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Recyclable immobilized rhodium catalysts in the diastereoselective hydrogenation of unsaturated steroids

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Dedicated to the memory of Prof. E. Derouane.

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ABSTRACT

Macroreticular anion exchange resins, Amberlite IRA-900 and Amberlite IRA-96, were used to bind monosulfonated triphenylphosphine ligand *via* noncovalent electrostatic interactions. The resin-phosphine system was found to be very efficient at promoting the immobilization of $[Rh_2(\mu\text{-}OMe)_2(cod)_2]$. The resulting stable Rh/TPPMS immobilized catalyst was tested in the hydrogenation of unsaturated oxosteroids (4-androstene-3,17-dione and 3β-acetoxypregna-5,16-dien-20-one). These immobilized catalysts could selectively reduce C=C bonds leading to the preferential formation of the α-diastereoisomer, as in the homogeneous systems. Furthermore, these new immobilized rhodium catalysts showed good performance, easy separation and recycling without loss of activity after at least three cycles.

When the immobilization of $[Rh_2(\mu\text{-}OMe)_2(cod)_2]$ was carried out *in situ* using either Amberlyst A27/TPPMS or the polystyrene-block-poly(*m*-vinyltriphenylphosphine) (PS-b-PPh_3), the catalytic activity was lower and a significant decrease was observed on recycling.

1. Introduction

Catalyst separation and reuse is often one of the major drawbacks in homogeneous catalysis [1]. Extensive research has been devoted to the development of new methods which combine the easy catalyst recovery inherent to heterogeneous catalysis with the desirable activity and selectivity characteristic of homogeneous catalytic systems. Key issues associated with supported catalysts are: (i) easy catalyst separation; (ii) catalyst recycling; (iii) preservation of high activity, and (iv) metal contaminant-free products [2–7].

It is generally accepted that immobilized catalysts can be prepared *via* a preformed cationic metal complex with an electrostatic link to the support (heterogenization of a homogeneous catalysis) or through the formation of the metal complex with a preformed covalently bound ligand matrix (polymer supported catalysts) [8]. Binding cationic active metal complexes to polyelectrolytes or ion exchange resins [8,9] or attaching metal to cross-linked polystyrene-phosphorus ligands [10] illustrate the above approaches.

Rh(I), Ru(II), Pd(II) and Ni(II) metal complexes are among the best immobilized catalysts employed for the hydrogenation of alkenes [11–13]. Diastereoselective reduction of carbon–carbon double bonds of α,β-unsaturated oxosteroids using palladium and rhodium homogeneous or heterogeneous catalytic systems have been extensively studied [14–16], but to the best of our knowledge the diastereoselective hydrogenation of steroids with immobilized catalysts has not yet been described.

We report here the diastereoselective hydrogenation of 4-androstene-3,17-dione **1** and 3β-acetoxypregna-5,16-dien-20-one **2** (Fig. 1) using two different approaches for the immobilization of rhodium complexes. One approach uses quaternary ammonium ion exchange resins (Amberlite IRA-900 and Amberlite IRA-96) linked to the (3-sulfonatophenyl)(diphenyl)phosphine monosodium salt (TPPMS) ligand, followed by rhodium complexation. The second uses a similar quaternary ammonium ion exchange resin, Amberlyst A27, ionically linked to TPPMS or the polystyrene-block-poly(*m*-vinyltriphenylphosphine) (PS-b-PPh_3), as a preformed ligand matrix, followed by *in situ* immobilization of $[Rh_2(\mu\text{-}OMe)_2(cod)_2]$.

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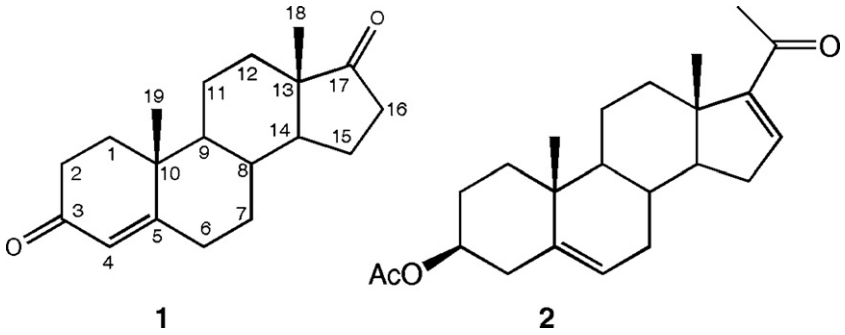


1 2

Fig. 1. Substrate structures.

