



# A Low Rhodium Content Smart Catalyst for Hydrogenation and Hydroformylation Reactions

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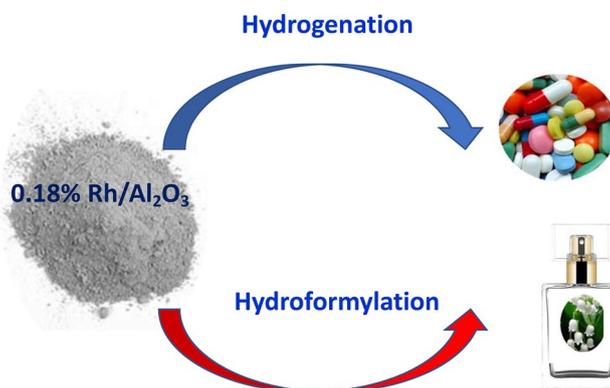
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## Abstract

This paper describes the preparation, broad characterization and study of activity in hydrogenation and hydroformylation reactions of an easily produced 0.18% Rh/Al<sub>2</sub>O<sub>3</sub>. Analytical studies on fresh and recycled samples shed light on the smart properties of such catalyst. Results showed high activity as well as fine/excellent chemoselectivity or regioselectivity, characteristics that may suggest a wide range of applicability.

## Graphic Abstract

The low metal content catalyst 0.18% Rh/Al<sub>2</sub>O<sub>3</sub> was very active in both hydrogenation and hydroformylation reactions so providing intermediates for valuable APIs, as Nabumetone and Eletriptan, and a fragrance with a fresh, green-floral smell, that recalls scent of lily of the valley.



**Keywords** Heterogeneous catalyst · Hydrogenation · Hydroformylation · Rhodium · Alumina · Low metal content

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## 1 Introduction

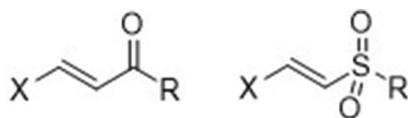
Nowadays, a lot of heterogeneous catalysts are commercially available on the market but often their performances (in terms of selectivity, activity, productivity and stability) and/or their cost are often seen as unsatisfactory or unsustainable. This is also due to the fact that they often show good activity only on specific and highly pure substrates. For these reasons finding a suitable catalyst for the investigated process can sometimes be very difficult [1]. Metal leaching in heterogeneous catalysts may sometimes be present, so catalyst recycle, one of the biggest advantages of heterogeneous

catalysts, is unfeasible [1]. In addition to this, if the level of metal residues is not acceptable from a regulatory point of view, which is especially true for the preparation of pharmaceutical substrates, further and expensive purification steps are required.

Many procedures were thus developed to overcome all these drawbacks and obtain efficient heterogeneous catalysts [2], the impregnation of metal/s on a support being probably the simplest and the most common one. Here, catalytic metallic species are dispersed on a pre-dried support by incipient wetness with an aqueous or non-aqueous solution of a suitable metallic salt precursor. A calcination step and a metallic activation is usually required to complete the procedure. As demonstrated in a very interesting paper on 1–5% Rh supported on CeO<sub>2</sub>, rhodium may undergo coalescence and various morphological changes during preparation, heat treatment, and reduction, as observed when X-ray photoelectron spectroscopy (XPS), high-resolution electron microscopy (HRTEM), and CO adsorption followed by diffuse reflectance infrared spectroscopy (DRIFTS) are used [3]. Therefore, a mild preparation method for the catalyst as well as no drastic conditions during its application are a relevant target.

As regards to the application, heterogeneous catalysts are used in many different reactions. One of the most interesting applications in the field of heterogeneous catalysis is the hydrogenation of  $\alpha,\beta$ -unsaturated carbonyl substrates or of unsaturated sulfones, often containing an aromatic or heteroaromatic ring (Fig. 1) to the corresponding saturated products.

The aim of this work is to describe a simple and reproducible protocol that allows to prepare and use a cheap, very active and chemoselective heterogeneous Rh catalyst, able to operate under mild conditions, minimizing the formation of non-target products, such as saturated or unsaturated alcohol, or by-products derived by partial or total hydrogenation of aromatic or heteroaromatic rings or by hydrogenolysis of C–S bond. While different metals, including non-noble metals and bimetallic species, have been considered and deemed effective in achieving this challenging goal [4–9], the literature concerning simple heterogeneous rhodium-based catalysts is quite scarce, probably due to the cost of this precious metal and to the reduced activity. The hydrogenation of  $\alpha,\beta$ -unsaturated carbonyl substrates to the corresponding



X = aryl or heteroaryl ring; R = H, alkyl, phenyl

Fig. 1 Substrates to be hydrogenated

saturated carbonyl derivatives is reported, working in methanol at room temperature, at low H<sub>2</sub> pressure, and using a non-commercial 1% Rh/AlPO<sub>3</sub> with a substrate/catalyst weight ratio between 300 and 500. However, the preparation of such catalyst is not simple and it was also reported that, while the reaction is fast, it is also sensitive to the steric hindrance [10]. 5% Rh on charcoal or alumina operating with a substrate/catalyst weight ratio equal to 20, seems one of the most used catalyst for the hydrogenation of hindered carbonyl compounds [11, 12], but in these cases the higher amount of metal on support and the lower substrate/catalyst molar ratio could be the limiting factors. Finally, a recyclable nanoparticle supported rhodium complex obtained by copolymerization of Rh(cod)(aaema) with acrylamides was used also for unsaturated aldehydes and ketones but for these substrates the results were not particularly relevant [13].

The authors of a patent [14] reported the selective reduction of an  $\alpha,\beta$ -unsaturated carbonyl compound, intermediate in the synthesis of Nabumetone (i.e. 4-(6-methoxy-2-naphthalenyl)-2-butanone) by using a low metal content Rh/Al<sub>2</sub>O<sub>3</sub>. Such catalyst was prepared in a simple way and showed very good properties: it was used industrially and recycled up to 20 times (with small additions of fresh catalyst) maintaining high activity and chemoselectivity; it proved to be a cheaper and much more efficient and selective solution than a commercial 5%Pd/C catalyst previously used in this application (Online Resource, Fig S1); the influence of K.F. and stirring rate were evidenced (Online Resource Fig. S2). Also, the characteristics of used alumina as support seemed to be important.

However, the overall characterization of fresh and used catalyst was not reported at that time. Therefore, the aim of this work was to evaluate the possibility of replicating the patent procedure for the preparation of such catalyst, 0.18% Rh/Al<sub>2</sub>O<sub>3</sub>, on a laboratory scale, characterizing the fresh and used catalyst and verifying the activity and selectivity with other challenging substrates and in other Rh-catalysed reactions.

In particular, here we describe the potential application in hydrogenation of some substituted olefins and in hydroformylation reactions.

About the hydrogenation of olefins, the attention here was focused on the reaction for precursors of Nabumetone (for comparison reasons) and Eleriptan (i.e. 5-[2-(benzenesulfonyl)ethyl]-3-[[2(R)-1-methylpyrrolidin-2-yl] methyl]-1H-indole), being it another important API.

In regard to the hydroformylation, even if this process is widely used in industry to synthesize many oxo-products with different fields of application, only few examples have been realized to this day using simple heterogeneous rhodium-based catalysts [15–18]. This reaction is usually carried out using catalytic complexes that work under homogeneous or biphasic conditions or are heterogeneously

encapsulated, in order to improve the selectivity of the catalyst. However, these synthetic protocols may present drawbacks as the low solubility in water of high molecular weight olefins, the possible degradation of the catalyst that can lead to inactive hydroxylated rhodium species or the cost of many catalysts may be quite expensive. After checking the activity of said catalyst on the typical model substrate, styrene, 0.18% Rh/Al<sub>2</sub>O<sub>3</sub> was here used in a synthesis of an aldehydic fragrance, containing a thiophene ring and the results were compared with some industrially used homogeneous Rh catalysts.

