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Full Paper

Microwave-Assisted Grafting to MCM-41 Silica and its Application as Catalyst in Flow Chemistry

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Finding environmentally gentle methods to graft Lewis acid on the surface of mesoporous materials is a topic of current interest. Herein we describe the optimization of a preparation procedure of a mesoporous silica-supported $\mathrm{Er^{III}}$ catalyst using the microwave-assisted post-calcination functionalization of Mobil Composition of Matter-41 silica as the key step. The required time for functionalization was reduced from several hours to 10 min using sealed-vessel microwave technology. Control experiments using conventional heating at the same temperature demonstrated that the rate increase is owing to a simple thermal/kinetic effect as a result of the higher reaction temperature. The resulting $\mathrm{Er^{III}}$ catalyst was tested for the first time as a catalyst in the continuous flow deprotection of benzaldehyde dimethylacetal and a complete leaching study was performed.

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Introduction

Heterogeneous catalysis offers several advantages in both organic synthesis and in industrial processes because catalyst recovery and recycling is often easier compared with homogeneous catalysts, without loss in reaction selectivity and yield. In addition, heterogeneous catalysts derived from homogeneous catalysts immobilized on an inorganic support, can be applied in continuous flow synthesis which is a particularly suitable technology for performing reactions in a fast, clean and scalable way.[1] Amorphous silica and mesoporous silica Mobil Composition of Matter-41 (MCM-41) have been extensively used as supports for immobilizing homogeneous catalysts and have recently also been used in continuous flow processes.[2] The advantages of mesoporous supports are related to their ordered array of hexagonal channels with pores up to 50 Å diameter. This results in superior access to the catalytically active sites located on the channels, a large superficial area, high catalyst loading and minimum diffusional resistance. On the other hand, these supports are generally temperature and solvent resistant, and easy to prepare and functionalize.[2]

Alternative heating methods such as microwave dielectric heating have been used in the past in order to synthesize functionalized mesoporous MCM-like materials by co-condensation,[3,4] while until date the reported methodologies to introduce organic groups on their surface by post-calcination grafting are often time-consuming, labour-intensive and involve the use of toxic solvents under conventional heating conditions.[5a] To the best of our knowledge, there are only two publications that describe the application of microwave-assisted procedures to the post-calcination grafting of organic molecules on the surface of silica-type materials. These involve the functionalization of controlled-pore glass as support for the solid phase synthesis of nucleic acids,[5b] and the immobilization of alkaloids on the surface of HPLC-grade silica gel via click chemistry.[5c] In both of these examples, microwave irradiation enhanced the rate and the yield of the functionalization compared with the classical procedure, but no rationalization of the observed phenomena was given. More recently, Garcìa and coworkers[6] proposed that microwave heating increases the silica functionalization rate and yield inducing autocondensation of polar silylating agents. Compared with the conventionally heated functionalized silica, a change in the grafted layer structure was observed.

In two of our recent publications we applied microwave heating to the synthesis of a new mesoporous silica-supported $\mathrm{Er^{III}}$ catalyst[7] and have performed an evaluation of microwave heating for the grafting of different organic moieties on the surface of the mesoporous silica support.[8] In these studies, we initially assumed the involvement of a 'specific microwave effect' on the silica functionalization reaction.[4] The aim of the present work was to re-evaluate the reaction conditions for the previously described post-calcination functionalization reactions using a dedicated single-mode microwave reactor with internal temperature measurement capabilities, in order to more carefully scrutinize the role of microwave irradiation on these types of grafting processes.

Results and Discussion

In our previous work[8] we performed a rough comparison between classical[9] and microwave-assisted grafting protocols involving different silylating agents and MCM-41 silica supports. Microwave experiments were performed in a multimode system with external IR temperature monitoring. MCM-41 silica was activated with a 25 % (v/v) HCl solution at room temperature for 3 h. The acid pretreatment allows to increase the OH-functionalities on the silica surface.[8,9] The classical functionalization was time and energy consuming (8 h at the reflux temperature of toluene, ~110°C) and the loading was lower or comparable with the loadings achieved after microwave irradiation within only 15 min. For graftings performed both in toluene and under solvent-free conditions, there was a strong dependence of the loading on the reaction time, with loadings ranging from 0.28–1.0 mmol g^{-1} in toluene up to 1.74 mmol g^{-1} using solvent-free conditions.[8]

In order to optimize these conditions more carefully and to re-evaluate the specific role of microwave irradiation on the grafting process, the functionalization of MCM-41 silica with 3-(chloropropyl)triethoxysilane (CPTES) was chosen as model reaction (Scheme 1). The grafting process was performed in single-mode microwave reactors with either external IR sensors or an internal fibre-optic probe temperature sensor, the latter allowing for very accurate reaction temperature measurements.[10]

In a first set of experiments, the microwave-assisted functionalizations were performed in a Biotage Emrys Initiator EXP 2.5 reactor.[10a] In a typical experiment 200 mg of pre-treated MCM-41 silica (see below) were reacted with a mixture of 1 mL of CPTES and 2 mL of toluene with magnetic stirring. The degree of functionalization was determined using Total Organic Carbon (TOC) measurements in triplicate and is given in mmol functionality per gram of silica. Using conventional reflux conditions, the loading after 8 h of reflux heating at 110°C was ~1.5 mmol g^{-1}, which represents an appropriate surface coverage for catalytic applications.