2. Experimental

2.1. Equipments and reagents

^{1}H NMR spectra were recorded in $CDCl_3$ solutions on Bruker Avance 300 operating at 300.13. TMS was used as internal reference. GC and GC-MS experiments were carried out on Agilent 6890 series equipped with Agilent HP5 column (30 m or 0.5 m, 0.32 mm × 0.25 μm). Rhodium content (wt.%) of the catalysts was determined by ICP-MS using a THERMO X series instrument equipped with a quadrupole analyser with a collision cell. The samples were extracted with a mixture of HNO_3, HCl and H_2O_2. The samples were measured with a 1000, 100 and 10 fold dilution using indium as internal standard. Alternatively, rhodium content was determined in a Kevex X-Ray spectrometer equipped with Am 241 source and a multichannel ORTEC analyser. The phosphine-resin complexes before and after catalytic reaction were examined by scanning electron microscopy (SEM) using a Philips-XL30 apparatus operated at 10 keV at 10^{-5} mbar and the elemental distribution surface analysis (EDS) was performed with EDAX.

Solvents were obtained from commercial sources (Aldrich) distilled and dried before use, according to standard procedures [17]. [Rh_2(μ-OMe)$_2$(cod)$_2$] [18] and (3-sulfonatophenyl) (diphenyl)phosphine monosodium salt [19] were synthesized according to literature procedures. Polystyrene-block-poly(*m*-vinyltriphenylphosphine) rhodium catalyst, the macroporous anion exchange resins Amberlite IRA-96 (IRA96), Amberlite IRA-900 (IRA900) and Amberlyst A27 (A27) were obtained from Fluka.

2.2. General procedure for the immobilization of rhodium into ion exchange resins

2.2.1. Rh/TPPMS complex-Amberlite IRA-96 resin

One gram of dry IRA96 resin (nominal ion-exchange capacity of 4.7 mEq/g) was first wetted with water and then washed with HCl (1 mol/L). The polymer was let in contact with 62 mL of an aqueous solution of TPPMS (6.7×10^{-2} mol/L) during 24 h with occasional stirring in order to exchange the chloride anion with the sulfonated phosphine anion. The TPPMS/IRA96 polymer was washed thoroughly with distilled water and then dried under vacuum. TPPMS/IRA96 (92 mg) was added to a solution of 2.5 mg of [Rh_2(μ-OMe)$_2$(cod)$_2$] in toluene (6.7×10^{-3} mol/L) and stirred for 24 h. The rhodium-TPPMS complex was formed and a concomitant discoloration of the toluene solution was observed. The resin was then washed with toluene and dried under vacuum. The Rh/TPPMS/IRA96 resin complex presented 11.319 mg Rh/g of resin. Rhodium content was determined by Kevex X-Ray spectrometry.

2.2.2. Rh/TPPMS complex-Amberlite IRA-900 resin

The chloride form of IRA900 resin (1 g, nominal ion-exchange capacity of 4.2 mEq/g), was kept in contact with 15 mL of an aqueous solution of TPPMS (6.6×10^{-2} mol/L) during 24 h to exchange the chloride anions with the sulfonated phosphine. The polymer was washed with distilled water and dried under vacuum. [Rh_2(μ-OMe)$_2$(cod)$_2$] was anchored by the same procedure described in Section 2.2.1. The Rh/TPPMS/IRA900 resin complex presents 9.158 mg Rh/g of resin. Rhodium content was determined by Kevex X-Ray spectrometry.

2.2.3. TPPMS-Amberlyst A-27 resin

The hydroxide form of Amberlyst A-27 resin (1 g, nominal ion-exchange capacity of 2.6 mEq/g), was alternately washed with NaOH (0.1 mol/L), HCl (0.1 mol/L) and NaOH (0.1 mol/L) solutions. After this treatment the resin was converted to the monosulfonated triphenylphosphine form by exchange with a solution of TPPMS (2.6 mmol, 10 mL) over 24 h. The resin was filtered, washed thoroughly with distilled water and then dried under vacuum.

