Active Base Hybrid Organosilica Materials based on Pyrrolidine Builder Units for Fine Chemicals Production

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The catalytic activity of "pyrrolidine type" fragments included or anchored in the mesoporous silica supports or polymeric frameworks have been fully reported for enantioselective transformation. Nevertheless, low attention was focused on their catalytic abilities to perform base-catalyzed reaction. Accordingly, hybrid materials including pyrrolidine fragments in the mesoporous silica supports were prepared following different synthesis methods, such as micellar and fluoride sol-gel routes in absence of structural directing agents. Their great catalytic performance was explored for various base-catalyzed reactions to the formation of C–C bond through Knoevenagel, Claisen-Schmidt and Henry condensations under microwave irradiation. The benefits of microwave irradiation combined with suitable catalytic properties of pyrrolidine hybrid materials with strong base sites and high accessibility to active centers, allowed carrying out successfully base-catalyzed condensation reactions for the production of fine chemicals. Moreover, the hybrid catalyst exhibited high selectivity and good stability over different catalytic cycles contributing to environmental sustainability.

Introduction

The area of hybrid materials in which organic and inorganic units are conjugated in their structure, perfectly assembled and regularly distributed in their framework, allows the generation of new families of materials, often with associated intrinsic porosity, that exhibit unique physico-chemical properties and reactivity, and above all, different from that of the building units in homogeneous phase when they are found separately.[1] This fact is favored by the positive synergy established between the active functional builders that make up the structure of the materials, where aspects such as the molecular distance between the different building units, their distribution and location in the network and the morphology of the structure in which they are integrated are keys in the properties of the hybrid organic-inorganic materials finally obtained.[2,3]

The appropriate combination of different builder units, organic and inorganic, through condensation, hydrothermal, solvothermal or even self-assembly processes allowed the generation of new families of advanced materials with varied properties and topologies, such as metal-organic materials (MOFs), coordination polymers, modified covalent organic frameworks (COFs) or mesoporous periodic organosilicas (PMOs), among the main ones.[4–6] These hybrid solids have found application in a large number of fields related to the adsorption-separation of gases, catalysis (including photocatalysis and electrocatalysis), sensors, molecular photodynamics or storage, covering aspects ranging from processes related to the specific production of chemicals through environmentally friendly catalytic routes to their intervention in green energy generation processes acting as efficient membranes in fuel cells, citing only a few relevant examples.[7] Base-catalyzed reactions allow the production of a large variety of products with high value added of interest in different sectors of chemical industry such as pharmaceuticals, fine chemicals, polymers, paints, drugs, cosmetics and ingredients for food. The main homogeneous bases usually used are NaOH, KOH, and trimethylamine in aqueous or alcoholic solution owing to their catalytic properties and low cost.[8] For the past century, with industrial revolution, humans have caused most of global warming by releasing greenhouse gases which levels are higher now than at any time in the last 800,000 years. Therefore, the urgency of caring for the planet, focusing on carbon neutrality and green chemistry principles that promote atomic efficiency, the use of non-toxic, degradable and environmentally friendly substances, as well as the utilization of catalysts, make the development of new robust and efficient hybrid functional catalysts crucial. Thus, the design and development of solid catalysts will allow avoiding the generation of large amount of waste, equipment corrosion, use of toxic substances and achieving easy catalyst separation from reaction products and recycling as well as higher process selectivity leading to environmentally benign and economical pathway being of large interest for chemical industry and scientific community.

Among all the possibilities offered by hybrid materials, their ability to house different active centers, perfectly stabilized and accessible, in their structure, coexisting in the same solid matrix, allows the creation of multi-functional materials with high potential to carry out consecutive chemical processes, using a

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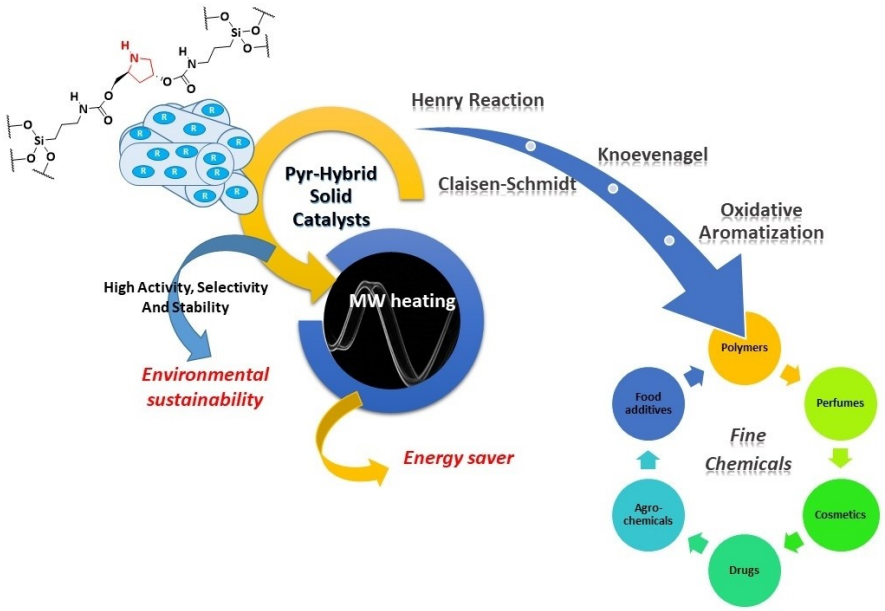
single reusable catalytic systems that act as a linear vector of combined reactive pathways.[9] Furthermore, the conjunction of alternate hydrophobic and hydrophilic sub-domains in the porous network, distributed homogeneously, facilitates the existence of high concentration gradients of substrates in active areas of the solid hybrid catalysts, favoring the performing of highly intensified chemical processes. The presence of nanospaces, in this type of organic-inorganic materials, would also facilitate a high selectivity associated with the formation of more energetically favorable intermediate species for obtaining specific products with high conversion. All this implies the performance of hybrid materials as true molecular machines acting in nanoconfined environments.[10]

Particularly relevant has been the development of new families of porous organosilicas, using suitable precursors based on bridged silsesquioxanes or disilanes, $(R'O)_3Si{-}R{-}Si(OR')_3$, which contain highly reactive terminal siloxane groups that facilitate their co-condensation and integration into the structure in which they are present. These precursors, moreover, contain organic bridge-type fragments with associated functional active centers, which are included in the walls of the porous structure.[11]

Besides the catalysts efficiency, the heating is an important parameter in the chemical conversions. In the last two decades, microwave technology was implanted for many chemical processes due to the benefits of microwave heating over conventional ovens such as higher rates of reaction, better yields and higher selectivity, high reproducibility owing to the homogeneity of microwave irradiation and finally energy saver.[2] Microwave energy provides efficient internal heat transfer by direct interaction of the electric field with all of the components of reaction system substrates, solvents and catalysts through dipolar rotation and ionic conduction. Accordingly, in this work, we describe the great catalytic activity of different hybrid materials containing pyrrolidine-type builder units in the framework with suitable catalytic properties for various base catalyzed reactions to the formation of C–C bond through Knoevenagel, Claisen-Schmidt and Henry condensations under microwave irradiation. We previously reported the preparation of hybrid materials incorporating pyrrolidine fragments in different mesoporous silica frameworks as well as their potential as enantioselective base catalysts for Michael addition.[3,4] Fluoride sol-gel route without structure-directing agents was followed to obtain non ordered mesoporous hybrid materials (N.O) and different structure-directing agents through suitable micellar processes were employed for the preparation of ordered materials (PMO-MCM-41 and PMO-SBA-15). Therefore, the benefits of microwave irradiation combined with suitable catalytic properties of pyrrolidine hybrid materials with strong base sites and high accessibility to active centers, allowed carrying out successfully base-catalyzed condensation reactions to the production of fine chemicals. Moreover, the hybrid catalyst exhibited high selectivity and good stability over different catalytic cycles contributing to environmental sustainability (Scheme 1). To evaluate the green aspects of a chemical process, some green chemistry metrics were established to quantify its efficiency or environmental performance such as atom economy, reaction mass efficiency or environmental factor (E factor). The reaction mass efficiency decreases dramatically on going downstream from bulk to fine chemicals and specialties such as pharmaceuticals because of the production involves multi-step syntheses and the use of stoichiometric reagents, excess of reactant and neutralization steps. In contrast, E factor that is the ratio of the mass of waste per mass of product increases rapidly and is in the range 5–50 for fine chemicals and 25–200 for pharmaceuticals. The use of catalytic process is a great strategy to maximize reaction mass efficiency and E factor. Therefore, we evaluated the E factor for the



Scheme 1. Pyrrolidine hybrid material as sustainable, efficient and stable base catalyst for the production of fine chemicals.

different processes studied in this work. The solvent and catalyst were not taken into account in the calculations since they can be fully reused after distillation or filtration, respectively.