Initially, the microwave grafting process using CPTES shown in Scheme 1 was performed at a set temperature of 150°C using either dry toluene as solvent (conditions a) or under solvent-free conditions (conditions c). Even after only 5 min reaction time the degree of functionalization was ~1 mmol g^{-1} using toluene as solvent, and 2 mmol g^{-1} under solvent-free conditions. Prolonged exposure to microwave irradiation at 150°C did not further increase the loading for both set of conditions. In a second series of experiments the functionalization was performed for 10 min constant reaction time, varying the temperature from 110 to 170°C. As expected, the degree of functionalization increased with higher temperatures for both the toluene and solvent-free experiments. In toluene, the optimum functionalization level of 1.5 mmol g^{-1} was obtained at 130°C, while under solvent-free conditions the loading was already around 2 mmol g^{-1} even at 110°C, too high for catalytic applications. In general, we found that when using toluene as solvent, the degree of functionalization could be better controlled than using solvent-free conditions. In this context, it should be emphasized that proper stirring in these heterogeneous silica functionalizations is required to ensure reproducible results. For example, using conical vials for the Biotage reactor (0.5–2.0 mL),[10a] the agitation induced by the small stir bar is not optimal and leads to significantly lower loadings and inhomogeneous samples as obtained in the larger cylindrical tubes, where appropriate stirring can be ensured.[11]

Finally we studied the dependence of the functionalization degree on the silica pre-activation step comparing the results obtained when the same MCM-41 silica sample was pre-treated with a freshly prepared 25 % (v/v) HCl solution, a one week old HCl solution and a one month old HCl solution of the same concentration.

As it can be seen in Fig. 1, no comparison is possible between samples activated with HCl solutions of different age. It can therefore be concluded that the activation step and the date of preparation of the HCl source are crucial for the silica surface coverage. The experiments described above have shown that the time required for the functionalization of mesoporous MCM-41 silica with 3-(chloropropyl)triethoxysilane (CPTES) using toluene as a solvent can be reduced from 8 h under reflux conditions to 10 min using sealed vessel microwave heating at 130°C. These conditions lead to a medium level of surface coverage (1.5 mmol g^{-1}), which makes this material suitable for use as a heterogeneous catalyst. In order to establish if the acceleration of the grafting performed under microwave conditions is owing to a specific microwave effect as presumed previously,[8] we have performed careful control experiments between microwave heating and conventional heating at the identical reaction temperature of 130°C.

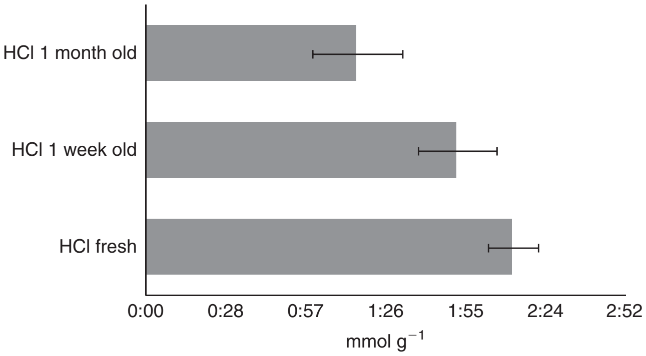
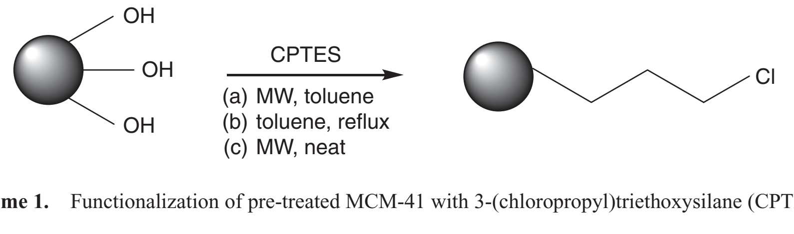


Fig. 1. Dependence of the loading in the microwave-assisted functionalization (Scheme 1) on the silica pre-activation step using different sources of 25 % (v/v) HCl.



Scheme 1. Functionalization of pre-treated MCM-41 with 3-(chloropropyl)triethoxysilane (CPTES).

For this purpose we have used a reactor system that allows us to perform both types of transformations *in the identical reaction vessel* and to monitor the internal reaction temperature in both experiments directly with a fibre-optic probe device.[12] This set-up can be either immersed into the cavity of a CEM Discover microwave reactor (CEM Microwave Technology, Buckingham, UK) or into a preheated and temperature equilibrated oil bath placed on a magnetic stirrer. In both cases, the software of the microwave instrument is recording the internal temperature and similar heating profiles can be obtained (see below). This system has the advantage that the same reaction vessel and the same method of temperature measurement are used. In this way all parameters apart from the mode of heating are identical and therefore a fair comparison between microwave heating and thermal heating can be made. The reaction conditions and the temperature profiles recorded for both the microwave and oil bath experiments at 130°C are shown in Fig. 2.