2.3. Hydrogenation procedure using rhodium catalysts with triphenylphosphine immobilized onto a polymeric support

2.3.1. Reduction of 4-androstene-3,17-dione **1** and 3β-acetoxypregna-5,16-dien-20-one **2** with rhodium catalysts immobilized onto anionic exchange resins Amberlite IRA 96 and Amberlite IRA 900

The substrate **1** or **2** (1.6×10^{-1} mmol) and the catalyst Rh/TPPMS/IRA96 or IRA900 (32 mg), together with a stirring bar, were introduced in a stainless steal autoclave. The system was closed and purged. Toluene (4 mL) was introduced in the reactor through an inlet cannula. The reactor was pressurized with hydrogen and, when the working temperature and pressure were reached, the stirring was started. After the catalytic reaction was stopped, the reactor was cooled and depressurized. The conversions and selectivities were determined by GC using previously isolated products as standards [16]. The catalytic results are presented in Table 1.

2.3.2. Reduction of 4-androstene-3,17-dione **1** and 3β-acetoxypregna-5,16-dien-20-one **2** with rhodium catalysts immobilized in situ onto anionic exchange resin Amberlyst A-27

The substrate **1** or **2** (7×10^{-2} mmol) and TPPMS/A27 (1.7 mg) were introduced in the autoclave, together with a stirring bar. The system was closed and purged. Then, a solution of [Rh(μ-OMe)(cod)]$_2$ (1.4×10^{-3} mmol) in toluene (2 mL) was introduced in the autoclave *via* an inlet cannula. The reactor was pressurized with hydrogen and, when the working temperature and pressure was reached, stirring was started. When the catalytic reaction was stopped, the reactor was cooled and depressurized. Conversion and selectivity were determined by GC using previously isolated products as standards [16]. The catalytic results are presented in Table 1.

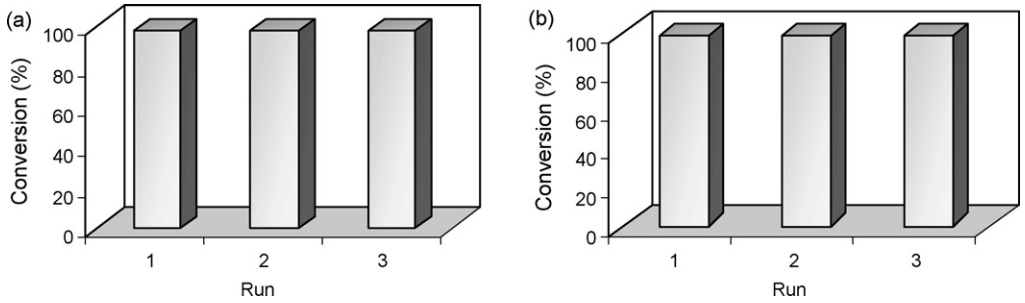


Fig. 2. Catalyst reuse in the hydrogenation of **1** with: (a) Rh/TPPMS/IRA96; (b) Rh/TPPMS/IRA900.

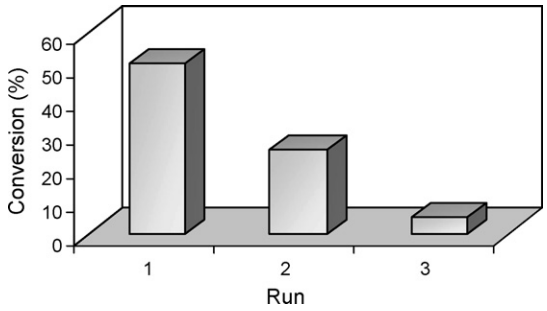


Fig. 3. Catalyst reuse in the hydrogenation of **1** with Rh/TPPMS/A27.

*2.3.3. Reduction of 4-androstene-3,17-dione **1** and 3β-acetoxypregna-5,16-dien-20-one **2** with rhodium immobilized on polystyrene-block-poly(m-vinyltriphenylphosphine)*

The catalytic hydrogenation reactions were performed according to the procedure described in Section 2.3.2 using substrates **1** or **2** (7.0×10^{-2} mmol) and polystryrene-block-poly(*m*-vinyltriphenylphosphine) (6 mg). The conversions and selectivities were determined by GC using previously isolated products as standards [16]. The results are presented in Table 2.

2.4. Catalysts recycling

After each reaction, the reactor was opened to air. Catalyst recovery was simply performed by filtration of the immobilized catalyst from the reaction mixture after each catalytic cycle. The reactor, containing the catalyst to be reused, was then closed and purged. A fresh substrate solution was introduced *via* an inlet cannula. The same catalytic conditions were used to perform the subsequent catalytic cycle. The results are presented in Figs. 2–4.

