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**Supported sulfonic acids: solid  
catalysts for batch and continuous  
flow synthetic processes**

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# 1 Green methods in organic chemistry

## 1.1 General introduction

In recent years the need to reduce production costs and the increasing regulations in pollution prevention prompted industries and academia to revise old processes in order to obtain safer and cleaner procedures for fine chemical and pharmaceutical synthesis. This trend towards what has become known as ‘Green Chemistry’ [1, 2, 3] or ‘Sustainable Technology’ necessitates a paradigm shift from traditional concepts of process efficiency, that are mostly based on chemical yield, to one that assigns economic value to eliminating waste at source and avoiding the use of toxic and/or hazardous substances.

Novel processes should encounter several requirements such as high chemo-, regio- and stereoselectivity, one pot reactions or multi-component reactions instead of multi-step procedures, use of non-toxic solvents or solvent-free reactions, elimination of toxic and/or harmful reagents, improvement of atom economy, etc.

A reasonable working definition of green chemistry can be formulated as follows: *“Green chemistry efficiently utilizes (preferably renewable) raw materials, eliminates waste and avoids the use of toxic and/or hazardous reagents and solvents in the manufacture and application of chemical products”*.

An alternative term, that is currently favoured by the chemical industry, is Sustainable Technologies. Sustainable development has been defined as [4]: *“meeting the needs of the present generation without compromising the ability of future generations to meet their own needs”*.

In order to reach the goal of Green Chemistry and Sustainable Technologies, organic synthesis should take advantage from new different methods. This work mainly deals with the application of the heterogeneous catalysis with special attention into the development of flow processes.

## 1.2 *Heterogeneous Catalysis*

A powerful tool to enhance the sustainability of chemical processes is undoubtedly catalysis. [5]

Furthermore, heterogeneous catalysis allows a few more improvements over the homogeneous one that can contribute to develop cleaner, safer and more economically feasible processes.

However, heterogeneous catalysts, in order to be practical, has to meet numerous requisites as:

- the catalyst preparation should be simple, efficient and of general applicability
- the performance of the immobilized catalyst should be comparable to (or better than) its homogeneous counterpart.
- the separation of the heterogeneous catalyst from the reaction mixture after reaction should be possible via a simple filtration in which more than the 95% of the catalyst should be recovered.
- the leaching of the active species from the heterogenized catalyst should be minimal.
- the recycling of the catalyst for several cycles should be possible without loss of activity.
- the supports carrying the catalyst should be mechanically, thermally and chemically stable; they should be compatible with the solvent and commercially available in a good quality.
- from an environmental (increasing disposal costs) and economical (cost of raw materials and of downstream separation) viewpoint, the catalyst selectivity might sometimes become more important than its activity or lifetime.

In recent years two preferential tendencies have been developed: that of the polymer-supported catalysts and that of the inorganic oxides heterogenized catalysts. [6,7] In particular the general area of cross-linked polymer supports has shown an explosive growth connected with the development of new macroporous materials, that are characterized by a rigid porous matrix that persists even in the dry state. [8] These polymers are typically produced as spherical beads by a suspension polymerization process, which is based on the mixture of cross-linking monomer, inert diluent and



the porogen. Otherwise, it has been reported the preparation of “molded” porous materials with high characteristics for catalysis and asymmetric catalysis too. On the other hand, inorganic oxides show several advantages, such as more mechanical stability, easier handling and a wider range of solvents that can be used.

Another class of solid catalysts that has generated a particular interest is that of the supported homogeneous catalysts, that combine the potential versatility and selectivity of homogeneous catalysts with the practical advantages of solid materials, such as easy catalyst separation from the reaction medium, recovery, and use of a large variety of reaction conditions. [9]

However the creation of the ideal supported catalyst is related to the need of new technologies and new supports since they play an important role in the outcome of the process. In fact, normally, the heterogenization procedure causes a decreasing in stereoselectivity and activity in comparison with the homogeneous counterpart. Besides, the solid support determines limited diffusion of reactants to the active sites and this results in lower reaction rates. The support surface and the catalyst site surrounding can also influence the extent of the reaction.

The focus of this dissertation regards the immobilization of homogeneous active catalysts onto solid supports for the production of fine chemicals in batch and continuous flow conditions.

### ***1.3 Supported catalysts***

In the last years many efforts have been devoted to the catalysts heterogenization and different strategies have been developed for the preparation of supported homogeneous catalysts.

The ideal supported catalyst should thus satisfy many requirements in order to combine both advantages of homogeneous and heterogeneous catalysis.

However, the creation of the ideal supported catalyst is far to be accomplished and indeed many problems related to this technology have to be overcome. First of all the heterogenization procedure usually causes a decreasing in both selectivity and activity of the homogeneous catalyst: in fact, the solid support determines limited

diffusion of reactants to the active sites and this results in lower reaction rates. The lower selectivity too, which often represents a drawback of the heterogeneous systems, has to be ascribed to the matrix effect. With its chemical and physical properties the support surface in close proximity of the anchored catalytic site can influence the extent of the reaction and determine a lower selectivity. As an example, when using silica as support, the polar surface can easily form hydrogen bonds with many organic polar functional groups or interact with metal atoms, and this effect can change the spatial orientation of reactants towards catalysts. On the other hand, organic polymeric supports have usually little porosity, therefore there is a spatial constriction of catalysts which are not completely free to assume the best orientation. Moreover, the recyclability of solid catalysts has not yet reached a good level of efficiency to be of practical interest. In this respect there are many problems related to the catalyst and support characteristics. The catalyst can be damaged during the reaction or can undergo partial leaching of the active species in the reaction medium that determines a partial deactivation of the catalyst itself. In some cases, however, the supporting procedure can improve the catalyst stability by eliminating, dimerization, and/or aggregation effects, which are the main causes of deactivation under homogeneous conditions. In fact “site isolation”, i.e. attaching the catalyst to a support in such a way that the active sites can no longer interact with each other, is a key concept that might lead to better performing heterogeneous catalysts. [10]

With a careful catalyst design and an appropriate support choice based on reaction conditions (e.g. solvent, temperature, reactant etc.) it is possible to overcome these drawbacks.

### 1.3.1 The anchoring methodologies

Concerning the catalyst heterogenization, there are almost three approaches that have been described in the literature (Figure 1) [11]: a) formation of covalent bonds; b) adsorption by ion pair formation; c) entrapment.

### *Covalent binding*

Covalent binding, by far the most frequently used strategy, can be made either by copolymerisation of conveniently functionalised catalysts or ligands with a suitable monomer, or by anchoring catalysts or ligands with reactive groups to a preformed surface. [12] With both strategies it is possible to prepare whole organic materials (polymeric materials) and organic-inorganic materials (mixed gels and organic molecules tethered on inorganic supports). [13, 14] Several specific methodologies used to covalently anchor to solid supports will be fully described in the following chapters.

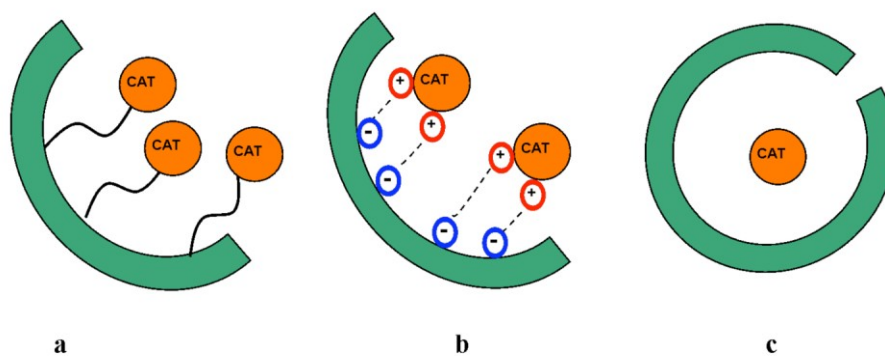
The heterogeneous catalysts are much more complex than their homogeneous counterparts, and many additional parameters such as type of support, spacer length and flexibility, surface coverage degree, surface area and porosity have to be optimised to achieve an acceptable catalytic performance.

### *Heterogenization via adsorption and ion pair formation*

This approach relies on various absorptive interactions between the carrier and the catalyst (usually a metal complex). [15, 16] In general this strategy suffers of limitations connected to the leaching of the active specie in the solution phase. The leaching makes problematic the recycling of the catalyst and the purification of the product from the released catalyst.

### *Heterogenization via entrapment*

Here, the size of the catalyst rather than a specific adsorptive interaction is important. There are two different preparation strategies. [17, 18] Often called 'ship in the bottle' approach, the first strategy is based on building up catalysts in well-defined cages of porous supports. The other approach is to build up an inorganic sol-gel or organic polymeric network around a preformed catalyst. However entrapped catalysts were much less active than their homogeneous counterparts.



**Figure 1.** Anchoring methodologies: a) covalent binding; b) adsorption; c) entrapment.

### 1.3.2 Solid supports

The development of supported catalysts for heterogeneous reactions prompted research groups all over the world to investigate many different solid supports as these play an important role in the outcome of the process. Solid supports can be roughly divided in two classes: inorganic materials and organic polymers.

#### *Inorganic materials*

Many different types of inorganic supports are known for the preparation of heterogenized catalysts. The most used can be divided mainly in three categories: a) amorphous materials (e.g. amorphous silica and alumina), b) mesoporous materials (e.g. MCM-41, MCM-48 and MSU silicas) and c) crystalline materials (e.g. zeolites). Inorganic materials described in this dissertation are mainly of two types: amorphous silica and mesoporous silica (MCM-41).

#### *Amorphous silica*

Amorphous silica has a non-ordered structure with irregular channels and pore diameter that can broadly vary. The amorphous silica utilised in the present work is commercially available (Merck) with an average pore diameter of 60 Å. This material has the advantage to be readily available and economically advantageous. However, due to the irregular pore sizes, part of the catalyst can penetrate into small

pores during the supporting procedure with the consequence that this part of the catalyst is not easily accessible from reactants.

### *Mesoporous synthetic silicas (MCM-41)*

Ordered mesoporous (alumino)silicates offer interesting catalytic properties. These materials are synthesized with the help of surfactant micelle templates. Exemplified by the Mobil M41S materials, of which MCM-41 [19, 20] is the most familiar, they possess uniform channels with tunable diameters in the range 1.5-10 nm.

M41S family is composed by three types of materials which have a very high surface area (often more than 700 m<sup>2</sup>/g) and which differ for the mesoporous spatial organization:

- MCM-41 with a mono-dimensional array of hexagonal channels
- MCM-48 with a three-dimensional network of cubic channels
- MCM-50 with a lamellar, but not very stable, organization of channels.

MCM-41 is the most studied and utilized material of the M41S family. The practical advantage in using MCM-41 as support for catalyst immobilization, lies in its high surface area and pore volume. Thus reactant and product molecules can easily diffuse and reach the catalytic sites, bulk catalysts can be accommodated in the mesopores (usually falling in the range 3-6 nm depending upon the synthesis conditions) and well-isolated and non-interacting catalytic site can be obtained. The typical XRD pattern of MCM-41 shows an intense peak at low diffraction angles (reflection line) and three less intense peaks at higher diffraction angles. This type of diffraction pattern is typical of a hexagonal symmetry distribution of regular sized cylindrical mesopores. MCM-41 is usually defined as a long-range ordered structure because the material at the atomic level is amorphous and does not present a short-range organisation (as for example zeolite aluminosilicates)

### *Organic Polymers*

Organic polymers as solid phases for heterogeneous catalysis [21] are mainly of three types: soluble polymers (linear non cross-linked), cross-linked insoluble polymers and macroreticulated resins. In this work the macroporous resins were employed.

### *Macroporous resins*

The term ‘macroporous’ resin is used to indicate a class of polymers which have a permanent well-developed porous structure even at the solid state. [22]

If a polymerization of styrene-divinylbenzene (DVB) mixture is carried out with the co-monomer mixture in the presence of an appropriate organic solvent (*diluent* or *porogen*) at some appropriate level, then the internal structure (morphology) of the product resin can be very different to that of a gel-type resin. Removal of the porogen at the end of the polymerization can leave a heterogeneous and non-uniform matrix: some areas consist of impenetrable cross-linked and entangled polymer chains, other areas are devoid of polymer. Unlike gel-type polymers, the macroporous resins do not need to swell in a solvent to allow access to the interior because they possess a permanent network of pores whose dimension can be manipulated by the precise conditions used in the polymerization. When a good solvent is contacted with a macroporous resin, it can swell the polymer matrix in some extent as well as filling the pore volume. The swelling often occurs rapidly because the permanent pore structure gives fast access to the solvent throughout the whole resin. [21]

### ***1.4 Continuous flow system***

In recent years the synthesis of organic compounds using supported catalysts (PS) or reagents [23, 24] has been of great interest in flow systems. [25, 26, 27]

This approach represents a relatively new area of study in rapid progress and it promises to improve the ease, efficiency and automation of liquid-phase synthesis. The flow systems have several advantages over conventional batch processes.

1. the supported catalyst should have longer useful time because the physical damage due to the magnetic stirring is minimized.
2. they allow easy or no work-up at the end of the process.
3. the support does not need to be removed from the reaction medium and continuous production is possible.
4. the reaction conditions should be easily reproducible and the flow system leads to

automation.

There are three different possibilities of working in flow system:

**I)** Type I is constituted by a simple packed catalytic bed (powder or beads polymer) in a glass column that is equipped with a jacket for column heating and cooling. The reactant solution is introduced to the column by gravity feed or by pumping through a syringe or peristaltic pump. The elute flows through the column then is collected in a reservoir.

**II)** Type II is constituted by long syringe needles that pump the solution from the top into the bottom of a glass tube containing powdered or beads polymer. The product flow upwards or overflow through a side arm into a receiver or is pumped out from the top of the column.

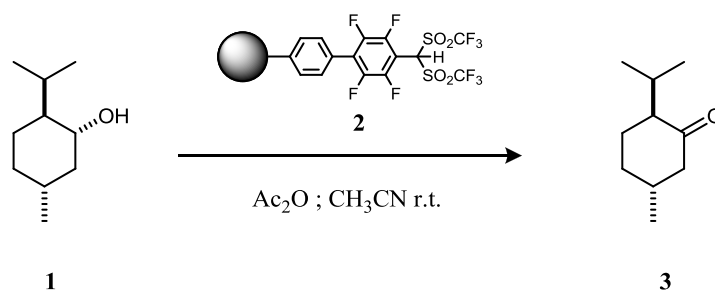
**III)** Type III uses a monolith that is tight to a plastic or glass cover. The solution generally is pumped down the column, and if it has the appropriate porosity and structure, the diffusion inside is smaller than with the Type I and II.

Together with the advantages above described, these systems show also drawbacks: for example it is well known that catalytic packed bed could promote the formation of preferential pathways for the mobile phase that decreases the catalyst accessibility and the productivity.

The first use of a supported catalyst in a solution phase system was almost certainly the use of column of acidic or basic ion-exchange resins. [28]

In Scheme 1 is reported an important example of organic reaction performed using supported super Brønsted acid (**2**) in flow system; the support is constituted by microporous 2% crosslinked polystyrene beads mixed with celite and packed into a 2 mL syringe. [29]

Many different reactions, such as ester formation, cyclic acetals synthesis, Mukaiyama aldol reaction, Sakurai-Hosomi reaction, and Mukaiyama-Michael addition reaction were performed achieving very good results. When a mixture of L-menthol and acetic anhydride in acetonitrile was passed once through the column over 1 hour at room temperature, the keton was formed in 99% yield. (Scheme 1).



**Scheme 1.** Continuous flow acid catalyzed oxidation of L-menthol.

There are specific studies of supported catalysts in flow system to produce enantioselective reactions [30, 31], for example the valerophenone was reduced to the corresponding alcohol using a polymer supported chiral aminoalcohol in a fluid-bed reactor.

In further similar experiments, by pumping solutions of aldehyde and diethylzinc into the reactor at a rate of 6 ml/h, the corresponding alcohol was obtained in 95% yield and 97% *ee*.

Annis and Jacobsen studied the hydrolytic kinetic resolution of epoxides (39% yield, *ee* 94%) by using a chiral catalyst supported on silica gel. The column could be regenerated successfully.

The Fréchet group performed different types of reactions by grafting the functionalities to polymer tubular monoliths with excellent flow properties. [32] Kirschning developed new monolithic material (polymer/glass) composites [33] and a new technique, named Passflow, applied to microreactor devices.

Ideally a catalytic continuous-flow reaction could go to completion with only one pass through the column. However most of the organic reactions are quite slow and require low flow rates in order to increase the residence time. In many cases this goal is achieved by recycling the reaction mixtures several times through the column reactor.



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## 2 Silica supported sulfonic acids

### 2.1 *Heterogeneous acid catalysis*

Brønsted and Lewis acids are the most important and common catalysts. [1] Many organic reactions such as aldol condensations, nucleophilic additions, hydrolysis, acylations, etc. are catalyzed by these acids. However, the use of soluble acids or corrosive mineral acids is associated with a great number of environmental and economical problems. Indeed, huge amounts of catalyst are needed, and troublesome work-up steps are also needed when Lewis acids are utilized. Moreover, usually more than stoichiometric amount of these acids is required, and a huge quantity of anions (specially chloride) is released in aqueous medium. The separation from the reaction mixture is very difficult and some related problems should be taken in account, such as the need of neutralization, the impossibility of the catalyst reuse and the reactor corrosion. It would be very useful to have a solid acid that can be separated by filtration and reused. [2]

Zeolites in their  $H^+$  form are the most widely used solid acids in petrochemistry [3] and gas phase reactions. Zeolites working in gas-phase, continuous-flow processes are the typical examples of non-toxic, reusable, highly selective solid catalysts. However, when moving from the scale of petrochemistry to fine chemistry and liquid phase reactions, zeolites are not the universal acid catalysts.

The small pore size available ( $<1.0$  nm even for the so called large-pore zeolites) that imposes a severe restriction for the accessibility of larger molecules to the internal surface of the catalyst, is probably the main drawback of zeolites.

In order to overcome the problem of pore size, the synthesis of mesoporous materials by Mobil researchers constituted a breakthrough due to the possibility of opening the catalysis by solid acids to the large molecules typical of fine chemistry. [4] The most widely used mesoporous silica is known as MCM-41. However, it was realized soon that the use of mesoporous silicas and aluminosilicates as solid acids will not meet the initial expectations, mainly due to the low acid strength of their acid sites. An alternative to the use of the mild acid sites of their aluminosilicate framework is to employ these mesoporous silicas as supports to which strong acid sites can be

covalently anchored. Sulfonic acids are organic compounds that exhibit an acid strength comparable to those of sulfuric and benzenesulfonic acids, strong acids frequently used in organic solvents. [5] Ford et al. prepared a strong acid catalyst consisting of silica containing alkanesulfonic acid groups. [6] The synthesis of silica supported sulfonic acid was achieved by anchoring 3-mercaptopropyltrialkoxysilane to the silanol groups of amorphous silica followed by oxidation of the terminal mercapto groups to sulfonic acid with hydrogen peroxide.

Subsequently, other groups have introduced variations in the preparation of this type of MCM-41-SO<sub>3</sub>H materials. [7,8,9] These improvements have focused on the synthesis of MCM-41-SO<sub>3</sub>H in a single step (instead of preparing a MCM-41 to which the alkylmercapto group is anchored), optimization of the mercapto/sulfonic oxidation step, control of the MCM-41 pore size, protection of the residual silanol groups, etc. The use of different structure-directing agents different from cetyltrimethylammonium halides leads to the formation of other mesoporous silicas besides MCM-41, such as those with structure of SBA-15 and SBA-12 using Pluronics 123 and Brij-76 as surfactant, respectively. [10] Analogous to alkanesulfonic acids, arenesulfonic acids covalently anchored to mesoporous silicas have also been prepared. [6] They can be obtained by sulfonation of phenyl groups linked to silica frameworks of MCM-41 or SBA-15. In many respects, particularly for those containing arenesulfonic groups, MCM-41-SO<sub>3</sub>H can be considered as the inorganic counterpart of polystyrenes and related polymers having phenylenesulfonic groups, a widely-used example of them being Amberlyst. [11] There are many acid-catalyzed reactions, including some large-scale industrial processes, that can be promoted using polystyrene bearing sulfonic groups. [12] The room temperature addition of alcohols to isobutene to form *tert*-butyl ethers used as isooctane number boosters is an example of an industrial process that can be performed with polyarenesulfonic resins. [13]

With respect to polymeric arenesulfonic acids, the obvious advantage of MCM-41-SO<sub>3</sub>H, and also of amorphous silica, is the large surface area of these materials (~1000 m<sup>2</sup>g<sup>-1</sup>) compared to cross-linked polystyrene (~50 m<sup>2</sup>g<sup>-1</sup>), this factor being reflected in a higher catalytic activity as a result of the easier accessibility of substrates to the acid sites. [14]

The present work deals with the synthesis and evaluation of the catalytic activity of some supported sulfonic acids as heterogeneous and reusable catalysts in different organic reactions showing synthetic interest.

### 2.2 *Materials and methods*

All the reagents were used as received without further purifications. Solvents were distilled under nitrogen and dried before use. Before functionalisation the siliceous supports were dried at 300 °C for 5 hours.

H<sub>2</sub>O (bidistilled), D<sub>2</sub>O (Euriso-top; 99.90%D) were purified in vacuo and rendered gas-free by several “freeze-pump-thaw” cycles to be employed in the IR spectroscopic measurements.

The amorphous silica used was the commercial Kieselgel 60 (KG-60) purchased from Merck. MCM-41 mesoporous silica was prepared, according to the procedure reported in the literature [15], by mixing, at room temperature and under vigorous stirring, 25% sodium silicate solution, tetramethylammonium hydroxide, 25% cetyltrimethylammonium chloride solution and water, (the resulting gel composition was: SiO<sub>2</sub>•0.39 Na<sub>2</sub>O•0.25 CTMACl•0.24 TMAOH•50.7) and aging at 110 °C for 4 days. The silica-alumina (SA) support was prepared by mixing and refluxing tetraethylorthosilicate (TEOS) (1.2 mL, 5.4 mmol), aluminium triisopropoxide (0.7 mL, 3.5 mmol) and EtOH (7.5 mL); to this homogeneous solution, H<sub>2</sub>O (130.0 mmol) and NH<sub>4</sub>OH (20.0 mmol) were added. The solution was maintained under reflux few minutes until gelation, the gel was dried at 70 °C and subsequently calcined at 400 °C for 72 h [16].

Gas-chromatographic analyses were accomplished on a TraceGC ThermoFinnigan instrument with a fused silica capillary column SPB-20 from Supelco (30 m x 0.25 mm).

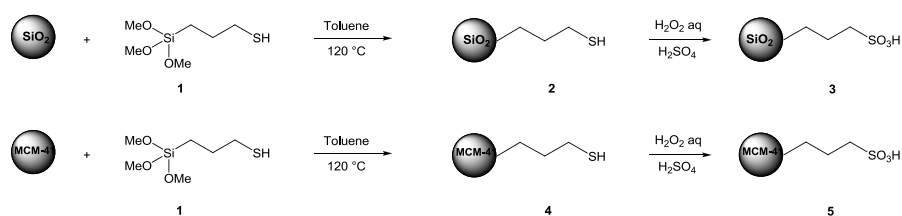
N<sub>2</sub> adsorption-desorption isotherms, obtained at 77 K on a Micromeritics PulseChemiSorb 2705, were used to determine specific surface areas (S.A.<sub>BET</sub>). Before each measurement the samples were outgassed at 383 K for 1 h.

The surface acidity and surface area of all catalysts were determined by a reported titration method [17] and by the BET method [18] respectively (Table 1).

### 2.3 Catalyst synthesis

The following materials were prepared according to well known literature procedures, with slight modifications. A new method was developed only for the preparation of the silica supported 4-propoxybenzensulfonic acid.

$SiO_2-(CH_2)_3-SO_3H$  and  $MCM-41-(CH_2)_3-SO_3H$  (method A) (Scheme 1): [6] the siliceous support (amorphous KG-60 silica or mesoporous MCM-41 silica) (8 g) has been refluxed under stirring for 24 h with (3-mercaptopropyl)trimethoxysilane (MPTS) (1.15 ml; 6.1 mmol) in toluene (120 ml) and the resulting supported propylmercaptane has been oxidized to propanesulfonic acid by treatment with 30% aq  $H_2O_2$  (100 ml; 1 mol) for 24 h under stirring at rt, adding few drops of concentrated sulfuric acid after 12 h.



**Scheme 1.** Preparation of propanesulfonic acids tethered onto silica (method A).

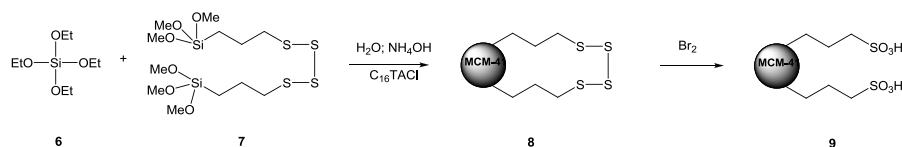
$MCM-41-(CH_2)_3-SO_3H$ : [19] (method B) (Scheme 2)  $C_{16}TACl$  solution in water (20.9 ml; 25 wt%) was added to a solution of  $NH_4OH$  (31.7 ml; 30 wt%) and the mixture was stirred for 30 min in a closed polyethylene bottle. A mixture of silane bis(3-triethoxysilylpropyl)-tetrasulfide (TESPT) and tetraethoxysilane (TEOS) (1.49 ml; 3.12 ml), was slowly added to the base/surfactant solution with slow stirring. After stirring for 30 min, the solutions were aged at 80 °C for 4 days in a closed polyethylene bottle.

The white powder produced was collected by filtration, washed thoroughly with water, and air-dried under ambient conditions.

