

Supported Sulfonic Acids: Solid Catalysts for Batch and Continuous-Flow Synthetic Processes

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Date Awarded: March 1st, 2012

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In recent years the need to reduce production costs and the increasing regulations in pollution prevention prompted industries and academia to revise old processes for fine chemical and pharmaceutical synthesis. A powerful tool to enhance the sustainability of chemical processes is, undoubtedly, heterogeneous catalysis, which allows a few improvements over homogeneous catalysis and can help develop cleaner, safer, and more economically feasible processes. In the field of heterogeneous catalysis, two preferential methods have been developed: the use of polymer-supported catalysts and the use of solid inorganic oxide catalysts. In the last years, much effort has been devoted to the heterogenization of catalysts, and different strategies have been developed for the preparation of supported homogeneous catalysts.

The ideal supported catalyst should satisfy many requirements in order to combine the advantages of both homogeneous and heterogeneous catalysis. With careful catalyst design and an appropriate support choice based on reaction conditions (e.g. solvent, temperature, reactant, etc.) it is possible to prepare highly efficient supported catalysts. Recently the synthesis of organic compounds using supported catalysts or reagents has been of great interest in flow systems. 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. They allow for prolonged use of the supported catalyst because physical damage due to 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.


Brønsted and Lewis acids are the most important and most common catalysts. 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 economic problems.

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 The full thesis is available as Supporting Information on the WWW under <http://dx.doi.org/10.1002/open.201402148>.

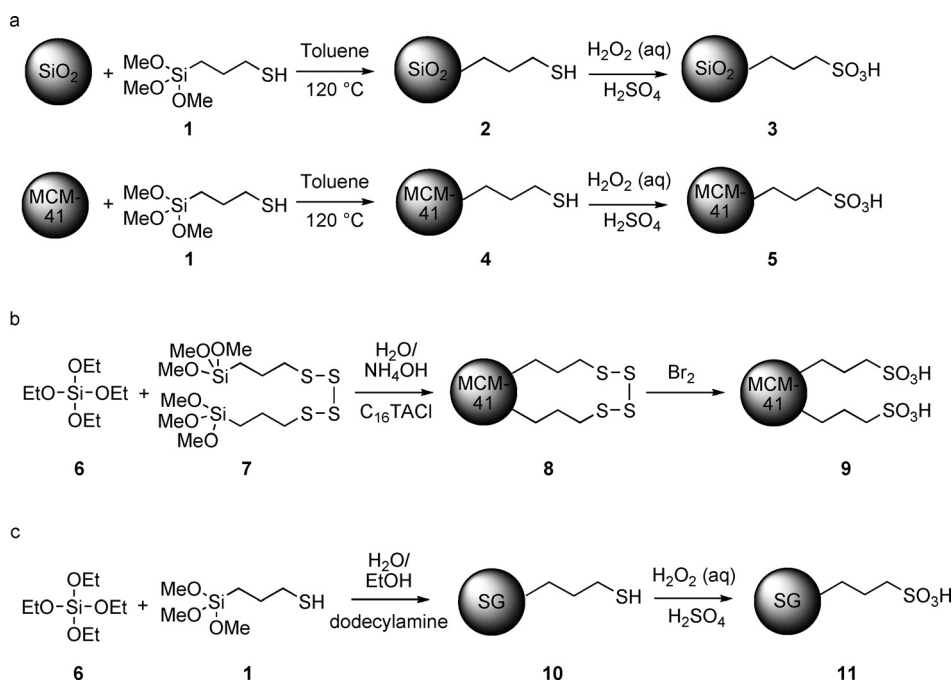
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Synthesis and characterization of supported sulfonic acids

Sulfonic acids are organic compounds that exhibit an acid strength comparable to that of sulfuric and benzenesulfonic acids, which are strong acids frequently used in organic solvents. The synthesis of silica-supported sulfonic acids can be achieved with different procedures. This thesis deals with the synthesis and evaluation of the catalytic activity of some supported sulfonic acids as heterogeneous and reusable catalysts in several organic reactions that are of synthetic interest.