Each functionalization has been performed in triplicate (experiments 1–3) and the results are shown in Table 1. As can be clearly seen, the TOC measurement results between microwave-heated and conventionally heated runs are nearly identical with loadings ranging from 1.88 to 2.33 mmol g^{-1}. All TOC measurements have been performed in triplicate on the same sample, and the standard deviations of these three measures ($\leq$0.15 in each case) can be interpreted as a parameter of sample homogeneity. It can therefore be concluded that the observed rate acceleration seen for this grafting process is the result of a purely thermal/kinetic phenomenon as a result of the higher reaction temperature, and can be duplicated in an autoclave experiment.[10c]

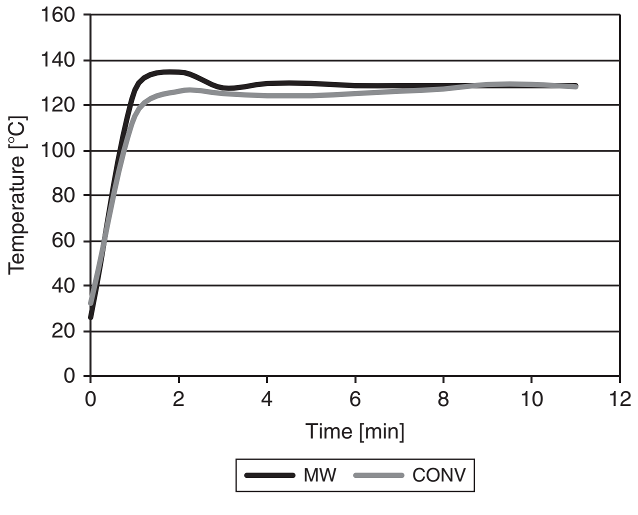


Fig. 2. Temperature profiles for the microwave-assisted (MW) and conventionally heated (CONV) silica functionalization reaction with CPTES (Scheme 1). Conditions: 200 mg of pre-treated MCM-41 (freshly prepared 25 % (v/v) HCl solution), 1 mL CPTES, 2 mL of dry toluene, 130°C, 10 min fixed hold time, 10 mL Pyrex vessel. MW: CEM Discover, max. magnetron output power 150 W, magnetic stirring 'high'. CONV: magnetic stirring 400 rpm.

Note that the results obtained with the CEM Discover instrument at 130°C (Table 1, internal fibre-optic temperature measurement) are in good agreement with the data obtained on the Biotage Initiator reactor (Fig. 1, external infrared temperature sensor). The most consistent results were obtained with high stirring rates, underscoring the importance of proper agitation in microwave-heated reactions.[11] Heating experiments performed with constant microwave power on suspensions of dried and pre-treated MCM-41 silica in microwave transparent CCl_4 in conjunction with quartz reaction vessels demonstrated that the silica material itself is only weakly microwave absorbing and can therefore not be selectively heated by microwave irradiation (data not shown). This type of experiment has been used in the past to quickly establish the microwave absorbance characteristics of materials.[13]

With an optimized microwave-assisted functionalization procedure in our hands, we again synthesized the Lewis acid heterogeneous Er^{III} catalyst that we have already previously applied in the cyanosilylation of aldehydes and ketones,[7] with the final aim to use this material as a heterogeneous catalyst in continuous-flow processes (Scheme 2).

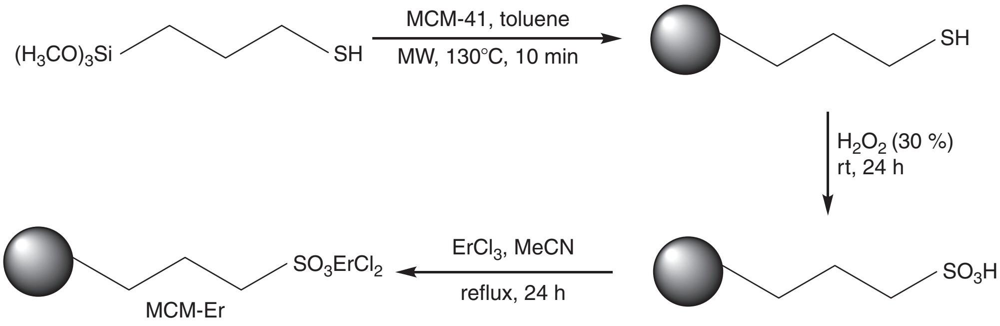
The MCM-Er catalyst was identified by comparison with the Raman and ^{13}C NMR spectra previously reported,[7] the Er^{III} amount present on the silica surface was quantified by inductively coupled plasma mass spectrometer (ICP-MS) (10.2 %, equivalent to 0.8 mequiv g^{-1} silica) and the porous structure was determined by N_2 adsorption/desorption isotherms (SBET = 575 $m^2 g^{-1}$; pore volume ($P/P_0 = 0.9$) = 0.41 $cm^3 g^{-1}$, see Accessory Publication). The flow experiments involving the Er^{III} silica catalyst were conducted in a high-pressure flow reactor (ThalesNano X-Cube; Thales Nanotechnology, Budapest, Hungary) where the heterogeneous Er catalyst is immobilized in a pre-packed, replaceable stainless steel cartridge (60 × 4 mm i.d., 200 mg MCM-Er).[14] The catalyst cartridge can be heated to 200°C and the reaction mixture is pumped through the cartridge using an HPLC pump at pressures up to 150 bar and flow rates of 0.1 to 3.0 mL min^{-1}. The list of the cartridges, the amount of Er^{III} and the support used for each cartridge is summarized in Table 2. Two cartridges, with two different amounts of Er^{III} (0.032 and 0.08 mequiv g^{-1}), were prepared with this catalyst. A non-swelling material such as amorphous silica K-60, sieved at 80 mesh, was used as inert material to dilute the catalyst to the desired concentration. Samples of ~200 mg of these materials were then packed in the stainless steel cartridge (C1 and C2, Table 2).