The solid material (2.5 g) was then stirred for 48 h in a refluxing solution of 10 g  $HCl$  (37 wt%) and 70 g of methanol to remove the surfactant. For ion exchange of the surfactant, the sample was stirred in a refluxing solution of 1 g  $NaCl$  and 100 g of ethanol. The solid material was filtered off, washed with water (3 x 50 ml), methanol (3 x 25 ml) and ethyl acetate (2 x 25 ml).

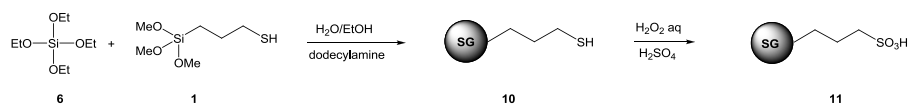
## 2. Silica supported sulfonic acids

The solvent-extracted sample (2.5 g) was kept under vacuum at 150 °C for 2 days, and then treated in refluxing CH<sub>2</sub>Cl<sub>2</sub> (150 ml) with Br<sub>2</sub> (1.3 ml; 25 mmol) for 4 h. The product was isolated on a Büchner funnel and washed with dichloromethane (3 x 25 ml).



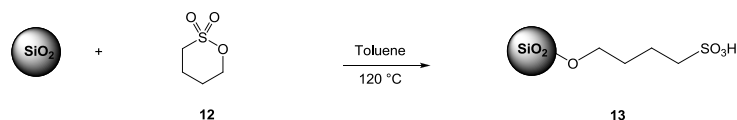
**Scheme 2.** Preparation of propanesulfonic acids tethered onto MCM-41 silica (method B).

*SG-(CH<sub>2</sub>)<sub>3</sub>-SO<sub>3</sub>H*: [20] (Scheme 3) in a beaker containing EtOH (20 ml) and H<sub>2</sub>O (25 ml), MPTS (1.9 ml; 10.1 mmol) and tetraethoxysilane (TEOS) (8.9 ml; 40 mmol) were added together with dodecylamine (2.54 g; 13.1 mmol) as porogenic compound [24]. When the mixture began to become opalescent, the stirrer was stopped and the formed gel aged for 24 h at rt in the same container covered with a filter paper. The so obtained white monolith was then finely ground in a mortar, washed in a Soxhlet apparatus with EtOH at reflux for 24 h, and the resulting supported propylmercaptane has been oxidized to propanesulfonic acid by treatment with 30% aq H<sub>2</sub>O<sub>2</sub> (100 ml; 1 mol) for 24 h under stirring at rt, adding few drops of concentrated sulfuric acid after 12 h.



**Scheme 3.** Preparation of propanesulfonic acid tethered onto silica via Sol-Gel (SG) method.

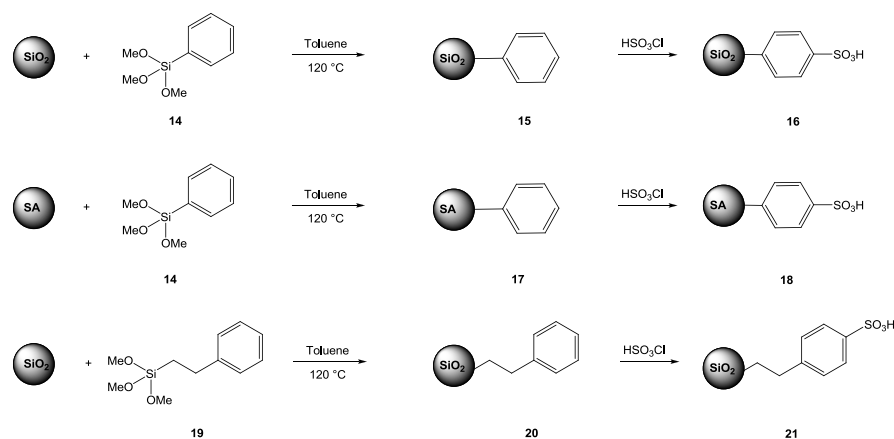
*SiO<sub>2</sub>-(CH<sub>2</sub>)<sub>4</sub>-SO<sub>3</sub>H*. [21] (Scheme 4) The amorphous silica (8 g) has been refluxed with 4-hydroxy-1-butananesulfonic acid  $\delta$ -sultone (2,04 g; 15 mmol) under stirring for 6 hours in toluene (120 ml). After that the solid was filtered off and washed with toluene (3 x 20 ml) and acetone (3 x 20 ml).



**Scheme 4.** Preparation of butanesulfonic acid tethered onto amorphous silica.

## 2. Silica supported sulfonic acids

$SiO_2-(C_6H_4)-SO_3H$ ,  $SA-(C_6H_4)-SO_3H$  and  $SiO_2-(CH_2)_2-(C_6H_4)-SO_3H$ . [6] (Scheme 5) The solid material (silica or SA) (8.0 g) was refluxed under stirring for 24 h with phenyltriethoxysilane (2.0 mL, 8.3 mmol) or phenylethyltrimethoxysilane (1.8 mL, 8.3 mmol) in toluene (120 mL), filtered and washed with toluene. The supported phenyl group was then sulfonated by refluxing the functionalized material with chlorosulfonic acid (10 mL, 150 mmol) under stirring for 4 h in 1,2-dichloroethane (60 mL). The solid material was then recovered by filtration and washed carefully with 1,2-dichloroethane (3 x 20 mL), acetone (3 x 20 mL) and water (3 x 50 mL).

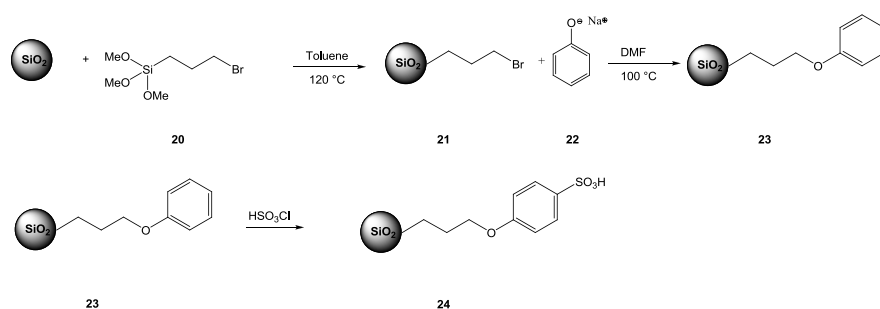


**Scheme 5.** Preparation of arylsulfonic acid tethered onto silica or silica-alumina.

$SiO_2-(CH_2)_3-O-(C_6H_4)-SO_3H$ . (Scheme 6) A mixture of amorphous silica gel (2.0 g) and bromopropyltrimethoxysilane BPTS (0.76 mL, 4.0 mmol) in toluene (80 mL) was refluxed, under stirring, for 24 h. The resulting silica supported 3-bromopropane was recovered by filtration and washed with toluene (3 x 50 mL). A mixture of this material (2.00 g) and sodium phenoxide (0.60 g, 6.0 mmol) in DMF (100 mL) was heated to 100 °C under stirring for 24 h. Afterwards the material was filtered and washed with DMF (3 x 20 mL) and acetone (3 x 20 mL). Finally a mixture of this material (2.0 g) and chlorosulfonic acid (4 mL, 60 mmol) in 1,2-dichloroethane (60 mL) was stirred for 4 h at reflux. The catalyst was recovered by filtration, washed with 1,2-dichloroethane (3 x 20 mL), acetone (3 x 20 mL) and water (3 x 50 mL).

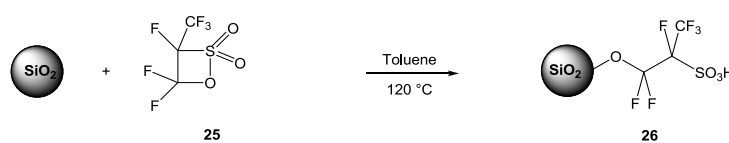


## 2. Silica supported sulfonic acids



**Scheme 6.** Preparation of 4-propoxybenzenesulfonic acid tethered onto silica.

$SiO_2-CF_2-CF-(CF_3)-SO_3H$ : (Scheme 7) [21] the amorphous silica (8 g) has been refluxed with 1,2,2-trifluoro-2-hydroxy-1-(trifluoromethyl)ethanesulfonic acid  $\beta$ -sultone (3,45 g; 15 mmol) under stirring for 6 hours in toluene (120 ml). After that the solid was filtered off and washed with toluene (3 x 20 ml) and acetone (3 x 20 ml).



**Scheme 7.** Preparation (2-trifluoromethyl)-perfluoroethanesulfonic acid tethered onto silica.

All the catalysts were carefully washed and dried for 24 h at 100 °C before use.

### 2.4 Catalyst characterisations

#### 2.4.1 Surface properties

Nitrogen adsorption-desorption measurements were performed at liquid nitrogen temperature (-196 °C) with an ASAP 2010 apparatus of Micromeritics. Before each measurement, the samples (0.1 g) were outgassed first at 100 °C for 12 h at  $5 \cdot 10^{-3}$  Torr and then at room temperature for 2 h at  $0.75 \cdot 10^{-6}$  Torr. The  $N_2$  isotherms were used to determine the specific surface areas through the BET equation ( $S.A._{BET}$ ), results are reported in Table 1.

The surface acidity was determined by a reported titration method [17] (Table 1): the concentration of acid sites of catalyst was determined by titration: 0.5 g of the

## 2. Silica supported sulfonic acids

catalyst sample was added to 50 mL of NaCl solution (200 g/L) and stirred at room temperature. The ion exchange between H<sup>+</sup> and Na<sup>+</sup> was allowed to proceed for 24 h. The catalyst was filtered off and washed with distilled water, then the mixture was titrated with 0.01 N NaOH solution using phenolphthalein as pH indicator, results are reported in Table 1.

**Table 1.** Surface area and surface acidity of the tested catalysts.

Catalyst	S.A. <sub>BET</sub> <sup>a</sup> (m <sup>2</sup> g <sup>-1</sup> )	Surface acidity (meq H <sup>+</sup> /g)
SiO <sub>2</sub>	540	-
MCM-41	1240	-
SiO <sub>2</sub> -(CH <sub>2</sub> ) <sub>3</sub> -SO <sub>3</sub> H ( <b>3</b> )	510	0.20
MCM-41-(CH <sub>2</sub> ) <sub>3</sub> -SO <sub>3</sub> H (A) ( <b>5</b> )	1100	0.42
SiO <sub>2</sub> -(CH <sub>2</sub> ) <sub>4</sub> -SO <sub>3</sub> H ( <b>9</b> )	470	0.37
SG-(CH <sub>2</sub> ) <sub>3</sub> -SO <sub>3</sub> H ( <b>11</b> )	340	0.32
MCM-41-(CH <sub>2</sub> ) <sub>3</sub> -SO <sub>3</sub> H (B) ( <b>13</b> )	970	2.53
SiO <sub>2</sub> -(C <sub>6</sub> H <sub>4</sub> )-SO <sub>3</sub> H ( <b>16</b> )	445	0.65
SA-(C <sub>6</sub> H <sub>4</sub> )-SO <sub>3</sub> H ( <b>18</b> )	371	0.90
SiO <sub>2</sub> -(CH <sub>2</sub> ) <sub>2</sub> -(C <sub>6</sub> H <sub>4</sub> )-SO <sub>3</sub> H ( <b>21</b> )	293	1.20
SiO <sub>2</sub> -(CH <sub>2</sub> ) <sub>3</sub> -O-(C <sub>6</sub> H <sub>4</sub> )-SO <sub>3</sub> H ( <b>24</b> )	415	0.70
SiO <sub>2</sub> -CF <sub>2</sub> -CF-(CF <sub>3</sub> )-SO <sub>3</sub> H ( <b>26</b> )	382	1.90
Amberlyst-15	53	4.70
Nafion NR-50	< 0.1	0.80

<sup>a</sup> Specific BET surface area

The specific pore volume (Vs) was calculated at p/p<sup>o</sup> = 0.98, and pore size distributions were calculated from the BJH [22] method calculated from the adsorption branch, these parameters were measured only for some catalysts, in order to distinguish between materials with different support or spacer, results are reported in Table 2.

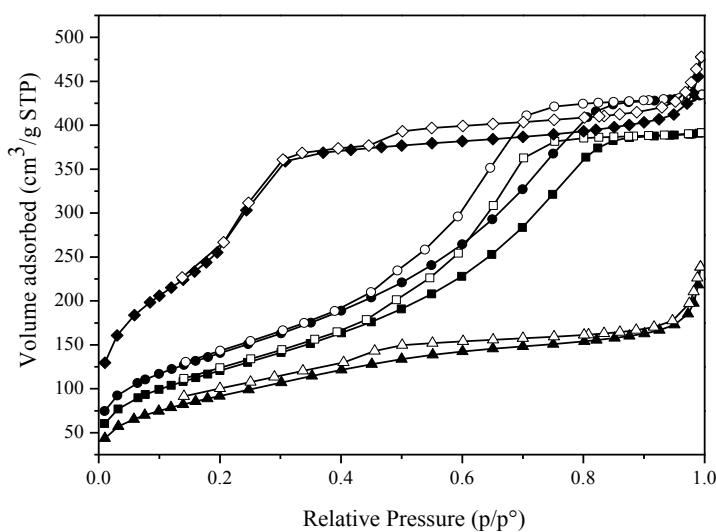
**Table 2.** Surface area and surface acidity of the tested catalysts.

Entry	Catalyst	$V_s^a$ ( $\text{cm}^3 \text{g}^{-1}$ )	$D_p^b$ (nm)
1	SiO <sub>2</sub>	0.80	4.0
2	MCM-41	1.13	2.5
3	SiO <sub>2</sub> -(CH <sub>2</sub> ) <sub>3</sub> -SO <sub>3</sub> H ( <b>3</b> )	0.67	4.7
4	MCM-41-(CH <sub>2</sub> ) <sub>3</sub> -SO <sub>3</sub> H ( <b>5</b> )	0.68	2.2
5	SG-(CH <sub>2</sub> ) <sub>3</sub> -SO <sub>3</sub> H ( <b>11</b> )	0.31	-
6	SiO <sub>2</sub> -(C <sub>6</sub> H <sub>4</sub> )-SO <sub>3</sub> H ( <b>16</b> )	0.60	5.3
7	Amberlyst-15	0.40	30.0

<sup>a</sup> Specific pore volume at P/P<sub>0</sub>=0.98

<sup>b</sup> Diameter of pores according to the maximum of the BJH pore size distribution

The N<sub>2</sub> adsorption–desorption isotherms of the functionalized mesoporous silica materials are shown in Figure 1. The isotherms of SiO<sub>2</sub>-(CH<sub>2</sub>)<sub>3</sub>-SO<sub>3</sub>H (**3**) and SiO<sub>2</sub>-(C<sub>6</sub>H<sub>4</sub>)-SO<sub>3</sub>H (**16**) materials are classified as type IV characteristic of the mesoporous materials [23]. Pore size distribution of these samples (Figure 2, Table 2), estimated by employing the BJH method, indicates the existence of uniform large mesopores. The MCM-41-(CH<sub>2</sub>)<sub>3</sub>-SO<sub>3</sub>H (**5**) exhibits a reversible type IV isotherm with a narrow hysteresis loop at  $p/p^\circ > 0.4$  and a sharp pore filling step at  $ca. 0.2 < p/p^\circ < 0.3$ , characteristic of uniform pores. The pore size distribution is very sharp and centred at 2.2 nm. The total pore volume  $V_s$  of these materials (Table 2) calculated from the N<sub>2</sub> amount adsorbed at  $p/p^\circ$  close to the saturation vapour pressure ( $p/p^\circ=0.98$ ) is almost the same value (about  $0.6 \text{ cm}^3 \text{ g}^{-1}$ ). Very different is the N<sub>2</sub> adsorption–desorption isotherm of the SG-(CH<sub>2</sub>)<sub>3</sub>-SO<sub>3</sub>H (**11**) sample. The material has a disordered porosity with a BET surface area and total pore volume about half of the other samples.

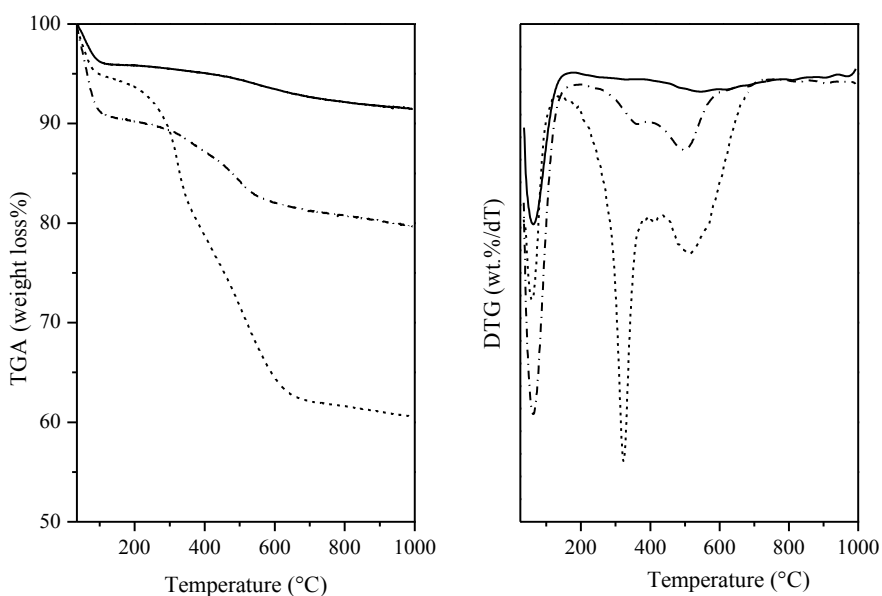


**Figure 1.** N<sub>2</sub> adsorption (full symbol) – desorption (empty symbol) isotherms of the functionalized silica materials MCM-41-(CH<sub>2</sub>)<sub>3</sub>-SO<sub>3</sub>H **5** (◆), SiO<sub>2</sub>-(CH<sub>2</sub>)<sub>3</sub>-SO<sub>3</sub>H **3** (●), SiO<sub>2</sub>-(C<sub>6</sub>H<sub>4</sub>)-SO<sub>3</sub>H **16** (■) and SG-(CH<sub>2</sub>)<sub>3</sub>-SO<sub>3</sub>H **11** (▲).

#### 2.4.2 Thermogravimetric and Differential Thermal Analyses

Thermogravimetric and Differential Thermal Analyses (TGA-DTG) were carried out with a Netzsch STA 409 instrument. Typically, 10 mg of sample were heated in a crucible made of alumina, at constant rate (10 °C/min) in a stream of air from 30 to 1000 °C. The temperature of maximum weight loss were obtained by derivative TGA (DTG) plots.

The thermal stability of these materials and the percentages of anchoring of the organic group were determined by means of TGA. Figure 2 shows the TGA-DTG profile of SiO<sub>2</sub>-(CH<sub>2</sub>)<sub>3</sub>-SO<sub>3</sub>H (**3**), MCM-41-(CH<sub>2</sub>)<sub>3</sub>-SO<sub>3</sub>H (**5**) and SG-(CH<sub>2</sub>)<sub>3</sub>-SO<sub>3</sub>H (**11**) samples. Desorption of physisorbed solvent was observed below 100 °C in all the synthesized organofunctionalized samples.

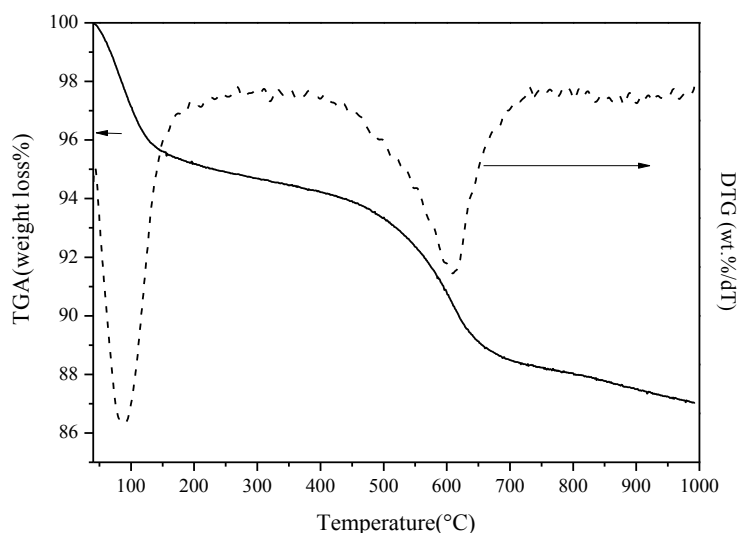


**Figure 2.** Thermogravimetric (left) and differential thermogravimetric (right) curves of  $\text{SiO}_2\text{-(CH}_2\text{)}_3\text{-SO}_3\text{H}$  (**3**) (solid line),  $\text{MCM-41-(CH}_2\text{)}_3\text{-SO}_3\text{H}$  (**5**) (dash-dot line) and  $\text{SG-(CH}_2\text{)}_3\text{-SO}_3\text{H}$  (**11**) (short dash line) samples.

The  $\text{MCM-41-(CH}_2\text{)}_3\text{-SO}_3\text{H}$  (**3**) DTG profile shows a large shoulder centred at about  $360^\circ\text{C}$  probably due to the decomposition of the supported propylmercaptane not oxidized to propylsulfonic acid by treatment with  $\text{H}_2\text{O}_2$  [24]. The decomposition of the propylsulfonic acid groups seems to occur in a large range of temperature as evidenced by the broad DTG peak, which coincides with an exothermic DSC peak, centered at about  $510^\circ\text{C}$ . Two-step weight loss, at  $320^\circ\text{C}$  and  $512^\circ\text{C}$ , both exothermic, was observed in the siliceous material prepared via sol-gel,  $\text{SG-(CH}_2\text{)}_3\text{-SO}_3\text{H}$  (**11**), the former due the decomposition of both the organic compounds that are part of the silica network and the not oxidized propylmercaptane, and the latter to the decomposition of the propylsulfonic acid groups.

From the TGA curve of the siliceous samples containing the organic alkylsulfonic group  $\text{-(CH}_2\text{)}_3\text{-SO}_3\text{H}$  (Figure 2) was calculated a weight loss, relative to the thermal decomposition of the tethered groups, always higher than that obtainable from the titration of the materials. The different data were ascribed to the incomplete oxidation of supported propylmercaptane to propylsulfonic acid [25].

The TGA-DTG profiles of the  $\text{SiO}_2\text{-(C}_6\text{H}_4\text{)-SO}_3\text{H}$  organic-inorganic hybrid material (Figure 3) clearly show that most of the arylsulfonic acid groups remained anchored to the silica matrix up to 610 °C which indicate the higher thermal stability of the  $\text{-(C}_6\text{H}_4\text{)-SO}_3\text{H}$  groups tethered to  $\text{SiO}_2$  respect to the  $\text{-(CH}_2\text{)}_3\text{-SO}_3\text{H}$  ones [26]. From the same TGA curve was calculated a 9% (w/w) weight loss relative to the thermal decomposition of the arylsulfonic acid groups accompanied by an exothermic DSC peak. In this case TGA results are quite in agreement with the surface acidity data obtained from titration method probably due to the different preparation approach. These results are also in agreement with previous studies carried out on aminopropyl silicas [27], and reflect the high thermal stability of the materials also in an oxidative environment.



**Figure 3.** Thermogravimetric (TGA - solid line) and differential thermogravimetric (DTG - dotted line) curves of the  $\text{SiO}_2\text{-(C}_6\text{H}_4\text{)-SO}_3\text{H}$  (**16**) sample.

### 2.4.3 Infrared analyses

Infrared spectra of the catalysts were performed in transmission mode on powders pressed in self-supporting pellets (“optical thickness” in the 8-10  $\text{mg}\cdot\text{cm}^{-2}$  range) and placed in a quartz IR cell equipped with KBr windows. The IR cell was connected to a conventional vacuum line (residual pressure  $p \leq 10^{-5}$  Torr), allowing adsorption/desorption experiments to be carried out in situ. A Bruker Vector 22

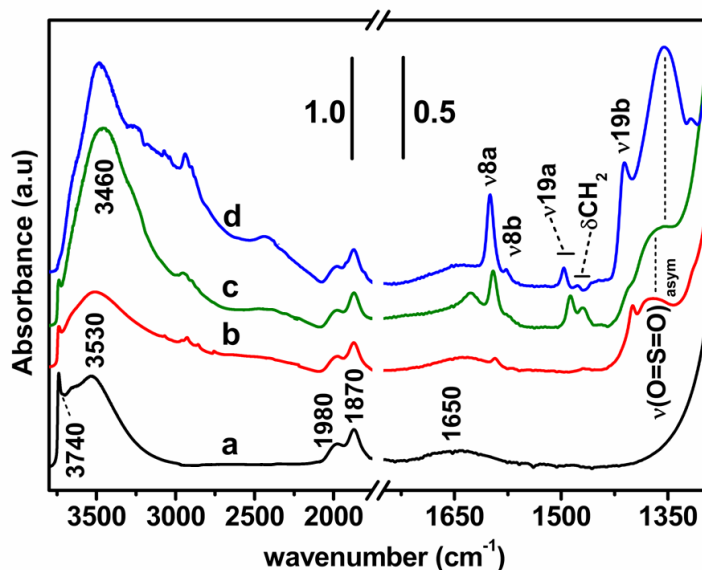
spectrometer was employed for spectra collection in the Mid-IR region, and a Jasco 6100 one for selected measurements extended to the Near-IR. In both cases, resolution was 4 cm<sup>-1</sup>, and a DTGS detector was employed.

All spectra were baseline corrected to remove the contribution of light scattering and were normalized with respect to the intensity of the signals at 1980 and 1870 cm<sup>-1</sup> due to the combinations of bulk framework modes [28] in order to render differences in intensity independent of differences in the thickness of the pellets.

