Available online at www.sciencedirect.com
SCIENCE DIRECT®
Journal of Organometallic Chemistry 689 (2004) 639–646
Journal of Organometallic Chemistry
www.elsevier.com/locate/jorganchem

Nanostructured ruthenium on γ-Al_2O_3 catalysts for the efficient hydrogenation of aromatic compounds

Guido Marconi [a], Paolo Pertici [a,*], Claudio Evangelisti [a], Anna Maria Caporusso [a], Giovanni Vitulli [a], Gustavo Capannelli [b], Manh Hoang [c], Terence W. Turney [c]

[a] *Istituto per la Chimica dei Composti Organometallici, ICCOM CNR, Sezione di Pisa, Dipartimento di Chimica e Chimica Industriale, Università di Pisa, via Risorgimento 35, 56126 Pisa, Italy*
[b] *Dipartimento di Chimica e Chimica Industriale, Università di Genova, via Dodecaneso 31, 16146 Genova, Italy*
[c] *CSIRO Manufacturing and Infrastructure Technology, Gate 4 Normandy Road, Clayton Vic. 3168, Australia*

Received 2 June 2003; accepted 10 November 2003

Abstract

Free and trioctylamine (TOA)-stabilized ruthenium nanoparticles have been prepared by decomposition of the metal precursor Ru(η^6-cyclooctа-1,3,5-triene)(η^4-cycloocta-1,5-diene) under mild conditions (room temperature, hydrogen atmospheric pressure). The nanoparticles have been deposited on γ-Al_2O_3 supports having different surface area. The resulting systems are active in the hydrogenation of methyl benzoate to methyl cyclohexanoate with a reaction rate decreasing in the order Ru(TOA)/γ-Al_2 O_3 (high surface area, catalyst **D**) > Ru(TOA)/γ-Al_2O_3 (catalyst **C**) > Ru/γ-Al_2O_3 (high surface area, catalyst **B**) > Ru/γ-Al_2O_3 (catalyst **A**). Catalysts **A**–**D** are long lived and can be reused without loss of activity; they are considerably more active than a commercial ruthenium on γ-Al_2O_3 sample. High Resolution Transmission Electron Microscopy analyses of such systems show that the nanoparticles are homogeneously dispersed on the support and that the size distribution decreases in the order catalyst **A**, 2.9 nm > catalyst **B**, 2.8 nm > catalyst **C**, 2.4 nm > catalyst **D**, 2.3 nm. Based on the easy hydrogenation of the aromatic ring to the cyclohexane derivative, an efficient synthesis of 4-carbomethoxyformylcyclohexane, important starting material in the preparation of pharmaceutical products, from the largely available methyl 4-formylbenzoate, has been set up in the presence of catalyst **D**.

Keywords: Arene hydrogenation; Ruthenium nanoparticles; Trioctylamine; Ruthenium on γ-Al_2O_3 catalysts; HRTEM

1. Introduction

The hydrogenation of aromatic compounds, which is typically performed with heterogeneous catalysts of VIII group metals, such as rhodium on alumina and Raney nickel, is still a very important research area in catalysis [1,2]. Nanosized metal particles, which are expected to have peculiar properties, different from those of atomic or molecular species and bulky metal [3,4], are of great interest in the development of new very efficient and selective catalytic systems [1,2,5–17]. Metal nanoparticles however are usually generated in the presence of stabilizers, such as organic ligands, surfactants and polymers. It has been observed that not only the cluster size, but also the stabilizing ligand can significantly affect the catalytic activity [13,15,18–20]. In this paper, we report the preparation of Ru/γ-Al_2O_3 systems by deposition of Ru nanoparticles obtained by the reduction and displacement of ligands from Ru(η^6-COT)(η^4-COD), COT = cycloocta-1,3,5-triene and COD = cycloocta-1,5-diene, [17,21,22], in the absence and in the presence of trioctylamine as a stabilizer, respectively. The catalysts were evaluated for the hydrogenation of monocyclic aromatic compounds such as methyl benzoate and methyl 4-formylbenzoate, an important intermediate in fine chemical synthesis [23,24], and their activity was compared with that of an analogous commercially available catalyst.

* Corresponding author. Tel.: ++39-050-2219224; fax: +39-050-2219260.
E-mail address: pertici@dcci.unipi.it (P. Pertici).

0022-328X/$ - see front matter © 2003 Elsevier B.V. All rights reserved.
doi:10.1016/j.jorganchem.2003.11.019

