

MgO nanoparticle-based multifunctional catalysts in the cascade reaction allows the green synthesis of anti-inflammatory agents

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Received 15 January 2007; revised 1 February 2007; accepted 2 February 2007

Available online 8 March 2007

Abstract

Up to now, the anti-inflammatory agent nabumetone has been synthesized by a two-step process involving either a Heck reaction between 6-bromo-2-methoxynaphthalene and methyl vinyl ketone or a condensation between 6-methoxy-2 naphthaldehyde and acetone to give an intermediate that is separated, purified, and hydrogenated in a second and separate process to give the final product, while producing a large amount of waste products. Here we report a residue-free catalytic process for the production of nabumetone with $\geq 98\%$ yield and 100% selectivity achieved through a cascade reaction system involving a multifunctional base/acid/hydrogenation catalyst based on nanocrystalline (~ 3 nm) MgO.

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Keywords: Aldol condensation; Anti-inflammatory; Cascade reaction; MgO; Multifunctional catalyst

1. Introduction

Nabumetone, 4-(6-methoxy-2-naphthyl)-2-butanone, like α -aryl propionic acids (e.g., ibuprofen, naproxen, ketoprofen) have nonsteroidal anti-inflammatory activity (NSAI). Besides being an effective anti-inflammatory and analgesic in the treatment of various rheumatic and arthritic diseases, nabumetone has fewer side effects and lower toxicity to the gastrointestinal tract than other anti-inflammatory agents [1].

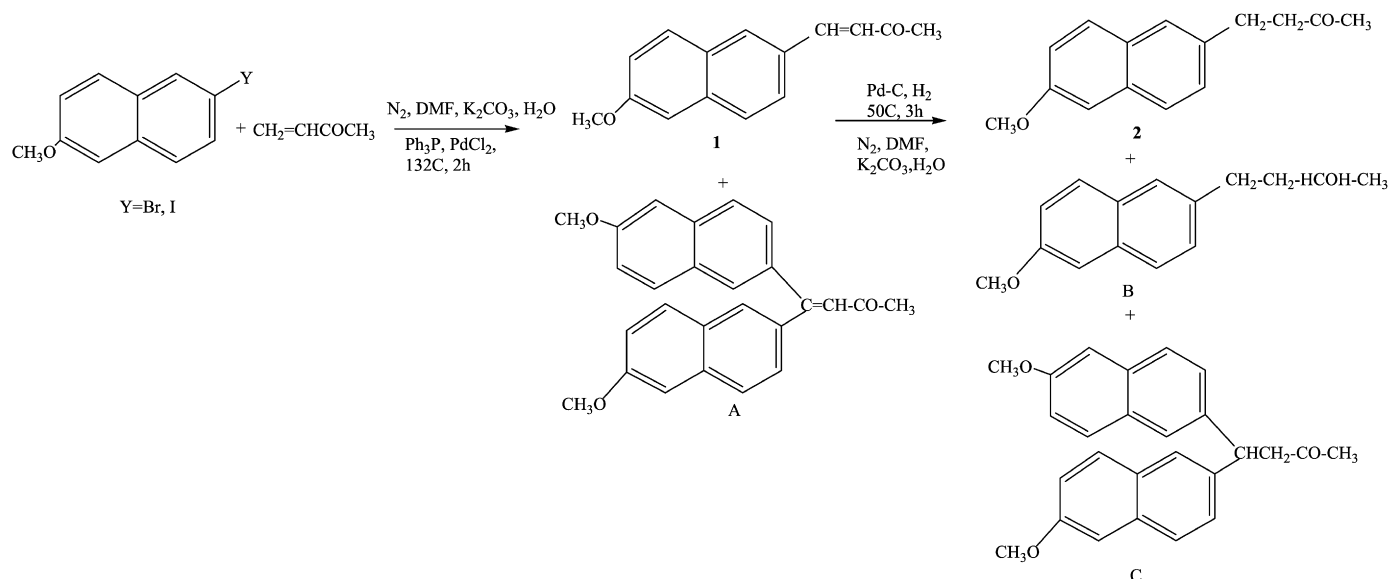
Various industrial processes for the preparation of nabumetone have been proposed that involve the preparation of an analogue compound with a double bond in the aliphatic chain 4-(6-methoxy-2-naphthyl)-3-buten-2-one (**1**), followed by hydrogenation of the double bond. It is interesting that although the unsaturated intermediary presents the same analgesic and/or anti-inflammatory activity as the final hydrogenated compound, it produces a certain degree of estrogenicity; for this reason, the final hydrogenated product is medically recommended. Two main standard methods for carbon–carbon formation have been used for the preparation of intermediate **1**: the Heck reaction [2] and aldol condensation. Thus, the Hoechst Celanese process re-

acts 6-bromo-2-methoxynaphthalene and methyl vinyl ketone (Heck reaction) in dimethylformamide as a solvent, using a homogeneous palladium (II) catalyst at 405 K. The Pd catalyst generally results from a Pd(II) salt and a phosphine ligand, such as triphenylphosphine (PPh₃). Hydrogenation of the unsaturated product formed during the Heck reaction with a palladium on carbon pretreated (Pd–C) catalyst in a second reaction step yields 87.4% of nabumetone [3] (**2**) (see Scheme 1) and leaves bromide salts as byproducts.