Results and Discussion

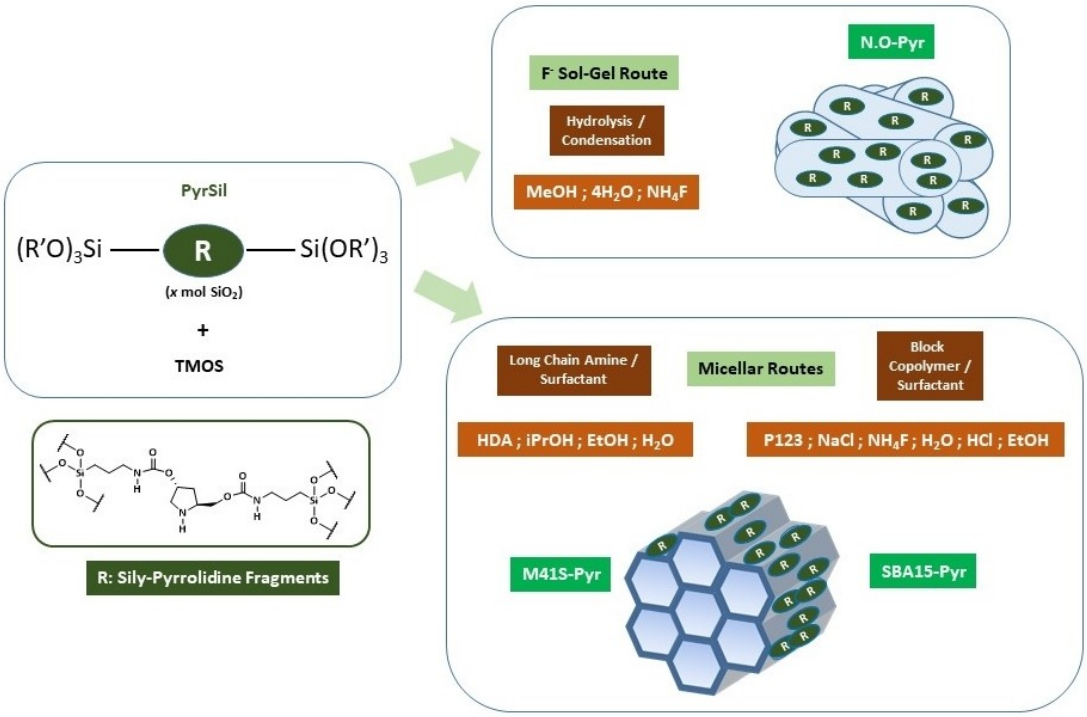
Synthesis and characterization

In this work, we report the catalytic activity of different hybrid materials containing pyrrolidine-type builder units in the framework. The pyrrolidine fragments were included in the mesoporous silica supports following different synthesis methods, being the physico-chemical properties and potential reactivity as base catalysts of the synthesized organic-inorganic materials previously characterized.[5] Non ordered mesoporous hybrid materials were obtained through fluoride sol-gel route without structure-directing agents (N.O), while the ordered materials were synthesized in the presence of different structure-directing agents through suitable micellar processes (PMO-MCM-41 and PMO-SBA-15) (Scheme 2).

Specifically, for the preparation of the hybrid materials was necessary the previous synthesis of a bis-silylated monomer used as an organosilicon precursor, which contained pyrrolidine-type fragments (PyrSil) like an organic bridge between reactive terminal siloxane groups (Scheme S1). In detail, non-ordered mesoporous hybrid materials were synthesized through a sol-gel process under soft conditions at neutral pH and at room temperature, acting the fluoride ions like a mineralizing agent and in absence of structure directing agents. These synthesis conditions favored the formation of penta-coordinated organosilicon species, which were reactive intermediates that allowed the rapid gelation of the synthesis gel. After the aging period at 36 °C, facilitating the assembly of the PyrSil monomers, the formation of non-ordered mesoporous structures (N.O), containing base pyrrolidine builder units in their framework, was achieved.

On the other hand, ordered hybrid materials with MCM-41- and SBA-15 morphologies (PMO-MCM-41 and PMO-SBA-15) were obtained by the employ of long chain neutral amine surfactants or block copolymers, respectively, through micellar processes in presence of the organosilicon bis-silylated precursor (PyrSil). In this latter case, the long-range order of the mesoporous hybrid materials decreased remarkably with the increase of the amount of pyrrolidine builder fragments incorporated in the network (from 5 mol.% to 30 mol.% of PyrSil), such as it is appreciated from X-ray diffraction patterns (Figure S1).

The micrographs obtained from transmission electronic microscopy (TEM) evidenced that the mesoporous distribution of the hybrid materials was present in the solids which were obtained with up to 5 mol.% of PyrSil in the synthesis gel, although it was observed a marked disorder and non-homogeneous distribution of internal channels. In the ordered hybrids, cavities of approximately 30–100 Å were appreciated, remembering SBA-15 or M41S topology (Figure S2). In the non-ordered mesoporous hybrid materials, an irregular morphology was detected, being present cavities of different internal diameters.



Scheme 2. Different synthesis routes for the mesoporous-hybrid materials containing pyrrolidine builder units incorporated in the framework.[12]

Chemical analysis (C, H, N, S) of the mesoporous hybrid materials showed that the organic content was higher when the amount of bis-silylated precursor (PyrSil) used in the synthesis process was more elevated (Table S1). The results confirmed that the extraction methodologies used to remove the internal surfactant molecules of hybrid materials with M41S and SBA-15 topologies were not completely effective. Overall, this drawback was more marked in the samples with lower number of pyrrolidine units inserted in the framework (5 mol.% of PyrSil), being this fact associated to the poorer order level achieved for the hybrid solids with a higher content of structural pyrrolidine moieties, which facilitated the removing of internal surfactants. In the case of non-ordered hybrid materials obtained in a fluoride medium in absence of structural directing agents, the organic content came exclusively from organosilicon precursor (PyrSil), being estimated a C/N molar ratio of 4.3 that was coincident with the theoretical value of pyrrolidine units. These results confirmed that the organic units were preserved as they were initially after their integration in the hybrid framework.

Thermogravimetric analysis (TGA) curves and their corresponding derivatives (DTA) of the hybrid mesoporous materials prepared confirmed that the thermal stability of the solids was established between 300 °C and 500 °C, considering the main weight losses (Figure S3). In detail, first weight loss was centered at 250–300 °C, corresponding to the residues of organic molecules used as structure directing agents (I), after the extraction post-synthesis processes. The second main weight loss (II), located in the temperature range of 300–500 °C, was assigned to the inserted pyrrolidine moieties included in the network from PyrSil monomer used in the synthesis. In the case of the organic-inorganic materials prepared in absence of organic templates, only one weight loss was appreciated at 300–500 °C attributed to pyrrolidine builder fragments units inserted in the framework.

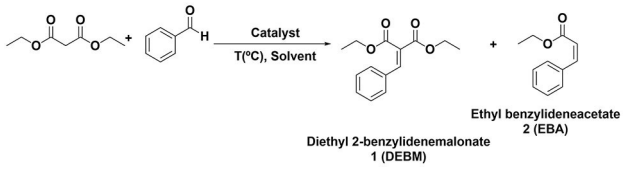
The presence and the integrity of the pyrrolidine fragments included in the framework of the porous hybrid materials was also evidenced by the NMR spectroscopic results (Figure S4). In fact, the ^{13}C NMR spectra showed the chemical shifts corresponding to all carbon atoms from the organosilicon precursor (PyrSil), being corroborated that the pyrrolidine organic units remained intact in the structure of the hybrids with the same composition as in the initial PyrSil precursor. Moreover, it was confirmed from ^{29}Si NMR spectra (Figure S5) that silyl-pyrrolidine moieties were covalently inserted into the architecture of the solids, being appreciated chemical shifts in the range between −60 and −80 ppm corresponding to T-type species of silicon atoms such as T^1 ($C–Si(OH)_2(OSi)$), T^2 ($C–Si(OH)(OSi)_2$) and T^3 ($C–Si(OSi)_3$). These spectroscopic results confirmed that the silyl-pyrrolidine groups were covalently included into the walls of the organic-inorganic materials through an effective hydrolysis and condensation process established between bis-silylated organosilicon precursors (PyrSil) and TMOS or TEOS used as purely siliceous sources. Specific surface area and free porous volume were analyzed in the hybrid materials from the nitrogen adsorption isotherms (Figure S6), being confirmed the mesoporous character of the solids. In all cases, it was detected that the accessibility of the internal porosity decreased substantially as the concentration of pyrrolidine groups present in the framework was higher, observing the collapse in the porous structure when 30 mol.% of PyrSil was used in the preparation process. Remarkably, in the case of non-ordered hybrid materials, the BET surface area achieved up to ~640 m^2/g^{-1} (Table S2). The analysis of the distribution of the BJH pore diameter allowed establishing that the hybrid materials exhibited diameters between 75–110 Å for SBA-15-type and 30–40 Å for M41S-type and non-ordered hybrid materials such as it was hoped for this class of mesoporous materials (Figure S6). The obtained results showed that the inclusion of pyrrolidine builder units in the structure of the solids markedly influenced the textural properties and porous nature of the organic-inorganic materials.

Catalytic Study

Knoevenagel condensation

Knoevenagel condensation is a specific aldol reaction between carbonyl compound and active methylene compound that produces alkenes and is a very useful tool in organic synthesis to form C–C bonds.[13,14] Knoevenagel condensation is usually catalyzed by nitrogen-based catalysts, categorized as tertiary amines, secondary amines, primary amines, and ammonium salts, and involves deprotonation of the active methylene compound to create a carbanion which, in turn, attacks the carbonyl compound. Homogeneous amines present certain toxicity and, taking into account the principles of green chemistry, there is a permanent interest in developing environmentally friendly processes using heterogeneous catalysts due to their advantageous characteristics such as activity and selectivity, robustness, easy recovery, possibility to recycle minimizing waste and its impact on the environment, opportunity to operate in flow and improvement of process costs.