## 2 Experimental

### 2.1 General Information

All commercially available reagents were purchased from Sigma-Aldrich and were used as received. Gamma-alumina was kindly offered by Chimet SpA (Arezzo, Italy). CO and H<sub>2</sub> for experiments and for heterogeneous support and catalyst characterization were purchased from SIAD SpA (Italy). 4-(2-methoxynaftalen-6-yl)but-3-en-2-one was prepared according to Ref. [14]. THF was dried following a known procedure [19]. The analysis of Rh content was performed by Chemi-Lab (Mestre Venezia, Italy) by adopting the UNI EN 13674:2004+EPA 6010C 2007 protocol. FT-IR spectra were collected by using a Bruker Equinox 55 spectrometer, equipped with MCT cryodetector, at a spectral resolution of 2 cm<sup>-1</sup> and accumulation of 32 scans. The interactions of Alumina and of Rh catalyst with NH<sub>3</sub>, CO<sub>2</sub> and CO were studied at room temperature in the relative pressure range 0.01–3 Pa. The samples were pressed into thin self-supporting pellets and then placed into a quartz IR cell. In particular, prior to the adsorption measurements, all samples were activated by a treatment in H<sub>2</sub> (20 kPa) at 150 °C (heating rate 2.5 °C/min) for 1 h, and then cooled to room temperature under Ar atmosphere. The sample of Al<sub>2</sub>O<sub>3</sub> was characterized by powder X-ray diffraction (XRD) through a Philips X'pert diffractometer (Cu K $\alpha$  radiation) and nitrogen adsorption measurements at 77 K were performed using a Quantachrome Autosorb 1. TEM-Philips model 208 operating at 80 kV was used for TEM imaging. GC analysis were carried out with an Agilent Technologies 6850 series equipped by HP-5 (Agilent) capillary column (30 m  $\times$  0.32 mm  $\times$  0.25  $\mu$ m film thickness) and flame ionizer detector (FID). GC-MS analysis were performed on a ThermoFinnigan (Trace CG 2000) equipped with an HP-5 capillary column (30 m  $\times$  0.32 mm  $\times$  0.25  $\mu$ m film thickness) and a quadrupole mass spectrometer (ThermoFinnigan Trace MS). HPLC analysis were performed on an Agilent 1100 series instrument, equipped with an YMC HPLC column, (150  $\times$  4.6 mm) and a peristaltic pump. The

flow of the eluent mixture Milli-Q ultrapure water/Acetonitrile/phosphoric acid (70/30/0.1%) was set at 1 mL/min, 5  $\mu$ L injection volume. <sup>1</sup>H and <sup>13</sup>C NMR spectra of the all organic compounds were recorded by using a Bruker Avance 300 MHz. spectrometer and samples were dissolved in deuterated chloroform.

### 2.2 Catalyst Preparation

50 mg of RhCl<sub>3</sub> (0.00023 mol of Rh), 0.36 mL (0.0008 mol) of Trioctylamine (TOA) (d=0.809 g/mL) and 10 mL of dry THF were introduced in a 150 mL stainless steel autoclave under nitrogen. The autoclave was pressurized with 0.5 Mpa of hydrogen and warmed at 25 °C for 24 h under stirring. After this time, the solution was introduced into a 250 mL double neck jacket round bottom flask containing 10 g of alumina and 30 mL of dry THF. The mixture was stirred for 24 h at 25 °C under hydrogen atmosphere. After this time, the solid was filtered by sintered glass filter and washed with 50 mL of dry THF. The recovered catalyst was dried under vacuum at 0.06 MPa. After analysis the detected amount of Rh was 0.18%. A similar procedure using CPME instead of THF had been reported by us [20] but the catalyst at that time was not characterized.

### 2.3 Substrate Preparations

#### 2.3.1 Synthesis of 5-((E)-2-(phenylsulfonyl)vinyl)-1H-indole (IV)

In a dry 50 mL three neck round bottom flask equipped with a reflux condenser under nitrogen atmosphere 10 mL of *N,N*-dimethylformamide was introduced; before the addition of all reagents the solvent was degassed by bubbling nitrogen through it, then palladium(II) acetate (0.034 g, 0.152 mmol), tri-*o*-tolylphosphine (0.309 g, 1.017 mmol), 5-bromoindole (1 g, 5.08 mmol), phenyl vinyl sulphone (1.28 g, 7.63 mmol) and triethylamine (1.02 g, 10.17 mmol) were added and the mixture was stirred at reflux temperature for 5–16 h. The reaction was monitored by TLC and GC-MS. After completion the reaction mixture was cooled at room temperature, filtered on diatomaceous earth to remove the spent catalyst and evaporated under reduced pressure. The solid obtained was purified by flash-chromatography (eluent: dichloromethane/MeOH/liquid ammonia 98/2/0.1): the title compound 5-((E)-2-(phenylsulfonyl)vinyl)-1H-indole (IV) was obtained as a white solid. (1.3 g, 90% yield).

5-((E)-2-(phenylsulfonyl)vinyl)-1H-indole (IV): <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  (ppm): 8.52 (broad s, 1H), 7.99–7.97 (m, 2H), 7.85–7.78 (m, 2H), 7.61–7.52 (m, 3H), 7.41–7.25 (m, 3H), 6.83–6.78 (d, *J* = 15 Hz, 1H), 6.60–6.58 (m, 1H); <sup>13</sup>C NMR (76 MHz, CDCl<sub>3</sub>)  $\delta$  (ppm): 144.64, 141.45, 137.43, 133.08, 129.76, 129.28, 127.47, 125.75, 124.31,

123.51, 123.28, 121.79; GC–MS *m/z*: 283 [M]<sup>+</sup>; 141 [M, –C<sub>6</sub>H<sub>6</sub>O<sub>2</sub>S]<sup>+</sup>; 115 [M, –C<sub>8</sub>H<sub>8</sub>O<sub>2</sub>S]<sup>+</sup>.

### 2.3.2 General Procedure for the Synthesis of 5-(2-(Phenylsulfonyl)ethyl)-1*H*-indole (V)

In a Schlenk tube, 1 g (3.53 mmol) of 5-((*E*)-2-(phenylsulfonyl)vinyl)-1*H*-indole (**IV**), 0.201 g of 0.18% Rh/Al<sub>2</sub>O<sub>3</sub> (substrate **IV**/catalyst molar ratio 1000/1) and 10 mL of toluene were added. The Schlenk tube was then transferred into a 150 mL stainless steel autoclave under nitrogen, pressurized with 0.2 MPa H<sub>2</sub> and stirred for 6.5 h at 80 °C. The reactor was then cooled to room temperature and the residual gases released. The catalyst was filtered off by using a sintered glass filter and the organic solution was analysed by GC and GC–MS: 96% conversion of substrate (**IV**) into product (**V**) was detected. Solvent was distilled off and the crude mixture was purified by flash-chromatography (eluent: dichloromethane/MeOH/liquid ammonia 98/2/0.1): the title compound (**V**) was obtained as a yellowish solid (0.96 g, 96% yield).

5-(2-(Phenylsulfonyl)ethyl)-1*H*-indole (**V**): <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm): 8.23 (broad s, 1H), 8.01–8.97 (m, 2H), 7.72–7.57 (m, 3H), 7.38–7.39 (d, 1H), 7.33–7.28 (dd, *J* = 9 Hz, 1H), 7.22–7.20 (m, 1H), 3.47–3.41 (m, 2H), 3.18–3.12 (m, 2H); <sup>13</sup>C-NMR (76 MHz, CDCl<sub>3</sub>) δ (ppm): 139.16, 134.78, 133.71, 129.32, 128.68, 128.20, 128.11, 124.87, 122.41, 120.08, 111.39, 102.30; GC–MS *m/z*: 285 [M]<sup>+</sup>; 143 [M, –C<sub>6</sub>H<sub>6</sub>O<sub>2</sub>S]<sup>+</sup>; 117 [M, –C<sub>8</sub>H<sub>8</sub>O<sub>2</sub>S]<sup>+</sup>.

### 2.3.3 Synthesis of 3-(((*S*)-1-methylpyrrolidin-2-yl)methyl)-5-((*E*)-2-(phenylsulfonyl)vinyl)-1*H*-indole (VII)

In a dry 100 mL three neck round bottom flask equipped with a reflux condenser and a thermometer, under inert atmosphere, 10 mL of acetonitrile was introduced; before the addition of all reagents, the solvent was degassed by bubbling dry nitrogen, then palladium(II) acetate (0.023 g, 0.102 mmol), tri-*o*-tolylphosphine (0.153 g, 0.476 mmol), 5-bromo-3-(((*S*)-1-methylpyrrolidin-2-yl)methyl)-1*H*-indole (1 g, 3.42 mmol), phenyl vinyl sulphone (0.863 g, 5.136 mmol) and triethylamine (0.691 g, 6.84 mmol) were added. The reaction mixture was stirred at reflux temperature for 14 h. After completion of reaction, the mixture was cooled at room temperature, filtered on celite to remove the spent catalyst and the filtrate evaporated under reduced pressure. The solid obtained was purified by flash-chromatography (eluent: dichloromethane/MeOH/liquid ammonia 98/2/0.1): the title compound 3-(((*S*)-1-methylpyrrolidin-2-yl)methyl)-5-((*E*)-2-(phenylsulfonyl)vinyl)-1*H*-indole (**VII**) was obtained as a foam. (0.95 g, 73% yield).