Various supported sulfonic acids were prepared according to well-known literature procedures, with slight modifications (Scheme 1 and Scheme 2). To probe the acid behavior of the supported species,



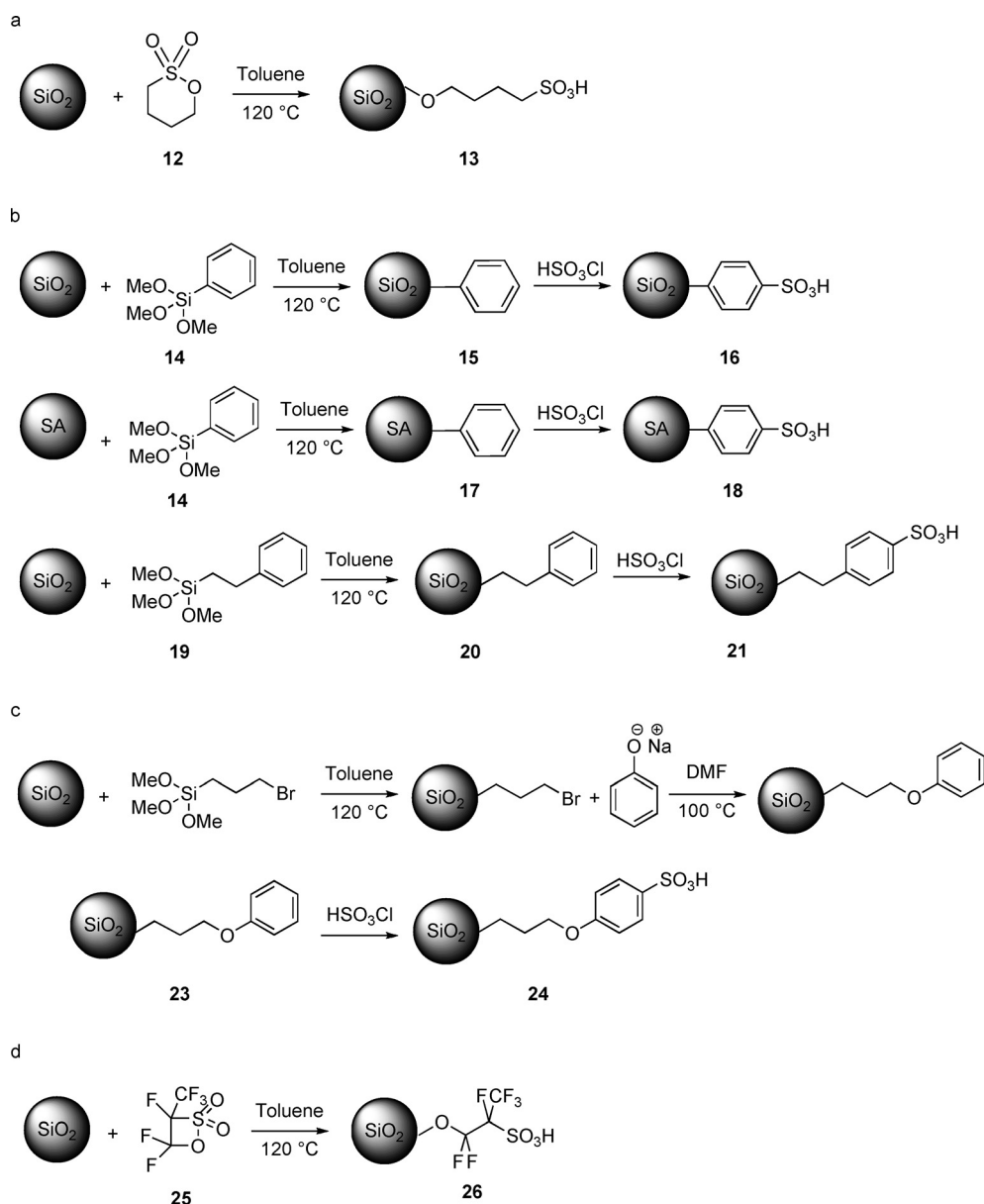
Scheme 1. Synthesis of the supported sulfonic acids used in this work. Preparation of propanesulfonic acids tethered onto a) silica (method A); b) mesoporous silica MCM-41 (method B); c) silica via sol-gel (SG) method.

the materials and the bare support (as a reference), were analyzed using infrared (IR) spectroscopy in degassed conditions (Figure 1) and under 20 mbar of water vapor (Figure 2). The 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 $3500\text{--}1700\text{ cm}^{-1}$. The latter is a kind of “fingerprint” of the formation of $\text{H}^+(\text{H}_2\text{O})_n$ clusters, and it probes the transfer of protons to the aqueous layers from $-\text{SO}_3\text{H}$ groups, which are converted into $-\text{SO}_3^-$. Thus, it can be stated that the contact with an aqueous medium results in complete deprotonation of the sulfonic groups.