2. Experimental

2.1. General considerations

All operations involving the use of ruthenium systems were performed under argon atmosphere using standard Schlenk techniques. Solvents were purified by standard methods. The commercial products were degassed and stored under argon before use. The commercial ruthenium on γ-Al_2O_3 catalyst (5 wt% Ru) was supplied by Aldrich. The complex Ru(η^6-COT)(η^4-COD) was obtained as described previously [22]. Commercial γ-Al_2O_3 (Chimet product, surface area SA = 110 m^2/g) and high surface area γ-Al_2O_3 (SA = 340 m^2/g) prepared by thermal decomposition of $NH_4Al(OH)_2CO_3$ [25], were used as supports of the ruthenium nanoparticles. The ruthenium loading on γ-Al_2O_3 supports was determined by Atomic Absorption Spectrometry using a Perkin–Elmer 4100ZL instrument at the Istituto per i Processi Chimico Fisici, CNR, Pisa, Italy. GC analyses were performed on a Perkin–Elmer 8600 gas chromatograph, equipped with a flame ionisation detector, using a SiO_2 "Wide Bore" column (DB1, 30 m × 0.53 mm, 5 μm) and helium as carrier gas. GC–MS spectra were recorded on a Perkin–Elmer Q-mass 910 spectrometer connected with a Perkin–Elmer gas chromatograph, equipped with a "split–splitless" injector, using a SiO_2 capillary column and helium as carrier gas. ^1H and ^{13}C NMR spectra were recorded on a Varian Gemini 300 spectrometer operating at 300 and 75 MHz, respectively; chemical shifts are reported relative to internal tetramethylsilane. Electron micrographs of the ruthenium on γ-Al_2O_3 catalysts (3.5 wt% Ru) were obtained with a JOEL 2010 Microscopy with EDS probe, model Oxford-Link, equipped with a top entry stage. The samples were ultrasonically dispersed in toluene and then deposited on copper grids covered with a holey carbon film. The metal particle size distribution was obtained by calculating the average particle diameter (d_a) of at least 300 particles on the micrograph using the equation, $d_a = \sum d_i n_i / \sum n_i$, where n_i is the number of particles of diameter d_i. Histograms of the metal particle size distribution, the average particle diameter (d_a) and the standard deviation (σ) were determined by HRTEM. The counting was carried out on electron micrographs taken at 130.000 magnification and in this condition the standard deviation resulted ±0.5 nm. Elemental analyses were carried out by the Laboratorio di Microanalisi, Facoltà di Farmacia, Università di Pisa, Italy.

2.2. Preparation of the ruthenium on γ-Al_2O_3 catalysts

In a typical experiment Ru(η^6-COT)(η^4-COD) (0.5 g, 1.58 mmol) was dissolved in THF (20 ml) and the resulting yellow solution was added to a suspension of the commercial γ-Al_2O_3 (4.41 g) in THF (10 ml). Argon was removed under reduced pressure and hydrogen (1 atm) was introduced. The suspension was stirred at room temperature until a complete decolourisation was obtained (8 h). The liquid was then removed by decantation and the Ru on commercial γ-Al_2O_3 was washed with pentane and dried in vacuo. A final 4.55 g catalyst containing 3.5 wt% Ru was obtained and hereafter designated as catalyst **A**.

Supported 3.5 wt% Ru on high surface area γ-Al_2O_3 (catalyst **B**) was prepared using the same procedure except that γ-Al_2O_3 with a surface area of 340 m^2 was used.

2.3. Preparation of supported ruthenium on γ-Al_2O_3 in the presence of trioctylamine as a stabilizer

In a typical experiment, trioctylamine, TOA, (2.1 ml, 4.75 mmol) was added to a yellow solution containing Ru(η^6-COT)(η^4-COD) (0.5 g, 1.58 mmol) dissolved in THF (20 ml). Argon was removed in vacuo and hydrogen (1 atm) was introduced. Commercial γ-Al_2O_3 (4.41 g) was then added to the solution and the suspension was stirred overnight at room temperature until complete decolourisation was obtained. The liquid was removed by decantation and the resulting supported Ru(TOA) on commercial γ-Al_2O_3 was washed with pentane and dried in vacuo. A 4.56 g catalyst containing 3.5 wt% Ru was obtained and hereafter designated as catalyst **C**.

The same procedure was used for supported Ru(TOA) on high surface area γ-Al_2O_3 (catalyst **D**).

2.4. Hydrogenation of methyl benzoate and 2-(4-carbomethoxyphenyl)-1,3-dioxane

Hydrogenation experiments were carried out under a hydrogen pressure of 20 atm in a 75 ml stainless-steel autoclave equipped with a removable Teflon liner, a magnetic bar, a stainless-steel sampling valve and a manometer (100 atm scale), submerged in an oil bath at constant temperature (±1.0 °C).

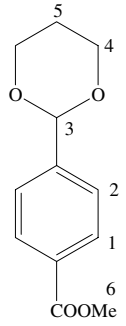
In a typical experiment, the reactant (3.5 mmol), catalyst (0.035 mg atom Ru) and reaction medium (10 ml) were charged into the autoclave under argon atmosphere. The autoclave was closed, argon was evacuated and hydrogen was introduced up to 20 atm. The progress of the reaction was monitored by analyzing liquid samples taken from the sampling tap by GC and NMR.

2.5. Preparation of 4-carbomethoxyformylcyclohexane from methyl 4-formylbenzoate, *1*

2.5.1. Synthesis of 2-(4-carbomethoxyphenyl)-1,3-dioxane, *2*

Methyl 4-formylbenzoate (4 g, 24.4 mmol), 1,3-propandiol (17.6 ml, 244 mmol) and anhydrous $CuSO_4$

(1.6 g, 10 mmol) were introduced in a Carius tube. The tube was closed and the reaction mixture was stirred at 95 °C for 3 h. After cooling the mixture was extracted with ether (4 × 25 ml). The combined ether extracts were dried over anhydrous sodium sulphate and concentrated under reduced pressure. The resulting solution (10 ml) was cooled to –30 °C for crystallisation of 2-(4-carbomethoxyphenyl)-1,3-dioxane, **2** (5.2 g, 23.4 mmol, yield 96%).

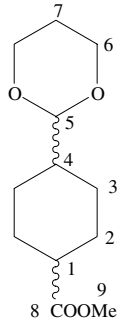


2

M.p. = 89–91 °C. Anal.: found: C, 65.04; H, 6.21%. $C_{12}H_{14}O_4$ requires: C, 64.85; H, 6.35%. ^{1}H NMR: δ 8.05 (d, 2H, H^1); 7.55 (d, 2H, H^2); 5.52 (s, 1H, H^3); 4.3 (m, 2H, H^4); 4.05 (m, 2H, H^4); 3.9 (s, 3H, H^6); 2.35–2.15 (m, 1H, H^5); 1.6–1.4 (m, 1H, H^5). GC–MS, *m/z* (rel. int. %): 222 (M^+, 71); 221 (68); 163 (29); 149 (10); 133 (42); 105 (65); 87 (28); 77 (76); 51 (52); 42 (100).