3-(((*S*)-1-methylpyrrolidin-2-yl)methyl)-5-((*E*)-2-(phenylsulfonyl)vinyl)-1*H*-indole (**VII**): <sup>1</sup>H-NMR

(300 MHz, CDCl<sub>3</sub>) δ (ppm): 8.52 (broad s, 1H), 8.00–7.98 (m, 2H), 7.87–7.85 (dd, 1H) 7.74 (s, 1H), 7.58–7.52 (m, 3H), 7.33 (s, 2H), 7.07 (s, 1H), 6.80–6.77 (d, *J* = 15.3 Hz, 1H), 3.20–3.16 (q, 2H), 2.65–2.59 (q, 1H), 2.49–2.47 (d, 4H), 2.25–2.21 (q, 2H), 1.84–1.69 (m, 4H); <sup>13</sup>C-NMR (76 MHz, CDCl<sub>3</sub>) δ 144.84, 142.04, 138.25, 133.73, 130.04, 127.79, 127.34, 125.63, 124.09, 123.52, 122.26, 121.94, 112.64, 112.16, 67.55, 56.61, 40.83, 40.55, 40.27, 39.99, 39.72, 39.44, 39.16, 30.36, 29.79, 27.49, 21.63. (lit: <sup>13</sup>C NMR, DMDS: δ 21.72, 28.11, 30.73, 39.29, 39.50, 39.71, 39.92, 40.13, 40.34, 40.55, 56.70, 66.96, 112.56, 113.04, 121.78, 122.29, 123.38, 123.92, 125.30, 127.34, 127.98, 130.02, 133.70, 138.21, 142.04, 144.92) [202]; GC–MS *m/z*: 380 [M]<sup>+</sup>; 296 [M, –C<sub>5</sub>H<sub>10</sub>N]<sup>+</sup>; 154 [M, –C<sub>11</sub>H<sub>16</sub>NO<sub>2</sub>S]<sup>+</sup>; 84 [M, –C<sub>17</sub>H<sub>14</sub>NO<sub>2</sub>S]<sup>+</sup>

### 2.3.4 General Procedure for the Hydrogenation of 3-(((*S*)-1-methylpyrrolidin-2-yl)methyl)-5-((*E*)-2-(phenylsulfonyl)vinyl)-1*H*-indole (VII) to Eletriptan

In a Schlenk tube, 0.1 g (0.263 mmol) 3-(((*S*)-1-methylpyrrolidin-2-yl)methyl)-5-((*E*)-2-(phenylsulfonyl)vinyl)-1*H*-indole (**VII**), 1.50 g of 0.18% Rh/Al<sub>2</sub>O<sub>3</sub> (substrate **VII**/catalyst molar ratio 10/1), and 4 mL of a mixture of Toluene and Methanol (4/1) were added. The Schlenk tube was then transferred into a 150 mL stainless steel autoclave under nitrogen, pressurized with 0.5 Mpa H<sub>2</sub> and stirred for 0.5 h at 80 °C. The reactor was then cooled to room temperature and the residual gases released. The catalyst was filtered off by using a sintered glass filter and the organic solution was analysed by HPLC vs reference standard: 84% of Eletriptan (**VI**) and (*S*)-5-ethyl-3-((1-methylpyrrolidin-2-yl)methyl)-1*H*-indole (**VIII**) were found.

### 2.3.5 General Procedure for the Hydrogenation of 4-(2-Methoxynaftalen-6-yl)but-3-en-2-one (I) to Nabumetone

In a Schlenk tube, 3.56 g (0.016 mol) of 4-(2-methoxynaftalen-6-yl)but-3-en-2-one (**I**), 0.180 g of 0.18% Rh/Al<sub>2</sub>O<sub>3</sub> (substrate **I**/catalyst molar ratio 5000/1) and 20 mL of toluene were added. The Schlenk tube was then transferred into a 150 mL stainless steel autoclave under nitrogen, pressurized with 0.5 MPa H<sub>2</sub> and stirred for 1 h at 50 °C. The reactor was then cooled to room temperature and the residual gases released. The catalyst was filtered off by using a sintered glass filter and the organic phase was analysed by GC and GC–MS. The recovered catalyst was washed with diethyl ether (3 × 10 mL), dried under vacuum and recycled by adopting the above described procedure.

### 2.3.6 General Procedure for the Hydroformylation of Styrene (IX) Catalysed by 0.18% Rh/Al<sub>2</sub>O<sub>3</sub>

In a Schlenk tube, 0.364 g (0.0035 mol) of styrene (IX) 0.8 g of 0.18% of Rh/Al<sub>2</sub>O<sub>3</sub> (equal to IX/catalyst molar ratio 800/1) and 5 mL of toluene were charged. The Schlenk tube was then transferred into a 150 mL stainless steel autoclave under nitrogen, pressurized with 4 MPa of syngas (CO/H<sub>2</sub> = 1) and heated at 50 °C for 20 h under stirring. After this time, the catalyst was filtered by using a sintered glass filter, washed with diethyl ether (3 × 5 mL) and dried under vacuum and recycled by adopting the above mentioned procedure.

### 2.3.7 General Procedure for the Hydroformylation of 2-Ethyl-5-(prop-1-enyl)thiophene (XIV) and 2-Allil-5-ethylthiophene (XV) by Rh/Al<sub>2</sub>O<sub>3</sub>

In a Schlenk tube, 0.010 g of 0.18% Rh/Al<sub>2</sub>O<sub>3</sub> (XIV or XV/ catalyst molar ratio 500/1), 0.013 g (0.087 mmol) of XIV or XV, both prepared in analogy with a literature procedure [21], and 10 mL of toluene were introduced under nitrogen. The Schlenk tube was then transferred into a 150 mL stainless steel autoclave under nitrogen, pressurized with 8 MPa of syngas (CO/H<sub>2</sub> = 1) and heated at 100 °C for 20 h under stirring. The reactor was then cooled to room temperature and the residual gases released. The organic phase was then analysed by GC and GC–MS.

## 3 Results and Discussion

### 3.1 Characterisation of Fresh Catalyst

The amount of metal on the fresh catalyst was 0.18% with a 75% yield compared to the theoretical metal amount used in the preparation as described in Experimental part. Also, after the recycle, the amount of metal was found substantially unchanged.

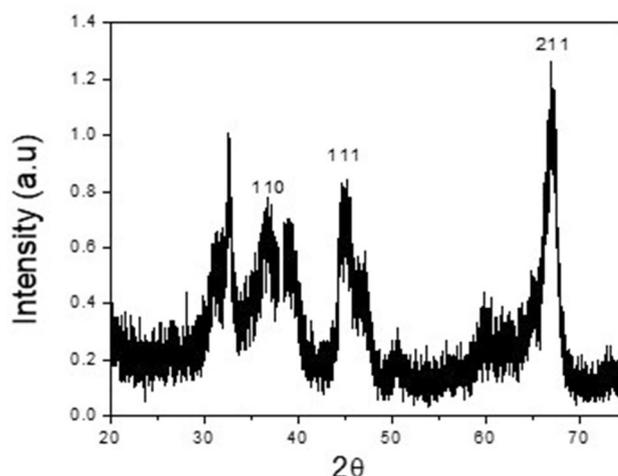
The used alumina, defined as  $\gamma$ -alumina from the supplier's specifications, had the following specifications (Table 1):

However, further analysis was made in order to improve the understanding of the support feature, to confirm the value obtained from the manufacturer and to verify possible changes after the Rh deposition. In Online Resource Fig. S3, a SEM image of the morphology of the support at 100× magnification is reported. As is evident, the sizes of the alumina particles are not uniform and the diameters of the particles range from 30 to 80  $\mu\text{m}$ .

According to the obtained X-ray refraction peaks (Fig. 2), the support could be a  $\gamma$ -alumina in agreement with some literature and with the supplier. However, on the basis of

**Table 1** Characteristics of used alumina kindly provided by the supplier

Characteristics	Value
Al <sub>2</sub> O <sub>3</sub> content	99.5%
Packed bulk density (PBD)	730 g/dm <sup>3</sup>
Specific surface area (BET)	115 m <sup>2</sup> /g
Particle size under 25 $\mu\text{m}$	0%
Particle size under 45 $\mu\text{m}$	31%
Particle size under 90 $\mu\text{m}$	93.5%
Water content	0.32%
Pore volume (water titration)	0.47 cm <sup>3</sup> /g



**Fig. 2** X-ray spectrum of used alumina

other literature data, the possibility of a  $\delta$ -alumina could be perhaps more likely [22, 23].

The adsorption–desorption analysis of the alumina before and after rhodium deposition (Fig. 3), is similar to that reported by the manufacturer and BET specific surface area slightly decreased to 119 m<sup>2</sup>/g.

The N<sub>2</sub> adsorption–desorption isotherms on the alumina and on 0.18% Rh/Al<sub>2</sub>O<sub>3</sub> are both of type IV which are typical of mesoporous materials. The average pore size resulted as calculated by DFT model of 8–9 nm [2, 3].