Reaction byproducts formed in this process are generated from the subsequent Heck C–C coupling of **1** to give product A and the corresponding hydrogenated (C), as well as the formation of 4-(6-methoxy-2-naphthyl)-2-butanol (B) (see Scheme 1).

Rhodia Chimie [4] synthesized **1** by reacting in an autoclave 1,6-dibromo-2-methoxynaphthalene with methyl vinyl ketone (MVK) in toluene anhydrous in the presence of Et₃N, Pd(OAc)₂, PPh₃, and H₂ at 423 K and 40 bar (yield of **1** $\sim 58\%$, and only a 5% of **2** was detected). Alternatives to MVK for the synthesis of nabumetone have been sought by industry due to its limited stability (due to competing side reactions, such as oligomerization) and toxicologic concerns associated with its use. An alternative method of obtaining **2** involves 2-bromo-6-methoxynaphthalene, 3-buten-2-ol, palladium acetate, PPh₃, in

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Scheme 1. Reaction steps involved in the Hoechst Celanese process.

1-methyl-2-pyrrolidone as solvent at 413 K for 5 h to give a yield of 60% [5].

Synthetic approaches to **2** via aldol condensation also have been reported in the literature [6]. Aldol condensation between 6-methoxy-2-naphthaldehyde and acetone was performed in the presence of an aqueous alkali metal hydroxide solution (NaOH and/or KOH) as catalyst, followed by acidification to give **1** (yield 95%). Then hydrogenation of **1** was carried out in a second step using Pd–C as catalysts, yielding the corresponding saturated ketone. This two-step process yields >90% of product **2** but generates high amounts of waste salts and effluents. To avoid this handicap, a two-step process using a solid catalyst (basic alumina) for the condensation step of 6-methoxy-2-naphthaldehyde and acetone has been described in the patent literature [7]. However, this procedure achieves only a 78% yield in the first reaction after 22 h, and the intermediate **1** must be hydrogenated in a second, separate process.

The present work demonstrates that a multifunctional acid–base–metal catalyst based on nanocrystallite (~3 nm) MgO is able to catalyze the synthesis of nabumetone with yields ≥ 98 and 100% selectivity through a one-pot cascade reaction system. The catalyst can be regenerated and recycled several times, resulting in high turnover numbers (TONs).

2. Experimental

2.1. Catalysts

The magnesium–aluminum layered double hydroxide sample (Mg–Al-LDH) was prepared from a gel produced by mixing two solutions. Solution A contained $(3 - x)$ mol of Mg(NO₃)₂·6H₂O and x mol of Al(NO₃)₃·9H₂O in the (Al + Mg) concentration of 1.5 mol/L, for a Al/Al + Mg molar ratio of 0.25. Solution B was formed by $(6 + x)$ mol of NaOH and 2 mol of Na₂CO₃ dissolved in the same volume as solu-

tion A. Both solutions were co-added at a rate of 1 mL/min under vigorous mechanical stirring at room temperature. The gel was aged under autogenous pressure conditions at 333 K for 12 h. Then the hydrotalcite was filtered and washed until pH 7 was reached, at which point the solid was dried. The Mg–Al mixed-oxide (HTc) base catalyst was obtained by calcination of Mg–Al-LDH at 723 K for 6 h in a dry nitrogen flow.

A MgO sample with a surface area of 120 m²/g was purchased from Aldrich. A MgO sample with a surface area of 320 m²/g was prepared starting from magnesium oxalate following the method described by Putanov et al. [8]. A MgO sample with a surface area of 670 m²/g was purchased from NanoScale Materials.

Pd catalysts with different Pd loadings (1, 1.5, and 2 wt% of palladium) were obtained by contacting the MgO or Mg–Al-LDH samples with an anhydrous toluene solution with different amounts of palladium acetylacetonate [Pd(acac)₂] for 12 h. After evaporation of toluene at reduced pressure, the solid was dried overnight at 353 K in vacuum and then calcined in nitrogen flow at 823 K (ramp rate, 5 °/min) for 3.5 h. In the case of Pd-HTc, the calcined sample (Pd-HTc) was hydrated at room temperature by the direct addition of decarbonated water (MilliQ) (36 wt%) just before their use as catalysts.