Through Knoevenagel condensation, a wide brand of chemically and biologically important products were prepared such as α-cyanocinnamates, α,β-unsaturated esters, α,β-unsaturated nitriles and cinnamic acid, with great purposes such as perfumes, cosmetics, pesticides, antifungal and antibacterial products, antivirals, antioxidants, anticancer activity and cytotoxic capacity.[15–19] Furthermore, Knoevenagel reaction is a complementary tool in the characterization of base catalysts and allows the evaluation of their basic strength owing to the use of active methylene compounds with different functional groups modifying the acidity of the acidic protons. With this purpose, the basic properties of the different hybrid catalysts in the Knoevenagel condensation between benzaldehyde and diethyl malonate (DEM) was explored (Scheme 3). The presence of two ester groups induces a decrease in the acidity of the acid protons and implies that the base involved in the Knoevenagel condensation has to present a high basic strength, since in the case of diethyl malonate the acid proton pKa is close to 13. Firstly, the reaction conditions (temperature, solvent and heating mode) were optimized in the presence of the non-ordered material with a 5% of PyrSil fragments (N.O-5%). The



Scheme 3. Knoevenagel condensation between benzaldehyde and diethyl malonate.

use of green and bio solvent such as ethanol, methanol or water is environmentally friendly preferred. Regarding the high temperature process required, the volatility of the solvent and the fact that water is a product of reaction, attempts to perform the reaction in ethanol were spent but low catalytic performance was observed (Table S3, Entries 7–8). However, in the bibliography, different tools and guides have been published for green solvent selection to reduce the use of the most hazardous solvents, as well as European regulation introduced restrictions on toluene, chloroform and dichloromethane. Likewise, anisole may be considered a green solvent as reported by the GlaxoSmithKline solvent sustainability guide.[20] The best catalytic results were achieved with diethyl malonate/ benzaldehyde ratio = 0.83, 20 mol.% of catalyst, anisole as solvent and 200 °C under microwave heating (MW) that allowed greatly reducing the reaction time reaching 94% total yield within 3 h (Table S3). Thus, under the same reaction conditions, the catalytic performance of different catalysts with a 5% of the pyrrolidine moiety in the framework, PMO-MCM-41 and PMO-SBA-15 mesoporous hybrid materials, was explored (Table 1, Entries 1, 4 and 7). A clear trend was observed, as the pyrrolidine content was increased for all hybrid catalysts family, N.O, PMO-MCM-41 and PMO-SBA-15, the reaction time increased whereas lower conversions were reached for the highest concentration of pyrrolidine units (30 mol.% of Si as PyrSil) (Table 1, Entries 3, 6 and 9).

In all the cases, the main product of the reaction was the monocarboxylic ester derivative **2** (EBA). This product is usually obtained via Doebner-Knoevenagel condensation between benzaldehyde and malonic acid in the presence of piperidine.[21] When the Knoevenagel reaction was carried out in the presence of non-ordered materials (N.O) with 5 and 10 wt.% of PyrSil content, the ratio EBA (**2**)/DEBM (**1**) products was closed to 7.5 and 1.7 at complete conversion, respectively. Nevertheless, in the presence of MCM-41 type hybrid material with 5, 10 and 30 wt.% of PyrSil content, the ratio EBA (**2**)/DEBM (**1**) products was 3.8, 4.9 and 29.7 at complete conversion. For hybrid materials obtained in presence of surfactant as structure-directing agent, with topology M41S (PMO-MCM-41), the nitrogen adsorption isotherms revealed that the specific surface area and the pore volume decreased markedly when increased the amount of pyrrolidine groups inserted in the framework. Then, materials with highest content of silyl-pyrrolidine fragments exhibited lowest BET surface. Moreover, it was notable that solids obtained with 5 or 10 mol.% of PyrSil monomers exhibited similar BET area, and lower that it could be expected due to probably the incomplete removal of surfactant molecules which blocked partially the pores and accessibility to active basic centers. Nevertheless, M41S type materials with a 30 mol.% of PyrSil fragments showed BET surfaces higher than non-ordered material, attributed to the better achieved organization owing to the presence of structure directing agents. According to the nitrogen adsorption results, the catalytic data showed that decarboxylation process is controlled by diffusion constrains and the number of active sites since in the presence of mesoporous ordered materials with high inserted pyrrolidine groups the ratio EBA (**2**)/DEBM (**1**) products was 29.

These results showed that void shapes and sizes controlled the diffusion of reactants and products in addition to confining transition states and reactive intermediates. Therefore, the differences in initial reaction rates and chemoselectivity exhibited by the different basic materials reflect differences in the geometry and accessibility to the active centers. Figure 1 illustrates the trend of **1** and **2** yield versus conversion reached over different type of hybrid catalysts with different PyrSil content and the influence of accessibility to active centers and number of active sites. When diffusion limitations are met, the dicarboxylic ester **1** derivative was the main product, in contrast, when higher accessibility and optimum content in the number of basic sites exist, the main product was the monocarboxylic ester **2** derivative. Kinetic curves (Figures S7–S9, Figure 2) revealed that N.O-5% and PMO-MCM-41-5% exhibited the best catalytic performance for Knoevenagel

Table 1. DEM conversion, yield and reaction rate obtained for the Knoevenagel condensation in the presence of different types of hybrid catalysts.[a]

Entry	Catalysts	t [h]	x [%]	Yield 1 [%]	Ratio 2/1	Yield 2 [%]	r_0 [mol/L*h]	TOF [h^{-1}]
1	N.O-5%	3	94	11	7.5	83	0.3	12.7
2	N.O-10%	3.5	95	35	1.7	60	0.1	9.2
3	N.O-30%	4	21	0	–	21	–	0
4	PMO-MCM41-5%	3.5	100	21	3.8	79	0.2	12.8
5	PMO-MCM41-10%	3.5	95	16	4.9	79	0.5	11.9
6	PMO-MCM41-30%	5	93	3	29.7	89	0.2	3.1
7	PMO-SBA15-5%	4	100	12	7.3	88	0.2	8.3
8	PMO-SBA15-10%	4	100	19	4.3	81	0.1	5.3
9	PMO-SBA15-30%	7	92	3	29.7	89	–	2.2

[a] Reaction conditions: DEM (0.1 mmol), benzaldehyde (0.12 mmol), 20 mol% catalyst, anisole (1 ml), 200 °C, microwave irradiation (MW). r_0 = initial rate. TOF calculated at 0.083 h.

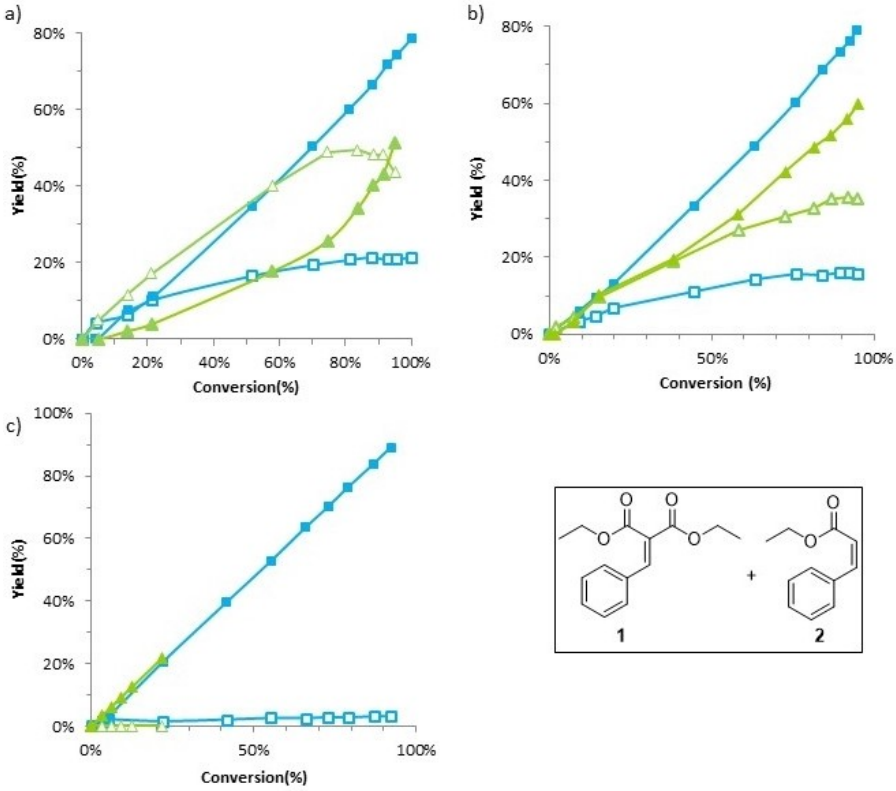


Figure 1. DEM conversion was plotted versus **1** and **2** yield when the Knoevenagel condensation was performed in the presence of the different hybrid materials. Reaction conditions: DEM (0.1 mmol, 16.02 mg), benzaldehyde (0.12 mmol, 12.73 mg), 20 mol% of catalyst, anisole, 200 °C under MW, a) PMO-MCM-41-5%, □ **1**, ■ **2**; N.O-5%, △ **1**, ▲ **2**, b) PMO-MCM-41-10%, □ **1**, ■ **2**; N.O-10%, △ **1**, ▲ **2**, c) PMO-MCM-41-30%, □ **1**, ■ **2**; N.O-30%, △ **1**, ▲ **2**.