To establish whether microwaves could have any effect on the distribution of the functionalities on the silica surface,

Table 1. Comparison of microwave (MW) and conventional heating (CONV) in the functionalization of MCM-41 silica with 3-(chloropropyl)triethoxysilane (CPTES) in toluene at 130°C[A]

Conditions	TOC [mmol g^{-1}] Experiment 1	TOC [mmol g^{-1}] Experiment 2	TOC [mmol g^{-1}] Experiment 3
MW	2.01 ± 0.15	1.94 ± 0.04	2.04 ± 0.14
CONV	2.33 ± 0.006	2.01 ± 0.04	2.08 ± 0.14

[A] For conditions, see Figure 2.



Scheme 2. Preparation of a heterogeneous $ErCl_3$ catalyst (MCM-Er).[7]

Table 2. List of the Er(III) silica catalyst cartridges for the continuous flow experiments

Cartridge	Inert Material	Er(III) Amount [mmol g^{-1}]
C1	K-60 silica	0.032
C2	K-60 silica	0.08
C3	MCM-41 silica	0.032
C4	MCM-41 silica	0.08
C5	K-60 silica	0.032^{A}
C6	K-60 silica	0.032^{B}
C7	K-60 silica	0.08^{B}

[A] Catalyst prepared in a conventional way.

[B] Cartridge prepared by mixing of $ErCl_3$, MCM-41 silica and K-60 silica.

leading to possible changes in activity, a small amount of catalyst was prepared in a conventional way and then mixed with the amorphous silica K-60 to prepare the last cartridge (C5 in Table 2). Two other cartridges were prepared by mixing the catalyst with commercial MCM-41 silica as support (C3 and C4, Table 2).

Finally, two additional cartridges (C6 and C7, Table 2) containing the same amount of $ErCl_3$ (respectively as C1 and C2 cartridges) and non-functionalized MCM-41 silica, were prepared by mixing these materials with the appropriate amount of K-60 silica as inert material.

As an initial trial to study the performance of this immobilized Er^{III} catalyst in continuous-flow mode we studied the deprotection of benzaldehyde dimethylacetal to benzaldehyde as a model transformation. Previous work from our laboratory on the Lewis acid activity of Er^{III} salts in homogeneous phase has demonstrated that it is possible to achieve full conversion of the acetal to the aldehyde within only 50 min simply mixing it with 1 mol % of $Er(OTf)_3$ in $MeNO_2$ saturated with water.[15] Gratifyingly, the same result was obtained when the reaction was performed in the presence of 1 mol % of the heterogeneous MCM-Er catalyst, as shown in Scheme 3, whereas only a partial deprotection was recorded when the reaction was performed both without any catalyst and with the same amount of commercial MCM-41 silica (10 and 20 % yield respectively after 6 h).

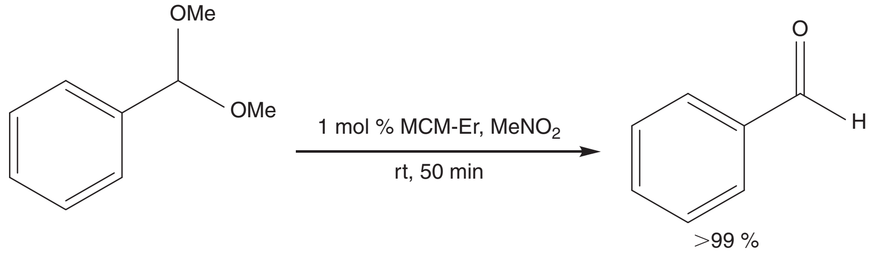
In light of this result, we planned to perform the reaction under continuous-flow conditions using the more diluted cartridges C1, C3, and C5. The cartridges were washed with wet nitromethane and used immediately, considering the optimum conditions found in the batch experiment (Scheme 3). Thus 1 mL of a solution of benzaldehyde dimethylacetal in nitromethane saturated with water (7.6 mg mL^{-1}, 0.05 mmol mL^{-1}) was passed through the MCM-Er cartridges at different flow rates at room temperature. After washing the system with 5 mL of pure solvent the mixture collected at the exit of the reactor was analyzed by GC/MS in order to determine the reaction conversion and yield. The results are summarized in Table 3. Using the C1 cartridge (Table 2) full conversion was achieved up to a flow rate of 1.4 mL min^{-1} (Table 3, entry 5). No differences were recorded using the cartridge C5 (data not shown), demonstrating that there are no differences in morphology between a microwave and conventionally prepared catalyst.