Mid-IR spectra are reported down to 1250 cm<sup>-1</sup>, that is the onset of the cut-off due to the fundamental absorptions of the siliceous lattice, that rendered opaque the samples at lower frequency, except for a narrow region (950-850 cm<sup>-1</sup> the so-called “silica window”). However, pellets of the catalysts appeared too fragile to be produced so thin to exhibit a reasonable transparency in such range.

IR spectra were recorded for catalysts **16**, **21**, **24**, these materials were chosen for IR analyses due to the presence of both alkyl and aryl components in the organic part of the supported silica.

Figure 4 shows the IR spectra recorded after outgassing at beam temperature (ca. 50 °C) for 1 h. Such treatment resulted in the complete desorption of water molecules initially adsorbed from air moisture, as witnessed by the essential invariance of the signal at ca. 1650 cm<sup>-1</sup> after subsequent exchange with D<sub>2</sub>O (inset). Actually, adsorbed water molecules are expected to contribute to that IR band through their deformation ( $\delta$ ) mode, and this contribution should be depleted after exchange with D<sub>2</sub>O, and substituted by the  $\delta$ D<sub>2</sub>O signal occurring at ca. 1200 cm<sup>-1</sup> (below the cut-off of the sample).



**Figure 4.** IR spectra of samples outgassed at beam temperature (ca. 50 °C) for 1 h: a) bare silica; b) catalyst 16; c) catalyst 24; d) catalyst 21.

Focusing on the spectral pattern of the bare SiO<sub>2</sub> support (curve a), on the basis of well assessed literature data [28], the various components can be assigned as follows

- narrow peak at 3740 cm<sup>-1</sup>: silanols in weak (van der Waals) interaction with neighbours Si-OH;
- shoulder at 3710 cm<sup>-1</sup>: terminal dangling OH of chains of interacting silanols;
- subband at 3660 cm<sup>-1</sup>: outer/inner silanols involved in weak hydrogen bonds;
- broad band at 3530 cm<sup>-1</sup>: silanols involved in stronger hydrogen bonds;
- signals at 1980, 1870 and 1650 cm<sup>-1</sup>: combinations (the first two) and overtone (the third one) of fundamental silica vibrational modes occurring at lower frequency.

As expected, the last three signals remained unaffected by the tethering of the organic moieties (curves b-d), whereas the peak at 3740 cm<sup>-1</sup> decreased in intensity, until depletion, as the amount of supported acids increases, and the series of absorptions at lower frequency were overcome by progressively more intense, broad and complex pattern spread over the 3700-2000 cm<sup>-1</sup> range. It is worthing to note that silanols present on the surface of the support can be involved in two kinds of events as a consequence of the functionalization with sulfonic acid molecules: i) consumption by reaction with the alcoxysilanes; ii) H-bond interaction with the



sulfonic groups, with related frequency downshift and increase in intensity of the  $\equiv\text{SiO-H}$  stretching band.

Of course, the other consequence of the functionalization of the support was the appearance of a series of bands below  $1650\text{ cm}^{-1}$ . For the sake of clarity, the assignment of these signals will be reported separately for the alkyl + aryl parts and for the sulfonic group.

*Bands due to alkyl + aryl parts.* All catalysts (curves b-d) exhibited bands at ca.  $1600$  and  $1410\text{ cm}^{-1}$ , that should be related to 8a and 19b modes (in the Wilson notation) [29, 30, 31] of the aromatic ring (Ar, in the following) [32, 33, 34], that can produce absorptions significantly more intense than their 8b and 19a partner modes [35, 36]. These latter are responsible of the components present at  $1580\text{ cm}^{-1}$  (8b mode) in the spectrum of catalyst **21** (curve d) and at ca.  $1490\text{ cm}^{-1}$  (19a mode) in the spectra of catalysts **21** and **24** [32, 33]. Noticeably, in the case of the catalyst **16** the 8a band appeared significantly weaker in intensity than expected with respect the other two catalysts on the basis of the relative amount of supported aromatic species. It can be considered that this band arises from a vibration in which the main dipole moment change is produced by the movements of the substituents on opposite sides of the ring acting in opposition, and then in the presence of one polar substituent or of two substituents with different polarity they should produce quite intense band [35].

Actually, in catalyst **16** the substituents on the aromatic ring are sulfonic and  $-\text{Si}(-\text{OSi}-)_3$  groups, exhibiting a significant different polarity. However, the  $-\text{Si}(-\text{OSi}-)_3$  is in turn directly linked to the support by O-Si bonds. The consequent possible coupling along the resulting (Ar)-Si-(OSi)<sub>3</sub>-(support) oscillators could affect the displacement of the Si atom bound to the aromatic ring, with a consequent effect on the dipole moment change. The same argument should hold for the 19a mode, in which the dipole-moment change is produced by the movements of the substituents on opposite sides of the ring, but moving in the same direction.

Furthermore, in the case of catalyst **24** a weak and broader component is present at  $1630\text{ cm}^{-1}$ , that can be due to the overtone of the aromatic 10a  $\gamma\text{CH}$  mode [32], the fundamental producing the strong band, expected around  $815\text{ cm}^{-1}$ , characteristic of *para*-disubstituted benzene rings [33].

As for the C-H stretching modes, they are responsible for the weak features in the 3100-3000  $\text{cm}^{-1}$  range.

The methylene groups of the alkyl links connecting the aromatic rings of catalysts **21** and **24** to the support produced the typical series of bands expected for their stretching modes in the 3000-2850  $\text{cm}^{-1}$  range, with the  $\nu_{\text{asym}}$  mode splitted in two components (at 2940 and 2900  $\text{cm}^{-1}$  in the spectrum of catalyst **21**, curve d) by Fermi resonance with the overtone of the deformation mode, then expected around 1460  $\text{cm}^{-1}$ . Actually, weak bands are present at 1470 and 1475  $\text{cm}^{-1}$  for catalyst **21** (curve d) and **24** (curve c), respectively. In particular, in the case of catalyst **21**, the weak component at 1475  $\text{cm}^{-1}$  should be due to the  $-\text{CH}_2-$  group linked to the support, as the other, because of the linking to the aromatic ring, should produce an absorption near 1420  $\text{cm}^{-1}$ , likely contributing to the onset of the 19b aromatic mode band.

No specific signals due to Ar-Si, Ar-C, Ar-O bonds were observed, because located below the limit of transparency of the self-supported pellet employed in this study [33, 37].

*Bands due to the sulfonic group.* The low frequency region of the spectra of the three catalysts is dominated by a broad band in the 1390-1325  $\text{cm}^{-1}$  range, assignable to the antisymmetric stretching mode of the O=S=O moiety [38]. Actually, the maximum of this band appeared located at ca. 1370  $\text{cm}^{-1}$  for catalyst **16** (curve b) and at 1355  $\text{cm}^{-1}$  for catalyst **21** (curve d). This is the maximum position also in the case of catalyst **24**, with a poorly resolved shoulder at ca. 1370  $\text{cm}^{-1}$  (curve c). The overall trend suggests that the  $(\text{O}=\text{S}=\text{O})_{\text{asym}}$  mode can monitor the interaction of the sulfonic group with at least two types of local environment. As for the sulphurylic symmetric stretching mode, it should produce a band at ca. 1100  $\text{cm}^{-1}$ , well below the limit of transparency of the samples [38].

However, the information on the sulfonic groups are extended by the presence of the spectral features due to the SO-H stretching mode, occurring in the high frequency region. Focussing on the comparison between the bare support (curve a) and catalyst **16** (curve b), it can be noticed that as a consequence of the surface functionalization, beside the decrease in intensity of the sharp peak at 3740  $\text{cm}^{-1}$ , the rest of the  $\nu\text{OH}$  pattern is constituted by an asymmetric absorption with maximum similar in position (3510  $\text{cm}^{-1}$ ) and intensity of that present for the bare silica (3530  $\text{cm}^{-1}$ ), and a tail

extended down to  $2800\text{ cm}^{-1}$ . This absorption should result from the superposition of subbands due to O-H stretching of sulfonic groups and silanols. The appearance of the low frequency tail suggests the occurrence of a H-bond interaction between SO-H (expected to act as a H-bond donor) and SiOH (expected to act as a H-bond acceptor). However, the supported acid molecules synthesised starting from phenyltriethoxysilane should be oriented with the sulphuric group pointing away from the support. Thus, the supposed interaction might involve acid molecular moieties formed in pores of the silica support, where silanols properly located on the facing pore wall could be present. Of course the presence of sulfonic groups involved in weaker H-bond interaction cannot be excluded, and, if present, they should contribute to the part of the asymmetric band close to the maximum at  $3510\text{ cm}^{-1}$ . Vice versa, significant amount of sulfonic groups not involved in any interaction should be negligible, as, on the basis of spectra of species entrapped in inert matrices [39] and of theoretical calculations [40], they should absorb at ca.  $3560\text{ cm}^{-1}$ . Focussing on catalyst **24**, the  $3740\text{ cm}^{-1}$  peak appeared slightly less intense, whereas the band at lower frequency, with maximum now located at  $3460\text{ cm}^{-1}$ , exhibited a significant increase in intensity, accompanied by the appearance of a shoulder at ca.  $3250\text{ cm}^{-1}$  and a partly resolved subband at ca.  $2400\text{ cm}^{-1}$ , and a further broadening toward lower frequency, tailing down to ca.  $2100\text{ cm}^{-1}$ . Such behaviour monitors the occurrence of stronger H-bond interactions, and the pattern appears typical of the occurrence of a Fermi resonance between overtones of low frequency bending modes, with the continuous distribution of levels resulting from the coupling of  $\nu(\text{A-H}\cdots)$  and  $\nu(\text{AH}\cdots\text{B})$  modes (where A and B represent H-donor and H-acceptor groups, respectively) [41, 42]. In the present case, the role of H-donor is played by the sulphuric groups, whereas the oxygen atoms of surface silanols can act as H-acceptor. Furthermore, it must be considered that in the present case the H-acceptor groups (the silanols) possess an internal mode, the  $\nu\text{OH}$  one, that absorb in the same region, and then can be involved in the coupling. This effect should be responsible for the increase in intensity of the high frequency part of the complex absorption, near the maximum at  $3510\text{ cm}^{-1}$ , related to less perturbed oscillators. Indeed, such intensification cannot be ascribed to a higher amount of silanols interacting each other, as, conversely,  $\equiv\text{Si-OH}$  should have been consumed in a slightly larger amount

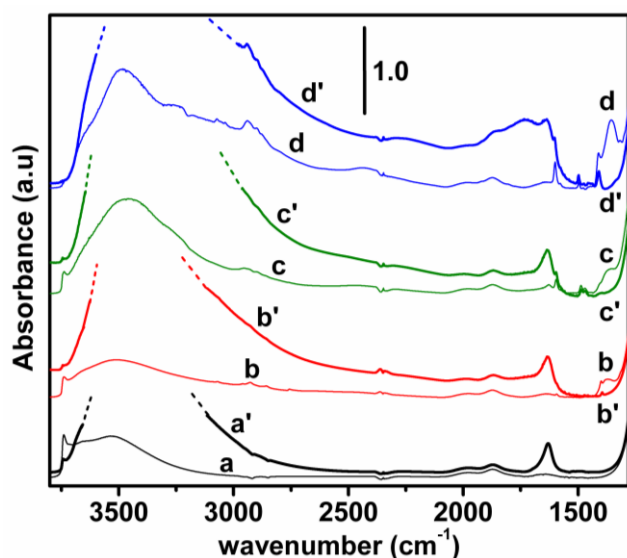
during the synthesis of the supported sulfonic acid molecules (by assuming the same Si-OH/alcoxyde stoichiometry for both phenyltriethoxy- and phenylethyltrimethoxysilane), slightly more numerous in catalyst **24** than in catalyst **16** (see Table 1). The stronger interaction between sulphonic groups and silanols should be related to possible orientations of the substituted aromatic ring different from the normal to the surface, because the link to the support through the alkyl moiety, with rotational degree of freedom around the C-C bonds.

Furthermore, the weak feature at ca.  $2400\text{ cm}^{-1}$  is similar in position to the low frequency component, with a more intense partner at ca.  $2900\text{ cm}^{-1}$ , of the  $\nu\text{OH}$  pattern obtained for dehydrated H-NAFION membranes [43], with sulfonic groups interacting each other via H-bonding. Actually, the increase in intensity of this component, and the more clear presence of a broad subband at ca.  $3000\text{ cm}^{-1}$ , are the distinctive features of the  $\nu\text{OH}$  pattern of catalyst **21** (curve d), that contains ca 40% additional supported acid moieties than catalyst **24** (see Table 1). Other consequences of such increased content in supported molecules are: i) the depletion of the  $3740\text{ cm}^{-1}$  peak, indicating that all isolated silanols have been chemically consumed and/or involved in interaction with supported species, and ii) the appearance of sharp minima at  $3300$  and  $3200\text{ cm}^{-1}$ , that might be narrow Evans windows resulting from Fermi resonance between the levels resulting from the coupling of  $\nu(\text{A-H}\cdots)$  and  $\nu(\text{AH}\cdots\text{B})$  modes (see above), and the overtones and combinations of internal modes of the base B involved in the H-bond, as observed in pyridine/acid zeolites systems [44]. In the present case, the base should be the part of the sulfonic group acting as H-bond acceptor.

Finally, it can be noticed that the difference in the interaction of sulfonic groups with different neighbours (silanols and/or other sulfonic groups) should affect, other than the SO-H band, also the S=O ones, and this could partly account for the difference in position and shape of the antisymmetric O=S=O stretching band observed for the three catalysts (see above).

To probe the acid behaviour of the supported species, the catalysts (and the bare support, for the sake of comparison), were contacted with 20 mbar of  $\text{H}_2\text{O}$  vapour, with the consequent formation of adsorbed multilayers of molecular water [45] and possible proton transfer from sulfonic groups to  $\text{H}_2\text{O}$  molecules. The

admission of water on the bare silica (Figure 5, a) simply resulted in the appearance of the bands due to the deformation ( $\delta$ , at  $1630\text{ cm}^{-1}$ ) and stretching modes ( $3730\text{--}2800\text{ cm}^{-1}$  range, maximum out of scale), these latter overimposed to the silanols pattern. As expected, the interaction with  $\text{H}_2\text{O}$  molecules heavily affected the peak at  $3740\text{ cm}^{-1}$ , as the related groups are now interaction via H-bond with adsorbed species. Nevertheless, a small portion of such signal, with maximum at  $3744\text{ cm}^{-1}$  still remained, indicating that some of the surface silanols are so widely distributed to form patches not hydrophilic enough for the adsorption of water [46].

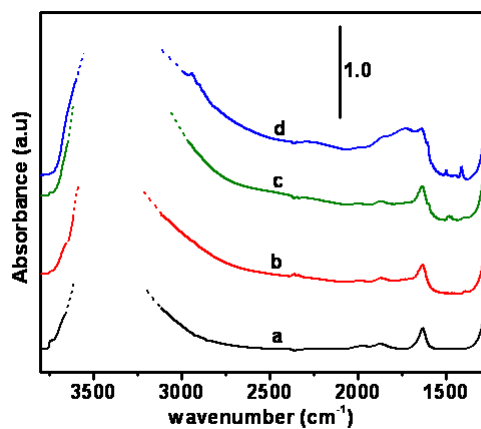


**Figure 5.** IR spectra of samples in contact with 20 mbar of  $\text{H}_2\text{O}$  vapour: a) bare silica; b) catalyst **16**; c) catalyst **24**; d) catalyst **21**.

In the case of catalysts (Figure 5, b-d), the additional consequences of the interaction with water were the depletion of the sulfurylic signal in the  $1390\text{--}1325\text{ cm}^{-1}$  range, and the appearance of a continuous absorption extended from  $3500\text{ to }1700\text{ cm}^{-1}$ . This latter is a kind of “fingerprint” of the formation of  $\text{H}^+(\text{H}_2\text{O})_n$  clusters [44], and then probes the transfer of protons to the aqueous layers from  $-\text{SO}_3\text{H}$  groups, converted into  $-\text{SO}_3^-$ , that are expected to absorb below the transparency limit of the samples [44].

Thus, it can be stated that the contact with an aqueous medium results in a complete deprotonation of the sulfonic groups. The same occurred for the materials in contact

with air, with the consequent formation of liquid-like molecular layers by adsorption of air moisture (Figure 6).



**Figure 6.** IR spectra of the samples in contact with air: a) bare SiO<sub>2</sub>; b) catalyst **16**; c) catalyst **24**; d) catalyst **21**. The maximum of the main absorption in the high frequency region was out of scale.

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## 3 Supported sulfonic acids as novel catalysts in green oxidation processes

### 3.1 General introduction

Nowhere there is a great need for green catalytic options in fine chemicals manufacture obtained by oxidation reactions. In contrast to reductions, oxidations are still largely carried out with stoichiometric inorganic (or organic) oxidants such as chromium(VI) reagents, potassium permanganate, manganese dioxide and periodates. Thus catalytic alternatives employing clean primary oxidants such as oxygen or hydrogen peroxide are strongly needed. Catalytic oxidation with O<sub>2</sub> is widely used in the manufacture of bulk petrochemicals [1], but application to fine chemicals is generally more difficult, due to the multifunctional nature of the target molecules. However, in some cases such technologies have been successfully applied. An elegant example is the BASF process [2] for the synthesis of citral, a key intermediate for fragrances and vitamins A and E. The key step is a catalytic vapor phase oxidation over a supported silver catalyst, basically the same as that used for the synthesis of formaldehyde from methanol.

Many other different oxidation reactions are of great interest at both academic and industrial level, such as epoxidation of alkenes, Baeyer-Villiger oxidation of ketones, oxidation of alcohols to aldehydes, sulfoxidation, etc.

As noted above, in all these cases there is an urgent call for greener methodologies, preferably employing O<sub>2</sub> or H<sub>2</sub>O<sub>2</sub> as clean oxidants and effective with a broad range of substrates.

Hydrogen peroxide is an ideal oxidant for many reasons, mainly due to the fact that it is cheap, and water is theoretically the sole by-product [3-5]. The activation of aqueous hydrogen peroxide is a challenge that has attracted many research groups in order to perform oxidation reactions, under environmentally friendly conditions [6,7].

From a mechanistic point of view, the activation of hydrogen peroxide can take place in three ways [8]. First, in the presence of metal catalysts, according to the well known Haber-Weiss reaction, involving the hydroxyl radical, that frequently leads to unselective processes in organic synthesis [9]; second, in the presence of a base,

### 3. Supported sulfonic acids as novel catalysts in green oxidation processes

through the formation of the strong  $\text{HOO}^-$  nucleophile, that can oxidize, for example, electrophilic alkenes [3]; third, according to the heterolytic oxidation process, that is probably the most important reaction from a synthetic point of view [10].

In the presence of catalysts containing different transition metals such as Ti, W, Mn, Re and Sn [11-15], hydrogen peroxide undergoes efficient oxidation reactions, for example alkene epoxidation [16-19], conversion of sulfides into sulfoxides and sulfones [20-23] and Baeyer-Villiger (BV) oxidation of ketones to lactones [24-27]. In all these cases the reaction involves an electrophilic activation of hydrogen peroxide; the same mechanism is reported with fluorinated solvents, as it was clearly shown by Sheldon and Berkessel [28,29].

With regard to the crucial role of peracids added to the reaction mixture or produced in situ from carboxylic acids, many studies are reported in the literature [30]; however the role of different acids such as sulfonic, arsonic and phosphonic acids showing a similar behavior is not as much studied and needs further deepening. For example, resin supported-sulfonic acids were reported to be good heterogeneous and reusable catalysts for the BV oxidation of cyclopentanone [31], and more recently Sato reported a very efficient procedure for the solvent-free dihydroxylation of alkenes with hydrogen peroxide in the presence of Nafion resin [32].

#### ***3.2 Silica supported sulfonic acids as efficient catalysts for Baeyer-Villiger oxidation with 30% aqueous hydrogen peroxide***

##### **3.2.1 Introduction**

In the past decades extensive studies have been devoted to the use of hydrogen peroxide to perform some of the most important oxidation reactions. Concerning, in particular, the efficient and selective BV oxidation, further investigations from both theoretical and applied point of view are required. Indeed, despite the numerous studies on this subject, some problems need further deepening such as the exploitation of heterogeneous, reusable catalysts [27] and the efficient use of hydrogen peroxide [33] avoiding unproductive decomposition reactions.

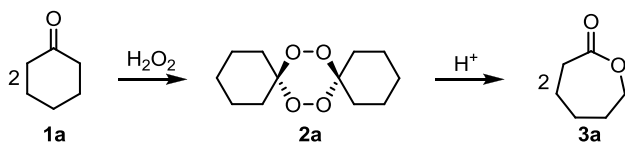
### 3. Supported sulfonic acids as novel catalysts in green oxidation processes

The BV oxidation under heterogeneous catalysis has been recently performed with  $\text{H}_2\text{O}_2$  for example in the presence of Sn-zeolite-beta, [15] Amberlyst-15, [31] redox molecular sieves MALPO-36 (M = Mn, Co) [34] and polymer anchored platinum complexes. Some of these catalysts still show poor selectivity; moreover the presence of transition metals as impurities in products designed for pharmaceutical or food application is a great problem, even if they are present only in traces.

A metal-free procedure has been reported by Berkessel to efficiently perform the BV oxidation of cyclohexanone with 50% aq hydrogen peroxide in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) as solvent in the presence of a Brønsted acid catalyst such as *para*-toluenesulfonic acid.[29]

The reaction has been shown to proceed via the spirobisperoxide intermediate **2a** which, in the presence of a protic acid, selectively rearranges to the corresponding lactone **3a** (Scheme 1). [35] Traces of 6-hydroxyhexanoic acid (**4a**) can be also produced.

The activity of some silica- and polystyrene-supported sulfonic acids as heterogeneous catalysts for BV oxidation with aq  $\text{H}_2\text{O}_2$  in HFIP has been evaluated.



**Scheme 1.** Baeyer-Villiger oxidation of cyclohexanone to  $\epsilon$ -caprolactone

#### 3.2.2 Results and discussion

The activity of the silica supported sulfonic acids catalysts and of the commercially available polystyrene supported benzenesulfonic acid (Amberlyst-15) was tested in the model reaction between cyclohexanone **1a** and 30% aq  $\text{H}_2\text{O}_2$  in HFIP as solvent.

### 3. Supported sulfonic acids as novel catalysts in green oxidation processes

**Table 1.** Textural properties and activity of the different catalysts in the model reaction between cyclohexanone (1d) and 30% aq H<sub>2</sub>O<sub>2</sub> in HFIP.<sup>(a)</sup>

Entry	Catalyst	Surface area (m <sup>2</sup> /g)	Total acidity (meqH <sup>+</sup> /g)	mg	<b>1a</b> conv. (%)	<b>3a</b> yield (%) <sup>(b)</sup>
a	Silica gel	540	-	50	<1	-
b	SiO <sub>2</sub> -(CH <sub>2</sub> ) <sub>3</sub> -SO <sub>3</sub> H	510	0.20	20	83	71
c	SiO <sub>2</sub> -(C <sub>6</sub> H <sub>5</sub> )-SO <sub>3</sub> H	445	0.65	7	82	69
d	SiO <sub>2</sub> -(CH <sub>2</sub> ) <sub>3</sub> -SO <sub>3</sub> H (sol-gel)	340	0.32	15	89	30
e	MCM-41-(CH <sub>2</sub> ) <sub>3</sub> -SO <sub>3</sub> H	1100	0.42	10	92	65
f	Amberlyst-15	53	4.70	5	88	42

<sup>(a)</sup> Reaction conditions: 0.95 mmol of cyclohexanone, 1 mmol of 30 % of H<sub>2</sub>O<sub>2</sub>, 2 mL of HFIP, 50°C for 90 minutes. <sup>(b)</sup>  $\epsilon$ -caprolactone (**3a**) was identified by GC and characterized by comparison with a reference sample.

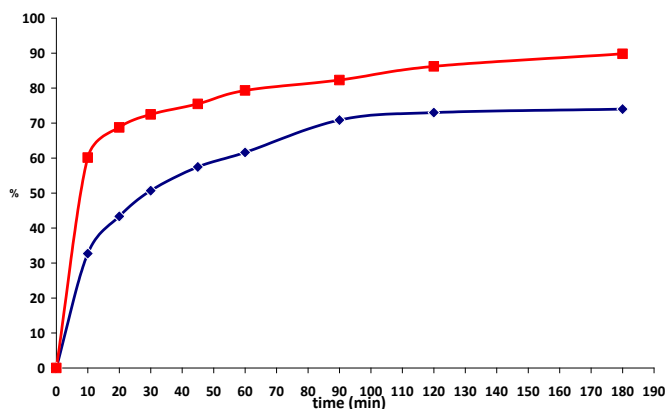
Reactivity parameters reported in Table 1 together with surface area and total acidity values of the catalysts, highlight similarities with the reaction performed under homogeneous catalysis.[35]

The cyclohexanone conversion reaches, in all cases, comparable high values (80-90%) independent of the acidity and surface area parameters of the catalyst utilized. On the contrary, the nature of the support, the acidity and the method utilized in the preparation of the catalyst play an important role in determining the yield and selectivity of the second step, namely the conversion of the intermediate **2a** into the product **3a**. The low yield of product **3a** observed in the reaction catalyzed by silica supported propylsulfonic acid prepared by sol-gel method (Table1, entry d) is, probably, a consequence of the fact that, despite the use of the porogenic dodecylamine in the preparation of the catalyst, the amount of sulfonic acid content as measured by acid/base titration [36] does not necessarily correspond to the same equivalent of catalytically active acid, since access to the active sites could be reduced or even hampered by the shape of the solid matrix (see chapter 2). A similar negative effect could be responsible for the low yield observed in the reaction catalyzed by Amberlyst-15 (Table1, entry f). In this case the cation-stabilizing solvent HFIP can give a lower swelling of the hydrophobic polystyrene support and consequently the accessibility to the sulfonic acid sites is reduced.[37] The best catalyst efficiency can be achieved by using the silica supported propylsulfonic acid prepared by tethering procedure (Table1, entry b). Furthermore, comparative

### 3. Supported sulfonic acids as novel catalysts in green oxidation processes

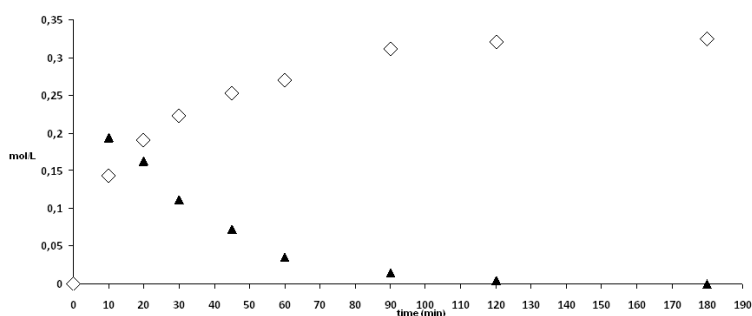
experiments performed with different solvents confirmed that HFIP plays a crucial role in the reaction (*i.e.* MeOH: 27% yield, 45% selectivity).