2.5.2. Catalytic hydrogenation of 2-(4-carbomethoxyphenyl)-1,3-dioxane, *2*, to 2-(4-carbomethoxy cyclohexyl)-1,3-dioxane, *3*

The hydrogenation of the aromatic ring in 2-(4-carbomethoxyphenyl)-1,3-dioxane to 2-(4-carbomethoxycyclohexyl)-1,3-dioxane was performed in a stainless-still autoclave following the experimental procedure described in Section 2.4. 2-(4-Carbomethoxyphenyl)-1,3-dioxane (5 g, 22.5 mmol) was dissolved in THF (20 ml) and Ru(TOA)/γ-Al_2O_3 (catalyst **D**, 0.664 g, 0.23 mg atom Ru) was added to the solution. The mixture was charged into the autoclave and heated to 80 °C in the presence of 20 atm of hydrogen. At complete conversion of 2-(4-carbomethoxyphenyl)-1,3-dioxane (ca. 24 h) the autoclave was cooled to room temperature, hydrogen was carefully evacuated and the catalyst was removed by filtration. The solvent was evaporated under reduced pressure and the residue was dissolved in THF (10 ml). The solution was filtered through a celite column followed by solvent removal in vacuo. 2-(4-Carbomethoxycyclohexyl)-1,3-dioxane, **3**, (4.63 g, 20.3 mmol, *trans*/*cis* ratio of 0.5) was obtained with a yield of 90%.



3

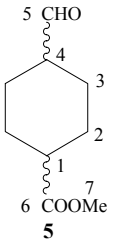
Anal.: found: C, 63.32; H, 8.64%. $C_{12}H_{20}O_4$ requires: C, 63.13; H, 8.83%. ^{1}H NMR: δ, *cis* isomer, 4.3 (d, H^5), 4.08 (m, $H^{6,ax}$), 3.7 (m, $H^{6,eq}$), 3.64 (s, H^9), 2.51 (m, H^1), 2.35 (m, H^7), 1.74 (m, H^3), 1.62 (m, H^2), 1.53 (m, H^4); *trans* isomer 4.21 (d, H^5), 4.02 (m, $H^{6,eq}$), 3.66 (m, $H^{6,ax}$), 3.64 (s, H^9), 2.4 (m, H^7), 2.18 (m, H^1), 1.81 (m, H^3), 1.69 (m, H^2), 1.47 (m, H^4). ^{13}C NMR: δ, *cis* isomer, 175 (C^8), 104.1 (C^5), 66.9 (C^6), 51.3 (C^9), 40.8 (C^4), 39.9 (C^1), 26.09 (C^3), 25.95 (C^7), 24.05 (C^2); *trans* isomer, 176 (C^8), 104.8 (C^5), 66.9 (C^6), 51.3 (C^9), 43.1 (C^1), 41.8 (C^4), 28.29 ($C^3 + C^7$), 26.23 (C^2). GC–MS, *m/z* (rel. int. %): 228 (M^+, 1); 227 (2.5); 226 (1); 197 (5); 169 (1); 152 (2); 93 (6); 87 (100); 81 (10); 67 (3); 59 (5).

2.5.3. Transacetalization reaction of 2-(4-carbomethoxycyclohexyl)-1,3-dioxane, *3*, to 4-carbomethoxycyclohexyl dimethyl acetal, *4*

A mixture of 2-(4-carbomethoxycyclohexyl)-1,3-dioxane (4.0 g, 17.5 mmol), methanol (80 ml) and concentrated HCl (1 ml) was refluxed in an one necked round-bottomed flask equipped with a reflux condenser and a magnetic stirrer for 24 h. The reaction mixture was extracted with ether (4 × 30 ml). After ether was evaporated, 4-carbomethoxycyclohexyl dimethyl acetal, **4**, was obtained and used in the next hydrolysis without purification.

2.5.4. Hydrolysis of 4-carbomethoxycyclohexyl dimethyl acetal, 4, to 4-carbomethoxy formylcyclohexane, *5*

4-Carbomethoxycyclohexyl dimethyl acetal, obtained from the above experiment, was placed in an one necked round bottomed flask equipped with a magnetic stirrer. Water (150 ml) and concentrated HCl (1 ml) were added and the mixture was stirred at room temperature for 4 h followed by extraction with ether (4 × 50 ml). The extracted phase was dried over sodium sulphate and ether was removed under reduced pressure. The residue was then distilled to give pure 4-carbomethoxyformylcyclohexane, **5**, (2.67 g, 15.7 mmol, yield = 90%, *trans*/*cis* = 2.3).