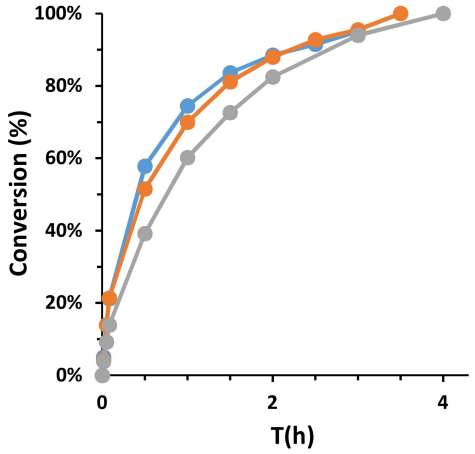


Figure 2. DEM conversion was plotted versus 2 and yield when the Knoevenagel condensation was performed in the presence of the different hybrid materials. Reaction conditions: DEM (0.1 mmol, 16.02 mg), benzaldehyde (0.12 mmol, 12.73 mg), 20 mol% of catalyst, anisole, 200 °C under MW, ● PMO-MCM-41-5%, ● N.O-5%, ● PMO-SBA-15-5%.

reaction with good 83% and 79% **2** yield, and 0.3 mol L^{-1} h^{-1} and 0.2 mol L^{-1} h^{-1} initial rate, respectively. Besides very similar results were achieved for both materials, from synthetic strategy standpoints and costs, N.O-5% was determined as the more suitable catalyst since it can be synthesized easily without structure directing agents avoiding washing and extraction process, exhibiting higher accessibility at lowest pyrrolidine inserted moieties (Table S2). Finally, the stability and recyclability of the N.O-5% was examined. The results showed that the mesoporous hybrid catalyst could be reused for four consecutive cycles without observing activity loss (Figure 3) and preserving the initial structure of the catalyst (Table S4). A leaching test confirmed the stability of included PyrSil fragments in the silicon framework since diethyl malonate conversion remained constant after hot filtration (Figure S10). To evaluate the sustainability of the Knoevenagel reaction herein set up, E factor was determined and close to 0.66 corresponding to reaction mass efficiency up to 54.6%.

To explore the scope of N.O-5% hybrid catalyst to promote Knoevenagel reaction and prepare different functionalized intermediates, the reaction between ethyl cyanoacetate and DEM with aliphatic aldehydes was investigated. The main issue is the self-condensation of aliphatic aldehydes having α-hydrogen with the consequent decrease of process efficiency. Therefore, various aldehydes were selected with or without α-hydrogen and the reaction performed in the presence of N.O-5% hybrid catalyst, under microwave irradiation (Schemes 4 and 5). The results summarized in the Tables 2 and 3 illustrate the great potential of N.O-5% hybrid material to catalyze Knoevenagel condensation with high product yield and selectivity. In the case of heptanal, self-condensation was

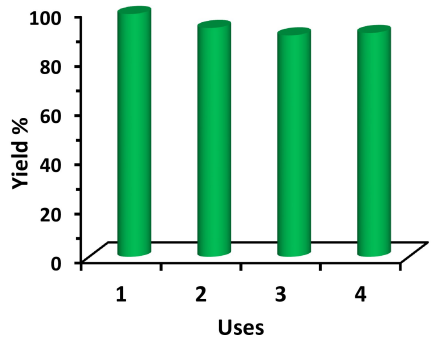
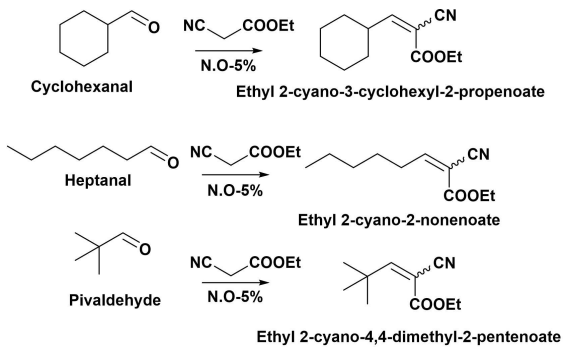
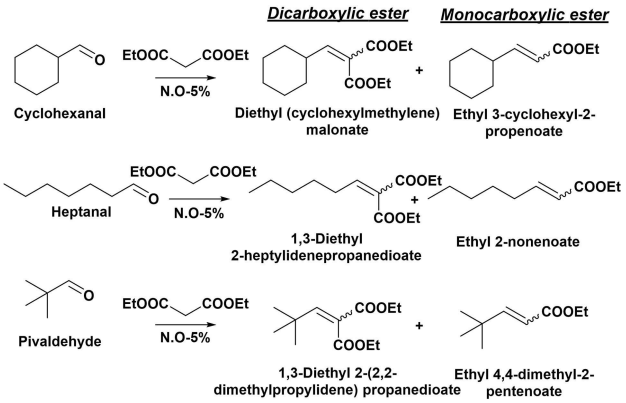


Figure 3. Reuses of the hybrid catalyst N.O-5% for the reaction between diethyl malonate and benzaldehyde in anisole at 200 °C under MW.



Scheme 4. Examples of Knoevenagel condensation between aliphatic aldehydes and ethyl cyanoacetate.



Scheme 5. Examples of Knoevenagel condensation between aliphatic aldehydes and DEM.

observed, thermodynamically favored under reaction conditions.

The high catalytic performance exhibited by N.O-5% to carry out the Knoevenagel condensation between diethyl malonate and benzaldehyde demonstrated the high basic strength of the pyrrolidine fragment included in the hybrid material and good stability observed for recycling study. These results evidence the suitable catalytic properties of the N.O-5% hybrid material with strong base active sites to perform base-catalyzed reactions and especially, the formation of carbon-carbon bonds which is crucial to produce valuable α,β-unsaturated compounds and which requires strong base catalysts. Therefore, to continue other reactions of C–C bond formation are explored.

Table 2. Ethyl cyanoacetate conversion and adduct yield obtained for the Knoevenagel condensation in the presence of N.O-5% hybrid catalyst.[a]

Entry	t [h]	Aldehyde	x [%]	Yield [%]	
				Z	E
1	5	Cyclohexanal	97.4	3.8	93.6
2	5	Heptanal	97	0.6	96.4
3	5	Pivaldehyde	85	85	–

[a] Reaction conditions: Ethyl cyanoacetate (0.1 mmol), aldehyde (0.12 mmol), 20 mol.% N.O-5%, anisole (1 mL), 120 °C under microwave irradiation.

Table 3. DEM conversion, adduct yield obtained for the Knoevenagel condensation in the presence of N.O-5% hybrid catalyst.[a]

Entry	t [h]	Aldehyde	x [%]	Yield [%]		
				Dicarboxylic ester		Monocarboxylic ester
				Z	E	E
1	8	Cyclohexanal	99.4	27.7	34.1	37.6
2	5	Heptanal	93.8	14.5	69.3	10
3	8	Pivaldehyde	92.2	18.6	48.5	25

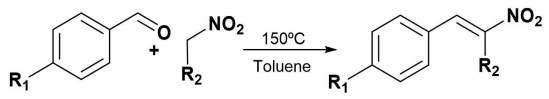
[a] Reaction conditions: DEM (0.1 mmol), aldehyde (0.12 mmol), 20 mol% N.O-5%, anisole (1 mL), 200 °C under microwave irradiation.

Nitroalkenes synthesis

Taking into account the high basic strength of pyrrolidine based hybrid materials exhibited for Knoevenagel condensation, the catalytic ability of N.O-5% catalyst was explored to carry out another C–C coupling to obtain nitroaldol compounds that is nearly analogous to the aldol reaction. The Henry reaction involves the deprotonation of the nitroalkane on the α-carbon position usually catalyzed by soluble bases such as alkali metal hydroxides, carbonates, alkoxides, alkaline earth metal hydroxide, and organic bases such as primary, secondary and tertiary amines.[22] The Henry reaction is a widely used synthetic tool in organic chemistry to produce nitroaldol intermediates of great synthetic value as primary precursors for subsequent reactions (oxidation/reduction, dehydration and condensation), while the nitro groups also give rise to a multitude of functionalities leading to products and intermediates with wide application in commodities, pharmaceuticals, agrochemicals and perfumes. Given the high catalytic activity demonstrated by the N.O-5% hybrid material for Knoevenagel condensation, it could be expected that this material would have suitable catalytic properties for the Henry reaction. Accordingly, a study of optimization of reaction conditions was performed and allowed preparing β-nitro-styrene with 100% yield, with