Subsequently, the reaction was carried out in three additional solvents; toluene, THF, and CH_3CN, different in polarity from nitromethane (entries 6 to 14, Table 3). Although nitromethane was the best performing solvent, we recorded full conversion also in toluene at 50°C (entry 7, Table 3) and, using a more concentrated cartridge, in CH_3CN at 75°C (entry 14, Table 3), whereas no conversion was observed in THF even using more drastic conditions (entries 8 to 11, Table 3).

A comparison between C1/C2 cartridges (made by functionalized silica) and C6/C7 cartridges (filled with a mixture of $ErCl_3$ and MCM-41 in the same amount present in C1 and C2 respectively) in terms of conversion efficiency was performed (entries 18 to and 20, Table 3). The cartridges containing the same amount of Er^{III} prepared mixed with non-functionalized MCM-41 silica are less effective compared with their analogues filled with functionalized silica.

A completely different behaviour was recorded for the C3 cartridge (Table 2) filled with mesoporous MCM-41 silica as inert material (Table 3, entries 15–17). Due to the small size of the particles, the recorded inlet pressure flushing the reaction mixture through this cartridge was very high, reaching almost the maximum value (150 bar) allowed by the instrument at 1.5 mL min^{-1} flow rate. For safety reasons we chose a flow rate of 1.0 mL min^{-1} to perform our experiments with this material.

An important parameter that has to be evaluated in all flow chemistry involving heterogeneous metal catalysts is the leaching of the metal from the support into the reaction mixture. In order to measure the leaching we performed ICP-MS measurements on the amount of Er^{III} found in the solution collected at the exit of the system (Table 4). This technique has been found quite useful in the past to establish if an immobilized catalyst is leached from the support or not. Leaching is likely to be a common problem for all metal-catalyzed transformations that involve a quasi-homogeneous mechanism where catalysis proceeds through a dissolution/re-adsorption process of the metal species from the support. Under flow conditions the active metal catalyst will be leached and transported away from the support, thereby constantly reducing the activity of the immobilized catalyst and contaminating the product with metal. In a conventional batch experiment the catalytically active metal will also



Scheme 3. Deprotection of benzaldehyde dimethylacetal using heterogeneous MCM-Er catalyst (Scheme 2). Conversion was determined by GC/MS and the product was identified by comparison with the data previously reported in the literature.[15]

Table 3. Catalytic efficiency of heterogeneous MCM-Er catalyst in the continuous-flow deprotection of benzaldehyde dimethylacetal (Scheme 3)[A]

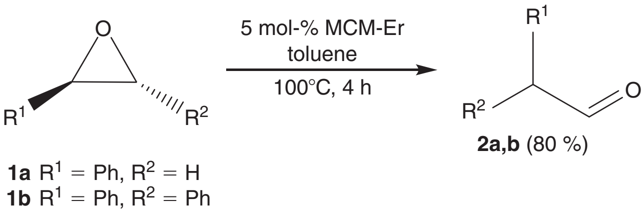
Entry	Cart	Solvent	Flow rate [mL min^{-1}]	T [°C]	Inlet pressure [bar]	Conv [%][B]
1	C1	CH_3NO_2	0.5	25	2	100
2	C1	CH_3NO_2	1	25	2	100
3	C1	CH_3NO_2	1.3	25	2	100
4	C1	CH_3NO_2	1.4	25	2	100
5	C1	CH_3NO_2	1.5	25	2	90
6	C1	Toluene	1.4	25	2	29
7	C1	Toluene	1.4	50	2	100
8	C1	THF	1.4	25	2	0
9	C1	THF	1.4	50	2	0
10	C1	THF	1.4	75	2	0
11	C2	THF	1.4	75	2	0
12	C1	CH_3CN	1.4	90	2	69
13	C2	CH_3CN	1.4	50	2	75
14	C2	CH_3CN	1.4	75	2	100
15	C3	CH_3NO_2	1	25	105	100
16	C3	CH_3NO_2	1.2	25	125	100
17	C3	CH_3NO_2	1.3	25	135	100
18	C6	Toluene	1.4	50	2	31
19	C7	Toluene	1.4	50	2	98
20	C7	CH_3CN	1.4	75	2	24

[A] For experimental details, see main text.
[B] Conversions were determined by GC/MS.