This reaction was successively analyzed comparing conversion of reagent **1a** and yield of product **3a** as a function of time (Figure 1).



**Figure 1.** Reaction trend for the oxidation of cyclohexanone to  $\epsilon$ -caprolactone employing 30% aq  $\text{H}_2\text{O}_2$  and 0.4% of  $\text{SiO}_2\text{-(CH}_2\text{)}_3\text{-SO}_3\text{H}$  [-■- **1a** conversion (%), -◆- **3a** yield (%)].

Cyclohexanone **1a** underwent a fast initial conversion reaching 62% after 10 minutes. On the contrary, a low value of lactone **3a** production (32%) was observed. The yield of product **3d** increased slowly but continuously with time and reached 72% after 90 minutes. The production of intermediate **2a** and the continuous conversion of **2a** into the final lactone **3a** has been demonstrated by carrying out the model reaction for 90 minutes and performing GC analyses every 10 minutes (Figure 2).



**Figure 2.** Plot of the concentration of spirobisperoxide **2a** and caprolactone **3a** versus time in the BV oxidation of cyclohexanone (-▲- spirobisperoxide **2a** concentration, -◆- caprolactone **3a** concentration).

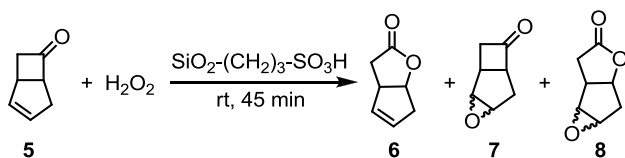
### 3. Supported sulfonic acids as novel catalysts in green oxidation processes

Results shown in Figure 2 confirm that intermediate **2a** starts to appear right from the very beginning of the reaction in combination with the final product. After 10 minutes the concentration of **2a** is 0.18 mmol/L accompanied by the product in 0.14 mmol/L. With ongoing reaction, the concentration of **3a** increases while the concentration of the spirobisperoxide **2a** decreases as would be expected if **2a** is an intermediate that decomposes to form **3a**. Possible leaching of active species into the solution and thus coexistence of homogeneous catalysis can be excluded by performing the hot-filtration test.[38] The catalyst was filtered at 50 °C after 10 min reaction time when the yield of **3a** was 32%. No increase in yield was observed by keeping the filtrate at 50 °C for further 3 hours. These results prompted us to investigate the possible catalyst recycling. Thus the catalyst recovered by filtration and washed with methanol, can be reused, in the model reaction, giving product **3a** in 71% yield after 150 minutes at 50 °C. The production of some by-products coming from spirobisperoxide and 6-hydroxyhexanoic acid **4a** can be responsible for the lowering of activity. To confirm this hypothesis, and to recover and recognize by-products adsorbed on the catalyst surface, the model reaction was carried out in a larger scale [H<sub>2</sub>O<sub>2</sub>: 5 mmol, cyclohexanone: 4.75 mmol, HFIP: 10 ml, SiO<sub>2</sub>-(CH<sub>2</sub>)<sub>3</sub>-SO<sub>3</sub>H: 0.4% mol]: product **3a** was isolated in 86% yield and 89% selectivity. Careful and repeated washing of the recovered catalyst with hot THF afforded 44 mg of 6-hydroxyhexanoic acid accompanied by traces of oligoesters. The washed catalyst can be reused in the same reaction for at least two successive cycles with the same level of activity and selectivity.

Moreover, the reaction shows a good level of chemoselectivity in the oxidation of unsaturated cis-bicyclo-[3.2.0]-hept-2-en-6-one (**5**) previously studied by Corma et al. as model substrate.[15] Thus compound **5** underwent selective conversion to lactone **6** (94% yield, 100% selectivity) without formation of epoxides **7** and **8** (Scheme 2). These results are comparable with those reported by Corma in the reaction promoted by Sn-Beta zeolite in ethereal solvents. [15]



### 3. Supported sulfonic acids as novel catalysts in green oxidation processes







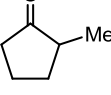

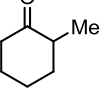
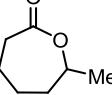

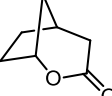

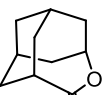


**Scheme 2.** BV oxidation of *cis*-bicyclo-[3.2.0]-hept-2-en-6-one with 30% aq  $\text{H}_2\text{O}_2$  catalyzed by  $\text{SiO}_2\text{-(CH}_2\text{)}_3\text{-SO}_3\text{H}$  catalyst.

The scope and general applicability of the oxidation process with respect to various cyclic ketones was finally investigated. Experimental results reported in Table 2 confirm the general applicability to different cyclic ketones. The ring size of the cyclic ketone has the expected influence as efficiency is affected by the ring strain (Table 2, entries a, b and d). Moreover in the reactions of 2-methylcyclohexanone, 2-methylcyclopentanone and norbornanone the only products detected were the corresponding lactones produced by migration of the more substituted group (Table 2, entries c, e and f).

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**Table 2.** BV oxidation of ketones<sup>a</sup>

Entry	Substrate	Product	Conv. (%)	Sel. (%) <sup>b</sup>
a			83	86
b			100	100
c			81	92
d			64	100
e			75	77
f			83	65
g			97	100

<sup>(a)</sup> Reaction conditions: ketone: 0.95 mmol, 30% of H<sub>2</sub>O<sub>2</sub>: 1 mmol, HFIP: 2 mL, SiO<sub>2</sub>-(CH<sub>2</sub>)<sub>3</sub>-SO<sub>3</sub>H: 0.4% mol, 50 °C, 1.5 h. <sup>(b)</sup> Formations of corresponding lactones were determined by GC analysis by comparison with reference samples.

The reaction shows, in general, a high selectivity: the only by-products (isolated and identified by <sup>13</sup>C NMR analysis in the model reaction and identified only by GC-MS in the other ones) were the intermediate spirobisperoxides and the ω-hydroxyalkanoic acids.

The reaction shows also a good level of efficient oxygen utilization as a 0.95/1.00 ketone/H<sub>2</sub>O<sub>2</sub> molar ratio was used in all experiments.

#### 3.2.3 Conclusions

In conclusion we have demonstrated that the BV-oxidation of cyclic ketones can be efficiently performed in 1,1,1,3,3,3-hexafluoro-2-propanol with 30% aqueous H<sub>2</sub>O<sub>2</sub> in the presence of propylsulfonic acid supported on silica used as heterogeneous and

### 3. Supported sulfonic acids as novel catalysts in green oxidation processes

reusable catalyst. The reaction involves the fast formation of a spirobisperoxide intermediate that rearranges to the corresponding lactone product. The catalytic oxidation reaction can be applied to different cyclic ketones showing good conversion and high selectivity combined with a good level of efficient oxygen utilization.

#### 3.2.4 Experimental Section

General procedure for the catalytic BV oxidation of cyclic ketones.

In a typical procedure cyclohexanone **1a** (0.95 mmol) and 30% aq H<sub>2</sub>O<sub>2</sub> (1.0 mmol) were dissolved in HFIP (2.0 mL) and were heated to 50°C under stirring in the presence of the selected catalyst for 90 minutes. The reaction was followed by GC analysis and the  $\epsilon$ -caprolactone product (**3a**) was identified by comparison with a reference sample, accompanied by variable amounts of intermediate **2a** and 6-hydroxyhexanoic acid.

### ***3.3 Dihydroxylation of methylcyclohexene catalyzed by supported sulfonic acids.***

#### **3.3.1 Introduction**

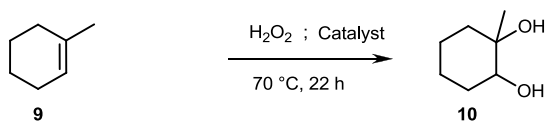
Despite the numerous examples reported in the literature concerning the catalytic dihydroxylation of olefins with hydrogen peroxide [39-41], the selectivity toward 1,2-diols is frequently very low, due to the formation of epoxides, alcohols, ketones, and/or ethers as by-products. Moreover in all the reported synthetic methods the use of chlorohydrocarbons or other organic solvents is required. For these reasons, we have evaluated the activity of some silica-supported sulfonic acids as heterogeneous catalysts for the dihydroxylation of 1-methylcyclohexene with hydrogen peroxide. In addition, molecular features of the supported acids and of the results of their interaction with H<sub>2</sub>O<sub>2</sub> have been investigated by IR spectroscopy in controlled atmosphere and DR UV-Vis spectroscopy of the catalysts in contact with H<sub>2</sub>O<sub>2</sub>/H<sub>2</sub>O solutions.

#### **3.3.2 Results and discussion**

The activity of different supported sulfonic acid catalysts has been evaluated in the 1,2-dihydroxylation of 1-methylcyclohexene with hydrogen peroxide (Table 3).

### 3. Supported sulfonic acids as novel catalysts in green oxidation processes

**Table 3.** Catalytic efficiency of supported sulfonic acids in the dihydroxylation of 1-methylcyclohexene<sup>a</sup>.



Entry	Catalyst (mol %)	Surf. acidity (mmol H <sup>+</sup> /g)	Surf. area (m <sup>2</sup> /g)	<b>10</b> Yield [Sel.] <sup>b</sup> (%)
1	SiO <sub>2</sub> -(C <sub>6</sub> H <sub>4</sub> )-SO <sub>3</sub> H (1)	0.65	445	70 [94]
2	SA-(C <sub>6</sub> H <sub>4</sub> )-SO <sub>3</sub> H (1)	0.90	371	23 [94]
3	Amberlyst-15 (1)	4.70	53	55 [93]
4	SiO <sub>2</sub> -(C <sub>6</sub> H <sub>4</sub> )-SO <sub>3</sub> H (2)	0.65	445	80 [94]
5	SiO <sub>2</sub> -(CH <sub>2</sub> ) <sub>2</sub> -(C <sub>6</sub> H <sub>4</sub> )-SO <sub>3</sub> H (2)	1.20	293	90 [96]
6	SiO <sub>2</sub> -(CH <sub>2</sub> ) <sub>3</sub> -O-(C <sub>6</sub> H <sub>4</sub> )-SO <sub>3</sub> H (2)	0.70	415	55 [93]

<sup>(a)</sup> Reaction conditions: 1-methylcyclohexene (0.5 mL, 4.2 mmol), 30% aq H<sub>2</sub>O<sub>2</sub> (0.86 mL, 8.4 mmol), 70 °C, 22 h. <sup>(b)</sup> Determined by GC analysis.

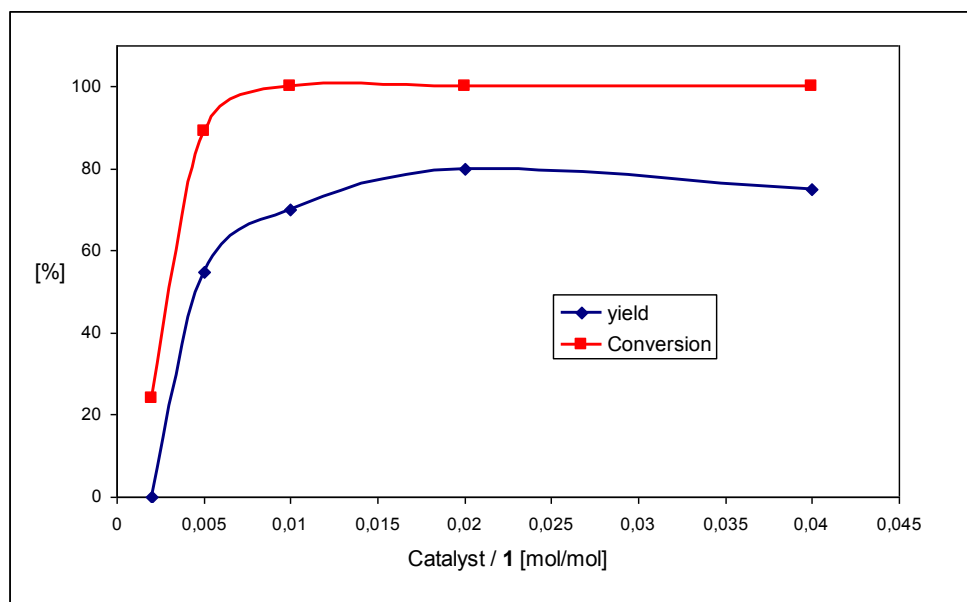
The experiments were carried out by adding 1-methylcyclohexene to a suspension of the catalyst in 30% aqueous hydrogen peroxide and by stirring the reaction mixture for 22 hours at 70 °C.

The model reaction was first tested with phenylsulfonic acid supported onto amorphous silica and SA and with the commercially available Amberlyst-15. In all cases 1-methyl-1,2-cyclohexanediol was obtained as the major product. The silica supported phenylsulfonic acid (1% molar ratio with respect to reagent **1**) showed the best activity, affording product **3** in 70% yield and 94% selectivity (Table 3, entry 1). Lower efficiency was observed Amberlyst-15 (53% yield, 93% selectivity) (Table 3, entry 3), whereas poor results were achieved with SA-supported phenylsulfonic acid (23% yield, 94% selectivity) (Table 3, entry 2).

In order to evaluate the possible catalytic activity of the bare supports, the reaction was performed in the presence of amorphous silica, SA and H-BEA zeolite; the siliceous support played no catalytic role, whereas SA gave product **10** in 12 % yield. It is important to underline that in the absence of catalyst hydrogen peroxide itself is not able to oxidize 1-methylcyclohexene.

### 3. Supported sulfonic acids as novel catalysts in green oxidation processes

The effect of catalyst amount was then evaluated (Figure 3).



**Figure 3.** Influence of the catalyst amount on the yield and selectivity in the reaction carried out with  $\text{SiO}_2\text{-(C}_6\text{H}_4\text{)-SO}_3\text{H}$  catalyst.

After increasing the catalyst/substrate molar ratio up to 0.005, the reaction shows a remarkable yield increase (55%) with a good level of selectivity (93%); a further yield increase was observed by using a 0.02 catalyst/substrate molar ratio value (80%), whereas with larger amount of catalyst a lowering in yield due to a non-controllable acid-catalyzed side reactions of the hydroxyl groups was observed (69%).

Concerning the optimum  $\text{H}_2\text{O}_2$  amount, the best result was achieved with a  $\text{H}_2\text{O}_2/9$  molar ratio = 2; with lower or higher amounts of  $\text{H}_2\text{O}_2$  product **10** was obtained in lower yield due to the competition of unproductive  $\text{H}_2\text{O}_2$  decomposition in the first case, and over oxidation reactions in the second one.

The effect of the concentration of the aqueous hydrogen peroxide on the efficiency of the process has been successively evaluated. In a series of experiments, the reaction was carried out in the presence of 1.2, 15, 30 and 50% hydrogen peroxide, by using the same amount of the oxidizing agent. The optimum hydrogen peroxide concentration was found to be 30% (80% yield, 94% selectivity), as the use of 50%  $\text{H}_2\text{O}_2$  afforded the diol in lower yield (72%) and selectivity (88%), probably due to overoxidation processes; on the contrary, when more diluted solutions of the

### 3. Supported sulfonic acids as novel catalysts in green oxidation processes

oxidizing agent were employed, lower yields and selectivities were detected for the competitive water addition reaction (15% H<sub>2</sub>O<sub>2</sub>: 49% yield, 80% selectivity; 1.2% H<sub>2</sub>O<sub>2</sub>: 8% yield, 65% selectivity).

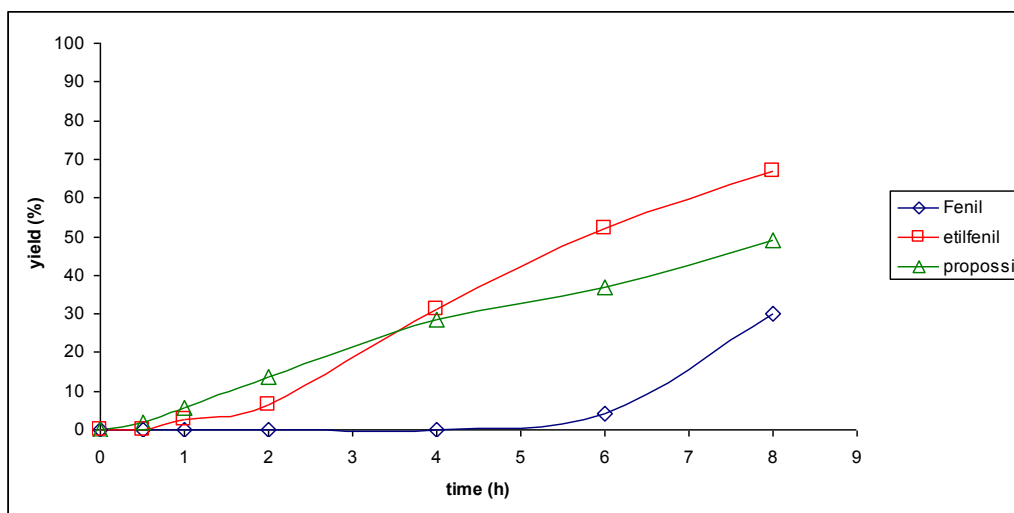
Concerning the efficiency of the hydrogen peroxide under the best reaction conditions, a value of 65%, calculated as product (mol) per consumed H<sub>2</sub>O<sub>2</sub> (mol) × 100, was found. The unreacted hydrogen peroxide was measured by iodimetric titration.

Addition of solvent (2 mL) such as toluene, acetonitrile, methanol or water, resulted in a dramatic lowering (<10%) or complete inhibition of compound **10** production, irrespective of the polarity. Among the by-products isolated in these reactions, 1-methylcyclohexan-1-ol, due to acid catalyzed addition of water to alkene, and 2-methylcyclohexanone, derived from the isomerisation of epoxide intermediate or from the pinacol rearrangement of 1-methyl-1,2-cyclohexanediol, were recognized in the final mixtures. When methanol was utilized, the expected 2-methoxy-1-methylcyclohexan-1-ol, derived from the reaction of the methanol with the intermediate epoxide, was also isolated in modest yield.

The catalytic activity of an additional series of sulfonic acids supported on silica through arms with different length has been successively studied in the reaction performed under the best conditions (2 mol% catalyst, 70 °C, 22 hours, H<sub>2</sub>O<sub>2</sub>/9 molar ratio = 2). The best result in terms of yield (90%) and selectivity (96%) of 1-methyl-1,2-cyclohexanediol was obtained with the silica supported 4-ethylphenylsulfonic acid (Table 1, entry 5). The lower activity (80% yield, 94% selectivity) of the silica-supported phenylsulfonic acid (Table 1, entry 4) could be ascribed to the fact that the direct anchoring of phenylsulfonic group to the silica surface can partly hamper the availability of the active acid sites with respect the more accessible ethylphenylsulfonic group. The surface area of these catalytic materials seems to be irrelevant in the present reaction.

To achieve further information on the behavior of these catalysts, the reactions with silica-supported phenylsulfonic, ethylphenylsulfonic and propoxyphenylsulfonic acids were analyzed during the first 10 hours under solventless condition. Results are reported in Figure 4.

### 3. Supported sulfonic acids as novel catalysts in green oxidation processes



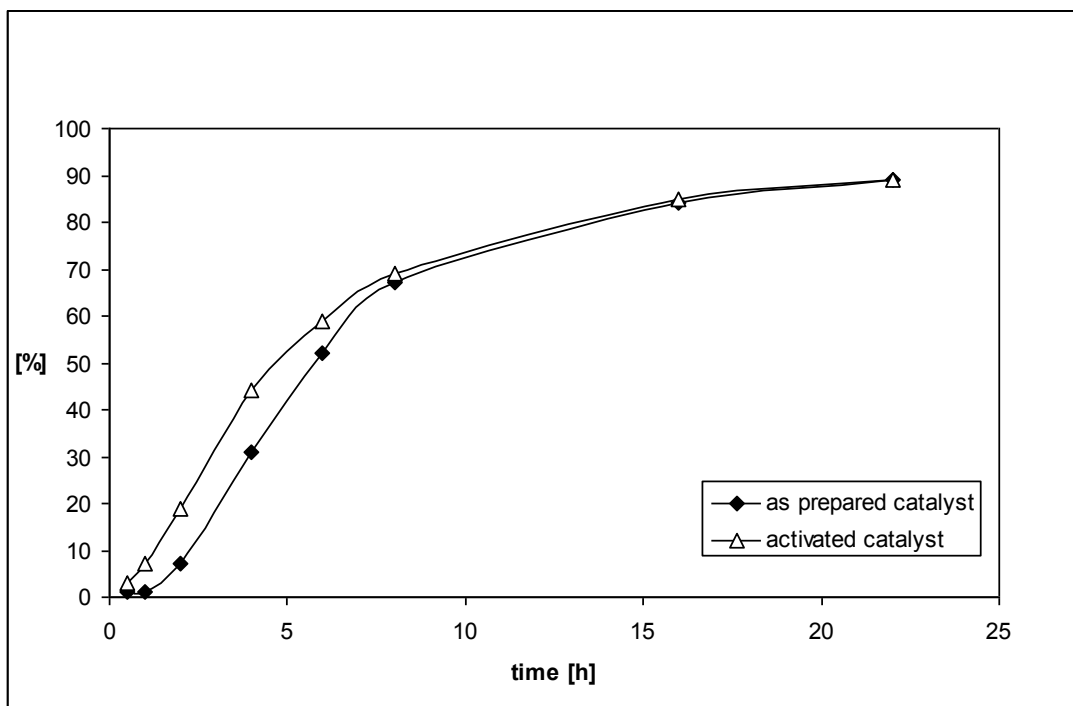
**Figure 4.** Yield versus time trend for the reactions carried out with  $\text{SiO}_2\text{-(C}_6\text{H}_4\text{)-SO}_3\text{H}$  (◆),  $\text{SiO}_2\text{-(CH}_2\text{)}_2\text{-(C}_6\text{H}_4\text{)-SO}_3\text{H}$  (▲) and  $\text{SiO}_2\text{-(CH}_2\text{)}_3\text{-O-(C}_6\text{H}_4\text{)-SO}_3\text{H}$  (■) catalysts.

It is interesting to note that the three catalysts show completely different reaction profiles. Propoxyphenylsulfonic acid (▲) shows a slightly higher initial rate with respect to the ethylphenylsulfonic (■) and phenylsulfonic acids (◆), without any induction period; nevertheless it rapidly reaches a plateau at ~ 50 % yield. Instead, variable induction periods were observed with ethylphenylsulfonic and phenylsulfonic acids; these induction times are expected to be due to the production of the active species.

This reaction is obviously affected by the accessibility of the sulfonic acid groups that depends on the length of the arm that binds them to the support surface, according to the order propoxyphenyl > ethylphenyl > phenyl. This hypothesis was, to some extent, confirmed by further experiments. Indeed we compared the activity of the as-prepared and the activated silica supported ethylphenylsulfonic acid; the activation was performed by heating at 70 °C for 2 hours a mixture of the catalyst with 30% aqueous hydrogen peroxide under stirring. After that period, the catalyst was recovered by filtration and used in the reaction. Comparative results in Figure 5 suggest that the as-prepared catalyst needs an induction period of about 2 hours; on the contrary when the preactivated catalyst is utilized the dihydroxylation reaction starts immediately.



### 3. Supported sulfonic acids as novel catalysts in green oxidation processes



**Figure 5.** Yield versus time trend for the reactions carried out with as-prepared (◆) and activated (▲)  $\text{SiO}_2\text{-(CH}_2\text{)}_2\text{-(C}_6\text{H}_4\text{)-SO}_3\text{H}$  catalysts.

Concerning the mechanism, we assumed that the reaction involves the initial production of the epoxide intermediate followed by the epoxide ring opening by a water molecule. The second step seems to be very fast; indeed in a blank experiment we confirmed that cyclohexene oxide was quantitatively converted into the *trans*-1,2-cyclohexanediol in 5 minutes by reaction with water at room temperature in the presence of silica supported 4-ethylphenylsulfonic acid.

In order to minimize the unproductive decomposition of hydrogen peroxide, we analyzed the reaction trend by adding  $\text{H}_2\text{O}_2$  dropwise to a suspension of 1-methylcyclohexene and the catalyst, through a syringe-pump during a period of 15 hours (the reaction mixture was stirred for further 7 hours to allow a total reaction time of 22 h). Comparable values of yield and selectivity of the desired product with respect to the one-pot addition of hydrogen peroxide were found (91% yield, 96% selectivity).