5

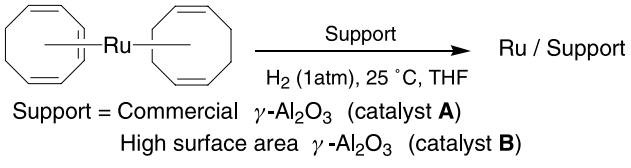
Anal.: found: C, 63.66; H, 8.14%. $C_9H_{14}O_3$ requires: C, 63.5; H, 8.29%. ^{1}H NMR: δ, *cis* isomer, 4.3 (d, H^5), 4.08 (m, $H^{6,\,ax}$), 3.7 (m, $H^{6,\,eq}$), 3.64 (s, H^9), 2.51 (m, H^1), 2.35 (m, H^7), 1.74 (m, H^3), 1.62 (m, H^2), 1.53 (m, H^4); *trans* isomer 4.21 (d, H^5), 4.02 (m, $H^{6,\,eq}$), 3.66 (m, $H^{6,\,ax}$), 3.64 (s, H^9), 2.4 (m, H^7), 2.18 (m, H^1), 1.81 (m, H^3), 1.69 (m, H^2), 1.47 (m, H^4). ^{13}C NMR: δ, *cis* isomer, 204 (C^5), 176 (C^6), 51.7 (C^7), 47.3 (C^4), 40.9 (C^1), 27.2 (C^3), 24.85 (C^2); *trans* isomer, 203 (C^5), 176 (C^6), 51.5 (C^7), 49.2 (C^4), 42 (C^1), 27.9 (C^3), 25.7 (C^2). GC–MS, *m/z* (rel. int. %): 170 (M^+, 2); 152 (1); 138 (10); 110 (27); 109 (15); 93 (14); 92 (15); 81 (100); 79 (15); 77 (10); 67 (12); 59 (8); 55 (11).

3. Results and discussion

3.1. Synthesis of the supported ruthenium on γ-alumina catalysts

3.1.1. Supported Ru/γ-Al_2O_3 prepared without trioctylamine (TOA) addition

Nanoparticles of ruthenium were deposited on γ-Al_2O_3 supports (both commercial low surface area and synthetic high surface area samples) by decomposition of Ru(η^6-COT)(η^4-COD) under atmospheric hydrogen at room temperature. This complex can be easily prepared by reduction of hydrated $RuCl_3$ with zinc dust in the presence of COD [21]. The formation of supported Ru/γ-Al_2O_3 is presented in Scheme 1.



Scheme 1.

3.1.2. Supported Ru/γ-Al_2O_3 catalysts prepared in the presence of TOA as a stabilizer

Deposition of the ruthenium nanoparticles stabilized by the trioctylamine on alumina involved two steps. Ru(η^6-COT)(η^4-COD) complex was first dissolved in THF containing TOA (TOA: Ru molar ratio = 3) under hydrogen atmosphere. The solution gradually became brown and no precipitation of metallic ruthenium was observed as a result of the interaction of TOA on the ruthenium nanoparticles. The solution was slowly discoloured upon addition of γ-Al_2O_3 and, at the completion of the reaction, a light brown solid, supported Ru(TOA)/γ-Al_2O_3 catalyst, was obtained. This overall reaction is illustrated in Scheme 2.

3.2. Hydrogenation of methyl benzoate

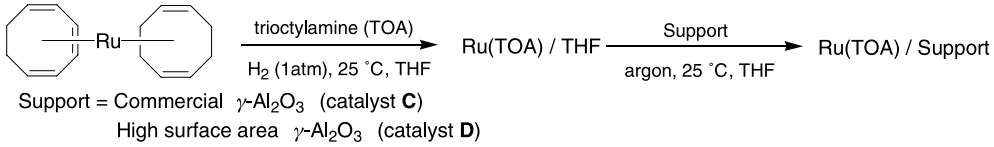
The hydrogenation of unsaturated aromatic hydrocarbons is a particularly important reaction in fine chemical synthesis [1,2] and the hydrogenation of methyl benzoate, as an example of deactivated aromatic compound, appears to be a useful model reaction of this type. Table 1 summarises the results obtained on the hydrogenation of methyl benzoate to methyl cyclohexanoate over different catalysts. The experiments were performed at 80 °C and 20 atm hydrogen in THF or cyclohexane.

As can be seen from Table 1, the catalyst activity of supported Ru catalyst, expressed as specific activity, was increased significantly as the support surface area increased. For both low and high surface area, the specific activity increased by a factor of almost 1.5 when THF was replaced by cyclohexane as reaction medium (runs 1–4). Further increase in catalyst activity was obtained when TOA was used as metal particle stabilizer (runs 5–8) and no evidence of catalyst deactivation was found (runs 9–12).

The catalyst activities for all catalysts prepared in this study were significantly higher than that obtained on commercial catalyst (run 13). The most active catalyst prepared in this study (run 8) exhibits almost 10 times higher in activity compared with a commercial available catalyst.

3.3. High Resolution Transmission Electron Microscopy (HRTEM) study of the Ru on γ-Al_2O_3 catalysts, A-D

The metal dispersion appears to be the main factor contributing to the catalyst activity as found by



Scheme 2.

Table 1
Hydrogenation of methyl benzoate to methyl cyclohexanoate with ruthenium on γ-Al_2O_3 catalysts at 20 atm hydrogen pressure and 80 °C[a]

Run	Catalyst[b]	Solvent	Time (h)	Conversion[c] (%)	Specific activity (SA)[d]
1	**A**	THF	5	5	
			24	70	2.9
2	**B**	"	5	15	
			24	100	4.2
3	**A**	Cyclohexane	5	20	
			22	100	4.5
4	**B**	"	5	50	
			16	100	6.2
5	**C**	THF	5	10	
			24	85	3.5
6	**D**	"	5	40	
			18	100	5.5
7	**C**	Cyclohexane	5	50	
			16	100	6.2
8	**D**	"	5	90	
			8	100	12.5
9	**A** (recovered from run 3)		22	100	4.5
10	**B** (recovered from run 4)	"	16	100	6.2
11	**C** (recovered from run 7)	"	16	100	6.2
12	**D** (recovered from run 8)	"	8	100	12.5
13	Ru on γ-Al_2O_3 (commercial)	"	24	35	1.4

[a] Methylbenzoate, 0.44 ml (3.5 mmol); catalyst (3.5 wt% Ru), 0.1 g (0.035 mg atom Ru); solvent, 10 ml.
[b] **A** = Ru on commercial γ-Al_2O_3; **B** = Ru on high surface area γ-Al_2O_3; **C** = Ru(TOA) on commercial γ-Al_2O_3; **D** = Ru(TOA) on high surface area γ-Al_2O_3.
[c] Determined by GC analysis.
[d] SA = moles of converted substrate/g atom ruthenium × h.