FT-IR spectra of samples after ammonia adsorption (pulse range 0.1–30 mbar) revealed the presence of Lewis and Brønsted acidic sites, both on alumina (Fig. 4) and on 0.18% Rh/Al<sub>2</sub>O<sub>3</sub> (Fig. 5).

The band at 1470 cm<sup>-1</sup>, which appears as a result of the adsorption of ammonia, is attributed to the bending vibration of ammonium ion formed by proton transfer reactions from Brønsted acid sites on the surface of alumina. The other two bands at 1625 cm<sup>-1</sup> and 1245 cm<sup>-1</sup>, respectively, are due to bending vibrations of ammonia adsorbed in molecular form.

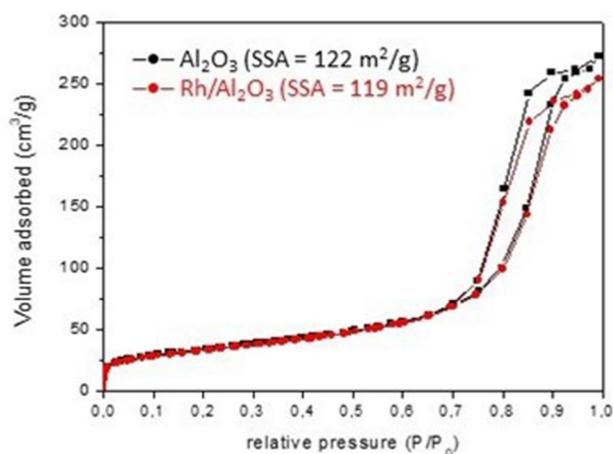


Fig. 3  $N_2$  Adsorption isotherms of  $Al_2O_3$  and 0.18%  $Rh/Al_2O_3$

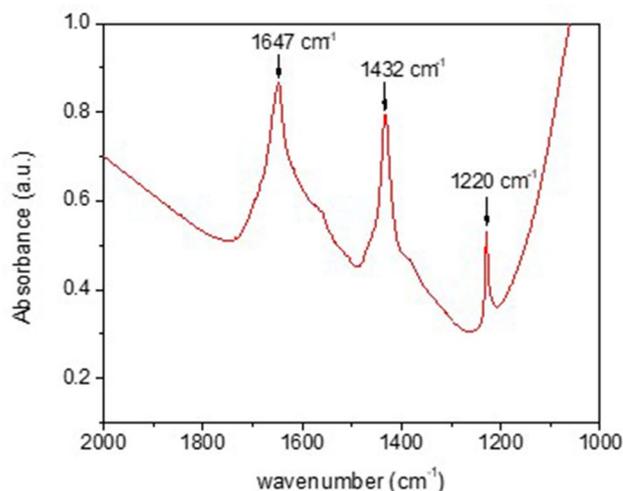


Fig. 6 FT-IR spectrum of  $CO_2$  adsorption on  $Al_2O_3$

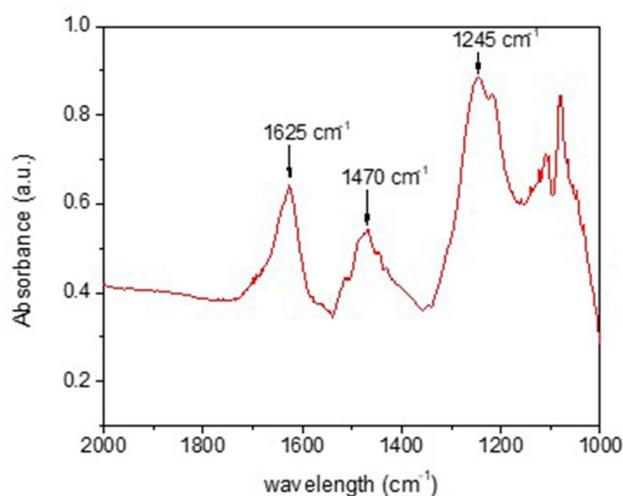


Fig. 4 FT-IR spectrum of  $NH_3$  adsorption on the used alumina

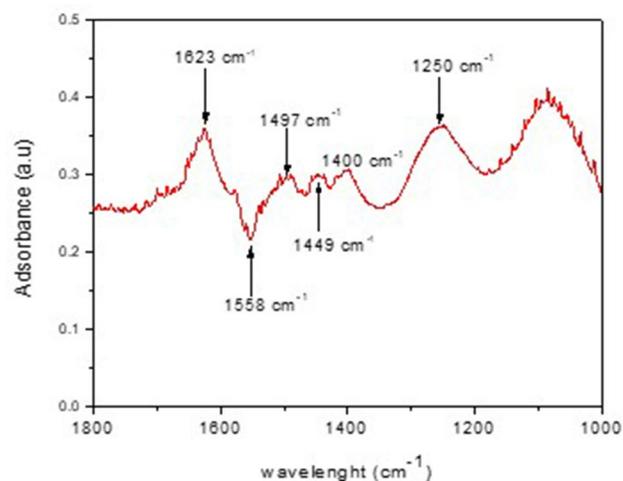


Fig. 5 FT-IR spectrum of  $NH_3$  adsorption on 0.18%  $Rh/Al_2O_3$

On the basis of literature, the latter band could be a prove of the presence of Lewis acid sites [24, 25].

The Brønsted acidity of the catalyst does not increase after the metal deposition and, after treatment with hydrogen, it seems to become negligible. Furthermore, it is interesting to note that this sample also presents carbonate species on the surface (Fig. 6 bands in the range 1600–1400  $cm^{-1}$ ). These species are probably formed by the interaction of atmospheric  $CO_2$  with the basic surface sites.

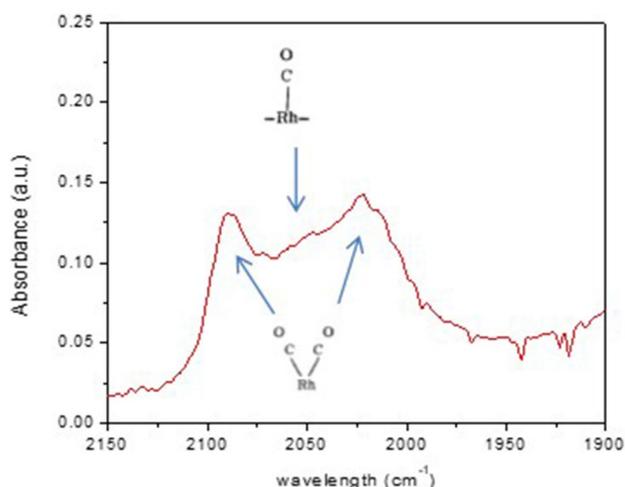
Therefore, a further analysis by  $CO_2$  adsorption was carried out in order to determine the presence of the basic sites on the alumina.

The  $CO_2$  absorption on the support ( $Al_2O_3$ ) revealed the formation of bicarbonate species (the three bands in the range 1800–1200  $cm^{-1}$ ) thus confirming the presence of basic sites (Fig. 6) [24].

In order to determine the dimension of Rh-particles on fresh  $Rh/Al_2O_3$  catalysts, an analysis by TEM spectroscopy was performed (Online Resource, Fig. S4). The analysis showed that the size of rhodium clusters ranges between 8 and 13 nm, which confirms a nanostructured catalyst. Probably, using a more controlled preparation protocol, for example adopting a one-pot procedure, as described in the patent [14], it should be possible to obtain lower sizes of rhodium cluster and a more regular distribution of metallic particles on the support. An upgraded TEM instrument would be also useful to achieve a more precise characterization.

Furthermore, the CO chemisorption analysis on  $Rh/Al_2O_3$  was carried out after pre-treatment of the sample with  $H_2$ , adopting the procedure reported in the experimental part, in order to elucidate the nature of carbonyl formed on Rh sites (Fig. 7).

Here it is possible to observe the formation of Rh-CO (band at 2050  $cm^{-1}$ ) and  $Rh(CO)_2$  species (bands at



**Fig. 7** FT-IR spectra of CO chemisorption analysis on 0.18% Rh/Al<sub>2</sub>O<sub>3</sub>

2086 cm<sup>-1</sup> and 2015 cm<sup>-1</sup>); the Rh(CO)<sub>2</sub> species are typical of small rhodium clusters, including isolated rhodium atoms, whereas monocarbonyl rhodium species [Rh(CO)] are formed only in the presence of more active rhodium atoms and usually require the presence of larger rhodium aggregates [26–31]. According to a suggestion of a referee, other adsorbed CO species could also be formed as it was demonstrated both on alumina and on titania-like supports [28, 30, 31]. Some analyses were also made on catalyst samples after use and will be described below.