Table 4. Leaching of Er(III) catalyst in the continuous-flow deprotection of benzaldehyde dimethylacetal (Scheme 3)[A,B]

Entry	Cart	T [°C]	Solvent	Washing solvent [mL][B]	Reaction mixture [mL]	Er leaching [%]
1	C1	25	CH_3NO_2	6	0	0.008
2	C1	25	CH_3NO_2	0	6	1.2
3	C1	25	Toluene	6	0	0.00077
4	C1	50	Toluene	0	6	0.00017
5	C1	25	THF	6	0	20.4
6	C1	75	THF	0	6	15.7
7	C2	75	THF	6	0	0.6
8	C1	90	CH_3CN	6	0	8.36
9	C2	75	CH_3CN	0	6	0.87
10	C3	25	CH_3NO_2	6	0	0.0002
11	C3	25	CH_3NO_2	0	6	0.00026
12	C6	25	Toluene	6	0	0.0007
13	C6	50	Toluene	0	6	0.00016
14	C7	50	Toluene	0	6	0.00003
15	C7	75	CH_3CN	6	0	1.76
16	C7	75	CH_3CN	0	6	1.4

[A] Leaching analysis was performed by ICP-MS measurements.
[B] Analysis performed on 6 ml of washing solvent/reaction mixture flowing at the rate of 1.4 mL min^{-1} for C1, C2, C6 and C7 cartridges and 1.0 mL min^{-1} for C3 cartridge.



Scheme 4. Epoxide rearrangement to aldehydes in heterogeneous phase.

be leached, but at the end of the reaction is likely to be redeposited/re-adsorbed on the support. Phenomena like this have been observed for Pd/C or Cu/C catalyzed processes such as Heck couplings or azide-alkyne cycloaddition reactions.[16]

The amount of catalyst lost during the reaction was calculated as % weight in comparison to the total amount of Er^{III} present in each cartridge, considering that ~23 versus ~57 mg of MCM-Er catalyst is present in each cartridge, with a total amount of ~3 versus ~7.5 mg Er^{III} per C1/C6 versus C2/C7 cartridges. As can be seen from the data presented in Table 4, there is a significant amount of leaching taking place when nitromethane (entries 1 and 2, Table 4), THF (entries 5 to 7, Table 4) and acetonitrile (entries 8 and 9, Table 4) are passed through the cartridges containing the Er catalyst. The leaching values are significantly lower using toluene as solvent (entries 3 and 4, Table 4). In general there was an inverse correlation between the conversion and the leaching: the lower the metal leaching was in a solvent, the higher the conversion. Note that despite the high inlet pressure, considerably less Er leaching is experienced for the cartridges filled with MCM-41 as solid support (Table 4, entries 10 and 11).

Regarding the C6 and C7 cartridges, the metal leaching was absolutely comparable to the corresponding cartridges filled with functionalized silica. In this case, the drop of conversion (see Table 3) was not directly related to the metal leaching but rather to the loss of the proximity effect between the metal centre and the pores within the silica.

As one would expect, the observed leaching was accompanied by a loss of activity in the cartridge. In a preparative experiment, a 7.6 mg mL^{-1} solution of benzaldehyde dimethylacetal in aqueous nitromethane was pumped through the cartridges C1 and C3, continuously measuring the conversion to benzaldehyde in the collected solution at the exit of the system. Under these conditions, the conversion drops from 100 to 90 % in only 15 min, and to 70 % in 25 min (see Accessory Publication).

As reported in the literature,[15] the deprotection reaction of benzaldehyde dimethylacetal is influenced by the solvent polarity. Polar solvents are the best choice in batch but, because of the high Er^{III} leaching associated to these solvents (entries 1, 2, 8, 9, 15, 16, Table 4,) we checked also less polar solvents in flow. The oxyphilic character of the Er^{III} could explain the high leaching/low yields obtained using THF as solvent (entries 5–7, Table 4).

From a comparison between the leaching data (Table 4) and the conversion results (Table 3), we decided to process benzaldehyde dimethylacetal in toluene as solvent at 50°C and 1.4 mL min^{-1} flow rate as optimized continuous-flow conditions. Considering a leaching of 0.00017 % after 4.28 min (corresponding to 6 mL of mixture passing through the cartridge at 1.4 mL min^{-1}), we can realize a scale up to roughly 400 kg of benzaldehyde dimethylacetal processed before that the catalyst loss 20 % of its activity.

In order to test the strength of the method, we checked the possibility to cleave some more resistant acetals such as the 2′,3′-*O*-isopropylidene-uridine and 2,3-*O*-isopropylidene-D-ribolactone.[17] For solubility reasons, we used nitromethane and acetonitrile as solvents. The reactions were performed using both C1 and C2 cartridges with a flow rate ranging from 0.3 to 0.5 mL min^{-1} and in a temperature region between 25 and 110°C. In all cases only the starting material was found in the processed samples, confirming that the solvent has critical importance for the outcome of the reaction.