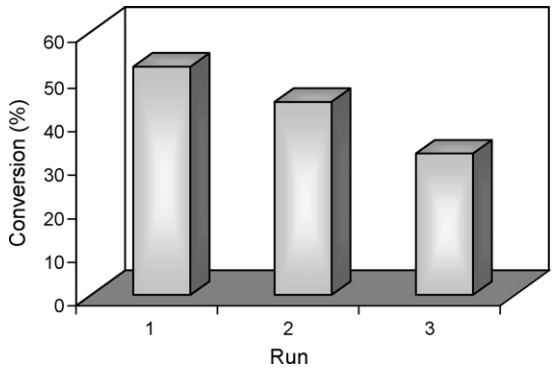


Fig. 4. Catalyst reuse in the hydrogenation of **1** with polymer supported Rh/PS-b-PPh_3 catalyst.

3. Results and discussion

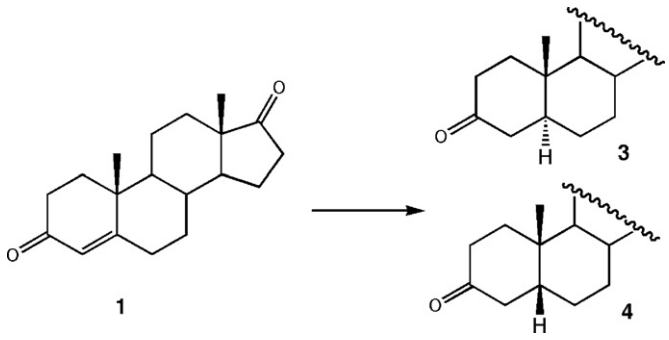
The aim of this work was to provide a simple and inexpensive protocol to prepare an anchored rhodium/triarylphosphine hydrogenation catalyst suitable for selective hydrogenation of the C=C double bonds of steroids **1** and **2**. For this purpose we chose the $[Rh_2((\mu\text{-}OMe)_2(cod)_2]$ complex, which is prepared in high yield in two straightforward steps from rhodium trichloride [18], and readily coordinates a phosphorous ligand. TPPMS is also simply prepared from triphenylphosphine by sulfonation with fuming sulfuric acid (20% SO_3) [19]. The macroporous anion exchange resins IRA-96, IRA-900 and A27 are commercial and inexpensive. The polystyrene-block-poly(*m*-vinyl-triphenylphosphine) is also commercial, although more expensive, and was employed for comparison purposes. The first approach to immobilize the catalyst was to previously anchor the rhodium complex on the polymers containing phosphorous ligands. To make the procedure even simpler, another approach was attempted: the components (i.e. rhodium complex and phosphinated polymer) were added directly to the reactor in order to form the anchored rhodium/triarylphosphine hydrogenation catalyst *in situ*.

3.1. Catalytic hydrogenation of steroids **1** and **2** using rhodium-triphenylphosphine ion exchange resin complexes

To prepare the neutral Rh(I) complexes, the TPPMS ligand was electrostatically bounded to the macroreticular strongly basic quaternary ammonium ion exchange resins Amberlite IRA-900 and Amberlite IRA-96 by stirring a solution of the ligand in toluene with the appropriate amount of the resin. After filtration and washing with water, the dried Amberlite IRA-900/TPPMS and Amberlite IRA-96/TPPMS ligand matrices were introduced in a toluene solution of $[Rh_2(\mu\text{-}OMe)_2(cod)_2]$ until the typical yellow colour disappeared yielding the desired immobilised Rh/TPPMS/IRA96 and Rh/TPPMS/IRA900 catalysts.

The hydrogenation of 4-androstene-3,17-dione **1** was firstly carried out using Rh/TPPMS/IRA96 as catalyst, at different pressures and temperatures. The product mixtures were analysed by ^1H NMR and GC against standards and the diastereoisomers **3** and **4**, Scheme 1, were identified as the main products of the catalytic hydrogenation of **1**. In addition, minor quantities of alcohols were observed as side products, resulting from further reduction of the carbonyl group.