## 3.2 Catalytic Test Activity and Some Characterizations of Used Catalyst

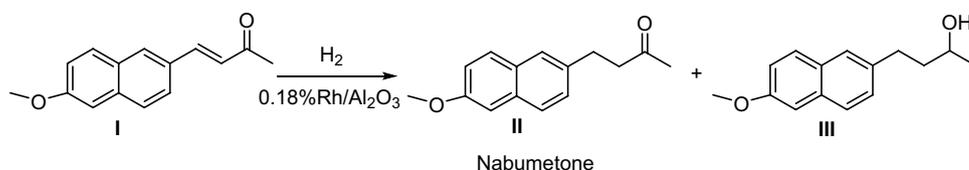
### 3.2.1 Hydrogenation

Initially the activity of this home-made 0.18% Rh/Al<sub>2</sub>O<sub>3</sub> catalyst was investigated on the hydrogenation of Nabumetone precursor (**I**) to compare the results with those industrially obtained [14] (Scheme 1).

Nabumetone (**II**), is an important anti-inflammatory pharmaceutical active ingredient (API) that belongs to the family of non-steroidal anti-inflammatory drugs (NSAIDs) and is used in the symptomatic treatment of rheumatic and inflammatory conditions [32]. The worldwide market in 2019 was 113 tons [33]. Many industrial and laboratory processes are known for its production and the hydrogenation step described in Scheme 1 is common to many of them [9, 34–38]. Usually the most important by-product is saturated alcohol (**III**) when the catalyst is a heterogeneous Pd based especially in absence of base additives (see also Fig. S1), but other impurities are due to the partial hydrogenation of the naphthalene ring. Therefore, it is important to increase the selectivity of this reaction toward the C=C, in order to improve the yield of the desired product (**II**). As matter of fact, 0.18% Rh/alumina produced on an industrial scale allowed to achieve a very high chemoselectivity (98–99%) [14]. Some experiments were therefore performed with our home-made catalyst and the results are summarized in Table 2.

The reaction was carried out under very mild conditions and high activity and selectivity towards C=C double bond

**Scheme 1** Hydrogenation of (**I**) to Nabumetone



**Table 2** Hydrogenation of compound (**I**) catalyzed by 0.18% Rh/Al<sub>2</sub>O<sub>3</sub>

Run <sup>a</sup>	P (MPa)	T (°C)	t (h)	I conv. (%)	II yield (%)	III yield (%)	TOF (h <sup>-1</sup> )
1	0.5	50	1	99	99	n.d	3663
2	0.5	30	1,5	97	97	n.d	2393
3	0.2	30	20	64	64	n.d	118
4 <sup>b</sup>	0.5	50	1	93	93	n.d	4650
5 <sup>c</sup>	0.5	50	1	80	80	n.d	4000

*n.d.* not detected

<sup>a</sup>Reaction conditions: substrate (**I**)=0.147 g (0.00065 mol); 0.18% Rh/Al<sub>2</sub>O<sub>3</sub>=0.010 g (substrate (**I**)/Rh molar ratio 3700/1); toluene = 5 mL

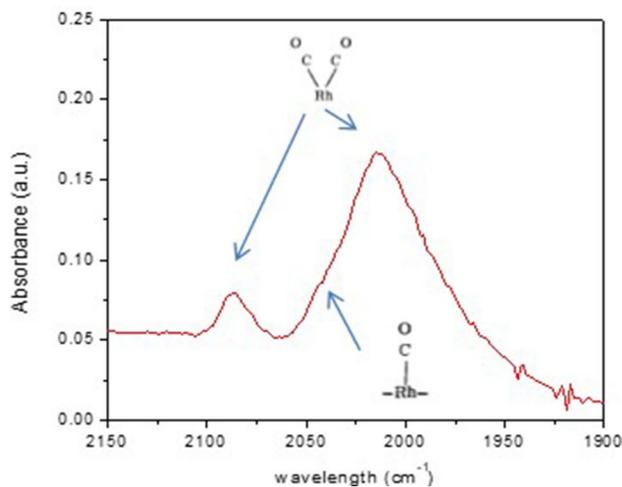
<sup>b</sup>Substrate (**I**)=3.56 g (0.016 mol); 0.18% Rh/Al<sub>2</sub>O<sub>3</sub>=0.180 g (substrate (**I**)/Rh molar ratio 5000/1); toluene = 20 mL

<sup>c</sup>Using the catalyst recovered from the previous run

were observed both in the experiments with the fresh catalyst (run 1 and 4, Table 2) and with a recycling one (run 5). However, it is also important to remark that better selectivity of the catalyst was obtained when the reaction was performed with a high substrate (**I**)/Rh molar ratio. In fact, in an experiment, not reported in Table 2, which was carried out at 50 °C and 0.5 MPa of H<sub>2</sub> pressure and using a substrate (**I**)/Rh molar ratio equal to 1000/1, a quantitative conversion of substrate (**I**) was observed but 2% of alcohol (**III**) and 5% of the sum of two other unidentified by-products were also detected.

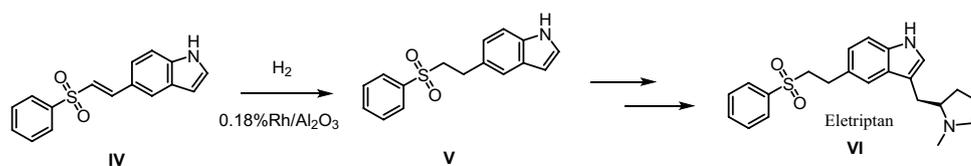
The catalyst used in run 5 (Table 2), was treated with CO, after a pre-treatment with hydrogen, and analysed by FT-IR (Fig. 8 to compare with Fig. 7 of the fresh catalyst).

Comparing the fresh catalyst (Fig. 7) and the recycled one (Fig. 8), it is possible to observe the significant reduction of signal due to monocarbonyl species at 2025–2050 cm<sup>-1</sup>. This is probably due to a partial aggregation of Rh particles and could perhaps explain the slight loss of activity. Furthermore, the intensity difference of signals due to bicarbonyl species in Figs. 7 and 8 might also suggest that they are not exactly the same, even if the wavelength does not change. As a matter of fact, the not symmetric peaks in Fig. 8 support the hypothesis that other adsorbed CO species may be formed, including carbonyl hydride rhodium species, as suggested by a referee.



**Fig. 8** FT-IR spectrum of the recycled 0.18% Rh/Al<sub>2</sub>O<sub>3</sub> catalyst in the Rh-Carbonyls signal area

**Scheme 2** Hydrogenation of (*E*)-5-(2(phenylsulfonyl)vinyl)-1*H*-indole (**IV**)



The presence of organic residues was also detected on the analysed recycled catalyst, despite a washing treatment. As a matter of fact, a very strong increasing signal appeared at about 1000 cm<sup>-1</sup> in the spectrum FT-IR which was not present in the fresh catalyst (Online Resource, Fig. S5 right and left respectively). We assume the presence of adsorbed naphthalene species and it could be a further cause of the observed reduced activity. The recycled catalyst was analysed to determine the metal content and no leaching phenomena was observed. Even if this result cannot completely rule out that, during the hydrogenation, colloidal rhodium species might be eventually formed and catalysed the reaction, surely, at the end, they should be totally reabsorbed by the alumina and maintain similar sizes. So, also on the basis of industrial results, it is highly unlikely, in our opinion, that the reaction may occur in the homogeneous phase. To support this hypothesis, we repeated a hydrogenation reaction and at the end, instead of a simple filtration, we centrifuged the reaction mixture to remove the heterogeneous species; on the supernatant we added fresh unsaturated substrate and tried to reduce it but without success.

The un-treated catalyst was analysed in order to verify the potential structural changes due to the pre-treatment with hydrogen, but no interesting data were obtained probably due to the oxidation of rhodium species. This result suggests that a pre-treatment with hydrogen is useful when the recycled catalyst is not so fully protected from atmospheric oxygen during the filtration step, as it is expected to happen in a laboratory but not in the plant.

Having been able to reproduce also in a small scale the patent procedure [14], including TOF, and the application, in spite of the fact that it is usual to have more problems working in a laboratory with heterogeneous catalysts (less efficient stirring, inefficient diffusion of hydrogen, partial deactivation for unwanted contact with air during the filtration and recycle, etc.) than in an industrial reactor, we decided to explore other difficult substrates to hydrogenate with high chemoselectivity. For this reason the hydrogenation of (*E*)-5-(2-(phenylsulfonyl)vinyl)-1*H*-indole (**IV**) to 5-(2-(phenylsulfonyl)ethyl)-1*H*-indole (**V**), possible intermediate of Eletriptan synthesis, was investigated (Scheme 2). Eletriptan (**VI**), (*S*)-3-((1-methylpyrrolidin-2-yl)methyl)-5-(2-(phenylsulfonyl)ethyl)-1*H*-indole, sold as HBr salt, is an important antimigraine and serotonin receptor agonist [39–41]. The worldwide market in 2019 was 1.9 tons [33].