Subsequently the interaction between the supported sulfonic acids and hydrogen peroxide was investigated. Hydrogen peroxide is an ideal oxidant for many reasons, mainly due to the fact that it is cheap, water is theoretically the sole byproduct, and its activation is a challenge that has attracted many research groups in order to perform oxidation reactions under environment-friendly conditions. The diffuse reflectance UV/Vis spectra of supported sulfonic acids contacted with an aqueous hydrogen peroxide solution suggested the possibility of an electrophilic activation of hydrogen peroxide via H-bonding.

Supported sulfonic acids as novel catalysts in green oxidation processes

The activity of some supported sulfonic acid catalysts was tested in the Baeyer–Villiger oxidation with 30% aqueous hydrogen peroxide, using cyclohexanone as model substrate and hexafluoroisopropanol (HFIP) as solvent. In all cases, the cyclohexanone conversion reached comparable high values (80–90%) independent from the acidity and surface area parameters of the catalyst used. The best catalyst efficiency was achieved by using a silica-supported propylsulfonic acid prepared by a tethering proce-



Scheme 2. Synthesis of the supported sulfonic acids used in this work. Preparation of a) butanesulfonic acid tethered onto amorphous silica; b) arylsulfonic acid tethered onto silica or silica alumina (SA); c) 4-propoxybenzenesulfonic acid tethered onto silica; d) (2-trifluoromethyl)perfluoroethanesulfonic acid tethered onto silica.

dure (**3**, Scheme 1a). Kinetic studies demonstrated that the desired lactone is produced through a spiro-bisperoxide intermediate.

In a flowing-case synthetic study, supported sulfonic acids were evaluated as catalysts in the 1,2-dihydroxylation of 1-methylcyclohexene with hydrogen peroxide. 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 (**21**, Scheme 2b). To achieve further information on the behavior of these catalysts, we analyzed the reactions with silica-supported phenylsulfonic, ethylphenylsulfonic, and propoxyphenylsulfonic acids under solvent-free conditions. Variable induction periods were observed with these supported acids; these induction times are expected to be due to the production of the active species. This reaction is obviously affected by the sulfonic acid group's accessibility, which depends on the length of the arm that binds them to the support surface: propoxyphenyl > ethylphenyl > phenyl.

Another relevant synthetic process that was investigated using supported sulfonic acid catalysts is the oxidation of methylhydroquinone to methylbenzoquinone with 30% aqueous hydrogen peroxide. The propylsulfonic acid tethered on both amorphous (**3**, Scheme 1a) and mesoporous MCM-