At the working temperature (80 °C) and pressure (30 bar), almost complete conversion was observed after 12 h, with 73% chemoselectivity for double bond reduction and 55% α-diastereoselectivity, (compound **3**, Scheme 1**)**. In order to improve the chemo and diasteroselectivity, the temperature was decreased to 60 °C and the pressure to 20 bar. Under these reaction conditions, the chemo and α-diastereoselectivity increased to 88% and 72%, respectively (Table 1, entry 1). It should be pointed out that at 80 °C/30 bar (12 h) complete carbon-carbon double bond reduction is reached followed by some carbonyl reduction.



Scheme 1. Diastereoselective hydrogenation reaction of 4-androstene-3,17-dione, **1**, using immobilized Rhodium catalysts.

The optimized reaction conditions, (60 °C and 20 bar H_2) were applied to the catalytic hydrogenation of 4-androstene-3,17-dione (**1**) using different rhodium-triphenylphosphine ion exchange resin complexes as catalysts. The results are presented in Table 1. Using the Rh/TPPMS/IRA900 complex, the hydrogenation of substrate **1** was performed and almost complete conversion was obtained, with 86% chemoselectivity and 71% α-diastereoselectivity (Table 1, entry 2).

Another strategy for the immobilization of $[Rh_2(\mu\text{-}OMe)_2(cod)_2]$ was accomplished by the *in situ* generation of the catalytic cationic rhodium species that coordinates to the phosphorous atom of the Amberlyst A27/TPPMS polymer. The hydrogenation of substrate **1** using the Rh/TPPMS/A27 catalyst generated *in situ* led to a lower conversion (51%, Table 1, entry 3) than the above mentioned Rh/TPPMS/IRA900 immobilized catalyst, but showed similar α-diastereoselectivity (73%, Table 1, entry 3). The improvement in the chemoselectivity is probably due to the lower activity of this catalyst, i.e. it is not able to additionally reduce the C=O double bonds under the conditions employed.

The comparative studies for the immobilization with the Rh/TPPMS/IRA900 and Rh/TPPMS/A27 catalysts were extended to the hydrogenation of the less hindered 3β-acetoxypregna-5,16-dien-20-one **2** (Scheme 2, Table 1, entries 4 and 5), applying the optimized reaction conditions described in Table 1, entry 2. With both catalytic systems, an almost complete conversion was obtained, after 12 h, with 100% regio and chemoselectivity for Δ^{16} reduction and very high α-diastereoselectivity (98%) for **5**. Rh/TPPMS/IRA900, again, showed higher activity than the *in situ* generated Rh/TPPMS/A27 catalyst.

It should be emphasized that, in the reduction of substrate **1**, all the anchored catalysts yielded lower activity, and only slightly lower chemo and diastereoselectivity than those obtained with the homogeneous rhodium catalytic system using the same reaction conditions (60 °C; 20 bar H_2; 100% conversion, 79% α-diastereoselectivity, and 74% chemoselectivity, after 12 h).

These and previous literature results [20] show that rhodium/phosphine complexes immobilized onto ion-exchange resins lead to catalysts that show similar selectivity to homogeneous ones, but with the advantage of easy separation and recovery of catalysts from the reaction medium.

3.2. Hydrogenation of steroids *1* and *2* using polystryrene-block-poly(m-vinyltriphenylphosphine) rhodium catalyst

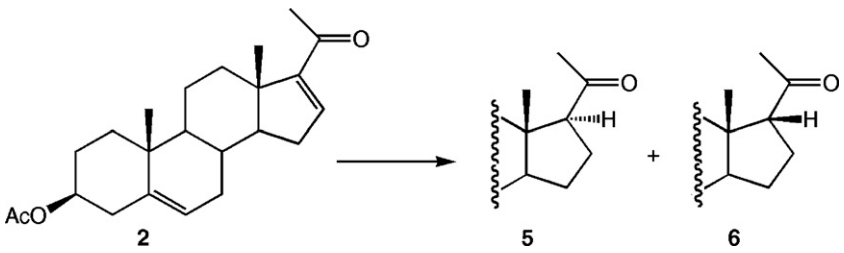
To highlight the influence of the anchoring support on the activity and selectivity of these catalytic systems, studies were carried out, for substrates **1** and **2**, using the polystryrene-block-poly(*m*-vinyltriphenylphosphine) as rhodium support, instead of the ion exchange resins. The product distribution for the hydrogenation reaction is presented in Table 2.