Samples of Pd-MgO and Pd-HTc were activated before reaction by heating the solid at 723 K under air atmosphere for 5 h and then for 5 h under nitrogen. Metal reduction was performed by heating the solid at 723 K in a flow of H₂/N₂ (90/10) for 2 h.

The catalysts thus prepared were characterized by XRD, TEM, and nitrogen adsorption. N₂ adsorption/desorption isotherms were performed at 77 K in a Micromeritics ASAP 2010 apparatus after the samples were pretreated under vacuum at 673 K overnight, and the BET surface areas were obtained using the BET methodology. The main characteristics of the catalysts are given in Table 1.

Table 1
Main characteristic of the catalyst

| Catalyst | Surface area (m ² g ⁻¹) | Total pore volume (cc/g) | Average pore diameter (Å) | Crystal size ^a (nm) |
|------------|--|--------------------------|---------------------------|--------------------------------|
| Pd-HTc-(1) | 264 | 0.553 | 84 | <50 |
| Pd-HTr-(1) | 18 | – | – | – |
| MgO-120 | 120 | 0.871 | 292.41 | 13 |
| MgO-320 | 320 | 0.563 | 70.80 | 5 |
| MgO-670 | 670 | 0.644 | 39.55 | 3 |

^a Crystallite size measured by X-ray diffraction spectrum.

2.2. Reaction procedure

For a typical experiment, a solution of 6-methoxy-2-naphthaldehyde (500 mg, 2.6 mmol) dissolved in an excess of acetone (26 mmol) was placed in a batch slurry reactor that was then immersed in a thermostat silicone oil bath at 333 K and magnetically stirred. When the desired temperature was reached, a 50-mg catalyst sample (10 wt% with respect to naphthaldehyde) was added, and hydrogen at a constant hydrogen pressure of 5 bar was applied. When Pd-HTr was used, the Pd-HTc precursor catalyst was previously hydrated at room temperature with decarbonated water (36 wt%). The course of the reaction was followed by gas chromatography (GC) using a Hewlett Packard GC 5988 A with a flame ionization detector and a HP-5 capillary column of 5% phenylmethylsilicone. In all of the experiments, dodecane was used as an internal standard. At the end of the reaction, after cooling, the reaction mixture was filtered to remove the catalyst. The solid was extracted thoroughly with dichloromethane, and the extract was considered in the mass balance. The reaction mixture was concentrated under reduced pressure, and the reaction products were analyzed

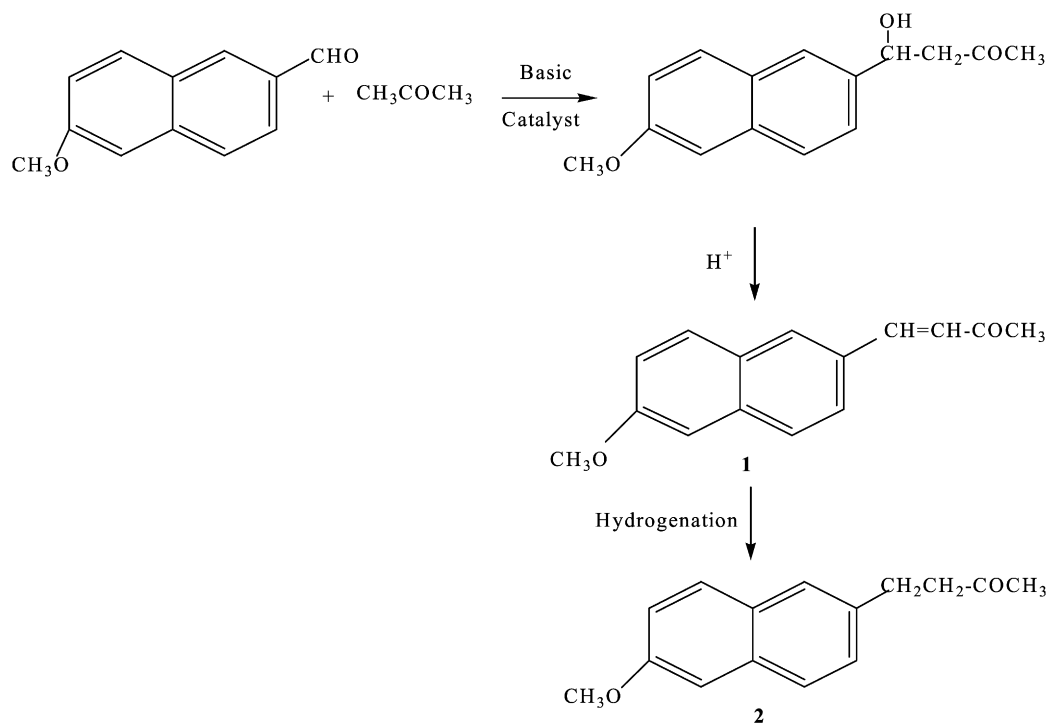
by GC–MS (Varian Saturn II, using the same column as for GC) and ¹H NMR spectroscopy (Varian Gemini, 300 MHz, with CDCl₃ as a solvent).