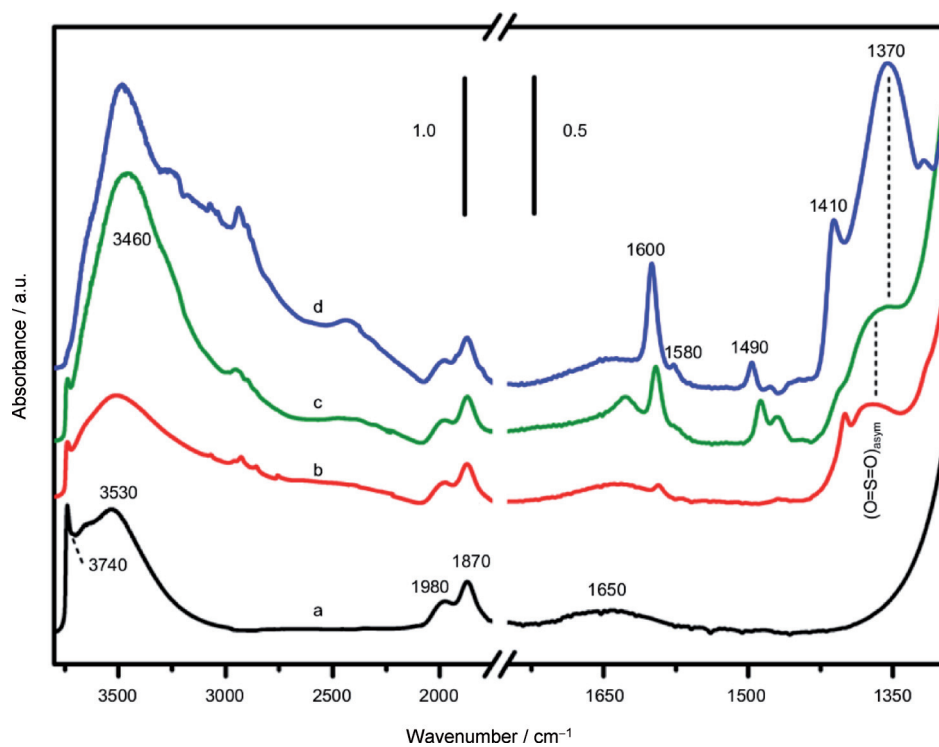


Figure 1. IR spectra of samples degassed at beam temperature (ca. 50 °C) for 1 h: a) bare silica; b) catalyst **16**; c) catalyst **24**; d) catalyst **21**.

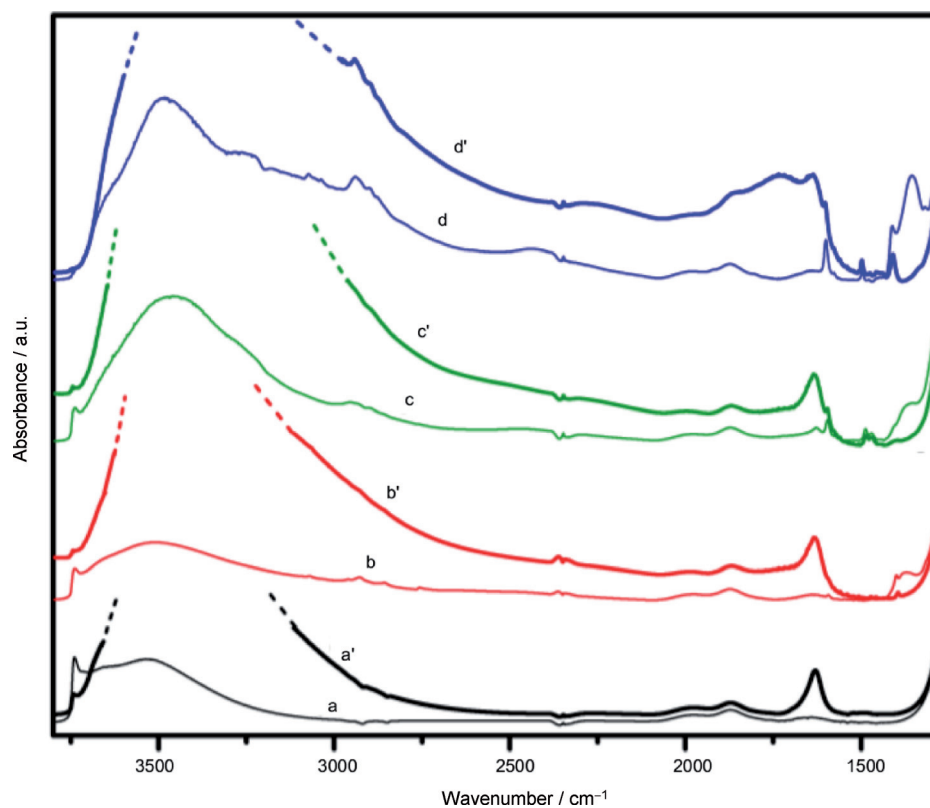


Figure 2. IR spectra of degassed samples and after contact with 20 mbar of water vapor (x, x'): a) bare silica; b) catalyst **16**; c) catalyst **24**; d) catalyst **21**.

41 silica (**5**, Scheme 1a) showed optimal activities. The reusability of $\text{SiO}_2-(\text{CH}_2)_3-\text{SO}_3\text{H}$ was then checked. The catalyst that is simply recovered by filtration and washed with hot methanol can be reused twice without loss of activity. The good synthetic results and, in particular, the effective catalyst recyclability achieved in the batch experiments were further developed on a continuous-flow catalytic system. The product was obtained in 55% yield, achieving a very high selectivity (95%), which is the most important parameter in a continuous-flow system.

