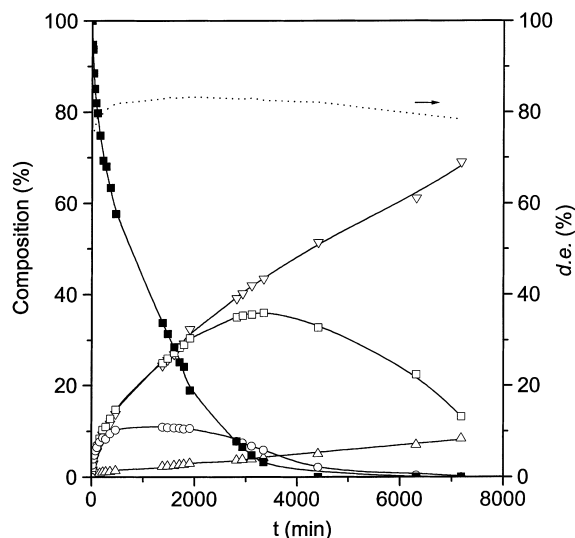


Fig. 3. Evolution of products distribution and d.e. with time in the hydrogenation of substrate **1'**, *N*-(2-methyl-benzoyl-*S*)-pyroglutamic acid methyl ester, over Ru/Al<sub>2</sub>O<sub>3</sub> catalyst, (■) substrate **1'**, (△) isomer **2'**, (▽) isomer **3'**, (□) SH', (○) unidentified, (...) d.e.

than the parent substrate. In addition, new products were detected: *S*-pyroglutamic acid methyl ester that was found in less than 5% and two other compounds, with GC retention times very close to that of SH' and detected in significant amounts (12%), particularly for the catalysts Ru/SiO<sub>2</sub> and Ru/Al<sub>2</sub>O<sub>3</sub>. These two latter products could not be identified, but it could be inferred that they have a similar structure to SH', because they are consumed in the reaction to form the *cis* isomers **2'** and **3'** since no more products were detected. On the other hand, although they were shown to have no influence on the diastereoselectivity, these molecules could be responsible for the progressive deactivation of the catalysts, because they would compete with the reactant for the surface active sites.

As in the case of the hydrogenation of substrate **1**, large amounts of cyclohexenic intermediate are formed. Cyclohexene and cyclohexene derivatives are known to be intermediates in the hydrogenation of benzenes and substituted benzenes, and ruthenium catalysts seem to be one of the most suitable catalysts to produce this partial hydrogenation of the aromatic ring [19]. The saturated products are formed by sub-

sequent hydrogenation, but as it is widely accepted, isomerization processes or double bond migration, and successive desorption and readsorption of these compounds on the catalysts lead to the *trans* isomers [19,20]. In spite of the high amounts of intermediates observed in the hydrogenation of both substrates, **1** and **1'**, the results presented in this paper show a very low production of the *trans* isomers, which contrast with the results of the hydrogenation of (*S*)-proline-2-methylanilide over Rh and Ru based catalysts, where up to 20% of *trans* isomers were observed [14]. This suggests that the structure of the molecule is crucial in the hydrogen addition and in the double bond migration, as has been pointed out after analysing the variable data obtained in the hydrogenation of unsaturated cyclic compounds [20]. In our case, the formation of *trans* isomers by isomerization processes in the hydrogenation of both substrates **1** and **1'** is inhibited.

As regards the diastereoselectivity, the chiral induction was in favour of the isomer **3'**, with the configuration (1*S*, 2*R*, 2'*S*) which is contrary to that obtained in the hydrogenation of substrate **1**. Moreover, as it has been earlier reported for Rh and Ru supported catalysts, the d.e. values are higher than in the reduction of substrate **1** [10,11]. Once again the catalysts supported on oxide materials showed better results than the catalyst supported on carbon. But, it is interesting to note that the d.e. values decrease when the cyclohexenic compound SH' is hydrogenated. So that, the favoured product in the SH' reduction is the isomer with configuration (1*R*, 2*S*, 2'*S*), as it was shown for the hydrogenation of SH. The differences found for the two substrates **1** and **1'** (the higher d.e. values achieved in the hydrogenation of **1'** and the inversion in the chiral induction) can be attributed to the molecule structure, which is determined by the chiral auxiliary. The presence of the new carbonyl bond in the chiral auxiliary of substrate **1'** stabilises only one of the two conformers observed for substrate **1**, that existing in a lower proportion for substrate **1** [11]. The haptophilic effect of ruthenium orientates the adsorption of this conformer via the side which holds the ester group yielding isomer **3'**. It was again observed a higher stereodifferentiation with the oxide supports. This can be explained considering that the oxygen atoms of the carboxylic group and the carbonylic groups of



the imide moiety would interact stronger with the species of ruthenium non totally reduced present on catalysts Ru/Al<sub>2</sub>O<sub>3</sub> and Ru/SiO<sub>2</sub>. The fact that in the hydrogenation of the two cyclohexene compounds SH and SH' the favoured isomer has the configuration (1*R*, 2*S*, 2'*S*) could be due to the spatial arrangement of the two molecules. This could indicate that the rigidity observed in compound 1', due to the presence of the new carbonyl bond, is lost in SH' and that the approach of the two intermediates towards ruthenium particles is similar. Molecular modelling of these compounds would help to clarify the results.

#### 4. Conclusions

The diastereoselective hydrogenation of *o*-toluic acid over ruthenium supported catalysts was studied using two auxiliaries, (*S*)-proline methyl ester and (*S*)-pyroglutamic acid methyl ester. With both auxiliaries the diastereoselectivity for the catalysts supported on alumina and on silica is higher than for the catalysts supported on carbon materials. This has been attributed to a stronger interaction between the metal and the oxygen atoms of the carbonyl and carboxylic groups of the substrate in the catalysts supported on oxidic supports, which orientates the adsorption of the molecule favouring preferentially one of the *cis* isomers. The addition of EDCA led to a decrease in the activity and in the diastereoselectivity that were more pronounced in the catalyst supported on alumina due to the higher coverage of the amine over the metal surface that causes greater steric constraints in the approach of the molecule to the active site.

When (*S*)-pyroglutamic acid methyl ester is used as auxiliary, the presence of the new C=O group induces only one stable conformer and as a result the d.e. obtained is higher than in the case of *S*-proline methyl ester.

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