2.3. Catalyst regeneration

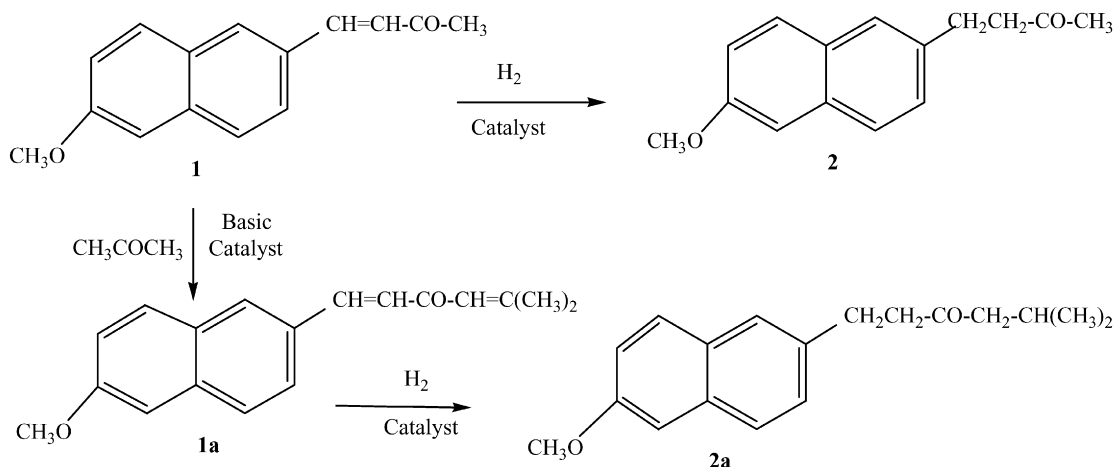
Pd-HTc(1) and Pd-MgO(1)-670 samples were regenerated after each use by calcination of the solids at 723 K under air atmosphere for 5 h and then under nitrogen for 5 h. Reduction of the Pd was performed by heating the solid at 723 K in a flow of H₂/N₂ (90/10) for 2 h.

3. Results and discussion

When we first approached the synthesis of **1** through the aldol condensation between 6-methoxy-2-naphthaldehyde and acetone, the solid base catalyst of choice was a calcined Mg/Al hydrotalcite. Calcined hydrotalcites are base compounds that have been successfully used in catalyzing condensation reactions for the production of chemicals and pharmaceuticals [9]. Furthermore, a series of excellent reports has shown that metal-supported hydrotalcites can be used to produce methyl isobutyl ketone [10], 2-methyl-3-phenyl propanal [11], and α -alkylated nitriles [12] in a single-stage condensation hydrogenation process. Therefore, and because three reaction steps are required for the synthesis of nabumetone, involving basic, acid, and hydrogenation sites (see Scheme 2), we used Pd on a calcined hydrotalcite (Pd-HTc-(1), with 1% wt/wt of Pd loading) as a catalyst, in which Lewis basic sites are associated with framework oxygens, Lewis acid sites are related to Al³⁺ and Mg²⁺ cations, and finally metal Pd as the hydrogenating func-



Scheme 2. Reaction steps involved in the formation of nabumetone.

Scheme 3. Reaction steps involved in the formation of compound **2a**.Table 2
Synthesis of nabumetone using Pd-supported hydrotalcites at different reaction temperatures

| Catalyst | <i>T</i> (K) | <i>r</i> ₀ ^a (mol min ⁻¹ g ⁻¹) 10 ⁴ | <i>r</i> ₀ ^b 2 (mol min ⁻¹ g ⁻¹) 10 ⁴ | Conversion (%) | Yield of 2 (%) |
|-----------|-----------------|---|--|-------------------|--------------------------|
| Pd-HTc(1) | 333 | 4.5 | 2.4 | 15 ^c | 15 ^c |
| Pd-HTr(1) | 333 | 5.2 | 2.8 | 32 ^c | 29 ^{c,e} |
| Pd-HTc(1) | 348 | 5.8 | 3.2 | 85 ^d | 85 ^d |
| Pd-HTc(1) | 373 | 7.8 | 4.8 | 98 ^d | 98 ^d |

Note. Reaction conditions: molar ratio acetone/aldehyde = 10, 10 wt%, of catalyst with respect to the aldehyde and working at constant pressure of hydrogen (5 bar). In brackets the amount of palladium content (wt%) of the catalyst.