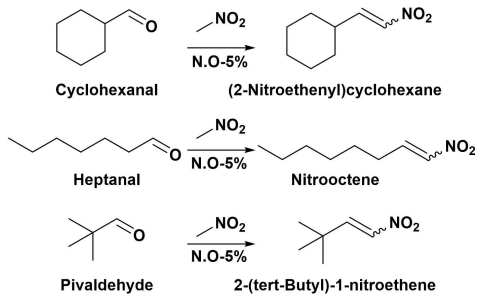
20 mol.% of N.O-5%, in toluene, at 150 °C (Table S5). Therefore, the scope of suitable catalytic properties of the hybrid material was evaluated with different benzaldehyde derivatives containing different functional groups in the para position of the aromatic ring. The influence of electron donating groups through mesomeric (-OMe) and inductive effects (-Me), and electron withdrawing groups through mesomeric (-NO_2) and inductive effects (-Br) was explored. All reactions were carried out within short reaction times (3–9 h) and >99% nitroalkene selectivity. Usually, resonance effect is stronger that inductive effect, except for the case of halogen as it could be observed in the present study. In the presence of OMe group, exhibiting electron-releasing effect inducing deactivation of carbonyl group, 86% nitroalkene yield was achieved in longer reaction time 9 h (Table 4, Entry 4). While when Me group was present, with donating inductive effect inducing deactivation of carbonyl group, 88% nitroalkene yield after 9 h longer reaction time (Table 4, Entry 2). When carbonyl reactant with substituted electron withdrawing groups in aromatic ring such as NO_2, an activation effect of carbonyl group should be observed. Nevertheless, high 88% yield after longer reaction (9 h) was reached, being this result attributed to diffusion limitation (Table 4, Entry 5). Finally, when Br with powerful withdrawing inductive effect was present, 97% yield after 4 h was reached (Table 4, Entry 3). Additionally, the Henry reaction was also successfully performed between nitroethane and benzaldehyde, reaching 90% trans-β-Methyl-β-nitrostyrene yield after 4 h of reaction with >99% selectivity (Table 4, Entry 6). It can be concluded that the N.O-5% catalyst exhibited high catalytic performance to carry out the Henry reaction with high yields and >99% trans adduct selectivity. The sustainability of this reaction process was evaluated and reaction mass efficiency was up to 43% for the nitroalkenes production corresponding to E factor close to 1.35 mainly attributed to the excess of nitro compound used. To show the scope of N.O-5% hybrid material as catalyst to promote Henry reaction, experiments involving nitromethane and aliphatic aldehydes were investigated (Scheme 6). As above-mentioned, the main issue is the self-condensation of aliphatic aldehydes having α-hydrogen with the consequent decrease of process selectivity. The results summarized in the Table 5 illustrate the great potential of N.O-5% hybrid material to catalyze Henry reaction with high product yield and selectivity. The worst yield and selectivity were reached when heptanal was used because of the thermodynamically favored self-condensation up to 27%.

Table 4. Scope of the Henry reaction in the presence of N.O-5% catalyst.[a]



Entry	R_1	R_2	t [h]	Yield [%]
1	H	H	3	100
2	Me	H	6	88
3	Br	H	4	97
4	OMe	H	9	86
5	NO_2	H	9	88
6	H	CH_3	4	90

[a] Reaction conditions: derivative of benzaldehyde (0.1 mmol), derivative of nitromethane (0.4 mmol), 20 mol.% N.O-5% and 1 mL of toluene at 150 °C.



Scheme 6. Examples of Henry reaction between aliphatic aldehydes and nitromethane.

Claisen-Schmidt condensation

Taking into account the suitable catalytic features of PyrSil-hybrid materials for the aldol-type condensation, the Claisen-Schmidt condensation was explored to the production of substrates with a wide range of application in the pharmaceutical industry such as chalcones that exhibit interesting biological activities[23] such as antimalarial,[24] anti-inflammatory,[25] cytotoxic,[26,27] anticancer.[28,29] Chalcones contain a three carbon α, β-unsaturated carbonyl system and are obtained from the condensation of aromatic aldehyde with acetophenones in the presence of a catalyst, leading to a variety of chemicals such as pyrazoline, isoxazole and heterocyclic compounds. Chalcones are usually synthesized through Claisen-Schmidt condensation in the presence of base catalysts such as barium hydroxides,[30] hydrotalcites[31] and natural phosphates[32] or using Lewis acids such as $RuCl_3$[33] and $TiCl_4$. The Claisen-Schmidt reaction is a specific aldol condensation between an aldehyde or ketone having an α-hydrogen with an aromatic carbonyl compound lacking an α-hydrogen catalyzed by base involving the deprotonation of the aldehyde or ketone derivative on the α-carbon position.[34]

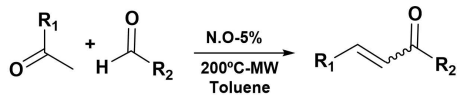
Therefore, the catalytic properties of N.O-5% were examined for the synthesis of chalcone **3** via Claisen-Schmidt reaction between acetophenone and benzaldehyde under

Table 5. Aldehyde conversion and adduct yield obtained for the Henry reaction in the presence of N.O-5% hybrid catalyst.[a]

Entry	t [h]	Aldehyde	x [%]	Yield [%]	
				Z	E
1	1	Cyclohexanal	99.7	33.6	63.1
2	1	Heptanal	98.7	35	36.4
3	1	Pivaldehyde	86.2	4.4	81.8

[a] Reaction conditions: aldehyde (0.1 mmol), nitromethane (0.4 mmol), 20 mol% N.O-5%, toluene (1 ml), 150 °C, microwave irradiation.

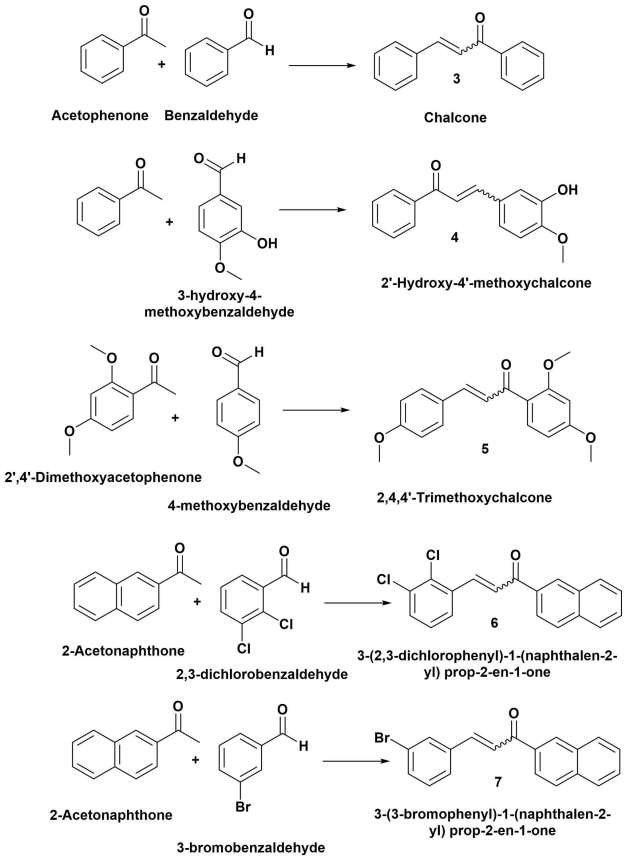
Table 6. Synthesis of chalcones with biological activities in the presence of N.O-5% hybrid material as catalyst, with 99% selectivity.[a]



Entry	R_1	R_2	Chalcone	T [°C]	t [h]	Yield [%]
1	Phenyl	Ph	3	200(MW)	5	95
2	Phenyl	3-OH-4-MeO-phenyl	4	200(MW)	12	36
3	Phenyl	3-OH-4-MeO-phenyl	4	150	45	91
4	4-MeO-phenyl	3,4-di-MeO-phenyl	5	200(MW)	10	89
5	Naphthalene	2,3-di-Cl-phenyl	6	200(MW)	8	93
6	Naphthalene	3-Br-phenyl	7	200(MW)	8	89

[a] Reaction conditions: Ketone (0.1 mmol, 12.02 mg), non-condensable aldehyde (0.23 mmol, 24.41 mg), 20 mol.% N.O-5% and 0.4 mL of toluene, 200 °C under MW heating.

different reaction conditions of temperature and solvent (Table S6). With 20 mol.% of catalyst (N.O-5%), toluene as solvent at 200 °C and MW irradiation, excellent 95% of acetophenone conversion and 99% selectivity to chalcone **3** were reached within 5 h. A recycling study revealed the catalytic stability over three uses, with a slight decrease of chalcone **3** yield from 95 to 90% (Figure S11). Using the same reaction conditions, the synthesis of different substituted chalcones of interest due to their biological properties were prepared with high ketone derivative conversion and 99% chalcone selectivity (Table 6, Scheme 7). The results showed that when the benzaldehyde derivative with electron donating substituents like hydroxy- and methoxy- groups (Table 6, Entries 2–4), the reaction time increased due to the presence of an electronically enriched aromatic ring together with steric effect. In contrast, when the Claisen-Schmidt condensation was performed between non-condensable aldehyde with substituted electron withdrawing groups in the aromatic ring and a hindered ketone (acetonaphthone), maximum conversion was achieved at shorter reaction time than reaction involving ketones with electron donor groups. Therefore, 93% and 89% conversions were reached after 8 h of reaction time (Table 6, Entries 5 and 6). These results showed the suitable catalytic properties and stability of N.O-5% hybrid catalyst to carry out the synthesis of chalcones derivatives under moderate reaction conditions within few hours. The sustainability of the Claisen-Schmidt condensation was evaluated and reaction mass efficiency was up to 53% corresponding to E factor close to 0.84 for the chalcones production.

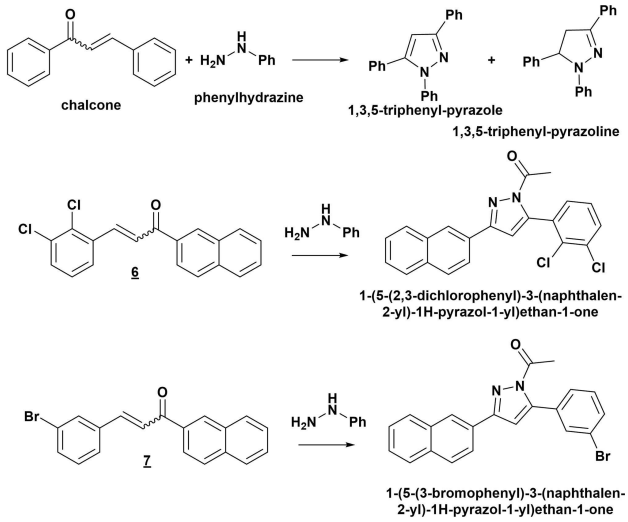


Scheme 7. Synthesis of chalcones with biological and pharmaceutical properties.