The higher steric hindrance of the Δ^4 double bond together with the poor diffusion of the substrate **1** through the polymer caused by the inefficient swelling of the microporous network [21,22] may be responsible for the low catalytic activity observed, 52% after 24 h (Table 2, entry 1). It should be emphasized that the reduction of the less hindered Δ^{16} double bond in substrate **2** occurred with almost complete conversion in 12 h (Table 2, entry 2). The immobilized Rh/PS-b-PPh_3 catalytic system also gave similar chemo and diastereoselectivity to those obtained with the homogeneous rhodium catalytic system.

Table 1
Hydrogenation of steroids **1** and **2** with Rhodium supported onto ion exchange resins (IRA 96, IRA 900 and A27).

Entry	Subs.	Time (h)	Catalyst	Conversion (%)[d]	Product distribution[d] (%)		
					3	**4**	Alcohol
1[a]	**1**	12	Rh/TPPMS/IRA96	98	63(72)[e]	25	12
2[b]	**1**	12	Rh/TPPMS/IRA900	97	61(71)[e]	25	14
3[c]	**1**	24	Rh/TPPMS/A27	51	72(73)[e]	27	1
Entry	Subs.	Time (h)	Catalyst	Conversion (%)[d]	Product distribution[d] (%)		
					5	**6**	Alcohol
4[b]	**2**	6	Rh/TPPMS/IRA900	98	98(98)[f]	2	–
5[c]	**2**	12	Rh/TPPMS/A27	98	98(98)[f]	2	–

Reaction conditions: $T = 60$ °C; $P_{H_2} = 20$ bar; (a) $[Rh_2(\mu\text{-}OMe)_2(cod)_2] = 8.8 \times 10^{-4}$ mmol, S/Rh = 90, 300 rpm, toluene = 4 mL; (b) $[Rh_2(\mu\text{-}OMe)_2(cod)_2] = 7.12 \times 10^{-4}$ mmol, S/Rh = 110, 300 rpm, toluene = 4 mL; (c) $[Rh_2(\mu\text{-}OMe)_2(cod)_2] = 1.4 \times 10^{-3}$ mmol, S/Rh = 25, 50 rpm, toluene = 2 mL, hydroxide counter ion; (d) the product mixtures obtained were analysed by ^{1}H NMR and GC against standards; (e) (α-diastereoselectivity): **3**/(**3**+**4**); (f) (α-diastereoselectivity): **5**/(**5**+**6**).



Scheme 2. Diastereoselective hydrogenation reaction of 3β-acetoxypregna-5,16-dien-20-one **2**, using immobilized Rhodium catalysts.

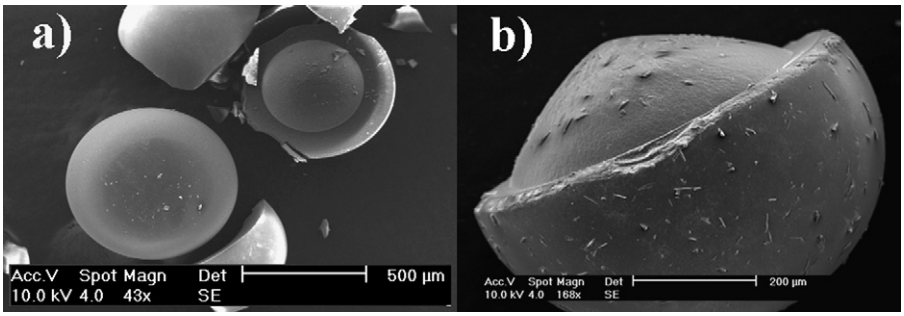


Fig. 5. SEM images of Rh/TPMMS/IRA96 supported catalyst beads before (a) and after (b) the third catalytic cycle (10 keV, 10^{-5} mbar).

3.3. Catalyst recycling

Catalyst recovery is of utmost environmental and economical relevance in fine chemical production, in particular in diastereoselective processes. In this context, we have evaluated the activity and selectivity of the immobilized catalysts Rh/TPPMS/IRA96, Rh/TPPMS/IRA900, Rh/TPPMS/A27 and Rh/PS-b-PPh_3 in the hydrogenation of substrate **1**, carrying out several subsequent runs. The results are presented in Figs. 2–4.

For all the catalytic systems studied, the reactor was opened to the air after each run, and the catalyst was filtered and immediately reused. The performance of the Rh/TPPMS/IRA96 and Rh/TPPMS/IRA900 catalysts remain almost unchanged after three subsequent runs (Fig. 2). In fact, the SEM images of the catalyst beads, before and after the third catalytic run, showed that the resin material was not affected (Fig. 5).