Similarly the thioanisole oxidation reaction with hydrogen peroxide was examined under continuous-flow conditions. A simple process was set up using a glass column packed with Amberlite IR 120H as a reactor; and precise control of the flow rate of the reagent solutions was assured by two syringe pumps. The model reaction was investigated by conducting a systematic variation of experimental parameters. The desired sulfoxide was obtained in 94% yield and 99% selectivity, using a stoichiometric amount of 30% aqueous hydrogen peroxide. The promising results achieved in these experiments suggested the possibility to perform the oxidation of thioanisole with even more dilute hydrogen peroxide. For this reason, we used a 3% aqueous hydrogen peroxide solution, which is very cheap and can be handled safely. The yield was 90%, which, surprisingly, was only a small decrease. Moreover, as the sulfoxide was the only product, the reaction was completely selective. Finally, the catalyst could be used for at least 3000 min without any loss of activity. These results represent the first example of the successful oxidation of aromatic sulfides with 3% aqueous hydrogen peroxide. It must be emphasized that this process avoids the use of any metals for the activation of the oxidizing reagent.

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

C–C bond formation represents a fundamental transformation in organic synthesis; in fact, the reactions that allow the formation of this bond are key steps in many synthetic routes of valuable organic chemicals and natural products, as well as in a variety of industrial applications. Thus, these reactions are important tools for synthetic chemists. In this work two different reactions that allow C–C bond formation were explored: the Friedel–Crafts acylation of aromatics and the coupling reaction between ketones and xanthen through C–H bond activation.

The acylation reaction of anisole, catalyzed by silica-supported sulfonic acids was carried out. The above method shows low environmental impact because it avoids the use of halogenated compounds, and acetic acid is the only byproduct. The activity of different catalysts was compared. In all cases, 4-methoxyacetophenone was the major product. The best result in terms of both yield (71%) and selectivity (95%) toward the desired product was achieved with the perfluoroalkyl sulfonic acid tethered onto silica (**26**, Scheme 2d). The different activities of the tested materials seem to be correlated to the strength of the supported sulfonic acids. In fact, catalyst **26** is undoubtedly a stronger acid used in this work due to the inductive effect played by the fluorine atoms; on the contrary, catalysts **13** (Scheme 2a) and **21** (Scheme 2b) are weaker acids, and consequently, their activity is lower.

The model reaction was then performed using different aliphatic anhydrides with anisole. Experimental results underline that the anisole conversion and the aromatic ketone yield increase with the number of carbon atoms of the anhydrides, going from acetic anhydride (two carbon atoms) to valeric anhydride (five carbon atoms). With longer alkyl chains, the reactivity slightly decreases. This behavior may be attributed to a hydrophobic positive effect, which can improve the reactivity until the maximum is reached with valeric anhydride; for longer anhydrides, this effect is overbalanced by a negative steric influence.

Among the wide panorama of C–C bond formation reactions, cross-dehydrogenative coupling (CDC) is becoming a highly attractive example because it can unlock new opportunities for greener synthetic strategies. To study this area of interest, we selected the CDC between cyclopentanone and xanthen as a model reaction. The catalytic tests carried out under an oxygen atmosphere showed that in all cases, 2-(9H-xanthen-9-yl)cyclopentanone was produced as the only product; in particular, the silica-supported 4-ethylphenylsulfonic acid (**21**, Scheme 2b) showed the best catalytic activity for this reaction (74% yield). Further studies on the parameters affecting the reaction were performed by using Amberlyst-15 as a solid catalyst, being commercially available, more economical, and safer to handle. The scope and generality of the oxidative coupling process with respect to various nucleophiles was then investigated. Experimental results confirmed the general applicability of the method 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%). Finally, the catalyst recyclability was tested in the reaction between xanthen and cyclohexanone.

The supported sulfonic acids used in this work showed very good catalytic activity in different classes of reactions. These catalysts have the advantage of being cheap, safe to handle, and easy to recycle. Reaction conditions are mild, with very good atom economy in most cases, and work-up steps are very easy, satisfying several essential parameters of the "green chemistry" philosophy. Furthermore the application of these catalytic systems to continuous-flow processes resulted in a considerable improvement in efficiency.

Keywords: continuous-flow synthesis · green chemistry · oxidation · solid acids · sulfonic acids · supported catalysts

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Received: December 10, 2014
Published online on January 16, 2015