^a Initial reaction rates for the condensation step.

^b Initial reaction rates of formation of nabumetone.

^c At 1 h reaction.

^d At 2 h reaction time.

^e 3% of compound **2a** was detected.

tion. The results, given in Table 2, show that this catalyst was not very active at 333 K, contrary to our expectations.

To increase the catalyst activity, the calcined hydrotalcite containing palladium metal was rehydrated [Pd-HTr(1)] (see Section 2), because rehydration restores the layered structure in which the CO₃²⁻ compensating anions in the interlayer space are replaced by OH⁻, resulting in strong Brønsted base catalysts that effectively catalyze a greater number of reactions [13–19].

The results in Table 2 indicate that the catalytic activity increased on rehydration, but a secondary product (**2a**) was formed by condensation of product **1** with a second acetone molecule, followed by hydrogenation (Scheme 3). The reaction temperature was increased to improve the yield to nabumetone; as shown in Table 2, a 98% yield of nabumetone could be achieved in a one-pot reaction after 2 h of reaction time using Pd-HTc(1) and working at 373 K. This yield is much higher than the values reported in the patent literature using a basic alumina for the condensation step, followed by hydrogenation of the product thus formed [7]. Unfortunately, the catalyst became deactivated, and regeneration was not achieved. Indeed, when the reaction was completed and the catalyst was

Table 3
Results of reuses of the Pd-HTc(1) catalyst

| Catalyst | Cycles | Conversion (%) | Yield of 2 (%) |
|-----------|----------------|----------------|-----------------------|
| Pd-HTc(1) | 1 | 81 | 81 |
| Pd-HTc(1) | 2 ^a | 66 | 66 |
| Pd-HTc(1) | 3 ^a | 62 | 62 |

Note. Reaction conditions: molar ratio acetone/aldehyde = 10, 10 wt% of catalyst with respect to the aldehyde, at 1 h reaction time, at 373 K, working at constant pressure of hydrogen (5 bar).

^a Reuse after calcination and reduction of the catalyst.

Table 4
Results of the use and reuses of Pd-HTr(1) catalyst

| Catalyst | Cycles | Conversion | Yield of 2 (%) | Yield of 2a (%) |
|-----------|----------------|------------|-----------------------|------------------------|
| Pd-HTr(1) | 1 | 100 | 89 | 11 |
| Pd-HTr(1) | 2 ^a | 18 | 17 | 1 |
| Pd-HTr(1) | 2 ^b | 44 | 35 | 9 |

Note. Reaction conditions: relation molar acetone/aldehyde = 10, 40 wt% of catalyst with respect to the aldehyde, 75 min, at 348 K, working at constant pressure of hydrogen (5 bar).

^a Reuse after washed and reduction.

^b Reuse after calcinations, reduction and rehydration of the catalyst. In brackets the amount of palladium content (wt%) of the catalyst.

filtered, washed with acetone, and reused, no activity was observed. In principle, this can be attributed to the presence of organic products remaining adsorbed on the catalyst. To eliminate these products, regeneration was attempted by calcination at 623 K for 5 h in the presence of air, followed by 5 h in a stream of N₂. After this regeneration procedure, the sample was reused in a second cycle and then in a third cycle. The results, given in Table 3, indicate an irreversible deactivation of the catalyst.

With the rehydrated hydrotalcite, improved yields of nabumetone also were obtained in shorter reaction times by increasing the temperature and the amount of catalyst (Table 4), but selectivity was lower than in the case of calcined hydrotalcite, due to formation of larger amounts of compound **2a**. Unfortunately, also in this case, catalyst deactivation occurred very rapidly, and regeneration of the solid by either washing or calcination and subsequent rehydration was not successful. Owing

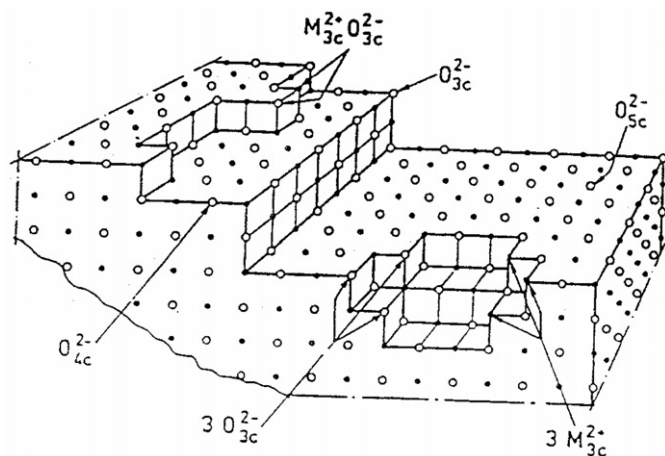


Fig. 1. Structure of MgO taken from Ref. [21].

to this, we have searched for another type of multifunctional acid–base metal catalyst.