HRTEM (Figs. 1–4). The average metal particle size of catalysts prepared in this study was in the range of 2.3–2.9 nm and the catalyst activity was found to be as a function of metal dispersion. Of the catalysts test, catalyst **D**, with a smallest average metal particle size, exhibits the highest activity. The metal dispersion was remained unchanged during the course of the reaction. A similar metal dispersion was found for catalyst **D** recovered from run 8 and, as can be seen from Table 1, this catalyst afforded similar activity when it was recycled for the next run.

3.4. Preparation of 4-carbomethoxyformylcyclohexane via catalytic hydrogenation of 2-(4-carbomethoxyphenyl)-1,3-dioxane to 2-(4-carbomethoxycyclohexyl)-1,3-dioxane

4-Carbomethoxyformylcyclohexane is an important material in the synthesis of *trans*-4-aminomethylcyclohexancarboxylic acid (known as tranexamic acid), a compound of considerable pharmaceutical interest [23,24]. In this study a new catalytic synthetic pathway for the preparation of 4-carbomethoxyformylcyclohexane from methyl 4-formylbenzoate has been studied and illustrated in Scheme 3.

Methyl 4-formylbenzoate cannot be directly hydrogenated to 4-carbomethoxyformylcyclohexane as the aldehyde group is reduced more easier than the aromatic ring. For this reason it is necessary to protect the aldehyde group in methyl 4-formylbenzoate by a reversible formation of a new functional group which is stable

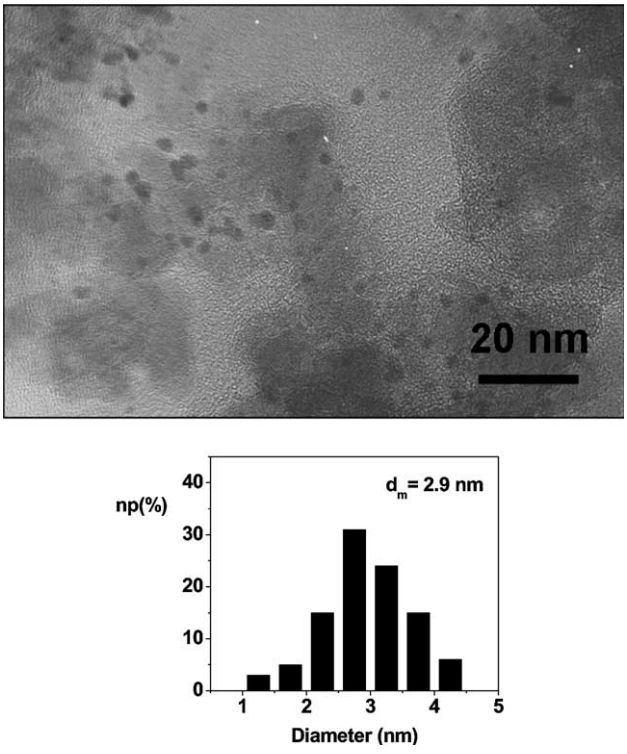


Fig. 1. Electron micrograph of the ruthenium on commercial γ-Al_2O_3 sample, catalyst **A**, and metal particle size distribution.

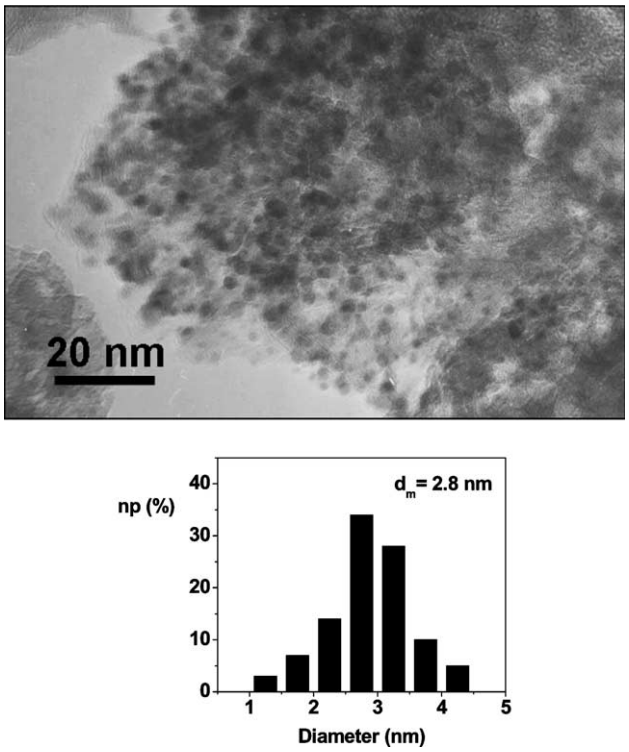


Fig. 2. Electron micrograph of the ruthenium on high surface γ-Al_2O_3 sample, catalyst **B**, and metal particle size distribution.