1,3,5-trisubstituted pyrazole and pyrazoline synthesis

Chalcones, besides being the central core for a wide range of biological compounds, give rise to a new family of compounds by reacting with hydrazine derivatives incorporating pyrazoline and/or pyrazole moieties leading to compounds with new biological activities and promising pharmacological, agrochemical, and analytical applications (Scheme 8).[35–37] The condensation between chalcone derivative and substituted hydrazine usually produced tri-substituted pyrazoline, further converted into pyrazole through oxidative aromatization in the presence of oxidizing agents such as zirconium nitrate,[38] activated carbon,[39] Pd/C,[40] HIO_3 and I_2O_5.[41]

Therefore, the catalytic performance of N.O-5% hybrid catalyst to carry out the reaction between chalcones and hydrazines derivatives was explored. Moreover, a study of optimization of reaction conditions to maximize pyrazoles yield was performed. Accordingly, the catalytic behavior of N.O-5% hybrid catalyst was evaluated controlling the nature of reaction atmosphere (air, inert atmosphere (N_2) and oxidant atmosphere



Scheme 8. Synthesis of 1,3,5-pyrazoles with biological and pharmaceutical properties.

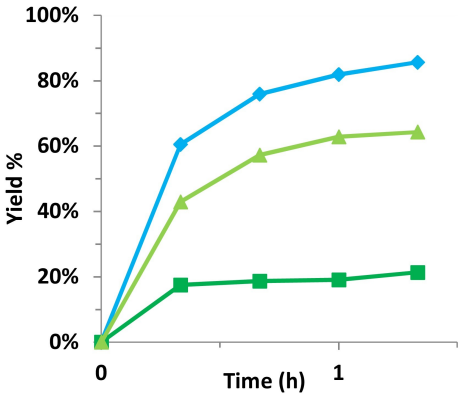


Figure 5. Chalcone conversion (♦), 1,3,5-triphenyl-pyrazoline (▲) and 1,3,5-triphenyl-pyrazole (■) yield were plotted versus time, when the reaction was performed under nitrogen atmosphere. Reaction conditions: (E)-Chalcone (0.1 mmol), phenylhydrazine (1.23 mmol), 20 mol.% N.O-5% and 1 mL of solvent, 180 °C (MW).

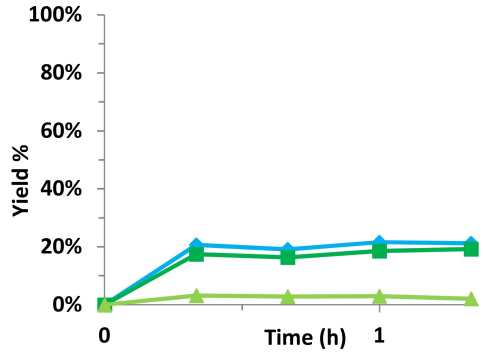


Figure 4. Chalcone conversion (♦), 1,3,5-triphenyl-pyrazoline (▲) and 1,3,5-triphenyl-pyrazole (■) yield were plotted versus time, when the reaction was performed under air atmosphere. Reaction conditions: (E)-Chalcone (0.1 mmol), phenylhydrazine (1.23 mmol), 20 mol.% N.O-5% and 1 mL of solvent, 180 °C (MW).

(O_2)). The results showed that under air atmosphere low yield to triphenyl pyrazole and pyrazoline were reached (Figure 4), while under inert atmosphere, very good 87–95% yield of 1,3,5-triphenyl-pyrazole and pyrazoline mixtures were obtained (Figure 5; Table 7, Entries 1, 3, 6–11). Moreover, when oxygen atmosphere was applied, maximum selectivity up to 95% towards 1,3,5-triphenyl-pyrazole was reached (Table 7, Entries 2, 4 and 12). Therefore, taking advantage of benefits of non-oxidant and oxidant atmosphere, under which a maximum yield to 1,3,5-triphenyl- pyrazoline and pyrazole were achieved, respectively, an experiment was then set up under nitrogen for the first hour and under oxygen for the following 2.5 h. Thus, maximum 97% chalcone conversion, 88% and 9%, 1,3,5-triphenyl- pyrazole and pyrazoline yield were reached, respectively (Figure 6; Table 7, Entry 14). These results revealed the suitable catalytic properties of N.O-5% hybrid catalyst to the

Table 7. Catalytic results for the synthesis of 1,3,5-phenyl pyrazole and pyrazoline in the presence of N.O-5% hybrid catalyst.[a]

Entry	Solvent	T [°C]	Atm	t [h]	Conversion [%]	Pyrazole [%]	Pyrazoline [%]
1	Anisole	150	N_2	40	88	43	45
2	Anisole	150	O_2	40	74	66	8
3	Toluene	150	N_2	15	87	27	61
4	Toluene	150	O_2	25	76	67	9
5	Toluene	150	N_2/O_2	20	95	90	5
6	Toluene	180[b]	N_2	1.1	93	34	59
7	Anisole	180[b]	N_2	2	92	43	49
8	iPrOH	180[b]	N_2	1.5	86	21	65
9	ACN	200[b]	N_2	1.25	62	26	36
10	Anisole	200[b]	N_2	1.5	92	45	47
11	Toluene	200[b]	N_2	1	95	47	48
12	Toluene	200[b]	O_2	3	62	59	3
13	Anisole	200[b]	O_2	3	21	19	2
14	Toluene	200[b]	N_2/O_2	2.5	97	88	9
15	Anisole	200[b]	N_2/O_2	4	90	74	16
16[c]	Toluene	200[b]	N_2/O_2	4	89	74	15

[a] Reaction conditions: (E)-Chalcone (0.1 mmol), phenylhydrazine (1.23 mmol), 20 mol% N.O-5% and 1 mL of solvent. [b] Microwave heating. [c] Tandem reaction: Acetophenone (0.1 mmol), benzaldehyde (0.23 mmol), 20 mol.% N.O-5%, 0.4 mL toluene at 200 °C (MW), followed by phenylhydrazine (1.23 mmol) and 0.6 mL of toluene at 200 °C (MW), combining atmospheres (N_2/O_2).

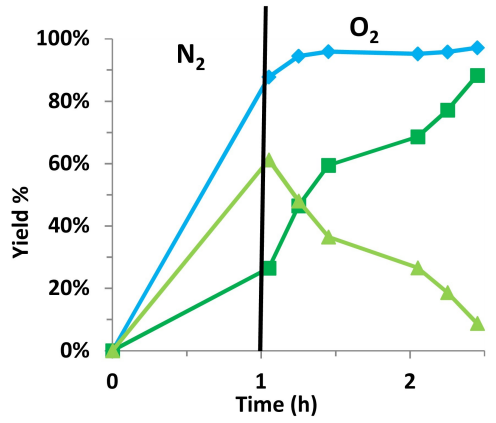


Figure 6. Chalcone conversion (♦), 1,3,5-triphenyl-pyrazoline (▲) and 1,3,5-triphenyl-pyrazole (■) yield were plotted versus time, when the reaction was performed, consecutively, under nitrogen and oxygen atmosphere. Reaction conditions: (E)-Chalcone (0.1 mmol), phenylhydrazine (1.23 mmol), 20 mol.% N.O-5% and 1 mL of solvent, 180 °C (MW).

preparation of pyrazole through oxidative aromatization free metal process.

Finally, an attempt of three steps, one-pot, consecutive reaction of Claisen-Schmidt condensation, chalcone and phenylhydrazine condensation and cyclisation followed by oxidative aromatization to the preparation of tri-phenyl pirazoline and pyrazole was successfully accomplished. After 5 h of reaction time, in toluene, 200 °C (MW) and complete conversion of acetophenone, the corresponding amount of phenylhydrazine was added to the reaction medium, to finally reach of 89% chalcone conversion, 74% of 1,3,5-triphenyl pyrazole and 15% of pyrazoline yields, after first 3 h under nitrogen atmosphere followed by 1 h under oxygen atmosphere (Table 7, Entry 16). The sustainability of the condensation-cyclisation of chalcone and hydrazine followed by oxidative aromatization to produce mainly pyrazole and pyrazoline was evaluated, and reaction mass efficiency was up to 19% corresponding to E factor close to 5.2 because of the high excess of hydrazine derivatives used. For the multistep one pot process, the reaction mass efficiency was close to 15.6% corresponding to E factor around 5.4. The decrease in the efficiency of the process was attributed to the high excess of hydrazine derivative required.