Alkaline earth oxides, and more specifically MgO, have shown to be active for aldol condensation reactions [20]. In this case, the basic sites able to abstract protons from a reactant molecule are those associated with $M^{2+}O^{2-}$ ion pairs, in which the O^{2-} acts as a Lewis basic site and the adjacent metal cation acts as a weak Lewis acid that catalyzes the dehydration of the intermediate benzylic alcohol to the corresponding enone, because this would be a facile reaction. Nevertheless, the benzylic alcohol intermediate also may undergo deoxygenation directly by C–O bond hydrogenolysis. We observed that MgO with $120 \text{ m}^2 \text{ g}^{-1}$ and 13 nm nanocrystalline size with 1 wt% Pd [Pd-MgO(1)-120] (see Section 2) had twice the activity for synthesis of nabumetone than rehydrated hydrotalcite [Pd-HTr(1)], whereas the former was 100% selective.

Based on this result, MgO appeared to be a promising candidate for performing the aldol condensation between 6-methoxy-2-naphthaldehyde and acetone, although the catalytic activity

had to be increased. To do this, we considered the MgO structural model of Coluccia et al. [21] who proposed a highly defective surface structure for MgO, with step edges, corners, and kinks, which provide O^{2-} sites of low coordination numbers (see Fig. 1). These low-coordinated O^{2-} sites (O_{5c}^{2-} on faces, O_{4c}^{2-} on edges, and O_{3c}^{2-} on corners) are expected to be responsible for the presence of basic sites with different strengths. The basic strength of surface O^{2-} sites increases as the coordination number drops, with $Mg_{3c}^{2+}O_{3c}^{2-}$ sites the most reactive for our purposes.

Taking the foregoing findings into account, we believed that the number of sites at the corners of the crystals should increase with decreasing crystallite size of MgO, and consequently the catalyst activity should increase accordingly. To evaluate this, we studied two new MgO catalysts with 320 and $670 \text{ m}^2 \text{ g}^{-1}$, and MgO crystallite sizes of 5 and 3 nm, respectively, as determined from the Debye–Scherrer equation (see Table 1 and Fig. 2). Thus, plotting the activity (initial reaction rates) for the first reaction step (i.e., the base-catalyzed condensation reaction (Scheme 2)) versus the crystallite size of the three MgO samples demonstrates that the initial reaction rate increases not linearly, but rather exponentially with decreasing crystallite size of the MgO (Fig. 3). The result indicates that this reaction is sensitive to the structure, following the nomenclature of Boudart [22]; in other words, the basic sites associated with corners and edges (which are the most basic) are also the most active for the condensation reaction. At this point, selecting the MgO sample with a nanocrystallite size of 3 nm (see Fig. 4) and depositing 1 wt% of Pd on the surface should yield a highly active and selective multifunctional catalyst. Indeed, carrying out a one-pot reaction at 333 K with the Pd-MgO(1)-670 sample produced a 98% yield of nabumetone with 100% selectivity after 60 min of reaction time; this yield was 87% for Pd-MgO(1)-120 after 150 min and 88% for Pd-MgO(1)-320 after 120 min (see Fig. 5).

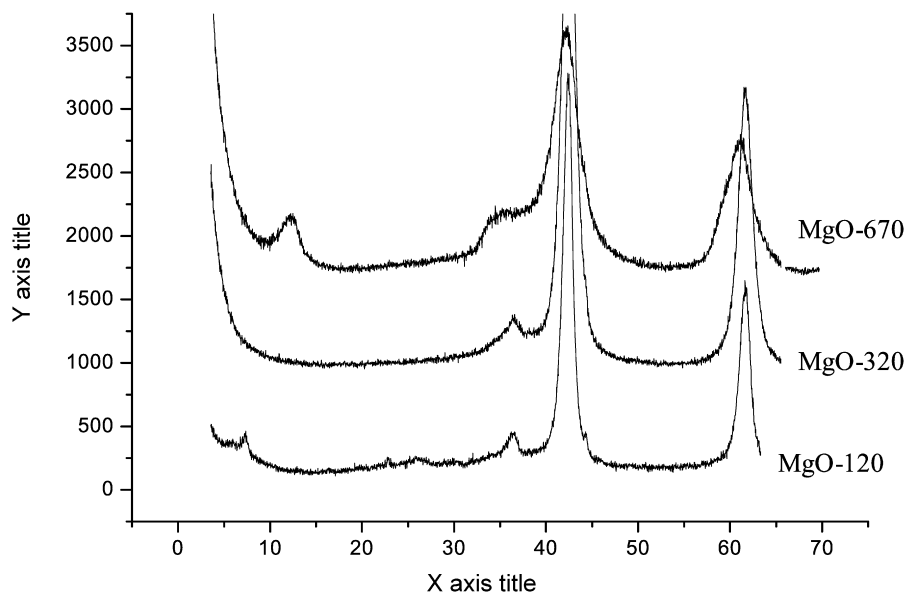


Fig. 2. XDR spectra of the MgO samples.