The Rh/TPPMS/A27 catalyst showed a significant decrease of activity after each run (Fig. 3). Upon reuse of the catalyst Rh/PS-b-PPh_3, deactivation was observed after each run, although this was less significant than with the above mentioned Rh/TPPMS/A27 (Fig. 4).

It should also be mentioned that in all the catalytic cycles the chemoselectivity and diastereoselectivity were not affected upon reutilization. Recycling studies were also carried out in the catalytic hydrogenation of substrate **2** and similar results were obtained. In all cases, the ICP-MS analysis of both liquid and solid phase, after completing three recycling runs, confirm that less than 0.1% of the rhodium mass was leached to the solution, while more than 99% of rhodium was retained in the solid phase. Furthermore, surface X-ray EDS microanalysis data showed the presence of rhodium, phosphorous and sulfur elements before and after the third catalytic run. These analytical results support the formation of the immobilized rhodium active catalytic system.

Therefore, the catalyst deactivation for the Rh/TPPMS/A27 cannot be explained by a leaching process. Considering the similarities in structure between the IRA900 and the A27 ion-exchange resins, the observed differences in deactivation during three cycles must be due to the method of utilization (*in situ vs*. pre-anchored complex).

Table 2
Hydrogenation reaction of substrates **1** and **2** with Rh/PS-b-PPh_3 catalyst.

Subs.	Time (h)	Conversion (%)	Product distribution (%)		
			3	**4**	Alcohols
1	24	52	64 (66)[a]	33	3
Subs.	Time (h)	Conversion (%)	Product distribution (%)		
			5	**6**	Alcohols
2	12	98	99 (99)[b]	1	–

Reaction conditions: S/Rh = 25, $P_{H_2} = 20$ bar, $T = 60\,^{\circ}C$, toluene = 2 mL; [$Rh_2(\mu\text{-}OMe)_2(cod)_2$] = 1.4×10^{-3} mmol; (a) (α-diastereoselectivity); **3**/(**3** + **4**). (b) (α-diastereoselectivity) (**5**/**5** + **6**).

During the *in situ* formation, the rhodium complex is heated in the presence of hydrogen before the coordination with the stabilizing phosphorous ligands. Probably, during this process, part of the rhodium complexes decompose to form metallic, catalytically inactive, rhodium particles which can impregnate the resin, lowering the catalytic activity. Although a detailed study of the degradation mechanism is beyond the scope of this study, we believe that the loss in activity upon reuse of the *in situ* generated catalyst stems from degradation of rhodium species upon exposure to air.

Although it is commonly reported that there is a decrease in activity upon recycling using ion exchange resin-supported catalysts [8,20–24] or metal-phosphine covalently bound to polystyrene catalysts [25], our results show a strong dependence of the catalytic stability with the method of rhodium immobilization. The preformed neutral catalysts, resulting from the previous coordination of the precursor [$Rh_2(\mu\text{-}OMe)_2(cod)_2$] with TPPMS/IRA900 or TPPMS/IRA96 are more stable and reusable than the *in situ* formed systems.

4. Conclusions

Two different approaches were implemented to prepare immobilized rhodium catalysts and tested in the diastereoselective hydrogenation of α,β-unsaturated oxosteroids.

The electrostatically bound TPPMS ligand matrix was easily prepared from cheap and commercially available IRA-96 and IRA-900 ion exchange resins, and yielded suitable supports for the immobilization of [$Rh_2(\mu\text{-}OMe)_2(cod)_2$]. These preformed immobilized single-site neutral rhodium catalysts were active in the hydrogenation of unsaturated steroids **1** and **2**, presenting chemo and diastereoselectivity similar to the homogeneous counterparts. Recycling studies showed no decrease in the activity after three subsequent runs. These new immobilized catalysts combine the selectivity of the homogeneous catalysts with easy product separation and the possibility of catalyst reuse. They enhance the application of diastereoselective steroid hydrogenation reactions leading to a more environmentally friendly pharmaceutical chemistry.

When a different [$Rh_2(\mu\text{-}OMe)_2(cod)_2$] immobilization strategy was performed, involving *in situ* anchoring to the ion exchange TPPMS/A27 or to the cross-linked polystyrene-triphenylphosphine a marked decrease in catalyst activity was observed, after recycling, showing that this strategy is not suitable to recover the catalyst.

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