Conclusion

The study of Knoevenagel reaction allowed evaluating the high strength of base active sites owing to the incorporation of pyrrolidine fragments in different mesoporous hybrid materials, obtained through micellar and fluoride sol-gel routes in absence of structural directing agents. N.O-5% hybrid catalyst exhibited the best catalytic properties, considering catalytic performance and synthetic strategy standpoints and costs. In addition, the base properties of the hybrid catalyst allowed to obtain six different nitroalkenes with $>99\%$ selectivity towards the trans-product. The hybrid catalyst exhibited very high catalytic properties and stability to synthesize valuable α, β-unsaturated compounds with large broad of applications such as different types of chalcones with high synthetic value, α, β-unsaturated esters and nitroalkenes. Furthermore, the synthesis of 1,3,5-trisubtitued pyrazoles and pyrazolines derivatives could be prepared with high yield and maximum selectivity, through 3-consecutive steps-one pot process, by combining an inert and oxidizing atmosphere. The catalyst was able to carry out a Claisen Schmidt, hydrazine addition-intramolecular cyclization and oxidative aromatization tandem reaction to obtain 1,3,5-trisubstituted pyrazole. The ability to carry out different base-catalyzed reactions combined to their ability to perform enantioselective reactions already reported, showed the high activity, selectivity, robustness and versatility of the synthesized mesoporous hybrid catalyst in different fields of chemistry.

Experimental Section

Characterization techniques

All reagents were purchased from commercial suppliers and used without further purification. CHN content was determined with a Carlo Erba 1106 elemental analyzer. Thermogravimetric and differential thermal analysis (TGA-DTA) were performed in an air stream with a Mettler Toledo TGA/SDTA 851E analyzer. Nitrogen adsorption isotherms were obtained at 77 K with a Micromeritics ASAP 2010 volumetric adsorption apparatus. Before the analysis, the solids were outgassed for 12 hours at 80 °C. The BET specific surface area was determined from the nitrogen adsorption data using the relative pressure range from 0.04 to 0.2. The total pore volume was evaluated from the amount of N_2 adsorbed at relative pressures around 0.99. External surface area and micropore volume were determined from *t*-plot method in the t range 3.5–5. The pore diameter and the pore size distribution were obtained using the Barret-Joyner-Halenda (BJH) methodology using adsorption branches of the isotherms. Solid state MAS-NMR spectra were obtained at room temperature under magic angle spinning (MAS) in a Brucker AV-400 spectrometer. Organic solutions were concentrated at reduced pressure using Büchi rotary evaporator.

Synthesis of hybrid mesoporous materials

Bis-silylated precursor PyrSil

The organosilane precursor, (3R,5S)-5-(8,8-diethoxy-3-oxo-2,9-dioxa-4-aza-8-silaundecyl)pyrrolidin-3-yl(3-(triethoxysilyl)propyl)carbamate (PyrSil) was synthesized from (2S,4R)-4-hydroxypyrrolidine-2-carboxilate hydrochloride in multistep reactions according to a reported procedure (see Scheme 1).[42] This precursor was used to synthesize mesoporous non-ordered (NOH-Pyr) and ordered (M41S-Pyr and SBA15-Pyr) hybrid materials.

Preparation of PMO-MCM-41 hybrid materials

Mesoporous PMO-MCM-41 hybrid materials were synthesized by co-condensation of bis-silylated precursor PyrSyl and TMOS with hexadecylamine as templating agent together with iPrOH, EtOH and water.[43] On the one hand, solution 1 was composed by TMOS and PyrSil compound solved with iPrOH and EtOH, being stirred at room temperature until homogeneity. On the other hand, solution 2 was composed by hexadecylamine solved with water at 40 °C for

3 h. Then, solution 1 was added to the solution 2 under vigorous stirring, being maintained during 24 h. The resultant mixture was aged at room temperature for 24 h. The molar ratio achieved in the synthesis gel was 1 [(1-x)TMOS + xPyrSil] SiO_2: 0.25 hexadecylamine: 2.05 iPrOH: 6.85 EtOH: 66.85 H_2O (x% SiO_2 mol respect to SiO_2 total mol). The formed gel was aged for 24 h at room temperature, filtrated and dried overnight at 60 °C. A fine white powder was obtained. The extraction of the surfactant from the as-synthesized solids was achieved with ethanol through four ultrasound cycles with subsequent filtration, employing 10 min for each cycle. A fine white powder was finally obtained.

Preparation of PMO-SBA-15 hybrid materials

Mesoporous PMO-SBA-15 hybrid materials were synthesized by co-condensation of chiral bis-silylated PyrSil and TMOS together with block copolymer P123 as templating agent.[44] P123, NaCl, and NH_4F solution (0,25 M) were mixed with HCl solution (0,1 M) and water to generate a homogeneous solution that was stirred at 40 °C for 3 h. Then, a mixture of TMOS, PyrSil bis-silylated precursor and ethanol was added to the solution under vigorous stirring. The resultant mixture was further stirred at 40 °C during 24 h and then aged at 80 °C for 24 h. The molar ratio achieved in the synthesis gel was 1 [(1-x)TMOS + xPyrSyl] SiO_2:0.017 P123:3.42 NaCl:0.0075 NH_4F:166 H_2O:0.03 HCl:8.7 EtOH (x% SiO_2 mol respect to SiO_2 total mol). As-synthesized materials were extracted with ethanol under refluxing conditions for 24 h to remove the structure directing agents. After filtration, resultant solids were dried at 100 °C overnight.

Preparation of mesoporous N.O hybrid materials

Non-ordered hybrid mesoporous organic-inorganic materials, N.O, were prepared from an initial mixture of tetramethoxysilane (TMOS) as silica precursor and the suitable amount of bis-silylated precursor PyrSil ($(R'O)_3Si$-R-$Si(OR')_3$), as bridged disilane, in methanol.[45] After dissolution of precursors, a water solution of NH_4F was incorporated dropwise to the solution containing organosilicon alkoxide compound under vigorous stirring. The reaction mixture presented the next molar composition: 1[(1-x)TMOS + xPyrSyl]: 4 MeOH: 4 H_2O: 0.00313 NH_4F (x% SiO_2 mol respect to SiO_2 total mol) where the Si/NH_4F and TMOS/disilane ratios were 479 and 4, respectively. Hydrolysis and condensation of the silicon species were performed under vigorous and continuous stirring in a glass beaker at room temperature. Agitation was maintained until gelation. The gel was aged for 24 h at 36 °C and, finally, dried at 150 °C for another 24 h. The obtained fine brown powder was profusely washed with ethanol and water in successive steps to remove the siloxane molecules which were not incorporated in the solids. Finally, solids were dried at 60 °C overnight.

General information about catalytic processes

The reaction products were identified by GC and GC-MS (Shimadzu, GCMS QP2010 Ultra), and liquid NMR. The ^1H and ^{13}C NMR spectra were recorded on a Bruker 300 spectrometer and the chemical shifts were given in ppm relative to the residual proton solvent signals. The data for the ^1H NMR spectra were given as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet, dd = double doublet, dddd = double doublet doublet), coupling constant and integration. All the reactions were carried out under an inert atmosphere of N_2 unless otherwise indicated, as well as all the solvents used were anhydrous, by using the MBraun 800 solvent purification system (SPS). For the reactions carried out carried out by microwave, the Biotage Initiator + microwave oven was used.

Catalytic tests

The calculation of conversion, yield and selectivity were performed from GC analysis (GC-2010-Ultra, Shimadzu, equipped with an FID and HP-5 column (0.25 mm × 0.25 μm × 30 m)) using dodecane as standard.

Knoevenagel condensation. General procedure

The reaction was carried out in sealed conical type 5 mL microwave vials with the presence of magnetic stirrers in the Biotage Initiator + microwave. Diethyl malonate (0.1 mmol) was added to the reaction vial, with benzaldehyde (0.12 mmol) and 20 mol.% of hybrid catalyst containing pyrrolidine units in its structure, in 1 mL of anisole at 200 °C under microwave heating. The products obtained were isolated by means of silica plates with an eluting phase (20:1) of hexane: ethyl acetate. The resulting products were analyzed by GC, GCMS and NMR.

Diethyl benzylidenemalonate: ^1H NMR (300 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.50–7.43 (m, 2H), 7.44–7.36 (m, 3H), 4.33 (dq, J = 8.7, 7.2 Hz, 4H), 1.32 (dt, J = 14.4, 7.2 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.44, 163.75, 141.63, 132.93, 130.50, 129.43(x2), 128.77(x2), 126.38, 61.62(x2), 14.13, 13.87.

Ethyl cinnamate: ^1H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, J = 15.9 Hz, 1H), 7.51–7.45 (m, 2H), 7.37–7.30 (m, 3H), 6.46–6.38 (d, J = 15.9 Hz, 1H), 4.24 (q, J = 7.2 Hz, 2H), 1.31 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.79, 144.47, 134.46, 128.83 (x2), 128.01(x2), 118.29, 60.36, 14.29.

Claisen-Schmidt reaction. General procedure

The reaction was carried out in sealed conical type 5 mL microwave vials with the presence of magnetic stirrers in the Biotage Initiator + microwave. The production of chalcones was carried out by mixing an aromatic ketone (acetophenone derivatives) (0.1 mmol) and a non-condensable aldehyde (benzaldehyde derivatives) (0.23 mmol) with 20 mol.% of N.O-5% as catalyst in 0.4 mL of toluene, at 200 °C under microwave. The chalcones were identified by GC and GC-MS (Shimadzu, GCMS QP2010 Ultra).