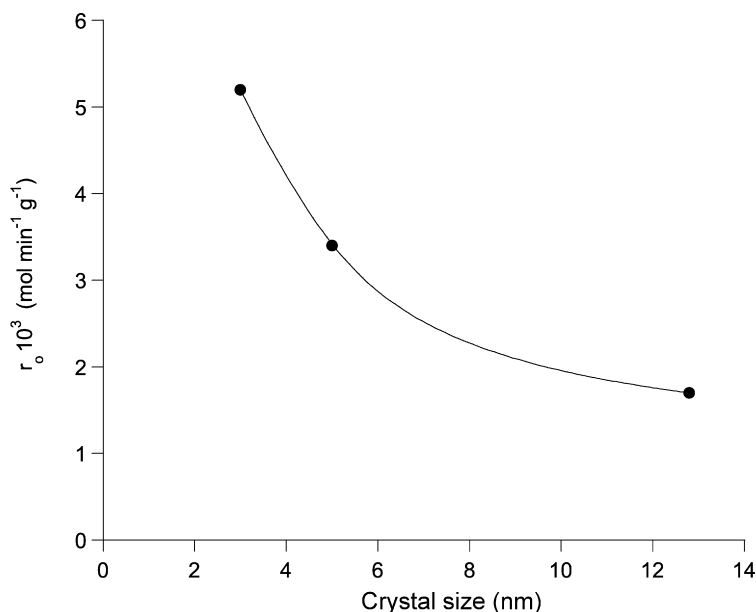


Fig. 3. Initial reaction rates for the condensation step using MgO of different crystal size. Reaction conditions: molar ratio acetone/aldehyde = 10, 10 wt%, of catalyst with respect to the aldehyde, at 333 K.

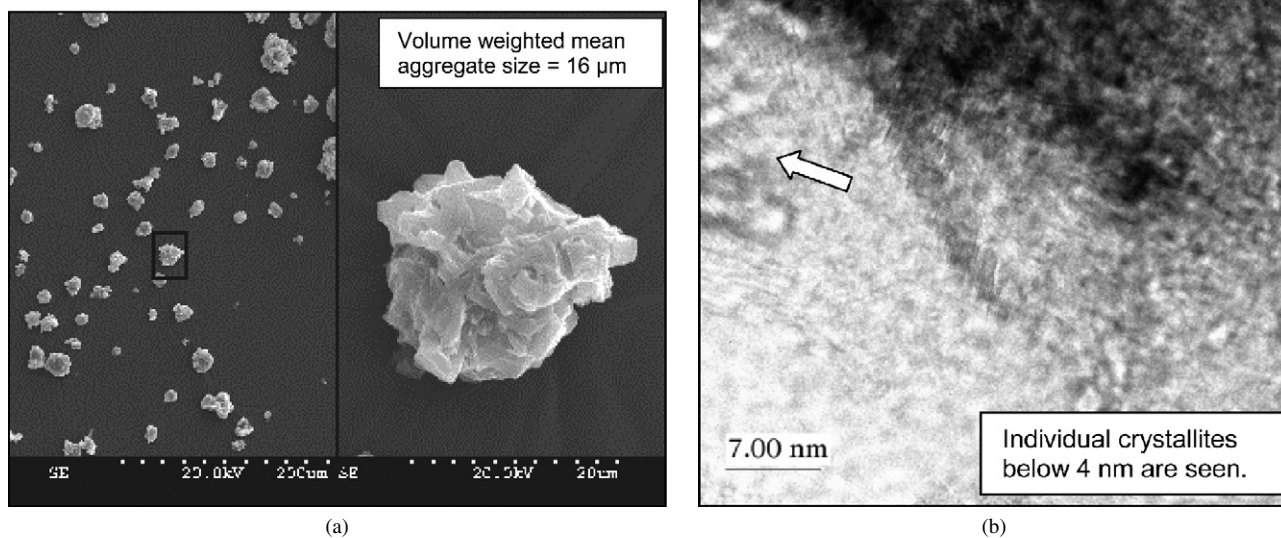


Fig. 4. (a) Scanning electron microscopy image and (b) transmission electron microscopy image of MgO-670 sample kindly supplied by NanoScale Materials Inc.