The recyclability of the silica supported 4-ethylphenylsulfonic acid catalyst was evaluated in the dihydroxylation of 1-methylcyclohexene. After the reaction, the catalyst was filtered off, washed with water, dried carefully and reused. The yield

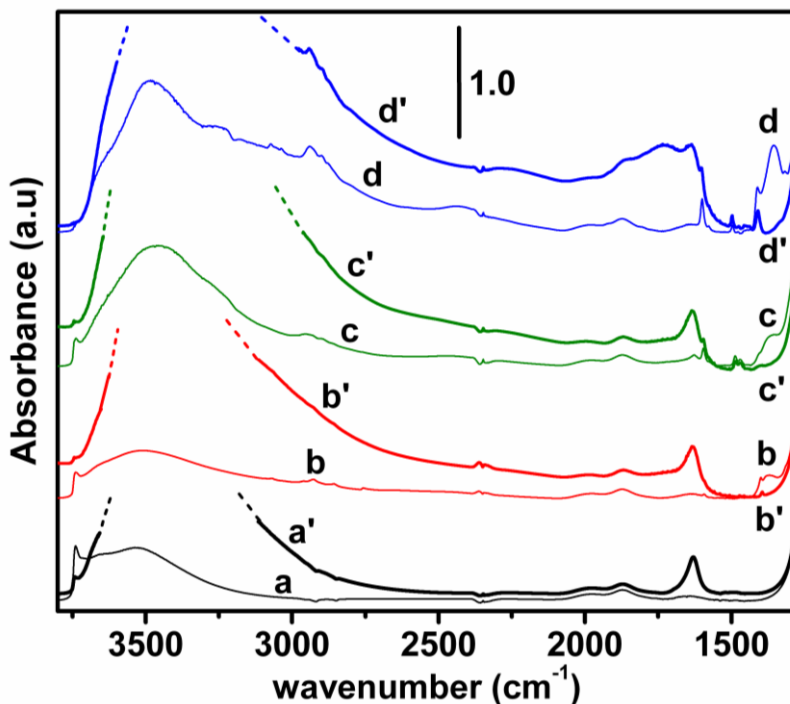
### 3. Supported sulfonic acids as novel catalysts in green oxidation processes

(and selectivities) were as follows: 1<sup>st</sup> run: 89 (95), 2<sup>nd</sup> run: 66 (94), 3<sup>rd</sup> run: 64 (96), 4<sup>th</sup> run: 64 (95). A remarkable loss of activity was observed during the first run, while maintaining a very high selectivity, whereas from the second cycle the catalyst shows a constant activity. Studies are in progress in order to understand the activity decrease during the first run.

#### 3.3.3 Interaction of catalysts with H<sub>2</sub>O<sub>2</sub>

##### *Interaction of catalysts with H<sub>2</sub>O*

To probe the acid behavior of the supported species, the catalysts (and the bare support, for the sake of comparison), were contacted with 20 mbar of H<sub>2</sub>O vapor, with the consequent formation of adsorbed multilayers of molecular water [42] and possible proton transfer from sulfonic groups to H<sub>2</sub>O molecules. The admission of water on the bare silica (Figure 6, a) simply resulted in the appearance of the bands due to the deformation ( $\delta$ , at 1630 cm<sup>-1</sup>) and stretching modes (3730-2800 cm<sup>-1</sup> range, maximum out of scale), these latter overimposed to the silanols pattern. As expected, the interaction with H<sub>2</sub>O molecules heavily affected the peak at 3740 cm<sup>-1</sup>, as the related groups are now interaction via H-bond with adsorbed species. Nevertheless, a small portion of such signal, with maximum at 3744 cm<sup>-1</sup> still remained, indicating that some of the surface silanols are so widely distributed to form patches not hydrophilic enough for the adsorption of water [43].



**Figure 6.** IR spectra of samples in contact with 20 mbar of H<sub>2</sub>O vapour: a) bare silica; b) catalyst SiO<sub>2</sub>-(C<sub>6</sub>H<sub>4</sub>)-SO<sub>3</sub>H; c) catalyst SiO<sub>2</sub>-(CH<sub>2</sub>)<sub>3</sub>-O-(C<sub>6</sub>H<sub>4</sub>)-SO<sub>3</sub>H; d) catalyst SiO<sub>2</sub>-(CH<sub>2</sub>)<sub>2</sub>-(C<sub>6</sub>H<sub>4</sub>)-SO<sub>3</sub>H.

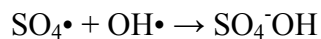
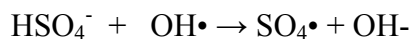
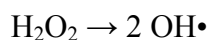
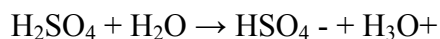
In the case of catalysts (Figure 2, b-d), the additional consequences of the interaction with water were the depletion of the sulfurylic signal in the 1390-1325 cm<sup>-1</sup> range, and the appearance of a continuous absorption extended from 3500 to 1700 cm<sup>-1</sup>. This latter is a kind of “fingerprint” of the formation of H+(H<sub>2</sub>O)<sub>n</sub> clusters [44], and then probes the transfer of protons to the aqueous layers from -SO<sub>3</sub>H groups, converted into -SO<sub>3</sub><sup>-</sup>, that are expected to absorb below the transparency limit of the samples [44].

Thus, it can be stated that the contact with an aqueous medium results in a complete deprotonation of the sulfonic groups. The same occurred for the materials in contact with air (as some of the UV-Vis measurements, see below), with the consequent formation of liquid-like molecular layers by adsorption of air moisture.

The deprotonation of sulfonic groups is quite relevant for the proposal of the nature of catalytically active species. Indeed, supported monoperoxysulfate species, were hypothesized to be active in the selective oxidation of cyclohexane to cyclohexanediol [32]. However, the formation of S-O-O-H groups by reaction

### 3. Supported sulfonic acids as novel catalysts in green oxidation processes

between sulphuric/sulfonic groups and  $\text{H}_2\text{O}_2$  requires the presence of a S-O-H moiety, as for instance in the case of sulphuric acid [45-47]:



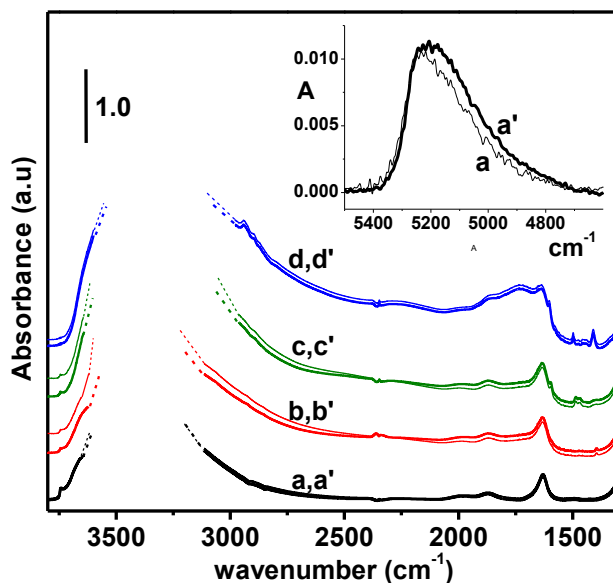
Conversely, IR data demonstrated the occurrence of a complete deprotonation of supported sulfonic acids when in contact with an aqueous environment.

#### *Interaction of catalysts with $\text{H}_2\text{O}_2/\text{H}_2\text{O}$*

Similar IR measurements were carried out by admitting the vapour (20 mbar) of a  $\text{H}_2\text{O}/\text{H}_2\text{O}_2$  mixture (30% vol  $\text{H}_2\text{O}_2$ ) onto the samples.

No significant changes were observed between the spectra collected after admission on the samples of  $\text{H}_2\text{O}$  or  $\text{H}_2\text{O}_2/\text{H}_2\text{O}$  vapor. However, the presence of  $\text{H}_2\text{O}_2$  in the liquid-like molecular layers formed on the sample surface was witnessed by the broadening towards the low frequency side of the  $\nu_{\text{OH}} + \delta_{\text{OH}}$  band of water at  $5230 \text{ cm}^{-1}$  (NIR region), likely due to the presence of an additional component due to the same combination mode of  $\text{H}_2\text{O}_2$  (Figure 7) Conversely, some information was obtained from the UV-Vis spectra of the systems contacted with  $\text{H}_2\text{O}$  and the  $\text{H}_2\text{O}/\text{H}_2\text{O}_2$  solution.

### 3. Supported sulfonic acids as novel catalysts in green oxidation processes



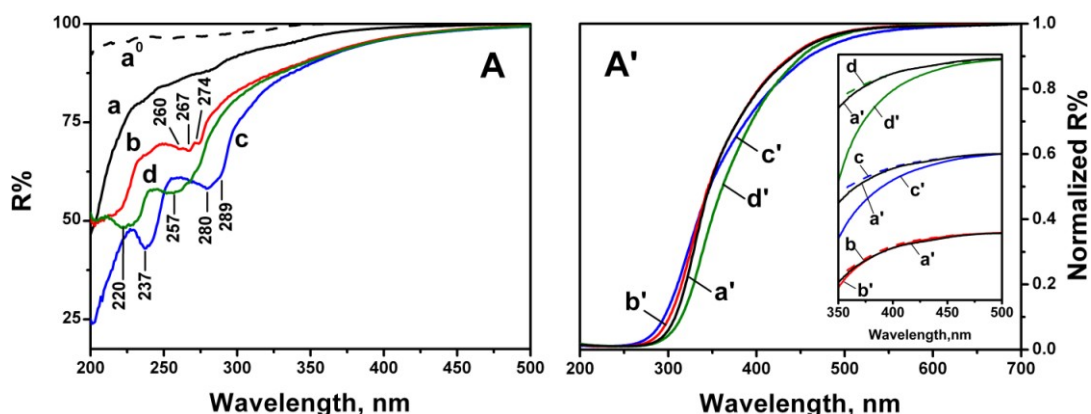
**Figure 7.** IR spectra of the samples in contact with 20 mbar of H<sub>2</sub>O vapour (curves x) or of H<sub>2</sub>O<sub>2</sub>/H<sub>2</sub>O (30% vol H<sub>2</sub>O<sub>2</sub>) (curves x'): a, a') bare SiO<sub>2</sub>; b,b') catalyst SiO<sub>2</sub>-(C<sub>6</sub>H<sub>4</sub>)-SO<sub>3</sub>H; c,c') catalyst SiO<sub>2</sub>-(CH<sub>2</sub>)<sub>3</sub>-O-(C<sub>6</sub>H<sub>4</sub>)-SO<sub>3</sub>H; d,d') catalyst SiO<sub>2</sub>-(CH<sub>2</sub>)<sub>2</sub>-(C<sub>6</sub>H<sub>4</sub>)-SO<sub>3</sub>H. The maximum of the main absorption in the high frequency region was out of scale. Inset: spectra, in the NIR region, of the bare SiO<sub>2</sub> in contact with 20 mbar of: a) H<sub>2</sub>O; a') H<sub>2</sub>O<sub>2</sub>/H<sub>2</sub>O (30% vol H<sub>2</sub>O<sub>2</sub>), as in the main frame. Similar data were obtained for the other samples.

As a first step, the electronic spectra of the materials in the form of an aqueous slurry were collected (Figure 8, panel A). The bare silica exhibited a continuous absorption, progressively increasing in intensity towards the shorter wavelengths, assignable to charge transfer transitions involving metal ion impurities (curve a). Conversely, the spectrum of the much more pure pyrogenic silica employed as diluent, appeared significantly less intense (curve a<sup>0</sup>). Overimposed to the feature due to the support, the spectra of the catalysts appeared characterized by a main band at ca. 220 nm (catalysts SiO<sub>2</sub>-(C<sub>6</sub>H<sub>4</sub>)-SO<sub>3</sub>H and SiO<sub>2</sub>-(CH<sub>2</sub>)<sub>2</sub>-(C<sub>6</sub>H<sub>4</sub>)-SO<sub>3</sub>H, curves b,d, respectively) or at ca. 240 nm (catalyst SiO<sub>2</sub>-(CH<sub>2</sub>)<sub>3</sub>-O-(C<sub>6</sub>H<sub>4</sub>)-SO<sub>3</sub>H, curve c), with a weaker partner, exhibiting a partially resolved fine structure, centred at ca. 260 nm (catalyst SiO<sub>2</sub>-(C<sub>6</sub>H<sub>4</sub>)-SO<sub>3</sub>H and SiO<sub>2</sub>-(CH<sub>2</sub>)<sub>2</sub>-(C<sub>6</sub>H<sub>4</sub>)-SO<sub>3</sub>H, curves b,d, respectively) or at ca. 280 nm (catalyst SiO<sub>2</sub>-(CH<sub>2</sub>)<sub>3</sub>-O-(C<sub>6</sub>H<sub>4</sub>)-SO<sub>3</sub>H, curve c). These components can be identified as the primary (p) and secondary (α) bands, this latter with the typical vibrational structure, due to transitions involving the π electron system of a benzylic aromatic ring [48]. Their displacement towards longer wavelengths in the case of catalyst B can depend on the presence as substituent at the *para* position with respect the sulfonic group of an oxygen atom, capable of a larger

### 3. Supported sulfonic acids as novel catalysts in green oxidation processes

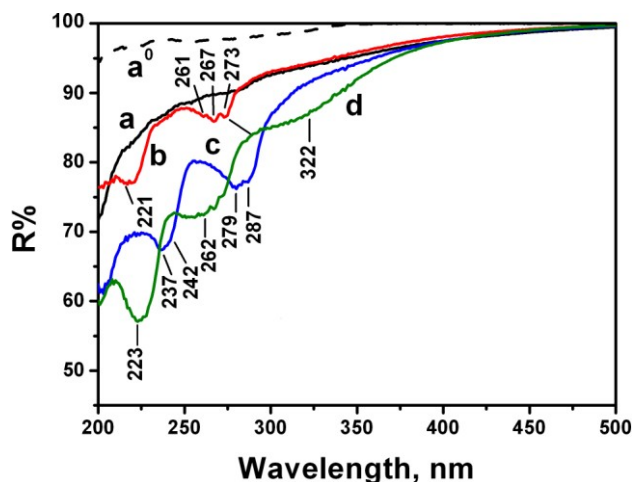
electron contributing effect than the Si atom and CH<sub>2</sub> present on the aromatic ring in catalysts SiO<sub>2</sub>-(C<sub>6</sub>H<sub>4</sub>)-SO<sub>3</sub>H and SiO<sub>2</sub>-(CH<sub>2</sub>)<sub>2</sub>-(C<sub>6</sub>H<sub>4</sub>)-SO<sub>3</sub>H, respectively. The spectra of the samples in air appeared similar to those of the aqueous slurries in terms of position of the absorption bands, that exhibited a lower intensity (Figure 9). This was likely due to the increased contribution of light scattering with respect absorption phenomena in the presence of only some layers of physisorbed water.

Subsequently, the slurries obtained by mixing the samples with the H<sub>2</sub>O/H<sub>2</sub>O<sub>2</sub> solution were analyzed. All spectra exhibited only a very intense and broad absorption band, with a deep reflectance minimum at ca. 250 nm and a tail towards longer wavelength (Figure 3, panel A'), due to H<sub>2</sub>O<sub>2</sub> molecules in aqueous solution. In order to render the spectral profiles independent on difference in intensity due to the not perfect equivalent density of all slurries, and better observe differences in shape, the data have been normalized to the minimum of reflectance.



**Figure 8.** DR UV-Vis spectra of slurries obtained by wetting the samples with different aqueous media. Panel A, samples in contact with H<sub>2</sub>O: a) bare silica used as support; a') highly pure silica used as diluent; b) catalyst A; c) catalyst B; d) catalyst C. Panel A': samples in contact with H<sub>2</sub>O<sub>2</sub>/H<sub>2</sub>O solution: a) bare silica; b) catalyst A; c) catalyst B; d) catalyst C. Inset, zoomed view of the 350-500 nm region, where the spectra (b'), (c'), (d') of the catalysts A, B, and C, respectively, in contact with the H<sub>2</sub>O<sub>2</sub>/H<sub>2</sub>O (the same as in panel A) are compared with the spectrum of the bare silica support in contact with the same medium (curves a', the same as in panel A') and with the spectra (b), (c) and (d) of catalyst the catalysts A, B, and C, respectively, in contact with H<sub>2</sub>O (the same as in panel A).

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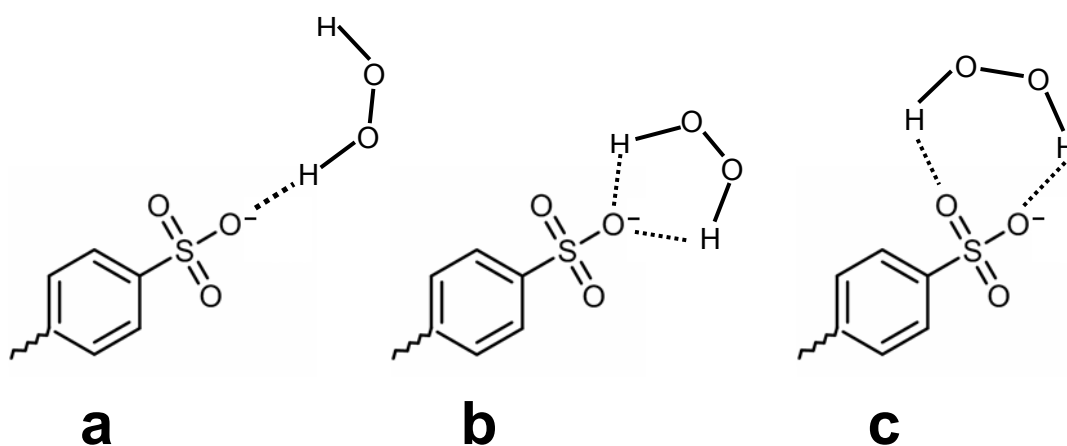


**Figure 9.** DR UV-Vis of samples in air: a<sup>0</sup>) pyrogenic silica used as diluents; a) bare silica support; b) catalyst SiO<sub>2</sub>-(C<sub>6</sub>H<sub>4</sub>)-SO<sub>3</sub>H; c) catalyst SiO<sub>2</sub>-(CH<sub>2</sub>)<sub>3</sub>-O-(C<sub>6</sub>H<sub>4</sub>)-SO<sub>3</sub>H; d) catalyst SiO<sub>2</sub>-(CH<sub>2</sub>)<sub>2</sub>-(C<sub>6</sub>H<sub>4</sub>)-SO<sub>3</sub>H.

It can be then noticed that the onset of the absorption of catalysts SiO<sub>2</sub>-(CH<sub>2</sub>)<sub>3</sub>-O-(C<sub>6</sub>H<sub>4</sub>)-SO<sub>3</sub>H and SiO<sub>2</sub>-(CH<sub>2</sub>)<sub>2</sub>-(C<sub>6</sub>H<sub>4</sub>)-SO<sub>3</sub>H, appeared shifted towards longer wavelength with respect to both the bare silica support and the catalysts simply in contact with H<sub>2</sub>O (Figure 8, panel A' inset). Such feature can be reasonably related to the interaction of H<sub>2</sub>O<sub>2</sub> molecules with supported organic species, that, apparently, occurred in a lower extent for catalyst SiO<sub>2</sub>-(C<sub>6</sub>H<sub>4</sub>)-SO<sub>3</sub>H, the spectrum of which appeared not so different with respect that obtained in the presence only of water. It is of interest to notice that catalyst A exhibited also the lowest catalytic activity, despite the similar content in supported sulphuric acids of catalyst SiO<sub>2</sub>-(CH<sub>2</sub>)<sub>3</sub>-O-(C<sub>6</sub>H<sub>4</sub>)-SO<sub>3</sub>H. Quantum chemical calculations indicate the possibility of the formation of complexes between H<sub>2</sub>O<sub>2</sub> and halide anions [49], and then it is proposed that some H-bonding interaction can occur between hydrogen peroxide (acting as an H-donor) and the sulphate groups (acting as H-acceptor) resulting from the deprotonation of supported sulfonic acids. As for the competition with water molecules for the interaction with sulphate groups, it can be recalled that H<sub>2</sub>O<sub>2</sub> in aqueous solution is a stronger H-bond donor (but a weaker acceptor) than H<sub>2</sub>O [49]. The result of the competition with hydrated H<sub>3</sub>O<sup>+</sup> ions should be the subject of a future modeling, as well as the effect of the sulphate-H<sub>2</sub>O<sub>2</sub> interaction on the electronic states of hydrogen peroxide molecules.

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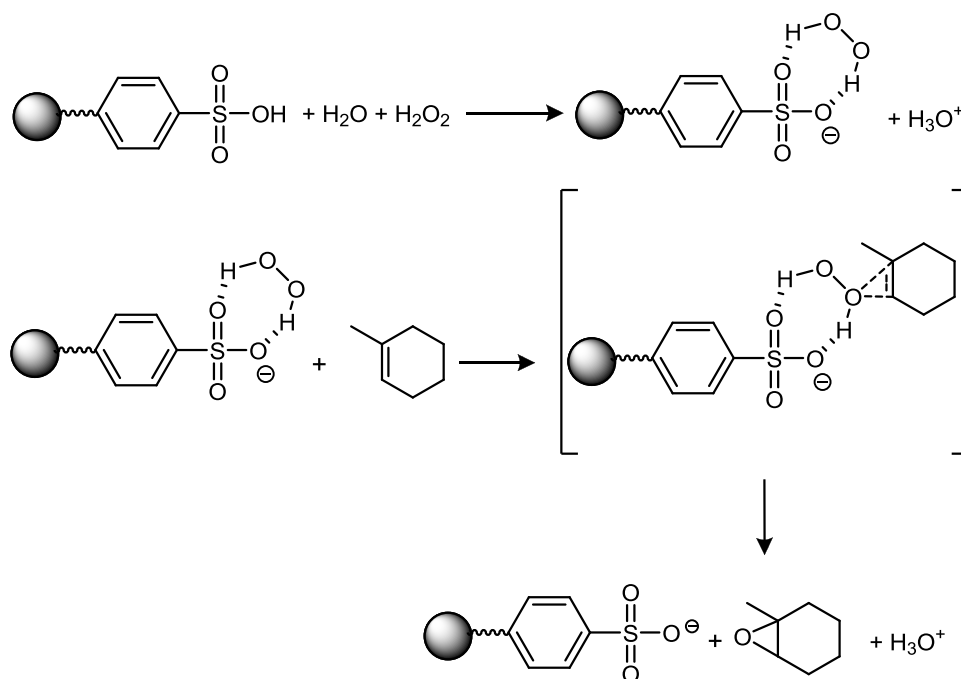
The occurrence of such interaction can be relevant for the catalytic process, as the results obtained by Neumann [10] on the selectivity attained in oxidation reactions by using  $\text{H}_2\text{O}_2$  in perfluorinated alcohol solvents suggested the possibility for an electrophilic activation of hydrogen peroxide via H-bonding. Tentative drawings are reported in Scheme 3, where no indication of the  $\text{H}_2\text{O}_2$  dihedral angle has been reported, intentionally. In general, it is known that hydrogen peroxide has a quite flexible molecular structure, easily distorted by molecular interactions [50, 51], as a result of the only weakly hindered rotation of the OH groups around the O-O bond [50,52]. According to these hypothesis the reaction mechanism could be tentatively considered as depicted in Scheme 4. The complex interaction between three different molecules may be responsible for the slow reaction rate.



**Scheme 3.** Possible interactions between sulfonic acid and hydrogen peroxide.



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**Scheme 4.** Possible reaction mechanism.

#### 3.3.4 Conclusions

Supported sulfonic acids can be used as eco-efficient catalysts for the dihydroxylation of 1-methylcyclohexene with aqueous  $\text{H}_2\text{O}_2$  under mild condition without using any additional solvent. The silica supported 4-ethylphenyl sulfonic acid shows the best activity giving 1-methyl-1,2-cyclohexanediol in 90 % yield and 96 % selectivity. The reaction requires an induction time before the product starts to be present in the reaction mixture. This period can be decreased by suspending the catalyst in aqueous hydrogen peroxide for two hours before adding the 1-methylcyclohexene. These results, together with the spectral analyses, suggest that the interaction between the catalyst and the hydrogen peroxide give rise to an activation of  $\text{H}_2\text{O}_2$  molecules, that produce the epoxide intermediate; this epoxide is immediately converted to the diol, by the addition of a water molecule.

#### 3.3.5 Experimental section

##### *Reaction procedure*

A 10-mL round-bottomed flask equipped with a magnetic stirring bar and reflux condenser was charged with the selected solid catalyst (2% mol with respect to 1-methylcyclohexene) and 30% aqueous H<sub>2</sub>O<sub>2</sub> (0.86 mL, 8.4 mmol). The mixture was stirred at rt for 10 min, after which 1-methylcyclohexene (0.50 mL, 4.2 mmol) was added. The mixture was heated at 70 °C under stirring for 22 h and then cooled to rt. The catalyst was removed by filtration and washed with methanol; MnO<sub>2</sub> (ca. 100 mg) was added to the solution to destroy any hydrogen peroxide excess. Subsequently, bromobenzene was added as internal standard, the mixture was diluted with methanol and analyzed by GC.

##### *Infrared and (DR) UV-vis analyses*

Infrared spectra of the catalysts were performed in transmission mode on powders pressed in self-supporting pellets (“optical thickness” in the 8-10 mg·cm<sup>-2</sup> range) and placed in a quartz IR cell equipped with KBr windows. The IR cell was connected to a conventional vacuum line (residual pressure  $p \leq 10^{-5}$  Torr), allowing adsorption/desorption experiments to be carried out in situ. A Bruker Vector 22 spectrometer was employed for spectra collection in the Mid-IR region, and a Jasco 6100 one for selected measurements extended to the Near-IR. In both cases, resolution was 4 cm<sup>-1</sup>, and a DTGS detector was employed.

All spectra were baseline corrected to remove the contribution of light scattering and were normalized with respect to the intensity of the signals at 1980 and 1870 cm<sup>-1</sup> due to the combinations of bulk framework modes [53] in order to render differences in intensity independent of differences in the thickness of the pellets.