Synthesis of 1,3,5-triphenylpyrazole. General procedure

The reaction was carried out in sealed conical type 5 mL microwave vials with the presence of magnetic stirrers in the Biotage Initiator + microwave. In the reaction vial (*E*)-chalcone (0.1 mmol) was added together with the phenylhydrazine (1.23 mmol) with 20 mol.% of N.O-5% as catalyst and 1 mL of toluene in an inert atmosphere of N_2 during 2 h at 200 °C under microwave irradiation. The reaction was followed by GC and at 90% conversions the atmosphere was changed from inert gas (N_2) to oxidant (O_2, 1 atm) and prolonged 1 h, at 200 °C (MW). The catalyst was filtered off and the mixture was treated with a $NaHCO_3$ solution (saturated) and the compound extracted with ethyl acetate (three times). The organic phase was dried with anhydrous $MgSO_4$ and, subsequently, concentrated on a rotary evaporator and purified by a column of silica chromatography with an eluent phase (30: 1) (hexane: AcOEt), to obtain the 1,3,5-triphenylpyrazole, as a white solid.

^1H NMR (300 MHz, $CDCl_3$) δ 7.85 (m, 2H), 7.41–7.14 (m, 13H), 6.75 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.99, 144.41, 140.19,133.09, 130.63, 128.91(x2), 128.77(x2), 128.65(x2), 128.49(x2), 128.30(x2), 127.99, 127.42, 125.83(x2), 125.32(x2), 105.22.

Henry reaction. General procedure

The reaction was carried out in sealed 3 mL vials with the presence of magnetic stirrers on heating plates. Benzaldehyde derivatives (0.1 mmol) and nitromethane (0.4 mmol) in 20 mol.% of N.O-5% were added to the reaction vial as catalyst at 150 °C and toluene as solvent. The reaction was monitored by GC and the products isolated by means of silica plates with an eluting phase (4:1) (hexane:AcOEt).

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Conflict of Interest

The authors declare no conflict of interest.

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[1] C. Sanchez, B. Julián, P. Belleville, M. Popall, *J. Mater. Chem.* **2005**, *15* (35–36), 3559–3592.
[2] B. Martins Estevão, I. Miletto, L. Marchese, E. Gianotti, *Phys. Chem. Chem. Phys.* **2016**, *18* (13), 9042–9052.
[3] U. Díaz, D. Brunel, A. Corma, *Chem. Soc. Rev.* **2013**, *42* (9), 4083–4097.
[4] M. Soldatov, Y. Wang, H. Liu, *Chem. Asian J.* **2021**, *16* (14), 1901–1905.
[5] M. Soldatov, H. Liu, *Prog. Polym. Sci.* **2021**, *119*, 101419.
[6] M. O'Keeffe, O. M. Yaghi, *Chem. Rev.* **2012**, *112* (2), 675–702.
[7] P. G. Parejo, A. Alvarez-Herrero, M. Zayat, D. Levy, *J. Mater. Sci.* **2015**, *50* (20), 6677–6687.
[8] W. Bing, M. Wei, *J. Solid State Chem.* **2019**, *269*, 184–194.
[9] A. Gaona, J. M. Moreno, A. Velty, U. Díaz, A. Corma, *J. Mater. Chem. A* **2014**, *2* (45).
[10] D. J. Tranchemontagne, J. L. Mendoza-Cortés, M. O'Keeffe, O. M. Yaghi, *Chem. Soc. Rev.* **2009**, *38* (5), 1257–1283.
[11] T. Asefa, M. J. MacLachlan, N. Coombs, G. A. Ozin, *Nature* **1999**, *402* (6764), 867–871.
[12] S. Llopis, A. Velty, U. Díaz, *Catalysts* **2019**, *9* (8), 654.
[13] K. Ebitani, 2.14 *Comprehensive Organic Synthesis II*; Knochel, P. B. T.-C. O. S. I. I. (Second E., Ed.; Elsevier: Amsterdam, **2014**; pp 571–605.
[14] E. Knoevenagel, *Ber. Dtsch. Chem. Ges.* **1896**, *29* (1), 172–174.
[15] S. Kim, E. Kim, J. H. Hong, *Nucleosides Nucleotides Nucleic Acids* **2015**, *34* (3), 163–179.
[16] M. Molnar, H. Brahmbhatt, V. Rastija, V. Pavić, M. Komar, M. Karnaš, J. Babić, *Molecules* **2018**, *23* (8), 1897.
[17] I. Ali, A. Haque, K. Saleem, M. F. Hsieh, *Bioorg. Med. Chem.* **2013**, *21* (13), 3808–3820.
[18] C. J. R. Bataille, M. B. Brennan, S. Byrne, S. G. Davies, M. Durbin, O. Fedorov, K. V. M. Huber, A. M. Jones, S. Knapp, G. Liu, A. Nadali, C. E. Quevedo, A. J. Russell, R. G. Walker, R. Westwood, G. M. Wynne, *Bioorg. Med. Chem.* **2017**, *25* (9), 2657–2665.
[19] K. van Beurden, S. de Koning, D. Molendijk, J. van Schijndel, *Green Chem. Lett. Rev.* **2020**, *13* (4), 349–364.
[20] C. M. Alder, J. D. Hayler, R. K. Henderson, A. M. Redman, L. Shukla, L. E. Shuster, H. F. Sneddon, *Green Chem.* **2016**, *18* (13), 3879–3890.
[21] O. Doebner, *Ber. Dtsch. Chem. Ges.* **1900**, *33* (2), 2140–2142.
[22] M. H. Abdellattif, H. M. Mohamed, *Green Sustainable Chem.* **2018**, *08* (02), 139–155.
[23] P. Singh, A. Anand, V. Kumar, *Eur. J. Med. Chem.* **2014**, *85*, 758–777.
[24] R. Li, G. L. Kenyon, F. E. Cohen, X. Chen, B. Gong, J. N. Dominguez, E. Davidson, G. Kurzban, R. E. Miller, E. O. Nuzum, P. J. Rosenthal, J. H. McKerrow, *J. Med. Chem.* **1995**, *38* (26), 5031–5037.
[25] J. F. Ballesteros, M. J. Sanz, A. Ubeda, M. A. Miranda, S. Iborra, M. Paya, M. J. Alcaraz, *J. Med. Chem.* **1995**, *38* (14), 2794–2797.
[26] J. R. Dimmock, N. M. Kandepu, M. Hetherington, J. W. Quail, U. Pugazhenthi, A. M. Sudom, M. Chamankhah, P. Rose, E. Pass, T. M. Allen, S. Halleran, J. Szydlowski, B. Mutus, M. Tannous, E. K. Manavathu, T. G. Myers, E. De Clercq, J. Balzarini, *J. Med. Chem.* **1998**, *41* (7), 1014–1026.
[27] C. C. Yit, N. P. Das, *Cancer Lett.* **1994**, *82* (1), 65–72.
[28] Y. Satomi, *Int. J. Cancer* **1993**, *55* (3), 506–514.
[29] L. W. Wattenberg, J. B. Coccia, A. R. Galbraith, *Cancer Lett.* **1994**, *83* (1–2), 165–169.
[30] A. Aguilera, A. R. Alcantara, J. M. Marinas, J. V. Sinisterra, *Can. J. Chem.* **1987**, *65* (6), 1165–1171.
[31] M. J. Climent, A. Corma, S. Iborra, A. Velty, *J. Catal.* **2004**, *221* (2).
[32] S. Sebti, A. Solhy, R. Tahir, S. Abdelatif, S. Boulaajaj, J. A. Mayoral, J. I. García, J. M. Fraile, A. Kossir, H. Oumimoun, *J. Catal.* **2003**, *213* (1), 1–6.
[33] N. Iranpoor, F. Kazemi, *Tetrahedron* **1998**, *54* (32), 9475–9480.
[34] L. J. Mazza, A. Guarna, *Synthesis (Stuttg.)* **1980**, *1980* (01), 41–44.
[35] K. Nepali, K. Kadian, R. Ojha, R. Dhiman, A. Garg, G. Singh, A. Buddhiraja, P. M. S. Bedi, K. L. Dhar, *Med. Chem. Res.* **2012**, *21* (10), 2990–2997.
[36] D. C. G. A. Pinto, A. M. S. Silva, J. A. S. Cavaleiro, J. Elguero, *Eur. J. Org. Chem.* **2003**, *2003* (4), 747–755.
[37] B. Han, Z. Liu, Q. Liu, L. Yang, Z.-L. Liu, W. Yu, *Tetrahedron* **2006**, *62* (11), 2492–2496.
[38] G. Sabitha, G. S. K. K. Reddy, C. S. Reddy, N. Fatima, J. S. Yadav, *Chem. Informationsdienst* **2003**, *34* (41).
[39] N. Nakamichi, Y. Kawashita, M. Hayashi, *Synthesis (Stuttg.)* **2004**, (7), 1015–1020.
[40] N. Nakamichi, Y. Kawashita, M. Hayashi, *Org. Lett.* **2002**, *4* (22), 3955–3957.
[41] L. Chai, Y. Zhao, Q. Sheng, Z.-Q. Liu, *Tetrahedron Lett.* **2006**, *47* (52), 9283–9285.
[42] S. Llopis, T. García, Á. Cantín, A. Velty, U. Díaz, A. Corma, *Catal. Sci. Technol.* **2018**, *8* (22).
[43] S. Inagaki, S. Guan, Y. Fukushima, T. Ohsuna, O. Terasaki, *J. Am. Chem. Soc.* **1999**, *121* (41), 9611–9614.
[44] P. Wang, X. Liu, J. Yang, Y. Yang, L. Zhang, Q. Yang, C. Li, *J. Mater. Chem.* **2009**, *19* (42), 8009–8014.
[45] U. Díaz, T. García, A. Velty, A. Corma, *J. Mater. Chem.* **2009**, *19* (33), 5970.

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