Finally, we decided to apply the heterogeneous Er^{III} catalyst in the rearrangement of epoxides to aldehydes (Scheme 4). We have previously found that $Er(OTf)_3$ is a very good catalyst for this interesting transformation in homogeneous phase, achieving full conversion both for the styrene oxide (**1a**) and the *trans*-stilbene oxide (**1b**) in 45 min at room temperature in presence of 1 mol % of Er catalyst.[18] Unfortunately, the reaction requires more drastic conditions when performed using the heterogeneous MCM-41 Er catalyst (Scheme 2) and only 80 % conversion was obtained when both starting materials were reacted in toluene at 100°C for 4 h in the presence of 5 mol % of MCM-Er (the conversions were determined by GC/MS and the products were identified by comparison with the data reported in the literature).[18] Clearly, given the long reaction/residence times, such a process is not well suited for a continuous flow approach.

Conclusions

Herein we have performed a detailed investigation on the role of microwave irradiation on the post-calcination functionalization of mesoporous MCM-41silica with CPTES. Control experiments using microwave and oil bath heating at the same internal reaction temperature of 130°C have confirmed that the observed rate enhancements compared with conventional reflux conditions are the results of a purely thermal/kinetic effect related to the higher reaction temperatures. Apart from temperature and reaction time, the effects of pre-activation and stirring efficiency were additionally studied. The optimized silica functionalization method was also applied to the synthesis of a heterogeneous Er^{III} catalyst and the application of this material in the continuous flow deprotection of benzaldehyde dimethylacetal was evaluated. The high reaction conversions and rates suggest a good potential application of these materials to a cleaner continuous flow technique; at the same time the leaching studies suggest that the efficiency of the method is strictly related to both the lowering of the metal leaching and the proximity between the catalytic active centre and the pores on the silica surface.

Experimental

All chemicals were obtained from Aldrich Chem. Co (Milan, Italy), Acros Organics (Geel, Belgium), or Alfa Aesar (Karlsruhe, Germany) and used as received. Microwave irradiation experiments in the Biotage Initiator EXP 2.5 single-mode reactor (2.45 GHz, 400 W) used an external IR sensor and followed standard procedures.[10a] Similarly, reactions in the CEM Discover LabMate single-mode instrument (2.45 GHz, 300 W) were performed using an internal fibre-optic sensor as previously reported.[11] Continuous-flow reactions were performed in an X-Cube from Thales Nanotechnology Inc.[19] TOC measurements were performed in triplicate for each sample on a Analytik Jena multi N/C 2100 analyzer equipped with a

HT 1300 oven. Raman spectra were recorded on a Renishaw inVia microRaman spectrophotometer using a laser power of 1.2 mW and a laser excitation wavelength of 514 nm. FT-IR spectra were performed on a Jasco 430 instrument ^{13}C HR-MAS NMR spectra were recorded on a Bruker Avance 500 MHz instrument at 298 K. The characterization of the porous structure was obtained by N_2 adsorption/desorption isotherms, measured at 77 K on a Micromeritics ASAP 2010 volumetric adsorption analyzer. Before measurements, samples were outgassed at 393 K for 6 h. These isotherms were used to evaluate Brunauer, Emmett, and Teller (BET) specific surface area, pore volume, and pore size distributions. The pore size distribution has been calculated using an algorithm based on the Barrett, Joyner and Halenda (BJH) theory. Er leaching in the reaction mixtures was determined with an Agilent 7500ce inductively coupled plasma mass spectrometer (Agilent, Waldbroinn, Germany). The effluents from the cartridges were collected and evaporated to dryness. The residues were quantitatively transferred with nitric acid into the 12 mL quartz vials of the MLS UIltraClave III. The temperature was ramped in 30 min to 250°C and kept at this temperature for a further 30 min. Er was quantitatively determined at *m/z* 166 with an ICP-MS. A calibration was performed with an external calibration curve established from 1.000 g Er L^{-1} standard (CPI International, Amsterdam, The Netherlands). Indium was used as an internal standard. GC-MS spectra were recorded using a Thermo Focus GC coupled with a Thermo DSQ II (EI, 70 eV). A HP5-MS column (30 m × 0.250 mm × 0.025 μm) was used with helium as carrier gas (1 mL min^{-1} constant flow). The injector temperature was set to 280°C. After 1 min at 50°C the temperature was increased in 25°C min^{-1} steps up to 300°C and kept at 300°C for 4 min. ^1H NMR spectra were recorded on a Bruker 300 MHz instrument. Low resolution mass spectra were obtained on an Agilent 1100 LC/MS instrument using atmospheric pressure chemical ionization in positive or negative mode.

General Procedures for the Microwave-assisted Functionalization of MCM-41

Pretreatment of MCM-41 Silica

Commercial MCM-41 (1 g) was treated with 25 mL of 25 % (v/v) HCl for 3 h at reflux temperature. The temperature was lowered to room temperature and the mixture was filtered. The solid material was washed with water and dried overnight at 100°C. The HCl solution was prepared by dilution of the commercial available HCl solution (33 % v/v) and stored in a Pyrex volumetric flask (amber glass) at room temperature. The solution had a shelf life of 1 week.