Diffuse reflectance (DR) UV-Vis spectroscopy measurements were performed with a Cary 5000 spectrophotometer, equipped with an integrating sphere internally coated with Spectralon<sup>®</sup>. The same material was used as reference for the collection of the background baseline. The samples, in the form of powder, were put on a quartz optical window, that was the bottom of a cylindrical cell, closed by screwing a piston, pressed toward the powder by a spring. The amount of sample was dosed in order to form a layer ca. 3 mm thick, to extinguish the radiation path within the

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powder [54]. The samples were investigated both in air and in the form of concentrated slurries, obtained by dropping H<sub>2</sub>O or H<sub>2</sub>O<sub>2</sub>/H<sub>2</sub>O solution in proper amounts to obtain an incipient wetness of the powders. In all cases, the materials were diluted in a 1:30 ratio by weight with a highly pure amorphous silica (AOX50, Aerosil), in order to attain the best compromise between the location above the 0% of Reflectance of the most intense signals and a satisfactory signal/noise ratio for the weakest ones. The conversion with the Kubelka-Munk function was then attempted, but not longer considered, as the most intense signals exhibited values of the function significantly higher than 1 (for the samples in the form of aqueous slurries), then outside the limits of applicability of such algorithm [54].

***3.4 Supported sulfonic acids: metal-free catalysts for the oxidation of hydroquinones to benzoquinones with hydrogen peroxide under batch and continuous flow condition***

**3.4.1 Introduction**

Eco-efficient oxidation of alcohols, phenols and their derivatives can be carried out by using atmospheric oxygen, hydrogen peroxide or alkyl hydroperoxides in the presence of an appropriate solid catalyst that activates the oxidizing agent [55].

In particular, oxidation of phenols and hydroquinones affords quinones that are found as structural units in a great variety of natural compounds showing antifungal, antibacterial, antiviral and anticancer activity. These properties made quinones valuable intermediates for the preparation of fine chemicals and pharmaceuticals [56-58]. Furthermore, their use as dienophiles in Diels-Alder reactions is well documented [59].

The oxidation of substituted hydroquinones to the corresponding quinones can be achieved by a variety of methods based on the use of noxious oxidants and metal-based catalysts. For example, the Fremy's salt (potassium nitrodisulfonate) [60], sodium dichromate/sulfuric acid mixtures [61], benzyltrimethylammonium tribromide [62], iodine or hydroiodic acid/hydrogen peroxide mixtures [63], diphenyl diselenide/hydrogen peroxide mixtures [64], ammonium ceric nitrate/Montmorillonite K10 mixtures [65], phenyl iodosoacetate on alumina under microwave irradiation [66], and a variety of transition metal derivatives [67] have been exploited.

Phenols and naphthols can be directly converted into quinones via one-pot hydroxylation oxidation process in the presence of different oxidizing [68-73]. Particular interest shows the dye sensitized photo-oxygenation of 1,5-dihydroxynaphthalene to Juglone (5-hydroxy-1,4-naphthalenedione) with oxygen in the presence of moderately concentrated sunlight [74].

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Moreover, some recent examples are reported showing the use of heterogeneous catalysts for the efficient oxidation of hydroquinone to *para*-benzoquinone with hydrogen peroxide. Thus, Cu(II) catalyst supported onto acrylic resin [75], mesoporous titanium-silicate catalyst [76], and a catalyst based on platinum nanoclusters incarcerated into polystyrene [77] allow the aerobic oxidation of hydroquinones to quinones.

Recently our group have demonstrated that a well known and established reagent such as silver oxide can also be utilized as catalyst with excellent results to perform these reactions [78]. Furthermore, solid polyaniline has been utilized as non metal heterogeneous catalyst to perform oxidation of hydroquinone to *para*-benzoquinone with hydrogen peroxide [79].

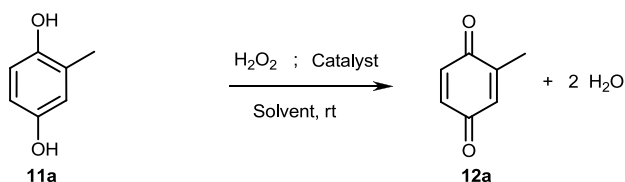
Catalysts based on polystyrene supported sulfonic acid (Nafion-NR50, Amberlyst-15) have shown successful results in various acid-catalyzed reactions [80, 81]. For this reason, we have evaluated the activity of silica-supported sulfonic acids as heterogeneous, metal-free catalysts for the oxidation of hydroquinones to benzoquinones with 30% aqueous hydrogen peroxide under batch and continuous flow conditions.

#### 3.4.2 Results and discussion

Methylhydroquinone, hereafter **11a**, has been utilized as model reagent in a series of experiments aimed at achieving the optimum conditions for the oxidation to methylbenzoquinone, hereafter **12a**, with 30% aqueous hydrogen peroxide catalyzed by some silica supported sulfonic acids catalysts and the commercially available Amberlyst-15. The experiments were carried out at room temperature in different solvents by adding dropwise aqueous hydrogen peroxide diluted in the same solvent during 30 minutes. The reaction mixture was stirred for a total time of 6 hours. Results are reported in Table 4.

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**Table 4.** Reaction of methylhydroquinone with aqueous H<sub>2</sub>O<sub>2</sub> in the presence of different solid catalysts and solvents.<sup>a</sup>



Entry	Catalyst	<b>11a</b> / H <sub>2</sub> O <sub>2</sub> ratio	Solvent	<b>12a</b> Yield [Sel.] <sup>b</sup> (%)
1	-	1/3	MeOH	~3
2	CH <sub>3</sub> SO <sub>3</sub> H	1/3	MeOH	49 [50]
3	SiO <sub>2</sub> -(CH <sub>2</sub> ) <sub>3</sub> -SO <sub>3</sub> H	1/2 <sup>c</sup>	MeOH	57 [93]
4	SiO <sub>2</sub> -(CH <sub>2</sub> ) <sub>3</sub> -SO <sub>3</sub> H	1/3	MeOH	79 [92] <sup>d</sup>
5	SiO <sub>2</sub> -(C <sub>6</sub> H <sub>4</sub> )-SO <sub>3</sub> H	1/2	MeOH	55 [61]
6	SiO <sub>2</sub> -(C <sub>6</sub> H <sub>4</sub> )-SO <sub>3</sub> H	1/3	MeOH	79 [79]
7	SG-(CH <sub>2</sub> ) <sub>3</sub> -SO <sub>3</sub> H	1/2	MeOH	32 [65]
8	SG-(CH <sub>2</sub> ) <sub>3</sub> -SO <sub>3</sub> H	1/3	MeOH	53 [62]
9	MCM-41-(CH <sub>2</sub> ) <sub>3</sub> -SO <sub>3</sub> H	1/2	MeOH	58 [91]
10	MCM-41-(CH <sub>2</sub> ) <sub>3</sub> -SO <sub>3</sub> H	1/3	MeOH	78 [90]
11	Amberlyst-15	1/2	MeOH	51 [93]
12	Amberlyst-15	1/3	MeOH	60 [92]
13	SiO <sub>2</sub> -(CH <sub>2</sub> ) <sub>3</sub> -SO <sub>3</sub> H	1/3	Acetone	71 [81]
14	SiO <sub>2</sub> -(CH <sub>2</sub> ) <sub>3</sub> -SO <sub>3</sub> H	1/3	H <sub>2</sub> O	10 [32]
15	SiO <sub>2</sub> -(CH <sub>2</sub> ) <sub>3</sub> -SO <sub>3</sub> H	1/3	MeCN	80 [85]
16	SiO <sub>2</sub> -(CH <sub>2</sub> ) <sub>3</sub> -SO <sub>3</sub> H	1/3	Dioxane	37 [73]

<sup>(a)</sup> Catalyst: 0.02 mmol, **1a**: 1 mmol, solvent: 2 ml, reaction time: 30 min addition and 5.5 h reaction.

<sup>(b)</sup> Determined by GC analysis. <sup>(c)</sup> When the reaction was performed with a stoichiometric amount of H<sub>2</sub>O<sub>2</sub>, product **3a** was obtained in a modest yield (41%). <sup>(d)</sup> When the reaction was performed on dark, product **3a** was obtained with the same yield (78%).

In the reactions carried out in methanol, methylbenzoquinone **12a** has been obtained in good yields. The propylsulfonic acid tethered onto both amorphous and mesoporous MCM-41 silica showed optimum activities [SiO<sub>2</sub>-(CH<sub>2</sub>)<sub>3</sub>-SO<sub>3</sub>H: 79% yield, 92% selectivity; MCM 41-(CH<sub>2</sub>)<sub>3</sub>-SO<sub>3</sub>H: 78% yield, 90% selectivity], better in terms of yield and selectivity to that obtained under homogeneous conditions performing the reaction with methanesulfonic acid [49% yield, 50% selectivity]; also the phenylsulfonic acid tethered onto silica [SiO<sub>2</sub>-(C<sub>6</sub>H<sub>4</sub>)-SO<sub>3</sub>H] gave product **12a** in good yield, but the selectivity was somewhat lower (79% yield, 79% selectivity).

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SG-(CH<sub>2</sub>)<sub>3</sub>-SO<sub>3</sub>H, prepared by sol-gel method, gave product **12a** in a lower yield (53%) and selectivity (62%); these results could be attributable to the method utilized in the catalyst preparation. In fact, in the material prepared by sol-gel technique it is expected that variable amounts of the sulfonic acid are incorporated within the siliceous framework and it appears that the sulfonic acid content, measured by the titration method [36], does not necessarily correspond to the same amount of catalytically active acid sites, since the access to these sites could be reduced or even hampered by the shape of the solid matrix. Moreover, the micropore structure of this material can hamper the reagent diffusion inside the catalyst (see chapter 2).

Amberlyst-15, utilized after water removal by heating at 100 °C for 24 hours, gave product **12a** in good yield (60%), however lower than that achieved with SiO<sub>2</sub>-(CH<sub>2</sub>)<sub>3</sub>-SO<sub>3</sub>H; this result could be ascribed to both the modest surface area and the hydrophobic nature of the polystyrenic support that could hamper the contact with the hydrophilic reagents.

Results from Table 4 also suggest that methanol was the solvent of choice in terms of yield, selectivity and solubility of both starting materials and products. The modest results achieved when the reaction was performed in acetone could be ascribed to the competitive production of the less reactive dimethyl dioxirane by reaction of hydrogen peroxide with acetone [82]. Similarly, the competitive interaction of the acid catalyst with the oxygen atoms of the solvent via H bond could account for the surprisingly low activity observed when the reaction was performed in 1,4-dioxane.

The successive studies were performed with the best catalyst [SiO<sub>2</sub>-(CH<sub>2</sub>)<sub>3</sub>-SO<sub>3</sub>H] in methanol with a methylhydroquinone/hydrogen peroxide molar ratio 1/3. The effect of the catalyst amount was first evaluated in the model reaction performed for 6 hours at room temperature. In Figure 10 the yield of product **12a** is plotted versus the catalyst amount.

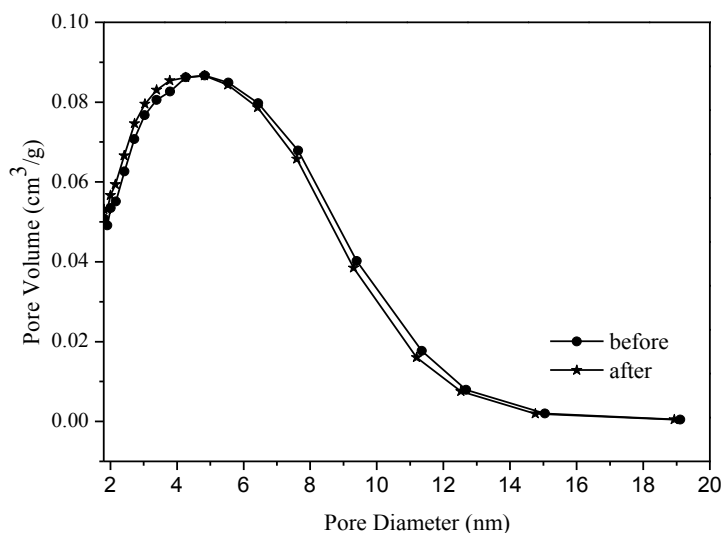
In the absence of catalyst, product **12a** was obtained only in traces (~3%). However, the **12a** yield was dramatically increased to 45% when only 0.01 g of SiO<sub>2</sub>-(CH<sub>2</sub>)<sub>3</sub>-SO<sub>3</sub>H (corresponding to 0.002 catalyst/1a molar ratio) was utilized. The maximum performance was achieved when the SiO<sub>2</sub>-(CH<sub>2</sub>)<sub>3</sub>-SO<sub>3</sub>H/ **11a** molar ratio was 0.02, being product **12a** obtained in 79% yield. By further increasing SiO<sub>2</sub>-(CH<sub>2</sub>)<sub>3</sub>-SO<sub>3</sub>H amount the yield of product **12a** did not show significant variations.

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The efficiency of hydrogen peroxide utilization in the model reaction, determined by evaluating the oxygen evolution after addition to the reaction crude of a suspension of manganese(IV) oxide, was found to be 52%.

The possible leaching of active species into solution and coexistence of homogeneous and heterogeneous catalysis was excluded by performing the Sheldon test [38]: the catalyst was removed by filtration after 1 hour when the methylbenzoquinone yield was 34%. Any yield increase was observed by keeping at room temperature the filtrate for further 5 hours.

The reusability of  $\text{SiO}_2\text{-(CH}_2\text{)}_3\text{-SO}_3\text{H}$  has then been checked in the model reaction. The catalyst, simply recovered by filtration and washed with hot methanol, can be reused two times, without further activation, giving product **12a** with the following yields and selectivities: 1st run 79% (92%); 2nd run 76% (91%); 3rd run 82 % (90%). It is important to underline that after the catalytic runs the catalyst maintained its textural characteristics: the BET surface area and the pore size distribution (Figure 11) of the material substantially did not change and no loss of specific pore volume was registered.



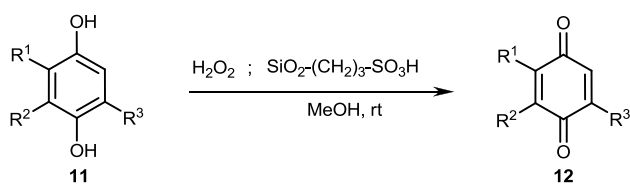
**Figure 11.** Pore size distribution (nm) of the functionalized mesoporous silica materials  $\text{SiO}_2\text{-(CH}_2\text{)}_3\text{-SO}_3\text{H}$  before and after catalytic cycle.

A variety of functionalized quinones were then prepared following the general optimized methodology. Synthetic results are described in Table 5.



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**Table 5.** Reaction of various hydroquinones with aqueous H<sub>2</sub>O<sub>2</sub>.<sup>a</sup>



Entry	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Benzoquinone	Yield [Sel.] <sup>b</sup> (%)
1	Me	H	H	<b>12a</b>	79 [92]
2	H	H	H	<b>12b</b>	80 [90]
3	Bu <sup>t</sup>	H	H	<b>12c</b>	44 [99]
4	Cl	H	H	<b>12d</b>	85 [99]
5	Me	Me	Me	<b>12e</b>	73 [78]
6	H	OMe	OMe	<b>12f</b>	53 [67]

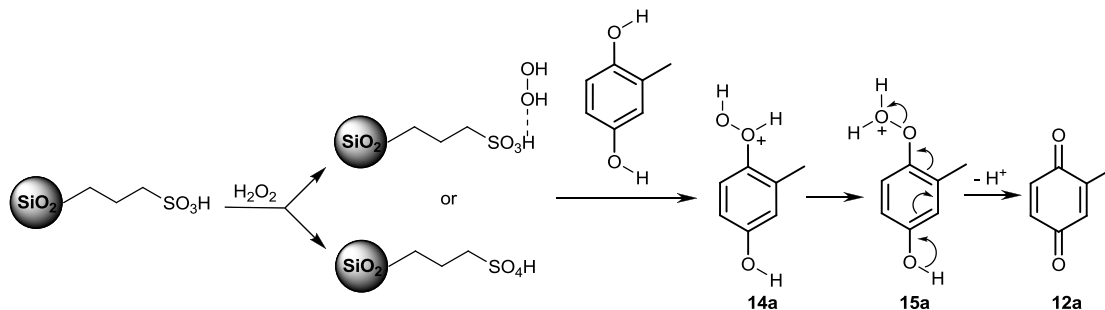
<sup>(a)</sup> Catalyst: 0.02 mmol, **11**: 1 mmol, MeOH: 2 ml, 30% aq H<sub>2</sub>O<sub>2</sub>: 3 mmol in MeOH 5 ml, reaction time: 30 min addition and 5.5 h reaction. <sup>(b)</sup> Determined by GC analysis.

The process gave quinones with satisfactory to good yields and selectivities starting from hydroquinones bearing both electronwithdrawing and electronreleasing groups. It is interesting to note that very good selectivities are obtained with hydroquinone, methylhydroquinone and chlorohydroquinone (Table 5, entries 1, 2 and 4); on the contrary, when the reaction is performed with hydroquinones bearing strong electronreleasing groups (entries 5 and 6), a drop in both yield and selectivity is observed, due to high reactivity of the starting materials that is responsible of the formation of overoxidation products.

Concerning a possible comment on the mechanism of the reaction, there are two different ways by which sulfonic acid can catalyze this oxidation reaction, as reported in literature: the hydrogen peroxide is probably activated by the sulfonic acid through hydrogen-bond formation; moreover it is also possible the in situ formation of the peroxysulfonic acid as a powerful oxidizing reagent [32, 83, 84]. In both cases the reaction proceeds through the formation of intermediates **14a** and **15a** [85] that produce the final methyl-1,4-benzoquinone (Scheme 5). It is important to underline that a possible radical mechanism contribution [1] can not be totally excluded as, by carrying out the reaction in the presence of stoichiometric amount of

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BHT (butylhydroxytoluene), a common radical inhibitor, variations in terms of yield and activity were observed (reaction carried out in the absence of BHT: 79% yield, 92% selectivity; reaction carried out in the presence of BHT: 52% yield, 90% selectivity).



**Scheme 5.** Possible ionic reaction mechanism.

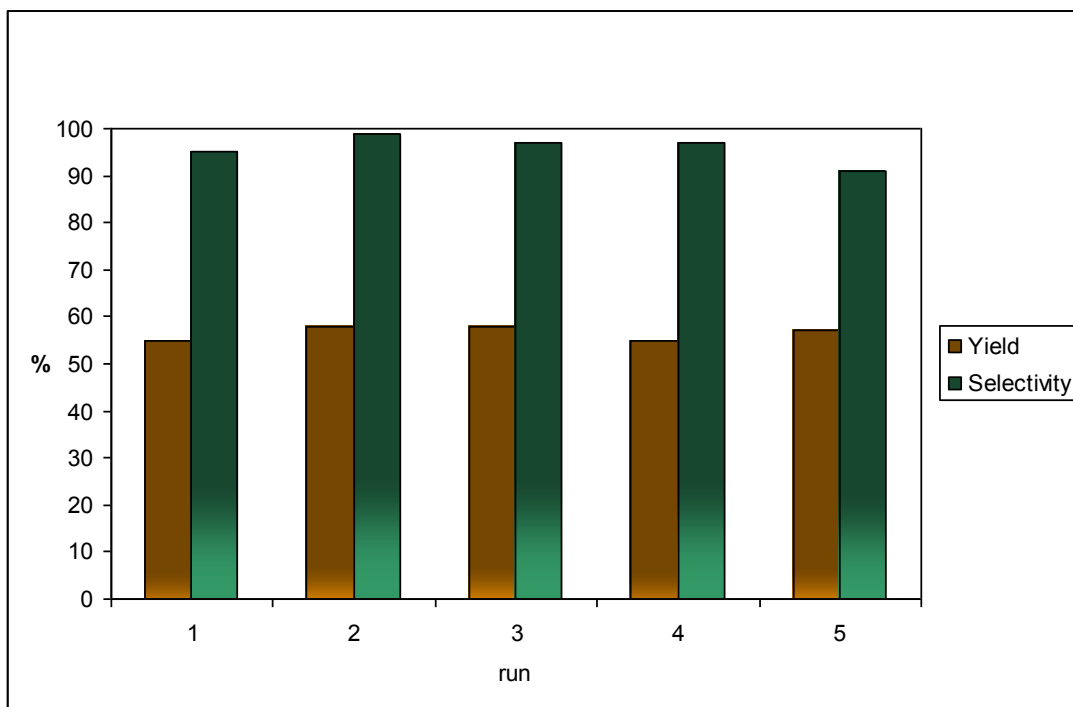
The good synthetic results and, in particular, the effective catalyst recyclability achieved in the batch experiments prompted us to develop a reaction method based on a continuous-flow catalytic system for performing the model reaction. Such a system, once optimized, can allow for a rapid, easy and efficient synthesis and purification of the target compounds [86]. To this end a simple apparatus was constructed using an HPLC column (10 cm length x 0.4 cm inner diameter) packed with the sulfonic resin Amberlyst-15 and equipped with a diaphragm metering pump to carefully control the flow rate.

Methylhydroquinone has been utilized as model reagent in a series of experiments aimed at achieving the optimum conditions for the oxidation with 30% aqueous hydrogen peroxide. The column-reactor was previously washed by flowing MeOH (10 mL) for 2 hours at 0.3 mL/min flow rate at room temperature, then a solution of methylhydroquinone **11a** (2 mmol) and 30% aq. H<sub>2</sub>O<sub>2</sub> (4 mmol) in MeOH (5 mL) was passed at room temperature with the flow rate of 0.080 ml/min and a minimum pressure applied (~ 1.2 bar). The column-reactor was then rinsed with additional MeOH (10 mL) and the combined eluates were analyzed by GC.

Amberlyst-15 is a commercial available sulfonic resin and it is quite different from the catalysts employed for the batch experiments, nevertheless this catalyst is

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produced in beads of 20-50 mesh and it is an ideal resin for continuous flow systems. We use a lower excess of H<sub>2</sub>O<sub>2</sub> (2:1) compared with the batch experiment and the product **12a** was obtained in 55% yield, however the selectivity was very high (95%) and this is the most important parameter in a continuous flow system. The reaction can be carried out for further four cycles without any loss of efficiency (Figure12).



**Figure 12.** Activity of Amberlyst-15 in five successive cycles of the model reaction, under continuous flow condition after washing with methanol.

#### 3.4.3 Conclusions

In conclusion we have found that sulfonic acids, tethered onto silica, represent good and reusable heterogeneous catalysts for the oxidation of hydroquinones to the corresponding quinones with 30% aqueous hydrogen peroxide under environmentally friendly conditions. Although this is a well-known oxidation reaction, the most important advantage of this protocol is that the use of metal catalysts is avoided. Moreover the reaction can be carried out under continuous flow conditions with a minimum pressure applied.

#### 3.4.4 Experimental section

##### *Reaction procedure*

To a mixture of the selected hydroquinone (1.0 mmol), SiO<sub>2</sub>-(CH<sub>2</sub>)<sub>3</sub>-SO<sub>3</sub>H (0.1 g, 0.02 mmol) and MeOH (2 ml), a solution of 30% aq H<sub>2</sub>O<sub>2</sub> (0.3 ml, 3.0 mmol) in MeOH (5 ml) was added dropwise under stirring during 30 min at rt. The mixture was continuously stirred for additional 5.5 h. The reaction mixture was then diluted with H<sub>2</sub>O (10 ml) and extracted with Et<sub>2</sub>O (2 x 15 ml). The combined organic layers were washed with H<sub>2</sub>O (2 x 10 ml) and dried over Na<sub>2</sub>SO<sub>4</sub>. The solvents were evaporated under reduced pressure affording the corresponding pure product after separation on a TLC plate using a mixture of hexane/EtOAc 10:1.

All the products gave melting points and spectral data consistent with values previously reported in the literature [87-90].

##### *Catalysts surface analyses*

Nitrogen adsorption-desorption measurements were performed at liquid nitrogen temperature (-196 °C) with an ASAP 2010 apparatus of Micromeritics. Before each measurement, the samples (0.1 g) were outgassed first at 100 °C for 12 h at  $5 \cdot 10^{-3}$  Torr and then at room temperature for 2 h at  $0.75 \cdot 10^{-6}$  Torr. The N<sub>2</sub> isotherms were used to determine the specific surface areas through the BET equation ( $S.A._{BET}$ ), the specific pore volume ( $V_s$ ) was calculated at  $p/p^\circ = 0.98$ , and pore size distributions were calculated from the BJH method calculated from the adsorption branch.

#### ***3.5 Oxidation of sulfides with diluted H<sub>2</sub>O<sub>2</sub> in a continuous flow reactor***

##### **3.5.1 Introduction**

Among oxidation processes, the chemoselective preparation of chiral/achiral sulfoxides and sulfones represents an extremely important class of reactions. In fact, sulfoxides and sulfones are valuable intermediates often utilized for the synthesis of fine chemicals and biologically active compounds. They often play an important role as therapeutic agents such as antiulcer, antibacterial, antifungal, cardiogenic, antihypertensive, antiarteriosclerotic and antihelminthic agents, as well as psychotropics and vasodilators. [91]

Nowadays the most important method for the preparation of these compounds involves the oxidation of thioethers. The sulfur atom can be easily oxidized by different electrophilic oxidants such as FeBr<sub>3</sub>-nitric acid, [92] mercury(II) oxide-iodine, [93] oxodiperoxo molybdenum complexes, [94] chromium(VI) oxide, [95] *meta*-chloroperbenzoic acid, [96] and benzeneseleninic peracid. [97]

Hence, in recent years, many studies have been devoted to replace common oxidants with aqueous hydrogen peroxide. There are many reports on the H<sub>2</sub>O<sub>2</sub>-based catalytic oxidation of sulfides by employing homogeneous and heterogeneous organocatalysts, acid catalysts, enzymes, metal catalysts (e.g. Ti, Mo, V, W, Fe, and Se), acid metal oxides, polyoxometalates, and the sulfonic resin Amberlyst 15. [1, 21, 22, 23, 98, 99, 100, 101, 102] More recently, the sulfoxides themselves, that are produced during the reaction, have been reported to be very effective catalysts for the selective oxidation of sulfides to sulfoxides without formation of sulfones as byproducts. [103] However, in some cases, a large excess of hydrogen peroxide must be utilized.