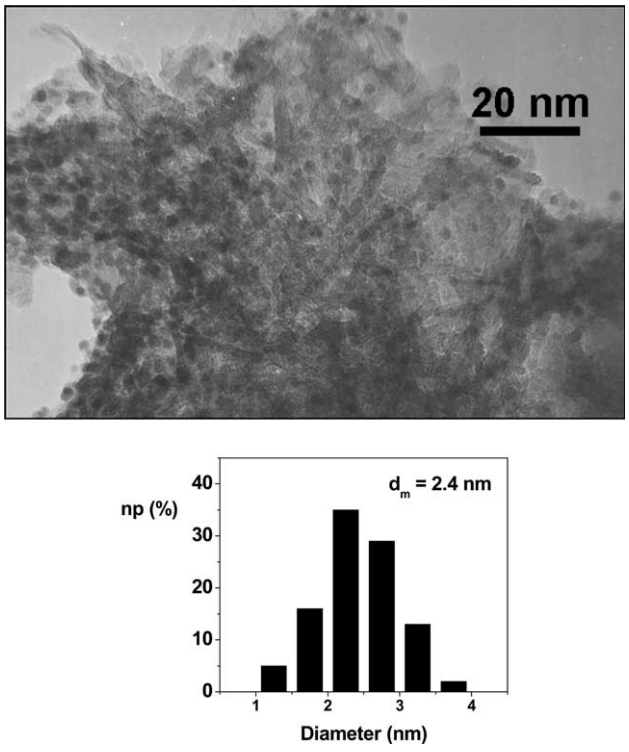


Fig. 3. Electron micrograph of the ruthenium on commercial γ-Al_2O_3 sample, containing trioctylamine, catalyst **C**, and metal particle size distribution.

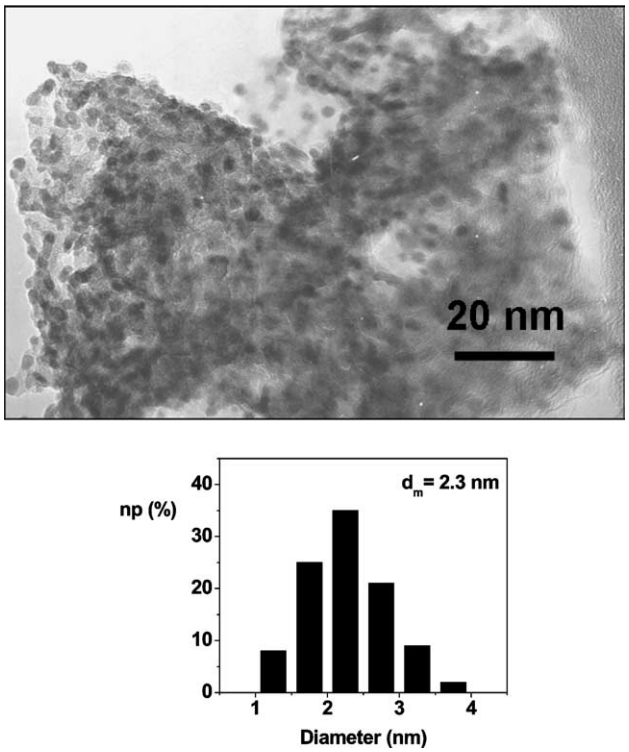
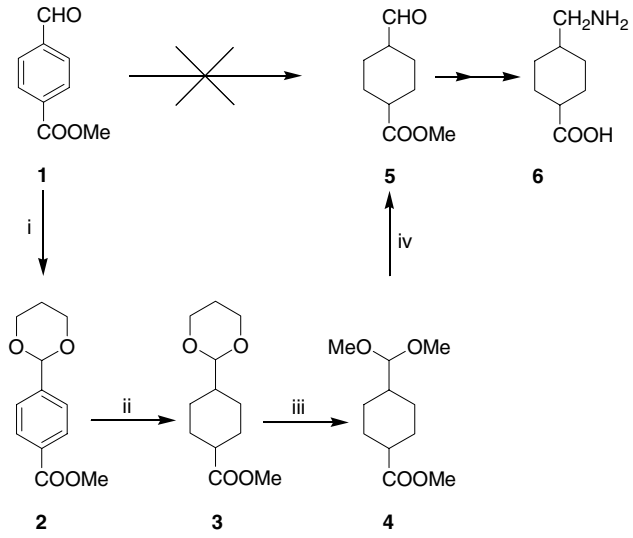


Fig. 4. Electron micrograph of the ruthenium on high surface γ-Al_2O_3 sample, containing trioctylamine, catalyst **D**, and metal particle size distribution.

under the hydrogenation conditions and can subsequently be removed. Cyclic acetals possess these features and the transformation of methyl 4-formylbenzoate to 2-(4-carbomethoxyphenyl)-1,3-dioxane was considered. This compound was synthesised by its reaction with



Scheme 3. (i) 1,3-Propandiol anhydrous $CuSO_4$, heat, yield 95%; (ii) H_2 (20 atm), Ru(TOA)/γ-Al_2O_3 (catalyst D), yield 90%; (iii) methanol, HCl, heat, and (iv) acidic water, 25 °C, yield 90%.

1,3-propandiol at 95 °C (Scheme 3, step i), in which anhydrous $CuSO_4$ was used both as a Lewis acidic catalyst and as a dehydrating agent to shift the equilibrium towards the formation of the product. The conversion of methyl 4-formylbenzoate was completed after 3 h and 2-(4-carbomethoxyphenyl)-1,3-dioxane can be recovered with a very high yield (95%), similar to that reported for the formation of 2-phenyl-1,3-dioxane by reaction of benzaldehyde and 1,3-propandiol [26].