MW-assisted Functionalization of MCM-41

Pre-treated MCM-41 (200 mg) suspended in 2.0 mL of dry toluene was reacted with CPTES (1 mL) for 10 min at 130°C in a sealed 10 mL microwave process vial equipped with a stirring bar (Initiator 2.5). At the end of the reaction the system was cooled to room temperature. The solid was filtered, washed three times with THF and extracted for 2 h in CH_2Cl_2/Et_2O mixture using a Soxhlet extractor, then dried under vacuum and stored overnight at 70°C. The functionalized mesoporous material obtained was stored under anhydrous conditions. The functionalized silica was identified by comparison with the FT-IR and ^{13}C NMR data reported in the literature.[8] TOC measurement (weight %) = 5.46 ± 0.5 (% C). Experiments performed in a CEM Discover instrument using microwave or oil bath conditions with internal temperature control were performed in a similar manner following the general protocols previously described.[12]

General Procedure for the Synthesis of the Heterogeneous Catalyst MCM-Er^{III}(Scheme 2)

Pre-treated MCM-41 (1 g) was reacted with 3-(mercaptopropyl) trimethoxysilane (5 mL) in dry toluene (10 mL) for 10 min at 130°C in a sealed 10–20 mL microwave process vial equipped with a stirring bar (Initiator 2.5). The resulting solid was filtered, washed three times with THF and extracted for 2 h in CH_2Cl_2/Et_2O mixture using a Soxhlet extractor, then dried under vacuum and stored overnight at 100°C. The solid materials possessing a thiol moiety bonded (1) was oxidized with 30 % H_2O_2 (20 mL) for 24 h at room temperature. After filtration and washing with water (3 × 3 mL) and ethanol (3 × 3 mL), the solid material (2) was treated with $ErCl_3$ (0.573 g) in acetonitrile (10 mL) at reflux temperature for 24 h. After cooling to room temperature the mixture was filtered, washed with acetonitrile, extracted for 2 h in a CH_2Cl_2/Et_2O mixture using a Soxhlet extractor, then dried under vacuum and finally kept at 90°C overnight. The resulting heterogeneous MCM-Er catalyst obtained was stored under anhydrous conditions. The catalyst was identified by comparison with the Raman and ^{13}C NMR data reported in the literature.[7] ICP-MS: (weight %) = 10.2 (% Er).

Deprotection of Benzaldehyde Dimethylacetal (Scheme 3)

Deprotection of Benzaldehyde Dimethylacetal Under Batch Conditions

A solution of benzaldehyde dimethylacetal (30.44 mg, 0.2 mmol) and 1 mol % MCM-Er (3 mg) in 4 mL of $MeNO_2$ saturated with water was stirred at room temperature for 50 min. The catalyst was removed by filtration and the yield was determined by GC/MS. The product was identified by comparison with the ^1H NMR and MS data reported in the literature.[15]

Deprotection of Benzaldehyde Dimethylacetal Under Continuous-flow Conditions

K-60 silica (310 mg) previously sieved to 80 mesh and dried at 350°C for 3 h, was mixed with the MCM-Er catalyst (40 mg, 0.032 mmol Er). The powder was packed in a stainless steel cartridge (60 × 4 mm i.d.) from ThalesNano. The cartridge was inserted in the X-cube reactor, warmed to 50°C and washed with toluene (10 mL). Subsequently, 1 mL of a solution of benzaldehyde dimethylacetal (7.6 mg mL^{-1}) in toluene was passed through the cartridge at a 1.4 mL min^{-1} flow rate. The crude solution was collected at the bottom of the cartridge after rinsing with toluene (5 mL). The yield was determined by GC/MS. The product was identified by comparison with the ^1H NMR and MS data reported in the literature.[15]

Er^{III}-Leaching Studies

A cartridge corresponding to each reaction test was prepared as previously described. Each new cartridge was inserted in the X-cube reactor, heated to the appropriate temperature and washed with solvent (10 mL). The flow rate (1.4 mL min^{-1}) was selected on the flow reactor and the processing was started, whereby only pure solvent was pumped through the system until a fraction of 6 mL was collected. At that point the inlet tube was switched to a 10 mL vial containing 6 mL of a solution of benzaldehyde dimethylacetal (7.6 mg mL^{-1}) in solvent. After the reaction mixture was consumed, the inlet tubing was moved back into a vial of pure solvent and further processing was continued. A fraction of 6 mL was collected (containing product). New processing was started once more with the same procedure. The fraction containing pure solvent and those containing the product were evaporated under reduced pressure and the samples were analyzed by ICP-MS.

Rearrangement of Styrene Oxide Under Batch Conditions (Scheme 4)

A solution of styrene oxide **1a** (25 mg, 24 µL, 0.2 mmol) and 5 mol % MCM-Er catalyst (12.5 mg) in 0.75 mL of toluene was stirred at 100°C in a sealed vial for 4 h. The catalyst was removed by filtration and the conversion was determined by GC/MS to be 80 %. The product was identified by comparison with the ^1H NMR and MS data reported in the literature.[18]

Accessory Publication

N_2 absorbtion and desorbtion curves for MCM-Er^{III} pores measurements and GC-MS profile for the continuous-flow deprotection of benzaldehyde dimethylacetal in nitromethane are available on the Journal's website.

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