These results clearly confirm that using nanocrystalline MgO, it is possible to synthesize nabumetone with very high yield and selectivity through a cascade or domino reaction in which the condensed product formed on the basic sites of the catalysts is rapidly dehydrated on an acid site and the resulting double bond is hydrogenated on the Pd. It should be noted that under our reaction conditions, increasing the amount of the hydrogenating function from 1 to 1.5 or 2 wt% Pd increased the rate of nabumetone formation, demonstrating that under these reaction conditions, hydrogenation is the controlling step. However, 1 and 1.5 wt% Pd have similar final conversion and selectivity.

Finally, the used catalyst was subjected to three cycles of reaction–regeneration (calcination)–reaction (see Section 2 for regeneration conditions). The catalyst maintained its activity (Fig. 6).

4. Conclusion

This study has demonstrated that using a multifunctional catalyst based on nanocrystalline MgO, it is possible to develop a new green process for the production of nabumetone in a one-pot reaction. This new process allows a yield $\geq 98\%$ with 100% selectivity.

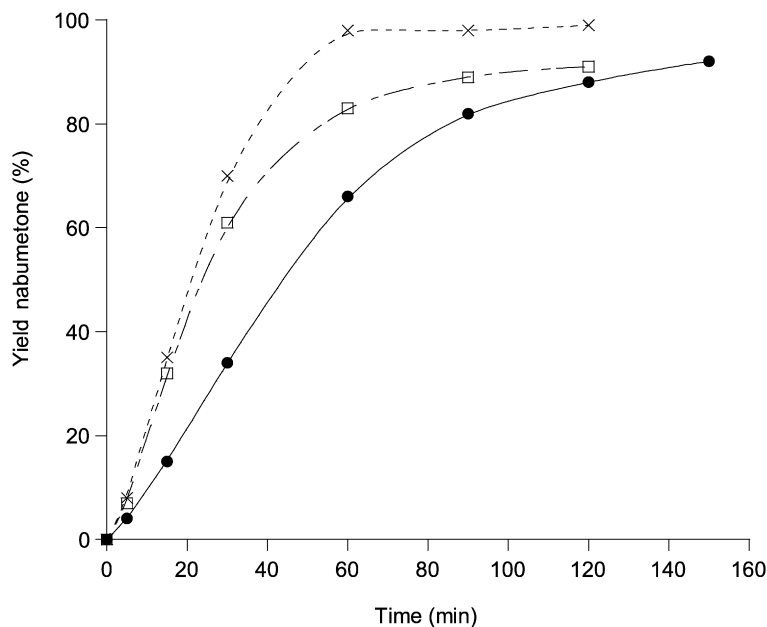


Fig. 5. Results of one pot synthesis of nabumetone using: (●) Pd-MgO(1)-120, (□) Pd-MgO(1)-320, (×) Pd-MgO(1)-670, as catalysts. Reaction conditions: molar ratio acetone/aldehyde = 10, 10 wt%, of catalyst with respect to the aldehyde, at 333 K and at constant pressure of hydrogen (5 bar).

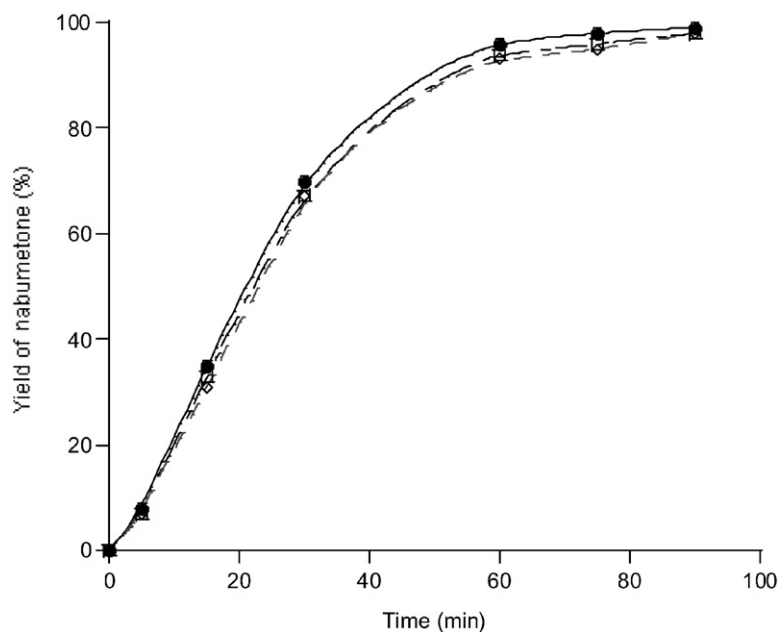


Fig. 6. Results of the regeneration of Pd-MgO(1)-670 catalyst: 1st (●), 2nd (□) and 3rd (◇) cycle.

Acknowledgment

Financial support by CICYT MAT2003-07769-C02-01 is acknowledged.

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