The next step consists in the catalytic hydrogenation of 2-(4-carbomethoxyphenyl)-1,3-dioxane to 2-(4-carbomethoxycyclohexyl)-1,3-dioxane (Scheme 3, step ii). This reaction is the key step in the synthesis of 4-carbomethoxyformylcyclohexane because of the difficulty to carry out the reduction of the aromatic ring without side reactions on other functional groups present in the molecule. The reaction was tested with ruthenium on γ-alumina catalysts prepared in this study at 80 °C and 20 atm of hydrogen. THF, being a good solvent for 2-(4-carbomethoxyphenyl)-1,3-dioxane, was used as a reaction medium. The results obtained are reported in Table 2. Catalysts **A** and **B** exhibit a similar activity giving 70 and 75% yield of 2-(4-carbomethoxycyclohexyl)-1,3-dioxane after 24 h, respectively (runs 14 and 15). Catalysts **C** and **D** in which TOA was used in the preparation procedure as a metal particle stabilizer are more active giving 95% and 100% yield of 2-(4-carbomethoxycyclohexyl)-1,3-dioxane after 20 h, respectively (runs 16 and 17). The reaction was also performed without solvent over catalyst **D** at 95 °C [melting point of 2-(4-carbomethoxyphenyl)-1,3-dioxane] (run 18). A complete conversion of 2-(4-carbomethoxyphenyl)-1,3-dioxane after 15 h was obtained with only a slight loss of selectivity to afford 2-(4-carbomethoxycyclohexyl)-1,3-dioxane, in 95% yield.

For this reason, in order to avoid difficult and expensive steps for the purification of 2-(4-carbomethoxycyclohexyl)-1,3-dioxane, the synthesis of 2-(4-carbomethoxycyclohexyl)-1,3-dioxane from 2-(4-carbomethoxyphenyl)-1,3-dioxane in large scale (see experimental section) was carried out in THF with catalyst **D**, following the conditions of run 17 (Table 2). 2-(4-Carbomethoxycyclohexyl)-1,3-dioxane was obtained as a mixture of *cis trans* isomers ratio of 0.5.

The final step consists of the removal of the protecting propandioxy group in 2-(4-carbomethoxycyclohexyl)-1,3-dioxane and the regeneration of the aldehyde group. The most common method employed for acetal breakage is acid-catalysed hydrolysis. However for cyclic acetals in 2-(4-carbomethoxycyclohexyl)-1,3-dioxane, the reaction rate is low. Attempts to perform the hydrolysis of 2-(4-carbomethoxycyclohexyl)-1,3-dioxane with HCl at different concentration, in water-acetone and water-dioxane mixtures, as reported for dioxolanic cycles [27,28] were unsuccessful due to a very low reaction rate at room temperature and side reactions under reflux conditions. The formation of an acyclic acetal, by a transacetalisation reaction, was considered as an alternative route, as acyclic acetals are less stable than the cyclic ones and their hydrolysis is easier to perform. Following this procedure, 2-(4-carbomethoxycyclohexyl)-1,3-dioxane was refluxed with methanol in the presence of concentrated HCl as a catalyst. This step formed 4-carbomethoxycyclohexyl dimethyl acetal, which was in turn hydrolysed in situ to give 2-(4-carbomethoxycyclohexyl)-1,3-dioxane with 90% yield (Scheme 3, steps iii and iv, respectively). Due to a partial conversion of *cis*- to *trans*-isomer occurring during these reactions, the product is enriched in *trans*-isomer (70%). This observation is of particular relevance as only the *trans*-isomer of 4-aminomethylcyclohexancarboxylic acid (tranexamic acid) is biologically active [23,24].

4. Conclusions

The Ru/γ-Al_2O_3 systems obtained using the complex Ru(η^6-COT)(η^4-COD) as source of nanoscale ruthenium particles appear to be valuable catalysts for

Table 2
Hydrogenation of 2-(4-carbomethoxyphenyl)-1,3-dioxane, **2**, to 2-(4-carbomethoxycyclohexyl)-1,3-dioxane, **3**, with ruthenium on γ-Al_2O_3 catalysts at 20 atm hydrogen pressure and 80 °C in THF[a]

Run	Catalyst[b]	Time (h)	Conversion[c] (%)	Compound **3**[c,d](%)	Specific activity[e] (SA)
14	**A**	24	70	70	2.9
15	**B**	24	75	75	3.1
16	**C**	20	95	95	4.7
17	**D**	20	100	100	5.0
18[f]	**D**	15	100	95	6.3

[a] 2-(4-Carbomethoxyphenyl)-1,3-dioxane, **2**, 0.77 g (3.5 mmol); catalyst (3.5 wt% Ru), 0.1 g (0.035 mg atom Ru); THF, 10 ml.
[b] **A** = Ru on commercial γ-Al_2O_3; **B** = Ru on high surface area γ-Al_2O_3; **C** = Ru(TOA) on commercial γ-Al_2O_3; **D** = Ru(TOA) on high surface area γ-Al_2O_3.
[c] Determined by GC and ^{1}H NMR analyses.
[d] *cis*/*trans* = 2.
[e] SA = moles of compound **3**/g atom ruthenium × h.
[f] Performed without solvent.

the hydrogenation of arenes containing electron-withdrawing groups such as methyl benzoate and 2-(4-carbomethoxyphenyl)-1,3-dioxane under mild conditions. The catalysts **C** and **D**, prepared in the presence of TOA as metal particle stabilizer, show the better catalytic activity, reasonably as result of a high metal dispersion, the ruthenium particles ranging 2.3–2.4 nm vs 2.8–2.9 nm in samples **A** and **B**. The effect of TOA on metal dispersion has been recently observed and widely discussed for rhodium-TOA on γ-Al_2O_3 systems [29,30]. It is reasonable to suppose a similar effect for Ru-TOA/γ-Al_2O_3 systems, in which Ru particles are surrounded by trioctylamine that stabilizes them in a form of high dispersion and prevents their agglomeration and poisoning. No evidence of catalyst deactivation was found and catalysts could be reused several times without loss of activity.