The unsaturated precursor (**IV**) was prepared by a Heck reaction [this work] [42–44], and used as such or after purification. A comparison of the activity of a commercial Pd/C [42–46] with 0.18% Rh/Al<sub>2</sub>O<sub>3</sub> was also carried out and the obtained results are summarized in Table 3.

At first, the hydrogenation of the isolated pure (**IV**) was studied. The reaction was carried out in toluene at 50 °C with 0.3 MPa of H<sub>2</sub> for 18 h, by using a commercially available 10% Pd/C, but the result was very poor with a very low conversion of the starting material (Table 3, run 1). On the contrary, the home-made 0.18% Rh/Al<sub>2</sub>O<sub>3</sub> proved to be a very active catalyst, allowing to work under milder conditions to obtain a full conversion into (**V**); the best compromise was obtained with run 7, even if it will probably be possible to repeat the result with a lower reaction time. It was also possible to hydrogenate directly the crude Heck reaction mixture, although, to achieve such result, a greater amount of this catalyst was necessary (Table 3, run 10). On this substrate the highest TOF was about 150.

Quite surprisingly the same catalyst was much less chemoselective in the hydrogenation step of 3-(((*S*)-1-methylpyrrolidin-2-yl)methyl)-5-((*E*)-2-(phenylsulfonyl)

vinyl)-1*H*-indole (**VII**) to afford Eletriptan (**VI**) (Scheme 3, Table 4). In this case, as by-product, (*S*)-5-ethyl-3-(((1-methylpyrrolidin-2-yl)methyl)-1*H*-indole (**VIII**) was found in relevant amount.

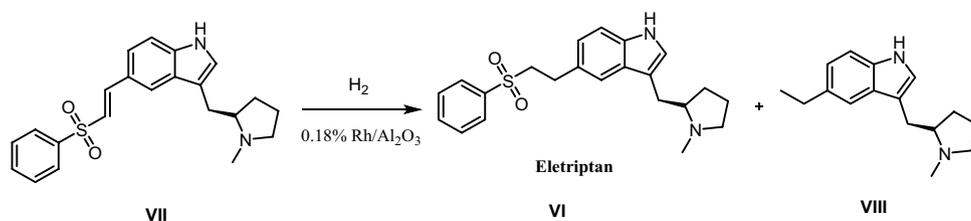
As shown in Table 4 and adopting the condition reported in run 1, a complete conversion was found; the reaction mixture was analysed by HPLC, as described in the experimental part, to give (**VI**) in 84 area % and by-product (**VIII**) in 16 area %. Many experiments were carried out using lower amount of catalyst and lower temperature (runs 2–6) in an effort to optimize the reaction parameters so to obtain high yield and better selectivity, but the results were unsatisfactory. Also lowering the H<sub>2</sub> pressure a high amount of hydrogenolysis by-product was observed (run 7). To verify if the by-product formation was dependent on the reaction time, it was carried out an experiment using the same reaction conditions adopted for run 1 but reducing the time to 30 min only instead of 17 h. It is worth nothing that in this case a full conversion was observed but without any improvement of selectivity (run 8 vs. run 1). The catalyst used in this experiment was recycled (run 9), observing practically the same activity but a worst selectivity. Finally, the reaction was carried out adding 1 equivalent of oxalic acid (run 10) or sodium acetate (run 11) with respect to the starting material, but even these experiments showed no improvement in selectivity while the amount of by-product observed working in the presence of oxalic acid was higher. Oxalic acid had been chosen so that Eletriptan could then be easily purified as hemioxalate salt [47]. The obtained result was surprising because the hydrogenation of this substrate or of the corresponding *N*-acetylindole derivative with palladium catalyst is often carried out in the presence of a strong acid such as methanesulfonic acid [40] or hydrobromic acid [41] and the alumina used as support for this Rh catalyst presents acidic characteristics too. No improvement was observed neither in selectivity nor conversion when lowering the hydrogen pressure. It was realized that using the reaction conditions adopted for run 8 as well as run 1 a full conversion was obtained but no change in selectivity occurs by changing reaction time; this fact was confirmed by other two experiments, not reported in the Table 4, where the reaction time was 1 h and 1.5 h, respectively. Also, the addition of sodium acetate was not effective. It

**Table 3** Hydrogenation of compound (**IV**)

Run	Catalyst	Sub/cat molar ratio	P(H <sub>2</sub> ) MPa	T (°C)/t (h)	V yield [%]
1 <sup>a</sup>	10% Pd/C	18/1	0.3	50/18	12.5
2 <sup>b</sup>	0.18% Rh/Al <sub>2</sub> O <sub>3</sub>	18/1	0.3	50/18	>99
3 <sup>c</sup>	0.18% Rh/Al <sub>2</sub> O <sub>3</sub>	100/1	0.3	50/18	>99
4 <sup>c</sup>	0.18% Rh/Al <sub>2</sub> O <sub>3</sub>	100/1	0.2	50/18	>99
5 <sup>d</sup>	0.18% Rh/Al <sub>2</sub> O <sub>3</sub>	500/1	0.2	50/18	>99
6 <sup>e</sup>	0.18% Rh/Al <sub>2</sub> O <sub>3</sub>	1000/1	0.2	50/18	80
7 <sup>e</sup>	0.18% Rh/Al <sub>2</sub> O <sub>3</sub>	1000/1	0.2	80/18	>99
8 <sup>e</sup>	0.18% Rh/Al <sub>2</sub> O <sub>3</sub>	1000/1	0.2	80/6.5	96
9 <sup>f</sup>	0.18% Rh/Al <sub>2</sub> O <sub>3</sub>	1000/1	0.2	80/6.5	17
10 <sup>g</sup>	0.18% Rh/Al <sub>2</sub> O <sub>3</sub>	100/1	0.2	80/8	98

Reaction conditions: <sup>a</sup>pure (**IV**)=(0.1 g, 0.353 mmol), 10% Pd/C=20.8 mg, Toluene=4 mL. <sup>b</sup>Same condition of run 1 but 0.18% Rh/Al<sub>2</sub>O<sub>3</sub>=1.12 g was used; <sup>c</sup>Same condition of run 1 but 0.18% Rh/Al<sub>2</sub>O<sub>3</sub>=0.20 g was used; <sup>d</sup>Same condition of run 1 but 0.18% Rh/Al<sub>2</sub>O<sub>3</sub>=40.1 mg was used; <sup>e</sup>Same condition of run 1 but 0.18% Rh/Al<sub>2</sub>O<sub>3</sub>=20.2 mg was used; <sup>f</sup>Same condition of run 8 but crude Heck reaction mixture containing (**IV**)=(0.1 g, 0.353 mmol) was used; <sup>g</sup>Same condition of run 9 but 0.18% Rh/Al<sub>2</sub>O<sub>3</sub>=0.20 g was used

**Scheme 3** Hydrogenation of (**VII**) to Eletriptan



**Table 4** Hydrogenation of compound (VII) catalysed by 0.18% Rh/Al<sub>2</sub>O<sub>3</sub>

Run	Sub/cat molar ratio	p(H <sub>2</sub> ) Mpa	T (°C)/t (h)	VII conv [%]	VI yield [%]	VIII yield [%]
1	10/1	0.5	80/17	100	84	16
2	50/1	0.5	80/17	97	55	42
3	50/1	0.5	60/17	97	60	37
4	50/1	0.5	50/17	77	57	20
5	50/1	0.5	40/17	78	60	18
6	50/1	0.5	30/17	64	53	11
7	50/1	0.2	80/17	82	46	36
8	10/1	0.5	80/0.5	100	84	16
9 <sup>a</sup>	1° recycle	0.5	80/0.5	96	52	44
10 <sup>b</sup>	10/1	0.5	80/0.5	88	55	33
11 <sup>c</sup>	10/1	0.5	80/0.5	100	74	26

Reaction conditions: (VII)=(0.1 g, 0.263 mmol), 0.18% Rh/Al<sub>2</sub>O<sub>3</sub> (1.50 g), toluene:methanol (4:1)=4 mL