Despite this recent progress the thioether oxidation reaction requires further improvements with particular focus on the chemoselectivity of the reaction, as well as effective oxygen utilization avoiding unproductive H<sub>2</sub>O<sub>2</sub> decomposition.

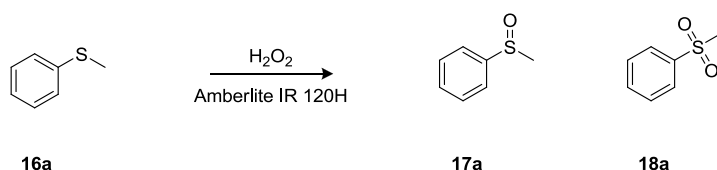
Here, we report on the highly chemoselective oxidation of sulfides with diluted hydrogen peroxide, catalyzed by Amberlite IR 120H in a continuous flow reactor. Continuous processing of catalytic reactions offers significant improvements

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compared to conventional batch processes due to a precise control of residence time, heat and mass transport. Continuous processes are thus contributing to more efficient and thus less wasteful and more sustainable syntheses. [104]

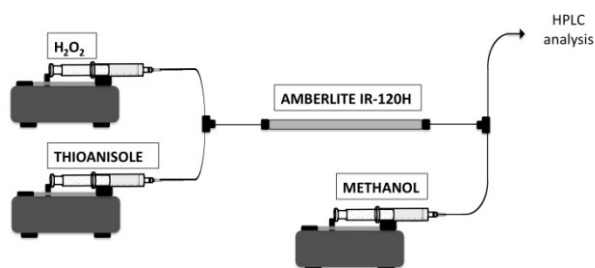
#### 3.5.2 Results and discussion

The catalyst Amberlite IR 120H used in this work is a commercially available polystyrene supported benzenesulfonic acid. In our studies, thioanisole **1a** was chosen as a model substrate for the oxidation reaction. In a first series of experiments a stoichiometric amount of 30% aqueous hydrogen peroxide was used (Scheme 6).



**Scheme 6.** Oxidation of thioanisole with H<sub>2</sub>O<sub>2</sub>.

In a preliminary batch experiment, the reaction was carried out at 4 °C using 1.40 g Amberlite IR 120H (loading: 4.4 meq H<sup>+</sup>/g), 7.44 g thioanisole (60 mmol) and 6.13 ml of 30% aqueous hydrogen peroxide (60 mmol). Methanol was used as solvent. After 60 min reaction time methylphenyl sulfoxide **17a** was obtained with 55% yield. For the continuous flow experiments a simple process was set up using a glass column (180 mm length × 11 mm inner diameter) packed with 6.8 grams of Amberlite IR 120H as a reactor. Three pulsation-free syringe pumps were connected to the reactor allowing a precise control of the flow rate of the two reagent solutions and of an additional methanol stream that was used for quenching the reaction at the outlet of the column reactor (Figure 13).



**Figure 13.** Schematic diagram of the reactor setup for the continuous flow oxidation of thioanisole with hydrogen peroxide.

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The continuous reaction has been performed at 4 °C by simultaneously pumping a mixture of thioanisole in methanol (0.89 mol L<sup>-1</sup>) and an equimolecular amount of 30% aqueous hydrogen peroxide through the reactor. At a residence time of 1.7 min, product **17a** was obtained in 11% yield. After increasing the residence time to 14 min by reducing the flow rates, the yield raised to 55%. Compared to the batch process the reaction was accelerated by a factor of more than 4. Given these excellent results, the model reaction was further investigated by conducting a systematic variation of experimental key parameters such as temperature, residence time and the molar ratio of thioanisole/hydrogen peroxide (Table 6).

**Table 6.** Continuous flow oxidation of thioanisole with 30% aq. H<sub>2</sub>O<sub>2</sub> catalyzed by Amberlite IR 120H<sup>a</sup>

Entry	Molar ratio H <sub>2</sub> O <sub>2</sub> /thioanisole	T [°C]	Residence time [min]	<b>16a</b> Conv. [%] <sup>b</sup>	<b>17a</b> Yield [%] <sup>b</sup>	<b>18a</b> Yield [%] <sup>b</sup>
1	1	6	50	85	85	-
2	1	6	25	83	83	-
3	1	6	17	80	80	-
4	1	22	50	97	95	2
5	1	22	25	95	94	1
6	1	22	17	94	92	2
7	1	30	50	98	94	4
8	1	30	25	97	94	3
9	1	30	17	96	94	2
10	1.07	6	50	97	97	-
11	1.07	6	25	94	94	-
12	1.07	22	50	98	94	4
13	1.07	22	25	96	92	4
14	1.07	30	50	100	88	12
15	1.07	30	25	100	94	6

<sup>(a)</sup> Reaction parameters: thioanisole **16a** solution in MeOH 0.89 mol/L, amount of catalyst: 6.80 g. <sup>(b)</sup> Determined by HPLC analysis

The best result was achieved by performing the reaction at 22 °C with a stoichiometric amount of 30% aqueous H<sub>2</sub>O<sub>2</sub> at a residence time of 25 min (Table 6, entry 5), obtaining sulfoxide **16a** in 94% yield and 99% selectivity. A little lowering of the selectivity was observed at higher temperatures, whereas lower temperature gave a reduction of the sulfoxide yield.

Further variation of residence time between 17 and 50 min did not produce very remarkable effects, however prolonged residence time gave rise to a little lowering in

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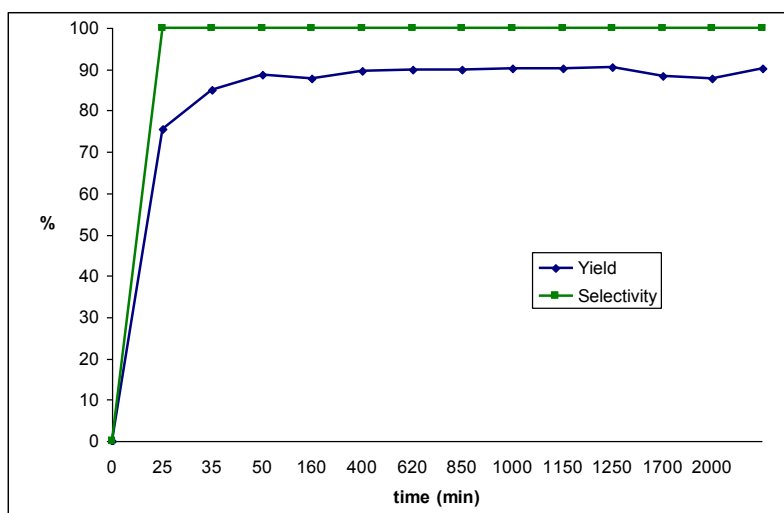
the selectivity, due to the increased formation of sulfone **18a**, whereas shorter residence times, while improving selectivity, caused a slight lowering in the thioanisole conversion.

Excellent results, both in terms of yield and selectivity, were achieved by performing the reaction at 6 °C (Table 6, entries 10 and 11) using an excess of hydrogen peroxide. However, from an environmental point of view, such over-stoichiometric conditions and the consumption of energy for cooling are less favored. In all other cases the excess of hydrogen peroxide caused a lowering in the yield of product **17a** and an increasing formation of sulfone **18a**.

The very promising results achieved in these experiments prompted us to perform the oxidation of thioanisole with more diluted hydrogen peroxide. For this reason we used a 3% aqueous hydrogen peroxide solution which is a very cheap chemical and can be handled safely.

The reaction was performed under the best conditions found by using 30% aqueous hydrogen peroxide (Table 6, entry 5). Surprisingly, only a small lowering in **17a** yield was found, being still very high at 90%. Moreover, as the sulfoxide was the only product, the selectivity was 100%.

The progress of yield and selectivity for the continuous oxidation with 3% H<sub>2</sub>O<sub>2</sub> is shown in Fig. 14. Obviously, the catalyst can be used for at least 3000 min without any loss of activity; under these conditions the ratio between the catalyst and the total thioanisole amount is 0.3.



**Figure 14.** Reaction trend for the continuous flow oxidation of thioanisole with 3% aqueous hydrogen peroxide catalyzed by Amberlite IR 120H (at 22 °C and under stoichiometric conditions).

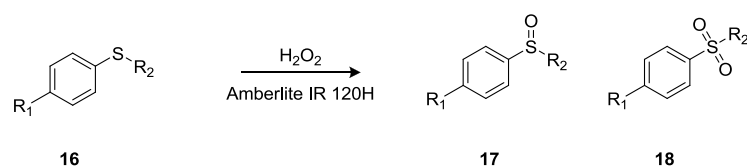


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These results represent the first example of the successful oxidation of aromatic sulfides with 3% aqueous hydrogen peroxide. Moreover, the process avoids the use of any metals for the activation of the oxidizing reagent.

The process was then applied to different aryl alkyl sulfides using an equimolecular amount of 3% hydrogen peroxide (Table 7).

**Table 7.** Continuous flow oxidation of various sulfides with 3% aqueous hydrogen peroxide catalyzed by Amberlite IR 120 H<sup>a</sup>



Entry	R <sub>1</sub>	R <sub>2</sub>	<b>16</b> Conv. [%] <sup>b</sup>	<b>17</b> Yield [%] <sup>b</sup>	<b>18</b> Yield [%] <sup>b</sup>
1	-H	-CH <sub>3</sub>	90	90	-
2	-OCH <sub>3</sub>	-CH <sub>3</sub>	99	96	3
3	-NO <sub>2</sub>	-CH <sub>3</sub>	97	93	4
4	-Cl	-CH <sub>3</sub>	81	81	-
5	-Br	-CH <sub>3</sub>	94	93	1
6	H	-Ph	87	84	3

<sup>(a)</sup> Reaction parameters: residence time 25 min, T = 22 °C, molar ratio H<sub>2</sub>O<sub>2</sub> / **16** = 1:1. <sup>(b)</sup> Determined by HPLC analysis. <sup>(c)</sup> Hydrogen peroxide diluted with methanol.

In all cases the yield and the selectivity obtained were excellent, and the process allowed the oxidation of arylsulfides carrying both electron-withdrawing and electron-donating groups at the *para* position of the aromatic ring. Due to the slight solubility of some substrates, hydrogen peroxide was sometimes diluted in methanol (Table 7, entries 2, 3, 5, and 6).

#### 3.5.3 Conclusions

In conclusion we have found that commercially available sulfonic resin Amberlite IR 120H represents a very promising heterogeneous catalyst for the chemoselective oxidation of sulfides to the corresponding sulfoxides with only 3% aqueous hydrogen

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peroxide under environmentally friendly conditions. Although this is a well-known oxidation reaction, an important advantage of this protocol is that the use of metal catalysts is avoided; in addition the process is carried out under continuous flow conditions with the additional resulting advantages.

#### 3.5.4 Experimental section

A glass column (180 mm length  $\times$  11 mm inner diameter) packed with 6.8 grams of Amberlite IR 120 H, dipped in a water bath, was utilized as reactor. Three pulsation-free syringe pumps were connected to the reactor allowing a precise control of the flow rate of the thioanisole solution in MeOH (0.89 mol L<sup>-1</sup>), the 3% aq H<sub>2</sub>O<sub>2</sub> and an additional methanol stream that was used for quenching the reaction at the outlet of the column reactor. The reagents were passed through the reactor in stoichiometric ratio, with a total flow rate of 0.200 mL min<sup>-1</sup>, allowing the oxidation reaction with a residence time of 25 min. The eluates, collected and diluted in MeOH, were analyzed by HPLC (Instrument: Agilent 1200; column: Zorbax Bonus RP 250  $\times$  4.6, 5  $\mu$ m; eluent: MeOH/H<sub>2</sub>O + 0.03% TFA with gradient–gradient: 0 min. 38% MeOH, 5 min. 38% MeOH, 5.1 min. 82% MeOH, 12 min. 82% MeOH; flow rate: 1 mL min<sup>-1</sup>; injection volume: 5  $\mu$ L; detector: DAD at 254 nm; temperature: 25 °C; calibration: external standards). All sulfoxides and sulfones were isolated and identified by comparison with pure reference samples.

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### 3. Supported sulfonic acids as novel catalysts in green oxidation processes

[104] B. P. Mason, K. E. Price, J. L. Steinbacher, A. R. Bogdan and D. T. McQuade, *Chem. Rev.*, **2007**, 107, 2300.



## 4 Catalytic C–C bond formation promoted by supported sulfonic acid catalysts

### 4.1 General introduction

The C–C bond formation represents a fundamental key transformation in organic synthesis; in fact, the reactions that allow the formation of this bond, are key steps in many syntheses of organic chemicals and natural products, as well as in a variety of industrial applications. Thus, these reactions are important tools for synthetic chemists. Examples of reactions which form carbon–carbon bonds are aldol, Diels-Alder, Grignard, Heck, Michael and Wittig reactions, as well as the Friedel-Crafts alkylations and acylations.

The aldol reaction is recognized as one of the most important tools for the construction of new carbon–carbon bonds in both biochemical and purely chemical domains. Concomitant with the carbon–carbon bond forming process is the formation of one or two adjacent new stereocenter(s), making the control of both the absolute and the relative configuration of the aldol products crucial. Both chiral and achiral groups attached to either substrate components, metal center in the enolate intermediate, or the catalyst/promoter can play a role in controlling stereochemistry during the aldol reaction.

Among the others, the Heck reaction is one of the most studied reaction in this field [1] during last years; it involves the palladium-catalysed arylation of olefinic double bonds and provides an alternative route to Friedel-Crafts alkylations or acylations for attaching carbon fragments to an aromatic rings. The reaction has broad scope and is currently being widely applied in the pharmaceutical and fine chemical industries. For example, Albemarle has developed a new process for the synthesis of the anti-inflammatory drug, naproxen, in which the key step is the Heck reaction. [2]

The present work focus on two different reactions that allow the C-C bond formation:

- Friedel-Crafts acylation of aromatics

#### 4. Catalytic C-C bond formation promoted by supported sulfonic acid catalysts

- Coupling reaction through C-H bond activation

The first one is undoubtedly one of the most studied organic reactions, and despite the huge number of scientific works on this subject, continues to inspire a great interests at both academic and industrial levels. From the other hand, the second reaction is not yet fully investigated, but may represent a very promising way for the future development of organic synthesis.

#### *4.2 Friedel-Crafts acylation reaction with anhydrides: silica supported sulfonic acids as green and efficient heterogeneous catalysts.*

##### 4.2.1 Introduction

The Friedel-Crafts acylation is one of the most investigated synthetic organic reactions [3, 4]. The great interest in the electrophilic acylation studies and in the optimization of the related synthetic processes was spurred by the considerable practical value of the aromatic ketones [5]. In fact aromatic ketones are of particular importance in the manufacture of intermediates for fragrance and pharmaceutical industries [6, 7]. Usually, electrophilic acylations are catalyzed by Lewis acids ( $\text{ZnCl}_2$ ,  $\text{AlCl}_3$  and  $\text{FeCl}_3$ ) or strong protic acids ( $\text{HF}$  and  $\text{H}_2\text{SO}_4$ ). However, the use of Lewis acid or corrosive mineral acids is associated with a great number of environmental and economical problems. Indeed, stoichiometric amounts of catalyst are needed, and troublesome work-up steps are also needed when Lewis acids are utilized. Besides, usually more than stoichiometric amounts of these acids are required, and a huge quantity of anions (specially chloride) is released in aqueous medium. For these reasons, during the past decade, the setting up of more eco-compatible Friedel-Crafts acylation reactions has become a fundamental goal of the general “green revolution” that has spread in all fields of synthetic chemistry [8, 9]. In particular, maximum efforts have been directed toward the use of solid acid catalysts. Heterogeneous catalysts can be easily separated from the reaction mixture

#### 4. Catalytic C-C bond formation promoted by supported sulfonic acid catalysts

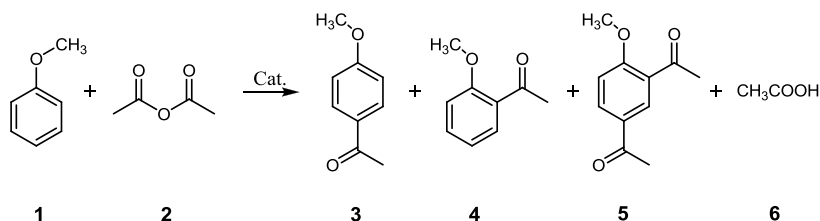
and reused; they are generally not corrosive and do not produce problematic side products [10, 11]. Different classes of materials have been studied and utilized as heterogeneous catalysts for Friedel-Crafts acylations, such as zeolites [12], metal oxides [13] and heteropoly acids [14].

In recent years this idea was further developed due to the design of hybrid organic–inorganic mesoporous silicas functionalized with sulfonic acid groups, that combine the acid strength with the high surface area of mesoporous materials [15,16,17].

The present work deals with the catalytic evaluation of a series of silica supported sulfonic acids in the acylation reaction of anisole, avoiding the use of metals and chlorinated reagents.

#### 4.2.2 Results and Discussion

A series of KG-60 silica supported alkyl-, aryl- and fluoroalkyl- sulfonic acids was prepared, according to well known literature procedures (see chapter 2), and their efficiency in the acylation of anisole was evaluated (Scheme 1).



**Scheme 1.** Acylation of anisole with acetic anhydride.

The above method shows low environmental impact, because it avoids the use of halogenated compounds, and acetic acid is the only by-product. However, since the anisole is a very activated reagent toward the electrophilic aromatic substitution reaction, the *para*-acylation product may be accompanied not only by the *ortho*-acylation isomer, but also by the diacylation product.

The first experiments, aimed to find the best reaction conditions, were carried out by using  $\text{SiO}_2\text{-(CH}_2\text{)}_2\text{-(C}_6\text{H}_4\text{)-SO}_3\text{H}$  catalyst. (Table 1)

#### 4. Catalytic C-C bond formation promoted by supported sulfonic acid catalysts

**Table 1.** Reaction of anisole with acetic anhydride, catalyzed by silica supported sulfonic acids.

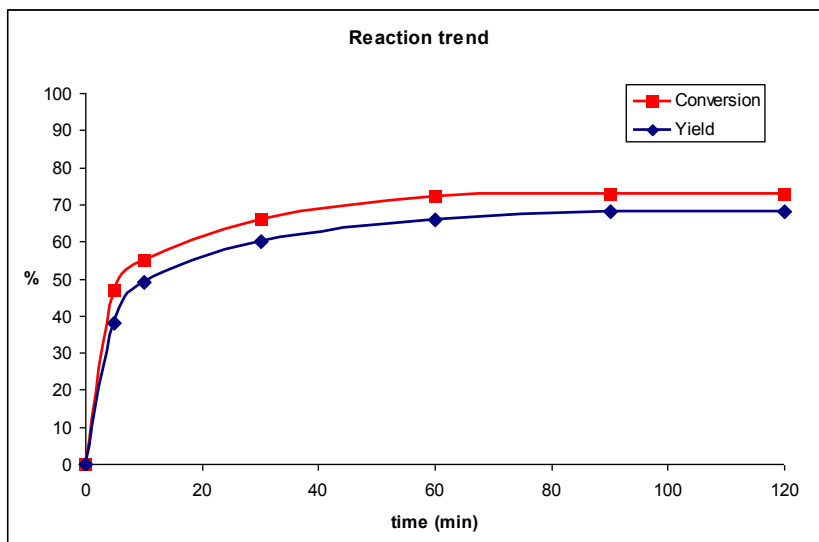
entry	Catalyst	T (°C)	1/2 molar ratio	Catalyst loading (%)	3 Yield (%)	3 Selectivity (%)
<i>Effect of experimental conditions</i>						
1	SiO <sub>2</sub> -(CH <sub>2</sub> ) <sub>2</sub> -(C <sub>6</sub> H <sub>4</sub> )-SO <sub>3</sub> H	60	1:1	5	27	87
2	SiO <sub>2</sub> -(CH <sub>2</sub> ) <sub>2</sub> -(C <sub>6</sub> H <sub>4</sub> )-SO <sub>3</sub> H	80	1:1	5	31	89
3	SiO <sub>2</sub> -(CH <sub>2</sub> ) <sub>2</sub> -(C <sub>6</sub> H <sub>4</sub> )-SO <sub>3</sub> H	120	1:1	5	38	83
4	SiO <sub>2</sub> -(CH <sub>2</sub> ) <sub>2</sub> -(C <sub>6</sub> H <sub>4</sub> )-SO <sub>3</sub> H	120	1:3	5	55	92
5	SiO <sub>2</sub> -(CH <sub>2</sub> ) <sub>2</sub> -(C <sub>6</sub> H <sub>4</sub> )-SO <sub>3</sub> H	120	1:3	2	43	88
<i>Effect of catalyst acidity</i>						
6	SiO <sub>2</sub> -(CH <sub>2</sub> ) <sub>3</sub> -SO <sub>3</sub> H	120	1:3	10	12	80
7	SiO <sub>2</sub> -(CH <sub>2</sub> ) <sub>4</sub> -SO <sub>3</sub> H	120	1:3	10	16	80
8	SiO <sub>2</sub> -(C <sub>6</sub> H <sub>6</sub> )-SO <sub>3</sub> H	120	1:3	10	45	94
9	SiO <sub>2</sub> -(CH <sub>2</sub> ) <sub>2</sub> -(C <sub>6</sub> H <sub>4</sub> )-SO <sub>3</sub> H	120	1:3	10	68	93
10	SiO <sub>2</sub> -CF <sub>2</sub> -CF-(CF <sub>3</sub> )-SO <sub>3</sub> H	120	1:3	10	71	95

By performing the model reaction at 60 °C with a 1/2 molar ratio = 1 with 5% of SiO<sub>2</sub>-(CH<sub>2</sub>)<sub>2</sub>-(C<sub>6</sub>H<sub>4</sub>)-SO<sub>3</sub>H catalyst, product **3** has been obtained in 27 % yield (Table 1, entry 1). When the same reaction was performed at 120 °C, the yield reached the value of 40 %, without any significant loss of selectivity (Table 1, entry 3). Successive experiments were performed to evaluate the effect of an excess of anhydride and results confirmed that product **3** could be obtained in 55% yield by using a molar ratio anisole/acetic anhydride = 1:3. The yield of product **3** was also considerably improved by increasing the catalyst amount (Table 1, entries 5, 4, 9): thus a proportional yield enhancement from 43%, to 55% and 68% was observed by increasing the amount of catalyst from 2, to 5 and 10%. From the environmental point of view, it should be underlined that the absence of any metals in the catalyst, makes it very attractive.

The model reaction has been studied in function of time (Figure 1): product **3** yield and anisole conversion values raise quickly in the first 30 minutes, reaching a plateau

#### 4. Catalytic C-C bond formation promoted by supported sulfonic acid catalysts

after the first hour. This trend is typical for acylation reaction performed with solid acid catalysts [18].



**Figure 1.** Reaction trend in function of time.

The comparison of the activity of different catalysts was also studied; the reactions were carried out under the best conditions found for  $\text{SiO}_2\text{-(CH}_2\text{)}_2\text{-(C}_6\text{H}_4\text{)-SO}_3\text{H}$  catalyst, highlighting great differences in the reactivity (Table 1, entries 6-10). In all cases 4-methoxyacetophenone (**3**) was the major product; 2-methoxyacetophenone (**4**) was also detected, while diacylation product **5** was not found even in traces. The best result in terms of both yield (71%) and selectivity (95%) toward 4-methoxyacetophenone product was achieved with the perfluoroalkyl sulfonic acid tethered onto silica catalyst [ $\text{SiO}_2\text{-CF}_2\text{-CF-(CF}_3\text{)-SO}_3\text{H}$ ].  $\text{SiO}_2\text{-(CH}_2\text{)}_2\text{-(C}_6\text{H}_4\text{)-SO}_3\text{H}$  catalyst showed similar good reactivity, while a little lowering of activity was observed by employing  $\text{SiO}_2\text{-(C}_6\text{H}_6\text{)-SO}_3\text{H}$  catalyst. The propyl- and butylsulfonic acids tethered onto silica gave the desired product in very low yields.

This behavior may be attributed to the different acidity of the tested materials, that seems to be correlated to the strength of the supported sulfonic acids. In fact the  $\text{SiO}_2\text{-CF}_2\text{-CF-(CF}_3\text{)-SO}_3\text{H}$  catalyst is undoubtedly the stronger one employed in this work, [19] due to the inductive effect played by the fluorine atoms; on the contrary,  $\text{SiO}_2\text{-(CH}_2\text{)}_3\text{-SO}_3\text{H}$  and  $\text{SiO}_2\text{-(CH}_2\text{)}_4\text{-SO}_3\text{H}$  catalysts are weaker acids [19] and consequently their activity is reduced.

#### 4. Catalytic C-C bond formation promoted by supported sulfonic acid catalysts

According to the classical reaction mechanism proposed for acylation with anhydrides, the acylating agent is the acylium ion. This highly reactive cation is generated by protonation of the anhydride. Hence the stronger the acidity of the catalyst, the higher the acylium ion concentration, in agreement with experimental results.