Acknowledgements

The authors thank CNR (Italy) and CSIRO (Australia) for the financial support in a CNR–CSIRO Collaborative Research Scheme; a partial support by Ministero dell'Istruzione, Università e Ricerca (MIUR, Italy) is also acknowledged.

References

[1] J.D. Aiken III, R.G. Finke, J. Mol. Cat. A 145 (1999) 1, and references therein.
[2] J.A. Widegren, R.G. Finke, J. Mol. Cat. A 191 (2003) 187, and references therein.
[3] S. Abbet, A. Sanchez, U. Heiz, W.-D. Schneider, A.M. Ferrari, G. Pacchioni, N. Rösch, J. Am. Chem. Soc. 122 (2000) 3453, and references therein.
[4] R. Rao, G.U. Kulkarni, P.J. Thomas, P.P. Edwards, Chem. Eur. J. 8 (2002) 29, and references therein.
[5] K.J. Klabunde, Free Atoms, Clusters and Nanoscale Particles, Academic Press, New York, 1994.
[6] M.T. Reetz, W. Helbig, S.A. Quaiser, in: A. Fürstner (Ed.), Active Metals: Preparation, Characterization, Applications, VCH, New York, 1996.
[7] H. Bönnemann, G. Braun, W. Brijoux, R. Brinkmann, A.S. Tilling, K. Seevogel, K. Siepen, J. Organomet. Chem. 520 (1996) 143.
[8] Y. Wang, H. Liu, N. Toshima, J. Phys. Chem. 100 (1996) 19533.
[9] G. Vitulli, A. Verrazzani, A.M. Caporusso, E. Pitzalis, P. Pertici, P. Salvadori, in: S. Daolio, E. Tondello, P.F. Vigato (Eds.), Syntheses and Metodologies in Inorganic Chemistry, New Compounds and Materials, vol. 7, 1997, p. 52.
[10] G. Vitulli, E. Pitzalis, A. Verrazzani, P. Pertici, P. Salvadori, G. Martra, Mater. Sci. Forum. 235-238 (1997) 929.
[11] K.S. Weddle, J.D. Aiken III, R.G. Finke, J. Am. Chem. Soc. 120 (1998) 5653.
[12] N. Toshima, T. Yonazawa, New J. Chem. 22 (1998) 1179.
[13] J. Schulz, A. Roucoux, H. Patin, J. Chem. Soc. Chem. Commun. (1999) 535.
[14] G.B. Sergeev, Russ. Chem. Rev. 70 (2001) 809.
[15] N. Toshima, Y. Shiraishi, T. Teranishi, M. Miyake, T. Tominaga, H. Watanabe, W. Brijoux, H. Bönnemann, G. Schmid, Appl. Organomet. Chem. 15 (2001) 178.
[16] H. Bönnemann, R. Richards, Eur. J. Inorg. Chem. (2001) 2455.
[17] A. Spitaleri, P. Pertici, N. Scalera, G. Vitulli, M. Hoang, T.W. Turney, M. Gleria, Inorg. Chim. Acta 352 (2003) 61.
[18] H. Hirai, H. Chawanya, N. Toshima, React. Polym. 3 (1985) 127.
[19] G. Schmid, Chem. Rev. 92 (1992) 1709.
[20] V.M. Frolov, Platinum Met. Rev. 40 (1996) 8.
[21] P. Pertici, G. Vitulli, Inorg. Syn. 22 (1983) 176.
[22] C. Pan, K. Peltzer, K. Philippot, B. Chaudret, F. Dassenoy, P. Lecante, M-J. Casanove, J. Am. Chem. Soc. 123 (2001) 7584.
[23] C. Runti, in: Fondamenti di Chimica Farmaceutica, vol. III, Lint, Trieste, Italy, 1989, 465.
[24] K. Maeda, M. Naganuma, J. Photochem. Photobiol. B 47 (1998) 136.
[25] M. Giannos, M. Hoang, T.W. Turney, Chem. Lett. 27 (1998) 793.
[26] R.P. Hanzlik, M. Leinwetter, J. Org. Chem. 43 (1978) 438.
[27] M.L. Bender, M.S. Silver, J. Am. Chem. Soc. 85 (1963) 3006.
[28] E.H. Cordes, H.G. Bull, Chem. Rev. 74 (1974) 580.
[29] G. Vitulli, C. Evangelisti, P. Pertici, E. Pitzalis, A.M. Caporusso, P. Salvadori, S. Coluccia, G. Martra, A. Balerna, S. Mobilio, Second European Catalysis Simposium, Pisa, Italy, 23–26 September 2001, abstract P75.
[30] G. Vitulli, C. Evangelisti, P. Pertici, A.M. Caporusso, N. Panziera, P. Salvadori, M.G. Faga, C. Manfredotti, G. Martra, S. Coluccia, A. Balerna, S. Colonna, S. Mobilio, J. Organomet. Chem. 681 (2003) 37.