<sup>a</sup>Using the catalyst recovered from run 8

<sup>b</sup>Same conditions of run 8 but 1 eq of oxalic acid was added

<sup>c</sup>Same conditions of run 8 but 1 eq of sodium acetate was added

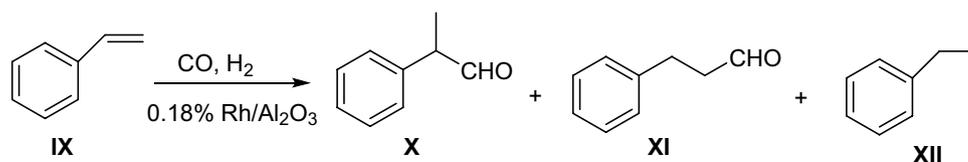
is to note that, on this substrate, the Rh catalyst proved to be active but much less selective, if compared to previous results obtained in the hydrogenation of substrate (IV). It is not easy to explain this different behaviour observed with this catalyst on substrates (IV) and (VI). Apparently, some interaction of heterogeneous rhodium species with the remote pyrrolidine ring should occur promoting the hydrogenolysis of the C–S bond. The worst result obtained with the recycled catalyst in term of chemoselectivity but not in term of activity would seem to confirm that the rhodium species remains, in any case, bonded to alumina and the hydrogenolysis is not due to colloidal free metallic Rh species stabilized by the nitrogen ligand. Luckily, a home-made 0.28% Pd/Al<sub>2</sub>O<sub>3</sub>, prepared with the same technique [48], that had not showed interesting performances on substrate (IV), permitted to obtain a better chemoselectivity ((VII)/(VIII)=94/6) in the hydrogenation of (VI) working at the following reaction conditions: [(VI)=(0.1 g, 0.263 mmol), 0.28% Pd/Al<sub>2</sub>O<sub>3</sub> (0.05 g), S/cat 200/1, solvent: toluene:methanol (4:1)=4 mL, p(H<sub>2</sub>)=0.1 Mpa., T=40 °C, t=16 h] [49]. The same result was observed also with this recycled home-made Pd catalyst. This difference in behaviour between these two catalysts in the hydrogenation of (VI), being the experimental conditions quite similar, could be due, according to our hypothesis, to

a higher possibility of heterogeneous Rh species to interact with *N*-methyl pyrrolidine than Pd species.

### 3.2.2 Hydroformylation

To test the activity of the Rh based home-made catalyst in the hydroformylation reaction, styrene (IX) was initially chosen as model substrate (Scheme 4, Table 5). 0.18% Rh/Al<sub>2</sub>O<sub>3</sub> showed high activity and selectivity (run 1, Table 5) and after the use, it was recovered from the crude mixture by filtration on sintered glass filter. The catalyst was recycled three times and in the first two recycles the activity and selectivity remained high (runs 2 and 3, Table 5) while in the third recycle (run 4) the activity decreased. However, the selectivity towards the branched aldehyde (X) remained high and even increased. It should be noted that both the fresh catalyst and the recycled one were treated, before use, with 2 MPa of CO for 20 h at room temperature: as a matter of fact, when the reaction was carried out by using a non pre-activated catalyst, the formation of acetophenone was observed, probably due to oxygen absorption on the catalyst surface during the filtration step.

Following the first usage, the recovered catalyst was analysed by FT-IR after CO chemisorption (Fig. 9a) and compared with the fresh one (Fig. 9b).

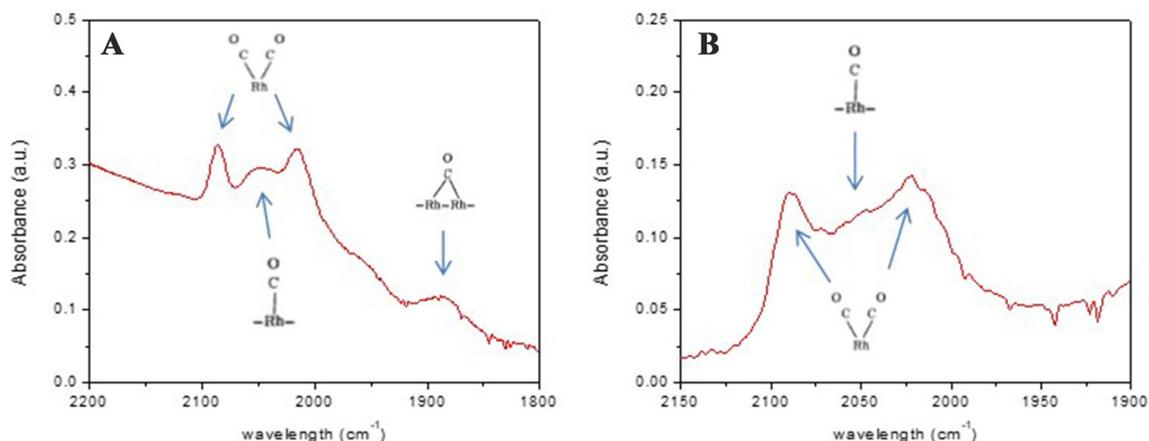
**Scheme 4** Hydroformylation of (IX)

**Table 5** Hydroformylation of (IX) catalysed by 0.18% Rh/Al<sub>2</sub>O<sub>3</sub>

Run	IX conv. (%)	X yield (%)	XI yield (%)	XII yield (%)	X/XI	TOF (h <sup>-1</sup> )
1	99	93	6	n.d	15.5	40
2 <sup>a</sup>	99	92	7	n.d	13	40
3 <sup>a</sup>	99	90	9	n.d	10	40
4 <sup>a</sup>	50	44	2	4	22	20

Reaction conditions: substrate (IX) = 0.364 g (0.0035 mol); Rh/Al<sub>2</sub>O<sub>3</sub> 0.18% = 0.8 g (substrate (IX)/catalyst molar ratio 800/1); toluene = 10 mL; p(H<sub>2</sub>) = (CO) = 2 MPa, T = 50 °C; t = 20 h

<sup>a</sup>The catalyst used was the same of the previous run



**Fig. 9** a Analysis of 0.18% Rh/Al<sub>2</sub>O<sub>3</sub> catalyst after the first use in styrene hydroformylation (run 1, Table 5); b analysis of the fresh catalyst

From the obtained data, it is possible to observe that after the first usage the catalyst (Fig. 9a) showed the formation of Rh<sub>2</sub>-CO species at ~ 1875 cm<sup>-1</sup> (and perhaps also Rh<sub>3</sub>-CO species at ~ 1975 cm<sup>-1</sup>), Rh-CO at 2050 cm<sup>-1</sup> and Rh-(CO)<sub>2</sub> at 2086 cm<sup>-1</sup> and 2150 cm<sup>-1</sup>. The occurrence of other species bonded to the metal, including H-CO, cannot be ruled out. There is, in this case, a very small difference in the recycled catalyst when confronted with the fresh one, which is perhaps due to a slight increase in the size of rhodium particles: this enhancement of the rhodium particle size was also confirmed by TEM analysis reported in supplementary material (Online Resource, Fig. 6Sb) as well as the deposition of organic material on the metal particles (Online Resource, Fig. S6 a, c). Also IR analysis confirmed this deposit in the region below 1250 cm<sup>-1</sup> (Online Resource, Fig. S7).

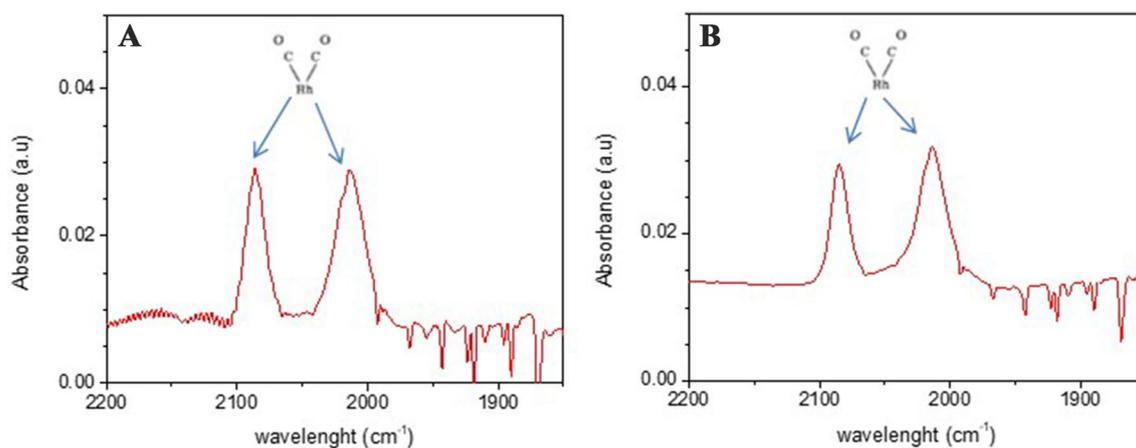
Before CO chemisorption, the used catalyst after the third recycle was analysed after H<sub>2</sub> pre-treatment or without any pre-treatment. In this case, it was possible to demonstrate that H<sub>2</sub> treatment does not affect the catalyst structure even if it is useful to clean the metal surface (Fig. 10).