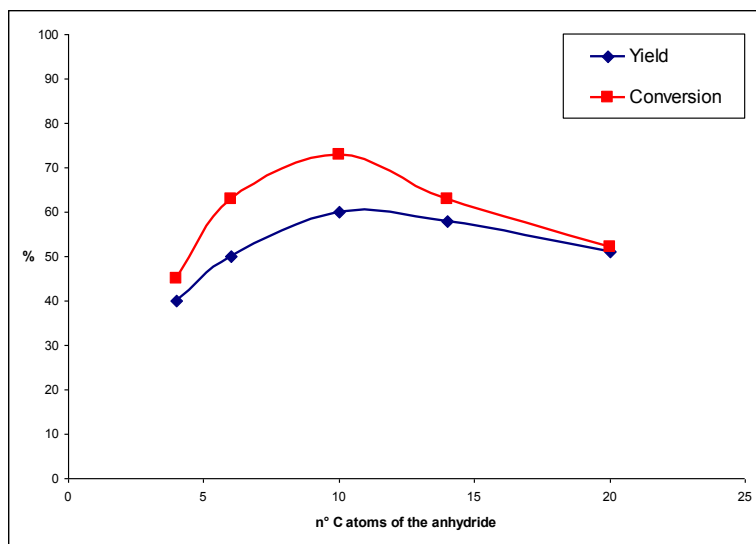
Another important parameter that can influence the catalyst activity, is the linker length. Comparing catalysts of similar or identical acidity, it seems that longer spacers improve the reactivity; indeed, as reported in Table 1, this effect is observed for both alkyl- and aryl-supported sulfonic acids.

Leaching of active species into the solution and thus coexistence of homogeneous catalysis was excluded by performing the Sheldon hot-filtration test [20]. The catalyst was filtered at 120 °C after 10 minutes reaction time (when the yield of product 3 was 48%); any yield increase was observed by keeping the filtrate at 120 °C for further 2 hours.

The model reaction (Scheme 1) was then performed with different aliphatic anhydrides with anisole in order to evaluate the effect of the length of the acylating reagent. Experiments were carried out under milder conditions: in fact, under the best conditions found for the acylation of anisole with acetic anhydride, the conversion of the reagent is too high to point out significant gap in reactivity.

The reaction was thus carried out for one hour at 100 °C, using a 3:1 excess of anhydride with respect to anisole, and 5 mol% of catalyst  $\text{SiO}_2-(\text{CH}_2)_2-(\text{C}_6\text{H}_4)-\text{SO}_3\text{H}$ . Figure 2 clearly shows that the reactivity of the different anhydrides seems to be correlated with the length of their alkyl chains.

#### 4. Catalytic C-C bond formation promoted by supported sulfonic acid catalysts



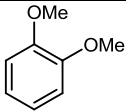
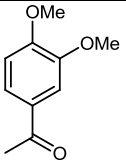
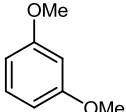
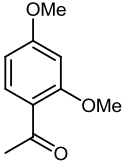
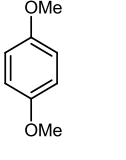
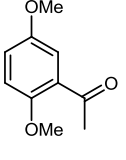

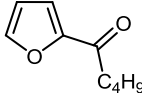

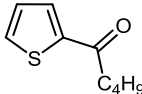
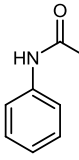
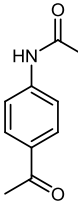
**Figure 2.** Acylation of anisole with different anhydrides.

The anisole conversion and the aromatic ketone yield raise with the number of carbon atoms of the anhydrides, going from acetic anhydride (4 carbon atoms ) to valeric anhydride (10 carbon atoms). With longer alkyl chains the reactivity slightly decreases. This behavior may be attributed to an hydrophobic positive effect, that can improve the reactivity until the maximum reached with valeric anhydride; for longer anhydrides, this effect is overbalanced by a negative steric influence.

The scope and generality of the acylation process with respect to various aromatics substrates was then investigated. Experimental results reported in Table 2 confirm the general applicability of the silica supported catalyst in the acylation reaction with acetic anhydride.

#### 4. Catalytic C-C bond formation promoted by supported sulfonic acid catalysts

**Table 2.** Friedel-Crafts acylation of aromatics <sup>a</sup>

Entry	Substrate	Product	Conv. (%)	Yield (%)
a			90	77
b			95	75
c			20	18
d			-	50
e			-	69
f			15	10

(a) Reaction conditions: substrate / acetic anhydride molar ratio 1:3, SiO<sub>2</sub>-(CH<sub>2</sub>)<sub>2</sub>-(C<sub>6</sub>H<sub>4</sub>)-SO<sub>3</sub>H: 5% mol, T = 120 °C, 1.5 h. (b) Reaction performed with valeric anhydride, T = 22 °C.

1,4-Dimethoxybenzene (entry c) shows a poor reactivity, compared to its regioisomers, because the *para* position of the ring is already occupied by another methoxy group. The slight solubility of *N*-acetylaniline in acetic anhydride may be responsible for the low reactivity.

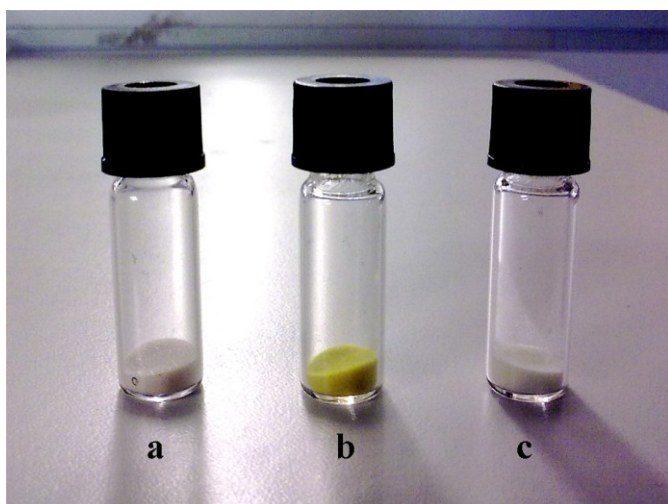
The reaction of heterocyclic compounds such as furane and thiophene (entries e, f), has been carried out at room temperature, due to the high volatility of these substrates. Unfortunately at this temperature the acetic anhydride is not reactive, for this reason the reaction has been performed with valeric anhydride.

Finally the solid catalyst recycle was tried; the recycle represent the most complicated issue of this catalytic system since, as reported in the literature, usually supported sulfonic acids lose their activity in acylation reaction after the first run.



#### 4. Catalytic C-C bond formation promoted by supported sulfonic acid catalysts

The “hot filtration test” has excluded the occurrence of leaching, thus the deactivation of this material is attributable to the formation of some ionic species that strongly interact with the catalyst. The presence of poisoning compounds is confirmed by the intense yellow color assumed by the solid acid after the first use, (Figure 3). Attempts to regenerate the catalyst by washing with ethanol, ethyl acetate and water did not give good results. The destruction of the adsorbed compounds by treatment with hydrogen peroxide was also attempted, but no improvements were obtained. Lastly, by washing the catalyst with a 2N HCl or HNO<sub>3</sub> solution, the loss of the intense yellow color of the solid was detected. The catalyst was further washed with water to eliminate any trace of mineral acid and subsequently dried at 100 °C for 2 hours: under these conditions the catalytic activity was partially restored. The acylation of anisole with the regenerated catalyst was performed with a 38 % yield. The deactivation pathway continues to be a complicate question for this process, however the reported results may open new chances to understand this issue.



**Figure 3.** a) as prepared catalyst; b) used catalyst; c) recovered catalyst washed with HCl 2N aq.

#### 4.2.3 Conclusions

In conclusion, silica supported sulfonic acids evidence an high activity in acylation processes as compared with other homogeneous and heterogeneous sulfonated acid catalysts.

#### 4. Catalytic C-C bond formation promoted by supported sulfonic acid catalysts

These new materials could constitute a competitive alternative to traditional homogeneous systems conventionally used as catalysts in acylation processes. In fact, most of the previous results describe examples of preparative methods in which the catalyst still represents the most expensive component of the process. This drawback creates economical and environmental problems that are particularly serious when transition metals, and in general, soluble metal derivatives, are utilized as catalysts, because they may adsorb some of the final products.

The results reported are also very important for the future development of new catalysts, in order to reach higher yield and selectivity values. For example the correlation between surface acidity and catalytic activity found for this reaction will allow the synthesis of even more active materials.

A further improvement might come from the detailed physico-chemical characterization of the catalytic materials, as well as from the studies of their interaction with reagents and products.

Deactivation and regeneration of these catalysts as well as their catalytic behavior with less activated aromatic compounds to settle their potential industrial applicability are currently under investigation.

##### 4.2.4 Experimental section

Reaction procedure: to a mixture of acetic anhydride **2** (0.286 ml, 3.0 mmol) and solid catalyst (0.10 mmol) the anisole **1** (0.108 ml, 1.0 mmol) was added under stirring at room temperature. The mixture was then heated to 120 °C and stirred for 90 minutes. After this period the mixture was diluted with ethanol, filtered off and washed with ethanol (3 x 5 ml).

The filtrate was analyzed by GC, using dodecane as external standard.

### ***4.3 Coupling reaction through C-H bond activation: supported sulfonic acids as heterogeneous catalysts for oxidative coupling of xanthene with nucleophiles.***

#### **4.3.1 Introduction**

Organic synthesis takes advantage from the high reactivity of some functional groups, that allows the transformation of the starting reagents into the targeted compounds. In fact, the general strategy for the formation of a new bond requires the presence of a heteroatom or an unsaturation in the carbon backbone of an organic molecule, as clearly stated by Corey.[21]

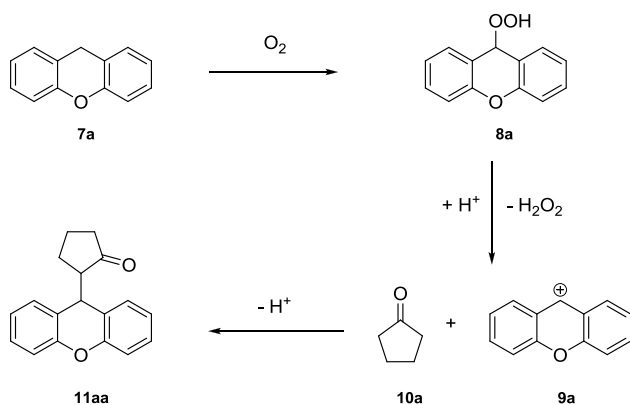
In this light, it is clear that the introduction of a new functionality through transformation of a (sp<sup>3</sup>)C-H bond, can unlock new opportunities for synthetic strategies.[22, 23] The high stability of this bond makes it generally unreactive, and not so useful from a synthetic point of view.[24] Furthermore, the direct insertion of a new group through the (sp<sup>3</sup>)C-H bond, can allow organic reactions with very good atom economy, that is one of the fundamental principles of the green chemistry.[25] For these reasons the activation of (sp<sup>3</sup>)C-H bond has attracted much attention at both the academic and industrial levels.

The production of a new C-C bond by coupling of two sp<sup>3</sup> carbons under oxidative conditions has been recently reported. In this reaction hydrogen acts as theoretical “leaving group” and in the best case water is the only by-product.[26] These oxidative coupling reactions can be catalytically performed simply by using metal salts or organic redox-active molecules for the activation of C-H bond. For example, the coupling of two (sp<sup>3</sup>)C-H bonds, one showing acid nature such as in nitromethane [27, 28] and in a methyl ketone,[29] and the other adjacent to a nitrogen atom, can be efficiently catalyzed by Cu(I) salts, in the presence of TBHP or even molecular oxygen. Furthermore, with (sp<sup>3</sup>)C-H bonds adjacent to different heteroatoms, such as oxygen, sulfur and nitrogen, a similar coupling reaction can be carried out by using an iron catalyst under similar conditions, generating the corresponding C-C bond.[30] However, often hard oxidants, harsh conditions, and

#### 4. Catalytic C-C bond formation promoted by supported sulfonic acid catalysts

expensive reagents are required, thus diminishing the overall efficiency and sustainability of the entire process.

Newly, Klussmann et al. reported an aerobic oxidative coupling of activated benzylic CH<sub>2</sub> groups in xanthene **7a** with ketones and 1,3-dicarbonyl compounds; the reaction proceeds smoothly under mild conditions without a metal reagent and requires only the cheap methane sulfonic acid and oxygen.[31] This reaction does not involve any redox-active catalyst and any reagent commonly used for C-H bond activation; thus it holds great potential for the design of sustainable syntheses with simple and cheap reagents with low level of environmental impact. A possible mechanistic rationalization, proposed by authors, involves the autoxidative formation of a xanthene hydroperoxide **8a**, which would react in an acid-catalyzed S<sub>N</sub>1 type reaction with nucleophiles like ketone **10a** to form the coupling product **11aa** and hydrogen peroxide (Scheme 2).



**Scheme 2.** Possible mechanism for the oxidative coupling of xanthene with cyclopentanone.

To enhance the sustainability of this process, the activity of some supported sulfonic acids as heterogeneous and reusable catalysts has been evaluated in the oxidative coupling reaction of xanthene and thioxanthene with nucleophiles.

#### 4.3.2 Results and discussion

The activity of two different supported sulfonic acids catalysts, in comparison with that of the commercially available sulfonic resins Amberlyst-15 and Nafion NR-50, was measured in the model reaction between cyclopentanone **10a** and xanthene **7a** carried out under oxygen atmosphere for 24 hours by using 5% mol of the supported

#### 4. Catalytic C-C bond formation promoted by supported sulfonic acid catalysts

sulfonic acid with respect to xanthene (Scheme 2). Results reported in Table 2 show that in all cases 2-(9H-xanthen-9-yl)cyclopentanone **11aa** was detected as the only product; in particular, the silica supported 4-ethylphenylsulfonic acid showed the best catalytic activity for this reaction (74% yield; Table 2, entry 2). Lower yields were observed with MCM-41 supported propanesulfonic acid catalyst and Nafion NR-50 (Table 2, entries 1 and 3 respectively).

**Table 2.** Oxidative coupling of xanthene with cyclopentanone.[a]

Entry	Catalyst	Surface acidity (mmol g <sup>-1</sup> )	Surface area (m <sup>2</sup> g <sup>-1</sup> )	<b>11aa</b> (%) <sup>[b]</sup>	Yield <b>11aa</b> (%) <sup>[c]</sup>	Selectivity
1	MCM-41-(CH <sub>2</sub> ) <sub>3</sub> -SO <sub>3</sub> H	2.53	970	54		93
2	SiO <sub>2</sub> -(CH <sub>2</sub> ) <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> -SO <sub>3</sub> H	1.14	293	74		95
3	Nafion NR-50	0.80	< 0.1	40		98
4	Amberlyst-15	4.70	53	71		96
5	Amberlyst-15	4.70	53	43		98 <sup>[d]</sup>
6	Amberlyst-15	4.70	53	4		25 <sup>[d, e]</sup>

[a] Reaction conditions: 1a (1.0 mmol), 4a (5.0 mmol), and solid catalyst (5% mol) were stirred under an atmosphere of oxygen at 40 °C for 24 h. [b] Yields were determined by GC analysis of the crude reaction mixture using dodecane as external standard. [c] Calculated on xanthene. [d] Air atmosphere. [e] Addition of 1.0 mmol of 30% aq H<sub>2</sub>O<sub>2</sub>.

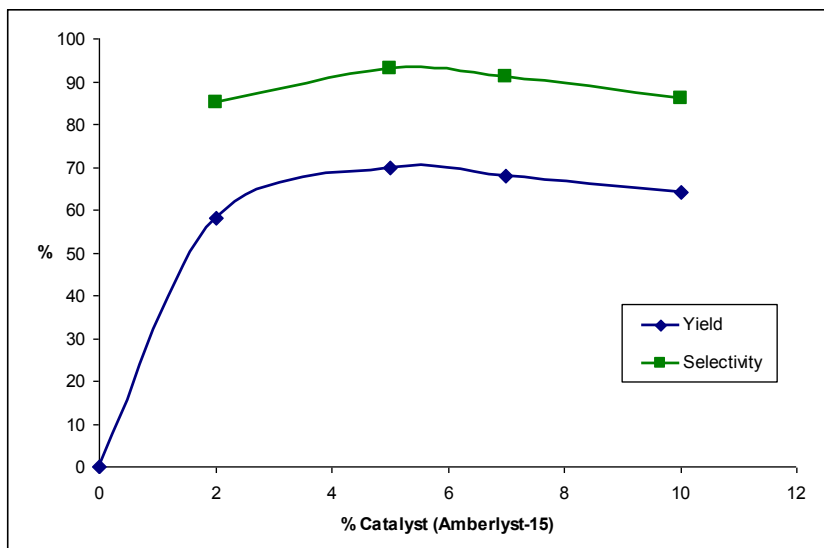
However, comparable results have been obtained with silica supported 4-ethylphenylsulfonic acid and Amberlyst-15 (Table 2, entries 2 and 4). The different activity showed by the four catalysts in the model reaction could be tentatively ascribed to the strength of the supported sulfonic acid rather than to the thickness of the acid sites and the surface area.[19, 32]

Further studies on the parameters affecting the reaction have been developed by using Amberlyst-15 as solid catalyst, being commercially available, more economic and safer to handle. Preliminary studies showed that the reaction was rather slow needing 24 hours to reach the plateau value of ~70% yield. For longer reaction times a slow, but continuous lowering of yield has been observed.

The effect of catalyst amount was then evaluated in the model reaction performed at 40 °C for 24 hours. Results of yield and selectivity showed in Figure 4 demonstrate that the reaction gives the desired product **11aa** in good yield and selectivity (58 and 85% respectively) with only 2% mol of catalyst. A further increase in yield was observed by increasing the amount of catalyst to 5% mol, reaching the maximum value of 70% yield and 93% selectivity. A slight lowering of yield and selectivity (to

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67 and 91% respectively) has been observed with a 7% mol catalyst amount; this negative trend was confirmed by further increasing the catalyst amount to 10% mol (64% yield and 85% selectivity).



**Figure 4.** Effect of Amberlyst-15 amount on the oxidative coupling of cyclopentanone with xanthene.

The model reaction can be performed with satisfactory yield (43%) under air atmosphere instead of oxygen (Table 1, entry 5), while the addition of one equivalent of  $\text{H}_2\text{O}_2$  completely blocked the reaction (Table 1, entry 6). Under the above conditions the methylene bridge of reagent **7a** could undergo oxidation as previously reported.[31] Although the mechanistic aspects of the reaction have not been deepened, the reaction mechanism proposed for the homogeneous reaction (Scheme 2) may occur also in this case. Indeed traces of hydroperoxide **8a** were detected in the reaction mixture and the presence of  $\text{H}_2\text{O}_2$  was confirmed by the  $\text{MnO}_2$  test.[33] The scope and generality of the oxidative coupling process with respect to various nucleophiles was then investigated. Experimental results reported in Table 3 confirm the general applicability to different cyclic and linear ketones and to 1,3-dicarbonyl compounds. Yields of isolated products are between 55 and 90%, accompanied by excellent selectivity values (83-99%).

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**Table 3.** Oxidative coupling of xanthene with different nucleophiles.[a]

Entry	X	R <sub>1</sub>	R <sub>2</sub>	Product	Yield <sup>[b]</sup> [Sel.] (%)
1	O	-(CH <sub>2</sub> ) <sub>3</sub> -		<b>11aa</b>	74 [95]
2	O	-(CH <sub>2</sub> ) <sub>4</sub> -		<b>11ab</b>	92 [98]
3	O	-CH(Me)(CH <sub>2</sub> ) <sub>3</sub> -		<b>11ac</b>	62 [89]
4	O	Me	Me	<b>11ad</b>	55 [89]
5	O	Ph	Me	<b>11ae</b>	86 [99]
6	O	<i>p</i> -MeO-(C <sub>6</sub> H <sub>4</sub> )	Me	<b>11af</b>	65 [99]
7	O	EtO(CO)	Me	<b>11ag</b>	73 [93]
8	O	CH <sub>3</sub> (CO)	Me	<b>11ah</b>	62 [83]
9	O	Ph(CO)	Me	<b>11ai</b>	66 [90] <sup>[c]</sup>
10	S	-(CH <sub>2</sub> ) <sub>4</sub> -		<b>11bb</b>	32 [99]
11	S	-(CH <sub>2</sub> ) <sub>4</sub> -		<b>11bb</b>	55 [98] <sup>[d]</sup>

[a] Reaction conditions: **1** (1.0 mmol), **4** (5.0 mmol), and Amberlyst-15 (11 mg; 0.05 mmol) were stirred under an oxygen atmosphere at 40 °C for 24 h. [b] Yields of isolated product. [c] Reaction temperature: 65 °C. [d] Reaction time: 72 h.

Furthermore the reaction of thioxanthene with cyclohexanone, was tested and the coupling product was obtained in good yield and excellent selectivity. It must be highlighted that, despite the oxidative reaction conditions, no traces of sulfone or sulfoxide were detected, even when the reaction was prolonged for 72 hours.

Finally the catalyst recyclability has been tested in the reaction between xanthene and cyclohexanone. After the first coupling reaction, the catalyst was filtered off, washed with methanol and water and reused for the next run. Eight runs can be efficiently performed with the recycled resin-supported sulfonic acid without a considerable decrease in its catalytic activity. The yield of each run was over 75% (Table 4).

**Table 4.** Oxidative coupling of xanthene with cyclohexanone.[a]

Run	<b>11ab</b> (%) <sup>[b]</sup>	yield	Run	<b>11ab</b> (%) <sup>[b]</sup>	yield
1	92		5	89	
2	83		6	77	
3	91		7	82	
4	82		8	76	

[a] Reaction conditions: **1a** (1.0 mmol), **4a** (5.0 mmol) and Amberlyst-15 (11 mg; 0.05 mmol) were stirred under an atmosphere of oxygen at 40 °C for 24 h. [b] Yields were determined by GC analysis of the crude reaction mixture using dodecane as external standard.

### 4.3.3 Conclusions

In summary, has been developed a clean and safe method for the oxidative coupling of xanthene and thioxanthene with methylene active compounds. The sulfonic resin catalyst has the advantage to be cheap, safe to handle and easy to recycle. Several important parameters of the “green chemistry” are satisfied: the atom economy is very high (99.2%), reaction condition are mild, the reaction is completely metal-free, and the work-up is very easy.

Since xanthene and its derivatives are very interesting pharmaceutical and biological active compounds, this reaction represent a valuable chance for the synthesis of these species.

### 4.3.4 Experimental Section

General procedure: xanthene (**7a**) (182 mg, 1.0 mmol), methylene active compound (**10**) (5.0 mmol) and Amberlyst-15 dried at 100 °C overnight (11 mg, 5 mol%) were mixed in a Schlenk tube equipped with a magnetic stirring bar. The tube was flushed with oxygen and then, after stirring at 40 °C for 24 h, the reaction mixture was purified directly by column chromatography (silica gel, eluant hexane/ethyl acetate 20:1) without further workup, giving the corresponding products **11**. Products **11ac** and **11af** are new compounds.

#### *Characterization of new products*

*rac* **2-Methyl-2-(9H-xanthen-9-yl)cyclohexanone (5ac)**: white solid, mp 128-30 °C; <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>, 25 °C, TMS): δ = 7.4-7.2 (m, 3H, 3 CH<sub>arom</sub>), 7.2-7.0 (m, 5H, 5 CH<sub>arom</sub>), 4.71 (s, 1H, CH), 2.7-2.3 (m, 2H, 2 CH<sub>aliph</sub>), 1.9-1.7 (m, 5H, 5 CH<sub>aliph</sub>), 1.4-1.2 (m, 1H, 1 CH<sub>aliph</sub>), 0.92 (s, 3 H, CH<sub>3</sub>); <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>, 25 °C, TMS): δ = 214.8, 154.2, 154.1, 130.4, 129.6, 128.0, 127.9, 123.0, 122.8, 122.4, 116.5, 55.9, 43.8, 39.7, 33.4, 26.1, 21.1, 20.6; IR (KBr): ν = 1699 (s) (C=O); MS (70 eV): *m/z* (%): 292 (3) [M]<sup>+</sup>, 181 (100) [C<sub>13</sub>H<sub>9</sub>O]<sup>+</sup>.



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***rac* 1-(4-Methoxyphenyl)-1-(9H-xanthen-9-yl)propan-2-one (5af)**: white solid, mp 118-21° C; <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>, 25 °C, TMS): δ = 7.36 (dd, <sup>3</sup>J(H,H)=7.6 Hz, <sup>4</sup>J(H,H)=1.2 Hz, 1H, CH<sub>arom</sub>), 7.25 (td, <sup>3</sup>J(H,H)=8.4 Hz, <sup>4</sup>J(H,H)=1.6 Hz, 1H, CH<sub>arom</sub>), 7.2-7.0 (m, 4H, 4 CH<sub>arom</sub>), 6.80 (d, <sup>3</sup>J(H,H)=8.8 Hz, 2H, 2 CH<sub>arom</sub>), 6.73 (td, <sup>3</sup>J(H,H)=7.6 Hz, <sup>4</sup>J(H,H)=1.2 Hz, 1H, CH<sub>arom</sub>), 6.71 (d, <sup>3</sup>J(H,H)=8.8 Hz, 2H, 2 CH<sub>arom</sub>), 6.57 (dd, <sup>3</sup>J(H,H)=7.6 Hz, <sup>4</sup>J(H,H)=1.2 Hz, 1H, CH<sub>arom</sub>), 4.66 (d, <sup>3</sup>J(H,H)=9.2 Hz, 1H, CH), 3.79 (d, <sup>3</sup>J(H,H)=9.2 Hz, 1H, CH), 3.78 (s, 3 H, OCH<sub>3</sub>), 1.87 (s, 3 H, CH<sub>3</sub>); <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>, 25 °C, TMS): δ = 207.8, 159.1, 153.2, 130.2, 129.7, 129.6, 127.8, 127.4, 125.2, 123.8, 123.3, 122.5, 116.4, 115.9, 113.7, 65.8, 55.2, 42.7, 31.1; IR (KBr): ν = 1709 (s) (C=O); MS (70 eV): *m/z* (%): 342 (77) [M-H<sub>2</sub>]<sup>+</sup>, 299 (30) [C<sub>21</sub>H<sub>15</sub>O<sub>2</sub>]<sup>+</sup>, 255 (100), 181 (35) [C<sub>13</sub>H<sub>9</sub>O]<sup>+</sup>.

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