Also, in this case, it is possible to observe the formation of the same rhodium species seen before while a relevant decrease of Rh-CO species can be noticed which suggests a further aggregation of the metal particles that could explain

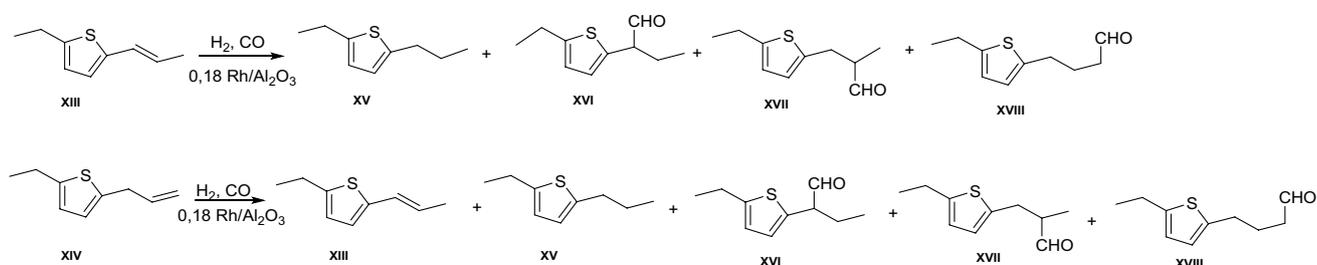
the reduction of activity. However, the observed partial deactivation could also be caused by the presence of an organic residue, due to insufficient washing or to partial polymerization of styrene (IX). The recovered catalyst analysed after the third recycle allowed to exclude any leaching phenomena as the content of Rh was not affected in any relevant manner. 0.18% Rh/Al<sub>2</sub>O<sub>3</sub> performances on styrene, that is the only comparable substrate, are much better in reactivity, chemoselectivity and regioselectivity than those of 8.5% Rh/Cu<sub>2</sub>O [18].

The activity of Rh/Al<sub>2</sub>O<sub>3</sub> in the hydroformylation reaction was then investigated on two different isomeric olefins ((*E*)-2-ethyl-5-(prop-1-en-1-yl)thiophene (XIII) and 2-allyl-5-ethylthiophene (XIV) to verify how the position of the double bond could affect the yield of the desired aldehyde (XVII), a fragrance with a fresh, green-floral smell, that recalls scent of lily of the valley (Scheme 5, Tables 6 and 7). Furthermore, for comparison, the hydroformylation reaction was also performed with two well-known homogeneous rhodium catalysts, (HRh(CO)(PPh<sub>3</sub>)<sub>3</sub> and Rh(CO)<sub>2</sub>(acac)/TPPTS) [50].

Working at 80 °C for 20 h at 8 MPa of syngas (CO/H<sub>2</sub> = 1) and with a substrate/0.18% Rh/Al<sub>2</sub>O<sub>3</sub> molar ratio to 100/1, a 79% conversion was obtained (run 1, Table 6), but the



**Fig. 10** Analysis of the recovered 0.18% Rh/Al<sub>2</sub>O<sub>3</sub> without H<sub>2</sub> treatment (**a**) and with H<sub>2</sub> treatment (**b**)



**Scheme 5** Hydroformylation of (**XIII**) and (**XIV**)

**Table 6** Hydroformylation of (**XIII**)

Run	Catalyst	Sub/cat molar ratio	<b>XIII</b> conv (%)	<b>XV</b> yield (%)	<b>XVI</b> yield (%)	<b>XVII</b> yield (%)	<b>XVIII</b> yield (%)
1 <sup>a</sup>	0.18% Rh/Al <sub>2</sub> O <sub>3</sub>	100	79	6	47	26	n.d
2 <sup>b</sup>	HRh(CO)(PPh <sub>3</sub> ) <sub>3</sub>	1000	94	6	71	17	n.d
3 <sup>c</sup>	Rh(CO) <sub>2</sub> (acac)/TPPTS	1000	27	1	15	11	n.d

Reaction condition: <sup>a</sup>substrate (**XIII**)=0.013 g (0.087 mmol); 0.18% Rh/Al<sub>2</sub>O<sub>3</sub>=0.05 g; toluene=10 mL; p(CO)=p(H<sub>2</sub>)=4 MPa; T=80 °C, t=20 h; <sup>b</sup>substrate (**XIII**)=0.195 g (1.3 mmol); HRh(CO)(PPh<sub>3</sub>)<sub>3</sub>=1.2 mg; toluene=2 mL; p(CO)=p(H<sub>2</sub>)=3.5 MPa; T=80 °C, t=24 h; <sup>c</sup>substrate (**XIII**)=0.195 g (1.3 mmol); Rh(CO)<sub>2</sub>(acac)<sub>2</sub>=1.2 mg; TPPTS=4.4 mg (cat/TPPTS molar ratio 1/6); toluene=2 mL; H<sub>2</sub>O=2 mL; p(CO)=p(H<sub>2</sub>)=3.5 MPa; T=80 °C; t=24 h

**Table 7** Hydroformylation of (**XIV**)

Run	Catalyst	Sub/cat molar ratio	<b>XIV</b> conv (%)	<b>XIII</b> yield (%)	<b>XV</b> yield (%)	<b>XVI</b> yield (%)	<b>XVII</b> yield (%)	<b>XVIII</b> yield (%)
1 <sup>a</sup>	0.18% Rh/Al <sub>2</sub> O <sub>3</sub>	500	99	5	1	3	44	46
2 <sup>b</sup>	HRh(CO)(PPh <sub>3</sub> ) <sub>3</sub>	1000	99	4	n.d	n.d	42	53
3 <sup>c</sup>	Rh(CO) <sub>2</sub> (acac)/TPPTS	1000	94	6	6	6	35	41

Reaction condition: <sup>a</sup>substrate (**XIV**)=0.013 g (0.087 mmol); 0.18% Rh/Al<sub>2</sub>O<sub>3</sub>=0.01 g; toluene=10 mL; p(CO)=p(H<sub>2</sub>)=4 MPa; T=100 °C, t=20 h; <sup>b</sup>substrate (**XIV**)=0.195 g (1.3 mmol); HRh(CO)(PPh<sub>3</sub>)<sub>3</sub>=1.2 mg; toluene=2 mL; p(CO)=p(H<sub>2</sub>)=3.5 MPa; T=80 °C, t=24 h; <sup>c</sup>substrate (**XIV**)=0.195 g (1.3 mmol); Rh(CO)<sub>2</sub>(acac)<sub>2</sub>=1.2 mg; TPPTS=4.4 mg (cat/TPPTS molar ratio 1/6); toluene=2 mL; H<sub>2</sub>O=2 mL; p(CO)=p(H<sub>2</sub>)=3.5 MPa; T=80 °C; t=24 h

main product was aldehyde (**XVI**) and only 26% of the target aldehyde (**XVII**) was obtained. With a homogeneous catalyst as Wilkinson hydride (run 2, Table 6) conversion was very high (94%) but the regioselectivity towards (**XVII**) was even lower than the previous run. The prevalence of the  $\alpha$ -aldehyde (**XVI**) can be explained by the favourite attack on the  $\alpha$ -carbon respect to the thiophene ring that allows to obtain an intermediate stabilized by resonance. The reaction was carried out also in an aqueous biphasic system in the presence of  $\text{Rh}(\text{CO})_2(\text{acac})$  modified with the water soluble phosphine TPPTS, but we observed a low activity (27% conversion) (run 3, Table 6).

On this substrate, 0.18%  $\text{Rh}/\text{Al}_2\text{O}_3$  showed high activity and a lower amount of the hydrogenated product was formed (run 1, Table 7); the amount of the  $\beta$ -branched (**XVII**) and linear aldehyde (**XVIII**) are practically the same.

The use of both  $\text{HRh}(\text{CO})(\text{PPh}_3)_3$  and the water soluble  $\text{Rh}(\text{CO})_2(\text{acac})/\text{TPPTS}$  did not improve the selectivity towards the desired (**XVII**) being the terminal aldehyde (**XVIII**) the prevailing reaction product (runs 2 and 3, Table 7).

In light of the obtained results, the use of the heterogeneous catalyst 0.18%  $\text{Rh}/\text{Al}_2\text{O}_3$  seems to be a good alternative to the use of homogeneous catalysts. The results obtained in the hydroformylation of the terminal olefin (**XIV**) are indeed able to compete with those obtained by using homogeneous catalysts. Even if the substrate (**XIV**)/cat molar ratio is higher than the one used with Wilkinson hydride, the heterogeneous catalyst is easy to recover and possibly to recycle.

## 4 Conclusion

In conclusion, a simple and efficient synthesis of a very active, low metal content, home-made  $\text{Rh}/\text{Al}_2\text{O}_3$  was reproduced in our laboratory with similar performances to those of the industrial catalyst in the hydrogenation of Nabumetone precursor. Its use was extended with good–excellent results to  $\text{C}=\text{C}$  bond reduction of other important substrates and in the hydroformylation reactions, obtaining comparable or even better results than the ones offered by the commercial and more expensive heterogeneous or homogeneous catalysts. Detailed information on the structure of the fresh and recycled catalyst allowed us to have a better understanding of its properties and paved the way for further improvements, especially in the recycling processes. The present protocol would be practical and economic for a wider use.

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## Compliance with Ethical Standards

**Conflict of interest** The authors declare no conflict of interest.

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